CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125085Orig1s332

Trade Name:	AVASTIN
Generic or Proper Name:	bevacizumab
Sponsor:	Genentech, Inc.
Approval Date:	May 29, 2020
Indication:	Avastin is a vascular endothelial growth factor inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, in combination with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen.

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer.

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and

paclitaxel for the first-line treatment.

- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma in combination with interferon alfa.
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
    - in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection
    - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistance recurrent disease who received no more than 2 prior chemotherapy regimens
    - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine followed by Avastin as a single agent, for platinum-sensitive recurrent disease.
- Hepatocellular Carcinoma (HCC)
    - in combination with atezolizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 125085/S-332

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Loan Ly
Program Manager, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Ly:

Please refer to your supplemental biologics license application (sBLA), dated and received January 24, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Avastin (bevacizumab).

This Prior Approval supplemental biologics application provides for a new indication of Avastin, in combination with atezolizumab, for the treatment of patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Gina Mehta, Regulatory Health Project Manager, at (301) 796-7910.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director (Acting)
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
    - Prescribing Information

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEVEN J LEMERY
05/29/2020 01:40:02 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s332

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN.

AVASTIN® (bevacizumab) injection, for intravenous use
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Indications and Usage, Hepatocellular Carcinoma (1.7)	05/2020
Dosage and Administration, Hepatocellular Carcinoma (2.8)	05/2020
Boxed Warning, Removed	06/2019
Warnings and Precautions (5 3, 5.9)	05/2020

----------INDICATIONS AND USAGE----------

Avastin is a vascular endothelial growth factor inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. (1.1)

Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer. (1.1)

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. (1.2)
- Recurrent glioblastoma in adults. (1.3)
- Metastatic renal cell carcinoma in combination with interferon alfa. (1.4)
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. (1.5)
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:
  - in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection (1.6)
  - in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens (1.6)
  - in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease (1.6)
- Hepatocellular Carcinoma (HCC)
  - in combination with atezolizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy (1.7)

----------DOSAGE AND ADMINISTRATION----------

Do not administer Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)
Metastatic colorectal cancer (2 2)
- 5 mg/kg every 2 weeks with bolus-IFL
- 10 mg/kg every 2 weeks with FOLFOX4
- 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Avastin containing regimen

First-line non–squamous non–small cell lung cancer (2.3)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent glioblastoma (2.4)
- 10 mg/kg every 2 weeks

Metastatic renal cell carcinoma **(**2.5)
- 10 mg/kg every 2 weeks with interferon alfa

Persistent, recurrent, or metastatic cervical cancer (2.6)
- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.7)
- 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week
- 15 mg/kg every 3 weeks with topotecan given every 3 weeks

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent
- 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

Hepatocellular Carcinoma (2.8)
- 15 mg/kg after administration of 1,200 mg of atezolizumab every 3 weeks

Administer as an intravenous infusion. (2 10)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Gastrointestinal Perforations and Fistula: Discontinue for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any organ (5.1)
- Surgery and Wound Healing Complications: Discontinue in patients who develop wound healing complications that require medical intervention or necrotizing fasciitis. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery, and until the wound is fully healed (5.2)
- Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3)
- Arterial Thromboembolic Events (ATE): Discontinue for severe ATE. (5.4)
- Venous Thromboembolic Events (VTE): Discontinue for Grade 4 VTE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue. (5.7)
- Renal Injury and Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine. (5.8)
- Infusion-Related Reactions: Decrease rate for infusion-related reactions. Discontinue for severe infusion-related reactions and administer medical therapy. (5.9)
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)
- Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)
- Congestive Heart Failure (CHF): Discontinue Avastin in patients who develop CHF. (5.12)

----------ADVERSE REACTIONS----------

Most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer

Avastin, in combination with intravenous fluorouracil-based chemotherapy, is indicated for the first-or second-line treatment of patients with metastatic colorectal cancer (mCRC).

Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line Avastin-containing regimen.

Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer *[see Clinical Studies (14.2)]*.

1.2 First-Line Non-Squamous Non–Small Cell Lung Cancer

Avastin, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).

1.3 Recurrent Glioblastoma

Avastin is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

1.4 Metastatic Renal Cell Carcinoma

Avastin, in combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

1.5 Persistent, Recurrent, or Metastatic Cervical Cancer

Avastin, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

1.6 Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Avastin, in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.

Avastin, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

1.7 Hepatocellular Carcinoma

Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Do not administer Avastin until at least 28 days following surgery and the wound is fully healed.

2.2 Metastatic Colorectal Cancer

The recommended dosage when Avastin is administered in combination with intravenous fluorouracil-based chemotherapy is:

- 5 mg/kg intravenously every 2 weeks in combination with bolus-IFL.
- 10 mg/kg intravenously every 2 weeks in combination with FOLFOX4.
- 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line Avastin-containing regimen.

2.3 First-Line Non-Squamous Non-Small Cell Lung Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel.

2.4 Recurrent Glioblastoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks.

2.5 Metastatic Renal Cell Carcinoma

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with interferon alfa.

2.6 Persistent, Recurrent, or Metastatic Cervical Cancer

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

2.7 Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Disease Following Initial Surgical Resection

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent for a total of up to 22 cycles or until disease progression, whichever occurs earlier.

Recurrent Disease

Platinum Resistant

The recommended dosage is 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week).

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

Platinum Sensitive

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

The recommended dosage is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

2.8 Hepatocellular Carcinoma

The recommended dosage is 15 mg/kg intravenously after administration of 1,200 mg of atezolizumab intravenously on the same day, every 3 weeks until disease progression or unacceptable toxicity.

Refer to the Prescribing Information for atezolizumab prior to initiation for recommended dosage information.

2.9 Dosage Modifications for Adverse Reactions

Table 1 describes dosage modifications for specific adverse reactions. No dose reductions for Avastin are recommended.

Table 1: Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.	• Gastrointestinal perforation, any grade • Tracheoesophageal fistula, any grade • Fistula, Grade 4 • Fistula formation involving any internal organ	Discontinue Avastin
Wound Healing Complications *[see Warnings and Precautions (5.2)]*.	• Wound healing complications requiring medical intervention • Necrotizing fasciitis	Discontinue Avastin
Hemorrhage *[see Warnings and Precautions (5.3)]*.	• Grade 3 or 4	Discontinue Avastin
	• Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more	Withhold Avastin
Thromboembolic Events *[see Warnings and Precautions (5.4, 5.5)]*.	• Arterial thromboembolism, severe	Discontinue Avastin
	• Venous thromboembolism, Grade 4	Discontinue Avastin
Hypertension *[see Warnings and Precautions (5.6)]*.	• Hypertensive crisis • Hypertensive encephalopathy	Discontinue Avastin
	• Hypertension, severe	Withhold Avastin if not controlled with medical management; resume once controlled
Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.7)]*.	• Any	Discontinue Avastin
Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.	• Nephrotic syndrome	Discontinue Avastin
	• Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome	Withhold Avastin until proteinuria less than 2 grams per 24 hours
Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.	• Severe	Discontinue Avastin
	• Clinically significant	Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve
	• Mild, clinically insignificant	Decrease infusion rate
Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.	Any	Discontinue Avastin

2.10 Preparation and Administration

Preparation

- Use appropriate aseptic technique.
- Visually inspect vial for particulate matter and discoloration prior to preparation for administration. Discard vial if solution is cloudy, discolored or contains particulate matter.
- Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- Store diluted Avastin solution at 2°C to 8°C (36°F to 46°F) for up to 8 hours.
- No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

Administration

- Administer as an intravenous infusion.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated. Administer all subsequent infusions over 30 minutes if second infusion over 60 minutes is tolerated.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) clear to slightly opalescent, colorless to pale brown solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations and Fistulae

Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies, with the highest incidence in patients with a history of prior pelvic radiation. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of perforations occurred within 50 days of the first dose *[see Adverse Reactions (6.1)]*.

Serious fistulae (including, tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites) occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from < 1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. The majority of fistulae occurred within 6 months of the first dose. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

Avoid Avastin in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ.

5.2 Surgery and Wound Healing Complications

In a controlled clinical study in which Avastin was not administered within 28 days of major surgical procedures, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery while receiving Avastin and 4% in patients who did not receive Avastin. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received Avastin and 0.7% in patients who did not receive Avastin *[see Adverse Reactions (6.1)]*.

Discontinue Avastin in patients with wound healing complications requiring medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following surgery and until the wound is fully healed.

Necrotizing fasciitis including fatal cases, has been reported in patients receiving Avastin, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue Avastin in patients who develop necrotizing fasciitis.

5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, which is most commonly Grade 1 epistaxis, and serious hemorrhage, which in some cases has been fatal. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-5 hemorrhagic events ranged from 0.4% to 7% in patients receiving Avastin *[see Adverse Reactions (6.1)]*.

Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving Avastin with chemotherapy compared to none of the patients receiving chemotherapy alone.

An evaluation for the presence of varices is recommended within 6 months of initiation of Avastin in patients with HCC. There is lack of clinical data to support the safety of Avastin in patients with variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding because these patients were excluded from clinical trials of Avastin in HCC *[see Clinical Studies (14.10)]*.

Do not administer Avastin to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grades 3-4 hemorrhage.

5.4 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3-5 ATE was 5% in patients receiving Avastin with chemotherapy compared to ≤2% in patients receiving chemotherapy alone; the highest incidence occurred in patients with GBM. The risk of developing ATE was increased in patients with a history of arterial thromboembolism, diabetes, or >65 years *[see Use in Specific Populations (8.5)]*.

Discontinue in patients who develop a severe ATE. The safety of reinitiating Avastin after an ATE is resolved is not known.

5.5 Venous Thromboembolic Events

An increased risk of venous thromboembolic events (VTE) was observed across clinical studies *[see Adverse Reactions (6.1)]*. In Study GOG-0240, Grades 3-4 VTE occurred in 11% of patients receiving Avastin with

chemotherapy compared with 5% of patients receiving chemotherapy alone. In EORTC 26101, the incidence of Grades 3-4 VTE was 5% in patients receiving Avastin with chemotherapy compared to 2% in patients receiving chemotherapy alone.

Discontinue Avastin in patients with a Grade 4 VTE, including pulmonary embolism.

5.6 Hypertension

Severe hypertension occurred at a higher incidence in patients receiving Avastin as compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-4 hypertension ranged from 5% to 18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuing Avastin. Withhold Avastin in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

5.7 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) was reported in < 0.5% of patients across clinical studies. The onset of symptoms occurred from 16 hours to 1 year after the first dose. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES.

Discontinue Avastin in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing Avastin, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin in patients who developed PRES is not known.

5.8 Renal Injury and Proteinuria

The incidence and severity of proteinuria was higher in patients receiving Avastin as compared to patients receiving chemotherapy. Grade 3 (defined as urine dipstick 4+ or > 3.5 grams of protein per 24 hours) to Grade 4 (defined as nephrotic syndrome) ranged from 0.7% to 7% in clinical studies. The overall incidence of proteinuria (all grades) was only adequately assessed in Study BO17705, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (15 days to 37 months) after initiating Avastin. Median time to resolution was 6.1 months (95% CI: 2.8, 11.3). Proteinuria did not resolve in 40% of patients after median follow-up of 11.2 months and required discontinuation of Avastin in 30% of the patients who developed proteinuria *[see Adverse Reactions (6.1)]*.

In an exploratory, pooled analysis of patients from seven randomized clinical studies, 5% of patients receiving Avastin with chemotherapy experienced Grades 2-4 (defined as urine dipstick 2+ or greater or > 1 gram of protein per 24 hours or nephrotic syndrome) proteinuria. Grades 2-4 proteinuria resolved in 74% of patients. Avastin was reinitiated in 42% of patients. Of the 113 patients who reinitiated Avastin, 48% experienced a second episode of Grades 2-4 proteinuria.

Nephrotic syndrome occurred in < 1% of patients receiving Avastin across clinical studies, in some instances with fatal outcome. In a published case series, kidney biopsy of 6 patients with proteinuria showed findings consistent with thrombotic microangiopathy. Results of a retrospective analysis of 5805 patients who received Avastin with chemotherapy and 3713 patients who received chemotherapy alone, showed higher rates of elevated serum creatinine levels (between 1.5 to 1.9 times baseline levels) in patients who received Avastin. Serum creatinine levels did not return to baseline in approximately one-third of patients who received Avastin.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Withhold for proteinuria greater than or equal to 2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome.

Data from a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24-hour urine protein [Pearson Correlation 0.39 (95% CI: 0.17, 0.57)].

5.9 Infusion-Related Reactions

Infusion-related reactions reported across clinical studies and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion-related reactions with the first dose occurred in < 3% of patients and severe reactions occurred in 0.4% of patients.

Decrease the rate of infusion for mild, clinically insignificant infusion-related reactions. Interrupt the infusion in patients with clinically significant infusion-related reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion-related reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).

5.10 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, Avastin may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.11 Ovarian Failure

The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or an FSH level < 30 mIU/mL during the post-treatment period. Long-term effects of Avastin on fertility are unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

5.12 Congestive Heart Failure (CHF)

Avastin is not indicated for use with anthracycline-based chemotherapy. The incidence of Grade $\geq$ 3 left ventricular dysfunction was 1% in patients receiving Avastin compared to 0.6% of patients receiving chemotherapy alone. Among patients who received prior anthracycline treatment, the rate of CHF was 4% for patients receiving Avastin with chemotherapy as compared to 0.6% for patients receiving chemotherapy alone.

In previously untreated patients with a hematological malignancy, the incidence of CHF and decline in left ventricular ejection fraction (LVEF) were increased in patients receiving Avastin with anthracycline-based chemotherapy compared to patients receiving placebo with the same chemotherapy regimen. The proportion of patients with a decline in LVEF from baseline of $\geq$ 20% or a decline from baseline of 10% to < 50%, was 10% in patients receiving Avastin with chemotherapy compared to 5% in patients receiving chemotherapy alone.

Time to onset of left-ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the Avastin arm compared to 82% in the placebo arm. Discontinue Avastin in patients who develop CHF.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.
- Surgery and Wound Healing Complications *[see Warnings and Precautions (5.2)]*.
- Hemorrhage *[see Warnings and Precautions (5.3)]*.
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.4)]*.
- Venous Thromboembolic Events *[see Warnings and Precautions (5.5)]*.
- Hypertension *[see Warnings and Precautions (5.6)]*.
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.7)]*.
- Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.
- Infusion-Related Reactions *[see Warnings and Precautions (5.9)]*.
- Ovarian Failure *[see Warnings and Precautions (5.11)]*.
- Congestive Heart Failure *[see Warnings and Precautions (5.12)]*.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety data in Warnings and Precautions and described below reflect exposure to Avastin in 4463 patients including those with mCRC (AVF2107g, E3200), non-squamous NSCLC (E4599), GBM (EORTC 26101), mRCC (BO17705), cervical cancer (GOG-0240), epithelial ovarian, fallopian tube, or primary peritoneal cancer (MO22224, AVF4095, GOG-0213, and GOG-0218), or HCC (IMbrave150) at the recommended dose and schedule for a median of 6 to 23 doses. The most common adverse reactions observed in patients receiving Avastin as a single agent or in combination with other anti-cancer therapies at a rate > 10% were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis.

Across clinical studies, Avastin was discontinued in 8% to 22% of patients because of adverse reactions *[see Clinical Studies (14)]*.

Metastatic Colorectal Cancer

In Combination with bolus-IFL

The safety of Avastin was evaluated in 392 patients who received at least one dose of Avastin in a double-blind, active-controlled study (AVF2107g), which compared Avastin (5 mg/kg every 2 weeks) with bolus-IFL to placebo with bolus-IFL in patients with mCRC *[see Clinical Studies (14.1)]*. Patients were randomized (1:1:1) to placebo with bolus-IFL, Avastin with bolus-IFL, or Avastin with fluorouracil and leucovorin. The demographics of the safety population were similar to the demographics of the efficacy population. All Grades 3–4 adverse reactions and selected Grades 1–2 adverse reactions (i.e., hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Adverse reactions are presented in Table 2.

Table 2: Grades 3-4 Adverse Reactions Occurring at Higher Incidence (≥2%) in Patients Receiving Avastin vs. Placebo in Study AVF2107g

Adverse Reaction[a]	Avastin with IFL (N=392)	Placebo with IFL (N=396)
Hematology		
Leukopenia	37%	31%
Neutropenia	21%	14%
Gastrointestinal		
Diarrhea	34%	25%
Abdominal pain	8%	5%
Constipation	4%	2%
Vascular		
Hypertension	12%	2%
Deep vein thrombosis	9%	5%
Intra-abdominal thrombosis	3%	1%
Syncope	3%	1%
General		
Asthenia	10%	7%
Pain	8%	5%

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In Combination with FOLFOX4

The safety of Avastin was evaluated in 521 patients in an open-label, active-controlled study (E3200) in patients who were previously treated with irinotecan and fluorouracil for initial therapy for mCRC. Patients were randomized (1:1:1) to FOLFOX4, Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity.

The demographics of the safety population were similar to the demographics of the efficacy population.

Selected Grades 3–5 non-hematologic and Grades 4–5 hematologic occurring at a higher incidence (≥2%) in patients receiving Avastin with FOLFOX4 compared to FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse reaction rates due to the reporting mechanisms.

First-Line Non Squamous Non-Small Cell Lung Cancer

The safety of Avastin was evaluated as first-line treatment in 422 patients with unresectable NSCLC who received at least one dose of Avastin in an active-controlled, open-label, multicenter trial (E4599) *[see Clinical Studies (14.3)]*. Chemotherapy naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel and carboplatin with or without Avastin (15 mg/kg every 3 weeks). After completion or upon discontinuation of chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving

therapeutic anticoagulation. The demographics of the safety population were similar to the demographics of the efficacy population.

Only Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions were collected. Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with paclitaxel and carboplatin compared with patients receiving chemotherapy alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thromboembolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Recurrent Glioblastoma

The safety of Avastin was evaluated in a multicenter, randomized, open-label study (EORTC 26101) in patients with recurrent GBM following radiotherapy and temozolomide of whom 278 patients received at least one dose of Avastin and are considered safety evaluable *[see Clinical Studies (14.4)]*. Patients were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine or lomustine alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. In the Avastin with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving Avastin with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

Metastatic Renal Cell Carcinoma

The safety of Avastin was evaluated in 337 patients who received at least one dose of Avastin in a multicenter, double-blind study (BO17705) in patients with mRCC. Patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks) or placebo with interferon alfa *[see Clinical Studies (14.5)]*. Patients were treated until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-5 adverse reactions occurring at a higher incidence (>2%) were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). Adverse reactions are presented in Table 3.

Table 3: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥5%) of Patients Receiving Avastin vs. Placebo with Interferon Alfa in Study BO17705

Adverse Reaction[a]	Avastin with Interferon Alfa (N=337)	Placebo with Interferon Alfa (N=304)
Metabolism and nutrition		
Decreased appetite	36%	31%
Weight loss	20%	15%
General		
Fatigue	33%	27%
Vascular		
Hypertension	28%	9%
Respiratory, thoracic and mediastinal		
Epistaxis	27%	4%
Dysphonia	5%	0%
Nervous system		
Headache	24%	16%
Gastrointestinal		
Diarrhea	21%	16%
Renal and urinary		
Proteinuria	20%	3%
Musculoskeletal and connective tissue		
Myalgia	19%	14%
Back pain	12%	6%

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The following adverse reactions were reported at a 5-fold greater incidence in patients receiving Avastin with interferon-alfa compared to patients receiving placebo with interferon-alfa and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of Avastin was evaluated in 218 patients who received at least one dose of Avastin in a multicenter study (GOG-0240) in patients with persistent, recurrent, or metastatic cervical cancer*[see Clinical Studies (14.6)]*. Patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin (15 mg/kg every 3 weeks), or paclitaxel and topotecan with or without Avastin (15 mg/kg every 3 weeks). The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 218 patients receiving Avastin with chemotherapy compared to 222 patients receiving chemotherapy alone were abdominal pain (12% vs. 10%), hypertension (11% vs. 0.5%), thrombosis (8% vs. 3%), diarrhea (6% vs. 3%), anal fistula (4% vs. 0%), proctalgia (3% vs. 0%), urinary tract infection (8% vs. 6%), cellulitis (3% vs. 0.5%), fatigue (14% vs. 10%), hypokalemia (7% vs. 4%), hyponatremia (4% vs. 1%), dehydration (4% vs. 0.5%), neutropenia (8% vs. 4%), lymphopenia (6% vs. 3%), back pain (6% vs. 3%), and pelvic pain (6% vs. 1%). Adverse reactions are presented in Table 4.

Table 4: Grades 1-4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0240

Adverse Reaction[a]	Avastin with Chemotherapy (N=218)	Chemotherapy (N=222)
General		
Fatigue	80%	75%
Peripheral edema	15%	22%
Metabolism and nutrition		
Decreased appetite	34%	26%
Hyperglycemia	26%	19%
Hypomagnesemia	24%	15%
Weight loss	21%	7%
Hyponatremia	19%	10%
Hypoalbuminemia	16%	11%
Vascular		
Hypertension	29%	6%
Thrombosis	10%	3%
Infections		
Urinary tract infection	22%	14%
Infection	10%	5%
Nervous system		
Headache	22%	13%
Dysarthria	8%	1%
Psychiatric		
Anxiety	17%	10%
Respiratory, thoracic and mediastinal		
Epistaxis	17%	1%
Renal and urinary		
Increased blood creatinine	16%	10%
Proteinuria	10%	3%
Gastrointestinal		
Stomatitis	15%	10%
Proctalgia	6%	1%
Anal fistula	6%	0%
Reproductive system and breast		
Pelvic pain	14%	8%
Hematology		
Neutropenia	12%	6%
Lymphopenia	12%	5%

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Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Following Initial Surgical Resection
The safety of Avastin was evaluated in GOG-0218, a multicenter, randomized, double-blind, placebo controlled, three arm study, which evaluated the addition of Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection *[see Clinical Studies (14.7)]*. Patients were randomized (1:1:1) to carboplatin and paclitaxel without Avastin (CPP), carboplatin and paclitaxel with Avastin for up to six cycles (CPB15), or carboplatin and paclitaxel with Avastin for six cycles followed by Avastin as a single agent for up to 16 additional doses (CPB15+). Avastin was given at 15 mg/kg every three weeks. On this trial, 1215 patients received at least one dose of Avastin. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the Avastin arms versus the control arm were fatigue (CPB15+ - 9%, CPB15 - 6%, CPP - 6%), hypertension (CPB15+ - 10%, CPB15 - 6%, CPP - 2%), thrombocytopenia (CPB15+ - 21%, CPB15 - 20%, CPP - 15%) and leukopenia (CPB15+ - 51%, CPB15 - 53%, CPP - 50%). Adverse reactions are presented in Table 5.

Table 5: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in GOG-0218

Adverse Reaction[a]	**Avastin with carboplatin and paclitaxel followed by Avastin alone[*] (N=608)**	**Avastin with carboplatin and paclitaxel[**] (N= 607)**	**Carboplatin and paclitaxel[***] (N= 602)**
General			
Fatigue	80%	72%	73%
Gastrointestinal			
Nausea	58%	53%	51%
Diarrhea	38%	40%	34%
Stomatitis	25%	19%	14%
Musculoskeletal and connective tissue			
Arthralgia	41%	33%	35%
Pain in extremity	25%	19%	17%
Muscular weakness	15%	13%	9%
Nervous system			
Headache	34%	26%	21%
Dysarthria	12%	10%	2%
Vascular			
Hypertension	32%	24%	14%
Respiratory, thoracic and mediastinal			
Epistaxis	31%	30%	9%
Dyspnea	26%	28%	20%
Nasal mucosal disorder	10%	7%	4%

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Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
The safety of Avastin was evaluated in 179 patients who received at least one dose of Avastin in a multicenter, open-label study (MO22224) in which patients were randomized (1:1) to Avastin with chemotherapy or chemotherapy alone in patients with platinum resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within < 6 months from the most recent platinum based therapy *[see Clinical*

Studies (14.8)]. Patients were randomized to receive Avastin 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks. Patients had received no more than 2 prior chemotherapy regimens. The trial excluded patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Patients were treated until disease progression or unacceptable toxicity. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 179 patients receiving Avastin with chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%).
Adverse reactions are presented in Table 6.

Table 6: Grades 2−4 Adverse Reactions Occurring at Higher Incidence (≥5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study MO22224

Adverse Reaction[a]	Avastin with Chemotherapy (N=179)	Chemotherapy (N=181)
Hematology		
Neutropenia	31%	25%
Vascular		
Hypertension	19%	6%
Nervous system		
Peripheral sensory neuropathy	18%	7%
General		
Mucosal inflammation	13%	6%
Renal and urinary		
Proteinuria	12%	0.6%
Skin and subcutaneous tissue		
Palmar-plantar erythrodysaesthesia	11%	5%
Infections		
Infection	11%	4%
Respiratory, thoracic and mediastinal		
Epistaxis	5%	0%

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Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g
The safety of Avastin was evaluated in 247 patients who received at least one dose of Avastin in a double-blind study (AVF4095g) in patients with platinum sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer *[see Clinical Studies (14.9]*. Patients were randomized (1:1) to receive Avastin (15 mg/kg) or placebo every 3 weeks with carboplatin and gemcitabine for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to placebo with chemotherapy were: thrombocytopenia (40% vs. 34%), nausea (4% vs. 1.3%), fatigue (6% vs. 4%), headache (4% vs. 0.9%), proteinuria (10% vs. 0.4%), dyspnea (4% vs. 1.7%), epistaxis (5% vs. 0.4%), and hypertension (17% vs. 0.9%). Adverse reactions are presented in Table 7.

Table 7: Grades 1−5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g

Adverse Reaction[a]	Avastin with Carboplatin and Gemcitabine (N=247)	Placebo with Carboplatin and Gemcitabine (N=233)
General		
Fatigue	82%	75%
Mucosal inflammation	15%	10%
Gastrointestinal		
Nausea	72%	66%
Diarrhea	38%	29%
Stomatitis	15%	7%
Hemorrhoids	8%	3%
Gingival bleeding	7%	0%
Hematology		
Thrombocytopenia	58%	51%
Respiratory, thoracic and mediastinal		
Epistaxis	55%	14%
Dyspnea	30%	24%
Cough	26%	18%
Oropharyngeal pain	16%	10%
Dysphonia	13%	3%
Rhinorrhea	10%	4%
Sinus congestion	8%	2%
Nervous system		
Headache	49%	30%
Dizziness	23%	17%
Vascular		
Hypertension	42%	9%
Musculoskeletal and connective tissue		
Arthralgia	28%	19%
Back pain	21%	13%
Psychiatric		
Insomnia	21%	15%
Renal and urinary		
Proteinuria	20%	3%
Injury and procedural		
Contusion	17%	9%
Infections		
Sinusitis	15%	9%

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Study GOG-0213

The safety of Avastin was evaluated in an open-label, controlled study (GOG-0213) in 325 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy*[see Clinical Studies (14.9)]*. Patients were randomized (1:1) to receive carboplatin and paclitaxel for 6 to 8 cycles or Avastin (15 mg/kg every 3 weeks) with carboplatin and paclitaxel for 6 to 8 cycles followed by Avastin as a single agent until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to chemotherapy alone were: hypertension (11% vs. 0.6%), fatigue (8% vs. 3%), febrile neutropenia (6% vs. 3%), proteinuria (8% vs. 0%), abdominal pain (6% vs. 0.9%), hyponatremia (4% vs. 0.9%), headache (3% vs. 0.9%), and pain in extremity (3% vs. 0%).
Adverse reactions are presented in Table 8.

Table 8: Grades 1−5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Musculoskeletal and connective tissue		
Arthralgia	45%	30%
Myalgia	29%	18%
Pain in extremity	25%	14%
Back pain	17%	10%
Muscular weakness	13%	8%
Neck pain	9%	0%
Vascular		
Hypertension	42%	3%
Gastrointestinal		
Diarrhea	39%	32%
Abdominal pain	33%	28%
Vomiting	33%	25%
Stomatitis	33%	16%
Nervous system		
Headache	38%	20%
Dysarthria	14%	2%
Dizziness	13%	8%
Metabolism and nutrition		
Decreased appetite	35%	25%
Hyperglycemia	31%	24%
Hypomagnesemia	27%	17%
Hyponatremia	17%	6%
Weight loss	15%	4%
Hypocalcemia	12%	5%
Hypoalbuminemia	11%	6%
Hyperkalemia	9%	3%
Respiratory, thoracic and mediastinal		
Epistaxis	33%	2%
Dyspnea	30%	25%
Cough	30%	17%
Rhinitis allergic	17%	4%
Nasal mucosal disorder	14%	3%
Skin and subcutaneous tissue		
Exfoliative rash	23%	16%
Nail disorder	10%	2%
Dry skin	7%	2%
Renal and urinary		
Proteinuria	17%	1%
Increased blood creatinine	13%	5%
Hepatic		

Adverse Reaction[a]	Avastin with Carboplatin and Paclitaxel (N=325)	Carboplatin and Paclitaxel (N=332)
Increased aspartate aminotransferase	15%	9%
General		
Chest pain	8%	2%
Infections		
Sinusitis	7%	2%

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Hepatocellular Carcinoma (HCC)

The safety of Avastin in combination with atezolizumab was evaluated in IMbrave150, a multicenter, international, randomized, open-label trial in patients with locally advanced or metastatic or unresectable hepatocellular carcinoma who have not received prior systemic treatment *[see Clinical Studies (14.10)]*. Patients received 1,200 mg of atezolizumab intravenously followed by 15 mg/kg Avastin (n=329) every 3 weeks, or 400 mg of sorafenib (n=156) given orally twice daily, until disease progression or unacceptable toxicity. The median duration of exposure to Avastin was 6.9 months (range: 0-16 months) and to atezolizumab was 7.4 months (range: 0-16 months).

Fatal adverse reactions occurred in 4.6% of patients in the Avastin and atezolizumab arm. The most common adverse reactions leading to death were gastrointestinal and esophageal varices hemorrhage (1.2%) and infections (1.2%).

Serious adverse reactions occurred in 38% of patients in the Avastin and atezolizumab arm. The most frequent serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%).

Adverse reactions leading to discontinuation of Avastin occurred in 15% of patients in the Avastin and atezolizumab arm. The most common adverse reactions leading to Avastin discontinuation were hemorrhages (4.9%), including bleeding varicose vein, hemorrhage and gastrointestinal, subarachnoid, and pulmonary hemorrhages; and increased transaminases or bilirubin (0.9%).

Adverse reactions leading to interruption of Avastin occurred in 46% of patients in the Avastin and atezolizumab arm; the most common (≥ 2%) were proteinuria (6%); infections (6%); hypertension (6%); liver function laboratory abnormalities including increased transaminases, bilirubin, or alkaline phosphatate (4.6%); gastrointestinal hemorrhages (3%); thrombocytopenia/decreased platelet count (4.3%); and pyrexia (2.4%).

Tables 9 and 10 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received Avastin and atezolizumab in IMbrave150.

Table 9: Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving Avastin in IMbrave150

Adverse Reaction	Avastin in combination with atezolizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Vascular Disorders				
Hypertension	30	15	24	12
General Disorders and Administration Site Conditions				
Fatigue/asthenia[1]	26	2	32	6
Pyrexia	18	0	10	0
Renal and Urinary Disorders				
Proteinuria	20	3	7	0.6
Investigations				
Weight Decreased	11	0	10	0
Skin and Subcutaneous Tissue Disorders				
Pruritus	19	0	10	0
Rash	12	0	17	2.6
Gastrointestinal Disorders				
Diarrhea	19	1.8	49	5
Constipation	13	0	14	0
Abdominal Pain	12	0	17	0
Nausea	12	0	16	0
Vomiting	10	0	8	0
Metabolism and Nutrition Disorders				
Decreased Appetite	18	1.2	24	3.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	12	0	10	0
Epistaxis	10	0	4.5	0
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction	11	2.4	0	0

[1] Includes fatigue and asthenia
[2] Graded per NCI CTCAE v4.0

Table 10: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving Avastin in IMbrave150

Laboratory Abnormality	Avastin in combination with atezolizumab (n=329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Chemistry				
Increased AST	86	16	90	16
Increased Alkaline Phosphatase	70	4	76	4.6
Increased ALT	62	8	70	4.6
Decreased Albumin	60	1.5	54	0.7
Decreased Sodium	54	13	49	9
Increased Glucose	48	9	43	4.6
Decreased Calcium	30	0.3	35	1.3
Decreased Phosphorus	26	4.7	58	16
Increased Potassium	23	1.9	16	2
Hypomagnesemia	22	0	22	0
Hematology				
Decreased Platelet	68	7	63	4.6
Decreased Lymphocytes	62	13	58	11
Decreased Hemoglobin	58	3.1	62	3.9
Increased Bilirubin	57	8	59	14
Decreased Leukocyte	32	3.4	29	1.3
Decreased Neutrophil	23	2.3	16	1.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: Avastin plus atezolizumab (222-323) and sorafenib (90-153) NA = Not applicable.
[1] Graded per NCI CTCAE v4.0

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bevacizumab in the studies described below with the incidence of antibodies in other studies or to other bevacizumab products may be misleading.

In clinical studies for adjuvant treatment of a solid tumor, 0.6% (14/2233) of patients tested positive for treatment-emergent anti-bevacizumab antibodies as detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-bevacizumab antibodies is not known.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Avastin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General: Polyserositis
Cardiovascular: Pulmonary hypertension, Mesenteric venous occlusion
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Hepatobiliary disorders: Gallbladder perforation
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation

7 DRUG INTERACTIONS

Effects of Avastin on Other Drugs

No clinically meaningful effect on the pharmacokinetics of irinotecan or its active metabolite SN38, interferon alfa, carboplatin or paclitaxel was observed when Avastin was administered in combination with these drugs; however, 3 of the 8 patients receiving Avastin with paclitaxel and carboplatin had lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel and carboplatin alone had a greater paclitaxel exposure at Day 63 than at Day 0.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Avastin may cause fetal harm in pregnant women. Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug-associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *(see Data)*. Furthermore, animal models link angiogenesis and VEGF and VEGFR2 to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included:

reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

Risk Summary

No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Avastin may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose.

Infertility

Females

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first-dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared to patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients *[see Warnings and Precautions (5.11), Adverse Reactions (6.1)]*.

8.4 Pediatric Use

The safety and effectiveness of Avastin in pediatric patients have not been established.

In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received Avastin. Avastin is not approved for use in patients under the age of 18 years.

Antitumor activity was not observed among eight pediatric patients with relapsed GBM who received bevacizumab and irinotecan. Addition of Avastin to standard of care did not result in improved event-free survival in pediatric patients enrolled in two randomized clinical studies, one in high grade glioma (n= 121) and one in metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma (n= 154).

Based on the population pharmacokinetics analysis of data from 152 pediatric and young adult patients with cancer (7 months to 21 years of age), bevacizumab clearance normalized by body weight in pediatrics was comparable to that in adults.

Juvenile Animal Toxicity Data
Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use
In an exploratory pooled analysis of 1745 patients from five randomized, controlled studies, 35% of patients were ≥ 65 years old. The overall incidence of ATE was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone, regardless of age; however, the increase in the incidence of ATE was greater in patients ≥ 65 years (8% vs. 3%) as compared to patients < 65 years (2% vs. 1%) *[see Warnings and Precautions (5.4)]*.

11 DESCRIPTION
Bevacizumab is a vascular endothelial growth factor inhibitor. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

Avastin (bevacizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brown solution in a single-dose vial for intravenous use. Avastin contains bevacizumab at a concentration of 25 mg/mL in either a 100 mg/4 mL or 400 mg/16 mL single-dose vial.

Each mL of solution contains 25 mg bevacizumab, α,α-trehalose dihydrate (60 mg), polysorbate 20 (0.4 mg), sodium phosphate dibasic, anhydrous (1.2 mg), sodium phosphate monobasic, monohydrate (5.8 mg), and Water for Injection, USP. The pH is 6.2.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

12.3 Pharmacokinetics
The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin every week, every 2 weeks, or every 3 weeks, bevacizumab pharmacokinetics are linear and the predicted time to reach more than 90% of steady state concentration is 84 days. The accumulation ratio following a dose of 10 mg/kg once every 2 weeks is 2.8.

Population simulations of bevacizumab exposures provide a median trough concentration of 80.3 mcg/mL on Day 84 (10^{th}, 90^{th} percentile: 45, 128) following a dose of 5 mg/kg once every two weeks.

Distribution
The mean (% coefficient of variation [CV%]) central volume of distribution is 2.9 (22%) L.

Elimination
The mean (CV%) clearance is 0.23 (33) L/day. The estimated half-life is 20 days (11 to 50 days).

Specific Populations

The clearance of bevacizumab varied by body weight, sex, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.26 L/day vs. 0.21 L/day) and a larger central volume of distribution (3.2 L vs. 2.7 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.25 L/day vs. 0.20 L/day) than patients with tumor burdens below the median. In Study AVF2107g, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess potential of bevacizumab for carcinogenicity or mutagenicity.

Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

13.2 Animal Toxicology and/or Pharmacology

Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer

Study AVF2107g

The safety and efficacy of Avastin was evaluated in a double-blind, active-controlled study [AVF2107g (NCT00109070)] in 923 patients with previously untreated mCRC who were randomized (1:1:1) to placebo with bolus-IFL (irinotecan 125 mg/m^2, fluorouracil 500 mg/m^2, and leucovorin 20 mg/m^2 given once weekly for 4 weeks every 6 weeks), Avastin (5 mg/kg every 2 weeks) with bolus-IFL, or Avastin (5 mg/kg every 2 weeks) with fluorouracil and leucovorin. Enrollment to the Avastin with fluorouracil and leucovorin arm was discontinued after enrollment of 110 patients in accordance with the protocol-specified adaptive design. Avastin was continued until disease progression or unacceptable toxicity or for a maximum of 96 weeks. The main outcome measure was overall survival (OS).

The median age was 60 years; 60% were male, 79% were White, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. The dominant site of disease was extra-abdominal in 56% of patients and was the liver in 38% of patients.

The addition of Avastin improved survival across subgroups defined by age (<65 years, ≥ 65 years) and sex. Results are presented in Table 11 and Figure 1.

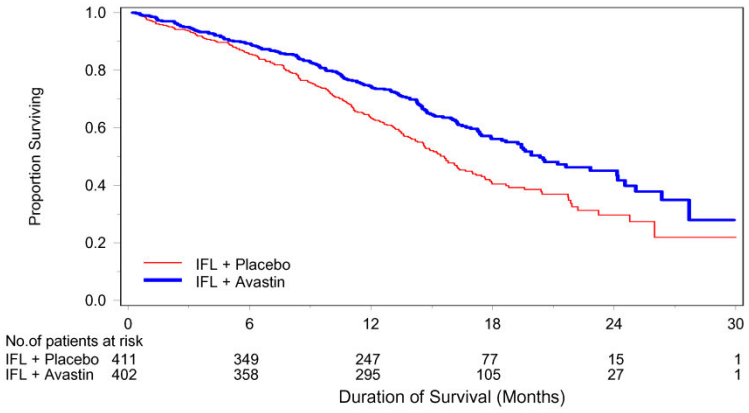
Table 11: Efficacy Results in Study AVF2107g

Efficacy Parameter	Avastin with bolus-IFL (N=402)	Placebo with bolus-IFL (N=411)
Overall Survival		
Median, in months	20.3	15.6
Hazard ratio (95% CI)	0.66 (0.54, 0.81)	
p-value[a]	< 0.001	
Progression-Free Survival		
Median, in months	10.6	6.2
Hazard ratio (95% CI)	0.54 (0.45, 0.66)	
p-value[a]	< 0.001	
Overall Response Rate		
Rate (%)	45%	35%
p-value[b]	< 0.01	
Duration of Response		
Median, in months	10.4	7.1

[a] by stratified log-rank test.

[b] by χ^2 test

Figure 1: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study AVF2107g



Among the 110 patients randomized to Avastin with fluorouracil and leucovorin, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, overall response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study E3200

The safety and efficacy of Avastin were evaluated in a randomized, open-label, active-controlled study [E3200 (NCT00025337)] in 829 patients who were previously treated with irinotecan and fluorouracil for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 concurrently, then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: leucovorin 200 mg/m^2, then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; every 2 weeks), Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The Avastin alone arm was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee based on evidence of decreased survival compared to FOLFOX4 alone.

The median age was 61 years; 60% were male, 87% were White, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan with or without fluorouracil for metastatic disease, and 1% received prior irinotecan and fluorouracil as adjuvant therapy.

The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone; median OS was 13.0 months vs. 10.8 months [hazard ratio (HR) 0.75 (95% CI: 0.63, 0.89), p-value of 0.001 stratified log-rank test] with clinical benefit seen in subgroups defined by age (<65 years, ≥ 65 years) and sex. PFS and ORR based on investigator assessment were higher in patients receiving Avastin with FOLFOX4.

Study TRC-0301

The activity of Avastin with fluorouracil (as bolus or infusion) and leucovorin was evaluated in a single arm study [TRC-0301 (NCT00066846)] enrolling 339 patients with mCRC with disease progression following both irinotecan- and oxaliplatin-based chemotherapy. Seventy-three percent of patients received concurrent bolus fluorouracil and leucovorin. One objective partial response was verified in the first 100 evaluable patients for an ORR of 1% (95% CI: 0%, 5.5%).

Study ML18147

The safety and efficacy of Avastin were evaluated in a prospective, randomized, open-label, multinational, controlled study [ML18147 (NCT00700102)] in 820 patients with histologically confirmed mCRC who had progressed on a first-line Avastin containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing Avastin as first-line treatment to receive fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy with or without Avastin (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks). The choice of second-line treatment was contingent upon first-line chemotherapy. Second-line treatment was administered until progressive disease or unacceptable toxicity. The main outcome measure was OS. A secondary outcome measure was ORR.

The median age was 63 years (21 to 84 years); 64% were male, 52% had an ECOG performance status of 1, 44% had an ECOG performance status of 0, 58% received irinotecan-based therapy as first-line treatment, 55% progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of OS and PFS. There was no significant difference in ORR. Results are presented in Table 12 and Figure 2.

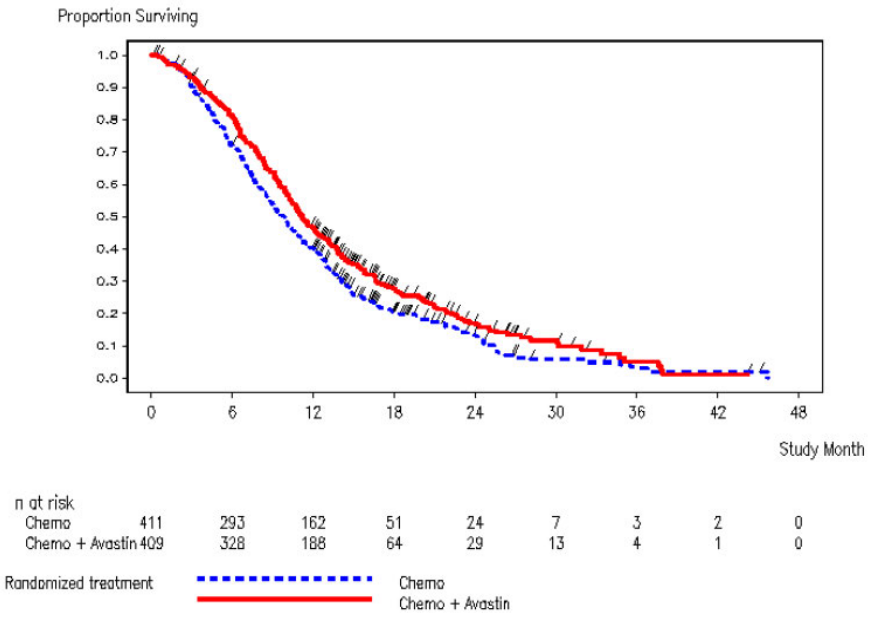
Table 12: Efficacy Results in Study ML18147

Efficacy Parameter	Avastin with Chemotherapy (N=409)	Chemotherapy (N=411)
Overall Survival[a]		
Median, in months	11.2	9.8
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival[b]		
Median, in months	5.7	4.0
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

[a] p=0.0057 by unstratified log-rank test.

[b] p-value < 0.0001 by unstratified log-rank test.

Figure 2: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study ML18147



14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of Avastin as an adjunct to standard chemotherapy for the adjuvant treatment of colon cancer was determined in two randomized, open-label, multicenter clinical studies.

The first study [BO17920 (NCT00112918)] was conducted in 3451 patients with high-risk stage II and III colon cancer, who had undergone surgery for colon cancer with curative intent. Patients were randomized to receive Avastin at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule with FOLFOX4 (N=1155) or on a 3-weekly schedule with XELOX (N=1145) or FOLFOX4 alone (N=1151). The main outcome measure was disease free survival (DFS) in patients with stage III colon cancer.

The median age was 58 years; 54% were male, 84% were White and 29% were ≥ 65 years. Eighty-three percent had stage III disease.

The addition of Avastin to chemotherapy did not improve DFS. As compared to FOLFOX4 alone, the proportion of stage III patients with disease recurrence or with death due to disease progression were numerically higher for patients receiving Avastin with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for Avastin with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for Avastin with XELOX versus FOLFOX4 alone. The hazard ratios for OS were 1.31 (95% CI: 1.03, 1.67) and 1.27 (95% CI: 1, 1.62) for the comparison of Avastin with FOLFOX4 versus FOLFOX4 alone and Avastin with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS was observed in the Avastin-containing arms compared to FOLFOX4 alone in the high-risk stage II cohort.

In a second study [NSABP-C-08 (NCT00096278)], patients with stage II and III colon cancer who had undergone surgery with curative intent, were randomized to receive either Avastin administered at a dose equivalent to 2.5 mg/kg/week with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The median age was 57 years, 50% were male and 87% White. Seventy-five percent had stage III disease. The main outcome was DFS among stage III patients. The HR for DFS was 0.92 (95% CI: 0.77, 1.10). OS was not significantly improved with the addition of Avastin to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

14.3 First-Line Non–Squamous Non–Small Cell Lung Cancer

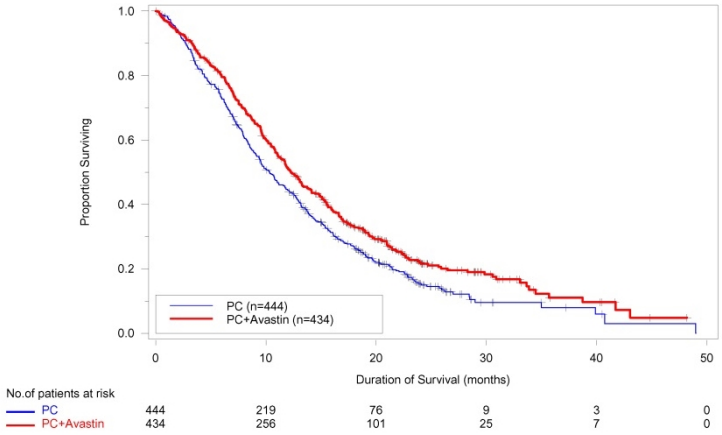
Study E4599

The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study [E4599 (NCT00021060)]. A total of 878 chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC 6) with or without Avastin 15 mg/kg. After completing or discontinuing chemotherapy, patients randomized to receive Avastin continued to receive Avastin alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The main outcome measure was duration of survival.

The median age was 63 years; 54% were male, 43% were ≥ 65 years, and 28% had ≥ 5% weight loss at study entry. Eleven percent had recurrent disease. Of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

OS was statistically significantly longer for patients receiving Avastin with paclitaxel and carboplatin compared with those receiving chemotherapy alone. Median OS was 12.3 months vs. 10.3 months [HR 0.80 (95% CI: 0.68, 0.94), final p-value of 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with Avastin with paclitaxel and carboplatin compared to chemotherapy alone. Results are presented in Figure 3.

Figure 3: Kaplan-Meier Curves for Duration of Survival in First-Line Non-Squamous Non-Small Cell Lung Cancer in Study E4599



In an exploratory analysis across patient subgroups, the impact of Avastin on OS was less robust in the following subgroups: women [HR 0.99 (95% CI: 0.79, 1.25)], patients ≥ 65 years [HR 0.91 (95% CI: 0.72, 1.14)] and patients with ≥ 5% weight loss at study entry [HR 0.96 (95% CI: 0.73, 1.26)].

Study BO17704

The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy was studied in another randomized, double-blind, placebo-controlled study [BO17704 (NCT00806923)]. A total of 1043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, Avastin 7.5 mg/kg or Avastin 15 mg/kg. The main outcome measure was PFS. Secondary outcome measure was OS.

The median age was 58 years; 36% were female and 29% were ≥ 65 years. Eight percent had recurrent disease and 77% had Stage IV disease.

PFS was significantly higher in both Avastin-containing arms compared to the placebo arm [HR 0.75 (95% CI: 0.62, 0.91), p-value of 0.0026 for Avastin 7.5 mg/kg and HR 0.82 (95% CI: 0.68; 0.98), p-value of 0.0301 for Avastin 15 mg/kg]. The addition of Avastin to cisplatin and gemcitabine failed to demonstrate an improvement in the duration of OS [HR 0.93 (95% CI: 0.78; 1.11), p-value of 0.420 for Avastin 7.5 mg/kg and HR 1.03 (95% CI: 0.86, 1.23), p-value of 0.761 for Avastin 15 mg/kg].

14.4 Recurrent Glioblastoma

Study EORTC 26101

The safety and efficacy of Avastin were evaluated in a multicenter, randomized (2:1), open-label study in patients with recurrent GBM (EORTC 26101, NCT01290939). Patients with first progression following radiotherapy and temozolomide were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine (90 mg/m^2 every 6 weeks) or lomustine (110 mg/m^2 every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. >0), steroid use (yes vs. no), largest tumor diameter (≤ 40 vs. > 40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment in Neuro-oncology (RANO) criteria, health related quality of life (HRQoL), cognitive function, and corticosteroid use.

A total of 432 patients were randomized to receive lomustine alone (N=149) or Avastin with lomustine (N=283). The median age was 57 years; 24.8% of patients were ≥ 65 years. The majority of patients with were male (61%); 66% had a WHO performance status score > 0; and in 56% the largest tumor diameter was ≤ 40 mm. Approximately 33% of patients randomized to receive lomustine received Avastin following documented progression.

No difference in OS (HR 0.91, p-value of 0.4578) was observed between arms; therefore, all secondary outcome measures are descriptive only. PFS was longer in the Avastin with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the Avastin with lomustine arm and 1.5 months in the lomustine arm. Among the 50% of patients receiving corticosteroids at the time of randomization, a higher percentage of patients in the Avastin with lomustine arm discontinued corticosteroids (23% vs. 12%).

Study AVF3708g and Study NCI 06-C-0064E

The efficacy and safety of Avastin 10 mg/kg every 2 weeks in patients with previously treated GBM were evaluated in one single arm single center study (NCI 06-C-0064E) and a randomized noncomparative multicenter study [AVF3708g (NCT00345163)]. Response rates in both studies were evaluated based on modified WHO criteria that considered corticosteroid use. In AVF3708g, the response rate was 25.9% (95% CI: 17%, 36.1%) with a median duration of response of 4.2 months (95% CI: 3, 5.7). In Study NCI 06-C-0064E, the response rate was 19.6% (95% CI: 10.9%, 31.3%) with a median duration of response of 3.9 months (95% CI: 2.4, 17.4).

14.5 Metastatic Renal Cell Carcinoma

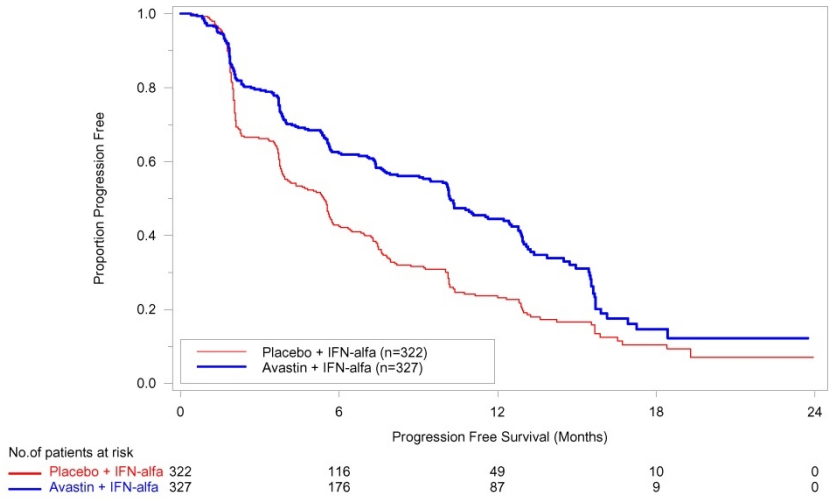
Study BO17705

The safety and efficacy of Avastin were evaluated in patients with treatment-naïve mRCC in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa and Avastin versus interferon alfa and placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks; N = 327) or placebo (every 2 weeks; N = 322) with interferon alfa (9 MIU subcutaneously three times weekly for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (18 to 82 years); 70% were male and 96% were White. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3–5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving Avastin compared to placebo; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI: 0.49, 0.72), p-value < 0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p-value < 0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the patients receiving Avastin with interferon alfa and 21 months in patients receiving interferon alone [HR 0.86, (95% CI: 0.72, 1.04)]. Results are presented in Figure 4.

Figure 4: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705



14.6 Persistent, Recurrent, or Metastatic Cervical Cancer

Study GOG-0240

The safety and efficacy of Avastin were evaluated in patients with persistent, recurrent, or metastatic cervical cancer in a randomized, four-arm, multicenter study comparing Avastin with chemotherapy versus chemotherapy alone [GOG-0240 (NCT00803062)]. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin, or paclitaxel and topotecan with or without Avastin.

The dosing regimens for Avastin, paclitaxel, cisplatin and topotecan were as follows:

- Day 1: Paclitaxel 135 mg/m^2 over 24 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours, Day 2: cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with cisplatin 50 mg/m^2 with Avastin;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with Avastin, Days 1-3: topotecan IV 0.75 mg/m^2 over 30 minutes

Patients were treated until disease progression or unacceptable adverse reactions. The main outcome measure was OS. Secondary outcome measures included ORR.

The median age was 48 years (20 to 85 years). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation, and 32% had a platinum-free interval of less than 6 months. Patients had a GOG performance status of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms.

Results are presented in Figure 5 and Table 13.

Figure 5: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240

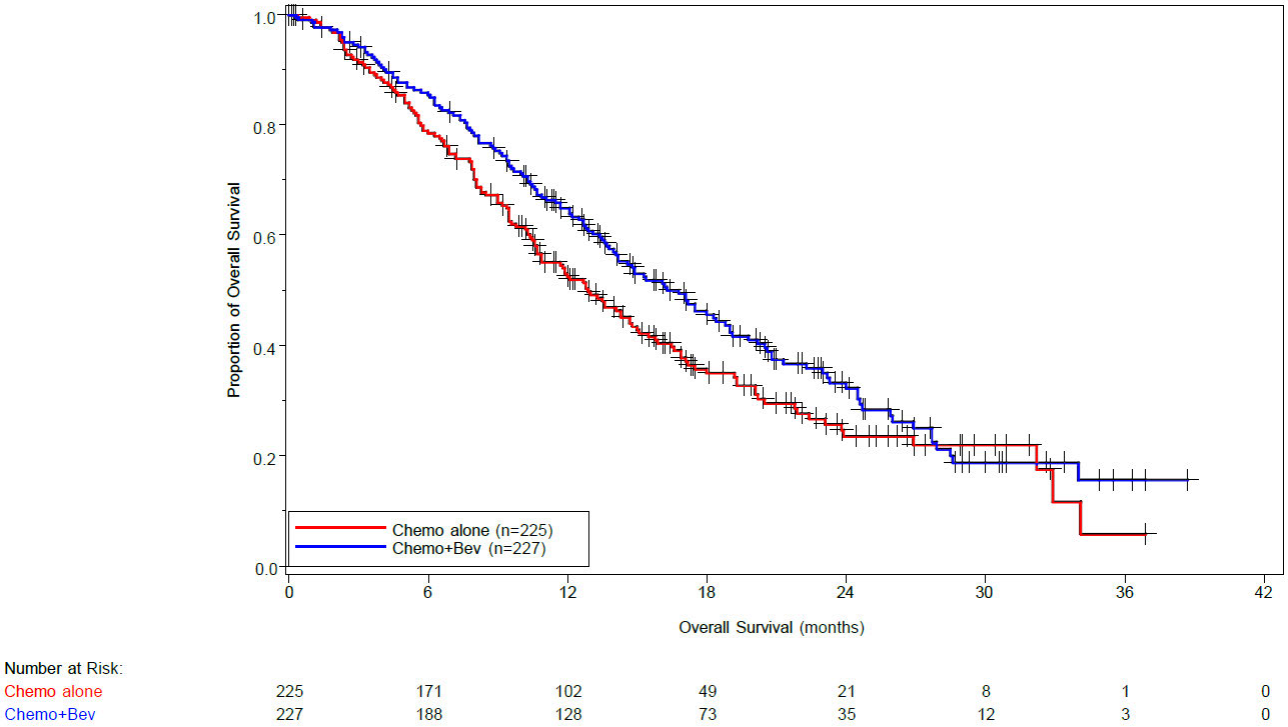


Table 13: Efficacy Results in Study GOG-0240

Efficacy Parameter	Avastin with Chemotherapy (N=227)	Chemotherapy (N=225)
Overall Survival		
Median, in months[a]	16.8	12.9
Hazard ratio (95% CI)	0.74 (0.58, 0.94)	
p-value[b]	0.0132	

[a] Kaplan-Meier estimates.
[b] log-rank test (stratified).

The ORR was higher in patients who received Avastin with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].

Table 14: Efficacy Results in Study GOG-0240

Efficacy Parameter	Topotecan and Paclitaxel with or without Avastin (N=223)	Cisplatin and Paclitaxel with or without Avastin (N=229)
Overall Survival		
Median, in months[a]	13.3	15.5
Hazard ratio (95% CI)	1.15 (0.91, 1.46)	
p-value	0.23	

[a] Kaplan-Meier estimates.

The HR for OS with Avastin with cisplatin and paclitaxel as compared to cisplatin and paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The HR for OS with Avastin with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

14.7 Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection

Study GOG-0218

The safety and efficacy of Avastin were evaluated in a multicenter, randomized, double-blind, placebo controlled, three arm study [Study GOG-0218 (NCT00262847)] evaluating the effect of adding Avastin to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer (N=1873) following initial surgical resection. Patients were randomized (1:1:1) to one of the following arms:

- CPP: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent placebo started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent Avastin started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15+: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent Avastin started at cycle 2, followed by Avastin as a single agent every three weeks for a total of up to 22 cycles of therapy (n=623).

The main outcome measure was investigator-assessed PFS. OS was a secondary outcome measure.

The median age was 60 years (range 22-89 years) and 28% of patients were >65 years of age.
Overall, approximately 50% of patients had a GOG PS of 0 at baseline, and 43% a GOG PS score of 1. Patients had either epithelial ovarian cancer (83%), primary peritoneal cancer (15%), or fallopian tube cancer (2%). Serous adenocarcinoma was the most common histologic type (85% in CPP and CPB15 arms, 86% in CPB15+ arm). Overall, approximately 34% of patients had resected FIGO Stage III with residual disease < 1 cm, 40% had resected Stage III with residual disease >1 cm, and 26% had resected Stage IV disease.

The majority of patients in all three treatment arms received subsequent antineoplastic treatment, 78.1% in the CPP arm, 78.6% in the CPB15 arm, and 73.2% in the CPB15+ arm. A higher proportion of patients in the CPP arm (25.3%) and CPB15 arm (26.6%) received at least one anti-angiogenic (including bevacizumab) treatment after discontinuing from study compared with the CPB15+ arm (15.6%).

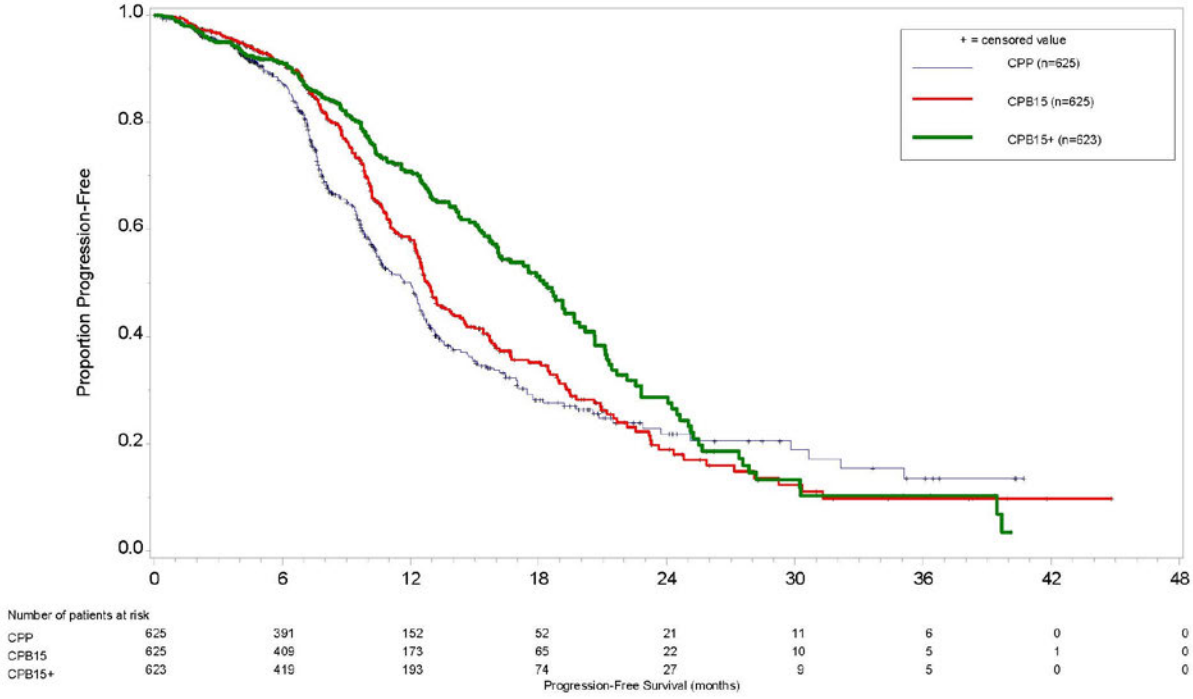
Study results are presented in Table 15 and Figure 6.

Table 15: Efficacy Results in Study GOG-0218

Efficacy Parameter	**Avastin with carboplatin and paclitaxel followed by Avastin alone (N=623)**	**Avastin with carboplatin and paclitaxel (N=625)**	**Carboplatin and paclitaxel (N= 625)**
Progression-Free Survival per Investigator			
Median, in months	18.2	12.8	12.0
Hazard ratio (95% CI)[a]	0.62 (0.52, 0.75)	0.83 (0.70, 0.98)	
p –value[b]	< 0.0001	NS	
Overall Survival[c]			
Median, in months	43.8	38.8	40.6
Hazard ratio (95% CI)[a]	0.89 (0.76, 1.05)	1.06 (0.90, 1.24)	

NS=not significant
[a] Relative to the control arm; stratified hazard ratio
[b] Two-sided p-value based on re-randomization test
[c] Final overall survival analysis

Figure 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection in Study GOG-0218



14.8 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study MO22224

The safety and efficacy of Avastin were evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing Avastin with chemotherapy versus chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within <6 months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following chemotherapy regimens at the discretion of the investigator: paclitaxel (80 mg/m^2 on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m^2 on day 1 every 4 weeks; or topotecan 4 mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25 mg/m^2 on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (25 to 84 years) and 37% of patients were ≥65 years. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥2 times ULN and 31% had ascites at baseline. Seventy-three percent had a platinum-free interval (PFI) of 3 months to 6 months and 27% had PFI of <3 months. ECOG performance status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Results for the ITT population are presented in Table 16 and Figure 7. Results for the separate chemotherapy cohorts are presented in Table 17.

Table 16: Efficacy Results in Study MO22224

Efficacy Parameter	Avastin with Chemotherapy (N=179)	Chemotherapy (N=182)
Progression-Free Survival per Investigator		
Median (95% CI), in months	6.8 (5.6, 7.8)	3.4 (2.1, 3.8)
HR (95% CI)[a]	0.38 (0.30, 0.49)	
p-value[b]	<0.0001	
Overall Survival		
Median (95% CI), in months	16.6 (13.7, 19.0)	13.3 (11.9, 16.4)
HR (95% CI)[a]	0.89 (0.69, 1.14)	
Overall Response Rate		
Number of Patients with Measurable Disease at Baseline	142	144
Rate, % (95% CI)	28% (21%, 36%)	13% (7%, 18%)
Duration of Response		
Median, in months	9.4	5.4

[a] per stratified Cox proportional hazards model
[b] per stratified log-rank test

Figure 7: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224

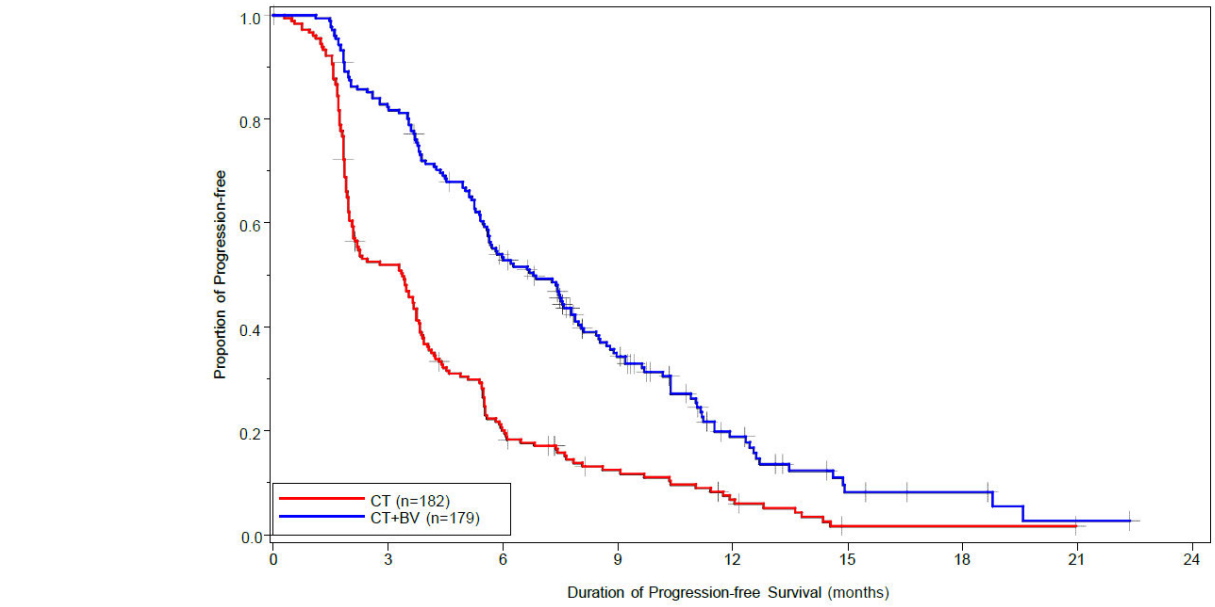


Table 17: Efficacy Results in Study MO22224 by Chemotherapy

Efficacy Parameter	Paclitaxel		Topotecan		Pegylated Liposomal Doxorubicin	
	Avastin with Chemotherapy (N=60)	Chemotherapy (N=55)	Avastin with Chemotherapy (N=57)	Chemotherapy (N=63)	Avastin with Chemotherapy (N=62)	Chemotherapy (N=64)
Progression-Free Survival per Investigator						
Median, in months (95% CI)	9.6 (7.8, 11.5)	3.9 (3.5, 5.5)	6.2 (5.3, 7.6)	2.1 (1.9, 2.3)	5.1 (3.9, 6.3)	3.5 (1.9, 3.9)
Hazard ratio[a] (95% CI)	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median, in months (95% CI)	22.4 (16.7, 26.7)	13.2 (8.2, 19.7)	13.8 (11.0, 18.3)	13.3 (10.4, 18.3)	13.7 (11.0, 18.3)	14.1 (9.9, 17.8)
Hazard ratio [a] (95% CI)	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Overall Response Rate						
Number of patients with measurable disease at baseline	45	43	46	50	51	51
Rate, % (95% CI)	53 (39, 68)	30 (17, 44)	17 (6, 28)	2 (0, 6)	16 (6, 26)	8 (0, 15)
Duration of Response						
Median, in months	11.6	6.8	5.2	NE	8.0	4.6

[a] per stratified Cox proportional hazards model
NE=Not Estimable

14.9 Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g

The safety and efficacy of Avastin were evaluated in a randomized, double-blind, placebo-controlled study [AVF4095g (NCT00434642)] studying Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment (N=484). Patients were randomized (1:1) to receive Avastin (15 mg/kg day 1) or placebo every 3 weeks with carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) a for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The main outcome measures were investigator-assessed PFS. Secondary outcome measures were ORR and OS.

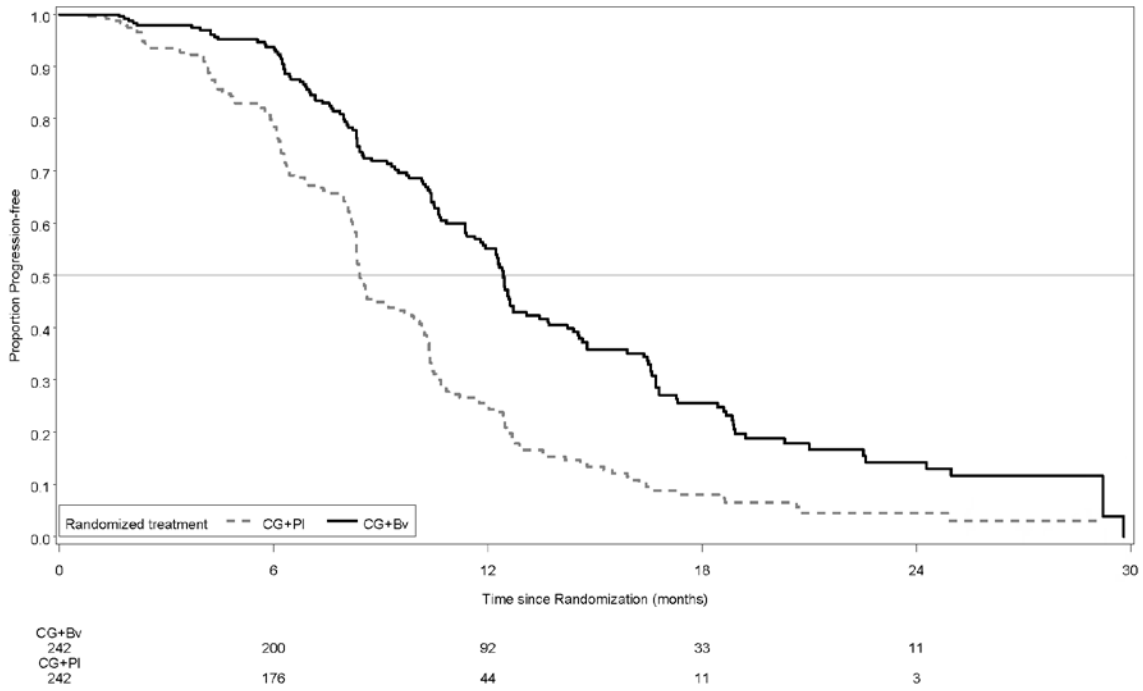
The median age was 61 years (28 to 87 years) and 37% of patients were ≥65 years. All patients had measurable disease at baseline, 74% had baseline CA-125 levels >ULN (35 U/mL). The platinum-free interval (PFI) was 6 months to 12 months in 42 % of patients and >12 months in 58% of patients. The ECOG performance status was 0 or 1 for 99.8% of patients.

A statistically significant prolongation in PFS was demonstrated among patients receiving Avastin with chemotherapy compared to those receiving placebo with chemotherapy (Table 18 and Figure 8). Independent radiology review of PFS was consistent with investigator assessment [HR 0.45 (95% CI: 0.35, 0.58)]. OS was not significantly improved with the addition of Avastin to chemotherapy [HR 0.95 (95% CI: 0.77, 1.17)].

Table 18: Efficacy Results in Study AVF4095g

Efficacy Parameter	**Avastin with Gemcitabine and Carboplatin (N=242)**	**Placebo with Gemcitabine and Carboplatin (N=242)**
Progression-Free Survival		
Median, in months	12.4	8.4
Hazard ratio (95% CI)	0.46 (0.37, 0.58)	
p-value	< 0.0001	
Overall Response Rate		
% patients with overall response	78%	57%
p-value	< 0.0001	

Figure 8: Kaplan-Meier Curves for Progression-Free Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study AVF4095g



Study GOG-0213

The safety and efficacy of Avastin were evaluated in a randomized, controlled, open-label study [Study GOG-0213 (NCT00565851)] of Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (N=673). Patients were randomized (1:1) to receive carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 to 8 cycles (N=336) or Avastin (15 mg/kg) every 3 weeks with carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) for 6 to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single agent until disease progression or unacceptable toxicity. The main outcome measure was OS. Other outcome measures were investigator-assessed PFS, and ORR.

The median age was 60 years (23 to 85 years) and 33% of patients were ≥ 65 years. Eighty-three percent had measurable disease at baseline and 74% had abnormal CA-125 levels at baseline. Ten percent of patients had received prior bevacizumab. Twenty-six percent had a PFI of 6 months to 12 months and 74% had a PFI of >12 months. GOG performance status was 0 or 1 for 99% of patients.

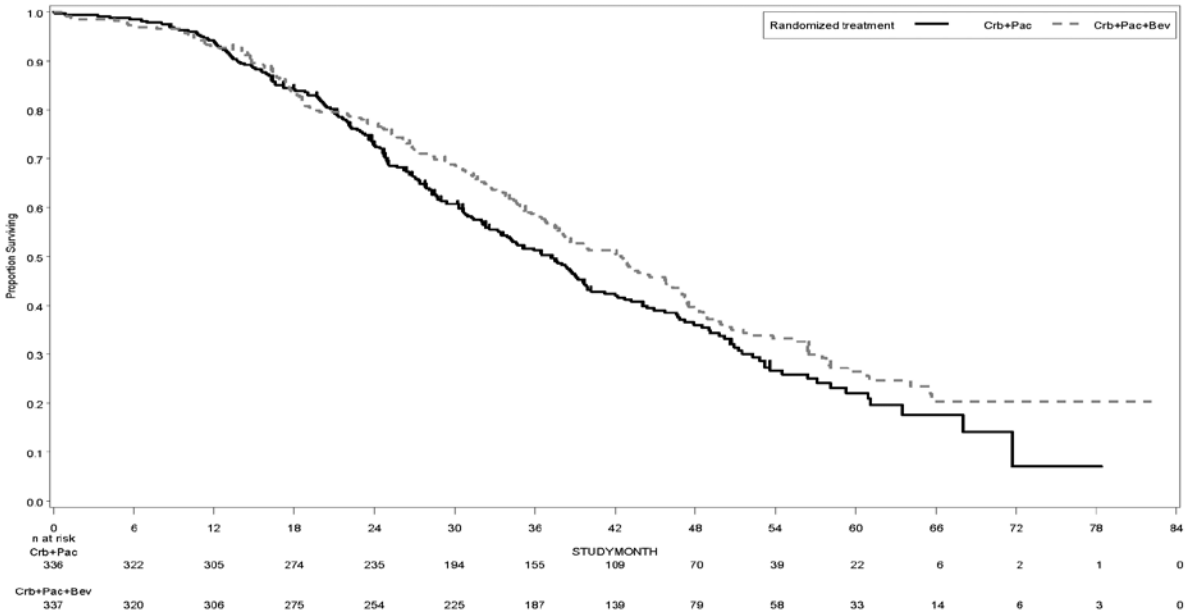
Results are presented in Table 19 and Figure 9.

Table 19: Efficacy Results in Study GOG-0213

Efficacy Parameter	Avastin with Carboplatin and Paclitaxel (N=337)	Carboplatin and Paclitaxel (N=336)
Overall Survival		
Median, in months	42.6	37.3
Hazard ratio (95% CI) (IVRS)[a]	0.84 (0.69, 1.01)	
Hazard ratio (95% CI) (eCRF)[b]	0.82 (0.68, 0.996)	
Progression-Free Survival		
Median, in months	13.8	10.4
Hazard ratio (95% CI) (IVRS)[a]	0.61 (0.51, 0.72)	
Overall Response Rate		
Number of patients with measurable disease at baseline	274	286
Rate, %	213 (78%)	159 (56%)

[a] HR was estimated from Cox proportional hazards models stratified by the duration of treatment free-interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.
[b] HR was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

Figure 9: Kaplan Meier Curves for Overall Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study GOG-0213



14.10 Hepatocellular Carcinoma

The efficacy of Avastin in combination with atezolizumab was investigated in IMbrave150 (NCT03434379), a multicenter, international, open-label, randomized trial in patients with locally advanced unresectable and/or metastatic hepatocellular carcinoma who have not received prior systemic therapy. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), baseline AFP (<400 vs. ≥400 ng/mL), and by ECOG performance status (0 vs. 1).

A total of 501 patients were randomized (2:1) to receive either atezolizumab as an intravenous infusion of 1200 mg, followed by 15 mg/kg Avastin, on the same day every 3 weeks or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. Patients could discontinue either atezolizumab or Avastin (e.g., due to adverse events) and continue on single-agent therapy until disease progression or unacceptable toxicity associated with the single-agent.

The study enrolled patients who were ECOG performance score 0 or 1 and who had not received prior systemic treatment. Patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding. Patients with Child-Pugh B or C cirrhosis, moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; administration of a live, attenuated vaccine within 4 weeks prior to randomization; administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; or untreated or corticosteroid-dependent brain metastases were excluded. Tumor assessments were performed every 6 weeks for the first 54 weeks and every 9 weeks thereafter.

The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 65 years (range: 26 to 88) and 83% of patients were male. The majority of patients were Asian (57%) or White (35%); 40% were from Asia (excluding Japan). Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ⩾400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). HCC risk factors were Hepatitis B in 48% of patients, Hepatitis C in 22% and 31% of patients had non-viral liver disease. The majority of patients had BCLC stage C (82%) disease at baseline, while 16% had stage B and 3% had stage A.

The major efficacy outcome measures were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) per RECIST v1.1. Additional efficacy outcome measures were IRF-assessed overall response rate (ORR) per RECIST and mRECIST.

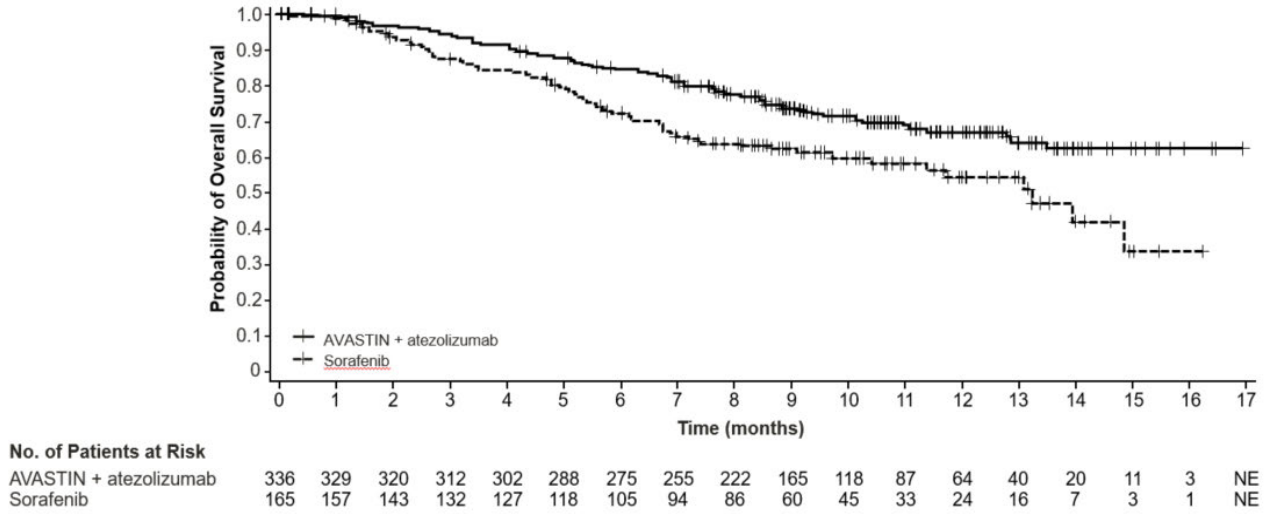
Efficacy results are presented in Table 20 and Figure 10.

Table 20: Efficacy Results from IMbrave150

	Avastin in combination with Atezolizumab (N= 336)	Sorafenib (N=165)
Overall Survival		
Number of deaths (%)	96 (29)	65 (39)
Median OS in months (95% CI)	NE (NE, NE)	13.2 (10.4, NE)
Hazard ratio[1] (95% CI)	0.58 (0.42, 0.79)	
p-value[2]	0.0006[2]	
Progression-Free Survival[3]		
Number of events(%)	197 (59)	109 (66)
Median PFS in months (95% CI)	6.8 (5.8, 8.3)	4.3 (4.0, 5.6)
Hazard ratio[1] (95% CI)	0.59 (0.47, 0.76)	
p-value	<0.0001	
Overall Response Rate[3,5] (ORR), RECIST 1.1		
Number of responders (%)	93 (28)	19 (12)
(95% CI)	(23, 33)	(7,17)
p-value[4]	<0.0001	
Complete responses, n (%)	22 (7)	0
Partial responses, n (%)	71 (21)	19 (12)
Duration of Response[3,5] (DOR) RECIST 1.1		
	(n=93)	(n=19)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.7, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)
Overall Response Rate[3,5] (ORR), HCC mRECIST		
Number of responders (%)	112 (33)	21 (13)
(95% CI)	(28, 39)	(8, 19)
p-value[4]	<0.0001	
Complete responses, n (%)	37 (11)	3 (1.8)
Partial responses, n (%)	75 (22)	18 (11)
Duration of Response[3,5] (DOR) HCC mRECIST		
	(n=112)	(n=21)
Median DOR in months (95% CI)	NE (NE, NE)	6.3 (4.9, NE)
Range (months)	(1.3+, 13.4+)	(1.4+, 9.1+)

[1] Stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline AFP (<400 vs. ≥400 ng/mL)
[2] Based on two-sided stratified log-rank test; as compared to significance level 0.004 (2-sided) based on 161/312=52% information using the OBF method
[3] Per independent radiology review
[4] Based on two-sided Cochran-Mantel-Haesnszel test
[5] Confirmed responses
+ Denotes a censored value
CI=confidence interval; HCC mRECIST= Modified RECIST Assessment for Hepatocellular Carcinoma; NE=not estimable; N/A=not applicable; RECIST 1.1= Response Evaluation Criteria in Solid Tumors v1.1

Figure 10: Kaplan-Meier Plot of Overall Survival in IMbrave150



16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin (bevacizumab) injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:

- 100 mg/4 mL: carton of one vial (NDC 50242-060-01); carton of 10 vials (NDC 50242-060-10).
- 400 mg/16 mL: carton of one vial (NDC 50242-061-01); carton of 10 vials (NDC 50242-061-10).

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.

17 PATIENT COUNSELING INFORMATION

Gastrointestinal Perforations and Fistulae: Avastin may increase the risk of developing gastrointestinal perforations and fistulae. Advise patients to immediately contact their health care provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, or vomiting *[see Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications: Avastin can increase the risk of wound healing complications. Advise patients that Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their health care provider for signs and symptoms of serious or unusual bleeding including coughing or spitting blood *[see Warnings and Precautions (5.3)]*.

Arterial and Venous Thromboembolic Events: Avastin increases the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their health care provider for signs and symptoms of arterial or venous thromboembolism *[see Warnings and Precautions (5.4, 5.5)]*.

Hypertension: Avastin can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their healthcare provider if they experience changes in blood pressure *[see Warnings and Precautions (5.6)]*.

Posterior Reversible Leukoencephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. Advise patients to immediately contact their health care provider for new onset or worsening neurological function *[see Warnings and Precautions (5.7)]*.

Renal Injury and Proteinuria: Avastin increases the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Avastin requires regular monitoring of renal function and to contact their health care provider for proteinuria or signs and symptoms of nephrotic syndrome *[see Warnings and Precautions (5.8)]*.

Infusion-Related Reactions: Avastin can cause infusion-related reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.9)]*.

Congestive Heart Failure: Avastin can increase the risk of developing congestive heart failure. Advise patients to contact their healthcare provider immediately for signs and symptoms of CHF *[see Warnings and Precautions (5.12)]*.

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise women not to breastfeed during treatment with Avastin and for 6 months after the last dose *[see Use in Specific Populations (8.2)]*.

Avastin® (bevacizumab)

Manufactured by:
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s332

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BLA Multi-disciplinary Review and Evaluation

FDA review of the atezolizumab application (BLA 761034 S25) was conducted in conjunction with other regulatory authorities under Project Orbis. While the application review is completed by the FDA, the application is still under review at the other regulatory agencies.

In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, and do not necessarily reflect the positions of the FDA or the other regulatory authorities.

Application Type	Efficacy supplements
Application Number(s)	BLA 761034 (S25) and 125085 (S332)
Priority or Standard	Priority
Submit Date(s)	January 24, 2020
Received Date(s)	January 24, 2020
PDUFA Goal Date	July 24, 2020
Division/Office	DO3/OOD
Review Completion Date	May 29, 2020
Established Name	Tecentriq and Avastin
Pharmacologic Class	Anti-programmed death cell ligand 1 (PD-L1) monoclonal antibody Anti-vascular endothelial growth factor A (VEGF-A) monoclonal antibody
Code name	Atezolizumab and bevacizumab
Applicant	Genentech
Formulation(s)	Atezolizumab: liquid for injection, 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL). Bevacizumab: liquid for injection, 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL)
Dosing Regimen	Atezolizumab 1200 mg IV every 3 weeks Bevacizumab 15 mg/kg IV every 3 weeks
Applicant Proposed Indication(s)/Population(s)	TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy. Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy.
Recommendation on Regulatory Action	Approval

Recommended Indication(s)/Population(s) (if applicable)	TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

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OPQ=Office of Pharmaceutical Quality; OPDP=Office of Prescription Drug Promotion; OSI=Office of Scientific Investigations; OSE= Office of Surveillance and Epidemiology; DEPI= Division of Epidemiology; DMEPA=Division of Medication Error Prevention and Analysis; DRISK=Division of Risk Management

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Glossary

AASLD	American Association for the Study of Liver Diseases
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADA	anti-drug antibody (also known as anti-therapeutic antibody [ATA])
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AFP	alpha feto-protein
AJCC-TNM	American Joint Committee on Cancer tumor size, lymph nodes affected, metastases
Atezo	atezolizumab
Atezo/bev	atezolizumab/bevacizumab
BCLC	Barcelona Clinic Liver Cancer
Bev	bevacizumab
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	Maximum serum or plasma concentration
CMC	chemistry, manufacturing, and controls
C_{min}	Minimum serum or plasma concentration
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CP	Child Pugh
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV%	percent coefficient of variation
DCR	disease control rate
DDI	drug-drug interaction
DMC	data monitoring committee
DOR	duration of response

ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EHS	extrahepatic spread
EORTC QLQ-HCC18	European Organization for the Research and Treatment of Hepatocellular Carcinoma Questionnaire 18 (HCC-specific 18-item)
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30
ER	Exposure-Response
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
HCC	hepatocellular carcinoma
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonization
iDMC	independent Data Monitoring Committee
IIV	inter-individual variability
imRECIST	immune modified Response Evaluation Criteria in Solid Tumors
IND	Investigational New Drug
IRF	Independent Review Facility
IRR	infusion-related reaction
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mRECIST	modified RECIST
mUC	metastatic urothelial bladder cancer
MVI	macrovascular invasion
NA	not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NE	not estimable

NME	new molecular entity
NSCLC	non-small cell lung cancer
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics or progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetics
PP	per protocol
PPES	palmar-plantar erythrodysesthesia
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
Q3W	every three weeks
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RTOR	real-time oncology review
SAE	serious adverse event
SADR	serious adverse drug reaction
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease or standard deviation
SGE	special government employee
SMQ	Standardized MedDRA Queries
SOC	standard of care
TACE	transarterial chemoembolization
TEAE	treatment emergent adverse event
TNBC	triple-negative breast cancer
TTD	time to deterioration
TTO	time to onset
ULN	upper limit of normal

US	United States
v	version
VEGF	vascular endothelial growth factor
vs	versus

1 Executive Summary

1.1 Product Introduction

Tecentriq (atezolizumab)

Atezolizumab is a humanized IgG1 monoclonal antibody that targets the programmed-death ligand 1 (PD-L1) and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1, both of which function as inhibitory receptors expressed on T cells. Blockade of PD-L1 binding increases the magnitude of tumor-specific T-cell responses, resulting in anti-tumor activity.

FDA first approved atezolizumab on May 18, 2016, for the treatment of patients with refractory urothelial and non-small cell lung cancer following platinum-containing chemotherapy. Prior to approval of these supplemental biologics license applications (sBLAs), atezolizumab was approved for the following indications:

- Non-small cell lung cancer (NSCLC)
  - in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
  - in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations
  - for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving atezolizumab
  - as a single agent, for first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression (PDL1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations
- Small Cell Lung Cancer (SCLC)
  - in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer
- Triple-Negative Breast Cancer (TNBC)
  - in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test.

  This indication is approved under accelerated approval.

- Urothelial carcinoma
  - adult patients with locally advanced or metastatic urothelial carcinoma who:
    - are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or
    - are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

This indication is approved under accelerated approval.

Atezolizumab is administered intravenously (IV) over 60 minutes for the first infusion, and subsequent infusions may be delivered over 30 minutes if the first infusion is tolerated. The approved dosages for atezolizumab are 840 mg every 2 weeks (Q2W), 1200 mg every 3 weeks (Q3W), or 1680 mg every 4 weeks (Q4W).

Tecentriq injection is supplied as a sterile, preservative-free, colorless to slightly yellow solution for intravenous infusion in cartons containing one 840 mg/14 mL single-dose vial or one 1200 mg/20 mL single-dose vial.

Avastin (bevacizumab)

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds the vascular endothelial growth factor (VEGF) ligand and inhibits angiogenesis. FDA first approved bevacizumab on February 26, 2004, for the first-line treatment of patients with metastatic colorectal cancer. Prior to approval of these sBLAs, bevacizumab was approved for the following indications:

- Metastatic colorectal cancer
  - in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment
  - in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen
- NSCLC
  - Unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC, in combination with carboplatin and paclitaxel for first-line treatment.
- Recurrent glioblastoma
- Metastatic renal cell carcinoma
  - in combination with interferon alfa
- Persistent, recurrent, or metastatic cervical cancer
  - in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer:

- in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection
- in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens
- in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting these sBLAs is Study IMbrave150 (IMbrave150), a multicenter, international, open-label, randomized (2:1) trial comparing the combination of atezolizumab and bevacizumab (atezolizumab/bevacizumab) to sorafenib for the first-line treatment of patients with locally advanced unresectable or metastatic hepatocellular carcinoma (HCC). A total of 501 patients were randomized and 485 received treatment (329 patients received atezolizumab 1200 mg IV in combination with bevacizumab 15 mg/kg IV every 3 weeks and 156 patients received sorafenib 400 mg orally twice daily). Treatment was administered until disease progression or intolerable toxicity. The primary endpoints of the trial were overall survival (OS) and progression-free survival (PFS) according to RECIST v1.1 as assessed by an independent review facility (IRF).

The IMbrave150 study demonstrated a clinically meaningful, statistically significant improvement in OS and IRF-assessed PFS. The hazard ratio (HR) for OS was 0.58 (95% confidence interval [CI]: 0.42, 0.79; p-value 0.0006) favoring the atezolizumab/bevacizumab arm. The median OS could not be estimated in the atezolizumab/bevacizumab arm and was 13.2 months (95% CI 10.4, NE) in the sorafenib arm. The HR for IRF-assessed PFS was 0.59 (95% CI: 0.47, 0.76); median PFS was 6.8 months (95% CI: 5.8, 8.3) in the atezolizumab/bevacizumab arm and 4.3 months (95% CI: 4.0, 5.6) in the sorafenib arm. Secondary endpoints, subgroup analyses, and sensitivity analyses were consistent with results of the primary endpoints and confirmed the robustness of the study results.

In addition, the Applicant submitted supportive data from a single arm cohort (Arm A) of Study GO30140, a multicenter, open label, multicohort trial of atezolizumab administered in combination with a variety of treatments in patients with solid tumors. conducted in the same patient population. One-hundred and four patients with HCC who had not received prior systemic treatment enrolled in Arm A and received atezolizumab and bevacizumab. The IRF-assessed response rate in Arm A was 35.6% (26.4; 45.6), with a median duration of response that could not be estimated (95% CI 11.8 months; NE). At the time of data cut-off, 76% of responders had ongoing responses. Isolation of effect of each component of the combination was demonstrated through analyses of pooled data from patients receiving atezolizumab monotherapy across several studies and data from Arm F of Study GO30140, Arm F randomized

(1:1) 119 patients with advanced unresectable or metastatic HCC to receive either atezolizumab monotherapy or the combination atezolizumab and bevacizumab. The HR for PFS favored the combination arm [0.55 (95% CI 0.34, 0.88);p=0.0108], demonstrating that the combination improved PFS over atezolizumab as a single agent.

An important issue considered by the review team was the incidence of anti-drug antibodies (ADAs) to atezolizumab observed in Study IMbrave 150. Although occurrence of ADAs has been previously described with atezolizumab, the incidence of ADAs in the HCC population was higher than expected (28%). Patients with ADAs appeared to benefit less from the combination atezolizumab and bevacizumab compared to patients who did not develop ADAs; however, there was no clear evidence indicating that the presence of ADAs conferred an increased risk of toxicities with atezolizumab/bevacizumab and the combination appears to be more tolerable than sorafenib overall, irrespective of the presence or absence of ADAs.

The submitted evidence meets the statutory evidentiary standard for regular approval of atezolizumab in combination with bevacizumab and bevacizumab in combination with atezolizumab for the first-line treatment of patients with locally advanced unresectable or metastatic HCC. The observed improvement in OS, with an HR of 0.58, is statistically robust and clinically meaningful. This finding is supported by improvements in PFS and ORR observed in the atezolizumab/bevacizumab arm when compared to the sorafenib arm.

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Atezolizumab is a monoclonal antibody that binds to programmed-death ligand 1 (PD-L1) and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1-mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody-dependent cellular cytotoxicity. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds the vascular endothelial growth factor (VEGF) ligand and inhibits angiogenesis. There is extensive clinical experience with atezolizumab and bevacizumab; both are approved by the FDA for multiple indications, either alone or in combination with other drugs. The safety and effectiveness of the combination of atezolizumab and bevacizumab (atezolizumab/bevacizumab) for the first-line treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) was established by the results of a single multicenter, international, open-label, randomized trial, Study IMbrave 150 (NCT03434379). These applications are also supported by data from two cohorts (Arms A and F) of Study GO30140, a multicenter, open label, multicohort trial of atezolizumab administered in combination with a variety of treatments in patients with solid tumors.

Study IMbrave was a multicenter, international, open-label, randomized trial in patients with locally advanced unresectable or metastatic hepatocellular carcinoma who had not received prior systemic therapy. Randomization was stratified by geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion or extrahepatic spread (presence vs. absence), baseline alpha fetoprotein level (<400 vs. ≥400 ng/mL), and by Eastern Cooperative Group (ECOG) performance status (0 vs. 1). Patients were randomized (2:1) to receive either atezolizumab as an intravenous infusion of 1200 mg, followed by 15 mg/kg bevacizumab, on the same day every 3 weeks or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. Patients could discontinue either atezolizumab or bevacizumab (e.g., due to adverse events) and continue on single-agent therapy until disease progression or unacceptable toxicity associated with the single-agent. Patients were required to be evaluated for the presence of varices within 6 months prior to treatment, and were excluded if they had variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding. Patients with Child-Pugh B or C cirrhosis, moderate or severe ascites; history of hepatic encephalopathy; a history of autoimmune disease; receipt of a live, attenuated vaccine within 4 weeks prior to randomization; receipt of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization; or untreated or corticosteroid-dependent brain metastases were excluded. Tumor assessments were performed every 6 weeks for the first 54 weeks and every 9 weeks thereafter.

A total of 501 patients were randomized, 336 to the atezolizumab/bevacizumab arm and 165 to the sorafenib arm. The demographics and baseline disease characteristics of the study population were balanced between the treatment arms. The median age was 65 years (range: 26 to 88) and 83% of patients were male. The majority of patients were Asian (57%) or White (35%); 40% were from Asia (excluding Japan). Approximately 75% of patients presented with macrovascular invasion and/or extrahepatic spread and 37% had a baseline AFP ≥400 ng/mL. Baseline ECOG performance status was 0 (62%) or 1 (38%). HCC risk factors were Hepatitis B in 48% of patients, Hepatitis C in 22%, and 31% of patients had non-viral liver disease. The majority of patients had BCLC stage C (82%) disease at baseline, while 16% had stage B, and 3% had stage A.

The major efficacy outcome measures were overall survival (OS) and independent review facility (IRF)-assessed progression free survival (PFS) per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were IRF-assessed overall response rate (ORR) per RECIST and ORR and PFS per modified RECIST (mRECIST). The IMbrave150 study demonstrated a clinically meaningful, statistically significant improvement in OS and IRF-assessed PFS. The hazard ratio (HR) for OS was 0.58 (95% confidence interval [CI]: 0.42, 0.79; p-value 0.0006) favoring the atezolizumab/bevacizumab arm. The median OS could not be estimated in the atezolizumab/bevacizumab arm and was 13.2 months (95% CI 10.4, NE) in the sorafenib arm. The HR for IRF-assessed PFS per RECIST v1.1 was 0.59 (95% CI: 0.47, 0.76); median PFS was 6.8 months (95% CI: 5.8, 8.3) in the atezolizumab/bevacizumab arm and 4.3 months (95% CI: 4.0, 5.6) in the sorafenib arm. Secondary endpoints, subgroup analyses, and sensitivity analyses were consistent with results of the primary endpoints and confirmed the robustness of the study results.

The efficacy results of Study IMbrave 150 are supported by the results of Arms A and Arm F of Study GO30140. One-hundred and four patients with HCC who had not received prior systemic treatment enrolled in Arm A and received atezolizumab and bevacizumab. The IRF-assessed response rate in Arm A was 35.6% (26.4; 45.6), with a median duration of response that could not be estimated (95% CI 11.8 months; NE). At the time of data cut-off, 76% of responders had ongoing responses. Isolation of effect of each component of the combination was demonstrated through analyses of pooled data from patients receiving atezolizumab monotherapy across several studies and data from Arm F of Study GO30140. Arm F randomized (1:1) 119 patients with advanced unresectable or metastatic HCC to receive either atezolizumab monotherapy or the combination of atezolizumab and bevacizumab. The HR for PFS favored the combination arm [0.55 (95% CI 0.34, 0.88);p=0.0108], demonstrating that the combination improved PFS over atezolizumab as a single agent

The adverse reaction profile observed in patients receiving atezolizumab and bevacizumab in Study IMbrave 150 and Study GO30140 is consistent with the adverse reaction profiles observed for each respective agent overall. The most common adverse reactions (reported in ≥ 20% of patients) in patients who received atezolizumab in combination with bevacizumab in Study IMbrave 150 were hypertension, fatigue and proteinuria. Serious adverse reactions occurred in 38% of patients in the atezolizumab and bevacizumab arm, and the most frequent

serious adverse reactions (≥ 2%) were gastrointestinal hemorrhage (7%), infections (6%), and pyrexia (2.1%). Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 12% of patients in the atezolizumab and bevacizumab arm.

The review team concluded that the overall risk:benefit assessment favored approval of atezolizumab in combination with bevacizumab (and bevacizumab in combination with atezolizumab) for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy. Unresectable and metastatic HCC is a serious and life-threatening disease with a poor prognosis, and available therapy in this setting, sorafenib and lenvatinib, confers a modest improvement in survival compared to supportive care alone and is associated with substantial toxicity. The demonstrated improvement in OS for patients randomized the atezolizumab and bevacizumab arm compared to patients randomized to sorafenib is clinically meaningful, statistically significant, and supported by improvements in PFS and ORR in Study IMbrave 150. The adverse reaction profile observed in patients in patients receiving atezolizumab and bevacizumab is consistent with the adverse reaction profiles observed for each respective agent. The most important risks are immune-mediated adverse reactions (secondary to atezolizumab); and hemorrhage, hypertension, and proteinuria (due to bevacizumab). These risks are largely manageable with patient surveillance, dose modification and supportive care . The risks of the combination of atezolizumab and bevacizumab are acceptable considering the life-threatening nature of unresectable and metastatic HCC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Locally advanced unresectable or metastatic HCC is a serious condition, with a 5-year relative survival of 12% for locoregional advanced disease and 2.5% for metastatic disease. In the U.S., the median survival of patients with metastatic disease is approximately one year.	Locally advanced or unresectable HCC is a serious, life-threatening condition with a poor prognosis.
Current Treatment Options	The standard of care for the first-line treatment of patients with advanced unresectable, or metastatic HCC is limited to two multi-tyrosine kinase inhibitors, sorafenib and lenvatinib. Sorafenib was approved in 2007 based on the results of the SHARP study, showing an improved median overall survival in the sorafenib arm (10.7 months) when compared with the placebo arm (7.9 months) with a HR 0.69 (95% CI 0.6, 0.9). Lenvatinib was approved based on the REFLECT study, a non-inferiority study comparing lenvatinib with sorafenib. The median overall survival in the lenvatinib arm was 13.6 months vs 12.3 months in the sorafenib arm, with a HR 0.92 (95% CI 0.79, 1.06), which	Although sorafenib and lenvatinib improved survival in patients with advanced unresectable or metastatic HCC, the outcome of these patients is still poor with an estimated median survival of approximately 1 year.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	demonstrated the non-inferiority of lenvatinib.	
Benefit	IMbrave150 was a randomized (2:1), open-label, international study in patients with locally advanced unresectable or metastatic HCC with no prior systemic treatment. The study enrolled 501 patients and 485 received treatment (329 patients received atezolizumab 1200 mg IV in combination with bevacizumab 15 mg/kg IV, both administered every 3 weeks and 156 patients received sorafenib 400 mg orally twice a day). Treatment was administered until disease progression or intolerable toxicity. Demographic and disease characteristics were similar in both arms and adequately reflect a population with advanced disease. Primary endpoints were overall survival and progression-free survival. The median OS in patients receiving atezolizumab/bevacizumab could not be estimated, while the median survival in patients receiving sorafenib was 13.24 months (95% CI: 10.4, NE) (HR = 0.58; 95% CI: 0.42, 0.79; p=0.0006); median PFS was 6.8 months (95% CI 5.8; 8.3) in the atezolizumab/bevacizumab arm and 4.3 months (95% CI 4.0; 5.6) in the sorafenib arm (HR 0.59, 95% CI 0.47; 0.76). Secondary endpoint analyses, subgroup analyses as well as sensitivity analyses confirm the benefit of atezolizumab in combination with bevacizumab and the robustness of the results. In addition, data from Arm A of Study GO30140, a single-arm cohort exploring the response rate (as assessed by an independent review facility by RECIST 1.1) and duration of response in 104 patients with advanced unresectable of metastatic HCC treated with atezolizumab/bevacizumab. The ORR was 35.6% (26.4; 45.6), with a	The submitted evidence meets the statutory evidentiary standard for approval. Results of a well-controlled randomized study showed a statistically significant and clinically meaningful improvement in overall survival and progression-free survival among patients who received atezolizumab/bevacizumab compared to those who received sorafenib in Study IMbrave 150. These results were consistent with observed improvement in ORR in Study IMbrave 150 and also supported by data from a second, multicohort study. Twenty-eight percent of patients developed anti-drug antibodies (ADAs). An exploratory analysis revealed that these patients still appeared to derive benefit from treatment; however, the benefit appeared less pronounced when compared to patients who did not develop ADAs. Product labeling for atezolizumab has been revised to provide this information to healthcare providers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	median duration of response that could not be estimated (95% CI 11.8 months; NE). At the time of data cut-off, 76% of responders had ongoing responses. Isolation of effect was demonstrated through analyses of pooled patients receiving atezolizumab monotherapy in several studies and Arm F of Study GO30140, a randomized (1:1) controlled study in the 119 patients with advanced unresectable or metastatic HCC receiving atezolizumab monotherapy or the combination atezolizumab/bevacizumab. The HR for PFS was 0.55 (95% CI 0.34, 0.88), demonstrating that the combination synergistically improved outcomes over atezolizumab monotherapy. Although occurrence of anti-drug antibodies (ADAs) has been previously described with atezolizumab, the incidence of ADAs in the HCC population was higher than expected (28%); patients with ADA appear to benefit less from the combination of atezolizumab and bevacizumab compared to patients who did not develop ADAs. However, patients with there was no clear evidence indicating that the presence of ADAs conferred an increased risk of toxicities with atezolizumab/bevacizumab and the combination appears to be more tolerable than sorafenib overall, irrespective of the presence or absence of ADAs.	
Risk and Risk Management	The toxicity profile of atezolizumab and bevacizumab observed in IMbrave150 was generally consistent with the established safety profile of each individual antibody and the morbidities associated with HCC and advanced liver disease. Almost all patients in both arms experienced adverse events (AEs); 60% and 58% patients experienced	The toxicity profile of the combination of atezolizumab and bevacizumab is acceptable when assessed in the context of the life-threatening nature of unresectable and metastatic HCC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Grade 3-4 AEs in the atezolizumab/bevacizumab and sorafenib arms, respectively, and 5% and 6% patients experienced fatal AEs in the atezolizumab/bevacizumab and sorafenib arms respectively. The median duration of treatment was 7.4 and 2.8 months in the atezolizumab/bevacizumab and sorafenib arms respectively, and the main reason for treatment discontinuation in both arms was disease progression; 49% and 61% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively required dose interruptions (and modifications in the sorafenib arm) to manage toxicities of the treatment regimen. The most common adverse reactions (reported in ≥ 20% of patients) with atezolizumab/bevacizumab in patients with HCC were hypertension, fatigue/asthenia and proteinuria; the most common AEs reported in the sorafenib arm were diarrhea, palmar-plantar erythrodysesthesia (PPES), fatigue/asthenia, hypertension, and decreased appetite. AEs observed with ≥ 5% difference in the atezolizumab/bevacizumab arm were proteinuria, infusion related reactions, pruritus, fever, hypothyroidism, epistaxis, peripheral edema, hypertension, musculoskeletal pain, and ALT increased. AEs observed with ≥ 5% difference in the sorafenib arm were PPES, diarrhea, decreased appetite, fatigue/asthenia, and alopecia. The nature and incidence of Grade 3-4 AEs are consistent with the known safety profiles of each study drug: patients treated with atezolizumab/bevacizumab experienced a higher incidence of Grade 3-4 hypertension, infusion-related reactions, and increased liver function tests; patients treated with sorafenib experienced higher incidences of Grade 3-4 diarrhea, PPES, and increased bilirubin. Of note, the increased length of exposure likely explains some of the AEs with increased incidence in the atezolizumab/bevacizumab arm.	No new significant safety concerns were identified during review of this supplemental application that would require a new risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of this combination. Significant and serious adverse reactions for the combination are predictable based on the each antibodies' mechanism of action and well-known toxicity profiles of each agent (primarily immune-mediated adverse reactions due to atezolizumab and hemorrhage, hypertension, and proteinurial for bevacizumab). These risks are adequately addressed in product labeling for atezolizumab and bevacizumab, and oncologists who treat patients with HCC are well-trained in the monitoring and treatment of these adverse reactions. The review team determined that standard postmarketing surveillance would be sufficient for continued assessment of the safety of atezolizumab in combination with bevacizumab in patients with unresectable or metastatic HCC, and that a postmarketing requirement (PMR) under the Food and Drug Administration Amendments Act of 2007 (FDAAA) was not needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Toxicities of bevacizumab are generally managed with treatment interruptions or discontinuations; selection of patients is crucial to avoid some potentially serious or fatal adverse events, particularly gastrointestinal hemorrhages. Although infrequent, serious immune-related AEs with atezolizumab can be managed with dose-interruptions and corticosteroids. The incidence of immune-related adverse reactions was the same as in other atezolizumab studies.	

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	☐ X	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
	X		☐	Patient reported outcome (PRO)	Sections 8.1.1 (Design of Studies Providing Key Information), 8.1.2 (Efficacy Results – Secondary or exploratory COA (PRO) endpoints) and 8.1.5 (Integrated Assessment of Effectiveness)
			☐	Observer reported outcome (ObsRO)	
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	

	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.		

X Martha Donoghue
Cross-Disciplinary Team Leader

2 Therapeutic Context/

2.1 Analysis of Condition

The Applicant's Position:

Hepatocellular carcinoma (HCC) is the sixth most common cancer type in the world, and the fourth most deadly cancer (Globocan 2018). There are over 700,000 new cases diagnosed each year worldwide with large geographic variation in both risk factors and incidence (El-Serag 2011; Ferlay et al 2010). The majority (>80%) of cases occur in Sub Saharan Africa and Eastern Asia, and China alone accounts for 55% of cases worldwide. In the United States, liver cancer incidence has tripled since 1980 and an estimated 42,030 new cases of liver cancer (including intrahepatic bile duct cancers) are expected to be diagnosed in the US during 2018 (American Cancer Society). Although HCC is a global disease, there is significant geographical heterogeneity in terms of efficacy outcomes attributed to several potential causes including regional differences in etiology and clinical practice patterns in Asia versus Western countries and Japan (Llovet et al 2003; Sanyal et al. 2010; Nault 2014).

Infection with Hepatitis B virus (HBV) or Hepatitis C virus (HCV), as well as heavy alcohol consumption are major drivers of cirrhosis and the downstream development of HCC. HBV infection is the main risk factor for HCC in Asia (>70%), while in Western countries and Japan, the main risk factor is HCV infection (50% to 70%) and excessive alcohol intake (20%), along with other causes of cirrhosis (10%) (Llovet et al 2003). The underlying etiology of HCC is an important consideration because of its association with differential mechanisms leading to the development of HCC as well as a possible relationship with response to treatment (Shirvani-Dastgerdi et al. 2016).

Up to 80% of patients first presenting with HCC have advanced, unresectable or metastatic disease because of the late appearance of symptoms, which may include jaundice, ascites, bruising/bleeding, upper abdominal pain, weight loss, and fatigue. It is a medically complex and difficult to treat disease as the majority of HCC patients have underlying cirrhosis requiring management of both the malignancy and underlying liver disease. HCC patients with locally advanced or metastatic disease have a poor prognosis, with rapid progression and short overall survival (OS). In HCC, tumor burden can be defined by the presence of extrahepatic disease (EHS) or macrovascular invasion (MVI) of the hepatic and/or portal vein branches, both of which are common and well described independent negative prognostic factors, and both are included in HCC staging criteria (Costentin et al. 2017; Forner et al 2012). Elevated AFP serum levels are also associated with a poorer prognosis in HCC patients with serum AFP concentrations ≥400 ng/mL consistently denoting poorer prognosis (Galle et al. 2019). In the United States, the 5-year OS rate of HCC patients is 18%, making it the second most lethal cancer behind pancreatic cancer (Jemal et al 2017).

The FDA's Assessment:
FDA agrees that advanced unresectable or metastatic HCC is a serious disease poor prognosis and short overall survival.

2.2 Analysis of Current Treatment Options

Sorafenib is a kinase inhibitor approved in the US for the treatment of patients with unresectable HCC based on the OS and PFS benefit in 299 patients with unresectable HCC in a randomized, double blind placebo controlled trial (SHARP) (Llovet et al 2008).
Lenvatinib is a multi-targeted receptor tyrosine kinase inhibitor approved in the US for the first-line treatment of patients with unresectable HCC based on the randomized, open-label, multicenter REFLECT study. Approval was based on lenvatinib being non-inferior to sorafenib in the primary efficacy endpoint of OS (Kudo et al. 2018).
A recent Phase III study (CheckMate 459) investigating nivolumab as monotherapy to treat patients with first line unresectable HCC failed to show superiority against sorafenib (Yau et al 2019).

Table 1 Summary of Treatment Armamentarium Relevant to Proposed Indication - Currently Available Treatments for Unresectable Hepatocellular Carcinoma (HCC)

Product Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Com-ments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Nexavar (sora-fenib)	For the treatment of patients with un-resectable hepato-cellular carcinoma	2007 (Full Approval)	400 mg (2x200 mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after a meal)	Randomized, double blinded, placebo-controlled trial Median OS: 10.7 months vs 7.9 months HR (95% CI): 0.69 (0.6, 0.9) Median PFS: 5.5 months vs 2.8 months HR (95% CI): 0.58 (0.45, 0.74)	Most common ADRs (>20%) are: diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, de-creased appetite, nausea, gastroin-testinal and abdominal pains, hyper-tension, and hemorrhage Rate of adverse reactions (including those associated with progressive disease) resulting in permanent discon-tinuation of Nexavar was 32%	
Lenvima (lenvati-nib)	First-line treatment of patients	2018 (Full Approval)	12 mg for patients greater than	Randomized open-label non-inferiority	Most common ADRs (≥20%) are: hyper-tension, fatigue,	

	with unre-sectable hepato-cellular carcinoma		or equal to 60 kg **OR** 8 mg for patients less than 60 kg	trial Median OS: 13.6 months vs 12.3 months HR (95% CI): 0.92 (0.79, 1.06) Median PFS (mRECIST): 7.3 months vs 3.6 months HR (95% CI): 0.64 (0.55, 0.75) ORR (95% CI) (mRECIST): 41% (36%, 45%) vs 12% (10%, 16%) Median PFS (RECIST 1.1): 7.3 months vs 3.6 months HR (95% CI): 0.65 (0.56, 0.77) ORR (95% CI) (RECIST 1.1): 19% (15%, 22%) vs 7% (4%, 9%)	diarrhea, decreased appetite, arthralgia/ myalgia, decreased weight, abdominal pain, palmar-plantar erythro-dysesthesia syndrome, protei-nuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea. Most common SADRs (≥2%): hepatic ence-phalopathy (5%), hepatic failure (3%), ascites (3%), decreased appetite (2%). Adverse reactions led to dose reduction or interruption in 62% of patients receiving LENVIMA. Treatment discontinuation due to adverse reactions occurred in 20% of patients in the LENVIMA-treated group.	

The Applicant's Position:

With the addition of just one additional treatment option for unresectable or advanced HCC which did not improve OS, the treatment standard has remained minimally changed for over a decade, highlighting the ongoing high unmet medical need for more efficacious and better tolerated treatments for patients with unresectable HCC.

The FDA's Assessment:

FDA agrees. The standard of care for the first-line treatment of patients with advanced, unresectable HCC that is not amenable to locoregional treatment and metastatic HCC is limited to two multi-tyrosine kinase inhibitors, sorafenib and lenvatinib. Although in the REFLECT study lenvatinib did not show a statistically improvement in OS over sorafenib, the median survival observed in studies evaluating first and second line therapies in HCC show an improved survival in all arms when compared with the median OS observed in the SHARP study; this likely reflects improvements in supportive care and the approval of several drugs for the second line

treatment of HCC (regorafenib, cabozantinib, ramucirumab for the subset of patients with baseline AFP levels ≥ 400 ng/mL, and the accelerated approvals of nivolumab and pembrolizumab).

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Tecentriq® (atezolizumab) was first approved under accelerated approval in the US on May 18, 2016 for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy, or, have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum- containing chemotherapy.
Tecentriq received full approval on April 30, 2018 for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving Tecentriq.
On June 19, 2018, Tecentriq was approved in the US under accelerated approval for patients with locally advanced or metastatic UC who:

- are not eligible for cisplatin-containing chemotherapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA approved test, or
- are not eligible for any platinum-containing chemotherapy regardless of level of tumor PD-L1 expression, or
- have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy.

Tecentric received full approval in the US on December 6, 2018,for use in combination with bevacizumab, paclitaxel, and carboplatin, for the firstline treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
On March 8, 2019, Tecentriq was approved in the US under accelerated approval for triple-negative breast cancer (TNBC) in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating IC of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test.
Tecentriq received full approval on March 18, 2019 for small cell lung Cancer (SCLC), in combination with carboplatin and etoposide, for the 1L treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
On December 2, 2019, Tecentriq received full approval in combination with paclitaxel protein-

bound and carboplatin, is indicated for the first-line treatment of patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations

The FDA's Assessment:
FDA concurs with the Applicant's description of U.S. regulatory actions and approved indications.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

On 19 October 2017 (Serial No. 0001), the Sponsor submitted to the FDA the investigational new drug application (IND) 135913 for the development of atezolizumab in combination with bevacizumab for the treatment of patients with gastrointestinal cancer. The regulatory history related to submission of the supplemental BLA are summarized in Table 2.

Table 2 Regulatory History

Date	Regulatory History
October 02 2017	Type B Pre-Phase III teleconference with the FDA to discuss the Phase III trial design for IMbrave150, as well as a potential accelerated approval pathway for Atezo + Bev in first-line HCC based on the Phase Ib Study GO30140
January 05 2018	FDA provided written feedback regarding the Sponsor's proposal for modifying the Phase Ib Study GO30140 to include a new arm ("Arm F") randomizing first-line HCC patients to atezolizumab monotherapy or Atezo + Bev combination therapy (received under IND 111271)
January 08 2018	Atezolizumab and bevacizumab received orphan drug designation for the treatment, when administered in combination, of HCC
March 08 2018	FDA provided written feedback regarding the Sponsor's proposal for modifying the Phase Ib Study GO30140 to include a new arm ("Arm F") randomizing first-line HCC patients to atezolizumab monotherapy or Atezo + Bev combination therapy
March 12 2018	Agency confirmed agreement with the Sponsor's submitted agreed iPSP for Tecentriq, in combination with bevacizumab, for the first-line treatment of patients with locally advanced or metastatic HCC
April 18 2018	Agency also confirmed agreement with the Sponsor's submitted agreed iPSP for Avastin, in combination with atezolizumab, for the first-line treatment of patients with locally advanced or metastatic HCC
July 13 2018	Breakthrough Therapy Designation for atezolizumab, in combination with bevacizumab, for the first-line treatment of patients with advanced or metastatic HCC

August 13 2018	Breakthrough Therapy Designation for bevacizumab, in combination with atezolizumab, for the first-line treatment of patients with advanced or metastatic HCC
August 17 2018	Type C teleconference with the FDA to discuss the Sponsor's proposed accelerated approval filing strategy for Atezo + Bev for the first-line treatment of patients with advanced or metastatic HCC and seek the Agency's feedback on the proposed change to the co-primary efficacy endpoints and interim and final statistical analysis plan for the Phase III Study IMbrave150
January 09 2019	Type C written feedback from the FDA regarding the proposed content and format of the sBLA to enable accelerated approval for the proposed indication in HCC
October 20 2019	Genentech request for Real Time Oncology Review on the basis of the topline results from IMbrave150
October 30 2019	Genentech request for consideration for inclusion into Project Orbis
November 05 2019	FDA and Genentech held a teleconference to discuss the sBLA submission under the RTOR program, the potential participation in Project Orbis, and other considerations for the sBLA submission
November 13 2019	First component of RTOR submission: Topline results and datasets for IMBrave150 and the complete study report and datasets for Study GO30140 were submitted to BLA 761034 (efficacy supplement 28)
November 21 2019	Second component of RTOR submission: IMbrave150 datasets and SAS programs
December 02 2019	Third component of RTOR submission: Module 1 documents, Module 5 eCRFs
December 09 2019	Preliminary comments received for the Type B pre-sBLA meeting
December 16, 2019	Fourth component of RTOR submission: USPI, IMbrave150 CSR, BIMO/OSI

The FDA's Assessment:

FDA concurs with the regulatory milestones described by the Applicant in Table 2. During the October 2, 2017 meeting, FDA expressed concern that neither Study YO40245 nor Study GO30140 will characterize the contributions of atezolizumab and of bevacizumab to the overall treatment effect. In response to this comment, the Applicant agreed to provide a proposal for modification of Study GO30140 to address this issue.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The review team determined that clinical site inspections were not necessary for several reasons. Bevacizumab has been approved since February 26, 2004, and it is been widely used for the treatment of several malignancies. Atezolizumab was initially approved on May 18, 2016, and there is ample clinical experience with its use in patients with cancer. Additionally, FDA review of the datasets did not show problematic outliers in results across study sites or novel safety signals. Protocol violations were minimal and unlikely to materially affect study results, and the vast majority of patients randomized in Study IMbrave150 study received their assigned treatment. Finally, the potential for bias in the results of the co-primary endpoints was deemed minimal given that overall survival is not subject to investigator bias and progression-free survival was determined by an independent review facility.

4.2 Product Quality

Refer to FDA OBP reviews. The applications are approvable from a CMC perspective.

4.3 Clinical Microbiology

This section is not applicable to this application.

4.4 Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current submission.

6 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

In this supplemental BLA submission, the Applicant seeks approval for atezolizumab in combination with bevacizumab for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy. The clinical data to support the proposed indication are from a randomized, open-label trial, Study IMbrave150, in which

atezolizumab was administrated at a fixed dose of 1200 mg by intravenous (IV) infusion every three weeks (Q3W) in combination with bevacizumab. Based on results from Study IMbrave150, and the well characterized atezolizumab pharmacokinetics (PK) and exposure-response relationships, the Applicant proposes atezolizumab dosing regimens (atezolizumab 1200 mg + bevacizumab 15 mg/kg Q3W, or 1200 mg Q3W; 840 mg Q2W; or 1680 mg Q4W if bevacizumab is discontinued) which are consistent with those in previously approved indications for atezolizumab as a monotherapy. Per FDA's previous analyses, atezolizumab AUCs and $C_{troughs}$ at steady state with 840 mg Q2W and 1680 mg Q4W are expected to be comparable to 1200 mg Q3W. In addition, C_{max} values at 1680 mg Q4W are generally comparable to those with 20 mg/kg Q3W where the safety was found to be acceptable (see Clinical Pharmacology review for supplement 13 and 14).

In Study IMbrave150, the ADA-positive rate is 28% (88/315 patients) overall, including 20% (58/288 patients) at the Week 6 timepoint. A majority (66% or 58/88) of ADA-positive patients tested positive for ADA prior to receiving the third dose of atezolizumab. Clearance of atezolizumab in the ADA-positive subgroup increased by 49% compared with the ADA-negative subgroup based on a post-hoc analysis. Based on the Applicant's proposed inverse probability weighting (IPW) analysis adjusting the imbalanced covariates between ADA-positive and ADA-negative subgroups, the overall survival (OS) hazard ratio (95% CI) compared with sorafenib for the Week 6 ADA-positive subgroup and the Week 6 ADA-negative group is 0.93 (0.57, 1.53) vs. 0.39 (0.26, 0.60), respectively, with 16 covariates adjusted.

FDA recommended the following labeling updates in Section 6.2, Section 12.3 and Section 14.5 to incorporate the above assessments.

Section 6.2 Immunogenicity:

Among 315 ADA-evaluable patients with HCC who received TECENTRIQ and bevacizumab in IMbrave150, 28% (n=88) tested positive for treatment-emergent ADA at one or more post-dose time points and 66% (58/88) of these 88 patients tested ADA-positive prior to receiving the third dose of TECENTRIQ. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA had lower systemic atezolizumab exposure as compared to patients who were ADA-negative *[see Clinical Pharmacology (12.3)]*. Exploratory analyses showed that the subset of patients who were ADA-positive by Week 6 (20%; 58/288) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by Week 6; *[see Clinical Studies (14.5)]*. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Section 12.3 Clinical Pharmacokinetics

In OAK, IMpower150 (TECENTRIQ, bevacizumab, paclitaxel, carboplatin arm only), IMpassion130 (TECENTRIQ and paclitaxel protein-bound) and IMbrave150 (TECENTRIQ and

bevacizumab), atezolizumab clearance in patients who tested positive for treatment-emergent anti-drug antibodies (ADA) was 25%, 18%, 22%, and 49% higher, respectively, as compared to clearance in patients who tested negative for treatment-emergent ADA.

Section 14.5 Clinical Studies

Exploratory analyses showed that the subset of patients (20%) who were ADA-positive by Week 6 appeared to have reduced efficacy (effect on OS) as compared to patients (80%) who tested negative for treatment-emergent ADA by Week 6 *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3)]*. ADA-positive patients by Week 6 appeared to have similar overall survival compared to sorafenib-treated patients. In an exploratory analysis, inverse probability weighting was conducted to compare ADA-positive patients and ADA-negative patients in the TECENTRIQ and bevacizumab arm to the sorafenib arm. Inverse probability weighting factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, age, race, geographic region, weight, neutrophil-to-lymphocyte ratio, AFP (<400 ng/mL vs ≥400 ng/mL), number of metastatic sites, MVI and/or EHS present at study entry, etiology (HBV vs. HCV vs. non-viral) and Child-Pugh Score (A5 VS. A6). The OS hazard ratio comparing the ADA-positive subgroup of the TECENTRIQ and bevacizumab arm to sorafenib was 0.93 (95% CI: 0.57, 1.53). The OS hazard ratio comparing the ADA-negative subgroup to sorafenib was 0.39 (95% CI: 0.26, 0.60).

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Following 1200 mg atezolizumab given every 3 weeks (Q3W) intravenously (IV), the PK results in all HCC studies were consistent with the known pharmacokinetics of atezolizumab. The observed inter-individual variability (IIV) of atezolizumab as the arithmetic mean CV% across studies ranged from 22% to 34% for C_{max} and 21% to 63% for C_{min} at Cycle 1.

No apparent PK drug–drug interaction (DDI) was observed when atezolizumab was administered in combination with bevacizumab.

Atezolizumab exposure was in concordance with historical data based on popPK analyses and well above the target concentration of 6 µg/mL (Deng et al 2016). Covariate effects impacting exposure of atezolizumab in IMbrave150 were consistent with those identified in the popPK model (which are body weight, gender, ADA status, albumin level, and tumor burden). Exposure-response (ER) analysis was not conducted for IMbrave150 given there were no clinically meaningful exposure-efficacy or exposure-safety relationships identified in previous analyses when atezolizumab was administered as monotherapy to patients with mUC or NSCLC in addition to potential confounding due to prognostic factors.

The proportion of patients who developed treatment-emergent ADAs to atezolizumab in HCC patients ranged from 23.8% to 37.9%. On average, the mean atezolizumab Cycle 1 C_{min} ranged from 6.06% to 39.1% lower in the ADA-positive patients compared to the ADA-negative patients, though remained 9-14 fold greater than the target minimum serum concentration of 6 μg/mL. (b) (4)

The imbalance in prognostic factors between ADA subgroups preclude definitive conclusions on the potential impact of ADA development on efficacy. There did not appear to be a clinically relevant impact of ADA status on safety.

Following 15 mg/kg of bevacizumab given Q3W IV, the PK results in HCC patients were consistent with the known pharmacokinetics of bevacizumab. The inter-individual variability (arithmetic mean CV%) of bevacizumab was up to 23% at C_{max} within Cycle 1. No apparent PK DDI was observed when bevacizumab was administered in combination with atezolizumab. The bevacizumab C_{max} and C_{min} with atezolizumab co-administration were comparable to historical studies in the absence of atezolizumab, showing a maximal percent difference of -11% and -14% respectively to historical studies, and the mean bevacizumab C_{min} was at least >8-fold above the target concentration of 10 μg/mL (Bergsland et al 2004). The proportion of patients who developed treatment-emergent ADAs to bevacizumab ranged from 2.1% to 3.7%. The clinical significance of an immune response to bevacizumab is limited by the small number of patients who developed ADA-positive status.

The FDA's Assessment:

FDA does not fully agree with the Applicant's position (b) (4) The clearance in ADA positive subgroup increased by 49% based on a post-hoc analysis compared with ADA negative subgroup. FDA does not agree with the Applicant that (b) (4) overall survival (OS) benefit appeared to be driven by ADA-negative patients as ADA positive patients had comparable OS with the sorafenib control patients. Please refer to Section 19.4 for FDA's analysis.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The Applicant's Position:

Genentech proposed a dosing regimen of atezolizumab administered at a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle) in combination with bevacizumab administered at a fixed dose of 15 mg/kg Q3W on Day 1 of each 21-day cycle.

Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In the Phase I Study GO27831 (PCD4989g) the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight based dose of 15 mg/kg Q3W) was selected on the

basis of both nonclinical studies (Deng et al. 2016) and available clinical PK, efficacy, and safety data.

Bevacizumab administered at a fixed dose of 15 mg/kg Q3W on Day 1 of each 21-day cycle is an approved dosage for bevacizumab (see Avastin approved label). The 15 mg/kg Q3W dose of bevacizumab aligns with the atezolizumab dosing schedule (1200 mg Q3W), and is also the dosage used in the IMbrave150 and GO30140 (Arms A and F) studies in combination with atezolizumab. This dose was well-tolerated without any new safety signal in these trials.

The FDA's Assessment:
FDA agrees with the Applicant's proposed recommended dosing regimen: atezolizumab 1200 mg Q3W in combination with bevacizumab 15 mg/kg Q3W, or atezolizumab 1200 mg Q3W; 840 mg Q2W; or 1680 mg Q4W if bevacizumab is discontinued. Atezolizumab at 1200 mg Q3W has demonstrated efficacy; Ctroughs at steady state with 840 mg Q2W and 1680 mg Q4W are expected to be comparable to 1200 mg Q3W; and Cmax values are generally comparable to the Cmax at 20 mg/kg Q3W, which had been demonstrated acceptable safety. Please refer to Clinical Pharmacology review for BLA 761034 Supplement-13 and Supplement-14 for details on the FDA's evaluation of the 840 mg Q2W and 1680 mg Q4W dosing regimens. Bevacizumab 15 mg/kg Q3W is an approved dosage.

2.2.2 Therapeutic Individualization

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees that no therapeutic individualization is needed. Please refer to the original BLA Clinical Pharmacology Review for FDA's assessment.

6.2.2.3 Outstanding Issues

The Applicant's Position:
None

The FDA's Assessment:
FDA agrees.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

The clinical pharmacology properties of atezolizumab were originally characterized using previous studies when atezolizumab 1200 mg IV Q3W was administered as monotherapy in

predominantly patients with mUC and NSCLC. The key general clinical pharmacology properties and those specific to HCC are listed below.

- Atezolizumab pharmacokinetics were linear over a dose range of 1 to 20 mg/kg of atezolizumab, including the fixed 1200 mg dose Q3W regimen of atezolizumab.
- The typical population total clearance of the drug (CL) was 0.2 L/day and the typical population volume of distribution in steady-state condition (V_{ss}) was 6.91 L.
- The typical terminal half-life ($t_{1/2}$) estimate is 27 days, and an approximate steady-state was reached after 3 cycles of treatment with accumulation of 2.75, 1.46, and 1.91-fold based on trough or C_{min}, C_{max}, and AUC.
- The majority of patients receiving 10 to 20 mg/kg atezolizumab Q3W, including the fixed 1200 mg dose of atezolizumab, maintained average atezolizumab C_{min} far above the target efficacy serum concentration of 6 μg/mL, regardless of ADA status.
- Atezolizumab PK data obtained in NSCLC (BIRCH, FIR, POPLAR, and OAK as monotherapy trials and IMpower150 as a combination therapy trial), in mUC (IMvigor210 and IMvigor211), and in renal cell carcinoma (a combination therapy trial IMmotion151) were consistent with the popPK model estimates using Phase I data.
- Based on the popPK analysis, the inter-individual variability (IIV) for CL is 29%, 18% for volume of distribution for the central compartment (V1), and 34% for volume of distribution for the peripheral compartment (V2). No patient-specific factors (e.g., body weight, gender, race, ADA status, or age) warrant changes to the dosing algorithm.
- No clinically meaningful exposure-efficacy or exposure-safety relationship was concluded when atezolizumab was administered as monotherapy in mUC and NSCLC.
- Mild to severe renal impairment and mild hepatic impairment did not appear to impact the pharmacokinetics of atezolizumab based on the popPK analysis.
- The overall treatment-emergent incidence of ADA to atezolizumab ranged from 16.7% to 54.5% in eight studies conducted previously (Studies PCD4989g, JO28944, IMvigor210, IMvigor211, BIRCH, POPLAR, FIR, and OAK).
- No clinically meaningful change in QTc was observed following 4 doses of atezolizumab (20 mg/kg IV Q3W).

The clinical pharmacology properties of atezolizumab have been characterized in studies in patients with HCC both as a monotherapy and mostly in combination with bevacizumab. The key properties in patients with HCC have been described in Section 6.2. The pharmacokinetic findings of atezolizumab when combined with bevacizumab in patients with HCC are similar to the Phase I monotherapy study (PCD4989g) following administration of 1200 mg of atezolizumab Q3W across other tumor types.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Following 1200 mg IV atezolizumab Q3W, the C_{min} for the majority of patients were well above the minimum target concentration of 6 µg/mL. Similarly, following the 15mg/kg IV dose of bevacizumab Q3W the C_{min} for bevacizumab were above the target concentration of 10 µg/mL, both of which are clinical targets based on in vitro and nonclinical extrapolation.

The Applicant's Position:

The clinical pharmacology information along with the efficacy results from IMbrave150 of 336 Atezo+Bev treated patients with locally advanced or metastatic HCC provide evidence of effectiveness.

The FDA's Assessment:
FDA agrees with Applicant's position.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

No exposure-efficacy or exposure-safety relationships were observed based on monotherapy trials. No clinically meaningful covariate was identified from the popPK analysis. The assessment of sparse pharmacokinetics from the pivotal trial did not appear to suggest DDI of atezolizumab and bevacizumab.

The Applicant's Position:

Yes. The pharmacokinetics of atezolizumab in previously untreated unresectable HCC patients are consistent with those observed previously from mUC and NSCLC studies. The proposed dosing regimen of 1200 mg of atezolizumab Q3W in combination with 15 mg/kg of bevacizumab Q3W is considered appropriate for patients with advanced or metastatic HCC.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

Based on the popPK analysis, no clinically meaningful covariates were identified that warrant dose adjustment.

The FDA's Assessment:

FDA agrees with the Applicant's position that no clinical meaningful covariates are identified for dose adjustment. However, FDA doesn't agree with the Applicant's assessment regarding the clinical impact of immunogenicity. In Study IMbrave150, the overall ADA-positive rate is 28% (88/315 patients) and 20% (58/288 patients) of patients were ADA-positive at the Week 6 landmark. A majority (66% or 58/88) of ADA-positive patients tested positive for ADA prior to receiving the third dose of atezolizumab. Clearance of atezolizumab in the ADA-positive subgroup increased by 49% compared with ADA-negative subgroup. Based on the Applicant-conducted IPW analysis adjusting the imbalanced covariates between ADA-positive and ADA-negative subgroups, overall survival (OS) hazard ratios (95% CI) compared with sorafenib for the Week 6 ADA-positive and Week 6 ADA-negative subgroups are 0.93 (0.57, 1.53) and 0.39 (0.26, 0.60), respectively, with 16 covariates adjusted. Please refer to Appendix 19.4 for FDA's assessment.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

No apparent DDI in either direction for atezolizumab or bevacizumab was observed.

The FDA's Assessment:

FDA agrees. Food-drug interaction is not expected for atezolizumab since it is administered as an IV infusion. The risk for drug-drug interactions between atezolizumab and concomitant drugs is also low given that atezolizumab is a monoclonal antibody.

X X

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7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 3 Listing of Clinical Trials Included with this sBLA

Trial Identity + NCT No.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
YO40245 (IMbrave150) NCT03434379	Phase III, open-label, multicenter, randomized, two-arm	• Atezo 1200 mg IV Q3W + Bev 15 mg/kg IV Q3W • Sorafenib 400 mg PO BID	Co-primary endpoints: OS, PFS per IRF RECIST v1.1 2° endpoints: PFS per IRF HCC mRECIST or Inv RECIST v1.1, ORR, DOR, TTP per all 3 RECIST criteria; OS and PFS by AFP level; TTD of physical functioning, role functioning and global health status/quality of life (GHS/QoL) per EORTC QLQ-C30 questionnaire	Treatment until radiographic disease progression per RECIST v1.1 or loss of clinical benefit as determined by the Investigator. Survival follow up following stop of study treatment.	501 (336 on Atezo+Bev, 165 on sorafenib)	Patients with locally advanced or metastatic HCC who have received no prior systemic treatment.	111 centers across 17 countries/ regions
GO30140 (Arms A and F) NCT02715531	Phase Ib, open-label, multicenter, non-randomized, single-arm (Arm A), and randomized, two-arm (Arm F)	Arm A: • Atezo 1200 mg IV Q3W + Bev 15 mg/kg IV Q3W Arm F: • Atezo 1200 mg IV Q3W + Bev 15 mg/kg IV Q3W • Atezo 1200 mg IV Q3W	Arm A: 1° EP: ORR per IRF RECIST v1.1 2° endpoints: ORR per IRF HCC mRECIST or Inv RECIST v1.1, PFS, DOR, TTP per all 3 RECIST criteria, OS Arm F: 1° EP: PFS per IRF RECIST v1.1 2° endpoints: PFS per IRF HCC mRECIST or Inv RECIST v1.1, ORR, DOR, TTP per all 3 RECIST criteria, OS	Treatment until radiographic disease progression per RECIST v1.1 or loss of clinical benefit as determined by the Investigator. Survival follow up following stop of study treatment.	223 (Arm A: 104 on Atezo+Bev. Arm F: 60 on Atezo+Bev, 59 on Atezo mono)	Patients with advanced or metastatic and/or unresectable HCC who have received no prior systemic treatment.	25 centers across 7 countries/ regions
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
PCD4989g (GO27831 NCT01375842 (HCC Cohort)	Phase Ia, open-label, dose-escalation and dose expansion stages	• HCC Cohort: Atezo 1200 mg IV Q3W	ORR, DOR PFS per Inv RECIST v1.1, OS, PK, Safety	Treatment continued as long as patients continued to experience clinical benefit in the opinion of the investigator	HCC = 15 1L = 5 2L+ = 10	Patients with locally advanced or metastatic HCC	7 centers in 4 countries

				until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation.			
YO29233 NCT02825940 (HCC Cohort)	Phase I, open-label, multicenter	• HCC Cohort: Atezo 1200 mg IV Q3W	ORR, DOR PFS per Inv RECIST v1.1 or HCC mRECIST, OS, PK, Safety	Treatment continued until disease progression per RECIST v1.1, loss of clinical benefit (for patients who continued atezolizumab treatment after disease progression per RECIST v1.1), unacceptable toxicity, patient or physician decision to discontinue, or death, whichever occurred first.	HCC = 21 1L = 7 2L+ = 14	Chinese patients with locally advanced or metastatic HCC that are refractory to standard therapeutic modalities and for whom no further standard therapy is available or who have refused standard therapy for solid tumors.	

Additional safety information from 8 previous studies is obtained from a total of 3178 patients treated with atezolizumab monotherapy in multiple indications. This safety population is pooled from different tumor types, mainly including patients in the 2L+ lines of anti-cancer therapies in NSCLC, UC and 1L+ RCC, providing a large comprehensive safety dataset for atezolizumab monotherapy. The list of all studies included and a description of their high-level study designs is provided in the Summary of Clinical Safety Module 2.7.4.

Furthermore, publications of two investigator initiated studies that investigated the effects of bevacizumab monotherapy in patients with HCC are also included and discussed in the submission (Siegel et al 2008, Boige et al 2012).

The FDA's Assessment:
FDA agrees with the content of Table 3. FDA considers Study IMbrave150 to be the primary study supporting the safety and effectiveness of atezolizumab in combination with bevacizumab for the first-line treatment of patients with unresectable, metastatic HCC. Arms A and F of Study GO30140, as well as cohorts of patients with HCC treated in other studies provide supportive evidence of the treatment effect of the combination and the contribution of each component.

8 Statistical and Clinical and Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 Design of Studies Providing Key Information

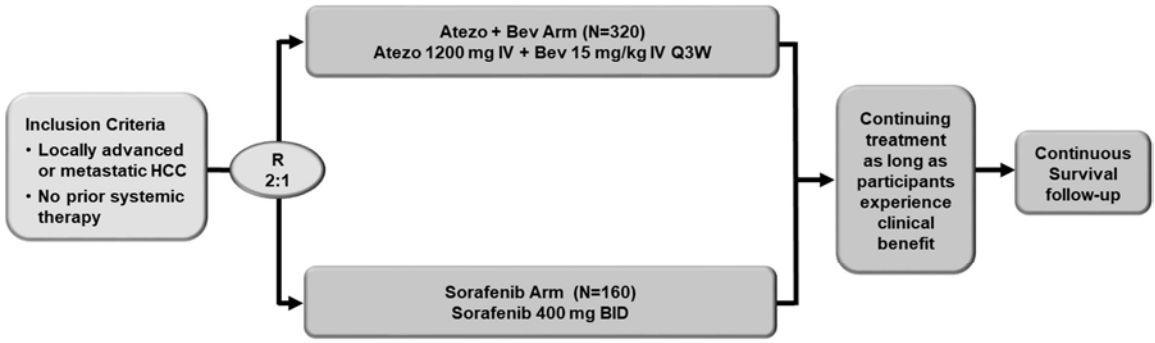
Pivotal Study: IMbrave150 (YO40245)

Trial Design

The Applicant's Description:

Trial Design Overview: IMbrave150 is an ongoing Phase III, randomized, multicenter, global, open-label, two-arm study designed to evaluate the efficacy and safety of Atezo + Bev versus sorafenib in patients with locally advanced or metastatic HCC who had not received prior systemic treatment. A schematic diagram of the study design is shown in Figure 1.

Figure 1 Study Design for IMbrave150



Randomization Stratification Factors

- Geographic Region (Asia excluding Japan vs rest of the world)
- Macrovascular invasion and/or extrahepatic spread (presence or absence)
- Baseline α feto-protein (<400 ng/mL vs ≥400 ng/mL)
- Baseline ECOG performance status (0 or 1)

Trial Location: This study was conducted globally. Geographic region (Asia [excluding Japan] vs. rest of world) was one of the stratification factors.

Choice of Control: At the time of study initiation, sorafenib was the only globally and locally approved targeted therapy for patients with unresectable HCC who have not received prior systemic therapy.

Diagnostic Criteria: IMbrave150 was to evaluate the efficacy and safety of Atezo + Bev vs sorafenib in patients with untreated locally advanced or metastatic HCC. This study population followed the recommended patient population for studies assessing a new agent or combination of agents in HCC, as noted by an expert panel convened by the AASLD. Key selection criteria were:

Key Inclusion Criteria:

- Locally advanced or metastatic and/or unresectable HCC with diagnosis confirmed by histology/cytology or clinically by AASLD criteria in cirrhotic patients
- Disease that was not amenable to curative surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies
- No prior systemic therapy (including systemic investigational agents) for HCC
- Patients who received prior local therapy (e.g., radiofrequency ablation, percutaneous ethanol or acetic acid injection, cryoablation, high-intensity focused ultrasound, transarterial chemoembolization, transarterial embolization, etc.) were eligible provided the target lesion(s) had not been previously treated with local therapy or the target lesion(s) within the field of local therapy had subsequently progressed in accordance with RECIST v1.1.
- Child-Pugh class A within 7 days prior to randomization. Patients with Child Pugh Class B or C were excluded from the study given the known increased risk of death
- Adequate hematologic and end organ function within 7 days prior to randomization
- Documented virology status of hepatitis, as confirmed by screening HBV and HCV serology test

- At least one measurable (per RECIST v1.1) untreated lesion
- ECOG Performance Status of 0 or 1 within 7 days prior to randomization
- For patients with active hepatitis B virus (HBV):
  - HBV DNA < 500 IU/mL obtained within 28 days prior to initiation of study treatment, ***and***
  - Anti-HBV treatment (per local standard of care; e.g., entecavir) for a minimum of 14 days prior to study entry and willingness to continue treatment for the length of the study

Key Exclusion criteria:

- Untreated or incompletely treated esophageal and/or gastric varices with bleeding or high risk for bleeding
  Patients must undergo an esophagogastroduodenoscopy (EGD), and all size of varices (small to large) must be assessed and treated per local standard of care prior to enrollment. Patients who have undergone an EGD within 6 months of prior to initiation of study treatment do not need to repeat the procedure.
- A prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study treatment
- History of malignancy other than HCC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death

Study Treatments / Dose Selection / Dose modification, Dose Discontinuation: The fixed dose and schedule of atezolizumab and bevacizumab are approved dosages for each drug and are the same as those used in Study GO30140. Both drugs were administered by IV infusion at a fixed dose of 1200 mg (atezolizumab) and of 15 mg/kg (bevacizumab) on Day 1 of each 21-day cycle. Atezolizumab was administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing.

The Atezo+Bev combination was to be administered until unacceptable toxicity or loss of clinical benefit as determined by the Investigator. Dose modifications were not allowed for atezolizumab and bevacizumab.

The selected sorafenib dose was 400 mg BID continuously as per the approved dose and schedule. Temporary interruption or dose modification were allowed for the management of toxicities as per protocol and applicable local prescribing information.

Assignment to Treatment: Patients were randomized via an interactive voice or web-based response system (IxRS) to one of the two treatment arms (Atezo+Bev or sorafenib) according to a 2:1 randomization ratio using a permuted-block randomization method. Randomization was stratified according to the following stratification factors which are also key disease related prognostic factors for HCC:

- Geographic region (Asia excluding Japan vs. rest of world)
- Macrovascular invasion and/or extrahepatic spread (presence vs. absence)
- Baseline AFP (<400 vs. $\geq$ 400 ng/mL)
- ECOG Performance Status (0 vs 1)

Blinding: An open-label (unblinded) study design was chosen due to the unique toxicity profile of each study drug that could allow identification of the assigned treatment. In addition, the open-label study design avoided unnecessary burden and excessive risk to patients from two

placebo infusions at every cycle in the control arm. Given the open-label nature of the study, co-primary and secondary efficacy endpoints were assessed by a blinded centralized IRF to minimize bias introduced due to the open-label design of the study.

Administrative Structure: An independent Data Monitoring Committee (iDMC) monitored accumulating patient safety data approximately every 6 months until the time of the primary PFS and first OS interim analysis. No efficacy interim analyses were conducted by the iDMC. An independent Data Coordinator Center performed all safety analyses (demographic data, AEs, SAEs, and relevant laboratory data) to support the periodic iDMC review.

Procedures and Schedule: Efficacy: Patients underwent tumor assessments at baseline, then every 6 weeks for the first 54 weeks, and every 9 weeks thereafter, regardless of dose delays, until radiographic disease progression per RECIST v1.1 or (for patients who continued treatment after radiographic disease progression) loss of clinical benefit as determined by the Investigator.

Patients who met RECIST v1.1 criteria for progression underwent tumor assessments until disease progression per imRECIST or loss of clinical benefit, whichever occurred later. In the absence of disease progression, tumor assessments were to continue regardless of whether patients started new anti-cancer therapy, until consent was withdrawn, death, or the study was terminated by the Sponsor, whichever occurred first. At the Investigator's discretion, tumor assessments may have been repeated at any time if progressive disease was suspected.

PROs: Patients were to complete paper versions of the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires at the clinic site on Cycle 1, Day 1 and Day 1 of every cycle thereafter until the treatment discontinuation visit (included). After treatment discontinuation, questionnaires were to be completed every 3 months (for 1 year), unless the patient withdrew consent.

Safety: After initiation of study drug, all AEs were collected up to 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurred first. SAEs and AESIs were reported until 90 days after the last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurred first. After the end of the AE reporting period, any SAE believed to be related to prior exposure to study treatment and all deaths continued to be collected.

Concurrent Medications: IMbrave150 CSR Section 3.7 discusses concomitant medications that were allowed, for which caution had to be exerted, or which were prohibited.

Prohibited therapies included other anti-cancer agents, investigational agents, live attenuated vaccines, systemic immunostimulatory or immunomodulatory medications, use of full dose anticoagulants, thrombolytic therapy at therapeutic doses, or anti-platelet therapy, use of warfarin or Coumadin like products, concomitant chronic use of NSAIDs.

Treatment Compliance: Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site were recorded on the Drug Inventory Log.

Subject Completion, Discontinuation, or Withdrawal: Patients were to receive atezolizumab and/or bevacizumab or sorafenib until unacceptable toxicity or loss of clinical benefit as determined by the Investigator after an integrated assessment of radiographic and biochemical data, and clinical status. Tumor assessments continued until disease progression, regardless of

whether treatment has been discontinued. Patients discontinuing study treatment prematurely were not replaced.

The FDA's Assessment:
FDA agrees with the Applicant's description of the IMbrave150 study design.

The protocol defined "adequate hematologic and end organ function" for eligibility as follows: ANC ≥ 1500/uL, platelets ≥75,000/uL, hemoglobin ≥9 g/dL; ALT/AST and alkaline phosphatase ≤ 5 x ULN, serum bilirubin ≤ 3x ULN, serum creatinine ≤1.5 x ULN or creatinine clearance ≥ 50 mL/min, albumin ≥ 2.8 g/dL, INR or aPTT ≤2x ULN, dipstick for proteinuria ≤ 2+.

Although serology for hepatitis C virus infection (HCV) was required, there were no eligibility criteria related to HCV infection.

Other important eligibility criteria include exclusion of patients with moderate to severe ascites, history of hepatic encephalopathy, uncontrolled pleural or pericardial effusion, uncontrolled tumor-related pain, uncontrolled or symptomatic hypercalcemia, and standard eligibility criteria for studies with checkpoint inhibitors and bevacizumab.

For decision-making regarding study treatment discontinuation, Immune-modified RECIST (imRECIST) was used to confirm disease progression in patients with disease progression per RECIST 1.1. While the definition of disease progression according to RECIST 1.1 requires ≥ 20% increase in the sum of the diameters of target lesions, unequivocal progression in non-target lesions, or appearance of new lesions, imRECIST defines progressive disease as a ≥ 20% increase in tumor burden.

Study Endpoints

The Applicant's Description:

Co-primary Efficacy Endpoints

- OS: time from randomization to death due to any cause
- PFS: time from randomization to the 1st documented disease progression as determined by an IRF according to RECIST Version 1.1, or death from any cause (whichever occurred first)

Secondary Efficacy Endpoints

- PFS as per IRF assessed HCC mRECIST and Investigator assessed RECIST v1.1
- Objective Response Rate (ORR) as per IRF assessed RECIST v1.1 and HCC mRECIST, and Investigator assessed RECIST v1.1
- Duration of Response (DOR) as per IRF assessed RECIST v1.1 and HCC mRECIST, and Investigator assessed RECIST v1.1
- Time to Progression (TTP) as per IRF assessed RECIST v1.1 and HCC mRECIST, and Investigator assessed RECIST v1.1
- OS and PFS per IRF assessed RECIST v1.1 by baseline serum AFP level (< 400 ng/mL vs ≥ 400 ng/mL)

Patient Reported Outcome Measures Pre-defined as Secondary Endpoints

- Time to Deterioration (TTD): time from randomization to first deterioration (decrease from baseline of ≥ 10 points), maintained for 2 consecutive assessments or one assessment followed by death from any cause within 3 weeks in the following subscales of the EORTC QLQ-C30 questionnaire: Physical functioning, Role functioning, GHS/QoL

The FDA's Assessment:

FDA agrees with the Applicant's summary of the study objectives and endpoints; however, OS and PFS are considered a family of primary endpoints which share alpha as described below, and are not co-primary endpoints.

Statistical Analysis Plan and Amendments

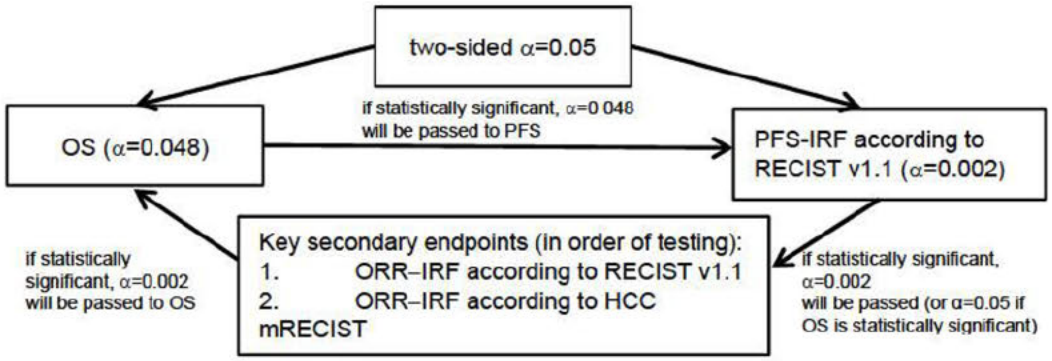
The Applicant's Description:

The analyses outlined in the SAP superseded those specified in the study protocol, as applicable. Version 1 of the SAP was submitted to FDA on 26-Feb-2019. There were no updates to the SAP. All statistical analyses performed are consistent with the SAP.

The IMbrave150 only and final PFS analysis was to be conducted when approximately 308 IRF-assessed PFS events per RECIST v1.1 had occurred in the ITT population. At the time of the final PFS analysis, the first interim OS analysis (OS IA1) was to be conducted in the same population.

Overall Type I Error Control: The overall type I error rate for this study was strongly controlled at a two-sided significance level of 0.05 by a graphical approach, i.e., alpha splitting and recycling (Bretz et al 2009). The overall two-sided significance level of 0.05 was split into a two-sided significance level of 0.048 for the testing of OS and a two sided significance level of 0.002 for the testing of PFS initially. If OS was statistically significant, the allocated two-sided significance level of 0.048 could be recycled to PFS such that PFS could be tested at a two sided significance level of 0.05 instead of 0.002. If the analysis of PFS was statistically significant, then the two-sided significance level of 0.002 (or 0.05 if OS was statistically significant) was to be recycled to key secondary endpoints (IRF-assessed ORR according to RECIST v1.1 and HCC mRECIST) to be formally tested in a hierarchical fashion. If PFS and both key secondary endpoints were statistically significant at a two-sided significance level of 0.002, then OS could be tested at a two-sided significance level of 0.05 instead of 0.048. Analyses of the co-primary efficacy endpoint of IRF-assessed PFS per RECIST v1.1 as well as analyses of all key secondary efficacy endpoints (confirmed IRF-assessed ORR per RECIST v1.1 and confirmed IRF-assessed ORR per HCC mRECIST) were to be conducted only once at the time of the primary PFS analysis. The detailed testing boundaries are described in the Statistical Analysis Plan. An overview of the type I error rate control strategy for the co primary and key secondary efficacy endpoints is shown in Figure 2.

Figure 2 Overview of the Type I Error Control for Co-Primary and Key Secondary Endpoints



Analysis Populations

- **Intent-to-Treat (ITT) Population:** All randomized patients, whether or not the patients received the assigned study treatment. Patients were grouped according to the treatment assigned at randomization by IxRS, whether or not the assigned treatment was received
- **PRO Evaluable Population:** All randomized patients who had a baseline and at least one post-baseline assessment. The PRO-evaluable population was used for descriptive analyses of visit summary and change from baseline and proportion analyses. The ITT population was used for the analyses of PRO completion and Time to Deterioration (TTD). All PRO analyses were performed per the treatment arm assigned at randomization by the IxRS, whether or not the assigned treatment was received.
- **PK Evaluable Population:** All patients who received any dose of study treatment and who had at least one post-baseline PK sample available.
- **Safety Evaluable (SE) Population:** All randomized patients who received at least one full or partial dose of any study treatment, with patients grouped according to the actual treatment received. Patients who received any amount of atezolizumab and/or bevacizumab were assigned to the Atezo+Bev treatment arm for safety analyses even if atezolizumab/bevacizumab was given in error.

Subgroup Analyses: The subgroup analyses presented in the report had been pre-specified in the SAP, with the exception of tobacco or alcohol use history, and prior local therapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's above statements, with the following comments:

- The Applicant's summary of the SAP above did not a include brief description of efficacy analyses including the primary analyses of OS, PFS, and key secondary endpoints. Per the SAP, the primary analysis of the OS primary endpoint would be the stratified log-rank test in the ITT population to compare OS between the two treatment arms. Three out of the 4 stratification factors used for randomization, geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and baseline AFP (< 400 vs. ≥ 400 ng/mL) per IxRS at randomization, would be used in the stratified analysis. The Kaplan-Meier method would be used to estimate median OS and its 95% CI for each treatment arm using Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982). The primary endpoint of PFS-IRF would be analyzed using the same

methodologies as OS. The two-sided Cochran-Mantel-Haenszel test would be used to compare ORR between the two treatment arms.

- Per the SAP, the analysis of ORR would be based on the subset of patients in the ITT population with measurable disease at baseline, which is a non-randomized subset of patients. Because between-arm comparisons of non-randomized subsets are difficult to interpret as there may be an imbalance in known or unknown factors between two arms , FDA conducts comparisons of ORR based on the ITT population.
- Per the SAP, TTD was defined as the time from randomization to the first deterioration (decrease from baseline of ≥ 10 points) in the patient-reported health-related global health status/quality of life (GHS /HRQoL), physical function or role function scales of the European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer (EORTC) QLQ-C30, maintained for two consecutive assessments, or one assessment followed by death from any cause within 3 weeks. The Kaplan-Meier analysis methods for the analysis of TTD were similar to those described for PFS. However, FDA does not agree that the 10 point threshold for TTD is appropriately justified as a clinically-meaningful threshold. FDA considers evaluation of the PRO endpoints to be exploratory.

Protocol Amendments

The Applicant's Description:

Protocol Version 2 (14 March 2018) was the 1st version under which patients were treated.

The protocol was amended to Version 3 on 15 Sep 2018 with the key modifications being a change in the co-primary endpoints from Investigator-assessed ORR and OS to IRF-assessed PFS and OS, given that ORR for Atezo+Bev was being extensively investigated in study GO30140.

Another amendment (to Version 4, 20 Feb 2019) was implemented primarily to modify the originally planned statistical analysis and to align with the SAP to include a second interim analysis for OS in anticipation of the changing HCC landscape. Other changes in the statistical analysis plan included:

- The method used for control of the overall type I error rate was updated from using a group sequential weighted Holm procedure to using a graphical approach to strongly control the type I error at 5% (two-sided).
- PFS was added as the primary endpoint of the China subpopulation analysis to align with the global study analysis.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the protocol amendments. Per the Applicant's statement above, Version 1 of the SAP (dated on 22-Feb-2019) was submitted to FDA on February 26, 2019. There were no updates to the SAP. The other changes in the statistical analysis plan in the protocol amendments that were not mentioned above are described below.

In Protocol Version 2, additional changes were as follows:

- The stratification factors used for the stratified analyses planned to be conducted for both primary efficacy endpoints, overall survival (OS) and overall response rate (ORR), were clarified. The following stratification factors were specified for the stratified analyses of both primary endpoints: geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence), and baseline α-fetoprotein level (<400 vs. ≥400 ng/mL). Results from unstratified analyses may be provided as sensitivity analyses (Sections 6.4.1.1 and 6.4.1.2, respectively).
- The testing order of the key secondary endpoints in Section 6.4.2 of the protocol was removed as formal testing of the time to progression endpoint was no longer planned.
- The optional interim analysis of OS was removed (previously, Section 6.10.2), and the section heading numbering changed accordingly.

In Protocol Version 3, additional changes were as follows:

- ORR and PFS as determined by the investigator were added as secondary endpoints. The primary efficacy endpoint of ORR was changed to PFS by IRF, and ORR by investigator assessment was made a secondary efficacy endpoint (Sections 2, 3.1.2, 3.3.5, 3.3.6, 6.1, 6.4, and 6.10).
- The secondary endpoint for patient reported outcomes of time to deterioration (TTD) was amended to align with the co-primary endpoints of progression-free survival and OS (Section 6.4.2). The previous TTD endpoint was made an exploratory endpoint (Section 6.4.3).

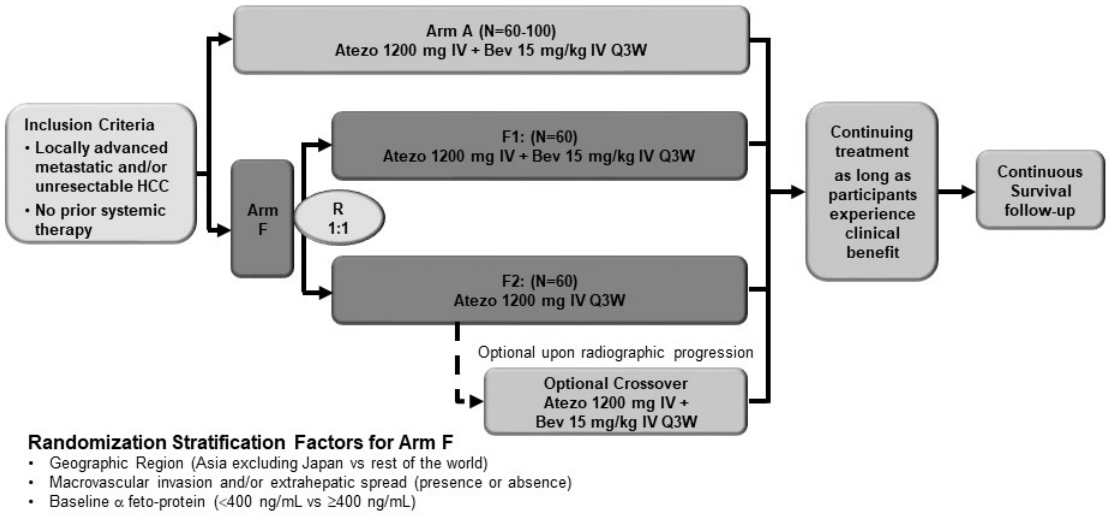
Supportive Study: GO30140 (Arm A and F)

Trial Design

The Applicant's Description:

Trial Design Overview: Study GO30140 is an ongoing open-label, multi-center, global Phase Ib study with non-randomized and randomized arms. The trial is evaluating the safety, efficacy, and pharmacokinetics of atezolizumab when administered with bevacizumab and/or other treatments in patients with a number of solid tumors. Arms A and F evaluated the combination of Atezo+Bev in patients with HCC. The single-arm cohort Arm A evaluated the safety and efficacy of atezolizumab administered in combination with bevacizumab. Arm F used a randomized design to evaluate the combination treatment against atezolizumab monotherapy. Figure 3 provides a schematic diagram of the study design.

Figure 3 Study Design for HCC Cohorts in GO30140



Trial Location: This study was conducted globally. Geographic region (Asia [excluding Japan] vs. rest of world) was one of the stratification factors for the randomization in Arm F.

Choice of Control: The purpose of Arm F was to compare Atezo+Bev vs Atezo monotherapy to assess the single-agent contribution to the overall effect of the combination. Arm A used a single-arm design without control.

Diagnostic Criteria: GO30140 recruited patients with locally advanced or metastatic and/or unresectable HCC who had received no prior systemic therapy.

Key Patient Selection Criteria: The key efficacy-related eligibility criteria for GO30140 were similar to those applied in IMbrave150 (see above). Similar to IMbrave150, Arm F of GO30140 recruited Child-Pugh A patients, while Arm A of GO30140 allowed for enrollment of patients with Child-Pugh score up to B7. The protocol specified for Arm F that patients had to have a life expectancy status determined by the Investigator as $\geq$ 3 months. No such eligibility criteria regarding life expectancy were applied in GO30140 Arm A or in IMbrave150. The exclusion criterion relating to prior malignancy history was only applicable to IMbrave150, but not for patients in GO30140 Arms A or F.

Study Treatments / Dose Selection / Dose modification, Dose Discontinuation: The same rules applied for the administration of atezolizumab or bevacizumab as described above in the context of IMbrave150.

Blinding: Similarly to IMbrave150, an open-label (unblinded) study design was chosen for Arm F to avoid unnecessary burden for patients from a placebo infusion at every cycle in the Atezo monotherapy arm. The primary and relevant secondary efficacy endpoints were assessed by a blinded centralized IRF to minimize bias due to the open-label design.

Assignment to Treatment: In Arm F, patients were randomized 1:1 via IxRS to Atezo+Bev or Atezo monotherapy using a permuted-block randomization method. Randomization was stratified according to the same stratification factors as used in IMbrave150, except for ECOG Performance Status.

Administrative Structure: There was no iDMC in place to monitor safety events.

Procedures and Schedule: Efficacy: Patients underwent tumor assessments at baseline, then every 8 ($\pm$ 1) weeks for the first 12 months following Cycle 1, Day 1, and every 12 ($\pm$ 3) weeks thereafter, with additional scans as clinically indicated. Tumor assessments continued until disease progression per RECIST v1.1 (except for patients treated past progression), withdrawal of consent, initiation of another anti-cancer therapy, death, or study termination by the Sponsor, whichever occurred first.

Safety: Very similar reporting rules for AEs were used in GO30140 as described above for IMbrave150, with the only relevant difference that also AESIs (rather than only SAEs) considered related to study treatment were reported beyond the 90-day reporting window.

Concurrent Medications: Section 3.7 of the GO30140 CSR discusses concomitant medications that were allowed, for which caution had to be exerted, or which were prohibited. While the wording differed in detail from the corresponding section in the IMbrave150 CSR, essentially the same therapies were excluded in both studies.

Treatment Compliance: Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site were recorded on the Drug Inventory Log.

Subject Completion, Discontinuation, or Withdrawal: Treatment with atezolizumab with or without bevacizumab could be continued as long as patients were experiencing clinical benefit in the opinion of the investigator. Patients were permitted to continue study treatment after investigator-assessed disease progression per RECIST v1.1 if they met certain criteria, including, but not limited to, evidence of clinical benefit as assessed by the investigator. Patients in the Atezo monotherapy group of Arm F who experienced investigator-assessed unequivocal radiographic progression as per RECIST v1.1 were allowed to cross over to Atezo+Bev treatment.

The FDA's Assessment:

FDA agrees with the overall description of Arms A and F of Study GO30140. Minor differences in eligibility criteria between Study GO30140 and IMbrave150 include, but are not limited to, exclusion of patients who received treatment for HCV within 2 weeks of Cycle 1 Day 1 and a provision allowing anti-HCV treatment after Cycle 8. Although patients with moderate or severe ascites were excluded in both studies, there were no exclusion criteria for patients with severe pleural or pericardial effusions.

Study Endpoints

The Applicant's Description:

Arm A: Primary Endpoint: ORR per IRF according to RECIST v1.1

Secondary Endpoints: ORR per Investigator according to RECIST v1.1 and per IRF according to HCC mRECIST; PFS, DOR, and TTP according to all three different RECIST assessments; OS.

Arm F: Primary Endpoint: PFS per IRF according to RECIST v1.1
Secondary Endpoints: PFS per Investigator according to RECIST v1.1 and per IRF according to HCC mRECIST; ORR, DOR, and TTP according to all three different RECIST assessments; OS.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study objectives and endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The details of the statistical analysis methods for the GO30140 study are described in the SAP dated 20 December 2018. An Addendum to this SAP was issued on 11 April 2019 to clarify the Sponsor's decision and rationale for not executing the previously planned interim analysis for PFS in Arm F. This was prior to the data cut-off date of 14 June 2019.

No formal statistical hypothesis testing was done for Arm A since this comprised just a single-arm cohort designed to obtain preliminary safety, PK, and efficacy data in HCC patients.

For Arm F, a formal statistical test for the primary efficacy endpoint of IRF-assessed PFS per RECIST v1.1 was conducted at a two-sided Type I error rate of 0.2. The primary analysis of the primary efficacy endpoint of PFS was to be performed when approximately 73 PFS events as determined by the IRF per RECIST v1.1 had occurred. All other efficacy endpoints were planned to be analysed for descriptive purposes without formal statistical testing.

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of the SAP and its amendments, with the following comments:

- The Applicant's summary of the SAP did not include a brief description of efficacy analyses including the analyses of the primary endpoint and key secondary endpoints. Per the SAP, the primary analysis of ORR in Arm A would be to estimate the confirmed ORR and its 95% CI using the Clopper-Pearson method. As specified in the SAP, the analysis of the primary endpoint PFS-IRF in Arm F would be the stratified log-rank test at the two-sided alpha level of 0.2 to compare PFS between Arm F1 and Arm F2. The stratification factors used in the analysis were geographic region (Asian excluding Japan vs. rest of world) and baseline AFP (< 400 vs. ≥400 ng/mL), which comprise 2 of the 3 stratification factors used for randomization. The Kaplan-Meier method would be used to estimate median OS and its 95% CI for each treatment arm using Brookmeyer-Crowley methodology (Brookmeyer and Crowley 1982).

- In general, the Type I error rate should be controlled at 0.05 (2-sided) for a trial that is used as a pivotal trial to support a marketing application. Study GO30140 was designed to be a supportive trial and was intended to characterize the contribution of bevacizumab to the treatment effect observed with the combination of atezolizumab and bevacizumab. In the teleconference between the Applicant and FDA on August 17, 2018, FDA cautioned that a

statistically significant result at a two-sided alpha level of 0.2 for Arm F may not adequately characterize the contribution of bevacizumab to the combination.

Protocol Amendments

The Applicant's Description:

Protocol **Version 2** (28 March 2016) was the 1st version under which patients were treated.

The protocol was amended to **Version 3** on 10 August 2016 to remove use of HCC mRECIST and PRO by the FHSI-8 questionnaire from Arm A. These parameters were later re-introduced in the amendment to Version 5.

Protocol **Version 4** (1 July 2017) increased the number of HCC patients enrolled in Arm A.

Protocol **Version 5** (12 January 2018) modified the primary and secondary objectives and corresponding statistical analyses for Arm A. Furthermore, Arm F was added to isolate the single agent contribution to the Atezo + Bev combination treatment effect.

Protocol **Version 6** (19 June 2018) increased the number of HCC patients in Arm F and added an interim analysis for the primary endpoint of PFS in Arm F. For Arm A, the assessment of the primary endpoint (ORR) was changed from determination by the investigator to determination by an IRF.

The FDA's Assessment:

In Version 3 of the protocol, RECIST was selected as the primary criteria to assess response (Arm A) although progression of disease was defined using imRECIST. Based on the clinical activity observed in Arm A, Protocol Version 4 expanded the sample size of this cohort to 40 patients, with the provision that if the ORR was at least 30%, 20-60 additional patients may be enrolled. The sample size increase to 100 patients allowed a 99.3% probability of detecting a true 20% improvement over a historical control. In Version 6 of the protocol, the sample size of Arm F was increased to 60 patients per arm. The protocol was revised once again (Version 7) to incorporate minor changes addressing safety issues, eligibility criteria, and other edits.

8.1.2 Study Results

Pivotal Study: IMbrave150 (YO40245)

Compliance with Good Clinical Practices

Data:

IMbrave150, GO30140, PCD4989g, and YO29233 studies were conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved the studies. The studies also took guidelines into consideration regarding statistical principles (ICH E9), and EMA and FDA guidelines on clinical trial endpoints for the approval of cancer drugs

(CPMP/EWP/205/95 Rev. 3 and the FDA Guidance to Industry, May 2007).The Roche Clinical Quality Assurance group or designee did not conduct any audits.

The Applicant's Position:

All studies were conducted in compliance with Good Clinical Practice guidelines.

The FDA's Assessment:
FDA acknowledges the Applicant's position.

Financial Disclosure

The Applicant's Position:

For Financial Disclosure information please refer to Module 1.3.4.2 of the sBLA, submitted on December 2, 2019 (Sequence No. 0820).

The FDA's Assessment:
FDA's complete assessment of the financial disclosures for both studies (IMbrave 150 and GO30140) can be found in Section 19.2 of this review. Genentech collected financial disclosure information for 1006 of the 1009 investigators in Study IMbrave150 and no investigator disclosed a financial conflict of interest. Three sub-investigators were found at the time of data reconciliation in October 2019 to have not submitted an initial financial disclosure form; these three sub-investigators had left the site and were not available for information requests. Principal investigators at these sites (enrolling 7 patients total) signed their forms. As the number of patients enrolled by these three sub investigators is 1% of the total study population and the study primary endpoints are overall survival and progression-free survival as per an independent facility review, it is unlikely that a conflict of interest, if present, for the three subinvestigators with missing financial disclosure forms would materially impact study results or affect the outcome of the IMbrave 150 trial.

Patient Disposition

Data:

Patients were randomized from 111 centers in 17 countries/regions. Patients were recruited in the following countries/regions: mainland China (78 pts, 15.6%), United States (74 pts, 14.8%), Japan (61 pts, 12.2%), Korea (47 pts, 9.4%), France (42 pts, 8.4%), Taiwan (41 pts, 8.2%), Russian Federation (24 pts, 4.8%), Poland (23 pts, 4.6%), Hongkong (18 pts, 3.6%), Singapore (17 pts, 3.4%), Italy (17 pts, 3.4%), Germany (16 pts, 3.2%), United Kingdom (13 pts, 2.6%), Spain (11 pts, 2.2%), Australia (9 pts, 1.8%), Canada (5 pts, 1.0%) and Czech Republic (5 pts, 1.0%). The first patient was randomized on 15 March 2018 and the last patient was randomized on 30 January 2019.

In total, 725 patients were screened for entry into this study and 224 patients failed screening based on information collected on the IxRS. Of the 501 patients randomized in a 2:1 ratio

(336 patients to Atezo+Bev and 165 patients to Sorafenib), 329 patients received Atezo+Bev and 156 patients received Sorafenib.

The primary reasons for the 16 patients (9 randomized to Sorafenib and 7 randomized to Atezo+Bev) who did not receive study treatment were Withdrawal by subject (11 pts), Physician decision and Symptom deterioration (2 pts each), and Protocol deviation (1 pt).

There were thus the following number of patients in the major analysis populations:

	Sorafenib	Atezo+Bev
All Randomized Intent-to-Treat Patients	165	336
All Safety Evaluable Patients	156	329
All PRO Evaluable Patients	145	309
All ADA Evaluable Patients	0	315
All PK Evaluable Patients	0	324

As of the clinical cut off date of 29 August 2019, 14.5% and 34.5% of patients in the Sorafenib arm and 43.5% and 24.4% of patients in the Atezo+Bev arm were continuing study treatment or were in survival follow up, respectively.

The Applicant's Position:

The global distribution of countries contributing patients to the IMbrave150 study is an adequate representation of the global incidence of HCC. Most of the patients randomized into the study were treated and there was no imbalance in the proportion of those patients who did not receive treatment.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition. Of the 111 centers enrolling patients, 13 centers enrolled ≥ 10 patients and only 3 enrolled ≥ 20 patients. Geographic region was a randomization stratification factor; 60% and 59% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively were enrolled in the "rest of the world" region and 40% and 41% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, were enrolled in Asia (excluding Japan).

A total of 108 (32%) and 84 (51%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, discontinued study participation; at the time of data cut-off, 143 (43%) and 82 (24%) patients in the atezolizumab/bevacizumab arm remained on treatment and in follow-up, respectively, and 24 (15%) and 57 (35%) patients in the sorafenib arm were still on treatment and in follow-up, respectively. Table 4 summarizes the reasons for treatment discontinuation in Study IMbrave150.

Table 4. Study IMbrave150: Treatment discontinuation

Reason for discontinuation	Atezo/bev N: 336; n (%)		Sorafenib N: 156; n (%)
	Atezolizumab	Bevacizumab	
AE	15 (4)	19 (6)	9 (5)
Death	15 (4)	16 (5)	7 (4)
Investigator's	1 (<1)	1 (<1)	1 (1)
PD	55 (16)	52 (15)	50 (30)

Reason for discontinuation	Atezo/bev N: 336; n (%)		Sorafenib N: 156; n (%)
	Atezolizumab	Bevacizumab	
Protocol violation	1 (<1)	1 (<1)	0
Symptomatic progression	9 (3)	8 (2)	4 (2)
Withdrawal	9 (3)	7 (2)	5 (3)
Other	0	0	1 (1)

AE: adverse event; PD: progressive disease
Source: FDA analysis of data from the ADSL dataset

A similar proportion of patients in each arm discontinued study treatment for AEs; there is an imbalance (15% vs 30% in the atezolizumab/bevacizumab and sorafenib arms respectively) in the proportion of patients across arms who discontinued treatment due to disease progression, supported by the PFS and OS data.

Although FDA does not disagree with the Applicant that the population enrolled in IMbrave150 is representative of the global incidence of HCC, the proportion of patients from each region is not a representation of the incidence of HCC across the globe; for example, about 50% of the world's HCC patients are from China (IARC data), and HCC is more prevalent in underdeveloped countries. FDA agrees that the population studied is representative of the US population.

Protocol Violations/Deviations

Data:

Major protocol deviations for the ITT population are summarized by category in Table 5.

Table 5 Major Protocol Deviations (ITT Population, IMbrave150)

Protocol Deviation Category Protocol Deviation Description	Sorafenib (N=165)	Atezo+Bev (N=336)	All Patients (N=501)
Total number of patient with at least one deviation	49 (29.7%)	120 (35.7%)	169 (33.7%)
Overall total number of deviations	70	224	294
EXCLUSION CRITERIA			
Total number of patient with at least one deviation	1 (0.6%)	5 (1.5%)	6 (1.2%)
Total number of events	1	5	6
Active or history of autoimmune disease or immune deficiency	1 (0.6%)	0	1 (0.2%)
Current or recent use of aspirin or trmt with dipyramidole, ticlopidine, clopidogrel, cilostazol	0	1 (0.3%)	1 (0.2%)
Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC	0	1 (0.3%)	1 (0.2%)
Major surgical procedure, open biopsy, significant traumatic injury w/in 28d prior to study start	0	1 (0.3%)	1 (0.2%)
Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of IP	0	1 (0.3%)	1 (0.2%)
chronic daily trmt w/ a non steroidal anti-inflammatory drug	0	1 (0.3%)	1 (0.2%)
INCLUSION CRITERIA			
Total number of patient with at least one deviation	6 (3.6%)	4 (1.2%)	10 (2.0%)
Total number of events	6	4	10
Adequate hematologic and end-organ function as defined in the protocol	3 (1.8%)	3 (0.9%)	6 (1.2%)
At least one measurable (per RECISTv1.1) untreated lesion	1 (0.6%)	0	1 (0.2%)
Child-Pugh class A	0	1 (0.3%)	1 (0.2%)
HBV DNA < 500 IU/ml w/in 28 days and antiHBV trmt for minimum of 14d and willing to continue trmt	1 (0.6%)	0	1 (0.2%)
no prior systemic treatment for HCC	1 (0.6%)	0	1 (0.2%)
MEDICATION			
Total number of patient with at least one deviation	9 (5.5%)	28 (8.3%)	37 (7.4%)
Total number of events	9	35	44
Received prohibited concomitant medication	2 (1.2%)	0	2 (0.4%)
Sig deviation from dose except AE management	2 (1.2%)	2 (0.6%)	4 (0.8%)
Sig deviation from scheduled drug admin visit	3 (1.8%)	12 (3.6%)	15 (3.0%)
Sig deviation from study med administration	1 (0.6%)	13 (3.9%)	14 (2.8%)
Use of protocol-prohibited therapy (Section 4.4.3)	1 (0.6%)	1 (0.3%)	2 (0.4%)
PROCEDURAL			
Total number of patient with at least one deviation	42 (25.5%)	105 (31.3%)	147 (29.3%)
Total number of events	54	180	234
Change in imaging modality impacting the primary endpoint	1 (0.6%)	0	1 (0.2%)
Deviation from reporting timelines SAEs	5 (3.0%)	10 (3.0%)	15 (3.0%)
Error with randomization	0	1 (0.3%)	1 (0.2%)
Error with stratification	9 (5.5%)	39 (11.6%)	48 (9.6%)
ICF not signed by patient or study personnel	0	2 (0.6%)	2 (0.4%)
Missing consent to updated ICF	2 (1.2%)	11 (3.3%)	13 (2.6%)
Missing or out of window assessment impact study integrity, safety	13 (7.9%)	33 (9.8%)	46 (9.2%)
No signed ICF for optional RBR	0	1 (0.3%)	1 (0.2%)
Omission of labs prior to drug administration	5 (3.0%)	24 (7.1%)	29 (5.8%)
Omission of tumor assessment	14 (8.5%)	31 (9.2%)	45 (9.0%)

A patient will be only counted once if received more than one deviation of the same type.

Source: t_dv_IT

As of the clinical cut off date of 29 August 2019, 33.7% of all randomized patients had at least one major protocol deviation. The overall frequency and type of major protocol deviations were generally similar across the treatment arms.

The Applicant's Position:

None of the major protocol deviations led to exclusion of data from the analysis, posed an increased safety risk to any patient continuing on study treatment, or were considered to have affected the integrity of the study findings.

The FDA's Assessment:

Protocol violations were reported in 77 (69%) centers. For Study IMbrave 150, the Applicant provided a dataset (ADDV) for major protocol violations. A slightly higher proportion of protocol violations (36% patients) was reported in the atezolizumab/bevacizumab arm compared to the sorafenib arm (30% patients). Although FDA was able replicate the Applicant's analysis of key protocol violations presented in the table above, FDA disagrees with the interpretation of some of these findings. Errors related to stratification in IxRS (10%) occurred more frequently in the atezolizumab/bevacizumab arm compared with the sorafenib arm (12% and 5.5%, respectively); however, FDA sensitivity analyses evaluating the primary endpoints using stratification factors as recorded in the CRF are consistent with the results of the primary analysis using stratification by IxRS (Table 69). FDA also notes that some of the eligibility criteria protocol violations (i.e., active history of autoimmune disease, major surgical procedure, inadequate organ function, etc.) or omission of labs prior to drugs administration could have potentially altered the prognosis or increased the affected patient's risk of adverse events in the study; however, these protocol violations occurred in a small number of patients (1.2% overall) and are unlikely to have affected the overall study results . Although there were one or more omissions of tumor assessments in 9% of patients, FDA agrees that these violations would not alter the results of the primary OS analysis; additionally FDA sensitivity analyses censoring patients with missing assessments for the determination of PFS, ORR, and DOR were consistent with the primary analyses of these endpoints. Despite the minor disagreements described above, FDA agrees with the Applicant's conclusion that protocol violations in Study IMbrave150 are unlikely to have an effect on the integrity of the study findings.

Demographic Characteristics

Data:

The patient population was predominantly Asian (56.7%) and White (34.9%), male (82.6%), and had a median age of 65.0 years (Table 6). Patients from Asia, excluding Japan, accounted for 40.1% of all patients. At baseline, an ECOG PS of 0 and 1 was reported for 62.3% and 37.7% of patients, respectively.

Collection of pre-treatment tumor tissue samples was optional for this study. In total, 182 samples (36.3% of all patients) were evaluable for PD-L1 Immunohistochemistry (IHC) status. In general, baseline PD-L1 expression in tumor or immune cells was well-balanced between the treatment arms for the three cutoffs based on tumor or immune cell expression. PD-L1 with at least 1%, 5%, or 10% in tumor or immune cell expression was reported in 61.5%, 34.6% and 9.3% of all tissue sample-available patients, respectively.

Table 6 Demographic and Baseline Disease Characteristics (ITT Population, IMbrave150)

	Sorafenib (N=165)	Atezo+Bev (N=336)	All Patients (N=501)
Age (yr)			
n	165	336	501
Median	66.0	64.0	65.0
Age group (yr)			
n	165	336	501
18-40	7 (4.2%)	18 (5.4%)	25 (5.0%)
41-64	67 (40.6%)	157 (46.7%)	224 (44.7%)
>= 65	91 (55.2%)	161 (47.9%)	252 (50.3%)
Sex			
n	165	336	501
Male	137 (83.0%)	277 (82.4%)	414 (82.6%)
Race			
n	165	336	501
Asian	96 (58.2%)	188 (56.0%)	284 (56.7%)
White	52 (31.5%)	123 (36.6%)	175 (34.9%)
Geographic Region (eCRF)			
n	165	336	501
Asia (excluding Japan)	68 (41.2%)	133 (39.6%)	201 (40.1%)
Rest of World	97 (58.8%)	203 (60.4%)	300 (59.9%)
ECOG Performance Status at Screening (eCRF)			
n	165	336	501
0	103 (62.4%)	209 (62.2%)	312 (62.3%)
1	62 (37.6%)	127 (37.8%)	189 (37.7%)
PD-L1 Category 1			
n	58	124	182
TC and IC < 1%	25 (43.1%)	45 (36.3%)	70 (38.5%)
TC or IC >= 1%	33 (56.9%)	79 (63.7%)	112 (61.5%)
PD-L1 Category 2			
n	58	124	182
TC and IC < 5%	41 (70.7%)	78 (62.9%)	119 (65.4%)
TC or IC >= 5%	17 (29.3%)	46 (37.1%)	63 (34.6%)
PD-L1 Category 3			
n	58	124	182
TC and IC < 10%	53 (91.4%)	112 (90.3%)	165 (90.7%)
TC or IC >= 10%	5 (8.6%)	12 (9.7%)	17 (9.3%)

Source: t_dm_IT_29AUG2019_40245

The Applicant's Position:

Patient demographics between the two treatment arms in the ITT population were generally well balanced and representative of an unresectable HCC patient population.

The FDA's Assessment:

FDA replicated the Applicant's analysis of the demographic characteristics of Study IMbrave150. Age and sex distribution are representative of the HCC population. Race distribution is representative of the geographic areas where the study was opened for enrollment and similar to the demographics of patients in similar studies planned for registration of drugs in the 1st line treatment of HCC. Of interest, in Study CALGB 80802 (Abou-Alfa G. 2019), conducted in the same disease setting but exclusively in the North American continent, the proportion of performance status is inverted (PS 0 36% and PS 1 60%) when compared to IMbrave150 (PS 0 62% and PS 1 38%). FDA agrees with the Applicant's conclusion that demographic characteristics were well balanced between arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

In the ITT population, the median time from initial diagnosis of HCC to randomization was 6.2 months (range: 0.2 – 227.9 months). The primary HCC etiology was HBV (47.9%) followed by non-viral and HCV (30.5% and 21.6%, respectively) (Table 7).

Approximately half of the patients received local therapy with the most common local therapy being transarterial chemoembolization (TACE; 39.9%).

At baseline, the majority of patients presented with advanced stage disease (50.3% AJCC TNM Stage IVB; 81.6% BCLC Stage C) and all but one patient (99.8%) were scored as Child-Pugh class A. The single Child-Pugh Class B7 patient was incorrectly scored as Child-Pugh Class A at the time of randomization into the Atezo+Bev arm and was reported as a protocol deviation.

At screening, AFP levels of ≥400 ng/mL were observed in 37.3% of patients in the ITT population. Other negative prognostic factors were common in these patients including the presence of macrovascular invasion (MVI; 39.9%) and extrahepatic spread (EHS; 60.9%). In total, 75.4% of patients presented with MVI and/or EHS at baseline. The median baseline sum of target lesion diameter for the ITT population as assessed by the Investigator was 74.0 mm (range: 10.0 – 321.0 mm).

Table 7 Hepatocellular Carcinoma History and Disease Characteristics (ITT Population, IMbrave150)

	Sorafenib (N=165)	Atezo+Bev (N=336)	All Patients (N=501)
BCLC Stage at Study Entry			
n	165	336	501
STAGE A1	3 (1.8%)	5 (1.5%)	8 (1.6%)
STAGE A4	3 (1.8%)	3 (0.9%)	6 (1.2%)
STAGE B	26 (15.8%)	52 (15.5%)	78 (15.6%)
STAGE C	133 (80.6%)	276 (82.1%)	409 (81.6%)
Etiology of HCC			
n	165	336	501
Hepatitis B	76 (46.1%)	164 (48.8%)	240 (47.9%)
Hepatitis C	36 (21.8%)	72 (21.4%)	108 (21.6%)
Non-viral	53 (32.1%)	100 (29.8%)	153 (30.5%)
Extrahepatic Spread (EHS) Present at Study Entry (eCRF)			
n	165	336	501
Yes	93 (56.4%)	212 (63.1%)	305 (60.9%)
Macro-Vascular Invasion (MVI) Present at Study Entry (eCRF)			
n	165	336	501
Yes	71 (43.0%)	129 (38.4%)	200 (39.9%)
EHS and/or MVI Present at Study Entry (eCRF)			
n	165	336	501
Yes	120 (72.7%)	258 (76.8%)	378 (75.4%)
Child Pugh Category			
n	165	334	499
A5	121 (73.3%)	239 (71.6%)	360 (72.1%)
A6	44 (26.7%)	94 (28.1%)	138 (27.7%)
B7	0	1 (0.3%)	1 (0.2%)
Baseline Sum of Target Lesion Diameter (mm) per INV			
n	164	336	500
Mean (SD)	92.32 (63.53)	84.51 (58.82)	87.08 (60.45)
Median	83.20	71.80	74.00
Min - Max	10.0 - 312.0	10.0 - 321.0	10.0 - 321.0
AFP Category at Screening (eCRF)			
n	165	336	501
<400 ng/mL	104 (63.0%)	210 (62.5%)	314 (62.7%)
>=400 ng/mL	61 (37.0%)	126 (37.5%)	187 (37.3%)
Varices at time of Enrollment			
n	165	336	501
Yes	43 (26.1%)	88 (26.2%)	131 (26.1%)
Type of Prior Local Therapy			
n	85	161	246
Radiofrequency Ablation (RFA)	24 (14.5%)	47 (14.0%)	71 (14.2%)
Transarterial Chemoembolization (TACE)	70 (42.4%)	130 (38.7%)	200 (39.9%)
Prior Cancer Radiotherapy			
n	165	336	501
Yes	17 (10.3%)	34 (10.1%)	51 (10.2%)

For patients whose cause of HCC was multifactorial as assessed by the Investigator, the viral cause was prioritized over non-viral causes to define the primary etiology of the patient.
Source: t_dm_IT_29AUG2019_40245

The Applicant's Position:

The baseline HCC history and disease characteristics between the two treatment arms in the ITT population were generally well balanced and were reflective of an advanced HCC population.

Previous and concurrent medical conditions reflect the expected comorbidities of a population of patients with unresectable HCC who have received no prior systemic therapy.

Previous (starting and ending prior to treatment start) and concurrent (starting prior to and ongoing at treatment start) medical conditions reported in the Safety population were balanced between treatment arms.

Overall, there were no notable differences between treatment arms with respect to the type and frequency of previous cancer therapies for HCC.

The FDA's Assessment:

FDA agrees with the Applicant's conclusion that the baseline HCC history and disease characteristics between the two treatment arms in the ITT population were generally well balanced and were reflective of an advanced HCC population. Although globally the main cause of HCC is hepatitis B infection and 48% patients in the IMbrave150 study had hepatitis B, in Western countries and Japan the main cause of HCC is hepatitis C infection. Less than 10% patients in Study CALGB 80802 (Abou-Alfa, G. 2019) had hepatitis B and approximately a quarter had hepatitis C. In an exploratory subgroup analysis of the ITT population of Study IMbrave150, the HR for survival was 0.51 (95% CI: 0.32; 0.81) in the hepatitis B subset and 0.43 (95% CI: 0.22; 0.87) in the hepatitis C subset; these results support the applicability of IMbrave150 results to the US population despite differences in viral etiology of HCC between the US population and patients outside the US and Japan.

Prior to enrollment, the previous medical conditions most frequently reported were infections (22% and 21% in the atezolizumab/bevacizumab and sorafenib arms respectively; most correspond to viral hepatitis) and gastrointestinal disorders (14% in each arm). The study arms were well-balanced in regards to baseline disease characteristics and prior comorbidities.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance: The median dose intensity as a measure of treatment compliance was 96% in the Sorafenib arm (range: 27–100%), and 98% (range: 54–104%) for atezolizumab and 97% (range: 44–104%) for bevacizumab in the Atezo+Bev arm (Table 8).

Table 8 Treatment Compliance (Safety-Evaluable Population, IMbrave150)

	Sorafenib (N=156)	Atezo+Bev (N=329)	
	Sorafenib	Atezolizumab	Bevacizumab
Dose Intensity (%)			
n	156	329	329
Mean (SD)	83.8 (20.1)	95.1 (6.9)	93.3 (9.6)
Median	96.0	98.0	97.0
Min - Max	27 - 100	54 - 104	44 - 104

Source: t_ex_SE_29AUG2019_40245.out

Concomitant Medications: During the study period, radiation therapy (predominantly to the bone) was given to a small number of patients for palliative reasons only: 1 patient in the Sorafenib arm and 5 patients in the Atezo+Bev arm.

A small number of patients received cancer-related surgery during the study period: 3 patients in each treatment arm. The primary intent for on-study surgeries was for palliative reasons (1.8% and 0.3% for the Sorafenib and Atezo+Bev arms, respectively).

Almost all patients in both treatment arms received previous/concomitant and concomitant non-cancer treatments: 98.7% and 99.7% in the Sorafenib and Atezo+Bev arms, respectively. By drug class, these medications had generally similar frequencies between treatment arms, with the exception of dermatologic agents and anti-diarrheals, which were more commonly used in the Sorafenib arm compared with Atezo+Bev (42.3% vs. 14.6% and 30.8% vs. 7.9%, respectively) and analgesics and loop diuretics, which were less commonly used in the Sorafenib arm compared with Atezo+Bev (25.6% vs. 35.6% and 15.4% vs. 25.8%, respectively).

The Applicant's Position:

Overall, treatment compliance was comparable between both arms based on the median dose intensity, although the lower mean dose intensity observed in sorafenib patients suggests that fewer of these patients received the full dose as intended. This is likely due to the fact that sorafenib is administered orally (vs infusions for atezolizumab and bevacizumab) and that the protocol allowed for sorafenib dose reductions as necessary, while no dose reduction were allowed for Atezo+Bev.

Concomitant treatments for HCC other than the study therapy were given only in isolated cases primarily for palliative reasons and did not influence the overall assessment of efficacy of the study treatments. Concomitant non-cancer therapies reflected either the general disease status of this patient population and any imbalances are due to treatments to deal with the different AE profiles associated with sorafenib vs. atezolizumab and bevacizumab.

The FDA's Assessment:

The median duration of treatment for atezolizumab was 7.4 months (range 0-16), 6.9 months (range 0-16) for bevacizumab, and 2.8 months (range 0-16) for sorafenib. The majority (57%) of patients in the sorafenib arm received less than 3 months of treatment, while the majority of patients in the atezolizumab/bevacizumab arm received more than 6 months of treatment (63% received atezolizumab for ≥ 6 months and 59% received bevacizumab for ≥ 6 months). Patients in the atezolizumab/bevacizumab arm received a median of 11 atezolizumab doses (range 1-24) and 10 bevacizumab doses (range 1-23). There were no dose reductions allowed for toxicity in the atezolizumab/bevacizumab arm; protocol-defined dose reductions for toxicity in the sorafenib arm are described in the safety section of this review.

Although FDA agrees with the Applicant's statement that concomitant treatments for HCC other than the study therapy and did not influence the overall assessment of efficacy of the study treatments, just for clarification, one patient in the atezolizumab/bevacizumab arm underwent surgery with curative intent.

FDA agrees with the Applicant's analysis of supportive care concomitant treatments. Four patients in the atezolizumab/bevacizumab arm required use of immunosuppressive agents other than corticosteroids (mycophenolate, tacrolimus, and tocilizumab). The most commonly used ancillary care drugs were proton pump inhibitors (46.5% vs. 48% in the atezolizumab/bevacizumab and sorafenib arms, respectively), dermatologic agents (15% vs. 42%), supplements (41% in each arm), opioid analgesics (33% vs. 36.5%), calcium channel blocking agents (41% vs. 35%), nucleoside/nucleotide analogues (40% vs. 34%), steroids (40% vs. 31%), anti-diarrheals (8% vs. 31%), and analgesics (36% vs. 25%).

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

There was a statistically significant and clinically meaningful improvement in OS (stratified HR: 0.58 [95% CI: 0.42, 0.79], log-rank p-value = 0.0006) with Atezo + Bev over Sorafenib in the ITT population (Table 9). The observed OS HR translated into a 42% reduction in the risk of death in the Atezo + Bev arm compared with Sorafenib.

The Kaplan-Meier estimated median OS was 13.2 (95% CI: 10.4, NE) months in the Sorafenib arm and was not reached in the Atezo + Bev arm (Table 9).

Of note, the Kaplan-Meier curves demonstrated early separation of the curves in favor of the Atezo + Bev arm (approximately one month after randomization) that was maintained over time (Figure 4).

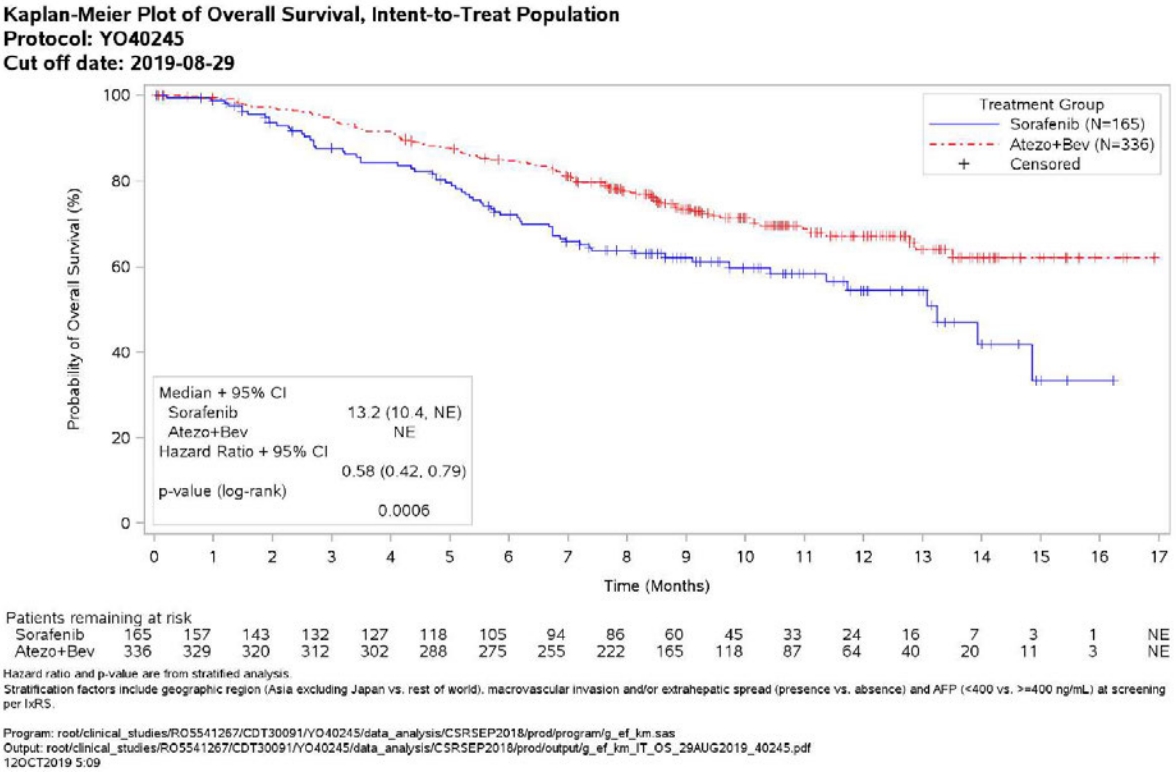
The 6-month event-free rate was higher in the Atezo + Bev arm (84.8%) compared with the Sorafenib arm (72.3%).

Table 9 Overall Survival (ITT Population, IMbrave150)

	Sorafenib (N=165)	Atezo+Bev (N=336)
Patients with event (%)	65 (39.4%)	96 (28.6%)
Death	65	96
Patients without event (%)	100 (60.6%)	240 (71.4%)
Time to Event (Months)		
Median	13.24	NE
95% CI	(10.41, NE)	NE
Stratified Analysis		
p-value (log-rank)	0.0006	
Hazard Ratio	0.58	
95% CI	(0.42, 0.79)	
Time Point Analysis		
6 Months		
Patients remaining at risk	105	275
Event Free Rate (%)	72.25	84.81
95% CI	(65.10, 79.40)	(80.93, 88.69)

Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.
Source: t_ef_tte01_IT_OS_29AUG2019_40245

Figure 4 Kaplan-Meier Plot of Overall Survival (ITT Population, IMbrave150)



A statistically significant and clinically meaningful improvement in PFS as assessed by IRF per RECIST v1.1 was observed (stratified HR: 0.59; 95% CI: 0.47, 0.76; log-rank p-value <0.0001) with Atezo + Bev over Sorafenib in the ITT population (Table 10). The observed PFS HR translated into a 41% reduction in the risk of disease progression or death in the Atezo + Bev arm compared with the Sorafenib arm.

The median PFS was longer in the Atezo + Bev arm (6.8 months, 95% CI: 5.8, 8.3) compared with the Sorafenib arm (4.3 months, 95% CI: 4.0, 5.6), with an increase of 2.5 months in the Atezo + Bev arm (Table 10).

The 6-month event-free rate was higher in the Atezo + Bev arm (54.5%) compared with the Sorafenib arm (37.2%) (Table 10).

The Kaplan-Meier curves showed early separation of the curves at the time of the first tumor assessment in favor of the Atezo + Bev arm compared with the Sorafenib arm that was maintained over time (Figure 5).

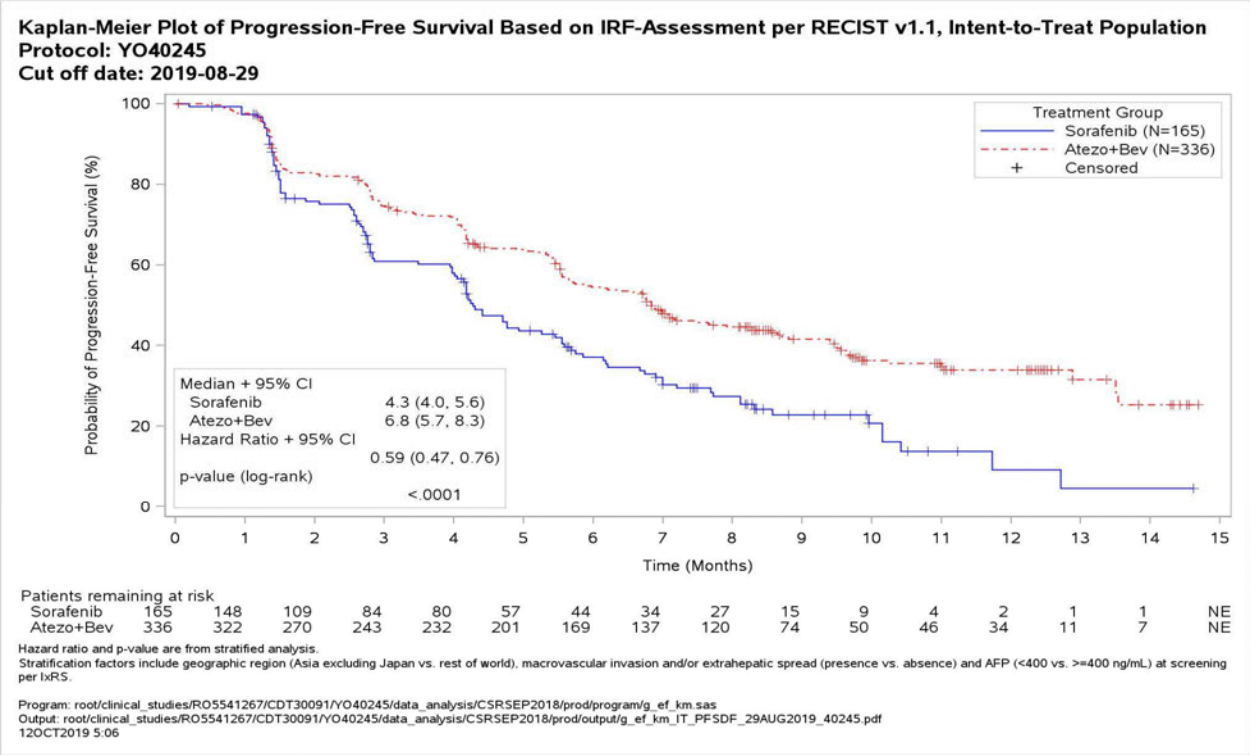
The impact of missing scheduled tumor assessments on IRF-assessed PFS per RECIST v1.1 was assessed as a sensitivity analysis. In this analysis, patients who missed two or more consecutive tumor assessments scheduled immediately prior to the date of PD or death in any treatment arm were censored at the last tumor assessment prior to the missed visit. The results of this sensitivity analysis were consistent with those observed in the primary analysis.

Table 10 Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 (ITT Population, IMbrave150)

	Sorafenib (N=165)		Atezo+Bev (N=336)
Patients with event (%)	109 (66.1%)		197 (58.6%)
Death	29		34
Disease Progression	80		163
Patients without event (%)	56 (33.9%)		139 (41.4%)
Time to Event (Months)			
Median	4.27		6.83
95% CI	(3.98, 5.55)		(5.75, 8.28)
Stratified Analysis			
p-value (log-rank)		<.0001	
Hazard Ratio		0.59	
95% CI		(0.47, 0.76)	
Time Point Analysis			
6 Months			
Patients remaining at risk	44		169
Event Free Rate (%)	37.17		54.51
95% CI	(29.00, 45.34)		(49.06, 59.96)

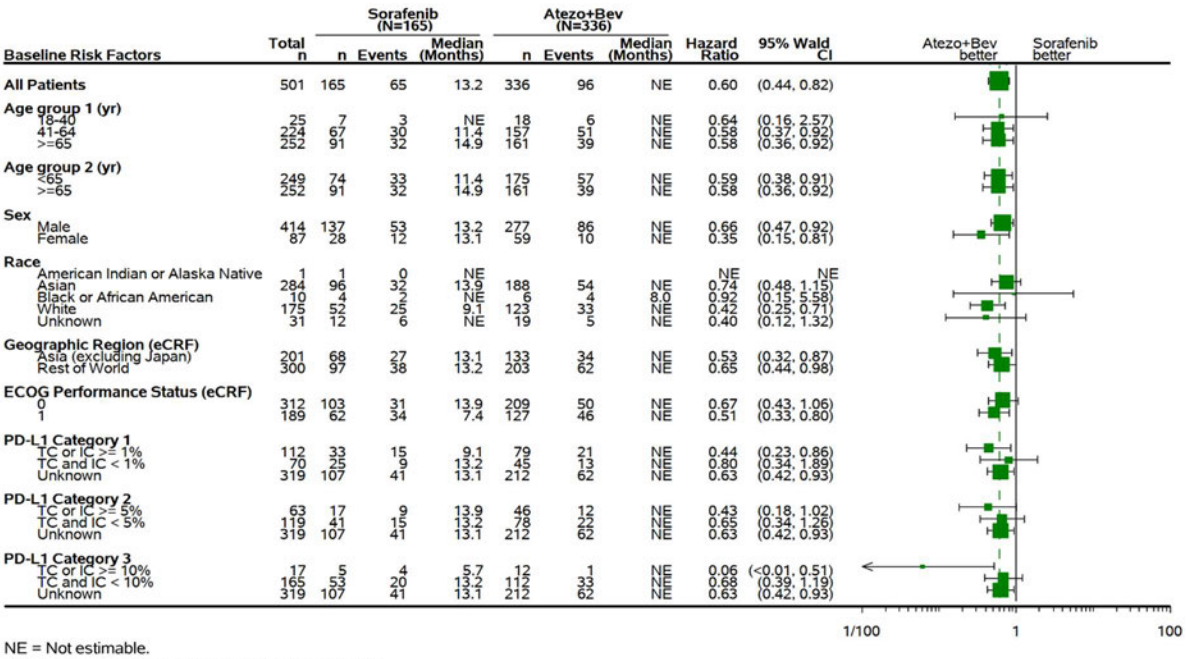
Summaries of Time-to-Event (median, percentiles) are Kaplan-Meier estimates. 95% CI for event (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed estimated by Cox regression.
Stratification factors include geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and AFP (<400 vs. >=400 ng/mL) at screening per IxRS.
Source: t_ef_tte01_IT_PFSDF_29AUG2019_40245

Figure 5 Kaplan-Meier Plot of Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 (ITT Population, IMbrave150)



The generalizability of the observed treatment effect with Atezo + Bev relative to Sorafenib on OS, IRF-assessed PFS, and ORR per RECIST v1.1 was investigated in predefined subgroups based on key baseline demographics and HCC disease characteristics, including stratification factors. There was an overall consistent trend for prolonged duration of OS (Figure 6) and PFS (Figure 7) for patients in the Atezo+Bev arm compared with those in the Sorafenib arm across subgroups, including those based on factors that are more clinically relevant to HCC such as geographical region (Asia, except Japan, vs. rest of the world), ECOG status, BCLC staging at study entry, etiology, presence or absence of macrovascular invasion and/or extrahepatic spread, and baseline AFP.

Figure 6 Subgroup Analysis of Overall Survival (ITT Population, IMbrave150)



Baseline Risk Factors	Total n	Sorafenib (N=165) n	Events	Median (Months)	Atezo+Bev (N=336) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	501	165	65	13.2	336	96	NE	0.60	(0.44, 0.82)
Age group 1 (yr)									
18-40	25	7	3	NE	18	6	NE	0.64	(0.16, 2.57)
41-64	224	67	30	11.4	157	51	NE	0.58	(0.37, 0.92)
>=65	252	91	32	14.9	161	39	NE	0.58	(0.36, 0.92)
Age group 2 (yr)									
<65	249	74	33	11.4	175	57	NE	0.59	(0.38, 0.91)
>=65	252	91	32	14.9	161	39	NE	0.58	(0.36, 0.92)
Sex									
Male	414	137	53	13.2	277	86	NE	0.66	(0.47, 0.92)
Female	87	28	12	13.1	59	10	NE	0.35	(0.15, 0.81)
Race									
American Indian or Alaska Native	1	1	0	NE				NE	NE
Asian	284	96	32	13.9	188	54	NE	0.74	(0.48, 1.15)
Black or African American	10	4	2	NE	6	4	8.0	0.92	(0.15, 5.58)
White	175	52	25	9.1	123	33	NE	0.42	(0.25, 0.71)
Unknown	31	12	6	NE	19	5	NE	0.40	(0.12, 1.32)
Geographic Region (eCRF)									
Asia (excluding Japan)	201	68	27	13.1	133	34	NE	0.53	(0.32, 0.87)
Rest of World	300	97	38	13.2	203	62	NE	0.65	(0.44, 0.98)
ECOG Performance Status (eCRF)									
0	312	103	31	13.9	209	50	NE	0.67	(0.43, 1.06)
1	189	62	34	7.4	127	46	NE	0.51	(0.33, 0.80)
PD-L1 Category 1									
TC or IC >= 1%	112	33	15	9.1	79	21	NE	0.44	(0.23, 0.86)
TC and IC < 1%	70	25	9	13.2	45	13	NE	0.80	(0.34, 1.89)
Unknown	319	107	41	13.1	212	62	NE	0.63	(0.42, 0.93)
PD-L1 Category 2									
TC or IC >= 5%	63	17	9	13.9	46	12	NE	0.43	(0.18, 1.02)
TC and IC < 5%	119	41	15	13.2	78	22	NE	0.65	(0.34, 1.26)
Unknown	319	107	41	13.1	212	62	NE	0.63	(0.42, 0.93)
PD-L1 Category 3									
TC or IC >= 10%	17	5	4	5.7	12	1	NE	0.06	(<0.01, 0.51)
TC and IC < 10%	165	53	20	13.2	112	33	NE	0.68	(0.39, 1.19)
Unknown	319	107	41	13.1	212	62	NE	0.63	(0.42, 0.93)

NE = Not estimable.
Medians were estimated from Kaplan-Meier method.
Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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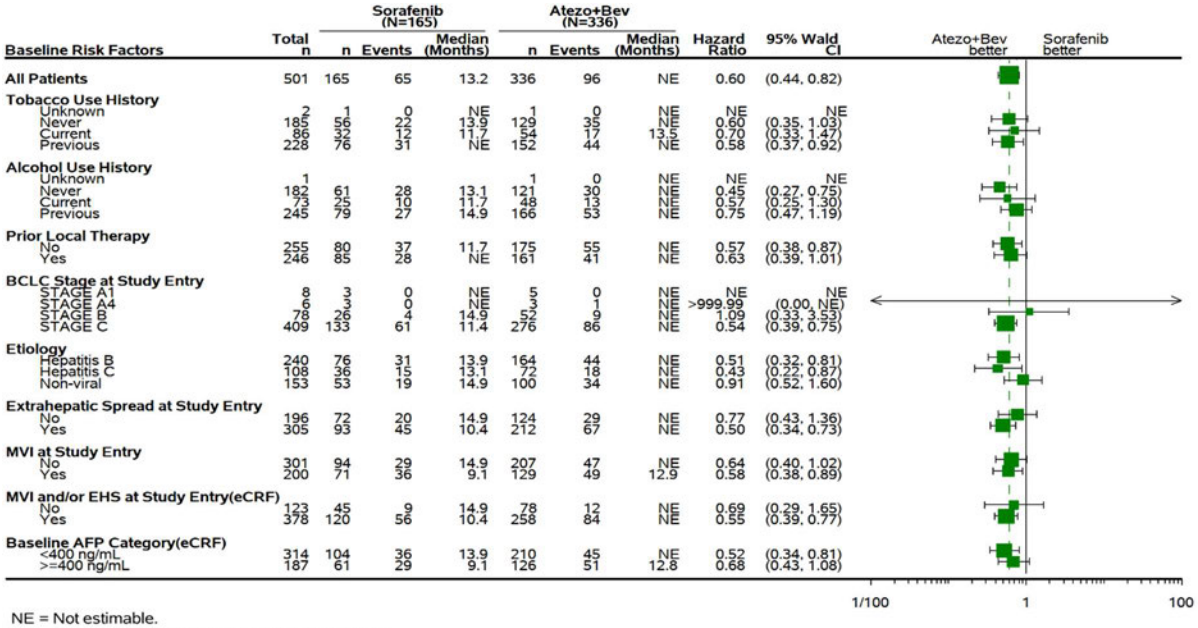
Figure 6 Subgroup Analysis of Overall Survival (ITT Population, IMbrave150) (cont.)



Baseline Risk Factors	Total n	Sorafenib (N=165) n	Events	Median (Months)	Atezo+Bev (N=336) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	501	165	65	13.2	336	96	NE	0.60	(0.44, 0.82)
Tobacco Use History									
Unknown	2	1	0	NE	1	0	NE	NE	NE
Never	185	56	22	13.9	129	35	NE	0.60	(0.35, 1.03)
Current	86	32	12	11.7	54	17	13.5	0.70	(0.33, 1.47)
Previous	228	76	31	NE	152	44	NE	0.58	(0.37, 0.92)
Alcohol Use History									
Unknown	1				1	0	NE	NE	NE
Never	182	61	28	13.1	121	30	NE	0.45	(0.27, 0.75)
Current	73	25	10	11.7	48	13	NE	0.57	(0.25, 1.30)
Previous	245	79	27	14.9	166	53	NE	0.75	(0.47, 1.19)
Prior Local Therapy									
No	255	80	37	11.7	175	55	NE	0.57	(0.38, 0.87)
Yes	246	85	28	NE	161	41	NE	0.63	(0.39, 1.01)
BCLC Stage at Study Entry									
STAGE A1	8	3	0	NE	5	0	NE	NE	NE
STAGE A4	6	3	0	NE	3	1	NE	>999.99	(0.00, NE)
STAGE B	78	26	4	14.9	52	9	NE	1.09	(0.33, 3.53)
STAGE C	409	133	61	11.4	276	86	NE	0.54	(0.39, 0.75)
Etiology									
Hepatitis B	240	76	31	13.9	164	44	NE	0.51	(0.32, 0.81)
Hepatitis C	108	36	15	13.1	72	18	NE	0.43	(0.22, 0.87)
Non-viral	153	53	19	14.9	100	34	NE	0.91	(0.52, 1.60)
Extrahepatic Spread at Study Entry									
No	196	72	20	14.9	124	29	NE	0.77	(0.43, 1.36)
Yes	305	93	45	10.4	212	67	NE	0.50	(0.34, 0.73)
MVI at Study Entry									
No	301	94	29	14.9	207	47	NE	0.64	(0.40, 1.02)
Yes	200	71	36	9.1	129	49	12.9	0.58	(0.38, 0.89)
MVI and/or EHS at Study Entry(eCRF)									
No	123	45	9	14.9	78	12	NE	0.69	(0.29, 1.65)
Yes	378	120	56	10.4	258	84	NE	0.55	(0.39, 0.77)
Baseline AFP Category(eCRF)									
<400 ng/mL	314	104	36	13.9	210	45	NE	0.52	(0.34, 0.81)
>=400 ng/mL	187	61	29	9.1	126	51	12.8	0.68	(0.43, 1.08)

NE = Not estimable.
Medians were estimated from Kaplan-Meier method.
Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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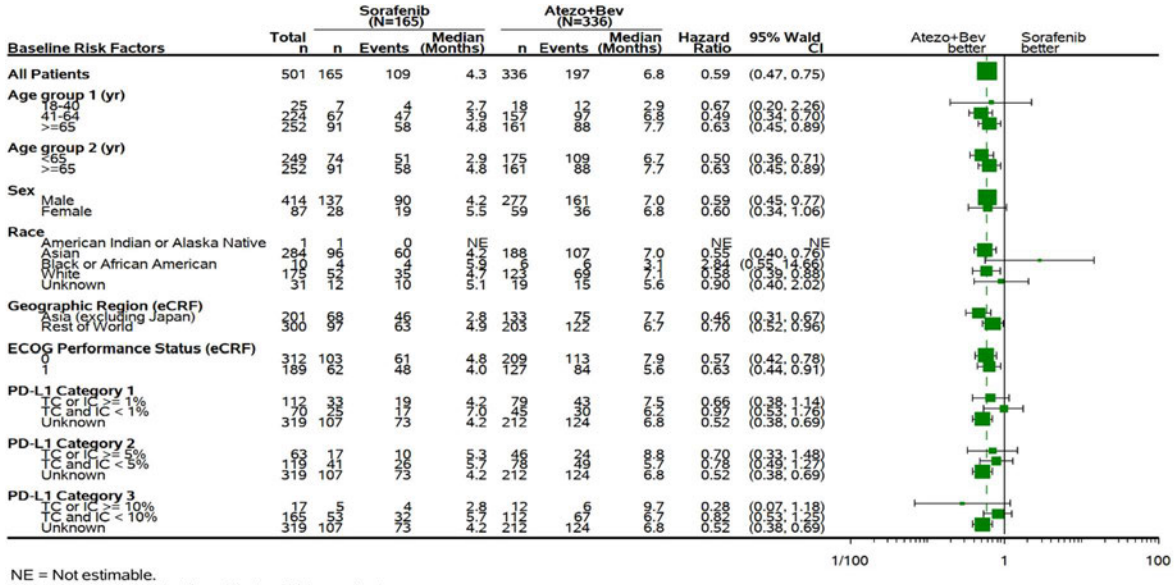
Figure 7 Subgroup Analysis of Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 (ITT Population, IMbrave150)



Baseline Risk Factors	Total n	Sorafenib (N=165) n	Events	Median (Months)	Atezo+Bev (N=336) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	501	165	109	4.3	336	197	6.8	0.59	(0.47, 0.75)
Age group 1 (yr)									
18-40	25	7	4	2.7	18	12	2.9	0.67	(0.20, 2.26)
41-64	224	67	47	3.9	157	97	6.8	0.49	(0.34, 0.70)
>=65	252	91	58	4.8	161	88	7.7	0.63	(0.45, 0.89)
Age group 2 (yr)									
<65	249	74	51	2.9	175	109	6.7	0.50	(0.36, 0.71)
>=65	252	91	58	4.8	161	88	7.7	0.63	(0.45, 0.89)
Sex									
Male	414	137	90	4.2	277	161	7.0	0.59	(0.45, 0.77)
Female	87	28	19	5.5	59	36	6.8	0.60	(0.34, 1.06)
Race									
American Indian or Alaska Native	1	1	0	NE				NE	NE
Asian	284	96	60	4.2	188	107	7.0	0.55	(0.40, 0.76)
Black or African American	10	4	4	5.9	6	6	3.1	2.84	(0.55, 14.66)
White	175	52	35	4.7	123	69	7.1	0.58	(0.39, 0.88)
Unknown	31	12	10	5.1	19	15	5.6	0.90	(0.40, 2.02)
Geographic Region (eCRF)									
Asia (excluding Japan)	201	68	46	2.8	133	75	7.7	0.46	(0.31, 0.67)
Rest of World	300	97	63	4.9	203	122	6.7	0.70	(0.52, 0.96)
ECOG Performance Status (eCRF)									
0	312	103	61	4.8	209	113	7.9	0.57	(0.42, 0.78)
1	189	62	48	4.0	127	84	5.6	0.63	(0.44, 0.91)
PD-L1 Category 1									
TC or IC >= 1%	112	33	19	4.2	79	43	7.5	0.66	(0.38, 1.14)
TC and IC < 1%	70	25	17	7.0	45	30	6.2	0.97	(0.53, 1.76)
Unknown	319	107	73	4.2	212	124	6.8	0.52	(0.38, 0.69)
PD-L1 Category 2									
TC or IC >= 5%	63	17	10	5.3	46	24	8.8	0.70	(0.33, 1.48)
TC and IC < 5%	119	41	26	5.7	78	49	5.7	0.78	(0.49, 1.27)
Unknown	319	107	73	4.2	212	124	6.8	0.52	(0.38, 0.69)
PD-L1 Category 3									
TC or IC >= 10%	17	5	4	2.8	12	6	9.7	0.28	(0.07, 1.18)
TC and IC < 10%	165	53	32	5.7	112	67	6.7	0.82	(0.53, 1.25)
Unknown	319	107	73	4.2	212	124	6.8	0.52	(0.38, 0.69)

NE = Not estimable.
Medians were estimated from Kaplan-Meier method.
Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
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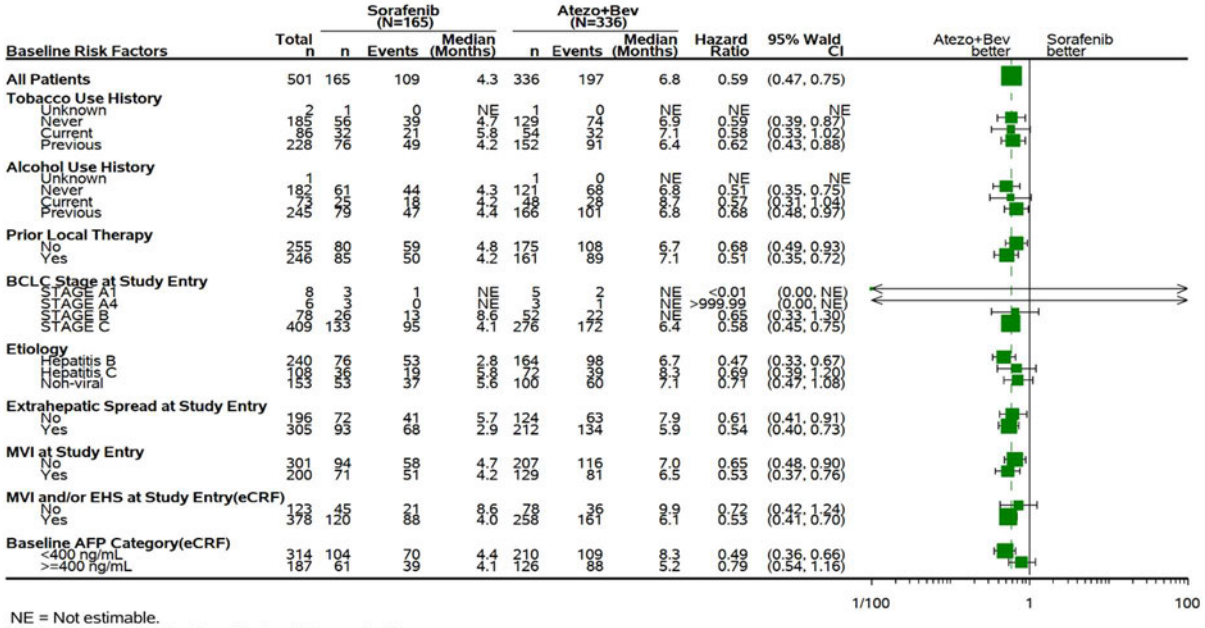
Figure 7 Subgroup Analysis of Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 (ITT Population, IMbrave150) (cont.)



Baseline Risk Factors	Total n	Sorafenib (N=165) n	Events	Median (Months)	Atezo+Bev (N=336) n	Events	Median (Months)	Hazard Ratio	95% Wald CI
All Patients	501	165	109	4.3	336	197	6.8	0.59	(0.47, 0.75)
Tobacco Use History									
Unknown	2	1	0	NE	1	0	NE	NE	NE
Never	185	56	39	4.7	129	74	6.9	0.59	(0.39, 0.87)
Current	86	32	21	5.8	54	32	7.1	0.58	(0.33, 1.02)
Previous	228	76	49	4.2	152	91	6.4	0.62	(0.43, 0.88)
Alcohol Use History									
Unknown	1				1	0	NE	NE	NE
Never	182	61	44	4.3	121	68	6.8	0.51	(0.35, 0.75)
Current	73	25	18	4.2	48	28	8.7	0.57	(0.31, 1.04)
Previous	245	79	47	4.4	166	101	6.8	0.68	(0.48, 0.97)
Prior Local Therapy									
No	255	80	59	4.8	175	108	6.7	0.68	(0.49, 0.93)
Yes	246	85	50	4.2	161	89	7.1	0.51	(0.35, 0.72)
BCLC Stage at Study Entry									
STAGE A1	8	3	1	NE	5	2	NE	<0.01	(0.00, NE)
STAGE A4	6	3	0	NE	3	1	NE	>999.99	(0.00, NE)
STAGE B	78	26	13	8.6	52	22	NE	0.65	(0.33, 1.30)
STAGE C	409	133	95	4.1	276	172	6.4	0.58	(0.45, 0.75)
Etiology									
Hepatitis B	240	76	53	2.8	164	98	6.7	0.47	(0.33, 0.67)
Hepatitis C	108	36	19	5.8	72	39	8.3	0.69	(0.39, 1.20)
Non-viral	153	53	37	5.6	100	60	7.1	0.71	(0.47, 1.08)
Extrahepatic Spread at Study Entry									
No	196	72	41	5.7	124	63	7.9	0.61	(0.41, 0.91)
Yes	305	93	68	2.9	212	134	5.9	0.54	(0.40, 0.73)
MVI at Study Entry									
No	301	94	58	4.7	207	116	7.0	0.65	(0.48, 0.90)
Yes	200	71	51	4.2	129	81	6.5	0.53	(0.37, 0.76)
MVI and/or EHS at Study Entry(eCRF)									
No	123	45	21	8.6	78	36	9.9	0.72	(0.42, 1.24)
Yes	378	120	88	4.0	258	161	6.1	0.53	(0.41, 0.70)
Baseline AFP Category(eCRF)									
<400 ng/mL	314	104	70	4.4	210	109	8.3	0.49	(0.36, 0.66)
>=400 ng/mL	187	61	39	4.1	126	88	5.2	0.79	(0.54, 1.16)

NE = Not estimable.
Medians were estimated from Kaplan-Meier method.
Hazard ratios relative to Sorafenib and the associated confidence intervals were estimated using unstratified Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.
Program: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/program/g_ef_tte_fp.sas
Output: root/clinical_studies/RO5541267/CDT30091/YO40245/data_analysis/CSRSEP2018/prod/output/g_ef_tte_fp_IT_PFSDF_p2_29AUG2019_40245.pdf 12OCT2019 5:43

The Applicant's Position:

The study met both of its co-primary efficacy endpoints of OS and of PFS as assessed by IRF per RECIST v1.1. The statistically significant improvements of Atezo+Bev over Sorafenib are clinically meaningful. A sensitivity analysis for PFS showed consistent results with those observed in the primary PFS analysis and thus supports the observed PFS benefit of Atezo+Bev in comparison to Sorafenib. PFS/OS benefits were generally consistent across subgroups.

The FDA's Assessment:

FDA agrees with the results of the OS interim analysis based on 161 OS events (52% of the planned events needed for the final OS analysis) presented by the Applicant. The significance level for the OS interim analysis was 0.004 (2-sided) using the O'Brien-Fleming method to control the type I error rate for OS at a significance level of 0.05 (2-sided). FDA also agrees with the Applicant's final PFS results based on 306 IRF-assessed PFS events per RECIST v1.1.

Per the SAP, PFS based on investigator-assessment per RECIST v1.1 and IRF-assessment using mRECIST for HCC were investigated as secondary endpoints. FDA agrees that the Applicant's results of these two secondary endpoints and the sensitivity analysis assessing the impact of missing scheduled tumor assessments on IRF-assessed PFS per RECIST 1.1 were consistent with the primary analysis of PFS according to IRF assessment per RECIST 1.1.

As stated above, there were stratification errors (10%) due to discordance between IxRS and eCRF, and these errors occurred more frequently in the atezolizumab/bevacizumab arm compared with the sorafenib arm (12% and 7%, respectively). FDA conducted sensitivity analyses of OS and PFS using stratified values based on eCRF. As shown in Table 69 in the Appendix, the sensitivity analyses are consistent with the primary analyses of OS and PFS.

FDA agrees with the results of the subgroup analyses presented in Figures 6 and 7, and considers these analyses exploratory.

Data Quality and Integrity

Data:

Information requested by the Office of Scientific Investigations (OSI) for Study IMbrave150 is provided in Module 5.3.5.4 as part of the submission to the sBLA on 16 December 2019 Sequence number 0834.

The FDA's Assessment:

The data and corresponding documents provided in the sBLA submissions were of adequate quality to enable reviewers to replicate the Applicant's major efficacy and safety results and conduct the analyses needed for a comprehensive risk/benefit assessment of this application.

Efficacy Results – Secondary and other relevant endpoints

Data:

The secondary efficacy endpoints of confirmed ORR based on either IRF-assessed RECIST v1.1 or IRF-assessed HCC mRECIST showed statistically significant and clinically meaningful improvements in the Atezo + Bev arm over the Sorafenib arm with differences between arms of 15.4% (95% CI; 7.9, 22.8; p-value <0.0001) or 19.9% (95% CI; 12.1, 27.8; p-value <0.0001), respectively in favor of Atezo + Bev (Table 11).

As per IRF-assessed RECIST v1.1, there were 18 patients (5.5%) with a confirmed complete response in the Atezo + Bev arm and no complete responders in the Sorafenib arm, while the IRF-assessment per HCC mRECIST showed 33 patients (10.2%) with a confirmed complete response in the Atezo + Bev arm vs. 3 patients (1.9%) in the Sorafenib arm.

IRF-assessed duration of response per RECIST v1.1 and per HCC mRECIST cannot yet be estimated in the Atezo+Bev arm, but the proportion of responding patients with an ongoing response at 6 months is greater in the Atezo+Bev arm compared to Sorafenib.

The results of the secondary endpoint of PFS analyzed by IRF-assessed HCC mRECIST (Table 11) were in line with the co-primary endpoint analysis of PFS by IRF-assessed RECIST v1.1. Other secondary endpoints (TTP, OS or PFS per baseline AFP) consistently showed a benefit for the Atezo+Bev treatment over Sorafenib.

Table 11 Overview of Efficacy (ITT Population, IMbrave150): Key Secondary Efficacy Endpoints

	RECIST v1.1		HCC mRECIST	
	Sorafenib N = 165	Atezo + Bev N = 336	Sorafenib N = 165	Atezo + Bev N = 336
IRF-Assessed ORR				
No. of evaluable patients	159	326	158	325
Confirmed ORR, N (%)	19 (11.9%)	89 (27.3%)	21 (13.3%)	108 (33.2%)
95% CI	(7.35, 18.03)	(22.54, 32.48)	(8.42, 19.60)	(28.13, 38.64)
CR, N (%)	0	18 (5.5%)	3 (1.9%)	33 (10.2%)
DCR, %	55.3%	73.6%	55.1%	72.3%
Difference in ORR, (%)	15.4%		19.9%	
95% CI	(7.90, 22.81)		(12.1, 27.8)	
p-value (Cochran-Mantel-Haenzel)	<0.0001		<0.0001	

IRF-Assessed DOR				
No. of evaluable patients	19	89	21	108
No. (%) of patients with event	6 (31.6%)	12 (13.5%)	8 (38.1%)	24 (22.2%)
Median, months	6.28	NE	6.28	NE
95% CI	(4.67, NE)	NE	(4.86, NE)	NE
6-month event free rate, %	59.1%	87.6%	62.5%	82.3%
		Sorafenib N = 165		**Atezo + Bev N = 336**
IRF-Assessed PFS per HCC mRECIST				
No. (%) of patients with event		111 (67.3%)		199 (59.2%)
Median, months		4.24		6.83
95% CI		(3.98, 5.45)		(5.72, 7.69)
Stratified hazard ratio (95% CI) [a]			0.59 (0.46, 0.74)	
p-value (log-rank)			<0.0001	
6-month PFS (%)		36.4%		54.3%

[a] Stratified by geographic region (Asia [excluding Japan] vs. rest of world), MVI and/or EHS (presence vs. absence), and baseline AFP (< 400 vs. ≥ 400 ng/mL).
Sources: t_ef_tte01_IT_OS, t_ef_tte01_IT_PFSDF, t_ef_rsp01_IT_MDF_CBORDF, t_ef_rsp01_IT_HMDF_hcbordf, t_ef_dor_IT_MDF_CRSDDF, t_ef_dor_IT_HMDF_hcrsddf, t_ef_tte01_IT_hpfsdf

The Applicant's Position:

All secondary endpoint analyses consistently showed a clinically meaningful improvement in Atezo+Bev treated patients over the Sorafenib arm. For the formally tested (see Figure 2) secondary endpoints of IRF-assessed ORR per RECIST v1.1 and HCC mRECIST, these improvements were demonstrated to be statistically significant.

The FDA's Assessment:

FDA does not agree with the results of the Applicant's ORR analyses presented in Table 11, which were calculated using a nonrandomized subset of patients excluding 16 patients in the ITT population with non-measurable disease at baseline as assessed by the IRF per RECIST 1.1. Interpretation of p-values derived from comparisons of non-randomized subsets is difficult because results may be confounded by imbalances in observed or non-observed factors. The same reasoning applies to the analysis result of ORR by IRF per HCC mRECIST. As FDA stated in Section 8.1.1, the analyses of IRF-assessed ORR per RECIST 1.1 and HCC mRECIST should be based on the ITT population consisting of all randomized patients. Based on the ITT population, Using the ITT population, ORR was 11.5% (95% CI: 7.1%, 17.4%) and 27.7% (95% CI: 23.0%, 32.8%) in the sorafenib atezolizumab/bevacizumab arms, respectively. Because the results of OS and PFS were statistically significant, the significance level for the two key secondary endpoints of ORR by IRF per RECIST 1.1 and HCC mRECIST 1.1 is 0.05 (2-sided) based on the pre-specified multiplicity adjustment procedure (Figure 2). Following the pre-specified hierarchical testing order of ORR by IRF per RECIST 1.1, then ORR by IRF per HCC mRECIST 1.1, FDA's ORR results show a statistically significant improvement in ORR in the atezolizumab/bevacizumab arm over the sorafenib arm with differences between arms of 16.2% (95% CI: 8.9%, 23.4%, p-

value<0.0001) in IRF-assessed ORR per RECIST 1.1 and 20.6% (95% CI: 13.0%, 28.2%) per HCC mRECIST (See Table 70 and Table 71 in the Appendix).

FDA agrees with the Applicant's analysis of the secondary endpoint of IRF-assessed PFS by HCC mRECIST presented in Table 11. However, because the testing of this endpoint was not pre-specified to be adjusted for multiplicity, FDA considers the p-value for the result of IRF-assessed PFS per HCC mRECIST cited in Table 11 to be nominal.

Dose/Dose Response

The Applicant's Position:

Exposure-response (ER) analysis was not conducted for IMbrave150 given there were no clinically meaningful exposure-efficacy or exposure-safety relationships identified in previous analyses when atezolizumab was administered as monotherapy to patients with mUC or NSCLC in addition to potential confounding due to prognostic factors.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Both atezolizumab and bevacizumab are marketed drugs and the doses used in this study follow the standard of care.

Durability of Response

The Applicant's Position:

The consistent prolongation in OS, PFS, and DOR (see Table 9 to Table 11) with Atezo+Bev as compared to sorafenib provide strong evidence that the effects of Atezo+Bev treatment are durable.

The FDA's Assessment:
FDA does not consider the 6-month event-free rates analysis summarized in Table 11 to be informative because these Kaplan-Meier estimates are not stable at the selected timepoint, which is also arbitrary. FDA conducted an updated DOR analysis based on the ITT population. Among the 19 responders in the sorafenib arm, 32% had an observed DOR ≥ 6 months compared with 48% of the 93 responders in the atezolizumab/bevacizumab arm (Table 70 in the Appendices section). Also see Table 71 in Appendices section for the summary of the analysis of ORR by IRF assessed per HCC mRECIST 1.1.

Persistence of Effect

The Applicant's Position:

The improvement in OS observed in Atezo+Bev patients vs sorafenib patients shows that the Atezo+Bev patients derive benefit even after their disease has progressed and they have stopped taking the study treatment.

The FDA's Assessment:

FDA does not agree with the Applicant's statement above. Treatment with atezolizumab/bevacizumab improved both PFS and OS in patients with unresectable or metastatic HCC with no prior systemic treatment. However, persistence of effect is a term better suited for continuous variables (hypertension, biomarker monitoring, etc.) than to characterize or compare the effect of treatment on two clinically related but statistically independent endpoints, each showing a statistically significant improvement. Although the OS analysis takes into account death events that occur after progressive disease (PD) and cessation of study treatment, a statistically significant improvement in OS does not necessarily demonstrate that the combination treatment provides benefit to patients after PD and after cessation of study treatment. Although disease progression and cessation of anticancer treatment generally precede deaths in patients with cancer and an improvement in OS was demonstrated in the atezolizumab/bevacizumab arm of Study IMbrave 150, neither the FDA nor the Applicant conducted an analysis to that conclusively shows that atezolizumab/bevacizumab continues to confer a benefit to patients after PD and cessation of the study treatment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

High compliance rates for the EORTC QLQ-C30 and EORTC QLQ-HCC18 questionnaires were seen in both treatment arms at baseline and through most of the treatment period.

At baseline, i.e. before initiating study treatment, mean scores in both treatment arms on the functioning, GHS/QoL, and symptom scales were comparable.

The times to deterioration (TTD) of patient-reported physical functioning, role functioning, and quality of life were analyzed as secondary efficacy endpoints. Treatment with Atezo + Bev resulted in a clinically meaningful delay in in these PROs in comparison to sorafenib (

Table 12).

Table 12 Summary of the PRO Secondary Efficacy Endpoints (ITT Population, IMbrave150)

Endpoint	Sorafenib N = 165	Atezo + Bev N = 336
TTD in Physical Functioning per EORTC-QLQ-C30		
No. (%) of patients with events	64 (38.8%)	114 (33.9%)
Median (95% CI) time to event, months	4.86 (3.48, 6.24)	13.14 (9.69, NE)
Stratified hazard ratio (95% CI) [a]	0.53 (0.39, 0.73)	
TTD in Role Functioning per EORTC-QLQ-C30		
No. (%) of patients with events	69 (41.8%)	136 (40.5%)
Median (95% CI) time to event, months	3.58 (2.20, 5.98)	9.13 (6.51, NE)
Stratified hazard ratio (95% CI) [a]	0.62 (0.46, 0.84)	
TTD in GHS/QoL per EORTC-QLQ-C30		
No. (%) of patients with events	66 (40.0%)	132 (39.3%)
Median (95% CI) time to event, months	3.58 (3.02, 6.97)	11.24 (5.98, NE)
Stratified hazard ratio (95% CI) [a]	0.63 (0.46, 0.85)	

[a] Stratified by geographic region (Asia [excluding Japan] vs. rest of world), MVI and/or EHS (presence vs. absence), and baseline AFP (< 400 vs. ≥ 400 ng/mL).

Sources: t_qs_tte_IT_pfnpt, t_qs_tte_IT_rfnpt and t_qs_tte_IT_ghsnpt

The Applicant's Position:

Treatment with Atezo + Bev resulted in a clinically meaningful delay in deterioration of patient-reported physical functioning, role functioning, and quality of life reported as secondary endpoints. Additional pre-specified exploratory analyses showed that treatment with Atezo+Bev also delayed deterioration of patient-reported symptoms in a clinically meaningful way, including appetite loss, diarrhea, fatigue, pain, and jaundice versus sorafenib, further supporting the overall clinical benefit of this combination treatment.

The FDA's Assessment:

FDA was able to replicate the results of the three PRO endpoints (TTD in physical functioning (PF), role functioning, and GHS/QoL subscales) summarized in Table 12. However, FDA considers the results of these PRO endpoints descriptive and should be interpreted with caution for the following reasons.

- The analyses were not pre-specified to be adjusted for multiplicity in the SAP.
- The 10-point threshold for deterioration has not been sufficiently justified.
- Among the 323 patients who were censored in the TTD PF analysis due to absence of a TTD PF deterioration event, 60% (194 patients) either had PD (48%) or died (12%). These PD or death events may compete with the deterioration of PF. Simply censoring these PD/death event in the analyses may not be adequate to capture the treatment effect on TTD PF.

- Higher censoring rates (61% in sorafenib arm vs 66% in Atezo + Bev arm) may result in unreliable estimate of TTD PF treatment effect.
- Low patient numbers in sorafenib arm for the QLQ-C30 evaluation, especially after Cycle 10 (<=26% of the total randomized patients), preclude a reliable comparison between the treatment arms.
- Bias may have been introduced due to the open-label nature of the study.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable

Supportive Study: GO30140

The data provided in this section refer to Arms A and F of the Phase 1b Study GO30140. Both arms investigated the combination of Atezo+Bev in patients with HCC. The focus is predominantly on Arm F that investigated the single-agent contribution of Atezo+Bev vs Atezo monotherapy. The data from the uncontrolled Atezo+Bev cohort in Arm A are presented as deemed appropriate to complement the IMbrave150 and GO30140 Arm F data.

Compliance with Good Clinical Practices

The Applicant's Position:

Please refer to statements provided above for the IMbrave150 study.

The FDA's Assessment:
FDA confirms the Applicant's position. Studies were conducted in compliance with GCP guidelines.

Financial Disclosure

The Applicant's Position:

For further information for financial disclosures for studies presented in the sBLA please see Module 1.3.4 submitted on December 2, 2019 (Sequence No. 0820).

The FDA's Assessment:
FDA's complete assessment of the financial disclosures for both studies (IMbrave 150 and

GO30140) can be found in Section 19.2 of this review. A total of 223 patients were enrolled in Arms A and F of Study GO30140 and 368 investigators participated in the study. Financial disclosure information was missing for one subinvestigator, and the following [redacted] had relevant financial disclosures:

- [redacted] patients enrolled) received > 25,000 USD for speaker honoraria
- [redacted] patients enrolled) received 50,000 USD for speaker honoraria and advisor fee.
- [redacted] patients enrolled) received 27,000 USD as honoraria
- [redacted] patients enrolled) received > 50,000 USD as honoraria.

The primary endpoint of Arm A was overall response rate and the primary endpoint of Arm F was progression-free survival. For both arms, the primary endpoint analyses are based on the outcome as assessed by an independent review facility, reducing the potential for bias related to investigator assessment. In addition, results of Study GO30140 do not provide the primary basis to support the effectiveness of atezolizumab/bevacizumab for the proposed indication and are considered supportive of the results of Study IMbrave150. It is therefore unlikely that these subinvestigators' conflict of interest or the lack of information for a single subinvestigator who did not provide a financial disclosure form affected the results of Study GO30140.

Patient Disposition

Data:

Patients were enrolled into Arms A and F from 25 investigational sites in 7 countries/regions. The highest recruiting countries/regions were Korea (111 pts, 49.8%), USA (57 pts, 25.6%), Taiwan (25 pts, 11.2%) and Japan (22 pts, 9.9%). Additional patients were recruited in Australia (5 pts, 2.2%), New Zealand (2 pts, 0.9%) and China (1 pt, 0.4%). For Arm A, the first patient was enrolled on 20 July 2016 and the last patient on 31 July 2018. For Arm F, the first patient was randomized on 18 May 2018 and the last one on 7 March 2019. The data presented for both arms are based on a clinical cut-off date of 14 June 2019.

For Arm A, 180 patients were screened: while 76 failed screening, 104 patients were enrolled. For Arm F, a total of 186 patients were screened, there were 67 screen failures due to not meeting the in- or exclusion criteria. Overall, 119 patients were randomized to treatment in Arm F (60 and 59 patients in the Atezo + Bev arm and Atezo monotherapy arm, respectively).

All 104 patients enrolled in Arm A received at least one dose of study treatment. Of the 119 patients randomized to Arm F, 118 received at least one dose of study treatment. One patient (randomized to Atezo monotherapy) was not treated because of elevated alkaline phosphatase levels at the intended dose of first dose.

There were thus the following number of patients in the major analysis populations:

	Arm A Atezo + Bev (N=104)	Arm F1 Atezo + Bev (N=60)	Arm F2 Atezo (N=59)
Intent-to-Treat Patients	0	60	59
Safety Evaluable Patients	104	60	58
Efficacy Evaluable Patients	104	60	59
PK Evaluable Patients	104	59	57
Atezolizumab ADA Evaluable Patients	101	58	57
Crossover Patients	0	0	26

Crossover is only allowed for Arm F2 patients.

As of the clinical cut off date of 14 June 2019, 25.0% of patients in Arm A and 41.7% and 49.2% of patients in the Arm F Atezo+Bev or Atezo mono groups, respectively, were still continuing study treatment. In addition, 27.9% of patients in Arm A and 30.0% and 16.9%, respectively, of Atezo+Bev or Atezo mono patients in Arm F were in survival follow-up.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition in Study GO30140. In all arms, the most common reason for atezolizumab treatment discontinuation was disease progression (13%, 50%, and 20% in Arms A, F1, and F2, respectively), followed by adverse events (1%, 13%, and 3% in Arms A, F1, and F2, respectively).

Protocol Violations/Deviations

Data:

Major protocol deviations were defined similarly to those for IMbrave150 and are summarized by category in Table 13.

As of the clinical cut off date of 14 June 2019, 19.2% of the Atezo+Bev patients in Arm A and 11.7% of Atezo+Bev and 1.7% of Atezo mono patients in Arm F had at least one major protocol deviation. The vast majority of deviations were of procedural nature with AE reporting and experimental sample collection errors being the most frequent ones.

Table 13 Major Protocol Deviations (Enrolled Patients, GO30140)

Protocol Deviation Category Protocol Deviation Subcategory	Arm A Atezo + Bev (N=104)	Arm F1 Atezo + Bev (N=60)	Arm F2 Atezo (N=59)
Total number of patients with at least one deviation	20 (19.2%)	7 (11.7%)	1 (1.7%)
Overall total number of deviations	35	12	3
PROCEDURAL			
Total number of patients with at least one deviation	19 (18.3%)	7 (11.7%)	1 (1.7%)
Total number of events	33	9	1
Adverse Event Reporting	6 (5.8%)	1 (1.7%)	1 (1.7%)
Experimental Sample Collection Error	5 (4.8%)	0	0
Missed Tumor Assessment	4 (3.8%)	1 (1.7%)	0
Missed Routine Lab	3 (2.9%)	0	0
Tumor Assessment out of window	3 (2.9%)	0	0
Safety Reporting	1 (1.0%)	1 (1.7%)	0
Study Conduct/Procedures	1 (1.0%)	1 (1.7%)	0
Treatment/Dosing Error	0	2 (3.3%)	0
Concomitant Medication/Therapy	1 (1.0%)	0	0
Data Collection Error	0	1 (1.7%)	0
Missed Screening Assessment	0	1 (1.7%)	0
Missed Visit	1 (1.0%)	0	0
Randomization	0	1 (1.7%)	0
INCLUSION			
Total number of patients with at least one deviation	1 (1.0%)	2 (3.3%)	1 (1.7%)
Total number of events	1	3	2
Missed Screening Assessment	1 (1.0%)	1 (1.7%)	1 (1.7%)
Screening	0	2 (3.3%)	0
EXCLUSION			
Total number of patients with at least one deviation	1 (1.0%)	0	0
Total number of events	1	0	0
Screening	1 (1.0%)	0	0

F2 included 1 protocol deviation that occurred during the crossover period.
Source: t_dv_EN

The Applicant's Position:

None of the major protocol deviations led to exclusion of data from the analysis, posed an increased safety risk to any patient continuing on study treatment, or were considered to have affected the integrity of the study findings.

The FDA's Assessment:

FDA replicated the Applicant's analysis and agrees with the conclusions. None of the protocol violations in Study GO30140 affected the integrity of the study results.

Demographic Characteristics

Data:

Arm A: The majority of patients enrolled in Arm A were male (80.8%), Asian (72.1%) with a median age of 62.0 years (Table 14). Patients from Asia excluding Japan accounted for 56.7% of patients. At baseline, an ECOG PS of 1 was reported in 50.0% of patients.

Arm F: The majority of patients randomized to Atezo + Bev or Atezo mono were male (90.0% vs 83.1%), Asian (75.0% vs 79.7%) with a median age of 59.5 years and 63.0 years, respectively. Patients from Asia, excluding Japan, accounted for 65.0% of patients in the Atezo + Bev arm vs 66.1% of patients in the Atezo mono arm (Table 14). At baseline, an ECOG PS of 1 was reported in 55.0% of patients in the Atezo + Bev arm and in 57.6% of patients in the Atezo mono arm.

Table 14 Demographic and Baseline Disease Characteristics (Efficacy Evaluable Patients, GO30140)

	Arm A Atezo + Bev (N=104)	Arm F1 Atezo + Bev (N=60)	Arm F2 Atezo (N=59)
Sex			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Male	84 (80.8%)	54 (90.0%)	49 (83.1%)
Female	20 (19.2%)	6 (10.0%)	10 (16.9%)
Age (year)			
n	104	60	59
Mean (SD)	61.0 (11.3)	59.9 (12.1)	61.8 (11.7)
Median	62.0	59.5	63.0
Min - Max	23 - 82	22 - 82	23 - 85
Age Group (year)			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
18-40	6 (5.8%)	3 (5.0%)	2 (3.4%)
41-64	61 (58.7%)	36 (60.0%)	32 (54.2%)
>=65	37 (35.6%)	21 (35.0%)	25 (42.4%)
Race			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Asian	75 (72.1%)	45 (75.0%)	47 (79.7%)
Black or African American	7 (6.7%)	1 (1.7%)	2 (3.4%)
Native Hawaiian or other Pacific Islander	0	0	1 (1.7%)
White	20 (19.2%)	14 (23.3%)	9 (15.3%)
Unknown	2 (1.9%)	0	0
Geographic Region			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Asia Excluding Japan	59 (56.7%)	39 (65.0%)	39 (66.1%)
ROW	45 (43.3%)	21 (35.0%)	20 (33.9%)
Geographic Region (IxRS)			
n	-	60 (100.0%)	59 (100.0%)
Asia Excluding Japan	-	40 (66.7%)	39 (66.1%)
ROW	-	20 (33.3%)	20 (33.9%)
Baseline ECOG			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
0	52 (50.0%)	27 (45.0%)	25 (42.4%)
1	52 (50.0%)	33 (55.0%)	34 (57.6%)

ROW: Rest of the world refers to the USA, Australia, New Zealand, and Japan.
Source: t_dm_EE

The Applicant's Position:

The patients enrolled in both Arms A and F were representative of a patient population with unresectable HCC. The two study groups in Arm F were generally well balanced with regards to the baseline characteristics.

The FDA's Assessment:

FDA replicated the Applicant's analysis of the demographic characteristics of Arms A and F of Study GO30140. Race distribution is representative of the geographic areas where the study was opened for enrollment and similar to the demographics of patients in similar studies planned for registration of drugs in the first-line treatment of HCC. FDA agrees with the Applicant's conclusion that demographic characteristics were well balanced between arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Arm A: HBV was the most frequent etiology of HCC in Arm A (49.0%), followed by HCV (29.8%) and non-viral etiology (21.2%) (Table 15). At baseline, the vast majority of patients had Child-Pugh class A, with 74.0% having Class A5 and 20.2% A6, 5.8% patients had B7. The majority of patients had advanced stage disease of BCLC Stage C (90.4%). MVI and/or EHS were present in most patients (87.5%). The proportion of patients with AFP $\geq$ 400 ng/mL was 35.6%. Prior local therapy for HCC was given to 61.5% of patients, with TACE being the most frequent (53.8%).

Arm F: The etiology of HCC was comparable between the 2 groups in Arm F, with most patients having HBV (56.7% vs 54.2%) followed by non-viral etiology (25.0% vs 28.8%) and HCV (18.3% vs 16.9%) (Table 15). At baseline, all patients in the Atezo + Bev and Atezo monotherapy arms had Child-Pugh class A, with 71.7% and 71.2% patients having Class A5. The majority of patients had advanced stage disease of BCLC Stage C (90.0% vs 89.8%). MVI and/or EHS were present in most patients (78.3% vs 84.7%). In the Atezo monotherapy arm, a greater proportion of patients had MVI compared to patients in the Atezo + Bev arm (42.4% vs 33.3%). The proportion of patients with AFP $\geq$ 400 ng/mL was comparable between the Atezo + Bev arm and the Atezo monotherapy arm (30.0% vs 32.2%). More patients on Atezo+Bev received prior local therapy for HCC (75%) than patients in the Atezo mono group (54.2%), the most frequent procedure was TACE (53.3% vs 47.5%).

Table 15 Hepatocellular Carcinoma History and Disease Characteristics (Efficacy Evaluable Patients, GO30140)

	Arm A Atezo + Bev (N=104)	Arm F1 Atezo + Bev (N=60)	Arm F2 Atezo (N=59)
Etiology of HCC			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Hepatitis B	51 (49.0%)	34 (56.7%)	32 (54.2%)
Hepatitis C	31 (29.8%)	11 (18.3%)	10 (16.9%)
Non-viral	22 (21.2%)	15 (25.0%)	17 (28.8%)
Child-Pugh-Class and Child-Pugh-Point			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
A5	77 (74.0%)	43 (71.7%)	42 (71.2%)
A6	21 (20.2%)	17 (28.3%)	17 (28.8%)
B7	6 (5.8%)	0	0
BCLC Staging Class at Study Entry			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Stage A4	0	0	2 (3.4%)
Stage B	10 (9.6%)	6 (10.0%)	4 (6.8%)
Stage C	94 (90.4%)	54 (90.0%)	53 (89.8%)
Macro-Vascular Invasion (MVI) Present			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Yes	55 (52.9%)	20 (33.3%)	25 (42.4%)
No	49 (47.1%)	40 (66.7%)	34 (57.6%)
Extrahepatic Spread (EHS) Present			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Yes	74 (71.2%)	40 (66.7%)	39 (66.1%)
No	30 (28.8%)	20 (33.3%)	20 (33.9%)
MVI and/or EHS Present			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Yes	91 (87.5%)	47 (78.3%)	50 (84.7%)
No	13 (12.5%)	13 (21.7%)	9 (15.3%)
AFP Categories (ng/mL) at Baseline			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
0 - <400	60 (57.7%)	36 (60.0%)	34 (57.6%)
>=400	37 (35.6%)	18 (30.0%)	19 (32.2%)
Missing	7 (6.7%)	6 (10.0%)	6 (10.2%)
Prior HCC Local Therapy			
n	104 (100.0%)	60 (100.0%)	59 (100.0%)
Yes	64 (61.5%)	45 (75.0%)	32 (54.2%)
No	40 (38.5%)	15 (25.0%)	27 (45.8%)
Prior HCC Local Therapy			
TACE	56 (53.8%)	32 (53.3%)	28 (47.5%)
RFA	21 (20.2%)	10 (16.7%)	7 (11.9%)
TARE	4 (3.8%)	4 (6.7%)	1 (1.7%)
Ethanol Ablation	2 (1.9%)	1 (1.7%)	1 (1.7%)
Other	10 (9.6%)	5 (8.3%)	5 (8.5%)

Non-viral HCC etiology includes unknown non-hepatitis B and C cause.
Source: t_dm_EE

The Applicant's Position:

The baseline HCC history and disease characteristics were generally well balanced between Arm A and the two treatment arms in the ITT population of Arm F, and in general also to what was observed in IMbrave150. They were reflective of an advanced HCC population.

The FDA's Assessment:

FDA agrees with the Applicant's conclusion that the baseline HCC history and disease characteristics in Arms A and F of Study GO30140 were reflective of an advanced HCC population and well balanced between arms F1 and F2. As stated above for the analysis of the

disease and baseline characteristics of patients enrolled in Study IMbrave150, although there are differences in the etiology of HCC – particularly in relationship with Hepatitis B and C – the results of the study can be extrapolated to the U.S. population .

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance: The median dose intensity as a measure of treatment compliance to atezolizumab was 99.9% in Arm A and 100.0% in the 2 groups of Arm F (Table 16). The compliance to bevacizumab (in the applicable groups) was similarly high.

Table 16 Treatment Compliance to Atezolizumab (Safety-Evaluable Population; GO30140)

	Arm A Atezo + Bev (N=104)	Arm F1 Atezo + Bev (N=60)	Arm F2 Atezo (N=58)	Arm F2-Crossover + Bev (N=26)
Dose intensity (%)				
n	104	60	58	26
Mean (SD)	97.5 (5.8)	98.0 (5.4)	98.8 (4.0)	99.5 (3.3)
Median	99.9	100.0	100.0	100.0
Min - Max	62 - 102	72 - 105	79 - 105	90 - 108

Source: t_ex_EXATEZO_SE

Concomitant Medications: No analyses were conducted in the GO30140 study for concomitant treatments given for palliative reasons.

Arm A: Concomitant non-cancer treatments given on or after the first dose of trial treatment were administered to 93.3% patients. Opioid analgesics were the most commonly prescribed concomitant treatments (45.2%), followed by analgesics (42.3%), supplements (41.3%), antihistamines (37.5%), and steroids (40.4%).

Arm F: A similar proportion of patients were administered concomitant non-cancer treatments given on or after the first dose of trial treatment in the Atezo + Bev arm (88.3%) compared to patients in the Atezo monotherapy arm (89.7%). Opioid analgesics were the most commonly prescribed concomitant treatments in both the Atezo + Bev arm and Atezo monotherapy arms (28.3% vs 34.5%), followed by analgesics (30.0% vs 25.9%), supplements (23.3% vs 24.1%), antihistamines (20.0% vs 25.9%), and steroids (21.7% vs 17.2%).

The Applicant's Position:

Treatment compliance was comparably high between all 3 treatment groups of GO30140, which was to be expected given that both study treatments were administered as IV infusions.

Concomitant non-cancer therapies reflected the general disease status of this patient population as well as the AE profile associated with atezolizumab and bevacizumab.

The FDA's Assessment:

Toxicity management for atezolizumab and bevacizumab does not include dose reductions; therefore, as expected, intensity measured as a function of the planned dose and actual dose received is close to 100% in the three arms. However, when assessing treatment delays for the

management of toxicity, 25 (24%), 6 (10%) and 6 (10%) patients in Arms A, F1, and F2, respectively, required treatment interruptions while on the main portion of the study (this analysis does not take into consideration patients in Arm F2 who crossed over to atezolizumab/bevacizumab).

Median duration of treatment with atezolizumab was 8.34 months (range 0-34.3), 5.21 months (range 0-11.3) and 3.22 months (range 0-9.2) in Arms A, F1 and F2, respectively, corresponding to a median of 11.5, 8.5, and 3 cycles, respectively. Due to different median follow-up times between Arms A and F, the number of patients on treatment for more than 6 months is not directly comparable.

This reviewer agrees with the Applicant's conclusion that treatment compliance was comparable between all arms of Study GO30140 and that concomitant non-cancer therapies reflected the general disease status of patients with advanced HCC receiving treatment with atezolizumab and bevacizumab.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Arm A

The primary efficacy endpoint in this single arm cohort of Atezo+Bev treated patients showed a clinically meaningful confirmed ORR of 35.6% (95% CI: 26.4%, 45.6%) based on IRF assessment per RECIST v1.1 in the efficacy-evaluable population (N = 104) (Table 17). There were 37 responders, 12 (11.5%) achieved a CR and 25 (24.0%) achieved a PR.

Table 17 Confirmed Objective Response Based on IRF-Assessment per RECIST v1.1 in Arm A (Efficacy Evaluable Patients, GO30140)

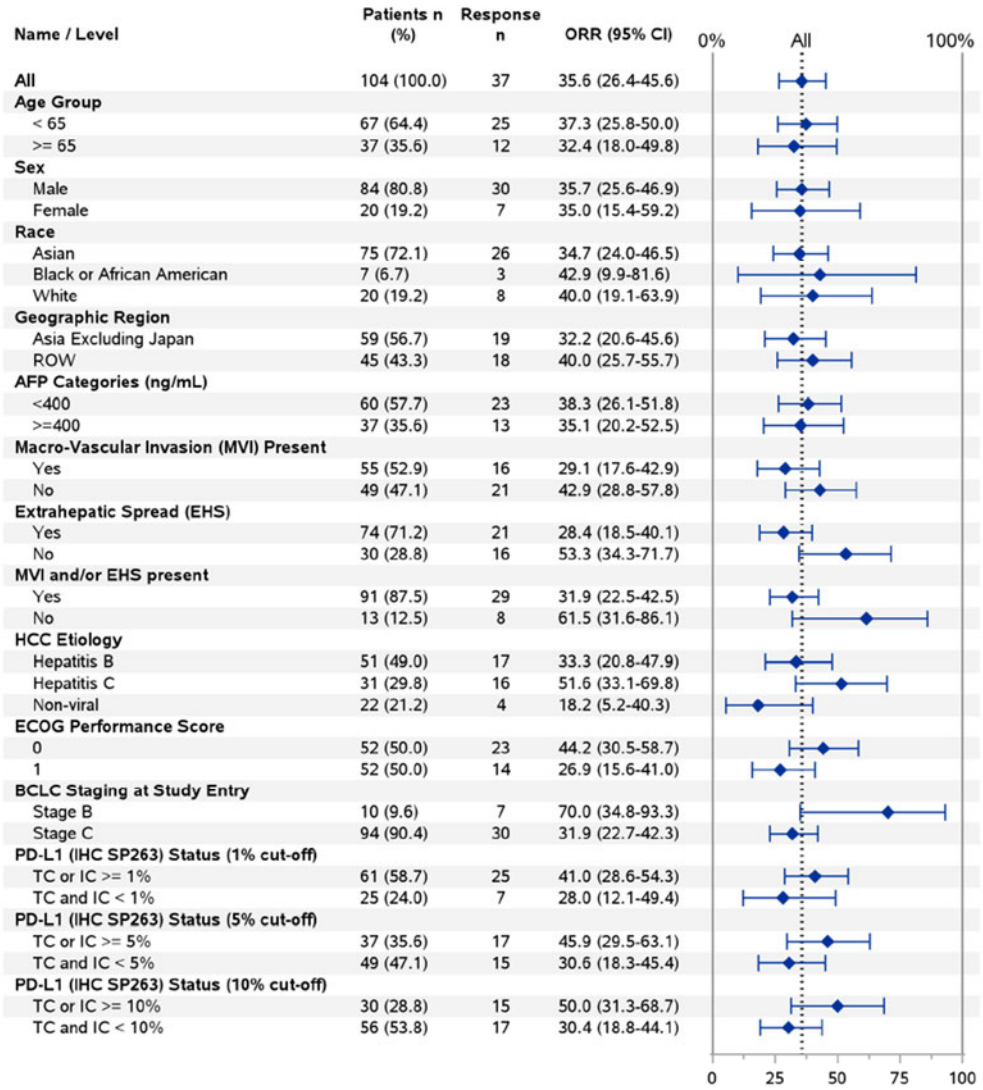
	Arm A Atezo + Bev (N=104)
Responders	37 (35.6%)
Non-Responders	67 (64.4%)
95% CI for Response Rate	(26.43, 45.57)
Complete Response (CR)	12 (11.5%)
95% CI	(6.11, 19.29)
Partial Response (PR)	25 (24.0%)
95% CI	(16.20, 33.41)
Stable Disease (SD)	37 (35.6%)
95% CI	(26.43, 45.57)
Progressive Disease (PD)	25 (24.0%)
95% CI	(16.20, 33.41)
Missing or Unevaluable	5 (4.8%)
Disease Control Rate (CR/PR/SD)	74 (71.2%)
95% CI	(61.45, 79.62)

Responses refer to either a (confirmed) CR or PR per RECIST v1.1.
Patients were classified as missing or unevaluable if no post-baseline response assessment was available or all post-baseline response assessments were unevaluable. 95% CI for rates were constructed using Clopper Pearson method.

Source: t_ef_orr_BESRSPR_ARMA_RFR_EE

Analyses of confirmed responses by IRF assessment per RECIST v1.1 (Figure 8) in pre-defined subgroups show antitumor responses in all subgroups, including those in patients with less favorable prognostic factors, such as macrovascular invasion and/or extrahepatic spread or AFP $\geq$ 400 ng/mL.

Figure 8 Subgroup Analyses of Confirmed Objective Response Based on IRF-Assessment per RECIST v1.1 in Arm A (Efficacy Evaluable Patients, GO30140)



ROW: Rest of the world refers to the USA, Australia, New Zealand and Japan. Non-viral HCC etiology includes unknown non-hepatitis B and C cause. Responses refer to either a (confirmed) CR or PR per RECIST v1.1. 95% CI for rates were constructed using Clopper Pearson method.
Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019

Program: root/clinical_studies/RO5541267/CDT30075/GO30140/data_analysis/CSR/prod/program/g_ef_orr_fp.sas
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14AUG2019 00:47

Arm F

Arm F of the study met its primary efficacy endpoint of PFS as assessed by IRF per RECIST v1.1. The Atezo+Bev combination showed a statistically significant and clinically meaningful improvement in PFS compared to Atezo monotherapy in the ITT population (N=119), with a stratified HR of 0.55 (80% CI: 0.40, 0.74, [p value=0.0108]) (Table 18).

The Kaplan Meier curves for PFS separated early (< 1 month post randomization) in favor of the Atezo + Bev arm vs. the Atezo monotherapy arm (Figure 9).

The 6-month PFS rate was higher in the Atezo +Bev arm (46%) compared with Atezo monotherapy (27%).

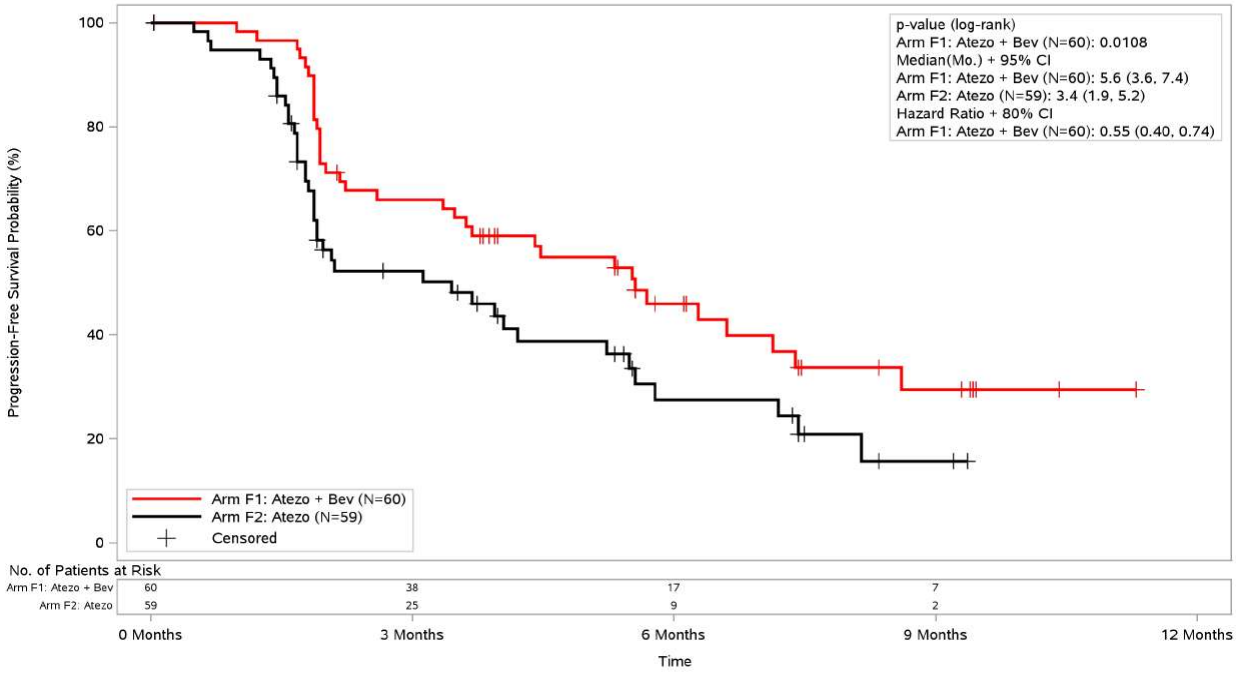
The sensitivity analyses planned for the primary efficacy endpoint in the event that ≥10% of the patients in either treatment arm missed two or more tumor assessments scheduled immediately prior to the date of disease progression or death were not conducted since the number of patients missing tumor assessments did not reach the pre-specified threshold.

Table 18 Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 in Arm F (Efficacy Evaluable Patients, GO30140)

	Arm F1 Atezo + Bev (N=60)		Arm F2 Atezo (N=59)
Patients with event (%)	35 (58.3%)		39 (66.1%)
Disease Progression	31		35
Death	4		4
Patients without event (%)	25 (41.7%)		20 (33.9%)
Time to event (months)			
Median	5.6		3.4
95% CI for Median	(3.6, 7.4)		(1.9, 5.2)
Stratified Analysis			
p-value (log-rank)		0.0108	
Hazard Ratio		0.55	
80% CI		(0.40, 0.74)	
Time Point Analysis			
6 months			
Patients remaining at risk	17		9
Event free probability	0.46		0.27
95% CI	(0.32, 0.59)		(0.14, 0.41)

* Censored. Summaries of time-to-event (median, percentiles) are Kaplan-Meier estimates.
95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression. Stratified analysis included geographic region (Asia excluding Japan vs. Rest of World) and AFP level (<400 ng/mL vs. >=400 ng/mL) at baseline obtained from IxRS as the stratification factors. Arm F2 is the reference.
Source: t_ef_km_PFSRAD_ARMF_RFR_EE

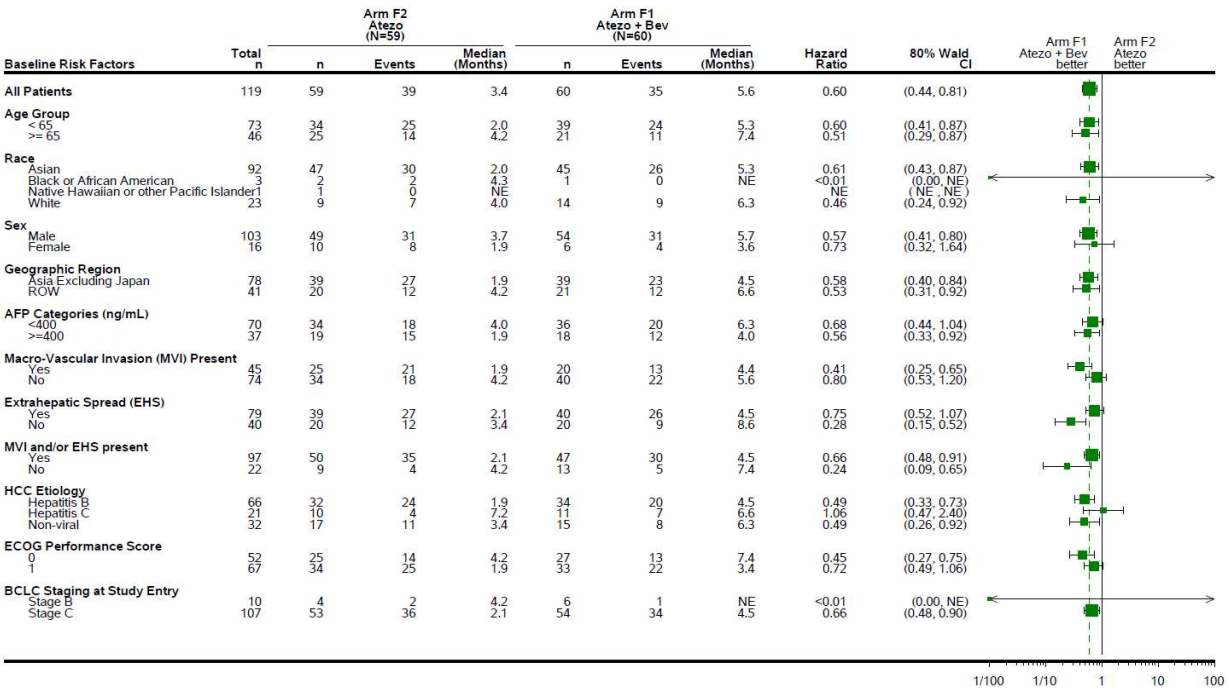
Figure 9 Kaplan-Meier Plot of Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 in Arm F (Efficacy Evaluable Patients, GO30140)



P-value and hazard ratio are based on stratified analyses with the stratification factors as geographic region (Asia excluding Japan vs. Rest of World) and AFP level (<400 ng/mL vs. >=400 ng/mL) obtained from IxRS.
Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019
Program: root/clinical_studies/RO5541267/CDT30075/GO30140/data_analysis/CSR/prod/program/g_ef_km.sas
Output: root/clinical_studies/RO5541267/CDT30075/GO30140/data_analysis/CSR/prod/output/g_ef_km_PFSRAD_ARMF_RFR_EE.pdf 14AUG2019 0:41

A consistent PFS benefit by IRF assessment per RECIST v1.1 was observed with Atezo+Bev compared with Atezo monotherapy across all pre-defined subgroups, with the exception of HCV, and was generally consistent with the benefit observed in the overall ITT population (Figure 10). The data for patients with HCV, which showed an unstratified HR of 1.06 (80% CI: 0.47-2.40), was based on a very small sample size (Atezo + Bev: 11 patients; Atezo monotherapy: 10 patients) and a limited number of events.

Figure 10 Subgroup Analyses of Progression-Free Survival Based on IRF-Assessment per RECIST v1.1 in Arm F (Efficacy Evaluable Patients, GO30140)



Hazard ratios were estimated by unstratified Cox regression. Arm F2 is the reference. NE: Not estimable.
ROW: Rest of the world refers to the USA, Australia, New Zealand and Japan. Non-viral HCC etiology includes unknown non-hepatitis B and C cause.
Data Extraction Date: 31JUL2019; Data Cut Date: 14JUN2019
Program: root/clinical_studies/RO5541267/CDT30075/GO30140/data_analysis/CSR/prod/program/g_ef_km_fp.sas
Output: root/clinical_studies/RO5541267/CDT30075/GO30140/data_analysis/CSR/prod/output/g_ef_km_fp_PFSRAD_ARMF_RFR_EE_PG1.pdf 27AUG2019 19:03

The Applicant's Position:

Arm A of GO30140 demonstrated encouraging response rates for the Atezo+Bev combination in patients with unresectable HCC. The ORR benefit was generally consistent across subgroups.

Arm F of GO30140 met its primary efficacy endpoint of PFS as assessed by IRF per RECIST v1.1. The statistically significant improvement of Atezo+Bev over Atezo monotherapy is clinically meaningful and demonstrates that combining bevacizumab with atezolizumab is necessary to provide meaningful clinical benefit to patients with unresectable HCC. The PFS benefit was generally consistent across subgroups.

The FDA's Assessment:

FDA agrees with the Applicant's results of ORR for Arm A and PFS for Arm F in Table 17 and Table 18. The 95% CI of the HR for PFS estimated by FDA is (0.34, 0.88) which is consistent with the primary analysis of PFS for Arm F. FDA does not consider DCR as an endpoint that demonstrates an effect of the study treatment on the disease and considers the analysis of DCR to be exploratory. FDA also considers the subgroup analyses presented in Figure 8 and Figure 9 to be exploratory.

Data Quality and Integrity

Data:

Information requested by the Office of Scientific Investigations (OSI) for Study GO30140 is provided in Module 5.3.5.4 as part of the submission to the sBLA on December 16 2019 (Serial No. 0834).

The FDA's Assessment:
The data and corresponding documents provided in the sBLA submissions were of adequate quality to enable reviewers to replicate the Applicant's major efficacy and safety results and conduct the analyses needed for a comprehensive risk/benefit assessment of this application.

Efficacy Results – Secondary and other relevant endpoints

Data:

Arm A

The results seen with secondary efficacy endpoints including confirmed ORR by IRF-assessed HCC mRECIST and investigator-assessed RECIST v1.1 were consistent with the results of the primary efficacy endpoint. Results for PFS were consistent across the three tumor assessment criteria.

Confirmed responses were durable with IRF assessed responses per RECIST v.1.1 ongoing in 76% of responders at time of the clinical data cut-off.

Arm F

Analyses of key secondary endpoints in Arm F showed for the Atezo+Bev group improvements in PFS assessed by IRF per HCC mRECIST and by the investigator per RECIST v1.1 compared to Atezo monotherapy (Table 19). These results confirmed the outcome of the primary endpoint (PFS by IRF assessed RECIST v1.1). In addition, the Atezo+Bev group showed numerically higher ORR by all three tumor assessment criteria in comparison to Atezo monotherapy (Table 20).

Table 19 Progression-Free Survival Based on IRF-Assessment per HCC mRECIST or Investigator-assessment per RECIST v1.1 in Arm F (Efficacy Evaluable Patients, GO30140)

	IRF-Assessment per HCC mRECIST		Investigator-assessed per RECIST v1.1	
	Atezo + Bev (N=60)	Atezo (N=59)	Atezo + Bev (N=60)	Atezo (N=59)
Number of events (%)	34 (56.7%)	39 (66.1%)	35 (58.3%)	44 (74.6%)
Median, months (95% CI)	5.6 (3.6 – 7.4)	3.4 (1.9 – 5.2)	5.7 (3.5 – 9.3)	2.0 (1.9 – 3.7)
Stratified HR* (80% CI)	0.54 (0.40, 0.74)		0.44 (0.33, 0.60)	

* Stratification factors included in the analysis were geographic region (Asia excluding Japan vs. Rest of World) and AFP level (<400 ng/mL vs. ≥400 ng/mL at baseline obtained from IxRS.

Table 20 Objective Response Rate Based on IRF-Assessments per RECIST v1.1 or HCC mRECIST in Arm F (Efficacy Evaluable Patients, GO30140)

	IRF-assessed per RECIST v1.1		IRF-assessed per HCC mRECIST	
Key Efficacy Endpoints	**Atezo + Bev (N=60)**	**Atezo (N=59)**	**Atezo + Bev (N=60)**	**Atezo (N=59)**
Objective Response Rate [a]	12 (20.0%)	10 (16.9%)	16 (26.7%)	10 (16.9%)
95% CI for Response Rates	(10.8, 32.3)	(8.4, 29.0)	(16.1, 39.7)	(8.4, 29.0)
CR	1 (1.7%)	3 (5.1%)	3 (5.0%)	3 (5.1%)
PR	11 (18.3)	7 (11.9%)	13 (21.7%)	7 (11.9%)
Difference in ORR (80% CI)	3.1% (-7.7, 13.8)		9.7% (-1.6, 21.0)	
SD	28 (46.7%)	19 (32.2%)	25 (41.7%)	19 (32.2%)
Non-CR/Non-PD	0	1 (1.7%)	0	1 (1.7%)
PD	17 (28.3%)	25 (42.4%)	16 (26.7%)	25 (42.4%)
Missing/Unevaluable	3 (5.0%)	4 (6.8%)	3 (5.0%)	4 (6.8%)
Disease Control Rate	40 (66.7%)	29 (49.2%)	41 (68.3%)	29 (49.2%)

[a] Only confirmed responders were included in analysis.

The Applicant's Position:

Analyses of secondary endpoints were all consistent with the outcomes of the primary endpoints for GO30140 Arms A and F.

The FDA's Assessment:

FDA agrees with the Applicant's results in Table 19 and Table 20.

Dose/Dose Response

The Applicant's Position:

No new information is available for GO30140

The FDA's Assessment:
Studies submitted to support the indication used the standard dose of atezolizumab and bevacizumab. No dose-response assessments were conducted.

Durability of Response

Data:

The median DOR in confirmed responders had not been reached yet in the Atezo+Bev groups of Arms A and Arm F. The 6-month event-free rates were 100% and 81%, respectively, in these groups .

The FDA's Assessment:
FDA agrees that the median DOR in confirmed responders had not been reached yet in the Atezo+Bev groups of Arms A and Arm F. However, FDA does not agree with the applicant that using the 6-month event-free rate to provide substantial evidence of effectiveness. In addition, the 6-month event-free rates in Table 18 are based on Kaplan-Meier estimates which are not stable especially in the situation of small number of events. Among the 37 responders in Arm A (Atezo + Bev), 64.9% of responders had observed DOR>=6 months while 25% of 12 responders in Arm F1 (Atezo + Bev).

Persistence of Effect

The Applicant's Position:

No new information is available for GO30140

The FDA's Assessment:
Not applicable.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable

The FDA's Assessment:
Not applicable.

8.1.3 Integrated Review of Effectiveness (supplements only)

The FDA's Assessment:
Not applicable.

8.1.4 Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Table 21 Comparison of IMbrave150 Co-Primary Endpoints with Corresponding Analyses in GO30140

	IMbrave150		GO30140		
	Sorafenib (N = 165)	Atezo + Bev (N = 336)	Arm A Atezo + Bev (N = 104)	Arm F1 Atezo + Bev (N = 60)	Arm F2 Atezo (N = 59)
Duration of Survival Follow-up					
Median, months (Min-Max)	8.1 (0.0 - 16.2)	8.9 (0.1-16.9)	12.4 (0.7-34.3)	6.6 (1.0-11.9)	6.7 (0.5-11.4)
Overall Survival					
No. (%) of patients with event	65 (39.4%)	96 (28.6%)	47 (45.2%)	16 (26.7%)	18 (30.5%)
Median, months (95% CI)	13.2 (10.4, NE)	NE (NE, NE)	17.1 (13.8, NE)	NE (8.3, NE)	NE (8.2, NE)
Stratified hazard ratio (CI), p-value *	0.58 (0.42, 0.79) [a], 0.0006		-	0.78 (0.50, 1.21) [b], -	
6-Month OS rate (%) (95% CI)	72% (65, 79)	85% (81, 89)	82% (74, 89)	88% (79, 96)	76% (65, 88)
Progression-Free Survival: IRF-Assessed per RECIST v1.1					
No. (%) of patients with event	109 (66.1%)	197 (58.6%)	69 (66.3%)	35 (58.3%)	39 (66.1%)
Median, months (95% CI)	4.3 (4.0, 5.6)	6.8 (5.8, 8.3)	7.3 (5.4, 9.9)	5.6 (3.6, 7.4)	3.4 (1.9, 5.2)
Stratified hazard ratio (CI), p-value *	0.59 (0.47, 0.76) [a], <0.0001		-	0.55 (0.40, 0.74) [b], 0.0108	
6-Month PFS rate (%) (95% CI)	37% (29, 45)	55% (49, 60)	54% (45, 64)	46% (32, 59)	27% (14, 41)

[a] Stratification factors included geographic region (Asia excluding Japan vs. rest of world), macrovascular invasion and/or extrahepatic spread (presence vs. absence) and baseline AFP levels (<400 vs. ≥400 ng/mL) per IxRS. Sorafenib is the reference. Two-sided 95% confidence interval is shown.

[b] Stratification factors included geographic region (Asia excluding Japan vs. rest of world) and baseline AFP levels (<400 vs. ≥400 ng/mL) per IxRS. Arm F2 is the reference. Two-sided 80% confidence interval is shown.

*. Based on two-sided stratified log-rank test, with stratification factors for IMbrave150 and GO30140 Arm F as outlined in footnotes a and b, respectively.

Sources: IMbrave150 and GO30140 CSRs.

The Applicant's Position:

Overall, the clinical benefit observed with treatment with Atezo+Bev in IMbrave150 was further supported by the clinical activity that was consistently observed in Arms A and F of GO30140 across efficacy endpoints, despite cross-study differences, and irrespective of some numerical differences in point estimates (Table 21).

The FDA's Assessment:

The administration of the combination of atezolizumab and bevacizumab demonstrated

improved survival and progression-free survival outcomes when compared with the standard of care for the first-line treatment of HCC in Study IMbrave 150. In addition, the combination resulted in improved response rates with durable responses; this benefit has been observed across Studies IMbrave150 and Arm A of Study GO30140, further supporting demonstration of clinical benefit with the use of the combination. In the analysis of time-to-event endpoints, FDA considers the totality of the data; analysis of outcomes at arbitrarily selected time endpoints like 6-months PFS or OS could are incomplete and unstable when using the Kaplan Meier method.

Secondary and Other Endpoints

Data:

Table 22 Comparison of Important Secondary Efficacy Endpoints of IMbrave150 with Corresponding GO30140 Analyses

	IMbrave150		GO30140		
	Sorafenib (N = 165)	Atezo + Bev (N = 336)	Arm A Atezo + Bev (N = 104)	Arm F1 Atezo + Bev (N = 60)	Arm F2 Atezo (N = 59)
Duration of Survival Follow-up					
Median, months (Min-Max)	8.1 (0.0 - 16.2)	8.9 (0.1-16.9)	12.4 (0.7-34.3)	6.6 (1.0-11.9)	6.7 (0.5-11.4)
Confirmed Objective Response Rate: IRF-Assessed per RECIST v1.1					
No. of evaluable patients	159	326	104	60	59
Confirmed ORR, N (%)[a] (95% CI)	19 (11.9%) (7.35, 18.03)	89 (27.3%) (22.54, 32.48)	37 (35.6%) (26.43, 45.57)	12 (20.0%) (10.78, 32.33)	10 (16.9%) (8.44, 28.97)
Difference in ORR, (%), (CI), p-value	15.4%, (7.9, 22.8), < 0.0001[b]		-	3.1%, (-7.7-, 13.8)[c], -	
Disease Control Rate: IRF-Assessed per RECIST v1.1					
DCR (%)	55.3%	73.6%	71.2%	66.7%	49.2%
Duration of Confirmed Response: IRF-Assessed per RECIST v1.1 *					
No. of evaluable patients	19	89	37	12	10
No. (%) of patients with event	6 (31.6%)	12 (13.5%)	9 (24.3%)	0	2 (20.0%)
Patients with ongoing response (%)	13 (68.4%)	77 (86.5%)	28 (75.7%)	12 (100.0%)	8 (80.0%)
Median time to event (months) (95% CI)	6.3 (4.67, NE)	NE	NE (11.8, NE)	NE	NE (3.7, NE)
6-Month event-free rate (%)	59%	88%	81%	100%	75%

CI=confidence interval; DCR=disease control rate; IRF=independent review facility; NE=Not estimable; ORR=objective response rate; RECIST v1.1=response evaluation criteria in solid tumors version 1.1

[a] Responses refer to either a (confirmed) CR or PR per RECIST v1.1.

[b] Two-sided 95% confidence interval is shown. P-value was based on stratified Cochran-Mantel-Haenszel test
[c] Two-sided 80% confidence interval is shown.
Sources: IMbrave150 and GO30140 CSRs

The Applicant's Position:

Overall, the clinical benefit observed with treatment with Atezo+Bev in IMbrave150 was further supported by the clinical activity that was consistently observed in Arms A and F of GO30140 across efficacy endpoints, despite cross-study differences, and irrespective of some numerical differences in point estimates (Table 22).

The FDA's Assessment:
FDA agrees with applicant that the clinical benefit in terms of ORR per RECIST/HCC mRECIST observed with Atezo+Bev treatment in IMbrave150 was supported by the corresponding clinical activity observed in Arms A and F of GO30140. However, FDA does not accept using the endpoint based on a time point or landmark such as 6-month event-free rates in Table 22 to provide substantial evidence of effectiveness for treatment effects because they are Kaplan-Meier estimates which are in general not stable in the situation of a small number of events.

Subpopulations

Data:

There were no analyses of subpopulations across studies

The FDA's Assessment:
Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:
Not applicable.

8.1.5 Integrated Assessment of Effectiveness

The Applicant's Position:

The IMbrave150 data demonstrated a statistically significant and clinically meaningful improvement in OS and PFS by IRF per RECIST v1.1 with Atezo+Bev over Sorafenib. The observed OS HR translated into a reduction in the risk of death by 42% with the Atezo+Bev arm compared with the Sorafenib arm. With a median duration of survival follow up for all patients was 8.6 months, the OS results are statistically significant with the pre-specified efficacy boundary crossed, representing the first study to demonstrate superior OS over Sorafenib, the standard of care in unresectable HCC. Furthermore, a clear separation of the OS Kaplan-Meier curves between the two treatment arms occurred early and remained over time despite a higher proportion of patients in the Sorafenib arm having received subsequent systemic therapy, including immunotherapy. The OS data, taken together with a reduction in risk of

disease progression or death of 41%, signify a pronounced improvement over the current standard of care.

A statistically significant and clinically meaningful improvement in ORR by IRF per RECIST v1.1 and HCC mRECIST was also observed. The clinical benefit was highlighted by the high rate of patients who experienced a CR in the Atezo + Bev arm compared with the Sorafenib arm. While the median DOR of the combination arm has not been reached yet, responders had a higher probability with a DOR $\geq$6 months (per RECIST v1.1) in the Atezo + Bev arm compared with the Sorafenib arm. Results for secondary endpoints of PFS, ORR, DOR, and TTP by IRF per HCC mRECIST and investigator per RECIST v1.1 were generally consistent to those of the IRF RECIST v1.1 analyses. OS, PFS, and ORR benefits were generally consistent across all pre-defined subgroups.

Pre-specified analyses of robust PRO data using psychometrically valid questionnaires indicated that, compared with Sorafenib, treatment with Atezo+Bev resulted in a clinically meaningful delay in deterioration of patient reported functioning and quality of life. These results are complemented by the clinically meaningful delay in deterioration of patient-reported symptoms (including appetite loss, diarrhea, fatigue, pain, and jaundice) observed with Atezo + Bev versus Sorafenib. All of these results are substantiated by additional pre-specified exploratory PRO analyses, which showed consistent and large treatment benefits in favor of Atezo+Bev.

Both atezolizumab and bevacizumab monotherapy studies have shown modest efficacy in HCC. GO30140 Arm F met its primary efficacy endpoint by demonstrating a statistically significant and clinically meaningful improvement in PFS as assessed by IRF per RECIST v1.1 with Atezo + Bev over atezolizumab monotherapy. The totality of Arm F results demonstrate that both atezolizumab and bevacizumab contribute to the overall treatment effect of the combination of Atezo + Bev. Taken together, the findings of these studies support the conclusion that combining atezolizumab with bevacizumab is necessary to improve clinical outcomes in HCC.

The FDA's Assessment:

FDA agrees with the Applicant that Study IMbrave150 demonstrated a statistically significant and clinically meaningful improvement in OS, PFS, and ORR with Atezo+Bev compared to sorafenib. Please note that FDA ORR is based on the ITT population and therefore differs from the Applicant's analysis.

Due to limitations in the design of Study IMbrave150 with respect to PRO assessment and analyses, FDA was not able to conclude that atezolizumab in combination with bevacizumab resulted in a clinically meaningful improvement or delay in deterioration of patient quality of life (see FDA's assessment regarding PRO results from Study IMbrave 150 in Section 8.2.6). FDA agrees with the Applicant that the PFS, ORR, and DOR results from Study GO30140 support the results of Study IMbrave150 and isolate the effect of the contribution of bevacizumab to the combination of Atezo + Bev..

8.2 Review of Safety

The Applicant's Position:

The assessment of the safety of the Atezo+Bev combination is based primarily on the comparison of the pooled safety data from the 3 Atezo+Bev cohorts investigated in the treatment of HCC patients (IMbrave150 and Arms A and F from GO30140) with the safety data obtained from the Sorafenib arm in IMbrave150.

The safety review was supplemented by the inclusion of a large pooled atezolizumab monotherapy population (3178 safety-evaluable patients from eight clinical trials mainly comprising patients with NSCLC, UC, and renal cell cancer [RCC]) to provide context and facilitate the characterization of the safety profile of atezolizumab in combination with bevacizumab. The side-by-side comparison of the pooled Atezo+Bev results with the Sorafenib data and the pooled Atezo monotherapy data across multiple indications is discussed in the Summary of Clinical Safety (SCS).

Safety information from cohorts of patients with 1L+ HCC in the Phase I open-label studies PCD4989g and YO29233 has been pooled with the data from Atezo monotherapy in GO30140 Arm F to provide additional supporting safety information about atezolizumab monotherapy when used in the HCC setting, in particular to help with interpretation of atezolizumab AESI findings (e.g. hepatic events) in HCC patients.

Based on the above, the following populations have been identified to be included in different analyses provided in the submission:

- Sorafenib population (N=156)
- Atezo+Bev population (N=493)
- Atezo Mono (HCC) population (N=93)
- Atezo Mono (Multiple Indications) population (N=3178)

The FDA's Assessment:

FDA agrees with the selection of the patient population to assess safety. FDA will focus on Studies IMbrave150 and GO30140, as the safety profile of atezolizumab is well established. The pooled data will be used for an integrated assessment of the toxicity of the combination.

8.2.1 Safety Review Approach

The Applicant's Position:

The safety and tolerability assessment was based on the frequency of adverse events (AEs), serious adverse events (SAEs), fatal AEs, AEs leading to discontinuation, AEs leading to dose reduction or interruption, AEs of Special Interest (AESIs) (both for atezolizumab as well as for bevacizumab), and clinical laboratory assessments and vital sign measurements.

The FDA's Assessment:

FDA agrees with the strategy for the safety analysis.

8.2.2 Review of the Safety Database

Overall Exposure

Data:

Table 23 Safety Population, Size, and Denominators

Safety Database for the Study Drug[1] Individuals exposed to the study drug in this development program for the indication under review N=493			
Clinical Trial Groups	Atezo+Bev (n=493)	Sorafenib (n= 156)	Atezo Monotherapy (n=3178)
Controlled trials conducted for this indication[2]	329	156	
All other than controlled trials conducted for this indication[3]	164 (GO30140 Arm F: 60; GO30140 Arm A: 104)		93 (GO30140 Arm F: 58 PCD4980g HCC: 14 YO29233 HCC: 21)
Controlled trials conducted for other indications[4]			3178 (incl. also 14 HCC patients from PCD4980g)

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

Table 24 Extent of Study Drug Exposure

	Sorafenib HCC (N=156)	Atezo+Bev HCC (N=493) Atezo	Atezo+Bev HCC (N=493) Bev	Atezo Mono HCC (N=93)	Atezo Mono Multiple Indications (N=3178)
Number of Doses					
n	156	493	493	93	3178
Mean (SD)	215.1 (194.6)	10.8 (7.0)	10.1 (6.6)	8.0 (6.4)	9.9 (9.8)
Median	149.0	10.0	10.0	6.0	6.0
Min-Max	6-908	1-50	1-44	1-35	1-64
Treatment Duration (Months)					
n	156	493	493	93	3178
Mean (SD)	4.1 (3.5)	7.1 (5.0)	6.8 (4.9)	5.1 (4.7)	6.6 (7.5)
Median	2.8	6.9	6.4	3.5	3.5
Min-Max	0-16	0-34	0-34	0-24	0-53

Source: t_ex_SE_29AUG2019_40245, t_ex_H234_atezo_29AUG2019_40245P, t_ex_H2_bev_29AUG2019_40245P.

The Applicant's Position:

There are 493 patients in the safety database for the Atezo+Bev combination in HCC patients, comprising the patients from IMbrave150 and Arms F and A from GO30140. In addition, data from 93 HCC patients who received atezolizumab as monotherapy and from a total of 3178 patients treated with atezolizumab monotherapy in multiple indications (primarily NSCLC, UC, and RCC) are also included in the submission.

Overall, Atezo+Bev population had longer median treatment durations than those in the Sorafenib, Atezo (Mono) and the Atezo Mono (Multiple Indications) populations. Therefore, the incidence of safety events in the Atezo+Bev population should be evaluated in context of longer median duration of treatment compared with the other populations.

The FDA's Assessment:

In Study IMbrave150, median duration of exposure to atezolizumab was 7.4 months (range 0-16 months) and median duration of exposure to bevacizumab was 6.9 months (range 0-16). The median dose intensity for both products was 98%; the median number of atezolizumab doses was 11 (range 1-24) and the median number of bevacizumab doses was 10 (rage 1-23).
The median duration of exposure in the sorafenib arm was 2.8 months (range 0-16). The median dose intensity was 96%; 57% patients received less than 3 months of treatment (23% patients in the atezolizumab/bevacizumab arm received less than 3 months of treatment).

As summarized below and in Table 35, Table 36, and Figure 11, most AEs in the sorafenib arm had an earlier onset than AEs in the atezolizumab/bevacizumab arm. Furthermore, the incidences of all AEs except pruritus, pyrexia, and proteinuria were higher in the sorafenib arm for the first 3 months of treatment. After Month 3, the incidence of AEs dropped dramatically in both arms, but because patients receiving atezolizumab/bevacizumab tended to remain on study treatment longer than patients receiving sorafenib, the incidence of some AEs increased over time in the atezolizumab/bevacizumab arm when compared to the sorafenib arm; however with the exception of 2 preferred terms (PTs) (pruritus and bilirubin increase), all AEs were below the incidence observed in the first 3 months of treatment. In addition, as the number of patients in the sorafenib arm decreased, estimates of incidences may be inaccurate. This reviewer agrees with the Applicant that the incidence of safety events in the atezolizumab/bevacizumab arm should be evaluated in the context of the longer median duration of treatment in patients receiving atezolizumab/bevacizumab compared to sorafenib-treated patients.

Relevant characteristics of the safety population:

Data:

The demographic and baseline characteristics of the pooled Atezo+Bev safety evaluable population were similar to that of the IMbrave150 ITT population (see Section 8.1.2). The median age of patients was 62.0 years (range: 22–88 years). The majority of patients were male Asians. Overall, the characteristics were reflective of an advanced HCC population. Baseline

demographic characteristics were generally balanced between the Atezo+Bev and Sorafenib populations.

The median age of patients in the two Atezo monotherapy populations was 60.0 years (range: 23–85 years) (HCC) and 64.0 years (range: 20–92 years) (Multiple Indications), respectively. The majority of patients in Atezo Mono (HCC) were Asian males, whereas, the majority of patients in Atezo Mono (Multiple Indications) were White men. Except for 36 patients (1.2%) in Atezo Mono (Multiple Indications) with an ECOG score of 2, all patients in both groups had an ECOG score of 0 or 1.

The FDA's Assessment:

Only 7 of 336 (2%) patients randomized to the atezolizumab/bevacizumab arm and 9 of 165 (5%) patients randomized to the sorafenib arm in Study IMbrave150 did not initiate study treatment; therefore, there are no important differences in the demographic and disease characteristics between the ITT and the safety population. Similarly, in Study GO30140, all patients in Arm A and F1 received the assigned/randomized treatment with atezolizumab/bevacizumab and 58 of 59 (98%) patients randomized to Arm F2 received atezolizumab; therefore, there are no differences in the demographic and baseline characteristics between the ITT and safety populations.

Adequacy of the safety database:

The Applicant's Position:

The safety profile of atezolizumab is now established, with a total exposure of more than 16,800 patients in clinical trials and more than (b) (4) patients in the postmarketing setting. The size of the IMbrave150 and GO30140 safety database is considered adequate to support the benefit-risk assessment for the proposed indication in unresectable HCC, which is a serious, life-threatening condition. The juxtaposition with the atezolizumab monotherapy populations demonstrates the consistency of the safety profile of atezolizumab in combination with bevacizumab.

The FDA's Assessment:

FDA considers the size of the dataset adequate to characterize the safety of atezolizumab in combination with bevacizumab for the first line treatment of patients with advanced, unresectable or metastatic HCC.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues relating to data integrity or quality were identified for the studies included in this submission.

The FDA's Assessment:

FDA conducted an audit of the safety datasets. In the IMbrave150 and GO30140 safety datasets, verbatim terms for safety events were accurately coded using the MedDRA dictionary. All discrepancies between verbatim terms and the preferred terms from the dictionary were minor and related to typographical errors, misspellings, or variations in wording of the events. For example, “acne-like rash” was coded as “dermatitis acneiform”, “drug-induced hepatitis” was coded as “drug-induced liver injuries”, etc. Overall, the safety datasets for Study IMbrave150 were of excellent quality.

Categorization of Adverse Event

The Applicant’s Position:

For classification purposes in the studies with HCC patients, lower level terms were assigned by the Sponsor to the original terms entered on the CRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA 22.0) terminology for adverse events and diseases and the Roche INN (International Non-proprietary Name) Drug Terms and Procedures Dictionary for medications and treatments. AEs were graded by the investigator in accordance with the extended NCI CTCAE v4, and laboratory values were graded according to these criteria by the Sponsor based on the reported results. Treatment-emergent AEs were summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade, and treatment arm. Multiple occurrences of the same event were counted once at the maximum grade.

AESIs for Atezolizumab: For the purpose of analysis, a set of comprehensive definitions using Standardized MedDRA Queries (SMQ), High Level Terms (HLTs), and Sponsor-defined AE Grouped Terms (AEGTs), were used to identify and summarize AESIs from the AE clinical database by medical concept. The medical concepts include atezolizumab-associated identified risks, potential risks and class effects reported with other immune-checkpoint inhibitors.

AESIs for Bevacizumab: The impact of the Atezo+Bev combination on bevacizumab toxicities, described as AESIs for bevacizumab, were summarized by medical concepts using MedDRA-standardized SMQs, Sponsor-defined AEGTs and Preferred Terms. The complete list of medical concepts with the constituting SMQs, HLTs, and AEGTs from MedDRA v22.0 is provided in the dossier.

The FDA’s Assessment:
FDA agrees with the review strategy as described above.

Routine Clinical Tests

The Applicant’s Position:

The schedules of assessments for IMbrave150 is provided in Appendix 1 of the study protocol and for GO30140 they are provided in protocol Appendices 1 and 6. Adverse events were collected continuously throughout the study until 30 days after the last dose of study treatment or initiation of a new anti-cancer therapy (the latter condition applied only to IMbrave150). Thereafter, any SAEs or AESIs were reported for up to 90 days, and deaths and SAEs considered related to prior treatment with study drug were reported beyond the 90 day window.

At each visit, patients underwent a physical examination and the assessment of routine laboratory tests (hematology, serum chemistry, pregnancy testing), vital signs, PK sampling and ADA assessment, and ECOG performance status. ECGs were conducted when clinically indicated.

The FDA's Assessment:
Monitoring for safety in all studies submitted is adequate and consistent with the standard of care. The schedule of assessments for both protocols are included in the Appendices section of this review (Section 19.6).

8.2.4 Safety Results

Major Safety Results

The FDA's Assessment:
The majority of patients in each arm experienced at least one AE. Table 25 summarizes the major safety results.

Table 25 Study IMbrave150: Major safety results

	Atezo/bev (n: 329) N; (%)	Sorafenib (n: 165) N; (%)
N patients with ≥ 1 AE	323 (98)	154 (99)
N AEs	3058	1299
N Grade 3-4 AEs	198 (60)	91 (58)
AEs with fatal outcomes	15 (5)	9 (6)
N pts with ≥ 1 SAE	125 (38)	48 (31)
AEs leading to atezolizumab withdrawal	28 (9)	NA
AEs leading to bevacizumab withdrawal	48 (15)	NA
AEs leading to atezo/bev withdrawal	23 (7)	NA
AEs leading to sorafenib withdrawal	NA	16 (10)

The incidence of SAEs was slightly higher in the atezolizumab/bevacizumab group compared to the sorafenib group (38% vs. 31%); however, the increased incidence did not result in increased toxicity-related deaths (5% and 6% in the atezolizumab/bevacizumab and sorafenib arms respectively) or treatment withdrawal (7% vs. 10% in the atezolizumab/bevacizumab vs. sorafenib arms respectively). Table 26 summarizes the AEs by system/organ (SOC).

Table 26 Study IMbrave150: AEs by SOC

SOC	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All grades	Grades 3-4	All grades	Grades 3-4
Blood and lymphatic system disorders	75 (23)	18 (5)	28 (18)	7 (4)
Cardiac disorders	17 (5)	5 (2)	5 (3)	0

SOC	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All grades	Grades 3-4	All grades	Grades 3-4
Congenital, familial and genetic disorders	2 (1)	0	0	0
Ear and labyrinth disorders	8 (2)	1 (<1)	1 (<1)	0
Endocrine disorders	39 (12)	1 (<1)	5 (3)	0
Eye disorders	13 (4)	1 (<1)	3 (2)	0
Gastrointestinal disorders	193 (59)	48 (15)	118 (76)	27 (17)
General disorders and administration site conditions	166 (50)	14 (4)	77 (49)	12 (8)
Hepatobiliary disorders	35 (11)	17 (5)	23 (15)	10 (6)
Immune system disorders	4 (1)	2 (1)	0	0
Infections and infestations	100 (30)	23 (7)	28 (18)	5 (3)
Injury, poisoning and procedural complications	46 (14)	13 (4)	6 (4)	2 (1)
Investigations	150 (48)	61 (19)	68 (44)	25 (16)
Metabolism and nutrition disorders	129 (39)	30 (9)	66 (42)	21 (13)
Musculoskeletal and connective tissue disorders	100 (30)	7 (2)	34 (22)	5 (3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (2)	1 (<1)	4 (3)	1 (1)
Nervous system disorders	68 (21)	8 (2)	25 (16)	5 (3)
Psychiatric disorders	42 (13)	5 (2)	12 (8)	0
Renal and urinary disorders	86 (26)	14 (4)	20 (13)	6 (4)
Reproductive system and breast disorders	16 (5)	1 (<1)	3 (2)	0
Respiratory, thoracic and mediastinal disorders	130 (40)	13 (4)	47 (30)	7 (4)
Skin and subcutaneous tissue disorders	123 (37)	2 (1)	107 (69)	21 (13)
Surgical and medical procedures	2 (1)	0	1 (<1)	0
Vascular disorders	108 (33)	53 (16)	42 (27)	21 (13)

A higher incidence (≥ 5% difference between arms) of AEs in the blood and lymphatic system disorders, endocrine, infections, nervous system, psychiatric, renal and urinary, respiratory, vascular disorders, and injury, poisoning and procedural complications SOCs was observed in the atezolizumab/bevacizumab arm compared to the sorafenib arm. In the blood and lymphatic system disorders SOC, although leukopenia (6% and 3% in the atezolizumab/bevacizumab and sorafenib arms respectively) and thrombocytopenia (8% and 5% in the atezolizumab/bevacizumab and sorafenib arms respectively) were more frequent with the combination, the increased incidence cannot be fully explained by an increased incidence in any particular preferred term (PT). Similarly, no particular event was more frequently reported in

the atezolizumab/bevacizumab arm nervous system disorders and psychiatric disorders SOCs; the increased incidence in these SOCs appears to be due to multiple unrelated events. The increased incidence of events in the injury, poisoning and procedural complications SOC is related to an increased incidence in infusion-related reactions (11% in the combination arms). All other SOCs are further explored in the significant adverse events and adverse events of special interest subsections.

An increased incidence (≥ 5% difference between arms) of AEs in the gastrointestinal and skin and subcutaneous tissue disorder SOCs was observed in the sorafenib arm. These differences are further explored in Table 27 and Table 28 and in subsequent sections of this review. Table 27 summarizes AEs by HLT.

Table 27 Study IMbrave150: AEs by HLT (incidence ≥ 5%)

HLT	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Liver function analyses	100 (30)	44 (13)	40 (26)	17 (11)
Vascular hypertensive disorders	98 (30)	50 (15)	39 (25)	20 (13)
Asthenic conditions	94 (29)	8 (2)	55 (35)	10 (6)
Urinary abnormalities	72 (22)	12 (4)	11 (7)	1 (1)
Pruritus	67 (20)	0	15 (10)	0
Diarrhea (excl infective)	62 (19)	6 (2)	77 (49)	8 (5)
Appetite disorders	58 (18)	4 (1)	38 (24)	6 (4)
Febrile disorders	59 (18)	4 (1)	15 (10)	2 (1)
Gastrointestinal and abdominal pains	54 (16)	5 (2)	32 (21)	5 (3)
Nausea and vomiting symptoms	54 (16)	3 (1)	29 (19)	2 (1)
Rashes, eruptions and exanthems	48 (15)	2 (1)	32 (21)	4 (3)
Musculoskeletal and connective tissue pain and discomfort	49 (15)	2 (1)	16 (10)	3 (2)
Gastrointestinal atonic and hypomotility disorders	47 (14)	1 (<1)	24 (15)	0
Coughing and associated symptoms	47 (14)	0 (<1)	20 (13)	1 (1)
Upper resp. tract signs/symptoms	45 (14)	1 (<1)	18 (12)	0
Physical examination procedures and organ system status	40 (12)	0	16 (10)	2 (1)
Platelet analyses	35 (11)	11 (3)	18 (12)	2 (1)
Non-site specific procedural complications	37 (11)	8 (2)	1 (1)	0
Breathing abnormalities	33 (10)	4 (1)	9 (6)	3 (2)
Upper respiratory tract infections	33 (10)	1 (<1)	10 (6)	1 (1)
Joint related signs and symptoms	33 (10)	0	8 (8)	1 (1)
Nasal disorders	34 (10)	0	7 (4)	1 (1)

HLT	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Edema	33 (10)	0	7 (4)	0
Anemias	30 (9)	9 (3)	15 (10)	4 (3)
Protein metabolism disorders	29 (9)	2 (1)	13 (8)	0
Disturbances in sleep	28 (9)	1 (<1)	11 (7)	0
Thyroid hypofunction disorders	29 (9)	0	3 (2)	0
Tissue enzyme analyses	25 (8)	4 (1)	13 (8)	0
Headaches	27 (8)	0	11 (7)	1 (1)
White blood cell analyses	26 (8)	9 (3)	11 (7)	3 (2)
Flatulence, bloating and distension	26 (8)	1 (<1)	9 (6)	2 (1)
Thrombocytopenias	27 (8)	6 (2)	8 (5)	3 (2)
Peritoneal and retroperitoneal disorders	23 (7)	6 (2)	9 (6)	2 (1)
Stomatitis and ulceration	24 (7)	3 (1)	10 (6)	1 (1)
Potassium imbalance	19 (6)	6 (2)	14 (9)	4 (3)
Sodium imbalance	19 (5)	9 (3)	9 (6)	3 (2)
Leukopenias	19 (6)	3 (1)	4 (3)	1 (1)
Dermal and epidermal conditions	16 (5)	0	8 (5)	2 (1)
Muscle pains	17 (5)	0	5 (3)	0
Neutropenias	17 (5)	1 (<1)	4 (3)	0
Non-site specific gastrointestinal hemorrhages	17 (5)	8 (2)	4 (3)	4 (3)
Urinary tract infections	17 (5)	2 (1)	3 (2)	0
Phosphorus metabolism disorders	8 (2)	2 (1)	11 (7)	6 (4)
Dermatitis ascribed to specific agent	3 (1)	0	76 (49)	15 (10)
Alopecias	4 (4)	0	22 (14)	0

Table 28 summarizes the preferred terms (PTs) with an incidence of at least 3%; lab-specific terms (i.e., neutrophils decreased) were not included as these will be analyzed in the lab subsection. Clinical terms related to these lab abnormalities (i.e., neutropenia) are included in the table.

Table 28 Study IMbrave150: AEs by PT (incidence ≥ 3%)

PT	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Hypertension	98 (30)	50 (15)	38 (24)	19 (12)
PPED	3 (1)	0	75 (48)	13 (8)
Fatigue/asthenia	67 (20)	24 (7)	29 (19)	11 (7)
Proteinuria	66 (20)	10 (3)	11 (7)	1 (1)

PT	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Diarrhea	62 (19)	6 (2)	77 (49)	8 (5)
Pruritus	64 (19)	0	15 (10)	0
Decreased appetite	58 (18)	4 (1)	38 (24)	6 (4)
Pyrexia	59 (18)	4 (1)	15 (10)	2 (1)
Constipation	44 (13)	0	22 (14)	0
Alopecia	4 (1)	0	22 (14)	0
Abdominal pain	40 (12)	4 (1)	27 (17)	4 (3)
Rash	41 (12)	0	27 (17)	4 (3)
Nausea	40 (12)	1 (1)	25 (16)	1 (1)
Cough	39 (12)	0	15 (10)	1 (1)
Weight decreased	37 (11)	0	15 (10)	1 (1)
Infusion related reaction	37 (11)	8 (2)	0	0
Hypophosphatemia	7 (2)	2 (1)	11 (7)	6 (4)
Vomiting	33 (10)	2 (1)	13 (8)	1 (1)
Arthralgia	32 (10)	0	8 (5)	1 (1)
Epistaxis	34 (10)	0	7 (4)	1 (1)
Hypokalemia	9 (3)	2 (1)	10 (6)	4 (3)
Anemia	30 (9)	9 (3)	15 (10)	4 (3)
Dysphonia	28 (9)	0	11 (7)	0
Insomnia	28 (9)	1 (<1)	11 (7)	0
Dyspnea	29 (9)	4 (1)	7 (4)	3 (2)
Edema peripheral	29 (9)	0	5 (3)	0
Hypothyroidism	29 (9)	0	3 (2)	0
Headache	27 (8)	0	11 (7)	1 (1)
Thrombocytopenia	27 (8)	6 (2)	8 (5)	3 (2)
Hypoalbuminemia	24 (7)	1 (<1)	12 (8)	0
Ascites	23 (7)	6 (2)	9 (6)	2 (1)
Abdominal distension	23 (7)	1 (<1)	5 (3)	2 (1)
Musculoskeletal pain	24 (7)	1 (<1)	3 (2)	0
Hyponatremia	19 (6)	9 (3)	9 (6)	3 (2)
Stomatitis	19 (6)	3 (1)	7 (4)	1 (1)
Back pain	19 (6)	1 (1)	5 (3)	1 (1)
Leukopenia	19 (6)	3 (1)	4 (3)	0
Abdominal pain upper	15 (5)	1 (<1)	6 (4)	1 (1)
Hyperglycemia	16 (5)	2 (1)	4 (3)	2 (1)
Myalgia	17 (5)	0	5 (3)	0
Nasopharyngitis	15 (5)	0	4 (3)	0
Neutropenia	17 (5)	1 (<1)	4 (3)	0
Upper respiratory tract infection	15 (5)	1 (<1)	2 (1)	0
Urinary tract infection	15 (5)	2 (1)	2 (1)	0
Hyperthyroidism	15 (5)	1 (<1)	0	0

* composite term for PTs fatigue and asthenia

Deaths

Data:

The leading cause of death was progressive disease in all populations (Table 29). In each group, the majority of deaths occurred more than 30 days after the last dose of study drug.

The incidence of deaths due to an AE was comparable between the Sorafenib, Atezo+Bev and Atezo Mono (Multiple Indications) populations (5.8%, 4.5% and 3.8%) but it was numerically lower (2.2%) in the Atezo Mono (HCC) population.

Table 29 Deaths and Causes of Death

	Sorafenib HCC (N=156)	Atezo+Bev HCC (N=493)	Atezo Mono HCC (N=93)	Atezo Mono Multiple Indications (N=3178)
All Death				
n	64	156	38	1898
<= 30 days after last dose	14 (21.9%)	22 (14.1%)	10 (26.3%)	352 (18.5%)
> 30 days after last dose	50 (78.1%)	134 (85.9%)	25 (65.8%)	1546 (81.5%)
Unknown time from last dose	0	0	3 (7.9%)	0
Primary cause of death				
n	64 (41.0%)	156 (31.6%)	38 (40.9%)	1898 (59.7%)
ADVERSE EVENT	9 (5.8%)	22 (4.5%)	2 (2.2%)	120 (3.8%)
PROGRESSIVE DISEASE	51 (32.7%)	127 (25.8%)	33 (35.5%)	1475 (46.4%)
OTHER	4 (2.6%)	7 (1.4%)	3 (3.2%)	303 (9.5%)

Source: t_dd_SE_29AUG2019_40245P

The Applicant's Position:

The types of Grade 5 AEs were distributed across several SOCs, and the incidence was not driven by events in any specific SOC. In the Atezo+Bev population, Grade 5 AEs had a numerically higher incidence of gastrointestinal bleeding events when compared with the Sorafenib and Atezo Mono (Multiple Indications) populations. However, it is important to note that bleeding (including fatal events) is a known adverse reaction for bevacizumab, and upper gastrointestinal bleeding is a common and life threatening complication in patients with HCC which can further confound this difference.

The FDA's Assessment:

As per the safety database of Study IMbrave150, 15 (5%) and 9 (6%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, had fatal AEs. The leading causes of death were hemorrhage (4 gastrointestinal hemorrhages and one subarachnoid hemorrhage in the atezolizumab/bevacizumab arm and one peritoneal hemorrhage in the sorafenib arm) and infection (4 in the atezolizumab/bevacizumab arm and one in the sorafenib arm). Table 30 summarizes fatal AEs in Study IMbrave150.

Table 30 Study IMbrave150: Fatal AEs

SOC	HLT	PT	Atezo/bev (N: 329)	Sorafenib (N: 156)
Cardiac	Heart failures	Cardiac failure	0	1
	Ventricular arrhythmias and cardiac arrest	Cardiac arrest	1	1
Gastrointestinal	Gastric and esophageal hemorrhages	Esophageal varices hemorrhage	1	0
	Gastric ulcers and perforation	Gastric ulcer perforation	1	0
	Non-site specific gastro intestinal haemorrhages	Gastrointestinal hemorrhage	3	0
	Peritoneal and retro peritoneal hemorrhages	Peritoneal hemorrhage	0	1
General disorders	Death and sudden death	Death	0	2
	General signs and symptoms	General physical health deterioration	0	1
		Multiple organ dysfunction syndrome	1	0
Hepatobiliary disorders	Hepatic enzymes and function abnormalities	Hepatic function abnormal	1	0
	Hepatic fibrosis and cirrhosis	Hepatic cirrhosis	0	2
	Hepatocellular damage	Liver injury	1	0
Infections and infestations	Hepatitis viral	Hepatitis E	0	1
	Infections	Empyema	1	0
	Lung infections	Pneumonia	2	0
	Sepsis	Sepsis	1	0
Nervous system	CNS hemorrhages	Subarachnoid hemorrhage	1	0
Respiratory	Breathing abnormalities	Respiratory distress	1	0

FDA agrees that the observed Grade 5 AEs are either commonly associated with unresectable or metastatic HCC or are consistent with the known toxicity profile of the investigational treatment received.

Serious Adverse Events

Data:

Overall, the incidence of SAEs was numerically lower in the Sorafenib population (30.8%) compared with the Atezo+Bev and Atezo Mono (Multiple Indications) populations (37.7% and 41.2%). The treatment-related SAEs had a comparable incidence between the Sorafenib (15.4%) and Atezo+Bev (17.8%) populations and the incidence of atezolizumab-related SAEs was also comparable between the Atezo+Bev and Atezo Mono (Multiple Indications) populations (13.2% and 11.1%). The most common SAEs in the Sorafenib population were gastrointestinal hemorrhage and hepatic encephalopathy (1.9% each), whereas pyrexia (2.6%), esophageal varices hemorrhage (2.0%), and gastrointestinal hemorrhage (1.8%) were the most common SAEs in the Atezo+Bev population. Pneumonia was the most common SAE in the Atezo Mono (Multiple Indications) population (3.1%). Except pneumonia, no SAEs showed a $\geq$ 2% difference between the populations.

The Applicant's Position:

The nature and incidence of serious adverse events observed with the Atezo+Bev combination in the HCC population was generally consistent with the known safety profile of the individual study drugs and/or the underlying disease.

The FDA's Assessment:

The code of federal regulations (Section 312.32) defines a serious adverse event (SAE) as an adverse event that in the view of either the investigator or sponsor results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Although 39 (12%) and 9 (6%) patients in the IMbrave150 study experienced "Grade 1-2" SAEs, some of these events (i.e., chronic myeloid leukemia, oropharyngeal neoplasm) are serious despite the low assigned severity grade. Some SAEs were erroneously graded (i.e., there is no Grade 1-2 sepsis or pulmonary embolism according to CTCAE).

A total of 114 (35%) and 44 (28%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, were hospitalized due to an SAE, and 24 SAEs resulted in 15 (5%) and 9 (6%) patients deaths in the atezolizumab/bevacizumab and sorafenib arms respectively. Overall the most frequent SAEs were gastrointestinal disorders (15% vs. 12% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively). When grouping terms for hemorrhagic events (PTs included bleeding varicose vein, epistaxis, gastric ulcer hemorrhage,

gastric varices hemorrhage, gastrointestinal hemorrhage, hematemesis, hemoptysis, hemorrhage, large intestinal hemorrhage, melena, esophageal hemorrhage, esophageal varices hemorrhage, peritoneal hemorrhage, pulmonary hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage), 28 (9%) and 12 (8%) patients in the atezolizumab/bevacizumab and sorafenib arms respectively had hemorrhages considered SAEs. SAEs of infections were more frequent in the atezolizumab/bevacizumab arm (7%) vs. the sorafenib arm (2%), with the most common infections in the lower respiratory tract and lung infections HLT (2% and 1% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively) and sepsis, bacteremia, viremia and fungemia HLT (7% vs 0% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively).

The nature and incidence of SAEs observed in both arms of Study IMbrave150 are generally consistent with the known safety profile of the individual study drugs or the underlying disease.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Per the IMbrave150 and GO30140 study protocols, patients who transiently or permanently discontinued either component of the Atezo+Bev combination could continue single agent treatment with the other component until disease progression, if the investigator considered this to be of clinical benefit to the patient.

The proportion of patients who discontinued any study treatment due to an AE was comparable between the Sorafenib and Atezo+Bev populations (10.3% and 15.2%) (withdrawal of any component of the Atezo+Bev combination was considered).

In addition, a comparable proportion of patients (8.5% and 7.1 %) withdrew from atezolizumab treatment (regardless of bevacizumab withdrawal) due to an AE in the Atezo+Bev and Atezo Mono (Multiple Indications) populations. The most common AE leading to any study treatment discontinuation was esophageal varices hemorrhage (6 patients, 1.2%) in the Atezo+Bev population. All other AEs leading to any study treatment discontinuation occurred in <1% of patients in the Sorafenib, Atezo+Bev, and Atezo Mono (Multiple Indications) populations.

The Applicant's Position:

Overall, the Atezo+Bev combination therapy in patients with HCC was generally well-tolerated with manageable toxicities.

The FDA's Assessment:

In Study IMbrave150, atezolizumab treatment was permanently discontinued due to toxicity in 28 (9%) patients. Most of the AEs leading to discontinuation of atezolizumab were of Grade 3-4 severity (20 patients). Bevacizumab was discontinued due to toxicity in 48 (15%) patients. Most of these patients had Grade 3-4 AEs (30 patients); atezolizumab and bevacizumab were discontinued due to fatal AEs in 3 patients (gastric ulcer perforation, gastrointestinal hemorrhage, and subarachnoid hemorrhage).

Sorafenib was permanently discontinued due to toxicity in 16 (10%) patients; all AEs leading to

discontinuation of sorafenib were Grade 3-4 (one patient had a "Grade 1" hepatic encephalopathy, but this is a coding mistake; hepatic encephalopathy is a manifestation of Grade 3 hepatic failure) with the exception of a fatal event of cirrhosis. The most frequent AEs leading to discontinuation of sorafenib were hemorrhage (24 events, only one in the sorafenib arm) and liver disorders (including hepatic encephalopathy, liver function-related laboratory abnormalities, cirrhosis and ascites). Table 66 in the Appendices section of this review summarizes the reasons for treatment discontinuation for each study drug. In contrast to sorafenib, dose reductions were not used to manage atezolizumab/bevacizumab toxicities. More patients in the combination arm required treatment withdrawal; however (see below analysis of drug interruptions/dose modifications), 61% patients in the sorafenib arm required dose reductions and/or interruptions, supporting the Applicant's statement that the atezolizumab/bevacizumab combination was generally better tolerated.

Dose Interruption/Reduction Due to Adverse Effects

Data:

No dose modifications were allowed for the patients treated with atezolizumab and/or bevacizumab.

Overall, the proportion of patients who reported AEs leading to dose modification or drug interruption of any study treatment was higher in the Sorafenib population (60.9%) compared with the Atezo+Bev and the Atezo Mono (Multiple Indications) populations (45.0% and 27.8%).

Palmar-Plantar Erythrodysesthesia syndrome, rash, asthenia, ascites, blood bilirubin increased, fatigue as well as gastrointestinal-related AEs such as diarrhea, abdominal pain, vomiting, nausea and decreased appetite led to more frequent (≥ 2% difference) dose modification/ interruptions in the Sorafenib population compared with Atezo+Bev. Proteinuria led to more frequent (≥ 2% difference) dose modification/interruptions in the Atezo+Bev population compared with the Sorafenib population (9.1% vs. 1.3%). Proteinuria is a known ADR for bevacizumab.

The Applicant's Position:

Overall, the Atezo+Bev combination in HCC was generally well-tolerated with manageable toxicities. The two components of the Atezo and Bev combination therapy likely have contributed to the higher incidence of dose modifications/interruptions in the Atezo+Bev population compared to Atezo monotherapy population.

The FDA's Assessment:

As stated above, no dose reductions of atezolizumab or bevacizumab were allowed in Study IMbrave150. A total of 163 patients (49%) in the atezolizumab/bevacizumab arm required interruption of one or more doses of either biologic for hypertension, proteinuria (bevacizumab toxicities) and liver function parameters (mostly atezolizumab interruptions). A total of 95 (61%) patients in the IMbrave150 study required dose reductions/interruptions of sorafenib to manage toxicities. The main toxicities requiring dose reductions/interruptions of

sorafenib were PPES (17%) and diarrhea (11%); other frequent toxicities leading to dose reduction or interruption of sorafenib were liver function lab abnormalities, other dermatological toxicities, and fatigue/asthenia.

Overall, the toxicities leading to dose reduction or interruption in Study IMbrave 150 are consistent with the established safety profiles of the study drugs and within the expected frequency for their individual safety profiles and condition of use.

Significant Adverse Events

Data:

The overall incidence of Grade 3–4 AEs was comparable between the Sorafenib and Atezo+Bev populations (55.1% vs. 53.3%), but it was numerically lower in the Atezo Mono (Multiple Indications) population (46.6%) (Table 31).

Hypertension was the most frequently reported Grade 3–4 AE in the Sorafenib and Atezo+Bev populations (12.2% vs 13.8%) and anemia was the most common Grade 3–4 AE in the Atezo Mono (Multiple Indications) population (5.0%).

The Grade 3–4 AEs of hypertension, proteinuria, platelet count decreased, blood bilirubin increased, and AST increased were reported in a higher proportion of patients in the Atezo+Bev population (≥2% difference) compared with the Atezo Mono (Multiple indications) population.

All other Grade 3–4 AEs had comparable incidences (<2% difference) in the Sorafenib, Atezo+Bev, and Atezo Mono (Multiple Indications) populations

Table 31 Adverse Events with NCI CTCAE Grade 3 – 4 Reported in ≥ 2% of Patients in Any Treatment Group by System Organ Class and Preferred Term

Adverse Events with NCI CTCAE Grade 3-4 in Any Treatment Group by Preferred Term, with an Incidence Rate of at Least 2%
Safety Evaluable Patients
Protocols: YO40245, GO30140

MedDRA Preferred Term	Sorafenib HCC (N=156)	Atezo+Bev HCC (N=493)	Atezo Mono HCC (N=93)	Atezo Mono Multiple Indications (N=3178)
ANAEMIA	4 (2.6%)	13 (2.6%)	3 (3.2%)	160 (5.0%)
DYSPNOEA	3 (1.9%)	9 (1.8%)	1 (1.1%)	117 (3.7%)
HYPERTENSION	19 (12.2%)	68 (13.8%)	1 (1.1%)	42 (1.3%)
FATIGUE	5 (3.2%)	9 (1.8%)	1 (1.1%)	109 (3.4%)
HYPONATRAEMIA	3 (1.9%)	15 (3.0%)	3 (3.2%)	98 (3.1%)
ASPARTATE AMINOTRANSFERASE INCREASED	8 (5.1%)	30 (6.1%)	6 (6.5%)	46 (1.4%)
PNEUMONIA	1 (0.6%)	6 (1.2%)	0	83 (2.6%)
URINARY TRACT INFECTION	0	3 (0.6%)	0	72 (2.3%)
ASTHENIA	4 (2.6%)	2 (0.4%)	0	63 (2.0%)
ALANINE AMINOTRANSFERASE INCREASED	2 (1.3%)	15 (3.0%)	1 (1.1%)	46 (1.4%)
DIARRHOEA	8 (5.1%)	10 (2.0%)	0	36 (1.1%)
BLOOD BILIRUBIN INCREASED	10 (6.4%)	16 (3.2%)	4 (4.3%)	17 (0.5%)
ABDOMINAL PAIN	4 (2.6%)	8 (1.6%)	0	34 (1.1%)
DECREASED APPETITE	6 (3.8%)	5 (1.0%)	0	35 (1.1%)
HYPOKALAEMIA	4 (2.6%)	3 (0.6%)	1 (1.1%)	32 (1.0%)
HYPOPHOSPHATAEMIA	6 (3.8%)	2 (0.4%)	0	22 (0.7%)
PROTEINURIA	1 (0.6%)	20 (4.1%)	0	6 (0.2%)
PLATELET COUNT DECREASED	2 (1.3%)	16 (3.2%)	0	6 (0.2%)
LYMPHOCYTE COUNT DECREASED	0	4 (0.8%)	2 (2.2%)	17 (0.5%)
RASH	4 (2.6%)	0	0	14 (0.4%)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	13 (8.3%)	0	0	0
HEPATIC FUNCTION ABNORMAL	2 (1.3%)	3 (0.6%)	2 (2.2%)	1 (<0.1%)
BILIARY TRACT INFECTION	0	0	2 (2.2%)	1 (<0.1%)

Source: t_ae_inc_pt_SE_grd34_2per_29AUG2019_40245P

The Applicant's Position:

Overall, the Grade 3-4 AEs observed in the Atezo+Bev population are consistent with the known safety profile of the individual study drugs and/or the underlying disease.

The FDA's Assessment:

Table 32 summarizes the most commonly observed severe (Grade 3-4) AEs in Study IMbrave150.

Table 32 IMbrave150: Grade 3-4 AEs (incidence ≥ 2%)

PT	Atezo/bev (n: 329) N; (%)	Sorafenib (n: 156) N; (%)
Hypertension	50 (15)	19 (12)
ALT/AST increased[a]	28 (9)	8 (5)
PPES	0	13 (8)
Fatigue/asthenia[b]	8 (2)	9 (6)
Blood bilirubin increased	8 (2)	10 (6)
Diarrhea	6 (2)	8 (5)
Decreased appetite	4 (1)	6 (4)
Hypophosphatemia	2 (1)	6 (4)
Anemia	9 (3)	4 (3)
Hyponatremia	9 (3)	3 (2)

PT	Atezo/bev (n: 329) N; (%)	Sorafenib (n: 156) N; (%)
Platelet count decreased	11 (3)	2 (1)
Proteinuria	10 (3)	1 (1)
Abdominal pain	4 (1)	4 (3)
Hypokalemia	2 (1)	4 (3)
Rash[c]	2 (1)	5 (3)
Infusion related reaction	8 (2)	0

[a, b]composite terms; [c]composite term including the PTs rash, rash erythematous, rash maculo-papular, rash pruritic, and drug eruption.

The nature and incidence of Grade 3-4 AEs are consistent with the known safety profiles of each study drug. Patients treated with atezolizumab/bevacizumab experienced a higher incidence of hypertension and increased liver function tests (LFTs), and as expected, infusion-related reactions were observed only in this arm. Patients treated with sorafenib experienced higher incidences of diarrhea and increased bilirubin; as expected, PPES was observed only in this arm.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

(b) (4)

Given the incidence of AEs observed in the HCC studies, a 10% cutoff is applied to highlight differences in adverse reactions between the two treatment arms in IMbrave150.

Overall, the most common treatment-emergent AEs (≥ 10%) observed in the Atezo+Bev arm are consistent with the known ADRs for atezolizumab or bevacizumab and the underlying disease, with the exception of infusion related reaction. An increased incidence of infusion-related reactions (IRRs) was observed in the Atezo+Bev population; however the clinical impact of these IRRs is considered very limited based on the following evidence: the majority of IRRs were of Grade 1–2 intensity, were non-serious, occurred in the first two cycles, resolved within a day, and did not recur in subsequent cycles; only 2 patients discontinued treatment due to IRRs, and most continued study treatment without drug interruption, demonstrating that IRRs were manageable.

Table 33 Adverse Reactions Occurring in ≥10% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Adverse Reaction	TECENTRIQ in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Vascular Disorders				
Hypertension	29.8	15.2	24.4	12.2

Adverse Reaction	TECENTRIQ in combination with bevacizumab (n = 329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
General Disorders and Administration Site Conditions				
Fatigue	20.4	2.4	18.6	3.2
Pyrexia	17.9	0	9.6	0
Renal and Urinary Disorders				
Proteinuria	20.1	3	7.1	<1
Investigations				
Aspartate Aminotransferase Increased	19.5	7.0	16.7	5.1
Alanine Aminotransferase Increased	14	3.6	9	1.3
Blood Bilirubin Increased	13.1	2.4	14.1	6.4
Weight Decreased	11.2	0	9.6	0
Platelet Count Decreased	10.6	3.3	11.5	1.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	19.5	0	9.6	0
Rash	12.5	0	17.3	2.6
Gastrointestinal Disorders				
Diarrhoea	18.8	1.8	49.4	5.1
Constipation	13.4	0	14.1	0
Abdominal Pain	12.2	0	17.3	0
Nausea	12.2	0	16	0
Vomiting	10	0	8.3	0
Metabolism and Nutrition Disorders				
Decreased Appetite	17.6	1.2	24.4	3.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	11.9	0	9.6	0
Epistaxis	10.3	0	4.5	0
Injury, Poisoning and Procedural Complications				
Infusion Related Reaction	11.2	2.4	0	0

[1] Graded per NCI CTCAE v4.0

The Applicant's Position:

As no clinically relevant differences between Atezo+Bev treatment in HCC patients (from IMbrave150 and GO30140 [Arms A and F1]) were noted in comparison to the adverse reactions for atezolizumab monotherapy described in the Warnings and Precautions section, no update was made to this section of the USPI.

The FDA's Assessment:

Of the most common AEs observed in Study IMbrave150 (FDA's Table 28 and Applicant's Table 33), AEs of special interest for atezolizumab and bevacizumab (hypertension, proteinuria, hemorrhages, autoimmune AEs, etc.), will be analyzed in the subsection of this review dedicated to these events. This section will focus on the AEs not considered to be AEs of special interest for atezolizumab/bevacizumab and those related to sorafenib administration. Table 34 summarizes the AEs with a ≥ 5% difference in incidence between arms.

Table 34 IMbrave150: AEs with ≥ 5% difference between arms.

PT	**Atezo/bev (n: 329) N; (%)**		**Sorafenib (n: 156) N; (%)**	
	All grades	**Grade 3-4**	**All grades**	**Grades 3-4**
Proteinuria	66 (20)	10 (3)	11 (7)	1 (1)
Infusion related reaction	37 (11)	8 (2)	0	0
Pruritus	64 (19)	0	15 (10)	0
Pyrexia	59 (18)	4 (1)	15 (10)	2 (1)
Hypothyroidism	29 (9)	0	3 (2)	0
Epistaxis	34 (10)	0	7 (4)	1 (1)
Edema peripheral	29 (9)	0	5 (3)	0
Hypertension	98 (30)	50 (15)	38 (24)	19 (12)
Musculoskeletal pain	24 (7)	1 (<1)	3 (2)	0
ALT increased	46 (14)	12 (4)	14 (9)	2 (1)
Abdominal pain	40 (12)	4 (1)	27 (17)	4 (3)
Decreased appetite	58 (18)	4 (1)	38 (24)	6 (4)
Fatigue/asthenia*	86 (26)	8 (2)	50 (32)	9 (6)
Alopecia	4 (1)	0	22 (14)	0
Diarrhea	62 (19)	6 (2)	77 (49)	8 (5)
PPES	3 (1)	0	75 (48)	13 (8)

* composite term

Infusion-related reactions (IRRs) in the IMbrave150 study were observed in 36 (11%) patients; 8 patients (2%) experienced Grade 3 events. The Applicant flagged IRRs in the dataset (CQ10NAM column). The following two additional TEAEs were appropriately not flagged by the Applicant as an IRR:

- A 73 year old man experienced an anaphylactic reaction after administration of a CT scan contrast agent 10 days after the Cycle 4 administration of atezolizumab/bevacizumab.
- A 34-year old man experienced a local reaction at the site of atezolizumab/bevacizumab

infusion.

Grade 4 cytokine release syndrome (CRS) was reported in a 43 year old man following receipt of atezolizumab and bevacizumab (Cycle 1 Day 1) . On Study Day 11, the patient developed fever and a rash. Despite treatment with paracetamol, fever was persistent and the patient was hospitalized on Day 13. Blood cultures were negative. During hospitalization he became hyponatremic, hypotensive, and developed severe metabolic acidosis and status epilepticus. He was transferred to the intensive care unit on Study Day 15. Dengue duo test, malaria film, urine, CSF and blood cultures, and viral tests were negative. He was diagnosed with non-infective meningoencephalitis and received treatment with prednisolone, mometasone, clobetasol, methylprednisolone, immunoglobulin, meropenem, vancomycin, acyclovir, clarithromycin, tocilizumab, and multiple supportive care medications. Following treatment, his condition improved and the patient was discharged from the hospital on Study Day 32. Treatment with atezolizumab/bevacizumab was discontinued and the patient died of progressive disease on Day 312.

Reviewer comment: Although the timing of this CRS event in relation to atezolizumab/bevacizumab administration is atypical, based on biological plausibility and the absence of any alternative explanation (particularly infection), this reviewer agrees that the event of CRS (or alternatively, systemic immune activation) is likely related to atezolizumab.

When analyzing events that occurred during infusion of atezolizumab, 28 (9%) patients experienced IRRs (23 patients), hypertension (2 patients), back pain, hypersensitivity, hypotension, pruritus, pyrexia, syncope, and vomiting (one event each). If one considers these events as related to the infusion (premedication and situational factors may confound the analysis), 4 additional patients had an event of IRR (increasing the total number of patients with IRR to 40 [12%] patients). Additional analyses of events occurring within 24 hours of atezolizumab/bevacizumab administration were consistent with the Applicant's analyses. In a pooled analysis of 2616 patients with various cancers who received atezolizumab as a single agent, IRRs occurred in 1.3% of patients, including Grade 3 (0.2%) (Tecentriq USPI); similar incidences were observed across pooled studies for the atezolizumab/bevacizumab combination. It is unclear why the IMbrave patient population experienced an increased incidence of IRRs (12%) compared to the incidences described in product labeling for atezolizumab alone (1.3%) and in the pooled study population for the combination.

Bevacizumab was administered after atezolizumab in Study IMbrave150. Fourteen (4%) patients experienced AEs while bevacizumab was being infused, including 9 (3%) patients with IRRs (2 patients had Grade 3 IRRs), 3 patients with Grade 3 hypertension, and one patient each with pyrexia and headache. The incidence of bevacizumab-related IRR is consistent with the historical experience with bevacizumab and information in the bevacizumab USPI.

The incidence of pruritus in IMbrave150 was 19% and 10% in the atezolizumab/bevacizumab and sorafenib arms, respectively. These incidences are consistent with the established incidence of pruritus with atezolizumab monotherapy (13-18%) and sorafenib (10-27%).

The incidence of pyrexia in IMbrave150 was 18% and 10% in the atezolizumab/bevacizumab and sorafenib arms, respectively; 4 patients in the atezolizumab/bevacizumab arm had pyrexia during or within 24 hour hours of the atezolizumab or bevacizumab infusions. These incidences are consistent with the known incidence of pyrexia with atezolizumab monotherapy (14-21%) and sorafenib (11%).

The incidence of peripheral edema in IMbrave150 was 9% and 3% in the atezolizumab/bevacizumab and sorafenib arms, respectively. When grouping all edema terms (scrotal, orbital, peripheral, edema, edema generalizes, and face edema), incidences were 10% and 4% in the atezolizumab/bevacizumab and sorafenib arms respectively. These incidences are consistent with the known incidence of peripheral edema with atezolizumab monotherapy (15-18%) and in the HCC population, where edema and ascites are common signs.

The incidence of musculoskeletal pain in IMbrave150 was 7% and 2% in the atezolizumab/bevacizumab and sorafenib arms, respectively. When grouping the PTs "musculoskeletal pain, myalgias, and chest musculoskeletal pain", incidences are 12% and 6% in the atezolizumab/bevacizumab and sorafenib arms, respectively. These incidences are consistent with the known incidence of musculoskeletal pain with atezolizumab monotherapy (20%), bevacizumab monotherapy (20%), and sorafenib (15% patients had pain in extremities and it is listed as "common" in the post-marketing section of the USPI).

The incidence of abdominal pain in IMbrave150 was 12% and 17% in the atezolizumab/bevacizumab and sorafenib arms, respectively. When grouping the PTs "abdominal pain, abdominal pain upper, and abdominal pain lower", incidences were 16% and 21% in the atezolizumab/bevacizumab and sorafenib arms, respectively. These incidences are consistent with the known incidence of abdominal pain with atezolizumab monotherapy (15-17%) and sorafenib (20%) and the earlier time of disease progression in the sorafenib arm.

The incidence of decreased appetite in IMbrave150 was 18% and 24% in the atezolizumab/bevacizumab and sorafenib arms, respectively. These incidences are consistent with the known incidence of decreased appetite with atezolizumab monotherapy (25%) and sorafenib (24%).

The incidence of asthenia/fatigue in IMbrave150 was 26% and 32% in the atezolizumab/bevacizumab and sorafenib arms, respectively. These incidences are consistent with the known incidence of asthenia/fatigue with atezolizumab monotherapy (49%) and sorafenib (41% fatigue and 12% asthenia).

In summary, pruritus, pyrexia, peripheral edema, and musculoskeletal pain/myalgia were more frequent in the atezolizumab arm. Abdominal pain, decreased appetite, fatigue/asthenia were more frequent in the sorafenib arm. The incidence of each of these adverse events fall within the expected range based on prior studies with these drugs. Although the incidence of IRRs was higher in the IMbrave150 study in comparison with previously reported incidences for atezolizumab monotherapy or in combination with other drugs, FDA assessment of the cases of IRR in Study IMbrave150 did not reveal a reason for this increased incidence. FDA agrees with the Applicant that most of the IRRs that occurred in Study IMbrave 150 were Grade 1-2, non-

serious, resolved rapidly after treatment, and did not recur after re-exposure.

All information presented by the Applicant in this section follows the standard analysis based on crude incidence rates. To assess the time to onset (TTO) of adverse events and the influence of exposure on the incidence of AEs, FDA conducted an analysis of the median TTO for all AEs with at least 5% incidence, summarized in Table 35.

Table 35 Study IMbrave150: TTO of the most common AEs

PT	Atezo/bev (n: 329)		Sorafenib (n: 156)	
	%	TTO (months)	%	TTO (months)
Hypertension	30	2.10	24	0.72
Fatigue	20	1.64	19	0.68
Proteinuria	20	3.51	7	3.97
AST increased	19	2.94	17	0.95
Pruritus	19	2.77	10	0.72
Diarrhoea	19	2.28	49	1.4
Pyrexia	18	0.52	10	1.11
Decreased appetite	18	1.36	24	0.75
ALT increased	14	3.77	9	1.75
Constipation	13	2.06	14	1.03
Blood bilirubin increased	13	3.53	14	1.28
Rash	12	2.82	17	0.42
Abdominal pain	12	2.49	17	1.28
Nausea	12	1.13	16	0.95
Cough	12	2.71	10	1.41
Infusion related reaction	11	0.72	0	
Weight decreased	11	2.85	10	3.23
Platelet count decreased	11	3.51	12	0.77
Epistaxis	10	2.72	4	1.90
Vomiting	10	1.41	8	1.21
Arthralgia	10	1.52	5	0.52
Anemia	9	4.17	10	4.13
Dyspnea	9	4.73	4	4.17
Hypothyroidism	9	3.48	2	2.66
Edema peripheral	9	3.80	3	3.05
Dysphonia	9	1.11	7	0.26
Insomnia	9	1.51	7	3.54
Headache	8	0.98	7	0.72
Thrombocytopenia	8	4.33	5	1.11
Hypoalbuminemia	7	3.79	8	1.34
Musculoskeletal pain	7	2.25	2	0.19
Abdominal distension	7	3.54	3	1.47

PT	Atezo/bev (n: 329)		Sorafenib (n: 156)	
	%	TTO (months)	%	TTO (months)
Ascites	7	4.69	6	6.07
Asthenia	7	1.87	13	1.41
Blood alkaline phosphatase increased	7	2.72	6	1.05
Back pain	6	1.54	3	0.75
Hyponatremia	6	2.08	6	1.28
Leukopenia	6	1.41	3	1.37
Stomatitis	6	2.89	4	0.72
Myalgia	5	1.05	3	2.44
Neutropenia	5	4.07	3	1.60
WBC decreased	4	3.38	5	3.95
Hypokalemia	3	4.79	6	2.44
Hypophosphatemia	2	2.52	7	1.41
Alopecia	1	3.94	14	1.41
PPES	1	3.05	48	0.49

Abbreviation: TTO- Time to Onset

Median treatment duration was longer in the combination arm (7.4 and 2.8 months in the atezolizumab/bevacizumab and sorafenib arms, respectively). The median TTO was shorter in the sorafenib arm and below the median duration of treatment for several adverse events, including hypertension, fatigue, diarrhea, PPES, rash, and stomatitis. The median TTO of the most common AEs related to atezolizumab/bevacizumab (with the exception of IRR, fever, fatigue, decreased appetite, constipation, nausea, etc.) was comparable to the median duration of exposure to atezolizumab/bevacizumab or longer. To further explore the impact of treatment duration on the incidence of AEs, the incidence of the most common AEs was analyzed by periods of time (Table 36).

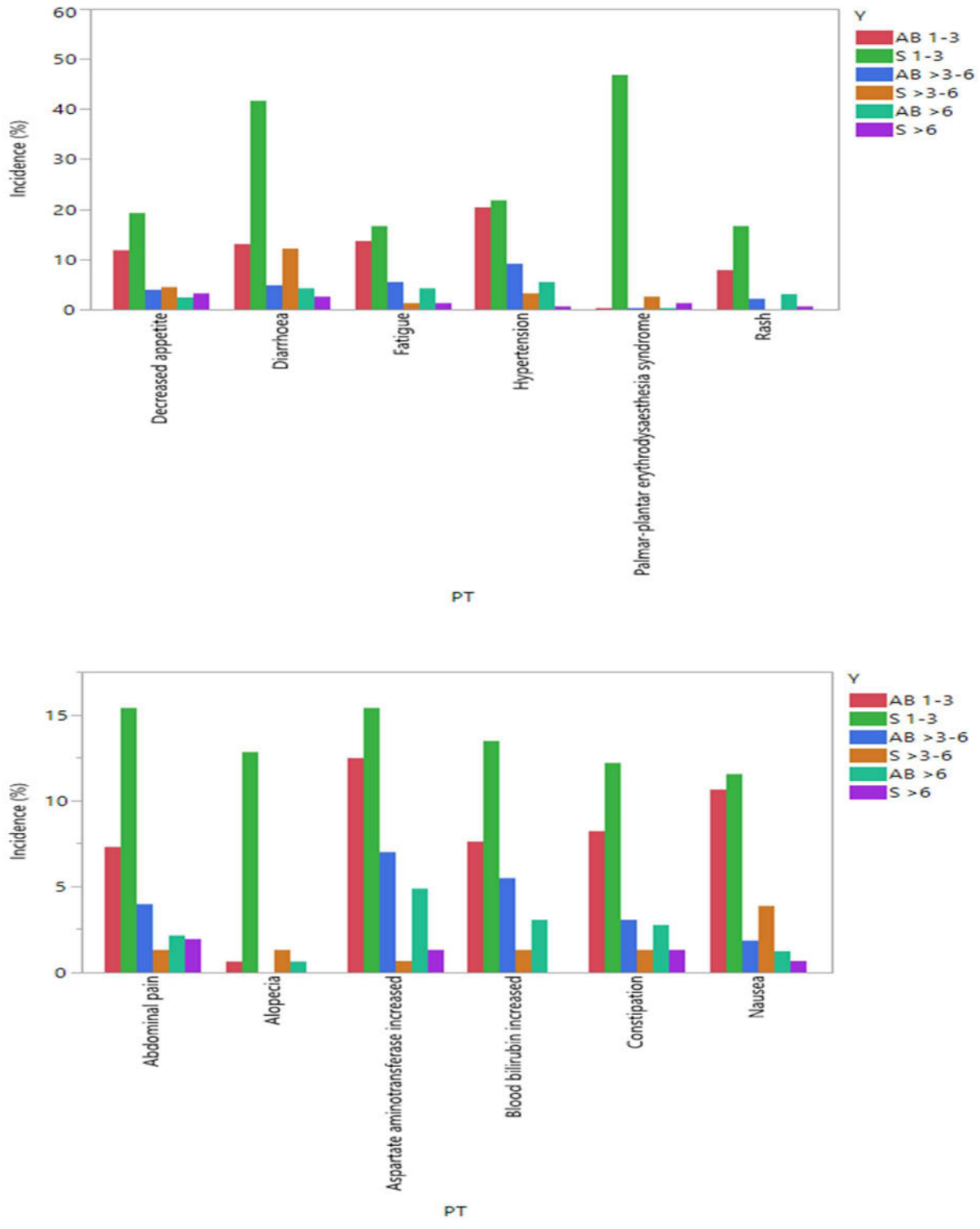
Table 36 Study IMbrave150: Incidence of the most common AEs by period of time

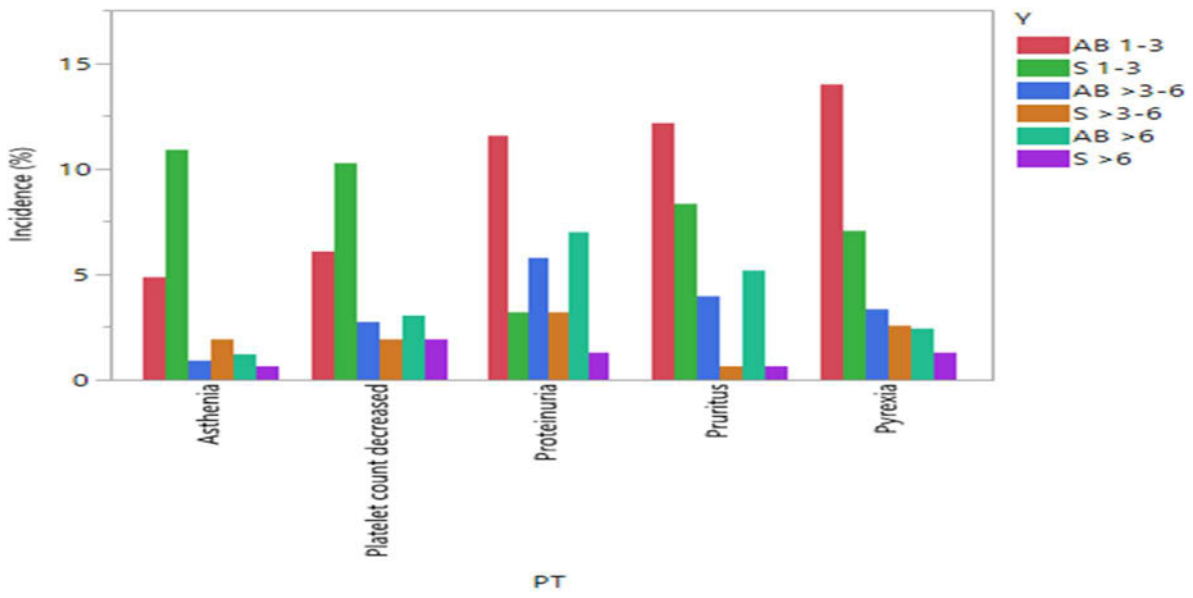
	Atezo/bev (n: 329) %			Sorafenib (n: 156) %		
Months	**0-3**	**> 3-6**	**> 6**	**0-3**	**> 3-6**	**> 6**
PT						
PPES	0	0	0	47	3	1
Diarrhea	13	5	4	42	12	3
Hypertension	20	9	5	22	3	1
Decreased appetite	12	4	2	19	4	3
Fatigue	14	5	4	17	1	1
Rash	8	2	3	17	0	1
Abdominal pain	7	4	2	15	1	2
AST increased	12	7	5	15	1	1
Blood bilirubin increased	8	5	3	13	1	0

	Atezo/bev (n: 329) %			Sorafenib (n: 156) %		
Months	**0-3**	**> 3-6**	**> 6**	**0-3**	**> 3-6**	**> 6**
PT						
Alopecia	1	0	1	13	1	0
Constipation	8	3	3	12	1	1
Nausea	11	2	1	12	4	1
Asthenia	5	1	1	11	2	1
Platelet count decreased	6	3	3	10	2	2
Pruritus	12	4	5	8	1	1
Pyrexia	14	3	2	7	3	1
Proteinuria	12	6	7	3	3	1

In this analysis, for the first 3 months of treatment, the incidence of all AEs except pruritus, pyrexia, and proteinuria were higher in the sorafenib arm. Although some AEs were more frequent in the atezolizumab/bevacizumab arm over time, in general, the between arm-differences for these AEs are small and not likely to be meaningful because numerical comparisons beyond 3 months may be unreliable due to the low number of patients in the sorafenib arm at later time periods. One possible reason for the higher incidence of AEs within the first 3 months in both arms could be explained by information bias, as patients may be more likely to report AEs in the beginning of treatment and patients with poor tolerance discontinue treatment. The incidence of AEs by period of time is further displayed in Figure 11.

Figure 11 Study IMbrave150: Incidence of the most common AEs by periods of time





AB: atezolizumab/bevacizumab; S: sorafenib; 1-3: incidence between start of treatment and 3 months; >3-6: incidence between > 3 and 6 months; > 6 months: incidence > 6 months.

Laboratory Findings

Data:

Laboratory data are presented in the dossier separately for each study, i.e. the data were not pooled.

In IMbrave150, laboratory data were classified according to NCI CTCAE v4.0 and summarized descriptively over time, including change from baseline by treatment arm. The majority of patients did not exhibit a clinically relevant shift in any laboratory test parameter during the study. The most common clinically relevant shifts were observed in chemistry tests.

A higher proportion of patients (≥ 5% difference between treatment arms) in the Sorafenib arm had clinically relevant shifts in bilirubin (high) (13.2% vs. 7.7%) and in phosphorus (low) (15.3% vs 4.4%) compared to Atezo+Bev. Clinically relevant laboratory safety test shifts were comparable between treatment arms for the remaining chemistry parameters.

Between arms, there were no clinically relevant laboratory safety test shifts with a ≥ 5% difference observed for coagulation or hematology parameters.

The shifts in chemistry observed in the Sorafenib and Atezo+Bev arm were confounded by the patients' underlying disease and concurrent illness of hepatitis. No unexpected findings were observed.

The proportion of patients who had normal TSH at baseline and treatment-emergent TSH abnormalities (high TSH) was lower in the Sorafenib arm (16.7%) compared to Atezo+Bev (28.0%). The proportion of patients who had normal TSH at baseline and treatment-emergent TSH abnormalities (low TSH) was numerically lower on Sorafenib (2.6%) compared to the

Atezo+Bev arm (8.2%). There were patients with both treatment-emergent TSH high and TSH low laboratory values in the Atezo+Bev arm.

Potential Hy's law cases were defined in the study protocol as ALT or AST increases above 3-fold the baseline with concomitant total bilirubin increases above 2-fold the ULN within 7 days.

A total of 26 patients had at least one elevated total bilirubin (>2x ULN) within 7 days after the latest elevated ALT or AST (>3x baseline) and were identified as potential Hy's law cases: 14 patients (9%) in the Sorafenib arm and 12 patients (3.6%) in the Atezo+Bev arm. Following detailed review, 24 of the 26 potential Hy's law cases (13 in the Sorafenib and 11 in the Atezo+Bev arm) did not qualify as true Hy's law cases, while the 2 remaining potential cases (1 patient in each treatment arm) were classified as true Hy's law cases due to the lack of alternate etiology.

(b) (4)

Table 37 Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with HCC Receiving TECENTRIQ in IMbrave150

Laboratory Abnormality	TECENTRIQ in combination with bevacizumab (n=329)		Sorafenib (n=156)	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
Chemistry				
Increased AST	86.1	16.1	89.5	15.7
Increased Alkaline Phosphatase	70.3	4.3	75.8	4.6
Increased ALT	61.9	7.7	69.9	4.6
Decreased Albumin	60.1	1.5	53.6	<1
Decreased Sodium	54.5	12.7	48.7	9.2
Increased Glucose	47.7	9.3	43.4	4.6
Decreased Calcium	30.3	<1	34.6	1.3
Decreased Phosphorus	26.1	4.7	58.3	15.9
Increased Potassium	23.2	1.9	16.3	2
Hypomagnesemia	21.7	0	22.4	0
Hematology				
Decreased Platelet	68.1	6.5	62.7	4.6
Decreased Lymphocytes	61.9	13.5	57.8	11.1
Decreased Hemoglobin	57.6	3.1	62.1	3.9
Increased Bilirubin	57	7.7	58.8	13.7
Decreased Leukocyte	31.9	3.4	29.4	1.3
Decreased Neutrophil	23.4	2.3	15.6	1.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ plus bevacizumab (222-323) and sorafenib (90-153) NA = Not applicable.
[1] Graded per NCI CTCAE v4.0

The results from GO30140 Arms A and F were in line with the above observations in IMbrave150.

The Applicant's Position:

The clinical laboratory results showed no unexpected safety findings for the Atezo+Bev combination.

The FDA's Assessment:

Grade 3-4 increases in LFTs (increased aspartate aminotransaminase [AST], alanine aminotransferase [ALT] and bilirubin [bili]) were reported in 59 (18%) and 24 (15%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively. LFTs were increased to at least 3 x ULN in 97 (29%) and 56 (36%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, and to at least 3 x baseline values in 71 (26%) and 36 (23%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively. Of patients who had LFTs ≥ 3 x ULN, bilirubin ≥ 2 x ULN was reported in 41 (12%) and 34 (22%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively; however, increased bilirubin was observed within 7 days after the latest elevated LFT only in 14 (9%) and 12 (8%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively. FDA agrees with the Applicant that many of the cases are confounded by underlying disease. Although immune-mediated hepatotoxicity is an established toxicity of atezolizumab, a definitive assessment of the role of atezolizumab and bevacizumab in development of hepatic injury is difficult in the context ongoing baseline liver disease and other concomitant conditions for many patients in Study IMbrave150. Overall, the pattern of liver injury evident by LFT elevation in the atezolizumab/bevacizumab arm does not appear to be worse than that observed in the sorafenib arm. Table 38 and Table 39 summarize shifts from baseline in LFTs, supporting this observation.

Table 38 IMbrave150: ALT shift

Grade shift	Atezo/bev baseline grade (n: 324); N (%)				Sorafenib baseline grade (n: 155); N (%)		
	0	**1**	**2**	**3**	**0**	**1**	**2**
0	118 (36)	2 (1)	0	0	45 (29)	1 (1)	0
1	92 (28)	57 (18)	2 (1)	0	1 (1)	34 (22)	0
2	9 (3)	13 (4)	5 (2)	0	0	14 (9)	2 (1)
3	9 (3)	14 (4)	2 (1)	1 (<1)	0	3 (2)	1 (1)
4	0	0	0	0	0	1 (1)	0

Table 39 IMbrave150: AST shift

Grade shift	Atezo/bev baseline grade (n: 324); N (%)			Sorafenib baseline grade (n: 155); N (%)			
	0	1	2	0	1	2	3
0	40 (12)	4 (1)	0	14 (9)	2 (1)	0	0
1	92 (28)	95 (29)	3 (1)	44 (28)	42 (27)	1 (1)	0
2	5 (2)	29 (9)	4 (1)	2 (1)	20 (13)	6 (4)	0
3	5 (2)	26 (8)	19 (6)	1 (1)	11 (7)	6 (4)	1 (1)
4	0	1 (<1)	1 (<1)	1 (1)	4 (3)	0	0

A higher proportion of patients (5% difference between treatment arms) treated with sorafenib arm had Grade 3-4 shifts in bilirubin (Table 40).

Table 40 IMbrave150: Bilirubin shift

Grade shift	Atezo/bev baseline grade (n: 324); N (%)			Sorafenib baseline grade (n: 154); N (%)		
	0	1	2	0	1	2
0	135 (42)	3 (1)	0	63 (51)	1 (1)	0
1	80 (2)	13 (4)	0	34 (22)	9 (6)	1 (1)
2	43 (13)	25 (8)	1 (<1)	12 (8)	11 (7)	3 (2)
3	8 (2)	5 (2)	8 (2)	10 (6)	5 (3)	3 (2)
4	3 (1)	0	0	2 (1)	0	0

Hyponatremia as an AE was reported in 6% of patients in each arm; as per the lab dataset, 54% and 49% patients had serum low sodium (12% and 9% Grade 3 low sodium) in the atezolizumab/bevacizumab and sorafenib arms, respectively. Hypoalbuminemia (as an AE) was reported in 7% and 8% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively (only one patient had a Grade 3 event); as per the lab dataset, 198 (60%) and 83 (53%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively had serum low albumin (all Grades 1-2). Shifts to high TSH (from normal baseline levels) were observed in 28% and 17% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively; shifts to low TSH were observed in 8% and 3% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively. Hyponatremia and hypoalbuminemia frequently occur in patients with cirrhosis and it is difficult to assess the effects of the drug on these two labs in the absence of a placebo control. There were no clinically significant differences between arms in other test shifts.

Vital Signs

The Applicant's Position:

Overall, no unexpected effects on vital signs were observed for HCC patients in the IMbrave150 and GO30140 studies following Atezo+Bev combination therapy. The observed changes in vital signs were consistent with the known safety profile of atezolizumab and bevacizumab.

The FDA's Assessment:
FDA's analysis of hypertension can be found in the Adverse Events of Special Interest subsection. FDA agrees that no new safety signals were found in Studies IMbrave150 and GO30140.

Electrocardiograms (ECGs)

Data:

Electrocardiography results are presented separately for studies IMbrave150 and GO30140. ECGs were conducted at baseline and postbaseline.

In IMbrave150, baseline incidence of clinically significant ECG abnormalities was comparable between treatment arms (Sorafenib: 1.9% and Atezo+Bev arm:2.1%). Clinically relevant postbaseline ECG abnormalities were reported as AEs in 3 patients (Sorafenib: 1 patient, Atezo+Bev: 2 patients). For the 2 patients in the Atezo+Bev arm these abnormalities were attributed to the underlying cardiac medical history or confounded by the concurrent conditions of sinus bradycardia or type 2 diabetes mellitus.

In Study GO30140, 1 patient in Arm A had a clinically significant ECG abnormality without a corresponding AE and 1 patient with a concurrent condition of atrial fibrillation in the Atezo+Bev group in Arm F had a clinically significant ECG abnormality at screening.

The Applicant's Position:

Overall, no unexpected effects on ECG were observed for HCC patients following Atezo+Bev combination therapy.

The FDA's Assessment:
FDA agrees with the Applicant's position.

QT

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
No data was requested for submission. Atezolizumab and bevacizumab do not have an effect on the QT interval.

Immunogenicity

Data:

The evaluation for the effect of ADAs on safety is based on pooled analyses from Studies IMbrave150 and GO30140 (Atezo+Bev population). A higher frequency (≥10% difference) of the following events was observed in ADA-positive patients compared with ADA-negative patients: SAEs (50.0% vs 31.5%), related SAEs (26.9% vs 13.8%), and AEs leading to dose interruption of any study treatment (54.5% vs 42.1%) (Table 41).

Gastrointestinal haemorrhage was the only SAE with a ≥ 2% difference between ADA-negative and -positive patients (0.9% vs 4.5%). These events are consistent with the underlying disease and the known safety profiles of the individual study treatments. After medical review, a relationship between these events and ADA status seems unlikely based on the lack of biological plausibility.

The incidence of AESIs was generally comparable across the majority of safety categories with the exception of Grade 3–4 AESIs (19% ADA-negative vs 31% ADA-positive). The difference in Grade 3–4 AESIs was mainly driven by more events of hepatitis laboratory abnormalities in the ADA-positive subgroup.

By medical concept, the most common (≥10% in either ADA-negative or ADA-positive) AESIs were hepatitis (diagnosis and laboratory abnormalities), rash, hypothyroidism and IRR.

The frequency of most AESIs was similar between the ADA subgroups except for hepatitis laboratory abnormalities (32% ADA-negative vs 37% ADA-positive) and IRRs (6% vs 15%). IRRs were mainly Grade 1–2 in both ADA subgroups (6% ADA-negative vs. 12% ADA-positive) and the overall incidence of Grade 3 IRRs was low (1% vs 3%). There were no Grade 4 or Grade 5 IRRs. Medical review of the individual cases indicated that there was limited clinical impact of ADA status on IRRs with regard to time to onset, severity, or outcome in these individual patients.

Table 41 Overview of AEs by ADA Status

	Atezo+Bev HCC (N=474)	
	ADA- (N=340)	ADA+ (N=134)
Total number of patients with at least one AE	331 (97.4%)	131 (97.8%)
Total number of events	3245	1294
Total number of patients with at least one		
Treatment-related AE	280 (82.4%)	114 (85.1%)
Atezo-related AE	250 (73.5%)	105 (78.4%)
Grade 3-4 AE	170 (50.0%)	79 (59.0%)
Treatment-related Grade 3-4 AE	111 (32.6%)	50 (37.3%)
Atezo-related Grade 3-4 AE	73 (21.5%)	35 (26.1%)
Grade 5 AE	11 (3.2%)	9 (6.7%)
Treatment-related Grade 5 AE	4 (1.2%)	4 (3.0%)
Atezo-related Grade 5 AE	3 (0.9%)	3 (2.2%)
Serious AE	107 (31.5%)	67 (50.0%)
Treatment-related serious AE	47 (13.8%)	36 (26.9%)
Atezo-related serious AE	37 (10.9%)	23 (17.2%)
AE leading to any Study Treatment withdrawal	47 (13.8%)	24 (17.9%)
AE leading to Atezo withdrawal	24 (7.1%)	14 (10.4%)
AE leading to any Dose modification or Study Treatment interruption	143 (42.1%)	73 (54.5%)
AE leading to Atezo interruption	106 (31.2%)	55 (41.0%)

The Applicant's Position:

Based on the case review of Grade 3–4 AEs, SAEs and assessment of biological plausibility, it is unlikely that there is a relationship between ADA status and these events. The poorer baseline prognostic factors in ADA-positive patients (see Section 6.2.1) may have contributed to the higher incidence of these events in ADA-positive vs ADA-negative patients.

The FDA's Assessment:

In Study IMbrave150, the incidence of Grade 3-4 AEs, SAEs, and treatment discontinuations were higher in the patients with known treatment emergent ADAs ("ADA+") when compared to patients with negative (n=227) or unknown (n=14) ADA status ("ADA-"). Grade 3-4 AEs were reported in 69% and 55% patients in the ADA+ and ADA-groups, respectively; SAEs were reported in 52% and 32% patients in the ADA+ and ADA-groups, respectively and AEs resulting in discontinuation of atezolizumab were reported in 11% and 7% patients in the ADA+ and ADA-groups, respectively.

Table 42 summarizes the most frequent AEs in the atezolizumab/bevacizumab arm in the ADA+ and ADA- subpopulations. Although most of the AEs that occurred more frequently in the ADA+ subgroup were general (fatigue, abdominal pain, nausea, diarrhea, etc.) or related to signs of hepatotoxicity, the incidence of infusion-related reactions (18% vs 8%), fever (26% vs. 15%), and pruritus (24% vs 17%) was also higher in ADA+ patients compared to ADA- patients.

Table 42 IMbrave150 Most frequent AEs (≥ 10%) by ADA status

PT	ADA-positive N: 88; N (%)		ADA negative or unknown N: 248; N (%)	
	All grades	Gr 3/4	All grades	Gr3/4
Hypertension	26 (30)	17 (19)	72 (29)	17 (7)
Fatigue	22 (25)	1 (1)	45 (18)	1 (<1)
Proteinuria	13 (15)	1 (1)	53 (21)	1 (<1)
AST increased	19 (22)	9 (10)	45 (18)	9 (4)
Pruritus	21 (24)	0	43 (17)	0
Diarrhea	20 (23)	2 (2)	42 (17)	2
Pyrexia	23 (26)	1 (1)	36 (15)	1 (<1)
Decreased appetite	13 (15)	1 (1)	45 (18)	1 (<1)
ALT increased	11 (13)	4 (5)	35 (14)	4 (2)
Constipation	18 (20)	0	26 (10)	0
Blood bilirubin increased	14 (16)	4 (5)	29 (12)	4 (2)
Rash	11 (13)	0	30 (12)	0
Abdominal pain	14 (16)	1 (1)	26 (10)	1 (<1)
Nausea	13 (15)	0	27 (11)	0
Cough	12 (14)	0	27 (11)	0
Infusion related reaction	16 (18)	4 (5)	21 (8)	4 (2)
Weight decreased	12 (14)	0	25 (10)	0
Platelet count decreased	7 (8)	4 (5)	28 (11)	4 (2)
Epistaxis	12 (14)	0	22 (9)	0
Vomiting	9 (10)	1 (1)	24 (10)	1 (<1)
Arthralgia	10 (11)	0	22 (9)	0
Anemia	12 (14)	3 (3)	18 (7)	3 (1)
Dyspnea	12 (14)	2 (2)	17 (7)	2 (1)
Hypothyroidism	9 (10)	0	20 (8)	0
Edema peripheral	11 (13)	0	18 (7)	0
Hyponatremia	9 (10)	5 (6)	10 (4)	5 (2)

Although it is plausible that the risk of some AEs such as infusion-related reactions may be higher in ADA+ patients, it is difficult to firmly attribute the increased incidence of AEs to the presence of ADA. As the Applicant stated, some demographic and disease characteristics were imbalanced between ADA+ and ADA- patients in the atezolizumab/bevacizumab arm (important prognostic characteristics are summarized in Table 43). A higher proportion of ADA+ patients had high risk features at baseline such as MVI/EHS, BCLC Stage C status, AFP ≥ 400 ng/mL, and CP A6 cirrhosis. However, none of these disease characteristics would explain the increase in general symptoms and infusion-related reactions, although caution should be taken in interpretation of an AE with low number of patients.

Table 43 IMbrave150: Demographic and disease characteristics by ADA status

	ADA-positive N: 88; N (%)	ADA negative or unknown N: 248; N (%)
Asian	38 (43)	150 (60)
White	41 (47)	82 (33)
Age ≥ 65	48 (55)	127 (51)
> 50% liver invasion	7 (8)	11 (4)
High risk features	25 (28)	39 (16)
MVI/EHS	73 (83)	185 (75)
BCLC C	79 (90)	197 (79)
AFP ≥ 400 ng/mL	41 (47)	85 (34)
ECOG PS 1	36 (41)	91 (37)
HBV	31 (35)	133 (54)
HCV	26 (30)	46 (19)
CP A5	58 (66)	181 (73)
CP A6	29 (33)	65 (26)

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Special Interest

Data:

AESIs for atezolizumab were closely monitored because they represent risks with an established or potential causal association with atezolizumab use. Though the AESIs are potentially causally associated with the use of atezolizumab (Atezo+Bev and Atezo Mono), these were also reported for patients in the Sorafenib population for comparison purpose. AESIs have been summarized by medical concepts. To provide a comprehensive analysis of these events in HCC, a side-by-side safety data comparison of the Atezo+Bev, Sorafenib and Atezo Mono (HCC and Multiple Indications) populations was performed (Table 44).

The incidence of atezolizumab-specific AESIs in the Atezo+Bev population was consistent with the known safety profile of atezolizumab. A lower proportion of Atezo+Bev patients experienced atezolizumab AESIs compared with the Sorafenib population (64.9% vs 82.1%). The difference was mainly driven by events reported under immune-related rash, which is a known ADR of Sorafenib. The majority of AESIs were Grade 1 or 2 in severity. The proportion of patients experiencing Grade 3-4 AESIs was lower in the Atezo+Bev population compared with Sorafenib (23.3% vs. 30.1%). The proportion of patients was comparable between Sorafenib and Atezo+Bev for Grade 5 AESIs (1.3% vs 1.2%), serious AESIs (10.9% vs 13.4%), and AESIs leading to any study treatment withdrawal (5.8% vs 5.9%). A lower proportion of patients in the Atezo+Bev population experienced atezolizumab AESIs leading to any dose

modification/interruption compared with Sorafenib (16.4% vs. 35.9%). Among the patients who experienced an AESI, a numerically higher proportion of patients on Atezo+Bev required systemic corticosteroid treatment compared with patients on Sorafenib (12.2% vs. 3.2%).

The spectrum, frequency, and severity of AESIs for bevacizumab were in line with the safety profile of bevacizumab and with the underlying disease. A numerically higher proportion of patients experienced bevacizumab AESIs in the Atezo+Bev population (57.2%) compared with the Sorafenib population (48.7%) (Table 45). A higher proportion of patients in the Atezo+Bev population experienced proteinuria (8.3% vs 24.7% [Atezo+Bev]) and bleeding/haemorrhage events (17.3% vs. 25.4% [Atezo+Bev]). The rate of hypertension was comparable between the two populations (25.6% vs 27.4%). The reported events are well known ADRs for bevacizumab. A comparable proportion of patients (<2% difference) in the Sorafenib and Atezo+Bev populations experienced events under the concept of upper gastrointestinal bleeding, which is a common complication in patients with HCC. Overall, the incidence of upper gastrointestinal bleeds observed in the Atezo+Bev population was as expected, based on the underlying disease and the known safety profile of bevacizumab.

Table 44 Overview of Adverse Events of Special Interest for Atezolizumab

	Sorafenib HCC (N=156)	Atezo+Bev HCC (N=493)	Atezo Mono HCC (N=93)	Atezo Mono Multiple Indications (N=3178)
Total number of patients with at least one AE of Special Interest	128 (82.1%)	320 (64.9%)	48 (51.6%)	1097 (34.5%)
Total number of events	271	753	144	2186
Total number of patients with at least one				
Treatment-related AE of Special Interest	115 (73.7%)	240 (48.7%)	28 (30.1%)	794 (25.0%)
Atezo-related AE of Special Interest	0	229 (46.5%)	28 (30.1%)	794 (25.0%)
Grade 3-4 AE of Special Interest	47 (30.1%)	115 (23.3%)	14 (15.1%)	248 (7.8%)
Treatment-related Grade 3-4 AE of Special Interest	39 (25.0%)	64 (13.0%)	10 (10.8%)	173 (5.4%)
Atezo-related Grade 3-4 AE of Special Interest	0	59 (12.0%)	10 (10.8%)	173 (5.4%)
Grade 5 AE of Special Interest	2 (1.3%)	6 (1.2%)	0	4 (0.1%)
Treatment-related Grade 5 AE of Special Interest	1 (0.6%)	5 (1.0%)	0	2 (<0.1%)
Atezo-related Grade 5 AE of Special Interest	0	5 (1.0%)	0	2 (<0.1%)
Serious AE of Special Interest	17 (10.9%)	66 (13.4%)	10 (10.8%)	151 (4.8%)
Treatment-related Serious AE of Special Interest	13 (8.3%)	34 (6.9%)	9 (9.7%)	127 (4.0%)
Atezo-related Serious AE of Special Interest	0	30 (6.1%)	9 (9.7%)	127 (4.0%)
AE of Special Interest leading to any Study Treatment withdrawal	9 (5.8%)	29 (5.9%)	4 (4.3%)	58 (1.8%)
AE of Special Interest leading to Atezo withdrawal	0	22 (4.5%)	4 (4.3%)	58 (1.8%)
AE of Special Interest leading to any Dose modification or Study Treatment interruption	56 (35.9%)	81 (16.4%)	7 (7.5%)	210 (6.6%)
AE of Special Interest leading to Atezo interruption	0	70 (14.2%)	7 (7.5%)	210 (6.6%)
AE of Special Interest Requiring the Use of Systemic Corticosteroids	5 (3.2%)	60 (12.2%)	3 (3.2%)	247 (7.8%)

Table 44 Overview of Adverse Events of Special Interest for Atezolizumab (cont.)

	Sorafenib HCC (N=156)	Atezo+Bev HCC (N=493)	Atezo Mono HCC (N=93)	Atezo Mono Multiple Indications (N=3178)
Special Interest AE Medical Concepts: patients with at least one				
Immune-Mediated Rash	96 (61.5%)	109 (22.1%)	9 (9.7%)	619 (19.5%)
Immune-Mediated Hepatitis (Diagnosis and Lab Abnormalities)	62 (39.7%)	191 (38.7%)	37 (39.8%)	343 (10.8%)
Immune-Mediated Hepatitis (Lab Abnormalities)	54 (34.6%)	171 (34.7%)	35 (37.6%)	315 (9.9%)
Immune-Mediated Hypothyroidism	4 (2.6%)	49 (9.9%)	4 (4.3%)	164 (5.2%)
Immune-Mediated Hepatitis (Diagnosis)	20 (12.8%)	60 (12.2%)	7 (7.5%)	62 (2.0%)
Immune-Mediated Pneumonitis	0	7 (1.4%)	0	87 (2.7%)
Infusion-Related Reactions	0	43 (8.7%)	2 (2.2%)	34 (1.1%)
Immune-Mediated Hyperthyroidism	0	16 (3.2%)	1 (1.1%)	30 (0.9%)
Immune-Mediated Colitis	1 (0.6%)	9 (1.8%)	0	34 (1.1%)
Immune-Mediated Pancreatitis	6 (3.8%)	11 (2.2%)	3 (3.2%)	18 (0.6%)
Immune-Mediated Severe Cutaneous Reactions	1 (0.6%)	0	0	22 (0.7%)
Immune-Mediated Diabetes Mellitus	0	10 (2.0%)	0	10 (0.3%)
Immune-Mediated Ocular Inflammatory Toxicity	0	1 (0.2%)	1 (1.1%)	16 (0.5%)
Immune-Mediated Myositis (Myositis+Rhabdomyolysis)	0	3 (0.6%)	0	13 (0.4%)
Immune-Mediated Meningoencephalitis	0	1 (0.2%)	0	14 (0.4%)
Immune-Mediated Adrenal Insufficiency	0	2 (0.4%)	0	12 (0.4%)
Immune-Mediated Meningitis	0	0	0	12 (0.4%)
Immune-Mediated Myositis	0	1 (0.2%)	0	8 (0.3%)
Immune-Mediated Vasculitis	0	1 (0.2%)	0	7 (0.2%)
Immune-Mediated Guillain-Barre Syndrome	0	1 (0.2%)	1 (1.1%)	5 (0.2%)
Rhabdomyolysis	0	2 (0.4%)	0	5 (0.2%)
Immune-Mediated Nephritis	0	3 (0.6%)	0	3 (<0.1%)
Autoimmune Hemolytic Anemia	0	2 (0.4%)	0	4 (0.1%)
Systemic Immune Activation	0	1 (0.2%)	0	2 (<0.1%)
Immune-Mediated Encephalitis	0	1 (0.2%)	0	2 (<0.1%)
Immune-Mediated Hypophysitis	0	0	0	2 (<0.1%)
Immune-Mediated Myasthenia Gravis	0	0	0	1 (<0.1%)
Immune-Mediated Myocarditis	0	1 (0.2%)	0	0

Source: t_ae_si_sum_SE_AAG6x5_29AUG2019_40245P

Table 45 Overview of Adverse Events of Special Interest for Bevacizumab

	Sorafenib HCC (N=156)	Atezo+Bev HCC (N=493)	Atezo Mono HCC (N=93)	Atezo Mono Multiple Indications (N=3178)
Total number of patients with at least one AE of Special Interest	76 (48.7%)	282 (57.2%)	12 (12.9%)	857 (27.0%)
Total number of events	106	581	25	1337
Total number of patients with at least one				
Treatment-related AE of Special Interest	52 (33.3%)	222 (45.0%)	2 (2.2%)	104 (3.3%)
Bevacizumab-related AE of Special Interest	0	221 (44.8%)	0	3 (<0.1%)
Grade 3-4 AE of Special Interest	29 (18.6%)	113 (22.9%)	5 (5.4%)	248 (7.8%)
Treatment-related Grade 3-4 AE of Special Interest	21 (13.5%)	85 (17.2%)	1 (1.1%)	28 (0.9%)
Bevacizumab-related Grade 3-4 AE of Special Interest	0	87 (17.6%)	0	0
Grade 5 AE of Special Interest	2 (1.3%)	8 (1.6%)	0	29 (0.9%)
Treatment-related Grade 5 AE of Special Interest	0	3 (0.6%)	0	2 (<0.1%)
Bevacizumab-related Grade 5 AE of Special Interest	0	3 (0.6%)	0	0
Serious AE of Special Interest	15 (9.6%)	60 (12.2%)	5 (5.4%)	242 (7.6%)
Treatment-related Serious AE of Special Interest	6 (3.8%)	33 (6.7%)	1 (1.1%)	20 (0.6%)
Bevacizumab-related Serious AE of Special Interest	0	33 (6.7%)	0	0
AE of Special Interest leading to any Study Treatment withdrawal	1 (0.6%)	39 (7.9%)	0	31 (1.0%)
AE of Special Interest leading to Bevacizumab withdrawal	0	39 (7.9%)	0	0
AE of Special Interest leading to any Dose modification or Study Treatment interruption	15 (9.6%)	87 (17.6%)	2 (2.2%)	83 (2.6%)
AE of Special Interest leading to Bevacizumab modification/interruption	0	79 (16.0%)	0	0
Special Interest AE Medical Concepts: patients with at least one				
Bleeding / Haemorrhage	27 (17.3%)	125 (25.4%)	8 (8.6%)	542 (17.1%)
Hypertension	40 (25.6%)	135 (27.4%)	2 (2.2%)	120 (3.8%)
Proteinuria	13 (8.3%)	122 (24.7%)	3 (3.2%)	47 (1.5%)
Thromboembolic Event - Venous	5 (3.2%)	12 (2.4%)	1 (1.1%)	156 (4.9%)
Thromboembolic Event - Arterial	2 (1.3%)	14 (2.8%)	1 (1.1%)	105 (3.3%)
Congestive heart failure	2 (1.3%)	2 (0.4%)	0	25 (0.8%)
Wound Healing Complications	0	4 (0.8%)	0	19 (0.6%)
Gastrointestinal Perforation	0	4 (0.8%)	0	15 (0.5%)
Fistula/Abscess (Non GI)	1 (0.6%)	0	0	16 (0.5%)
Posterior Reversible Encephalopathy Syndrome	0	1 (0.2%)	0	1 (<0.1%)

Source: t_ae_bevsi_sum_SE_29AUG2019_40245P

The Applicant's Position:

The incidence of atezolizumab-specific or bevacizumab-specific AESIs in the Atezo+Bev population was consistent with the known safety profiles of the corresponding drugs and with the underlying disease. No new safety signals were identified.

The FDA's Assessment:

Liver toxicity and causality of liver toxicity AEs are difficult to assess in the HCC population. Although IMbrave150's eligibility criteria restricted enrollment to patients with Child-Pugh A score, LFTs ≤ 5 x ULN, bilirubin ≤ 3 x ULN, albumin ≥ 2.8 g/dL, and without moderate or severe ascites or history of hepatic encephalopathy, patients may experience liver function deterioration that is unrelated to treatment, as the underlying etiology of HCC (cirrhosis, NASH, viral hepatitis, etc.) continues to progress. In addition, disease progression may manifest as deteriorating liver function before being radiologically diagnosed. Based on a customized query of the IMbrave150 safety dataset for immune-mediated hepatitis (diagnosed hepatitis based on clinical manifestations and investigations), 12% and 13% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, experienced an event; of these, 8 (2%) patients in the atezolizumab/bevacizumab arm required treatment with steroids for events (Grades 2-5) of autoimmune hepatitis/immune-mediated hepatitis (3 patients), hepatitis, liver injury, esophageal varices, and hepatobiliary disease. Based on analyses using the same query, the Applicant reported the same incidence for the combination of atezolizumab/bevacizumab across HCC studies and an incidence of 7.5% in patients with HCC and 2% in patients with a variety of cancer types who received atezolizumab as a single agent. Table 46 summarizes the AEs included in the Applicant's broad query for "immune-mediated hepatitis". Please note that this is a broad query that included many terms that are not specific for autoimmune hepatitis.

Table 46 IMbrave150: Hepatic toxicity SMQ

PT	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All grades	Grades 3-4	All grades	Grades 3-4
AST increased	64 (19)	23 (7)	26 (17)	8 (5)
ALT increased	46 (14)	12 (4)	14 (9)	2 (1)
Bilirubin increased	43 (13)	8 (2)	22 (14)	10 (6)
Ascites	23 (7)	6 (2)	9 (6)	2 (1)
GGT increased	8 (2)	5 (2)	7 (4)	3 (2)
Hepatic function abnormal	6 (2)	2 (1)	5 (3)	2 (1)
Bilirubin conjugated increased	8 (2)	0	3 (2)	1 (1)
Hepatic encephalopathy	5 (2)	2 (1)	3 (2)	2 (1)
Hyperbilirubinemia	6 (2)	3 (1)	3 (2)	1 (1)
Hepatic pain	5 (2)	1 (<1)	2 (1)	0
Esophageal varices haemorrhage	7 (2)	6	1 (1)	1 (1)
Transaminases increased	5 (2)	3 (1)	1 (1)	0

PT	Atezo/bev (n: 329) N; (%)		Sorafenib (n: 156) N; (%)	
	All grades	Grades 3-4	All grades	Grades 3-4
Blood bilirubin unconjugated increased	3 (1)	0	1 (1)	0
Hepatitis	3 (1)	2 (1)	1 (1)	0
Total bile acids increased	2 (1)	0	1 (1)	0
Autoimmune hepatitis	2 (1)	1 (<1)	0	0
Hyperammonemia	2 (1)	1 (<1)	0	0
Varices esophageal	3 (1)	2 (1)	0	0
Ammonia increased	0	0	1 (1)	0
Drug-induced liver injury	0	0	2 (1)	1 (1)
Gastric varices hemorrhage	1 (<1)	1 (<1)	1 (1)	1 (1)
Hepatic failure	0	0	2 (1)	2 (1)
Liver disorder	0	0	2 (1)	1 (1)
Liver function test increased	0	0	2 (1)	1 (1)
Liver injury	0	0	1 (1)	1 (1)
Gastric varices	1 (<1)	0	0	0
Hepatic cirrhosis	1 (<1)	1 (<1)	0	0
Hepatobiliary disease	1 (<1)	1 (<1)	0	0
Hepatorenal failure	1 (<1)	1 (<1)	0	0
Hypertransaminasemia	1 (<1)	0	0	0
Immune-mediated hepatitis	1	1	0	0
Liver function test abnormal	1	1	0	0
Portal hypertension	1	0	0	0

The CTCAE dictionary defines hepatic failure as “a disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase”. There is no Grade 1-2 hepatic failure in the CTCAE dictionary. Grade 3 hepatic failure is defined by the presence of asterixis; mild encephalopathy; limiting self-care; Grade 4 is defined by moderate to severe encephalopathy; coma; life-threatening consequences. Although the dictionary does not define “hepatic encephalopathy”, Grade 1-2 encephalopathy is defined as encephalopathy with mild or moderate symptoms with limited instrumental daily activities. Table 47 summarizes FDA’s review of SMQs (investigation-related SMQs not included) indicative of liver injury and hepatic liver failure/dysfunction.

Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase. There is no Grade 1-2 hepatic failure in the CTCAE dictionary. Grade 3 hepatic failure is defined by the presence of asterixis; mild encephalopathy; limiting self-care; Grade 4 is defined by moderate to severe encephalopathy; coma; life-threatening consequences. Although the dictionary does not define “hepatic encephalopathy”, Grade 1-2 encephalopathy is defined as encephalopathy with mild or moderate symptoms with limited instrumental daily activities. Table 47 summarizes FDA’s review of SMQs (investigation-related SMQs not included) indicative of liver injury and hepatic liver failure/dysfunction.

Table 47 IMbrave150: Summary of liver injury SMQs (excluding labs)

SMQ	PT	Atezo/bev (n: 329); n (%)	Sorafenib (n: 156); n (%)
Hepatic disorders	Ascites	23 (7)	9 (6)
	Autoimmune hepatitis	2 (1)	0
	Cholestasis	0	1 (1)
	Drug-induced liver injury	0	2 (1)
	Gastric varices	1 (<1)	0
	Gastric varices hemorrhage	1 (<1)	1 (1)
	Hepatic cirrhosis	1 (<1)	2 (1)
	Hepatic encephalopathy	5 (2)	3 (2)
	Hepatic failure	0	2 (1)
	Hepatic pain	5 (2)	2 (1)
	Hepatitis	3 (1)	1 (1)
	Hepatobiliary disease	1 (<1)	0
	Hepatorenal failure	1 (<1)	0
	Immune-mediated hepatitis	1 (<1)	0
	Jaundice	1 (<1)	2 (1)
	Liver disorder	0	2 (1)
	Liver injury	1 (<1)	1 (1)
	Esophageal varices hemorrhage	8 (2)	1 (1)
	Portal hypertension	1 (<1)	0
	Varices esophageal	3 (1)	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	Ascites	23 (7)	9 (6)
	Drug-induced liver injury	0	2 (1)
	Gastric varices	1 (<1)	0
	Gastric varices hemorrhage	1 (<1)	1 (1)
	Hepatic cirrhosis	1 (<1)	2 (1)
	Hepatic encephalopathy	5 (2)	3 (2)
	Hepatic failure	0	2 (1)
	Hepatobiliary disease	1 (<1)	0
	Hepatorenal failure	1 (<1)	0
	Liver disorder	0	2 (1)
	Liver injury	1 (<1)	1 (1)
	Esophageal varices hemorrhage	8 (2)	1 (1)
	Portal hypertension	1 (1)	0
	Varices esophageal	3 (1)	0
Hepatitis, non-infectious	Autoimmune hepatitis	2 (1)	0
	Hepatitis	3 (3)	1 (1)
	Immune-mediated hepatitis	1 (<1)	0
Noninfectious encephalopathy/delirium	Amnesia	3 (1)	0
	Confusional state	5 (2)	0
	Delirium	2 (1)	0
	Dementia	0	1 (1)

SMQ	PT	Atezo/bev (n: 329); n (%)	Sorafenib (n: 156); n (%)
	Encephalopathy	0	2 (1)
	Hallucination	1 (<1)	0
	Hepatic encephalopathy	5 (2)	3 (2)
	Irritability	1 (<1)	0
	Lethargy	1 (<1)	0
	Mental status changes	1 (<1)	0
	Metabolic encephalopathy	0	1 (1)
	Muscular weakness	5 (2)	0
	Senile dementia	1 (<1)	0
	Somnolence	1 (<1)	0
	Tremor	4 (1)	0

A customized query for hepatic failure (including non-lab hepatic terms and the central nervous system terms hepatic encephalopathy, metabolic encephalopathy, mental status changes, lethargy, and encephalopathy) showed that these events were more frequent in the sorafenib arm; 31 (9%) and 23 (15%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, had an event indicative of serious liver injury or hepatic failure. As stated above (in the laboratory data section), although immune-mediated hepatotoxicity is an established risk of atezolizumab, it is difficult to firmly establish a causal role for atezolizumab/bevacizumab (or sorafenib) in many of the cases of hepatotoxicity in Study IMbrave150 due to the presence of ongoing liver disease and other concomitant conditions; however, the pattern of liver function deterioration observed in the atezolizumab/bevacizumab arm does not appear to be worse than the sorafenib arm. Treatment with atezolizumab was interrupted/withdrawn due to hepatic events in 12 (4%) patients.

Hyponatremia is a common electrolyte disturbance in patients with advanced liver disease. In cirrhotic patients, hyponatremia can be hypovolemic (generally related to diuretic use or excessive losses from the gastrointestinal tract) or hypervolemic (resulting in decreased effective circulating volume from increased arterial splanchnic vasodilatation leading to excessive secretion of arginine vasopressin). Although incidences vary by country and hospitalization status at the time of diagnosis, approximately half of all patients with cirrhosis had at least one laboratory assessment documenting a serum sodium concentration of ≤ 135 mmol/L, and about 21% to 28% had values < 130 mmol/L. Several studies have confirmed the relationship between hyponatremia and the severity of liver disease, and hyponatremia appears to be associated with manifestations of decompensated liver disease such as ascites, hepatic encephalopathy, and hepatorenal syndrome. (Angeli N. 20106 and Yu C. 2013). The SMQ for “Hemodynamic edema, effusions and fluid overload” (including the PTs of ascites, generalized edema, joint swelling, edema, edema peripheral, pelvic fluid collection, pericardial effusion, peripheral swelling, pleural effusion, and swelling) showed an increased incidence in the atezolizumab/bevacizumab arm (19%) when compared with the sorafenib arm (11%). Hyponatremia (as an AE) was reported in 6% of patients in each arm; as per the lab dataset, 54% and 49% patients had serum low serum sodium (12% and 9% Grade 3 low sodium).

Hypoalbuminemia was reported as an AE in 7% and 8% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively (only one patient had a Grade 3 event); as per the lab dataset, 198 (60%) and 83 (53%) patients in the atezolizumab/bevacizumab and sorafenib arms respectively had at least one laboratory measurement documenting low serum albumin (all Grades 1-2).

An increased incidence in edema/ascites, hyponatremia, and hypoalbuminemia has also been observed in patients with HCC treated with ramucirumab, a monoclonal antibody targeting VEGFR2, compared to those receiving placebo (Cyramza USPI).

In summary, events of autoimmune/immune-related hepatitis (PTs) were reported in only 3 patients in the IMbrave150 study, all in the atezolizumab/bevacizumab arm. The customized query – which includes many PTs that are nonspecific – did not reveal a meaningful imbalance between arms in Study IMbrave150 (40% vs. 43% in the atezolizumab/bevacizumab vs. sorafenib arms respectively); there was a higher incidence of events when compared to the incidence observed in a pooled safety population comprising other studies of atezolizumab in patients with HCC. Liver failure/injury occurred more frequently in the sorafenib arm of Study IMbrave150. Ascites/hyponatremia/hypoalbuminemia were more frequent in the combination arm, which is consistent with prior experience with monoclonal antibodies targeting the VEGF pathway; these adverse reactions can be monitored and managed clinically.

Skin toxicities were more common in the sorafenib arm (per-patient incidence of 37% and 69% in the atezolizumab/bevacizumab and sorafenib arms, respectively) and the patterns of adverse reactions observed in Study IMbrave150 are consistent with the known safety profile of atezolizumab, bevacizumab, and sorafenib. Table 48 summarizes the incidence of skin AEs that occurred in at least 3% of patients. Of these, 3 patients in the atezolizumab/bevacizumab arm had Grade 3 events (rash maculopapular and psoriasis) and 21 patients had Grade 3 events in the sorafenib arm (rash [4], PPES [13], skin eruption [2], skin toxicity and dry skin [one each]). One patient in the sorafenib arm had a Grade 4 skin ulcer. Using the Applicant's customized search for immune-related rash, the incidence is 61.5% and 19.5% in the atezolizumab/bevacizumab and sorafenib arms respectively (only 3 patients per arm required systemic steroids therapy for these events).

Table 48 IMbrave150: Skin toxicity (incidence ≥3%)

PT	Atezo/bev (n: 329) N; (%)	Sorafenib (n: 156) N; (%)
PPES	3 (1)	75 (48)
Pruritus	64 (19)	15 (10)
Rash*	49 (15)	35 (22)
Dry skin	13 (4)	4 (3)
Dermatitis acneiform	5 (2)	4 (3)

* composite term. PTs included: drug eruption, rash, rash erythematous, rash maculo-papular, rash popular, rash

pruritic, toxic skin eruption.

Overall, 66 (20%) and 78 (50%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively experienced diarrhea or colitis. Colitis was reported in 6 patients in the atezolizumab/bevacizumab arm and 1 patient in the sorafenib arm; two events were Grade 3 (one per arm) and one patient in the atezolizumab/bevacizumab arm experienced Grade 4 colitis. Diarrhea occurred in 19% of patients in the atezolizumab/bevacizumab arm and in 49% of patients in the sorafenib arm.

Thyroid toxicity was observed in both arms of Study IMbrave150. Forty-four (13%) and 4 (3%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, experienced a clinical or laboratory thyroid abnormality reported as an adverse event. Hypothyroidism was reported in 29 (9%) and 3 (2%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively. Hyperthyroidism was reported in 15 (5%) patients in the atezolizumab/bevacizumab arm; no patients with hyperthyroidism were reported in the sorafenib arm. During treatment, 120 (36%) patients in the atezolizumab/bevacizumab arm had above normal thyrotropin-releasing hormone (TRH) values and 37 (11%) had below normal TRH values; some patients had TRH levels that were both above and below normal values. Patients in the sorafenib arm experienced less TRH fluctuation (15% had above normal values and 3% had below normal values during treatment). Free T3 was increased in 7% of patients and decreased in 16% of patients in the atezolizumab/bevacizumab arm. Free T3 was increased in 1% of patients and decreased in 15% of patients in the sorafenib arm. Free T3 was increased in 7% of patients and decreased in 16% of patients in the atezolizumab/bevacizumab arm. Free T3 was increased in 1% of patients and decreased in 15% of patients in the sorafenib arm.

Other AEs of probable autoimmune etiology in Study IMbrave150 (observed only in the atezolizumab/bevacizumab arm) were diabetes (8 patients), nephritis (3 patients), pneumonitis/ILD (4 patients), vasculitis, systemic immune activation, and adrenal insufficiency (1 patient each). The Applicant considered events of ulcerative keratitis that occurred in 1 patient randomized to the atezolizumab/bevacizumab arm as immune-related ocular inflammatory disease. Ocular toxicity was observed in 4% and 2% of patients in the atezolizumab/bevacizumab and sorafenib arms, respectively. On Study Day 83, one patient randomized to the atezolizumab/bevacizumab arm experienced a SAE of intermittent Grade 3 blindness of the left eye. The vision loss was attributed to palliative radiotherapy the patient had received on Day 41 for treatment of temporal brain metastases. The patient continued atezolizumab/bevacizumab despite disease progression (after Cycle 4) and he received a total of 8 cycles of treatment.

Overall, 12% and 3% patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, required corticosteroids for the management of toxicity. In addition, in the atezolizumab/bevacizumab arm, 2 patients were treated with mycophenolate mofetil (for treatment of hepatobiliary disease and immune-related hepatitis) and one patient received tocilizumab for treatment of cytokine release syndrome.

Treatment in both arms of Study IMbrave150 targeted the VEGF pathway. VEGF-related AESIs (proteinuria, hemorrhage, hypertension, thromboembolisms, perforation/fistulas, etc.) were observed in 190 (58%) and 76 (49%) patients in the atezolizumab/bevacizumab and sorafenib arms, respectively; 23% and 19% of patients in the atezolizumab/bevacizumab and sorafenib arms, respectively, experienced Grade 3-4 events. Table 49 summarizes the VEGF-related AESIs.

Table 49 IMbrave150: VEGF-inhibition related AESI

	Atezo/bev (n: 329) N (%)	**Sorafenib (n: 156) N (%)**
Hypertension	102 (31)	40 (26)
Hemorrhage	83 (25)	27 (17)
Proteinuria	70 (21)	17 (8)
Venous thrombosis	10 (3)	5 (3)
Arterial thromboembolism	9 (3)	2 (1)
Congestive heart failure	1 (<1)	2 (1)
Wound healing complication	2 (1)	0
Non-GI fistula	0	1 (1)
Gastrointestinal perforation	1 (<1)	0

VEGF-associated Grade 5 AESIs in the atezolizumab/bevacizumab arm were gastrointestinal hemorrhage (3 patients), gastric ulcer perforation, esophageal varices hemorrhage, and subarachnoid hemorrhage (1 of each). VEGF-related Grade 5 AESIs in the sorafenib arm were cardiac failure and peritoneal hemorrhage, occurring in 1 patient each.

Grade 3 hypertension (no Grade 4 was reported) was observed in 15% and 12% of patients in the atezolizumab/bevacizumab and sorafenib arms, respectively. Most hemorrhagic events were Grade 1-2; Grade 3-4 hemorrhage incidence was 6% in each arm. As expected, proteinuria was observed at a higher incidence with bevacizumab (21% vs. 8% in the atezolizumab/bevacizumab vs. sorafenib arms respectively); 3% of patients receiving bevacizumab experienced Grade 3 proteinuria and one patient had nephrotic syndrome.

In summary, the pattern of VEGF-related AEs observed in Study IMbrave150 are consistent with the established safety profiles of bevacizumab and sorafenib.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
COA analyses to inform the safety and tolerability of atezolizumab in combination with bevacizumab were not provided in this application. Safety and tolerability of the combination are extensively analyzed in other parts of the safety section of this review.

8.2.7 Safety Analyses by Demographic Subgroups

Data:

Pooled subgroup analyses for safety were performed on the Atezo+Bev population. The safety profile of Atezo+Bev was generally comparable across all age groups. Consistent with the disease demographics for HCC, the majority of patients were male and the overall safety profile of Atezo+Bev was mostly comparable between males and females.

The majority of patients in the Atezo+Bev population were Asians (62.1%) followed by Whites, which accounted for 31.0%. While there was a numerical increase in the incidence of events in AE categories in White patients when compared to Asian patients, these increases were not driven by any specific system organ class or PT.

Approximately half of the patients in the Atezo+Bev population had the etiology of Hepatitis B infection, followed by non-viral etiologies and Hepatitis C infection. A higher proportion of patients in the HCV subgroup reported Grade 3–4 AEs when compared to the HBV or non-viral subgroups. Hypertension, aspartate aminotransferase increased, and proteinuria contributed to this higher incidence of Grade 3–4 AEs in the HCV subgroup. These events are known adverse reactions with atezolizumab or bevacizumab. While a higher proportion of patients in the HCV and non-viral subgroups reported SAEs when compared to the HBV subgroup, no specific preferred terms (PTs) contributed to this difference.

The majority of patients in the Atezo+Bev population were from Asia-Pacific, followed by North America, and Europe and Middle East; the overall safety profile was mostly comparable among patients in these three regions.

The FDA's Assessment:
Overall no major differences in the toxicity profile of atezolizumab/bevacizumab were observed between the Asian and non-Asian populations in Study IMbrave150. Table 50 and Table 51 summarize the most frequent AEs by race. It appears that the incidence of some VEGF-related toxicities is higher in Asian patients in both arms (proteinuria, PPES, and dysphonia); however, the results of these subset analyses should be interpreted with caution due to the small sample sizes of these subpopulations.

Table 50 IMbrave150: Most frequent (≥ 5%) AEs in Asian vs. non-Asian subpopulations

PT	Atezo/bev; n:329 N (%)		Sorafenib; n: 156 N (%)	
	Asian N: 186	Non-Asian N: 143	Asian N: 88	Non-Asian N: 68
Diarrhea	30 (16)	32 (22)	41 (47)	36 (53)
Hypertension	58 (31)	40 (28)	24 (27)	14 (21)
Decreased appetite	31 (17)	27 (19)	19 (22)	19 (28)
Fatigue	30 (16)	37 (26)	10 (11)	19 (28)
AST increased	37 (20)	27 (19)	18 (20)	8 (12)
Pruritus	34 (18)	30 (21)	9 (10)	6 (9)
PPES	1 (1)	2 (1)	54 (61)	21 (31)
Proteinuria	46 (25)	20 (14)	7 (8)	4 (6)
Pyrexia	32 (17)	27 (19)	9 (10)	6 (9)
Rash	25 (13)	16 (11)	10 (11)	17 (25)
Abdominal pain	19 (10)	21 (15)	13 (15)	14 (21)
Constipation	21 (11)	23 (16)	11 (13)	11 (16)
Blood bilirubin increased	23 (12)	20 (14)	10 (11)	12 (18)
Nausea	21 (11)	19 (13)	13 (15)	12 (18)
ALT	27 (15)	19 (13)	7 (8)	7 (10)
Cough	19 (10)	20 (14)	9 (10)	6 (9)
Platelet count decreased	24 (13)	11 (8)	13 (15)	5 (7)
Weight decreased	18 (10)	19 (13)	6 (7)	9 (13)
Vomiting	17 (9)	16 (11)	6 (7)	7 (10)
Anemia	18 (10)	12 (8)	10 (11)	5 (7)
Asthenia	6 (3)	16 (11)	3 (3)	18 (26)
Epistaxis	20 (11)	14 (10)	5 (6)	2 (3)
Arthralgia	9 (5)	23 (16)	2 (2)	6 (9)
Dysphonia	21 (11)	7 (5)	9 (10)	2 (3)
Insomnia	14 (8)	14 (10)	4 (5)	7 (10)
Infusion related reaction	22 (12)	15 (10)	0	0
Ascites	11 (6)	12 (8)	2 (2)	7 (10)
Abdominal distension	20 (11)	3 (2)	5 (6)	0
Alopecia	1 (1)	3 (2)	15 (15)	7 (10)
Hypophosphatemia	3 (2)	4 (3)	9 (10)	2 (3)

Table 51 IMbrave150: Most frequent (≥%) Grade 3-4 AEs in Asian vs. non-Asian subpopulations

PT	Atezo/bev; n:329 N (%)		Sorafenib; n: 156 N (%)	
	Asian N: 186	Non-Asian N: 143	Asian N: 88	Asian N: 68
Diarrhea	3 (2)	3 (2)	4 (5)	4 (6)
Hypertension	30 (16)	20 (14)	11 (13)	8 (12)
Decreased appetite	2 (1)	2 (1)	1 (1)	5 (7)
Fatigue	4 (2)	4 (3)	1 (1)	4 (6)
AST increased	11 (6)	12 (8)	3 (3)	5 (7)
PPES	0	0	9 (10)	4 (6)
Proteinuria	7 (4)	3 (2)	1 (1)	0
Rash	0	0	1 (1)	3 (4)
Blood bilirubin increased	3 (2)	5 (3)	4 (5)	6 (9)
ALT increased	10 (5)	2 (1)	1 (1)	1 (1)
Platelet count decreased	6 (3)	5 (3)	0	2 (3)
Asthenia	0	1 (1)	0	4 (6)
Dyspnea	2 (1)	2 (1)	0	3 (4)
Hyponatremia	3 (2)	6 (4)	0	3 (4)
Hypokalemia	1 (1)	1 (1)	4 (5)	0
Hypophosphatemia	2 (1)	0	4 (5)	2 (3)
GGT increased	5 (3)	0	3 (3)	0
Gastrointestinal hemorrhage	1 (1)	3 (2)	0	3 (4)

An increased proportion of patients in the sorafenib arm were 65 years of age or older compared to the atezolizumab/bevacizumab arm (48% vs. 56% of patients in the atezolizumab/bevacizumab and sorafenib groups, respectively were ≥ 65 years of age). As summarized in Table 67 and Table 68 in the Appendices section, although patients ≥ 65 years of age in the atezolizumab/bevacizumab arm experienced an increased incidence (by at least 4%) of diarrhea, hypertension, decreased appetite, fatigue, arthralgia, peripheral edema, and stomatitis compared to younger patients; younger patients experienced higher incidence of some AEs such as increased ALT/AST/bilirubin, proteinuria, and rash. The tolerability of the combination regimen, however, does not appear to substantially differ between younger and older patients. In contrast, on the sorafenib arm, it appears that patients ≥ 65 years of age had increased toxicity overall; in particular, the incidence of diarrhea, decreased appetite, fatigue, PPES, proteinuria, and rash was higher in this age group.

8.2.8 Supportive Safety Data/Study GO30140

All patients enrolled in Arms A (n: 104) and F1 (n: 60) received treatment with atezolizumab/bevacizumab. Fifty-eight of the 59 patients enrolled in Arm F2 received atezolizumab monotherapy.

The median duration of exposure to study treatment for atezolizumab and bevacizumab in Arm A was 8.34 months and 8.16 months, respectively. The majority of patients (96%) experienced at least one AE. The median duration of exposure to study treatment for atezolizumab was 5.21 months in Arm F1 and 1.61 months in Arm F2. Most patients experienced at least one AE (95% and 90% in arms Arm F1 and F2 respectively). Table 52 summarizes the major safety results (excluding events that occurred in the crossover portion of Arm F2). Table 52 summarizes the major safety results (excluding events that occurred in the crossover portion of Arm F2).

Table 52 GO30140: Major safety results

	A (n: 104) N (%)	**F1 (n: 60) N (%)**	**F2 (n: 58) N (%)**
Patients with Grade 5 AEs	3 (3)	0	0
Patients with Grade 3-4 AEs	55 (53)	22 (37)	8 (14)
Patients with SAEs	46 (44)	15 (25)	6 (10)
AE leading to treatment withdrawal	10 (10)	9 (15)	5 (9)
AE leading to atezolizumab withdrawal	11 (11)	3 (5)	1 (2)
AE leading to bevacizumab withdrawal	17 (16)	5 (8)	NA
AE leading to dose interruption	50 (48)	9 (15)	5 (9)

These results, particularly the ones in Arm A, are consistent with the major safety results described in the atezolizumab/bevacizumab arm of Study IMbrave150 (Table 25). The lower incidence of Grade 3-4 AEs and SAEs in Arm F1 is likely related to the shorter duration of treatment exposure.

Table 53 provides the analysis of AEs by SOC for Study GO30140. Overall, the analysis, particularly for Arm A, is consistent with the analysis of AEs by SOC for Study IMbrave150, with the exception of the renal and urinary SOC; the incidence of AEs in the atezolizumab/bevacizumab arm of Study IMbrave150 for this SOC was 26% vs. 44% in Arm A and 27% in Arm F1 of Study GO30140. The higher incidence of AEs in the renal and urinary SOC for Arm A is exclusively driven by an increased incidence of proteinuria (40%, including 7% Grade 3 events). This degree of proteinuria has been described for Avastin and other VEGF/R targeting agents; differences observed between Studies IMbrave150 and GO30140 are likely to be random and related to the small sample sizes of the two trials.

Table 53 Study GO30140: AEs by SOC

SOC	A (n: 104) N (%)		F1 (n: 60) N (%)		F2 (n: 58) N (%)	
	All grades	Grades 3-4	All grades	Grades 3-4	All grades	Grades 3-4
Blood and lymphatic system	22 (21)	7 (7)	3 (5)	1 (2)	5 (9)	0
Cardiac	4 (4)	0	2 (3)	0	2 (3)	0
Ear and labyrinth	6 (6)	0	3 (5)	1 (2)	1 (2)	0
Endocrine	10 (10)	1 (1)	3 (5)	0	2 (3)	0
Eye	4 (4)	1 (1)	0	0	2 (3)	1 (2)
Gastrointestinal	71 (68)	20 (19)	34 (57)	6 (10)	22 (38)	1 (2)
General disorders and administration site conditions	62 (60)	5 (5)	23 (38)	1 (2)	19 (33)	0
Hepatobiliary	14 (13)	11 (11)	3 (5)	2 (3)	2 (3)	1 (2)
Infections and infestations	45 (43)	10 (10)	17 (28)	3 (5)	8 (14)	0
Injury, poisoning and procedural complications	14 (13)	0	3 (5)	0	4 (7)	1 (2)
Investigations	52 (50)	23 (22)	17 (28)	4 (7)	18 (31)	4 (7)
Metabolism and nutrition	46 (44)	11 (11)	13 (22)	3 (5)	11 (19)	1 (2)
Musculoskeletal and connective tissue	33 (32)	3 (3)	17 (28)	0	13 (22)	0
Neoplasms benign, malignant and unspecified	0	0	2 (3)	0	0	0
Nervous system	25 (24)	7 (7)	15 (25)	2 (3)	8 (14)	0
Psychiatric	20 (19)	2 (2)	3 (5)	1 (2)	5 (9)	0
Renal and urinary	46 (44)	8 (8)	16 (27)	3 (5)	4 (7)	0
Reproductive system and breast	7 (7)	0	3 (5)	0	1 (2)	0
Respiratory, thoracic and mediastinal	48 (46)	5 (5)	22 (37)	4 (7)	11 (19)	0
Skin and subcutaneous tissue	43 (41)	0	24 (40)	0	15 (26)	0
Surgical and medical procedures	2 (2)	0	2 (3)	0	1 (2)	0
Vascular	23 (22)	15 (14)	14 (23)	5 (8)	3 (5)	1 (2)

Overall, toxicity by SOC in Study GO30140, particularly Arm A is consistent with the profile observed in IMbrave150, with the exception of the renal and urinary SOC: incidence of AEs in the atezolizumab/bevacizumab arm in IMbrave 150 was 26% vs. 44% in Arm A and 27% in Arm F1 of Study GO30140. The higher incidence of AEs in Arm A is exclusively driven by an increased incidence of proteinuria (40%, including 7% Grade 3 events). This level of proteinuria has been described before in other Avastin and VEGF/R targeting agents; differences observed between

Studies IMbrave150 and GO30140 are likely a random variation between studies. Table 54 summarizes the incidence of AEs by HLT.

Table 54 Study GO30140: AEs by HLT (incidence ≥ 5%)

HLT	A (n: 104) N (%)		F1 (n: 60) N (%)		F2 (n: 58) N (%)	
	All grades	Grades 3-4	All grades	Grades 3-4	All grades	Grades 3-4
Urinary abnormalities	40 (38)	7 (7)	14 (23)	3 (5)	1 (2)	0
Asthenic conditions	37 (36)	2 (2)	13 (22)	0	6 (10)	0
Appetite disorders	36 (35)	1 (1)	8 (13)	0	8 (14)	0
Gastrointestinal and abdominal pains	28 (27)	4 (4)	13 (22)	0	6 (10)	0
Liver function analyses	27 (26)	11 (11)	6 (10)	3 (5)	11 (19)	4 (7)
Rashes, eruptions and exanthems	27 (26)	0	15 (25)	0	7 (12)	0
Febrile disorders	24 (2)	2 (2)	6 (10)	1 (2)	8 (14)	0
Diarrhea	23 (3)	3 (3)	9 (15)	1 (2)	7 (12)	0
Gastrointestinal atonic and hypomotility disorders	22 (22)	1 (1)	5 (8)	0	3 (5)	0
Pruritus	22 (21)	0	3 (5)	0	8 (14)	0
Vascular hypertensive disorders	22 (21)	15 (14)	10 (17)	3 (5)	1 (2)	1 (2)
Coughing and associated symptoms	21 (20)	0	6 (10)	0	8 (14)	0
Edema	21 (20)	0	6 (10)	0	5 (9)	0
Upper respiratory tract infections	21 (20)	0	9 (15)	0	5 (9)	0
Platelet analyses	19 (18)	5 (5)	5 (8)	0	4 (7)	0
Upper respiratory tract signs and symptoms	18 (17)	0	8 (13)	0	1 (2)	0
Musculoskeletal and connective tissue pain and discomfort	17 (16)	1 (1)	9 (15)	0	11 (19)	0
Nausea and vomiting symptoms	17 (16)	2 (2)	4 (7)	0	8 (14)	0
Joint related signs and symptoms	16 (15)	0	8 (13)	0	4 (7)	0
Anemias	15 (14)	3 (3)	1 (2)	1 (2)	2 (3)	0
Protein metabolism disorders	14 (13)	2 (2)	4 (7)	1 (2)	3 (5)	0
Nasal disorders	13 (13)	0	7 (12)	0	1 (2)	0
Disturbances in initiating and maintaining sleep	12 (12)	0	1 (2)	0	4 (7)	0
Dyspeptic signs and symptoms	12 (12)	0	2 (3)	0	1 (2)	0
Stomatitis and ulceration	12 (12)	1 (1)	6 (10)	0	4 (7)	0
Breathing abnormalities	11 (11)	2 (2)	4 (7)	3 (5)	3 (5)	0
Physical examination procedures and organ system status	11 (11)	2 (2)	2 (3)	0	2 (3)	0
Tissue enzyme analyses	11 (11)	2 (2)	0	0	3 (5)	0
Flatulence, bloating and distension	10 (10)	0	3 (5)	1 (2)	4 (7)	0

The HLT analysis of Study GO30140 is generally consistent with the HLT analysis of IMbrave150, taking into account the variability expected between studies and considering the difference in the incidence of proteinuria described above.

Table 55 summarizes the most frequently observed AEs by PT (occurring at an incidence of at least 10%); lab-specific terms (i.e., neutrophils decreased) were not included in this table as these will be analyzed in the lab subsection. Clinical terms related to these lab abnormalities (i.e., neutropenia) are included in the table.

Table 55 Study GO30140: AEs by PT (incidence ≥ 10%)

PT	A (n: 104) N (%)		F1 (n: 60) N (%)		F2 (n: 58) N (%)	
	All grades	Grades 3-4	All grades	All grades	Grades 3-4	All grades
Proteinuria	38 (37)	7 (7)	14 (23)	3 (5)	0	0
Decreased appetite	36 (35)	1 (1)	8 (13)	0	8 (14)	0
Fatigue	29 (28)	1 (1)	12 (20)	0	5 (9)	0
Pyrexia	24 (23)	2 (2)	6 (10)	1 (2)	8 (14)	0
Rash	24 (23)	0	12 (20)	0	6 (10)	0
Diarrhea	23 (23)	3 (3)	9 (15)	1 (2)	7 (12)	0
Hypertension	22 (21)	15 (14)	9 (15)	3 (5)	1 (2)	1 (2)
Abdominal pain	21 (20)	4 (4)	9 (15)	0	4 (7)	0
Pruritus	21 (20)	0	3 (5)	0	8 (14)	0
Constipation	20 (19)	1 (1)	5 (8)	0	3 (5)	0
Cough	17 (16)	0	4 (7)	0	5 (9)	0
Edema peripheral	17 (16)	0	5 (8)	0	4 (7)	0
Arthralgia	16 (15)	0	8 (13)	0	4 (7)	0
Anemia	15 (14)	3 (3)	1 (2)	1 (2)	2 (3)	0
Dysphonia	14 (13)	0	3 (5)	0	0	0
Nausea	14 (13)	2 (2)	4 (7)	0	6 (10)	0
Epistaxis	13 (13)	0	7 (12)	0	1 (2)	0
Hypoalbuminemia	13 (13)	2 (2)	4 (7)	1 (2)	3 (5)	0
Dyspepsia	12 (12)	0	1 (2)	0	1 (2)	0
Insomnia	12 (12)	0	1 (2)	0	4 (7)	0
Upper respiratory tract infection	11 (11)	0	5 (8)	0	3 (5)	0

The analysis of AEs by preferred term shows variability in the incidence of several toxicities between the atezolizumab/bevacizumab combination arm in Study IMbrave150 and Arms A and F1 in Study GO30140. The incidence of proteinuria, decreased appetite, fatigue, fever, rash, abdominal pain, constipation, arthralgia, anemia, hypoalbuminemia, and upper respiratory tract infection was ≥ 5% higher in Arm A than in Study IMbrave150; diarrhea and hypertension

were ≥ 5% higher in Study IMbrave150 than in Arm A (and F1). The incidence of rash in Arm F1 was ≥ 5% higher than in IMbrave 150, but proteinuria, fever, hypertension, constipation, and anemia were higher in IMbrave150 when compared to Arm F1. These differences are likely related to the inherent variability observed in clinical studies, particularly those with small sample sizes.

Table 56 summarizes the hepatobiliary SOC and liver labs reported as AEs (for Arms F, data limited before the crossover period) in at least 2 patients.

Table 56 Study GO30140: Hepatobiliary and liver-related labs AEs

	A (n: 104) N (%)	**F1 (n: 60) N (%)**	**F2 (n: 58) N (%)**
AST increased	16 (15)	3 (5)	8 (14)
Bilirubin increased	14 (13)	4 (7)	7 (12)
ALT increased	12 (12)	3 (5)	5 (9)
Alkaline phosphatase increased	11 (11)	0	3 (5)
Hyperbilirubinemia	4 (4)	0	0
GGT increased	2 (2)	0	0
Hepatic function abnormal	1 (1)	2 (3)	0

At the time of the data cutoff date, there were 47 deaths (45%) in Arm A. The most common cause of death was PD (40/47). The following fatal AEs were reported in 7 patients: cirrhosis, hepatic function abnormal, bacteremia, bacterial peritonitis, cardiac arrest, upper gastrointestinal hemorrhage, and pneumonitis. Most (85%) deaths occurred more than 30 days after the last dose of the combination treatment.

At the time of the data cutoff date there were 16 deaths (27%) in Arm F1 and 17 deaths (29%) in the F2 arm. All deaths in the F1 arm and 16 deaths in Arm F2 were attributed to PD. The majority (75% and 82% in Arms F1 and F2 respectively) of deaths occurred more than 30 days after the last dose of the treatment.

Median treatment duration in Arm A was 8.34 months (range 0-34.3 months) and the median number of atezolizumab doses was 11.5 (range: 1.0-50.0). In Arm A, 18 patients (17%) discontinued at least one treatment component due to toxicity. The most common cause (38%) of toxicity-related treatment discontinuation was hemorrhage (esophageal hemorrhage varices [2], gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, intraperitoneal hemorrhage, and subarachnoidal hemorrhage); other AEs leading to discontinuation of treatment were dyspnea, bacterial peritonitis, proteinuria, cervical cord compression, increased bilirubin, leukoencephalopathy, cholangitis, drug-induced liver injury, autoimmune encephalitis, hepatic liver function abnormal, adrenal insufficiency, and duodenal ulcer perforation. AEs leading to interruption of any treatment component were reported in 50 patients (48); the most commonly reported AE leading to treatment interruption was proteinuria (19%).

In Arm F1, median treatment duration was 5.21 months (range: 0 -11.3 months and) the median number of atezolizumab doses was 8.5 months (range: 1-17). Six patients (10%) discontinued treatment because of an AE; AEs leading to treatment discontinuation included hypertensive nephropathy, proteinuria, duodenal ulcer hemorrhage, epistaxis, fever, Guillain Barre syndrome, and anxiety. In the F1 arm, 15% of patients required treatment interruption, with proteinuria being the only AE leading to treatment interruption in at least 5% of patients.

AESIs for atezolizumab were reported in 67%, 40%, and 41% of patients in Arms A, F1, and F2, respectively. The most common AESIs in Arm A were immune-related hepatitis (38%), immune-related rash (29%), immune-related hypothyroidism (10%), and infusion-related reaction (5%). In Arm F1, the most common atezolizumab-related AESIs were immune-related rash (25%), immune-related hepatitis (17%), and immune-related hypothyroidism (5%). In Arm F2, the most common atezolizumab-related AESIs were immune-related hepatitis (22%) and immune-related rash (14%). Fourteen percent, 8%, and 3% of patients in Arms A, F1, and F2, respectively, required systemic corticosteroid treatment for AESIs.

Hepatobiliary events (excluding cross-over period) are summarized in Table 56. The vast majority of rashes are non-descript (PT; rash). All events were Grade 1-2, none of these AESIs led to drug interruption or withdrawal of atezolizumab; three patients required treatment with corticosteroids.

The incidence and nature of AESIs for atezolizumab observed in Study GO30140 are consistent with the profile observed in Study IMbrave150.

AESIs for bevacizumab that occurred in at least 2 patients in Study GO30140 are summarized in Table 57. The most common hemorrhage-related AE reported as a single PT was epistaxis (13% and 12% of patients in Arms A and F1, respectively), followed by gastrointestinal hemorrhages (excluding gingival bleeding) which were reported in 13% and 7% of patients, respectively.

Table 57 Study GO30140: bevacizumab-related AESIs

	A (n: 104) N (%)	**F1 (n: 60) N (%)**	**F2 (n: 58) N (%)**
Proteinuria	38 (37)	14 (23)	1 (2)
Hemorrhage	30 (29)	12 (20)	4 (7)
Hypertension	22 (21)	11 (18)	1 (2)
Gastrointestinal perforation	3 (3)	0	0
Thromboembolic arterial event	3 (3)	2 (3)	0
Thromboembolic venous event	2 (2)	0	1 (2)

Of note, there was one event each of congestive heart failure and posterior reversible encephalopathy (both in Arm A) and two events of wound healing complications (Arms A and F1). Grade 3-4 events were observed in 7 (7%), 3 (5%) and 1 (2%) patients in Arms A, F1 and F2, respectively. One patient in Arm A died of upper gastrointestinal hemorrhage.

The incidence and nature of AESIs for bevacizumab are consistent with the profile observed in Study IMbrave150 and the know toxicity profile of Avastin.

Table 58 summarizes the clinically significant shifts in laboratory parameters (from Grade 0-2 to 3-4); shifts in potassium, calcium, and coagulation parameters were observed in ≤2% patients and are therefore not included in this table.

Table 58 Study GO30140: Lab shifts to Grade 3-4

	A (n: 104) N (%)	**F1 (n: 60) N (%)**	**F2 (n: 58) N (%)**
Chemistry			
Low albumin	6 (6)	3 (5)	0
ALT	4 (4)	1 (2)	2 (3)
AST	16 (16)	8 (14)	8 (14)
ALK	7 (7)	1 (2)	1 (2)
Bilirubin	10 (10)	6 (10)	4 (7)
Glucose (high)	10 (10)	5 (9)	5 (9)
Sodium (low)	15 (15)	7 (12)	9 (15)
Phosphorus (low)	4 (4)	5 (9)	1 (2)
Hematology			
Lymphocytes (low)	16 (15)	5 (9)	5 (9)
ANC (low)	5 (5)	0	1 (2)
Platelets (low)	5 (5)	3 (5)	1 (2)
Hemoglobin (low)	3 (3)	1 (2)	1 (2)

TSH abnormalities were reported in 38%, 23%, and 8% of patients in Arms A, F1, and F2, respectively; most patients with TSH abnormalities had high TSH levels, indicative of hypothyroidism.

These laboratory shifts are consistent with the underlying disease in patients enrolled in Study GO30140, the known toxicity profile of atezolizumab and bevacizumab, and the results of Study IMbrave150.

In conclusion, overall, the safety profile of atezolizumab and bevacizumab observed in Study GO30140 is consistent with the findings of Study IMbrave150, the known safety profile of each drug, and the underlying disease of patients enrolled in this trial. No new safety signals related to the combination therapy and no unexpected AEs were identified.

8.2.9 Specific Safety Studies/Clinical Trials

The Applicant's Position:

No studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:
Not applicable.

8.2.10 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
Not relevant to this application.

Human Reproduction and Pregnancy
The Applicant's Position:

No new information is provided in the current submission. No pregnancies were reported in the HCC studies.

The FDA's Assessment:
The atezolizumab USPI contains a warning that its use can cause fetal harm when administered to pregnant women. The bevacizumab USPI contains a warning that bevacizumab may cause fetal harm in pregnant women. No new information is provided in the current submission.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:

No new information related to pediatrics is provided in the current submission.

The FDA's Assessment:
The Avastin USPI contains data on physeal dysplasia and the use of bevacizumab in children. There is no data on the safety and effectiveness of atezolizumab in children in the atezolizumab USPI. No new information is provided in the current submission.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
Not relevant to this application.

8.2.11 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:

As of 17 May 2019, atezolizumab has been globally approved for the treatment of a variety of cancers, including NSCLC, SCLC, UC and triple-negative breast cancer. Since the International Birth Date (18 May 2016) through 17 May 2019, an estimated cumulative total of (b) (4) patients have received atezolizumab from marketing experience (United States N= (b) (4); European Economic Area N= (b) (4); Japan N= (b) (4); Rest of the World N= (b) (4)).
No new safety signals were identified in the post-marketing setting for atezolizumab used as monotherapy or in approved combination therapies

The FDA's Assessment:
The safety profile observed in Studies IMbrave150 and GO30140 are consistent with the known safety profile of each of these biologics products, which are well characterized. The post-marketing database may be used for the identification of rare immune-mediated toxicities or autoimmune diseases related to atezolizumab that have not been identified to date. Bevacizumab has been on the market since 2004 and no new safety signals have been identified in recent years.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:

Not Applicable

The FDA's Assessment:
No safety-related PMRs or PMCs are planned.

8.2.12 Integrated Assessment of Safety

The Applicant's Position:

Overall, the Atezo+Bev combination in HCC was generally well-tolerated with manageable toxicities. The incidence of the safety events should be interpreted in the context of the considerably longer duration of treatment with Atezo+Bev compared with sorafenib. While the spectrum of AEs differed between Sorafenib and Atezo+Bev, the safety profile observed in both HCC populations was consistent with the known risks of the individual study treatments and the underlying disease.

The incidences of AEs, Grade 3-4 AEs, Grade 5 AEs, and AEs leading to any treatment withdrawal were comparable between the Sorafenib and the Atezo + Bev populations. From a clinical perspective, the two most common AEs of hypertension and proteinuria with Atezo+Bev are generally not associated with symptoms and therefore, have less detrimental impact on the

patients' quality of life compared with the most common AEs observed in the Sorafenib arm; diarrhea and palmar-plantar erythrodysesthesia syndrome. These AEs are by nature symptomatic requiring intervention and with likely impact on patients' quality of life. The proportion of patients with SAEs was numerically higher in the Atezo+Bev population compared with the Sorafenib population. However, the incidence of treatment-related SAEs was comparable between the two arms, with no particular pattern of certain events driving the numerical increase observed between the two populations. The incidence of AEs leading to dose modification/interruption of any study treatment was lower in the Atezo+Bev population compared with the Sorafenib population. Clinical laboratory results, vital signs and ECG observations showed no unexpected safety findings for the Atezo + Bev combination.

The incidence of atezolizumab-specific AESIs in the Atezo+Bev population was consistent with the known safety profile of atezolizumab and the underlying disease. No new atezolizumab AESIs were identified in the Atezo+Bev population. An increased incidence of immune-mediated hepatitis was expected in the Atezo+Bev population given the underlying liver disease. This was further affirmed by the similar incidence of immune-mediated hepatitis observed in the Atezo Mono (HCC) and Sorafenib populations. An increased incidence of IRRs was also observed in the Atezo + Bev population, however the clinical impact of these IRRs was very limited as these events were predictable, reversible and manageable.

The spectrum, frequency, and severity of bevacizumab AESIs were in line with the safety profile of bevacizumab and with the underlying disease. No new bevacizumab AESIs were identified in the Atezo+Bev population. A comparable proportion of patients (<2% difference) in the Sorafenib and Atezo+Bev populations experienced events under the concept of upper gastrointestinal bleeding, which is a common complication in patients with HCC. Overall, the incidence of upper gastrointestinal bleeds observed in the Atezo+Bev population was as expected, based on the underlying disease and the known safety profile of bevacizumab, and consistent with historical data in other HCC trials with bevacizumab monotherapy (Boige et al 2012 and Siegel et al 2008).

The FDA's Assessment:

The Applicant submitted data from studies including 493 patients with HCC treated with atezolizumab/bevacizumab, 93 patients with HCC treated with atezolizumab monotherapy, 156 patients with HCC treated with sorafenib, and a pooled database of 3085 patients treated with atezolizumab monotherapy for different solid tumors. Across clinical studies (IMbrave150 and Arm F of Study GO30140), the safety profile of the combination of atezolizumab/bevacizumab is consistent. Although an increased incidence (11%) of infusion-related reactions was observed when compared with a historical incidence of these reactions of <2% in a pooled data analysis across atezolizumab clinical development, the IRR occurring in IMbrave150 were mostly Grade 1-2 and did not result in an increased incidence of treatment discontinuation. All AEs observed are either known adverse reactions of one or more of the combination components or are anticipated in the studied population; no new safety signals were identified. In the pivotal study IMbrave150, most patients (99% and 98% in the atezolizumab/bevacizumab and sorafenib arms, respectively) experienced an AE; a similar proportion of patients (60% and 58% of patients in the atezolizumab/bevacizumab and sorafenib arms, respectively) experienced Grade

3-4 AEs and fatal AEs (5% and 6% of patients in the atezolizumab/bevacizumab and sorafenib arms, respectively). As expected, the safety profile observed was different in the two treatment arms. The most common AEs in the atezolizumab/bevacizumab arm were hypertension (30%), fatigue/asthenia (26%), proteinuria (20%), pruritus (19%), and fever (18%). The most common AEs in the sorafenib arm were diarrhea (49%), PPES (48%), fatigue/asthenia (32%), hypertension (24%), and decreased appetite (24%). Hypertension was the most commonly reported Grade 3-4 AE in both populations (15% vs. 12%), followed by fatigue/asthenia (7% in both arms). Grade 3-4 proteinuria was the only AE with a higher incidence (difference of at least 2%) in the atezolizumab/bevacizumab arm (3% vs. 1% respectively); Grade 3-4 PPES, diarrhea, decrease appetite, rash, and hypophosphatemia were more frequent in the sorafenib arm. Deaths due to gastrointestinal hemorrhage were numerically higher in the combination arm (4 vs. 1 in the combination and sorafenib arms, respectively), but the incidence is very similar. The rates of discontinuation of atezolizumab and sorafenib due to AEs were comparable (9% vs. 10%), although more patients required discontinuation of bevacizumab treatment; however, the majority of patients (61%) required sorafenib dose modifications or interruptions. Importantly, the median duration of treatment was 7.4 months in the combination arm and 2.8 months in the sorafenib arm. Although the incidence of AEs was similar between arms (and the incidence of AEs was higher in both arms for the first 3 months of treatment), as patients in the atezolizumab/bevacizumab arm had a much longer median duration of exposure, the increased incidence of AEs observed in the atezolizumab/bevacizumab arm compared to the sorafenib arm over time should be interpreted in the context of the differences in exposure between arms. The reason for discontinuation of treatment was disease progression for the majority of patients in both arms.

When comparing AESI between the HCC population treated with atezolizumab/bevacizumab and the pooled atezolizumab monotherapy population, no new immune-mediated events were identified but the incidence of AESI was higher in the atezolizumab/bevacizumab population (65%) compared with the monotherapy HCC population (52%) and the pooled solid tumor population (34%). This difference was mainly driven by the SMQ immune-mediated hepatitis and infusion-related reactions. As analyzed above, due to the composition of the SMQ, a similar proportion of patients in both arms of IMbrave150 experienced an event of “immune-related hepatitis” (12% and 13% patients in the atezolizumab/bevacizumab and sorafenib arms respectively). Eight (2%) patients in the atezolizumab/bevacizumab arm required treatment with steroids for events (Grades 2-5) of autoimmune hepatitis/immune-mediated hepatitis. Both “autoimmune hepatitis” and “infusion-related reactions” SMQs are too broad to accurately characterize the true incidences of autoimmune hepatitis and infusion-related reactions, and these data should be interpreted with caution.

Sorafenib and lenvatinib are the current standard of care for the first-line treatment of patients with unresectable or metastatic HCC. Sorafenib has a modest benefit-risk profile given the known toxicity and modest efficacy conferred by sorafenib treatment. The toxicity profile of atezolizumab/bevacizumab in patients with HCC is different than the sorafenib profile. Although similar incidences of AEs, Grade 3-4 AEs, deaths, and treatment discontinuation were observed in the arms of Study IMbrave150, these events occurred over a longer period of time

in the atezolizumab/bevacizumab arm compared to the sorafenib arm, reflecting a more favorable safety profile overall for atezolizumab/bevacizumab. The risk:benefit relationship for the use of atezolizumab/bevacizumab in patients with unresectable or metastatic HCC is favorable.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

Other than the issue found in the primary analyses of ORR per RECIST/mRECIST regarding the analysis population in Study IMbrave150 which was not the ITT population, the statistical reviewer found no major statistical issue that impacted the overall conclusions.

8.4 Conclusions and Recommendations

The FDA's Assessment:

Based on data from Study IMbrave150, patients randomized to Atezo+Bev had a statistically significant and clinically meaningful improvement in OS (p-value=0.0006), PFS (p-value<0.0001) and ORR (p-value<0.0001) by IRF-assessment per RECIST 1.1 and by IRF-assessment per HCC mRECIST 1.1 compared to the patients randomized to Sorafenib. The estimated HR for OS and PFS are 0.58 (95% CI: 0.42, 0.79) and 0.59 (95% CI 0.47, 0.76) in favor of Atezo+Bev, respectively. The estimated median OS for Atezo + Bev had not been reached yet at the time of the OS analysis, while the estimated median OS was 13.2 months (95% CI: 10.4, not reached) in the Sorafenib arm.

X Xiaoping (Janet) Jiang	X Lisa Rodriguez
Primary Statistical Reviewer	**Statistical Team Leader**
X Sandra Casak	X Martha Donoghue
Primary Clinical Reviewer	**Clinical Team Leader**

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

These supplemental applications were not referred to an Advisory Committee meeting given the improvement in overall survival which represents unequivocal benefit.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

The Applicant's Position:

Not Applicable as the applicant has not proposed any pediatric sections in the proposed labeling.

The FDA's Assessment:
Atezolizumab and bevacizumab received orphan drug designation for the treatment of HCC on January 8, 2018; therefore, these supplemental applications are exempt from the requirements under the Pediatric Research Equity Act (PREA).

11 Labeling Recommendations

Data:

TECENTRIQ label		
Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1.5 Indications and Usage, Hepatocellular Carcinoma	Extended the indication to include the use of TECENTRIQ in combination with bevacizumab for the treatment of patients with unresectable HCC who have not received prior systemic therapy.	Indication changed: TECENTRIQ in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy
2.2.6 Recommended Dosage	Included dosing information for TECENTRIQ in combination with bevacizumab in HCC.	Minor editorial changes to GNE's proposal
2.7 Dose Modifications	Included recommendations for the occurrence of Hepatitis for patients with HCC	Minor editorial changes to GNE's proposal
6.1 Adverse Reactions, Clinical Trial Experience with HCC	Included information from Study IMbrave150	Information edited to group terms (e.g., (b) (4) , etc.) thus avoiding

		granularity and adding value to prescribers.
6.2 Immunogenicity		Addition of immunogenicity data from Study IMbrave150 and the impact of ADA development in efficacy outcomes
8.5 Use in Specific Populations, Geriatric Use	Modified language to incorporate data from Study IMbrave150.	No edits.
12.3 Special Populations	Included language to reflect moderate hepatic impairment data from IMbrave150	Addition of ADA language.
14 Clinical Studies, HCC	Included information from Studies IMbrave150 (b) (4).	Deletion of (b) (4) Deletion of (b) (4) Addition of outcomes for ADA+ patients. Deletion of (b) (4)

AVASTIN label		
Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1.7 Indications and Usage, Hepatocellular Carcinoma	Extended the indication to include the use of Avastin in combination with atezolizumab for the treatment of patients with unresectable HCC who have not received prior systemic therapy.	Indication changed: TECENTRIQ in combination with bevacizumab for the treatment of patients with <u>unresectable or metastatic</u> HCC who have not received prior systemic therapy
2.8 Recommended Dosage	Included dosing information for Avastin in combination with atezolizumab in HCC.	

5 Warnings and Precautions		Updated and/or verified incidence rates reported "across all studies". 5.3 Hemorrhage: Added evaluation for the presence of varices in patients with HCC and Avastin not recommended in patients with variceal bleeding within 6 months prior to treatment, untreated or incompletely treated varices with bleeding, or high risk of bleeding.
6.1 Adverse Reactions, Clinical Trial Experience with HCC		Included information from Study IMbrave150.
14.10 Clinical Studies, HCC	Included information from Study IMbrave150.	Deletion of (b) (4) [redacted]

The Applicant's Position:

The results presented in the dossier from Study IMbrave150 supported by the data from Study GO40140 which provides meaningful information regarding the single agent attribution to the combination, demonstrates the benefits of TECENTRIQ in combination with bevacizumab for HCC patients in clinical practice.

The Applicant believes that the magnitude of clinical benefit and the acceptable safety profile seen in both studies, confirm the positive benefit-risk balance of treatment in the patient population enrolled in the clinical trial. As such, the Applicant recommends that TECENTRIQ in combination with bevacizumab should be made available to patients with HCC according to the following proposed indication:

"TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy."

The FDA's Assessment:

FDA agrees that the risk:benefit for the use of atezolizumab and bevacizumab for the treatment

of patients with advanced unresectable or metastatic HCC is favorable.

APPEARS THIS WAY
ON ORIGINAL

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS have been requested. Both antibodies have been used extensively in cancer patients.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
No PMRs and PMCs have been requested.

APPEARS THIS WAY ON ORIGINAL

14 Division Director (DHOT) Comments (NME Only)

X X

X X

APPEARS THIS WAY
ON ORIGINAL

15 Division Director (OCP) Comments

X X

X X

APPEARS THIS WAY
ON ORIGINAL

16 Division Director (OB) Comments

X X

X X

APPEARS THIS
WAY ON ORIGINAL

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X X

X X

APPEARS THIS WAY
ON ORIGINAL

17 Division Director (Clinical) Comments

I agree with the review teams' recommendations regarding the approvability of these applications for atezolizumab and bevacizumab for the treatment of patients with hepatocellular carcinoma. Given the improvement in overall survival observed in IMbrave 150, atezolizumab in combination with bevacizumab will represent a new standard of care in properly selected patients with hepatocellular carcinoma and Child-Pugh class A cirrhosis.

X Steven Lemery

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.1 References

The Applicant's References:

American Cancer Society. Key Statistics About Liver Cancer. www.cancer.org/cancer/liver-cancer/about/what-is-key-statistics.html. Accessed 12-Dec.

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YauT, Park JW, Finn RS, et al. LBA38_PR 'Checkmate 459: A randomized, multi-center phase 3 study of nivolumab (nivo) vs sorafenib (sor) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (AHCC)' Annals of Oncology, Volume 30, Supplement 5, October 2019.

Additional references in FDA's sections:

Abou-Alfa G., Shi Q., Knox J. et al. Assessment of Treatment With Sorafenib Plus Doxorubicin vs Sorafenib Alone in Patients With Advanced Hepatocellular Carcinoma: Phase 3 CALGB 80802 Randomized Clinical Trial JAMA Oncol 2019 Sep 5;5(11):1582-1588.

19.2 Financial Disclosure

The Applicant's Position:

For further information for financial disclosures for studies presented in the sBLA please see Module 1.3.4 submitted on December 2, 2019 (Sequence No. 0820).

The FDA's Assessment:

[FDA will complete this section.]

Covered Clinical Study (Name and/or Number):*

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1009		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): none		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____		

Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study #2: GO30140: An Open-label, Multicenter Phase Ib Study of the Safety and Efficacy of Atezolizumab (Anti-PD-L1 Antibody) Administered in Combination with Bevacizumab and/or Other Treatments in Patients with Solid Tumors (Arms A and F only)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 368		
Number of investigators who are sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: yes Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in sponsor of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) one		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

19.3 Nonclinical Pharmacology/Toxicology

Data:

None

The FDA's Assessment:
New non-clinical data were not reviewed as part of these efficacy supplements.

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

Summary of Findings

The clinical pharmacology review is mainly focusing on the assessment of treatment-emergent anti-drug antibodies (ADA) for atezolizumab on PK and efficacy:

1. ADA positive rate is 27.9% (88/315 patients) and 20% (58/288 patients) at week 6 landmark. Majority (66%) of these patients were tested ADA positive prior to receiving the third dose of atezolizumab.
2. Clearance in ADA positive subgroup increased by 49% compared with ADA negative subgroup by post-hoc comparison.
3. Sponsor-proposed IPW analysis to adjust the imbalanced covariates between ADA positive and ADA negative subgroups. Based on IPW analysis, overall survival hazard ratio with 95% confidence interval (95%CI) compared with sorafenib for ADA week 6 positive and ADA week 6 negative group is 0.93 (0.57, 1.53) vs. 0.39 (0.26, 0.60) with 16 covariates adjusted.

19.4.1 What is the impact of immunogenicity on pharmacokinetics in Study IMbrave150?

Clearance in ADA positive subgroup increased by 49% (Ratio of ADA+ clearance vs. ADA- clearance: 0.289/0.194=1.49) compared with ADA negative subgroup by post-hoc comparison (Table 59). In the population pharmacokinetics analysis, the clearance was increased by 16% after accounting for other important baseline covariates in treatment emergent ADA-positive patients as compared to treatment-emergent ADA-negative patients.

Table 59: Summary of Geometric Mean [CV%] on Atezolizumab Clearance and Exposure Metrics by ADA Status

Variable (unit)	ADA Negative N=227	ADA Positive N=88	p-value	Ratio (95%CI)
Clearance (L/d)	0.194 [36.5]	0.289 [35.6]	2.81E-16	0.671 (0.616,0.732)
C_{max}, Cycle 1 (μg/mL)	387 [20.4]	362 [18.3]	6.21E-03	1.07 (1.02,1.12)
C_{min}, Cycle 1 (μg/mL)	77.1 [37.6]	56.6 [40.3]	1.31E-09	1.36 (1.24,1.5)
AUC_{0-21}, Cycle 1 (μg.day/mL)	3000 [21.3]	2500 [20.5]	5.98E-11	1.2 (1.14,1.26)

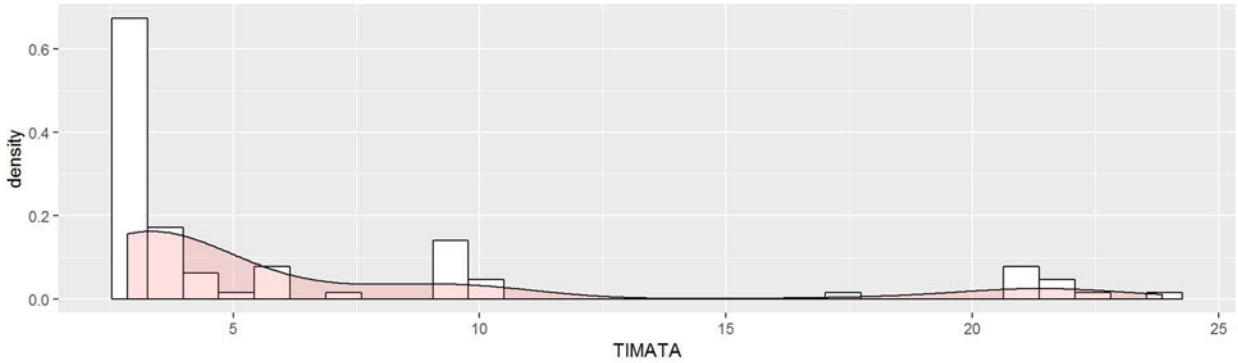
Source: Table 9 of population PK report (Report # 1099305)

19.4.2 What is ADA Onset Rate and Onset Time in Study IMbrave150?

ADA positive rate is 27.9% (88/315 patients) tested as ADA positive in study IMbrave150 with 6.25% (21/336) ADA status missing.

Consistent with previous findings for atezolizumab monotherapy treatments, ADA for atezolizumab onset time is very early. Around 66% (58/88) of ADA were produced after the first or second injection and were detectable at week 6 before patients received the third dose of atezolizumab (Figure 12). The median time to onset of ADAs among treatment-emergent ADA-positive patients was 3.14 weeks, which corresponding to the first scheduled ADA sampling timepoint (3 weeks) following the start of treatment in atezolizumab plus bevacizumab arm. The median duration of ADA-positive status was 0.14 weeks (range: 0.1 – 42.1 weeks) indicating most patients could only be tested positive for one occasion. However, this is likely due to the relative low drug tolerance of ADA assay (200 ug/mL with 500ng/mL ADA) used in study IMbrave150 and lead to a under detection of later ADA. Steady state atezolizumab Cmin is 163 ug/mL [61.9] which is more than 2 times of first cycle Cmin (70.8 ug/mL [40.8]). Atezolizumab ADA week 6 positive rate is 20 (58/288). The following landmark analysis was based on ADA status by week 6.

Figure 12: Summary of Atezolizumab ADA Onset Time in Study IMbrave150



Source: Reviewer's independent analysis (X axis unit week).

19.4.3 Landmark Analysis of Atezolizumab ADA on Efficacy

An exploratory landmark analysis based on ADA status at week 6 were conducted. HCC patients in both arms who had event or censored before week 6 were removed. There is a little discrepancy between FDA's ADA week 6 positive rate (57/312) versus sponsor's ADA week 6 positive rate (58/288). Sponsor's denominator excluded 28 later onset ADA positive patients and lead to 58 ADA week 6 positive patients and 230 ADA negative patients. FDA's early ADA status grouped based on status at week 6 is listed in Table 60. FDA's analysis has 57 ADA week 6 positive patients and 255 ADA week 6 negative patients (including 227 ADA negative patients and 28 later ADA onset patients). This minor difference should not significantly change the result.

Table 60: ADA Status at Week 6 in IMbrave150

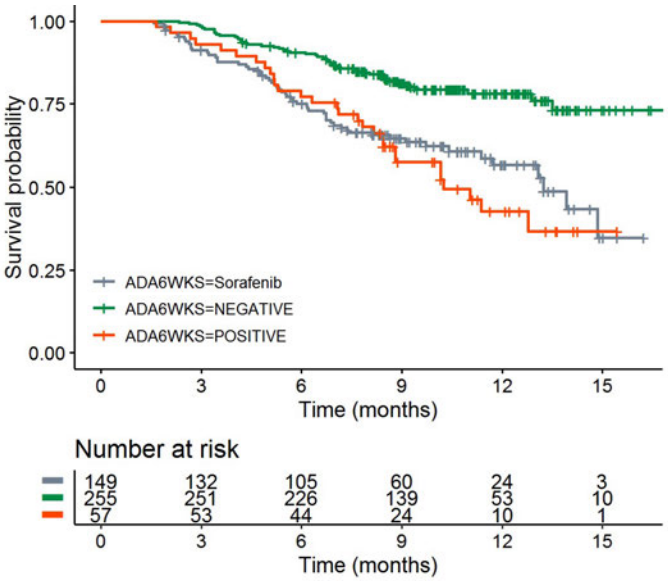
ADA week 6 status	N (%)
MISSING	11/ 323 (3.4%)
ADA+ week 6	57/ 312 (18.3%)
ADA- week 6	255/312 (81.3%)

Source: Reviewer's independent analysis

OS results based on ADA status at week 6:

The results of landmark OS analysis were shown in (Figure 13, Table 61, Figure 14). Patients had death event before week 6 were removed from the analysis. Shown in Table 61, the death rate is 51% in atezolizumab early ADA positive subgroup, which is higher than the 20% death rate in the ADA negative group. The death rate is 40% in the sorafenib arm for the landmark analysis. The median OS time in the ADA positive subgroup is 10.3 (8.44, NA) months which is shorter than the median OS time (not reached) for the ADA negative subgroup. The median survival time is 13.2 (11.37, NA) months in the sorafenib arm. The hazard ratio compared to the sorafenib arm without adjustment for stratification factors was 1.19 (0.76, 1.85) in the ADA positive group, compared with 0.42 (0.29, 0.61) in the ADA negative group. Based on the multivariate Cox regression analysis, the hazard ratio with 95% confidence interval (95%CI) compared with sorafenib for ADA week 6 positive and ADA week 6 negative group is 0.95 (0.61, 1.49) vs. 0.41 (0.28, 0.59) adjusted for stratification factors including: geographic region (Asian excluding Japan vs. rest of the world), macrovascular invasion MVI and/or EHS (yes or no), baseline alpha-fetoprotein (AFP <400 vs. >= 400 ng/mL) and baseline ECOG (0 vs. 1). The forest plot of OS HR for the adjusted with stratification factors was shown in Figure 14. In summary, the overall survival benefit seems to be driven by the ADA negative arm and the ADA positive arm seems to have comparable OS with sorafenib.

Figure 13: Overall Survival in HCC Patients in IMbrave150 by ADA Week 6 Status in Atezolizumab plus Bevacizumab Arm



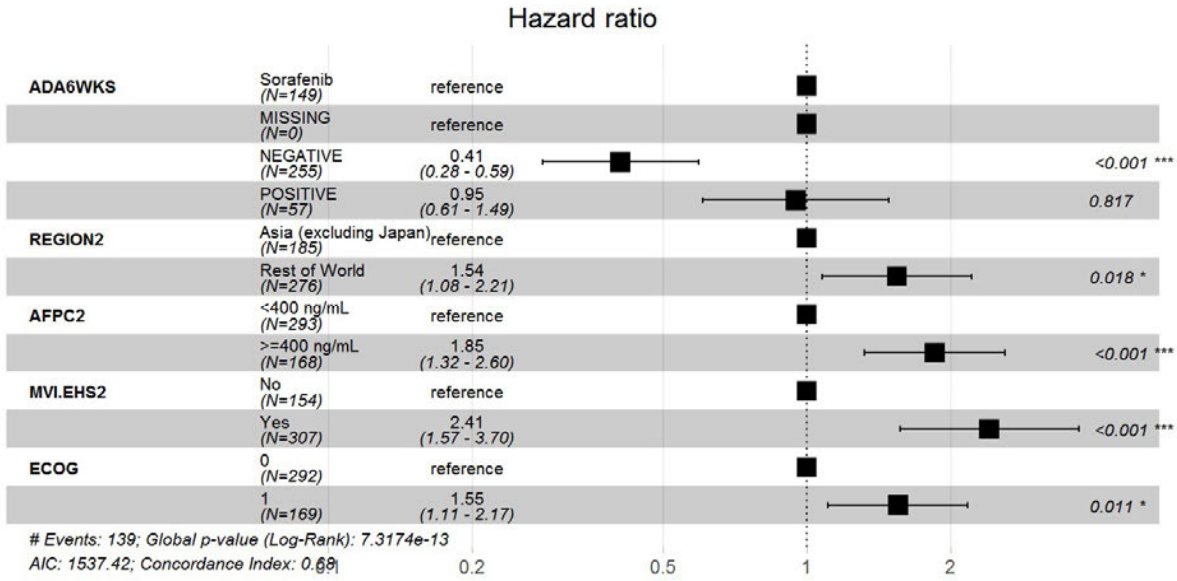
Source: Reviewer's independent analysis

Table 61: Overall Survival Result in Landmark ADA Subgroups (ADA Week 6)

ADA Status	N	Events	Median	HR_ unadjusted	HR adjusted*
ADA+ 6wks	57	29 (50.9%)	10.3 (8.44, NA)	1.19 (0.76, 1.85)	0.95 (0.61, 1.49)
ADA- 6wks	255	51 (20%)	NA (NA, NA)	0.42 (0.29, 0.61)	0.41 (0.28, 0.59)
Sorafenib	149	59 (39.6%)	13.2 (11.37, NA)		

Source: Reviewer's independent analysis. * HR was conducted by multivariate Cox regression analysis with stratification factors adjusted including geographic region (Asian excluding Japan vs. rest of the world), macrovascular invasion MVI and/or EHS (yes or no), baseline alpha-fetoprotein (AFP <400 vs. >= 400 ng/mL) and baseline ECOG (0 vs. 1).

Figure 14: Forest Plot of Overall Survival in 1L HCC Patients in IMbrave150 by ADA Week 6 Status

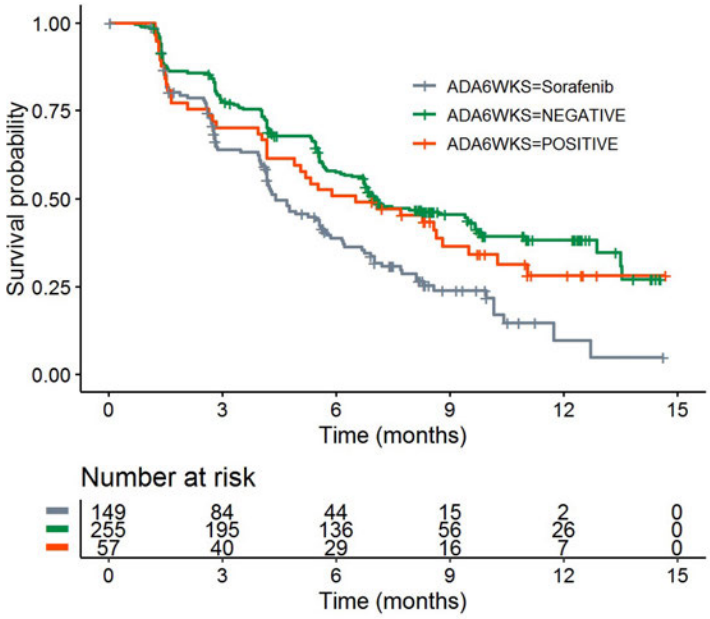


Source: Reviewer's independent analysis

PFS results based on ADA status at Week 6:

The results of landmark PFS were shown in (Figure 15, Table 61, Figure 16). Median survival time for the ADA week 6 positive, ADA week 6 negative subgroups in atezolizumab + bevacizumab arm and the sorafenib arm were 6.51 months (4.17, 8.8), 7 months (6.41, 9.49) and 4.4 months (4.14, 5.59) respectively (Table 62). Based on the multivariate Cox regression analysis, the hazard ratio with 95% confidence interval (95%CI) compared with sorafenib for the ADA week 6 positive group and the ADA week 6 negative group is 0.61 (0.42, 0.89) vs. 0.57 (0.44, 0.73) with adjustment for stratification factors: geographic region (Asian excluding Japan vs. rest of the world), macrovascular invasion MVI and/or EHS (yes or no), baseline alpha-fetoprotein (AFP <400 vs. >= 400 ng/mL) and baseline ECOG (0 vs. 1). The forest plot for HRs adjusted with stratification factors was shown in Figure 16.

Figure 15: Progression Free Survival in HCC Patients in IMbrave150 by ADA Week 6 Status in Atezolizumab plus Bevacizumab Arm



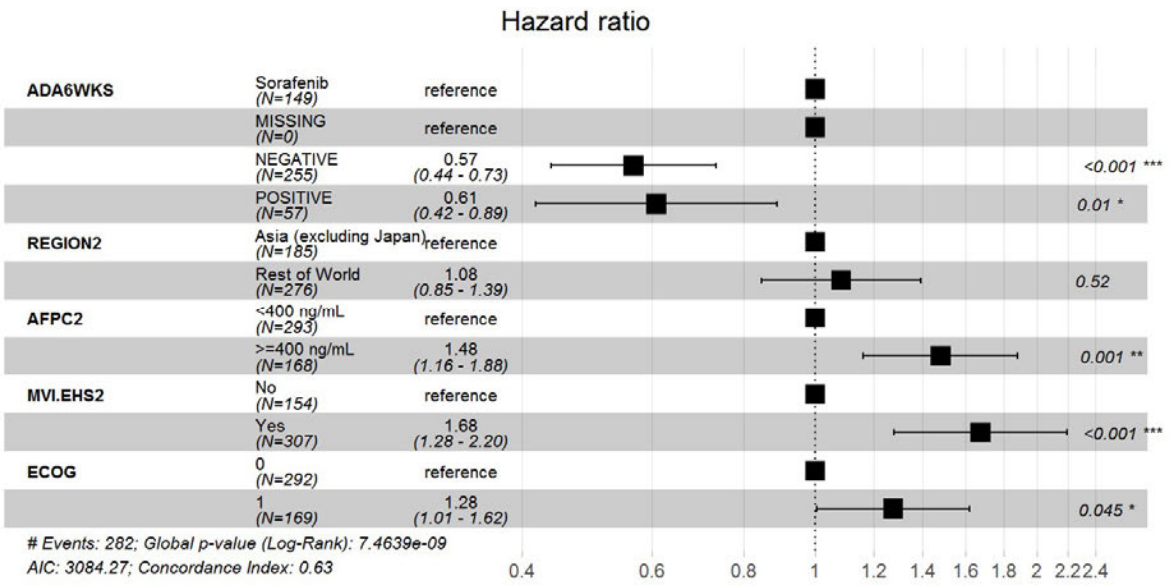
Source: Reviewer's independent analysis

Table 62: Progression Free Survival Result in Landmark ADA Subgroups (ADA 6wks)

ADA Status	N	Events	Median	HR_ unadjusted	HR adjusted*
ADA+ 6wks	57	38 (66.7%)	6.51 (4.17, 8.8)	0.68 (0.47, 1.0)	0.61 (0.42, 0.89)
ADA- 6wks	255	142 (55.7%)	7 (6.41, 9.49)	0.56 (0.44, 0.73)	0.57 (0.44, 0.73)
Sorafenib	149	102 (68.5%)	4.4 (4.14, 5.59)		

Source: Reviewer's independent analysis * HR was conducted by multivariate Cox regression analysis with stratification factors adjusted including geographic region (Asian excluding Japan vs. rest of the world), macrovascular invasion MVI and/or EHS (yes or no), baseline alpha-fetoprotein (AFP <400 vs. >= 400 ng/mL) and baseline ECOG (0 vs. 1).

Figure 16: Forest Plot of Progression Free Survival in 1L HCC Patients in IMbrave150 by ADA Week 6 Status



Source: Reviewer's independent analysis

19.4.4 Comparison of Atezolizumab Treatment Effect in ADA positive (by week 6) subgroup using Inverse Probability Weighting Analysis

Given the exploratory nature of the post-hoc landmark analyses based on ADA status by week 6, sponsor conducted inverse probability weighting (IPW) as one sensitivity analysis of efficacy by ADA status in IMbrave150 to reduce the confounding effect due to differences in baseline factors among ADA subgroups.

Demographic and Baseline Characteristics Comparison by ADA Status at Landmark (Week 6)

ADA positive patients were associated with a worse baseline characteristic including: higher proportion of patients with ECOG performance status of 1; higher level of baseline LDH, baseline tumor size, neutrophil/ lymphocytes ratio; higher proportion of patients with AFP>=400 ng/ml; higher proportion of patients with MVI and/or EHS. The imbalanced factor favoring the ADA positive group is the lower proportion of patients have age greater than 65. However the imbalanced baseline factors cannot totally explain the OS difference between the ADA positive and negative groups after adjustment with the IPW approach.

ADA-Positive versus ADA-Negative Patients

The following differences were observed in the ADA-positive subgroup compared with the ADA-negative subgroup

- Imbalances expected to be associated with worse prognosis for ADA-positive patients:
  - 10.4% higher proportion of patients with ECOG performance status of 1
  - 14.9% higher median baseline lactate dehydrogenase (LDH)
  - 33.5% higher median baseline SLD
  - 27.3% higher median baseline neutrophil-to-lymphocyte ratio
  - 18% higher proportion of patients with AFP ≥400 ng/mL
  - 16% higher proportion of patients with MVI and/or EHS
- Imbalances expected to be associated with better prognosis for ADA-positive patients:
  - 12.5% lower proportion of patients ≥65 years of age

Covariates Selected for Adjustment

The covariates(factors) considered for IPW and PSM adjusted analyses were selected and summarized in Table 63. Covariates for the TGI-OS model were selected by a multivariate model.

Table 63: IMbrave150: Covariates Selected for Adjustment

Covariate (Baseline Factor) [Variable ID in Model]	IPW and PSM	TGI-OS [a]
Sex (female vs. male) [SEX]	✓	
Age (<65 years vs. ≥65 years) [AGEGR1]	✓	
Race (Asian vs. White vs. others) [RACEGRP]	✓	
Geographic region (Asia excluding Japan vs. rest of world) [REGION1]	✓	
Weight (continuous) [BWGHTSI]	✓	
ECOG performance status (0 vs. 1) [ECOG]	✓	
SLD (continuous) [BSLD]	✓	✓
Albumin level (continuous) [BALBUM]	✓	
LDH level (continuous) [BLDH]	✓	✓
NLR (continuous) [BNLR]	✓	
AFP (<400 vs. ≥400 ng/mL) [AFPC]	✓	
No. of metastatic sites (continuous) [METSITES]	✓	
MVI and/or EHS at study entry (Y vs. N) [MVI_EHS)	✓	✓
Etiology (HBV vs. HCV vs. non-viral) [ETIOLOGY]	✓	
Child-Pugh score (A5 vs. A6) [CHPGSC]	✓	✓

Source: Table 8 of ADA Report (ADA report for study IMbrave150)

Inverse Propensity Weighting Result

Sponsor proposed IPW analysis to adjust the imbalanced covariates between the ADA positive and ADA negative subgroups. Based on the IPW analysis, the overall survival hazard ratio with 95% confidence interval (95%CI) compared with sorafenib for the ADA week 6 positive and ADA week 6 negative group is 0.93 (0.57, 1.53) vs. 0.39 (0.26, 0.60) adjusted with 16 covariates listed in Table 63. The progression free survival hazard ratio with 95% confidence interval (95% CI) compared with sorafenib for the ADA week 6 positive and the ADA week 6 negative group is 0.51 (0.33, 0.79) vs. 0.54 (0.41, 0.72).

19.5 Additional Clinical Outcome Assessment Analyses

The FDA's Assessment:
[FDA will complete this section.]

19.6 Additional Clinical Tables and Charts

Study IMbrave150 – Schedule of activities

	Screening [b]		Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
Assessment Window (Days) [a]	–28 to –1	–7 to –1	Day 1 of Each Cycle [c]	≤30 Days after Last Dose	
Signed Informed Consent Form(s) [b]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information [d]	x				
Complete physical examination [e]	x				
Limited physical examination [f]			x [g]	x	
ECOG Performance Status		x	x [g]	x	
Patient-reported outcomes [h]			x [g]	x	x [h]
Tumor assessment [i]	x		See footnote [i]	x	x
Vital signs [j]	x		x	x	
Weight	x		x [k]	x	
Height	x				
12-lead ECG [l]	x		Perform as clinically indicated		
EGD [m]	x				
Hematology [n, z]		x	x [g]	x	
Serum chemistry [o, z]		x	x [g]	x	
HIV, HBV, HCV serology [p]	x				

Assessment Window (Days) [a]	Screening [b]		Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
	–28 to –1	–7 to –1	Day 1 of Each Cycle [c]	≤30 Days after Last Dose	
Quantitative HBsAg, HBV DNA, HCV RNA [q]	x		x	x	
α-fetoprotein	x		x	x	
Coagulation panel (aPTT, INR) [z]		x	x [ε]	x	
Urinalysis [r, z]		x	x [ε]	x	
TSH, free T3, free T4	x		Cycles 5, 9, 13, etc. (every 4 cycles)	x	
Pregnancy test		x [s]	x [t]	x	
Serum PK sample			See Appendix 2		
Serum ADA sample			See Appendix 2		
Pharmacodynamic samples for biomarkers			See Appendix 2	x	
Plasma sample for RBR (optional)			Any time (at investigator's discretion)		
Archival tumor tissue sample (or optional fresh biopsy if archival tissue is not available) for biomarkers	x				
Concomitant medications [u]		x	x	x	
Adverse events [v]	x		x	x	
Study treatment infusion [w]			x		
Sorafenib dispensing [x]			x		
Survival and anti-cancer therapy follow-up [y]					x

Table 64 Study GO30140 - Arm A: Schedule of activities

Schedule of Activities

Assessment Window (Days) [a]	Screening [b]		Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
	–28 to –1	–7 to –1	Day 1 of Each Cycle [c]	≤30 Days after Last Dose	
Signed Informed Consent Form(s) [b]	x				
Review of eligibility criteria	x				
Medical, surgical, and cancer histories, including demographic information [d]	x				
Complete physical examination [e]	x				
Limited physical examination [f]			x [g]	x	
ECOG Performance Status		x	x [g]	x	
Patient-reported outcomes [h]			x [g]	x	x [h]
Tumor assessment [i]	x		See footnote [i]	x	x
Vital signs [j]	x		x	x	
Weight	x		x [k]	x	
Height	x				
12-lead ECG [l]	x		Perform as clinically indicated		
EGD [m]	x				
Hematology [n, z]		x	x [g]	x	
Serum chemistry [o, z]		x	x [g]	x	
HIV, HBV, HCV serology [p]	x				

Assessment Window (Days) [a]	Screening [b]		Treatment Phase (Q3W)	Treatment Discontinuation [c]	Survival Follow-Up
	–28 to –1	–7 to –1	Day 1 of Each Cycle [c]	≤30 Days after Last Dose	
Quantitative HBsAg, HBV DNA, HCV RNA [q]	x		x	x	
α-fetoprotein	x		x	x	
Coagulation panel (aPTT, INR) [z]		x	x [g]	x	
Urinalysis [r, z]		x	x [g]	x	
TSH, free T3, free T4	x		Cycles 5, 9, 13, etc. (every 4 cycles)	x	
Pregnancy test		x [s]	x [t]	x	
Serum PK sample			See Appendix 2		
Serum ADA sample			See Appendix 2		
Pharmacodynamic samples for biomarkers			See Appendix 2	x	
Plasma sample for RBR (optional)			Any time (at investigator's discretion)		
Archival tumor tissue sample (or optional fresh biopsy if archival tissue is not available) for biomarkers	x				
Concomitant medications [u]		x	x	x	
Adverse events [v]	x		x	x	
Study treatment infusion [w]			x		
Sorafenib dispensing [x]			x		
Survival and anti-cancer therapy follow-up [y]					x

Assessment Window (Days)	Screening [a] Days –28 to –1	All Cycles 1 [b]	8 (±3)	15 (±3)	End of Treatment [c] ≤30 Days after Last Dose	Follow-Up
Optional fresh biopsy [cc, dd]	x [cc, dd]	*C1D12–C3D1* [dd]				
Survival and anti-cancer therapy follow-up [ee]						x

AFP – alpha-fetoprotein; anti-HBc – antibody to hepatitis B core antigen; anti-HBs – antibody to hepatitis B surface antigen; *ADA – anti-drug*

Table 65 Study GO30140 Arm F: Schedule of activities

Assessment Window (Days)	Screening [a] Days –28 to –1	All Cycles 1 [b]	8 (±3)	15 (±3)	End of Treatment [c] ≤30 Days after Last Dose	Follow-Up
Signed Informed Consent Form(s) [a]	x					
Review of eligibility criteria	x					
Medical, surgical, and cancer histories, including demographic information [d]	x					
HIV, HBV, and HCV serology [e]	x [f]					
Concomitant medications [g]	x	x	x [h]	x [h]	x	
Tumor assessment [i]	x	See footnote [i]			x	x
Head CT or MRI scan	x					
Complete physical examination [j]	x				x	
Limited physical examination [k]		x [l]				
ECOG performance status	x	x [l]			x	
Vital signs [m]	x	x	x [h]	x [h]	x	
12-lead ECG [n]	x	Perform as clinically indicated				
EGD [o]	x					
Weight	x	x	x [h]	x [h]	x	
Height	x					
Hematology [p]	x [f]	x [l]	x [h]	x [h]	x	
Serum chemistry [q]	x [f]	x [l]	x [h]	x [h]	x	

Assessment Window (Days)	Screening [a] Days –28 to –1	All Cycles 1 [b]	8 (±3)	15 (±3)	End of Treatment [c] ≤30 Days after Last Dose	Follow-Up
Coagulation panel (aPTT, INR)	x [f]	x		x [h]	x	
C-reactive protein testing	x	x [l]				
Urine dipstick (+24-hr urine dipstick protein ≥2+) [r]	x [f]	x			x	
Pregnancy test (women of childbearing potential only)	x [s]	x [t]			x	
Quantitative HBsAg, HBV DNA, HCV RNA [u]	x	x [u]			x	
TSH, free T3, free T4	x [f]	every 3 months			x	
Auto-antibody testing [v]	x					
Serum sample for atezolizumab *ADA* assessment [w]		x			x	x
Serum sample for bevacizumab *ADA* assessment (Group F1 only) [w]		x			x	x
Serum sample for atezolizumab PK sampling [w]		x			x	x
Serum sample for bevacizumab PK sampling (Group F1 only) [w]		x			x	x
Blood samples for pharmacodynamic biomarkers [w, x]	x [w, x]	x [w, x]				
Blood samples for AFP testing [y]	x	x			x	
Adverse events [z]		x	x [h]	x [h]	x	
Atezolizumab infusion [aa]		x				
Bevacizumab infusion (Group F1 only) [aa]		x				

Assessment Window (Days)	Screening [a] Days –28 to –1	All Cycles 1 [b]	8 (±3)	15 (±3)	End of Treatment [c] ≤30 Days after Last Dose	Follow-Up
Archival/screening FFPE tumor tissue specimen or 16 unstained slides [bb]	x					
Optional fresh biopsy [cc, dd]	x [cc, dd]	*C1D12–C3D1* [dd]				
Survival and anti-cancer therapy follow-up [ee]						x

AFP=alpha-fetoprotein; anti-HBc=antibody to hepatitis B core antigen; anti-HBs=antibody to hepatitis B surface antigen; *ADA=anti-drug antibody;* CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; EGD=esophagogastroduodenoscopy; FFPE=formalin fixed paraffin embedded; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCC mRECIST=hepatocellular carcinoma–specific modified Response Evaluation Criteria in Solid Tumors; HCV=hepatitis C virus; MRI=magnetic resonance imaging; PD-L1=programmed death-ligand 1; PET=positron emission tomography; PK=pharmacokinetic; RCR=Roche Clinical Repository; RECIST=Response Evaluation Criteria in Solid Tumors; TBNK=T, B, and natural killer; TSH=thyroid-stimulating hormone.

Notes: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted. Each cycle is 21 days in length.

The same treatment schedule of assessment and procedures for Group F1 will apply to the crossover patients. Specifically, patients will begin on Cycle 1 (now to be called Cycle 1A) and will follow the same assessments and procedures as outlined in this protocol for Group F1, Cycle 1 as well as for all subsequent cycles (i.e., Cycle 2, now to be called Cycle 2A, etc.). Prior to crossover, end of treatment assessments and procedures must be performed after progression on atezolizumab monotherapy. If subsequent progression occurs on combination therapy, end of treatment procedures must be repeated.

[a] Written informed consent can be obtained up to 30 days prior to study entry and is required before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests. Screening local laboratory assessments obtained ≤96 hours prior to Cycle 1, Day 1 do not have to be repeated for Cycle 1. Test results should be reviewed prior to administration of study treatment.

Table 66 IMbrave150: Treatment withdrawal AEs

PT	N total; n: 485	Atezo; n: 329	Bev; n:329	Sorafenib; n: 156
Gastrointestinal hemorrhage	5	2	3	0
Esophageal varices hemorrhage	4	0	4	0
Autoimmune hepatitis	3	2	1	0
Blood bilirubin increased	3	1	1	1
Infusion related reaction	3	2	1	0
Pancreatitis	3	1	1	1
Pleural effusion	3	1	1	1
Transaminases increased	3	2	1	0
Ascites	2	1	1	0
AST increased	2	1	1	0
Chronic myeloid leukemia	2	1	1	0
Cytokine release syndrome	2	1	1	0
Gastric mucosal lesion	2	1	1	0
Gastric ulcer perforation	2	1	1	0
Hepatobiliary disease	2	1	1	0
Herpes simplex encephalitis	2	1	1	0
Hypersensitivity	2	1	1	0
Hyperthyroidism	2	1	1	0
Hypotension	2	1	1	0
Nephritis	2	1	1	0

PT	N total; n: 485	Atezo; n: 329	Bev; n:329	Sorafenib; n: 156
Esophageal hemorrhage	2	0	2	0
Esophageal squamous cell carcinoma	2	1	1	0
Proteinuria	2	0	2	0
Pulmonary hemorrhage	2	1	1	0
Septic shock	2	1	1	0
Subarachnoid hemorrhage	2	1	1	0
Acute myocardial infarction	1	0	1	0
Arthralgia	1	1	0	0
Bleeding varicose vein	1	0	1	0
Cellulitis	1	0	0	1
Cerebral infarction	1	0	1	0
Drug eruption	1	0	0	1
Drug-induced liver injury	1	0	0	1
Duodenal ulcer	1	0	1	0
Embolism venous	1	0	1	0
Fatigue	1	0	0	1
Gastric cancer	1	0	0	1
Gastritis erosive	1	0	1	0
General physical condition abnormal	1	0	0	1
General physical health deterioration	1	0	0	1
Hemorrhage	1	0	1	0
Hepatic cirrhosis	1	0	0	1
Hepatic encephalopathy	1	0	0	1
Hypoproteinemia	1	0	1	0
Liver function test increased	1	0	0	1
Melena	1	0	1	0
Nephrotic syndrome	1	0	1	0
Peritoneal hemorrhage	1	0	0	1
Pharyngeal inflammation	1	1	0	0
Platelet count decreased	1	0	1	0
Portal vein thrombosis	1	0	1	0
Pulmonary embolism	1	0	1	0
Rash	1	0	0	1
Rectal hemorrhage	1	0	1	0
Skin toxicity	1	0	0	1
Splenic infarction	1	0	1	0
Toxic skin eruption	1	0	0	1
Ulcerative keratitis	1	1	0	0
Upper gastrointestinal hemorrhage	1	0	1	0

Table 67 IMbrave150: Most frequent AEs by age group

PT	Atezo/bev (n: 329)				Sorafenib (n: 156)			
	<65 y.o. (n: 171)		≥65 y.o. (n: 158)		<65 y.o. (n: 69)		≥65 y.o. (n: 87)	
	N	%	N	%	N	%	N	%
Diarrhea	28	16	34	22	30	43	47	54
Hypertension	47	27	51	32	17	25	21	24
Decreased appetite	26	15	32	20	7	10	31	36
Fatigue	24	14	43	27	6	9	23	26
AST increased	39	23	25	16	15	22	11	13
Pruritus	35	20	29	18	8	12	7	8
PPES	1	1	2	1	29	42	46	53
Proteinuria	39	23	27	17	3	4	8	9
Pyrexia	29	17	30	19	7	10	8	9
Rash	25	15	16	10	6	9	21	24
Abdominal pain	22	13	18	11	10	14	17	20
Constipation	23	13	21	13	8	12	14	16
Blood bilirubin increased	28	16	15	9	10	14	12	14
Nausea	21	12	19	12	9	13	16	18
ALT increased	28	16	18	11	4	6	10	11
Cough	19	11	20	13	8	12	7	8
Platelet count decreased	17	10	18	11	8	12	10	11
Weight decreased	22	13	15	9	5	7	10	11
Vomiting	18	11	15	9	6	9	7	8
Anemia	17	10	13	8	8	12	7	8
Asthenia	9	5	13	8	6	9	15	17
Epistaxis	18	11	16	10	3	4	4	5
Arthralgia	12	7	20	13	4	6	4	5
Dysphonia	16	9	12	8	5	7	6	7
Insomnia	17	10	11	7	4	6	7	8
Headache	15	9	12	8	7	10	4	5
Infusion related reaction	18	11	19	12	0	0	0	0
Dyspnea	13	8	16	10	2	3	5	6
Hypoalbuminemia	10	6	14	9	4	6	8	9
Thrombocytopenia	17	10	10	6	4	6	4	5
Edema peripheral	11	6	18	11	2	3	3	3
Ascites	10	6	13	8	4	6	5	6
Hypothyroidism	17	10	12	8	1	1	2	2
ALK increased	13	8	9	6	5	7	4	5

PT	Atezo/bev (n: 329)				Sorafenib (n: 156)			
	<65 y.o. (n: 171)		≥65 y.o. (n: 158)		<65 y.o. (n: 69)		≥65 y.o. (n: 87)	
	N	%	N	%	N	%	N	%
Abdominal distension	15	9	8	5	4	6	1	1
Hyponatremia	11	6	8	5	3	4	6	7
Musculoskeletal pain	14	8	10	6	3	4	0	0
Alopecia	3	2	1	1	10	14	12	14
Stomatitis	7	4	12	8	2	3	5	6
Back pain	13	8	6	4	3	4	2	2
Leukopenia	11	6	8	5	4	6	0	0
Myalgia	7	4	10	6	1	1	4	5
Abdominal pain upper	10	6	5	3	2	3	4	5
Neutropenia	12	7	5	3	3	4	1	1
WBC decreased	8	5	5	3	5	7	3	3
Hyperglycemia	11	6	5	3	2	3	2	2
Hypokalemia	4	2	5	3	7	10	3	3
Nasopharyngitis	3	2	12	8	0	0	4	5
Hypophosphatemia	4	2	3	2	7	10	4	5
Dry skin	3	2	10	6	2	3	2	2
Upper respiratory tract infection	12	7	3	2	1	1	1	1
Urinary tract infection	5	3	10	6	1	1	1	1
Malaise	1	1	10	6	2	3	3	3
Hyperkalemia	3	2	8	5	1	1	3	3
Pain in extremity	2	1	6	4	4	6	2	2
Muscle spasms	3	2	4	3	0	0	5	6
LDH increased	2	1	2	1	4	6	3	3
Blood sodium decreased	3	2	2	1	5	7	1	1
Hemorrhoids	3	2	2	1	0	0	5	6

Table 68 IMbrave150: Grade 3-4 AEs by age group

PT	**Atezo/bev (n: 329)**				**Sorafenib (n: 156)**			
	< 65 y.o. (n: 171)		**≥ 65 y.o. (n: 158)**		**< 65 y.o. (n: 69)**		**≥ 65 y.o. (n: 87)**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hypertension	17	10	33	21	7	10	12	14

PT	Atezo/bev (n: 329)				Sorafenib (n: 156)			
	< 65 y.o. (n: 171)		≥ 65 y.o. (n: 158)		< 65 y.o. (n: 69)		≥ 65 y.o. (n: 87)	
	N	%	N	%	N	%	N	%
AST increased	14	8	9	6	4	6	4	5
Proteinuria	4	2	6	4	0	0	1	1
Fatigue	3	2	5	3	1	1	4	5
Blood bilirubin increased	3	2	5	3	4	6	6	7
Platelet count decreased	6	4	5	3	1	1	1	1
Decreased appetite	0	0	4	3	2	3	4	5
ALT increased	8	5	4	3	1	1	1	1
Anemia	5	3	4	3	2	3	2	2
Dyspnea	0	0	4	3	1	1	2	2
Hyponatremia	5	3	4	3	0	0	3	3
Diarrhea	3	2	3	2	2	3	6	7
Abdominal pain	1	1	3	2	2	3	2	2
Infusion related reaction	5	3	3	2	0	0	0	0
Ascites	3	2	3	2	0	0	2	2
GGT increased	3	2	2	1	0	0	3	3
Esophageal varices hemorrhage	4	2	2	1	0	0	1	1
Hepatic encephalopathy	0	0	2	1	0	0	2	2
Asthenia	0	0	1	1	0	0	4	5
Thrombocytopenia	5	3	1	1	2	3	1	1
Hypokalemia	1	1	1	1	3	4	1	1
Hypophosphatemia	1	1	1	1	3	4	3	3
Gastrointestinal hemorrhage	3	2	1	1	0	0	3	3
Pancreatitis	0	0	1	1	0	0	2	2
PPES	0	0	0	0	3	4	10	11
Rash	0	0	0	0	0	0	4	5
Abdominal distension	1	1	0	0	2	3	0	0
Hepatic function abnormal	2	1	0	0	0	0	2	2
Amylase increased	1	1	0	0	0	0	2	2
Acute kidney injury	1	1	0	0	1	1	2	2

PT	Atezo/bev (n: 329)				Sorafenib (n: 156)			
	< 65 y.o. (n: 171)		≥ 65 y.o. (n: 158)		< 65 y.o. (n: 69)		≥ 65 y.o. (n: 87)	
	N	%	N	%	N	%	N	%
Upper gastrointestinal hemorrhage	2	1	0	0	0	0	2	2
Anal fissure	0	0	0	0	0	0	2	2
General physical health deterioration	0	0	0	0	0	0	2	2
Hepatic failure	0	0	0	0	0	0	2	2

Table 69 IMbrave150: FDA's Sensitivity analyses of OS and PFS

	Sorafenib (n=165)	Atezo + Bev (n=336)
OS sensitivity analysis (using eCRF values in stratified analysis)		
Number of Event (%)	65 (39.4)	96 (28.6)
Median OS in Months (95%CI)	13.2 (10.4, NE)	NE
Hazard Ratio* (95%CI)	0.56 (0.41, 0.77)	
PFS sensitivity analysis (using eCRF values in stratified analysis)		
Number of Event (%)	109 (66.1)	197 (58.6)
PD	80	163
Death	29	34
Median PFS in Months (95%CI)	4.3, (4.0, 5.6)	6.8 (5.7, 8.3)
Hazard Ratio* (95%CI)	0.58 (0.46, 0.74)	

**Stratified by Geographic region (Asia excluding Japan vs. rest of world), Macrovascular invasion and/or extrahepatic spread (presence vs. absence), Baseline AFP (a-fetoprotein [<400 vs. >= 400 ng/mL])*

Table 70 IMbrave150: FDA's Results of ORR and DOR analyses (IRF-assessment per RECIST v1.1.)

	Sorafenib (n=165)	Atezo + Bev (n=336)
Response rate (95% CI)	11.5% (7.1%, 17.4%)	27.7% (23.0%, 32.8%)
Responders (CR+PR), n (%)	19 (12)	93 (28)
Complete responders (CR)	0	22 (7)
Partial responders (PR)	19 (12)	71 (21)
p-value (CMH test)	<0.0001	
difference of ORR	16.2% (8.9%, 23.4%)	
Duration of Response (DOR)	**n=19**	**n=93**
Median DOR in months* (95%CI)	6.3 (4.7, NA)	NA (NA, NA)
DOR>=6 months, n(%)	6 (32)	45 (48)
DOR>=12 months, n (%)	0	5 (5)

**Observed DOR*

Table 71 IMbrave150: FDA's Results of ORR and DOR analyses (IRF-assessment per HCC mRECIST v1.1.)

	Sorafenib (n=165)	**Atezo + Bev (n=336)**
Response rate (95% CI)	12.7% (8.1%, 18.8%)	33.3% (28.3%, 38.7%)
Responders (CR+PR), n (%)	21 (13)	112 (33)
Complete responders (CR)	3 (1.8)	37 (11)
Partial responders (PR)	18 (11)	75 (22)
p-value (CMH test)	<0.0001	
difference of ORR	20.6% (13.0%, 28.2%)	
Duration of Response (DOR)	**n=21**	**n=112**
Median DOR in months* (95%CI)	6.3 (4.9, NA)	NA (NA, NA)
DOR>=6 months, n (%)	8 (38)	53 (47)
DOR>=12 months, n (%)	0	5 (5)

**Observed DOR*

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Alexander Putman	OOD/DHOT	Sections: 5	Select one: X Authored ___ Approved
	Signature: Alexander Putman -S Digitally signed by Alexander Putman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000207705, cn=Alexander Putman -S Date: 2020.05.27 10:08:08 -04'00'			
Nonclinical Team Leader	Matthew Thompson	OOD/DHOT	Sections: 5	Select one: ___ Authored X Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001270689, cn=Matthew D. Thompson -S Date: 2020.05.26 18:10:29 -04'00'			
Clinical Pharmacology Reviewer	Xiling Jiang	CDER/DCP II	Sections: 6 and 19.4	Select one: X Authored ___ Approved
	Signature: Xiling Jiang -S Digitally signed by Xiling Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656 Date: 2020.05.27 14:14:26 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	CDER/DCP II	Sections: 6 and 19.4	Select one: X Authored X Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2020.05.26 15:47:58 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Pharmacometrics Reviewer	Yuan Xu	CDER/OCP/DPM	Sections: 6 and 19.4	Select one: x Authored ___ Approved
	Signature: Yuan Xu -S Digitally signed by Yuan Xu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan Xu -S, 0.9.2342.19200300.100.1.1=2001686060 Date: 2020.05.26 15:53:44 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	CDER/OCP/DPM	Sections: 6 and 19.4	Select one: x Authored x Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.05.26 15:52:03 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman	CDER/DCP II	Sections: 6 and 19.4	Select one: ___ Authored x Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.05.27 09:22:21 -04'00'			
Clinical Reviewer	Sandra Casak	DO3	Sections: 1, 2, 3, 4.1, 7, 8.1, 8.2, 8.4, 11, 13, 19.5, 19.6	Select one: x Authored ___ Approved
	Signature: Sandra Casak -S Digitally signed by Sandra Casak -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sandra Casak -S, 0.9.2342.19200300.100.1.1=2000518303 Date: 2020.05.27 07:14:36 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Martha Donoghue	DO3	Authored: Section 1 Approved Sections: 1, 2, 3, 4.1, 7, 8.1, 8.2, 8.4, 11, 13, 19.5,19.6	**Select one:** X Authored X Approved
	Signature: Refer to final assessment aid.			
Statistical Reviewer	Xiaoping Jiang	OB/DBV	Sections: 1, 7, 8.1. 8.3, 8.4	**Select one:** x Authored x Approved
	Signature: Xiaoping Jiang -S Digitally signed by Xiaoping Jiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaoping Jiang -S, 0.9.2342.19200300.100.1.1=1300369835 Date: 2020.05.26 17:35:27 -04'00'			
Statistical Team Leader	Lisa Rodriguez	OB/DBV	Sections: 1, 7, 8.1. 8.3, 8.4	**Select one:** ___ Authored x Approved
	Signature: Lisa R. Rodriguez -S Digitally signed by Lisa R. Rodriguez -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001011155, cn=Lisa R. Rodriguez -S Date: 2020.05.27 08:50:16 -04'00'			
Division Director (OB)	Yuan-Li Shen	OB/DBV	Sections: 1, 7, 8.1. 8.3, 8.4	**Select one:** ___ Authored x Approved
	Signature: Yuan-li Shen -S Digitally signed by Yuan-li Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan-li Shen -S, 0.9.2342.19200300.100.1.1=1300142755 Date: 2020.05.27 17:08:14 -04'00'			
Associate Director for Labeling (ADL)	William Pierce	OOD/IO	Section: 11, Prescribing Information (USPI)	**Select one:** X Authored X Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2020.05.26 20:58:45 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Martha Donoghue	DO3	Authored Section :1 Approved Section : All	**Select one:** X Authored X Approved
	Signature: Refer to final assessment aid.			

Division Director (Clinical)	Steven Lemery	DO3	Sections: All	**Select one:** ___ Authored _X_ Approved
	Signature: Refer to final assessment aid			

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/s/

SHUBHANGI H MEHTA
05/29/2020 01:14:19 PM

MARTHA B DONOGHUE
05/29/2020 01:16:31 PM

STEVEN J LEMERY
05/29/2020 01:18:50 PM

Memorandum – Clinical Review	
BLA	125085
Supplement	332
Submission date	January 24, 2020
Product	Avastin (bevacizumab)
Applicant	Genentech
Reviewer	Sandra J. Casak
Team Leader	Martha Donoghue
Indication: Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy.	
The clinical review is complete and has been added to the BLA Assessment Aid document. My recommendation for this application is approval.	

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/s/

SANDRA J CASAK
05/26/2020 08:06:37 PM

MEMORANDUM

Date: May 15, 2020
TO: To the file for BLA 761034-S025 (atezolizumab; Genentech, Inc.) and BLA 125085-S332 (bevacizumab; Genentech, Inc.)
FROM:
Alexander Putman, PhD
Nonclinical Reviewer
Division of Hematology Oncology Toxicology (DHOT)
THROUGH:
Matthew Thompson, PhD, MPH
Nonclinical Team Lead (Acting)
Division of Hematology Oncology Toxicology (DHOT)
RE: Nonclinical Review

Application Type	Efficacy supplements
Application Number(s)	BLA 761034 (S25) and 125085 (S332)
Priority or Standard	Priority
PDUFA Goal Date	July 24, 2020
Division/Office	DO3/OOD
Established Name	Tecentriq and Avastin
Pharmacologic Class	Anti-programmed death cell ligand 1 (PD-L1) monoclonal antibody Anti-vascular endothelial growth factor A (VEGF-A) monoclonal antibody
Code name	Atezolizumab and bevacizumab
Applicant	Genentech
Formulation(s)	Atezolizumab: liquid for injection, 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL). Bevacizumab: liquid for injection, 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL)
Dosing Regimen	Atezolizumab: 1200 mg IV every 3 weeks Bevacizumab: 15 mg/kg IV every 3 weeks
Applicant Proposed Indication(s)/Population(s)	TECENTRIQ, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy.

No new nonclinical information was provided in the submission and there were no labeling changes requiring pharmacology/toxicology input. Therefore, a nonclinical review was not conducted. From a pharmacology/toxicology perspective, there are no issues that would prevent approval of this efficacy supplement. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

ALEXANDER H PUTMAN
05/15/2020 01:57:17 PM

MATTHEW D THOMPSON
05/15/2020 02:18:16 PM
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #:	761034, 125085
Supplement #:	25, 332
Drug Names:	Tecentriq® (atezolizumab), Avastin® (Bevacizumab)
Indications:	Tecentriq®, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy Avastin®, in combination with atezolizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy
Applicant:	Genentech
Received Date:	January 24, 2020
PDUFA Date:	July 27, 2020
Review Type:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Xiaoping (Janet) Jiang, PhD
Concurring Reviewers:	Lisa Rodriguez, PhD, Team Leader Yuan-Li Shen, Dr. P.H., Deputy Division Director (Acting)
Medical Division:	Division of Oncology 3
Clinical Team:	Sandra Casak, MD, Clinical Reviewer Martha Donoghue, MD, Clinical Team Leader Steven Lemery, MD, Division Director (Acting)
Project Manager:	Shubhangi (Gina) Mehta, PharmD
Keywords:	Stratified log-rank test, Kaplan-Meier method, Cox model

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation/Assessment Aid, which will be uploaded to DARRTS when it is finalized. Refer to

the Multi-disciplinary Review and Evaluation Aid for additional details. From a statistical standpoint, the proposed indications are supported by the applications.

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/s/

XIAOPING JIANG
05/27/2020 09:31:30 AM

LISA R RODRIGUEZ
05/27/2020 09:38:30 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s332

CHEMISTRY REVIEW(S)

Memorandum of Assessment:

Submission Tracking Number (STN):	125085/332
Subject:	Rolling efficacy supplement (RTOR Pilot) to support a new proposed indication for bevacizumab in combination with atezolizumab
Date Received:	01/24/20
Assessment/Revision Date:	04/23/20
Primary Assessor:	Eric Hales, Ph.D., Product Quality Reviewer (Biologist), DBRR1/OBP/CDER
Secondary Assessor:	Kristen Nickens, Ph.D., Product Quality Team Lead (Lead Biologist), DBRR1/OBP/CDER
Tertiary Assessor:	Qing (Joanna) Zhou, Ph.D., Review Chief (Supervisory Biologist), DBRR1/OBP/CDER
RBPM:	Anh-Thy Ly (CDER/OPRO) and Shubhangi Mehta (CDER/OND)
Applicant:	Genentech, Inc.
Products:	Bevacizumab (Avastin) is a recombinant, humanized IgG1κ monoclonal antibody manufactured in Chinese hamster ovary cells that targets human vascular endothelial growth factor (VEGF). Atezolizumab (Tecentriq) is a recombinant, humanized IgG1κ monoclonal antibody (b) (4) to prevent glycosylation/effector function and is manufactured in (b) (4) Atezolizumab targets programmed death-ligand 1 (PD-L1).
Proposed Indication:	For the use of bevacizumab in combination with atezolizumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy
Filing Action Date:	03/24/20
Action Due Date:	07/24/20

Note: *This assessment only covers bevacizumab (Avastin). Assessment of Tecentriq is deferred to the assigned atezolizumab assessor. Cross-reference is provided in BLA 125085/332 to the relevant clinical information (Modules 2 and 5) and environmental assessment under BLA 761034/25 supporting this efficacy supplement. The proposed draft USPI for Avastin is included in Module 1 of BLA 125085/332.*

1. Recommendation: We recommend approval from the product quality perspective for bevacizumab.

2. Assessment:

This efficacy supplement was provided to support a new indication for bevacizumab in combination with atezolizumab, for adult patients with unresectable HCC who have received no prior systemic therapy. Clinical data supporting this combination were derived from the pivotal Phase 3 Study YO40245 (IMbrave150) and the supportive Phase 1b Study GO30140 (Arms A and F). Bevacizumab was administered intravenously at 15 mg/kg once every

three weeks (Q3W) in Arm A of YO40245 and in Arms A and F1 of GO30140 (Module 2.5, Table 2). The draft USPI for Avastin was updated with the proposed indication and administration information; no changes were made to the bevacizumab storage, formulation, presentation, preparation for administration, and in-use condition in the label. The low incidence of anti-drug antibodies (ADA) to bevacizumab in previous studies (e.g., GO30140) precluded the need to further evaluate bevacizumab pharmacokinetics (PK) and anti-drug antibodies (ADA) in pivotal Study YO40245 to support the proposed indication.

Assessor comment: *An information request (IR) was sent to the applicant on April 14, 2020 to clarify the source of the bevacizumab batches administered in clinical studies YO40245 and GO30140 to support the proposed indication. The applicant confirmed in the response received on April 17, 2020 that all bevacizumab batches were manufactured by the approved U.S.-licensed commercial manufacturing process. The bevacizumab dose is within the range of the other approved indications under BLA 125085; therefore, the maximum allowable endotoxin and host cell DNA exposure are within acceptable limits.*

Clinical pharmacology review team was contacted to clarify if ADA to bevacizumab were being evaluated to support the immunogenicity incidence for this indication. The pharmacology assessor confirmed (by email on April 1, 2020) that the incidence of ADA to bevacizumab was not assessed in the pivotal study YO40245 by the applicant, and that the incidence of ADA to bevacizumab in supportive study GO30140 will not be further assessed considering bevacizumab immunogenicity was previously characterized and didn't appear to have significant clinical impact. Therefore, assessment of the ADA assay for bevacizumab (validation report AVF.017.AVR_0 in Module 5.3.1.4 of BLA 761034/Supplement 9) is not necessary for the action taken on the proposed indication (confirmed with the clinical team at the mid-cycle meeting on April 15, 2020).

Environmental Assessment:
A categorical exclusion from the requirements of preparing an environmental assessment is requested by the applicant under 21 CFR 25.31(b). Under this regulation, an exclusion is warranted if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

Assessor comment: *Considering that the potential approval action for this supplement would result in the increased use of the active moiety, this regulation appears appropriate for EA exclusion. This supplement also appears to qualify for categorical exclusion as a biological product under 21 CFR 25.31(c) because it is not expected to significantly affect the concentration or distribution of naturally occurring substances in the environment based on an understanding that antibody products degrade into its constituent amino acid components in the environment.*

Eric Hales

Digitally signed by Eric Hales
Date: 4/23/2020 12:43:49PM
GUID: 57d6a5ef01b1162fe9ae3a025d49565e

Kristen Nickens

Digitally signed by Kristen Nickens
Date: 4/23/2020 12:45:20PM
GUID: 54b821c400083afe9702573df3fd56c4

Qing Zhou

Digitally signed by Qing Zhou
Date: 4/23/2020 12:59:29PM
GUID: 508da7430002bbad737ae8d4b9c59845

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125085Orig1s332

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 5, 2020

To: Shubhangi Mehta, PharmD, Regulatory Project Manager, Division of Oncology 3 (DO3)

William Pierce, PharmD, Associate Director for Labeling

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for AVASTIN® (bevacizumab) injection, for intravenous use

BLA: 125085/Supplement-332

In response to DO3's consult request dated December 26, 2019, OPDP has reviewed the proposed product labeling (PI) for Avastin. This supplement (S-332) pertains to the proposed indication in combination with atezolizumab for the treatment of patients with unresectable and metastatic HCC who have not received prior systemic therapy.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DO3 (Shubhangi Mehta) on April 27, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

39 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ROBERT L NGUYEN
05/05/2020 02:23:00 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 18, 2020
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	BLA 761034/S-25
Product Name, Dosage Form, and Strength:	Tecentriq (atezolizumab) injection, 840 mg/14 mL (60 mg/mL), 1,200 mg/20 mL (60 mg/mL)
Application Type and Number:	BLA 125085/S-332
Product Name, Dosage Form, and Strength:	Avastin (bevacizumab) injection, 100 mg/4 mL (25 mg/mL), 400 mg/16 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	January 24, 2020, March 4, 2020, and March 11, 2020
OSE RCM #:	2020-2
DMEPA Safety Evaluator:	Sarah Thomas, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

Genentech submitted BLA 761034/S-25 and BLA 125085/S-332 to extend the use of Tecentriq and Avastin to the following new indications:

- Tecentriq, in combination with bevacizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy.
- And Avastin, in combination with atezolizumab, is indicated for the treatment of patients with unresectable hepatocellular carcinoma who have not received prior systemic therapy.

This review responds to the Division of Oncology 3 (DO3) consult for DMEPA to evaluate the proposed Tecentriq Prescribing Information (PI) and Medication Guide (MG) and Avastin PI for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed PIs and MG and note edits to Section 2, Dosage and Administration section, of the PIs as well as to the Tecentriq MG. We identified areas where the PI labeling may be improved to promote the safe use of the products.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Avastin and Tecentriq PIs may be improved to promote the safe use of the products as described in Section 4.1.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 3 (DO3)

A. Avastin Prescribing Information

1. Dosage and Administration Section, Highlights and Full PI

    a. We recommend adding a comma to the 1200 mg dose (e.g., 1,200 mg), as using commas for dosing units at or above 1,000 improves readability.[a]

B. Tecentriq Prescribing Information

1. Dosage and Administration Section, Highlights and Full PI

    a. We recommend adding a comma to the 1200 mg and 1680 mg doses (e.g., 1,200 mg and 1,680 mg), as using commas for dosing units at or above 1,000 improves readability.[a]

2. Dosage and Administration Section, Full PI

    a. In Table 1, place the abbreviation "ULN" in parenthesis after the first time the words "upper limit of normal" are included in the table (e.g., in Hepatitis/non-HCC adverse reaction row under the first "Severity of Adverse Reaction" description: "AST or ALT more than 3 and up to 8 times the upper limit of normal (ULN)…"). This will help define the ULN abbreviation prior to its use in the proposed Hepatitis/HCC adverse reaction row.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2020 FEB 28]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tecentriq received on March 4, 2020 from Genentech, Inc.

Table 2. Relevant Product Information for Tecentriq	
Initial Approval Date	May 18, 2016
Proper Name	atezolizumab
Indication	Urothelial Carcinoma • for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who: o are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), as determined by an FDA-approved test, or o are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status, or o have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Non-Small Cell Lung Cancer (NSCLC) • in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations. • in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations • for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving Tecentriq. Triple-Negative Breast Cancer (TNBC) • in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (PD-L1 stained tumor-

	infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA approved test. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Small Cell Lung Cancer (SCLC) • in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). *Proposed:* *Heptatocellular Carcinoma (HCC)* *• in combination with bevacizumab for the treatment of patients with unresectable HCC who have not received prior systemic therapy*
Route of Administration	Intravenous
Dosage Form	Injection
Strength	840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL)
Dose and Frequency	Administer Tecentriq intravenously over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Urothelial Carcinoma • Administer Tecentriq as a single agent as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. NSCLC • Administer Tecentriq as a single agent as 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. • When administering with chemotherapy with or without bevacizumab, administer Tecentriq 1200 mg every 3 weeks prior to chemotherapy and bevacizumab • Following completion of 4-6 cycles of chemotherapy, and if bevacizumab is discontinued, administer Tecentriq 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. Metastatic Treatment of TNBC • Administer Tecentriq 840 mg, followed by 100 mg/m^2 paclitaxel protein-bound. For each 28 day cycle, Tecentriq is administered on days 1 and 15, and paclitaxel protein-bound is administered on days 1, 8, and 15. Small Cell Lung Cancer

	• When administering with carboplatin and etoposide, administer Tecentriq 1200 mg every 3 weeks prior to chemotherapy. • Following completion of 4 cycles of carboplatin and etoposide, administer Tecentriq 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks. *Proposed:* *Hepatocellular Carcinoma* *• Administer TECENTRIQ 1200 mg, followed by 15 mg/kg bevacizumab on the same day every 3 weeks* *• If bevacizumab is discontinued, administer TECENTRIQ as:* *• 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks*
How Supplied	Carton containing one 840 mg/14 mL single-dose vial (NDC 50242-918-01) or 1200 mg/20 mL single-dose vial (NDC 50242-917-01)
Storage	Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
Container Closure	Primary packaging for atezolizumab Drug Product is a 20 mL colorless USP/Ph. Eur./JP (b) (4) glass vial sealed with a 20 mm rubber stopper and crimped with a 20 mm aluminum seal fitted with a plastic (b) (4) cap

Table 3 presents relevant product information for Avastin received on March 11, 2020 from Genentech, Inc.

Table 2. Relevant Product Information for Avastin	
Initial Approval Date	February 26, 2004
Proper Name	bevacizumab
Indication	Avastin is a vascular endothelial growth factor inhibitor indicated for the treatment of: • Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. • Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. Limitations of Use: Avastin is not indicated for adjuvant treatment of colon cancer.

	• Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. • Recurrent glioblastoma in adults. • Metastatic renal cell carcinoma in combination with interferon alfa. • Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. • Epithelial ovarian, fallopian tube, or primary peritoneal cancer: o in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for stage III or IV disease following initial surgical resection o in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens o in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by Avastin as a single agent, for platinum-sensitive recurrent disease *Proposed:* • *Hepatocellular Carcinoma (HCC)* o *in combination with atezolizumab for the treatment of patients with unresectable HCC who have not received prior systemic therapy*
Route of Administration	intravenous
Dosage Form	injection
Strength	100 mg/4 mL (25mg/mL) or 400 mg/16 mL (25mg/mL)
Dose and Frequency	Do not administer Avastin for 28 days following major surgery and until surgical wound is fully healed. Metastatic colorectal cancer • 5 mg/kg every 2 weeks with bolus-IFL • 10 mg/kg every 2 weeks with FOLFOX4 • 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Avastin containing regimen First-line non-squamous non-small cell lung cancer • 15 mg/kg every 3 weeks with carboplatin and paclitaxel Recurrent glioblastoma • 10 mg/kg every 2 weeks

	Metastatic renal cell carcinoma • 10 mg/kg every 2 weeks with interferon alfa Persistent, recurrent, or metastatic cervical cancer • 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection • 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer • 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week • 15 mg/kg every 3 weeks with topotecan given every 3 weeks Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer • 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent • 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent *Proposed:* *Hepatocellular Carcinoma* • *15 mg/kg after administration of 1200 mg of atezolizumab every 3 weeks* Administer as an intravenous infusion.
How Supplied	• 100 mg/4 mL: carton of one vial (NDC 50242-060-01); carton of 10 vials (NDC 50242-060-10). • 400 mg/16 mL: carton of one vial (NDC 50242-061-01); carton of 10 vials (NDC 50242-061-10).
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. Do not freeze or shake the vial or carton.
Container Closure	(b) (4) 6 cc USP/EP vial and (b) (4) 20 cc USP/EP vial with (b) (4) stopper (Complies with USP/Ph. Eur. Requirements) and (b) (4) aluminum, two-piece cap assembly. Upper part consists of a (b) (4) plastic cap, and the lower par consists of the aluminum seal.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 26, 2020, we performed 2 searches for the most recent DMEPA reviews that are relevant to this current review and evaluated Tecentriq PI and MG and Avastin PI, using the terms, Tecentriq, atezolizumab, BLA# 761034 for the first search and Avastin and BLA# 125085 for the second search. Our search identified 2 previous reviews[b,c], and we considered our previous recommendations in the reviews to see if they are applicable to this current review.

[b]Thomas, S. Label and Labeling Review for Tecentriq (BLA 761034/S-27). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 20. RCM No.: 2020-76.

[c] Gao, T. Label and Labeling Review for Avastin (BLA 125085/S-323). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MARCH 8. RCM No.: 2017-2107.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Tecentriq and Avastin labeling submitted by Genentech, Inc.

- Tecentriq Prescribing Information and Medication Guide (Image not shown) received on March 4, 2020, available from \\cdsesub1\evsprod\bla761034\0887\m1\us\annotated-label-text.pdf
- Avastin Prescribing Information (Image not shown) received on March 11, 2020, available from \\cdsesub1\evsprod\bla125085\1045\m1\us\redlined-label-text-20200311.pdf

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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