CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761034Orig1s019

Trade Name: TECENTRIQ

Generic or Proper Name: atezolizumab

Sponsor: Genetech Inc

Approval Date: March18, 2019

Indication:

TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated:

Urothelial Carcinoma

for the treatment of 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 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. (1.2)
- 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).

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s019

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761034/S-019

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Kimberly Smith, eMBA
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Smith:

Please refer to your Supplemental Biologics License Application (sBLA), dated September 18, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tecentriq (atezolizumab) Injection, 1200 mg/20 mL (60 mg/mL).

This Prior Approval supplemental biologics application provides for a new indication for the use of Tecenriq, in combination with carboplatin and etoposide, for the first-line treatment of adult patient with extensive-stage small cell lung cancer.

APPROVAL & LABELING

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

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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.

We are waiving the pediatric study requirement for this application because studies are impossible or highly impracticable for extensive-stage small cell lung cancer.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 3587-1 To provide updated overall survival (OS) results from the IMpower133 study based upon the protocol-specified timing for the final analysis of OS to better characterize survival differences at late time points in order to inform labeling.

The timetable you submitted on March 12, 2019, states that you will conduct this study according to the following schedule:

Study Completion:	03/2019
Final Report Submission:	09/2019

Submit all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report,

and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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/

PATRICIA KEEGAN
03/18/2019 08:00:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s019

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TECENTRIQ® (atezolizumab) injection, for intravenous use
Initial U.S. Approval: 2016

RECENT MAJOR CHANGES

Indications and Usage, Urothelial Carcinoma (1.1)	7/2018
Indications and Usage, Non-Small Cell Lung Cancer (1.2)	12/2018
Indications and Usage, Triple-Negative Breast Cancer (1.3)	3/2019
Indications and Usage, Small Cell Lung Cancer (1.4)	3/2019
Dosage and Administration (2.1, 2.3, 2.4, 2.5, 2.7)	3/2019
Warnings and Precautions (5.1, 5.2, 5.3, 5.4)	3/2019
Warnings and Precautions (5.6, 5.7)	12/2018

INDICATIONS AND USAGE

TECENTRIQ is a programmed death-ligand 1 (PD-L1) blocking antibody indicated:

Urothelial Carcinoma

- for the treatment of 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. (1.1)

  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). (1.1)

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. (1.2)
- 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. (1.2)

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). (1.3)

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). (1.4)

DOSAGE AND ADMINISTRATION

Urothelial Carcinoma

- TECENTRIQ 1200 mg intravenously over 60 minutes every 3 weeks.

NSCLC

- TECENTRIQ 1200 mg intravenously over 60 minutes every 3 weeks. If administering in combination, administer TECENTRIQ prior to chemotherapy or other antineoplastic drugs when administered on the same day.

Metastatic Treatment of TNBC

- TECENTRIQ 840 mg IV over 60 minutes, 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

- TECENTRIQ 1200 mg intravenously over 60 minutes every 3 weeks. When administering in combination, administer TECENTRIQ prior to chemotherapy when administered on the same day.

If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. (2.2, 2.3, 2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Immune-Mediated Pneumonitis: Withhold or permanently discontinue based on severity of pneumonitis. (2.6, 5.1)
- Immune-Mediated Hepatitis: Monitor for changes in liver function. Withhold or permanently discontinue based on severity of transaminase or total bilirubin elevation. (2.6, 5.2)
- Immune-Mediated Colitis: Withhold or permanently discontinue based on severity of colitis. (2.6, 5.3)
- Immune-Mediated Endocrinopathies (2.6, 5.4):
  - Hypophysitis: Withhold based on severity of hypophysitis.
  - Thyroid Disorders: Monitor for changes in thyroid function. Withhold based on severity of hyperthyroidism.
  - Adrenal Insufficiency: Withhold based on severity of adrenal insufficiency.
  - Type 1 Diabetes Mellitus: Withhold based on severity of hyperglycemia.
- Infections: Withhold for severe or life-threatening infection. (2.6, 5.6)
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue based on severity of infusion reactions. (2.6, 5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

- Most common adverse reactions (reported in ≥ 20% of patients) with TECENTRIQ as a single-agent were fatigue/asthenia, nausea, cough, dyspnea, and decreased appetite. (6.1)
- Most common adverse reactions (reported in ≥ 20% of patients) with TECENTRIQ in combination with other antineoplastic drugs in patients with NSCLC and SCLC were fatigue/asthenia, nausea, alopecia, constipation, diarrhea, and decreased appetite (6.1)
- The most common adverse reactions (reported in ≥ 20% of patients) with TECENTRIQ in combination with paclitaxel protein-bound in patients with TNBC were alopecia, peripheral neuropathies, fatigue, nausea, diarrhea, anemia, constipation, cough, headache, neutropenia, vomiting, and decreased appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech 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 and Medication Guide.

Revised: 3/2019

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 Urothelial Carcinoma

TECENTRIQ is indicated for the treatment of 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 *[see Dosage and Administration (2.1)]*, 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 based on tumor response rate and durability of response *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2 Non-Small Cell Lung Cancer

- TECENTRIQ, in combination with bevacizumab, paclitaxel, and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations.
- TECENTRIQ, as a single-agent, is indicated 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.

1.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

TECENTRIQ, in combination with paclitaxel protein-bound, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (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 *[see Dosage and Administration (2.1)]*.

This indication is approved under accelerated approval based on progression free survival *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.4 Small Cell Lung Cancer

TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for Treatment of Urothelial Carcinoma and Triple-Negative Breast Cancer

Select cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial carcinoma for treatment with TECENTRIQ based on the PD-L1 expression on tumor-infiltrating immune cells *[see Clinical Studies (14.1)]*.

Select patients with locally advanced or metastatic triple-negative breast cancer for treatment with TECENTRIQ in combination with paclitaxel protein-bound based on the PD-L1 expression on tumor infiltrating immune cells *[see Clinical Studies (14.3)]*.

Information on FDA-approved tests for the determination of PD-L1 expression in locally advanced or metastatic urothelial carcinoma or triple-negative breast cancer are available at: http://www.fda.gov/CompanionDiagnostics

2.2 Recommended Dosage for Urothelial Carcinoma

The recommended dosage of TECENTRIQ is 1200 mg intravenously over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

2.3 Recommended Dosage for NSCLC

The recommended dosage of TECENTRIQ is 1200 mg intravenously over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion of TECENTRIQ is tolerated, all subsequent infusions may be delivered over 30 minutes.

When administering TECENTRIQ in combination with chemotherapy or other antineoplastic drugs, administer TECENTRIQ prior to chemotherapy or other antineoplastic drugs when given on the same day.

Refer to the Prescribing Information for the chemotherapy agents or other antineoplastic drugs administered in combination with TECENTRIQ for recommended dosing information.

2.4 Recommended Dosage for Locally Advanced or Metastatic TNBC

The recommended dosage of TECENTRIQ is 840 mg administered as an intravenous infusion over 60 minutes, 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 until disease progression or unacceptable toxicity.

TECENTRIQ and paclitaxel protein-bound may be discontinued for toxicity independently of each other.

If the first infusion is tolerated, all subsequent infusions of TECENTRIQ may be delivered over 30 minutes. See also the prescribing information for paclitaxel protein-bound prior to initiation.

2.5 Recommended Dosage for SCLC

The recommended dosage of TECENTRIQ is 1200 mg intravenously over 60 minutes every 3 weeks until disease progression or unacceptable toxicity. If the first infusion of TECENTRIQ is tolerated, all subsequent infusions may be delivered over 30 minutes.

When administering TECENTRIQ in combination with chemotherapy, administer TECENTRIQ prior to chemotherapy when given on the same day.

Refer to the Prescribing Information for the chemotherapy agents administered in combination with TECENTRIQ for recommended dosing information.

2.6 Dosage Modifications for Adverse Reactions

No dose reductions of TECENTRIQ are recommended. Recommendations for dosage modifications are provided in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity of Adverse Reaction[1]	Dosage Modifications
Pneumonitis *[see Warnings and Precautions (5.1)]*	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 3 or 4	Permanently discontinue
Hepatitis *[see Warnings and Precautions (5.2)]*	AST or ALT more than 3 and up to 8 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	AST or ALT more than 8 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Colitis or diarrhea *[see Warnings and Precautions (5.3)]*	Grade 2 or 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Endocrinopathies (including but not limited to hypophysitis, adrenal insufficiency, hyperthyroidism, and type 1 diabetes mellitus) *[see Warnings and Precautions (5.4)]*	Grade 2, 3, or 4	Withhold dose until Grade 1 or resolved and clinically stable on hormone replacement therapy.
Other immune-mediated adverse reactions involving a major organ *[see Warnings and Precautions (5.5)]*	Grade 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Infections *[see Warnings and Precautions (5.6)]*	Grade 3 or 4	Withhold dose until Grade 1 or resolved
Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)	Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last TECENTRIQ dose	Permanently discontinue

Adverse Reaction	Severity of Adverse Reaction[1]	Dosage Modifications
Inability to taper corticosteroid	Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after last TECENTRIQ dose	Permanently discontinue
Recurrent Grade 3 or 4 adverse reaction	Recurrent Grade 3 or 4 (severe or life-threatening) adverse reaction	Permanently discontinue

[1] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

2.7 Preparation and Administration

Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed. Do not shake the vial.

Prepare the solution for infusion as follows:

- Select the appropriate vial(s) based on the prescribed dose.
- Withdraw the required volume of TECENTRIQ from the vial(s).
- Dilute into a 250 mL polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO) infusion bag containing 0.9% Sodium Chloride Injection, USP.
- Dilute with only 0.9% Sodium Chloride Injection, USP.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard used or empty vials of TECENTRIQ.

Storage of Infusion Solution

This product does not contain a preservative.

Administer immediately once prepared. If diluted TECENTRIQ infusion solution is not used immediately, store solution either:

- At room temperature for no more than 6 hours from the time of preparation. This includes room temperature storage of the infusion in the infusion bag and time for administration of the infusion, or
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from time of preparation.

Do not freeze.

Do not shake.

Administration

Administer the initial infusion over 60 minutes through an intravenous line with or without a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Do not coadminister other drugs through the same intravenous line.

Do not administer as an intravenous push or bolus.

3 DOSAGE FORMS AND STRENGTHS

Injection: 840 mg/14 mL (60 mg/mL) and 1200 mg/20 mL (60 mg/mL) colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis

TECENTRIQ can cause immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of systemic corticosteroids, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher pneumonitis. Withhold or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.6)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, pneumonitis occurred in 2.5% of patients, including Grade 3 (0.6%), Grade 4 (0.1%), and Grade 5 (< 0.1%) immune-mediated pneumonitis. The median time to onset of pneumonitis was 3.6 months (3 days to 20.5 months) and median duration of pneumonitis was 1.4 months (1 day to 15.1 months). Pneumonitis resolved in 67% of patients. Pneumonitis led to discontinuation of TECENTRIQ in 0.4% of the 2616 patients. Systemic corticosteroids were required in 1.5% of patients, including 0.8% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 45 days) followed by a corticosteroid taper.

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, immune-mediated pneumonitis occurred in 5.5% of patients, including Grades 3-4 in 1.4% of patients. Systemic corticosteroids were required in 4.2% of patients, including 3.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 5 days (1 day to 98 days) followed by a corticosteroid taper.

5.2 Immune-Mediated Hepatitis

TECENTRIQ can cause liver test abnormalities and immune-mediated hepatitis, defined as requiring use of systemic corticosteroids. Fatal cases have been reported. Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of TECENTRIQ, including clinical chemistry monitoring. Administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 or higher elevations of ALT, AST and/or total bilirubin. Interrupt or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.6)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, hepatitis occurred in 9% of patients, including Grade 3 (2.3%), Grade 4 (0.6%), and Grade 5 (< 0.1%). The median time to onset of hepatitis was 1.4 months (1 day to 25.8 months) and median duration was 24 days (1 day to 13 months). Hepatitis resolved in 71% of patients. Hepatitis led to discontinuation of TECENTRIQ in 0.4% of 2616 patients. Systemic corticosteroids were required in 2% of the patients, with 1.3% requiring high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 3 days (1 day to 35 days) followed by a corticosteroid taper.

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, immune-mediated hepatitis occurred in 14% of patients, including Grades 3-4 in 4.1% of patients. Systemic corticosteroids were required in 4.8% of patients, including 3.4% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 6 days (1 day to 144 days) followed by a corticosteroid taper.

5.3 Immune-Mediated Colitis

TECENTRIQ can cause immune-mediated colitis or diarrhea, defined as requiring use of systemic corticosteroids. Monitor patients for signs and symptoms of diarrhea or colitis. Withhold treatment with TECENTRIQ for Grade 2 or 3 diarrhea or colitis. If symptoms persist for longer than 5 days or recur, administer corticosteroids, prednisone 1–2 mg/kg/day or equivalents, followed by a taper for Grade 2 diarrhea or colitis. Interrupt or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.6) and Adverse Reactions (6.1)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, diarrhea or colitis occurred in 20% of patients, including Grade 3 (1.4%) events. The median time to onset of diarrhea or colitis was 1.5 months (1 day to 41 months). Diarrhea and colitis resolved in 85% of the patients. Diarrhea or colitis led to discontinuation of TECENTRIQ in 0.2% of 2616 patients. Systemic corticosteroids were required in 1.1% of patients and high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) was required in 0.4% patients with a median duration of 3 days (1 day to 11 days) followed by a corticosteroid taper.

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, diarrhea or colitis occurred in 29% of patients, including Grade 3-4 in 4.3% of patients. Systemic corticosteroids were required in 4.7% of patients, including 2.9% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 170 days) followed by a corticosteroid taper.

5.4 Immune-Mediated Endocrinopathies

TECENTRIQ can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, and type 1 diabetes mellitus, including diabetic ketoacidosis, and hypophysitis/hypopituitarism.

Thyroid Disorders: Monitor thyroid function prior to and periodically during treatment with TECENTRIQ. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Continue TECENTRIQ for hypothyroidism and interrupt for hyperthyroidism based on the severity *[see Dosage and Administration (2.6)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, hypothyroidism occurred in 4.6% of patients, and 3.8% of patients required the use of hormone replacement therapy. Hyperthyroidism occurred in 1.6% of patients. One patient experienced acute thyroiditis.

In clinical studies enrolling 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with platinum-based chemotherapy *[see Adverse Reactions (6.1)]*, hypothyroidism occurred in 11% of patients, including Grades 3-4 in 0.3% of patients; 8.2% of the 2421 patients required the use of hormone replacement therapy. The frequency and severity of hyperthyroidism and thyroiditis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

Adrenal Insufficiency: Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate prednisone 1to 2 mg/kg/day or equivalents, followed by a taper and hormone replacement as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.6)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, adrenal insufficiency occurred in 0.4% of patients, including Grade 3 (< 0.1%) adrenal insufficiency. Median time to onset was 5.7 months (3 days to 19 months). There was insufficient information to adequately characterize the median duration of adrenal insufficiency. Adrenal insufficiency resolved in 27% of patients. Systemic corticosteroids were required in 0.3% of 2616 patients, including 0.1% who required high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent). The frequency and severity of adrenal insufficiency were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

Type 1 Diabetes Mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.6)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, type 1 diabetes mellitus occurred in < 0.1% of patients. Insulin was required in one patient. The frequency and severity of diabetes mellitus were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

Hypophysitis: For Grade 2 or higher hypophysitis, initiate prednisone 1–2 mg/kg/day or equivalents, followed by a taper and hormone replacement therapy as clinically indicated. Interrupt TECENTRIQ based on the severity *[see Dosage and Administration (2.6)]*.

In clinical studies enrolling 2616 patients who received TECENTRIQ as a single-agent, Grade 2 hypophysitis occurred in < 0.1% of patients. The frequency and severity of hypophysitis were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.5 Other Immune-Mediated Adverse Reactions

TECENTRIQ can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with TECENTRIQ, immune-mediated adverse reactions can also manifest after discontinuation of TECENTRIQ.

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grades 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 2 mg/kg/day or equivalents, followed by a taper. Interrupt or permanently discontinue TECENTRIQ, based on the severity of the reaction *[see Dosage and Administration (2.6)]*.

If uveitis occurs in combination with other immune-mediated adverse reactions, evaluate for Vogt-Koyanagi-Harada syndrome, which has been observed with other products in this class and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of < 1% in 2616 patients who received TECENTRIQ as a single-agent and in 2421 patients who received TECENTRIQ in combination with platinum-based chemotherapy or were reported in other products in this class *[see Adverse Reactions (6.1)]*:

Cardiac: myocarditis

Dermatologic: bullous dermatitis, pemphigoid, erythema multiforme, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).

Gastrointestinal: pancreatitis, including increases in serum amylase or lipase levels

General: systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis

Hematological: autoimmune hemolytic anemia, immune thrombocytopenic purpura.

Musculoskeletal: myositis, rhabdomyolysis.

Neurological: Guillain-Barre syndrome, myasthenia syndrome/myasthenia gravis, demyelination, immune-related meningoencephalitis, aseptic meningitis, encephalitis, facial and abducens nerve paresis, polymyalgia rheumatica, autoimmune neuropathy, and Vogt-Koyanagi-Harada syndrome.

Ophthalmological: uveitis, iritis.

Renal: nephrotic syndrome, nephritis.

Vascular: vasculitis

5.6 Infections

TECENTRIQ can cause severe infections including fatal cases. Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold TECENTRIQ and resume once clinically stable *[see Dosage and Administration (2.6) and Adverse Reactions (6.1)]*.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, infections occurred in 42% of patients, including Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%). In patients with urothelial carcinoma, the most common Grade 3 or higher infection was urinary tract infections, occurring in 6.5% of patients. In patients with NSCLC, the most common Grade 3 or higher infection was pneumonia, occurring in 3.8% of patients. The frequency and severity of infections were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.7 Infusion-Related Reactions

TECENTRIQ can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue TECENTRIQ based on the severity *[see Dosage and Administration (2.6)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single-agent *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The frequency and severity of infusion-related reactions were similar whether TECENTRIQ was given as a single-agent in patients with various cancers or in combination with other antineoplastic drugs in NSCLC and SCLC.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death.

Verify pregnancy status of females of reproductive potential prior to initiating TECENTRIQ. Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.2)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.3)]*
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Infections *[see Warnings and Precautions (5.6)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

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

The data described in WARNINGS AND PRECAUTIONS reflect exposure to TECENTRIQ as a single-agent in 2616 patients in two randomized, active-controlled studies (POPLAR, OAK) and four open-label, single arm studies (PCD4989g, IMvigor210, BIRCH, FIR) which enrolled 524 patients with metastatic urothelial carcinoma, 1636 patients with metastatic NSCLC, and 456 patients with other tumor types. TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks in all studies except PCD4989g. Among the 2616 patients who received a single-agent TECENTRIQ, 36% were exposed for longer than 6 months and 20% were exposed for longer than 12 months.

Using the dataset described for patients who received TECENTRIQ as a single-agent, the most common adverse reactions in ≥ 20% of patients were fatigue/asthenia (48%), decreased appetite (25%), nausea (24%), cough (22%), and dyspnea (22%).

In addition, the data reflect exposure to TECENTRIQ in combination with other antineoplastic drugs in 2421 patients with NSCLC (N = 2223) or SCLC (N = 198) enrolled in five randomized, active-controlled trials, including IMpower150 and IMpower133. Among the 2421 patients, 53% were exposed to TECENTRIQ for longer than 6 months and 29% were exposed to TECENTRIQ for longer than 12 months.

Among the 2421 patients with NSCLC and SCLC who received TECENTRIQ in combination with other antineoplastic drugs, the most common adverse reactions in ≥20% of patients were fatigue/asthenia (49%), nausea (38%), alopecia (35%), constipation (29%), diarrhea (28%) and decreased appetite (27%).

The data described below in this section were obtained from one open-label, single arm, multiple cohort study (IMvigor210) and three randomized open-label, active-controlled studies (OAK, IMpower150 and IMpower133). In these trials, TECENTRIQ was administered at a dose of 1200 mg intravenously every 3 weeks. This section also describes data from one randomized, placebo-controlled study (IMpassion130) in which TECENTRIQ was administered (at a dose of 840 mg

intravenously every 2 weeks) in combination with paclitaxel protein-bound to 452 patients with metastatic TNBC.

Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor 210 (Cohort 1), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy *[see Clinical Studies (14.1)]*. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until either unacceptable toxicity or disease progression. The median duration of exposure was 15 weeks (0 to 87 weeks).

The most common Grades 3–4 adverse reactions (≥ 2%) were fatigue, urinary tract infection, anemia, diarrhea, blood creatinine increase, intestinal obstruction, ALT increase, hyponatremia, decreased appetite, sepsis, back/neck pain, renal failure, and hypotension.

Five patients (4.2%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, cardiac arrest, myocardial infarction, respiratory failure, or respiratory distress. One additional patient (0.8%) was experiencing herpetic meningoencephalitis and disease progression at the time of death.

Serious adverse reactions occurred in 37% of patients. The most frequent serious adverse reactions (≥ 2%) were diarrhea, intestinal obstruction, sepsis, acute kidney injury, and renal failure.

TECENTRIQ was discontinued for adverse reactions in 4.2% of patients. The adverse reactions leading to discontinuation were diarrhea/colitis (1.7%), fatigue (0.8%), hypersensitivity (0.8%), and dyspnea (0.8%).

Adverse reactions leading to interruption occurred in 35% of patients; the most common (≥ 1%) were intestinal obstruction, fatigue, diarrhea, urinary tract infection, infusion- related reaction, cough, abdominal pain, peripheral edema, pyrexia, respiratory tract infection, upper respiratory tract infection, creatinine increase, decreased appetite, hyponatremia, back pain, pruritus, and venous thromboembolism.

Tables 2 and 3 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 1).

Table 2: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
General		
Fatigue[1]	52	8
Peripheral edema[2]	17	2
Pyrexia	14	0.8
Gastrointestinal		
Diarrhea[3]	24	5

Adverse Reaction	TECENTRIQ N = 119	
	All Grades (%)	Grades 3–4 (%)
Nausea	22	2
Vomiting	16	0.8
Constipation	15	2
Abdominal pain[4]	15	0.8
Metabolism and Nutrition		
Decreased appetite[5]	24	3
Musculoskeletal and Connective Tissue		
Back/Neck pain	18	3
Arthralgia	13	0
Skin and Subcutaneous Tissue		
Pruritus	18	0.8
Rash[6]	17	0.8
Infections		
Urinary tract infection[7]	17	5
Respiratory, Thoracic, and Mediastinal		
Cough[8]	14	0
Dyspnea[9]	12	0

[1] Includes fatigue, asthenia, lethargy, and malaise
[2] Includes edema peripheral, scrotal edema, lymphedema, and edema
[3] Includes diarrhea, colitis, frequent bowel movements, autoimmune colitis
[4] Includes abdominal pain, upper abdominal pain, lower abdominal pain, and flank pain
[5] Includes decreased appetite and early satiety
[6] Includes rash, dermatitis, dermatitis acneiform, rash maculo-papular, rash erythematous, rash pruritic, rash macular, and rash papular
[7] Includes urinary tract infection, urinary tract infection bacterial, cystitis, and urosepsis
[8] Includes cough and productive cough
[9] Includes dyspnea and exertional dyspnea

Table 3: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 1)

Laboratory Abnormality	Grades 3–4 (%)
Chemistry	
Hyponatremia	15
Hyperglycemia	10
Increased Alkaline Phosphatase	7
Increased Creatinine	5
Hypophosphatemia	4
Increased ALT	4

Laboratory Abnormality	Grades 3–4 (%)
Increased AST	4
Hyperkalemia	3
Hypermagnesemia	3
Hyperbilirubinemia	3
Hematology	
Lymphopenia	9
Anemia	7

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The safety of TECENTRIQ was evaluated in IMvigor210 (Cohort 2), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following at least one platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen *[see Clinical Studies (14.1)]*. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. The median duration of exposure was 12.3 weeks (0.1 to 46 weeks).

The most common Grades 3–4 adverse reactions (≥ 2%) were urinary tract infection, anemia, fatigue, dehydration, intestinal obstruction, urinary obstruction, hematuria, dyspnea, acute kidney injury, abdominal pain, venous thromboembolism, sepsis, and pneumonia.

Three patients (1%) who were treated with TECENTRIQ experienced one of the following events which led to death: sepsis, pneumonitis, or intestinal obstruction.

TECENTRIQ was discontinued for adverse reactions in 3.2% of patients. Sepsis led to discontinuation in 0.6% of patients.

Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions (> 2%) were urinary tract infection, hematuria, acute kidney injury, intestinal obstruction, pyrexia, venous thromboembolism, urinary obstruction, pneumonia, dyspnea, abdominal pain, sepsis, and confusional state.

Adverse reactions leading to interruption occurred in 27% of patients; the most common (> 1%) were liver enzyme increase, urinary tract infection, diarrhea, fatigue, confusional state, urinary obstruction, pyrexia, dyspnea, venous thromboembolism, and pneumonitis.

Tables 4 and 5 summarize the adverse reactions and Grades 3–4 selected laboratory abnormalities, respectively, in patients who received TECENTRIQ in IMvigor210 (Cohort 2).

Table 4: Adverse Reactions in ≥ 10% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

Adverse Reaction	TECENTRIQ N = 310	
	All Grades (%)	Grades 3–4 (%)
General		
Fatigue	52	6
Pyrexia	21	1

Adverse Reaction	TECENTRIQ N = 310	
	All Grades (%)	Grades 3–4 (%)
Peripheral edema	18	1
Metabolism and Nutrition		
Decreased appetite	26	1
Gastrointestinal		
Nausea	25	2
Constipation	21	0.3
Diarrhea	18	1
Abdominal pain	17	4
Vomiting	17	1
Infections		
Urinary tract infection	22	9
Respiratory, Thoracic, and Mediastinal		
Dyspnea	16	4
Cough	14	0.3
Musculoskeletal and Connective Tissue		
Back/Neck pain	15	2
Arthralgia	14	1
Skin and Subcutaneous Tissue		
Rash	15	0.3
Pruritus	13	0.3
Renal and Urinary		
Hematuria	14	3

Table 5: Grades 3–4 Laboratory Abnormalities in ≥ 1% of Patients with Urothelial Carcinoma in IMvigor210 (Cohort 2)

Laboratory Abnormality	Grades 3–4 (%)
Chemistry	
Hyponatremia	10
Hyperglycemia	5
Increased Alkaline Phosphatase	4
Increased Creatinine	3
Increased ALT	2
Increased AST	2

Laboratory Abnormality	Grades 3–4 (%)
Hypoalbuminemia	1
Hematology	
Lymphopenia	10
Anemia	8

Non-small Cell Lung Cancer (NSCLC)

Metastatic Non-Squamous NSCLC

The safety of TECENTRIQ with bevacizumab, paclitaxel and carboplatin was evaluated in IMpower150, a multicenter, international, randomized, open-label trial in which 393 chemotherapy-naïve patients with metastatic non-squamous NSCLC received TECENTRIQ 1200 mg with bevacizumab 15 mg/kg, paclitaxel 175 mg/m^2 or 200 mg/m^2, and carboplatin AUC 6 mg/mL/min every 3 weeks for a maximum of 4 or 6 cycles, followed by TECENTRIQ 1200 mg with bevacizumab 15 mg/kg every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*. The median duration of exposure to TECENTRIQ was 8.3 months in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin.

The most common Grades 3–4 adverse reactions (≥2%) in patients receiving TECENTRIQ were fatigue/asthenia, hypertension, febrile neutropenia, diarrhea, pneumonia, nausea, decreased appetite, dehydration, and pulmonary embolism.

Fatal adverse reactions occurred in 6% of patients receiving TECENTRIQ; these included hemoptysis, febrile neutropenia, pulmonary embolism, pulmonary hemorrhage, death, cardiac arrest, cerebrovascular accident, pneumonia, aspiration pneumonia, chronic obstructive pulmonary disease, intracranial hemorrhage, intestinal angina, intestinal ischemia, intestinal obstruction and aortic dissection.

Serious adverse reactions occurred in 44%. The most frequent serious adverse reactions (>2%) were febrile neutropenia, pneumonia, diarrhea, and hemoptysis.

TECENTRIQ was discontinued due to adverse reactions in 15% of patients; the most common adverse reaction leading to discontinuation was pneumonitis (1.8%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 48%; the most common (>1%) were neutropenia, thrombocytopenia, fatigue/asthenia, diarrhea, hypothyroidism, anemia, pneumonia, pyrexia, hyperthyroidism, febrile neutropenia, increased ALT, dyspnea, dehydration and proteinuria.

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in patients receiving TECENTRIQ with bevacizumab, paclitaxel, and carboplatin in IMpower150. Study IMpower150 was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TECENTRIQ, as compared to the control arm, for any specified adverse reaction or laboratory abnormality listed in Tables 6 and 7.

Table 6: Adverse Reactions Occurring in ≥15% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

Adverse Reaction	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 393		Bevacizumab, Paclitaxel and Carboplatin N = 394	
	All Grades* (%)	Grades 3–4* (%)	All Grades* (%)	Grades 3–4* (%)
Nervous System				
Neuropathy[1]	56	3	47	3
Headache	16	0.8	13	0
General				
Fatigue/Asthenia	50	6	46	6
Pyrexia	19	0.3	9	0.5
Skin and Subcutaneous Tissue				
Alopecia	48	0	46	0
Rash[2]	23	2	10	0.3
Musculoskeletal and Connective Tissue				
Myalgia/Pain[3]	42	3	34	2
Arthralgia	26	1	22	1
Gastrointestinal				
Nausea	39	4	32	2
Diarrhea[4]	33	6	25	0.5
Constipation	30	0.3	23	0.3
Vomiting	19	2	18	1
Metabolism and Nutrition				
Decreased appetite	29	4	21	0.8
Vascular				
Hypertension	25	9	22	8
Respiratory				
Cough	20	0.8	19	0.3
Epistaxis	17	1	22	0.3
Renal				
Proteinuria[5]	16	3	15	3

* Graded per NCI CTCAE v4.0

[1] Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy.

[2] Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, contact dermatitis, rash erythematous, rash macular, pruritic rash, seborrheic dermatitis, dermatitis psoriasiform.

[3] Includes pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain, backpain, myalgia, and bone pain.

[4] Includes diarrhea, gastroenteritis, colitis, enterocolitis.

[5] Data based on Preferred Terms since laboratory data for proteinuria were not systematically collected.

Table 7: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in IMpower150

Laboratory Abnormality	TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin[2]		Bevacizumab, Paclitaxel and Carboplatin[2]	
	All Grades[1] (%)	Grades 3–4 (%)	All Grades[1] (%)	Grades 3–4 (%)
Hematology				
Anemia	83	10	83	9
Neutropenia	52	31	45	26
Lymphopenia	48	17	38	13
Chemistry				
Hyperglycemia	61	0	60	0
Increased BUN	52	NA	44	NA
Hypomagnesemia	42	2	36	1
Hypoalbuminemia	40	3	31	2
Increased AST	40	4	28	0.8
Hyponatremia	38	10	36	9
Increased Alkaline Phosphatase	37	2	32	1
Increased ALT	37	6	28	0.5
Increased TSH	30	NA	20	NA
Hyperkalemia	28	3	25	2
Increased Creatinine	28	1	19	2
Hypocalcemia	26	3	21	3
Hypophosphatemia	25	4	18	4
Hypokalemia	23	7	14	4
Hyperphosphatemia	25	N/A	19	N/A

NA = Not applicable.

[1] NCI CTCAE does not provide a Grades 3-4 definition for these laboratory abnormalities

[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ with bevacizumab, paclitaxel, and carboplatin range: 337-380); bevacizumab, paclitaxel, and carboplatin (range: 337-382)

Previously Treated Metastatic NSCLC

The safety of TECENTRIQ was evaluated in OAK, a multicenter, international, randomized, open-label trial in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression *[see Clinical Studies (14.2)]*. A total of 609 patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel (n=578) 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. The study excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids. The study population characteristics were: median age of 63 years (25 to 85 years), 46% age 65 years or older, 62% male, 71% White, 20% Asian, 68% former smoker, 16% current smoker, and 63% had ECOG performance status of 1. The median

duration of exposure was 3.4 months (0 to 26 months) in TECENTRIQ-treated patients and 2.1 months (0 to 23 months) in docetaxel-treated patients.

The most common Grades 3–4 adverse reactions (≥2%) were dyspnea, pneumonia, fatigue, and pulmonary embolism.

Fatal adverse reactions occurred in 1.6% of patients; these included pneumonia, sepsis, septic shock, dyspnea, pulmonary hemorrhage, sudden death, myocardial ischemia or renal failure.

Serious adverse reactions occurred in 33.5% of patients. The most frequent serious adverse reactions (>1%) were pneumonia, sepsis, dyspnea, pleural effusion, pulmonary embolism, pyrexia and respiratory tract infection.

TECENTRIQ was discontinued due to adverse reactions in 8% of patients. The most common adverse reactions leading to TECENTRIQ discontinuation were fatigue, infections and dyspnea. Adverse reactions leading to interruption of TECENTRIQ occurred in 25% of patients; the most common (>1%) were pneumonia, liver function test abnormality, dyspnea, fatigue, pyrexia, and back pain.

Tables 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in OAK.

Table 8: Adverse Reactions Occurring in ≥10% of Patients with NSCLC Receiving TECENTRIQ in OAK

Adverse Reaction[1]	TECENTRIQ N = 609		Docetaxel N = 578	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
General				
Fatigue/Asthenia[2]	44	4	53	6
Pyrexia	18	<1	13	<1
Respiratory				
Cough[3]	26	<1	21	<1
Dyspnea	22	2.8	21	2.6
Metabolism and Nutrition				
Decreased appetite	23	<1	24	1.6
Musculoskeletal				
Myalgia/pain[4]	20	1.3	20	<1
Arthralgia	12	0.5	10	0.2
Gastrointestinal				
Nausea	18	<1	23	<1
Constipation	18	<1	14	<1
Diarrhea	16	<1	24	2
Skin				
Rash[5]	12	<1	10	0

[1] Graded per NCI CTCAE v4.0
[2] Includes fatigue and asthenia
[3] Includes cough and exertional cough
[4] Includes musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia
[5] Includes rash, erythematous rash, generalized rash, maculopapular rash, papular rash, pruritic rash, pustular rash, pemphigoid

Table 9: Laboratory Abnormalities Worsening From Baseline Occurring in ≥20% of Patients with NSCLC Receiving TECENTRIQ in OAK

Laboratory Abnormality	TECENTRIQ		Docetaxel	
	All Grades[1] (%)[2]	Grades 3-4 (%)	All Grades[1] (%)[2]	Grades 3-4 (%)
Hematology				
Anemia	67	3	82	7
Lymphocytopenia	49	14	60	21
Chemistry				
Hypoalbuminemia	48	4	50	3
Hyponatremia	42	7	31	6
Increased Alkaline Phosphatase	39	2	25	1
Increased AST	31	3	16	0.5
Increased ALT	27	3	14	0.5
Hypophosphatemia	27	5	23	4
Hypomagnesemia	26	1	21	1
Increased Creatinine	23	2	16	1

[1] Graded according to NCI CTCAE version 4.0
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 546–585) and docetaxel (range: 532–560)

Metastatic Triple Negative Breast Cancer (TNBC)

The safety of TECENTRIQ in combination with paclitaxel protein-bound was evaluated in IMpassion130, a multicenter, international, randomized, double-blinded placebo-controlled trial in patients with locally advanced or metastatic TNBC who have not received prior chemotherapy for metastatic disease *[see Clinical Studies (14.3)]*. Patients received 840 mg of TECENTRIQ (n=452) or placebo (n=438) intravenously followed by paclitaxel protein-bound (100 mg/m^2) intravenously. For each 28 day cycle, TECENTRIQ was administered on days 1 and 15 and paclitaxel protein-bound was administered on days 1, 8, and 15 until disease progression or unacceptable toxicity. In the safety-evaluable population, the median duration of exposure to TECENTRIQ was 5.5 months (range: 0-32 months) and paclitaxel protein-bound was 5.1 months (range: 0 – 31.5 months) in the TECENTRIQ plus paclitaxel protein-bound arm. The median duration of exposure to placebo was 5.1 months (range: 0-25.1 months) and paclitaxel protein-bound was 5.0 months (range: 0-23.7 months) in the placebo plus paclitaxel protein-bound arm.

The most common Grades 3-4 adverse reactions occurring in ≥2%, were neutropenia (8%), peripheral neuropathies (9%), neutrophil count decreased (4.6%), fatigue (4%), anemia (2.9%), hypokalemia (2.2%), pneumonia (2.2%), and aspartate aminotransferase increased (2.0%). Adverse reactions leading to discontinuation of TECENTRIQ occurred in 6% (29/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm. The most common adverse reaction leading to TECENTRIQ discontinuation was peripheral neuropathy (<1%). Fatal adverse reactions occurred in 1.3% (6/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm; these included septic shock, mucosal inflammation, auto-immune hepatitis, aspiration, pneumonia, pulmonary embolism. Adverse reactions leading to interruption of TECENTRIQ occurred in 31% of patients; the most common (≥ 2%) were neutropenia, neutrophil count decreased, hyperthyroidism, and pyrexia. Serious adverse reactions occurred in 23% (103/452) of patients. The most frequent serious adverse reactions were pneumonia (2%), urinary tract infection (1%), dyspnea (1%), and pyrexia (1%).

Immune-related adverse reactions requiring systemic corticosteroid therapy occurred in 13% (59/452) of patients in the TECENTRIQ and paclitaxel protein-bound arm.

Table 10 summarizes adverse reactions that occurred in at least 10% of patients treated with TECENTRIQ and paclitaxel protein-bound. Table 11 summarizes selected laboratory abnormalities worsening from baseline that occurred in at least 20% of patients in the TECENTRIQ treated patients.

Table 10: Adverse Reactions Occurring in ≥10% of Patients with TNBC (IMpassion130)

Adverse Reaction[1]	TECENTRIQ in combination with paclitaxel protein-bound (n=452)		Placebo in combination with paclitaxel protein-bound (n=438)	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
	Percentage (%) of Patients			
Skin and Subcutaneous Tissue Disorders				
Alopecia	56	<1	58	<1
Rash	17	<1	16	<1
Pruritus	14	0	10	0
Nervous System				
Peripheral neuropathies[2]	47	9	44	5
Headache	23	<1	22	<1
Dysgeusia	14	0	14	0
Dizziness	14	0	11	0
General Disorders and administration site conditions				
Fatigue	47	4	45	3.4
Pyrexia	19	<1	11	0
Peripheral Edema	15	<1	16	1.4
Asthenia	12	<1	11	<1
Gastrointestinal Disorders				
Nausea	46	1.1	38	1.8
Diarrhea	33	1.3	34	2.1
Constipation	25	<1	25	<1
Vomiting	20	<1	17	1.1
Abdominal pain	10	<1	12	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	25	0	19	0
Dyspnea	16	<1	15	<1
Metabolism and Nutrition Disorders				
Decreased Appetite	20	<1	18	<1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	<1	16	<1
Back pain	15	1.3	13	<1
Myalgia	14	<1	15	<1

Pain in extremity	11	<1	10	<1
Endocrine Disorders				
Hypothyroidism	14	0	3.4	0
Infections and infestations				
Urinary tract infection	12	<1	11	<1
Upper respiratory tract infection	11	1.1	9	0
Nasopharyngitis	11	0	8	0

[1] Graded per NCI CTCAE v4.0
[2] Includes peripheral neuropathy, peripheral sensory neuropathy, paresthesia, and polyneuropathy

Table 11: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with TNBC (IMpassion130)

Laboratory Abnormality Test	Percentage of Patients with Worsening Laboratory Test from Baseline			
	TECENTRIQ in combination with paclitaxel protein-bound (n=452)		Placebo in combination with paclitaxel protein-bound (n=438)	
	All Grades[1] (%)[2]	Grades 3–4 (%)	All Grades[1] (%)[2]	Grades 3–4 (%)
Chemistry				
Increased ALT	43	6	34	2.7
Increased AST	42	4.9	34	3.4
Decreased Calcium	28	1.1	26	<1
Decreased Sodium	27	4.2	25	2.7
Decreased Albumin	27	<1	25	<1
Increased Alkaline Phosphatase	25	3.3	22	2.7
Decreased Phosphate	22	3.6	19	3.7
Increased Creatinine	21	<1	16	<1
Hematology				
Decreased Hemoglobin	79	3.8	73	3
Decreased Leukocytes	76	14	71	9
Decreased Neutrophils	58	13	54	13
Decreased Lymphocytes	54	13	47	8
Increased Prothrombin INR	25	<1	25	<1

[1] Graded per NCI CTCAE v4.0, except for increased creatinine which only includes patients with creatinine increase based on upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).
[2] Based on the number of patients with available baseline and at least one on-treatment laboratory test.

Small Cell Lung Cancer (SCLC)

The safety of TECENTRIQ with carboplatin and etoposide was evaluated in IMpower133, a randomized, multicenter, double-blind, placebo-controlled trial in which 198 patients with ES-SCLC received TECENTRIQ 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles, followed by TECENTRIQ 1200 mg every 3 weeks until disease progression or unacceptable toxicity *[see Clinical Studies (14.4)]*. Among 198 patients receiving TECENTRIQ, 32% were exposed for 6 months or longer and 12% were exposed for 12 months or longer.

The most common Grades 3–4 adverse reactions (≥2%) were fatigue/asthenia (5%), febrile neutropenia (3.5%), pneumonia (3.0%), asthenia (2.5%), diarrhea (2.0%), and infusion related reaction (2.0%).

Fatal adverse reactions occurred in 2% of patients receiving TECENTRIQ. These included pneumonia, respiratory failure, neutropenia, and death (1 patient each).

Serious adverse reactions occurred in 37% of patients receiving TECENTRIQ. Serious adverse reactions in >2% were pneumonia (4.5%), neutropenia (3.5%), febrile neutropenia (2.5%), and thrombocytopenia (2.5%).

TECENTRIQ was discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction requiring permanent discontinuation in >2% of patients was infusion-related reactions (2.5%).

Adverse reactions leading to interruption of TECENTRIQ occurred in 59% of patients; the most common (>1%) were neutropenia (22%), anemia (9%), leukopenia (7%), thrombocytopenia (5%), fatigue (4.0%), infusion-related reaction (3.5%), pneumonia (2.0%), febrile neutropenia (1.5%), increased ALT (1.5%), and nausea (1.5%).

Tables 12 and 13 summarize adverse reactions and laboratory abnormalities, respectively, in patients who received TECENTRIQ with carboplatin and etoposide in IMpower133.

Table 12: Adverse Reactions Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Adverse Reaction	TECENTRIQ with Carboplatin and Etoposide N = 198		Placebo with Carboplatin and Etoposide N = 196	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
General				
Fatigue/asthenia	39	5	33	3
Gastrointestinal				
Nausea	38	1	33	1
Constipation	26	1	30	1
Vomiting	20	2	17	3
Skin and Subcutaneous Tissue				
Alopecia	37	0	35	0
Metabolism and Nutrition				
Decreased appetite	27	1	18	0

[1] Graded per NCI CTCAE v4.0

Table 13: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients with SCLC Receiving TECENTRIQ in IMpower133

Laboratory Abnormality	TECENTRIQ with Carboplatin and Etoposide[2]		Placebo with Carboplatin and Etoposide[2]	
	All Grades[1] (%)[2]	Grades 3–4[1] (%)[2]	All Grades[1] (%)[2]	Grades 3–4[1] (%)[2]
Hematology				
Anemia	94	17	93	19
Neutropenia	73	45	76	48
Thrombocytopenia	58	20	53	17
Lymphopenia	46	14	38	11
Chemistry				
Hyperglycemia	67	10	65	8
Increased Alkaline Phosphatase	38	1	35	2
Hyponatremia	34	15	33	11
Hypoalbuminemia	32	1	30	0
Decreased TSH[3]	28	NA[3]	15	NA[3]
Hypomagnesemia	31	5	35	6
Hypocalcemia	26	3	28	5
Increased ALT	26	3	31	1
Increased AST	22	1	21	2
Increased Blood Creatinine	22	4	15	1
Hyperphosphatemia[3]	21	NA[3]	23	NA[3]
Increased TSH[3]	21	NA[3]	7	NA[3]

[1] Graded per NCI CTCAE v4.0
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 181-193); Placebo (range: 181-196)
[3] NA= Not applicable. NCI CTCAE v4.0 does not include these laboratories.

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 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 atezolizumab in the studies described above with the incidence of antibodies in other studies or to other products may be misleading.

Among 565 patients with NSCLC in OAK, 30% tested positive for treatment-emergent anti-drug antibodies (ADA) at one or more post-dose time points. The median onset time to ADA formation was 3 weeks. The ability of these binding ADA to neutralize atezolizumab is unknown. Patients who tested positive for treatment-emergent ADA also had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%; 118/560) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 *[see Clinical Studies (14.2)]*. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 275 patients with urothelial carcinoma in IMvigor210 (Cohort 2), 42% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 111 patients in IMvigor210 (Cohort 1), 48% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA also had decreased

systemic atezolizumab exposures. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

Among 364 ADA-evaluable patients with NSCLC who received TECENTRIQ with bevacizumab, paclitaxel and carboplatin in IMpower150, 36% (n=132) tested positive for treatment-emergent ADA at one or more post-dose time points and 83% of these 132 patients tested ADA positive prior to receiving the second dose of atezolizumab. 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)]*. The presence of ADA did not increase the incidence or severity of adverse reactions *[see Clinical Studies (14.2)]*.

Among 434 patients with TNBC in IMpassion130, 13% tested positive for treatment-emergent ADA at one or more post-dose time points. Among 178 patients in PD-L1 positive subgroup with TNBC in IMpassion130, 12% tested positive for treatment-emergent ADA at one or more post-dose time points. Patients who tested positive for treatment-emergent ADA had decreased systemic atezolizumab exposure *[see Clinical Pharmacology (12.3)]*. There are insufficient numbers of patients in the PD-L1 positive subgroup with ADA to determine whether ADA alters the efficacy of atezolizumab. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (12.1)]*, TECENTRIQ can cause fetal harm when administered to a pregnant woman. There are no available data on the use of TECENTRIQ in pregnant women.

Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to increased risk of immune-related rejection of the developing fetus resulting in fetal death *(see Data)*. Advise females of reproductive potential 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

Animal reproduction studies have not been conducted with TECENTRIQ to evaluate its effect on reproduction and fetal development. A literature-based assessment of the effects on reproduction demonstrated that a central function of the PD-L1/PD-1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to a fetus. Blockage of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to a fetus and to result in an increase in fetal loss; therefore, potential risks of administering TECENTRIQ during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-L1/PD-1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to atezolizumab may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of atezolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from TECENTRIQ, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating TECENTRIQ *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Based on its mechanism of action, TECENTRIQ can 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 TECENTRIQ and for at least 5 months following the last dose.

Infertility

Females

Based on animal studies, TECENTRIQ may impair fertility in females of reproductive potential while receiving treatment *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 2481 patients with urothelial carcinoma, lung cancer, and triple-negative breast cancer who were treated with TECENTRIQ in clinical studies, 45% were 65 years and over and 11% were 75 years and over. No overall differences in safety or effectiveness were observed between patients aged 65 years or older, and younger patients.

11 DESCRIPTION

Atezolizumab is a programmed cell death ligand 1 (PD-L1) blocking antibody. Atezolizumab is an Fc-engineered, humanized, non-glycosylated IgG1 kappa immunoglobulin that has a calculated molecular mass of 145 kDa.

TECENTRIQ (atezolizumab) injection for intravenous use is a sterile, preservative-free, colorless to slightly yellow solution in single-dose vials. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. Each 14 mL vial contains 840 mg of atezolizumab and is formulated in glacial acetic acid (11.5 mg), L-histidine (43.4 mg), polysorbate 20 (5.6 mg), and sucrose (575.1 mg) with a pH of 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PD-L1 may be expressed on tumor cells and/or tumor infiltrating immune cells and can contribute to the inhibition of the anti-tumor immune response in the tumor microenvironment.

Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is a monoclonal antibody that binds to 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. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

12.3 Pharmacokinetics

Patients' exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including a dose of 1200 mg administered every 3 weeks. The clearance (CV%) was 0.20 L/day (29%), the volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. Steady state was achieved after 6 to 9 weeks following multiple doses. The systemic accumulation ratio for every 2 weeks administration and every 3 weeks administration was 3.3- and 1.9- fold, respectively. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV%) from baseline value of approximately 17% (41%); however, the decrease in clearance was not considered clinically relevant.

Specific Populations

Age (21 to 89 years), body weight, sex, albumin levels, tumor burden, region or race, mild or moderate renal impairment [estimated glomerular filtration rate (eGFR) 30 to 89 mL/min/1.73 m^2], mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1 to 1.5 × ULN and any AST), level of PD-L1 expression, or performance status had no clinically significant effect on the systemic exposure of atezolizumab. In OAK, IMpower150 (TECENTRIQ, bevacizumab, paclitaxel, carboplatin arm only), and IMpassion130 (TECENTRIQ and paclitaxel protein-bound) atezolizumab clearance in patients who tested positive for treatment-emergent anti-drug antibodies (ADA) was 25%, 18%, and 22% higher, respectively, as compared to clearance in patients who tested negative for treatment-emergent ADA.

The effect of severe renal impairment or moderate or severe hepatic impairment on the pharmacokinetics of atezolizumab is unknown.

Drug Interaction Studies

The drug interaction potential of atezolizumab is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to test the potential of atezolizumab for carcinogenicity or genotoxicity.

Animal fertility studies have not been conducted with atezolizumab; however, an assessment of the male and female reproductive organs was included in a 26-week, repeat-dose toxicity study in cynomolgus monkeys. Weekly administration of atezolizumab to female monkeys at the highest dose tested caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries. This effect occurred at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible. There was no effect on the male monkey reproductive organs.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased

bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice and mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Urothelial Carcinoma

Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of TECENTRIQ was investigated in IMvigor210 (Cohort 1) (NCT02951767), a multicenter, open-label, single-arm trial that included 119 patients with locally advanced or metastatic urothelial carcinoma who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant or adjuvant chemotherapy. Patients were considered cisplatin-ineligible if they met any one of the following criteria at study entry: impaired renal function [creatinine clearance (CLcr) of 30 to 59 mL/min], Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, hearing loss of ≥ 25 decibels (dB) at two contiguous frequencies, or Grades 2-4 peripheral neuropathy. This study excluded patients who had: a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrollment; or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Patients received TECENTRIQ 1200 mg as an intravenous infusion every 3 weeks until unacceptable toxicity or disease progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed overall response rate (ORR) as assessed by independent review facility (IRF) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), duration of response (DoR) and overall survival (OS).

In this study, the median age was 73 years, 81% were male, and 91% were White. Thirty-five percent of patients had non-bladder urothelial carcinoma and 66% had visceral metastases. Eighty percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 70% had impaired renal function, 20% had an ECOG PS of 2, 14% had a hearing loss of ≥ 25dB, and 6% had Grades 2-4 peripheral neuropathy at baseline. Twenty percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 119 patients, 27% were classified as having PD-L1 expression of ≥ 5% (defined as PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area). The remaining 73% of patients were classified as having PD-L1 expression of < 5% (PD-L1 stained tumor-infiltrating IC covering < 5% of the tumor area).

Among the 32 patients with PD-L1 expression of ≥ 5%, median age was 67 years, 81% were male, 19% female, and 88% were White. Twenty-eight percent of patients had non-bladder urothelial carcinoma and 56% had visceral metastases. Seventy-two percent of patients had an ECOG PS of 0 or 1. Reasons for ineligibility for cisplatin-containing chemotherapy were: 66% had impaired renal function, 28% had an ECOG PS of 2, 16% had a hearing loss ≥ 25 dB, and 9% had Grades 2-4 peripheral neuropathy at baseline. Thirty-one percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy.

Confirmed ORR in all patients and the two PD-L1 subgroups are summarized in Table 14. The median follow-up time for this study was 14.4 months. In 24 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 33% (95% CI: 16%, 55%).

Table 14: Efficacy Results in IMvigor210 (Cohort 1)

	All Patients	PD-L1 Expression Subgroups	
	N = 119	PD-L1 Expression of < 5% in ICs[1] N = 87	PD-L1 Expression of ≥ 5% in ICs[1] N = 32
Number of IRF-assessed Confirmed Responders	28	19	9
ORR % (95% CI)	23.5% (16.2, 32.2)	21.8% (13.7, 32)	28.1% (13.8, 46.8)
Complete Response (CR) (%)	6.7%	6.9%	6.3%
Partial Response (PR) (%)	16.8%	14.9%	21.9%
Median DoR, months (range)	NR (3.7, 16.6+)	NR (3.7, 16.6+)	NR (8.1, 15.6+)

NR = Not reached
+ Denotes a censored value
[1] PD-L1 expression in tumor-infiltrating immune cells (ICs)

IMvigor130 (NCT02807636) is an ongoing multicenter, randomized study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum-containing chemotherapy. The study contains three arms: TECENTRIQ monotherapy, TECENTRIQ with platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine), and platinum-based chemotherapy alone (comparator). Both cisplatin-eligible and cisplatin-ineligible patients are included in the study. Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that patients classified as having PD-L1 expression of <5% when treated with TECENTRIQ monotherapy had decreased survival compared to those who received platinum-based chemotherapy. The iDMC recommended closure of the monotherapy arm to further accrual of patients with low PD-L1 expression, however, no other changes were recommended for the study, including any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of TECENTRIQ was investigated in IMvigor210 (Cohort 2) (NCT02108652), a multicenter, open-label, single-arm trial that included 310 patients with locally advanced or metastatic urothelial carcinoma who had disease progression during or following a platinum-containing chemotherapy regimen or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. This study excluded patients who had: a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, or administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Patients received TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity or either radiographic or clinical progression. Tumor response assessments were conducted every 9 weeks for the first 54 weeks and every 12 weeks thereafter. Major efficacy outcome measures included confirmed ORR as assessed by IRF using RECIST v1.1 and DoR.

In this study, the median age was 66 years, 78% were male, 91% of patients were White. Twenty-six percent had non-bladder urothelial carcinoma and 78% of patients had visceral

metastases. Sixty-two percent of patients had an ECOG PS of 1 and 35% of patients had a baseline CLcr < 60 mL/min. Nineteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Forty-one percent of patients had received 2 or more prior systemic regimens in the metastatic setting. Seventy-three percent of patients received prior cisplatin, 26% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 32% were classified as having PD-L1 expression of ≥ 5%. The remaining 68% of patients were classified as having PD-L1 expression of < 5%.

Confirmed ORR and median DOR in all patients and the two PD-L1 subgroups are summarized in Table 15. The median follow-up time for this study was 32.9 months. In 59 patients with disease progression following neoadjuvant or adjuvant therapy, the ORR was 22.0% (95% CI: 12.3%, 34.7%).

Table 15: Efficacy Results in IMvigor210 (Cohort 2)

	All Patients	**PD-L1 Expression Subgroups**	
	N = 310	**PD-L1 Expression of < 5% in IC[1] N = 210**	**PD-L1 Expression of ≥ 5% in IC[1] N = 100**
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	14.8% (11.2, 19.3)	9.5% (5.9, 14.3)	26% (17.7, 35.7)
Complete Response (CR) (%)	5.5%	2.4%	12.0%
Partial Response (PR) (%)	9.4%	7.1%	14.0%
Median DOR, months (range)	27.7 (2.1+, 33.4+)	20.9 (2.1+, 33.4+)	29.7 (4.2, 31.2+)

+ Denotes a censored value
[1] PD-L1 expression in tumor-infiltrating immune cells (IC)

14.2 Non-Small Cell Lung Cancer

Metastatic Chemotherapy-Naive Non-Squamous NSCLC

The efficacy of TECENTRIQ with bevacizumab, paclitaxel, and carboplatin was evaluated in IMpower150 (NCT02366143), a multicenter, international, randomized (1:1:1), open-label trial in 1202 patients with metastatic non-squamous NSCLC. IMpower150 enrolled patients with stage IV non-squamous NSCLC who had received no prior chemotherapy for metastatic disease, but could have received prior EGFR or ALK kinase inhibitor if appropriate, regardless of PD-L1 or T-effector gene (tGE) status and ECOG performance status 0 or 1. The trial excluded patients with a history of autoimmune disease, administration of a live attenuated vaccine within 28 days prior to randomization, active or untreated CNS metastases, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomization, or clear tumor infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions as seen on imaging.

Randomization was stratified by sex, presence of liver metastases, and PD-L1 expression status on tumor cells (TC) and tumor-infiltrating immune cells (IC) as follows: TC3 and any IC vs.

TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1. Patients were randomized to one of the following three treatment arms.

- Arm A: TECENTRIQ 1200 mg, paclitaxel 175 mg/m² or 200 mg/m² and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm B: TECENTRIQ 1200 mg, bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles
- Arm C: bevacizumab 15 mg/kg, paclitaxel 175 mg/m² or 200 mg/m², and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for a maximum of 4 or 6 cycles

Patients who had not experienced disease progression following the completion or cessation of platinum-based chemotherapy, received:

- Arm A: TECENTRIQ 1200 mg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm B: TECENTRIQ 1200 mg and bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity
- Arm C: bevacizumab 15 mg/kg intravenously on Day 1 of each 21-day cycle until disease progression or unacceptable toxicity

Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumor specimens were evaluated prior to randomization for PD-L1 tumor expression using the VENTANA PD-L1 (SP142) assay at a central laboratory. Tumor tissue was collected at baseline for expression of tGE signature and evaluation was performed using a clinical trial assay in a central laboratory prior to the analysis of efficacy outcome measures.

The major efficacy outcome measures for comparison of Arms B and C were progression free survival (PFS) by RECIST v1.1 in the tGE-WT (patients with high expression of T-effector gene signature [tGE], excluding those with EGFR- and ALK-positive NSCLC [WT]) and in the ITT-WT subpopulations and overall survival (OS) in the ITT-WT subpopulation. Additional efficacy outcome measures for comparison of Arms B and C or Arms A and C were PFS and OS in the ITT population, OS in the tGE-WT subpopulation, and ORR/DoR in the tGE-WT and ITT-WT subpopulations.

A total of 1202 patients were enrolled across the three arms of whom 1045 were in the ITT-WT subpopulation and 447 were in the tGE-WT subpopulation. The demographic information is limited to the 800 patients enrolled in Arms B and C where efficacy has been demonstrated. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were White (82%), 13% of patients were Asian, 10% were Hispanic, and 2% of patients were Black. Clinical sites in Asia (enrolling 13% of the study population) received paclitaxel at a dose of 175 mg/m^2 while the remaining 87% received paclitaxel at a dose of 200 mg/m^2. Approximately 14% of patients had liver metastases at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). PD-L1 was TC3 and any IC in 12%, TC0/1/2 and IC2/3 in 13%, and TC0/1/2 and IC0/1 in 75%. The demographics for the 696 patients in the ITT-WT subpopulation were similar to the ITT population except for the absence of patients with EGFR- or ALK-positive NSCLC.

The trial demonstrated a statistically significant improvement in PFS between Arms B and C in both the tGE-WT and ITT-WT subpopulations, but did not demonstrate a significant difference for either subpopulation between Arms A and C based on the final PFS analyses. In the interim analysis of OS, a statistically significant improvement was observed for Arm B compared to Arm C, but not for Arm A compared to Arm C. Efficacy results for the ITT-WT subpopulation are presented in Table 16 and Figure 1.

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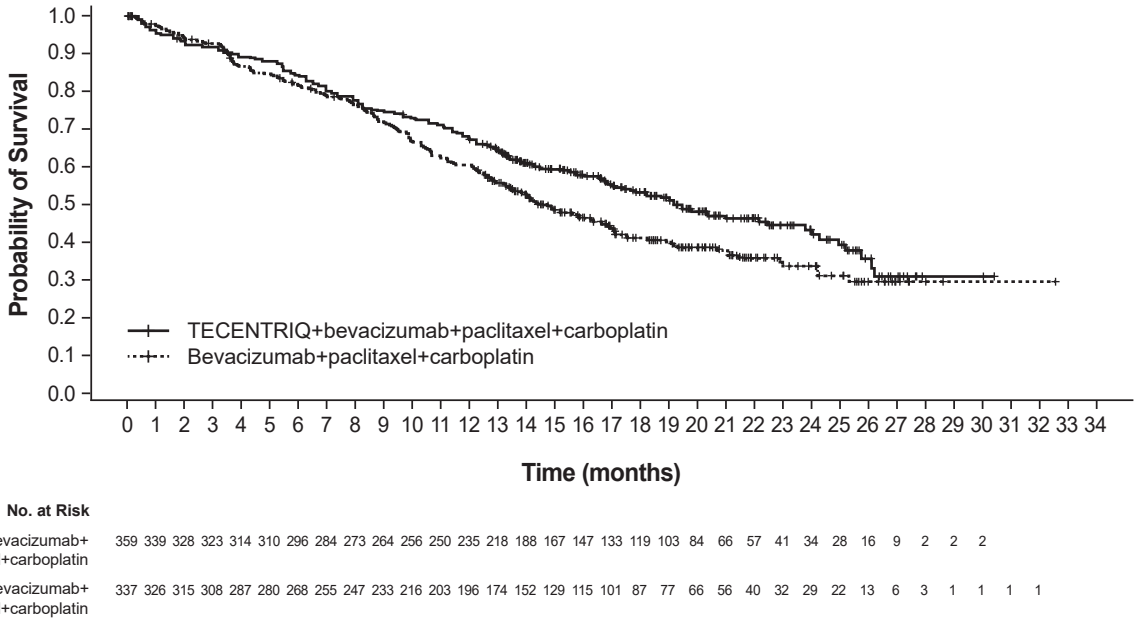
Table 16: Efficacy Results in ITT-WT Population in IMpower150

	Arm C: Bevacizumab, Paclitaxel and Carboplatin N = 337	Arm B: TECENTRIQ with Bevacizumab, Paclitaxel, and Carboplatin N = 359	Arm A: TECENTRIQ with Paclitaxel, and Carboplatin N = 349
Overall Survival[1]			
Deaths (%)	197 (59%)	179 (50%)	179 (51%)
Median, months	14.7	19.2	19.4
(95% CI)	(13.3, 16.9)	(17.0, 23.8)	(15.7, 21.3)
Hazard ratio[2] (95% CI)	---	0.78 (0.64, 0.96)	0.84 (0.72, 1.08)
p-value[3]	---	0.016[4]	0.204[5]
Progression-Free Survival[6]			
Number of events (%)	247 (73%)	247 (69%)	245 (70%)
Median, months	7.0	8.5	6.7
(95% CI)	(6.3, 7.9)	(7.3, 9.7)	(5.6, 6.9)
Hazard ratio[2] (95% CI)	---	0.71 (0.59, 0.85)	0.94 (0.79, 1.13)
p-value[3]	---	0.0002[7]	0.5219
Objective Response Rate[6]			
Number of responders (%)	142 (42%)	196 (55%)	150 (43%)
(95% CI)	(37, 48)	(49, 60)	(38, 48)
Complete response	3 (1%)	14 (4%)	9 (3%)
Partial response	139 (41%)	182 (51%)	141 (40%)
Duration of Response[6]	n = 142	n = 196	n = 150
Median (months)	6.5	10.8	9.5
(95% CI)	(5.6, 7.6)	(8.4, 13.9)	(7.0, 13.0)

[1]Based on OS interim analysis .
[2]Stratified by sex, presence of liver metastases, and PD-L1 expression status on TC and IC
[3]Based on the stratified log-rank test compared to Arm C
[4]Compared to the allocated α=0.0174 (two sided) for this interim analysis.
[5]Compared to the allocated α=0.0128 (two sided) for this interim analysis.
[6]As determined by independent review facility (IRF) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[7]Compared to the allocated α=0.006 (two sided) for the final PFS analysis.
CI=confidence interval

Figure 1: Kaplan-Meier Curves for Overall Survival in ITT-WT Population in IMpower150



Exploratory analyses showed that the subset of patients in the four drug regimen arm who were ADA positive by week 4 (30%) appeared to have similar efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (70%) *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3)]*. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Similarly ADA negative patients in the TECENTRIQ, bevacizumab, paclitaxel, and carboplatin arm were compared with a matched population in the bevacizumab, paclitaxel, and carboplatin arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, baseline albumin, baseline LDH, sex, tobacco history, metastatic site, TC level, and IC level. The hazard ratio comparing the ADA-positive subgroup with its matched control was 0.69 (95% CI: 0.44, 1.07). The hazard ratio comparing the ADA-negative subgroup with its matched control was 0.64 (95% CI: 0.46, 0.90).

Previously Treated Metastatic NSCLC

The efficacy of TECENTRIQ was evaluated in a multicenter, international, randomized (1:1), open-label study (OAK; NCT02008227) conducted in patients with locally advanced or metastatic NSCLC whose disease progressed during or following a platinum-containing regimen. Patients with a history of autoimmune disease, symptomatic or corticosteroid-dependent brain metastases, or requiring systemic immunosuppression within 2 weeks prior to enrollment were ineligible. Randomization was stratified by PD-L1 expression tumor-infiltrating immune cells (IC), the number of prior chemotherapy regimens (1 vs. 2), and histology (squamous vs. non-squamous).

Patients were randomized to receive TECENTRIQ 1200 mg intravenously every 3 weeks until unacceptable toxicity, radiographic progression, or clinical progression or docetaxel 75 mg/m^2 intravenously every 3 weeks until unacceptable toxicity or disease progression. Tumor assessments were conducted every 6 weeks for the first 36 weeks and every 9 weeks thereafter. The major efficacy outcome measure was overall survival (OS) in the first 850 randomized patients and OS in the subgroup of patients with PD-L1-expressing tumors (defined as ≥ 1% PD-L1 expression on tumor cells [TC] or immune cells [IC]). Additional efficacy outcome measures

were OS in all randomized patients (n = 1225), OS in subgroups based on PD-L1 expression, overall response rate (ORR), and progression free survival as assessed by the investigator per RECIST v.1.1.

Among the first 850 randomized patients, the median age was 64 years (33 to 85 years) and 47% were ≥ 65 years old; 61% were male; 70% were White and 21% were Asian; 15% were current smokers and 67% were former smokers; and 37% had baseline ECOG PS of 0 and 63% had a baseline ECOG PS of 1. Nearly all (94%) had metastatic disease, 74% had non-squamous histology, 75% had received only one prior platinum-based chemotherapy regimen, and 55% of patients had PD-L1-expressing tumors.

Efficacy results are presented in Table 17 and Figure 2.

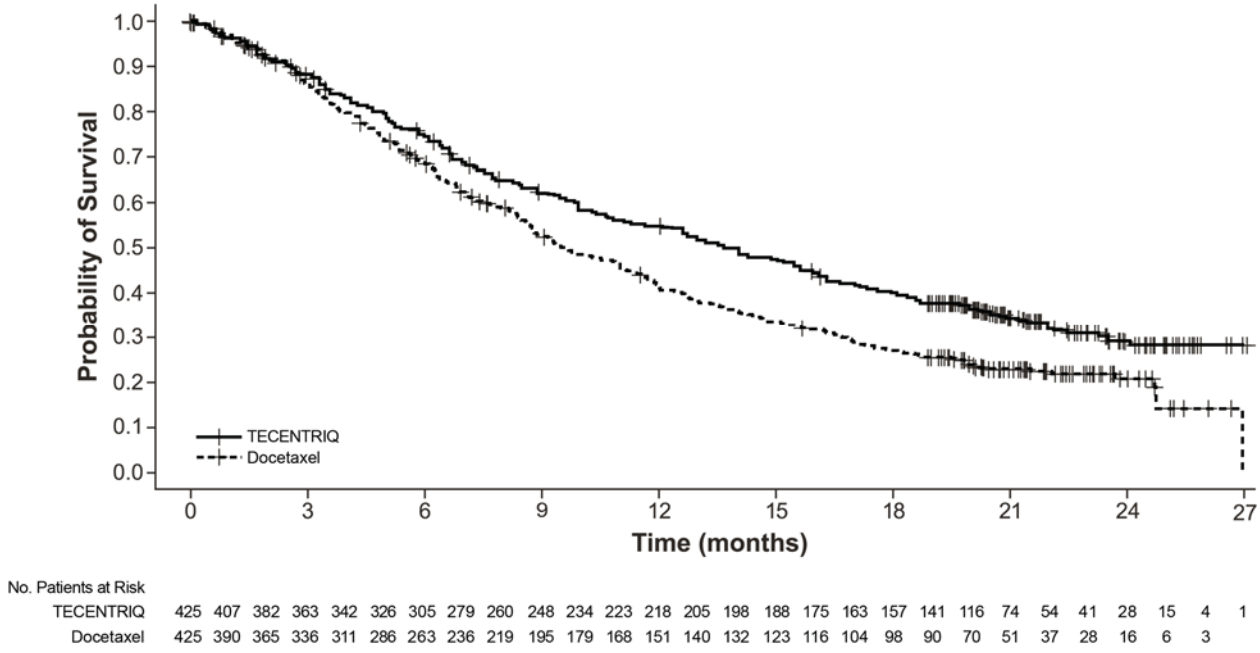
Table 17: Efficacy Results in OAK

	TECENTRIQ	Docetaxel
Overall Survival in first 850 patients		
Number of patients	N=425	N=425
Deaths (%)	271 (64%)	298 (70%)
Median, months	13.8	9.6
(95% CI)	(11.8, 15.7)	(8.6, 11.2)
Hazard ratio[1] (95% CI)	0.74 (0.63, 0.87)	
p-value[2]	0.0004[3]	
Progression-Free Survival		
Number of Patients	N=425	N=425
Events (%)	380 (89%)	375 (88%)
Progression (%)	332 (78%)	290 (68%)
Deaths (%)	48 (11%)	85 (20%)
Median, months	2.8	4.0
(95% CI)	(2.6, 3.0)	(3.3, 4.2)
Hazard ratio[1] (95% CI)	0.95 (0.82, 1.10)	
Overall Response Rate [4]		
Number of Patients	N=425	N=425
ORR, n (%)	58 (14%)	57 (13%)
(95% CI)	(11%, 17%)	(10%, 17%)
Complete response	6 (1%)	1 (0.2%)
Partial response	52 (12%)	56 (13%)
Duration of Response[3]	N=58	N=57
Median (months)	16.3	6.2
(95% CI)	(10.0, NE)	(4.9, 7.6)
Overall Survival in all 1225 patients		
Number of patients	N=613	N=612
Deaths (%)	384 (63%)	409 (67%)
Median, months	13.3	9.8
(95% CI)	(11.3, 14.9)	(8.9, 11.3)

	TECENTRIQ	Docetaxel
Hazard ratio[1] (95% CI)	0.79 (0.69, 0.91)	
p-value[2]	0.0013[5]	

[1] Stratified by PD-L1 expression in tumor infiltrating immune cells, the number of prior chemotherapy regimens, and histology
[2] Based on the stratified log-rank test
[3] Compared to the pre-specified allocated α of 0.03 for this analysis
[4] Per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[5] Compared to the allocated α of 0.0177 for this interim analysis based on 86% information using O'Brien-Fleming boundary
CI=confidence interval; NE=not estimable

Figure 2: Kaplan-Meier Curves of Overall Survival in the First 850 Patients Randomized in OAK



Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used to define the PD-L1 expression subgroups for pre-specified analyses. Of the 850 patients, 16% were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥ 50% of TC or ≥ 10% of IC. In an exploratory efficacy subgroup analysis of OS based on PD-L1 expression, the hazard ratio was 0.41 (95% CI: 0.27, 0.64) in the high PD-L1 expression subgroup and 0.82 (95% CI: 0.68, 0.98) in patients who did not have high PD-L1 expression.

Exploratory analyses showed that the subset of patients who were ADA positive by week 4 (21%) appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for treatment-emergent ADA by week 4 (79%) *[see Adverse Reactions (6.2), Clinical Pharmacology (12.3)]*. ADA positive patients by week 4 appeared to have similar OS compared to docetaxel-treated patients. In an exploratory analysis, propensity score matching was conducted to compare ADA positive patients in the atezolizumab arm with a matched population in the docetaxel arm and ADA negative patients in the atezolizumab arm with a matched population in the docetaxel arm. Propensity score matching factors were: baseline sum of longest tumor size (BSLD), baseline ECOG, histology (squamous vs. non-squamous), baseline albumin, baseline LDH, gender, tobacco history, metastases status (advanced or local), metastatic site, TC level, and IC level. The hazard ratio comparing the ADA positive subgroup

with its matched control was 0.89 (95% CI: 0.61, 1.3). The hazard ratio comparing the ADA negative subgroup with its matched control was 0.68 (95% CI: 0.55, 0.83).

14.3 Locally Advanced or Metastatic Triple-Negative Breast Cancer

The efficacy of TECENTRIQ in combination with paclitaxel protein-bound was investigated in IMpassion130 (NCT02425891), a multicenter, international, double-blinded, placebo-controlled, randomized trial that included 902 unresectable locally advanced or metastatic triple-negative breast cancer patients that had not received prior chemotherapy for metastatic disease. Patients were stratified by presence of liver metastases, prior taxane treatment, and by PD-L1 expression status in tumor infiltrating immune cells (IC) (PD-L1 stained tumor-infiltrating immune cells [IC] <1% of tumor area vs. ≥ 1% of the tumor area) by the VENTANA PD-L1 (SP142) Assay. Of the 902 patients in the intent to treat population (ITT), 41% (369 patients) were classified as PD-L1 expression ≥ 1%. Patients were randomized (1:1) to receive either TECENTRIQ (840 mg) or placebo intravenous infusions on Days 1 and 15 of every 28-day cycle, plus paclitaxel protein-bound (100 mg/m^2) administered via intravenous infusion on Days 1, 8 and 15 of every 28-day cycle. Patients received treatment until radiographic disease progression per RECIST v1.1, or unacceptable toxicity.

Patients were excluded if they had 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. Tumor assessments were performed every 8 weeks (± 1 week) for the first 12 months after Cycle 1, day 1 and every 12 weeks (± 1 week) thereafter.

In IMpassion130, the median age was 55 years (range: 20-86). Overall, most patients were women (99.6%) and the majority of patients were white (68%), Asian (18%), Black or African American (7%), and American Indian or Alaskan Native (4.4%). The demographic and baseline disease characteristics of the study population were well balanced between the treatment arms. Baseline ECOG performance status was 0 (58%) or 1 (41%). Overall, 41% of enrolled patients had PD-L1 expression ≥ 1%, 27% had liver metastases and 7% brain metastases at baseline. Approximately half the patients had received a taxane (51%) or anthracycline (54%) in the (neo)adjuvant setting. Patient demographics and baseline tumor disease in the PD-L1 expressing population were generally representative of the broader study population.

Tumor specimens (archival or fresh) were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay at a central laboratory and the results were used as a stratification factor for randomization and to define the PD-L1 expression subgroups for pre-specified analyses.

The major efficacy outcomes were investigator-assessed progression free survival (PFS) in the ITT and PD-L1 expressing patient population per RECIST v1.1 and overall survival (OS) in the ITT population. Overall survival data were immature with 43% deaths in the ITT population. The efficacy results of IMpassion130 for the patient population with PD-L1 expression ≥ 1% are presented in Table 18 and Figure 3.

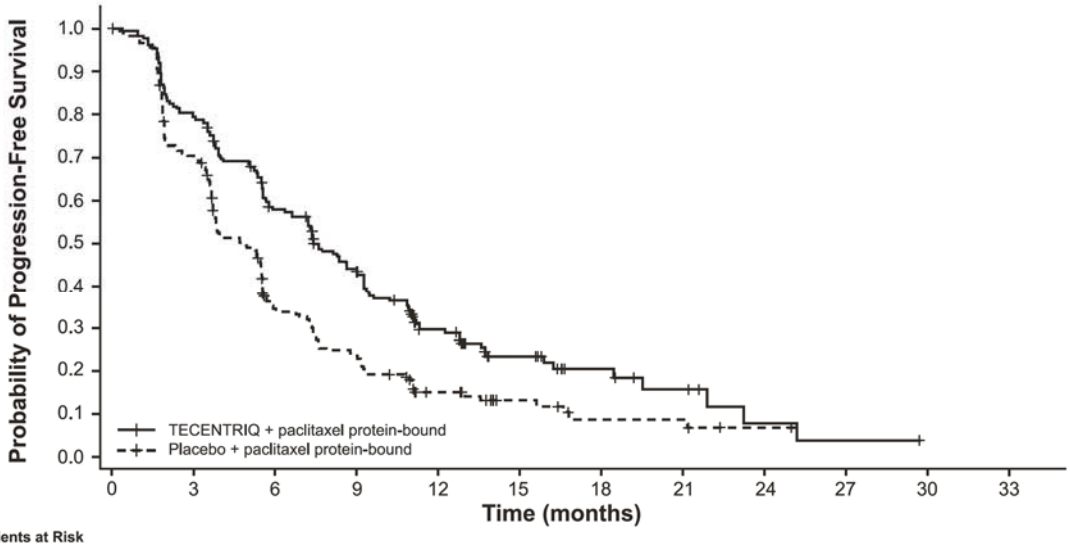
Table 18: Efficacy Results from IMpassion130 in Patients with PD-L1 Expression ≥ 1%

	PD-L1 Expression ≥ 1%[1]	
	TECENTRIQ in combination with paclitaxel protein-bound	**Placebo in combination with paclitaxel protein-bound**
Progression-Free Survival[2,3]	(n=185)	(n=184)
Events (%)	136 (74)	151 (82)
Median, months	7.4 (6.6, 9.2)	4.8 (3.8, 5.5)
Stratified Hazard ratio (95% CI)[4]	0.60 (0.48, 0.77)	

p-value	<0.0001	
Objective Response Rate[2,3,5,6]	n=185	n=183
Number of responders (%)	98 (53)	60 (33)
(95% CI)	(45.5, 60.3)	(26.0, 40.1)
Complete response (%)	17 (9)	1 (<1)
Partial response (%)	81 (44)	59 (32)
Duration of Response[2,3,6]	n=98	n=60
Median (months)	9.2	6.2
(95% CI)	(7.5, 11.9)	(5.5, 8.8)

[1] PD-L1 expression in tumor-infiltrating immune cells (IC)
[2] As determined by investigator assessment
[3] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[4] Stratified by presence of liver metastases, and by prior taxane treatment
[5] patients with measurable disease at baseline
[6] confirmed responses
PFS=Progression-Free Survival; CI=Confidence Interval; ORR=Objective Response Rate; DOR=Duration of Response; NE=Not Estimable

Figure 3: Kaplan-Meier Plot of Progression-Free-Survival in IMpassion130 in Patients with PD-L1 Expression ≥1%



14.4 Small Cell Lung Cancer

The efficacy of TECENTRIQ with carboplatin and etoposide was investigated in IMpower133 (NCT02763579), a randomized (1:1), multicenter, double-blind, placebo-controlled trial in 403 patients with ES-SCLC. IMpower133 enrolled patients with ES-SCLC who had received no prior chemotherapy for extensive stage disease and ECOG performance status 0 or 1. The trial excluded patients with active or untreated CNS metastases, history of autoimmune disease, administration of a live, attenuated vaccine within 4 weeks prior to randomization, or administration of systemic immunosuppresive medications within 1 week prior to randomization.

Randomization was stratified by sex, ECOG performance status, and presence of brain metastases. Patients were randomized to receive one of the following two treatment arms:

- TECENTRIQ 1200 mg and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2 and 3 of each 21-day cycle for a maximum of 4 cycles followed by TECENTRIQ 1200 mg once every 3 weeks until disease progression or unacceptable toxicity, or
- placebo and carboplatin AUC 5 mg/mL/min on Day 1 and etoposide 100 mg/m^2 intravenously on Days 1, 2, and 3 of each 21-day cycle for a maximum of 4 cycles followed by placebo once every 3 weeks until disease progression or unacceptable toxicity.

Administration of TECENTRIQ was permitted beyond RECIST-defined disease progression. Tumor assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Patients treated beyond disease progression had tumor assessment conducted every 6 weeks until treatment discontinuation.

Major efficacy outcome measures were OS and PFS as assessed by investigator per RECIST v1.1 in the intent-to-treat population. Additional efficacy outcome measures included ORR and DoR as assessed by investigator per RECIST v1.1.

A total of 403 patients were randomized, including 201 to the TECENTRIQ arm and 202 to the chemotherapy alone arm. The median age was 64 years (range 26 to 90) and 65% were male. The majority of patients were White (80%); 17% were Asian, 4% were Hispanic and 1% were Black. Baseline ECOG performance status was 0 (35%) or 1 (65%); 9% of patients had a history of brain metastases, and 97% were current or previous smokers.

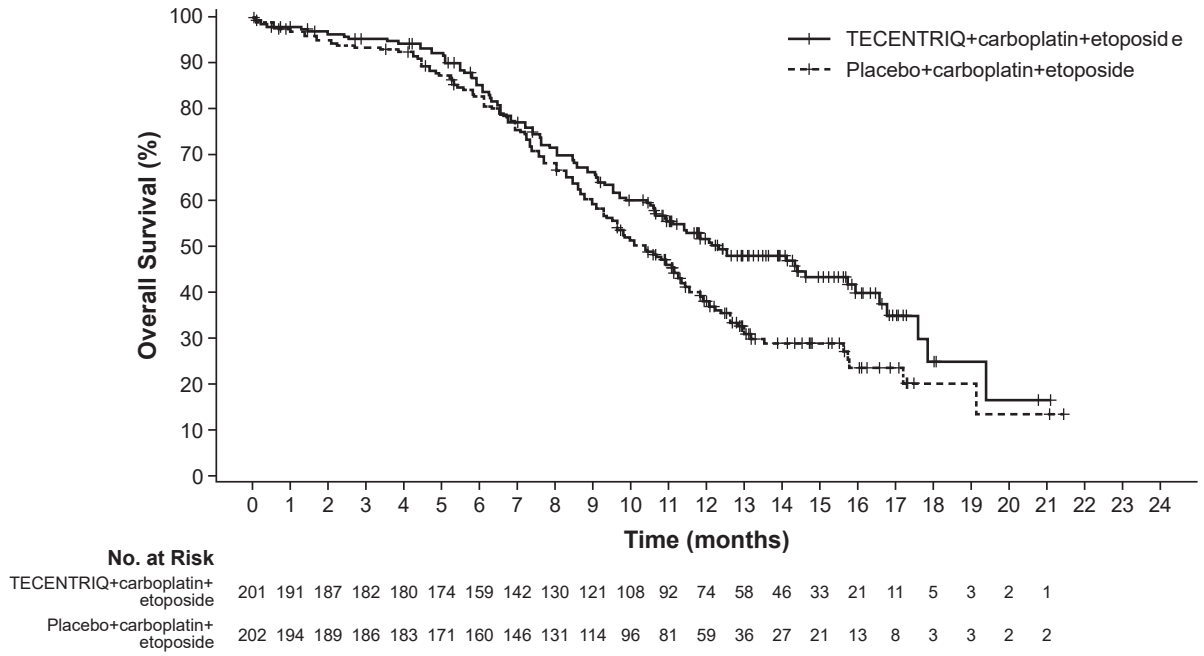
Efficacy results are presented in Table 19 and Figure 4.

Table 19: Efficacy Results from IMpower133

	TECENTRIQ with Carboplatin and Etoposide	Placebo with Carboplatin and Etoposide
Overall Survival	N=201	N=202
Deaths (%)	104 (52%)	134 (66%)
Median, months	12.3	10.3
(95% CI)	(10.8, 15.9)	(9.3, 11.3)
Hazard ratio[3] (95% CI)	0.70 (0.54, 0.91)	
p-value[4, 5]	0.0069	
Progression-Free Survival[1,2]	N=201	N=202
Number of events (%)	171 (85%)	189 (94%)
Median, months	5.2	4.3
(95% CI)	(4.4, 5.6)	(4.2, 4.5)
Hazard ratio[3] (95% CI)	0.77 (0.62, 0.96)	
p-value[4, 6]	0.0170	
Objective Response Rate[1,2,7]	N=201	N=202
Number of responders (%)	121 (60%)	130 (64%)
(95% CI)	(53, 67)	(57, 71)
Complete response	5 (2%)	2 (1%)
Partial response	116 (58%)	128 (63%)
Duration of Response[1,2,7]	N=121	N=130
Median (months)	4.2	3.9
(95% CI)	(4.1, 4.5)	(3.1, 4.2)

[1]As determined by investigator assessment
[2] per RECIST v1.1 (Response Evaluation Criteria in Solid Tumors v1.1)
[3]Stratified by sex and ECOG performance status
[4]Based on the stratified log-rank test
[5]Compared to the allocated α of 0.0193 for this interim analysis based on 78% information using O'Brien-Fleming boundary
[6]Compared to the allocated α of 0.05 for this analysis.
[7]Confirmed response
CI=confidence interval

Figure 4: Kaplan-Meier Plot of Overall Survival in IMpower133



16 HOW SUPPLIED/STORAGE AND HANDLING

TECENTRIQ injection is a sterile, preservative-free, and colorless to slightly yellow solution for intravenous infusion supplied as a 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).

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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of TECENTRIQ, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.2)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain *[see Warnings and Precautions (5.3)]*.

- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, hyperthyroidism, hypothyroidism, adrenal insufficiency, or type 1 diabetes mellitus, including diabetic ketoacidosis *[see Warnings and Precautions (5.4)]*.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of other potential immune-mediated adverse reactions *[see Warnings and Precautions (5.5)]*.

Infections

Advise patients to contact their healthcare provider immediately for signs or symptoms of infection *[see Warnings and Precautions (5.6)]*.

Infusion-Related Reactions

Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.7)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential that TECENTRIQ can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of TECENTRIQ *[see Use in Specific Populations (8.3)]*.

Lactation

Advise female patients not to breastfeed while taking TECENTRIQ and for at least 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

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MEDICATION GUIDE
TECENTRIQ® (te-SEN-trik)
(atezolizumab)
Injection

What is the most important information I should know about TECENTRIQ?

TECENTRIQ is a medicine that may treat certain cancers by working with your immune system. TECENTRIQ can cause your immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

Call or see your healthcare provider right away if you get any symptoms of the following problems or these symptoms get worse:

Lung problems (pneumonitis). Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

Liver problems (hepatitis). Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- drowsiness
- dark urine (tea colored)
- bleeding or bruising more easily than normal
- feeling less hungry than usual

Intestinal problems (colitis). Signs and symptoms of colitis may include:

- diarrhea (loose stools) or more bowel movements than usual
- blood or mucus in your stools or dark, tarry, sticky stools
- severe stomach area (abdomen) pain or tenderness

Hormone gland problems (especially the thyroid, adrenal glands, pancreas, and pituitary). Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- extreme tiredness
- weight gain or weight loss
- dizziness or fainting
- feeling more hungry or thirsty than usual
- hair loss
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- feeling cold
- constipation
- your voice gets deeper
- urinating more often than usual
- nausea or vomiting
- stomach area (abdomen) pain

Problems in other organs. Signs and symptoms may include:

- severe muscle weakness
- numbness or tingling in hands or feet
- confusion
- blurry vision, double vision, or other vision problems
- changes in mood or behavior
- extreme sensitivity to light
- neck stiffness
- eye pain or redness
- skin blisters or peeling
- chest pain, irregular heartbeat, shortness of breath or swelling of the ankles

Severe infections. Signs and symptoms of infection may include:

- fever
- cough
- flu-like symptoms
- pain when urinating, frequent urination or back pain

Severe infusion reactions. Signs and symptoms of infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- swelling of your face or lips
- dizziness
- fever
- feeling like passing out
- back or neck pain

Getting medical treatment right away may help keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during your treatment with TECENTRIQ. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with TECENTRIQ if you have severe side effects.

What is TECENTRIQ?

TECENTRIQ is a prescription medicine used to treat adults with:

- **a type of bladder and urinary tract cancer called urothelial carcinoma.** TECENTRIQ may be used when your bladder cancer has spread or cannot be removed by surgery, **and if you have any one of the following conditions:**
  - you are not able to take chemotherapy that contains a medicine called cisplatin, and your cancer tests positive for "PD-L1", **or**
  - you are not able to take chemotherapy that contains any platinum regardless of "PD-L1" status, **or**
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- **a type of lung cancer called non-small cell lung cancer (NSCLC).**
  - **TECENTRIQ may be used with bevacizumab and the chemotherapy medicines carboplatin and paclitaxel as your first treatment when your lung cancer:**
    - has spread or grown, **and**
    - is a type of lung cancer called "non-squamous NSCLC
    - your tumor does not have an abnormal "EGFR" or "ALK" gene
  - **TECENTRIQ may be used when your lung cancer:**
    - has spread or grown, **and**
    - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
    - if your tumor has an abnormal "EGFR" or "ALK" gene, you should have also tried an FDA-approved therapy for tumors with these abnormal genes, and it did not work or is no longer working.
- **a type of breast cancer called triple-negative breast cancer (TNBC).** TECENTRIQ may be used with the medicine paclitaxel protein-bound when your breast cancer:
  - has spread or cannot be removed by surgery, **and**
  - your cancer tests positive for "PD-L1".
- **a type of lung cancer called small cell lung cancer (SCLC).**

TECENTRIQ may be used with the chemotherapy medicines carboplatin and etoposide as your first treatment when your lung cancer

is a type called "extensive-stage SCLC," which means that it has spread or grown.

It is not known if TECENTRIQ is safe and effective in children.

Before you receive TECENTRIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are being treated for an infection
- are pregnant or plan to become pregnant. TECENTRIQ can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with TECENTRIQ.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with TECENTRIQ.
  - You should use an effective method of birth control during your treatment and for at least 5 months after the last dose of TECENTRIQ.
- are breastfeeding or plan to breastfeed. It is not known if TECENTRIQ passes into your breast milk. Do not breastfeed during treatment and for at least 5 months after the last dose of TECENTRIQ.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive TECENTRIQ?

- Your healthcare provider will give you TECENTRIQ into your vein through an intravenous (IV) line over 30 to 60 minutes.
- TECENTRIQ is usually given every 2 or 3 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will test your blood to check you for certain side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of TECENTRIQ?

TECENTRIQ can cause serious side effects, including:

- **See "What is the most important information I should know about TECENTRIQ?"**

The most common side effects of TECENTRIQ when used alone include:

- feeling tired
- nausea
- cough
- shortness of breath
- decreased appetite

The most common side effects of TECENTRIQ when used in lung cancer with other anti-cancer medicines include:

- feeling tired or weak
- nausea
- hair loss
- constipation
- diarrhea
- decreased appetite

The most common side effects of TECENTRIQ when used in triple-negative breast cancer with paclitaxel protein-bound include:

- hair loss
- tingling or numbness in hands or feet
- feeling tired
- nausea
- diarrhea
- low red blood cells (anemia)
- constipation
- cough
- headache
- low white blood cells
- vomiting
- decreased appetite

TECENTRIQ may cause fertility problems in females, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of TECENTRIQ. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TECENTRIQ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about TECENTRIQ, talk with your healthcare provider. You can ask your healthcare provider for information about TECENTRIQ that is written for health professionals.

What are the ingredients in TECENTRIQ?

Active ingredient: atezolizumab

Inactive ingredients: glacial acetic acid, L-histidine, sucrose, polysorbate 20

Manufactured by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990 USA

U.S. License No. 1048 TECENTRIQ is a registered trademark of Genentech, Inc.

For more information, call 1-*844-832-3687* or go to www.TECENTRIQ.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 3/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s019

MULTI-DISCIPLINARY REVIEW

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	761034/ S-019
Priority or Standard	Priority
Submit Date(s)	09/18/2018
Received Date(s)	09/18/2018
PDUFA Goal Date	03/18/2019
Division/Office	DOP2/OHOP
Review Completion Date	March 18, 2019
Established Name	atezolizumab
(Proposed) Trade Name	TECENTRIQ
Pharmacologic Class	Programmed death-ligand 1 (PD-L1) blocking antibody
Applicant	Genentech
Formulation(s)	Injection
Dosing Regimen	1200 mg as an intravenous infusion over 60 minutes every 3 weeks
Applicant Proposed Indication(s)/Population(s)	TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

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Safety Analyst (OHOP IO)	Yutao Gong

OSE= Office of Surveillance and Epidemiology

Reference ID: 4405439

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
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
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
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
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

Reference ID: 4405439

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

Reference ID: 4405439

1 Executive Summary

1.1. Product Introduction

Atezolizumab (TECENTRIQ) is a programmed death-ligand 1 (PD-L1) blocking antibody (IgG1 kappa) that directly binds to PD-L1 and blocks its interactions with the PD-1 and B7.1 receptors on lymphocytes and other cells.

Atezolizumab is approved for the following indications:

- In combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations.

- For the treatment of 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.

- For the treatment of 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.

  The indication for treatment of patients with urothelial carcinoma is approved under the provisions of accelerated approval based on tumor response rate and duration of response.

- For the treatment, in combination with paclitaxel protein-bound, of of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (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).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The primary trial supporting this sBLA is the IMpower133 study (IMpower133), a multicenter, international, randomized, double-blind, placebo-controlled trial comparing carboplatin and etoposide with atezolizumab to a control arm of carboplatin and etoposide with placebo as first-line systemic therapy in patients with extensive stage small cell lung cancer (ES-SCLC), who had received no prior chemotherapy for extensive stage disease.

IMpower133 demonstrated a hazard ratio (HR) for overall survival (OS) favoring the atezolizumab arm of 0.70 (95% CI 0.54, 0.91; p-value 0.0069 as compared to an allocated alpha of 0.0193). The median OS was 12.3 months in the atezolizumab arm and 10.3 months in the control arm. The HR for progression-free survival (PFS) as assessed by investigator also favored the atezolizumab arm with a HR of 0.77 (95% CI 0.62, 0.96, p-value 0.0170 as compared to an allocated alpha of 0.05), corresponding to an estimated median PFS of 5.2 months in the atezolizumab arm and 4.3 months in the control arm. There was no difference in overall response rate (ORR) between the two arms, with an ORR of 60% in the atezolizumab arm and 64% in the control arm, and the estimated median durations of response were 4.2 months and 3.9 months, respectively.

The submitted evidence meets the statutory evidentiary standard for approval of atezolizumab, in combination with carboplatin and etoposide, for the first-line treatment of patients with ES-SCLC. The improvement in OS, with an HR of 0.70 and a 2-month difference in median OS, observed for the atezolizumab, carboplatin and etoposide arm as compared with the placebo, carboplatin and etoposide arm in IMpower133 is statistically robust and clinically meaningful. While the observed difference in median PFS is not considered clinically meaningful on its own, the finding of a statistically significant difference in PFS is supportive of the OS findings.

Finally, evidence of the development of anti-drug antibodies (ADA) against atezolizumab (18.6% incidence of ADA in 188 evaluable patients) was observed in IMpower133. This finding has also been observed in other studies supporting prior approvals for atezolizumab as a single agent. In analyses from these other studies, development of ADA has consistently resulted in reduced exposure to atezolizumab, but the effects of ADA on efficacy are less certain. In contrast, based upon the limited data available from IMpower133, the development of ADAs did not appear to impact the exposure to atezolizumab with clearance of atezolizumab of 0.25 L/Day in ADA-positive patients as compared to 0.22 L/Day in ADA-negative patients. As noted in the approval letter for sBLA 761034/S-009, Genentech agreed to conduct several post-marketing commitments to systematically assess the potential effects of ADA on pharmacokinetics, safety and efficacy across multiple clinical studies in the atezolizumab clinical development program. FDA's integrated assessment of the effect of ADAs on atezolizumab efficacy and safety will be conducted when Genentech submits the final reports for these PMCs.

1.3. Benefit-Risk Assessment

Reference ID: 4405439

Benefit-Risk Summary and Assessment

Atezolizumab is a human monoclonal antibody that directly binds to PD-L1 and blocks its interactions with PD-1 and B7.1 receptors. At the time of submission of this supplemental BLA, atezolizumab was approved as a single agent for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy and has accelerated approval for the treatment of patients with metastatic urothelial carcinoma.

Extensive stage small cell lung cancer (ES-SCLC) is a life-threatening condition with poor survival. Platinum-based (cisplatin or carboplatin) doublet chemotherapy is the standard of care for the first-line treatment of patients with ES-SCLC. Etoposide, which is FDA-approved "in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer", is the most commonly used partner for platinum-based doublet chemotherapy for ES-SCLC in the US; alternative doublets involve cisplatin or carboplatin with irinotecan. Demonstrated median overall survival (OS) with such doublet regimens is approximately 8 to 10 months.

This application is primarily supported by a single, multicenter, international, randomized, double-blind, placebo-controlled trial comparing atezolizumab, carboplatin and etoposide to a control arm of placebo, carboplatin and etoposide as first-line systemic therapy in 403 patients with extensive stage small cell lung cancer (ES-SCLC), IMPower133. The HR for OS of 0.70 (95% CI 0.54, 0.91; p-value 0.0069 as compared to an allocated alpha of 0.0193) favoring the atezolizumab arm (median OS 12.3 months in the atezolizumab arm and 10.3 months in the control arm) is statistically robust and clinically meaningful. While the observed difference in median PFS of 0.9 months (median PFS of 5.2 months in the atezolizumab arm and 4.3 months in the control arm) is not considered clinically meaningful on its own, the finding of a statistically significant difference in PFS with a HR of 0.77 (95% CI 0.62, 0.96, p-value 0.0170 as compared to an allocated alpha of 0.05) is supportive of the OS findings. ORR and median DOR were similar between arms (ORR 60% with median DOR of 4.2 months in the atezolizumab arm and ORR 64% with median DOR of 3.9 months in the control arm).

The observed safety profile of atezolizumab administered in combination carboplatin and etoposide is acceptable when assessed in the context of the treatment of a life-threatening disease. The most common adverse reactions were fatigue/asthenia (39%), nausea (38%), alopecia (37%), decreased appetite (27%), constipation (26%), and vomiting (20%). Atezolizumab was discontinued for adverse reactions in 11% of patients; the most common adverse reaction resulting in discontinuation of atezolizumab was infusion-related reactions (2.5%). Adverse reactions leading to interruption of atezolizumab occurred in 59% of patients; the most common were (>1%) neutropenia, anemia, leukopenia, thrombocytopenia, fatigue, infusion-related reactions, pneumonia, febrile neutropenia, increased alanine aminotransferase (ALT), and nausea. The incidence of the most common immune-mediated adverse reactions in the atezolizumab arm in IMpower133 is similar to (hypothyroidism, hyperthyroidism) or lower (pneumonitis, hepatitis, and colitis) than that observed in patients with NSCLC treated with atezolizumab in combination with platinum-

based chemotherapy with or without bevacizumab in IMpower150. The incidence of infusion-related reactions in atezolizumab-treated patients in IMpower133 was similar to that in IMpower150 (6% vs 3.8%). There was no increase in the incidence of Grade 3-4 adverse events of special interest (AESI), which included immune-mediated adverse reactions and infusion-related reactions as well as infections, in atezolizumab-treated patients in IMpower133 relative to atezolizumab-treated patients in IMpower150 or a pooled population of patients who received atezolizumab administered as a single agent. Significant and serious adverse reactions, including immune-mediated adverse reactions and infusion-related reactions, are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for regular approval of atezolizumab, in combination with carboplatin and etoposide, for the first-line treatment of patients with ES-SCLC. The demonstrated treatment effect on OS is statistically robust and clinically meaningful and is consistent with a significant improvement in the treatment of patients with ES-SCLC, which has been associated with a median survival of 8 to 10 months following treatment with standard first-line platinum-based doublet chemotherapy. This benefit is supported by a statistically significant improvement in PFS. The clinical benefits outweigh the risks associated with atezolizumab administered in combination with carboplatin and etoposide. The reviewers recommend granting regular approval of atezolizumab for the following indication: "in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer death in the US; SCLC accounts for approximately 13% of all lung cancer cases. • Approximately 75% of patients with SCLC present with extensive stage disease; the reported median OS is 8 to 10 months following treatment with standard first-line chemotherapy.	Extensive stage SCLC (ES-SCLC) is a life-threatening disease with poor survival.
Current Treatment Options	• The US current standard first-line treatment for patients with ES-SCLC is a platinum-based (cisplatin or carboplatin) doublet chemotherapy. • Etoposide, which is FDA-approved "in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer", is the most commonly used partner for combination therapy in	There is an unmet medical need for patients with previously untreated ES-SCLC, given the median OS with standard of care platinum-based doublet chemotherapy regimens is 8-10 months.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the US. Alternative doublets involve cisplatin or carboplatin with irinotecan. • Demonstrated median overall survival (OS) with such doublet regimens is approximately 8 to 10 months.	
Benefit	• The primary trial supporting this sBLA is IMpower133, a multicenter, international, randomized, double-blind, placebo-controlled trial comparing atezolizumab, carboplatin and etoposide to a control arm of placebo, carboplatin and etoposide as first-line systemic therapy in 403 patients with extensive stage small cell lung cancer (ES-SCLC). • IMpower133 demonstrated a robust and clinically meaningful improvement in survival, with a HR for OS favoring the atezolizumab arm of 0.70 (95% CI 0.54, 0.91; p-value 0.0069 as compared to an allocated alpha of 0.0193). The median OS was 12.3 months in the atezolizumab arm and 10.3 months in the control arm. • The HR for PFS as assessed by investigator also favored the atezolizumab arm, with a HR of 0.77 (95% CI 0.62, 0.96, p-value 0.0170 as compared to an allocated alpha of 0.05). • ORR and median DOR were similar between arms (66% and 4.2 months in the atezolizumab arm compared to 64% and 3.9 months in the control arm).	The submitted evidence meets the statutory evidentiary standard for regular approval of atezolizumab, in combination with carboplatin and etoposide, for the first-line treatment of patients with ES-SCLC. The observed improvement in OS is statistically robust and clinically meaningful. This finding is supported by a modest but statistically significant improvement in PFS.
Risk and Risk Management	• Safety data from IMpower133 included 198 patients with who received atezolizumab in combination with carboplatin and etoposide. The application also contained safety data from the pooled population of 2421 patients with ES-SCLC (IMpower133) and metastatic NSCLC treated with atezolizumab in combination with platinum-based chemotherapy, as well as data from a pooled population of 2616 patients who received atezolizumab as a single agent across multiple clinical trials previously submitted to the BLA. The safety database is considered adequate to assess safety with reference to the overall US population. • The incidence of AESI, including immune-mediated adverse reactions and	The observed safety profile is acceptable when assessed in the context of the treatment of a life-threatening disease. The incidence of the most common immune-mediated adverse reactions in the atezolizumab arm in IMpower133 is similar to or lower than that observed in patients with NSCLC treated with atezolizumab in combination with platinum-based chemotherapy (with or without bevacizumab) in IMpower150, the study which

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	infusion-related reactions, in the atezolizumab arm of IMpower133 was also compared with the incidence observed in the two atezolizumab combination arms from IMpower150. • Atezolizumab was discontinued for adverse reactions in 11% of patients; the most common adverse reaction resulting in discontinuation of atezolizumab was infusion-related reactions (2.5%). • Adverse reactions leading to interruption of atezolizumab occurred in 59% of patients; the most common were (>1%) neutropenia, anemia, leukopenia, thrombocytopenia, fatigue, infusion-related reactions, pneumonia, febrile neutropenia, increased alanine aminotransferase (ALT), and nausea. • The most common adverse reactions were fatigue/asthenia (39%), nausea (38%), alopecia (37%), decreased appetite (27%), constipation (26%), and vomiting (20%). • The incidence of the most common immune-mediated adverse reactions in the atezolizumab arm in IMpower133 is similar to (hypothyroidism, hyperthyroidism) or lower (pneumonitis, hepatitis, and colitis) than that observed in patients with NSCLC treated with atezolizumab in combination with platinum-based chemotherapy with or without bevacizumab in IMpower150. • The incidence of infusion-related reactions in atezolizumab-treated patients in IMpower133 was similar to that in IMpower150 (6% vs 3.8%). • There was no increase in the incidence of Grade 3-4 AESI in atezolizumab-treated patients in IMpower133 relative to atezolizumab-treated patients in IMpower150 or the pooled population of patients who received atezolizumab administered as a single agent.	supported the prior approval of atezolizumab in combination with platinum-based chemotherapy with bevacizumab for the first-line NSCLC indication. The incidence of infusion-related reactions was also similar in atezolizumab-treated patients in IMpower133 and IMpower150. Significant and serious adverse reactions, including immune-mediated adverse reactions and infusion-related reactions, are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

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			
	X		□	Patient reported outcome (PRO)	Section 19.6
			□	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			
	□	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.				

Erin Larkins, M.D.
Cross-Disciplinary Team Leader

Reference ID: 4405439

2 Therapeutic Context

Analysis of Condition

Lung cancer is the leading cause of cancer and cancer-related mortality world wide[1] and the leading cause of cancer-related deaths in the United States (US)[2]. SCLC accounts for approximately 13% of all lung cancer cases, with approximately 30,500 patients diagnosed annually with SCLC.[3] Approximately 75% of patients present with extensive stage disease. Limited stage disease is defined as disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field, while extensive stage disease is defined as disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion and/or distant metastases.[4] Although the overall incidence of SCLC has been decreasing, the incidence in women has increased and the male-to-female incidence ratio is now approximately 1:1.[4, 5]

The US standard of care for the first-line systemic treatment for patients with extensive stage SCLC is platinum-based doublet chemotherapy, consisting of carboplatin or cisplatin and etoposide. The median survival of patients with extensive stage (ES)-SCLC when managed with chemotherapy is about 8 to 10 months. Since ES-SCLC is incurable and survival is limited, there is a need for more effective therapeutic options.

2.2. Analysis of Current Treatment Options

The US current standard first-line treatment for patients with ES-SCLC is a platinum-based (cisplatin or carboplatin) doublet chemotherapy. Etoposide, which is FDA-approved "in combination with other approved chemotherapeutic agents as first line treatment in patients with small cell lung cancer", is the most commonly used partner for combination therapy in the US. Alternative doublets involve cisplatin or carboplatin with irinotecan.[4] Demonstrated median overall survival (OS) with such doublet regimens is approximately 8 to 10 months.

The initial adoption by the oncology community of cisplatin plus etoposide as standard first-line therapy for extensive stage SCLC was based upon demonstration of improved efficacy and a better toxicity profile in the treatment of patients with limited stage SCLC compared to historically used alkylator and/or anthracycline based regimens[4] and high response rates reported in patients with extensive stage SCLC in single arm trials. Carboplatin is often used in place of cisplatin in order to avoid specific toxicities associated with cisplatin. Table 1 provides results from several randomized studies in patients with extensive stage SCLC which included a platinum doublet chemotherapy arm.

Table 1: Randomized Trials for First-Line Extensive Stage SCLC

Reference ID: 4405439

Publications	Study Title	Study Endpoints
Fukuoka et al, J Natl Cancer Inst, 1991[6]	Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer Note: included patients with limited stage disease (51%)	N =142 with ES-SCLC **ORR** (n=137): EP 78%, CAV 59%, CAV/EP 63% **Median OS (months)**: EP 8.3, CAV 8.7, CAV/EP 9.0
Roth et al, J Clin Oncol, 1992[7]	Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group	N = 437 **ORR**: EP 61%, CAV 51%, CAV/EP 59% **Median OS (months)**: EP 8.6, CAV 8.3, CAV/EP 8.1
Hanna et al, J Clin Oncol, 2006[8]	Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-disease small cell lung cancer	N = 331 **ORR**: IP 48%, EP 44% **Median OS (months)**: IP 9.3, EP 10.2
Schmittel et al, Ann Oncol, 2011[9]	A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive disease small-cell lung cancer	N=216 **ORR**: I-Carb 54%, E-Carb 52% **Median OS (months)**: I-Carb 10.0, E-Carb 9.0

CAV: cyclophosphamide, doxorubicin and vincristine; EP: etoposide and cisplatin; IP: irinotecan and cisplatin; E-Carb: etoposide and carboplatin; I-Carb: irinotecan and carboplatin

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Atezolizumab (TECENTRIQ®) is not a new molecular entity. It is currently marketed in the United States for the indications listed in Section 1.1 of this review. The initial approval for atezolizumab was accelerated approval for the treatment of patients with urothelial carcinoma on May 18, 2016 (under BLA 761034). On October 18, 2016, atezolizumab was approved for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy; the reviews supporting that approval were conducted under BLA 761041. BLA 761041 is a Type 9 BLA that was administratively closed upon approval of BLA 761041; all supplements for atezolizumab are reviewed under BLA 761034.

3.2. Summary of Presubmission/Submission Regulatory Activity

On October 13, 2016, Orphan Drug Designation was granted by the FDA (designation number 16-5412) for atezolizumab for "Treatment of patients with SCLC".

On June 30, 2017, a meeting request letter was granted as a Type B Written Response Only. The Type B Meeting Request-Written Response Only letter was issued on September 12, 2017. In this communication, FDA provided comments on the proposed contents of several planned BLA supplements, including supplemental BLA 761034/S-019, based on the results of the IMpower133 study.

On January 26, 2018, FDA issues a Meeting Request Granted Letter for a Type C Written Response Only meeting and on March 27, 2018, the FDA issued the Meeting Request-Written Responses Only minutes. In this response FDA agreed to the strategy to pool safety data from the IMpower130, IMpower131, IMpower132, IMpower133, and IMpower150 studies for this efficacy supplement (sBLA 761034-019).

Genentech submitted a [redacted] (b) (4) Application on August 8, 2018. [redacted] (b) (4), noting the survival curves separate at approximately 8 months, after approximately 40% of deaths have occurred in both arms and it is unclear whether the survival curve for the atezolizumab with chemotherapy arm plateaus or the curves come together.

On September 18, 2018, Genentech submitted sBLA 761034/S-019.

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

4.1. Office of Scientific Investigations (OSI)

Clinical study site inspections were not requested for this application, given the primary endpoint and number of prior approvals for atezolizumab.

4.2. Product Quality

There was no new CMC information or data submitted in supplement 019.

4.3. Clinical Microbiology

No clinical microbiology data were submitted in supplement 019 application.

4.4. Devices and Companion Diagnostic Issues

There was no device or companion diagnostic test reviewed in support of this sBLA.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical data needed to support the approval of atezolizumab was reviewed under the original BLA (BLA 761034). No new nonclinical data was submitted in this application (761034/S-019).

6 Clinical Pharmacology

6.1. Executive Summary

Among 188 post-baseline evaluable patients with ES-SCLC in Impower133, 35 (18.6%) patients tested positive for treatment-emergent ADAs at one or more post-dose time points. Production of ADA had limited effects on the pharmacokinetics of atezolizumab with clearance of atezolizumab of 0.25 (SD=0.08) L/Day in the ADA positive arm as compared to 0.22 (SD=0.06) L/Day in the ADA negative arm. The integrated assessment on the effect of ADAs to atezolizumab on efficacy and safety will be conducted when Genentech submits the final reports to the previously agreed upon PMCs regarding immunogenicity. No changes will be made at this time to the Immunogenicity section of the label.

Yuan Xu; Xiling Jiang
Primary Reviewers

Jiang Liu & Hong Zhao
Team Leaders

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7 Sources of Clinical Data and Review Strategy

Table of Clinical Studies

This review focuses primarily on the results of the IMpower133 study, entitled, "A phase I/III, randomized, double blind, placebo-controlled study of carboplatin plus etoposide with or without atezolizumab (anti-PD-L1 antibody) in patients with untreated extensive-stage small cell lung cancer".

Table 2: IMpower133 Study Design

Arm	**Atezolizumab and CE**	**Placebo and CE**
Line of therapy	1L	
Sample size	201 patients	202 patients
PD-L1 status	Patients with ES-SCLC whose disease is unselected for PD-L1 expression	
Dose	Atezolizumab: 1200 mg IV Day 1 q3w	Placebo
	Carboplatin: Target AUC of 5 mg/mL/min IV Day 1 q3w Etoposide 100 mg/m^2 IV Days 1-3 q3w	
Response assessment	Investigator assessment	
Follow-up assessment	All patients are followed for survival approximately every 3 months from study treatment discontinuation until death, loss to follow-up, or study termination by the Sponsor, whichever occurs first.	
	All patients are followed for subsequent anti-cancer therapy.	

Abstracted from Applicant Table. IMpower133; CSR.

1L=first-line; AUC=area under the concentration-time curve;

CE =carboplatin + etoposide; ES-SCLC=extensive stage small cell lung cancer;

IV=intravenous; PD-L1=programmed death-ligand 1; q3w=every 3 weeks.

In addition to the data from IMpower133, safety data from a pooled population of 2421 patients with NSCLC and SCLC who received atezolizumab 1200 mg IV every 3 weeks in combination with platinum-based chemotherapy across four randomized, open-label, active-controlled NSCLC trials (IMpower130, IMpower131, IMpower132, and IMpower150 [included patients who also received bevacizumab]) and one randomized, double-blinded, placebo-controlled SCLC trial (IMpower133) were evaluated. This safety profile (N=2421) consisting of all drug reactions (ADRs) and Grade 3-4 ADRs from patients who received atezolizumab in combination with chemotherapy was compared with the safety profile of atezolizumab administered as a single agent in a pooled safety population comprising 2616 patients. Across the studies included in the pooled monotherapy safety database, atezolizumab was administered at dose of 1200 mg IV every 3 weeks in all studies except Study PCD4989g, in

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which some patients received weight-based rather than flat doses of atezolizumab (up to 20 mg/kg). An overview of the studies included in the pooled safety populations is listed below.

Table 3: Studies Included in the Atezolizumab and Chemotherapy Pooled Population

Study Number, Study Name	Proposed atezolizumab and chemotherapy combination population and CCOD (n=2421)
GO29436, IMpower150	n=793 with NSCLC 22 January 2018
GO29537, IMpower130	n=473 with NSCLC 15 March 2018
GO29437, IMpower131	n=666 with NSCLC 20 April 2018
GO29438, IMpower132	n=291 with NSCLC 22 May 2018
GO30081, IMpower133	n=198 with SCLC 24 April 2018

(Abstracted from Applicant Table. IMpower133; CSR)

Table 4: Studies Included in Pooled Atezolizumab Monotherapy Population

Study Number, Study Name (number of patients receiving atezolizumab monotherapy and disease)	CCOD (MedDRA Version) Monotherapy Population N=2616
GO28915 OAK (n=609 with NSCLC) GO28753	7 July2016 (v20.1)
POPLAR (n=142 with NSCLC) GO28754 BIRCH	1 December 2015 (v20.1)
(n-659 with NSCLC) GO28625 FIR (n=137	1 December 2015 (v20.1)
with NSCLC)	7 January 2015 (v20.1)
GO29293 IMvigor210 (n=429 with UC)	4 July 2016 (v 20.1)
PCD4989g (n=89 with NSCLC, n=95 with UC, n=456 other	31 March 2016 (v20.1)

(Abstracted from Applicant Table. IMpower133; CSR)

Table 5: Summary of Studies in Pooled Atezolizumab and Chemotherapy Safety Population

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Pivotal Study					
IMpower133 (GO30081)	Phase I/III, global, randomized, multicenter, double-blind, placebo-controlled study	Patients with chemotherapy-naïve extensive-stage small cell lung cancer (per the VALG staging system). Patients were stratified by sex (male vs. female), ECOG performance status (0 vs. 1), and presence of brain metastases (yes vs. no).	394 patients: Atezo + CE = 198 Placebo + CE = 196	Atezolizumab 1200 mg IV q3w; Carboplatin AUC of 5 mg/mL/min IV q3w; Etoposide 100 mg/m^2 IV Days 1, 2, and 3, q3w	Primary analysis: 24 April 2018
Atezolizumab Combination Therapy Studies in First-Line Non-Small Cell Lung Cancer					
IMpower130 (GO29537)	Phase III, global, open-label, multicenter, randomized study	Patients with 1L chemotherapy-naive non-squamous NSCLC. Patients were stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and by PD-L1 tumor expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1).	473 patients treated with atezolizumab in combination with Carboplatin + Nab-paclitaxel	Atezolizumab 1200 mg IV q3w; Carboplatin AUC of 6 mg/mL/min IV q3w; Nab-paclitaxel 100 mg/m^2 IV qw	Primary analysis: 15 March 2018

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Atezolizumab Combination Therapy Studies in First-Line Non-Small Cell Lung Cancer (cont.)					
IMpower131 (GO29437)	Phase III, global, open-label, multicenter, randomized study	Patients with 1L chemotherapy-naive squamous NSCLC. Patients were stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and by PD-L1 tumor expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1).	666 patients treated with atezolizumab in combination with chemotherapy: Atezo + Carboplatin + Nab-paclitaxel = 334 Atezo + Carboplatin + Paclitaxel = 332	Atezolizumab 1200 mg IV q3w; Carboplatin AUC of 6 mg/mL/min IV q3w; Nab-paclitaxel 100 mg/m^2 IV qw OR Paclitaxel 200 mg/m^2 IV q3w	Second interim OS analysis: 20 April 2018
IMpower132 (GO29438)	Phase III, global, open-label, multicenter, randomized study	Patients with 1L chemotherapy-naive non-squamous NSCLC. Patients were stratified by sex (male vs. female), smoking status (never vs. current and/or former), ECOG performance status (0 vs. 1) and chemotherapy regimen (carboplatin vs. cisplatin)	291 patients treated with atezolizumab in combination with Carboplatin or Cisplatin + Pemetrexed	Atezolizumab 1200 mg IV q3w; Carboplatin AUC of 6 mg/mL/min IV q3w OR Cisplatin 75 mg/m^2 IV q3w; Pemetrexed 500 mg/m^2 IV q3w	Primary analysis: 22 May 2018

Study No.	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Atezolizumab Combination Therapy Studies in First-Line Non-Small Cell Lung Cancer (cont.)					
IMpower150 (GO29436)	Phase III, global, open-label, multicenter, randomized study	Patients with 1L chemotherapy-naive non-squamous NSCLC. Patients were stratified by sex (male vs. female), presence of liver metastases at baseline (yes vs. no), and by PD-L1 tumor expression by IHC (TC3 and any IC vs. TC0/1/2 and IC2/3 vs. TC0/1/2 and IC0/1).	793 patients treated with atezolizumab in combination with chemotherapy with or without Bevacizumab: Atezo + CP = 400 Atezo + Bev + CP = 393	Atezolizumab 1200 mg IV q3w; Bevacizumab 15 mg/kg IV q3w; Carboplatin AUC of 6 mg/mL/min IV q3w; Paclitaxel 200 mg/m^2 IV q3w	Updated analysis: 22 January 2018

(Abstracted from Applicant's Table. IMpower133; CSR)

7.2. Review Strategy

The clinical review strategy included review and analysis of the Clinical Study Report for IMpower133, the Summary of Clinical Safety (SCS), the Summary of Clinical Efficacy (SCE), Genentech's risk:benefit assessment, a subset of individual case report forms (CRFs), a subset of narratives, the Integrated Summary of Efficacy (ISE), the Integrated Summary of Safety (ISS), and the submitted datasets. Analyses of key safety datasets were performed using the AutoSafety Tool via the safety analysis query request form and MedDRA-based Adverse Events Diagnostics tool (MAED) software. The statistical review of efficacy endpoints was conducted by Johnathon Vallejo. The safety review was conducted by Luckson Mathieu and Yutao Gong.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study GO30081 (IMpower133)

Trial Design

Study GO30081 (IMpower133) is a randomized, multicenter, double-blind, placebo-controlled trial in 403 patients with chemotherapy-naïve extensive stage small cell lung cancer (ES-SCLC). Randomization completed on 05/31/2017. Randomization was stratified by sex (male vs. female), ECOG performance status (0 vs. 1), and brain metastases (yes vs. no). Patients were accrued in 106 centers across 21 countries, including the US. Eligible patients were randomly assigned in a 1:1 ratio to two treatment arms:

- atezolizumab with carboplatin and etoposide (atezolizumab/CE) for four 21-day cycles ("induction phase") followed by atezolizumab given in 21-day cycles ("maintenance phase")
- placebo with carboplatin and etoposide (placebo/CE) for four 21-day cycles ("induction phase") followed by placebo given in 21-day cycles ("maintenance phase")

Treatment is continued until disease progression, unacceptable treatment-related toxicity, or patient or physician decision to discontinue. Patients can be considered for treatment beyond radiographic progression per RECIST v1.1 at the discretion of the investigator and after appropriate discussion with the patient and obtaining informed consent, if all of the following criteria are met:

- Evidence of clinical benefit as assessed by the investigator
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression.

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Tumor assessments are performed at baseline and every 6 weeks (±7 days) for 48 weeks. After completion of the Week 48 tumor assessment, tumor assessments are required every 9 weeks (±7 days) thereafter. Tumor assessments will continue until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first.

The study schema is shown in Figure 1 below.

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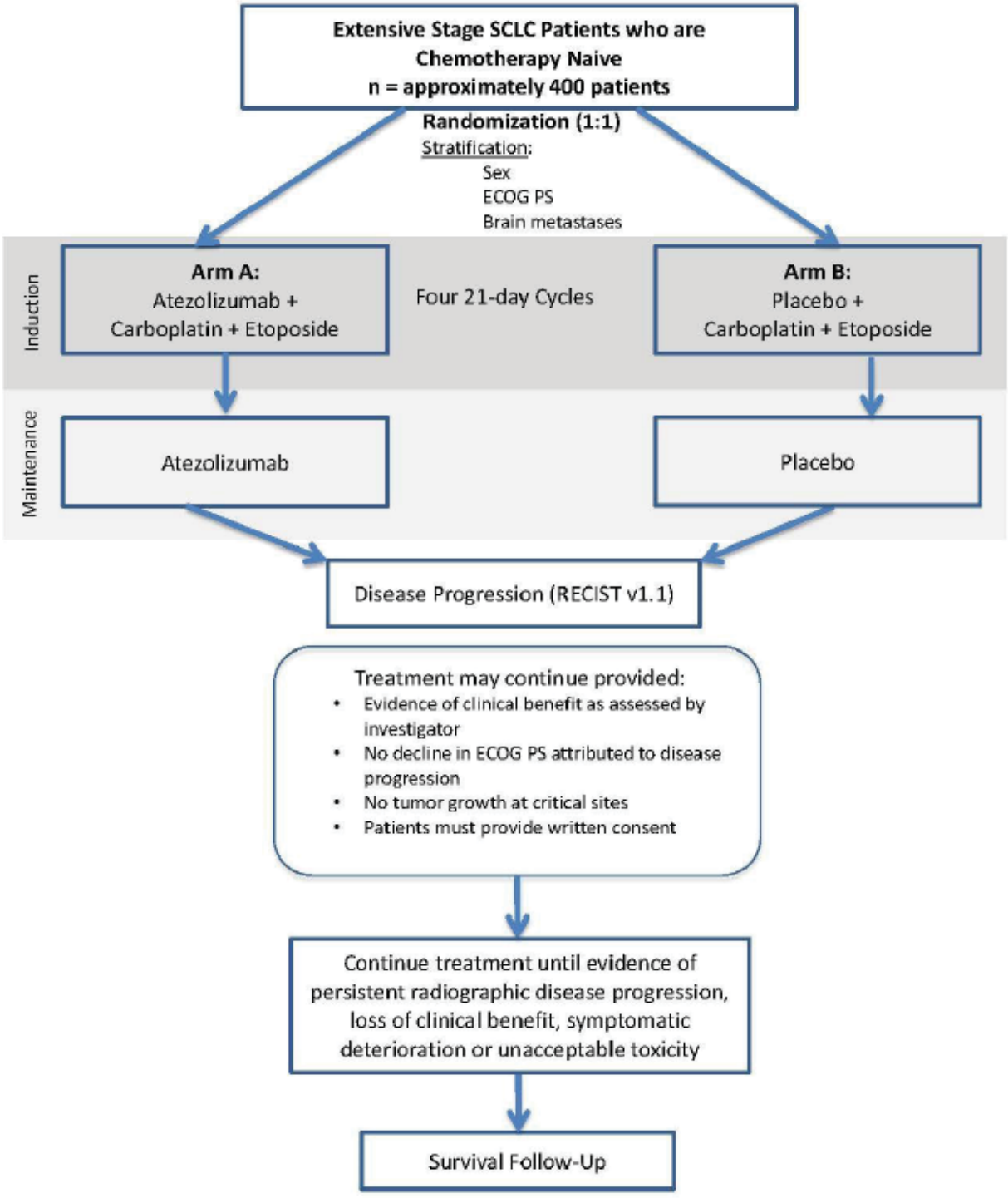
Figure 1: Study Schema of IMpower133



ECOG PS = Eastern Cooperative Oncology Group performance status; SCLC = small cell lung cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

Source: Figure 1 of CSR, pg. 41.

Study Endpoints
The family of primary endpoints in IMpower133 are OS and PFS as assessed by investigator according to RECIST v1.1.

Major secondary endpoints include overall response rate (ORR) as assessed by investigator, duration of response (DOR), and time to deterioration (TTD) in selected patient-reported lung cancer symptoms from the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the supplemental lung cancer module (QLQ-LC13).

Statistical Analysis Plan
The primary analysis for both primary endpoints is a stratified log-rank test performed on the intent-to-treat (ITT) population. In the original version of the statistical analysis plan (SAP), the log-rank test was specified to be stratified by all factors used for stratification at randomization. Amendment 2 of the SAP defined a rule by which a stratification factor would be dropped if there were 10 or fewer events in a single stratum (see Table 6).

Assuming the median OS would be 10 months in the control arm and 14.7 months in the treatment arm, a total of 306 deaths were needed to detect a HR of 0.68 with 91% power at a two-sided alpha level of 0.045. Assuming the median PFS would be 13 months in the control arm and 10.9 months in the treatment arm, a total of 295 events were needed to detect a HR of 0.55 with 99% power at a two-sided alpha level of 0.005.

A group sequential Holm procedure was specified to control for multiplicity arising from testing multiple endpoints. To control the overall two-sided Type I error rate at 0.05, the two-sided significance levels of 0.005 and 0.045 were allocated to PFS and OS, respectively. If the test for PFS was significant, the two-sided 0.005 alpha would be recycled to OS; if the test for OS was significant at either the interim or final analysis, the two-sided 0.045 alpha would be recycled to PFS. No alpha was allocated to ORR.

One interim analysis was planned to be performed at approximately 240 (78% information) deaths. The O'Brien-Fleming boundary method was utilized to adjust for the interim analysis. If PFS was not significant, this boundary specified that the two-sided p-value boundary was 0.0200 for the interim analysis and 0.0390 for the final analysis. If PFS was significant, this boundary specified that the two-sided p-value boundary was 0.0228 for the interim analysis and 0.0433 for the final analysis.

Protocol Amendments
Key protocol and SAP amendments for IMpower133 are summarized in Table 6.

Table 6: Key Protocol and SAP Amendments to IMpower133

Amendment	Significant changes
Protocol Amendment 1 (06/08/2015)	• To clarify that in the case of an early termination of the study, patients who are deriving clinical benefit from treatment with atezolizumab will be permitted to continue treatment with atezolizumab at the discretion of the investigator
Protocol Amendment 2 (08/25/2018)	• Inclusion and exclusion criteria clarified • Evaluation frequency of PRO measures modified. Patients who discontinue study treatment for any reason other than disease progression per RECIST v1.1 were specified to complete these instruments at each tumor assessment until disease progression per RECIST v1.1, unless the patient withdraws consent or the Sponsor terminates the study, whichever occurs first. • The requirement for a tumor response assessment at the treatment discontinuation visit was removed
Protocol Amendment 3 (08/27/2017)	• The timing of OS analyses was updated. The timing of the final analysis was changed from 298 events to 280 events. A second interim analysis planned for 258 events was removed. The first interim analysis was updated to occur at 258 events (55% information). • The multiplicity strategy was adjusted from the Bonferroni procedure to a group sequential Holm procedure. • Modifications were made to the statistical analysis plan for the efficacy analyses for PFS and OS in the China extension cohort to align with the updated timing of analyses. • The definition of the end of the study was updated. The end of study was updated to occur when all of the following criteria had been met: the last patient last visit (LPLV) had occurred (i.e., last patient in the global and extended China enrollment phases combined); approximately 280 deaths had been observed among the randomized patients in the global enrollment phase; and there were sufficient OS events in the ITT population enrolled in the China enrollment phase • A time window for PRO instruments administered during survival follow-up was added. Visits were updated to occur within 30 days of the 3 month and 6 month visits following radiographic disease progression per RECIST v1.1 • PFS defined by additional censoring rule for missed visits was changed to a sensitivity analysis to be consistent with other studies in the atezolizumab first-line lung cancer program • A sensitivity analysis to account for the effect of non-protocol-specified anti-cancer therapy on OS was specified.
Protocol Amendment 5 (02/27/2018)	• The protocol was amended to comply with the Spanish health authority's (Agencia Española de Medicamentos y Productos Sanitarios) requirement to include guidelines on the management of atezolizumab-specific adverse events, which are also included in the Atezolizumab Investigator's Brochure.
SAP Amendment 1 (02/27/2018)	• The planned number of deaths for the interim and final analyses was updated from 220 and 280 to 240 and 306, respectively.
SAP Amendment 2 (05/14/2018)	• The SAP was amended to implement a rule which removes a stratification factor in the case that any stratum had less than 10 events.

Source: FDA reviewer's summary of changes based on Protocol versions 2-5 and SAP versions 2 & 3.

On May 14, 2018, Genentech submitted an updated version of the SAP for IMpower133 that included a rule which would remove a stratification factor in the case that any stratum had less than 10 events. This amendment was detailed in the cover letter submitted with this amendment (pg. 2):

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> "The Study IMpower133 Statistical Analysis Plan (SAP) Version 2 is being amended due to the potential risk of over-stratification (Akazawa et al. 1997). If at least one stratum (i.e., a combination of stratification factor levels across sex [male vs female], Eastern Cooperative Oncology Group [ECOG] performance status [0 vs 1], and brain metastasis [Yes vs No] per interactive voice/Web response system [IxRS]) has less than 10 events (progression-free survival [PFS] or overall survival [OS] events), the stratification factor (one of 3 stratification factors: sex, ECOG performance status, and brain metastasis per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with less than 10 events (PFS or OS events). The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned."

FDA did not comment on this amendment.

8.1.2. Study Results

Compliance with Good Clinical Practices

Genentech stated that the trial was performed in accordance with the principles of the Good Clinical Practice (GCP) and that Genentech and all clinical investigators followed the International Conference on Harmonization (ICH) GCP guidelines for good clinical practice.

Financial Disclosure

During the study site initiation process, Genentech provided study-specific financial disclosure forms to all principal investigators and sub-investigators for IMpower133 for disclosure of financial interests in or receipt of significant payments from Genentech, Roche or Chugai.

Genentech reported that a total of 1329 out of 1340 (99.2%) principal investigators and sub-investigators responded. Genentech states that 11 investigators who enrolled did not provide a completed financial disclosure form, but no patients were enrolled by these investigators; Genentech conducted due diligence to reach these investigators but were unable to obtain a completed financial disclosure form for these 11 investigators. The sites at which these sub-investigators worked enrolled a total of 7 patients.

Of the investigators who provided completed forms, disclosable financial interests were recorded by 4 of the 1340 (0.30%) investigators in IMpower133: (b) (6) (Site: (b) (6), (b) (6) (Site: (b) (6)), (b) (6) (Site (b) (6), and (b) (6) (Site: (b) (6). The total number of patients enrolled at any of these (disclosable financial interests) sites was 5, with 3 enrolled at site (b) (6) (where (b) (6) was the principal investigator and (b) (6) (b) (6) was the sub-investigator), and 2 at site (b) (6) (where (b) (6) was a sub-investigator). (b) (6) was the only investigator or sub-investigator to enroll patients, enrolling all 3 of the patients at site (b) (6).

Please refer to the Clinical Investigator Financial Disclosure review form (appended in Section 19.2).

Reviewer Comment: *IMpower133 is a randomized, double-blind study that enrolled 403 patients across 110 investigational sites (that enrolled at least one patient). The endpoints used to assess efficacy are OS and PFS. The financial interests identified above are not expected to affect the study results for OS and PFS given the limited number of patients (3 of 403 enrolled) enrolled by the investigators identified as having disclosable financial interests.*

Analysis Population

The dataset supporting this application was based on the data cut-off date used for the interim analysis, which occurred after 238 deaths and 360 PFS events. In this review, the analysis population is the ITT population (all randomized patients) in IMpower133 as of the data cut-off date.

Patient Disposition

Figure 2 shows the patient disposition for all patients who were randomized in IMpower133. At the time of data cut-off date, more patients remained on protocol-specified treatment in the atezolizumab arm (23) than in the control arm (11). Table 7 and Table 8 show the reasons for study treatment discontinuation, respectively.

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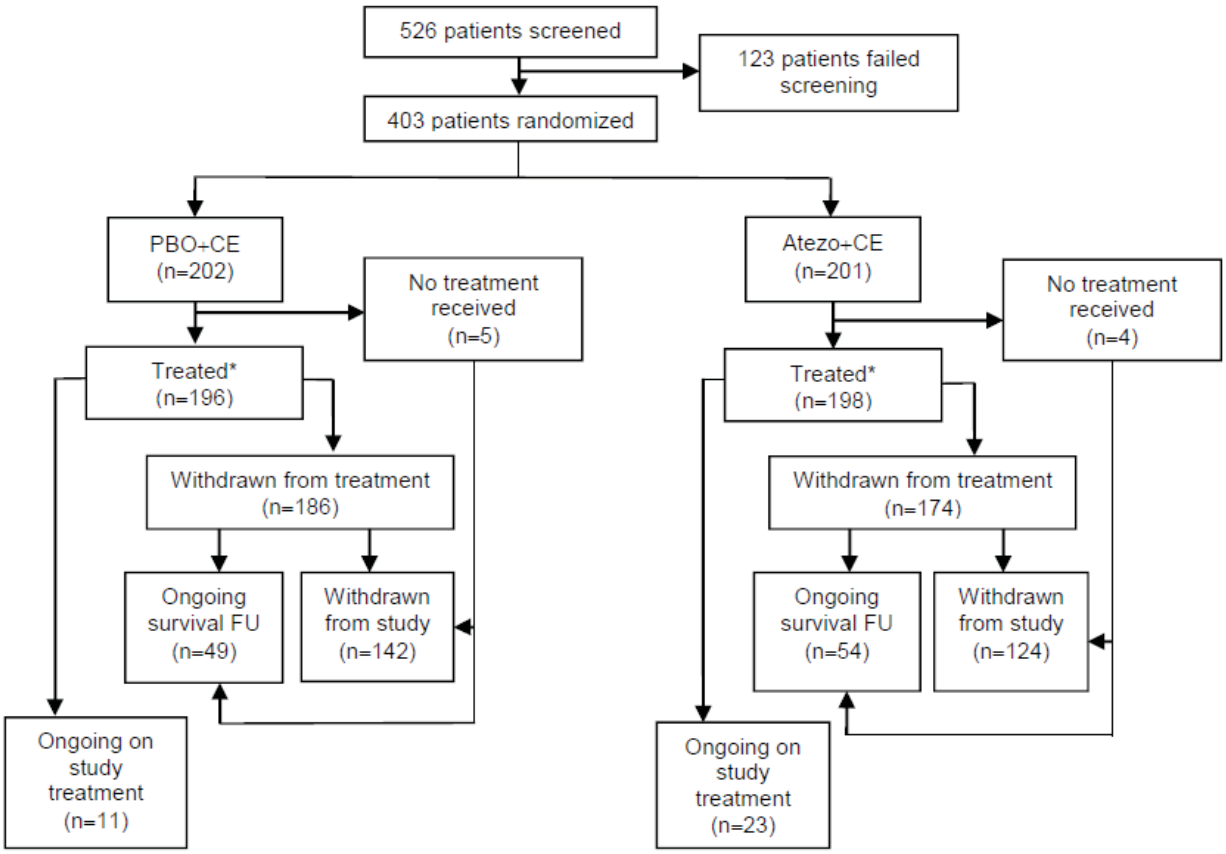
Figure 2: Diagram of Patient Disposition for all Patients Screened in IMpower133



Atezo = atezolizumab; CP = carboplatin + etoposide; FU = follow up; PBO = placebo.

*One Safety Population patient randomized to the PBO + CE arm received Atezo and was therefore counted in the Atezo + CE arm.

Source: Figure 3 from the CSR, pg. 84.

Table 7: Study Discontinuation in IMpower133

	Atezolizumab/CE	Placebo/CE
n	201	202
Received Treatment (%)	197 (98)	197 (98)
On Study (%)	77 (38)	60 (30)
Alive: In Follow-Up	54 (27)	49 (24)
Alive: On Treatment	23 (11)	11 (5)
Study Discontinuation (%)	124 (62)	142 (70)
Death	101 (50)	132 (65)
Lost to Follow-Up	3 (1)	1 (0)
Physician Decision	2 (1)	0 (0)
Withdrawal by Subject	18 (9)	9 (4)

Table 8: Treatment Discontinuation in IMpower133

	Atezolizumab/CE			Placebo/CE		
	Atezo	Carboplatin	Etoposide	Placebo	Carboplatin	Etoposide
n	198	198	198	196	196	196
Treatment Status (%)						
Ongoing	23 (12)	0 (0)	0 (0)	11 (6)	1 (1)	1 (1)
Completed	0 (0)	171 (86)	168 (85)	0 (0)	174 (89)	173 (88)
Discontinued	175 (88)	27 (14)	30 (15)	185 (94)	21 (11)	22 (11)
Reason for Treatment Discontinuation (%)						
Non-Compliance with Study Drug	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Protocol Deviation	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Death	8 (5)	4 (15)	4 (13)	10 (5)	7 (33)	7 (32)
Adverse Event	21 (12)	5 (19)	8 (27)	5 (3)	1 (5)	2 (9)
Symptomatic Deterioration	7 (4)	3 (11)	3 (10)	1 (1)	0 (0)	0 (0)
Progressive Disease	126 (72)	8 (30)	8 (27)	158 (85)	8 (38)	8 (36)
Physician Decision	2 (1)	1 (4)	1 (3)	3 (2)	1 (5)	1 (5)
Withdrawal by Subject	9 (5)	6 (22)	6 (20)	7 (4)	3 (14)	3 (14)
Lost to Follow-Up	0 (0)	0 (0)	0 (0)	1 (1)	1 (5)	1 (5)

Protocol Violations/Deviations

Table 9 shows the major protocol deviations by treatment arm in IMpower133. The deviations are generally similar across both arms, though a larger number of patients had inclusion criteria deviations in the atezolizumab arm (16) than the control arm (9).

Table 9: Major Protocol Deviations in Study IMpower133

	Atezolizumab/CE	Placebo/CE
Procedural	91	80
Error with Stratification	12 (13)	8 (10)
Failure to Report SAEs or Pregnancy per Protocol	5 (5)	6 (8)
ICF - Other (E.g. Procedural Issues)	29 (32)	26 (32)
No Pre-Treatment Tumor Tissue Sample Submitted	0 (0)	1 (1)
Omission of Safety Labs Required by Protocol	9 (10)	9 (11)
Omission of Tumor Assessment	4 (4)	4 (5)
Other Proc. Deviation for Safety and/or Efficacy	21 (23)	23 (29)
Tumor Assessment Significantly Out of Window	11 (12)	3 (4)
Medication	7	10
Induction Treatment not Given as per Protocol	1 (14)	1 (10)
Received Incorrect Study Drug or Wrong Dose	1 (14)	1 (10)
Significant Deviation from Planned Study Drug Dose	5 (71)	8 (80)
Inclusion Criteria	16	9
Incl/Excl-Related Test not Done/Out of Window	13 (81)	7 (78)
Inclusion Lab Values Outside Allowed Limits	0 (0)	1 (11)
Ineligible History or Current SCLC Stage	2 (12)	1 (11)
Received Prior Treatment for ES-SCLC	1 (6)	0 (0)
Exclusion Criteria	4	5
Active or Untreated CNS Metastases	0 (0)	4 (80)
Excluded Positive Viral Test (HIV, HBV, HCB, TB)	1 (25)	0 (0)
Other Exclusion Criteria	3 (75)	1 (20)

Table of Demographic Characteristics

Table 10 shows the demographic characteristics in the efficacy analysis (ITT) population. The median age was 64 years (range 26 to 90). Sex, brain metastases at baseline, and ECOG status are shown as reported on the electronic case report forms (eCRFs). The results for the values that were recorded by the by the interactive voice/Web response system (IxRS) for stratification at randomization were similar.

Table 10: Demographic Characteristics in the ITT Population

	Atezolizumab/CE	Placebo/CE
n	201	202
Age (%)		
< 65	111 (55)	106 (52)
>= 65	90 (45)	96 (48)
Sex[1] (%)		
Female	72 (36)	70 (35)
Male	129 (64)	132 (65)
Race (%)		
American Indian or Alaska Native	0 (0)	1 (0)
Asian	33 (16)	36 (18)
Black or African American	1 (0)	2 (1)
White	163 (81)	159 (79)
Unknown	4 (2)	4 (2)
Region (%)		
Asia Pacific	40 (20)	40 (20)
EU	116 (58)	107 (53)
North America	39 (19)	51 (25)
South America	6 (3)	4 (2)
Ethnicity (%)		
Hispanic or Latino	8 (4)	8 (4)
Not Hispanic or Latino	187 (93)	185 (92)
Not Reported	4 (2)	4 (2)
Unknown	2 (1)	5 (2)

[1] As reported on the eCRFs.

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

Other baseline characteristics are shown in Table 11.

Table 11: Other Baseline Characteristics in the Analysis Population of IMpower133

	Atezolizumab/CE	Placebo/CE
n	201	202
Brain metastases at baseline[1] (%)		
No	184 (92)	184 (91)
Yes	17 (8)	18 (9)
ECOG Performance Status[1] (%)		
0	73 (36)	67 (33)
1	128 (64)	135 (69)
bTMB biomarker expression ≥ 10 (%)		
>=10	102 (51)	110 (54)
Missing	28 (14)	24 (12)
bTMB biomarker expression ≥ 16 (%)		
<16	133 (66)	138 (68)
>=16	40 (20)	40 (20)
Missing	28 (14)	24 (12)
Prior Anti-Cancer Treatment (%)		
No	192 (96)	190 (94)
Yes	9 (4)	12 (6)
Prior Radiotherapy for SCLC (%)		
No	176 (88)	174 (86)
Yes	25 (12)	28 (14)
Prior Surgery SCLC (%)		
No	168 (84)	177 (88)
Yes	33 (16)	25 (12)

[1] As reported on the eCRFs.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

At the time of study enrollment and prior to randomization date, the majority of the safety population (90.6%) were receiving at least one concomitant medication (89.6% Atezo/CE versus 91.6% placebo/CE). The most commonly used class of drugs was opioid analgesics. The majority of the safety population also received at least one concomitant medication initiated on or after randomization date. The most commonly used classes of drugs were 5-HT3 antagonists (78% Atezo/CE vs 74% placebo/CE), steroids (66% vs 63%), colony stimulating factors (42% vs 42%), supplements (41% vs 36%), antiemetics (39% vs 35%), and opioid analgesics (33% vs 34%).

Efficacy Results – Primary Endpoint

In contrast to the analysis plan in the clinical protocol, which proposed to include all stratification variables in the stratified log-rank test, the stratification of brain metastases at baseline was not included in the model for analyses of OS and PFS, since, as shown in Table 11, the number of patients who were reported to have brain metastases at screening was small 8%

and 9% of patients in the atezolizumab and control arms, respectively). This resulted in strata with less than 10 events. As a result, brain metastases at baseline was removed as a stratification factor in the primary analyses, as specified in version 3 of the SAP.

OS

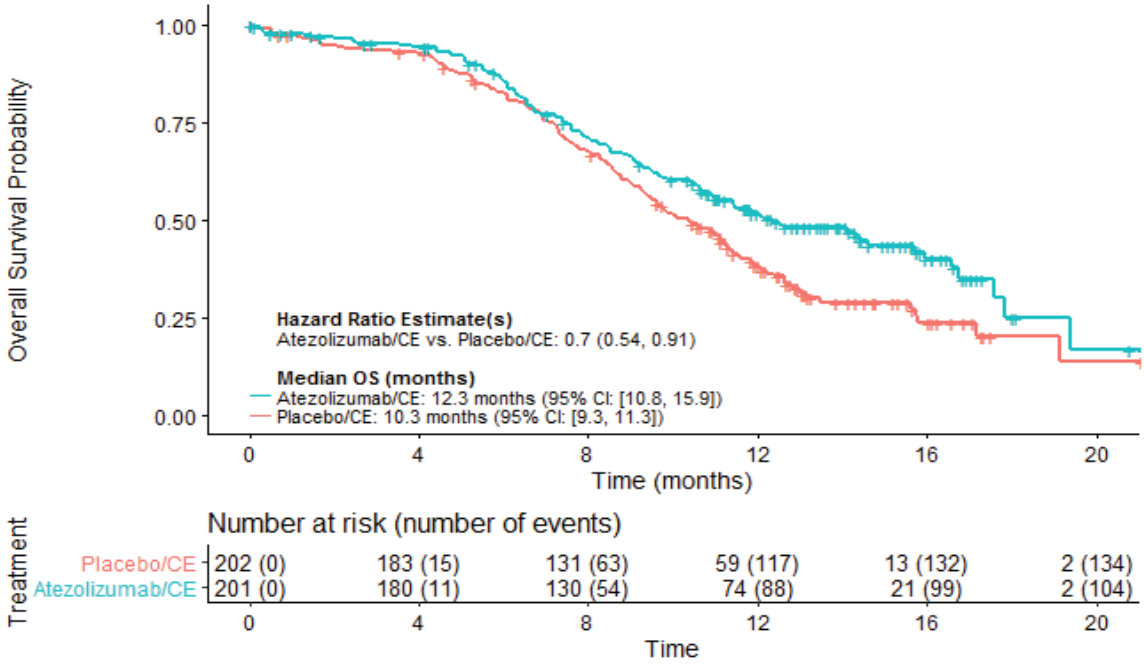
Table 12 presents the analysis of OS. Patients in the atezolizumab/CE arm demonstrated a statistically significant and clinically important improvement in OS compared to those in the control (placebo/CE) arm, with a hazard ratio (HR) of 0.70 (95% CI: [0.54, 0.91]) and a stratified log-rank test p-value of 0.0069 (compared to an alpha of 0.0193 due to the interim boundary specified in the protocol). The estimated median OS was 12.3 months (95% CI: [10.8, 15.9]) for the atezolizumab/CE arm and was 10.3 months (95% CI: [9.3, 11.3]) for the placebo/CE arm. Figure 3 shows the OS curves, estimated using the Kaplan-Meier method.

Table 12: Overall Survival in the Analysis Population

	Placebo/CE N = 202	Atezolizumab/CE N = 201
Number of events	134	104
Median in months (95% CI)[1]	10.3 (9.3, 11.3)	12.3 (10.8, 15.9)
Hazard Ratio (95% CI)[2]	0.70 (0.54, 0.91)	
p-value[3]	0.0069[4]	

[1] Estimated using the Kaplan-Meier method
[2] Estimated using a Cox proportional hazards model stratified by ECOG status (0 vs. 1) and sex (male vs. female).
[3] Two-sided p-value estimated using a stratified log-rank test
[4] Compared to an alpha of 0.0193 due to the interim boundary specified in the protocol.

Figure 3: Kaplan-Meier Plot of Overall Survival in the Analysis Population



PFS per Investigator (INV)

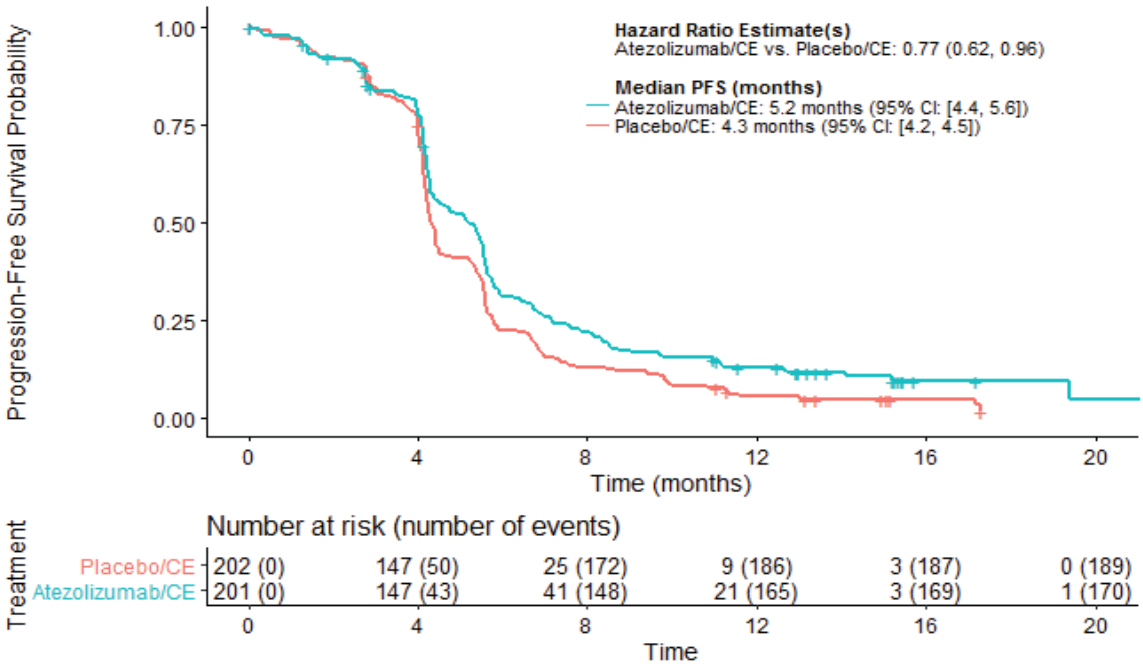
Table 13 presents the analysis of PFS as assessed by investigator. Patients in the atezolizumab/CE arm demonstrated a statistically significant but clinically unimportant improvement in progression-free survival when compared to those in the placebo//CE arm, with a HR of 0.77 (95% CI: [0.62, 0.96]) and a stratified log-rank test p-value of 0.017 (compared to an alpha of 0.05 due to the pre-specified recycling of alpha if OS was significant). The estimated median PFS time was 5.2 months (95% CI: [4.4, 5.6]) for the atezolizumab/CE arm and 4.3 months (95% CI: [4.2, 4.5]) for the placebo/CE arm. Figure 4 shows the PFS curves, estimated using the Kaplan-Meier method.

Table 13: Progression-Free Survival in the Analysis Population

	Placebo/CE N = 202	Atezolizumab/CE N = 201
Number of events	189	171
Median in months (95% CI)[1]	4.3 (4.2, 4.5)	5.2 (4.4, 5.6)
Hazard Ratio (95% CI)[2]	0.77 (0.62, 0.96)	
p-value[3]	0.017[4]	

[1] Estimated using the Kaplan-Meier method
[2] Estimated using a Cox proportional hazards model stratified by ECOG status (0 vs. 1) and sex (male vs. female).
[3] Two-sided p-value estimated using a stratified log-rank test
[4] Compared to an alpha of 0.05 due to the pre-specified recycling of alpha if OS was significant.

Figure 4: Kaplan-Meier Plot of Progression-Free Survival in the Analysis Population



Reviewer's Comment: Though the test for PFS was statistically significant, the difference in PFS between the two arms at all time points was not clinically meaningful. The curves are overlapping for the first 4 months with modest separation of the curves thereafter. Because of this delayed treatment effect, the hazard ratio may not adequately characterize the treatment effect.

Data Quality and Integrity

Data, statistical programs, and study reports for the analyses of this application were submitted electronically on September 18, 2018. The overall quality of the submissions was acceptable, and the reviewer was able to perform all analyses using the submitted data. Derivations for key variables were verified, as well as demographic variables. No inconsistencies were found in the reported efficacy results or patient baseline characteristics.

Efficacy Results – Secondary and other relevant endpoints

Confirmed ORR and DOR per INV
Table 14 presents the analysis of confirmed ORR per INV. The estimated ORR was 64% (95% CI: [57, 71]) for the placebo/CE arm and was 60% (95% CI: [53%, 67%]) for the atezolizumab/CE arm. The estimated duration of response was 3.9 months (95% CI: [3.1, 4.2]) for the placebo/CE arm and was 4.2 months (95% CI: [4.1, 4.5]) for the atezolizumab/CE arm.

Table 14: Confirmed ORR and DOR per INV in the Analysis Population

	Placebo/CE N = 202	Atezolizumab/CE N = 201
ORR	64%	60%
(95% CI)[1]	(57%, 71%)	(53%, 67%)
Complete Response	1%	2%
Partial Response	63%	58%
Duration of Response in months		
Median (range)	3.9 (3.1, 4.2)	4.2 (4.1, 4.5)

[1] Estimated using the Clopper-Pearson method

The median duration of follow-up for response was 4.1 months (range: [1.4, 19.5])

Reviewer's Comment: The ORR and DOR are similar in both arms.

Dose/Dose Response

Not applicable for this supplement. All patients received atezolizumab 1200 mg IV Q3W.

Durability of Response

Duration of response is included in "Efficacy Results – Secondary and other relevant endpoints".

Persistence of Effect

Duration of response is included in "Efficacy Results – Secondary and other relevant endpoints".

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Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Three patient-reported outcome (PRO) instruments were administered in IMpower133: EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-5D-5L. Time to deterioration (TTD) was defined as a secondary endpoint. The following subscales of the EORTC QLQ-LC13 were pre-specified to be analyzed: cough, dyspnea, chest pain, and arm/shoulder pain. Refer to Section 19.6 for PRO results.

Reviewer's comment: The results described in Section 19.6 show that the treatment effect on TTD was not in the same direction across the four pre-specified subscales. These results are exploratory, as no formal test was specified for these endpoints.

Other Analyses Performed on Trial

Sensitivity Analyses on OS
Sensitivity analyses were performed to assess the effect of protocol amendments and protocol violations. These subsets are described below.

- **SAP version 1**: Amendment 1 of the SAP updated the timing of the interim analysis to occur at 240 events rather than the originally specified 240 events. The primary analysis as specified in SAP v1 is conducted on a data set with a cut-off at the 220th death. No stratification factors are dropped in this analysis (consistent with the plan in SAP v1).
- **SAP version 2**: Amendment 2 of the SAP specified the following rule for dropping a stratification factor: "*If at least one stratum (i.e., a combination of stratification factor levels across sex [male vs female], Eastern Cooperative Oncology Group [ECOG] performance status [0 vs 1], and brain metastasis [Yes vs No] per interactive voice/Web response system [IxRS]) has less than 10 events (progression-free survival [PFS] or overall survival [OS] events), the stratification factor (one of 3 stratification factors: sex, ECOG performance status, and brain metastasis per IxRS) which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factor will continue until there is no stratum with less than 10 events (PFS or OS events).*" The primary analysis is conducted per the specifications of SAP v2, which did not implement this rule.
- **No protocol violations**: The estimated treatment effect on OS may not be representative of the population in the indication sought if the result is driven primarily by patients who enrolled in the trial in error (due to violation of inclusion or exclusion criteria) and/or patients who received the treatment in a way not consistent with the protocol. In this analysis, any patients who had protocol violations in inclusion criteria, exclusion criteria, or medication were removed. Patients with procedural protocol violations were retained, as these violations were not thought to have an impact on OS. The analysis method is the same as that utilized in the primary analysis.
- **Financial disclosure**: All sites that employed at least one investigator or sub-investigator who had disclosable financial interests or who did not submit a completed financial disclosure forms are removed from the data set. As reported in "Financial Disclosure", 7 patients were enrolled at sites where at least one investigator or sub-investigator did

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not submit a completed financial disclosure form, and 5 patients were enrolled at sites where at least one investigator or sub-investigator had disclosable financial interests. The primary analysis is performed on the resulting data set.

Table 15 shows the results from these analyses.

Table 15: Sensitivity Analyses Performed on OS

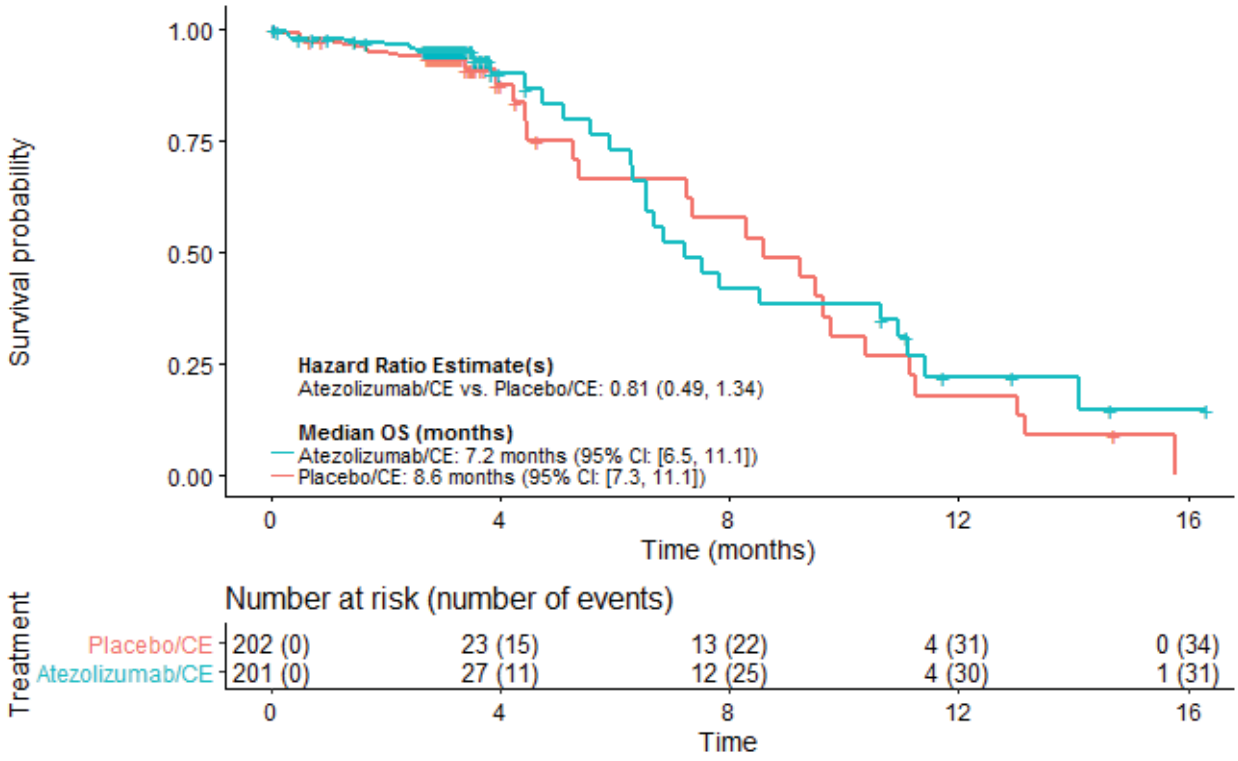
Sensitivity Analysis	N	HR (95% CI)
SAP version 1	403	0.68 (0.52, 0.89)
SAP version 2	403	0.69 (0.53, 0.89)
No protocol violations	356	0.74 (0.57, 0.98)
Financial disclosure	391	0.67 (0.52, 0.87)

Reviewer's note: Although 12 patients were removed for the "financial disclosure" sensitivity analysis, only 3 patients were enrolled by investigators who had disclosable financial interests or who did not submit a completed financial disclosure form. These 3 patients were enrolled at site (b) (6) *by* (b) (6) *. The hazard ratios for OS in these analyses are similar to that reported in the primary analysis. This suggests neither the changes to the statistical plan nor the protocol deviations had a large effect on the results.*

OS Prior to Maintenance Therapy

The Kaplan-Meier curves of OS show separation beginning around 7 months. This is after the initial treatment ("induction") period, in which patients were to receive four 21-day cycles of atezolizumab or placebo in combination with carboplatin and etoposide. A sensitivity analysis was conducted to assess the treatment effect on OS prior to maintenance therapy. Patients who received any dose during the maintenance period were censored at the beginning of the maintenance period, and patients who did not receive any dose during the maintenance period were censored in the same fashion as the primary analysis. The results are shown in Figure 5.

Figure 5: Overall Survival Prior to the Maintenance Period in the Analysis Population



Reviewer's Comment: As in the primary analysis of OS, the probability of survival is numerically higher in the atezolizumab/CE arm than the placebo/CE arm during the first four months. For patients who reached the maintenance period, the median time from randomization to initiation of the maintenance period was 3.0 months (range: [2.6, 4.6]). The graph does not show any detrimental treatment effect on OS prior to maintenance therapy.

Quantifying the Effect on OS

Because the Kaplan-Meier curves do not clearly separate until around 7 months, the proportional hazards assumption may not be reasonable. Figure 6 shows the estimated difference in OS between the placebo and atezolizumab arms. This figure highlights early difference in survival followed by a dissipation of effect around 7 months.

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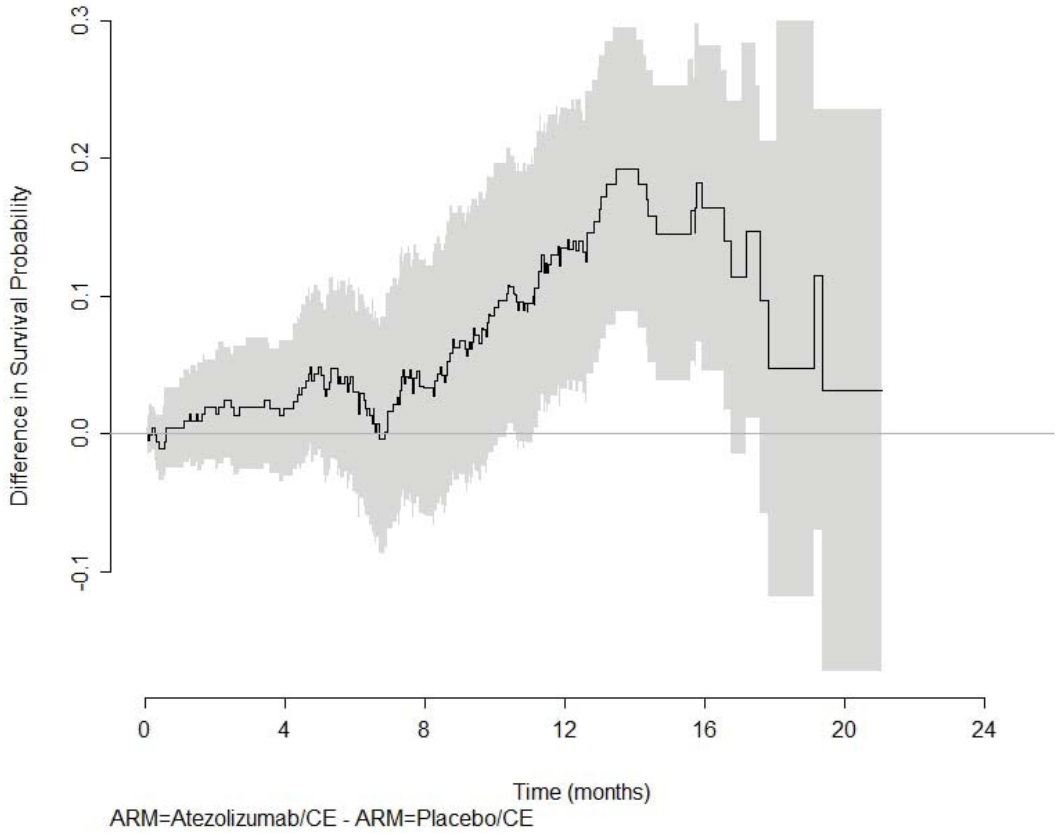
Figure 6: Difference in Survival over Time (Atezolizumab/CE – Placebo/CE)



Because the proportional hazard assumption may not be reasonable, the hazard ratio may not adequately describe the treatment effect. Consequently, we report other measures of the treatment effect that do not rely on this assumption. Table 16 shows the probability of survival at different landmarks, and Table 17 show the restricted mean survival time (RMST) over different lengths of time.

The time points chosen in Table 16 and Table 17 reflect key points in the trial. The induction period ended at 3 months. The percentiles of follow-up for OS also roughly correspond to these landmarks: the 25th percentile of OS follow-up was 6.5 months, the 75th percentile of OS follow-up was 12.9 months, and the maximum follow-up time was 21.4 months.

Table 16: Probability of Survival at Landmarks (with 95% CI)

	Placebo/CE	**Atezo/CE**
At 3 months	94% (90, 97)	95% (93, 98)
At 6 months	83% (78, 88)	86% (81, 91)
At 12 months	38% (31, 45)	52% (44, 59)
At 18 months	20% (11, 29)	25% (11, 39)

Table 17: RMST in Months (Unadjusted)

	Placebo/CE	**Atezo/CE**	**Difference (Atezo – Placebo)**
Over 12 months	9.2 (8.7, 9.6)	9.7 (9.2, 10.1)	0.5 (-0.1, 1.1)
Over 18 months	10.8 (10.1, 11.6)	12.2 (11.4, 13.0)	1.4 (0.3, 2.5)
Over 21 months	11.3 (10.4, 12.2)	12.9 (11.9, 13.9)	1.5 (0.2, 2.9)

Subpopulations

The hazard ratio of OS in the atezolizumab/CE arm vs. the placebo/CE arm is shown by subgroups in Table 18.

Table 18: Hazard Ratio of OS by Subgroup (Atezolizumab/CE vs. Placebo/CE)

Factor	Subgroup	N	HR (95% CI)
Region	Asia-Pacific	80	0.97 (0.51, 1.86)
	EU	223	0.62 (0.44, 0.89)
	North America	90	0.77 (0.47, 1.28)
	South America	10	0.79 (0.13, 4.76)
Age	< 65	217	0.92 (0.64, 1.32)
	>= 65	186	0.53 (0.37, 0.77)
ECOG	0	145	0.73 (0.46, 1.17)
	1	258	0.69 (0.51, 0.95)
Brain Metastases	N	371	0.67 (0.51, 0.87)
	Y	32	1.40 (0.58, 3.34)
Sex	F	141	0.63 (0.41, 0.98)
	M	262	0.75 (0.54, 1.03)
Smoking Status	Current	149	0.65 (0.42, 0.98)
	Never	12	0.89 (0.08, 10.37)
	Previous	242	0.77 (0.55, 1.07)
bTMB	<10	139	0.70 (0.45, 1.07)
	>=10	212	0.68 (0.47, 0.97)
	<16	271	0.71 (0.52, 0.98)
	>=16	80	0.63 (0.35, 1.15)
Prior Anti-Cancer Treatment	N	382	0.71 (0.55, 0.93)
	Y	21	0.82 (0.24, 2.8)
Prior Radiotherapy for SCLC	N	350	0.65 (0.49, 0.86)
	Y	53	1.34 (0.67, 2.67)
Prior Surgery for SCLC	N	345	0.71 (0.54, 0.94)
	Y	58	0.74 (0.37, 1.48)

Reviewer's Comment: There does not seem to be any outlying treatment effect on OS in the subgroups shown above. Analyses of RMST by subgroup are presented in Section 19.5.

8.1.3. Integrated Assessment of Effectiveness

An integrated assessment of efficacy was not conducted as this application relied on the results of a single major efficacy study, IMpower133.

8.2. Review of Safety

Safety Review Approach

The clinical safety review of IMpower133 included review and analysis of the clinical study report (CSR) for IMpower133, Genentech's risk:benefit assessment, CRFs, selected narratives, the integrated summary of safety (ISS), and the primary datasets submitted by Genentech. The reviewers analyzed key safety datasets using several safety analysis queries, MedDRA based Adverse Events Diagnostics tool, JMP and JMP Clinical Software. Subgroup analyses were performed as necessary to further characterize the safety profile of atezolizumab in combination with carboplatin and etoposide. Adverse events (AEs) occurring in patients treated

with atezolizumab, carboplatin and etoposide were compared AEs occurring in patients treated with placebo, carboplatin and etoposide.

The total population randomized in IMpower133 comprised 403 patients with ES-SCLC. Among these patients, 9 did not receive any study treatment (4 patients in the atezolizumab, carboplatin and etoposide arm and 5 patients in the placebo, carboplatin and etoposide arm). These 9 patients are excluded from the safety evaluable population. In addition, the total safety analysis population from IMpower133 is comprised of 394 patients, including 198 patients who received atezolizumab, carboplatin and etoposide and 196 patients who received placebo, carboplatin and etoposide.

Safety data for adverse events of special bevacizumab interest (AESI), including immune-mediated adverse reactions, from IMpower133 was compared to data for patients with metastatic NSCLC treated with atezolizumab, carboplatin, and paclitaxel with or without in the IMpower150 study and to data from a pooled population comprising 2616 patients with various cancers who received atezolizumab as a single agent. In order to inform the Warnings and Precautions section of product labeling, data was also analyzed for a pooled population of 2421 patients treated with atezolizumab in combination with platinum-based chemotherapy across IMpower133 (n=198) and four randomized, active-controlled studies (IMpower130 [N=473], IMpower131 [N=666], IMpower132 [N=291], and IMpower150 [N=793, including patients who also received bevacizumab]) in patients with metastatic NSCLC.

8.2.2. Review of the Safety Database

Overall Exposure

In IMpower133, 198 patients received at least one dose of atezolizumab. As shown in the table below, the median duration of treatment for patients in the atezolizumab arm is 4.7 months (range 0 to 30 months). Among the 198 patients receiving atezolizumab, 32% were exposed to atezolizumab for 6 months or longer and 12% were exposed for > 12 months or longer.

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Table 19: Exposure to Atezolizumab or Placebo (Safety Population)

	Treatment group		
	PLACEBO + CARBOPLATIN + ETOPOSIDE	**ATEZOLIZUMAB + CARBOPLATIN + ETOPOSIDE**	**All doses**
Number of subjects			
N	196	198	394
Total treatment duration (months)			
0 to <=3	41 (20.9%)	47 (23.7%)	88 (22.3%)
>3 to <=6	113 (57.7%)	88 (44.4%)	201 (51%)
>6 to <=12	30 (15.3%)	40 (20.2%)	70 (17.8%)
>12	12 (6.1%)	23 (11.6%)	35 (8.9%)
Mean (SD)	5 (3.4)	5.7 (4.3)	5.4 (3.9)
Median	4.2	4.7	4.2
Range	(0.1; 21.4)	(0; 20.9)	(0; 21.4)
Dose intensity (%)			
Mean (SD)	92.9 (7.2)	92.1 (9.3)	92.5 (8.4)
Median	94.7	94.9	94.7
Range	(59.7; 102.4)	(15.8; 100.5)	(15.8; 102.4)
Number of doses received			
Mean (SD)	7.7 (4.8)	8.5 (5.9)	8.1 (5.4)
Median	6	7	7
Range	(1; 30)	(1; 30)	(1; 30)
Total cumulative dose			
Mean (SD)	0 (0)	10193 (7166.6)	5122.4 (7196.2)
Median	0	8400	340
Range	(0; 0)	(80; 36000)	(0; 36000)

Source: aex.xpt. Variables used: USUBJID, SAFFL, TRT01A, EXDINT, EXDOSNT, EXTCAT, EXTCATT, TRTDUR. Generated by OCE Safety Team reviewer using datasets for IMpower133 submitted by the Applicant

Relevant characteristics of the safety population:

The characteristics of the safety population of IMpower133 are consistent with the epidemiology and natural history of patients with extensive stage SCLC. The median age was 64

years (range: 26 to 90) with 46% of the patients 65 years or older; 65% of the patients were male. The majority of patients were either former (60%) or current (37%) smokers; 80% were White and 17% Asian; 100% had an ECOG performance status of 0 or 1 at baseline.

Adequacy of the safety database:

Overall, the safety database of 198 atezolizumab-treated patients with ES-SCLC submitted by Genentech was sufficient to evaluate safety given the established safety profile of the combination of carboplatin and etoposide and of atezolizumab as a single agent, given the availability of data from additional studies of atezolizumab administered in combination with platinum-based chemotherapy in patients with NSCLC reviewed under sBLA 761034/S-009.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted was organized and adequate to perform a complete review of the safety of atezolizumab. To assess the reliability and quality of the data, the clinical reviewer conducted random cross-validation of datasets with CRFs from IMpower133; this assessment raised no concerns regarding data integrity. Information requests were sent to Genentech during the review to confirm data or clarify minor discrepancies.

Categorization of Adverse Events

All AEs regardless of causality were collected during the study and for up to 30 days after the last dose or until start of non-protocol treatment, which ever occurred first. All SAEs and AESIs (non-serious or serious) regardless of causality were recorded up to 90 days after the last dose or until start of non- protocol treatment, whichever occurred first.

Genentech used the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 to map verbatim terms from the CRFs to preferred terms (PTs) to code all AEs reported by investigators. Genentech defined treatment-emergent AEs (TEAEs) as AEs that first occurred or worsened any time between the first dose of study treatment until the earliest of one of the following: 30 days after the last dose of study treatment, initiation of a non-protocol anti-cancer therapy after the last administration of study drug or the clinical cutoff date. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 was used to grade the severity of AEs. For all TEAEs, the Investigator provided his/her opinion regarding the relationship of the event to atezolizumab. All events were assessed for causality of the study drug by the Investigator based on five tiers: definite/certain, probable, possible, not likely, or unrelated to the study therapy. All TEAEs assessed by the Investigator as at least possibly related to the study drug were reported in the datasets as ”related”. AEs were collected at every visit regardless of investigator-assessed relationship to study drug. All patients were followed until resolution or stabilization of any study-related AE.

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TEAEs were summarized by the MedRA (version 20.1) System Organ Class (SOC) and PT. The incidence and percentage of patients with at least one occurrence of a PT were included, per the most severe NCI-CTCAE version 4.0 grade. Verbatim terms in the AE dataset were analyzed to determine the correctness of the coding of the MedRA preferred terms.

The safety monitoring period was from the time of randomized treatment assignment until 30 days following the discontinuation of the assigned treatment for all adverse events or serious adverse events and AESIs reported beyond 90 days regardless of relationship to study drug.

Genentech reported that for the purpose of analysis, a set of comprehensive definitions using Standardized MedDRA Queries (SMQ), Sponsor-defined AE Grouped Terms (AEGTs), and High Level Terms (HLTs) were used to identify AESIs from the AE clinical database by medical concept. A complete list of medical concepts including the SMQs, HLTs, and AEGTs from MedDRA (Version 20.1) is provided in the Appendix. In addition, AESI were further analyzed by their temporal relationship with the use of systemic corticosteroids. The immune-mediated AEs (imAEs) requiring the use of systemic corticosteroids were collected on the concomitant medication eCRFs and AE eCRFs. AESI using systemic corticosteroids includes AEs per all the following criteria:

- Date of systemic corticosteroid initiation was on or up to 30 days after the AE onset date
- Date of systemic corticosteroid initiation was before the AE resolution date

Corticosteroids were identified through the ROCHE corticosteroids basket (Version 6) with the Thesaurus Management System (TMS). The routes of corticosteroids administration were provided on the concomitant medication eCRF page. Immunosuppressive agents other than corticosteroids were identified using the WHO drug class of tumor necrosis factor antagonists, immunomodulators, and immunostimulants.

According to Genentech, an external independent Data Monitoring Committee (IDMC) evaluated safety data on an ongoing basis. The incidence, time of event onset, time to resolution, and proportion of patients who were treated with corticosteroids were reviewed.

Routine Clinical Tests

Screening tests and evaluations were performed within 28 days prior to cycle 1, day 1. Laboratory assessments were performed at regular scheduled intervals. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle were performed prior to study treatment infusion unless otherwise noted. ECOG performance status, limited physical examination, local laboratory tests were obtained $\leq$96 hours before Day 1 of each cycle. TSH, free T3, and free T4 were checked at screening, cycle 1, day 1 and every fourth cycle thereafter. Vital signs assessment included pulse rate, respiratory rate, blood pressures, and temperature.

Vital signs were determined within 60 minutes prior to atezolizumab/placebo infusion, during the atezolizumab/placebo infusion (approximately every 15 minutes) and within approximately 30 minutes after the atezolizumab/placebo infusion, if clinically indicated. Vital signs were also

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assessed during the carboplatin and etoposide infusions and within 30 minutes after etoposide infusion if clinically indicated. During subsequent infusions, vital signs were collected 30 minutes after carboplatin and etoposide infusion only if clinically indicated or if symptoms occurred during the prior infusion.

8.2.4. Safety Results

An overview of the AEs in IMpower 133 is presented in Table 20. More patients receiving the atezolizumab regimen discontinued any drug in the three-drug regimen due to an AE (11%) compared to the control arm (3%). The incidence of Grade 3 to 4 AEs was similar between the two treatment arms. The incidence of serious AEs was also similar in the atezolizumab arm (37%) and the control arm (35%).

Table 20: Overview of Adverse Events

	PBO/CE N=196 %	Atezo/CE N=198 %	All Pts (N = 394) %
No. of patients with one or more AEs	96	100	98
Grade 3 to 4	64	67	66
Serious AEs	35	37	36
Death due to AE	6	2	4
AE leasing to treatment withdrawal	3	11	7
AE leading to dose modification/interruption	52	59	56

Deaths

Genentech performed an analysis of the cause of death for all patients who died as of the data cut-off April 24, 2018. Genentech provided detailed narratives of all patients' deaths attributed to the study drug in the atezolizumab treatment arm. Table 21 summarizes the proportion of deaths attributed to AE versus progressive disease reported for the safety population in IMpower133. Genentech reported that fatal events categorized as "other" included deaths that were deemed unrelated to study treatment and occurred outside the reporting period.

Table 21: Death and AEs in Safety Population

	PBO/CE n=196	Atezo/CE n=198	All Patients (n=394)
Data cut-off date: April 24, 2018			
Patient status:			
All Deaths	130	103	233
Adverse Events	11 (6%)	4 (2%)	15 (3.8%)
Progression	115 (59%)	90 (46%)	205 (52%)
Other	4 (2%)	9 (4.5%)	13 (3.3%)

Source: AdaM dataset: adsl.xpt and adae.xpt. DCO: April 2018

Deaths due to AE were reported for 4 patients (2%) receiving atezolizumab, carboplatin and etoposide. Fatal AEs were pneumonia (1), respiratory failure (1), death not otherwise specified (1), and neutropenia (1).

Brief narratives for these four fatal AEs are presented below.

(1) Subject (b) (6), a 50-year-old White male, diagnosed with extensive stage SCLC on study day -38. On study day 1 he experienced Grade 2 vomiting and Grade 2 decreased appetite, and Grade 2 fatigue. On study day 8 he received metoclopramide for vomiting and on that same day vomiting was considered resolved. On study day 9, the patient experienced Grade 3 diarrhea. He received fluids in the from emergency services. On day 11 the patient was found dead in bed at home. The cause of death was reported as Death NOS. An autopsy was not performed.

(2) Subject (b) (6), a 59-year-old White male with medical history of peripheral artery stenosis, peripheral arterial occlusive disease and coronary artery stenosis was diagnosed with extensive stage SCLC on study day -26. On study day 9, the patient presented with fever and severe dyspnea. The patient received treatment with theophylline, ethyl morphine, morphine, and steroids. The patient died on study day 9. An autopsy report confirmed pneumonia as the cause of death.

(3) Subject (b) (6), a 67-year-old White female with medical history of sacral cyst, COPD, hypertension, and impaired glucose tolerance. She was diagnosed with extensive stage SCLC with brain metastasis (cerebellum) on study day -48. On study day 4, the patient had a fall at home and was hospitalized with Grade 3 femur fracture. On Day 39, the patient had a Grade 4 respiratory failure at the hospital where the patient was undergoing rehabilitative therapy for her femur fracture and died on the same day. It is unknown if an autopsy was performed.

(4) Subject (b) (6), a 64-year-old White female with medical history of breast cyst, ovarian cyst and chronic sinusitis. She was diagnosed with extensive stage SCLC on

study day -26. On study day 5, the patient developed Grade 2 chest pain and elevated BUN, Grade 3 anemia, Grade 3 transaminitis, Grade 3 neutropenia, Grade 4 leukopenia, and Grade 4 thrombocytopenia all resulting in hospitalization. The patient received treatment, but on study day 8 she died. An autopsy was not performed.

Reviewer Comment: *Based on the available information within the reviewed narratives, the deaths due to an adverse event from the atezolizumab arm do not suggest a new safety signal.*

Serious Adverse Events

In IMpower133, the incidence of SAEs was similar between the atezolizumab-containing arm (37.4%) and the control arm (34.7%). Serious adverse reactions occurring in > 1% of patients in the atezolizumab plus chemotherapy arm were pneumonia (4.5%), neutropenia (3.5%), febrile neutropenia (2.5%), thrombocytopenia (2.5%), anemia (1.5%), diarrhea (1.5%), fatigue (1.5%), syncope (1.5%), and vomiting (1.5%). Table 22 below summarizes the SAEs reported in > 1% of patients in IMpower 133.

Table 22: SAEs Reported in >1% of Patients in IMpower133

	PBO/CE N=196 (%)	Atezo/CE N=198 (%)
Total pts with at least one SAE	68 (34.7)	74 (37.4)
Pneumonia	7 (3.6)	9 (4.5)
Neutropenia	8 (4.1)	7 (3.5)
Febrile Neutropenia	9(4.6)	5 (2,5)
Thrombocytopenia	4 (2)	5 (2.5)
Anemia	2 (1)	3 (1.5)
Diarrhea	1 (0.5)	3 (1.5)
Fatigue	0 (0)	3 (1.5)
Syncope	0 (0)	3 (1.5)
Vomiting	3 (1.5)	3 (1.5)

Source: Reviewer Table and ADaM dataset: adae.xpt and SDTM dataset AE.xpt. DCO: April 2018

Dropouts and/or Discontinuations Due to Adverse Effects

Table 23 summarizes the adverse reactions leading to atezolizumab interruption. Adverse reactions leading to interruption of atezolizumab occurred in 59% of patients in the atezolizumab arm; the most common (>1%) were neutropenia (22%), anemia (9%), leukopenia (7%), thrombocytopenia (5%), fatigue (4.0%), infusion-related reaction (3.5%), pneumonia (2.0%), febrile neutropenia (1.5%), increased ALT (1.5%), and nausea (1.5%).

Reference ID: 4405439

Table 23: Adverse Reactions Leading to Atezolizumab Interruption

	Atezo/CE N=198 (%)			
Total pts with at least one SAE	All Grades (N)	All Grade (%)	Grade 3-4 (N)	Grade 3-4 (%)
All	117	59.1	75	37.9
Neutropenia	43	21.7	24	12.1
Neutrophil count decreased	21	10.6	17	8.6
Anemia	17	8.6	8	4
Leukopenia	13	6.6	3	1.5
Thrombocytopenia	10	5.1	7	3.5
Fatigue	8	4.0	3	1.5
Infusion related reaction	7	3.5	2	1
Pneumonia	4	2.0	3	1.5
Increased ALT	3	1.5	1	0.5
Febrile neutropenia	3	1.5	3	1.5
Nausea	3	1.5	0	0
Decreased platelet count	3	1.5	1	0.5
Decreased WBC count	3	1.5	2	1

Source: Reviewer Table and ADaM dataset: adae.xpt and SDTM dataset AE.xpt. DCO: April 2018

Atezolizumab was permanently discontinued due to adverse reactions in 11% of patients. The most frequent adverse reaction, requiring permanent discontinuation in > 2% of patients, was infusion-related reactions (2.5%). Table 24 presents AEs leading to discontinuation of study treatment in ≥1% of patients.

Table 24: Adverse Reactions Leading to Atezolizumab Discontinuation

	Atezo/CE N=198 (%)			
Total pts with at least one SAE	All Grades (N)	All Grade (%)	Grade 3-4 (N)	Grade 3-4 (%)
All	21	10.6	16	8.1
Infusion related reaction	5	2.5	3	1.5
Abdominal distension	1	0.5	0	0
Anal hemorrhage	1	0.5	0	0
Anaphylactic reaction	1	0.5	1	0.5
Asthenia	1	0.5	1	0.5
Erythema	1	0.5	1	0.5
Gastritis	1	0.5	0	0
Health deterioration	1	0.5	1	0.5
Hypotension	1	0.5	0	0
Ileus	1	0.5	1	0.5
Jaundice	1	0.5	1	0.5
Pneumonia	1	0.5	1	0.5
SVC syndrome	1	0.5	1	0.5

Source: Reviewer Table and ADaM dataset: adae.xpt and SDTM dataset AE.xpt. DCO: April 2018

Significant Adverse Events

Treatment-emergent AEs were AEs considered by the investigator to have a reasonable suspected causal relationship to the study treatment. AEs reported in ≥10% of patients in the atezolizumab plus chemotherapy arm, along with incidence in the control arm, are presented in Table 25.

Reference ID: 4405439

Table 25: Adverse Reactions Occurring in ≥10% of Patients Receiving TECENTRIQ in IMpower133

Adverse Reaction	TECENTRIQ with Carboplatin and Etoposide N = 198		Placebo with Carboplatin and Etoposide N = 196	
	All Grades[1] (%)	Grades 3–4[1] (%)	All Grades[1] (%)	Grades 3–4[1] (%)
General				
Fatigue/Asthenia	39	5	33	3
Headache	12	0	12	0
Pyrexia	10	0	8	0
Dizziness	10	0	6	0
Gastrointestinal				
Nausea	38	1	33	1
Constipation	26	1	30	1
Vomiting	20	2	17	3
Diarrhea	18	2	16	1
Skin and Subcutaneous Tissue				
Alopecia	37	0	35	0
Metabolism and Nutrition				
Decreased appetite	27	1	18	0
Decreased weight	10	0	5	1
Respiratory				
Cough	14	1	16	1
Dyspnea	10	2	9	1

[1] Graded per NCI CTCAE v4.0

Laboratory Findings

Laboratory abnormalities were analyzed using the laboratory datasets. Table 26 below summarizes laboratory abnormalities worsening from baseline that occurred in ≥20% of patients in receiving atezolizumab, along with incidence in the control arm.

Table 26: Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients Receiving TECENTRIQ in IMpower133

Laboratory Abnormality	TECENTRIQ with Carboplatin and Etoposide[2]		Placebo with Carboplatin and Etoposide[2]	
	All Grades[1] (%)[2]	Grades 3–4[1] (%)[2]	All Grades[1] (%)[2]	Grades 3–4[1] (%)[2]
Hematology				
Anemia	94	17	93	19
Neutropenia	73	45	76	48
Thrombocytopenia	58	20	53	17
Lymphopenia	46	14	38	11
Chemistry				
Hyperglycemia	67	10	65	8
Increased Alkaline Phosphatase	38	1	35	2
Hyponatremia	34	15	33	11
Hypoalbuminemia	32	1	30	0
Decreased TSH[3]	28	NA[3]	15	NA[3]
Hypomagnesemia	31	5	35	6
Hypocalcemia	26	3	28	5
Increased ALT	26	3	31	1
Increased AST	22	1	21	2
Increased Blood Creatinine	22	4	15	1
Hyperphosphatemia[3]	21	NA[3]	23	NA[3]
Increased TSH[3]	21	NA[3]	7	NA[3]

[1] Graded per NCI CTCAE v4.0
[2] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TECENTRIQ (range: 181-193); Placebo (range: 181-196)
[3] NA= Not applicable. NCI CTCAE v4.0 does not include these laboratories.

Vital Signs

Vital signs were collected at baseline and every 21 days +/- 3 days. Baseline labs was defined as the measurement obtained on Cycle1, Day 1 before the first dose of study drug was administered. Changes in vital signs were summarized over time by treatment arm, which included change from baseline. No clinically meaningful changes from baseline were noted in the safety population.

Electrocardiograms (ECGs)

Electrocardiograms (12-lead ECG) were performed at screening and when clinically indicated. The number of patients with clinically significant abnormal baseline and unscheduled ECG was low in both arms.

Table 27: ECG Abnormalities by Visit in IMpower133 (Safety Population)

Analysis Visit Window	PBO/CE N=196	Atezo/CE N=198
Baseline		
n	194	196
Abnormal, clinically significant	4	1
Normal	119	121
Unscheduled		
n	9	11
Abnormal, not clinically significant	1	9
Abnormal, clinically significant	3	0
Normal	5	2

(Adapted from Applicant's Table. IMpower133; CSR)

QT

There is no dedicated QTc study submitted in this supplement. As with most monoclonal antibodies, there is no expectation that atezolizumab would affect the QT interval.

Immunogenicity

Among 188 post-baseline evaluable patients with ES-SCLC in Impower133, 35 (18.6%) patients tested positive for treatment-emergent ADAs at one or more post-dose time points. See section 6.1 for additional information.

8.2.5. Analysis of Submission-Specific Safety Issues

Immune-mediated Adverse Events

Immune-mediated adverse events (imAE) are known toxicities of checkpoint inhibitor class of products, including atezolizumab. Adverse events of special interest (AESI) were defined as immune-related AEs based on Genentech's predefined list of preferred AE terms (Table 39 in the Appendix) that are potentially associated with an immune etiology. Additional AESI, based on inclusion as subsections in Section 5 (Warnings and Precautions) of the labeling for atezolizumab, are infusion-related reactions and infections.

Safety data from a pooled population comprising 2616 patients (refer to Table 4) treated with atezolizumab as a single agent across various clinical trials was previously analyzed to inform the Warnings and Precautions section of product labeling. Table 28 below compares the incidence of AESI in the atezolizumab arm of IMpower133 with the incidence observed in the two atezolizumab combination arms from IMpower150 and the pooled single agent atezolizumab data.

Table 28: Summary of imAEs to Atezolizumab

	Atezolizumab Monotherapy N = 2616		Atezolizumab/ Anti-neoplastic agents IMpower 150 N = 793		Atezolizumab/CE IMpower133 N = 198	
Total pts with at least one SAE	**All Grade (%)**	**Grade 3-4 (%)**	**All Grade (%)**	**Grade 3-4 (%)**	**All Grade (%)**	**Grade 3-4 (%)**
Pneumonitis	2.5	0.7	4.5	1.8	2	0.5
Hypothyroidism	4.6	0	11	0	12	0
Hepatitis	9	2.9	12	4.0	7	1.5
Infusion-related reactions	1.3	0.2	3.8	0.8	6	2
Hyperthyroidism	1.6	0	3.4	0	6	0
Colitis and Diarrhea	20	1.4	27	4.3	19	3
Infections	42	10	50	14	32	7

Reviewer Note: *The incidence of pneumonitis, hepatitis, and colitis/diarrhea in atezolizumab-treated patients in IMpower133 is similar to atezolizumab administered as a single agent and lower than in atezolizumab-treated patients in IMpower150. The incidence of infusion-related reactions, hyperthyroidism, and hypothyroidism is higher in atezolizumab-treated patients in IMpower133 compared to atezolizumab administered as a single agent but similar to that in atezolizumab-treated patients from IMpower150. The incidence of infections is lower in atezolizumab-treated patients in IMpower133 (32%) relative to atezolizumab administered as a single agent (42%) and atezolizumab-treated patients in IMpower150 (50%). There is no increase in the incidence of Grade 3-4 AESI in atezolizumab-treated patients in IMpower133 relative to atezolizumab administered as a single agent or atezolizumab-treated patients in IMpower150.*

In order to further inform the Warnings and Precautions section of product labeling, the safety data from a pooled population of 2421 patients (refer to Table 3) treated with atezolizumab with platinum-based chemotherapy across five clinical trials (IMpower133 and four randomized,

active-controlled NSCLC studies, IMpower130, IMpower131, IMpower132, and IMpower150 [including patients who also received bevacizumab]) was analyzed during this review. These results are compared to data for the previously analyzed pooled safety population of 2,616 patients treated with atezolizumab as a single agent.

This section of the review will discuss in detail the most common AESIs. Tables 29 and 30 present the incidence of AESI in the pooled population of patients (which includes IMpower133) treated with atezolizumab in combination with platinum-based chemotherapy and in atezolizumab-treated patients from IMpower133. The characteristics of key AESIs, including incidence, time to event onset, time to resolution, and proportion of patients who were treated with corticosteroids (for relevant immune-mediated adverse reactions) were reviewed, and this data is presented for the pooled population of patients treated with atezolizumab in combination with platinum-based chemotherapy, with data for the pooled single agent atezolizumab population included for comparison.

Table 29: Summary of AESI to Atezolizumab Plus Chemotherapy (Pooled Population)

	Pooled Safety Data N = 2421			
Total pts with at least one SAE	All Grades (N)	All Grade (%)	Grade 3-4 (N)	Grade 3-4 (%)
Pneumonitis	134	5.5	33	1.4
Hypothyroidism	272	11.2	8	0.3
Hepatitis	344	14.2	100	4.1
Infusion-related reactions	73	3	13	0.5
Hyperthyroidism	91	3.8	4	0.2
Colitis and Diarrhea	702	29	104	4.3
Pancreatitis	17	0.7	8	0.3
Nephritis	12	0.5	8	0.3
Rash	616	25.4	53	2.2
Vasculitis	6	0.2	1	0
Myopathies	5	0.2	1	0
Hypophysitis	7	0.3	2	0.1
Guillain-Barre syndrome	2	0.1	1	0
Adrenal insufficiency	18	0.7	3	0.1
Infections	1043	43.1	289	11.9
Diabetes	16	0.7	8	0.3
Meningoencephalitis	38	0.4	4	0.2
Severe skin rash	10	0.8	6	0.2
AIHA	19	0.2	2	0.1
Myositis	6	0.2	1	0
Ocular inflammatory	5	0.3	2	0.1
Systemic immune activation	7	0	1	0

Source: Reviewer Table and ADaM dataset: adsl.xpt and aae.xpt. DCO: April 2018

Reference ID: 4405439

Table 30: Summary of AESI to Atezolizumab Plus Chemotherapy (IMpower133)

	Atezo/CE (IMpower133) N = 198			
Total pts with at least one SAE	All Grades (N)	All Grade (%)	Grade 3-4 (N)	Grade 3-4 (%)
Pneumonitis	4	2	1	0.5
Hypothyroidism	23	12	0	0
Hepatitis	14	7	3	1.5
Infusion-related reactions	11	6	4	2
Hyperthyroidism	11	6	0	0
Colitis and Diarrhea	37	19	6	3
Pancreatitis	1	0.5	1	0.5
Nephritis	1	0.5	1	0.5
Rash	37	19	4	2
Vasculitis	0	0	0	0
Myopathies	2	1	1	0.5
Hypophysitis	1	0.5	0	0
Guillain-barre syndrome	1	0.5	1	0.5
Adrenal insufficiency	0	0	0	0
Infections	64	32	14	7
Diabetes	1	0.5	0	0
Meningoencephalitis	0	0	0	0
Severe skin rash	2	1	0	0
AIHA	0	0	0	0
Myositis	0	0	0	0
Ocular inflammatory	0	0	0	0
Systemic immune activation	0	0	0	0

Source: Reviewer Table and ADaM dataset: adsl.xpt and aae.xpt. DCO: April 2018

Pneumonitis:

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent, pneumonitis occurred in 2.5% of patients, including Grade 3 (0.6%), Grade 4 (0.1%), and Grade 5 (<0.1%) immune-mediated pneumonitis. Systemic corticosteroids were required in 1.5% of patients, including 0.8% who received high-dose corticosteroids (prednisone ≥40 mg per day or equivalent) for a median duration of 4 days (1 day to 45 days) followed by a corticosteroid taper.

In clinical studies enrolling 2421 patients with lung cancers who received TECENTRIQ with chemotherapy, pneumonitis occurred in 5.5% of patients, including Grade 3-4 (1.4%) events.

Systemic corticosteroids were required in 4.2% of patients, including 3.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 5 days (1 day to 98 days) followed by a corticosteroid taper.

The PTs used to identify cases of pneumonitis include pneumonitis, alveolar lung disease, bronchiolitis, interstitial lung disease, lung infiltration, pulmonary fibrosis, pulmonary radiation injury, and radiation pneumonitis.

Hepatitis:
In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ, hepatitis occurred in 9% of patients, including Grade 3 (2.3%), Grade 4 (0.6%), and Grade 5 (<0.1%). Systemic corticosteroids were required in 2% of the patients, with 1.3% requiring high-dose corticosteroids for a median duration of 3 days (1 day to 35 days) followed by a corticosteroid taper.

The incidence of hepatitis in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 14.3%, including Grade 3-4 (4.1%) events. Systemic corticosteroids were required in 4.8% of patients, including 3.4% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 5 days (1 day to 144 days) followed by a corticosteroid taper.

The PTs used to identify cases of hepatitis include aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, transaminases increased, hepatic enzyme increased, liver function test increased, autoimmune hepatitis, ascites, bilirubin conjugated increased, drug-induced liver injury, hepatic cirrhosis, hepatic congestion, hepatic enzyme abnormal, hepatic failure, hepatic function abnormal, hepatic lesion, hepatic pain, hepatic steatosis, hepatitis, hepatitis acute, hepatitis toxic, hepatobiliary disease, hepatocellular injury, hepatomegaly, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver disorder, liver function test abnormal, oesophageal varices haemorrhage, varices oesphageal, and blood bilirubin increased.

Colitis and diarrhea:
In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent, diarrhea or colitis occurred in 20%, including Grade 3 (1.4%) events. Systemic corticosteroids were required in 1.1% of patients and high-dose corticosteroids was required in 0.4% patients with a median duration of 3 days (1 day to 11 days).

The incidence of colitis and diarrhea in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 29.1%, including Grade 3-4 (4.3%) events. Systemic corticosteroids were required in 4.7% of patients, including 2.9% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 4 days (1 day to 170 days) followed by a corticosteroid taper.

The PTs used to identify cases of colitis and diarrhea include colitis, autoimmune colitis, diarrhoea, diarrhea, colitis microscopic, and frequent bowel movement.

Hypothyroidism:
In clinical studies enrolling 2616 patients who received TECENTRIQ, hypothyroidism occurred in 4.6% of patients, and 3.8% of patients required the use of hormone replacement therapy.

The incidence of hypothyroidism in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 11.4%, including Grade 3-4 (0.3%) events. Among the 2421 patients, 8.2% required the use of hormone replacement therapy.

The PTs used to identify cases of hypothyroidism include hypothyroidism, autoimmune thyrioditis, blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, thyroiditis, thyroxine free increased, tri-iodothyronine free increased, tri-iodothyronine free increased, autoimmune hypothyroidism, blood thyroid stimulating hormone abnormal, thyroiditis, thyroxine free increased, tri-iodothyronine free increased, blood thyroid stimulating hormone abnormal, euthyroid sick syndrome, goitre, myxoedema coma, thyroxine free decreased, thyroxine increased, tri-iodothyronine abnormal, tri-iodothyronine decreased, and tri-iodothyronine free decreased.

Hyperthyroidism:
In clinical studies enrolling 2616 patients who received TECENTRIQ, hyperthyroidism occurred in 1.6% of patients. One patient experienced acute thyroiditis.

The incidence of hyperthyroidism in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 3.8%, including Grade 3-4 (0.2%) events.

The PTs used to identify cases of hyperthyroidism include hyperthyroidism, basedow's disease, endocrine opthalmopathy, and exophthalmos.

Adrenal Insufficiency:
In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, adrenal insufficiency occurred in 0.4% of patients, including Grade 3 (<0.1%) adrenal insufficiency. Systemic corticosteroids were required in 0.3% of 2616 patients, including 0.1% who required high-dose corticosteroids.

The incidence of adrenal insufficiency in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.7%, including Grade 3-4 (0.1%) events. Systemic corticosteroids were required in 0.6% of patients, including 0.2% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 7.0 days (1 day to 21 days) followed by a corticosteroid taper.

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The PTs used to identify cases of adrenal insufficiency include ACTH stimulation test abnormal, adrenal insufficiency, adrenalitis, adrenocortical insufficiency acute, adrenocorticotropic hormone deficiency, primary adrenal insufficiency, and secondary adrenocortical insufficiency.

Diabetes Mellitus:
In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, type 1 diabetes mellitus occurred in <0.1% of patients. Insulin was required in one patient.
The incidence of diabetes mellitus in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.7%, including Grade 3-4 (0.3%) events.

The PT used to identify cases of diabetes mellitus include diabetes mellitus, diabetic ketoacidosis, ketoacidosis, and type 1 diabetes mellitus.

Hypophysitis:
In clinical studies enrolling 2616 patients who received TECENTRIQ as a single agent, Grade 2 hypophysitis occurred in <0.1% of patients.

The incidence of hypophysitis in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.3%, including Grade 3-4 (< 0.1%) events. Systemic corticosteroids were required in 0.2% of patients, including < 0.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 18.0 days (18 days to 18 days) followed by a corticosteroid taper.

The PT used to identify cases of hypophysitis is hypophysitis.

Infections:
In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent, infections occurred in 42% of patients, including Grade 3 (8.7%), Grade 4 (1.5%), and Grade 5 (1%). In patients with urothelial carcinoma, the most common Grade 3 or higher infection was urinary tract infections, occurring in 6.5% of patients. In patients with NSCLC, the most common Grade 3 or higher infection was pneumonia, occurring in 3.8% of patients.

The incidence of infections in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 43.1%, including Grade 3-4 (11.9%) events.

The PT used to identify cases of infection include infection, infectious, sepsis, septic shock, pneumonia, urinary tract infection, sinusitis, otitis media, staphylococcal infection, upper respiratory tract infection, viral infection, viral upper respiratory tract infection, bacterial infection, catheter site infection, clostridium difficile infection, device related infection, ear infection, ear infection fungal, eye infection, febrile infection, fungal infection, fungal skin infection, gastrointestinal viral infection, helicobacter infection, gastrointestinal viral infection, localized infection, lower respiratory tract infection, lung infection, localized infection, mucosal infection, mycobacterium avium complex infection, nail infection, oral fungal infection, oral

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infection, oral viral infection, parainfluenza virus infection, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection fungal, respiratory tract infection viral, rhinovirus infection, skin infection, staphylococcal infection, upper respiratory treact infection, gastrointestinal candidiasis, gastrointestinal infection, genital candidiasis, genital herpes, genital infection fungal, gingival abscess, gingivitis, groin abscess, groin infection, helicobacter gastritis, hepatitis A, hepatitis C, herpes ophthalmic, herpes simplex, herpes virus infection, herpes zoster, hordeolum, human ehrlichiosis, infected bite, infected cyst, infected dermal cyst, infectious colitis, infectious disease carrier, infectious pleural effusion, infective exacerbation of chronic obstructive airways disease, influenza, injection site cellulitis, klebsiella sepsis, laryngitis, lip infection, lyme disease, mastitis fungal, mastoiditis, meningitis, mumps, myringitis, nasalvestibulitis, nasopharyngitis, neutropenic sepsis, oesophagealcandidiasis, onychomycosis, ophthalmic herpes simplex, ophthalmic herpes zoster, oral candidiasis, oral herpes, orchitis, oropharyngeal candidiasis, oropharyngitis fungal, osteomyelitis, otitis externa, paronychia, parotitis, penile infection, periodontitis, peripheral nerve infection, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, pleural infection, pneumonia adenoviral, pneumonia bacterial, pneumonia legionella, pneumonia staphylococcal, pneumonia streptococcal, post procedural infection, postoperative wound infection, prostatic abscess, pseudomembranous colitis, pseudomonal sepsis, pulmonary mycosis, pulmonary sepsis, pulpitis dental, pyelonephritis, pyelonephritis chronic, pyopneumothorax, pyuria, rash pustular, respiratory syncytial virus bronchitis, respiratory syncytial virus infection, rhinitis, salmonellosis, skin candida, soft tissue infection, staphylococcal bacteraemia, staphylococcal sepsis, staphylococcal skin infection, stomatococcal infection, subcutaneous abscess, systemic candida, tinea cruris, tinea infection, tinea manuum, tinea pedis, tongue fungal infection, tonsillitis, tonsillitis bacterial, tooth abscess, tooth infection, tracheitis, tracheobronchitis, trichomoniasis, upper respiratory tract infection bacterial, urinary tract infection bacterial, urinary tract infection enterococcal, urinary tract infection staphylococcal, urosepsis, vaginal infection, varicella zoster virus infection, viral diarrhoea, viral pharyngitis, vulva l abscess, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis trichomonal.

Infusion-related Reactions:

In clinical studies enrolling 2616 patients with various cancers who received TECENTRIQ as a single agent, infusion-related reactions occurred in 1.3% of patients, including Grade 3 (0.2%). The incidence of infusion-related reactions in atezolizumab-treated patients in IMpower150 was 3.8%, including Grade 3 to 4 (0.8%).

The incidence of infusion-related reactions in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 3%, including Grade 3-4 (0.5%) events. Systemic corticosteroids were required in 0.3% of patients, including < 0.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 1.0 days (1 day to 1 day) followed by a corticosteroid taper.

The PT used to identify cases of infection include infusion related reaction and cytokine release syndrome.

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of < 1% in 2616 patients who received TECENTRIQ as a single agent and in 2421 patients who received TECENTRIQ in combination with platinum-based chemotherapy or were reported in other products in this class.

Pancreatitis:
The incidence of pancreatitis in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.7%, including Grade 3-4 (0.3%) events. Systemic corticosteroids were required in 0.1% of patients, including <0.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 19.5 days (7 day to 32 days) followed by a corticosteroid taper.

The PT used to identify cases of pancreatitis include lipase increased, pancreatitis, pancreatitis acute, amylase increased, and autoimmune pancreatitis.

Nephritis:
The incidence of nephritis in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.5%, including Grade 3-4 (0.3%) events. Systemic corticosteroids were required in 0.4% of patients, including 0.2% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 11.0 days (2 days to 18 days) followed by a corticosteroid taper.

The PT used to identify cases of nephritis include lipase increased, pancreatitis, pancreatitis acute, amylase increased, and autoimmune pancreatitis.

Vasculitis:
The incidence of vasculitis in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.2%, including Grade 3-4 (< 0.1%) events. Systemic corticosteroids were required in < 0.1% of patients, including 0% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent).

The PT used to identify cases of vasculitis include polymyalgia rheumatica and vasculitis.

Myopathies:
The incidence of myopathies in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.2%, including Grade 3-4 (< 0.1%) events. Systemic corticosteroids were required in 0% of patients.

The PT used to identify cases of myopathies include myopathy, rhabdomyolysis, and myoglobin urine present.

Myositis:
The incidence of myositis in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.2%, including Grade 3-4 (< 0.1%) events.

Systemic corticosteroids were required in 0.2% of patients, including 0% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent).

The PT used to identify cases of myositis include myositis, polymyalgia rheumatica, and polymyositis.

Guillain-Barre Syndrome:
The incidence of Guillain-Barre syndrome in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was < 0.1%, including Grade 3-4 (< 0.1%) events. Systemic corticosteroids were required in < 0.1% of patients, including < 0.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 1.0 days (1 day to 1 day) followed by a corticosteroid taper.

The PT used to identify cases of Guillain-Barre Syndrome include guillain-barre syndrome and demyelinating polyneuropathy.

Meningoencephalitis:
The incidence of meningoencephalitis in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.4%, including Grade 3-4 (0.2%) events. Systemic corticosteroids were required in 0.2% of patients, including < 0.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 3.5 days (3 days to 4 days) followed by a corticosteroid taper.

The PT used to identify cases of meningoencephalitis include encephalitis, meningitis, and photophobia.

Severe cutaneous rash:
The incidence of severe cutaneous skin rash in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.8%, including Grade 3-4 (0.2%) events. Systemic corticosteroids were required in 0.2% of patients, including 0% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent).

The PT used to identify cases of severe cutaneous reaction include dermatitis bullous, toxic skin eruption, erythema multiforme, and exfoliative rash.

Autoimmune Hemolytic Anemia (AIHA):
The incidence of AIHA in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was 0.2%, including Grade 3-4 (< 0.1%) events. Systemic corticosteroids were required in < 0.1% of patients, including 0% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent).

The PT used to identify cases of AIHA include autoimmune haemolytic anaemia, haemoglobinuria, haemolysis, haemolytic uraemic syndrome, haptoglobin decreased, and transfusion reaction.

Ocular inflammatory toxicity:
The incidence of ocular inflammatory toxicity in 2421 TECENTRIQ-treated patients in clinical studies where TECENTRIQ was administered with chemotherapy was was 0.3%, including Grade 3-4 (< 0.1%) events. Systemic corticosteroids were required in 0.1% of patients, including 0.1% who received high-dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) for a median duration of 12.0 days (1 day to 189 days) followed by a corticosteroid taper.

The PT used to identify cases of ocular inflammatory toxicity include episcleritis, eye inflammation, keratitis, noninfective conjunctivitis, optic neuritis, optic neuropathy, retinal detachment, retinopathy, ulcerative keratitis, and uveitis.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D were used to assess HRQoL, physical functioning, symptom severity, and to generate utility scores for use in economic models for reimbursement. Results of the PRO analysis are presented below in section 19.

8.2.7. Safety Analyses by Demographic Subgroups

Age

In IMpower133, 90 (45%) of the patients receiving atezolizumab were age 65 years or older. Table 31 presents an overview of the incidence of AEs by age <65 years and ≥65 years of age.

Table 31: Overview of Adverse Events by Age Group (Safety Population)

	PBO/CE N=196 (%)		Atezo/CE N=198 (%)	
Years of age	<65	≥65	<65	≥65
N	103	93	109	89
N with any AE	97 (94)	92 (99)	109 (100)	89 (100)
Grade 3 to 4 AEs	59 (57)	66 (71)	70 (64)	63 (71)
Serious AE	30 (29)	38 (41)	44 (40)	30 (34)
Died due to a TEAE	3 (2.9)	8 (9)	3 (3)	1 (1)
Discontinued due to AE	2 (2)	3 (3.2)	13 (12)	8 (9)
Discontinued due to SAE	2 (2)	3 (3.2)	10 (9)	3 (3)

***Reviewer* comments:** *The proportion of patients age 65 or older who experienced grade 3 to 4*

AEs and serious AEs was higher than in patients age <65 in the placebo arm; this was not observed in the atezolizumab arm. In the atezolizumab arm, the proportion of patients age less than 65 discontinuing treatment do to an AE or SAE (21%) was higher than for patients age 65 or older (12%).

Gender
In IMpower133, 262 (65%) of the patients were male and 141 (35%) were female. Table 32 summarizes the incidence of AEs by gender in IMpower133.

Table 32: Overview of Adverse Events by Gender (Safety Population)

	PBO/CE N=196 (%)		Atezo/CE N=198 (%)	
Gender	Male	Female	Male	Female
N	129	67	127	71
N with any AE	124 (96)	65 (97)	127 (100)	71 (100)
Grade 3 to 4 AEs	80 (62)	45 (67)	82 (65)	51 (72)
Serious AE	44 (34)	24 (36)	44 (35)	30 (42)
Died due to a TEAE	8 (6)	3 (5)	2 (2)	2 (3)
Discontinued due to AE	3 (2.3)	2 (3)	12 (9)	9 (13)
Discontinued due to SAE	3 (2.3)	2 (3)	7 (6)	6 (9)

Reviewer comments: *No major differences were noted in the overall incidence of AEs between male and female patients enrolled in IMpower133. The proportion of females with Grade 3-4 AEs and SAEs in the atezolizumab arm was slightly higher than for males.*

8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies were included in this submission.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No carcinogenicity studies were conducted.

Human Reproduction and Pregnancy

No reproductive toxicity studies were conducted.

Pediatrics and Assessment of Effects on Growth

Not applicable for this supplement.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses were reported with atezolizumab in IMpower133, according to Genentech.

Based on atezolizumab' s mode of administration and pharmacological properties, there are no concerns regarding the potential for abuse, withdrawal, or rebound.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Based on information provided by Genentech, as of August 21, 2018, atezolizumab has been registered or approved in several foreign markets for the second line treatment of patients with metastatic NSCLC. On December 6, 2018, atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin received regular approval for the first-line treatment of patients with NSCLC in the U.S. under sBLA 761034/S-009.

There have been no withdrawals or suspensions from marketing in any country.

Table 33: Summary of Foreign Marketing Developments

Indication: TECENTRIQ as a single agent for 2L metastatic Non-Small Cell Lung Cancer		
Country	**Date Approved**	**Marketing Status**
Albania	01 June 2018	Not marketed
Argentina	25 August 2017	Marketed
Aruba	26 April 2018	Marketed
Australia	27 July 2017	Marketed
Bolivia	10 May 2018	Not marketed
Bosnia and Herzegovina	02 July 2018	Marketed
Brazil	09 October 2017	Marketed
Canada	06 April 2018	Marketed
Chile	31 August 2017	Marketed
Indication: TECENTRIQ as a single agent for 2L metastatic Non-Small Cell Lung Cancer		
Country	**Date Approved**	**Marketing Status**
Costa Rica	28 February 2018	Not marketed
Cuba	16 October 2017	Marketed
Dominican Republic	19 September 2017	Marketed
Ecuador	10 March 2018	Marketed
Egypt	29 March 2018	Marketed
El Salvador	17 July 2017	Marketed
EU*	21 September 2017	Marketed
Georgia	17 December 2017	Marketed

Guatemala	27 April 2018	Marketed
Honduras	07 March 2018	Marketed
Hong Kong	29 January 2018	Marketed
India	13 November 2017	Not marketed
Israel	19 June 2017	Marketed
Japan	19 January 2018	Marketed
Jordan	25 March 2018	Not marketed
Kosovo	02 March 2017	Marketed
Kuwait	03 November 2016	Marketed
Lebanon	22 March 2017	Marketed
Macao	26 April 2018	Marketed
Macedonia	13 July 2018	Not marketed
Malaysia	28 February 2018	Marketed
New Zealand	06 April 2017	Not marketed
Oman	28 December 2017	Marketed
Pakistan	12 July 2018	Not marketed
Panama	14 February 2018	Marketed
Paraguay	14 August 2017	Marketed
Peru	04 December 2017	Marketed
Qatar	12 February 2017	Marketed
Russia	18 January 2018	Marketed
Saudi Arabia	08 August 2017	Marketed
Serbia	02 March 2018	Not marketed
Singapore	09 February 2018	Marketed
South Korea	02 May 2017	Marketed
Switzerland	23 May 2017	Marketed
Taiwan	15 September 2017	Marketed

Expectations on Safety in the Postmarket Setting

Atezolizumab has been marketed in the U.S. since 2016 and the safety profile of atezolizumab, as well as the safety profiles of carboplatin and etoposide is well-established. FDA will continue to monitor atezolizumab safety in the postmarketing setting, specifically regarding the anti-drug antibody formation to atezolizumab.

8.2.11. Integrated Assessment of Safety

To compare the incidence of immune-related AEs associated to atezolizumab, the incidence of AESI observed in IMpower133 was compared to the safety data of 2616 patients from studies in which atezolizumab was administered as a single agent (Atezolizumab Monotherapy Safety Dataset), data for atezolizumab-treated patients with NSCLC from IMpower150, and data for a pooled population of 2421 patients from studies in which atezolizumab was administered with chemotherapy (IMpower133 and four NSCLC studies) to support the consistency of the atezolizumab safety profile across indications (see Section 8.2.5 of this review).

Table 34 below summarizes the comparison between the all ADRs and Grade 3-4 ADRs of 2421 patients from studies in which atezolizumab was administered with chemotherapy to the atezolizumab treated arm in IMpower133 (N= 198).

Table 34 AEs in Pooled Safety Population and IMpower133

	Pooled Study (N = 2421)		**IMpower133 (Atezo-treated arm) N = 198**	
Preferred Terms	All Grades (%)	Grade 3-4 (%)	All Grade (%)	Grade 3-4 (%)
Fatigue and Asthenia	49	7	39	5
Nausea	38	2.2	38	0.5
Alopecia	35	0	37	0
Fatigue	32	4.3	27	2.5
Constipation	29	0.6	26	1
Diarrhea	28	3.5	18	2
Decreased Appetite	27	2	27	1

Source: Reviewer Table and ADaM dataset: adsl.xpt and aae.xpt. DCO: April 2018

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There were no significant statistical issues in the review of this application. The review team does note that because the treatment effect was delayed for both OS and PFS, the hazard ratio may not adequately describe the treatment effect.

8.4. Conclusions and Recommendations

The primary trial supporting this sBLA is IMpower133, a randomized, multicenter, double-blind, placebo-controlled trial comparing atezolizumab in combination with carboplatin and etoposide to placebo plus carboplatin and etoposide as first-line systemic therapy in 403 patients with extensive stage small cell lung cancer.

IMpower133 demonstrated a hazard ratio for OS favoring the atezolizumab-containing arm of 0.70 (95% CI 0.54, 0.91; p- value 0.0069 as compared to a pre-specified significance level for alpha of 0.0193); the median OS was 12.3 months in the atezolizumab arm and 10.3 months in the control arm. The HR for PFS as assessed by investigator also favored the atezolizumab-containing arm with a HR of 0.77 (95% CI 0.62, 0.96, p-value 0.0170), corresponding to median PFS of 5.2 months in the atezolizumab arm and 4.3 months in the control arm, although this difference in PFS is not considered clinically meaningful. ORR and DOR were similar between arms, with ORR 60% in the atezolizumab arm and 64% in the control arm and estimated median durations of response of 4.2 months and 3.9 months, respectively.

The safety profile of atezolizumab administered in combination with carboplatin and etoposide is acceptable relative to the demonstrated clinical benefit in the context of the treatment of a life-threatening disease. The AEs observed are consistent with the known AE profile of atezolizumab administered as a single agent and with the combination of carboplatin and etoposide. No new safety signals for atezolizumab were identified during the safety review. The incidence of the most common immune-mediated adverse reactions in the atezolizumab arm in IMpower133 is similar to (hypothyroidism, hyperthyroidism) or lower (pneumonitis, hepatitis, and colitis) than that observed in patients with NSCLC treated with atezolizumab in combination with platinum-based chemotherapy with or without bevacizumab in IMpower150. The incidence of infusion-related reactions in atezolizumab-treated patients in IMpower133 was similar to that in IMpower150. The incidence of infections was lower in atezolizumab-treated patients in IMpower133 (32%) relative to atezolizumab administered as a single agent (42%) and atezolizumab-treated patients in IMpower150 (50%). There was no increase in the incidence of Grade 3-4 AESI in atezolizumab-treated patients in IMpower133 relative to atezolizumab-treated patients in IMpower150 or the pooled population of patients who received atezolizumab administered as a single agent. The safety concerns of immune-mediated adverse reactions, infections, and infusion-related reactions are adequately addressed by information in the Warnings and Precautions and dose modification sections of the USPI to allow appropriate management by treating oncologists.

The submitted evidence meets the statutory evidentiary standard for regular approval. The observed improvement in OS is statistically robust and clinically meaningful. The review team recommends approval of atezolizumab, in combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive stage SCLC based on the determination that atezolizumab in combination with carboplatin and etoposide presents a favorable risk:benefit profile for the proposed indication.

Jonathan Vallejo, Ph.D.
Primary Statistical Reviewer

Lisa Rodriguez, Ph.D.
Statistical Team Leader

Luckson Mathieu, M.D.
Primary Clinical Reviewer

Erin Larkins, M.D.
Clinical Team Leader

Reference ID: 4405439

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this efficacy supplement to an advisory committee because atezolizumab is not the first drug in this class, the safety profile is acceptable in this indication, and the clinical trial design is similar to that used previously in this class. The safety profile of atezolizumab alone is well established in patients with metastatic cancer and no new safety signals were identified in IMpower133 when atezolizumab was administered with carboplatin and etoposide to patients with extensive stage SCLC. The demonstrated benefit-risk profile for atezolizumab, administered in combination with carboplatin and etoposide, is favorable given the improvement in overall survival and does not provide substantial increase in risks over available therapy for patients with previously untreated extensive stage SCLC.

Reference ID: 4405439

10 Pediatrics

Genentech submitted a copy of the FDA's Agreed Initial Pediatric Study Plan-3 (iPSP-3) letter, issued on June 23, 2018, in the application alone with a Request for Waiver of Pediatric Studies for the proposed indication. The Agreed iPSP-3 described "Genentech plans to request a full waiver from the requirements of the Pediatric Research Equity Act (PREA) under Section 505B(a)(4)(A)(i) of the Federal Food, Drug, and Cosmetic Act for all pediatric age groups (0 to 17 years of age) for Tecentriq, in combination with carboplatin and etoposide, for first-line treatment of extensive-stage SCLC. The justification for the proposed waiver is that the necessary studies are impossible or highly impracticable to conduct because the number of patients is so small."

The request for waiver from the requirements of PREA for all pediatric age groups was reviewed and approved by the OCE Pediatric Research Committee (PeRC) on March 6, 2019.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The approved TECENTRIQ labeling was modified to help ensure that the product information is complaint with regulations, consistent with labeling guidance recommendations and current best labeling practices and policies, and conveys the essential scientific information needed for the safe and effective use of TECENTRIQ.

Section 1, Indications and Usage

FDA recommended that "age groups should be included in indications" as summarized in the FDA Guidance on the Indications and Usage section of labeling. Therefore, the word "adult" is included in all of the indication statements, including the new indication statement as shown below.

TECENTRIQ, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Section 5, Warnings and Precautions:

The revised labeling includes a statement in each subsection that the rate of an immune-mediated or another adverse reaction was similar in patients receiving TECENTRIQ as a single agent or in combination with platinum-based chemotherapy or includes a paragraph that summarizes the risks of an adverse reaction following administration of TECENTRIQ in combination if the risk was higher in patients who received TECENTRIQ in combination

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compared to single agent. The revised labeling for atezolizumab in combination with platinum-based chemotherapy is based on the analysis of a pooled safety dataset of five clinical trials conducted in patients with lung cancer.

Section 6, Adverse Reactions

Subsection 6.1, Clinical Trials Experience

The labeling was modified to include the most common adverse reactions in patients receiving TECENTRIQ as a single agent and in combination with other neoplastic agents before a description of the individual studies. The revised labeling is based on pooled analyses across studies. The list of the most common adverse reactions (b) (4) was removed, because the most common reactions can be found in the tables for each trial.

The table entitled "Laboratory Abnormalities Worsening from Baseline Occurring in ≥20% of Patients (b) (4) TECENTRIQ in IMpower133" was modified to remove (b) (4), (b) (4), and (b) (4) since there is no mechanistic association between these lab abnormalities and the use of TECENTRIQ. (b) (4) was also removed from the table, because neutropenia and lymphopenia are included. Added footnotes to indicate laboratory abnormalities included in the table but not included in NCI CTCAE v4.0.

Subection 6.2, Immunogenicity

(b) (4)

. A more detailed assessment of the effects of development of ADA will be further assessed following review of the final study reports for PMC 3459-1, 3459-2, and 3459-3 in the December 6, 2018, approval letter for sBLA 760134/S-009.

Section 8.5, Geriatric Use:

The information in this section was integrated across all indications rather than presented separately by study since each study yielded similar findings.

Section 10, Overdose:

This section was deleted as no clinically useful information is provided.

Section 14, Clinical Studies

Added footnotes to the table entitled "Efficacy Results from IMpower133" to indicate the stratification factors used for the statistical analyses and the allocated alpha for the analyses of OS and PFS.

The results for the Physical Function and Patient Reported Treatment Related Symptoms using

EORTC QLQ C30 and EORTC QLQ LC13 measures were not included in the labeling as these exploratory analyses do not provide robust evidence of the absence of clinically important effects on patient reported outcomes.

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend that a risk evaluation and mitigation strategy (REMS) be required to ensure safe and effective use of atezolizumab for the indicated population given the established safety profile of atezolizumab; lack of new safety signals when atezolizumab is administered with carboplatin and etoposide for the treatment of ES-SCLC; and the experience of the medical oncology community in managing immune-mediated adverse reactions. Adequate recommendations for safe and effective use of atezolizumab, including monitoring for immune-mediated adverse events, are contained in the agreed-upon full prescribing information and the medication guide.

13 Postmarketing Requirements and Commitment

Due to the increased incidence of ADA observed with atezolizumab, Genentech agreed to conduct PMCs to further characterize the risks of ADA, including effects on atezolizumab's pharmacokinetics, efficacy and safety as described in the December 2018 approval letter for sBLA761034/S-009.

The following PMC was recommended and agreed upon with Genentech under this sBLA:

Provide updated OS results from the IMpower133 study based upon the protocol-specified timing for the final analysis of OS to better characterize survival differences at late time point to inform labeling.

Study/Trial Completion (Updated OS database lock):	03/2019
Final Report Submission (Supplemental Results Report Submission):	09/2019

Reference ID: 4405439

14 Division Director (DHOT)

Not applicable.

15 Division Director (OCP)

Brian Booth

16 Division Director (OB)

Rajeshwari Sridhara, Ph.D.
Division of Biometrics V
Office of Biometrics

17 Division Director (Clinical)

I concur with the recommendations of the review team that the application be approved based on demonstration of substantial evidence of effectiveness [statistically robust and clinically important improvement in survival, supported by a clinically modest effect on PFS] and a favorable risk:benefit assessment. Based on the lack of new safety signals, the clinical benefit observed, and the life-threatening nature of ES-SCLC, a REMS is not required to ensure safe use. The pending PMCs (under sBLA 761034/S-009) and the agreed-upon PMC will further characterize the risks and benefits of atezolizumab for the treatment of ES-SCLC, administered in combination with first-line chemotherapy.

Patricia Keegan, M.D.
Division of Oncology Products 2
Office of Hematology and Oncology Products

18 Office Director (or designated signatory authority)

Not applicable.

19 Appendices

19.1. References

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19.2. Financial Disclosure

Table 35: Financial Disclosure Summary IMpower133

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1340		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
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: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.5. Statistical Appendices

Subgroup analyses of restricted mean survival time (RMST) of atezolizumab/CE vs. placebo/CE are shown in Table 36.

Table 36: RMST of OS by Subgroup (Atezolizumab/CE vs. Placebo/CE)

Factor	Subgroup	N	RMST in months (95% CI)
Region	Asia-Pacific	80	0.4 (-1.9, 2.7)
	EU	223	2.1 (0.5, 3.7)
	North America	90	1.7 (-0.9, 4.3)
	South America	10	0.4 (-2.6, 3.3)
Age	< 65	217	0.3 (-1.4, 2)
	>= 65	186	2.9 (1.1, 4.8)
ECOG	0	145	0.8 (-1, 2.6)
	1	258	1.8 (0.2, 3.4)
Brain Metastases	N	371	1.9 (0.5, 3.3)
	Y	32	-1.3 (-5.2, 2.6)
Sex	F	141	1.7 (-0.3, 3.7)
	M	262	1.3 (-0.4, 2.9)
Smoking Status	Current	149	1.4 (-0.3, 3)
	Never	12	0.3 (-6.3, 6.9)
	Previous	242	1.2 (-0.5, 2.9)
bTMB	<10	139	1.6 (-0.3, 3.5)
	>=10	212	1.5 (-0.3, 3.4)
	<16	271	1.5 (-0.1, 3.1)
	>=16	80	1.9 (-1, 4.9)
Prior Anti-Cancer Treatment	N	382	1.5 (0.1, 2.9)
	Y	21	0 (-3.9, 3.9)
Prior Radiotherapy for SCLC	N	350	1.9 (0.5, 3.4)
	Y	53	-1.6 (-4.7, 1.4)
Prior Surgery for SCLC	N	345	1.6 (0.1, 3)
	Y	58	1.1 (-1.4, 3.6)

19.6. Additional Clinical Outcome Assessment Analyses

Time to deterioration (TTD) was defined as the time from baseline to the first time the patient's score shows a ≥ 10-point increase above baseline in the specified subscale. In order for the symptom to be considered "deteriorated," a score increase of ≥ 10 points above baseline must have been held for at least two consecutive assessments or an initial score increase of ≥ 10 points is followed by death within 3 weeks from the last assessment.

Reviewer's comment: The 10-point threshold which defines "deterioration" is arbitrary and was not discussed between Genentech and FDA. There was no agreement between Genentech and FDA on this definition of TTD prior to submission of the marketing application.

Analyses for TTD were to be performed on all patients in the ITT population who had a baseline score. If no post-baseline assessment is performed, patients will be censored at the randomization date plus 1 day. The analyses specified were the same as those specified for OS and PFS.

The protocol for IMpower133 also specified summary statistics for the PRO instruments as exploratory outcomes. These analyses included mean and change from baseline. These analyses were to be performed on all patients in the ITT population who had a baseline score and at least one non-missing post-baseline score.

Completion rates for the EORTC QLQ-C30 and EORTC QLQ-LC13 are shown in Table 37 and Table 38.

Table 37: Completion Rates by Visit for the EORTC QLQ-C30

	Atezolizumab/CE		Placebo/CE	
Visit	% of Expected Forms Completed	# Forms Expected	% of Expected Forms Completed	# Forms Expected
Baseline	89	197	89	197
Week 3	85	196	83	197
Week 6	81	178	88	185
Week 9	84	174	83	179
Week 12	81	162	86	169
Week 15	85	150	87	156
Week 18	88	117	89	112
Week 21	85	101	86	85
Week 24	84	77	79	57
Week 27	86	64	89	44
Week 30	90	58	86	36
Week 33	92	52	93	29
Week 36	76	41	92	25
Week 39	87	38	83	24
Week 42	97	35	90	20
Week 45	94	33	94	18
Week 48	89	27	88	16
Week 51	96	26	83	12
Week 54	91	22	92	12

Reference ID: 4405439

Week 57	85	20	80	10
Week 60	83	18	100	8
Week 63	92	12	88	8
Week 66	82	11	83	6
Week 69	75	8	100	5
Week 72	83	6	100	4
Week 75	67	3	100	3
Week 78	67	3	100	1
Week 81	100	2	0	1
Week 84	100	2	100	1
Week 87	100	2	100	1
Week 90	0	1	0	1
Week 93	0	0	0	1
END OF TREATMENT	91	174	83	186

Table 38: Completion Rates by Visit for the EORTC QLQ-LC13

	Atezolizumab/CE		Placebo/CE	
Visit	% of Expected Forms Completed	# Forms Expected	% of Expected Forms Completed	# Forms Expected
Baseline	88	197	85	197
Week 3	83	196	81	197
Week 6	80	178	86	185
Week 9	80	174	83	179
Week 12	81	162	86	169
Week 15	85	150	86	156
Week 18	88	117	89	112
Week 21	85	101	86	85
Week 24	84	77	77	57
Week 27	86	64	89	44
Week 30	90	58	86	36
Week 33	92	52	93	29
Week 36	76	41	92	25
Week 39	84	38	83	24
Week 42	97	35	90	20
Week 45	94	33	94	18
Week 48	89	27	88	16
Week 51	96	26	83	12
Week 54	91	22	92	12
Week 57	85	20	80	10
Week 60	83	18	100	8
Week 63	92	12	88	8
Week 66	73	11	83	6
Week 69	75	8	100	5
Week 72	83	6	100	4
Week 75	67	3	100	3
Week 78	67	3	100	1
Week 81	100	2	0	1

Week 84	100	2	100	1
Week 87	100	2	100	1
Week 90	0	1	0	1
Week 93	0	0	0	1
END OF TREATMENT	90	174	84	186

Kaplan-Meier plots with associated hazard ratios are shown for TTD in the pre-specified subscales in Figure 7, Figure 8, Figure 9, and Figure 10.

Figure 7: Time to Confirmed Deterioration in Arm and Shoulder Pain

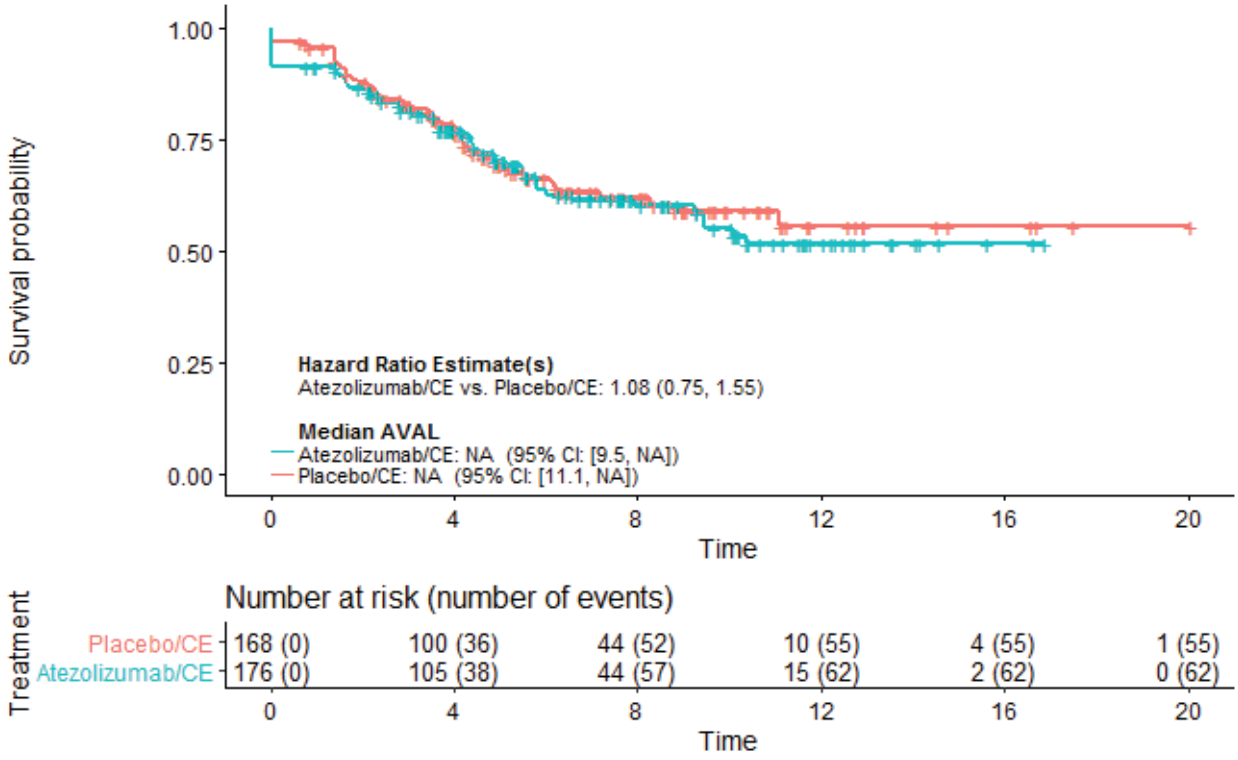


Figure 8: Time to Confirmed Deterioration in Chest Pain

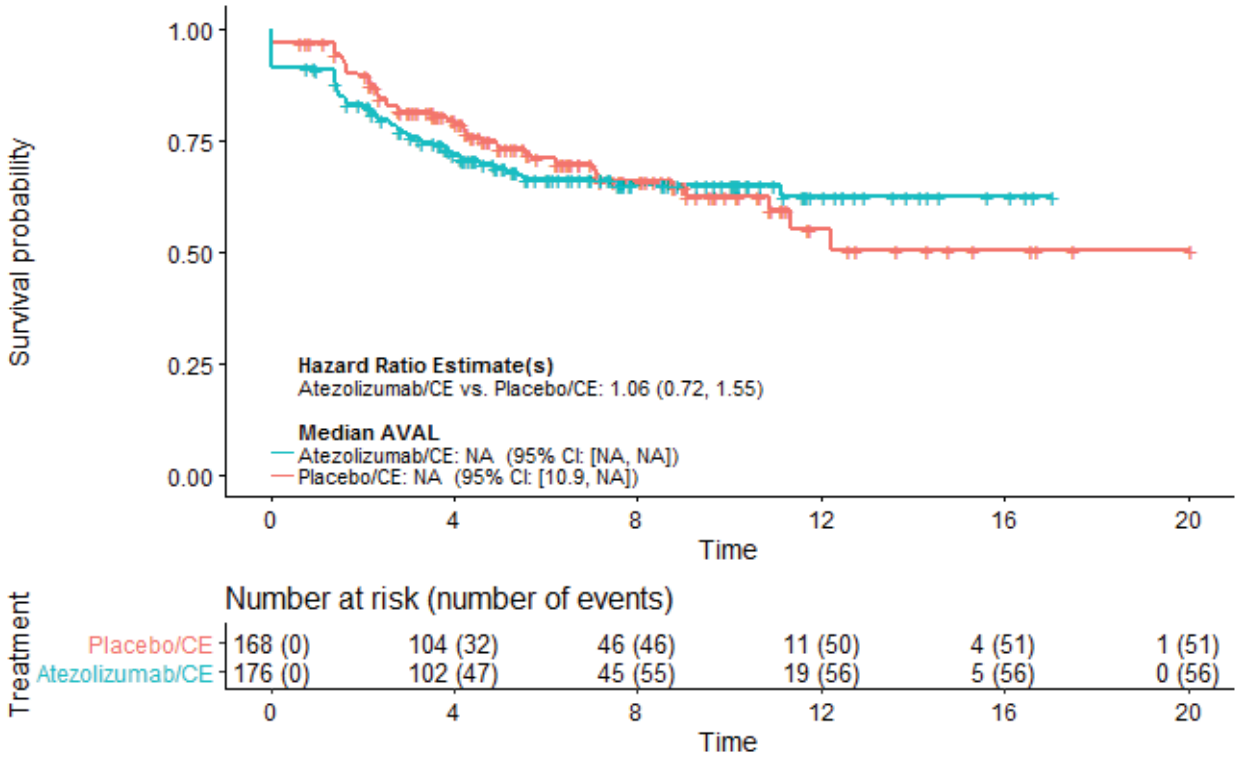


Figure 9: Time to Confirmed Deterioration in Cough

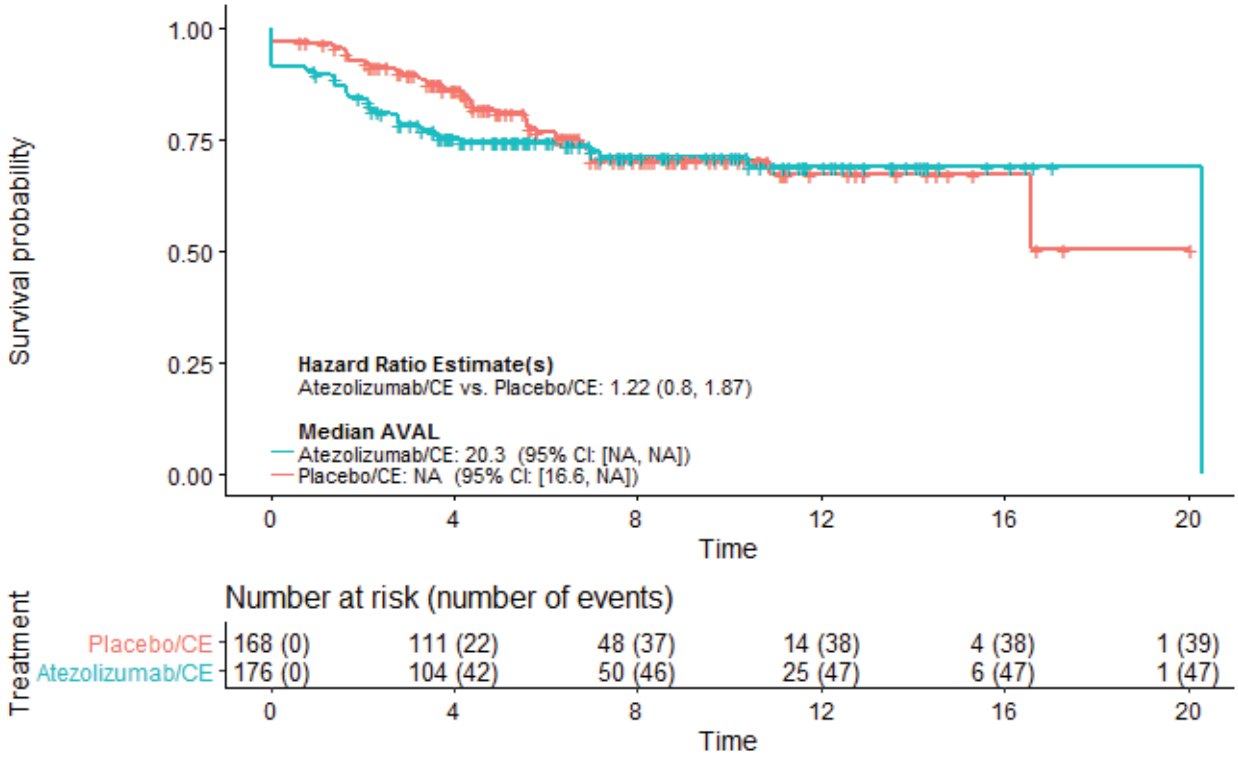
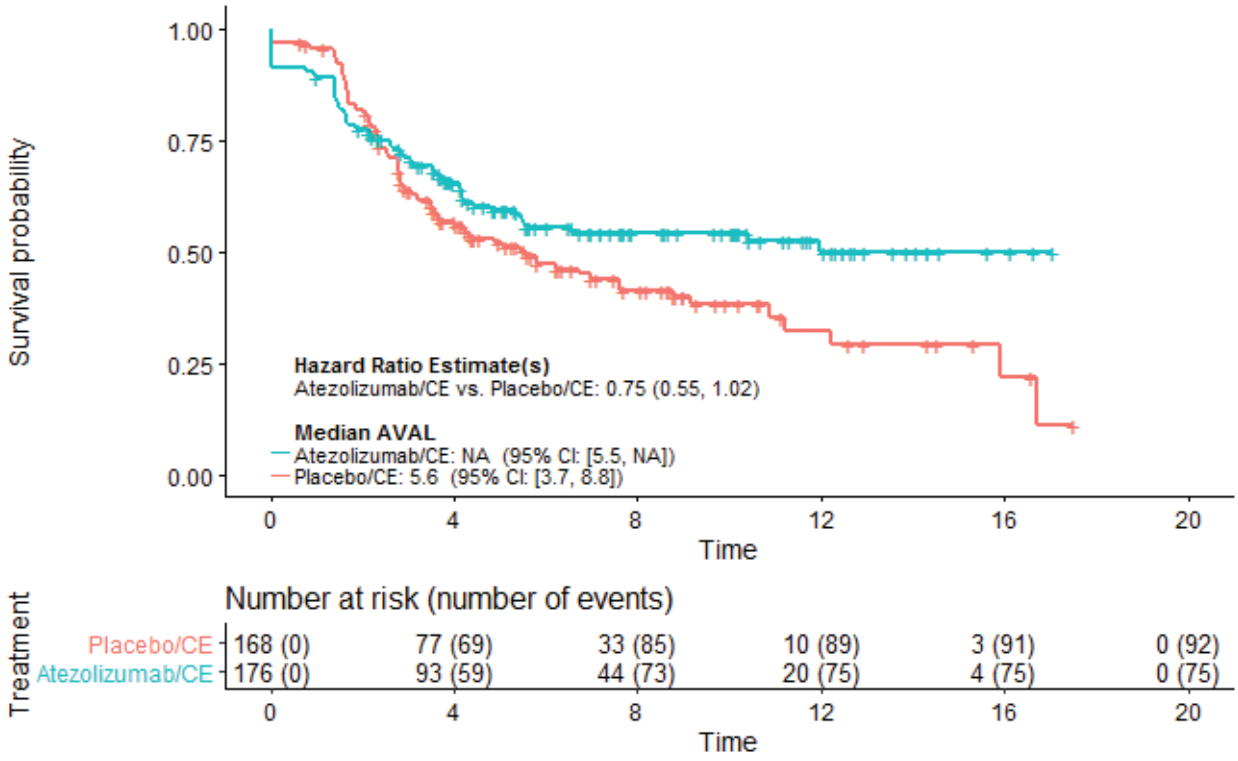


Figure 10: Time to Confirmed Deterioration in Dyspnoea



Mean and change from baseline score by visit are shown for these subscales in Figure 11 and Figure 12, respectively.

Figure 11: Mean EORTC QLQ-LC13 Scores by Visit for Selected Subscales

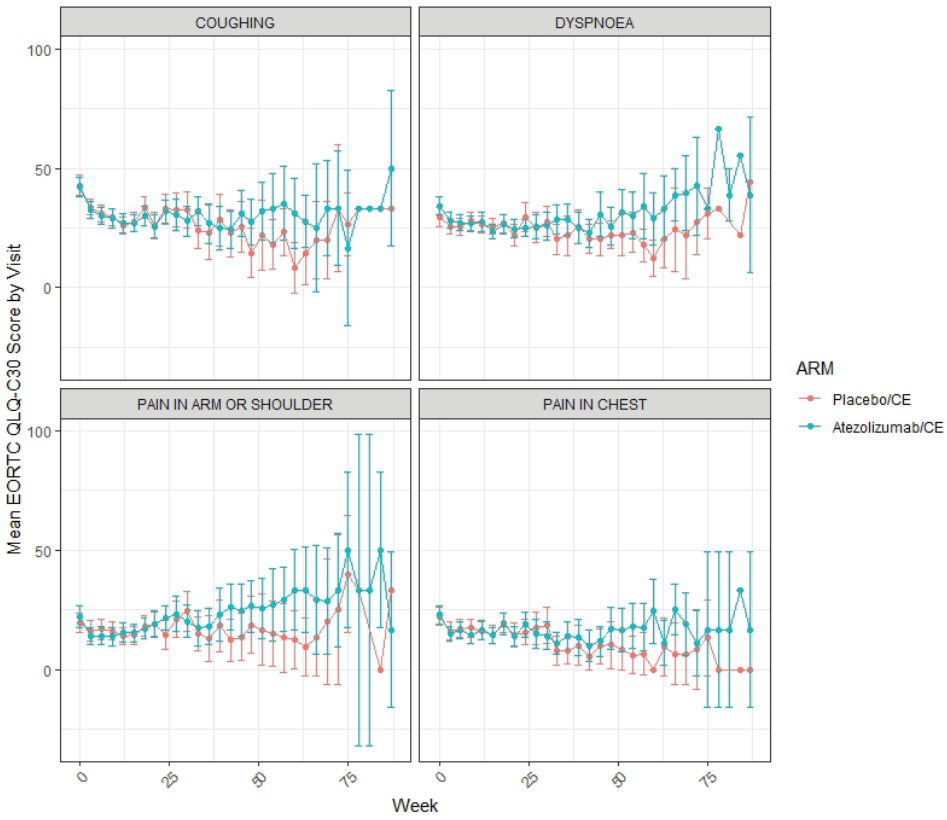
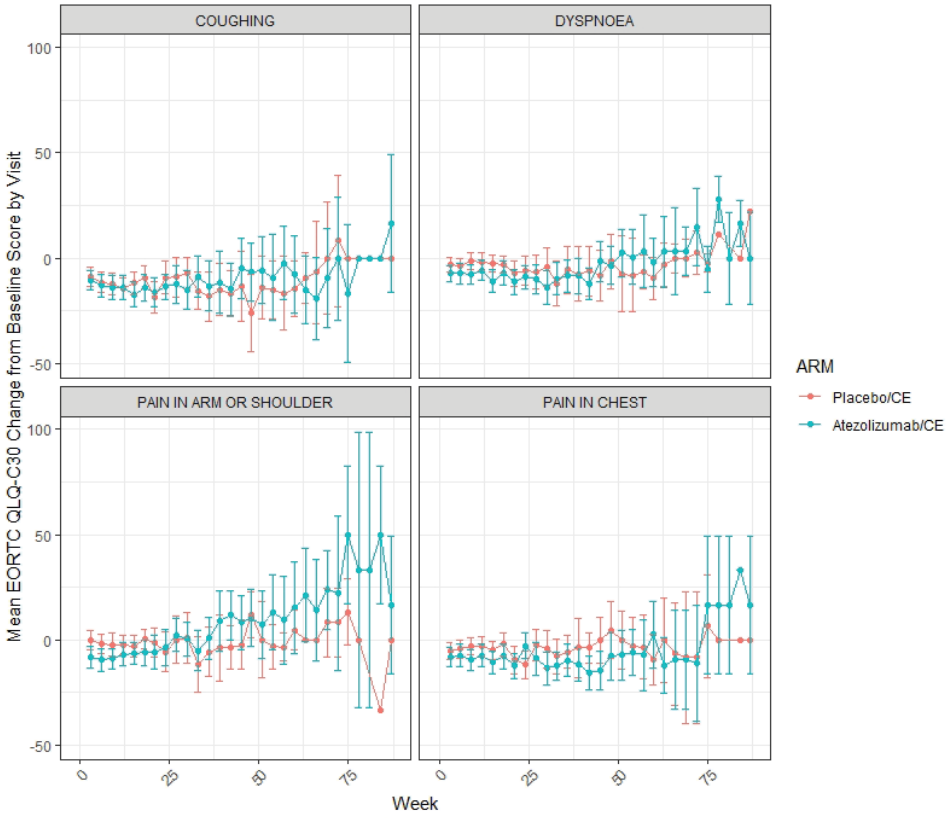


Figure 12: Mean Change from Baseline EORTC QLQ-LC13 by Visit for Selected Subscales



Reviewer's Comment: Because this trial was double-blind, the possibility of bias arising from a patient's knowledge of treatment assignment is lower than it would be in an open-label trial. However, there does not appear to be any consistent treatment effect across the four pre-specified subscales.

Table 39: List of AESI Preferred Terms Used in IMpower133

List of Adverse Events of Special Interest (AESIs) for Atezolizumab Study GO30081 (IMpower133)

AESI	Reference Type (MedDRA v21.0)	Methodology
Immune-Related Hepatitis	SMQ	Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) narrow
	SMQ	Hepatitis, non-infectious (SMQ) narrow
	SMQ	Liver related investigations, signs and symptoms (SMQ) narrow
Immune-Related Hypothyroidism	SMQ	Hypothyroidism (SMQ) wide
Immune-Related Hyperthyroidism	SMQ	Hyperthyroidism (SMQ) narrow
Immune-Related Adrenal Insufficiency	Sponsor defined AEGT	Atezolizumab adrenal insufficiency AEGT consisting of the following PTs: Addison's disease, Adrenal atrophy, Adrenal insufficiency, Adrenal insufficiency neonatal, Adrenal suppression, Adrenocortical insufficiency acute, Adrenocortical insufficiency neonatal, Aldosterone urine decreased, Biopsy adrenal gland abnormal, Blood aldosterone abnormal, Blood aldosterone decreased, Blood corticosterone abnormal, Blood corticosterone decreased, Blood corticotrophin abnormal, Blood corticotrophin decreased, Blood corticotrophin increased, Cortisol free urine decreased, Hydroxycorticosteroids urine decreased, Hypoaldosteronism, Secondary adrenocortical insufficiency, Steroid withdrawal syndrome, Primary adrenal insufficiency, Dexamethasone suppression test positive, Dexamethasone suppression test, Urine cortisol/creatinine ratio decreased, Urine cortisol/creatinine ratio abnormal, Glucocorticoids abnormal, Glucocorticoids decreased, Aldosterone urine abnormal, Adrenogenital syndrome, Scan adrenal gland abnormal, Hydroxycorticosteroids urine abnormal, Adrenalitis, Acth stimulation test abnormal, Glucocorticoid deficiency, Mineralocorticoid deficiency, Corticotropin-releasing hormone stimulation test, Adrenocorticotropic hormone deficiency, Triple a syndrome, Hypothalamic pituitary adrenal axis suppression, Adrenal androgen deficiency, Apituitarism, Cortisol deficiency
Immune-Related Pneumonitis	SMQ	Interstitial lung disease (SMQ) narrow
Immune-Related Colitis	HLT	Colitis (excl infective)
Immune-Related Guillan-Barre	SMQ	Guillain-Barre syndrome (SMQ) narrow
Immune-Related Myasthenia Gravis	HLT	Myasthenia gravis and related conditions
Immune-Related Meningoencephalitis	SMQ	Noninfectious meningitis (SMQ) narrow
	SMQ	Noninfectious encephalitis (SMQ) narrow
Infusion-Related Reaction	PT	Infusion Related Reaction (Only include if occurred on same day or within 1 day of atezolizumab infusion)
	PT	Cytokine release syndrome (Only include if occurred on same day or within 1 day of atezolizumab infusion)

AESI	Reference Type (MedDRA v20.1)	Methodology
Immune-Related Pancreatitis	Sponsor defined AEGT	Atezolizumab pancreatitis AEGT consisting of the Acute pancreatitis SMQ (narrow) plus the following MedDRA PTs: Amylase abnormal, amylase increased, autoimmune pancreatitis, lipase abnormal, lipase increased
Immune-Related Diabetes Mellitus	Sponsor defined AEGT	Atezolizumab Diabetes/DKA (excludes hyperglycemia) AEGT consisting of the following MedDRA PTs: Diabetes mellitus, Diabetic coma, Diabetic hyperglycaemic coma, Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Ketoacidosis, Latent autoimmune diabetes in adults, Type 1 diabetes mellitus, Fulminant type 1 diabetes mellitus
Immune-Related Myositis	HLT	Muscle infections and inflammations
	HLT	Muscular autoimmune disorders
Immune-Related Nephritis	HLT	Glomerulonephritis and nephrotic syndrome
	HLT	Nephritis NEC
Immune-Related Rash	Sponsor defined AEGT	EGFR Associated Skin Reactions AEGT consisting of the following PTs: Acne, Acne cystic, Acne pustular, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalised, Dermatitis infected, Drug eruption, Eczema, Eczema infected, Erythema, Erythema multiforme, Erythema of eyelid, Fixed eruption, Folliculitis, Furuncle, Palmar-plantar erythrodysaesthesia syndrome, Rash, Rash erythematous, Rash follicular, Rash generalised, Rash macular, Rash maculo-papular, Rash morbilliform, Rash papular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash scarlatiniform, Rash vesicular, Seborrhoeic dermatitis, Skin exfoliation, Skin necrosis, Skin ulcer, Stevens-johnson syndrome, Toxic epidermal necrolysis, Vasculitic rash, Acute generalised exanthematous pustulosis, Acne fulminans, Rash maculovesicular, Generalised erythema, Mucocutaneous rash, Eyelid folliculitis, Toxic skin eruption, Rash rubelliform, Eczema vesicular, Hand dermatitis, Epidermal necrosis, Skin toxicity, Exfoliative rash, Butterfly rash, Application site acne, Drug reaction with eosinophilia and systemic symptoms, Eyelid rash, Toxic erythema of chemotherapy, Nodular rash, Vascular access site rash, Symmetrical drug-related intertriginous and flexural exanthema
Rhabdomyolysis	SMQ	Rhabdomyolysis/myopathy (SMQ) narrow
Systemic Immune Activation	PT	Systemic immune activation
	PT	Cytokine release syndrome
Immune-Related Meningitis	SMQ	Noninfectious meningitis (SMQ) narrow
Immune-Related Encephalitis	SMQ	Noninfectious encephalitis (SMQ) narrow

AESI	Reference Type (MedDRA v20.1)	Methodology
Immune-Related Ocular Inflammatory Toxicity	Sponsor defined AEGT	Atezolizumab Ocular Inflammation Toxicity AEGT consisting of the following PTs: Chorioretinitis, Choroidal detachment, Choroiditis, Episcleritis, Eye inflammation, Iridocyclitis, Iritis, Keratitis, Keratitis interstitial, Optic neuritis, Papillitis, Punctate keratitis, Retinal detachment, Retinal vasculitis, Retinitis, Retinopathy, Scleritis, Uveitis, Vitritis, Necrotising scleritis, Detachment of retinal pigment epithelium, Anterior chamber inflammation, Optic neuropathy, Retinoschisis, Corneal endotheliitis, Chorioretinopathy, Ulcerative keratitis, Necrotising retinitis, Ocular vasculitis, Rheumatoid scleritis, Ocular pemphigoid, Non-infectious endophthalmitis, Atopic keratoconjunctivitis, Detachment of macular retinal pigment epithelium, Autoimmune retinopathy, Diffuse lamellar keratitis, Noninfective chorioretinitis, Noninfective retinitis, Noninfective conjunctivitis, Autoimmune uveitis, Immune recovery uveitis, Superior limbic keratoconjunctivitis
Immune-Related Vasculitis	SMQ	Vasculitis (SMQ) narrow
Immune-Related Hypophysitis	HLT	Hypothalamic and pituitary disorders NEC
Immune-Related Myocarditis	Sponsor defined AEGT	Atezolizumab Myocarditis Immune-Related AEGT consisting of the following PTs: Eosinophilic myocarditis, Myocarditis, Autoimmune myocarditis, Hypersensitivity myocarditis
Immune-Related Severe Cutaneous Reaction	SMQ	Severe cutaneous adverse reactions (SMQ) narrow
Autoimmune Hemolytic Anaemia	SMQ	Haemolytic disorders (SMQ) narrow

AEGT = Adverse Event Group Term; AESI = adverse event of special interest; EGFR = epidermal growth factor receptor; HLT = High Level Term; MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified; PT = Preferred Term; SMQ = Standardized MedDRA Query.

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s019

STATISTICAL REVIEW(S)

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

NDA/BLA #:	BLA 761034
Supplement #:	19
Drug Name:	Atezolizumab
Indication(s):	Extensive-stage small cell lung cancer
Applicant:	F. Hoffmann-La Roche
Date(s):	Received Date: September 18, 2018
	PDUFA Date: March 18, 2019
Review Priority:	Priority
Biometrics Division:	V
Statistical Reviewer:	Jonathon Vallejo, PhD
Concurring Reviewers:	Lisa Rodriguez, PhD
	Rajeshwari Sridhara, PhD
Medical Division:	Division of Oncology Products 2
Clinical Team:	Luckson Mathieu, MD
	Erin Larkins, MD
	Patricia Keegan, MD
Project Manager:	Gina Davis, MT

Keywords: Overall survival

The statistical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. From a statistical standpoint, the proposed indication is supported by the application.

Reference ID: 4395585

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02/25/2019 04:00:05 PM

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02/25/2019 04:17:09 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761034Orig1s019

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 4, 2019

To: Gina Davis, MT, Senior Regulatory Health Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products

Stacy Shord, PharmD, Associate Director for Labeling, (DOP2)

From: Emily Dvorsky, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for TECENTRIQ® (atezolizumab) injection, for intravenous use

BLA: 761034/Supplement-019

In response to DOP 2's consult request dated February 6, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for TECENTRIQ® (atezolizumab) injection, for intravenous use. This supplement (S-019) allows for the indication of first-line treatment of extensive small cell lung cancer.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP 2 (Gina Davis) on February 22, 2019 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on March 1, 2019.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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/s/

EMILY M DVORSKY
03/04/2019 02:47:45 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 28, 2019
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TECENTRIQ (atezolizumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761034
Supplement Number:	S-019
Applicant:	Genentech, Inc.

1 INTRODUCTION

On September 18, 2018, Genentech, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 761034/S-019 for TECENTRIQ (atezolizumab) injection. With this supplement, the Applicant proposes to include a new indication for TECENTRIQ, in combination with carboplatin and etoposide, for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on February 6, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TECENTRIQ (atezolizumab) injection.

2 MATERIAL REVIEWED

- Draft TECENTRIQ (atezolizumab) injection MG received on September 18, 2018, and received by DMPP and OPDP on February 25, 2019.
- Draft TECENTRIQ (atezolizumab) injection Prescribing Information (PI) received on September 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 25, 2019.
- Approved TECENTRIQ (atezolizumab) injection labeling dated December 6, 2018.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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SUSANNAH O'DONNELL on behalf of EMILY M DVORSKY
03/01/2019 09:26:36 AM

BARBARA A FULLER
03/01/2019 09:32:51 AM

LASHAWN M GRIFFITHS
03/01/2019 09:51:18 AM