# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 125377Orig1s000

# SUMMARY REVIEW

# Addendum to Division Director Summary Review

| | |
|---|---|
| **Date** | March 24, 2011 |
| **From** | Patricia Keegan, M.D. |
| **Subject** | Division Director Summary Review |
| **BLA #** | STN BL 125377/0 |
| **Applicant Name** | BMS |
| **Date of Submission** | June 25, 2010 |
| **PDUFA Goal Date** | March 25, 2011 |
| **Proprietary Name / Established (USAN) Name** | Yervoy<br>Ipilimumab |
| **Dosage Forms / Strength** | Solution for injection in strengths of 50 mg/10 mL and 200 mg/40 mL |
| **Proposed Indication(s)** | "for the treatment of advanced melanoma (unresectable Stage III and Stage IV melanoma) in patients who have received prior therapy" |
| **Recommended Action for NME:** | Approval |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Addendum to Medical Officer Review | Kaushikkumar Shastri |

# Addendum to Division Director Summary Review

A March 18, 2011 addendum to the Medical Officer Review was generated describing re-analysis of safety results based on safety findings limited to a 4-dose treatment regimen and excluding data obtained in 40 patients who underwent a second course of ipiliumumab. The safety analyses, abstracted from the addendum to the medical officer review, are presented below:

**Incidence of Grade 3-5 Immune Mediated Adverse Reactions In Patients Receiving A Single Course of Treatment in MDX010-20**

| | Ipilimumab (n=131) | Ipilumumab +gp100 (n=380) |
|---|---|---|
| **Any Immune-mediated Adverse Reaction** | 15% | 12% |
| **Enterocolitis**[a,b] | 7% | 7% |
| **Hepatitis or hepatic failure**[a] | 1% | 2% |
| **Dermatitis**[a] | 2% | 3% |
| **Neuropathy**[a] | 1% | <1% |
| **Endocrinopathies** | 4% | 1% |
| Hypopituitarism | 4% | 1% |
| Adrenal insufficiency | 0 | 1% |
| **Other** | | |
| Pneumonitis | 0 | <1% |
| Meningitis | 0 | <1% |
| Nephritis | 1% | 0 |
| Eosinophilia[c] | 1% | 0 |
| Pericarditis[c] | 0 | <1% |

[a] Including fatal outcome.

[b] Including intestinal perforation.

[c] Underlying etiology not established.

**Incidence of Common (≥5%) Adverse Reactions and of Severe (Grade 3-5) Adverse Reactions In Patients Receiving A Single Course of Treatment in MDX010-20**

| | Percentage (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| | YERVOY 3 mg/kg n=131 | | YERVOY 3 mg/kg+gp100[a] n=380 | | gp100[a] n=132 | |
| **System Organ Class Preferred Term** | Any Grade | Grade 3-5 | Any Grade | Grade 3-5 | Any Grade | Grade 3-5 |
| **Gastrointestinal Disorders** | | | | | | |
| Diarrhea | 32 | 5 | 37 | 4 | 20 | 1 |
| Colitis | 8 | 5 | 5 | 3 | 2 | 0 |
| **Skin and Subcutaneous Tissue Disorder** | | | | | | |
| Pruritus[a] | 31 | 0 | 21 | 0.3 | 11 | 0 |
| Rash[a] | 29 | 1 | 25 | 2 | 8 | 0 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 41 | 7 | 34 | 5 | 31 | 3 |

[a] included appropriate combining/remapping of the preferred terms by the applicant

Dr. Shastri's review also summarizes the information provided in the February 24, 2011 amendment to the BLA, which characterized the time to onset of common immune-mediated toxicities, proportion of patients requiring steroids, and outcome (e.g.,resolved, improved, hospitalization, death). This information served as the basis for specific data provided in the Warnings and Precautions section of the final product label.

The Division Director review is also amended to note that, based on the February 25, 201 publication of the "Draft Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)", the Medication Guide for Yervoy (ipilimumab) is required as labeling but not part of a REMS. In discussions between the OND review staff and OSE, we have determined that the Medication Guide is not necessary to ensure the benefits of the drug outweigh its risks, and therefore has not been included as a component of the REMS.

## SIGNATURES PAGE

Patricia Keegan, M.D./s/
Patricia Keegan, M.D.
Director, Division of Biologic
Oncology Products
Office of Oncology Drug Products

March 24, 2011
Date

# Division Director Summary Review

| | |
|---|---|
| **Date** | March 12, 2011 |
| **From** | Patricia Keegan, M.D. |
| **Subject** | Division Director Summary Review |
| **BLA #** | STN BL 125377/0 |
| **Applicant Name** | BMS |
| **Date of Submission** | June 25, 2010 |
| **PDUFA Goal Date** | March 25, 2011 |
| **Proprietary Name / Established (USAN) Name** | Yervoy<br>Ipilimumab |
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| **Recommended Action for NME:** | Approval |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Regulatory Project Manager Review | Erik Laughner |
| Medical Officer Review | Kaushikkumar Shastri |
| Statistical Review | Yuan Li Shen |
| Pharmacology Toxicology Review | Andrew McDougal |
| Pharmacology Toxicology TL Review | Anne Pilaro |
| OBP Review | Subramanian Muthukkumar & Carla Lankford |
| OBP TL Review | Barbara Rellahan |
| Drug Substance Facilities Review | Kalavati Suvarna |
| Drug Product Facilities Review | Don Obenhuber |
| Clinical Pharmacology Review | Aakanksha Khandelwal |
| Pharmacogenomics Review | Christian Grimstein |
| Clinical Pharmacology TL Review | Hong Zhao |
| DDMAC | Carole Broadnax & Cynthia Collins |
| DSI | Lauren Iacono-Connors |
| OSE/DMEPA | Jibril Abdus-Samad & Todd Bridges, TL |
| OSE/DRISK - REMS | Joyce Weaver – Senior Drug Risk Management Analyst<br>Kate Heinrich- Health Education Reviewer<br>Suzanne Robottom, TL |
| OSE/DRISK _ Patient Labeling | Steve Morin – Patient Labeling Reviewer<br>Sharon Mills, TL<br>LaShawn Griffiths, TL |
| CDRH/CBER OBRR – PMA review | Donna Roscoe |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

# Division Director Summary Review

## 1. Introduction

Yervoy (ipilimumab) is a fully human IgG1 kappa monoclonal antibody that is directed against the human cytotoxic lymphocyte antigen-4 (CTLA-4) present on activated T-cells. The mechanism of action is believed to be through prevention of the inhibition of the interaction between antigen presenting cells (APCs) and T-cells. The CTLA-4 antigen on T-cells out-competes CD28 for binding to CD80/86 on APCs and induces a negative or inhibitory signal which acts to down-regulate T cell activity. Ipilimumab binds to CTLA-4, thus preventing its interaction with CD80/86. This results in potentiation or up-regulation of T-cell activity. It is believed that ipilimumab acts by permitting development of an immune response to tumor (self) antigens presented by APCs. This is also thought to be the primary mechanism of ipilimumab toxicity, an unintended pharmacologic effect of enhanced immune response to self-antigens presented by APCs. As noted by the applicant, "[b]locking CTLA-4 function may permit the emergence of immune-mediated adverse events that result in clinical syndromes resembling autoimmunity."

Cutaneous melanoma, arising from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin, with increasing rate of incidence in the latest decades. The National Cancer Institute estimates that in 2010 there will be 68, 130 new cases of melanoma and 8.700 deaths due to melanoma in the United States; based on trend analyses, the incidence of melanoma has been increasing over the past several decades. Current TNM melanoma staging is based on AJCC classification since 2001; refinements to the classification system include new prognostic features such as histopathologic ulceration in AJCC stages I and II and lymph node micro- and macrometastases in AJCC stage III. Manola and colleagues (J Clin Oncol 2000 Nov 15;18(22):3782-93) evaluated prognostic characteristics for metastatic melanoma based on a review of eight clinical trials conducted by ECOG, enrolling 1362 patients with metastatic melanoma. In this overview, the overall response rate was 12% and the median survival was 6.4 months. The following poor prognostic factors were identified across these trials: number of metastatic sites (relative risk [RR] 1.12), ECOG performance status of 1 or more (RR 1.49), and metastatic disease in the gastrointestinal (GI) tract (RR 1.49), liver (RR 1.44), pleura (RR 1.35), or lung (RR 1.19). Additional poor prognostic factors, based on three trials, were increased LDH, increased alkaline phosphatase, and Favorable prognostic factors were prior immunotherapy (RR = 0.84) and female sex (RR = 0. 87).

Dacarbazine and aldesleukin (interleukin-2) are the only FDA-approved treatments for treatment of metastatic melanoma. Commonly used off-label treatments include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens, and interferon alone or in combination with chemotherapy, as

well as investigational immunotherapy treatments. All currently used treatment approaches are characterized by low objective tumor response rates (<20%) and no evidence of improved survival.

A single double-blind, double-dummy, efficacy trial (MDX010-20) was submitted in support of this application. MDX010-20 was a randomized, double-blind, multicenter study conducted in HLA-A*0201-positive patients with Stage III or IV melanoma and who had relapsed/progressed after one or more of the following treatments: aldesleukin, dacarbazine, temozolomide, fotemustine, and/or carboplatin. Randomization was stratified for TNM status (M0, M1a, M1b vs M1c) and prior treatment with aldesleukin (IL-2); patients were randomized (3:1:1) to receive 3 mg/kg ipilimumab plus gp100 vaccine every 3 weeks, 3mg/kg ipilimumab plus vaccine placebo, or gp100 plus placebo (for ipilimumab), respectively. All study drugs were to be administered every three weeks for a total of 4 doses. The protocol allowed for a second course, termed "re-induction", with the assigned treatment regimen for subjects with an initial response of stable disease (SD) or better after induction with subsequent disease progression after study week 12.

The study met the endpoint for the revised primary efficacy analysis, demonstrating a statistically significant improvement in overall survival for the ipilimumab plus gp100 combination arm compared to the gp100 alone arm [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004} with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively. Specific issues raised during the review of this application are as follows

- Acceptability of the control arm
- Reliance on a single study
- Use of genomic, proteomic, or other "enrichment" strategies
- Revisions to the planned primary endpoint during the conduct of the study
- Adequacy or inadequacy of dose-finding; recommended doses
- Novel safety concerns
- REMS

With regard to the control arm, the applicant was asked to provide evidence that the gp100 peptide vaccine arm did not adversely affect survival, resulting in a spurious "improvement" for the ipilimumab arm as compared to the gp100 arm. Several pieces of evidence were provided, including evidence that the combination arm containing gp100 was not inferior to ipilimumab alone, literature reports of a randomized trial of interleukin-2 alone or with gp100 peptides, showing that survival was not adversely impacted with the addition of gp100 peptide vaccines as compared to interleukin-2 alone, and replication of the treatment effect of ipilimumab on overall survival in the high-level results of CA 184024.

With regard to use of a single study, the treatment effects on survival were statistically robust and consistent across relevant subgroups; however the effects on tumor response rate and on progression-free survival (efficacy endpoints traditionally considered supportive in clinical trials of patients with metastatic cancer) were very modest and did not provide direct evidence of efficacy.

With regard to the enrichment strategy, the study population was limited to patients with a single HLA phenotype, a subset for which there is no information regarding its prognostic relevance and for which, based on the trial design, the relationship to treatment effect could not be determined. The trial was designed to show that ipilimumab administered in combination with two HLA-A*0201-specific tumor peptides resulted superior anti-tumor activity (objective tumor shrinkage) as compared to peptide vaccination alone or ipilimumab alone. Since the peptides were designed for presentation to and recognition by the HLA-A*0201 molecule, enrollment was limited to the 50% of the general population with the HLA-A*0201 phenotype.

With regard to study conduct, the trial was revised shortly prior to unblinding, with modifications of the primary endpoint (from objective response rate to survival) and the primary comparisons (from comparisons of the single agents to the combination to comparisons of the ipilimumab-gp100 combination to the gp-100 peptide vaccine arm). This raised concerns regarding the maintenance of the study blind and potential for use of ongoing trial information to direct protocol modifications.

The availability during the review of high-level results from Protocol CA 184024, addressed two major deficiencies in the application, specifically reliance on a single study and extrapolation of results from a selected population to a general population. The results of CA 184024 demonstrated that treatment with ipilimumab resulted in improved survival, thus providing replication of the treatment effects from MDX010-20 and also provided information indicating that the treatment effect was not limited to patients with HLA-A*0201 phenotype. The CA 184024 results, in conjunction with a directed inspection of the applicant's study records, also alleviated concerns with late modifications to the protocol.

Issues with regard to the dose optimization, novel safety concerns, and the proposed REMS were satisfactorily addressed such that they do not preclude approval; however these issues require further assessment in the post-marketing setting. The issues are discussed in greater detail under sections 5 (Clinical Pharmacology) and 8 (Safety) of this review.

# 2. Background

The original developer for ipilimumab was Medarex, which submitted three INDs for clinical development in 2000: IND (b) (4) , IND 9186 for development of ipilimumab alone or in combination with chemotherapy for treatment of melanoma, and IND (b) (4) . Following the reorganization of CBER in 2003, with transfer of regulatory oversight of therapeutic biologics to CDER, INDs 9186 (b) (4) were transferred to CDER, while regulatory oversight of IND (b) (4) remained in CBER in the Office of Tissue, Cellular, and Gene Therapy as the primary mode of action under investigation in the IND (b) (4) In June

2004, ipilimumab was granted orphan drug designation of the treatment of melanoma. In 2005, Medarex transferred sponsorship of their INDs for ipilimumab to Bristol Myers Squibb (BMS). Key regulatory interactions regarding Protocol MDX010-20, Protocol CA 184024, and BL STN 125377 are summarized below:

*Protocol MDX010-20 regulatory history*

- Feb 23, 2004
  An end-of-Phase 2 (EOP2) meeting was held between CBER and Medarex to discuss the clinical development program intended to support a Biologics License Application (BLA) for ipilimumab at a dose of 3 mg/kg (b) (4)
- August 2004:
  Protocol MDX010-20 was accepted under a request for Special Protocol Assessment (SPA). The co-primary objectives of MDX010-20 were demonstration of efficacy of the ipilimumab/gp100 peptide combination through effects on best overall response rate and to demonstrate the independent contributions of the gp100 melanoma peptide vaccine and of ipilimumab. Key secondary objectives were assessment of overall survival and progression-free survival in the three study arms.
- Sept. 27, 2004
  MDX010-20 was "initiated" on September 27, 2004, with enrollment of the first patient. .
- November 2006
  Fast-track designation granted for second-line treatment of unresectable stage III or metastatic melanoma
- July 24, 2008
  Last patient enrolled.
- September 2008:
  (b) (4)
  BMS further stated their intent to withdraw the SPA agreement for Protocol MDX010-20. BMS also confirmed that no interim analysis had been conducted for MDX010-20.
- January 15, 2009:
  BMS modified Protocol MDX010-20 to change primary endpoint to OS
- October 29, 2009:
  A revised statistical analysis plan was submitted for MDX010-20. The major revisions included a change in the primary efficacy analysis to comparison of overall survival in the combination arm to that in the gp100 peptide vaccine arm with secondary objectives of comparison of survival in the combination arm to the ipilimumab alone arm and comparison of survival between the gp100 arm and the ipilimumab alone arm.
- Nov 13, 2009:
  BMS contacted CBER stating that the analysis of overall survival were significant and the results would be submitted to IND w/ OS results from ipilimumab vaccine study under CBER IND

- January 13, 2010:
  Type C meeting with BMS to discuss whether the results of Protocol MDX010-20 could be used as the sole study supporting an application for ipilimumab for the treatment of metastatic melanoma. BMS presented the results of MDX010-20 for comparisons of overall survival, best overall response rate, and progression-free survival between the combination ipilimumab and gp100 arm to the gp100 arm. BMS proposed submission of a BLA based primarily safety and efficacy data from Protocol MDX010-20 with supportive safety data Protocols CA184008, CA184007, CA184004 and CA184022. Key issues identified by FDA that would need to be addressed in a BLA were:

  - The gp100 "control" arm for MDX010-20 utilized an investigational product; BMS should provide data in the BLA which demonstrate that gp100 administration does not impair survival.
  - The BLA should include all known, relevant data regarding effects on survival; specifically, the high-level results of Study, CA184024.
  - Evidence of an effect on overall survival is limited to MDX010-20, conducted in an HLA-A*0201-restricted population. Expansion of labeling to an unrestricted population would be dependent on the results of CA184024.
  - The BLA should contain detailed information on the method(s) used to identify patients with HLA-A*0201 phenotype in MDX010-20 and plans for development of an assay for identification of patients with an HLA-A*0201 phenotype.
  - CDER would be the primary review center for a BLA supported by MDX010-20 (b) (4)

- March 4, 2010: Pre-BLA meeting held and following key agreements were reached:

  - The BLA should include all known, relevant data regarding effects on survival, including the high-level results of Study, CA184024. BMS agreed to provide the data in a manner that maintained the study blind for BMS staff.
  - Data from MDX010-20 alone would support an indication for HLA-A*0201-positive patients with previously treated melanoma.
  - Proposed product labeling should include a Boxed Warning for immune-related adverse events and the BLA should contain a proposal for a REMS
  - MDX010-20 data would support a proposed dose of 3 mg/kg every 3 weeks for four doses
  - The size of the proposed safety database (MDX010-20 results supplemented by data from CA184004, 184007,184008, and 184022) was acceptable to support a BLA filing.
  - Agreements were also reached regarding the proposed BLA contents for clinical pharmacology, nonclinical toxicology, and chemistry, manufacturing and controls data.

*Regulatory history of ipilimumab as monotherapy under IND 9186*

- Nov 28, 2005:
  An end-of-Phase 1 (EOP1) meeting was held to discuss the acceptability of the design of a single arm study, CA 184008, to determine if the results would support accelerated approval based on evidence of durable objective tumor responses; the key parameter of adequate activity was that the lower bound of the 95% confidence interval (CI) around the observed response rate should exclude a response rate of less than 10%. Protocol CA 184008 was designed to enroll 155 patients who had received at prior systemic therapy for treatment of metastatic melanoma and all patients were to receive ipilimumab at a dose of 10 mg/kg weekly.

  The proposed trial intended to verify clinical benefit was Protocol CA 184024, a randomized (1:1), double blind, placebo-controlled trial to be conducted in 500 patients receiving initial treatment for metastatic or unresectable melanoma. Patients would receive dacarbazine in combination with placebo/ipilimumab at a dose of 10 mg/kg weekly. The primary endpoint of this study was progression-free survival (PFS), with overall survival as a secondary endpoint.

- April 25 2008
  A pre-BLA meeting was held at which the results of CA 184008 were presented. **This study was reviewed under Special Protocol Assessment (SPA) for consideration of accelerated approval, 21 CFR 601.40 (Subpart E), for ipilimumab monotherapy in the second-line setting based on objective response rate as a surrogate endpoint. The prespecified agreement for overall response rate stated that** *"the lower boundary of the two-sided exact 95% confidence interval for the best overall response rate (BORR) will be at least 10% when 23 or more responses are observed (i.e. BORR ≥15.3%). Such observation would be considered clinically important."*

  (b) (4)

  BMS informed FDA that Protocol CA 184024 would now serve as the primary efficacy study in support of a BLA. In addition, BMS proposed to change primary endpoint from progression-free survival to overall survival for CA 184024. The amended protocol was submitted and FDA acknowledged the protocol amendment in 2009.

*Regulatory History of STN BL 125377*

- Application Received: June 25, 2010.
  A substantial number of amendments (more than 50) addressing FDA requests for additional information and analyses were submitted and one meeting held with the applicant during the BLA review period.
- Filed with priority review designation: August 16, 2010
- BMX submitted a proposal for submission of top line CA184024 overall survival data on August 16, 2010.
- FDA provided a written response on September 16, 2010, indicating that the proposal was acceptable. .

- 74-day Letter for deficiencies: September 7, 2010
- BMS 90-Day Safety Update Amendment: September 23, 2010
- The analysis of survival data from CA 184024 was performed and results presented to the Data Monitoring Committee during an *ad hoc* meeting held September 27, 2010 and these results were provided to a single individual within BMS. FDA received the top-line OS data from ongoing CA184024 trial on October 5, 2010.
- Receipt of major amendment on October 22, 2010; BMS notified via letter on October 28, 2010 of the extension of PDUFA goal date to March 26, 2011.

# 3. CMC/Device

I concur with the conclusions reached by the quality review team regarding the acceptability of the manufacturing of the drug product and drug substance. Ipilimumab is a full length IgG1 kappa fully human monoclonal antibody that is directed against the human cytotoxic T-lymphocyte antigen 4 (CTLA-4), also characterized as CD152. It is produced through (b) (4) Chinese Hamster Ovary (CHO) cell line (b) (4) Based on the quality and facilities reviews, the manufacturing process is adequately described and contains appropriate quality controls. Manufacturing site inspections for drug substance were acceptable; inspections were waived for drug product due to recent acceptable inspection of this facility in 2009. The final drug product is sterile, pure, and potent and is supplied as a liquid for intravenous infusion in vials of 50 mg/mL and 200 mg/40 mL. Stability testing supports an expiry of 36 months at 2-8°C for the drug product. The quality reviewer determined that the product met the requirements for categorical exclusion from environmental assessment. There are no outstanding quality issues which would preclude approval however the FDA and BMS have agreed-upon several non-506B post-marketing commitments to enhance product quality. In addition, post-marketing requirements have been identified for development and validation of assays capable of detecting anti-product antibodies in the presence of ipilimumab (see Section 5 of this review).

# 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding nonclinical pharmacology or toxicology issues that preclude approval. The applicant provided a summary of *in-vitro* and *in-vivo* studies assessing the pharmacodynamic properties of ipilimumab. The pharmacodynamic data indicated that administration of ipilimumab with various novel antigens resulted in an augumented humoral and cellular (as manifested by delayed-type hypersensitivity) as compared to vaccination alone.

Non-clinical studies were limited to non-human primates as these were the only relevant animal models and the non-clinical studies conducted were generally of short duration, which may have been insufficient exposure to allow for development or observation of an

immune response, which is necessary in order to observe toxicity for this product. Of the 66 cynomolgus monkeys evaluated for more than 3 months, only ten monkeys were evaluated for up to 6 months. These animals received 5 doses, once per month, with a one-month recovery period. An additional limitation of the non-clinical program was the lower affinity of the ipilimumab for cynomolgus CTLA-4 as compared to human CTLA-4. The non-clinical studies generally under-represented the toxicity of ipilimumab as compared with the human clinical trial experience. Although nearly all animals were asymptomatic with multiple doses of 3 mg/kg and 10 mg/kg, there was evidence of leukocytic infiltration of organs on histopathology consistent with the expected pharmacology. Given the proposed indication, and in accordance with current ICH Guidances, carcinogenicity and mutagenicity studies were not required. Safety pharmacology studies for cardiac effects did not reveal drug-related findings.

The major finding of concern identified in non-clinical studies were derived from the interim results of an ongoing reproductive toxicology study, which revealed an increased incidence of third-trimester spontaneous abortions, stillbirths, and premature delivery in pregnancy cynomolgus monkeys treated with ipilimumab from gestation day 20 through parturition as compared to controls. A post-marketing requirement to submit the final study report has been established, in order to further evaluate the possible mechanism for third-trimester losses.

# 5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The proposed dose is 3 mg/kg administered as an intravenous infusion over 90 minutes, every 21 days for a total of four doses. Detailed pharmacokinetic sampling was performed only in studies which used an earlier manufacturing process and utilized a different assay. The data characterizing pharmacokinetics with the current manufacturing process were obtained by BMS in sparse PK sampling across multiple single-arm and one dose-ranging trial but not in the major efficacy trial. Sparse PK sampling demonstrate that the pharmacokinetics of ipilimumab are linear over the doses evaluated in clinical studies (0.3, 3, and 10 mg/kg) with an elimination half-life of 15 days and steady state achieved after the third dose. Clearance of ipilimumab is affected by body weight, however the recommended dose is adjusted by body mass and no additional adjustments based on weight are necessary. The pharmacokinetics of ipilimumab are not affected by renal or hepatic function or by age or gender. There were insufficient numbers of non-White patients to assess for differences in pharmacokinetics based on race. There was no indication that pharmacokinetics is affected by HLA-A*0201 phenotype in exploratory analyses of patients retrospectively evaluated for HLA type.

The dose-response relationship of ipilimumab is inadequately characterized, having been limited to a single dose-ranging trial that evaluated objective tumor response as the

primary endpoint at the primary endpoint in patients with metastatic melanoma. This trial did not suggest that there were important dose-response differences between the 3 mg/kg and the 10 mg/kg doses for the outcomes of response rate or survival, which may have been difficult to detect given the very low response rate across all groups and the relatively short survival times in this disease. However there was evidence of an increased rate of severe toxicity in patients receiving 10 mg/kg as compared to those receiving 3 mg/kg ipilimumab. Exploratory analyses pooling data from dose-ranging or single-arm studies in which sparse pharmacokinetic sampling was conducted suggest a possible relationship between exposure and survival. These analyses are confounded by between-study differences in patient populations and by imbalances in important prognostic factors across subgroups (quartiles or tertiles) defined by exposure, which may account for all observed differences in survival outcomes. It remains unclear whether 3 mg/kg or 10 mg/kg every three weeks is the optimal dose, defined as the dose providing lowest risk in light of the survival benefit. Therefore, FDA has required that a dose-comparison study be performed to characterize the relative risks and benefits of these two doses, as described under the post-marketing required studies at the end of this summary review.

Assessment for anti-product antibody responses was conducted in the clinical development program. A low incidence of anti-product antibodies were detected, however this finding is not considered reliable because of the interference of circulating ipilimumab with the assay results. Interpretation on the impact of immunogenicity on safety is limited due to the small number of patients with serologic evidence of an anti-product antibody response.

ECG monitoring was conducted in 25 patients receiving 3 mg/kg and 32 patients receiving 10 mg/kg, with triplicate serial ECGs obtained at baseline, and pre- and post-infusion on dose 1 and dose 4 in Protocol CA184004. No clinically meaningful changes from baseline in heart rate, or in QRS, PR, or QTc intervals were identified in this assessment.

FDA also evaluated the results submitted by the applicant for exploratory analyses of the relationship between genetic factors and risks or benefits. Based on DNA samples collected in patients enrolled in CA184004, CA184007, CA184008, or CA184022, an assessment for correlations was conducted between immune-related gene variants and the incidence or severity of immune-related adverse events were assessed. FDA confirmed the applicant's analyses, which identified an association between a missense mutation in CD86 (rs2681417) with increased relative risk of enterocolitis. As noted by the pharmacogenomics reviewer, these analyses were exploratory and the strength of the associations were limited by 1) lack of uniform DNA sample acquisition across all patients enrolled in these four trials; 2) no DNA samples obtained in MDX010-20; 3) lack of justification for candidate gene/SNP selection; 4) limited numbers of patients treated with doses other than 10 mg/kg; and 5) lack of a uniform criteria in the four trial for defining an immune-related adverse events. Given these limitations, this information was not included in product labeling, however a post-marketing requirement has been

established to further assess the relationship between the missense mutation encoding for CD86 and the incidence/severity of immune-related adverse events.

# 6. Clinical Microbiology

No clinical microbiology data were provided in this application. Microbiology assessments conducted as part of product assessment were evaluated by the CMC review team.

# 7. Clinical/Statistical-Efficacy

The determination of efficacy was supported primarily by the results of Protocol MDX010-20, the details of which will be summarized in greater detail in this section. In addition, at FDA's request, the high-level survival results for Protocol CA 184024 were supplied in order to provide replication of the treatment effects observed in MDX010-20 as well as to address FDA's concerns regarding the ability to extrapolate of the results of MDX010-20 to an unselected population (i.e., patients with other HLA phenotypes). Since the full results of CA 184024 were not provided, the trial design and survival data will be summarized in less detail. The results of single-arm trials and dose-ranging trials do not provide substantial support for product efficacy based on the very low response rates observed both in these studies and across the entire development program in metastatic melanoma. These additional single-arm trials were evaluated primarily for characterization of safety and are discussed in more detail in Section 8 of this review.

Protocol MDX010-20: "A Randomized, Double-Blind, Multicenter Study Comparing MDX-010 Monotherapy, MDX-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A*0201-Positive Patients with Previously Treated Unresectable Stage III or IV Melanoma."

*Study Design:*
The trial design was a placebo-controlled, double-blind, double-dummy trial with unbalanced allocation (3:1:1) to one of three treatment arms. Randomization was stratified for tumor stage (M0, M1a. or M1b vs. M1c) and prior interleukin-2 therapy (yes/no). Key eligibility criteria included metastatic melanoma with measurable disease, HLA-A*0201 phenotype, evidence of disease progressive following one or more cycles of IL-2, dacarbazine, temozolamide, fotomustine or carboplatin containing regimen *or* inability to tolerate prior therapy due to unacceptable toxicity. Patients with any of the following were ineligible for enrollment: primary ocular melanoma, untreated CNS metastases (patients with CNS metastases that were stable following appropriate local treatment were eligible), history of autoimmune disease, an active second primary cancer,

*Treatment plan:*
- Ipilimumab at a dose of 3 mg/kg administered as an IV infusion over 90 minutes and gp100 melanoma peptide vaccine administered in two divided doses by deep

subcutaneous injection. Treatment was to be administered every three weeks (study days 1, 22, 42, and 64) for a total of 4 treatments or until completion of 16 weeks on study, whichever occurred earlier.

- Ipilimumab 3 mg/kg as an IV infusion every three weeks with vaccine placebo injections, administered every three weeks for 4 treatments.
- Placebo (for ipilimumab) administered as an IV infusion and gp100 peptide vaccine by deep subcutaneous injection administered every three weeks for 4 treatments.

The gp100 melanoma peptide vaccine consisted of (b) (4) One mL of each peptide was to be administered in emulsion of incomplete Freund's adjuvant as a deep subcutaneous injection into right and left thigh for a total of 4 injections at each administration.

The protocol permitted administration of a second course of study drug/placebo beginning on or after week 24 in patients with no significant toxicity and who achieved stable disease for a minimum of three months following the end of first course (between weeks 12 to 24) or patients or a complete or partial response by week 24.

*Protocol-specified dose modifications:*
Patients were encouraged to remain until week 12, even in the presence of disease progression, provided that the rate of progression was not rapid, that disease progression not symptomatic, and that performance status remained stable. If new visceral lesions were identified prior to study week 12, the investigator and the Medarex medical monitor were to confer on whether to continue treating patient.

Treatment was allowed to continue for any of the following: potentially reversible inflammation of Grade 3 or lower if attributed to a local antitumor reaction that could potentially be a therapeutic response (e.g., inflammatory reactions at sites of tumor resection, draining lymph nodes, or sites of metastatic disease); hospitalization for Grade 1 or 2 adverse events where the primary reason for hospitalization was to expedite the work-up; and in patients with immune-mediated endocrinopathies where clinical symptoms were controlled with hormone replacement therapy.

Study drug/placebo were to be delayed for "drug-related" Grade 2-3 skin or immune-mediated toxicity until the adverse event had fully resolved or improved to Grade 1 severity. Treatment was not to be restarted while a patient was receiving systemic corticosteroids with the exception of stable doses of hormone replacement therapy.

Gp100 peptide vaccine/placebo was to be delayed or discontinued if ipilimumab/placebo was delayed or discontinued.

Treatment was to be discontinued for Grade 4 skin or immune-related toxicity or for other toxicities that were Grade 3 or higher in severity and for progressive disease beyond week 12.

*Study monitoring*
During study drug administration, monitoring included physical examination, pharmacokinetic and pharmacodynamic sampling, ECOG performance status evaluation, clinical laboratory testing, and the collection of treatment-emergent adverse events. All adverse events (AEs) were to be reported through 70 days following the last dose of study treatment, or until adverse events resolved or stabilized; AEs occurring > 70 days following the last dose of study treatment and assessed by the investigator as probably or definitely related to study medication were also to be reported.

Tumor measurements were obtained at baseline with restaging at week 12. For those with stable or responding disease, tumor restaging was performed again at weeks 16, 24, and every three months thereafter until investigator-determined disease progression. Responses were determined by the investigator utilizing modified WHO criteria. In addition, patients who asymptomatic disease progression prior to week 12 were permitted to remain on study and be considered for response at later timepoints, based on the premise that such increases in tumor might occur with inflammatory response leading to "tumor flare" and anecdotal reports of delayed responses after initial disease progression.

Patients with disease progression were to be followed for survival status by telephone every 3 months.

*Statistical analysis plan*
In the final version of the protocol and final analysis plan, the primary objective was to compare the overall survival between the ipilimumab and gp100 melanoma peptide vaccine combination arm and the ipilimumab placebo and melanoma peptide vaccine. Secondary objectives included comparison of survival between the ipilimumab/gp100 combination arm and the ipilimumab/placebo arm, best overall response rate, major durable response rate, duration of response, progression-free survival, time-to-progression, health-related quality of life, and toxicity profile.

Due to the change in the primary endpoint, the final sample size was adjusted to account for analysis of the primary objective. On the basis of a simulation using the collected blinded survival data from this study and historical literature data, a total of 385 events and a total of 500 enrolled patients in the two arms (at the 3:1 ratio) would be expected to achieve a 90% power to detect a difference in survival between these two treatment arms at the 0.05 significance level using the log-rank test.

**Results**
MDX010-20 was "initiated" on September 27, 2004, with enrollment of the first patient. The last patient was enrolled on July 24, 2008, and the study was considered 'completed" on October 7, 2009. A total of 1783 patients were evaluated in the screening phase of Protocol MDX010-20; of these 676 patients were randomized (403 subjects to ipilimumab plus gp100, 137 to ipilimumab monotherapy, and 136 to gp100 monotherapy) and included in the intent to treat (ITT) population. The safety analysis population consists of 643 patients who received at least one dose of study drug and are analyzed "as treated" rather than "as randomized". The safety population consists of 380

patients who received ipilimumab plus gp100, 131 who received ipilimumab alone, and 132 patients who received gp100 alone) and included in the safety, as treated population. One patient who was randomized to ipilimumab plus gp100 instead received ipilimumab placebo plus gp100 (i.e., gp100 alone).

Regarding study conduct, several areas of concerns were identified during the BLA review. As noted by the statistical reviewer, there were some inconsistencies between the disease characteristics as recorded at randomization and those recorded on case report forms. Analytic results were similar regardless of which source was used for stratification variables in stratified log-rank tests, thus the statistical reviewer utilized the data in the randomization tables in presenting data. A large number of queries were required to resolve address inability to replicate analysis results, requiring submission of additional analysis programs or based on the failure to provide information in all analysis datasets or all analysis programs. In addition, based on queries regarding inconsistencies between case narratives and analysis datasets, the applicant stated that case narratives had not been fully quality controlled, and that analysis datasets should be relied upon as more reliable than the case narratives. Finally, the Division of Scientific Integrity determined that data from one of the clinical trial sites (Site 0301) was not reliable and that a decision regarding approvability should not considered this information. Analyses excluding these data were consistent with the full dataset.

In the ITT population, the median age of the study population was 57 years, with 29% age 65 years or older. Slightly more than half the patients (59%) were male, approximately 94.4% were White and 4.4% were Hispanic. Regarding stratification variables, 71% of patients had stage M1c disease at study entry and approximately three-quarters (77%) had not received prior interleukin-2 therapy. With regard to other prognostic characteristics, 38% of patients had elevated LDH (above the upper limit of normal), 12% had CNS metastases and 1.5% had an ECOG performance status of 2 or 3. Approximately half the patients were enrolled at clinical sites in North America, 40% at sites in Europe, and 10% from other geographic regions.

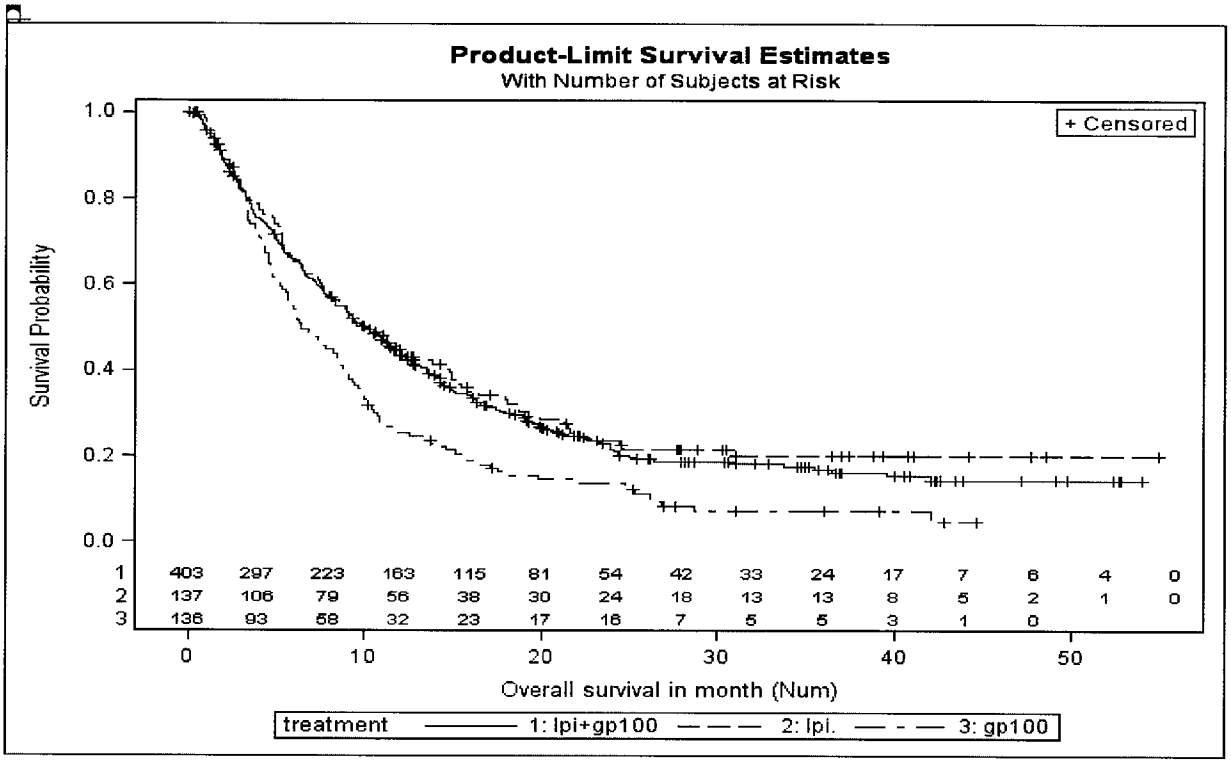
*Overall Survival*

The data cut-off data for the final analysis was June 19, 2010, at which time there were 525 deaths and a median follow-up of 8.9 months. The final analysis of overall survival demonstrated a statistically significant increase in overall survival for the ipilimumab plus gp100 combination arm compared to the gp100 arm alone. These results are displayed in the table below, abstracted from Dr. Shen's review, and are displayed in the Kaplan-Meier curves in the figure below. The secondary analyses of overall survival also indicate that there is a longer survival for the ipilimumab alone arm compared to the gp100 arm and no apparent differences in survival between the ipilimumab plus gp100 combination arm and the ipilimumab alone arm. Since there was no alpha allocation between these two secondary analyses, and one of these analyses was not significant, the p-values in the table below are considered nominal and not definitive. In a series of subgroup analyses, there was no evidence of substantial differences in treatment effect on overall survival, based on subgroups defined by gender, age, baseline tumor prognostic characteristics, or geographic region of the world.

**Table 4 Summary of Overall Survival Results (using data from randomization list)**

| | Ipi+gp100 N=403 | Ipi N=137 | gp100 N=136 | Total N=676 |
|---|---|---|---|---|
| Number of events | 306 | 100 | 119 | 525 |
| Median (months) [a] | 9.95 | 10.12 | 6.44 | 9.10 |
| 95% CI for median [a] | (8.48, 11.50) | (8.02, 13.80) | (5.49, 8.71) | (8.31, 10.12) |
| HR vs. gp100 with 95% CI [b] | 0.68 (0.55, 0.85) | 0.66 (0.51, 0.87) | | |
| Log-rank p value vs. gp100 [b] | 0.0004 | 0.0026 | | |
| HR vs. ipi alone with 95% CI [b] | 1.04 (0.83, 1.3) | | | |
| Log-rank p value vs. ipi alone [b] | 0.7575 | | | |

[a] 95% confidence intervals (CI) for median were computed using Brookmeyer and Crowley method.
[b] Cox model for Hazard ratios (HR) and log-rank test p-values were stratified by baseline M-stage at randomization (M0, M1a, M1b vs. M1c) and prior treatment with IL-2 (Yes vs. No) using the data from the randomization. 95% confidence intervals (CI) for HR were computed using Cox model.




*Secondary endpoints*

The key secondary efficacy endpoints in Protocol MDX010-20 were progression-free survival and best overall response rates. The objective response rates in this trial were low across all treatment arms and do not provide substantial evidence supporting the clinical effectiveness of ipilimumab. Similarly, progression-free survival times were very short (median survivals of less than 3 months) across all three treatment arms and do not provide substantial evidence supporting the clinical effectiveness of ipilimumab. These data, abstracted from Dr. Shen's review, are presented in the following table.

| | Ipilimumab + gp100 (n=403) | Ipilimumab (n=137) | gp-100 (n=136) |
|---|---|---|---|
| BORR | 5.7% (23/403) | 10.9% (15/137) | 1.5% (2/136) |
| (95% CI) | (3.7, 8.4) | (6.3, 17.4) | (0.2, 5.2) |
| Nominal p-value[1,2] | 0.0433 | 0.0012 | |
| Progression-free survival | | | |
| Median (mos) | 2.76 | 2.86 | 2.76 |
| Hazard Ratio[1] | 0.81 | 0.64 | |
| (95% CI) | (0.66, 1.00) | (0.50, 0.83) | |
| Nominal p-value[1,3] | 0.0464 | 0.0007 | |

[1] compared to gp100 arm

[2] CMH test stratified by M-stage and prior IL-2 therapy

[3] log-rank test stratified by M-stage and prior IL-2 therapy

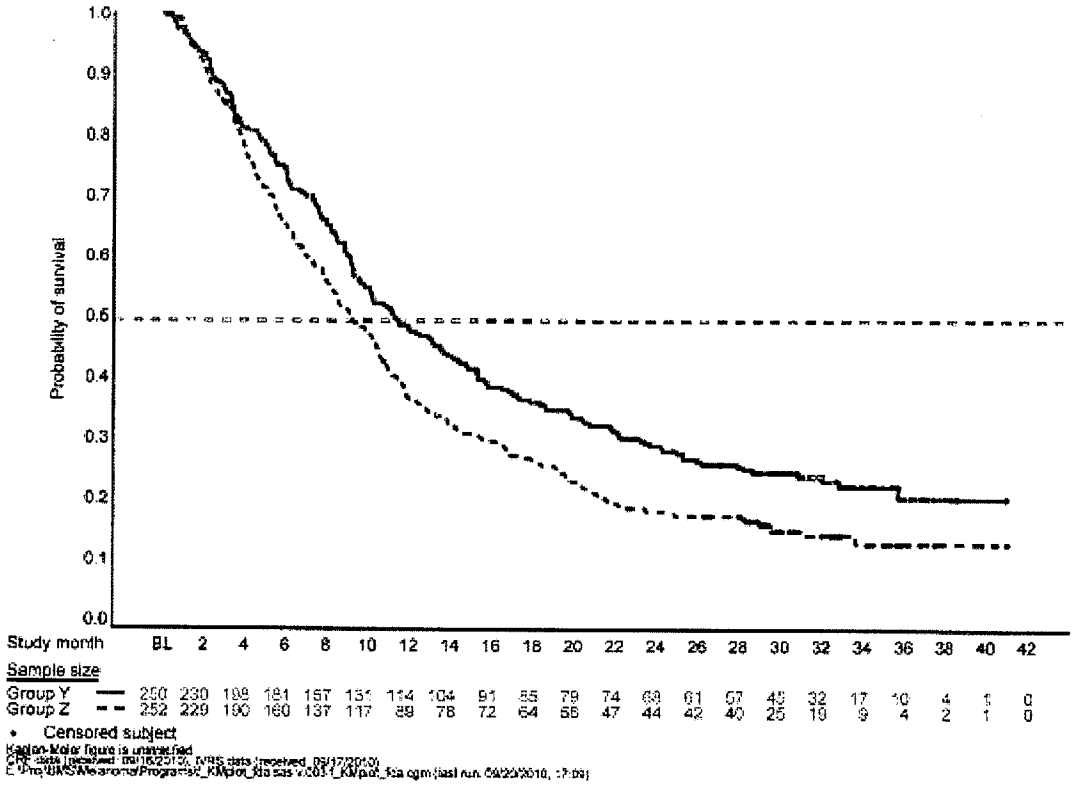
*Replication of treatment effect*
As noted in the background section of the review, FDA requested the near final results of Protocol CA 184024 to provide supportive evidence of the reproducibility of the findings of MDX010-20 on overall survival and to provide insight into whether treatment effects might be different in the HLA-A*0201-restricted population as compared to an unselected population.

Protocol CA184024 is a multi-center, randomized, double-blind, two-arm, clinical trial that enrolled patients with unresectable AJCC stage III or metastatic melanoma who had received no prior systemic therapy for metastatic or unresectable disease. The study was designed to enroll 500 patients who were equally allocated to receive dacarbazine at standard doses plus ipilimumab at a dose of 10 mg/kg intravenously every 3 weeks or dacarbazine with placebo. The primary efficacy endpoint of overall survival is to be analyzed after 416 deaths to provide 90% power to detect an improvement in overall survival with a hazard ratio of 0.727 at a two-sided alpha of 0.05. Sample size assumptions were that the median survival would be 8 months in the control arm and 11 months in the dacarbazine plus ipilimumab arm.

The high level results of Protocol CA 184024 were provided at FDA's request; this analysis conducted based on approximately 97% of the planned number of events for the final (and only) analysis of survival. FDA informed BMS that the analysis requested could be provided without need for a penalty for an unplanned look because the results where being provided at FDA's request.

At the time of the analysis, there were (b) (4) deaths among the 502 patients enrolled in this trial. The results were show an improvement in overall survival [HR 0.85 (95% CI: 0.76, 0.93)] with a nominal p-value of 0.001, stratified log-rank test. BMS provided the analysis program and datasets, which allowed Dr. Shen to confirm these analysis results. The Kaplan-Meier curves for overall survival in this trial are similar to those in MDX010-20 in showing a relatively early separation of the curves and that is maintained throughout later timepoints.

Figure 1. **Kaplan-Meier curve: overall survival**




# 8. Safety

The size of the safety database was sufficient to characterize toxicity in support of licensure. I concur with the proposal by BMS and recommendations of the clinical reviewer, that a REMS containing a communication plan for healthcare providers on the unique risks of this novel agent and recommended patient management is necessary and appropriate to mitigate risks to human subjects. In addition, I concur with recommendations for additional post-marketing requirements to determine the relative risks and benefits of the 3 mg/kg and the 10 mg/kg dosing regimens, further characterization of the potential genetic marker (mis-sense mutation encoding for CD86) that may be associated with an increased risk of toxicity, and requirement for a sensitive assay and more reliable characterization of the incidence anti-ipilimumab antibody development following exposure to ipilimumab.

Analysis of the safety of ipilimumab, when administered at a dose of 3 mg/kg every three weeks for 4 doses, relies primarily of data collected in Protocol MDX010-20, in which 511 patients received ipilimumab alone (n=131) or in combination with gp100 (n=380) and 132 patients received gp100 vaccine. One patient who was randomized to

ipilimumab plus gp100 instead received ipilimumab placebo plus gp100 (i.e., gp100 alone). Additional safety information, characterizing immunogenicity and serious adverse events, was obtained in studies 184004, 184007, 184008, and 184022. Study CA184022, a randomized dose-ranging trial of 0.3, 3, and 10 mg/kg, also provides information regarding the dose-toxicity relationship. The design of the these four studies is briefly summarized below:

Supportive Safety Studies

- CA184022: Conducted in 214 patients with previously treated advanced melanoma. The study design was a double-blind, randomized, three-arm trial, in which patients were randomized to receive ipilimumab at doses of 0.3 mg/kg (n=72), 3 mg/kg (n=71) or 10 mg/kg (n=71) every three weeks for 4 doses, followed by the same dose administered every 12 weeks. The primary objective was characterization of best overall response rate.
- CA184008: Conducted in 155 patients with previously treated advanced melanoma. The study design was a single arm trial, in which patients received ipilimumab at a dose of 10 mg/kg every three weeks for 4 doses, followed by 10 mg/kg administered every 12 weeks. The primary objective was characterization of best overall response rate.
- CA184004: Conducted in 82 patients with either previously treated or previously untreated advanced melanoma. The study design was a double-blind, randomized study to assess potential predictive biomarkers for response in which patients were randomized to receive ipilimumab at a dose of 3 mg/kg (n=40) or 10 mg/kg (n=42)
- CA 184007: Conducted in 115 patients with previously treated or untreated advanced melanoma. The study design was a double-blind, randomized trial in which patients were randomized to receive ipilumumab at 10 mg/kg either with (n=57) or without budesonide (n=58). The objective of the study was to assess the effects of concurrent corticosteroid administration on safety and activity.

As noted by the applicant, blocking CTLA-4 function through ipilimumab permits the emergence of immune-mediated adverse events that result in clinical syndromes resembling autoimmunity. At the time of initiation of MDX010-20, the following adverse reactions were identified as drug-related, immune-mediated events which would be specifically identified and further characterized in this trial: rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypopituitarism. Protocol MDX010-20 stated that an immune-related adverse event (irAE) would be defined as an adverse event of unknown etiology, associated with drug exposure, and consistent with an immune phenomenon. Investigators were instructed to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as a clinically significant systemic (e.g., systemic lupus erythematosus-like diseases) or organ-specific irAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). In addition, investigators were instructed to obtain serological, immunological, and histological (biopsy) data to support the diagnosis of an immune-mediated toxicity.

As noted in Dr. Shastri's and Dr. Shen's review, analysis of safety was challenging due to discontinuation of use of a case report form during the conduct of MDX010-20 which

was specifically designed to capture information on immune-related adverse events and failure to further follow the agreed-upon analysis plan for identification of immune-related events, as discussed with FDA in the pre-BLA meeting. In addition, many of the supportive documents (hospital summaries, pathology reports) were not contained in the BLA and the case narratives were not reliable per the applicant. While most of these deficiencies were address through information requests, characterization of the duration and of assurance of complete resolution of immune-related adverse reactions is suboptimal, and will need to be ascertained in the trial of 3 mg/kg vs. 10 mg/kg identified as a post-marketing requirement.

Protocol MDX010-20 contained directions for patient management in the event of an immune-related adverse event but also referenced the treatment algorithm in the current investigator brochure for ipilimumab, which was changed during the course of MDX010-20. Therefore, patients were not managed in a uniform manner for toxicity. In general, these instructions recommended a dose-delay for NCI CTCAE version 3 grade 2 or moderate toxicity, with institution of palliative treatment and, if unresolved, systemic steroids. For grade 3 or greater toxicities, the recommendation was to permanently discontinue both study drugs (ipilimumab, gp100 or their placebos) and to institute systemic corticosteroid, with one exception. Patients with grade 3 or 4 endocrinopathies were allowed to resume study treatment on resolution of toxicity with hormone replacement therapy.

There was no attempt, other than in Protocol 184007 where corticosteroids were administered prophylactically, to study the efficacy of corticosteroid therapy in managing immune-related adverse events. However a review of case narratives suggests that systemic corticosteroids are useful in reducing the severity of such adverse reactions. There is insufficient information on the use of other immunosuppressive agents (e.g., infliximab, mycophenolate, anti-thymocyte globulin) to determined their utility in the management of adverse reactions that do not respond or are inadequately controlled by corticosteroids.

As noted above, safety information for ipilimumab at the proposed dose and schedule is supported by data from 131 patients (median age 57 years, 60% male) who received ipilimumab as a single agent and 380 patients (median age 56 years, 61% male) who received ipilimumab with an investigational gp100 peptide vaccine (gp100), in comparison to the safety experience in 132 patients (median age 57 years, 54% male) who received gp100 peptide vaccine alone. Patients enrolled in MDX010-20 received a median of 4 doses of study medication. Iplimumab treatment was discontinued prematurely in 10% of patients for adverse reactions. The most common adverse reactions, by preferred term, leading to study drug discontinuation in the ipilimumab plus gp100- and ipilimumab-treated patients were colitis [10 (2.6%) and 3 (2.3%) patients, respectively] and diarrhea (10 (2.6%) and 2 (1.5%) patients, respectively].

The most common adverse reactions among patients who received ipilimumab at a dose of 3 mg/kg every three weeks for up to 4 doses were fatigue, diarrhea, pruritus, rash, and colitis. The following table lists those discrete preferred terms which occurred in at least

5% of ipilimumab-treated patients (1% for grade 3-5 adverse reactions) and at a higher incidence in patients who received ipilimumab than in those who received only gp100.

[Note: additional analyses limited to adverse reactions occurring only in conjunction with the initial 12-16 week treatment course are pending at the time of this review. The numbers in the tables below may be updated in product labeling to reflect these additional analyses]

(b) (4)

The following table presents the per-patient incidence of severe, life-threatening, or fatal immune-mediated adverse reactions reported in MDX010-20.


Characterization of common immune-related adverse reactions, abstracted from the proposed package insert, are summarized further below. Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appears to be dose dependent.


In addition, the clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients in MSX010-20: fatal Guillain-Barré syndrome, peripheral motor neuropathy nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia. Across the clinical development for ipilimumab, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

*Anti-product antibody Responses (Immunogenicity)*
In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. This assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected.

The incidence of anti-product antibodies is likely to have been underestimated due to the limitations of assay sensitivity in the presence of circulating ipilimumab. In a subset analysis of patients who received 0.3 mg/kg, 6.9% of 58 evaluable patients tested positive for binding antibodies against ipilimumab.

# 9. Advisory Committee Meeting

Advice regarding the approvability of this application was not sought from the Oncologic Drugs Advisory Committee since demonstration of overall survival in two controlled, clinical trials provided sufficient evidence of clinical benefit, particularly in this malignancy where there is currently no highly effective treatment. Evidence of improved survival also provides assurance that the benefits generally outweigh the risks. .

# 10. Pediatrics

The safety and efficacy of ipilimumab have not be evaluated in pediatric patients. Ipilimumab for the treatment of metastatic melanoma, was designated as an orphan drug product and is therefore exempt from the requirements of the Pediatric Research and Equity Act.

# 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

# 12. Labeling

[Note: Labeling negotiations for physician labeling, Medication Guide, and REMS template are ongoing at the time of this review]

- Proprietary name: I concur with the recommendation by DMEPA and the clinical reviewer that the proprietary name of YERVOY is acceptable.

- Physician labeling (major issues that were discussed, resolved, or not resolved)
  - Indications and Usage
    BMS proposed Indication was not limited to patients with HLA-A*0201-; FDA accepted this proposal based on the high-level results of CA 184024 rather than the exploratory retrospective analyses based on uncontrolled single arm studies. In addition, based on the results of CA 184024 and the lack of highly effective therapies for initial treatment of metastatic melanoma, the indication was written broadly to encompass this population. Dosage and Administration
  - Dosage Forms and Strength
    - This section was extensively revised to brevity and clarity.

(b) (4)

- Information regarding routine patients monitoring for, and treatment of, adverse reactions was moved to the appropriate Warnings and Precautions subsections
- Preparation for Administration subsection retitled (Preparation and Administration); (b) (4)

- Contraindications
  No modifications to proposed labeling
- Warnings and Precautions
  - The term (b) (4)' was replaced with "immune-mediated" to describe adverse reactions of ipilimumab.
  - Extensively revised to include information on incidence of Grade 2 and Grade 3-5 events identified using agreed-upon case definitions and time to onset updated based on new case definitions for immune-related adverse events. Data on time to resolution was not adequately captured on the case report forms to permit detailed characterization, resolution of immune-mediated adverse reactions provided in general terms and characterized by the proportion of patients with improvement or resolution.
  - Revised to include a description of severe and fatal outcomes, and description of the patient management actually employed in clinical study, MDX010-20.
  - Specific information on use of alternative immunosuppressant regimens for patients with an inadequate response were described based on data obtained in MDX010-20 or other studies replaced vague language on (b) (4) of such alternative treatments

(b) (4)

- Adverse Reactions
  - Limited tables describing adverse events to those with controlled studies.

(b) (4)

(b) (4)

- Added data noting the apparent relationship and risk of immune-mediated enterocolitis and immune-mediated hepatitis.
- Immunogenicity subsection revised to include standard language per FDA Guidance for Industry and regulations. Also revised to note the insensitivity of the assay results in the presence of circulating ipilimumab as well as results of higher anti-product antibody responses identified at lower (0.3 mg/kg) doses.

- Drug Interactions
  Edited for brevity and consistency with product labeling for monoclonal antibodies
- Use in Specific Populations
  - Subsections 8.1and 8.3 modified as request by the maternal fetal health team reviewer; non-clinical data moved to section 13 of the labeling
  - Subsection on Geriatric Use – minor editorial changes only
  - Subsections on Renal and Hepatic Impairment modified in accordance with standard language and recommendations by Clinical Pharmacology staff
- Overdosage:
  - Modified to reflect available data. As noted by Dr. Shastri, the application does not contain the primary safety data from studies in which patients received 20 mg/kg of ipilimumab.
- Description: minor editorial revisions
- Clinical Pharmacology
  - Mechanism of Action: minor editorial revisions
  - (b) (4)
  - Pharmacokinetics: editorial revisions to the first and second paragraphs with reformatting. (b) (4)
    (b) (4)
- Non-Clinical Toxicology:
  - Revised to include subheadings under 13.1 for consistency with general approach to product labeling for this section
  - Section 13.2 added to describe the interim results of the non-clinical reproductive toxicology study and knock-out mouse model. This information was moved from section 8.1 to section 13.2
- Clinical Studies
  - (b) (4)
  - (b) (4), however overall response rate is described in text since

prescribers should be aware that reduction in tumor size does not occur in 90-95% of patients

- (b) (4)
- Edited description of the study design for MDX010-20 for brevity, (b) (4)
- (b) (4)

- How Supplied/Storage and Handling
  Retitled, subsections combined, and edited for brevity
- Information for Patients
  - Edited for brevity and "command" language.
  - Medication Guide referenced

- Carton and immediate container labels: All major issues have been resolved.

- Patient labeling/Medication guide: A medication guide was submitted to as part of the proposed REMS. I concur that risks to patients will by mitigated by use of this additional tool, in combination with discussions of risks provided by the healthcare provider, through early recognition and prompt treatment of immune-related adverse reactions. The proposed medication guide was revised for format and to address recommendations of the clinical and OSE/DRISK review staff.

# 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment

  In concur with the recommendations of the review team that this product should be approved. The benefits of ipilimumab, which is demonstration of a reproducible increase in overall survival time, outweighs the sometimes substantial and unique adverse reactions of this product. As noted by Dr. Shastri, there are no effective treatments for the treatment of metastatic melanoma which prolong survival and none which are likely to provide symptomatic relief through tumor shrinkage in a substantial number of patients or which have been shown to delay time to disease progression. Although the major efficacy trial, MDX010-20, raised questions regarding study conduct (late change in primary analysis plan and alteration of hypothesis regarding mechanism of action) as well as concerns regarding extrapolation to a general population (i.e., not genetically restricted to HLA-A*0201), these concerns have been satisfactorily addressed through replication of the treatment effects of ipilimumab in Protocol CA 184024.

In addition, since CA 184024 was conducted in a first-line patient population, this trial also provided evidence to support approval for a broad population, including those who had not received prior treatment for metastatic melanoma.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  Given the novel toxicities of this product, FDA requested that BMS proposed a Risk Evaluation and Mitigation Strategy to educate healthcare providers, patients, and their caregivers on the possible risks. In addition, FDA determined that a communication plan to educate medical oncology healthcare providers was necessary to ensure adequate communication on recommended evaluation and patient management in order to mitigate risks to patients. A restricted distribution was not felt to be necessary because of the targeting of the communication plan and evidence that the use of anti-neoplastic agents is generally limited to medical oncologists under the practice of medicine.

  The goal of the REMS is to inform healthcare providers about the serious risks of ipilimumab, including risks of fatal immune-mediated enterocolitis (including gastrointestinal perforation), fatal immune-mediated hepatitis (including hepatic failure), fatal immune-mediated toxicities of skin (including toxic epidermal necrolysis), fatal nervous system toxicity, and endocrinopathies resulting from treatment with ipilimumab.

  The communication plan will include a proposal to send communications, every 6 months for the next three years, on the toxicity profile of ipilimumab U.S. cancer treatment infusion centers, and to the following U.S.-licensed healthcare providers: oncologists, gastroenterologists, dermatologists, endocrinologists, emergency room physicians, hepatologists, neurologists, oncology nurses, oncology pharmacists and health-system pharmacists,

  The communications to be provided include a "Dear Healthcare Provider" letter informing healthcare providers about the incidence, type, severity and management of immune-mediated adverse reactions caused by YERVOY and the following patient management tools (Immune-Mediated Adverse Reaction Management Guide and the Immune-Mediated Adverse Reaction Symptom Checklist) directed to healthcare providers. In addition, healthcare providers will be provided with the Patient Wallet Card as an additional educational tool for distribution to patients.

  As an additional element to the REMS, a Medication Guide has been developed that is to be distributed to patients at the initiation of each treatment course and whenever the Medication Guide is updated.

- Recommendation for other Postmarketing Requirements and Commitments

1. To submit the Final Report for study DN10020 (Intravenous Study of Pre-and Postnatal Development in Cynomolgus Monkeys with a 6-Month Postnatal Evaluation).

2. Following the assessment of data from Trial CA184024, the applicant will design and conduct a trial to compare the efficacy, with the primary endpoint of overall survival, and the safety of ipilimumab at doses of 3mg/kg versus 10mg/kg given as monotherapy every three weeks for four doses in patients with unresectable stage III or Stage IV melanoma.

3. To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ipilimumab, including procedures for accurate detection of antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

4. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ipilimumab, including procedures for accurate detection of neutralizing antibodies to ipilimumab in the presence of ipilimumab levels that are expected to be present in the serum or plasma at the time of patient sampling. In the event such an assay can not be developed, evidence of due diligence in attempting to develop the assay will be provided.

5. To conduct an assessment of anti-drug antibody (ADA) response and neutralizing ADA responses to ipilimumab with a validated assay (as described under other PMRs) capable of sensitively detecting ADA responses in the presence of ipilimumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 ipilimumab-treated patients enrolled in the required postmarketing study comparing 3 mg/kg versus 10 mg/kg of ipilimumab monotherapy. The final report will include information on the level of ipilimumab in each patient's test sample at each sampling time point.

6. During the conduct of the required postmarketing study comparing 3mg/kg vs. 10mg/kg ipilimumab monotherapy, you will obtain comprehensive DNA sample acquisition (target ≥95%) and conduct pharmacogenomic association analyses to establish the clinical utility of specific candidate gene polymorphisms (CD86) as genetic determinants of immune related adverse events. The final report will contain primary data in electronic datasets.

Post-marketing Commitments

7. To identify further genetic determinants of immune-related adverse events caused by ipilimumab. DNA samples from the required post-marketing study comparing 3 mg/kg vs. 10 mg/kg ipiliumab monotherapy will be used to

conduct genome-wide association analyses. The design of these analyses will be reviewed by FDA and a Final Report with electronic datasets will be provided.

## SIGNATURES PAGE

Patricia Keegan, M.D./s/ March 12, 2011

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Date