CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s000

MEDICAL REVIEW(S)

Addendum to the safety section of the clinical Review completed on 2/25/11

Application # STN 125377/0
Established Name: ipilimumab
(Proposed)Trade Name: Yervoy
Indication: Unresectable or metastatic melanoma
Dosing Regimen: 3mg/kg every 3 weeks for 4 doses

Reviewer: Kaushik Shastri, MD
Division/Office: DBOP/OODP

Date of Addendum: March 23, 2011

Background: As noted in the safety section of the clinical review, the applicant submitted additional analysis to characterize the immune mediated adverse reactions. This information was only received by the FDA on February 24, 2011. The information contained in that submission was intended to support the accompanying proposed label as described in the supporting document for proposed labeling changes. The information included all of the safety assessments for subjects in primary study MDX010-20, which included the safety experience of the 40 subjects who received more than 4 doses of treatment. Since the indicated treatment regimen is only for the 4 doses of Yervoy treatment (3 mg/kg by intravenous infusion every 3 weeks for 4 doses), the applicant was asked to provide data characterizing the adverse reactions, including the immune-mediated adverse reactions occurring only during and after the 4 doses. The applicant submitted this information on March 14, 2011 as an amendment to the BLA. This clinical review addendum incorporates the information from this latest amendment that forms the basis for description of adverse reactions in the product label. The original clinical review had a discussion on the safety of the re-treatment group in section 7.5.

This clinical review addendum summarizes a more detailed characterization of the immune-mediated adverse events based on submissions received after completion of the clinical review. It does not change this reviewer's recommendation for approval of Yervoy or the risk/benefit assessment contained in the original review.

Immune mediated Adverse Reactions:

The overall incidence of immune-mediated adverse reactions, excluding those that occurred during re-treatment, is shown in the table below and was not significantly different from table 28 of the original review.

MDX010-20: ≥ Grade 3 Immune Mediated Adverse Reactions (induction phase)

	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.

Immune-mediated enterocolitis:

In Study MDX010-20, severe, life-threatening or fatal (diarrhea of 7 or more stools above baseline, fever, ileus, peritoneal signs; Grade 3–5) immune-mediated enterocolitis occurred in 34 (7%) YERVOY-treated patients, and moderate (diarrhea with up to 6 stools above baseline, abdominal pain, mucus or blood in stool; Grade 2) enterocolitis occurred in 28 (5%) of YERVOY-treated patients. Across all YERVOY-treated patients (n=511), 5 (1%) patients developed intestinal perforation, 4 (0.8%) patients died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.
The median time to onset was 7.4 weeks (range 1.6–13.4) and 6.3 weeks (range 0.3–18.9) after the initiation of YERVOY for patients with Grade 3–5 enterocolitis and with Grade 2 enterocolitis, respectively.

Twenty-nine patients (85%) with Grade 3–5 enterocolitis were treated with high-dose (≥40 mg prednisone equivalent per day) corticosteroids, with a median dose of 80 mg/day of prednisone or equivalent; the median duration of treatment was 2.3 weeks (ranging up to 13.9 weeks) followed by corticosteroid taper. Of the 28 patients with moderate enterocolitis, 46% were not treated with systemic corticosteroids, 29% were treated with <40 mg prednisone or equivalent per day for a median duration of 5.1 weeks, and 25% were treated with high-dose corticosteroids for a median duration of 10 days prior to corticosteroid taper. Infliximab was administered to 5 of the 62 patients (8%) with moderate, severe, or life-threatening immune-mediated enterocolitis following inadequate response to corticosteroids.

Of the 34 patients with Grade 3–5 enterocolitis, 74% experienced complete resolution, 3% experienced improvement to Grade 2 severity, and 24% did not improve. Among the 28 patients with Grade 2 enterocolitis, 79% experienced complete resolution, 11% improved, and 11% did not improve.

Immune-mediated Hepatitis:

In clinical trial MDX010-20, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations of more than 5 times the upper limit of normal or total bilirubin elevations more than 3 times the upper limit of normal; Grade 3–5) occurred in 8 (2%) YERVOY-treated patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4% of YERVOY-treated patients. An additional 13 (2.5%) patients experienced moderate hepatotoxicity manifested by liver function test abnormalities (AST or ALT elevations of more than 2.5 times but not more than 5 times the upper limit of normal or total bilirubin elevation of more than 1.5 times but not more than 3 times the upper limit of normal; Grade 2). The underlying pathology was not ascertained in all patients but in some instances included immune-mediated hepatitis. There were insufficient numbers of patients with biopsy-proven hepatitis to characterize the clinical course of this event.

In CA184-007, 3 subjects (CA184007-2-7002, CA184007-24-7044 and CA184007-13-7101) with severe immune-mediated hepatitis were considered to be steroid-refractory and received mycophenolate. In all 3 subjects, liver function tests continued to rise despite introduction of corticosteroids. The durations of corticosteroid treatment prior to the addition of mycophenolate were: 17 days, 13 days, and 17 days, respectively. Following the introduction of mycophenolate, all 3 severe hepatitis events completely resolved.

Immune-mediated Dermatitis:

Severe, life-threatening or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3–5) occurred in 13 (2.5%) YERVOY-treated patients in clinical trial MDX010-20. One (0.2%) patient

died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis. There were 63 (12%) patients with moderate (Grade 2) dermatitis.

The median time to onset of moderate, severe, or life-threatening immune-mediated dermatitis was 3.1 weeks and ranged up to 17.3 weeks from the initiation of YERVOY. Seven (54%) YERVOY-treated patients with severe dermatitis received high-dose corticosteroids (median dose 60 mg prednisone/day or equivalent) for up to 14.9 weeks followed by corticosteroid taper. Of these 7 patients, 6 had complete resolution; time to resolution ranged up to15.6 weeks.

Of the 63 patients with moderate dermatitis, 25 (40%) were treated with systemic corticosteroids (median of 60 mg/day of prednisone or equivalent) for a median of 2.1 weeks, 7 (11%) were treated with only topical corticosteroids, and 31 (49%) did not receive systemic or topical corticosteroids. Forty-four (70%) patients with moderate dermatitis were reported to have complete resolution, 7 (11%) improved to mild (Grade 1) severity, and 12 (19%) had no reported improvement.

Immune-mediated Neuropathies

In clinical trial MDX010-20, there was one case of fatal Guillain-Barré Syndrome and one case of severe (Grade 3) peripheral motor neuropathy. Across the clinical development program of YERVOY, myasthenia gravis and additional cases of Guillain-Barré syndrome have been reported.

Immune-mediated Endocrinopathies

Severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3–4) occurred in 9 (1.8%) YERVOY-treated patients in clinical trial MDX010-20. All 9 patients had hypopituitarism and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. Six of the 9 patients were hospitalized for severe endocrinopathies. Moderate endocrinopathy (requiring hormone replacement or medical intervention; Grade 2) occurred in 12 (2.3%) patients and consisted of hypothyroidism, adrenal insufficiency, hypopituitarism, and one case each of hyperthyroidism and Cushing's syndrome. The median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after the initiation of YERVOY.

Of the 21 patients with moderate to life-threatening endocrinopathy, 17 patients required long-term hormone replacement therapy including, most commonly, adrenal hormones and thyroid hormones.

Other Immune-mediated Adverse Reactions, Including Ocular Manifestations

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of YERVOY-treated patients in Study 1: nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis, and hemolytic anemia.

Across the clinical development program for YERVOY, 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.

Common Adverse events occurring only during induction phase

The incidences of common adverse events, when limited to those occurring during or after induction phase(i.e. excluding those occurring in the subjects during retreatment), are shown below. Only adverse reactions that occurred in at least 5% of patients in the YERVOY-containing arms and with at least 5% increased incidence over the control gp100 arm for all-grade events or at least 1% incidence over the control group for Grade 3–5 events are shown in the Table.

Common Adverse Reactions during induction phase:

	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 3/4
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

Dose Delays: As noted in the original review, case report forms did not specifically capture which adverse event resulted in dose delays, when more than one was present. At the request of FDA, the applicant attempted to analyze by combining the adverse events datasets with the dosing datasets. Of the 23 dose delays, due to adverse events, 20 could be matched to ongoing adverse events, which included 14 grade 2 events and 6 grade 3-5 events. Enterocolitis and dermatitis accounted for majority of dose delays.

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(b) (6)

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CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125377/0
Priority or Standard	Priority
Submit Date(s)	June 25, 2010
Received Date(s)	June 25, 2010
PDUFA Goal Date	March 26, 2011
Division / Office	DBOP/OODP
Reviewer Name(s)	Kaushik Shastri, MD KS 2/25/11
Review Completion Date	February 25, 2011
Established Name	ipilimumab
(Proposed) Trade Name	Yervoy
Therapeutic Class	Monoclonal antibody
Applicant	Bristol Myers Squibb
Formulation(s)	50 mg and 200 mg (5mg/ml) single use vials for intravenous infusion
Dosing Regimen	3mg/kg every 3 weeks for 4 doses
Indication(s)	Unresectable or metastatic melanoma
Intended Population(s)	advanced (unresectable Stage III and Stage IV) melanoma

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of ipilimumab (Yervoy) in patients with advanced melanoma (unresectable stage 3, and stage 4), based on improved overall survival (OS) shown in clinical trial MDX010-20 described in this application. Ipilimumab is the first drug that has shown improved overall survival in patients with advanced melanoma. The improvement in survival was consistent across all important prognostic groups such as stage of disease, prior interleukin 2 use, and lactose dehydrogenase (LDH) levels. The survival advantage was also consistent for age groups, gender and across regions.

MDX010-20 was a multicenter, placebo controlled, double-blind clinical trial that randomized six hundred and seventy six HLA-A2*0201 positive patients with previously treated unresectable stage III or stage IV malignant melanoma in a 3:1:1 ratio to receive (a) ipilimumab (3mg/kg intravenously every 3 weeks up to 4 doses) in combination with gp100 (1 mg peptide A and 1 mg peptide B deep subcutaneously every 3 weeks up to 4 doses) or (b) ipilimumab (3mg/kg every 3 weeks up to 4 doses) plus gp100 placebo every 3 weeks for 4 doses, or (c) ipilimumab placebo (every 3 weeks up to 4 doses) plus gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses). Randomization was stratified by baseline disease stage and prior treatment with interleukin-2.

The primary endpoint of the trial was overall survival. The applicant had changed the end point from best objective response rate (BORR) to overall survival at a later stage of the study, but the study data were not unblinded at that time and the end point of overall survival provides an unbiased assessment of the efficacy of ipilimumab.

Both the ipilimumab containing arms had a significantly longer survival than the gp100 vaccine arm. Overall survival was longer for the ipilimumab monotherapy arm compared to gp100 alone [hazard ratio=0.66, (95% CI:0.51, 0.87), p-value= 0.0026, stratified log rank test], with a median survival time for the ipilimumab monotherapy arm was 10.22 months compared to a median survival of 6.44 months for the gp100 arm. Overall survival was longer for the ipilimumab plus gp100 arm compared to gp100 alone [hazard ratio 0.68 (95% CI: 0.55, 0.85), p =0.0004 stratified log rank test] with a median survival time in the ipilimumab+gp100 arm of 9.95 months as compared 6.44 months in the gp100 . The comparison of overall survival between the two ipilimumab-containing arms was not significantly different. The survival advantage for patients receiving ipilimumab was consistent across all important prognostic groups such as stage of disease, prior interleukin 2 use, LDH, as well as for age, gender and across regions.

[Note to FOIA staff: the information in the next three paragraphs is commercial confidential and should be redacted prior to posting

Although not submitted as a part of this application, another ongoing but nearly complete clinical trial CA184-024 is viewed as providing important corroborative evidence of the efficacy of ipilimumab. This was a multi-center, randomized, double-blind, two-arm, phase III clinical trial in patients with untreated stage III (Unresectable) or IV melanoma receiving Dacarbazine (DTIC) plus 10mg/kg of Ipilimumab vs. Dacarbazine with placebo.

This trial was planned to accrue 500 randomized patients (250 per arm). A total of 416 deaths are needed to provide approximately 90% power to detect a 38% increase in median OS (i.e. Assuming a median OS of 8 months for dacarbazine with placebo vs. 11 months for dacarbazine+ipilimumab) based on a 2-sided α=0.05. The median overall survival time difference corresponds to a hazard ratio of 0.727). The primary efficacy endpoint of this study is overall survival. The study has been fully accrued and already there were (b) (4) events as of 9/16/11. FDA had asked the applicant to provide high-level overall survival results for Study CA184-024. The high level OS results include the hazard ratio with confidence intervals, p-values from the log-rank statistic, the K-M curve for OS and the number of patients at risk. FDA agreed that the applicant will not incur a statistical penalty. At the request of the applicant, the applicant organization remained blinded to the results and on 10/7/10, the top-line results were sent to FDA and the corresponding OS data was also submitted in a CD by an independent statistician. The data cutoff date for this top-line data is 9/16/10. The FDA statistician reviewed the top line results of this study, and based on the results of this study, this reviewer is reassured of the findings of Study MDX10-20.

Since Study CA184-024 was done in patients who had no HLA restriction, and in first line treatment of metastatic or unresectable advanced melanoma, and since there is no alternative treatment that has shown survival advantage in any line of treatment for this disease, FDA has agreed to grant the indication for ipilimumab in unresectable Stage 3 or Stage IV melanoma without restriction of HLA type or prior treatment status.]

The Study MDX010-20 protocol allowed retreatment with the originally assigned treatment in patients who had progressed following either stable disease of $\geq$ 3 months duration (beginning Week 12) or an initial objective response (PR or CR) to the first cycle of therapy . No patient was to be re-treated if they experienced a Grade 3 non-dermatologic immune related adverse event (except enodcrinopathies that were well controlled with hormone replacement therapy) or Grade 4 toxicity of any organ system considered related to ipilimumab or placebo administration. Forty subjects (5.9%) received re treatment. Of the forty subjects, 29 (7.2%) were assigned to the ipilimumab +gp100 treatment group, 9 (6.6%) were assigned to the ipilimumab arm, and 2 (1.5%) were assigned to the gp100 arm. The safety and efficacy experience with retreatment was thus very limited, hence it can not be recommended as a treatment strategy. Censoring of the retreated subjects at the time of re-treatment did not have significant impact on overall survival results.

1.2 Risk Benefit Assessment

Advanced (unresectable stage III and stage IV) melanoma is a disease with uniformly poor prognosis, with a reported median overall survival ranging from 6 to 9 months. Among the available therapies, including the two drugs that are FDA-approved for this indication, dacarbazine and interleukin 2 (aldesleukin), none has shown improvement in overall survival.

As per the results of the clinical trial MDX010-20, contained in this application, there was a 32 to 34% risk reduction for death, and a 4 month improvement in median survival for ipilimumab-treated patients compared to the control arm of gp100 vaccine. The survival advantage was consistent across the prognostic groups including disease stage, prior interleukin 2 use, and LDH levels.

Yervoy has unique toxicities due to its novel mechanism of action. Due to its potentiation of T-cell function by CTLA-4 blockade, Yervoy is postulated to causes disruption of immune tolerance to antigens on cancer cells and thus produce anti-tumor effects. However, it also produces pathological immune response and autoimmunity. Yervoy can result in severe and fatal immune-mediated adverse reactions, which may involve any organ system and have included enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy (including Gullian Barre syndrome), and endocrinopathies. In study MDX010-20, the incidence of severe immune-mediated enterocolitis was 7%, dermatitis was 2.5%, endocrinopathies and hepatitis was 2% each, and neuropathy was less than 1%. In clinical trial MDX010-20, subjects with immune mediated toxicities received systemic corticosteroids with benefit. Early recognition and treatment with immunosuppressants appear to be helpful in mitigating the severity or duration of these toxicities.

Despite the unique and significant toxicities associated with Yervoy, the benefit of Yervoy in prolonging survival in patients with metastatic and unresectable stage III melanoma, outweighs the associated risks.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies (REMS)

The applicant has proposed a REMS, which includes a medication guide and a communication plan. The plan will be finalized once the safety characterization for the package insert is finalized.

1.4 Recommendations for Post-market Requirements and Commitments

There is evidence of more toxicity with the 10 mg/kg dose as compared to the 3 mg/kg dose. With the survival advantage seen with the 3 mg/kg dose in the study presented in this

application, and the review of the top line survival results of the 10 mg/kg clinical trial CA 84-024, the correct dose (3 mg/kg vs 10 mg/kg) that will provide the optimal benefit for the risk is unclear. The applicant has agreed to a post-marketing requirement (PMR) trial for evaluation of efficacy and safety comparing the 3 and the 10 mg/kg doses in melanoma patients. The final wording and the milestones of the PMR are still under negotiation.

2 Introduction and Regulatory Background

2.1 Product Information

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1k) specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T cells. Ipilimumab is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system.

The mechanism of action of ipilimumab exploits a unique approach to the treatment of cancer, which differs from traditional cytotoxic chemotherapy or other targeted treatment approaches. Specifically, the purported mechanism of action involves interference with host immune-tolerance, representing a novel experimental approach to cancer therapy. Cancer cells escape immune activation and surveillance, at least in part, due to the development of immunologic tolerance to their antigens. T-cells play a pivotal role in the development of immune tolerance to self and tumor antigens. Conversely, upon activation, T-cells are central to anti-tumor responses and the development of autoimmunity. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a key surface receptor on T-lymphocytes that modulates immune responses. Interference of the interaction of CTLA-4 with B7 (CD80 or CD86) molecules on antigen presenting cells by ipilimumab results in blockade of the inhibitory function of CTLA-4. This results in potentiation of T-cell function, thereby causing disruption of immune tolerance to antigens on cancer cells and producing anti-tumor effects. Disruption of tolerance to self antigens, on the other hand produces autoimmune adverse effects.

2.2 Tables of Currently Available Treatments for Proposed Indications

For the first line treatment of metastatic melanoma, there are two approved treatments in the US, both of which have failed to show an improvement in overall survival. Dacarbazine, approved more than 30 years ago, has a response rate of about 15%. High dose interleukin 2 (Proleukin®; IL-2, aldesleukin) received an expanded labeling claim in 1998 for the treatment of metastatic melanoma based on a response rate of 16% in single arm trials. Interferon alpha and a variety of chemotherapeutic agents including temozolamide, cisplatin, vinblastine etc, either singly or in various combinations have been used off-label without consistent evidence of durable and clinically meaningful objective tumor response rates and no evidence of improvement in overall survival.

Currently, there is no FDA approved treatment for previously treated advanced melanoma, i.e. in a second line setting.

2.3 Availability of Proposed Active Ingredient in the United States

Ipilimumab is a new molecular entity and is not currently marketed in any country.

2.4 Important Safety Issues with Consideration to Related Drugs

Tremelimumab is another anti-CTLA4 antibody for which there are published reports of its use in melanoma. In a published report of a Phase II trial of previously treated patients with unresectable stage 3 or 4 melanoma[1], the response rate was 6.6% among 251 patients. Thirteen patients (5%) discontinued because of treatment related adverse events. Most common adverse events reported by the authors were diarrhea (11%) and colitis (4%). Endocrine adverse events occurred in 9 (4%) of patients, including 8 patients with thyroid disorders (hyperthyroidism, hypothyroidism, autoimmune thyroiditis, or Basedow's disease) and 1 patient with hypophysitis and pituitary insufficiency.

As seen above, the safety issues observed with the other CTAA-4 antibody are similar to those observed with ipilimumab.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The first investigational new drug applications (INDs) for ipilimumab were submitted by Medarex to the FDA's Center for Biologics Evaluation and Research (CBER) in 2000. (b) (4)

Another IND contained the development program for ipilimumab alone or in combination with other cytotoxic drugs for the treatment of melanoma. (b) (4) . When the regulatory review of therapeutic biologic products was re-assigned to the Center for Drugs

Evaluation and Research (CDER), two of the ipilumumab INDs were transferred to CDER, while one IND remained with CBER in the Office of Tissue, Cellular, and Gene Therapies due to the stated mechanism of action under investigation (b) (4).

In 2004, Medarex met with CBER for a pre-phase 3 meeting to discuss the development program for ipilimumab (b) (4) in patients with refractory unresectable melanoma. Agreement was reached under a request for special protocol assessment (SPA) on the design of study MDX010-20 in 2005. This study was a double blind, double-dummy, three-arm, randomized (3:1:1) study with the primary objective of determining the effect, in terms of objective response rate, of ipilimumab in combination with gp 100 melanoma peptide and to determine the independent contributions of the vaccine therapy and ipilimumab in patients with previously treated unresectable stage III or IV melanoma.

In 2005, the sponsorship of the ipilimumab INDs were transferred from Medarex to Bristol Myer Squibb (BMS) and an end of phase 1 meeting was held between BMS and CDER to discuss the clinical development program (b) (4). The clinical benefit of ipilimumab would be verified by demonstration of a clinically important prolongation of progression free survival in study CA 184024, a double blind, randomized (1:1), multicenter study of dacarbazine with or without ipilimumab (10 mg/kg) to be conducted in 500 patients with previously untreated, advanced melanoma. The development program was agreed to by CDER and both the studies were subsequently accepted under SPA.

On April 25, 2008, BMS met with FDA/CDER for a pre-BLA meeting to discuss the results of the single arm study CA 184008, (b) (4) (b) (4)). During the meeting, BMS indicated that they would like to change the primary endpoint of study CA 184024 from progression free survival to overall survival. CDER agreed that the change in the primary endpoint to overall survival for study CA 184024 was acceptable but specific details would need to be formally reviewed. In a letter dated March 3, 2009, CDER formally agreed to the change in the primary endpoint in response to submissions dated October 20, 2008 and December 22, 2008 containing clean and red-lined versions, respectively of the amended protocol for study CA 184024.

On July 25, 2008, BMS notified FDA/CBER its decision to change the primary end point of the MDX010-20 vaccine/ipilimumab trial to overall survival and end further enrollment. (b) (4)

(b) (4)

On December 1, 2009, BMS requested a Type C meeting with the CDER review team responsible for the two of the ipilimumab INDs to discuss the overall development plan for melanoma in light of the analysis of survival in study MDX010-20. During the meeting, FDA agreed that that the survival data were of interest, but expressed reservations regarding a BLA supported only by the results of MDX010-20, noting the small study size and concerns as to whether the gp100 peptide vaccine was a valid control for purposes of the survival comparison. FDA further noted that the final analysis of survival in study CA184024 would be necessary to provide confirmatory evidence of the treatment effect on survival. BMS indicated that CA184024 was ongoing and that the number of events needed for the final analysis of survival was likely not going to be available until October 2010 at the earliest. A subsequent pre-BLA meeting was held on March 4, 2010.

2.6 Other Relevant Background Information

Ipilimumab has not received regulatory approval in any other country.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality of the submission was not adequate. There were multiple requests for additional information from almost all review disciplines. As of 2/10/11, there were 55 amendments to the BLA.
From a clinical review stand point, the following were the major challenges in evaluating this application:

- There were major issues with the applicant's presentation and characterization of the immune-mediated adverse events, which is detailed in section 7. These issues resulted in submission of a major amendment.
- The applicant did not provide a package insert describing dose modifications and interventions for significant adverse events that were supported by actual data from the clinical study itself, but rather based these on the opinion of the applicant's experts. The clinical study report, for example, lacked information on dose delay for toxicity.

- The case report forms did not contain the necessary supporting documents, such as hospital reports, imaging or pathology results. It was therefore extremely difficult to follow the patient narratives while reviewing the case report forms.

3.2 Compliance with Good Clinical Practices

The clinical trials were generally conducted in accordance with acceptable ethical standards and in compliance with good clinical practices with one notable exception (see specific comments regarding site 301). The pivotal study was conducted at 125 sites in North America, Europe, South America, and Africa. An FDA Division of Scientific Integrity (DSI) audit was requested for the top 4 highest enrolling sites, all of which were US sites. The selection of the sites was based on the highest number of subjects enrolled in the primary study MDX10-20.

DSI inspection did not find any significant issues with three of the sites [at one site a single observation form 483 was issued for reporting of the serious adverse events (SAEs) after the 24 hour requirement, but no other deficiencies noted] and the audit of the applicant; however, there were significant issues with site # 301. This site had enrolled a total of 19 subjects (11, 4 and 4 assigned to the ipilimumab+gp100, ipilimumab monotherapy and gp100 arms, respectively). As per DSI's assessment of data integrity at this site, the data for this site site, associated with Study MDXOI0-20 submitted to the Agency in support of BLA 125377, appear unreliable based on available information. This conclusion is based largely on the totality of protocol compliance violations, numerous missed protocol-specified periodic assessments, calling into question important safety assessments based on this data. In addition, there were inadequate drug storage and accountability records, calling into question how and when drug was prepared and administered and whether it was expired or not prior to use. DSI recommended that data from this site not be used to support a regulatory decision. During the course of investigation, as preliminary findings raised a concern about overall data reliability from the site, DSI suggested that the review division conduct sensitivity analyses in which data from this site is removed to assess the impact on overall efficacy and safety conclusions. Please see sections 6 and 7 were, the analyses was performed excluding the subjects from this site.

The applicant was also inspected by DSI. The FDA field investigators reported that inspection of the applicant, Bristol-Myers Squibb Company, covered organization and personnel, selection and monitoring of clinical investigators, selection of monitors, monitoring procedures and activities, QA, Adverse events/effects and reporting, data collection, data tabulations, test article integrity and accountability. In addition, primary efficacy endpoint data were assessed. No deficiencies were noted. Inspectional findings revealed no evidence that BMS or MDX personnel had inappropriate access to unblinded data from Study MDXOI0-20 prior to database unblinding that occurred on October 30, 2009.

3.3 Financial Disclosures

The applicant has supplied financial arrangements from clinical investigators as recommended in the FDA's Guidance for Industry Financial Disclosure by Clinical Investigators. Review of these disclosures does not raise questions about the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

As per the CMC review, the data submitted in this application are adequate to support the conclusion that the manufacture of ipilimumab is well controlled, and leads to a product that is pure and potent. From a CMC standpoint it is recommended that this product be approved for human use (under conditions specified in the package insert).

4.2 Clinical Microbiology

There were no clinical microbiology issues.

4.3 Preclinical Pharmacology/Toxicology

Upon review of the nonclinical pharmacology and toxicology sections of the original BLA submission and amendments, the preclinical pharmacology toxicology reviewer did not identify any basis for objecting to the approval of ipilimumab. Evaluation indicates that the nonclinical models underpredicted potential toxicity, compared with clinically-observed adverse events. The ongoing enhanced pre- and post-natal development (ePPND) study in monkeys raises serious concerns for the use of ipilimumab during pregnancy; the current version of the draft label appropriately reflects these concerns and their basis. In addition, one postmarketing requirement (PMR) to ensure submission by the applicant of the results of nonclinical study # DN10020, "Ipilimumab (BMS-734016): intravenous study of pre- and postnatal development in cynomolgus monkeys with a 6-month postnatal evaluation" is recommended. This study is ongoing and is being conducted in compliance with United States Code of Federal Regulations part 58 (21CFR58), Good Laboratory Practices (GLP) for Nonclinical Laboratory Studies.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The proposed mechanism of action for ipilimumab is interference with the interaction of CTLA-4 (cytotoxic T lymphocyte antigen 4; CD152) with the B7 molecules (CD80/CD86) on antigen-presenting cells. This results in subsequent blockade of the inhibitory modulation of T cell activation and potentiation of the immune response.

4.4.2 Pharmacodynamics

According to the clinical pharmacology review, exposure-response analysis revealed an increase in overall survival with increasing drug exposures at 0.3, 3, and 10 mg/kg doses in Phase II studies. Steady state trough concentration was found to be an independent predictor of overall survival using a stepwise Cox proportional hazard model after correcting for confounding risk factors (ECOG performance status and baseline lactate dehydrogenase). Positive exposure-response relationship provides supportive evidence of the effectiveness of ipilimumab. 98% patients in the upper (3rd and 4th) quartiles for drug exposure, with a median survival greater than 10 months received the 10 mg/kg dose. Patients who received the 3 mg/kg dose were in the lower (1st and 2nd) quartiles. The exposure-response relationship suggests that there might be an increased survival benefit at the higher dose of 10 mg/kg.

Clinical review comment: The above analysis was based on small Phase 2 studies with variable follow-up and studies not designed to evaluate the survival endpoint. There is evidence of increased toxicity at the 10 mg/kg dose. The applicant has agreed to a PMR to evaluate the safety and efficacy at 3 and 10 mg doses.

4.4.3 Pharmacokinetics

Rich pharmacokinetic (PK) data were available from 84 patients enrolled into 3 clinical studies and sparse PK data is available from 499 patients across 4 clinical studies. Ipilimumab exhibited linear PK over 0.3 to 10 mg/kg with a mean half-life of 15 days.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Primary Efficacy and Safety Study

Study	Population	Design	Primary endpoint	Ipilumumab dose and duration	Number of Subjects Randomized/Treated
MDX10-20	HLA A2 + Pre-treated Unresectable stage 3 or metastatic melanoma	Double blind Randomized (3:1:1), ipilimumab +gp100, ipilimumab, gp100	Overall Survival	Ipilimumab 3 mg/kg IV q 3 wks X 4; Re-treatment under very specific circumstances	676/643

Table 2: Other Efficacy Study of interest (ongoing- top line survival curves provided for confidential review by FDA)

Study	Population	Design	Primary endpoint	Ipilumumab dose and duration	Number of Subjects Treated
CA184024	Untreated, stage 3 (unresectable) or 4 ,malignant melanoma	Phase 3, Double-blind randomized (1:1); DTIC ± ipilimumab	Overall Survival	Placebo or Ipilimumab 10 mg/kg IV q3 wks x 4 doses <u>Maintenance</u> Ipilimumab 10 mg/kg or placebo q12 wks until PD, toxicity	497

Table 3: Other Studies

Study	Population	Design	Primary endpoint	Ipilumumab dose and duration	# of Subjects Treated
CA184022	Pre-treated Unresectable or metastatic melanoma	Double blind Randomized (1:1:1), Phase 2	BORR	Induction IV Ipilimumab 0.3 3 or 10 mg/kg IV q3 wks x 4 doses Maintenance q12 weeks until PD, toxicity	214
CA184008	Pretreated stage 3 (unresectable) or stage 4 melanoma	Phase 2, open-label, single-arm, multicenter	BORR	Induction IV Ipilimumab 10 mg/kg IV q3 wks x 4 Maintenance IV Ipilimumab 10 mg/kg IV q12 weeks until PD, toxicity	155
CA184007	Pretreated and untreated subjects with unresectable stage 3 or 4 malignant melanoma	Double-blind randomized (1:1) phase 2	Safety of ipilimumab with either prophylactive oral budesonide or placebo	Induction Ipilimumab 10 mg/kg IV q3 wks x 4 Maintenance: Ipilimumab 10 mg/kg q12 wks Budesonide: 9 mg QD until wk 12, 6 mg until wk 14, and 3 mg until Wk 16	115 (ipilimumab +placebo=57; Ipilimumab+ budesonide=58)
CA184004	Pretreated and previously untreated subjects with unresectable stage 3 or 4 malignant melanoma	Double-blind randomized (1:1) phase 2, exploratory	Determine potential predictive markers of response or toxicity	Induction IV Ipilimumab 3 or 10 mg/kg IV q3 wks x 4 doses Maintenance IV Ipilimumab 3 or 10 mg/kg IV q12 weeks until PD, toxicity	82

Table 4: Other studies (continued)

Study	Population	Design	Primary endpoint	Ipilumumab dose and duration	# of Subjects Treated
MDX010-08	Chemo-naïve Unresectable or metastatic melanoma	Randomized Open label, Phase 2	Safety and activity profile	Ipilimumab 3 mg/kg IV q4 wks x 4 doses ± dacarbazine	74
CA184042	Subjects with Melanoma Brain Metastases	Phase 2, open label	Disease Control Rate at Week 12	Induction Ipilimumab 10 mg/kg IV q3 wks x 4 doses Maintenance IV Ipilimumab 10 mg/kg IV q12 weeks	28 (interim study report)
MDX010-28	Metastatic melanoma	Phase 2, follow-up	Collect disease status and survival information on patients alive after completing studies MDX010-02, MDX010-08 or MDX010-15	None	Total 181

5.2 Review Strategy

The application is primarily supported by a single study MDX10-20, showing improved survival in the ipilimumab containing arms for patients with pre-treated advanced melanoma. This study is reviewed in sections 5.3, 6 and 7. The eligibility and protocol amendments are discussed in section 5.3, the efficacy information is discussed in section 6. The safety from this study is discussed in section 7.

FDA asked the applicant to provide top line results on Study CA184024, which were reviewed by the FDA statistician, and the implications of that review are discussed in efficacy summary of section 6.

Because the primary efficacy and safety study MDX010-20 only enrolled subjects with HLA-A2+ genotype, the applicant included in this application, data on the HLA test results in their Phase 2 studies, making an argument that the efficacy results were not dependent on the HLA type. These small Phase 2 studies are not adequate to exclude the possibility of that HLA type is either prognostic or predictive of clinical benefit that however, these exploratory results in these Phase 2 studies based on the subset of patients who were assessed by HLA typing are discussed briefly in section 6.

The incidence of common adverse events and the characterization of important immune-mediated adverse events primarily relied on Study MDX10-20 because of the internal control of the gp100 vaccine alone arm and the large size of the study. However, Phase 2, studies were used to explore toxicity at the higher dose, and for characterization of infusion reactions, immunogenicity and rarer adverse events and these findings are described in section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Study MDX010-20:

Title of the Study: 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 Stage IV Melanoma

Study Period: Study initiated: 27 September 2004
Study Completed: 7 October 2009

Investigators/Study Centers: 125 sites across North America, Europe, South America and Africa

Inclusion Criteria

Subjects who met all of the following criteria on screening examination (within 35 days of HLA-A2*0201 confirmation by either the local or central laboratory) were eligible for inclusion in the study:

1) Histologic diagnosis of malignant melanoma;
2) Measurable unresectable Stage III or Stage IV melanoma;
3) At least 18 years of age;
4) Positive for HLA-A2*0201;

5) Subject demonstrated 1 of the following in response to at least 1 cycle of 1 or more regimens containing 1 or more of the following: IL-2, dacarbazine, temozolamide, fotemustine and/or carboplatin: 1) relapse following an objective response (PR/CR); 2) failed to demonstrate an objective response (PR/CR); or 3) inability to tolerate treatment due to unacceptable toxicity;
6) At least 28 days since treatment with chemotherapy, biochemotherapy, surgery, radiation, or immunotherapy, and 14 days for gamma knife treatment and recovered from any clinically significant toxicity experienced during treatment (prior treatment must be completed by the time of study drug administration);
7) Women met 1 of the following criteria: post-menopausal for at least 1 year; surgically incapable of bearing children; or utilizing a reliable form of contraception. Women of childbearing potential had a negative serum ß-human chorionic gonadotropin (HCG) hormone pregnancy test conducted during screening and a negative urine ß-HCG pregnancy test conducted prior to study drug administration;
8) Men who could have fathered a child agreed to the use of male contraception for the duration of their participation in the trial;
9) Life expectancy $\geq$ 4 months;
10) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
11) Required values for initial laboratory tests:

- White blood cell (WBC) count $\geq$ 2500/µL
- Absolute neutrophil count (ANC) = 1500/µL
- Platelet count $\geq$ 100 x 10^3/µL
- Hematocrit (Hct) $\geq$ 30%
- Hemoglobin (Hb) $\geq$ 10 g/dL
- Creatinine $\geq$ 2 upper limit of normal (ULN)
- Aspartate aminotransferase (AST) $\leq$ 2xULN, except for subjects with AST $\leq$ 5xULN attributed to liver metastases
- Total Bilirubin < 2xULN, except subjects with Gilbert's Syndrome, who must have had a total bilirubin < 3.0 mg/dL

12) Negative screening tests for human immunodeficiency virus (HIV), Hepatitis B, and Hepatitis C.

Exclusion Criteria:

1) Any other prior malignancy from which the subject has been disease-free for less than 5 years, with the exception of adequately treated and cured basal or squamous cell skin cancer, superficial bladder cancer, or adequately treated carcinoma in situ of the cervix, breast, or bladder;
2) Primary ocular melanoma;
3) Active, untreated central nervous system (CNS) metastasis (subjects with brain metastases identified at screening may have been rescreened after the lesion(s) were appropriately treated);
4) Prior treatment with an anti-CTLA4 antibody;

5) Prior treatment with any cancer therapeutic vaccine, including gp100 peptides;
6) Any active autoimmune disease or a history of autoimmune disease except for vitiligo and adequately controlled endocrine deficiencies such as hypothyroidism;
7) Pregnant or nursing;
8) Hypersensitivity to Incomplete Freund's Adjuvant (IFA) [Montanide ISA-51] or any component of the vaccine;
9) Any underlying medical condition, which in the opinion of the Investigator, will make the administration of study drug hazardous or obscure the interpretation of adverse events (AEs), such as a condition associated with frequent diarrhea;
10) Concomitant therapy with any of the following: IL-2, interferon or other non-study anti-melanoma immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids; or
11) Inability to provide adequate informed consent.

Study Treatment:

Six hundred and seventy six patients in this study were randomized in 3:1:1 ratio (stratified by baseline M-stage and prior treatment with IL-2) to the following three arms:

Arm 1: ipilimumab + gp100: ipilimumab (3mg/kg every 3 weeks up to 4 doses) in combination with gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses);

Arm 2: ipilimumab monotherapy: ipilimumab (3mg/kg every 3 weeks up to 4 doses) plus gp100 placebo every 3 weeks for 4 doses;

Arm 3: gp100 monotherapy: ipilimumab placebo (every 3 weeks up to 4 doses) arm plus gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses).

The melanoma peptide vaccine consisted of (b) (4) (b) (4). The ipilimumab placebo consisted of a similar formulation of ipilimumab without the active component. The vaccine placebo consisted of normal saline. Intravenous (IV) infusions of ipilimumab or ipilimumab placebo were administered on Days 1, 22, 43 and 64 (i.e. 12-week treatment cycle). Both gp100 and placebo vaccine were administered subcutaneously by injection, immediately following the infusion of ipilimumab or ipilimumab placebo.

Retreatment: Patients who had progressed following either stable disease of ≥ 3 months duration (beginning Week 12) or an initial objective response (PR or CR) to the first cycle of therapy with the originally assigned treatment regimen until PD, was offered additional cycles of therapy with the originally assigned treatment regimen, provided they met the eligibility laboratory requirement and did not have active brain metastasis. Patients experiencing a Grade 3 non-dermatologic irAE or Grade 4 toxicity of any organ system considered related to ipilimumab or placebo administration or placebo were not to be re-treated. Patients with the following

ipilimumab or placebo related toxicities that are <Grade 4 will be permitted re-treatment when in the treating physician's opinion re-treatment is justified:

- Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy; or
- Dermatologic toxicity

If a patient has experienced a study medication-related Grade 2 or Grade 3 irAE, then the event must have improved to Grade 1 before re-treatment can be considered. Patients eligible for additional treatment cycles were to repeat the treatment phase as outlined above.

Dose Modifications:

Treatment with ipilimumab or placebo will be discontinued if patients experience an adverse event considered to be "possibly," "probably," or "definitely" related to ipilimumab or placebo that meets the following criteria:

- Any non-skin-related adverse event of ≥ Grade 3 with the following exceptions:
  - Potentially reversible inflammation < Grade 4 that can be attributable to a local antitumor reaction that could potentially be a therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or in sites suspicious for, but not diagnostic of metastasis.
  - Hospitalization for ≤ Grade 2 events where the primary reason for hospitalization is to expedite work-up.
  - Patients with endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy.
- Any adverse event ≥ Grade 4 that is considered to be "possibly," "probably," or "definitely" related to ipilimumab or placebo.

In patients with a drug-related Grade 2 skin immune-mediated toxicity or Grade 3 skin immune-mediated event regardless of causality, additional treatment will be delayed until the event improves to ≤ Grade 1 severity.

In patients with a non-skin-related immune mediated toxicity of Grade 2 severity or permissible Grade 3 immune toxicities (see above), additional treatment will be delayed until the event improves to ≤ Grade 1 severity. Treatment may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

Following a delay, treatment may commence as soon as the event improves to ≤ Grade 1 severity. Additional dosing with study medication, if applicable, should be administered every 3

weeks from the time of restarting treatment. In the initial treatment phase, in the event of a prolonged delay or multiple delays, no dosing will be allowed after Week 16.

Study Assessments:

During the treatment period, patients were required to visit the Investigator's office or clinic for administration of study medications, pharmacokinetic and pharmacodynamic sampling, vital signs measurements, physical examinations, ECOG performance status evaluation, clinical laboratory testing, and the collection of treatment-emergent adverse events. Responses were determined by the investigator utilizing modified WHO criteria. All patients were to be restaged at Week 12, and for patients with stable disease or better responses, again at Week 16, Week 24, and every 3 months thereafter. Confirmatory scans were to be obtained 4 weeks following documentation of response improvement from the preceding re-staging scan; e.g., if a patient demonstrates improvement at Week 16 or Week 24 then confirmatory re-staging assessments must be performed at Week 20 or Week 28, respectively.

Patients with disease progression, who are not eligible for re-treatment during the follow-up period, were to be followed for survival status by telephone every 3 months.

Protocol Amendments: There were a total of six protocol amendments; significant amendments are described below:

Amendment #1 (dated 7/01/04 before beginning of the study on 9/27/04):
The primary endpoint was changed from objective response rate (ORR) to best objective response rate (BORR). Study design was adapted to 1 stage for subject enrollment instead of 2 stages. One additional stratification factors MI status (M1a or M1b vs. M1c). The randomization ratio was changed from 4:1:1 to 3:1:1 for Arm 1 vs. Arm 2 vs. Arm 3 to achieve for a total of 450:150:150 sample size. Modified criteria for discontinuation of ipilimumab/ipilimumab placebo to include any related ≥ Grade 4 event and added reasons for a delay in treatment; clarified stopping rules for toxicity; statistical methods section was rewritten and the sample size was re-estimated based on the revised study design.

Amendment #3 (dated 3/17/06):

Assessment of patient-reported outcomes using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 for health-related quality of life assessment was specified as a study objective. The MI stratification factor was changed to TNM status and added M0 (i.e. now the level includes M0, M1a or M1b vs. M1c). The major durable response rate was clarified to be CR/PR ≥6 months duration. The duration of serious adverse events (SAE) reporting was changed from 4 weeks to 70 days following study treatment.

Amendment #5 (dated 10/17/07)

Laboratory results were to be reviewed prior to study drug infusion; if central laboratory results were not available, results from a local laboratory could be used. If significant abnormalities were noted, administration of study drug was to be postponed for workup and possible treatment. Appendix 4 updated, to refer to the Investigator's Brochure for the most current version of suggested treatment algorithms for management of immune-related adverse events (irAEs).

Amendment #6 (dated 1/15/09):

The primary endpoint was changed from best overall response rate (BORR) to overall survival (OS). The primary comparison was the same as that in earlier amendment (i.e. between ipilimumab in combination with gp100 vs. gp100 arm). However, the secondary comparisons were now to be conducted between ipilimumab monotherapy vs. gp100 and between two ipilimumab containing arms. The sample size was revised based on the new primary efficacy endpoint.

Protocol Violations/Deviations: There were a total of 32 protocol violations representing 4.7% of the randomized population. Of these, 8 are considered of limited medical importance (3 cases of concomitant steroid use, 1 of a concomitant topical anti-neoplastic; 1 case of completing prior chemotherapy within 26 days rather than 28 days of study start; 2 cases of surgical excision of local lesions within 28 days of study start; and 1 erroneous qualifying platelet counts. The other violations were fairly well distributed among the three treatment groups and are unlikely to have an impact on the interpretation of the results of the study. Inadequate prior chemotherapy and active CNS metastasis accounted of seven violations each, while 4 patients had a history of actie autoimmune disease and 3 had received therapeutic vaccine in the past.

6 Review of Efficacy

Efficacy Summary

Ipilimumab is the first drug that has shown improved overall survival in patients with advanced melanoma (unresectable stage 3 and stage 4), a disease with uniformly dismal prognosis.
The demonstration of efficacy of ipilimumab is primarily based on improvement in overall survival observed in Study MDX10-20, described below. Since this study had patient selection criteria that only included patients with HLAA2 positive phenotype and had a control arm that received of a tumor vaccine, which could not be assumed to be a non-toxic placebo, FDA insisted on reviewing the top line results in the form of survival curves from an ongoing but nearly completed study CA 184024, which was a double-blind study in unselected (no HLA restriction) patients with advanced melanoma who received DTIC with or without ipilimumab, which is also briefly mentioned below. Having reviewed the top line survival results from that study, this reviewer is comfortable with the validity of the results of the Study MDX10-20 contained in this application. Since there is no first-line treatment for advanced melanoma that has been shown to improve survival, although the population studied in MDX10-20 was that of HLA A2 positive, pretreated advanced melanoma, the approved indication for ipilimumab will

be all subjects with advanced melanoma, i.e. regardless of HLA phenotype or prior treatment status.

Major Efficacy Study
Study MDX010-20 enrolled patients with diagnosis of malignant melanoma or measurable Stage III or IV melanoma, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, who were HLA-A2*0201 positive, received at least 1 cycle of one or more regimens (containing IL-2, dacarbazine, temozolamide, fotemustine and/or carboplatin) for metastatic/unresectable disease, and had relapsed, failed to respond or did not tolerate the treatment due to toxicity. Six hundred and seventy six patients in this study were randomized in 3:1:1 ratio (stratified by baseline M-stage and prior treatment with IL-2) to the following three arms:

Arm 1: ipilimumab + gp100: ipilimumab (3mg/kg every 3 weeks up to 4 doses) in combination with gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses);

Arm 2: ipilimumab monotherapy: ipilimumab (3mg/kg every 3 weeks up to 4 doses) plus gp100 placebo every 3 weeks for 4 doses;

Arm 3: gp100 monotherapy: ipilimumab placebo (every 3 weeks up to 4 doses) arm plus gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses).

Intravenous (IV) infusions of ipilimumab or ipilimumab placebo were administered on Days 1, 22, 43 and 64 (i.e. 12-week treatment cycle). Both gp100 and placebo vaccine were administered subcutaneously by deep injection, immediately following the infusion of ipilimumab or ipilimumab placebo. Following treatment, patients entered the follow-up phase.

The primary endpoint of the study was overall survival. The applicant had changed the endpoint from best objective response rate (BORR) to overall survival at a later stage of the study, but the study data were not unblinded at that time and the endpoint of overall survival provides an unbiased assessment of the efficacy of ipilimumab.

Patients in both of the ipilimumab-containing arms had a significantly longer survival than those in the gp100 vaccine arm. The median survival time for the ipilimumab monotherapy arm was 10.22 months compared to a median survival of 6.44 months for the gp100 arm. The hazard ratio (HR) for overall survival was 0.66 (95% CI: 0.51, 0.87), at p-value0.0026 based on the stratified log rank test.

The ipilimumab+gp100 arm also had statistically significant longer median overall survival time as compared with that of the gp100 monotherapy arm (9.95 vs. 6.44 months; the HR for overall survival was 0.68 (95% CI:0.55, 0.85), at p-value=0.0004 based on the stratified log rank test. The comparison of overall survival between the two ipilimumab-containing arms was not significantly different [HR 1.04 (95% CI 0.83, 1.30), p=0.76].

Supportive Efficacy Information

Although not submitted as a part of this application, Study CA184024 is viewed as providing important corroborative was a multi-center, randomized, double-blind, two-arm, Phase 3 study in patients with untreated stage III (Unresectable) or IV melanoma receiving Dacarbazine (DTIC) plus 10mg/kg of ipilimumab (MDX-010) vs. Dacarbazine with placebo.

This study was planned to accrue 500 randomized patients (250 per arm). A total of 416 deaths are needed to provide approximately 90% power to detect a 38% increase in median OS (i.e. assuming a median OS of 8 months for dacarbazine with placebo vs. 11 months for dacarbazine with ipilimumab) based on a 2-sided α=0.05. The assumed difference in median overall survival times corresponds to a hazard ratio of 0.727. The primary efficacy endpoint of this study is overall survival. The study has been fully accrued and already there were (b) (4) events as of 9/16/11. During review of the BLA, FDA asked the applicant to conduct an unplanned analysis (prior to the required 414 events) and to provide with the high-level OS results from this analysis for Study CA184024, consisting of the hazard ratio with confidence intervals, p-values from the log-rank statistic, the K-M curve for OS and the number of patients at risk. FDA agreed that the applicant should not incur a statistical penalty for this unplanned look, which was disclosed only to FDA and limited personnel conducting the analysis at BMS. At the request of the applicant, the applicant organization remained blinded to the results and on 10/7/10, the top-line results were sent to FDA and the corresponding OS data was also submitted in a CD by an independent statistician. The data cutoff date for this top-line data is 9/16/10. The FDA statistician reviewed the top line results of this study, and based on the results of this study, this reviewer is reassured of the findings of Study MDX10-20.

Since Study CA184024 was conducted in a patient population who had no HLA restriction for study entry, and in first line treatment of metastatic or unresectable advanced melanoma, and since there is no alternative treatment that has shown survival advantage in any line of treatment for this disease, FDA has agreed to grant the indication for ipilimumab in this application without restriction of HLA type or prior treatment status.

Utility of Retreatment

Study MDX010-20 protocol allowed retreatment of patients who had progressed following either stable disease of $\geq$ 3 months duration (beginning Week 12) or an initial objective response (PR or CR) to the first cycle of study therapy with additional cycles of therapy with the originally assigned treatment. No patient was to be re-treated if they experienced a Grade 3 non-dermatologic immune related adverse event (except enodcrinopathies that are well controlled with hormone replacement therapy) or Grade 4 toxicity of any organ system considered related to ipilimumab or placebo administration. Forty subjects (5.9%) of the randomized population received re-induction treatment. Of the forty subjects 29 (7.2%) were in the ipilimumab +gp100 treatment group, 9 (6.6%) were in the ipilimumab arm, and 2 (1.5%) were in the gp100 arm. The experience of re-induction was very limited, hence it can not be recommended as a treatment strategy. Censoring of the retreated subjects at the time of re-treatment did not have significant impact on overall survival results.

Conclusions

The application originally specified an indication for ipilimumab for the treatment of advanced melanoma in patients who have received prior chemotherapy. However, since there is no effective first line therapy and none has shown survival advantage, there is no question that ipilimumab will de-facto be used in the first line setting by the oncology community. Therefore, following the receipt of top line survival curves for the nearly completed first line study of ipilimumab, the review division and the office is comfortable in giving ipilimumab indication for advanced melanoma with or without prior chemotherapy.

6.1 Indication

Ipilimumab is indicated for unresectable stage 3 or metastatic malignant melanoma.

6.1.1 Methods

This application is based on overall survival results form a single trial MDX010-20, which included patients with diagnosis of malignant melanoma or measurable Stage III or IV melanoma, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, were HLA-A2*0201 positive, received at least 1 cycle of one or more regimens (containing IL-2, dacarbazine, temozolamide, fotemustine and/or carboplatin) and had relapsed, failed to respond or did not tolerate the treatment due to toxicity. Six hundred and seventy six patients in this study were randomized in 3:1:1 ratio (stratified by baseline M-stage and prior treatment with IL-2) to the following three arms:

Arm 1: ipilimumab + gp100: ipilimumab (3mg/kg every 3 weeks up to 4 doses) in combination with gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses);

Arm 2: ipilimumab monotherapy: ipilimumab (3mg/kg every 3 weeks up to 4 doses) plus gp100 placebo every 3 weeks for 4 doses;

Arm 3: gp100 monotherapy: ipilimumab placebo (every 3 weeks up to 4 doses) arm plus gp100 (1 mg peptide A and 1 mg peptide B every 3 weeks up to 4 doses).

Intravenous (IV) infusions of ipilimumab or ipilimumab placebo were administered on Days 1, 22, 43 and 64 (i.e. 12-week treatment cycle). Both gp100 and placebo vaccine were administered subcutaneously by injection, immediately following the infusion of ipilimumab or ipilimumab placebo. Following induction cycle, patients entered the follow-up phase.

The primary endpoint of the study was overall survival. The applicant had changed the end point from best objective response rate (BORR) to overall survival at a later stage of the study. This modification of the study was acceptable since study data were not unblinded at that time and the end point of overall survival provides an unbiased assessment of the efficacy of ipilimumab.

As per the protocol, the primary comparison was between combination of ipilimumab and gp 100 with the gp100 arm alone.

Secondary endpoint included overall survival between combination therapy and ipilimumab monotherapy, and between ipilimumab and vaccine monotherapy. Other secondary end points included best objective response rate (BORR) as determined by site investigator tumor assessment up to week 24 and confirmed at least 4 weeks later, duration of response, progression free survival, time to progression, and health-related Quality of Life.

6.1.2 Demographics

The following table shows the demographics for clinical trail MDX010-20.

Table 5: Demographics (MDX010-20)

	Ipi+gp100 N=403	**Ipi N=137**	**gp100 N=136**	**Total N=676**
Age (years)				
Mean (Min-Max)	55.6 (24-84)	56.8 (19-88)	57.4 (23-90)	56.2 (19-90)
Median	57.0	57.0	57.0	57.0
<65 years	291 (72.2)	95 (69.3)	94 (69.1)	480 (71.0)
≥ 65 years	112 (27.8)	42 (30.7)	42 (30.9)	196 (29.0)
Sex (n %)				
Male	247 (61)	81 (59)	73 (54)	401 (59)
Female	156 (39)	56 (41)	63 (46)	275 (41)
Race (n %)				
White	380 (94.3)	129 (94.2)	129 (94.9)	638 (94.4)
Black	3 (0.7)	1 (0.7)	1 (0.7)	5 (0.7)
Hispanic	18 (4.5)	7 (5.1)	5 (3.7)	30 (4.4)
Other	2 (0.5)	0	1 (0.7)	3 (0.4)

The baseline tumor prognostic and prior treatment characteristics are shown below:

Table 6: Baseline tumor prognostic and prior treatment characteristics

	Ipi+gp100 N=403	Ipi N=137	gp100 N=136	Total N=676
Melanoma Duration	401	137	136	674
Mean (Min-Max)	5.09 (0.2-38.9)	4.34 (-0.0-35.9)	5.65 (0.3-31.2)	5.05 (-0.0-38.9)
Median	3.14	2.93	3.67	3.11
M Stage [b]				
M0, M1a,M1b	118 (29.3)	37 (27.0)	38 (27.9)	193 (28.6)
M1c	285 (70.7)	100 (73.0)	98 (72.1)	483 (71.4)
Prior IL-2 [b]				
No	314 (77.9)	105 (76.6)	103 (75.7)	522 (77.2)
Yes	89 (22.1)	32 (23.4)	33 (24.3)	154 (22.8)
LDH				
>ULN	149 (37.0)	53 (38.7)	52 (38.2)	254 (37.6)
≤ULN	252 (62.5)	84 (61.3)	81 (59.6)	417 (61.7)
Unknown	2 (0.5)	0	3 (2.2)	5 (0.7)
Brain Metastasis				
Yes	46 (11)	15 (10.9)	21 (15.4)	82 (12.2)
No	357 (89)	122 (89.1)	115 (84.6)	592 (87.8)
ECOG status				
ECOG 0, 1	398 (99)	136 (99)	132 (97)	666 (98.5)
2, 3	5 (1)	1 (1)	4 (3)	10 (1.5)

The patient demographic and baseline characteristics appear to be comparable between treatment arms (shown in the following table). The median age of the study population was 57 years old. More than 54% of the patients were male. Approximately 94% of the patients were White. The median time from diagnosis of melanoma to study entry appears to be longer in the gp100 arm (3.67 years) as compared with the median duration in the ipi+gp100 (3.14 years) and ipilimumab monotherapy arm (2.93 years), respectively. More than 70% of the patients had M1c stage disease and more than 75% of the patients had not received prior IL-2. About 62% of the patients had baseline LDH values below the upper limit of normal value. The Gp100 arm had the highest percentage of patients with brain metastasis (15% in gp100 arm vs. 11% in each of the ipilimumab+gp100 and ipilimumab monotherapy arm). Approximately 99% of patients had ECOG performance status of 0 or 1 (as required in the inclusion criteria).

The use of prior antineoplastic therapies related to melanoma was also summarized. The result shows that all but 2 patients in ipilimumab+gp100 arm had undergone surgery for treatment of

melanoma and all patients received prior anti-neoplastic medication for melanoma. There were 38%, 44% and 38% of the patients who had received radiotherapy in ipilimumab+gp100, ipilimumab monotherapy and gp100 arm, respectively. The distribution of therapy type appears to be compatible across all three arms. The most common systemic therapy was chemotherapy, then immunotherapy. Over 90% of the patients received chemotherapy. There was higher percentage of patients received immunotherapy in gp100 arm (59%) compared with the number of patients in ipilimumab+gp100 arm (50%) and ipilimumab monotherapy arm (45%).

6.1.3 Subject Disposition

Of the 1783 subjects who enrolled and were screened for study participation, a total of 676 subjects were randomized between 27-Sep-2004 and 24-July-2008. Among the 1107 subjects who failed screening, the most common reason for screen failure noted by site monitors was a negative HLA-A2*0201 test (approximately two-thirds of failures). The second most common reason for screen failure was the presence of pre-existing active brain metastases, accounting for approximately 10% of screen failures. Other less frequent reasons included withdrawal of consent and ineligibility based on study eligibility criteria such as ECOG performance status or prior treatment status.

The following table shows disposition of the randomized subjects:

Table 7: Patient Disposition

	Ipi+gp100	Ipi	gp100	Total
Randomized	403 (100.0)	137 (100.0)	136 (100.0)	676 (100.0)
Not Treated	22 (5.5)	6 (4.4)	5 (3.7)	33 (4.9)
Treated[a]	381 (94.5)	131 (95.6)	131 (96.3)	643 (95.1)
Discontinued Study				
Death (all causes)	306 (75.9)	100 (73.0)	119 (87.5)	525 (77.7)
Subject withdrew consent	10 (2.5)	2 (1.5)	3 (2.2)	15 (2.2)
Other	3 (0.7)	3 (2.2)	2 (1.5)	8 (1.2)
Lost to follow-up	3 (0.7)	2 (1.5)	1 (0.7)	6 (0.9)
Protocol violation	0	0	1 (0.7)	1 (0.1)
Trial completed	81 (20.1)	30 (21.9)	10 (7.4)	121 (17.9)

a Data is presented based on randomization; however, 1 subject (M20-392-0066) was randomized to Ipi+gp100 but treated with gp100. Therefore dosing and safety analyses will count this subject in the gp100 treatment group.

6.1.4 Analysis of Primary Endpoint(s)

Overall Survival (Study MDX010-20)

At the time of the data cutoff date (6/19/10), the median follow-up time was 8.9 months. The ipilimumab+gp100 arm had statistically significantly longer overall survival as compared with that of the gp100 monotherapy arm [hazard ratio (HR) 0.68 (95% CI: 0.55, 0.85), p-value=0.0004 stratified log rank test] and, median survival times of 9.95 vs. 6.44 months;. The comparison of survival between two ipilimumab-containing arms was not significantly different, but the ipilimumab monotherapy arm was significantly longer survival as compared with that of the gp100 arm [HR 0.66 (95% CI: 0.51, 0.87), p-value= 0.0026 stratified log rank test], with median survival times of 10.12 vs. 6.44 months, respectively. The survival results from the three treatment arms are presented in the following table:

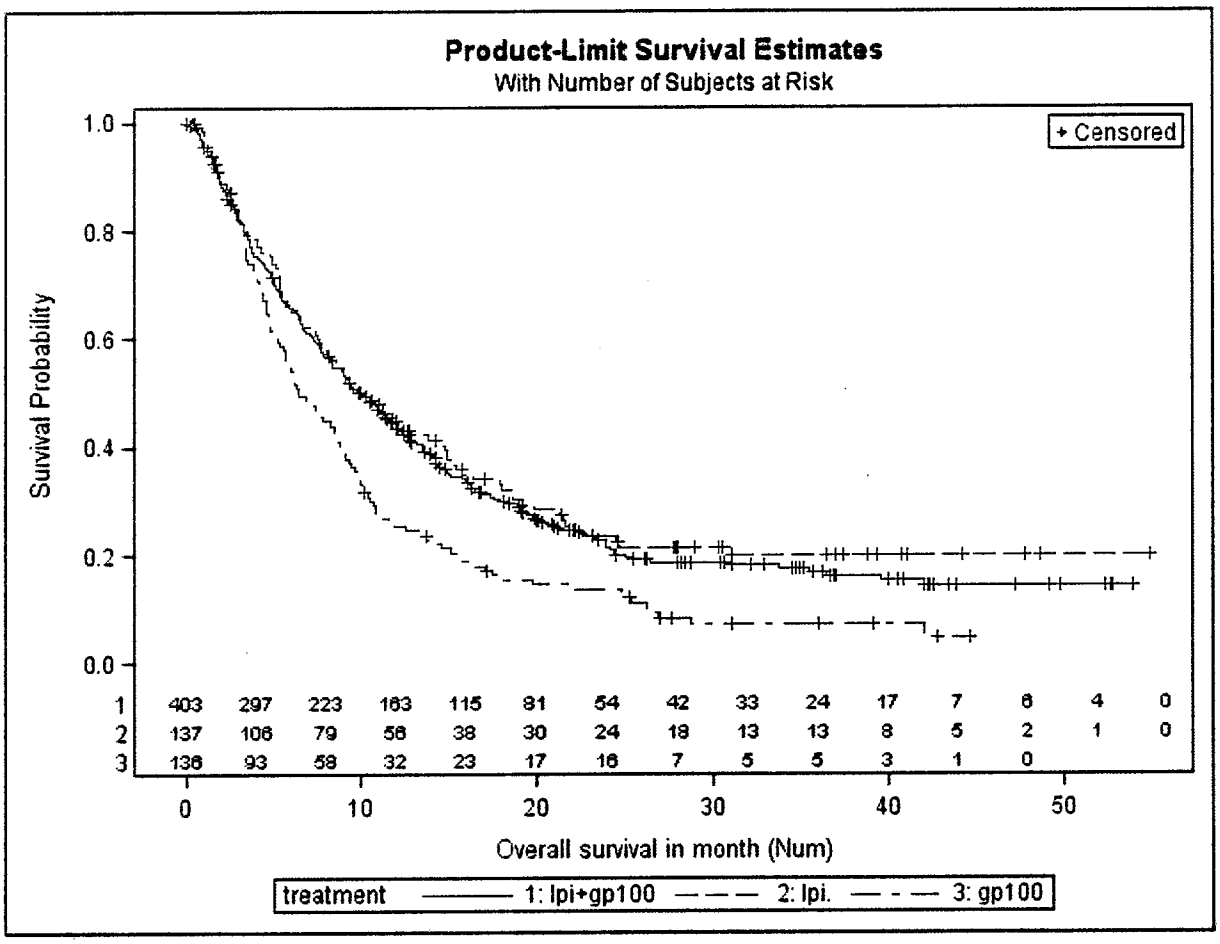
Table 8: Summary of Overall Survival

	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.

The following figure showing the Kaplan Meier estimates of overall survival was generated by the statistical reviewer:

Figure 1: Overall Survival: MDX010-20



Exploratory Analyses:

Results Excluding Study Site 301: Based on their inspection of study site, DSI recommended that data from this site not be used to support a regulatory decision. This site enrolled 19 patients (11, 4 and 4 from ipilimumab+gp100, ipilimumab monotherapy and gp100 arm, respectively). The results (shown in the following table) of the analysis conducted by the statistical reviewer excluding this site indicate that the impact of this site on the overall survival results is minor.

Table 9: Summary of Overall Survival results excluding Site 301

	Ipi+gp100 N=392	**Ipi N=133**	**gp100 N=132**
Number of events	298	97	115
Median (months) (95% CI)[a]	9.66(8.38, 11.43)	10.12 (7.72, 13.8)	6.44 (5.06, 8.71)
HR vs. gp100 with 95% CI[b]	0.70 (0.56, 0.86)	0.68 (0.52, 0.89)	
Stratified log-rank p value vs. gp100 [a]	0.0010	0.0050	
HR vs. ipi alone with 95% CI [a]	1.04 (0.83, 1.31)		
Stratified log-rank p value vs. ipi alone [a]	0.7378		

[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 randomization. 95% confidence intervals (CI) for HR were computed using Cox model.

Results Censoring patients who received "reinduction": There were 40 patients who received at least one dose of study treatment as part of a re-induction (second) cycle (7.2%, 6.6% and 1.5% of the patients in ipilimumab+gp100, ipilimumab and gp100 arm, respectively). Among these 40 patients who received re-induction dose, there were 6 deaths from ipilimumab+gp100, 3 deaths from ipilimumab and 2 deaths from gp100 arm. To explore the possible confounding effect for patients who received re-induction dose, the statistical reviewer performed the overall survival analysis by censoring the retreated patients at the time when the first re-induction dose was administered. The results are shown in the following table:

Table 10: Summary of overall survival results censoring at the time of re-induction.

	Ipi+gp100 N=403	Ipi N=137	gp100 N=136
Number of events	306	100	119
Median (months) (95% CI) [a]	9.66 (8.38, 11.40)	9.72 (7.72, 12.45)	6.44 (5.36, 8.61)
HR vs. gp100 with 95% CI [a]	0.70 (0.57, 0.87)	0.67 (0.51, 0.88)	
Stratified log-rank p value vs. gp100 [a]	0.0013	0.0035	
HR vs. ipi alone with 95% CI [a]	1.05 (0.84, 1.33)		
Stratified log-rank p value vs. ipi alone [a]	0.6659		

[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 randomization. 95% confidence intervals (CI) for HR were computed using Cox model.

Figure 2: Subgroup Analysis for Overall Survival (Ipilimumab+gp100 versus gp100; MDX010-20)

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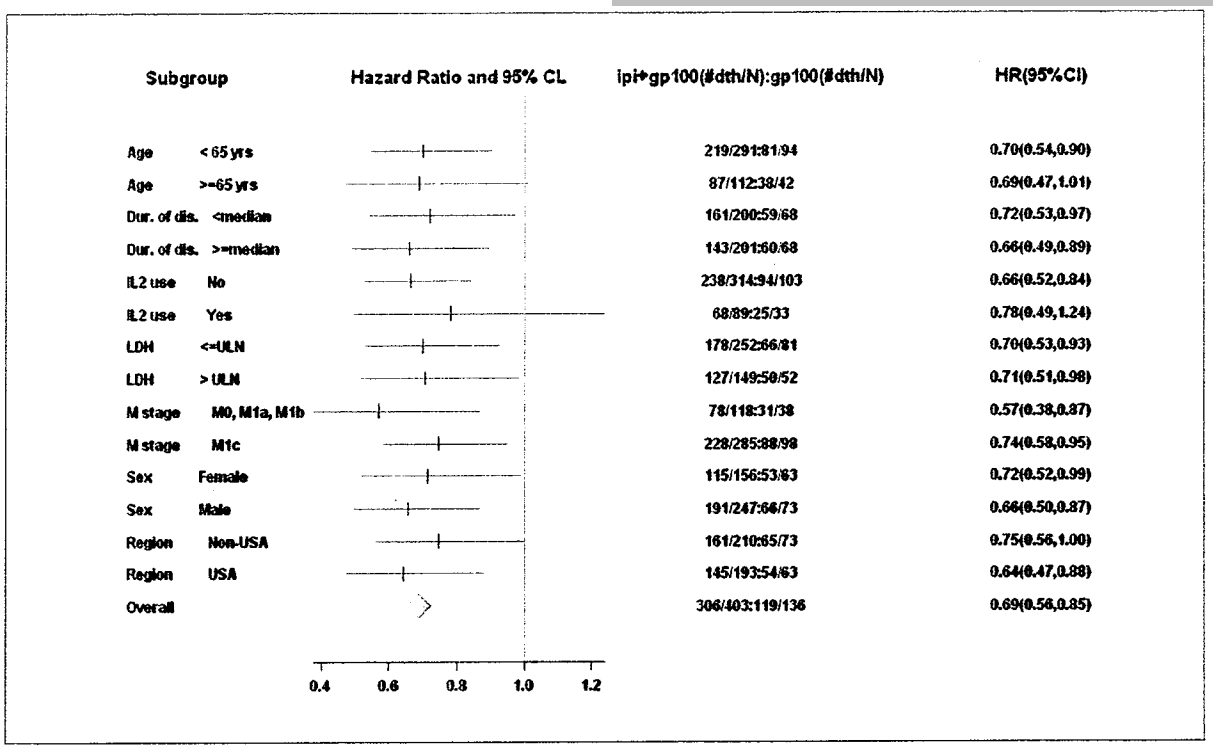

Figure 3: Subgroup Analysis for Overall Survival (Ipilimumab versus gp100; MDX010-20)

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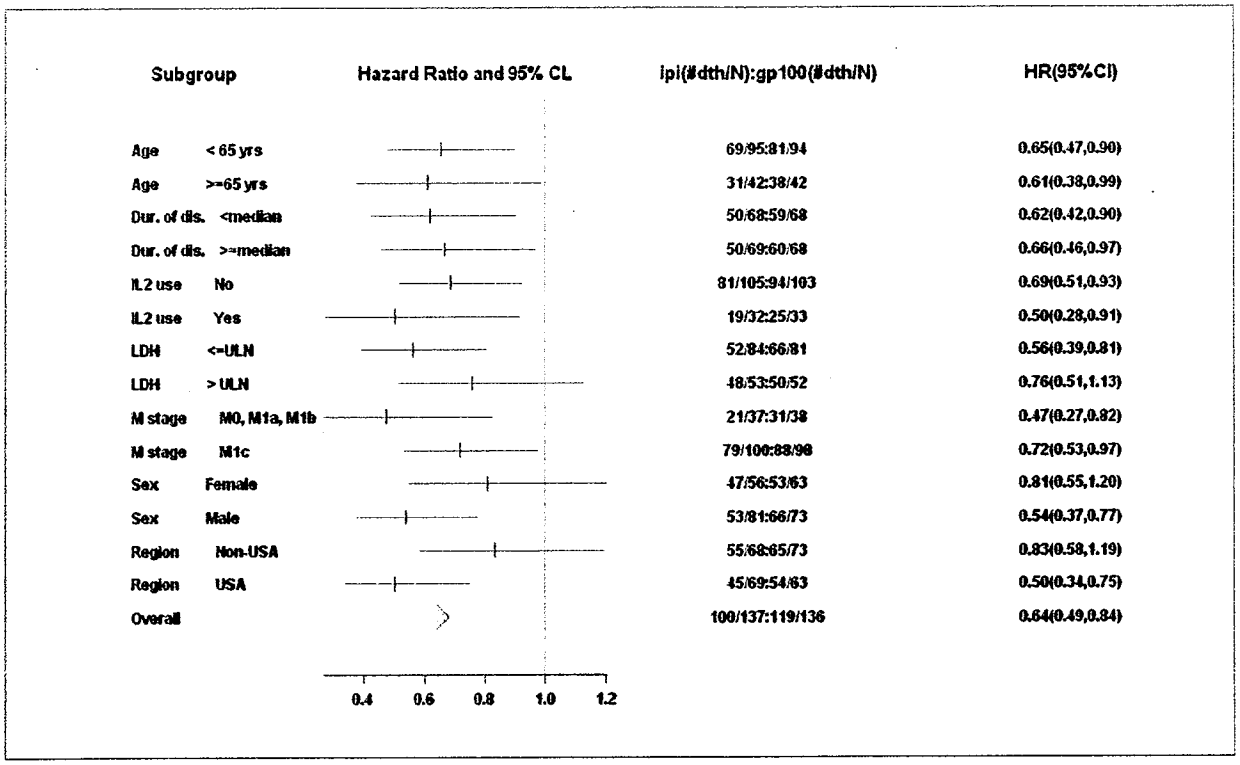

As seen in the above two figures, both the ipilimumab containing arms showed consistent effect across various subgroups.

Overall Survival (Phase 2 Studies: CA184-022 and CA184-008):

For completeness of review, the statistical reviewer also analyzed the overall survival results from the two studies CA184-022 and CA184-008 because these two studies also enrolled patients with previously treated advanced melanoma and each study has more subjects than the other phase 2 studies. The following table is taken from the statistical review:

Table 11: Summary of Overall Survival Results: MDX010-20 and Phase 2 studies

Study	Treatment	#deaths/total subjects	Median Survival in months (95% CI)
MDX010-20	Ipi 3mg/kg+Gp100	306/403	10.0(8.4,11.5)
	Ipi. 3mg/kg	100/137	10.1(7.7,13.8)
	Gp100	119/136	6.4(5.4,8.6)
CA184-022	0.3mg/kg_pre-treated	57/72	8.6(7.4,11.3)
	3mg/kg_pre-treated	53/71	8.7(6.8,11.4)
	10mg/kg_pre-treated	50/72	11.4(6.9,16.1)
CA184-008	10mg/kg_pre-treated	109/155	10.2(7.6,16.3)

As seen in the above table, estimated median survival across dose levels can be inconsistent when determined in small studies. For example, the median survival time for 3 mg arm from study MDX010-20 was closer to what had been observed in the 10 mg/kg arm in studies CA184008 and the median survival time for gp100 arm is even shorter than what was observed in the 0.3 mg/kg arm of study CA184022.

6.1.5 Analysis of Secondary Endpoints(s)

Best Overall Response Rate (Study MDX010-20)

Best overall response rate (BORR) was based on the investigator's assessment using the WHO response criteria and was calculated based on the data from the first cycle only and included response assessments up to week 24 (confirmed at week 28 if needed). The BORR were 5.7% (95% CI:3.7, 8.4), 10.9% (95% CI:6.3, 17.4) and 1.5%(95% CI:0.2, 5.2) for the ipilimumab+gp100, ipilimumab monotherapy and gp100 arms, respectively. The nominal p-values based on Cochran Mantel Haenszel test for the comparison of BORR with ipilimumab + gp100 compared with gp100 monotherapy was p=0.043, favoring the combination arm and for the comparison of BORR with of ipilimumab + gp100 with ipilimumab monotherapy arm was p=0.040, favoring the ipilimumab monotherapy arm. The nominal p-value for comparison between ipilimumab monotherapy arm versus gp100 was 0.0012, favoring the ipilimumab monotherapy arm.

Table 12: Summary of Best Overall Response Rate (MDX010-20)

	Ipi+gp100 N=403	Ipi N=137	gp100 N=136	Total N=676
BORR (n[%]) (95%CI) [a]	23 (5.7) (3.7,8.4)	15 (10.9) (6.3,17.4)	2 (1.5) (0.2,5.2)	40(5.9) (4.3,8.0)
CR	1(0.2)	2(1.5)	0	3(0.4)
PR	22(5.5)	13(9.5)	2(1.5)	37(5.5)
SD	58(14.4)	24(17.5)	13(9.6)	95(14.1)
PD	239(59.3)	70(51.1)	89(65.4)	398(58.9)
NE	83(20.6)	28(20.4)	32(23.5)	143(21.2)
Nominal P-value [b] (vs. gp100)	0.0433	0.0012		
Nominal P-value [b] (vs. Ipilimumab)	0.0402			

CR = confirmed complete response, PR = confirmed partial response, SD = stable disease, PD = progressive disease, NE = not evaluated, missing, or unknown.
a Non-responder is defined as SD, PD, unknown and missing. Responder is defined as a confirmed CR/PR.
b P-values were computed using CMH test stratified by baseline M-stage at randomization (M0, M1a, M1b vs. M1c) and prior IL-2 treatment (Yes vs. No).

As noted in the statistical review, since there was no specified hierarchical testing rule for various secondary end points, the p-value can not be interpreted for the comparison of BORR between treatment arms.
Although the above data appear to support the primary treatment effect seen in terms of improvement in overall survival, response rates in this range do not necessarily point to a convincing treatment effect.

A similar pattern of low response rates was seen among the Phase 2 studies included in the application.

Table 13: Best Objective Response Rate: MDX010-20 and Phase II studies

Study	Treatment	# responders /total	Response rate (%) (95% CI)
MDX010-20	Ipi 3mg/kg+Gp100	23/403	5.7(3.7,8.4)
	Ipi. 3mg/kg	15/137	10.9(6.3,17.4)
	Gp100	2/136	1.5(0.2,5.2)
CA184-004	3mg/kg_pre-treated	2/26	7.7(0.9,25.1)
CA184-022	0.3mg/kg_pre-treated	0/72	0 (0,5.0)
	3mg/kg_pre-treated	3/71	4.2(0.9, 11.9)
	10mg/kg_pre-treated	8/72	11.1(4.9,20.7)
CA184-008	10mg/kg_pre-treated	9/155	5.8(2.7,10.7)

The above data are provided primarily to show that the BORR has not been particularly consistent across these small studies with ipilimumab. For example, the BORR for 3 mg arm from study MDX010-20 was closer to what had been observed in the 10 mg arm in studies CA184-022. The BORR for 10 mg arm (11%) observed for study CA184-022 was almost double of what had been observed for 10 mg arm from study CA184-008 (5.8%).

Progression Free Survival MDX010-20:
Progression-free survival (PFS) was one of the secondary end points in the MDX010-20 trial, but not specified as a key secondary end point. Based on the investigator-assessed PFS, the median PFS time was similar across the three treatment arms.

The following summary table of the investigator-determined PFS was generated by the statistical reviewer:

Table 14: MDX010-20: Investigator Assessed PFS

	Ipi+gp100 N=403	Ipi N=137	gp100 N=136
Number of events	371	122	127
Median (months) [a] 95% CI [a]	2.76 2.73, 2.79	2.86 2.76, 3.02	2.76 2.73, 2.83
HR (vs. gp100) (95% CI) [b]	0.81 (0.66, 1.00)	0.64 (0.50, 0.83)	
Stratified log-rank nominal p value (vs. gp100) [a]	0.0464	0.0007	
HR (vs. ipi alone) (95% CI) [b]	1.25 (1.01, 1.53)		
Stratified log-rank test: nominal p value (vs. ipi alone) [a]	0.0371		

[a] 95% confidence intervals (CI) 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 (M0, M1a, M1b vs. M1c) and prior treatment with IL-2 (Yes vs. No) at randomization.
95% confidence intervals (CI) for HR computed using Cox model.

The both ipilimumab +gp100 and ipilimumab monotherapy arm appear to have reduced risk as compared with that of the gp100 arm. Comparison of the two ipilimumab arms appear to indicate a 25% higher risk for the ipilimumab + gp100 as compared with that of the ipilimumab monotherapy arm (Hazard ratio=1.25, 95% CI= [1.01, 1.53]).

6.1.6 Other Endpoints

Duration of Response: The median duration of response was 11.47 months (95% CI: 5.36, NR) for the 23 subjects in the ipilimumab plus gp100 group who achieved an objective tumor response, as determined by the investigator using modified WHO criteria. The median duration of response was not reached for responders in the ipilimumab monotherapy arm because of the number of objective tumor responses that were ongoing as of the data cut-off date(10 of 15). Likewise, 1 of the 2 patients with an objective responses in the gp100 monotherapy group had not progressed as of the data cut-off date thus the median duration cannot be calculated.

Time to Progression and Time to response could not be assessed because the first tumor assessment was done at 12 weeks.

Heath-related quality of life (HRQoL) was assessed using the EORTC QLQ C-30 HRQoL questionnaire. Questionnaire completion rate at baseline was approximately 95% dropped to the range of 61 to 65% during week 12 and less than 15% at week 24. There were no meaningful changes in any of the functional or global scales.

6.1.7 Subpopulations

Age

Subgroup analyses based on 65 years as the age cutoff points (<65, ≥ 65 years old) for OS were performed by the statistical reviewer. Both ipilimumab+gp100 and ipilimumab monotherapy appear to have a similar beneficial effect on overall survival when compared with the gp100 arm in both younger and older patient population.

Table 15: Summary of Overall Survival by Age Subgroup (MDX010-20)

Comparison	Age subgroup	# events/# Patients Ipi +gp100	# events/# Patients Gp100	Hazard Ratio[a] (95% CI) *Ipi containing arm vs control*
Ipi.+gp100 vs gp100	< 65 yrs	219/291	81/94	0.70(0.54,0.90)
	>=65 yrs	87/112	38/42	0.69(0.47,1.01)
Ipi vs. gp100		**Ipi**	**Gp100**	
	< 65 yrs	69/95	81/94	0.65(0.47,0.90)
	>=65 yrs	31/42	38/42	0.61(0.38,0.99)

[a]Hazard ratio based on the unstratified Cox's proportional hazards model.

Gender

Subgroup analyses comparing overall survival between treatment arms within subgroups defined by gender were performed by the statistical reviewer. These subgroup analyses showed that patients of both gender benefited from ipilimumab treatment.

Table 16: Summary of Overall Survival by Gender Subgroup (MDX-010-20)

Comparison	Age subgroup	# of events/# of Patients Ipi +gp100	# of events/# of Patients Gp100	Hazard Ratio[a] (95% CI) *Ipi containing arm vs control*
Ipi.+gp100 vs gp100	Female	115/156	53/63	0.72(0.52,0.99)
	Male	191/247	66/73	0.66(0.50,0.87)
Ipi vs. gp100		**Ipi**	**Gp100**	
	Female	47/56	53/63	0.81(0.55,1.20)
	Male	53/81	66/73	0.54(0.37,0.77)

Geographic Region

Subgroup analysis comparing overall survival between arms within different regions was summarized by North America, Europe and other regions, in the following analyses performed by the statistical reviewer. In most of the subgroup analyses, the hazard ratio were less than 1.0 indicating a beneficial effect of OS in the ipilimumab-containing arm.

Table 17: Summary of Overall Survival by Region (MDX010-20)

Comparison	Comparison	Age subgroup	# of events/# of Patients Ipi +gp100	# of events/# of Patients Gp100
Ipi+gp100. vs gp100	Europe	121/154	47/54	0.77(0.55,1.08)
	North America	155/209	58/68	0.65(0.48,0.88)
	Other	30/40	14/14	0.73(0.38,1.38)
Ipi vs. gp100		**Ipi**	**Gp100**	
	Europe	38/49	47/54	0.70(0.46,1.08)
	North America	51/75	58/68	0.58(0.39,0.84)
	Other	11/13	14/14	0.80(0.34,1.86)

[a]Hazard ratio based on the unstratified Cox's proportional hazards model.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The efficacy of ipilimumab in malignant melanoma is supported by a single study that showed improved overall survival when ipilimumab was used at a dose of 3 mg/kg. Hence this is the recommended dose. The sponsor has agreed to a post-marketing commitment to do a head to heads comparison of safety and efficacy of 3 mg/kg dose with the 10 mg/kg dose in this patient population.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary endpoint of the study MDX010-20, on which this application is based, was overall survival in a disease which has a dismal prognosis. Persistence of efficacy and/or tolerance effects is therefore not discussed.

6.1.10 Additional Efficacy Issues/Analyses

The trial supporting the efficacy of ipilimumab, MDX010-20 had an active control of gp100 vaccine. Therefore there was a concern whether the overall survival results were driven by a poor outcome in the control arm. The fact that the ipilimumab monotherapy and the ipilimumab + gp100 arm both showed robustly superior overall survival compared to the gp100 arm was an argument in favor of a true drug effect of ipilimumab. However, to be reassured further, the review division asked for and reviewed the top line survival curves for the nearly completed study CA184-024, which is also conducted in advanced melanoma population. This action provided the necessary reassurance.

Another issue with the Study MDX010-20 was that it was limited to patients with HLA-A2+ phenotype. This was done for in order to adequately assess response to the vaccine component, which required HLA-A2 phenotype to ensure successful presentation of the peptide vaccine. However, there is a possibility that the HLA selection contributed to the positive results seen in the study. Again, review of the top line results of the CA184024 study, which did not have HLA phenotype restriction as part of eligibility criteria, provided the necessary reassurance.

The applicant tried to address this issue of the prognostic and predictive significance of the HLA-A2 phenotype by exploratory analysis based on the subset of patients with HLA A2 assessments obtained in Phase 2 studies. The following table lists the available sample sizes for the HLA A2 positive and HLA A2 negative subjects across these trials and as a percentage of the total trial participants.

Table 18: HLA Typing in Phase 2 studies

Study	Objective	Population	Dose	HLA test/Total	HLA -	HLA +
184004	Explore pre-treatment characteristics with response and/or toxicity	Unresectable III/IV Pre-treated Not-Pretreated	3 mg 10 mg	37/40 39/42	16 (9 prior treated) 18 (11 prior treated)	21 (15 prior treated) 21 (14 prior treated)
007	Estimate rate of ≥ Grade 2 diarrhea with ipilimumab with prophylactic oral budesonide or placebo	Unresectable III/IV Pre-treated Not-Pretreated	10 mg +/- budenoside	100/115	38	62
008	Best overall response rate	Previously treated	10 mg	148/155	87	61
022	Best overall response rate	Previously treated	0.3 mg 3 mg 10mg	69/73 70/72 69/72	44 38 47	25 32 22

As seen above, none of the studies had adequate sample sizes and none of the studies above could exclude the possibility of impact of HLA A2 phenotyping on as a prognostic or predictive biomarker, especially since none of the studies had the primary end point of survival. However, as noted above, since Study CA184024 was done in patients who had no HLA restriction, it is not considered necessary that ipilimumab be only indicated for HLA A2 positive advanced melanoma patients.

Response Rates in the Re-treatment Population:

As noted, only 40 subjects in study MDX010-20 received more than 1 cycle of treatment. The protocol was not followed in determining the eligibility for the re-treatment population. The applicant analyzed the response rates in 32 of these subjects since eight subjects were considered ineligible from the analysis perspective; 5 subjects had a progressive disease at week 24 and 3 subjects did not meet the original eligibility criteria for study entry. Additional scrutiny of these 32 subjects show that 10 of these did not have a PD recorded in the database, 1 had unknown assessment, and 2 subjects had a stable disease of less than 90 days to be eligible. Therefore only 19 subjects were eligible for response assessment. The applicant states that there were 6 responses (1 CR and 5 PR) in the 32 patients. However, from these six subjects at least 3 subjects

(M20-3950625, M20-447-0739 and M20-422-0740) did not have a PD recorded in the database to be eligible.

The applicant also did a retrospective review of their dataset to determine how many subjects met the re-treatment criteria from the study dataset and how many were actually treated. Of the 41 subjects who would have been eligible, 21 actually received treatment.

Given the uncertainty of the benefit and the extremely small sample size, re-treatment of ipilimumab can not be recommended.

7 Review of Safety

Reviewer's NOTE: The applicant was asked to provide a thorough characterization of all the immune-mediated events that occurred in clinical trial MDX010-20. This information was only received by FDA on February 24, 2011. This new information has not been reviewed. Appropriate sections of this safety section will be revised upon review of this new information.

Safety Summary

Ipilimumab, due to its mechanism of action of potentiating T cell function by blocking the binding of CTLA-4 to B7, is can cause the development of severe immune-mediated adverse reactions. Ipilimumab at the recommended dose of 3 mg/kg was evaluated in the primary efficacy study MDX010-20, in which 511 subjects received this drug and another 131 subjects received gp100 vaccine. Because of its control arm and the large size, this study was used to describe the incidence of adverse events, and characterization of the important immune related adverse reactions. A Phase 2, Study CA184022, is the only study submitted in the application that evaluated the safety of three different doses of ipilimumab; investigator-assessed immune mediated adverse events from this study are discussed separately in this safety assessment. Information regarding rare adverse reactions and immunogenicity was supplemented from other Phase 2 studies included in this application, as well as case narratives of ongoing studies.

The major issue with the application was the identification and characterization of immune-related adverse reactions. As per the protocol, MDX010-20, an Immune-Related Adverse Event (irAE; or autoimmune breakthrough event as it was previously called) is defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. The protocol specified that efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event an irAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. This information was to be captured in a supplemental page of case report form.

However, the applicant discontinued use of this form approximately half-way through the study. Instead the applicant used a programmatic approach to label all treatment-related events (in this double-blind study) within a group of MedDRA preferred terms categorized as immune related. Accurate identification of immune-mediated adverse event is important for the appropriate characterization of these events, and what interventions were effective. The applicant was therefore asked to devise a case definition of these events, to confirm the appropriateness of the case definition through review of the events identified, and to provide all the supportive information in their database used to define the immune-mediated adverse reactions. The overall strategy for this adjudication is described in section 7.1.2.

In clinical trial MDX010-20, of the 511 subjects treated with ipilimumab, 330 subjects completed the planned 4 doses. Fifty-two subjects discontinued ipilimumab and gp100/vaccine placebo due to an adverse event. According to the applicant's analysis conducted with the BMS-adjudicated case definitions of immune-mediated enterocolitis, immune-mediated adverse reactions accounted for a total of 38 discontinuations among the ipilimumab-treated patients, with enterocolitis, dermatitis and hepatitis accounting for permanent ipilimumab treatment discontinuation in 24, 7 and 6 patients, respectively. There were dose delays due to adverse events in 23 instances in ipilimumab-treated subjects. There were 10 deaths from immune related toxicities that are probably related to ipilimumab treatment; these included 5 deaths due to enterocolitis with 4 of these having intestinal perforation, one death due to toxic epidermal necrolysis, 1 death due to Guillian Barre syndrome and 1 death due to hepatic failure. The other deaths were due to myelodysplastic syndrome in a subject who received multiple cycles of chemotherapy in the past, and death due to 'vascular leak syndrome' in a patient with edema prior to study entry and a history of hemochromatosis.

Overall, 262 subjects reported at least 1 serious adverse event (SAE). The similarilty in the rates of SAEs across the three treatment groups (41% in the ipilimumab + gp100 group, 42% in the ipilimumab group and 39% in the gp100 group) reflect the gravity of the underlying disease.

In MDX010-20, the most significant adverse reactions were immune-mediated adverse reactions. Severe colitis occurred in 7% of subjects, while severe hepatitis occurred in 2%, severe dermatitis in 2.5%, neuropathies in <1%, and severe endocrinopathies in 9 of 511 subjects. Other severe immune-mediated adverse events included nephritis, pneumonitis, meningitis, eosinophilia, and pericardial effusion.

Immune-mediated adverse reactions appeared to occur more frequently with the 10 mg/kg dose than with the recommended dose of 3 mg/kg. In a randomized, three-arm, dose-ranging, double-blind Phase 2 clinical trial, CA184022, which employed 0.3 mg/kg, 3 mg/kg and 10 mg/kg doses, investor-assessed immune-mediated adverse reactions occurred at a higher rate (25%) compared to 3 mg/kg dose (7%). The applicant has agreed to a post-marketing requirement (PMR) to perform a clinical trial directly comparing the safety and efficacy of the 3 mg/kg and 10 mg/kg doses.

The applicant developed management algorithms, particularly regarding systemic corticosteroid and immunosuppressant use, during the development of ipilimumab. The applicant was asked to provide analyses of the safety experience for ipilimumab when the management algorithm was followed and when it was not to determine if such an approach mitigates the risk of immune-mediated adverse reactions. That information is pending. However, review of the case narratives show that corticosteroids appear to be effective in treatment of these immune-mediated adverse events.

Since ipilimumab produces unusual and severe immune-mediated side effects, the applicant has proposed a REMS program which includes a communication plan for healthcare professionals and a medication guide patients.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical trials used to evaluate safety are listed in section 5.1.

Safety analysis populations
The safety evaluation primarily depends on Study MDX010-20, because of its large size compared to the Phase 2 studies and since it is the only study which had a non-ipilimumab control. Other than local injection site reactions, the gp100 vaccine is not generally expected to produce severe adverse reactions. The safety data for the three arms of the MDX010-20 study are generally presented separately. The characterization of interventions and outcome of immune-mediated events are presented for the combined population of the two ipilimumab-containing arms.
The safety evaluation primarily depends on Study MDX010-20, because of its large size compared to the smaller Phase II studies, and since it is the only study which had a non-ipilimumab control. Other than local injection site reactions, GP100 vaccine is not generally expected to produce severe adverse reactions. The safety data for the three arms of the study are generally presented separately. The characterization of interventions and outcome of immune-mediated events are presented for the combined population of the two ipilimumab containing arms.

The applicant summarized the experience of the Phase 2 studies by pooling the data across studies according to the dose (3 mg and 10 mg). The following four studies which enrolled patients with pre-treated advanced melanoma were used for this integrated safety assessment by dose (CA184008, CA184022, CA184007, and CA184004; 111 subjects treated at 3 mg/kg and 325 subjects treated at 10 mg/kg). This integrated safety analysis is further discussed in section 7.1.3. There appears to be an increased incidence of immune-mediated adverse events at the 10 mg/kg dose compared with the 3 mg/kg dose. Since Study CA184022 is the only study that directly compared the safety of different doses of ipilimumab, immune-mediated adverse events from this study are discussed separately in this safety assessment.

The applicant included case narratives from subjects with death, serious adverse events and study drug discontinuation from ongoing studies in their entire development program. This was reviewed to note selected rare adverse events.

The applicant also included adverse events dataset and summary table showing the incidence of common adverse events from all melanoma studies in their database (n=1498) for inclusion of all preferred terms describing adverse events with incidence < 10% in the package insert, as part of labeling support document (labeling support document dated 1/6/11, amendment 40). This summary table included the following studies: CA184004, CA184007, CA184008, CA184022, CA184042, (b) (4); MDX010-08, (b) (4) and MDX010-20. The clinical study reports for the studies numbers that are underlined were not included in the application package. Since this list of preferred terms (which included terms such as upper respiratory infection, night sweats, dry skin etc) are derived from these mostly single arm studies, it is not considered informative to the prescribing physician and hence not recommended for inclusion in the final product label.

7.1.2 Categorization of Adverse Events

The applicant used MedDRA version 12.1 for coding the adverse events. The coding terms used by the applicant were appropriate.

The major issue regarding analysis of safety which arose during the review of this application was the approach taken by the applicant in describing the important category of immune-mediated adverse events. As discussed in Section 6.9.2 of the MDX10-20 protocol, an Immune-Related Adverse Event (irAE; or autoimmune breakthrough event as it was previously called) was defined as an adverse event of unknown etiology, associated with drug exposure and consistent with an immune phenomenon. Efforts were to be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event an irAEs. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. In Appendix 3 of the protocol, it is stated that documentation of test results should be included on the appropriate CRF pages and/or forwarded to Medarex, Inc. The appendix also refers to the most current versions of the investigator brochure for the suggested treatment algorithms for immune mediated adverse events.

The investigator was required to make a medical assessment of the potential immune-based nature of an adverse event on a case-by-case basis and manually document these on case report forms (CRFs) (check box on the Adverse Event CRF page supported by a supplemental page for diagnostic detail). According to the applicant's response to FDA information request, (October 12, 2010; amendment # 24), after the partnership between BMS and Medarex was established, the protocol was amended (Amendment 3), and thereafter, the use of the supplemental CRF page for individual investigator assessments of irAEs in MDX010-20 was discontinued.

Reviewer's Comment: According to the information submitted to the BLA, protocol amendment 3 did not describe discontinuation of the supplemental case report form for autoimmune breakthrough (immune related) adverse events. It was only in the last amendment amendment 6, dated 15 January 2009 that the supplemental CRF was discontinued. This amendment to the protocol occurred more than 6 months after the applicant notified FDA/CBER that it was ending further enrollment to the study. Thus the applicant did not collect the appropriate case report forms during the study as stipulated in the protocol.

Instead, all the investigator-designated treatment related preferred terms that were supposed to be used to further investigate immune related adverse events, were designated as immune related adverse events. In addition, establishing causal attribution was challenging due to the fact that this was a double-blind study, making it difficult for the investigator to assign relationship to the study drug. Additionally, the CRF had check boxes for relationship to be ascribed to blinded gp100 or ipilimumab. The applicant, in their presentation in the CSR, elected to consider checking of either of the check-box as related to the assigned treatment. While the case report forms had check boxes for relationship to be ascribed to blinded gp100/placebo or to blinded ipilimumab/placebo therapy, in the safety analysis presented in the clinical study report (CSR), elected to group all adverse events, regardless of the investigator's designation to a single drug, as related to the assigned treatment.

The 'programatic' approach of the applicant in designating all 'treatment-related' adverse events that belonged to a particular preferred term as immune-mediated, without the benefit of further investigation, was problematic for accurately characterizing the severity, outcome or response to intervention of these events, as was the failure to identify adverse events attributed to a single component of therapy. For example, using this approach and as reported in the CSR for MDX010-20, 32% subjects in the gp100 arm were considered to have any grade irAE, which was not credible.

A major deficiency of the safety database was that posed significant difficulties in the review of the application was that the case report forms submitted with application referenced supportive information which was provided in the application. This made it impossible to match the case narratives with the case report forms.

Considering the importance of determining the immune-mediating events as accurately as possible, during the course of the review of this application, the applicant was asked to follow the approach originally proposed but not followed in the safety analysis. Specifically, the applicant was asked to develop a case definition of specific, commonly reported immune-related adverse events and to provide supporting data (such as imaging, endoscopy or biopsy findings) which verified that basis for designation as an immune-related adverse event. This resulted in a major amendment. The required supporting information was mainly available to the applicant for grade 3 and 4 events, which were likely to be associated with serious adverse events.

The purpose of developing these case definitions and further analyses based on identification of cases meeting such a definition is to simulate the condition stipulated in the protocol; i.e. patients with adverse events would be further investigated as noted above to define immune related adverse events. Such as retrospective look has is not without deficiencies, particularly where there is lack of information. Also, investigator in this blinded study would have initiated treatment at times without knowing whether the patient was exposed to ipilimumab. However, analyses of treatment intervention in strictly defined cases would provide a reasonable guidance to management of these cases.

Case definitions were designed to characterize adverse events (AEs) in MDX010-20 as either "likely", "definitely" or "not" an ipilimumab-associated AE. The case definitions are for the most common and potentially severe AEs of special interest involving the gastrointestinal, skin, liver and endocrine system, as well as other less frequent AEs that are known to be potentially inflammatory in nature (i.e., neuropathy, uveitis, non-infectious myocarditis).

The data sources used by the applicant for adjudication were the clinical database (CRFs) and patient narratives [Corporate Adverse Event Reporting and Evaluation System (CARES) and clinical database]. The CARES database includes communication from the investigator to BMS (SAE and queries) and, in some cases, primary source documentation (pathology, microbiology, radiology and hospital discharge reports).

This type of adjudication exercise does have its flaws, in that it is dependent on the amount of additional information available. Where information was not available as in many grade 2 events, it was not simply possible to adjudicate the events. These events which the applicant was unable to adjudicate were conservatively listed as immune-mediated events. Also, using the response to corticosteroids as part of definition, biases the evaluation of the necessity for administration of steroids as a required treatment for such events.
These unable to events were conservatively listed as immune mediated events. Also, using the response to corticosteroids as part of definition, does bias the evaluation of steroids as the treatment of such events.

Adverse events with the following terms diarrhea (PT diarrhea), colitis (PT colitis, enterocolitis, large intestinal ulcer, proctitis), intestinal perforation (PT intestinal perforation, large intestinal perforation, peritonitis) were adjudicated under the composite term of enterocolitis as follows:

Table 19: Enterocolitis case definition

A Definitely	B Likely	C Not Attributed
Evidence of inflammation by (A1) biopsy or (A2) endoscopy[b]	With concomitant immunosuppression, (B1) AE improves or (B2) resolves	(C1) Intervening treatment with chemotherapy proximal to the event and known to cause diarrhea or colitis
Presence of concomitant (A3) fecal leukocytes or (A4) elevated calprotectin	(B3) Concomitant to AE, evidence of bowel wall inflammation by-abdominal imaging	(C2) Document tumor progression at site of perforation
	(B4) The AE persists ≥ 1 week or worsens	(C3) Same grade AE present at baseline or (C4) in medical history
	(B5) Subject has at least one other ipilimumab-associated inflammatory GI AE.[a]	(C5) Evidence that AE likely due to infection or (C6) concomitant medication
		(C7) AE rapidly (< 1 week) resolves **without initiating concomitant immunosuppression**.

a. For another inflammatory AE in same organ criteria, the other AE can be any grade (even grade 1) and can occur before or after the Grade 3 AE of interest (i.e., regardless of timing)

b. If patient narrative has text describing results of either biopsy or endoscopy, we will assume that a biopsy or endoscopy, respectively were performed.

Adverse events with the following preferred terms were adjudicated as Hepatitis: under composite term of increase in ALT/AST (PT ALT, ALT increased, AST, AST increased, Liver function tests abnormal, hepatic function abnormal), composite term of Autoimmune hepatitis (PT hepatitis, autoimmune hepatitis), under composite term of Liver failure (PT hepatic failure, acute hepatic failure)

Table 20: Hepatitis Case Definition

A Definitely	B Likely	C Not Attributed
(A1) Evidence of inflammation by biopsy	(B1) Subject has at least one other ipilimumab-associated inflammatory liver AE[a].	(C1) Intervening treatment with chemotherapy proximal to the event and known to cause hepatitis
	With concomitant immunosuppression, (B2) AE improves or (B3) resolves	(C2) Document tumor progression or (C3) documented bile duct obstruction
		(C4) Same grade AE present at baseline or (C5) in medical history
		(C6) Evidence that AE likely due to infection, (C7) concomitant medication, or (C8) other documented medical etiology

a. For another inflammatory AE in same organ criteria, the other AE can be any grade (even grade 1) and can occur before or after the Grade 3 AE of interest (i.e., regardless of timing)

Dermatitis: All preferred terms describing rash and pruritis, dermatitis, toxic epidermal necrolysis, Steven Johnson Syndrome etc were adjudicated as follows:

Table 21: Dermatitits case defintion

A Definitely	B Likely	C Not Attributed
(A1) Evidence of inflammation by biopsy	(B1) Subject has at least one other ipilimumab-associated inflammatory skin AE[a].	(C1) Intervening treatment with chemotherapy proximal to the event and known to cause skin AE
	With concomitant immunosuppression, (B2) AE improves or (B3) resolves	(C2) Same grade AE present at baseline or (C3) in medical history
	(B4) Skin AE persists ≥ 1 week or worsens	(C4) Evidence that AE likely due to infection, (C5) other concomitant medication or (C6) radiation
		(C7) AE rapidly (< 1 week) resolves without initiating concomitant immunosuppression.
		(C8) Injection site reaction

a. For another inflammatory AE in same organ criteria, the other AE can be any grade (even grade 1) and can occur before or after the Grade 3 AE of interest (i.e., regardless of timing)

Endocrinopathy: Preferred terms indicating various endocrine dysfunction were adjudicated as follows:

Table 22: Endocrinopathy case definition

A Definitely	B Likely	C Not Attributed
(A1) Evidence of inflammation by biopsy	(B1) Hypopituitarism without evidence of pituitary enlargement	(C1) Intervening treatment with chemotherapy proximal to the event and known to cause endocrine AE
(A2) Hypopituitarism with pituitary enlargement	(B2) Subject has at least one other ipilimumab-associated inflammatory endocrine AE[b]	(C2) Document tumor progression at endocrine organ of AE
	With concomitant immunosuppression, (B3) AE improves or (B4) resolves[a]	(C3) Same grade AE present at baseline or (C4) in medical history
		(C5) Evidence that AE likely due to infection, (C6) other concomitant medication or (C7) other documented medical etiology

a. With the exception of adrenal insufficiency that responds to corticosteroids

b. For another inflammatory AE in same organ criteria, the other AE can be any grade (even grade 1) and can occur before or after the Grade 3 AE of interest (i.e., regardless of timing)

Evaluation of the preferred terms uvetitis, nephritis, pneumonitis, and myocarditis, as well as other preferred terms which might been immune-related were adjudicated as follows:

Table 23: Other Infrequent immune-mediated Adverse Reactions case definitions

A Definitely	B Likely	C Not Attributed
(A1) Evidence of inflammation by biopsy	(B1) Subject has at least one other ipilimumab-associated inflammatory AE in the same organ.	(C1) Intervening treatment with chemotherapy proximal to the event and known to cause AE
	With concomitant immunosuppression, (B2) event improves or (B3) resolves	(C2) Document tumor progression at site of organ of AE
		(C3) Same grade AE present at baseline or (C4) in medical history
		(C5) Evidence that AE likely due to infection, (C6) metabolic disorder, (C7) concomitant medication, or (C8) other documented medical etiology

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Since MDX010-20 clinical trial was the only clinical trial with a non-ipilimumab containing control arm, it provided the best opportunity to estimate the incidences of adverse events against the background of the underlying cancer. Also, as noted in 7.1.2, the approach taken by the applicant to designate immune mediated adverse events required further adjudication of adverse events data.

The applicant summarized the experience of the Phase 2 studies by pooling the data across studies according to the dose (3 mg and 10 mg). The following four studies were used for this: CA184008, CA184022, CA184007, and CA184004. A summary description of the studies is included in section 5.1.

The 3 mg/kg dose pooled data summarized by the applicant included a total of 111 subjects, 71 subjects from CA184022 and 40 subjects from CA184004. The 10 mg/kg pooled data summarized by the applicant included a total of 325 patients; these included 71 subjects from CA184022, 155 subjects in CA184008, 57 subjects who had not received budesonide in CA184007, and 42 subjects in CA184004.

For this review, pooled data is not used to characterize the incidence of common adverse events, since eliciting common adverse events in the advanced melanoma population enrolled in these studies is limited by the lack of a control arm. The number of patients in the primary clinical trial MDX010-20, which has an internal control, is sufficient for this purpose.
However, to explore the dose relationship of the adverse events of interest, namely immune related adverse events, comparison of investigator assessed immune related events is made between 0.3, 3 mg and 10 mg doses of ipilimumab using study CA184022. The investigator-assessed immune-related adverse reactions from the pooled 10 mg/kg group (which included the 72 subjects from CA184022) are also described in section 7.3.4.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In clinical trial MDX010-20, 511 subjects received ipilimumab (380 in ipilimumab plus gp100 and 131 in ipilimumab monotherapy groups) and 132 received gp100 monotherapy group in this study. The exposure to ipilimumab for the first four doses (also called induction phase) is summarized below.

Table 24: MDX010-20: Ipilimumab Exposure

Number of ipilimumab doses received	Ipilimumab +gp100 (n=380)	Ipilimumab (n=131)
1	30 (7.9%)	10 (7.6%)
2	56 (14.7%)	16 (12.2%)
3	52 (13.7%)	17 (13%)
4	242 (63.7%)	88 (67.2%)
Mean (SD)	3.3 (1.00)	3.3 (0.96)
Median (SD)	4	4

Thirty-eight of the Yervoy-treated subjects received more than 1 cycle of treatment (also called re-induction); this included 29 (7.2%) subjects in the ipilimumab + gp100 group and 9 (6.6%) subjects in the ipilimumab group. Of these, 3 subjects each in the ipilimumab + gp100 group and in the ipilimumab group received 2 cycles and 1 subject in the ipilimumab + gp100 group received 3 cycles of treatment. The number of subjects receiving more than one cycle of treatment was thus very limited. However, the exposure was adequate to describe the safety of the recommended dosing regimen of 3 mg/kg every 3 weeks for 4 doses.

However, the exposure was adequate to describe the safety of the recommended dosing regimen of 3 mg/kg every 3 weeks for 4 doses.

The demographics of clinical trial MDX010-20 are described in section 6.1.2 for efficacy population. The safety population is described below:

Table 25: MDX010-20: Demographics of Safety Population

Characteristic	Ipilimumab N =131	Ipilimumab + gp100 N=380	Gp 100 N=132
Age ≥ 65	39 (30%)	102 (27%)	39 (29%)
Age < 65	92 (70%)	278 (73%)	93 (71%)
Female	52 (40%)	150 (39%)	61 (46%)
Male	79 (60%)	230 (61%)	71 (54%)
M0, M1a, or M1b			
M1c	95 (73%)	266 (70%)	94 (71%)
ECOG PS 0	71 (54%)	222 (58 %)	70 (53)
ECOG PS 1	69 (45%)	154 (41%)	58 (44)

7.2.2 Explorations for Dose Response

The "response" in this application was measured by overall survival, which was assessed in only one study, MDX010-20. The dose used was 3 mg/kg every 3 weeks for a total of 4 doses.

7.2.3 Special Animal and/or In Vitro Testing

Please see section 4.3 of this review.

7.2.4 Routine Clinical Testing

Routine clinical testing in the clinical trial MDX010-20 was adequate. The results are summarized in 7.42 and 7.4.3.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please also see section 4.3. Ipilimumab is an immunoglobulin, which is not metabolized by liver cytochrome P450 enzymes or other drug metabolizing enzymes. Ipilimumab as a monoclonal antibody targeting CTLA-4 is unlikely to have an effect on CYPs or other drug metabolizing enzymes in terms of inhibition or induction.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other CTLA4 inhibitors approved in the US or elsewhere. CTLA4 inhibitors currently being evaluated as investigational drugs in clinical trials under IND show a similar safety profile. Please see section 2.4.

7.3 Major Safety Results

7.3.1 Deaths:

The following list shows the deaths in Yervoy treated patients Study MDX010-20,that potentially are related to the study drug.

Table 26: MDX010-20: Potential Ipilimumab Related Deaths

Subject ID	Treatment group	Age/gender	Study day of death	Principle Toxicity
M20-001-0468	Ipilimumab + gp100	70/M	108	Colitis
M20-291-0506	Ipilimumab + gp100	58/F	91	Colitis with perforation
M20-360-0339	Ipilimumab + gp100	53/M	489	MDS with myelofibrosis[1]
M20-384-0636	Ipilimumab + gp100	59/M	25	Intestinal perforation
M20-400-0119	Ipilimumab + gp100	42/M	18	Toxic Epidermal Necrolysis
M20-426-1133	Ipilimumab + gp100	69/M	66	Peritonitis[2]
M20-442-1092	Ipilimumab + gp100	62/M	102	Guillain-Barre Syndrome
M20-007-0059	Ipilimumab	62/M	25	Liver failure
M20-393-0903	Ipilimumab	77/F	193	Colon perforation
M20-433-1045	Ipilimumab	55M	20	vascular leak syndrome[3]

[1] Subject had received multiple cycles of chemotherapy in the past
[2] Subject had peritoneal carcinomatosis in addition to ulcerating colitis in the sigmoid colon
[3] Many confounding factors; patient had edema, weight gain prior to study entry, had history of hemochromatosis, and was thought to have disease progression at the time of death.

The following subject, listed by the applicant as a treatment-related death, appears to be due to co-morbid disease and complications of underlying melanoma.

M20-163-0223: Ipilimumab + vaccine group; 46 year old with extensive metastatic disease, with an infected melanoma neck mass and abscess, died of sepsis on day 22 of the study.

The following deaths which occurred in subjects on the gp 100 arm were listed by the applicant as related to the study drug. Upon review, these do not appear to be study drug-related.

M20-378-0723: This 67 year old female with Stage IV melanoma with disease in the lymph nodes, reported grade 1 loss of appetite, recorded as an adverse event on day 22, which continued until her death. On day 75 she presented with pain with worsening left groin nodal mass, and was started on morphine sulfate. She died on day 85, with the investigator attribution of death due to disease progression, and unrelated to study therapy.

M20-495-0558: This 43-year-old white male had Stage IV, M1c disease metastatic to adrenal gland, lymph nodes, and soft tissue, and received treatment with gp100 monotherapy in MDX010-20. He also had a medical history significant for right sided inguinal and axillary lymphadenopathy. He was hospitalized on Day 32 (dose 2 given Day 24) due to lymphedema of

lower extremities and right arm (Grade 3) and thrombosis of the right arm (Grade 3). Doppler echocardiography showed deep vein thrombosis of the right femoral, tibial, and fibular veins in the context of compression from tumor mass, and thrombosis of the right axillary and subclavian veins. Subcutaneous enoxaparin 60 mg once daily was begun. On Day 37 broad spectrum antibiotics were begun for presumptive pneumonia; blood cultures were negative. He died later that day in the setting of sudden hypotension and decreased consciousness. The differential included sepsis, massive pulmonary embolism and systemic inflammatory reaction. An autopsy was not performed.

In the Phase 2 studies, the following deaths are considered by this reviewer as ipilimumab related according to the review of the narratives provided in this application.

Table 27: Phase 2 studies: Ipilimumab related deaths

Subject ID	Ipilimumab dose	Age/gender	Study day of death	Principle Toxicity
CA184004-18-4045	Ipilimumab 3 mg/kg	67/M	59	Intestinal perforation
CA184004-7-4002	Ipilimumab 10mg/kg	58/F	91	Colitis with perforation
CA184008-50-8076	Ipilimumab 10mg/kg	53/M	489	Acute Glomerulonephritis
CA184008-60-8011	Ipilimumab 10mg/kg	70/F	115	Hypovolemic shock, history of hypopituitarism
CA184008-66-8072	Ipilimumab 10mg/kg	67/F	87	Hepatic failure (hx of liver mets confounding)
CA184042-4-3	Ipilimumab 10mg/kg	66/M	44	Intestinal perforation with sepsis

7.3.2 Nonfatal Serious Adverse Events

Overall, 262 subjects in clinical trial MDX010-20 suffered at least 1 serious adverse event (SAE). Consistent with the gravity of the underlying disease, the proportion of subjects with SAEs were similar across the three treatment groups (41% in the ipilimumab + gp100 group, 42% in the ipilimumab group and 39% in the gp100 group. Drug-related SAEs, as per the investigator's attribution, were reported in 52 (13.7%), 23 (17.6%), and 5 (3.8%) of the subjects in the ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy groups, respectively. The most common drug-related SAEs reported in the ipilimumab plus gp100 and ipilimumab monotherapy groups were colitis (14 [3.7%] and 7 [5.3%] subjects, respectively) and

diarrhea (15 [3.9%] and 5 [3.8%] subjects, respectively), neither was reported as a drug-related SAE in the gp100 monotherapy group.

Drug-related SAEs reported under the MedDRA system organ classification (SOC) of endocrine disorders were the next most common events reported in the ipilimumab plus gp100 and ipilimumab monotherapy groups, most commonly hypopituitarism (3 [0.8%] and 2 [1.5%] subjects, respectively) and hypophysitis (1 [0.3%] and 2 [1.5%] subjects, respectively); there were no reports of hypopituitarism or hypophysitis as drug-related SAEs in the gp100 monotherapy group.

The most significant adverse events are those that are due to the pathologic immune response to ipilimumab. These frequently resulted in hospitalizations and are further described under significant adverse events (section 7.3.4).

7.3.3 Dropouts and/or Discontinuations

In clinical trial MDX010-20, on-study adverse events resulting in discontinuation of study drug at any time during the study occurred in 51 (10%) subjects in the ipilimumab-treated groups (35 [9.2%] subjects in ipilimumab plus gp100, and 17 [13.0%] subjects in ipilimumab monotherapy) compared to five (3.8%) subjects in the gp100 monotherapy group. The most common AEs leading to study drug discontinuation reported in the ipilimumab plus gp100 and ipilimumab monotherapy groups were colitis (10 [2.6%] and 3 [2.3%] subjects, respectively) and diarrhea (10 [2.6%] and 2 [1.5%] subjects, respectively); neither diarrhea or colitis was reported as leading to discontinuation for any subject in the gp100 monotherapy group.

According to the applicant's analysis using the BMS-adjudicated case definitions of immune mediated enterocolitis, immune-mediated adverse reactions accounted for a total of 38 patients with permanent discontinuation of treatment among the ipilimumab-treated patients, with enterocolitis, dermatitis and hepatitis accounting for permanent discontinuation of treatment in 24, 7 and 6 subjects, respectively.

Although the case report forms captured the reason that a dose delay occurred (due to AE, scheduling conflict or other), the case report forms did not specify which AE, if more than one was present at the time of treatment delay. According to the MDX dataset (submitted as part of the analysis dataset), dose delay due to AE occurred in 23 instances in ipilimumab-treated subjects. The applicant was asked to provide information on dose delays due to specific toxicity. The dose delay information is still pending at the time of this review.

In pooled data from subjects in phase 2 studies using the 3 mg/kg dose (n=111), drug toxicity was the reason for ipilimumab discontinuation in 7% of subjects. In the pooled data from subjects in the phase 2 studies using 10 mg/kg dose (n=325), study drug toxicity resulted in discontinuation of ipilimumab in 17% of subjects.

7.3.4 Significant Adverse Events

The most significant adverse events of ipilimumab are related to the pathologic immune response including autoimmunity due to T-cell activation, which result from the mechanism of action of ipilimumab. The programmatic approach adopted by the applicant in identification of these adverse events was unsatisfactory in accurately describing these immune-mediated events, the time-course of these events and the response to interventions such as immunosuppressant therapy. The applicant was asked to develop case definitions as discussed in section 7.1.2 for important categories of immune-mediated adverse events. The applicant carried out the adjudication of immune-mediated adverse reaction for subjects in clinical trial MDX010-20.

Immune-mediated adverse events

Since most of the information was available for ≥grade 3 events, there were very few grade ≥3 events in the "unable to adjudicate" category. Among Grade ≥ 3 adverse events, the following adverse event identified by the "programmatic" search for immune-mediated adverse events could not be assessed for the following reasons

Of the 48 immune-mediated events (12.6 %) in the ipilimumab+gp100 group, 6 were in the "unable to adjudicate" category; of the 20 events in the ipilimumab group (15.3%), 2 were in the "unable to adjudicate" category. In the gp100 group there was a single event, which was in the "unable to adjudicate" category.

In addition, data from site 301 was excluded based on the recommendation of DSI that these data not be used to support the application:

Site 301: Immune-mediated events ≥Grade 3 occurred in 1 subject at this site in the ipilimumab + gp 100 arm who had diarrhea. Exclusion of this patient from the safety dataset (based on the recommendations of the Division of Scientific Integrity due to the findings during the audit of this site) would not affect the percentage of patients with enterocolitis.

The following table shows the ≥ grade 3 immune-mediated adverse events:

Table 28: MDX010-20: ≥ Grade 3 Immune Mediated Adverse Reactions

	Ipilimumab (n=131)	Ipilumumab +gp100 (n=380)
Any Immune-mediated Adverse Reaction	15%	13%
Enterocolitis	7%[a]	7%[a,b]
Hepatitis or hepatic failure[a]	1%	2%
Dermatitis	2%	3%
Neuropathy	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
Pericardial effusion[c]	0	<1%

a Including fatal outcome.
b Including intestinal perforation.
c Underlying etiology not established.

Adjudication for grade 1 events was not possible, since the applicant stated that there was no additional information.

For grade 2 events, where information was sparse, the results of adjudication showed the following: Of the 62 events in the ipilimumab + gp100 group, 8 were in the "unable to adjudicate" category, of the 35 in the ipilimumab 8 were in the "unable to adjudicate" category, while of the gp100 group 6 of the 12 events were in the "unable to adjudicate" category. The six events considered likely in the gp 100 group were dermatitis in 4, and colitis and neuropathy in 1 each.

Yervoy-induced grade 2 immune-mediated events were most frequently identified as dermatitis (40 events in ipi+gp100 group, 25 in ipilimumab group), endocrinopathy (7 in ipi+gp100 and 6 in ipi), colitis (13 in the ipi +gp100 group and 8 in the ipi group), and hepatitis (6 in ipi+gp100 group and 8 in ipi group).

The FDA statistical reviewer performed a time-to-event analysis for grade 3 to 5 immune-mediated adverse events. For gastrointestinal events where the numbers were sufficient, the 25 events in the ipi+gp100 arm occurred with a median time of onset of 7 weeks (min 1.6 weeks

and max 17.9 weeks), 18 of which resolved with a median time to resolution of 8.6 weeks (min 2.4 weeks, macx10 weeks). For the 9 events in the ipilimumab group, the median time to onset was 9.4 weeks (range 5 weeks to 13.4 weeks) 8 of which were documented to have resolved, with a median time to resolution of 5.1 weeks (range 0.6 weeks to 18.7 weeks).

The applicant provided time to onset and resolution analysis for grade 3 to 5 immune mediated adverse events based on KM estimates. However, given the small number of subjects and unclear censoring, the applicant was asked to provide descriptive statistics for subjects who resolved and those who did not resolve based on interventions recommended by the applicant for inclusion in the package insert. This information is still pending. The applicant was asked to further characterize all the adjudicated immune mediated adverse events, including hospitalizations, for inclusion in the package insert. The applicant's response is pending at this time. This section will be updated at that time.

Phase 2 Clinical Trial CA184022: Adjudication for immune-mediated adverse reactions per the case definitions used in MDX010-20 was not done by the applicant for clinical trial CA184022. The applicant used the 'programatic' approach to describe these events, i.e. all treatment related adverse events (as per the investigator) that fall into a predefined list of MedDRA terms were considered immune-mediated. This trial, although double-blind, used ipilimumab in all three arms at 0.3 mg/kg, 3 mg/kg and 10 mg/kg doses. The following table depicts the investigator assessed grade 3 and 4 immune-mediated adverse events according to the dose during the induction period.

Table 29: CA184022: Investor Assessed Immune Mediated Adverse Reactions

Category of Grade 3/4 immune related event	0.3 mg/kg N=72	3 mg/kg N=71	10 mg/kg N=71
overall	0	5 (7%)	18 (25%)
GI	0	2 (3%)	11 (16%)[2]
Liver	0	0	2 (3%)
Endocrine	0	2 (3%)	1 (1%)
Skin	0	1 (1%)	3 (4%)
Other	0	0	1* (1%)

* other included pneumonitis

In the pooled safety group of subjects receiving 10 mg/kg dose (n=325), which included the 71 subjects from trial CA184022, grade 3-5 immune related adverse events during induction period were 24% (GI 11.7%, Hepatic 7.1%, endocrine and skin 2.5% each, others 2.8%; the others included 1 myocarditis, 1 scleritis, 1 arthritis, 2 pneumonitis, 1 glomerulonephritis, 3 with pancreatinc enzyme elevations, 1 with multi-organ failure). Thus, severe immune mediated adverse events appear to occur at a higher frequency at 10 mg/kg dose than the recommended 3 mg/kg dose.

Across clinical studies with YERVOY, 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, diverticulitis, and arthritis, autoimmune thyroiditis, hyperthyroidism.

Among cases of neuropathies, myasthenia gravis has been reported in other clinical studies. Subject CA184087-1-22, developed dysphagia and pneumonia on day 34 (12 days post 2nd dose of ipilimumab at 10 mg/kg, and exhibited increasing muscle weakness. On day 47 she had positive ANA 1:640 (negative at baseline), and positive acetyl choline (Ach) receptor binding, blocking and modulating antibodies. The subject was treated with systemic corticosteroids, and the event was reported as resolved on day 147.

7.3.5 Submission Specific Primary Safety Concerns

Ipilimumab can cause immune-mediated/autoimmune adverse reactions due to its mechanism of action. Such reactions can manifest in any organ system. Additional immune-mediated adverse reactions are likely to be identified when this drug is more widely used. The steps taken to mitigate risks (boxed warning in the proposed product label, the medication guide, the communication plan in the REMS, and the fact that this drug is administered as an infusion and hence under the supervision of an oncologist), should lead to prompt recognition and intervention for such adverse reactions.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events in the Study MDX010-20, defined as those which occurred in at least 5% of patients in ipilimumab-containing arms and with a greater than 5% increased incidence over the control gp100 arm for events of any severity (grade 1-5) and those with a greater than 1% higher incidence as compared to the control group for ≥ grade 3 events are shown below:

Table 30: MDX010-20: Common Adverse Events

	Percentage (%) of Patients					
	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg+gp100[a] n=380		gp100[a] n=132	
System Organ Class[a]/ Preferred Term	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Gastrointestinal Disorders						
Diarrhea	32	5	37	4	19	1
Colitis	8	5	5	3	2	0
Skin and Subcutaneous Tissue Disorder						
Pruritus	29	0	19	0.3	11	0
Rash	21	1	20	1	7	0
General Disorders and Administration Site Conditions						
Fatigue	41	7	34	5	31	3

Common Adverse Events Excluding site 301: The incidence (expressed as %) of above adverse events were also analyzed excluding the data from site 301. There was no change in the results.

7.4.2 Laboratory Findings

Hematology: Ipilimumab treatment did not have significant impact on hematological parameters of hemoglobin, absolute neutrophil count (ANC) or platelets, in Study MDX10-20. There were no grade 3-4 events of thrombocytopenia. Grade 3-4 anemia occurred in 1.7%, 0.8% and 4% of subjects in the ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy groups, respectively. Grade 3-4 abnormalities in white blood cell count (WBC) and ANC were reported in < 1% of subjects in each group. The differential white counts, including absolute lymphocyte counts remained within normal range through the study.

Liver Function Tests: In clinical trial MDX010-, the on-study abnormalities in ALT, AST, total bilirubin, and alkaline phosphatase (ALP) were primarily Grade 1-2 in severity. As shown below, Grade 3-4 abnormalities in ALT and AST were each reported in < 2% of subjects and Grade 3-4 abnormalities in total bilirubin were reported in < 1% of subjects. Grade 3-4 abnormalities in ALP were reported in 1.7%, 3.3%, and 0.8% of subjects in the ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy groups, respectively.

Table 31: Liver Function Test Abnormalities (MDX010-20)

	Percentage (%) of Patients					
	YERVOY 3 mg/kg n=131		YERVOY 3 mg/kg+gp100[a] n=380		gp100[a] n=132	
Test	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
ALT	29 (24%)	2 (2%)	59 (17%)	4 (1%)	19 (15%)	1(1%)
AST	34 (28%)	2(2%)	69 (20%)	6 (2%)	23(18%)	1(1%)
Total Bilirubin	8 (7%)	1 (1%)	16 (5%)	2 (1%)	2 (2%)	0
Alkaline Phosphatase	34 (28%)	4 (3.3%)	93 (26%)	6 (2%)	37 (29%)	1 (1%)

Renal Function: Ipilimumab treatment did not have significant impact on renal function as measured by serum creatinine. Abnormalities in serum creatinine, which were primarily of Grade 1 and 2 (10 to 11%) severity, were equally distributed in the three study groups.

Baseline values for rheumatoid factor (RF) were similar across the 3 treatment groups. At Week 12, a majority of subjects (189/206 subjects, 91.7% ipilimumab plus gp100; 70/72 [97.2%] ipilimumab monotherapy and 61/65 [93.8%] gp100 monotherapy) who were normal at baseline continued to have normal RF values. No difference in the grade shift pattern for RF was noted across treatment groups. Anti-nuclear antibody (ANA) tests was positive at baseline in 53, 54 and 54 % of subjects in Ipi+gp100, ipi alone and gp100 groups respectively. At week 12, ANA was positive in 40%, 37% and 38% respectively in the three groups.

Review Comment: The number of subjects with positive ANA at baseline is striking, compared to what would be usually expected based on clinical experience, and perhaps reflects on the assay methodology.

Changes in thyroid function, as measured by thyroid stimulating hormone (TSH) levels, is shown by the shift table below. Baseline mean values for TSH were comparable across the 3 treatment groups. At Week 12, a majority of subjects (178/206 subjects, 86% ipilimumab plus gp100; 59/74, 80% ipilimumab monotherapy and 60/65, 92% gp100 monotherapy), that were normal at baseline continued to have normal TSH values. No difference in shift pattern for TSH was noted across treatment groups. An equal number of subjects shifted from normal to high or normal to low.

Table 32: MDX010-20: TSH: Baseline Versus Week 12 levels

Week 12 visit	Ipilimumab + gp 100 (baseline)			Ipilimumab (baseline)			gp 100 (baseline)		
	Low	Normal	High	Low	Normal	High	Low	Normal	High
Low	7	14	0	2	9	0	3	2	0
Normal	7	178	16	1	59	5	4	60	4
High	0	14	10	0	6	2	0	3	6

Thyroid function tests may be difficult to interpret in this fairly sick population. However, it is still important to perform these tests because they are routinely available and may point to hypopituitarism, which has very non-specific symptoms, or to primary thyroid disease.

7.4.3 Vital Signs

In study MDX010-20, vital signs were collected at baseline and at 30, 60, 90 and 150 minutes from the start of infusion. There were no clinically meaningful changes in vital signs. Similarly, there were no significant changes in vital signs among subjects in the pooled safety dataset in which patients received 3 mg/kg or 10 mg/kg during ipilimumab infusions.

7.4.4 Electrocardiograms (ECGs)

In study MDX010-20, ECGs were only collected at baseline. Study CA184004 collected serial, triplicate ECGs at screening, baseline (Day -1), Day 1, and Day 64 (prior to infusion, and 90 minutes and 150 minutes after starting infusion) in 25 subjects treated with 3 mg/kg and 32 subjects treated with 10 mg/kg ipilimumab. ECGs were sent to an ECG Core Laboratory for interval duration measurement adjudication and wave form analysis. A limited number of subjects also had ECGs collected at Week 24.

No clinically-meaningful changes from baseline heart rate, QRS, or PR intervals or wave forms were observed after treatment with 3 mg/kg or 10 mg/kg ipilimumab. QTcF was generally comparable between the 3 mg/kg and 10 mg/kg groups at measured time points. Mean QTcF interval changes from time-matched baseline were small.

7.4.5 Special Safety Studies/Clinical Trials

As part of ipilimumab development program, the applicant had performed some exploratory pharmacogenomic studies. Please see genomics review for details. The following is excerpted from that review. DNA was collected in four phase 2 studies (CA184004, CA184007, CA184008, CA184022) and associations between immune-related gene variants and irAEs were assessed. Consistent with the sponsor's analyses, a missense mutation in CD86 (rs2681417) was associated with increased risk of GI irAEs in patients receiving ipilimumab. Other associations with skin, hepatobiliary, and GI events were seen. However, several limitations preclude definitive conclusions regarding the strength of the associations, including 1) lack of uniform DNA sample acquisition from analyzed phase 2 studies; 2) no DNA collection in the pivotal phase 3 study; 3) lack of justification for candidate gene/SNP selection; 4) limited numbers of patients treated with doses other than 10 mg/kg; and 5) questionable irAE definition. No definitive label modifications are warranted at this time.

7.4.6 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. None of the subjects in Study MDX10-20 developed antibodies. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients and neutralizing antibodies against ipilimumab detected.

Because trough levels of ipilimumab interfere with the ECL assay results, a subset analysis was performed. In this analysis it was observed that 6.9% of 58 evaluable patients, who were treated with 0.3 mg/kg dose, tested positive for binding antibodies against ipilimumab.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The recommended dose of ipilimumab in unresectable stage 3 or stage 4 is 3 mg/kg every 21 days for a total of 4 doses, based on improved overall survival seen with MDX010-20 study contained in this application. The application contained a Phase 2 double-blind trial CA184022 that randomized patients to three fixed doses 0.3 mg/kg, 3 mg/kg and 10 mg/kg doses. The investigator-assessed severe immune-mediated adverse events (grade 3-4) occurred at a higher frequency at 10 mg/kg dose than the recommended 3 mg/kg dose. These finding are discussed in section 7.3.4

Safety During Re-induction:

A limited number of patients (40) in study MDX010-20 received more than 4 doses of originally assigned treatment. The safety assessments in the tables 28 and 30 incorporate these subjects. Here the safety of these subjects is summarized separately. Thirty four of the retreated subjects completed the four doses during re-induction. Five of the seven who started the second re-induction cycle completed the four additional doses. Only one subjects received a third re-induction cycle and he completed the four doses during that cycle. One subject discontinued treatment due to an adverse event of grade 3 colitis. Including that patient, there were a total of 4 immune-mediated adverse reactions were seen that were of grade 3 in severity and included diarrhea, rash and eosinophilia. There were no deaths attributed to ipilimumab during re-induction.

7.5.2 Time Dependency for Adverse Events

The time dependency of the important and severe immune-related adverse reaction of enterocolitis is discussed in section 7.3.4. The applicant was asked to provide analyses of the time to onset of applicant-adjudicated immune-mediated adverse events, combining the two arms that utilized ipilimumab. This information is still pending at the time of this review.

7.5.3 Drug-Demographic Interactions

The overall safety profile of ipilimumab at 3 mg/kg was similar between subjects ≥ 65 years of age and those < 65 years of age. Similarly there were no notable differences in safety profile in men compared to women.

7.5.4 Drug-Disease Interactions

The majority of subjects had stage M1c at baseline, with small numbers of subjects for other M stages (M0, M1a, and M1b). Overall, the observed safety profile of ipilimumab was similar across all M-Stage subgroups.

7.5.5 Drug-Drug Interactions

Since ipilimumab is a monoclonal antibody, like most therapeutic proteins, it is not metabolized by liver cytochrome P450 metabolizing enzymes and is not expected to have an effect on cytochrome P450 or other drug metabolizing enzymes in terms of inhibition or induction. Thus, no formal drug-drug interaction study was conducted with ipilimumab.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The application did not contain any information on human carcinogenicity. The applicant is seeking an indication for the use of ipilimumab in advanced melanoma, a malignancy with very poor outcome and a short lifespan.

7.6.2 Human Reproduction and Pregnancy Data

As per the applicant, there were no pregnancies reported among subjects while on treatment with ipilimumab or within 70 days of last dose within the clinical development program.

7.6.3 Pediatrics and Assessment of Effects on Growth

Ipilimumab has not been studied in the pediatric population. Metastatic or unresectable advanced melanoma is uncommon in the pediatric age group.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no experience with drug overdose. In clinical trials patients received up to 20 mg/kg as a single dose (the applicant did not provide information as to the source of this statement; this reviewer found from the investigator's brochures for ipilimumab submitted to the application that the PK-Study MDX010-15 included a single dose of 20 mg; no information regarding this study was not included in this application). There is no known drug abuse potential and no data on withdrawal or rebound phenomenon with this intravenously administered monoclonal antibody.

7.7 Additional Submissions / Safety Issues

As described in section 7.1.2, the applicant's approach to categorization of immune-mediated adverse events was not satisfactory. The applicant was asked to develop a case definition for each of the categories of immune-mediated adverse events. The applicant provided the listing, narratives, and supporting documents when available, for subjects meeting the definitions of ≥ grade 3 adverse reactions, on 12/14/2010. The applicant provided the listing and results of their adjudication of ≥ grade 2 immune-mediated reactions on 12/23/2010. These are discussed in section 7.3. Upon review of the ≥ grade 3 immune-mediated adverse reactions, it was clear that although the applicant separated the categories of diarrhea and colitis, all cases of diarrhea, where an endoscopic biopsy was performed, showed features consistent with colitis. Also, the applicant separated intestinal perforation as a separate category, it was merely a complication of colitis. The applicant was therefore asked to combine these three terms (diarrhea, colitis, intestinal perforation) as enterocolitis for analysis of time to onset, time to resolution and effect of interventions such as high dose corticosteroids. Similarly, the review of the cases of endocrinopathies showed that all cases had primary hipopituitarism with only one subject having additional adrenal insufficiency. The applicant was asked to add this information for inclusion in the package insert. For the category of skin related manifestations, the applicant separated the categories of dermatitis and pruritus, but the only case of ≥ grade 3 pruritus had dermatitis. Hence the applicant was asked to combine these two terms for analyses of time to onset, resolution, and effect of interventions such as topical steroids or systemic corticosteroids. The results of information regarding the results of the analyses for characterization of immune-mediated adverse reactions requested as above are still pending at the time of this review and will be appended to section 7.3.4.

8 Postmarket Experience

Ipilimumab is not marketed in any country and there is no post-marketing experience.

9 Appendices

9.1 Literature Review/References

1. Kirkwood et al, Phae II Trial of Tremelimumab (CP-675,206) in Patients with Advanced Refractory or Relapsed Melanoma. Clin Cancer Res; 16: OF 1-7, 2010

9.2 Labeling Recommendations

The labeling negotiations are ongoing at the time of this review. However, the following major recommendations were conveyed to the applicant:

Black Box warning: The applicant used the term (b) (4)' adverse reactions (AR) to describe the immune-mediated or autoimmune AR of ipilimumab. FDA recommended the term (b) (4)' to describe these events. The applicant counter proposed the term 'immune mediated'. Final determination has not yet been made.

Indications and Usage: The indication was changed to all patients with advanced melanoma and not just pre-treated patients

Dosage and administration: (b) (4)n . The applicant proposed dose modifications such as permanent discontinuation or omission of doses based on their evolving strategy in their entire development program. The applicant was asked to describe the dose modifications based on the actual conduct of the study MDX010-20.

Warning and Precautions: The applicant was asked to adjudicate the immune-mediated adverse events not based on programmatic approach, but actual review of cases as noted in section 7.1.2. These would then be used in the warnings and precaution section and in the adverse reactions section of the label. The applicant completed this review and provided a revised package insert on January 12, 2010. The characterization of the immune-mediated adverse reactions and the proposed interventions was still not satisfactory. For example, the applicant was asked to describe the characterization of enterocolitis in terms of how many developed complications such as intestinal perforation, how many were hospitalized, how many died as a result of complications, what was the time of onset, what was the time of resolution, how many subjects received high dose corticosteroids and what was the outcome in them compared to subjects who did not receive corticosteroids. The applicant's response is still pending at the time of this review.

Clinical Trial Experience: The applicant was asked to only include adverse reactions that occurred in $\geq$ 5% of subjects in the ipilimumab containing arms and with a higher incidence than the gp100 arm.

For the immune-related adverse reactions, the applicant was asked to provide the listing of severe adverse reactions of the adjudicated adverse reactions.

For the additional list of adverse reactions in the proposed PI, the applicant will be asked to only include those adverse reactions which are well defined adverse reactions and not a list of preferred terms, such as (b) (4) (b) (4)

Immunogenicity: This section was revised to convey the limitations of the assay used in detection of the anti-drug antibodies.

Pregnancy and Animal Toxicology sections: Information was added regarding the increased incidences of third-trimester abortion, stillbirth, premature delivery, low birth weight, and infant mortality, that occurred following intravenous administration of ipilimumab to pregnant cynomolgus monkeys.

Geriatric Use: The applicant was asked to include information based on the 511 subjects who received the study drug [redacted] (b) (4).

Clinical studies section was extensively revised for brevity and clarity. [redacted] (b) (4)

9.3 Advisory Committee Meeting

An advisory committee meeting was not convened for this application. Advanced melanoma has uniformly dismal prognosis and ipilimumab is the first drug to have shown survival advantage in this disease. During the review cycle, after top line data for another nearly completed study were made available to FDA for review, the review team felt comfortable in recommending approval of ipilimumab without seeking input from the advisory committee.

Signature page for file (DO NOT FOR POST):

(b) (6)

Kaushik Shastri 2/25/11
Medical Officer
CDER/OND/OODP/DBOP

Through

(b) (6)

2-25-2011

Patricia Keegan
Acting Team Leader
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