CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125377Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	March 24, 2011
From	/Richard Pazdur/ Richard Pazdur, MD
Subject	Office Director Decisional Memo
BLA #	STN BL 125377/0
Applicant Name	BMS
Date of Submission	June 25, 2010
PDUFA Goal Date	March 26, 2011
Proprietary Name/ Established (USAN) Name	Yervoy Ipilimumab
Dosage Forms / Strength	Solution for injection in strengths of 50 mg/10 mL and 200 mg/40 mL
Proposed Indication(s)	"for the treatment of advanced melanoma (unresectable Stage III and Stage IV melanoma) in patients who have received prior therapy"
Recommended Action for NME:	Approval

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

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

1. Introduction

Ipilimumab is a fully human monoclonal immunoglobulin (IgG1k) that is directed against the human cytotoxic lymphocyte antigen-4 (CTLA-4) present on activated T-cells. The mechanism of action is believed to be through prevention of the inhibition of the interaction between antigen presenting cells (APCs) and T-cells. The CTLA-4 antigen on T-cells out-competes CD28 for binding to CD80/86 on APCs and induces a negative or inhibitory signal which acts to down-regulate T cell activity. Ipilimumab binds to CTLA-4 preventing its interaction with CD80/86, which results in potentiation or up-regulation of T-cell activity. It is believed that ipilimumab acts by permitting development of an immune response to tumor (self) antigens presented by APCs.

Cutaneous melanoma is the most aggressive malignancy arising from the skin. The National Cancer Institute estimates that in 2010 there will be 68,130 new cases of melanoma and 8,700 deaths due to melanoma in the United States.

Dacarbazine and aldesleukin (interleukin-2) are the only FDA-approved treatments for treatment of metastatic melanoma. Commonly used off-label treatments include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens, and interferon alone or in combination with chemotherapy, as well as investigational immunotherapy treatments. All currently used treatment approaches are characterized by low objective tumor response rates (<20%) and no evidence of improved survival.

2. Efficacy

The pivotal trial in support of this application, MDX010-20, was a multicenter, placebo controlled, double-blind clinical trial that randomized 676 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 every 3 weeks up to 4 doses) in combination with gp100 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 every 3 weeks up to 4 doses.

The study met the endpoint for the revised primary efficacy analysis, demonstrating a statistically significant improvement in overall survival for the ipilimumab plus gp100 combination arm compared to the gp100 alone arm [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively. See Table 1 below.

Table 1 Summary of Overall Survival Results (using data from randomization list)

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

The treatment effect on survival for this single study were statistically robust and consistent across relevant subgroups; however the effects on tumor response rate and on progression-free survival were very modest and did not provide direct evidence of efficacy. See Table 2 below.

Table 2.

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

[1] compared to gp100 arm
[2] CMH test stratified by M-stage and prior IL-2 therapy
[3] log-rank test stratified by M-stage and prior IL-2 therapy

Although not submitted as a part of this application, FDA requested to receive high-level results of another ongoing but nearly complete clinical trial, CA184-024. This was a multi-center, randomized, double-blind, two-arm, phase 3 clinical trial in patients with untreated stage III (Unresectable) or IV melanoma receiving Dacarbazine (DTIC) plus 10mg/kg of Ipilimumab vs. Dacarbazine with placebo.

CA 184024 demonstrated that treatment with ipilimumab resulted in improved survival providing replication of the treatment effects from MDX010-20 and information indicating that the treatment effect was not limited to patients with HLA-A*0201 phenotype.

3. Safety

The safety database was comprised of 643 patients, which was sufficient to characterize toxicity to support licensure. Analysis of the safety of ipilimumab, when administered at a dose of 3 mg/kg every three weeks for 4 doses, relies on data primarily collected in Protocol MDX010-20, in which 511 patients received ipilimumab alone (n=131) or in combination with gp100 (n=380) and 132 patients received gp100 vaccine. One patient who was randomized to ipilimumab plus gp100 instead received ipilimumab placebo plus gp100 (i.e., gp100 alone). Additional safety information, characterizing immunogenicity and serious adverse events, was obtained in the following studies:

Supportive Safety Studies

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

Ipilimumab treatment was discontinued prematurely in 10% of patients for adverse reactions. The most common adverse reactions leading to study drug discontinuation in the ipilimumab plus gp100- and ipilimumab-treated patients were colitis [10 (2.6%) and 3 (2.3%) patients, respectively] and diarrhea (10 (2.6%) and 2 (1.5%) patients, respectively].

The most common adverse reactions among patients who received ipilimumab at a dose of 3 mg/kg every three weeks for up to 4 doses were fatigue, diarrhea, pruritus, rash, and colitis.

The applicant submitted additional analysis to characterize the immune mediated adverse reactions after the original clinical review was complete. 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 ipililumab 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. Dr. Shastri, the clinical reviewer wrote an addendum to the original clinical review incorporating this information. The overall incidence of immune-mediated adverse reactions excluding those that occurred during re-treatment, is shown in Table 3 below and was not significantly different from Table 28 of Dr. Shastri's original review.

Table 3. 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.

Based on the experience in the entire clinical program for melanoma, the incidence and severity of enterocolitis and hepatitis appears to be dose dependent.

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

Anti-product antibody Responses (Immunogenicity)
In clinical studies, 1.1% of 1024 evaluable patients tested positive for binding antibodies against ipilimumab in an electrochemiluminescent (ECL) based assay. However, this assay has substantial limitations in detecting anti-ipilimumab antibodies in the presence of ipilimumab. Infusion-related or peri-infusional reactions consistent with hypersensitivity or anaphylaxis were not reported in these 11 patients nor were neutralizing antibodies against ipilimumab detected. In a subset analysis of patients who received 0.3 mg/kg, 6.9% of 58 evaluable patients tested positive for binding antibodies against ipilimumab.

To mitigate certain risks of ipililumab, a REMS containing a communication plan for healthcare providers is required. In addition, there are postmarketing requirements (PMRs) to determine the relative risks and benefits of the 3 mg/kg and 10 mg/kg dosing regimens, as well as PMRs to further characterize the potential genetic marker that may be associated with an increased risk of toxicity, and a PMR to develop a sensitive assay and more reliable characterization of the incidence anti-ipilimumab antibody development following exposure to ipilimumab. Please refer to the action letter for these PMRs.

4. Other Discipline Reviews

There are no other outstanding issues that preclude approval from other disciplines and a summary of other discipline reviews is below.

CMC:

Based on quality and facility reviews, the manufacturing process is adequately described and contains appropriate quality controls. Manufacturing site inspections for drug substance were acceptable; inspections were waived for drug product due to recent acceptable inspection of the facility in 2009. There are several postmarketing commitments (PMCs) to enhance product quality and PMRs for the development and validation of assays to detect anti-product antibodies. Please refer to the approval letter for these PMCs and PMRs.

Nonclinical:

Nonclinical studies were conducted in non-human primates—the only relevant animal models. Of the 66 cynomolgus monkeys evaluated for more than 3 months, 10 monkeys were evaluated for up to 6 months. These animals received 5 doses, once per month, with a one-month recovery period. The nonclinical studies generally under-represented the toxicity of ipilimumab as compared with the human clinical trial experience. Although nearly all animals were asymptomatic with multiple doses of 3 mg/kg and 10 mg/kg, there was evidence of leukocytic infiltration of organs on histopathology consistent with the expected pharmacology. Safety pharmacology studies for cardiac effects did not reveal drug-related findings.

The major finding of concern were derived from interim results of an ongoing reproductive toxicology study, which revealed an increased incidence of third-trimester spontaneous abortions, stillbirths, and premature delivery in pregnancy cynomolgus monkeys treated with ipilimumab as compared to controls. A PMR to submit the final study report has been included in the action letter.

Clinical Pharmacology:

The proposed dose for ipilimumab is 3 mg/kg administered as an intravenous infusion over 90 minutes, every 21 days for a total of 4 doses. Sparse PK sampling demonstrate that the pharmacokinetics of ipilimumab are linear over the doses evaluated in clinical studies (0.3, 3, and 10 mg/kg) with an elimination half-life of 15 days and steady state achieved after the third dose. Clearance of ipilimumab is affected by body weight; however, the recommended dose is adjusted by body mass and no additional adjustments based on weight are necessary. The pharmacokinetics of ipilimumab are not affected by renal or hepatic function or by age or gender.

The dose-response relationship of ipilimumab is inadequately characterized, having been limited to a single dose-ranging trial. This trial did not suggest that there were important dose-response differences between the 3 mg/kg and the 10 mg/kg doses for the outcomes of response rate or survival, which may have been difficult to detect given the very low response rate across all groups and the relatively short survival times in this disease. However there was evidence of an increased rate of severe toxicity in patients receiving 10 mg/kg as compared to those receiving 3 mg/kg ipilimumab. It remains unclear whether 3 mg/kg or 10 mg/kg every three weeks is the optimal dose, defined as the dose providing lowest risk in light of the survival benefit. Therefore, FDA has required that a dose-comparison study be performed to characterize the relative risks and benefits of these two doses as a PMR.

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

5. Other Regulatory Issues

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

Advisory Committee:
Advice regarding the approvability of this application was not sought from the Oncologic Drugs Advisory Committee since demonstration of overall survival in two controlled, clinical trials provided sufficient evidence of clinical benefit, particularly in this malignancy where there is currently no highly effective treatment.

Proprietary name:
DMEPA and the division have concluded that the proprietary name of YERVOY is acceptable.

Labeling:
All major issues have been resolved. YERVOY will also have a MedGuide to describe risks to patients.

6. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

- Risk Benefit Assessment

  I concur with the assessment and recommendations of the Division Director summary review written by Dr. Keegan. Additionally, I concur with the review team that this product should be approved. There are no effective treatments for the treatment of metastatic melanoma which prolong survival and the benefits of ipilimumab, which has shown to increase overall survival time outweighs the unique adverse reactions of this product. Additionally, REMS are set in place to mitigate risks of ipilimumab.

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

  The communication plan will include a proposal to send communications, every 6 months for the next three years, on the toxicity profile of ipilimumab U.S. cancer treatment infusion centers, and to the following U.S.-licensed healthcare providers: oncologists, gastroenterologists, dermatologists, endocrinologists, emergency room physicians, hepatologists, neurologists, oncology nurses, oncology pharmacists and health-system pharmacists. The communications to be provided includes a "Dear Healthcare Provider" letter and the following patient management tools: Immune-Mediated Adverse Reaction Management Guide and the Immune-Mediated Adverse Reaction Symptom Checklist. In addition, healthcare providers will be provided with the Patient Wallet Card as an additional educational tool for distribution to patients.

- Please refer to the action letter for description of the PMRs and PMCs for this action.