CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translation Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES- TEAM LEADER'S MEMO

BLA/Serial Number:	125377/000
Drug Name:	YERVOY ® (ipilimumab)
Indication(s):	Treatment of Pretreated Advanced Melanoma
Applicant:	Bristol-Myers Squibb Company
Date of Receipt:	05-25-2010
Date of Amendment:	10-28-2010
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Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
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Clinical Team:	Kaushikkumar Shastri, M.D., Clinical reviewer Patricia Keegan, M.D., Division Director
Project Manager:	Mr. Eric Laughner

The Applicant submitted a Biologics License Application (BLA) for YERVOY ® (ipilimumab), STN BL 125377/000, and is seeking a labeling claim for the treatment of pretreated advanced melanoma.

The application was based on a pivotal trial MDX010-20, and two Phase 2 trials (CA184022 and CA184004). In this memo, this reviewer will briefly summarize the design, statistical analyses, and efficacy results of the MDX010-20 trial. This reviewer agrees with Dr. Yuan-Li Shen's primary statistical review for this application. Please refer to her review for the detailed analyses and results.

The efficacy of ipilimumab was investigated in a randomized, double-blind, double-dummy trial MDX010-20. Six hundred and seventy six patients were randomized using the stratification factors baseline M-stage (M0, M1a or M1b vs. M1c) and prior treatment with Interleukin-2 (IL2) (yes vs. no) in a 3:1:1 ratio with advanced melanoma previously treated with one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin. Of these 676 patients, 403 were randomized to receive ipilimumab 3 mg/kg in combination with an investigational gp100 peptide vaccine (gp100), 137 were randomized to receive ipilimumab 3 mg/kg monotherapy, and 136 were randomized to receive gp100 alone. Ipilimumab was administered at 3 mg/kg as an intravenous infusion every 3 weeks for four doses. Gp100 was administered at a dose of 2 mg peptide by deep subcutaneous injection every 3 weeks for four doses. The trial was initiated in September 2004 and completed in October 2009, and was conducted at 125 sites in 13 countries in Europe, North America, South America, and Africa.

The modified primary efficacy endpoint was overall survival (OS). The primary analysis was a stratified log-rank test to compare OS between the ipilimumab+gp100 arm and the gp100 arm. The secondary analyses were to compare OS between the ipilimumab+gp100 arm and the ipilimumab monotherapy arm, and between the ipilimumab monotherapy arm and the gp100 arm.

Of the randomized patients, 61%, 59% and 54% in the ipilimumab+gp100, ipilimumab monotherapy, and gp100 arms, respectively, were men. Overall, 29% were ≥65 years of age, the median age was 57 years, 71% had M1c stage, 11% had a history of previously treated brain metastasis, 99% had ECOG performance status of 0 and 1, 23% had prior IL-2 use and 38% had elevated LDH level.

The primary analysis of the stratified log-rank test for OS gives a p-value of 0.0004 (not adjusted for unplanned adaptations) in comparing the ipilimumab+gp100 arm with the gp100 arm. The primary comparison of OS is shown in Table 1.

Table 1 Primary Comparison of Overall Survival

Overall Survival	Ipilimumab + gp100 N=403	Gp100 N=136
Number of deaths (%)	306 (75.9%)	119 (87.5%)
Median (95% CI)	10.0 (8.5, 11.5)	6.4 (5.5, 8.7)
Hazard ratio (95% CI)	0.68 (0.55, 0.85)	
p-value	0.0004	

The secondary comparisons of OS are shown in Table 2.

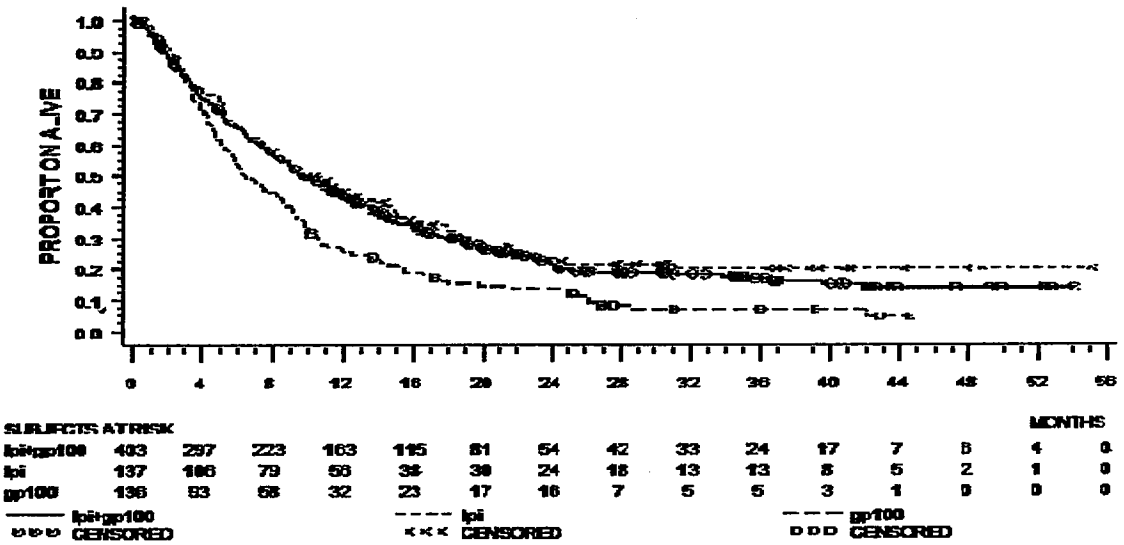
Table 2 Secondary Comparisons of Overall Survival

Overall Survival	Ipilimumab N=137	Gp100 N=136
Number of deaths (%)	100 (73.0%)	119 (87.5%)
Median (95% CI)	10.1 (8.0, 13.8)	6.4 (5.5, 8.7)
Hazard ratio (95% CI)	0.66 (0.51, 0.87)	
p-value	0.0026	
	Ipilimumab + gp100 N=403	**Ipilimumab N=137**
Number of deaths (%)	306 (75.9%)	100 (73.0%)
Median (95% CI)	10.0 (8.5, 11.5)	10.1 (8.0, 13.8)
Hazard ratio (95% CI)	1.04 (0.83, 1.3)	
p-value	0.7575	

Note that a statistical procedure was not pre-specified for adjusting multiple secondary comparisons in the Statistical Analysis Plan, thus, p-values in Table 2 for the secondary comparisons were not adjusted.

Figure 1 presents the Kaplan-Meier curve of OS.

Figure 1 Kaplan-Meier curve of Overall Survival



There were several protocol amendments during the trial. A key modification was to change the primary endpoint of best objective response rate (BORR) to OS. However, the sample size was still in the ratio of 450:150:150 as planned in the original design using BORR as the primary endpoint. The applicant provided a rationale using a simulation to support its original sample size calculation.

The main concerns regarding the OS results were their reliability and robustness since the primary endpoint of OS was changed from the originally designed primary endpoint of BORR and the current OS results were derived using the original sample size calculation

for BORR. However, the preliminary results from a larger trial showed that ipilimumab treated patients had longer survival, which may provide some supportive evidence to the OS results derived from the MDX010-20 trial.

Whether the results based on the MDX010-20 trial provide a favorable benefit to risk analysis will be based on an overall evaluation by the clinical review team.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Drug Name:	Ipilimumab
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1 EXECUTIVE SUMMARY

The applicant, Bristol-Myers Squibb Company (BMS), Inc., is seeking a labeling claim of YERVOY® (Ipilimumab) as the treatment of advanced melanoma (unresectable stage III and IV melanoma) in patients who have received prior therapy.

Based on study MDX010-20 and the preliminary information from study CA184-024, the results appear to demonstrate a statistically significant reduction in the risk of death in favor of ipilimumab containing arm (as compared to the gp100 peptide vaccine) for patients with advanced melanoma (unresectable stage III and IV melanoma) who have received prior treatment. The hazard ratios for the comparison between ipilimumab combination arm vs. gp100 was 0.68 (95% CI=0.55, 0.85; p-value=0.0004) and for the comparison between ipilimumab monotherapy arm vs. gp100 was 0.66 (95% CI=0.51, 0.87, p-value=0.0026). The median OS time was 9.95(95% CI: 8.5, 11.5), 10.12(95% CI: 8.0, 13.8), and 6.4(95% C: 5.5, 8.7) months for ipilimumab combination, ipilimumab monotherapy and gp100 arm, respectively, based on study MDX010-20.

Also, the results from study MDX-010-20 (for HLA-A2*-2-1 positive only), Phase II studies (studies CA184-004, CA194-022) and study CA184-024 (no HLA typing) did not suggest the requirement for an HLA typing.

The overall survival benefit of the ipilimumab containing arms was consistently demonstrated based on several sensitivity analyses and appears to be consistent across various subgroups.

The beneficial effect of ipilimumab treated arm based on the single, small study (MDX010-20) does not appear to be convincing due to several deficiencies identified, e.g. the concerns of the reliability and robustness of the treatment effect, many unplanned modifications to the protocol, patients not well allocated and the results based on the secondary endpoints not being persuasive. However, the demonstration of the overall survival benefit based on the preliminary results from a larger study (study CA184-024) provides a replication of the beneficial effect for the ipilimumab treated arm.

2 INTRODUCTION

This section provides an overview of the submitted trials.

2.1 Overview

The applicant submitted a randomized, double-blind, multicenter study (MDX010-20) to support an indication claim in patients with previously treated unresectable stage III or IV melanoma. The applicant also submitted several phase II studies to support the efficacy and safety information. A more detailed descriptions of these phase II trials are provided in the appendix.

FDA emphasized in 3/2/2010 pre-BLA meeting that a top line survival data from study CA184-024 should be provided to FDA for review. Study CA184-024 is a multi-center, randomized, double-blind, two-arm, phase III study in patients with untreated stage III (unresectable) or IV melanoma receiving Dacarbazine plus 10mg/kg of ipilimumab (MDX-010) vs Dacarbazine with placebo. The primary efficacy endpoint for this study is overall survival. FDA indicated that the summary results for overall survival were required in order for FDA to take a final action on this BLA. The applicant acknowledged and agreed to permit the Data Monitoring Committee to release the results to FDA.

The focus of this review will be on study MDX010-20, the preliminary overall survival results from study CA184-024 and the efficacy results from study CA184-022 and CA184-008 that included previously treated melanoma patients and 3 or 10 mg/kg dose arm will also be discussed if deemed appropriate.

2.2 Data Sources

Data used for the majority of the review is from the electronic submission received on 06/25/10. The network path is in :

\\cber-fs3\m\eCTD_Submissions\STN125377\0000\m5\datasets

Data used to evaluate the ipilimumab-associated inflammatory adverse event is in the following paths:
\\cber-fs3\m\eCTD_Submissions\STN125377\0039\m5\datasets and
\\cber-fs3\m\eCTD_Submissions\STN125377\0040\m5\datasets.

3 STATISTICAL EVALUATION

The efficacy and safety analysis results were presented in this section for protocol MDX010-20.

3.1 Data and Analysis Quality

In general, documentation and supporting SAS programs for the efficacy analyses are easy to follow. The reviewer was able to calculate the derived variables from the raw datasets and confirm the efficacy results.

However, the documentation and supporting SAS programs are harder to follow for the safety data analyses. Some of the datasets used in the SAS programs were not submitted and variables for merging (e.g. study ID, patient ID, treatment indicator) were not consistently defined or named through out the safety datasets (i.e. between the individual datasets vs. the combined datasets for Integrated Summary of Safety). The reviewer had to spend more time to work on data manipulation and request for more datasets and clarification in order to perform the safety data analyses. Nevertheless, the reviewer was able to confirm the safety results based on the submitted derived safety datasets.

3.2 Evaluation of Efficacy

3.2.1 Introduction

Study MDX010-20 included patients who had histologic 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 relapse, failed to respond or can not tolerate due to toxicity. Patients could not use chemotherapy, biologics, surgery, radiation or immunotherapy within 28 days of the first dose of study drug and gamma knife

treatment within 14 days of the first dose of study drug. Patients who had other malignancy, had been disease-free for less than 5 years, had active, untreated central nervous system metastasis, had prior treatment with an anti-CTLA4 antibody, cancer vaccine (including gp100 peptides), had any active autoimmune disease or history of autoimmune disease, had hypersensitivity to Incomplete Freund's Adjuvant [Montanide ISA-51] or any component of the vaccine, had any underlying medical condition and had concomitant therapy with any of the non-study anti-melanoma therapy were excluded from the study. Also, patients with primary ocular melanoma were excluded from entering into the trial. Patients in this study were randomized in 3:1:1 ratio 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) ;

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).

IV infusions of ipilimumab or ipilimumab placebo were administered on Days 1, 22, 43 and 64 (i.e. induction cycle which lasted for 9 weeks). 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.

Patients who 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 may be offered additional cycles of therapy with the originally assigned treatment regimen until off-treatment criteria are met. No patient was retreated if they experienced a Grade 3 non-dermatologic irAE (immune related Adverse Event) or Grade 4 toxicity of any organ system considered related to ipilimumab or placebo administration.

The randomization was stratified by 1) baseline M-stage (M0, M1a or M1b vs M1c) and 2) prior treatment with Interleukin-2 (IL-2) or not. A total of 125 centers in 13 countries (in Europe, North America, South America and Africa) participated the study.

Patients could not use IL-2, interferon or other non-study anti-melanoma immunotherapy regimens, cytotoxic chemotherapy, immunosuppressive agents, other investigational therapies or chronic use of systemic corticosteroids during the course of the study. However, patients with progressive disease (PD) who were not eligible for continued treatment or for re-induction were permitted to receive non-study antimelanoma medications at the discretion of the investigators.

A list of protocol amendments that may affect statistical analyses are shown 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 one stage for subject enrollment instead of two stages and one additional stratification factor MI status (M1a or M1b vs. M1c) was added to the M-stage stratification factor. 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.

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

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 for health-related quality of life assessment was specified. 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 $\geq$6 months duration. The duration of SAE reporting was changed from 4 weeks to 10 weeks following study treatment.

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

The primary endpoint was changed from 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 between ipilimumab monotherapy vs. gp100 and between two ipilimumab containing arms. The sample size was revised based on the new primary efficacy endpoint, assuming delay effect at 8 months based on simulation methods.

Reviewer's comments:

- *The applicant notified FDA that* (b) (4) *the primary efficacy endpoint would be changed from BORR to OS in a teleconference on 7/25/08. At that time, FDA requested that the SPA (Special Protocol Assessment) to be withdrawn for MDX010-20 since it is no longer considered a pivotal study for registration. Approximately, 6 months later the protocol was revised (dated on 1/15/09).*

The data cutoff date was 6/19/09, the statistical analysis was signed off on 10/28/09 and the data were unblended on 10/30/09 .

Disease Assessments Schedule

All treated patients were to be restaged at Week 12 to assess response. Those with stable disease (SD) or a response reflecting improvement were staged again at Weeks 16 and 24 and every 3 months thereafter. Also, re-staging assessments (i.e. confirmatory scans) were performed at a minimum of 28 days from the preceding assessments if an objective response is noted.

3.2.2 Efficacy Endpoints

Primary Efficacy variable

The amended primary efficacy endpoint is overall survival (OS) derived as the time from randomization until death from any cause. For patients who were alive were censored at the time of last contact (last known alive date). The primary comparison was between ipilimumab in combination with gp100 vs. gp100 arm.

Investigator assessed progression

The tumor response (Complete response [CR], partial response [PR], Stable disease

[SD] and progressive disease [PD]) was evaluated by the investigator based on the modified WHO criteria described in Appendix 1 of the protocol.

Secondary efficacy variables

The secondary endpoints include the comparison of overall survival between ipilimumab in combination with gp100 vs. ipilimumab monotherapy and between ipilimumab monotherapy vs. gp100.

Other secondary endpoints are described below:

- Best overall response rate (BORR): defined by the number of patients whose BOR was CR or PR divided by the total number of patients.

  It is noted by the applicant that the baseline tumor assessment was reset at each cycle. BOR for the first induction course was determined between Weeks 12 and Weeks 24 with confirmation at least 4 weeks later. Complete response (CR) and partial response (PR) need to be confirmed. For patients who had surgical resection or radiotherapy, only pre-surgical or pre-radiotherapy tumor assessments conducted on or prior to the date of surgery or radiotherapy were used in the determination BOR. Early progression (i.e. PD occurring prior to Week 12) did not preclude a BOR of SD, PR or CR resulting from the Week 12 or later assessment. However, an overall response assessment of PD at or after Week 12 precluded a subsequent BOR of SD, PR or CR.
- Disease Control Rate (DCR): defined by the number of patients whose BOR was CR, PR or SD divided by the total number of patients
- Duration of response (DOR): defined as the number of days between date of response (CR or PR) and the date of PD or death whichever occurred first. For patients who remained alive and had not progressed following response, DOR was censored at the date of the last assessments.
- Time to response: defined as the number of days from date of randomization to the date when a BOR of CR or PR occurred. For patients who did not have progression and remained alive will be censored at the last assessment date. For patients who remained alive and who have no recorded post-baseline assessment or who were randomized and were not treated were censored at the date of

randomization. Patients who died were censored at the time of death.

- Progression Free Survival (PFS): defined as the number of days between the date of randomization to the date of progression or death. The censoring rules are similar to those described in the time to response except for patients who die without any reported progression were considered as having an event at the time of death.
- Delayed response: defined as the post Week 24 overall response for the patients who have PD before or at Week 24. Late response includes late CR, late PR, late SD, continued PD, unknown, and missing after Week 24.

Additional secondary endpoints listed in the statistical analysis plan included PFS at Week 12, survival rates at 12, 18 and 24 months.

3.2.3 Sample Size Consideration

Prior to amendment #6, the sample size of 540 patients was required for the combination therapy and gp100 arms (135 for gp100 arm and 405 for combination therapy). This sample size was calculated to provide 90% power to detect a 10% improvement in BORR (assume 5% response rate in the gp100), assuming 2-sided 0.05 alpha level. Assuming 10% drop rate, 750 patients (450: 150: 150 for ipilimumab+gp100, ipilimumab monotherapy and gp100 arm, respectively) were required to be enrolled.

Reviewer's comments:

- [redacted] (b) (4)

At amendment #6, the sample size had been revised using the new primary efficacy endpoint OS based on the comparison of ipilimumb+gp100 versus gp100 monotherapy arm.

The applicant indicates that the new sample size calculation was based on a simulation using the collected blinded survival data from this study and historical literature. From the simulation, a total of 385 events (3:1 ratio for ipilimumab+gp100 vs. gp100 arm) and a total of 500 enrolled patients for the two groups were required based on the following

assumptions:

- A simulation based on two arms was generated assuming the distribution of OS as follows: *55% survival rate for both arms before Month 8, 48% survival rate for ipilimumab+gp100 arm and 28% survival rate for gp100 arm, between Month 8 to Month 12 and 30% survival rate for ipilimumab+gp100 arm and 13% survival rate for gp100 arm after Month 24. Based on the assumed survival rates,* the assumed hazard ratios for the OS of ipilimumab+gp100 vs. gp100 at 8, 12 and 24 months are 1, 0.2017 and 0.6126, respectively. The simulated data was then summarized and the median OS time of 10.8 and 8.6 months were obtained for ipilimumab+gp100 and gp100 arms, respectively.

Based on the simulation, it shows that a total of 385 deaths in ipilimumab+gp100 vs. gp100 arm can achieve a 90% power. It is estimated that approximately a total of 481 events are required in all 3 groups (assuming events are evenly distributed among the 3 arms according to the randomization ratio) to observe 385 events in the ipilimumab+gp100 and gp100 treated arms.

3.2.4 Efficacy Analysis Method

The following statistical analysis populations were proposed for the analyses:

- Intent-to-treat population: including all patients randomized. This population was applied to all primary and secondary analyses.
- Per-protocol population (PPP): including all patients randomized who had a diagnosis of malignant melanoma, had at least one on-study tumor assessment and had no major protocol violations. This population was applied to the secondary efficacy analyses.
- Re-induction population: including all per-protocol population who also met all the re-induction criteria (See section 3.1.1 for the criteria). This population was applied to OS and safety analyses.
- Safety population: including all patients randomized who took at least one study medication. This population was applied to safety analyses.

The primary analysis for all time-to-event endpoints was based on a stratified log-rank test stratified by the baseline stratification factors (i.e. baseline M-stage [M0, M1a or

M1b vs. M1c] and prior treatment with IL-2 or not). The Kaplan-Meier method was used to plot the survival estimates for OS. The median OS and its 95% confidence interval were calculated using the method of Brookmeyer and Crowley. The hazard ratio and the corresponding 2-sided confidence intervals were estimated using the Cox's proportional hazards model stratified by baseline M-stage and prior treatment IL-2.

Cochran-Mantel-Haenszel (CMH) test stratified by baseline M-stage and prior treatment IL-2 was used for analyses of BORR and DCR. A 2-sided 95% confidence intervals were computed for the BORR based on the Clopper and Pearson method.

Sensitivity analyses for PFS

No pre-specified sensitivity analysis was proposed in the statistical analysis plan or in the protocol. However, a sensitivity analysis was performed both by the applicant (per FDA's request) and the reviewer by censoring patients in the following situations :

a. at time of the last assessment before patients discontinued treatment for toxicity or other reason prior to progression;
b. at the time of the last assessment before patients took anti-cancer treatment prior to progression;
c. at the time of the last assessment before patients died or progressed after more than one missed assessment visit.

Subgroup analysis

A list of subgroup analysis was specified in the statistical analysis plan for OS:

- M-stage (M0, M1a, M1b, M1c);
- Prior IL-2 treatment (Yes, No);
- Baseline LDH (≤ULN, > ULN);
- Age (<65, ≥65 years);
- Gender (male, female).

Quality of Life (QoL) analysis

Statistical analysis was performed for EORTC QLQ-C30. EORTC QLQ-C30 scores at Weeks 1, 12, and 24 and the change from baseline (week 1) to each post-baseline visit was summarized using descriptive statistics for each treatment.

For Week 12 at cycle 1, score changes were analyzed using analysis of covariance model (ANCOVA) including treatment and baseline M-stage and prior treatment with IL-2 as covariates. Missing scores were not imputed since most patients missing Week 12 assessment did not have any post-treatment data. Since this quality of life analysis is considered as exploratory, the results of this analysis will not be discussed.

3.2.5 Applicant's Results and Statistical Reviewer's Findings/Comments

A total of 676 patients were randomized between 9/27/04 to 7/24/08: 403 to ipilimumab+gp100, 137 to ipilimumab monotherapy and 136 to gp100 monotherapy.

The patient disposition is shown in the following table. There were a total of 33 patients who were randomized, but not treated. Deaths were the main reasons (approximately 73-76% in ipilimumab+gp100 and Ipilimumab monotherapy arm and over 87% in gp100 arm were due to deaths) that the patients discontinued from study.

Table 1 Applicant's Summary of 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.

The study populations are summarized in the following table. The 33 patients who were randomized but not treated were excluded from the safety as treated population. The

safety analysis was based on safety as treated population.

Approximately 7% of the patients in ipilimumab+gp100 and ipilimumab monotherapy arms received re-induction dose while only 1.5% of the patient in the gp100 arm received re-induction dose.

Table 2 Summary of Study Populations

	Ipi+gp100	Ipi	gp100	Total
Study populations (n %)				
Intent-to-Treat as Randomized[a]	403 (100.0)	137 (100.0)	136 (100.0)	676 (100.0)
Safety as Treated – safety analyses[b]	380 (94.3)	131 (95.6)	132 (97.0)	643 (95.1)
Per-protocol as Randomized	315 (78.2)	106 (77.4)	101 (74.3)	522 (77.2)
Re-induction as Randomized-efficacy analyses	29 (7.2)	9 (6.6)	2 (1.5)	40 (5.9)
≥ 1 Cycle	29 (7.2)	9 (6.6)	2 (1.5)	40 (5.9)
≥ 2 Cycles	4 (1.0)	3 (2.2)	0	7 (1.0)
≥ 3 Cycles	1 (0.2)	0	0	1 (0.1)

a All randomized, as randomized; includes subjects who were randomized but not treated.
b All treated, as treated; 1 subject (M20-392-0066) was randomized to Ipi+gp100 but treated with gp100. Therefore, the dosing and safety analyses count this subject in the gp100 treatment group.

The patient demographic and baseline characteristics information appear to be compatible 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 duration of melanoma 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 and more than 75% of the patients did not take prior IL-2. About 62% of the patients had LDH value within upper limit of normal value. Gp100 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). There were approximately 99% of patients had ECOG performance status 0 and 1 (as require in the inclusion criteria).

Table 3 Summary of Demographic and Baseline Characteristics - ITT

	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
Age by Category (n %)				
<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)
Duration of melanoma (years) [a]				
n	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 performance status				
0, 1	398 (99)	136 (99)	132 (97)	666 (98.5)
2, 3	5 (1)	1 (1)	4 (3)	10 (1.5)

[a]Calculated based on the date of initial diagnosis to the date of randomization.

[b] M stage and prior IL-2 use are based on the data from CRF.

Reviewer's comments:

- *There were some disagreement of the M-stage classification and IL2 use between the CRF data and the data reported from the randomization. In general, there were over 95% agreement of patients who had M1c level between the two data sources, but there were only about 74% to 79% of the agreement rates across three treatment for patients who had M0, M1a or M1b levels. The agreement rates appear to be good both in patients reported not to have IL2 use (approximately 98%) and in patients reported to have IL2 use (ranged from 89% to 91% for 3 arms). There were 11%, 9% and 11% of the patients who reported to have IL2 use in the randomization list, but not on the CRF in ipilimumab+gp100, ipilimumab and gp100, respectively. The disagreement of the stratification factors between the CRF data and the data reported from the randomization had minor impact on the study results.*

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 surgery and all patients received medication. There were 38%, 44% and 38% of the patients receiving 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 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%).

3.2.5.1 Primary Efficacy Endpoint Analyses

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 significant longer median overall survival time as compared with that of the gp100 monotherapy arm (9.95 vs. 6.44 months; hazard ratio=0.68, 95% CI=[0.55, 0.85], p-value=0.0004 based on the stratified log rank test). The comparison between two ipilimumab containing arms did not show statistical significance, but the ipilimumab monotherapy arm appears to have significantly longer median survival time as compared with that of the gp100 arm (10.12 vs. 6.44 months; hazard ratio=0.66, 95% CI=[0.51, 0.87], p-value= 0.0026 based on the stratified log rank test). The overall survival results based on the three treatment arms are presented in the following table:

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

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

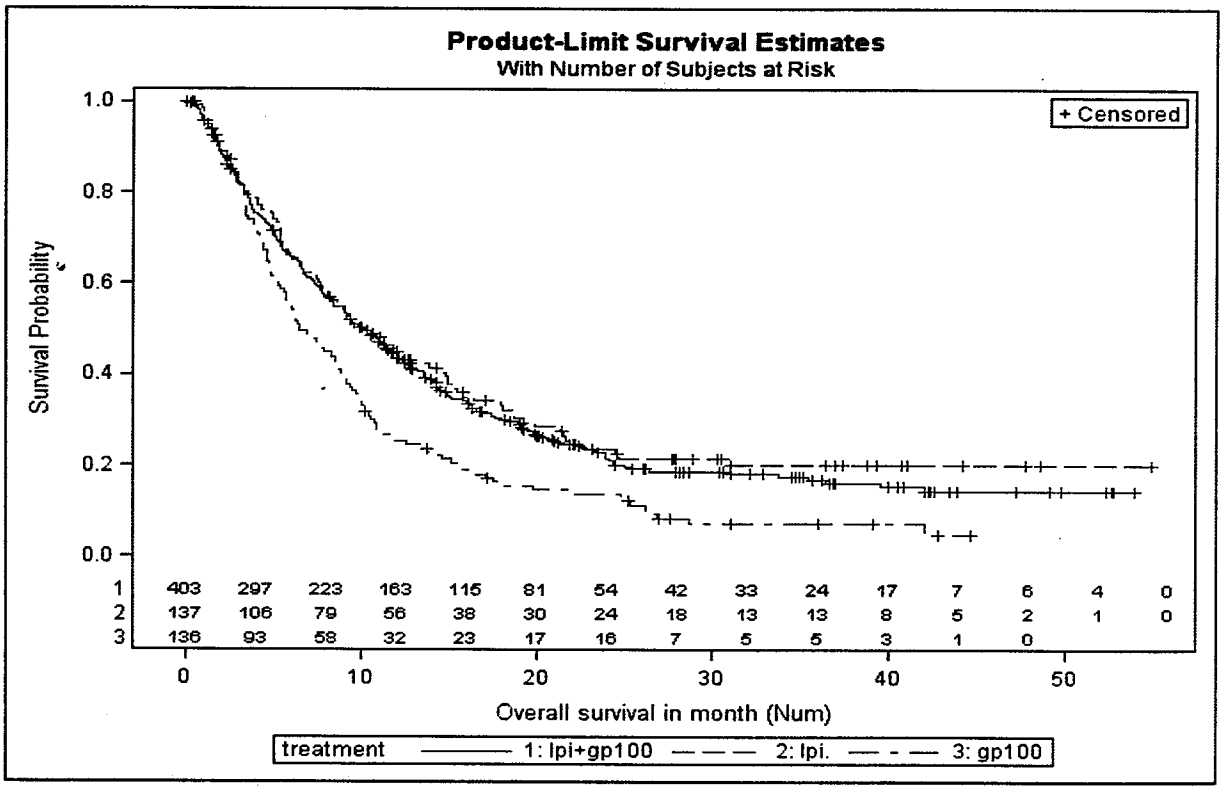
[a] 95% confidence intervals (CI) for median were computed using Brookmeyer and Crowley method.
[b] Cox model for Hazard ratios (HR) and log-rank test p-values were stratified by baseline M-stage at randomization (M0, M1a, M1b vs. M1c) and prior treatment with IL-2 (Yes vs. No) using the data from the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

Reviewer's comments:

- *To evaluate how current of the follow-up data, this reviewer observed 4.2%, 3.7% and 5.9% of the patients who had a last date know to be alive obtained more than 3 months before data cut-off date for ipilimumab+gp100, ipilimumab alone and gp100 arm, respectively. It appears that only small percentages of patients in all three arms had their last contact date more than 3 months earlier than the cutoff date, so the follow-up data appears to be up-to-date.*
- *To evaluate the censoring distribution among treatment arms, stratified log.rank tests were performed for all paired comparisons by switching the censoring indicator. The results show that the censoring distribution appears to be compatible between arms (the nominal p-values for all pair-wise comparisons are >0.8).*

The corresponding Kaplan-Meier curve for OS is presented in the following figure:

Figure 1 Kaplan-Meier estimates for Overall Survival (MDX010-20)



Reviewer's comments:

As commented in Section 3.1.5, there were disagreement of the M-stage classification and IL2 use between the CRF data and the data reported from the randomization. The disagreement had resulted in minor discrepancies in the p-values and hazard ratio estimates from the primary results. The summary of the OS results using the data from CRF as the stratification factor values are presented below:

Table 5 Summary of Overall Survival Results (MDX010-20, using data from CRF for stratified analysis)

	Ipi+gp100 N=403	**Ipi N=137**	**gp100 N=136**
Number of events	306	100	119
Median (months) (95% CI) [a]	9.95 (8.48, 11.50)	10.12 (8.02, 13.80)	6.44 (5.49, 8.71)
HR vs. gp100 with 95% CI [b]	0.70 (0.57, 0.87)	0.66 (0.50, 0.86)	
Stratified log-rank p value vs. gp100 [b]	0.0013	0.0022	
HR vs. ipi alone with 95% CI [b]	1.07 (0.85, 1.34)		
Stratified log-rank p value vs. ipi alone [b]	0.5711		

[a] 95% confidence intervals (CI) for median were computed using Brookmeyer and Crowley method.

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

Reviewer's comments:

- *There were 40 patients who received at least one re-induction dose (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,, patients were censored at the time when the first re-induction dose was administered. The results are shown in the following table and are similar to the applicant's primary efficacy results.

Table 6 Summary of Overall Survival Results (MDX010-20, using data from randomization for stratified analysis) censoring at 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 [b]	0.70 (0.57, 0.87)	0.67 (0.51, 0.88)	
Stratified log-rank p value vs. gp100 [b]	0.0013	0.0035	
HR vs. ipi alone with 95% CI [b]	1.05 (0.84, 1.33)		
Stratified log-rank p value vs. ipi alone[b]	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.

Overall Survival excluding Site 0301

According to the Clinical Inspection Summary, it stated in the general observations/comments section for site 301: "While the primary efficacy endpoint data of overall survival were verifiable against source documents found at the site the totality of protocol deviations and deficient record keeping practices calls into question the overall efficacy and safety data generated by this site. The inspection revealed multiple protocol deviations and inadequate recordkeeping.". Due to the stated reasons, Dr. Lauren Iacono-Connors recommended that the analysis results should be re-evaluated by excluding site 301. Site 301 enrolled 19 patients (11, 4 and 4 from ipilimumab+gp100,

ipilimumab monotherapy and gp100 arm, respectively). The results (shown in the following table) indicate that the impact on the overall survival results is minor after excluding site 301.

Table 7 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, 13.80)	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 [b]	0.0010	0.0050	
HR vs. ipi alone with 95% CI [b]	1.04 (0.83, 1.31)		
Stratified log-rank p value vs. ipi alone [b]	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.

Preliminary Overall Survival Results for Study CA184-024

Based on the 8/10/10 submitted letter, the applicant agreed to provide high-level OS results for Study CA184-024 through the data monitoring committee. The preliminary results from this trial showed that ipilimumab treated patients had longer survival, which may provide some supportive evidence to the OS results derived from the MDX010-20 trial.

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

For completeness of the review, the overall survival results are also presented for studies CA184-022 and CA184-008 because these two studies are for previously treated patient population for melanoma and the sample sizes are relatively larger than those of the

other Phase II trials. Study CA184-022 was a randomized, double-blind, multi-center, phase II fixed dose study of multiple doses of Ipilimumab (MDX-010) monotherapy in patients with previously treated unresectable stage III or IV melanoma. Study CA184-008 was a multi-center, single arm phase II Study of MDX-010 (BMS-734016) monotherapy (10 mg/kg) in patients with previously treated unresectable stage III or IV melanoma. A more detailed summary of these two studies are presented in the Appendix.

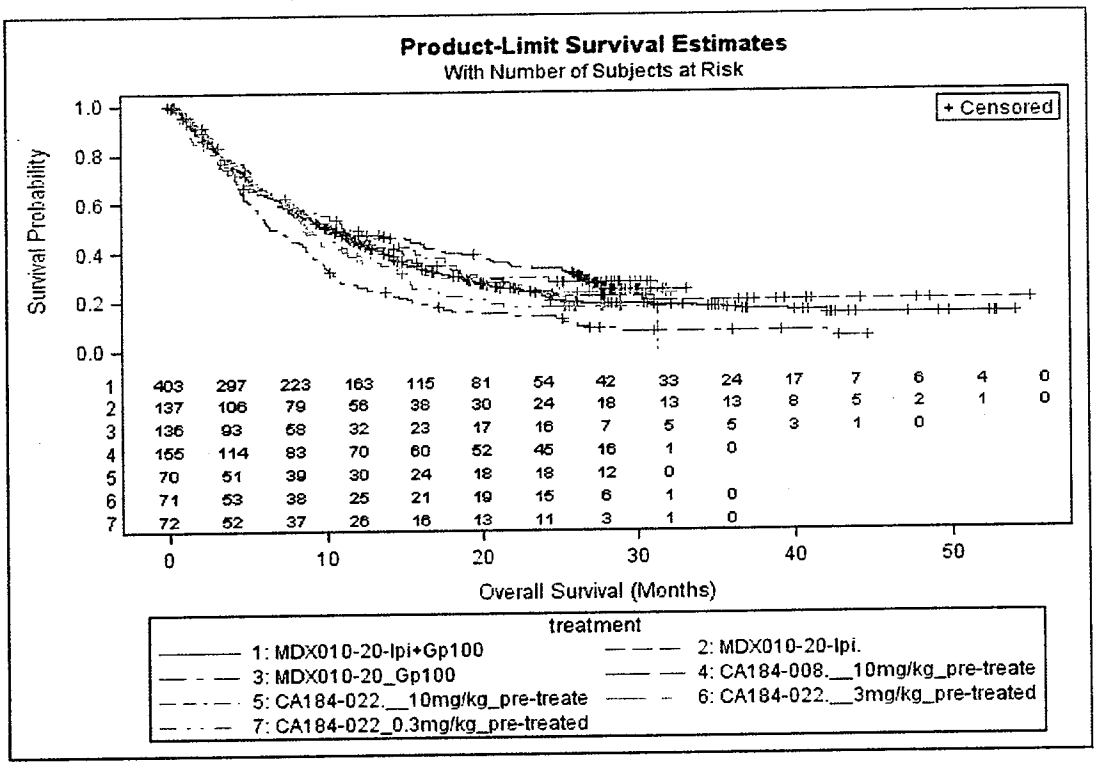
The intention of the summary is not for cross-study comparison, but to show that the overall survival estimates across dose levels may be inconclusive based on small studies. For example, the median survival time for 3 mg arm from study MDX010-20 was closer to what had been observed in the 10 mg/kg arm in studies CA184-008 and the median survival time for gp100 arm is even shorter than what was observed in the 0.3 mg/kg arm of study CA184-022.

Table 8 Summary of Overall Survival Results (MDX010-20, Phase II studies)

Study	Treatment	#deaths/total	Median Survival time (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)

The corresponding Kaplan-Meier estimates for the treatment arms shown above are presented in the following figure:

Figure 2 **Kaplan-Meier estimates for Overall Survival (MDX010-20, Phase II studies)**



3.2.5.2 Secondary Efficacy Endpoint Analyses

Best Overall Response Rate (Study MDX010-20)

Best Overall Response Rate was based on the investigator's assessment using the WHO 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 ipilimumab+gp100, ipilimumab monotherapy and gp100 arm, respectively. The nominal p-values based on Cochran Mantel Haenszel test were 0.043 and 0.040 for Ipilimumab + gp100 compared with gp100 monotherapy and ipilimumab monotherapy arm, respectively. The nominal p-value for comparison between ipilimumab monotherapy arm versus gp100 was 0.0012.

Table 9 Summary of Best Overall Response Rate (MDX010-20, Up to Week 24)

	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).

Reviewer's comments:

- *The disease response after week 24 was evaluated every 3 months, so BORR after week 24 was not adequately assessed.*
- *Since there was no hierarchical testing rule specified for testing the secondary endpoint. The p-value can not be interpreted for the comparison of BORR between treatment arms.*

The median duration for responders was 11.5 months for ipilimumab+gp100 arm, but the median duration for responders had not been reached for ipilimumab monotherapy arm and gp100 arm.

Table 10 Summary of Duration of Response for Responders (MDX010-20)

	Ipi+gp100 N=23	Ipi N=15	gp100 N=2	Total N=40
Number of Events	12	5	1	18
Number of censors	11	10	1	22
Median (months) (95% C.I.)	11.47 (5.36, NA)	NA (28.09, NA)	NA (2.0, NA)	28.9 (8.54, NA)
25% (months) (95% C.I.)	4.8 (1.9, 8.6)	8.5 (2.8, NA)	2.0 (2.0, NA)	5.4 (82.8,8.8)

Best Overall Response Rate (Phase II Studies: CA184-022 and CA184-008)

For completeness of the review, Best Overall Response Rates for studies CA184-022 and CA184-008 are also presented to demonstrate that BORR estimates were not robust among various dose levels based on small studies. 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%).

Table 11 Summary of Best Overall Response Rate (up to 24 weeks, for MDX010-20, Phase II studies)

Study	Treatment	#deaths/total	Median Survival time (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)

Progression Free Survival

Based on the investigator-assessed PFS, the median PFS time was similar in all 3 treatment arms. The ipilimumab +gp100 appears to have marginally lower risk as compared with that of the gp100 arm (Hazard ratio=0.81, 95% CI= [0.66, 1.00]) while it had 25% higher risk as compared with that of the ipilimumab monotherapy arm (Hazard ratio=1.25, 95% CI= [1.01, 1.53]). Ipilimumab monotherapy arm appears to have reduced risk as compared with that of the gp100 arm (Hazard ratio=0.64, 95% CI= [0.50, 0.83]). The summary of the investigator determined PFS is shown in the following table:

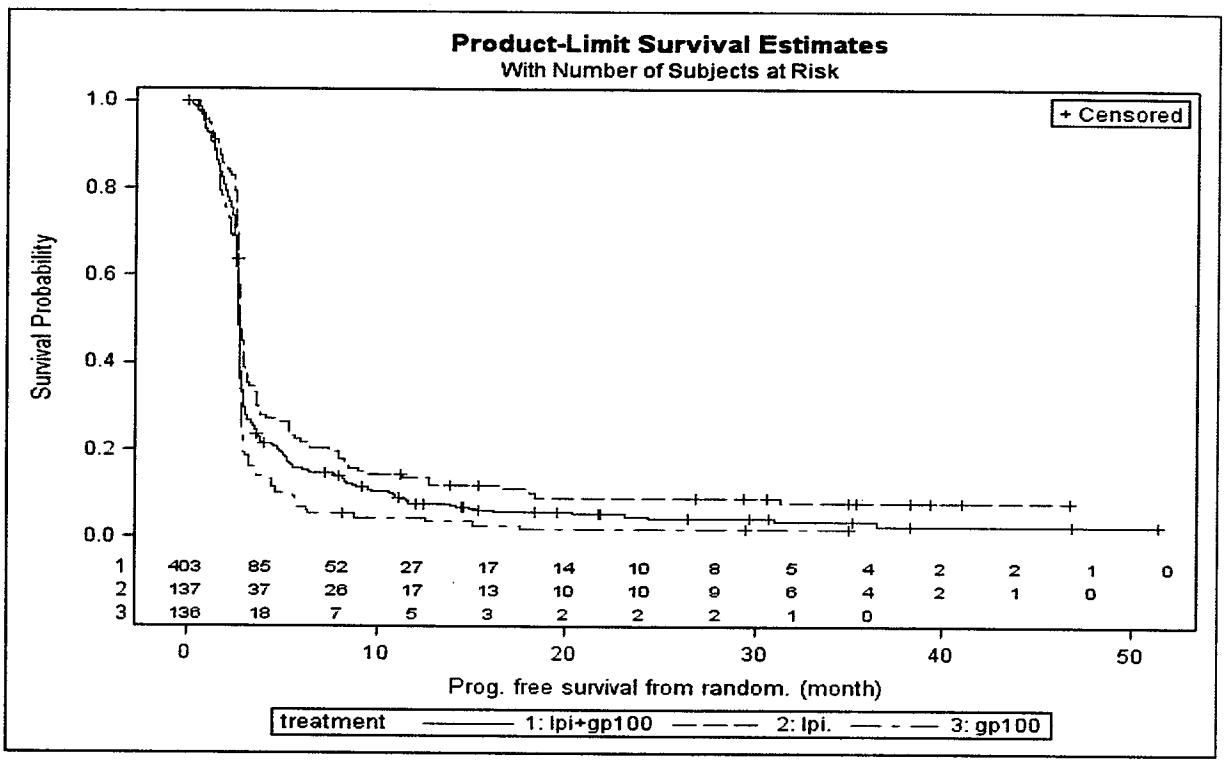
Table 12 Summary of the Investigator-assessed Progression Free Survival (MDX010-20)

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

[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 corresponding Kaplan-Meier curve for the investigator assessed PFS is presented in the following figure:

Figure 3 **Kaplan-Meier estimates for Investigator-assessed Progression-free Survival (MDX010-20)**



Reviewer's comments:

- *Because PFS was not a pre-specified key secondary endpoint, the p-values can not be interpreted.*
- *The majority of the PFS events resulted in death after progression (56%, 52% and 68% for ipilimumab+gp100, ipilimumab monotherapy and gp100 arm, respectively). Only 16% in ipilimumb+gp100 arm and ipilimumab monotherapy arm and 6% in gp100 arm of the PFS events were attributed to disease progression only.*
- *Disease assessment for study MDX010-20 started at week 12, so any disease progression prior to week 12 was not collected.*
- *Small percentages of patients had lost to follow-up (0.7%, 1.5% and 0.7% for ipilimumab+gp100, ipilimumab alone and gp100 arm, respectively) according to the CRF data. Seven percent, 6% and 6% of patients censored at the last assessment date before having more than 1 missing assessment*

prior to progression or death date for ipilimumab+gp100, ipilimumab monotherapy and gp100 arm, respectively. Four percent, 5% and 4% of the patients from ipilimumab+gp100, ipilimumab monotherapy and gp100 arm, respectively, were censored at the last assessment date prior to receiving concomitant antineoplastic agents or immunomodulating agents. Ten percent of the ipilimumab+gp100 arm, 14% from ipilimumab monotherapy arm and 7% from gp100 arm were censored at the last assessment date prior to early withdrawal from the study due to adverse events. The summary of censorings for PFS evaluation is displayed in the following table:

Table 13 Summary of the Censoring for Missing Assessments, Receiving Anti-cancer Therapy and Early Withdrawal due to AE for PFS (MDX010-20)

	Ipi+gp100 N=403	**Ipi N=137**	**gp100 N=136**
>1 missing assessment prior to event	28 (7%)	8 (6%)	8 (6%)
Receive anti-cancer therapy [a]	15 (4%)	7 (5%)	6 (4%)
Early withdrawal due to AE	40 (10%)	19 (14%)	9 (7%)

- *A sensitivity analysis was performed for PFS by censoring patients at the last response assessment date prior to the adverse event. The results appear to be similar to the original results for PFS (shown below).*

Table 14 Summary of the Investigator-assessed Progression Free Survival – Censored at Last Assessment Date if Withdrawal due to Toxicity (MDX010-20)

	Ipi+gp100 N=403	Ipi N=137	gp100 N=136
Number of events	356	115	121
Median (months)	2.79	2.86	2.76
95% CI for median [a]	2.76, 2.79	2.76, 3.06	2.73, 2.83
HR vs. gp100 with 95% CI [b]	0.81(0.65, 1.00)	0.62 (0.47, 0.82)	
HR vs. ipi alone with 95% CI [b]	1.27 (1.01, 1.59)		

[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.

- *Another sensitivity analysis was performed for PFS to evaluate the robustness of the results by censoring patients at the last disease assessment time prior to taking anti-cancer therapy. The results appear to be similar to the primary results: the hazard ratio between combination therapy vs. gp100 arm was 0.81 (95% C.I.=[0.65, 0.99]) and between ipilimumab monotherapy vs. gp100 arm was 0.66 (95% C.I.=[0.50, 0.85]).*
- *The other PFS was performed by censoring patients at the last disease assessment date prior to the time when patients had more than 1 missing assessments prior to a progression or death. The results again appear to be similar to the primary results: the hazard ratio between combination therapy vs. gp100 arm was 0.81 (95% C.I.=[0.66, 1.00]) and between ipilimumab monotherapy vs. gp100 arm was 0.63 (95% C.I.=[0.48, 0.82]).*
- *The dates for patients who took antineoplatic agents may not be adequately collected, so the calculation for the sensitivity analyses may not be accurate. The majority of the data (n=350) was based on telephone follow-up questionnaire which only captured the date of contact, not the time when the antineoplatic agents were administered. It is noted that only small portion of*

the patients who took antineoplatic agents were captured in the concomitant medication page (n=45) in which date of starting the antineoplatic agents were more adequately captured.

3.2.6 Applicant's Conclusions and Reviewer's Conclusions/Comments

Based on the MDX010-20 efficacy results, the applicant concluded that

- Ipilimumab reduced the risk of death from melanoma (hazard ratios of 0.68 [95% CI: 0.55, 0.85; p=0.0004] and 0.66 [95% CI: 0.51, 0.87; p=0.0026] for comparisons of ipilimumab+gp100 vs. gp100 and ipilimumab monotherapy arm vs. gp100, respectively.
- There was no difference in OS between the ipilimumab monotherapy and ipilimumab plus gp100 groups.
- Ipilimumab demonstrated a consistent survival benefit across prognostic factor subsets, including M stage, LDH, prior IL-2 therapy, age, and sex,etc.
- There was no difference in survival outcomes observed between HLA-A2*0201-positive and –negative patients across the Phase 2 studies, demonstrating that the ipilimumab effect is similar in these groups.
- Long-term survival (up to 2 years) and durable responses are observed.
- Statistically significant results in favor of ipilimumab-treated groups were observed for other efficacy endpoints (BORR, DCR, and PFS) indicating internal consistency of efficacy results.

Based on study MDX010-20 efficacy results, this reviewer summarized the results as follows:

- The results show that Ipilimumab combined with gp100 arm had 32% reduction in the risk of deaths (hazard ratios of 0.68 [95% CI: 0.55, 0.85]) while the Ipilimumab monotherapy arm had 23% reduction in the risk of deaths (hazard ratios of 0.66 [95% CI: 0.51, 0.87]) as compared with the results in the gp100 arm. Both comparisons appear to be statistically significant.
- The hazard ratio for ipilimumab combined with gp100 arm vs. ipilimumab monotherapy arm was 1.04 (95% C.I.: 0.83, 1.3).
- The hazard ratio estimates were consistently lower than 1 (both for ipilimumab combination arm vs. gp100 and ipilimumab monotherapy arm vs. gp100 arm)

across different subgroups (age, gender, M stage, prior IL-2 use, etc).

- The hazards ratio estimate for ipilimumab combined with gp100 arm vs. ipilimumab monotherapy arm was greater than 1 in several subgroups, e.g. male, ≥ 65 years old, < 65 years old, US, etc.
- The results from study MDX010-20 data and phase II data did not demonstrate whether there was differential overall survival results in HLA positive and negative subtypes.
- Since the best overall response rate is not a pre-specified key secondary endpoint, the p-value can not be interpreted. Also, due to the magnitude of the response rates (11% for ipilimumab monotherapy arm and 6% for ipilimumab combination arm), the best overall response rate can not support the overall survival results.
- Since the progression free survival is not a pre-specified key secondary endpoint, the p-value can not be interpreted. Also, due to the magnitude of the median PFS time (2.8, 2.9 and 2.8 months for ipilimumab combination arm, ipilimumab monotherapy arm and gp100 arm, respectively), the median progression free survival time can not support the overall survival results.

Reviewer's comment:

(b) (4)

and hence the treatment allocation was 3:1:1 resulted in a small sample size for the monotherapy arm. As with any small trial, the results comparing ipilimumab monotherapy with gp100 based on 273 patients for both arms combined should be evaluated cautiously. During the review of this application, preliminary results from a second independent study showing OS benefit support the results from this initial small study.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section provides summary statistics (hazard ratio, median survival time, count of patients and events) based on selected subgroups for overall survival.

4.1 Gender, Race, Age and Geographic Region

Gender

This reviewer performed analysis of OS by gender subgroup. The results for the comparisons between the combination therapy vs. gp100 and ipilimumab monotherapy vs. gp100 appear to be in favor of the ipilimumab containing arms in both genders. The comparison between combination arm vs. ipilimumab monotherapy arm is less clear. The ipilimumab+gp100 arm appear to have higher risk in male (based on the hazard ratio estimate) as compared with the ipilimumab monotherapy arm. However, because of the small sample sizes in the gender subgroups, the interpretation of the subgroup should be taken with caution.

Table 15 Reviewer's 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)
Ipi+gp100 vs. Ipi		**Ipi+gp100**	**Ipi**	
	Female	115/156	47/56	0.88(0.63,1.24)
	Male	191/247	53/81	1.28(0.94,1.74)

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

Race

Subgroup analysis by race can not be performed because race information was not

collected.

Age

Subgroup analyses based on 65 years as the age cutoff points (<65, ≥ 65 years old) for OS were performed. Both ipilimumab+gp100 and ipilimumab monotherapy appear to demonstrate lower risk in overall survival as compared with the gp100 arm in both younger and older patient population. The comparison between combination arm vs. ipilimumab monotherapy arm is not as clear. The ipilimumab combination arm appears to have higher risk (based on the hazard ratio estimate) as compared with the ipilimumab monotherapy arm. However, due to the small sample sizes in the age subgroups, the interpretation of this subgroup should be taken with caution.

Table 16 Reviewer's Summary of Overall Survival by Age Subgroup (MDX010-20)

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	< 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)
Ipi+gp100 vs. Ipi		**Ipi + gp100**	**Ipi**	
	< 65 yrs	219/291	69/95	1.07(0.81,1.40)
	>=65 yrs	87/112	31/42	1.10(0.73,1.66)

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

Geographic Region

The overall survival was summarized by North America, Europe and other region The majority of the hazard ratio estimates were lower than 1 demonstrating the beneficial effect of OS in the ipilimumab containing arm. The combination arm appears to have higher risk (based on the hazard ratio estimate) in Europe and North America as compared to that of the ipilimumab monotherapy arm. However, the higher risk does not appear to be statistically significant.

Table 17 Reviewer's 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)
Ipi+gp100 vs. Ipi		**Ipi+gp100**	**Ipi**	
	Europe	121/154	38/49	1.11(0.77,1.60)
	North America	155/209	51/75	1.13(0.82,1.54)
	Other	30/40	11/13	0.75(0.38,1.51)

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

4.2 Other Special/Subgroup Population

HLA-A2*0201 subtypes

To evaluate the overall survival in HLA subtypes, the pre-treated, 3 mg/kg dose group from two Phase II studies (study CA184-004 and CA18-4022) were combined. Ninety six percent of the patients had HLA status available. Among these phase II data, 46 and 47 patients had HLA positive and HLA negative, respectively.

The summary of the median survival time and its 95% confidence intervals based on study MDX010-20 and the combined phase II studies are presented in the following table. The median overall survival time estimates appear to be compatible among all HLA-positive subtypes. The median overall survival time in the HLA-negative subgroup appear to be shorter. However due to the small sample in the subgroup, more data is required for further analyses.

Table 18 Summary of the Median Survival Time by HLA-A2*0201 Subtypes (MDX010-20, Phase II studies)

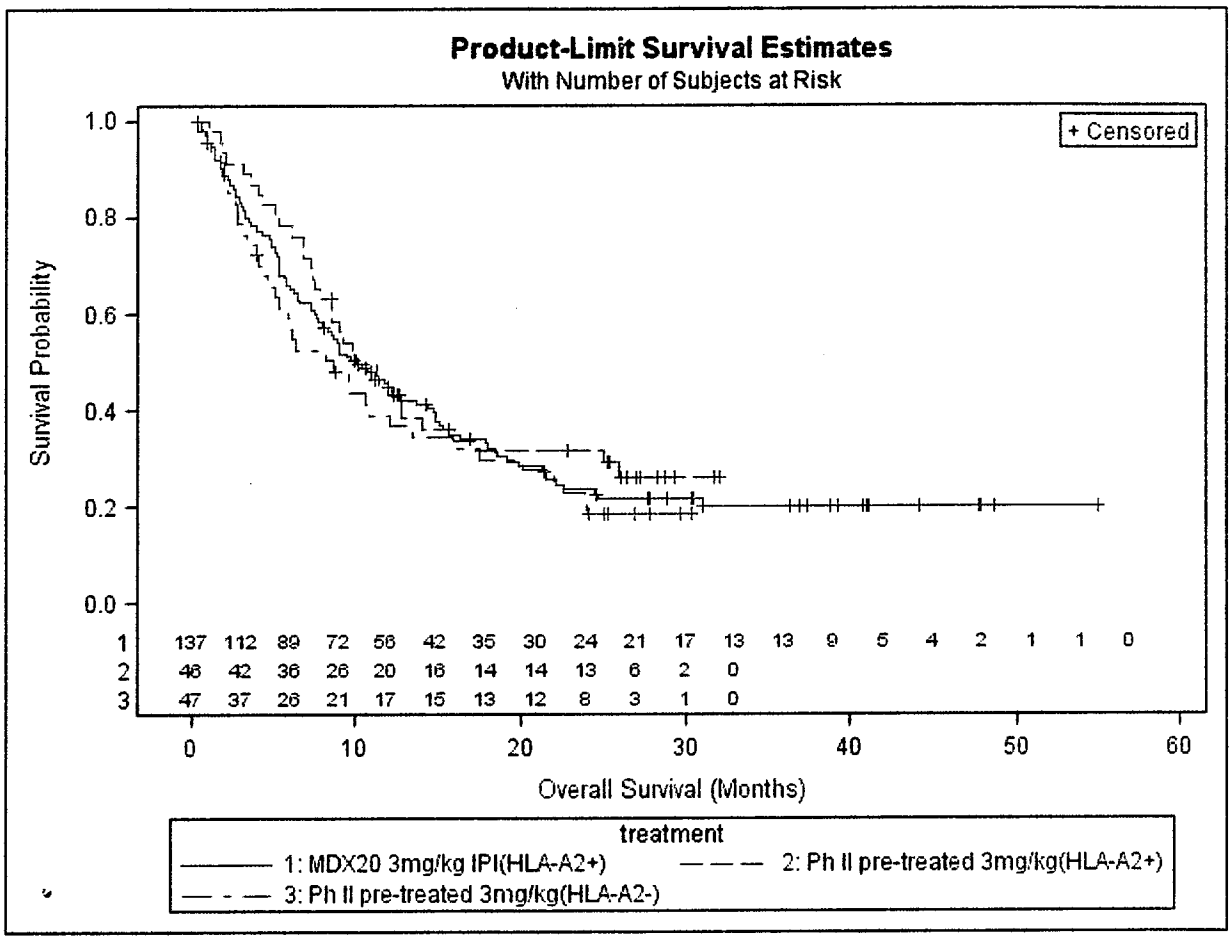
Study	HLA status	Treatment	#deaths/Total	Median (95% CI)
MDX-010-20	Positive	Ipi (3mg/kg)+gp100	306/403	9.95 (8.5,11.5)
	Positive	Ipi (3mg/kg)	100/137	10.1 (8.0,13.8)
	Positive	Gp100	119/136	6.44 (5.5, 8.7)
PhII study CA184004+ CA184022	Positive	Ipi (3mg/kg)	33/46	10.1 (7.6,14.2)
	Negative	Ipi (3mg/kg)	37/47	8.7 (5.1,13.5)

Reviewer's comments:

- *The cross-study comparison is not recommended and due to the small size, the results from the phase II data did not demonstrate whether there was differential overall survival results in HLA positive and negative subtypes.*
- *Due to the positive overall survival results observed in study CA184-024 (where study was based on unselected population, i.e. not require HLA typing), the data observed so far did not provide sufficient evidence that an HLA typing is required.*

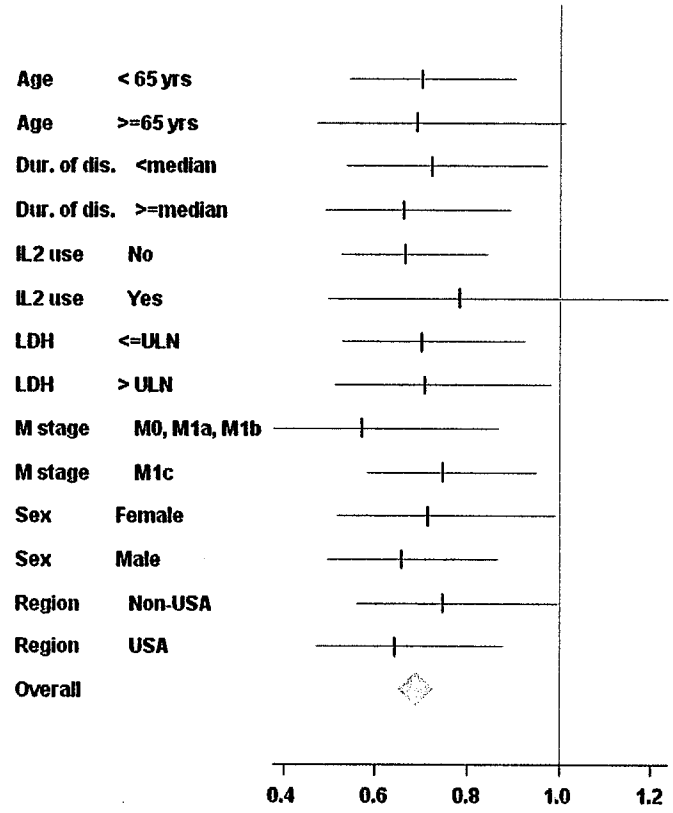
The corresponding Kaplan-Meier plots are presented follows:

Figure 4 Kaplan-Meier estimates for Overall Survival by HLA-A2*0201 Subtypes (MDX010-20, Phase II studies)



Subgroup analyses were also performed based on baseline duration of disease and LDH in addition to the age, gender, region, M-stage and IL-2 use. These subgroup analysis results were presented in the following three forest plots.

Figure 5 Subgroup Analysis for Overall Survival (Ipilimumab+gp100 versus gp100; MDX010-20)



Subgroup		ipi+gp100(#dth/N):gp100(#dth/N)	HR(95%CI)
Age	< 65 yrs	219/291:81/94	0.70(0.54,0.90)
Age	>=65 yrs	87/112:38/42	0.69(0.47,1.01)
Dur. of dis.	<median	161/200:59/68	0.72(0.53,0.97)
Dur. of dis.	>=median	143/201:60/68	0.66(0.49,0.89)
IL2 use	No	238/314:94/103	0.66(0.52,0.84)
IL2 use	Yes	68/89:25/33	0.78(0.49,1.24)
LDH	<=ULN	178/252:66/81	0.70(0.53,0.93)
LDH	> ULN	127/149:50/52	0.71(0.51,0.98)
M stage	M0, M1a, M1b	78/118:31/38	0.57(0.38,0.87)
M stage	M1c	228/285:88/98	0.74(0.58,0.95)
Sex	Female	115/156:53/63	0.72(0.52,0.99)
Sex	Male	191/247:66/73	0.66(0.50,0.87)
Region	Non-USA	161/210:65/73	0.75(0.56,1.00)
Region	USA	145/193:54/63	0.64(0.47,0.88)
Overall		306/403:119/136	0.69(0.56,0.85)

Figure 6 Subgroup Analysis for Overall Survival (Ipilimumab versus gp100; MDX010-20)

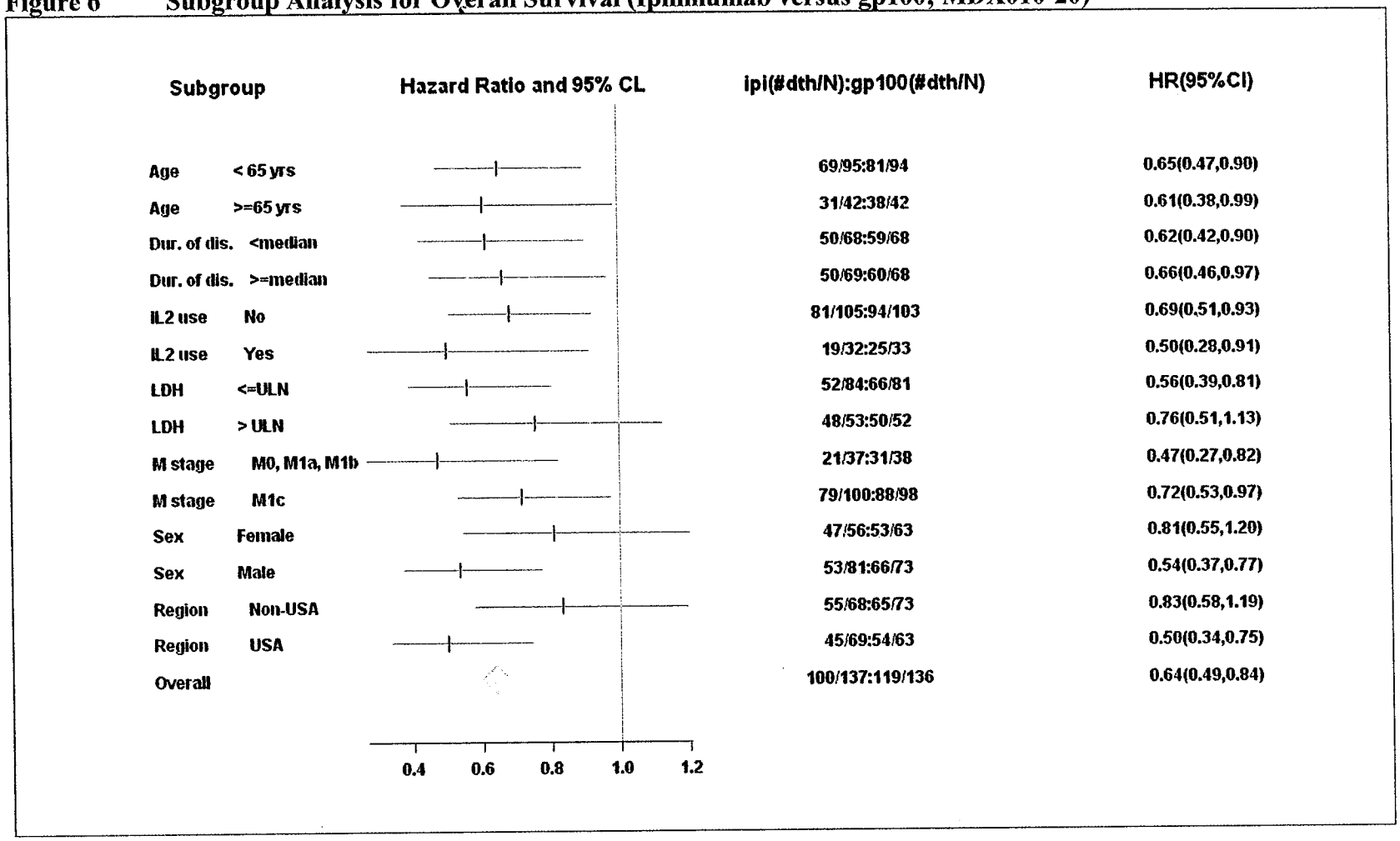
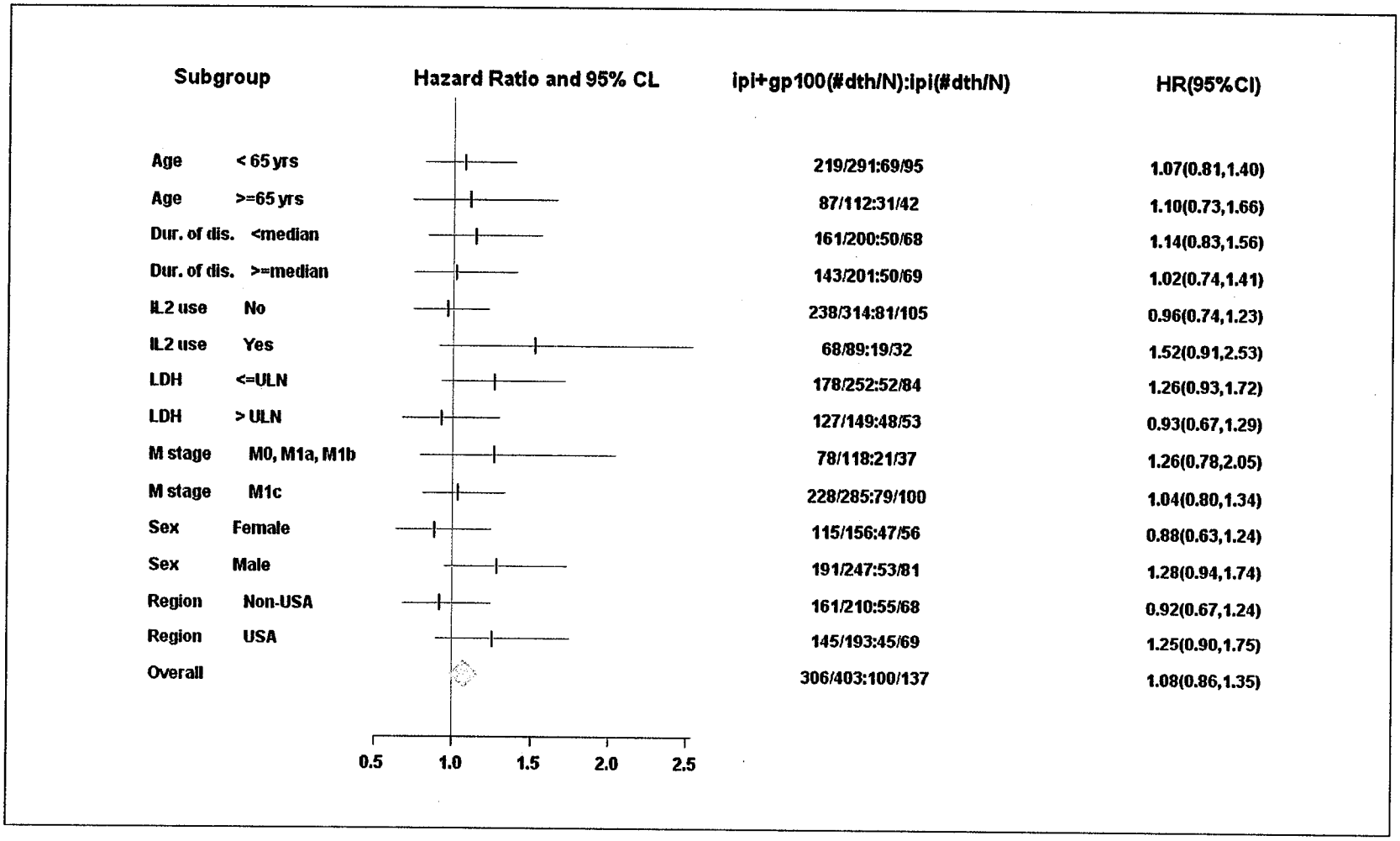


Figure 7 Subgroup Analysis for Overall Survival (Ipilimumab+gp100 versus Ipilimumab; MDX010-20)



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Based on study MDX010-20 and the supporting overall survival results from study CA184-024, ipilimumab in combination with gp100 and ipilimumab monotherapy arm appear to have prolonged overall survival time as compared with the gp100 arm in patients with advanced melanoma (unresectable stage III and IV melanoma) who have received prior treatment. The hazard ratios for the comparison between ipilimumab combination arm vs. gp100 was 0.68 (95% CI=0.55, 0.85) and for the comparison between ipilimumab monotherapy arm vs. gp100 was 0.66 (95% CI=0.51, 0.87). The median OS time was 9.95 (95% CI: 8.5, 11.5), 10.12(95% CI: 8.0, 13.8), and 6.44 (95% C: 5.5, 8.7) months for ipilimumab combination, ipilimumab monotherapy and gp100 arm, respectively, based on study MDX010-20. However, the comparison between two ipilimumab containing arms did not show statistically significant difference.

Also, the results from study MDX-010-20 (for HLA-A2*-2-1 positive only), Phase II studies (studies CA184-004, CA194-022) and study CA184-024 (no HLA typing) did not suggest the requirement for an HLA typing.

The beneficial treatment effect of the ipilimumab containing arms was consistently demonstrated based on several sensitivity analyses and appears to be consistent across various subgroups.

The major statistical/data issues are summarized as follows:

- The concerns of the reliability and robustness of the treatment effects based on one single small study.
- MDX010-20 was not a well designed study (b) (4)
- The concerns of potential bias that may be introduced as a results of many unplanned modifications to the protocol, e.g. change of the primary endpoint from BORR to OS, adding additional secondary comparison (i.e. compare between ipilimumab monotherapy arm vs. gp100), recalculation of the sample size. The impact of the potential bias may be difficult to evaluate. Therefore,

the interpretation based on this single trial may be problematic.

- The secondary endpoints, such as best overall response rate and progression free survival, are not persuasive, so the study did not demonstrate robustness of the results across different endpoints.

The beneficial effect of ipilimumab treated arm based on the single, small study does not appear to be convincing due to many deficiencies as cited. However, the demonstration of the overall survival benefit based on the preliminary results from a larger study (study CA184-024) provides a replication of the beneficial effect for the ipilimumab treated arm.

5.2 Conclusions and Recommendations

Based on study MDX-010-20 and the supporting information from study CA184-024, the results appear to demonstrate a statistically significant reduction in the risk of death in favor of ipilimumab containing arm (as compared to the gp100 peptide vaccine) for patients with advanced melanoma (unresectable stage III and IV melanoma) who have received prior treatment.

The beneficial treatment effect of the ipilimumab containing arms was consistently demonstrated based on several sensitivity analyses and appears to be consistent across various subgroups

Also, the results from study MDX-010-20 (for HLA-A2*-2-1 positive only), Phase II studies (studies CA184-004, CA194-022) and study CA184-024 (no HLA typing) did not suggest the requirement for an HLA typing.

6 APPENDIX

Study	Population	Design/type of control	Primary Endpoint /objectives	Test Drugs Dose and Duration	Number of Treated Subjects
Studies with Induction plus Maintenance Treatment					
CA184022	Pretreated stage 3 (unresectable) or stage 4 melanoma	Double-blind randomized (1:1:1) Phase 2	BORR (by Wold Health Organization criteria)	Induction IV Ipilimumab 0.3 3 or 10 mg/kg IV q3 wks x 4 doses Maintenance IV Ipilimumab 0.3 3 or 10 mg/kg IV q12 weeks until disease progression, toxicity requiring study drug discontinuation withdrawal of consent or study closure	214
CA184008	Pretreated stage 3 (unresectable) or stage 4 melanoma	Phase 2, open-label, single-arm, multicenter	BORR (by Wold Health Organization criteria)	Induction IV Ipilimumab 10 mg/kg IV q3 wks x 4 doses Maintenance IV Ipilimumab 10 mg/kg IV q12 weeks until disease	155

				progression, toxicity requiring study drug discontinuation withdrawal of consent or study closure	
CA184007	Pretreated and previously untreated subjects with unresectable stage 3 or 4 malignant melanoma	Double-blind randomized (1:1) phase 2	Safety /Estimate the rate of grade ≥ 2 diarrhea with ipilimumab when given with either prophylactive oral budesonide or placebo	IV Ipilimumab and oral budesonide or placebo <u>Induction</u> Ipilimumab 10 mg/kg IV q3 wks x 4 doses Maintenance: Ipilimumab 10 mg/kg q12 wks <u>Budesonide</u>: 9 mg QD until wk 12, 6 mg until wk 14, and 3 mg until Wk 16	115 (# in ipilimumab+placebo =57; # in ipilimumab+budesonide=58)
Biomarker Biopsy Study					
CA184004	Pretreated and previously untreated subjects with unresectable stage 3 or 4	Double-blind randomized (1:1) phase 2, exploratory	Determine potential predictive markers of response or toxicity	<u>Induction</u> IV Ipilimumab 3 or 10 mg/kg IV q3 wks x 4 doses <u>Maintenance</u>	82

	malignant melanoma		/Correlate pretreatment characteristics of patient and/or tumor with clinical tumor response to identify candidate markers predictive of response and/or serious toxicity to ipilimumab	IV Ipilimumab 3 or 10 mg/kg IV q12 weeks until disease progression, toxicity requiring study drug discontinuation, withdrawal of consent	

/S/

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2/25/2010

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2/25/2010

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2/25/2010

7 SIGNATURES/DISTRIBUTION LIST PAGE

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