Name of Sponsor/Company: Medarex, Inc. / Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Ipilimumab		
Name of Active Ingredient: MDX-010		

SYNOPSIS

Clinical Study Report for Study MDX010-20

TITLE OF 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

INVESTIGATORS/STUDY CENTERS: Of the 1783 subjects who enrolled and were screened for study participation, a total of 676 subjects were randomized at 125 sites in Europe, North America, South America, and Africa.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 27 September 2004 **CLINICAL PHASE:** 3

Last Patient First Visit: 24 July 2008

Study Completion Date: 7 October 2009

OBJECTIVES:

Primary Objective: To compare the overall survival (OS) of subjects administered ipilimumab (MDX-010; BMS-734016) in combination with gp100 melanoma peptide vaccine (MDX-1379, BMS-734019; the combination is herein referred to as ipilimumab plus gp100 and in tables as ipi+gp100) versus those administered ipilimumab placebo in combination with melanoma peptide vaccine (herein referred to as gp100 monotherapy and in tables as gp100).

Secondary Objectives:

- Comparison of OS of subjects administered ipilimumab plus gp100 to those administered ipilimumab in combination with vaccine placebo (herein referred to as ipilimumab montherapy and in tables as ipi), and of subjects administered gp100 monotherapy vs. those administered ipilimumab monotherapy
- Determination of safety
- Evaluation of best overall response rate (BORR)
- Determination of major durable response rate
- Determination of duration of response
- Determination of progression-free survival (PFS)
- Determination of time-to-progression
- Evaluation of health-related Quality of Life (HRQoL)

METHODOLOGY: This was a Phase 3, randomized, double-blind, multicenter study in HLA-A*0201-positive (herein referred to as HLA-A2*0201-positive) subjects with a diagnosis of unresectable Stage III or Stage IV melanoma who had relapsed, failed, or were not able to tolerate at least 1 or more prior treatment regimens. In order to evenly balance factors that may influence outcome, subjects enrolled into the study were stratified on the basis of baseline TNM status (M0, M1a, or M1b vs. M1c) and prior treatment with interleukin-2 (IL-2).

The study consisted of 3 phases: Screening, Treatment, and Follow-up. Subjects who met the selection criteria were randomized in a double-blind fashion in a 3:1:1 ratio to receive ipilimumab plus gp100, ipilimumab monotherapy, or gp100 monotherapy. Ipilimumab or ipilimumab placebo was administered intravenously (IV) every 3 weeks for a total of 4 doses to the subjects in all 3 treatment groups. In addition, gp100 or vaccine placebo was administered by subcutaneous injection, immediately after administration of the ipilimumab dose. An induction cycle was defined as 4 doses of study medication administered 3 weeks apart. At the completion of the initial induction cycle, subjects entered the follow-up phase to be followed for response, survival, and safety.

Subjects who progressed following stable disease (of ≥ 3 months duration beginning at Week 12), or who had experienced an initial objective response (partial response [PR] or complete response [CR]) to the initial induction cycle could have been offered additional cycles of treatment with the originally assigned treatment regimen (re-induction) until off-treatment criteria were met, provided they continued to meet re-induction eligibility requirements. All adverse events (AEs) were to be reported through 70 days following the last dose of study treatment, or until adverse events resolved or stabilized; AEs occurring > 70 days following the last dose of study treatment and assessed by the investigator as probably or definitely related to study medication were also to be reported. No subject was to receive re-induction if they experienced a Grade 3 non-skin irAE (except for endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy) or a Grade 4 toxicity of any organ system considered related to study drug administration. No subject with disease progression following induction was permitted to receive re-induction with study medication.

All subjects who prematurely discontinued treatment due to a drug-related adverse event prior to Week 12 (in the absence of disease progression) were to return for all study visits and procedures including Week 12 and, if appropriate, further restaging assessments. Any subject with documented progression at any scheduled restaging visit who was not eligible for continued treatment was not required to have additional restaging assessments. Subjects with stable disease (SD), PR, or CR, who prematurely discontinued treatment due to a drug-related adverse event (AE) were to continue all study visits as per the protocol and have all study procedures performed.

Subjects who were not eligible or chose not to receive re-induction were to be followed for survival status by telephone every 3 months and were permitted to receive non-study antimelanoma medications at the discretion of the Investigator. All subjects randomized to the study were to be followed until at least 481 events (deaths) occurred in the study.

NUMBER OF SUBJECTS (Planned and Analyzed): The sample size was based on the primary objective, comparison of OS of ipilimumab plus gp100 and gp100 monotherapy. On the basis of a simulation using the collected blinded survival data from this study and historical literature data, a total of 385 events and a total of 500 enrolled subjects for the 2 groups would be expected to achieve a 90% power to detect a difference in OS between the 2 groups at the 0.05 significance level using the log-rank test.

A total of 676 subjects were randomized (403 subjects to ipilimumab plus gp100, 137 to ipilimumab monotherapy, and 136 to gp100 monotherapy) and included in the intent to treat (ITT) population; 643 subjects were treated (380 subjects with ipilimumab plus gp100, 131 to ipilimumab monotherapy, and 132 to gp100 monotherapy) and included in the safety, as treated population. One subject was randomized to ipilimumab plus gp100 but received a full induction cycle of treatment with gp100 monotherapy.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: HLA-A2*0201-positive subjects with a diagnosis of unresectable Stage III or Stage IV melanoma who, in response to 1 or more regimens containing 1 or more of the following: IL-2, dacarbazine, temozolomide, fotemustine and/or carboplatin, had (1) relapsed following an objective response (PR/ CR); (2) failed to demonstrate an objective response (PR/CR); or (3) could not tolerate such a regimen due to unacceptable toxicity. All subjects must have received at least 1 course of first-line therapy.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: The 2 test product treatment groups were ipilimumab plus gp100 and ipilimumab monotherapy. Ipilimumab was administered at a dosage of 3 mg/kg as an intravenous (IV) infusion administered over 90 minutes every 3 weeks for a total of 4 doses, together with gp100 or matching vaccine placebo. Gp100 consisted of 2 separate peptide components: Peptide A, a peptide with sequence YLEPGPVTV (gp100:280-288[288V]) and Peptide B, a peptide with the sequence IMDQVPFSV (gp100:209-217[210M]). Each peptide was prepared with Montanide ISA-51. One dose of gp100 consisted of the administration of Peptide A, at a dosage of 2 mL or 1 mg, and Peptide B, at a dosage of 2 mL or 1 mg. The vaccine placebo consisted of sterile 0.9% sodium chloride. After Week 12, subjects who met re-induction criteria could receive further cycles of their randomized study therapy.

Relevant study drug components were administered from the following batches:

Ipilimumab: M31A-03-02FC, M31A-03-04FC, M31A-04-03FC, M31A-04-06FC, M31A-05-02FC, M31A-06-03FC

gp100 vaccine: MPS22-03-02FC, MPS22-05-01FC, MPS22-07-01FC, MPS21-05-01FC, MPS21-07-01FC, MPS21-03-02FC

gp100 placebo (vaccine placebo): Saline # 13-074-DK, Saline # 13-494-DK, and as of Amendment 2, the site was to supply saline to use as placebo and Medarex (MDX) supplied only the labels.

Montanide for subjects receiving gp100 vaccine: IFA-04-02FC, IFA-04-03FC, IFA-05-01FC, IFA-06-01FC

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: The reference therapy group for this study was gp100 monotherapy. One dose of gp100 consisted of the administration of Peptide A, at a dosage of 2 mL or 1 mg, and Peptide B, at a dosage of 2 mL or 1 mg. Each peptide was prepared with Montanide ISA-51. Gp100 was administered every 3 weeks together with matching ipilimumab placebo, administered as an IV infusion. After Week 12, subjects who met re-induction criteria could receive further cycles of their randomized study therapy (matching ipilimumab placebo plus gp100).

Relevant study drug components were administered from the following batches:

Ipilimumab Placebo: PLCB-04-01FC, PLCB-07-01FC

gp100 vaccine: Peptide A - MPS22-03-02FC, MPS22-05-01FC, MPS22-07-01FC; Peptide B- MPS21-05-01FC, MPS21-07-01FC, MPS21-03-02FC

Montanide for subjects receiving gp100 vaccine: IFA-04-02FC, IFA-04-03FC, IFA-05-01FC, IFA-06-01FC

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy endpoint was the comparison of OS for subjects administered ipilimumab plus gp100 versus those administered gp100 monotherapy. Secondary efficacy endpoints included comparison of OS for subjects administered ipilimumab plus gp100 vs. those administered ipilimumab monotherapy, and for subjects administered gp100 monotherapy vs. those administered ipilimumab monotherapy. Other secondary endpoints were based on investigator reported response (no IRC review)

and included: BORR up to Week 24 (as determined by site Investigator tumor response assessment based on modified WHO criteria), duration of response, PFS, and time-to-progression. The European Organization for Research and treatment of Cancer (EORTC) QLQ-C30 questionnaire was the primary instrument used to measure QOL.

Safety: Safety was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. The key safety endpoints were: deaths, the incidence of on-study AEs, particularly irAEs, discontinuation due to AEs, clinical laboratory tests, physical examinations, and vital sign measurements. An independent Data Monitoring Committee (DMC) monitored safety and made recommendations on study continuation or modification to the Sponsor Steering Committee.

STATISTICAL CONSIDERATIONS: The original sample size of 750 subjects was based on a primary endpoint of BORR, comparing the combination group to each of the 2 monotherapy groups. Subsequently, the primary endpoint was amended to be OS and the protocol design was amended to have a single primary comparison of ipilimumab plus gp100 and gp100 monotherapy. The change in the primary endpoint was made for 2 reasons. First, previous Health Authority advice had included a recommendation to use overall survival as the primary endpoint for this study. Second, as the Phase 2 data matured, it became clear that the survival endpoint more accurately captures the clinical benefit of ipilimumab than do conventional tumor response endpoints. The use of BORR were designed to capture the benefit of conventional chemotherapy where progressive disease by the standard criteria is never expected to be followed by durable tumor suppression and/or objective response, whereas the biology of immunotherapy is substantially different as has been described in subjects treated with immunotherapies. Since validated endpoints that reflect the mechanisms underlying immunotherapy are not yet available, the gold-standard endpoint of overall survival becomes the most appropriate measure for assessing the clinical efficacy and safety of ipilimumab.

The sample size was revised based on the new primary comparison, OS of ipilimumab plus gp100 and gp100 monotherapy. On the basis of a simulation using the collected blinded survival data from this study and historical literature data, a total of 385 events and a total of 500 enrolled subjects for the 2 groups (ipilimumab plus gp100 and gp100 monotherapy) were required to achieve a 90% power to detect a difference in OS between the 2 groups at the 0.05 significance level using the log-rank test. Therefore, a total of 481 events were required in all 3 groups (assuming that the events are distributed with ratios at 3:1:1 in ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively). On the basis of these assumptions, and with study enrollment over 650 subjects, enrollment into the study was closed effective 25 July 2008. The observed 219 events out of 273 subjects randomized in a 1:1 ratio (ipilimumab monotherapy vs. gp100) yields at least 80% power with a two-sided alpha of 0.05.

For the primary efficacy analysis, the difference in OS between ipilimumab plus gp100 vs. gp100 monotherapy was compared using stratified log-rank test along with the depiction of the Kaplan-Meier survival curve. The 2 stratification factors were baseline TNM status (M0, M1a, or M1b versus M1c), and prior or no prior treatment with IL-2. The median estimates with 95% confidence intervals (CIs) were computed using Brookmeyer and Crowley method. The other time-to-event parameters (PFS and time-to-progression) were also analyzed using the same methods as for OS.

The secondary efficacy analysis of survival compared the OS of ipilimumab monotherapy to gp100 monotherapy and ipilimumab plus gp100 to ipilimumab monotherapy. Treatment differences for the BORR (as determined by site Investigator up to Week 24 and confirmed at least 4 weeks later) were compared using the stratified CMH test. The duration of response was summarized by treatment group using descriptive statistics for responder subjects only. The HRQoL was compared for treatment differences using an Analysis of Covariance (ANCOVA) model.

Safety parameters were summarized using descriptive statistics (frequency tabulation), including the following items: any AE, any serious AE (SAE), any study drug related AE, any irAE, death, and discontinuation of study medication due to AE. Routine clinical laboratory findings were summarized using descriptive statistics for each treatment group. Changes from baseline to each visit were determined for quantitative variables.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics:

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: 403 to ipilimumab plus gp100, 137 to ipilimumab monotherapy, and 136 to gp100 monotherapy. **Table 1** presents subject disposition according to randomized treatment assignment; however, 1 subject was randomized to ipilimumab plus gp100 but treated with gp100 monotherapy. This subject is counted in the ipilimumab plus gp100 group for baseline characteristics and efficacy analyses, and in the gp100 monotherapy group for dosing and safety analyses.

Table 1: Subject Disposition - All Subjects

	Ipi+gp100	Ipi	gp100	Total
Enrolled	-	-	-	1783
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[b]				
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[c]	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 are presented based on randomization; however, 1 subject was randomized to Ipi+gp100 but treated with gp100. Therefore dosing and safety analyses will count this subject in the gp100 treatment group.

[b] Percentage based on all randomized subjects

[c] Reasons for study discontinuation for 2 subjects under 'Other' were study completion (ipi + gp100) and overall study closed (ipi), respectively; these subjects should have been included under Trial completed.

The median age of subjects was 57 years, and a majority (59%) was male. Over 90% of subjects were white, and 98% had Stage IV disease. The majority of subjects were M1c stage (71.4%) and approximately

one-third of subjects had an elevated LDH at baseline. The 3 treatment groups were well balanced for demographic characteristics, including baseline M-stage at randomization and prior IL-2 use, as would be expected since these were stratification factors contributing to the randomization (**Table 2**). ECOG performance status was 0 or 1 for all but 11 subjects (9 with status of 2; 1 each with status of 3 or unknown).

Table 2: Demographic and Baseline Characteristics - ITT as Randomized

Characteristic	Ipi+gp100 n=403	Ipi n=137	gp100 n=136	Total n=676
Age (years)				
Mean	55.6	56.8	57.4	56.2
Median	57.0	57.0	57.0	57.0
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)
M Stage				
M0	5 (1.2)	1 (0.7)	4 (2.9)	10 (1.5)
M1a	37 (9.2)	14 (10.2)	11 (8.1)	62 (9.2)
M1b	76 (18.9)	22 (16.1)	23 (16.9)	121 (17.9)
M1c	285 (70.7)	100 (73.0)	98 (72.1)	483 (71.4)
Prior IL-2				
No	314 (77.9)	105 (76.6)	103 (75.7)	522 (77.2)
Yes	89 (21.1)	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)

ULN = upper limit of normal; Min = minimum; Max = maximum

Exposure: Most subjects (603/643; 94%) were treated only during the induction cycle of treatment; forty (40) subjects (6%) received re-induction. Four-hundred eight (408) subjects (63.5%) received the target number of doses of ipilimumab/ipilimumab placebo, 407 subjects (63.3%) received the target number of doses of gp100/placebo Peptide A component and 406 subjects (63.1%) received the target number of doses of gp100/vaccine placebo Peptide B component.

Efficacy Results:

*Overall Survival*Survival follow-up was current (defined as having died or last known alive date occurring on or after the 19-June-2009 cutoff) for 83% of subjects, while 4% of subjects had a last known alive date that was obtained more than 3 months before the cutoff for follow-up. Median follow-up for alive subjects was 21 months for the ipilimumab plus gp100 group, 28 months for the ipilimumab monotherapy group, and 17 months for the gp100 monotherapy groups. Subjects known to be alive were followed for as long as 55 months.

The primary objective of this study was the comparison of OS in subjects administered ipilimumab plus gp100 versus gp100 monotherapy. The hazard ratio (HR) for comparison of OS between the ipilimumab plus gp100 and gp100 monotherapy groups was 0.68 (95% CI: 0.55, 0.85; p = 0.0004) (**Table 3**), indicating a 32% risk reduction in OS for the ipilimumab plus gp100 group compared with the gp100 monotherapy group. The HR for comparison of OS between the ipilimumab monotherapy and gp100 monotherapy groups was 0.66 (95% CI: 0.51, 0.87; p = 0.0026), indicating a 34% risk reduction in OS for the ipilimumab monotherapy group compared with the gp100 group. The HR for comparison of OS between the ipilimumab plus gp100 and ipilimumab monotherapy groups was 1.04 (95% CI: 0.83, 1.30; p = 0.7575) demonstrating no difference in survival outcomes between both groups.

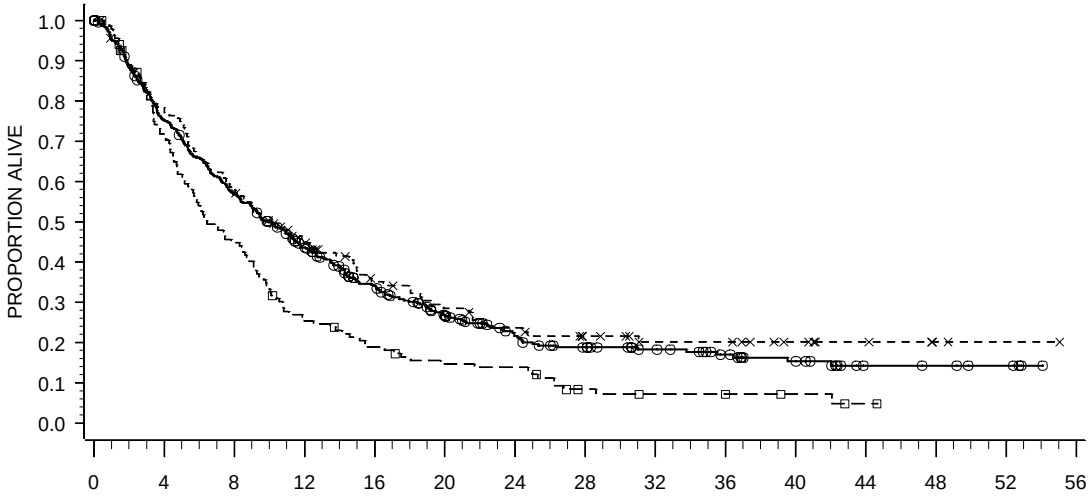
Table 3: Overall Survival by Treatment - ITT as Randomized

	Ipi+gp100 (n=403)	**Ipi (n=137)**	**gp100 (n=136)**	**Total (n=676)**
Number of events	306	100	119	525
HR vs.gp100 with 95% CI	0.68 (0.55, 0.85)	0.66 (0.51, 0.87)		
Log-rank p value vs. gp100	0.0004	0.0026		
HR vs. Ipilimumab with 95% CI	1.04 (0.83, 1.30)			
Log-rank p value vs. Ipilimumab	0.7575			

The Kaplan-Meier survival curves are similar for the 3 treatment groups through approximately the first 4 months of treatment (**Figure 1**), after which a separation in the curves suggests a favorable OS advantage for the ipilimumab plus gp100 and ipilimumab monotherapy groups compared with the gp100 group.

Median OS was 9.95 months (95% CI: 8.48, 11.50) in the ipilimumab plus gp100 group, 10.12 months (95% CI: 8.02, 13.80) in the ipilimumab monotherapy group, and 6.44 months (95% CI: 5.49, 8.71) in the gp100 monotherapy group.

Figure 1: Overall Survival by Treatment - ITT as Randomized



SUBJECTS AT RISK

Ipi+gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

Ipi+gp100 ⊙⊙⊙ CENSORED
Ipi ××× CENSORED
gp100 □□□ CENSORED

GROUP	# DEATHS / # RANDOMIZED	MEDIAN (95% CI)
Ipi+gp100	306/403	9.95 (8.48 - 11.50)
Ipi	100/137	10.12 (8.02 - 13.80)
gp100	119/136	6.44 (5.49 - 8.71)

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The estimated 1-year and 2-year survival rates were consistently higher in the ipilimumab-treated groups. The estimated 1-year survival rates were 43.6% in the ipilimumab plus gp100 group, 45.6% in the ipilimumab monotherapy group, and 25.3% in the gp100 group. The estimated 2-year survival rates were 21.6%, 23.5%, and 13.7%, respectively. Long-term survival (at least 2 years) was observed in the ipilimumab plus gp100 and ipilimumab monotherapy groups by 54 and 24 subjects, respectively, alive for at least 2 years, compared with 16 subjects in the gp100 group.

Subgroup comparisons for OS were performed across 5 pre-specified categories M-stage (M0, M1a or M1b versus M1c), prior IL-2, baseline LDH (≤ ULN versus > ULN), age (< 65 years versus ≥ 65 years), and gender. The subgroup categories of M-stages, prior IL-2 and baseline LDH represent prognostic factors affecting outcome in late stage melanoma. In addition, prior IL-2 treatment and M-stage were used as stratification factors for randomization in this study. The results from the subgroup analyses demonstrate a consistent pattern with HRs favoring either of the ipilimumab-treated groups relative to the gp100 monotherapy group. Subgroup analyses for ipilimumab plus gp100 versus ipilimumab monotherapy consistently showed HRs whose 95% CIs overlap 1, indicating comparable activity across the 2 ipilimumab-treated groups. These pre-specified analyses demonstrate that the performance of ipilimumab within relevant prognostic subgroups is highly consistent with the survival advantage that was demonstrated for the overall study population.

BORR, Disease Control Rate (DCR), PFS, PFS Rate, duration of response, time to progression (TTP)

Secondary endpoints of BORR, DCR, PFS, PFSR, duration of response, time-to-progression are summarized (**Table 4**). The responses observed with ipilimumab treatment were durable. Among the subjects in the ipilimumab-treated groups that achieved an objective response; response was maintained for at least 2 years for 17.4% (4/23) of subjects treated with ipilimumab plus gp100 (range: 27.9+ to 44.4+) and 60.0% (9/15) of subjects treated with ipilimumab monotherapy (range: 26.5+ to 44.2+ months). Of these, 3 subjects maintained their response for more than 36 months. None of the subjects treated with gp100 remained in response at the 2-year time point.

Table 4: MDX010-20 - Secondary Efficacy Endpoints (ITT Population)

	Ipi + gp100 n = 403	**Ipi n = 137**	**gp100 n = 136**
BORR (CR and PR)			
n (%)	23 (5.7)	15 (10.9)	2 (1.5)
95% CI	(3.7, 8.4)	(6.3, 17.4)	(0.2, 5.2)
Treatment comparison - BORR	p-value[a]		
Ipi + gp100 vs.gp100	0.0433		
Ipi vs. gp100	0.0012		
Ipi + gp100 vs. Ipi	0.0402		
DCR (CR, PR, SD)			
n (%)	81 (20.1)	39 (28.5)	15 (11.0)
95% CI	(16.3, 24.3)	(21.1, 36.8)	(6.3, 17.5)
BOR, N (%)			
CR	1 (0.2)	2 (1.5)	0
PR	22 (5.5)	13 (9.5)	2 (1.5)
SD	58 (14.4)	24 (17.5)	13 (9.6)
PD	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated	83 (20.6)	28 (20.4)	32 (23.5)

Table 4: MDX010-20 - Secondary Efficacy Endpoints (ITT Population)

	Ipi + gp100 n = 403	Ipi n = 137	gp100 n = 136
PFS (months)			
Median (95% CI)	2.76 (2.73, 2.79)	2.86 (2.76, 3.02)	2.76 (2.73, 2.83)
Treatment comparison - PFS	Hazard Ratio (95% CI)[b]		
Ipi + gp100 vs.gp100	0.81 (0.66, 1.00)		
Ipi vs. gp100	0.64 (0.50, 0.83)		
Ipi + gp100 vs. Ipi	1.25 (1.01, 1.53)		
Time to Progression (months)			
Median (95% CI)	2.76 (2.73, 2.79)	2.86 (2.76, 3.02)	2.76 (2.73, 2.83)
Time to Response (months)			
N	23	15	2
Mean (95% CI)	3.324 (2.991, 3.737)	3.176 (2.753, 3.598)	2.743 (2.117, 3.370)
Duration of Response (months)			
N	23	15	2
Median (95% CI)	11.47 (5.36, NR)	NR (28.09, NR)	NR (2.00, NR)

BORR = best overall response rate, BOR = best overall response, DCR = disease control rate, PFS = progression free survival, CI = confidence interval, CR = confirmed complete response, PR = confirmed partial response, SD = stable disease, PD = progressive disease, NE = not evaluated, missing, or unknown, NR = not reached

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

[a] The comparison for P-values was performed between ipi + gp100 vs. gp100, ipi vs. gp100, and ipi+gp100 vs. ipi. 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).

[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 IL-2 with (Yes vs. No).

Safety Results: Safety was evaluated using the safety population which consisted of all treated subjects, as treated. Unless otherwise specified in this document, overall safety is described based on events observed throughout the on-study period (defined as starting from the first date of induction dosing and ending at 70 days after the last dose of study therapy, including re-induction doses). Progressive disease was the most frequent reason of death across treatment groups. Adverse events with an outcome of death were reported for 44 subjects, of which 14 were judged by the Investigator to be related to study drug: 8 (2.1%) subjects in the ipilimumab plus gp100, 4 (3.1%) in the ipilimumab monotherapy and 2 (1.5%) in the gp100 monotherapy groups (**Table 5**). Of these, a total of 7 deaths resulting from study-defined irAEs occurred in the 2 ipilimumab-containing treatment groups (5 ipilimumab plus gp100, 2 ipilimumab monotherapy, none gp100 monotherapy): 5 in association with complications of colitis, 1 hepatic failure, and 1 Guillain-Barre syndrome. On-study AEs, severe AEs (≥ Grade 3), and SAEs were reported in a similar proportion of

subjects across treatment groups. Study drug-related AEs (ie, related to either ipilimumab or gp100), were reported for 547 (85.1%) of subjects, and were ≥ Grade 3 in 72 (18.9%) of subjects treated with ipilimumab plus gp100, 33 (25.2%) with ipilimumab monotherapy, and 16 (12.1%) with gp100 monotherapy.

The most frequently reported drug-related AEs were irAEs. The incidence of irAEs was higher in the ipilimumab-treated groups (ipilimumab plus gp100 in 221 subjects, 58.2%; ipilimumab monotherapy in 80 subjects, 61.1%) compared to gp100 monotherapy (42 subjects, 31.8%) (**Table 5**). Across treatment groups, the most frequently (≥ 2%) reported irAEs were skin and subcutaneous tissue disorders and gastrointestinal (GI) disorders and, less commonly, liver and endocrine disorders. The most frequently (≥ 5%) reported GI irAE were diarrhea and colitis. Intestinal perforation occurred on-study in 5 subjects in the ipilimumab plus gp100 group. In addition, 1 subject in the ipilimumab monotherapy group had a large intestine perforation that occurred > 70 days after the last dose of study drug. The most frequently reported skin irAEs were pruritus, rash, erythema, vitiligo, and urticaria. Toxic epidermal necrolysis occurred in 1 subject in the ipilimumab plus gp100 group. The most frequently reported endocrine irAEs were hypothyroidism and hypopituitarism. Liver irAEs were infrequent in all 3 treatment groups with the highest rate of events (4.5% for all grades and 2.3% for ≥ Grade 3) in the gp100 monotherapy group. Hepatic failure (Grade 5) occurred in 1 subject in the ipilimumab monotherapy group.

Table 5: Summary of On-Study Safety (Safety Population)

	Ipi+gp100 (n=380)	**Ipi (n=131)**	**gp100 (n=132)**
Subjects with any on-study AE[a] (n %)	374 (98.4)	127 (96.9)	128 (97.0)
Severe (≥Grade 3)	193 (50.8)	72 (55.0)	69 (52.3)
Serious	155 (40.8)	55 (42.0)	52 (39.4)
Related	338 (88.9)	105 (80.2)	104 (78.8)
AEs leading to study drug discontinuation	35 (9.2)	17 (13.0)	5 (3.8)
AE with outcome of death (n%)	23 (6.1)	13 (9.9)	8 (6.1)
Related AE with outcome of death	8 (2.1)	4 (3.1)	2 (1.5)
Immune Related Adverse Events (irAE)[b]			
Subjects with any on-study irAE (n %)	221 (58.2)	80 (61.1)	42 (31.8)
Severe (≥ Grade 3) irAE	43 (11.3)	20 (15.3)	4 (3.0)
Serious irAE	40 (10.5)	17 (13.0)	1 (0.8)
irAE leading to study drug discontinuation	22 (5.8)	11 (8.4)	1 (0.8)
Death due to irAE (n %)	5 (1.3)	2 (1.5)	0
Gastrointestinal irAEs (any grade)	122 (32.1)	38 (29.0)	19 (14.4)
Severe (≥ Grade 3)	24 (6.3)	10 (7.6)	1 (0.8)
Liver irAEs (any grade)	8 (2.1)	5 (3.8)	6 (4.5)
Severe (≥ Grade 3)	4 (1.1)	1 (0.8)	3 (2.3)

Table 5: Summary of On-Study Safety (Safety Population)

	Ipi+gp100 (n=380)	Ipi (n=131)	gp100 (n=132)
Endocrine irAEs (any grade)	15 (3.9)	10 (7.6)	2 (1.5)
Severe (≥ Grade 3)	4 (1.1)	5 (3.8)	0
Skin irAEs (any grade)	152 (40.0)	57 (43.5)	22 (16.7)
Severe (≥ Grade 3)	9 (2.4)	2 (1.5)	0
Neurological irAEs (any grade)	2 (0.5)	0	0
Severe (≥ Grade 3)	2 (0.5)	0	0
Other[c] irAEs (any grade)	15 (3.9)	6 (4.6)	3 (2.3)
Severe (≥ Grade 3)	8 (2.1)	3 (2.3)	1 (0.8)

AE = adverse event, irAE = immune-related adverse event

[a] On-study AEs are AEs reported after the first dose that occurred within 70 days of the last dose or any AE related to the study drug.

[b] irAEs are adverse events of unknown etiology associated with study drug exposure and consistent with an immune phenomenon that were reported by the Investigator to be possibly, probably, or definitely related to study drug or with unknown causality.

[c] Includes blood, eye, immune system, infections, renal and respiratory system.

Re-induction: A total of 40 subjects were exposed to at least 1 cycle of re-induction. Of these, 32 were evaluated for efficacy. The disease control rate in the ipilimumab-treated groups was 65% to 75% compared to 0% in the gp100 monotherapy group upon re-induction. The safety profile was similar to that seen for the duration of the study. Drug-related AEs were reported in 25 (86.2%), 7 (77.8%), and 2 (100%) subjects in the ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy groups, respectively. The most common drug-related AEs reported during re-induction were AEs affecting the GI tract and skin in the ipilimumab-treated groups and injection site reactions in gp100-treated groups, Immune-related AEs were reported in 15 (51.7%), 7 (77.8%), and 1 (50%) subjects in the ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy groups, respectively. The most common irAEs reported during re-induction were irAEs affecting the skin and GI tract. In nearly all cases, irAEs were Grade 1-2 in severity.

Quality of Life: Most changes from baseline in HRQoL domains were "no change" to "moderate" across the three treatment groups. The trend in global health status was towards return to baseline. There was no difference between treatment groups.

CONCLUSIONS:

- Ipilimumab reduced the risk of death from melanoma by 32% to 34% (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 the 2 comparisons of ipilimumab vs. gp100)
- 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.
- 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.
- Adverse events are expected in this population with late stage melanoma; irAEs reflect the immune-mediated mechanism of action of ipilimumab and occur frequently (any irAE in 60% of subjects treated with an ipilimumab-containing regimen; ≥ Grade 3 events in 11-15%).
  - Rates for subcategories of irAEs vary by the organ system involved, with skin and GI events occurring more frequently than endocrine, liver and other events.
  - The temporal onset of irAEs also varies by the organ system involved; median time to onset of Grade 2-5 skin irAEs was 3-4 weeks and Grade 2-5 GI irAEs was 6-9 weeks.
- The use of steroids or alternate immunosuppression can reverse the irAE-associated inflammatory process. Overall, systemic steroid use occurred in approximately 35% of subject in both ipilimumab containing groups and in 25% of the gp100 group. In this study the observed time to resolution was 4 to 5 weeks for Grade 2-4 skin irAEs and 3 to 4 weeks for Grade 3-4 GI irAEs.
- AEs leading to study drug discontinuation occurred more frequently with ipilimumab treatment (9.2%-13.0% versus 3.8% for gp100); the majority of the discontinuations in the 2 ipilimumab-containing arms were due to irAEs.
- Drug-related deaths were reported in 8 (2.1%) subjects treated with ipilimumab plus gp100, 4 (3.1%) ipilimumab monotherapy and 2 (1.6%) gp100 monotherapy. A subset of 7 drug-related deaths occurred as a consequence of an irAE (4 GI irAEs and 1 neurologic irAE in the ipilimumab plus gp100 group; 1 GI irAE and 1 liver irAE in the ipilimumab montherapy group).
- Re-induction treatment was followed by additional objective responses or stable disease and the safety profile for re-induction was consistent with the overall safety profile for ipilimumab.
- The findings showing “no change” to “a little” decline in HRQoL after treatment with ipilimumab plus gp100 or ipilimumab monotherapy over 12 weeks in this advanced stage melanoma population suggest that ipilimumab is well tolerated in the induction phase. Further research is required to determine long-term HRQoL in patients with advanced stage melanoma.

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