The Emerging Role of Combination Immunotherapy

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Immunotherapy Categories

Passive

- Monoclonal antibodies
- Cell therapy
  - Lymphokine-activated killer cells
  - Tumor infiltrating lymphocytes (TILs)

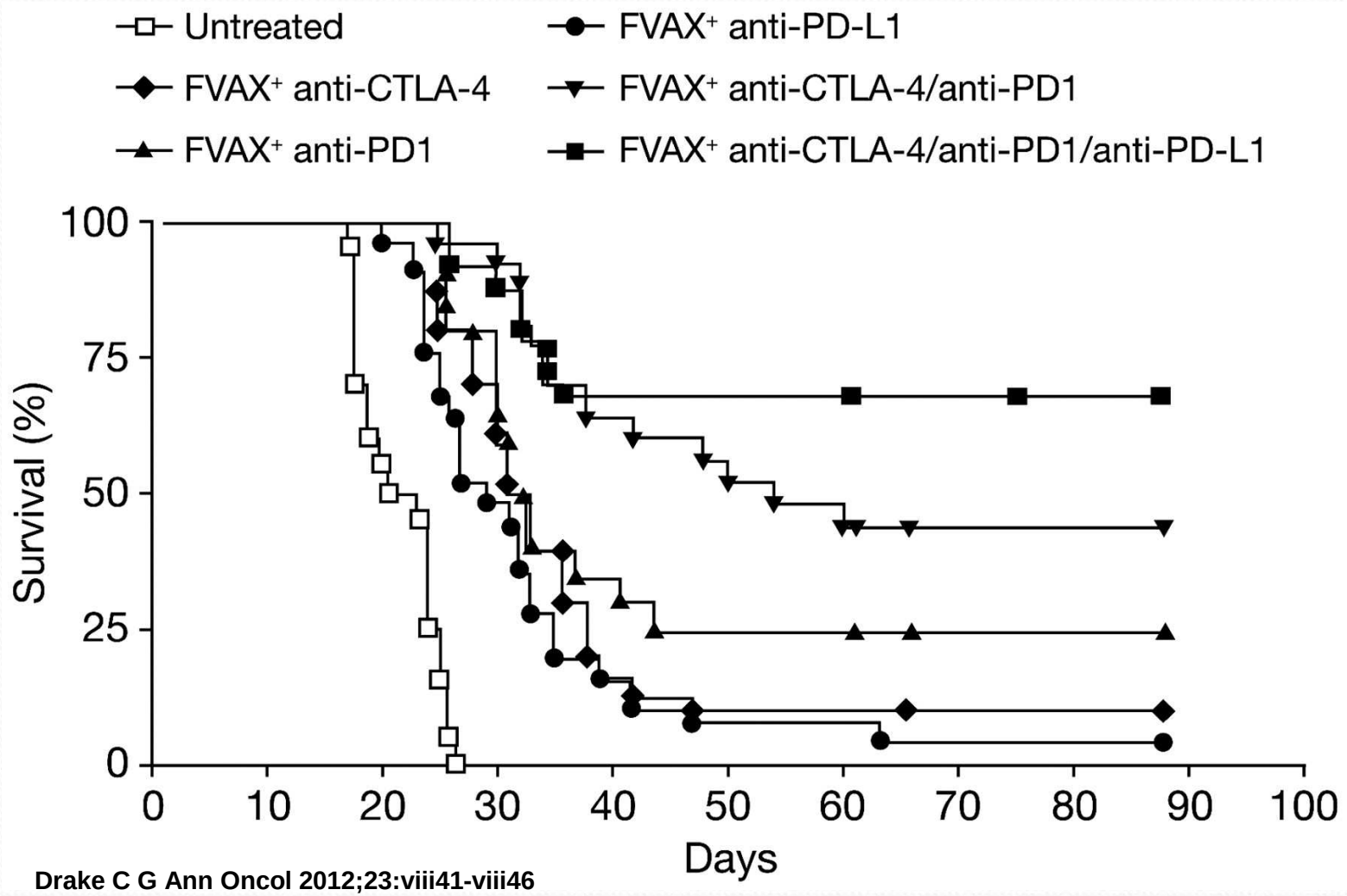
Active

- Vaccines
  - Dendritic cell vaccines
  - Tumor vaccines
  - Peptide vaccines
- Cytokines
  - Interleukin-2
  - Interferon
  - GM-CSF
- Immune checkpoint inhibitors
  - CTLA-4
  - PD-1/PD-L1

Combination Therapy: Issues to Consider

- Improved response?
- Improved survival?
- Combining? Sequencing?
- Time to response
- Toxicity
- Cost of therapy
- Feasibility of trials , i.e., different pharma
- Feasibility in the “real world”

Combination blockade of the PD1, CTLA-4 and PD-L1 coinhibitory molecules coupled with Fvax vaccination increased survival of mice challenged with antigen-presenting melanoma cells.



Drake C G Ann Oncol 2012;23:viii41-viii46

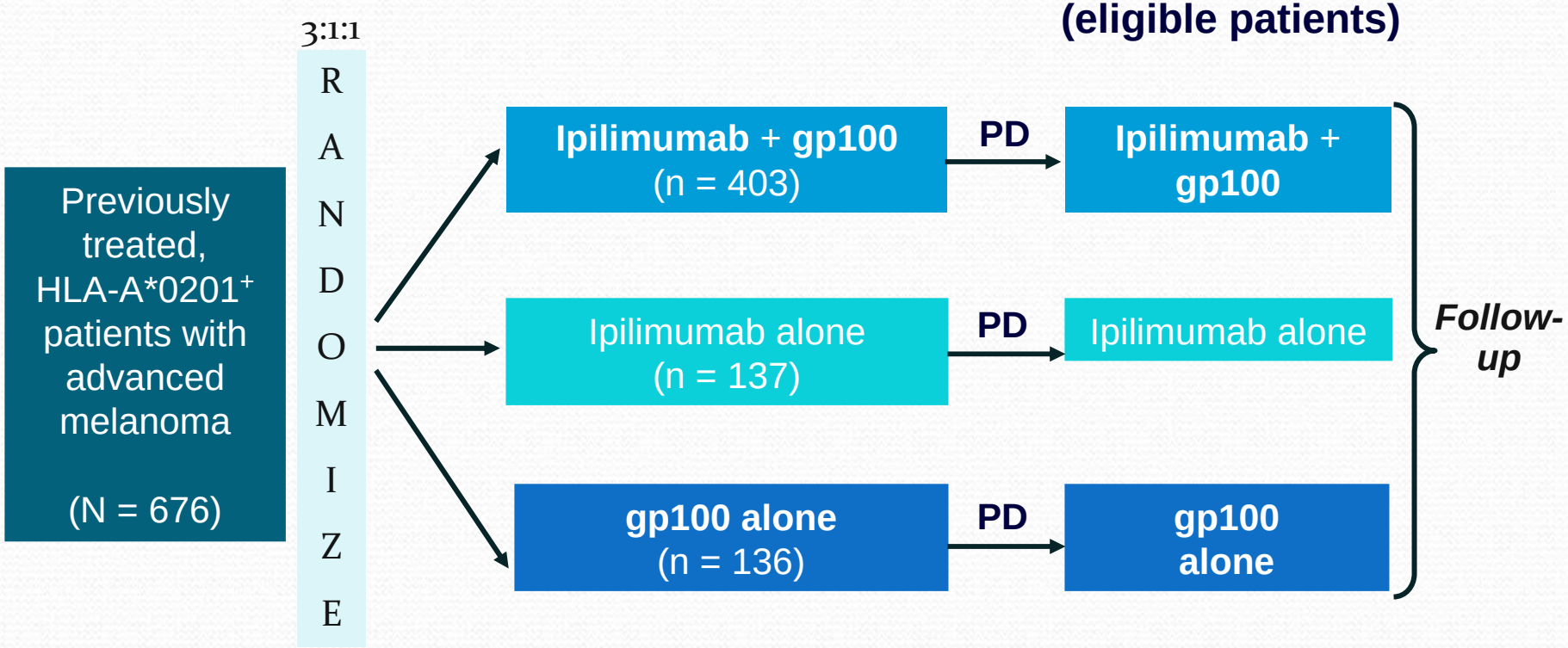
Original Article

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

N Engl J Med
Volume 363(8):711-723
August 19, 2010

MDX010-20 Study Schema



Induction: Ipilimumab at 3 mg/kg, with or without gp100, q3w for 4 treatments.
Reinduction: Patients with SD for 3 months' duration from Wk 12, or a confirmed CR or PR, could receive additional therapy with their assigned treatment regimen upon PD.

Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Patient Baseline Characteristics

Table 1. Baseline Characteristics of the Patients.*

Variable	Ipilimumab plus gp100 (N = 403)	Ipilimumab Alone (N = 137)	gp100 Alone (N = 136)	Total (N = 676)
Mean age — yr	55.6	56.8	57.4	56.2
Sex — no. (%)				
Male	247 (61.3)	81 (59.1)	73 (53.7)	401 (59.3)
Female	156 (38.7)	56 (40.9)	63 (46.3)	275 (40.7)
ECOG performance status — no. (%)†				
0	232 (57.6)	72 (52.6)	70 (51.5)	374 (55.3)
1	166 (41.2)	64 (46.7)	61 (44.9)	291 (43.0)
2	4 (1.0)	1 (0.7)	4 (2.9)	9 (1.3)
3	1 (0.2)	0	0	1 (0.1)
Unknown	0	0	1 (0.7)	1 (0.1)
M stage — no. (%)‡				
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)
Lactate dehydrogenase level — no. (%)				
≤Upper limit of the normal range	252 (62.5)	84 (61.3)	81 (59.6)	417 (61.7)
>Upper limit of the normal range	149 (37.0)	53 (38.7)	52 (38.2)	254 (37.6)
Unknown	2 (0.5)	0	3 (2.2)	5 (0.7)
CNS metastases at baseline — no. (%)	46 (11.4)	15 (10.9)	21 (15.4)	82 (12.1)
Received study drug	42 (10.4)	15 (10.9)	20 (14.7)	77 (11.4)
Had had previous treatment for CNS metastases	39 (9.7)	15 (10.9)	19 (14.0)	73 (10.8)
Previous systemic therapy for metastatic disease — no. (%)	403 (100.0)	137 (100.0)	136 (100.0)	676 (100.0)
Previous interleukin-2 therapy — no. (%)	89 (22.1)	32 (23.4)	33 (24.3)	154 (22.8)

* Percentages may not total 100 because of rounding. CNS denotes central nervous system.
† The Eastern Cooperative Oncology Group (ECOG) status ranges from 0 to 5, with higher scores indicating greater impairment (5 indicates death).
‡ The metastasis (M) stage was classified according to the tumor–node–metastasis (TNM) categorization for melanoma of the American Joint Committee on Cancer.

Hodi FS, et.al. *N Engl J Med* 2010;363:711-723.

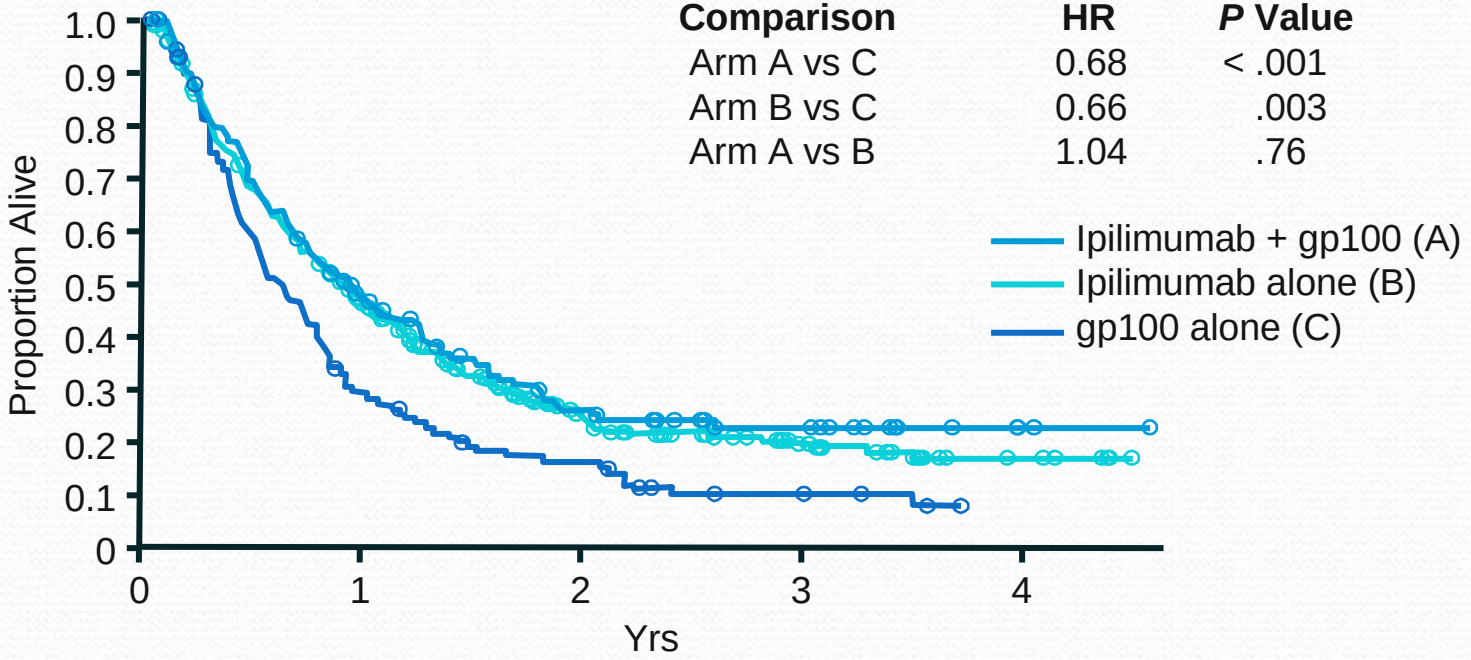
Ipilimumab Improves BORR

	Arm A Ipi + gp100 (n = 403)	Arm B Ipi + pbo (n = 137)	Arm C gp100 + pbo (n = 136)
BORR (%)	5.7	10.9	1.5
p Value: A vs. C	.0433		
p Value: B vs. C	.0012		
DCR[a] (%)	20.1	28.5	11.0
p Value: A vs. C	.0179		
p Value: B vs. C	.0002		

Hodi Fs, et.al. *N Engl J Med* 2010;363:711-723.

[a]DCR: Percent of patients with CR, PR, or SD.
BORR = best objective response rate; DCR = disease control rate; SD = stable disease.
Hodi et al, 2010.

MDX010-20: Kaplan-Meier Analysis of Overall Survival



Comparison	HR	*P* Value
Arm A vs C	0.68	< .001
Arm B vs C	0.66	.003
Arm A vs B	1.04	.76

OS	Ipilimumab + gp100	Ipilimumab Alone	gp100 Alone
1 yr, %	44	46	25
2 yr, %	22	24	14
Median, mos	10.0	10.1	6.4

Hodi FS, et al. N Engl J Med. 2010;363:711-723.

Adverse Events

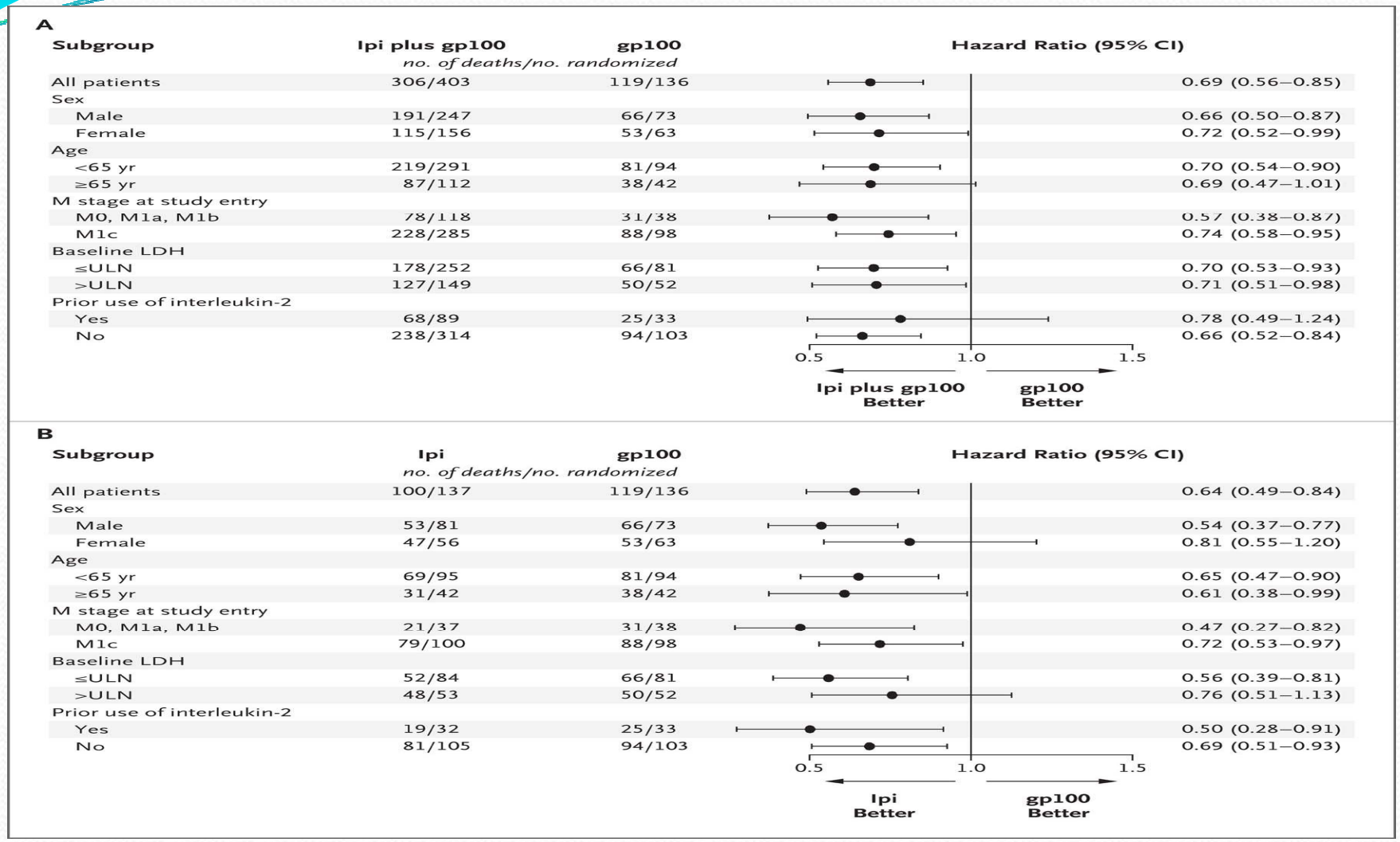
Table 3. Adverse Events in the Safety Population.*

Adverse Event	Ipilimumab plus gp100 (N=380)			Ipilimumab Alone (N=131)			gp100 Alone (N=132)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number of patients (percent)								
Any event	374 (98.4)	147 (38.7)	26 (6.8)	127 (96.9)	49 (37.4)	11 (8.4)	128 (97.0)	54 (40.9)	8 (6.1)
Any drug-related event	338 (88.9)	62 (16.3)	4 (1.1)	105 (80.2)	25 (19.1)	5 (3.8)	104 (78.8)	15 (11.4)	0
Gastrointestinal disorders									
Diarrhea	146 (38.4)	16 (4.2)	1 (0.3)	43 (32.8)	7 (5.3)	0	26 (19.7)	1 (0.8)	0
Nausea	129 (33.9)	5 (1.3)	1 (0.3)	46 (35.1)	3 (2.3)	0	52 (39.4)	3 (2.3)	0
Constipation	81 (21.3)	3 (0.8)	0	27 (20.6)	3 (2.3)	0	34 (25.8)	1 (0.8)	0
Vomiting	75 (19.7)	6 (1.6)	1 (0.3)	31 (23.7)	3 (2.3)	0	29 (22.0)	3 (2.3)	0
Abdominal pain	67 (17.6)	6 (1.6)	0	20 (15.3)	2 (1.5)	0	22 (16.7)	6 (4.5)	1 (0.8)
Other									
Fatigue	137 (36.1)	19 (5.0)	0	55 (42.0)	9 (6.9)	0	41 (31.1)	4 (3.0)	0
Decreased appetite	88 (23.2)	5 (1.3)	1 (0.3)	35 (26.7)	2 (1.5)	0	29 (22.0)	3 (2.3)	1 (0.8)
Pyrexia	78 (20.5)	2 (0.5)	0	16 (12.2)	0	0	23 (17.4)	2 (1.5)	0
Headache	65 (17.1)	4 (1.1)	0	19 (14.5)	3 (2.3)	0	19 (14.4)	3 (2.3)	0
Cough	55 (14.5)	1 (0.3)	0	21 (16.0)	0	0	18 (13.6)	0	0
Dyspnea	46 (12.1)	12 (3.2)	2 (0.5)	19 (14.5)	4 (3.1)	1 (0.8)	25 (18.9)	6 (4.5)	0
Anemia	41 (10.8)	11 (2.9)	0	15 (11.5)	4 (3.1)	0	23 (17.4)	11 (8.3)	0
Any immune-related event	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)	42 (31.8)	4 (3.0)	0
Dermatologic	152 (40.0)	8 (2.1)	1 (0.3)	57 (43.5)	2 (1.5)	0	22 (16.7)	0	0
Pruritus	67 (17.6)	1 (0.3)	0	32 (24.4)	0	0	14 (10.6)	0	0
Rash	67 (17.6)	5 (1.3)	0	25 (19.1)	1 (0.8)	0	6 (4.5)	0	0
Vitiligo	14 (3.7)	0	0	3 (2.3)	0	0	1 (0.8)	0	0
Gastrointestinal	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0	19 (14.4)	1 (0.8)	0
Diarrhea	115 (30.3)	14 (3.7)	0	36 (27.5)	6 (4.6)	0	18 (13.6)	1 (0.8)	0
Colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0	1 (0.8)	0	0
Endocrine	15 (3.9)	4 (1.1)	0	10 (7.6)	3 (2.3)	2 (1.5)	2 (1.5)	0	0
Hypothyroidism	6 (1.6)	1 (0.3)	0	2 (1.5)	0	0	2 (1.5)	0	0
Hypopituitarism	3 (0.8)	2 (0.5)	0	3 (2.3)	1 (0.8)	1 (0.8)	0	0	0
Hypophysitis	2 (0.5)	2 (0.5)	0	2 (1.5)	2 (1.5)	0	0	0	0
Adrenal insufficiency	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0	0	0	0
Increase in serum thyrotropin level	2 (0.5)	0	0	1 (0.8)	0	0	0	0	0
Decrease in serum corticotropin level	0	0	0	2 (1.5)	0	1 (0.8)	0	0	0
Hepatic	8 (2.1)	4 (1.1)	0	5 (3.8)	0	0	6 (4.5)	3 (2.3)	0
Increase in alanine aminotransferase	3 (0.8)	2 (0.5)	0	2 (1.5)	0	0	3 (2.3)	0	0
Increase in aspartate aminotransferase	4 (1.1)	1 (0.3)	0	1 (0.8)	0	0	2 (1.5)	0	0
Hepatitis	2 (0.5)	1 (0.3)	0	1 (0.8)	0	0	0	0	0
Other	12 (3.2)	5 (1.3)	0	6 (4.6)	2 (1.5)	1 (0.8)	3 (2.3)	1 (0.8)	0

* The adverse events listed here were reported in at least 15% of patients. The most common immune-related adverse events and those of particular clinical relevance are also listed. Patients could have more than one adverse event. Included are all patients who received at least one dose of a study drug (643 patients). A total of 14 deaths (2.2%) were determined by the investigators to be related to the study drug (8 in the ipilimumab-plus-gp100 group, 4 in the ipilimumab-alone group, and 2 in the gp100-alone group). Seven of the 14 deaths related to the study drug were associated with immune-related adverse events: 5 in the ipilimumab-plus-gp100 group (1 patient had grade 3 colitis and septicemia; 3 patients had bowel perforation—inflammatory colitis, bowel perforation, or multiorgan failure—peritonitis; and 1 patient had Guillain–Barré syndrome, which is considered to be consistent with a neurologic immune-related adverse event) and 2 in the ipilimumab-alone group (1 patient had colic bowel perforation and the other had liver failure). Deaths related to the study drug that were not associated with immune-related adverse events included deaths from sepsis, myelofibrosis, and acute respiratory distress syndrome (3 patients in the ipilimumab-plus-gp100 group); severe infection—renal failure—septic shock, and vascular leak syndrome (2 patients in the ipilimumab-alone group), and cachexia and septic shock (2 patients in the gp100-alone group).

Hodi FS, et.al. *N Engl J Med* 2010;363:711-723.

Subgroup Analyses of Overall Survival



Hodi FS, et.al. *N Engl J Med* 2010;363: 711-723.

Best Response to Treatment and Time-to-Event Data

Table 2. Best Response to Treatment and Time-to-Event Data.*

Response and Time to Event	Ipilimumab plus gp100 (N = 403)	Ipilimumab Alone (N = 137)	gp100 Alone (N = 136)
Overall survival			
Total no. of deaths	306	100	119
Comparison with gp100 alone			
Hazard ratio (95% CI)	0.68 (0.55–0.85)	0.66 (0.51–0.87)	—
P value by log-rank test	<0.001	0.003	—
Comparison with ipilimumab alone			
Hazard ratio (95% CI)	1.04 (0.83–1.30)	—	—
P value by log-rank test	0.76	—	—
Evaluation of therapy			
Induction			
Best overall response — no. (%)			
Complete response	1 (0.2)	2 (1.5)	0
Partial response	22 (5.5)	13 (9.5)	2 (1.5)
Stable disease	58 (14.4)	24 (17.5)	13 (9.6)
Progressive disease	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated	83 (20.6)	28 (20.4)	32 (23.5)
Best overall response rate — % (95% CI)	5.7 (3.7–8.4)	10.9 (6.3–17.4)	1.5 (0.2–5.2)
P value for comparison with gp100 alone	0.04	0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Disease control rate — % (95% CI)†	20.1 (16.3–24.3)	28.5 (21.1–36.8)	11.0 (6.3–17.5)
P value for comparison with gp100 alone	0.02	<0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Time to event — mo			
Time to progression — median (95% CI)	2.76 (2.73–2.79)	2.86 (2.76–3.02)	2.76 (2.73–2.83)
Time to response — mean (95% CI)	3.32 (2.91–3.74)	3.18 (2.75–3.60)	2.74 (2.12–3.37)
Duration of response — median (95% CI)	11.5 (5.4–NR)	NR (28.1–NR)	NR (2.0–NR)
Reinduction‡			
Best overall response — no./total no. (%)			
Complete response	0	1/8 (12.5)	0
Partial response	3/23 (13.0)	2/8 (25.0)	0
Stable disease	12/23 (52.2)	3/8 (37.5)	0
Progressive disease	8/23 (34.8)	2/8 (25.0)	1/1 (100.0)

* Of the 143 patients who could not be evaluated for a response, 33 patients did not receive any study drug and 110 patients did not have baseline or week-12 tumor assessments (or both). Percentages may not total 100 because of rounding. NR denotes not reached.

† The disease control rate is the percentage of patients with a partial or complete response or stable disease.

‡ A total of 40 patients (29 in the ipilimumab-plus-gp100 group; 9 in the ipilimumab-alone group, and 2 in the gp100-alone group) were given reinduction therapy, but 8 were not included in the efficacy analyses: 3 had major protocol violations and 5 were not eligible owing to the fact that they had had a best overall response of progressive disease during induction and were given reinduction therapy inadvertently.

Hodi FS, et.al. *N Engl J Med* 2010;363:711-723.

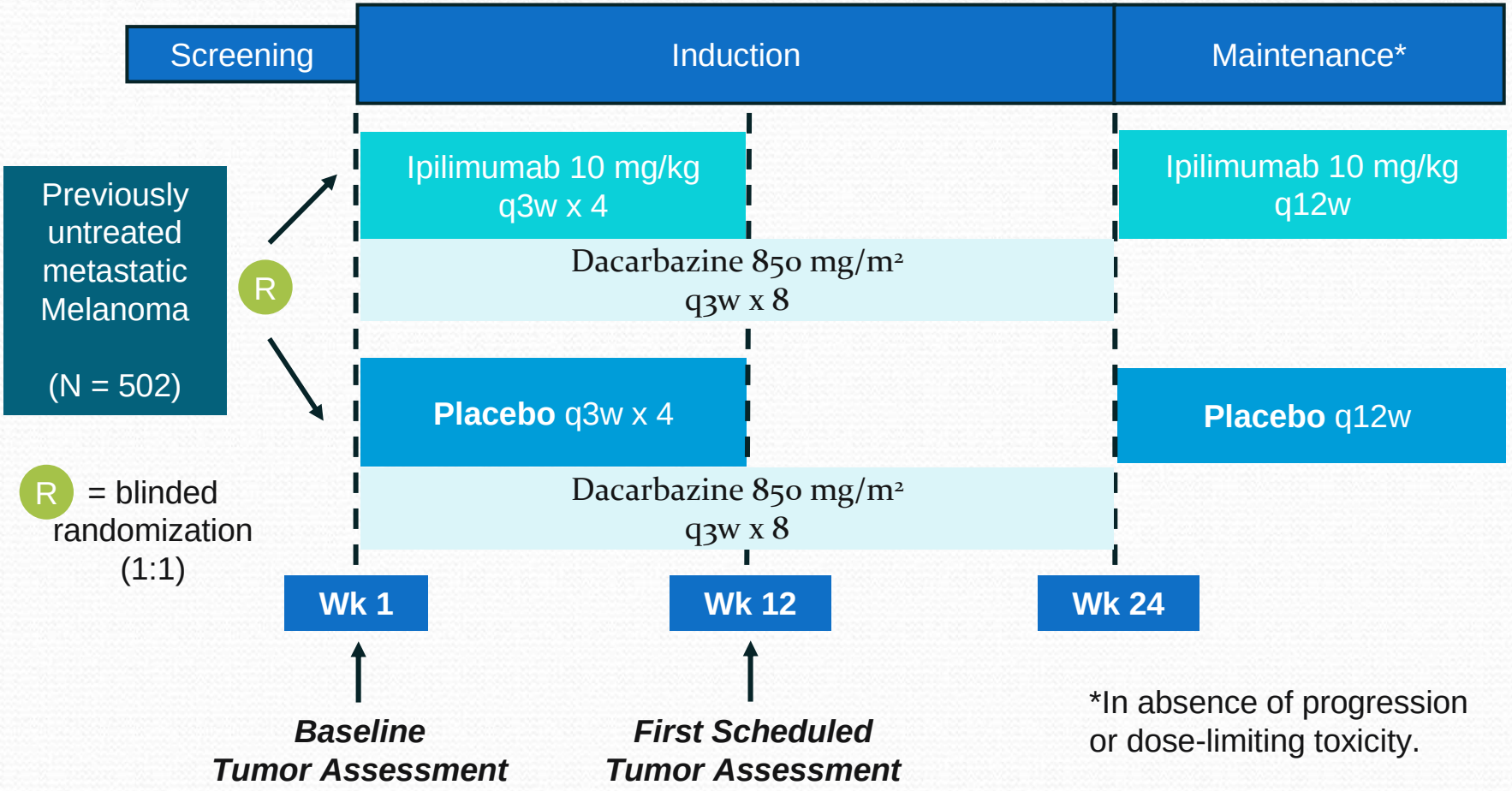
Original Article

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

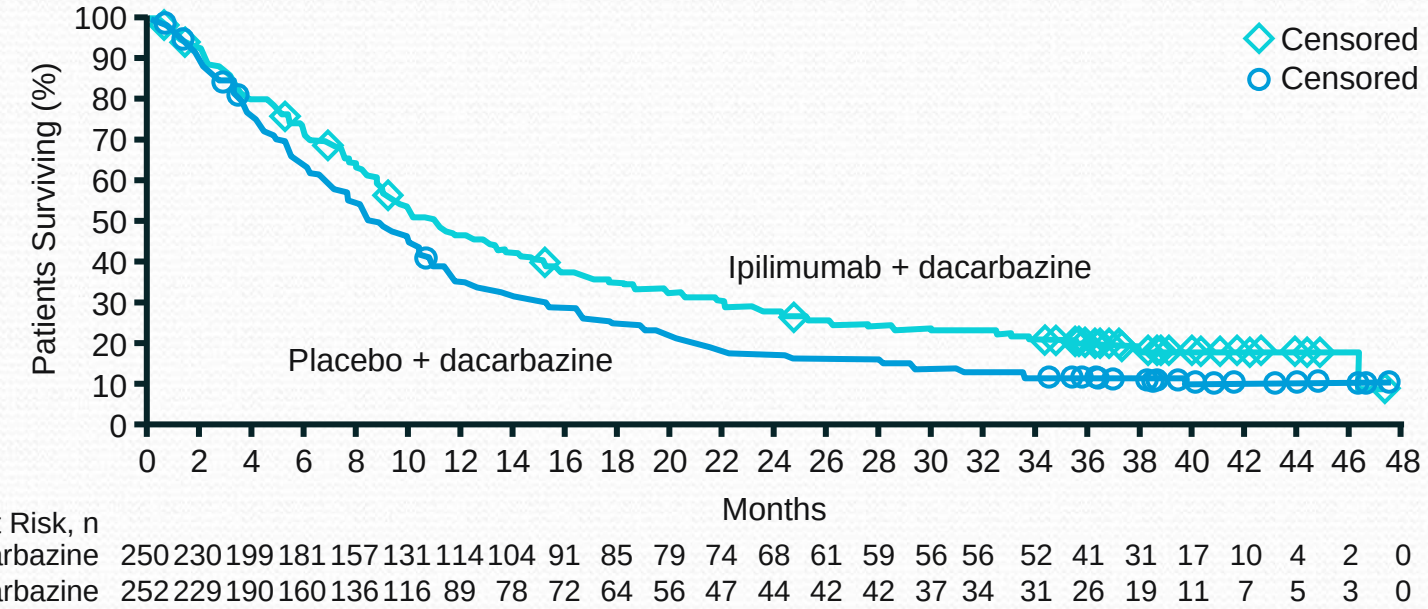
N Engl J Med
Volume 364(26):2517-2526
June 30, 2011

Study 024: Design



Robert C, et al. N Engl J Med. 2011;364:2517-2526.

Study 024: Overall Survival



Patients at Risk, n																								
Ipilimumab + dacarbazine	250	230	199	181	157	131	114	104	91	85	79	74	68	61	59	56	56	52	41	31	17	10	4	2	0
Placebo + dacarbazine	252	229	190	160	136	116	89	78	72	64	56	47	44	42	42	37	34	31	26	19	11	7	5	3	0

Estimated Survival Rate, %	Ipilimumab + Dacarbazine (n = 250)	Placebo + Dacarbazine (n = 252)
Yr 1	47.3	36.3
Yr 2	28.5	17.9
Yr 3*	20.8	12.2

*3-yr survival was a post hoc analysis.

Robert C, et al. N Engl J Med. 2011;364:2517-2526.

Original Article

gp100 Peptide Vaccine and Interleukin-2 in Patients with Advanced Melanoma

Douglas J. Schwartzentruber, M.D., David H. Lawson, M.D., Jon M. Richards, M.D., Ph.D., Robert M. Conry, M.D., Donald M. Miller, M.D., Ph.D., Jonathan Treisman, M.D., Fawaz Gailani, M.D., Lee Riley, M.D., Ph.D., Kevin Conlon, M.D., Barbara Pockaj, M.D., Kari L. Kendra, M.D., Ph.D., Richard L. White, M.D., Rene Gonzalez, M.D., Timothy M. Kuzel, M.D., Brendan Curti, M.D., Phillip D. Leming, M.D., Eric D. Whitman, M.D., Jai Balkissoon, M.D., Douglas S. Reintgen, M.D., Howard Kaufman, M.D., Francesco M. Marincola, M.D., Maria J. Merino, M.D., Steven A. Rosenberg, M.D., Ph.D., Peter Choyke, M.D., Don Vena, B.S., and Patrick Hwu, M.D.

N Engl J Med
Volume 364(22):2119-2127
June 2, 2011

High Dose IL-2 + Peptide Vaccine

- Inclusion:
  - Stage III/Stage IV melanoma patients (n=185)
  - HLA*A0201 haplotype
  - No brain metastases
  - Previous therapy allowed (no high-dose IL-2)
- Treatment:
  - High dose IL-2 (720,000 units/kg) q 8 hours X 12 doses every 3 weeks, 4 cycles max
  - High dose IL-2 + gp100 peptide vaccine

Schwartzentruber DJ, et.al. *N Engl J Med* 2011;364:2119-2127.

Baseline Characteristics of the Patients.

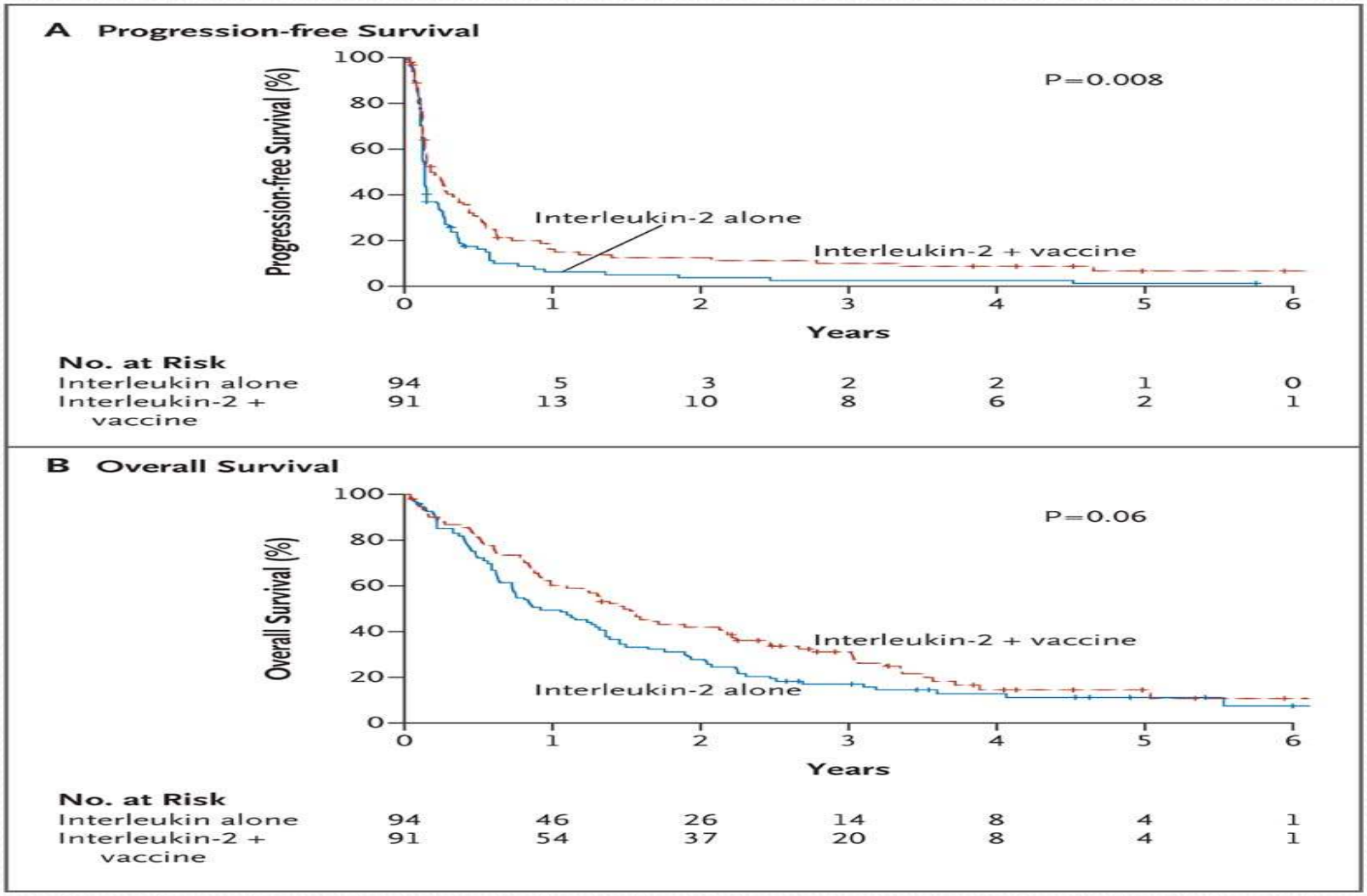
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Interleukin-2 Alone (N=94)	Vaccine–Interleukin-2 (N=91)	P Value
Sex — no. (%)			0.53
Male	63 (67)	57 (63)	
Female	31 (33)	34 (37)	
Mean age — yr	50.3	46.9	0.04
Race or ethnic group — no. (%)†			1.00
White	91 (97)	90 (99)	
Hispanic	2 (2)	1 (1)	
Other	1 (1)	0	
ECOG performance status — no. (%)‡			0.92
0	78 (83)	76 (84)	
1	16 (17)	15 (16)	
Site of disease — no. (%)			
Cutaneous or subcutaneous only	8 (9)	8 (9)	0.95
Any other site	86 (91)	83 (91)	
Disease stage — no. (%)§			0.33
Locally advanced III	3 (3)	5 (5)	
IV	91 (97)	83 (91)	
M1a	25 (27)	22 (24)	
M1b	29 (31)	32 (35)	
M1c	37 (39)	29 (32)	
Data missing	0	3 (3)	
Previous treatment — no. (%)			
Surgery	86 (91)	86 (95)	0.42
Interferon-alfa	39 (41)	50 (55)	0.07
Chemotherapy	11 (12)	11 (12)	0.94
Radiation	14 (15)	14 (15)	0.93
Low-dose interleukin-2	7 (7)	11 (12)	0.29

* Interleukin-2 was administered in patients in both groups at a dose of 720,000 IU per kilogram of body weight every 8 hr. The vaccine administered in the vaccine–interleukin-2 group was a gp100:209-217(210 M) peptide vaccine (1 mg) plus incomplete Freund's adjuvant (Montanide ISA-51). P values were calculated with the use of a Wilcoxon rank-sum test for skewed continuous variables and a chi-square test or Fisher's exact test for categorical variables.
† Race or ethnic group was determined by the study coordinators.
‡ The Eastern Cooperative Oncology Group (ECOG) performance status ranges from 0 to 5, with higher scores indicating greater impairment (5 indicates death). ECOG 0 indicates that the patient is fully active, and ECOG 1 that a patient is restricted in the performance of physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature.
§ The stage was determined according to the criteria of the American Joint Committee on Cancer, 6th edition, which are based on the sites of disease. (No measurements of lactate dehydrogenase levels were performed.)

Schwartzentruber DJ, et.al. *N Engl J Med* 2011;364:2119-2127.

Progression-free and Overall Survival.



Schwartzentruber DJ, et.al. *N Engl J Med* 2011;364:2119-2127.

Response to Treatment, as Assessed by Investigators and by Central Review.

Table 2. Response to Treatment, as Assessed by Investigators and by Central Review.

Response	Assessment by Investigators		Assessment by Central Review	
	Interleukin-2 Alone (N=93)	Vaccine–Interleukin-2 (N=85)	Interleukin-2 Alone (N=93)	Vaccine–Interleukin-2 (N=85)
	number (percent)			
Complete*	2 (2)	9 (11)	1 (1)	8 (9)
Partial	7 (8)	8 (9)	5 (5)	6 (7)
Complete or partial†	9 (10)	17 (20)	6 (6)	14 (16)
Stable disease	25 (27)	21 (25)	25 (27)	20 (24)
Progressive disease	59 (63)	47 (55)	62 (67)	51 (60)

* P=0.02 for complete response as assessed by investigators, and P=0.01 for complete response as assessed by central review.

† P=0.05 for response as assessed by investigators, and P=0.03 for response as assessed by central review.

Schwartzentruber DJ, et.al. *N Engl J Med* 2011;364:2119-2127.

Grades 3 to 5 Toxic Effects of Treatment over the Course of All Cycles.

Table 3. Grades 3 to 5 Toxic Effects of Treatment over the Course of All Cycles.*

Toxic Effect	Interleukin-2 Alone (N=93)	Vaccine–Interleukin-2 (N=85)†	P Value
	no. of patients (%)		
Hearing	0	1 (1)	0.48
Blood or bone marrow	33 (35)	41 (48)	0.08
Cardiovascular			
Arrhythmia	4 (4)	16 (19)	0.002‡
General	25 (27)	31 (36)	0.17
Coagulation	2 (2)	3 (4)	0.67
Constitutional symptoms	15 (16)	24 (28)	0.06
Skin	6 (6)	6 (7)	0.87
Gastrointestinal	17 (18)	18 (21)	0.63
Hemorrhage	1 (1)	2 (2)	0.61
Hepatic	36 (39)	34 (40)	0.86
Infection or febrile neutropenia	6 (6)	7 (8)	0.65
Lymphatic system	0	1 (1)	0.48
Metabolic or laboratory-testing results	19 (21)§	36 (42)	0.002‡
Musculoskeletal	3 (3)	6 (7)	0.31
Neurologic	11 (12)	22 (26)	0.02
Ocular or visual	0	1 (1)	0.48
Pulmonary	19 (21)§	19 (22)	0.81
Pain	10 (11)	11 (13)	0.65
Renal or genitourinary	14 (15)	16 (19)	0.50
Sexual or reproductive function	1 (1)	0	1.00
Syndromes¶	1 (1)	2 (2)	0.61
Maximum reported grade 3–5	74 (80)	73 (86)	0.27

* Toxic effects were assessed according to the National Cancer Institute Common Toxicity Criteria, version 2.0. P values were calculated with the use of the chi-square test or Fisher's exact test.
† A total of 86 patients in this group were treated, but 1 was not assessed for toxic effects.
‡ After Bonferroni adjustment, P values of 0.002 or less were considered to be significant in order to maintain the 0.05 error rate.
§ Data for two patients were missing.
¶ Included are tumor flare, the tumor lysis syndrome, and other syndromes.

Schwartzentruber DJ, et.al. *N Engl J Med* 2011;364:2119-2127.

Original Article

Nivolumab plus Ipilimumab in Advanced Melanoma

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N Engl J Med
Volume 369(2):122-133
July 11, 2013

Baseline Characteristics of All Treated Patients.

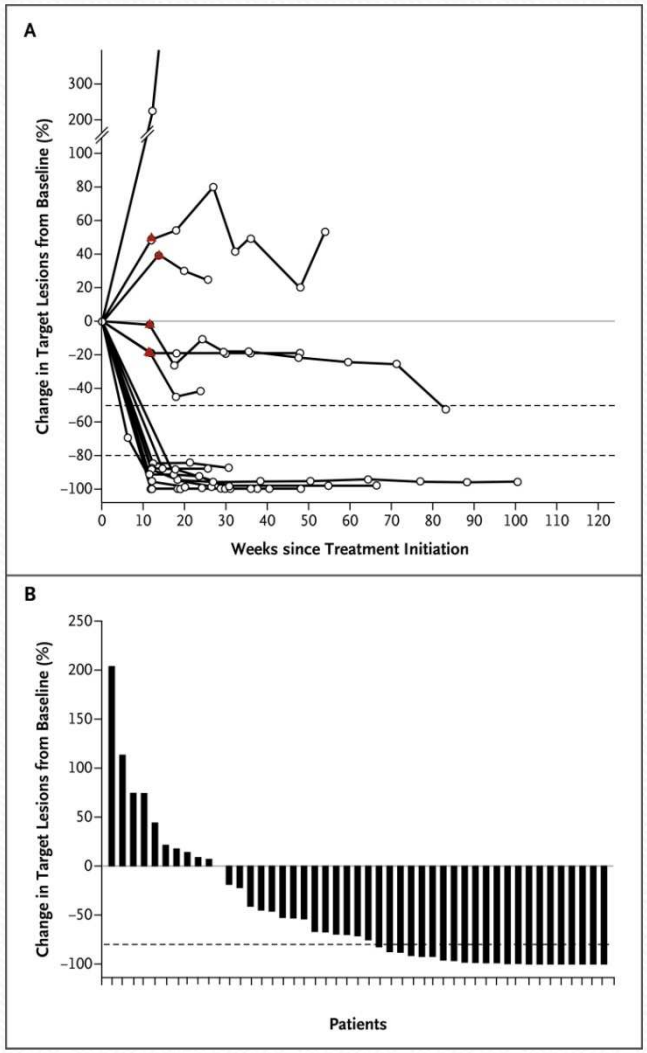
Table 1. Baseline Characteristics of All Treated Patients.*

Characteristic	Concurrent Treatment (N = 53)	Sequenced Treatment (N = 33)
Age — yr		
Median	58	64
Range	22–79	23–89
Sex — no. (%)		
Male	32 (60)	18 (55)
Female	21 (40)	15 (45)
ECOG performance status — no. (%)†		
0	44 (83)	22 (67)
1	8 (15)	11 (33)
Unknown	1 (2)	0
Disease status — no. (%)‡		
M1a	8 (15)	5 (15)
M1b	11 (21)	5 (15)
M1c	30 (57)	18 (55)
Unknown	4 (8)	5 (15)
Lactate dehydrogenase — no. (%)		
≤Upper limit of the normal range	33 (62)	21 (64)
>Upper limit of the normal range	20 (38)	12 (36)
Prior therapy — no. (%)		
Surgery	51 (96)	31 (94)
Radiotherapy	11 (21)	17 (52)
Systemic therapy	20 (38)	33 (100)
Immunotherapy	9 (17)	33 (100)
Interleukin-2	8 (15)	1 (3)
BRAF inhibitor	3 (6)	2 (6)
No. of prior systemic therapies — no. (%)		
0	33 (62)	0
1	14 (26)	18 (55)
2	5 (9)	10 (30)
≥3	1 (2)	5 (15)
Lesions — no. (%)		
Bone	5 (9)	1 (3)
Central nervous system	0	1 (3)
Liver	16 (30)	13 (39)
Lung	25 (47)	16 (48)
Lymph node	26 (49)	8 (24)
Soft tissue or other organ	34 (64)	19 (58)

* Treatment groups were not formally compared in this phase 1 trial.
† An Eastern Cooperative Oncology Group (ECOG) performance status of 0 indicates that the patient is asymptomatic, and 1 indicates that the patient is ambulatory but restricted in strenuous activity.[8]
‡ M1a indicates metastases to the skin, subcutaneous tissue, or distant lymph nodes; M1b metastases to the lung; and M1c metastases to all other visceral sites or distant metastases to any site combined with an elevated serum lactate dehydrogenase level.

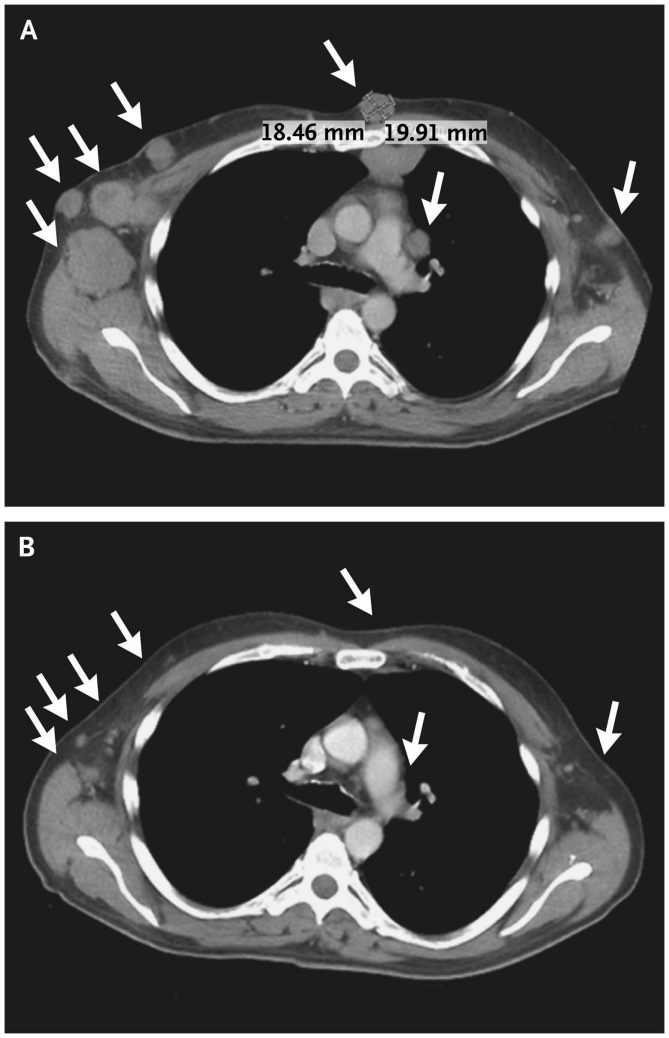
Wolchok JD, et.al. *N Engl J Med* 2013;369:122-123.

Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.



Wolchok JD, et.al. *N Engl J Med* 2013;369:122-133.

Computed Tomographic (CT) Scans of the Chest Showing Tumor Regression in a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab



Wolchok JD, et.al. *N Engl J Med* 2013;369:122-133.

Highest Grade of Selected Treatment-Related Adverse Events That Occurred in at Least One of the Patients Who Received the Concurrent Regimen.

Table 2. Highest Grade of Selected Treatment-Related Adverse Events That Occurred in at Least One of the Patients Who Received the Concurrent Regimen.*

Event	Cohort 1 (N=14)		Cohort 2 (N=17)		Cohort 2a (N=16)		Cohort 3 (N=6)		All Patients in Concurrent-Regimen Group (N=53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	number of patients (percent)									
Pneumonitis	1 (7)	0	2 (12)	1 (6)	0	0	0	0	3 (6)	1 (2)
Endocrinopathy	1 (7)	0	3 (18)	0	1 (6)	0	2 (33)	1 (17)	7 (13)	1 (2)
Hypothyroidism	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hypophysitis	0	0	1 (6)	0	0	0	1 (17)	1 (17)	2 (4)	1 (2)
Thyroiditis	0	0	1 (6)	0	1 (6)	0	1 (17)	0	3 (6)	0
Adrenal insufficiency	0	0	2 (12)	0	0	0	0	0	2 (4)	0
Hyperthyroidism	0	0	1 (6)	0	0	0	1 (17)†		2 (4)†	0
Thyroid-function results abnormal	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Hepatic disorder	4 (29)	3 (21)	5 (29)	3 (18)	2 (12)	1 (6)	1 (17)	1 (17)	12 (23)	8 (15)
Aspartate aminotransferase increased	4 (29)	3 (21)	4 (24)	2 (12)	2 (12)	1 (6)	1 (17)	1 (17)	11 (21)	7 (13)
Alanine aminotransferase increased	3 (21)	2 (14)	5 (29)	3 (18)	2 (12)	0	1 (17)	1 (17)	11 (21)	6 (11)
Gastrointestinal disorder	5 (36)	1 (7)	6 (35)	2 (12)	6 (38)	2 (13)	3 (50)	0	20 (38)	5 (9)
Diarrhea	5 (36)	0	5 (29)	1 (6)	5 (31)	2 (13)	3 (50)	0	18 (34)	3 (6)
Colitis	1 (7)	1 (7)	2 (12)	1 (6)	1 (6)	0	1 (17)	0	5 (9)	2 (4)
Renal disorder	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Blood creatinine increased	1 (7)	1 (7)	1 (6)	1 (6)	1 (6)	1 (6)	0	0	3 (6)	3 (6)
Acute renal failure	0	0	1 (6)	1 (6)	1 (6)	1 (6)	0	0	2 (4)	2 (4)
Renal failure	0	0	1 (6)	1 (6)	0	0	0	0	1 (2)	1 (2)
Tubulointerstitial nephritis	1 (7)	0	0	0	0	0	0	0	1 (2)	0
Skin disorder	10 (71)	1 (7)	14 (82)	0	10 (62)	1 (6)	3 (50)	0	37 (70)	2 (4)
Rash	8 (57)	1 (7)	11 (65)	0	7 (44)	1 (6)	3 (50)	0	29 (55)	2 (4)
Pruritus	6 (43)	0	11 (65)	0	7 (44)	0	1 (17)	0	25 (47)	0
Urticaria	0	0	0	0	1 (6)	0	0	0	1 (2)	0
Blister	0	0	1 (6)	0	0	0	0	0	1 (2)	0
Infusion-related reaction	0	0	1 (6)	0	0	0	0	0	1 (2)	0

* Only the highest grade of event was counted for each patient. Adverse events that require more frequent monitoring or intervention with immune suppression or hormone replacement are listed, according to a prespecified list of terms from the *Medical Dictionary for Regulatory Activities*, version 15.1. The dose levels in the cohorts were as follows: cohort 1 received 0.3 mg of nivolumab per kilogram of body weight and 3 mg of ipilimumab per kilogram, cohort 2 received 1 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram, cohort 2a received 3 mg of nivolumab per kilogram and 1 mg of ipilimumab per kilogram, and cohort 3 received 3 mg of nivolumab per kilogram and 3 mg of ipilimumab per kilogram. The doses in cohort 3 exceeded the maximum doses that were associated with an acceptable level of adverse events, and the doses in cohort 2 were identified as the maximum doses that were associated with an acceptable level of adverse events. The numbers reported for the specific adverse events within an organ category may be greater than the total number reported for the organ category because patients who had more than one adverse event were counted for each event but were counted only once for the organ category.

† Data include one patient with an event of unknown grade.

Wolchok JD, et.al. *N Engl J Med* 2013;369:122-123.

Clinical Activity in Patients Who Received the Concurrent Regimen.

Table 3. Clinical Activity in Patients Who Received the Concurrent Regimen.

Cohort No.	Dose	Patients with a Response*	Response				Stable Disease for ≥24 Wk	Immune-Related Stable Disease for ≥24 Wk†	Objective-Response Rate (95% CI)‡	Aggregate Clinical-Activity Rate (95% CI)§	≥80% Tumor Reduction at 12 Wk
			Complete	Partial	Unconfirmed Partial¶	Immune-Related Partial†					
	mg/kg		*no.*						%		*no. (%)*
1	Nivolumab, 0.3; ipilimumab, 3	14	1	2	0	2	2	0	21 (5–51)	50 (23–77)	4 (29)
2	Nivolumab, 1; ipilimumab, 3	17	3	6	0	0	0	2	53 (28–77)	65 (38–86)	7 (41)‖
2a	Nivolumab, 3; ipilimumab, 1	15	1	5	2	1	2	0	40 (16–68)	73 (45–92)	5 (33)
3	Nivolumab, 3; ipilimumab, 3	6	0	3	0	1	0	1	50 (12–88)	83 (36–100)	0
All	—	52	5	16	2	4	4	3	40 (27–55)	65 (51–78)	16 (31)

* Data are for patients who had a response that could be evaluated, defined as patients who received at least one dose of study therapy, had measurable disease at baseline, and had one of the following: at least one tumor evaluation during treatment, clinical progression of disease, or death before the first tumor evaluation during treatment.

† Data include patients who had a reduction in the target tumor lesion in the presence of new lesions, which was consistent with an immune-related partial response or stable disease.[11]

‡ The objective-response rate was calculated as the number of patients with either a complete response or a partial response, divided by the number of patients with a response that could be evaluated, times 100. Unconfirmed or immune-related responses were not included in this calculation. Confidence intervals (CIs) were estimated by the Clopper–Pearson method.

§ The aggregate clinical-activity rate was calculated as the number of patients with a complete response, a partial response, an unconfirmed complete response, an unconfirmed partial response, an immune-related partial response, stable disease for at least 24 weeks, or immune-related stable disease for at least 24 weeks, divided by the number of patients with a response that could be evaluated, times 100.

¶ Data include patients who had a partial response after one tumor assessment but did not have sufficient follow-up time for confirmation of the initial partial response.

‖ Two additional patients in cohort 2 had tumor reduction of 80% or more at their first scheduled assessment, which was conducted after week 12.

Wolchok JD, et.al. *N Engl J Med* 2013;369:122-133.

ECOG 1608: Multicenter, Randomized Phase II Trial of GM-CSF Plus Ipilimumab vs. Ipilimumab Alone in Metastatic Melanoma

- 245 previously treated patients with metastatic melanoma
- Ipilimumab 10 mg/kg q 3 weeks X 4 cycles, followed by maintenance ipilimumab 10 mg/kg q 12 weeks vs. same ipilimumab schedule + GM-CSF 250 mcg SQ daily days 10-14 q 21 days X 4 cycles

Hodi FS, et.al. *Proc Am Soc Clin Oncol* 2013; Abstract CRA 9007

ECOG 1608: Results

- Median followup 13.3 months
- Median overall survival
  - 17.5 months (combo) vs. 12.7 months (ipilimumab)
  - HR =0.64 p=.014
- No significant improvement in progression-free survival
- 1 Year survival
  - 67.9% (combo) vs. 51.2 % (ipilimumab)
- No significant improvement in response rate
  - 11.3% (combo) vs. 14.7% (ipilimumab)
- Grade 3-5 events
  - 45% (combo) vs. 58% (ipilimumab)

Hodi FS, et.al. *Proc Am Soc Clin Oncol* 2013;Abstract CRA9007.

Safety, Efficacy and Biomarkers of Nivolumab with Vaccine in Ipilimumab-Refractory or –Naïve Melanoma

- Weber JS, et.al. *J Clin Oncol* 2013;31.
- 90 patients with unresectable stage III or stage IV melanoma
- Cohorts 1-3: ipilimumab-naïve patients, received nivolumab at 1, 3 or 10 mg/kg q 2 weeks X 24 weeks, then every 12 weeks (up to 2 years) + multipeptide vaccine
- Cohorts 4-5: patients progressing after ipilimumab, received nivolumab 3 mg/kg + multipeptide vaccine
- Cohort 6: patients progressing after ipilimumab, received nivolumab 3 mg/kg, no vaccine

Efficacy

		Objective Response		
Cohort	N	N	%	95% CI (%)
Ipilimumab-naïve patients				
Cohort 1	10	3	30	6.7 to 65.3
Cohort 2	13	4	31	9.1 to 61.4
Cohort 3	11	1	9	0.2 to 41.3
Patients previously treated with ipilimumab				
Cohort 4	10	3	30	6.7 to 65.3
Cohort 5	5	1	20	0.5 to 71.6
Cohort 6	38	10	26	13.4 to 43.1
All cohorts	87	22	25	16.6 to 35.8

Weber Js, et.al. *J Clin Oncol* 2013;31.

Efficacy (Cont.)

		Stable Disease ≥ 24 Weeks			
Cohort	# Responders	Response Duration (wks)	N	%	PFS 24 weeks (%)
Ipilimumab-naïve patients					
Cohort 1	3	140+, 128+, 76+	2	20	50
Cohort 2	4	84+, 36,24,24	1	8	39
Cohort 3	1	84+	4	36	45
Patients previously treated with ipilimumab					
Cohort 4	3	60+, 60+, 60+	2	20	50
Cohort 5	1	36+	2	40	60
Cohort 6	10	48+, 36+, 36+, 36+	7	18	44

Toxicities (All Cohorts)

- All grades
  - Fatigue
  - Pruritis
  - Injection site reaction
- Grade 3 or 4
  - 2 case of interstitial pneumonitis (cohort 2, 5)
  - 1 case of optic neuritis (cohort 2)
  - 2 cases of rash (cohort 6)

Weber Js, et.al. *J Clin Oncol* 2013;31.

Conclusions

- Combination nivolumab + peptide vaccine was well tolerated.
- RECIST 1.1 response rate for ipilimumab-naïve and previously treated patients was 25%
- Elevated pre-treatment levels of NY-ESO-1 and

  MART-1 specific $CD8^+$ T cells were associated with progression of disease
- At week 12, increased peripheral T regulatory cells and decreased antigen specific T cells were associated with progression.
- PD-L1 tumor staining was associated with responses to nivolumab, but negative staining did not rule out a response.

Ongoing Combination Immunotherapy Trials: Melanoma

- CA 220-007 IL21+ ipilimumab
- CA 209-067/069 Nivolumab monotherapy vs ipilimumab monotherapy vs. combination
- ECOG 3611 Ipilimumab +/- interferon
- LUD 2012-004 NY-ESO-1 vaccine + ipilimumab
- LUD 2012-005 Ipilimumab + Anti-OX40
- PROCLIVITY 02 High dose IL-2 + ipilimumab
- MCC 16755 Ipilimumab + pegylated interferon
- CA 209-064 Nivolumab + ipilimumab sequence

Ongoing Combination Immunotherapy Trials: Melanoma

• PROCLIVITY 02	High dose IL-2 + ipilimumab
• MCC 16755	Ipilimumab + pegylated IFN
• CA 209-064	Nivolumab/ipilimumab sequence
• CA 184-213	Ipilimumab + lymphodepletion + adoptive cell transfer and high-dose IL-2

Ongoing Combination Immunotherapy Trials: Other Tumor Types

- CA 184-041 Ipilimumab + vaccine (pancreas)
- UCSF 12552 Ipilimumab + GM-CSF (prostate)
- CA 209-016 Nivolumab + sunitinib, pazopanib or ipilimumab (renal cell)