ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Melanoma

Jade Homsi, MD

University of Texas Southwestern

Dallas, Texas

ADVANCES IN Cancer IMMUNOTHERAPY™

- **Genentech: Consulting**
- **Merck: Consulting**

- **I will be discussing non-FDA approved indications during my presentation.**

Cancer statistics, 2017

Estimated New Cases

Males			Females		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**	**All Sites**	**852,630**	**100%**

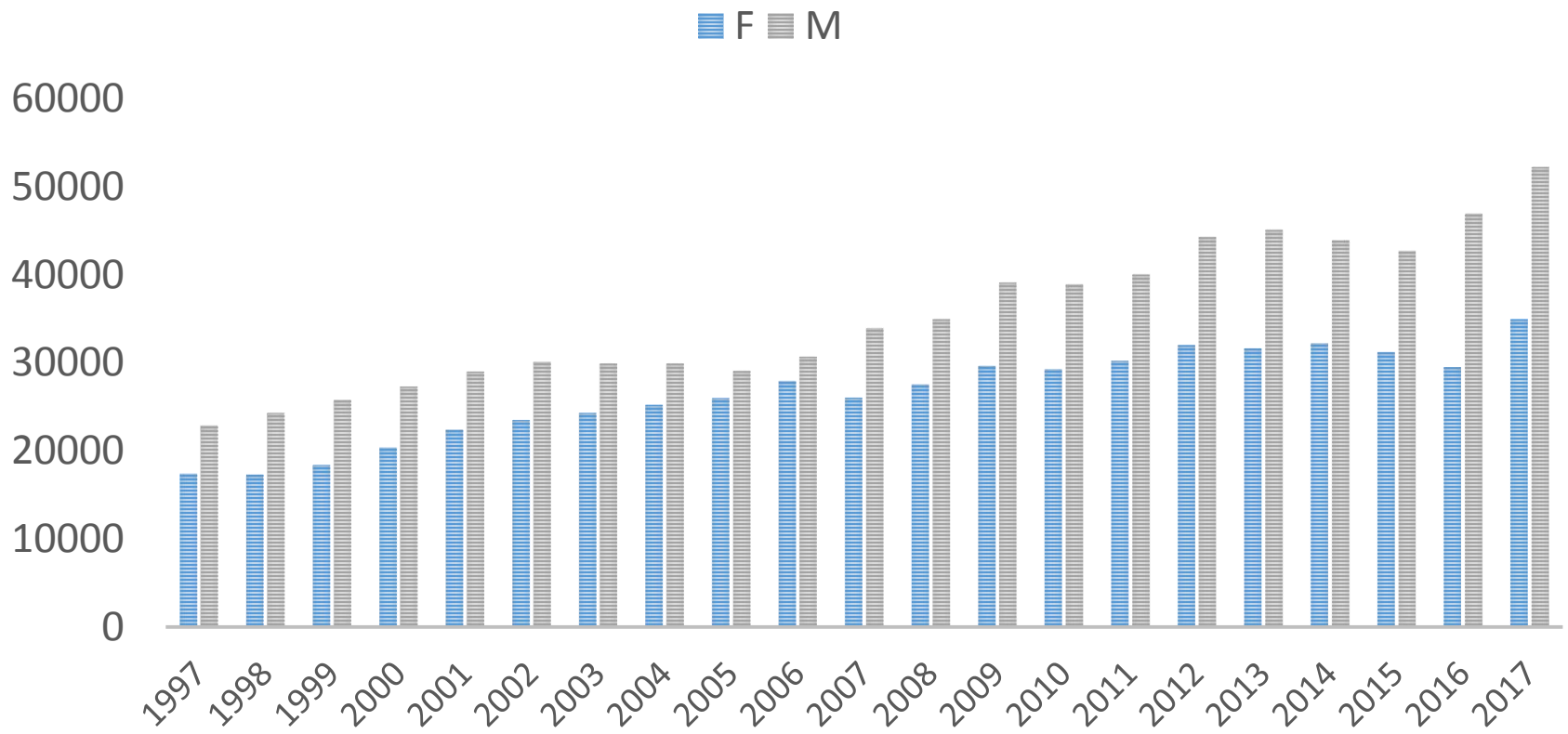
Estimated Deaths

Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**

CA: A Cancer Journal for Clinicians Volume 67, Issue 1

ADVANCES IN Cancer IMMUNOTHERAPY™

Melanoma Estimated New Cases



ADVANCES IN Cancer IMMUNOTHERAPY™

Life Time Probability of Developing Melanoma in the US

	All Sites	Melanoma 1996-1998	Melanoma 2011-2013
Female	1 in 3	1 in 82	1 in 44
Male	1 in 2	1 in 58	1 in 28

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for Melanoma

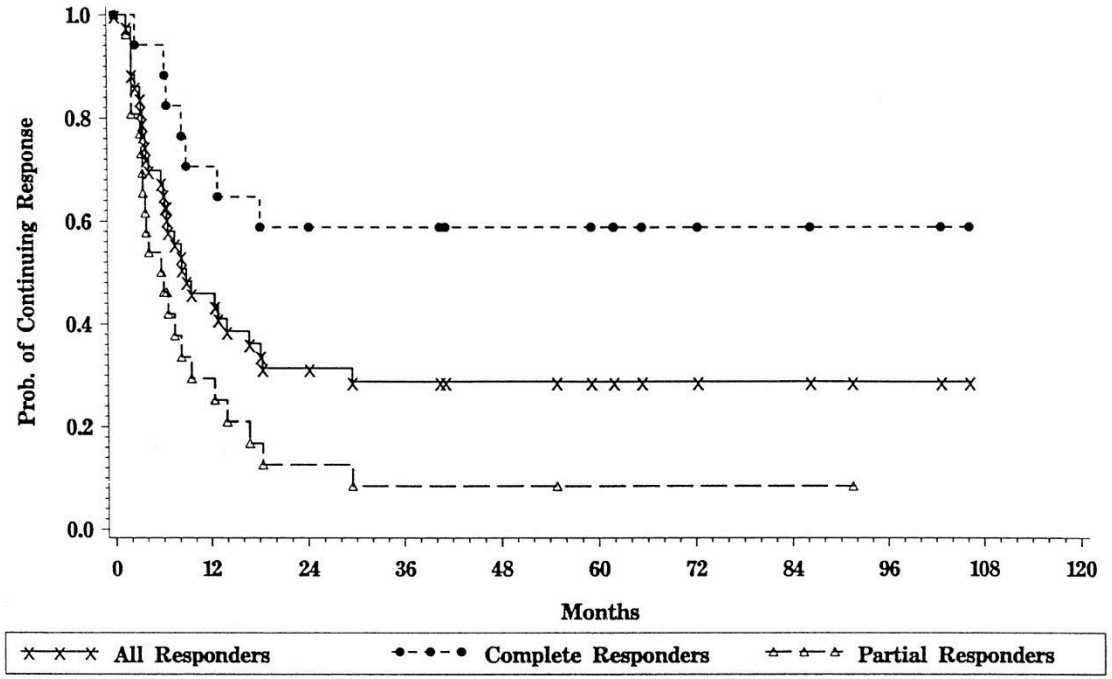
Adjuvant

- Interferon alpha-2b (1996)
- Peginterferon-alfa-2b (2011)
- Ipilimumab (2015)
- Nivolumab (2017)

Uresectable/Metastatic

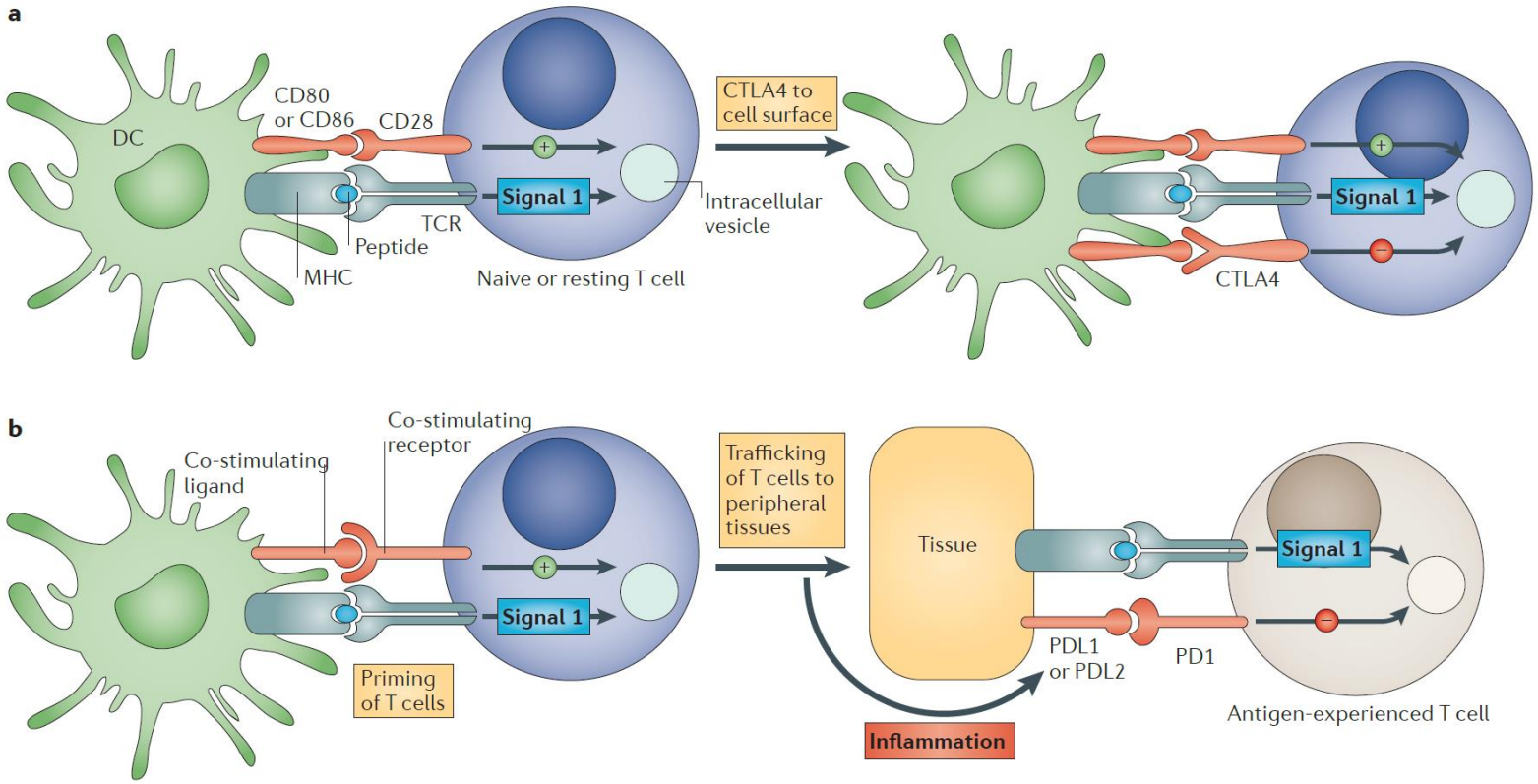
- High Dose Interleukin-2 (1998)
- Ipilimumab (2011)
- Nivolumab (2014)
- Pembrolizumab (2014)
- Ipilimumab + Nivolumab (2015)
- T-VEC (2015)

HDIL-2: Durable Response in Metastatic Melanoma



Atkins. J Clin Oncol 1999 Jul;17(7):2105

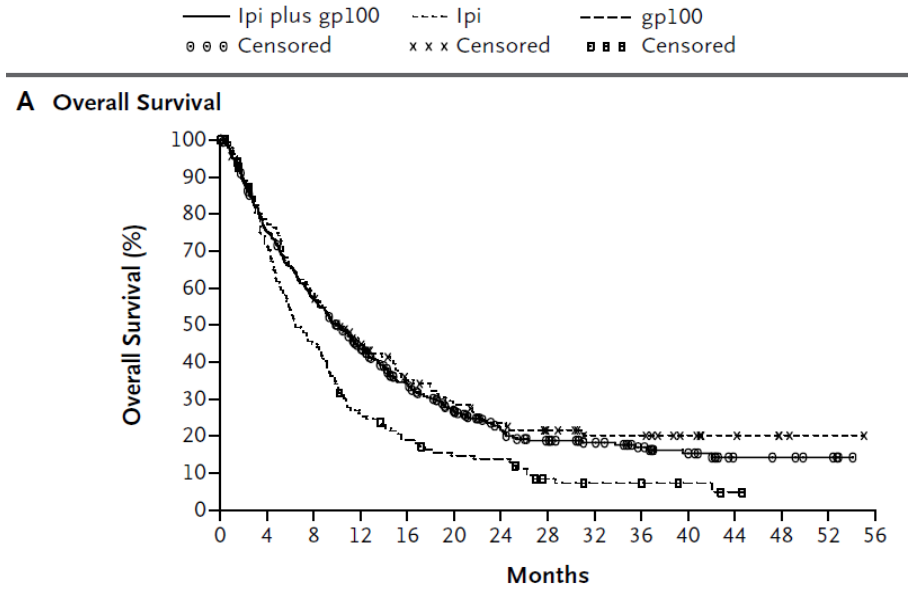
The blockade of immune checkpoints in cancer immunotherapy



Pardoll. Nat Rev Cancer. 2012: 22

Ipilimumab improves survival compared to gp100 vaccine

- Low response rate: 10% but some durable
- Median survival: 10 vs 6.4 months
- Grade 3 or 4 in up to 15%
- Most common: diarrhea/colitis any grade 27-31%
- Deaths related to the study drug 2.1%



No. at Risk															
Ipi plus 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

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

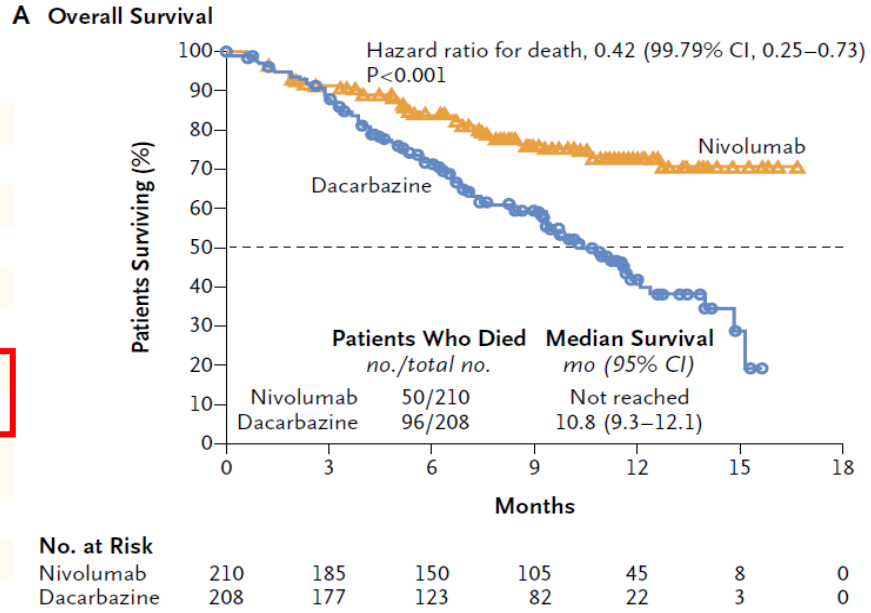
Characteristic	Nivolumab (N=210)	Dacarbazine (N=208)	Total (N=418)
Age — yr			
Median	64	66	65
Range	18–86	26–87	18–87
Sex — no. (%)			
Male	121 (57.6)	125 (60.1)	246 (58.9)
Female	89 (42.4)	83 (39.9)	172 (41.1)
Geographic region — no. (%)			
Europe or Canada	145 (69.0)	145 (69.7)	290 (69.4)
Israel, Australia, or South America	65 (31.0)	63 (30.3)	128 (30.6)
ECOG performance-status score — no. (%)†			
0	148 (70.5)	121 (58.2)	269 (64.4)
1	60 (28.6)	84 (40.4)	144 (34.4)
2	1 (0.5)	3 (1.4)	4 (1.0)
Metastasis stage — no. (%)‡			
M1c	128 (61.0)	127 (61.1)	255 (61.0)
M0, M1a, or M1b	82 (39.0)	81 (38.9)	163 (39.0)
Lactate dehydrogenase — no. (%)			
≤ULN	120 (57.1)	125 (60.1)	245 (58.6)
>ULN	79 (37.6)	74 (35.6)	153 (36.6)
≤2× ULN	178 (84.8)	177 (85.1)	355 (84.9)
>2× ULN	21 (10.0)	22 (10.6)	43 (10.3)
Not reported	11 (5.2)	9 (4.3)	20 (4.8)
History of brain metastases — no. (%)			
Yes	7 (3.3)	8 (3.8)	15 (3.6)
No	203 (96.7)	200 (96.2)	403 (96.4)
PD-L1 status — no. (%)§			
Positive	74 (35.2)	74 (35.6)	148 (35.4)
Negative or indeterminate	136 (64.8)	134 (64.4)	270 (64.6)
BRAF status — no. (%)			
Mutation	0	0	0
No mutation	202 (96.2)	204 (98.1)	406 (97.1)
Not reported	8 (3.8)	4 (1.9)	12 (2.9)
Prior systemic therapy — no. (%)			
Adjuvant therapy	32 (15.2)	36 (17.3)	68 (16.3)
Neoadjuvant therapy	1 (0.5)	1 (0.5)	2 (0.5)

Nivolumab vs Chemotherapy Metastatic Braf wild type

Robert. N Engl J Med 2015;372

Nivolumab improves survival compared to chemotherapy

Response	Nivolumab (N=210)	Dacarbazine (N=208)
Best overall response — no. (%)†		
Complete response	16 (7.6)	2 (1.0)
Partial response	68 (32.4)	27 (13.0)
Stable disease	35 (16.7)	46 (22.1)
Progressive disease	69 (32.9)	101 (48.6)
Could not be determined	22 (10.5)	32 (15.4)
Objective response‡		
No. of patients (% [95% CI])	84 (40.0 [33.3–47.0])	29 (13.9 [9.5–19.4])
Difference — percentage points (95% CI)	26.1 (18.0–34.1)	
Estimated odds ratio (95% CI)	4.06 (2.52–6.54)	
P value	<0.001	



Robert. N Engl J Med 2015;372

ADVANCES IN Cancer IMMUNOTHERAPY™

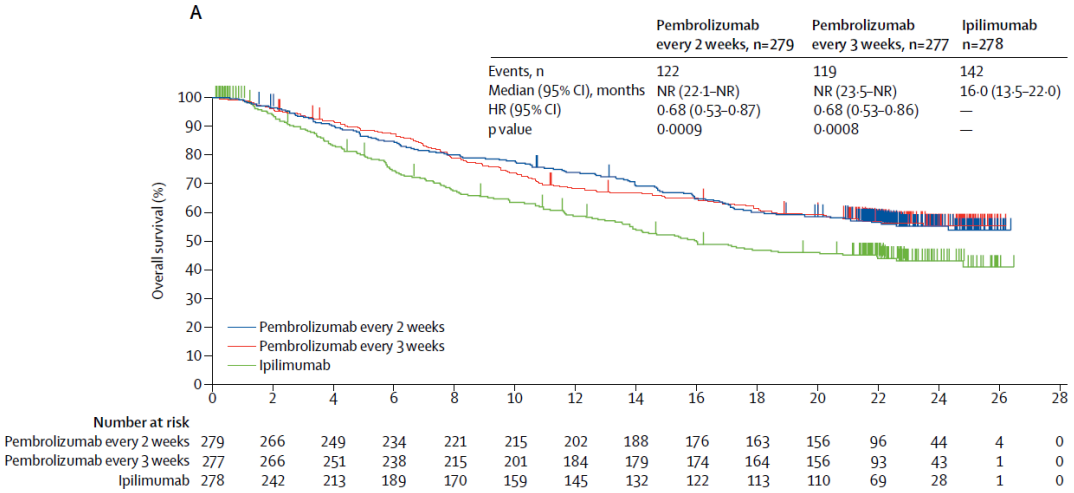
	Pembrolizumab every 2 weeks n=279	Pembrolizumab every 3 weeks n=277	Ipilimumab n=278
Age, median (range), years	61 (18–89)	63 (22–89)	62 (18–88)
Sex			
Male	161 (58%)	174 (63%)	162 (58%)
Female	118 (42%)	103 (37%)	116 (42%)
ECOG performance status			
0	196 (70%)	189 (68%)	188 (68%)
1	83 (30%)	88 (32%)	90 (32%)
LDH			
Normal	194 (70%)	175 (63%)	178 (64%)
Elevated	81 (29%)	98 (35%)	91 (33%)
Missing	4 (1%)	4 (1%)	9 (3%)
BRAF$^{V600E/K}$ status			
Wild-type	177 (63%)	178 (64%)	170 (61%)
Mutant	98 (35%)	97 (35%)	107 (39%)
Undetermined	4 (1%)	2 (1%)	1 (<1%)
PD-L1 expression			
Positive*	225 (81%)	221 (80%)	225 (81%)
Negative	49 (18%)	54 (20%)	47 (17%)
Unknown	5 (2%)	2 (1%)	6 (2%)
M staging of the extent of metastasis†			
M0	9 (3%)	8 (3%)	13 (5%)
M1	6 (2%)	4 (1%)	5 (2%)
M1a	21 (8%)	35 (13%)	30 (11%)
M1b	64 (23%)	41 (15%)	52 (19%)
M1c	179 (64%)	189 (68%)	178 (64%)
Lines of previous therapy			
0	183 (66%)	185 (67%)	181 (65%)
1	96 (34%)	91 (33%)	97 (35%)
2	0	1 (<1%)	0
Previous (neo)adjuvant therapy	42 (15%)	30 (11%)	37 (13%)
Previous chemotherapy	36 (131%)	41 (15%)	29 (10%)
Previous BRAF or MEK inhibitor	50 (18%)	45 (16%)	56 (20%)
Previous immunotherapy	8 (3%)	7 (2%)	12 (4%)
Interferon	3 (1%)	2 (<1%)	6 (2%)
Peg-interferon	1 (<1%)	0	0
IL-2	1 (<1%)	3 (1%)	2 (<1%)
Baseline tumour size, median (range) mm	58·5 (10–390)	63·4 (11–554)	55·6 (10–465)
Brain metastases			
Yes	24 (9%)	27 (10%)	29 (10%)
No	252 (90%)	248 (90%)	248 (89%)
Missing	3 (1%)	2 (1%)	1 (<1%)

Pembrolizumab vs Ipilimumab Metastatic Braf wild and mutant 2 year survival update

Schachter. Lancet 2017; 390: 1853

Pembrolizumab improves survival compared to ipilimumab

	Pembrolizumab every 2 weeks n=279	Pembrolizumab every 3 weeks n=277	Ipilimumab n=278
Objective response rate, % (95% CI)	37 (31–43)	36 (30–42)	13 (10–18)
Best overall response			
Complete response	33 (12%)	36 (13%)	14 (5%)
Partial response	70 (25%)	64 (23%)	23 (8%)
Stable disease	30 (11%)	30 (11%)	43 (16%)
Non-complete response or non-progressive disease*	12 (4%)	14 (5%)	9 (3%)
Progressive disease	107 (38%)	115 (42%)	137 (49%)
Not evaluable†	19 (7%)	15 (5%)	50 (18%)
No assessment‡	8 (3%)	3 (1%)	2 (<1%)
Ongoing responses§	69 (67%)	60 (60%)	23 (62%)
Duration of response, median (range), months	NR (1·8 to >22·8)	NR (2·0 to >22·8)	NR (>1·1 to >23·8)



24-month overall survival rate 55% vs 43%

Schachter. Lancet 2017; 390: 1853

	Pembrolizumab every 2 weeks n=278		Pembrolizumab every 3 weeks n=277		Ipilimumab n=256	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any	229 (82%)	47 (17%)	213 (77%)	46 (17%)	190 (74%)	50 (20%)
Serious	34 (12%)	0	32 (12%)	0	44 (17%)	0
Led to discontinuation	19 (7%)	0	30 (11%)	0	23 (9%)	0
Led to death	1 (<1%)*	0	0	0	0	0
Observed in ≥10% of patients in any treatment group						
Fatigue	79 (28%)	1 (<1%)	64 (23%)	3 (1%)	43 (17%)	3 (1%)
Pruritus	56 (20%)	0	55 (20%)	0	67 (26%)	0
Diarrhoea	54 (19%)	7 (3%)	46 (17%)	3 (1%)	59 (23%)	7 (3%)
Rash	44 (16%)	0	48 (17%)	0	40 (16%)	0
Arthralgia	35 (13%)	0	38 (14%)	0	13 (5%)	0
Nausea	36 (13%)	0	37 (13%)	0	24 (9%)	0
Hypothyroidism	30 (11%)	0	23 (8%)	0	2 (1%)	0

Pembrolizumab vs Ipilimumab
Less grade 3-4 toxicity

Schachter. Lancet 2017; 390: 1853

ADVANCES IN Cancer IMMUNOTHERAPY™

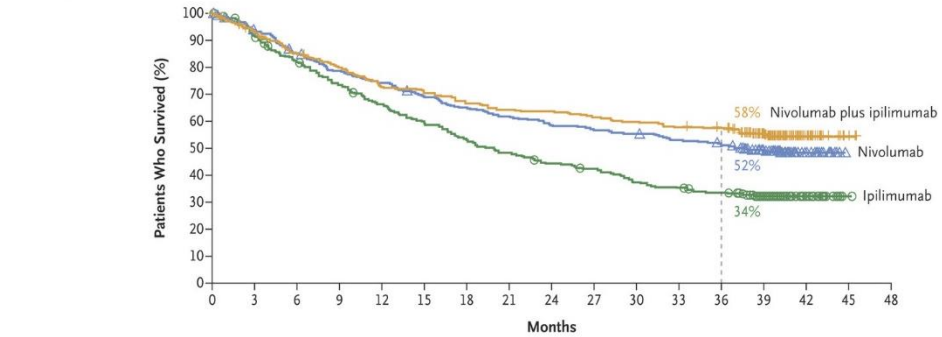
Characteristic	Nivolumab (N=316)	Nivolumab plus Ipilimumab (N=314)	Ipilimumab (N=315)	Total (N=945)
Age — yr				
Mean	59	59	61	60
Range	25–90	18–88	18–89	18–90
Age category — no. (%)				
<65 yr	198 (62.7)	185 (58.9)	182 (57.8)	565 (59.8)
≥65 to <75 yr	79 (25.0)	94 (29.9)	89 (28.3)	262 (27.7)
≥75 yr	39 (12.3)	35 (11.1)	44 (14.0)	118 (12.5)
Sex — no. (%)				
Male	202 (63.9)	206 (65.6)	202 (64.1)	610 (64.6)
Female	114 (36.1)	108 (34.4)	113 (35.9)	335 (35.4)
ECOG performance-status score — no. (%)†				
0	238 (75.3)	230 (73.2)	224 (71.1)	692 (73.2)
1	77 (24.4)	83 (26.4)	91 (28.9)	251 (26.6)
2	1 (0.3)	0	0	1 (0.1)
Not reported	0	1 (0.3)	0	1 (0.1)
Metastasis stage — no. (%)				
M1c	184 (58.2)	181 (57.6)	183 (58.1)	548 (58.0)
M0, M1a, or M1b	132 (41.8)	133 (42.4)	132 (41.9)	397 (42.0)
Lactate dehydrogenase — no. (%)				
≤ULN	196 (62.0)	199 (63.4)	194 (61.6)	589 (62.3)
>ULN	112 (35.4)	114 (36.3)	115 (36.5)	341 (36.1)
≤2× ULN	271 (85.8)	276 (87.9)	279 (88.6)	826 (87.4)
>2× ULN	37 (11.7)	37 (11.8)	30 (9.5)	104 (11.0)
Unknown	8 (2.5)	1 (0.3)	6 (1.9)	15 (1.6)
Brain metastases — no. (%)				
Yes	8 (2.5)	11 (3.5)	15 (4.8)	34 (3.6)
No	308 (97.5)	303 (96.5)	300 (95.2)	911 (96.4)
PD-L1 status — no. (%)				
Positive	80 (25.3)	68 (21.7)	75 (23.8)	223 (23.6)
Negative	208 (65.8)	210 (66.9)	202 (64.1)	620 (65.6)
Could not be determined or evaluated	28 (8.9)	36 (11.5)	38 (12.1)	102 (10.8)
BRAF status — no. (%)				
Mutation	100 (31.6)	101 (32.2)	97 (30.8)	298 (31.5)
No mutation	216 (68.4)	213 (67.8)	218 (69.2)	647 (68.5)

Ipi +Nivo vs Nivo vs Ipi
Metastatic Braf wild and mutant
3 year survival update

Wolchok. N Engl J Med 2017; 377:1345

Nivo+Ipi and Nivo improves survival compared to Ipi

Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	61 (19)	52 (16)	16 (5)
Partial response	122 (39)	88 (28)	43 (14)
Stable disease	38 (12)	31 (10)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	28 (9)
Objective response‡			
No. of patients with response	183	140	59
% of patients (95% CI)	58 (53–64)	44 (39–50)	19 (15–24)
Estimated odds ratio (95% CI)§	6.46 (4.45–9.38)	3.57 (2.48–5.15)	—
P value	<0.001	<0.001	—
Median duration of response (95% CI) — mo	NR	NR (36.3–NR)	19.3 (8.3–NR)

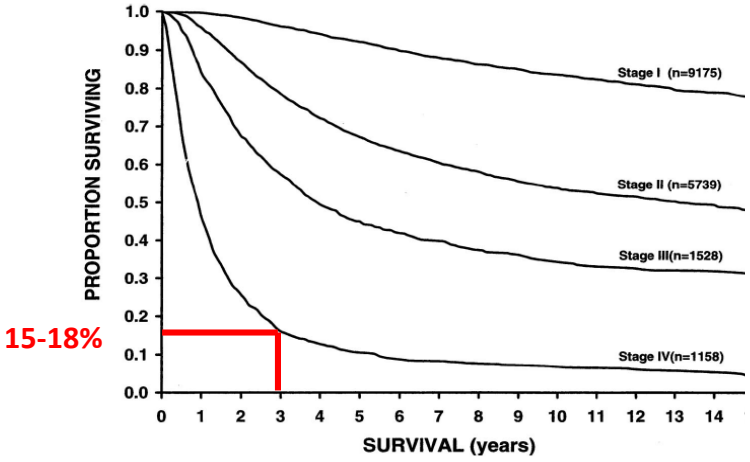


No. at Risk

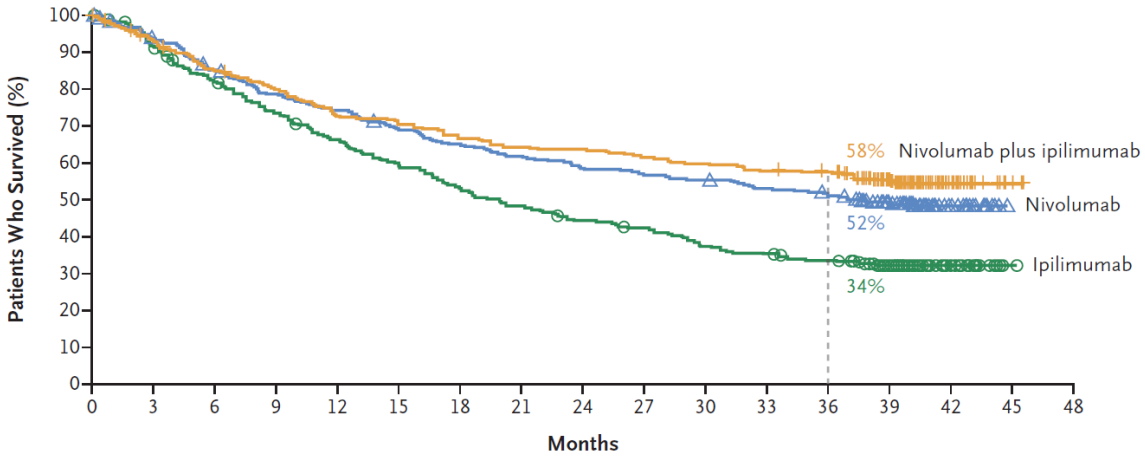
Nivolumab plus ipilimumab	314	292	265	247	226	221	209	200	198	192	186	180	177	131	27	3	0
Nivolumab	316	292	265	244	230	213	201	191	181	175	171	163	156	120	28	0	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	117	107	100	68	20	2	0

Wolchok. N Engl J Med 2017; 377:1345

Melanoma: Survival in the past 2 decades

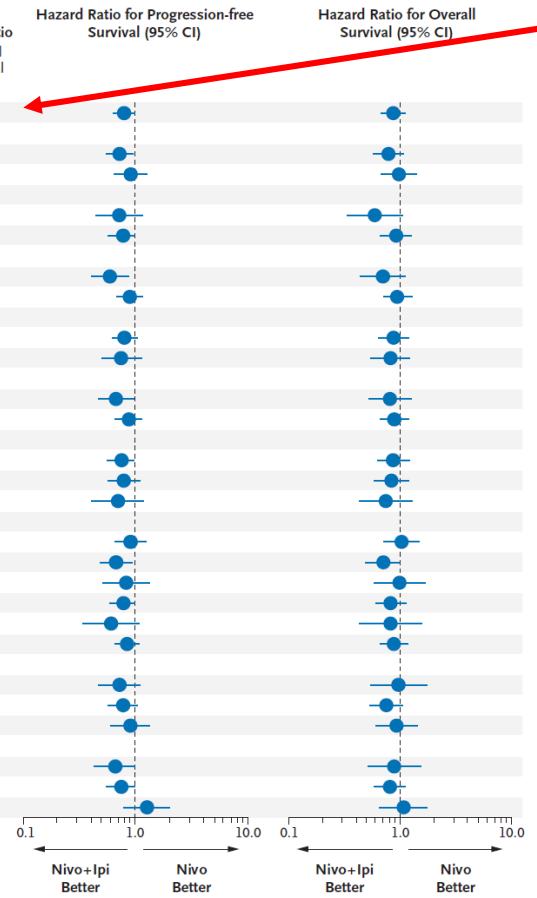


Balch. J Clin Oncol. 2001;19:3635



Wolchok. N Engl J Med 2017; 377:1345

Subgroup	No. of Patients		3-Yr Progression-free Survival Rate		3-Yr Overall Survival Rate		Unadjusted Hazard Ratio	
	Nivo+ Ipi	Nivo	Nivo+ Ipi	Nivo	Nivo+ Ipi	Nivo	Progression-free Survival	Overall Survival
			%		%			
All patients	314	316	39	32	58	52	0.79	0.85
Age								
<65 yr	185	198	39	31	61	51	0.73	0.78
≥65 yr	129	118	37	34	54	52	0.90	0.96
Geographic region								
United States	64	68	45	31	70	57	0.71	0.59
Europe	177	170	34	28	53	49	0.77	0.91
BRAF mutation								
Yes	102	98	40	22	68	56	0.59	0.69
No	212	218	38	36	53	50	0.89	0.94
ECOG performance-status score								
0	230	237	39	33	64	58	0.80	0.85
1	83	79	37	27	43	32	0.75	0.81
Metastasis stage								
M0, M1a, or M1b	129	132	50	39	72	64	0.67	0.79
M1c	185	184	31	27	48	42	0.87	0.88
LDH level								
≤ULN	199	197	45	37	66	61	0.75	0.86
>ULN	114	112	28	21	44	34	0.79	0.83
>2×ULN	37	37	17	11	31	14	0.69	0.73
PD-L1 expression level								
≥1%	155	171	43	39	62	60	0.90	1.02
<1%	123	117	35	26	54	42	0.67	0.70
≥5%	68	80	49	41	65	61	0.83	0.99
<5%	210	208	36	31	56	50	0.78	0.82
≥10%	46	59	58	39	67	58	0.61	0.82
<10%	232	229	35	32	57	51	0.84	0.87
Tumor burden								
≤31 mm	78	85	45	38	72	69	0.72	0.96
>31 mm and ≤97 mm	154	150	38	30	59	48	0.76	0.74
>97 mm	82	80	33	29	41	39	0.89	0.92
No. of lesion sites								
1	89	80	47	37	70	65	0.65	0.88
2 or 3	166	176	38	28	57	48	0.74	0.80
>3	59	59	27	36	42	44	1.25	1.06



HR for death
0.85 (95% CI, 0.68 to 1.07)

Ipi +Nivo vs Nivo

Wolchok. N Engl J Med 2017; 377:1345

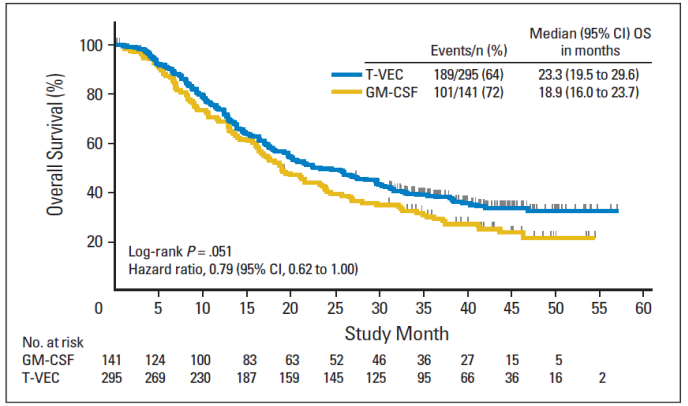
Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

Ipi +Nivo vs Nivo vs Ipi
More than double grade 3-4 toxicity with combo (59%, 21%, 28%)

Wolchok. N Engl J Med 2017; 377:1345

T-VEC (Talimogene Laherparepvec)

- **Intralesionally delivered oncolytic immunotherapy**
- **Genetically engineered attenuated herpes simplex virus**
- **Secretes granulocyte macrophage–colony stimulating (GM-CSF)**



Response	T-VEC (n = 295)	GM-CSF (n = 141)	*P*
DRR			< .001
Patients with durable response, No.	48	3	
DRR, %*	16.3	2.1	
95% CI	12.1 to 20.5	0 to 4.5	
Unadjusted odds ratio	8.9		
95% CI	2.7 to 29.2		
ORR			< .001†
CR			
No.	32	1	
%	10.8	< 1	
PR			
No.	46	7	
%	15.6	5.0	
ORR, %*	26.4	5.7	
95% CI	21.4 to 31.5	1.9 to 9.5	

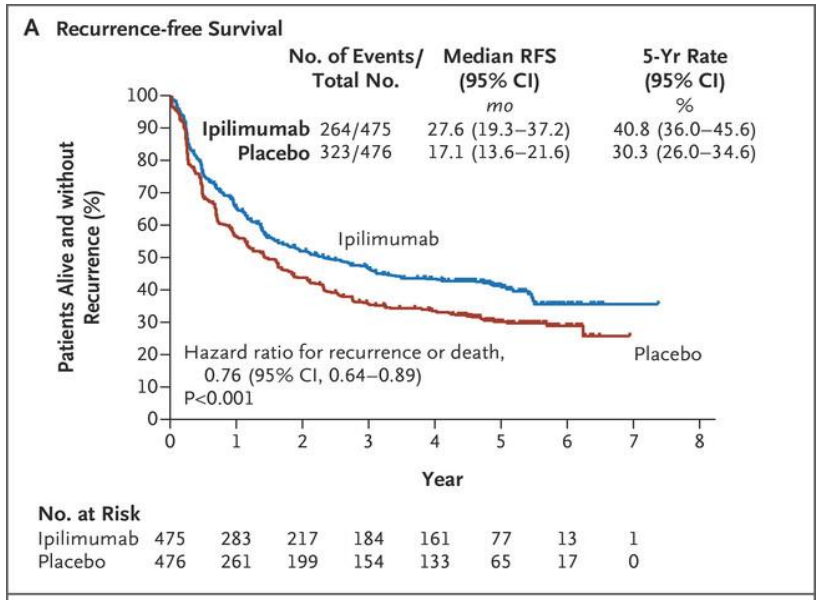
Ott. Clin Cancer Res; 22(13); 3127

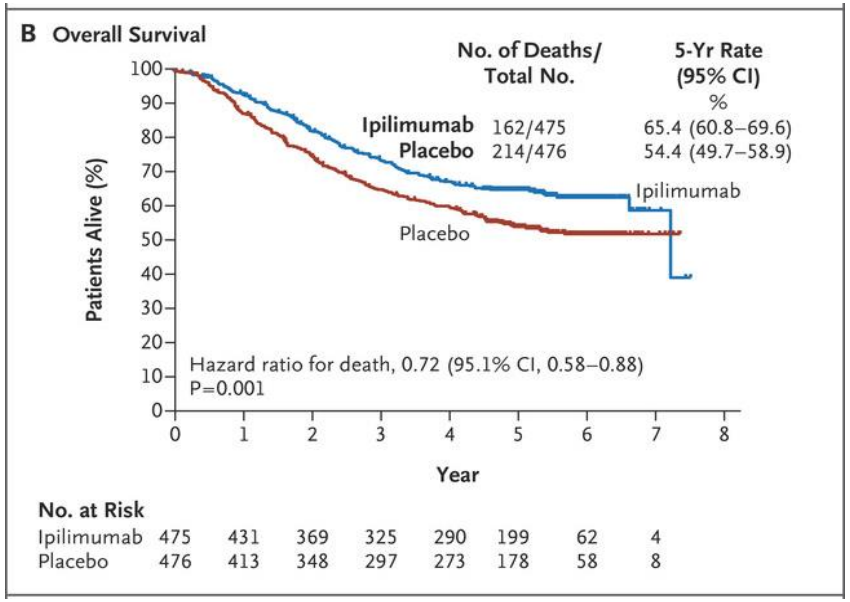
Characteristic	Ipilimumab (N=475)	Placebo (N=476)
Sex — no. (%)		
Male	296 (62.3)	293 (61.6)
Female	179 (37.7)	183 (38.4)
Age		
Median (range) — yr	51 (20–84)	52 (18–78)
Distribution — no. (%)		
<50 yr	214 (45.1)	211 (44.3)
51 to <65 yr	180 (37.9)	178 (37.4)
≥65 yr	81 (17.1)	87 (18.3)
Disease stage — no. (%)		
At randomization		
IIIA	98 (20.6)	98 (20.6)
IIIB	182 (38.3)	182 (38.2)
IIIC with 1–3 positive lymph nodes	122 (25.7)	121 (25.4)
IIIC with ≥4 positive lymph nodes	73 (15.4)	75 (15.8)
According to AJCC 2002 criteria†		
IIIA	98 (20.6)	88 (18.5)
IIIB	213 (44.8)	207 (43.5)
IIIC with 1–3 positive lymph nodes	69 (14.5)	83 (17.4)
IIIC with ≥4 positive lymph nodes	95 (20.0)	98 (20.6)
Type of lymph-node involvement — no. (%)†		
Microscopic	210 (44.2)	193 (40.5)
Macroscopic	265 (55.8)	283 (59.5)
No. of positive lymph nodes on pathological testing — no. (%)†		
1	217 (45.7)	220 (46.2)
2 or 3	163 (34.3)	158 (33.2)
≥4	95 (20.0)	98 (20.6)
Ulceration — no. (%)†		
Yes	197 (41.5)	203 (42.6)
No	257 (54.1)	244 (51.3)
Unknown	21 (4.4)	29 (6.1)

Ipilimumab 10 mg/kg vs Placebo Stage 3 Adjuvant 5 year Update

N Engl J Med 2016; 375:1845

Adjuvant Ipilimumab vs Placebo: Better RFS and Survival





N Engl J Med 2016; 375:1845

Adjuvant Ipilimumab vs Placebo
High grade 3-4 toxicity

Event	Ipilimumab (N=471)				Placebo (N=474)			
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
Any immune-related adverse event	426 (90.4)	169 (35.9)	27 (5.7)	5 (1.1)	188 (39.7)	12 (2.5)	1 (0.2)	0
Any dermatologic event	298 (63.3)	20 (4.2)	0	0	99 (20.9)	0	0	0
Rash	161 (34.2)	5 (1.1)	0	0	52 (11.0)	0	0	0
Any gastrointestinal event†	217 (46.1)	70 (14.9)	6 (1.3)	3 (0.6)	85 (17.9)	3 (0.6)	1 (0.2)	0
Diarrhea	194 (41.2)	46 (9.8)	0	0	80 (16.9)	2 (0.4)	0	0
Colitis	73 (15.5)	32 (6.8)	4 (0.8)	3 (0.6)	7 (1.5)	1 (0.2)	1 (0.2)	0
Any endocrine-system event	178 (37.8)	34 (7.2)	3 (0.6)	0	38 (8.0)	1 (0.2)	0	0
Hypophysitis	77 (16.3)	20 (4.2)	1 (0.2)	0	1 (0.2)	0	0	0
Any hepatic event	115 (24.4)	38 (8.1)	13 (2.8)	0	20 (4.2)	1 (0.2)	0	0
Increase in liver-enzyme levels	83 (17.6)	14 (3.0)	6 (1.3)	0	18 (3.8)	0	0	0
Any neurologic event	21 (4.5)	5 (1.1)	4 (0.8)	0	9 (1.9)	0	0	0
Other‡	111 (23.6)	34 (7.2)	2 (0.4)	2 (0.4)	23 (4.9)	8 (1.7)	0	0

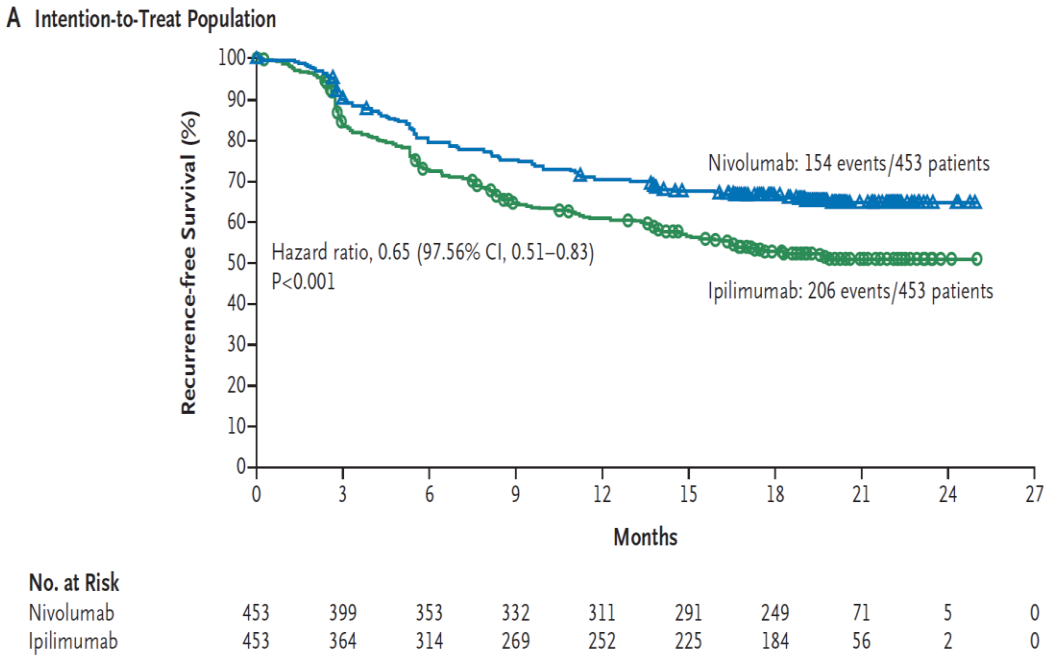
N Engl J Med 2016; 375:1845

ADVANCES IN Cancer IMMUNOTHERAPY™

Characteristic	Nivolumab (N=453)	Ipilimumab (N=453)
Sex — no. (%)		
Male	258 (57.0)	269 (59.4)
Female	195 (43.0)	184 (40.6)
Median age (range) — yr	56 (19–83)	54 (18–86)
Disease stage — no. (%)		
IIIB	163 (36.0)	148 (32.7)
IIIC	204 (45.0)	218 (48.1)
IV	82 (18.1)	87 (19.2)
Other or not reported	4 (1.0)	0
Type of lymph-node involvement in stage III — no./total no. (%)		
Microscopic	125/369 (33.9)	134/366 (36.6)
Macroscopic	219/369 (59.3)	214/366 (58.5)
Not reported	25/369 (6.8)	18/366 (4.9)
Tumor ulceration in stage III — no./total no. (%)		
Yes	153/369 (41.5)	135/366 (36.9)
No	201/369 (54.5)	216/366 (59.0)
Not reported	15/369 (4.1)	15/366 (4.1)
Metastasis status in stage IV — no./total no. (%)		
M1a	50/82 (61.0)	51/87 (58.6)
M1b	12/82 (14.6)	15/87 (17.2)
M1c	20/82 (24.4)	21/87 (24.1)
Tumor PD-L1 expression — no. (%)		
<5%	275 (60.7)	286 (63.1)
≥5%	152 (33.6)	154 (34.0)
Could not be determined or not reported	26 (5.7)	13 (2.9)
BRAF status — no. (%)		
Mutation	187 (41.3)	194 (42.8)
No mutation	197 (43.5)	214 (47.2)
Not reported	69 (15.2)	45 (9.9)

Adjuvant Nivolumab vs Ipi Resected Stage III or IV Melanoma

Weber. N Engl J Med 2017; 377:19



Adjuvant Nivo vs Ipi Better RFS with nivo

At 12-month RFS 70.5% for nivo and 60.8% for ipi

Weber. N Engl J Med 2017; 377:19

Event	Nivolumab (N=452)		Ipilimumab (N=453)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event	438 (96.9)	115 (25.4)	446 (98.5)	250 (55.2)
Treatment-related adverse event†	385 (85.2)	65 (14.4)	434 (95.8)	208 (45.9)
Fatigue	156 (34.5)	2 (0.4)	149 (32.9)	4 (0.9)
Diarrhea	110 (24.3)	7 (1.5)	208 (45.9)	43 (9.5)
Pruritus	105 (23.2)	0	152 (33.6)	5 (1.1)
Rash	90 (19.9)	5 (1.1)	133 (29.4)	14 (3.1)
Nausea	68 (15.0)	1 (0.2)	91 (20.1)	0
Arthralgia	57 (12.6)	1 (0.2)	49 (10.8)	2 (0.4)
Asthenia	57 (12.6)	1 (0.2)	53 (11.7)	4 (0.9)
Hypothyroidism	49 (10.8)	1 (0.2)	31 (6.8)	2 (0.4)
Headache	44 (9.7)	1 (0.2)	79 (17.4)	7 (1.5)
Abdominal pain	29 (6.4)	0	46 (10.2)	1 (0.2)
Increase in ALT level	28 (6.2)	5 (1.1)	66 (14.6)	26 (5.7)
Increase in AST level	25 (5.5)	2 (0.4)	60 (13.2)	19 (4.2)
Maculopapular rash	24 (5.3)	0	50 (11.0)	9 (2.0)
Hypophysitis	7 (1.5)	2 (0.4)	48 (10.6)	11 (2.4)
Pyrexia	7 (1.5)	0	54 (11.9)	2 (0.4)
Any adverse event leading to discontinuation	44 (9.7)	21 (4.6)	193 (42.6)	140 (30.9)
Treatment-related adverse event leading to discontinuation	35 (7.7)	16 (3.5)	189 (41.7)	136 (30.0)

Adjuvant Nivo vs Ipi
More than double grade 3-4 toxicity with ipi

Weber. N Engl J Med 2017; 377:19

ADVANCES IN Cancer IMMUNOTHERAPY™

Lessons from immunotherapy in melanoma

- Improved survival in mets melanoma: 15% vs 58% alive at 3 years
- Response could take weeks but mostly durable
- Pseudoprogression is a challenge
- Braf mutant and wild type benefit
- PDL-1 status: for now does not matter
- PD-1 inhibitors superior and better tolerated than CTLA-4 inhibitors
- Choice of single agent vs combination mostly clinical
- Duration of therapy: 2 years?
- Benefits in brain mets
- Synergy with radiation therapy
- Unique, Multiorgan and sometime life threatening side effects
- Close monitoring, early use of steroids and supportive care save lives
- Cost of therapy
- The end of interferon?
- Combination with Braf targeted therapy is being explored

ADVANCES IN Cancer IMMUNOTHERAPY™

Case: 46 year old, primary cutaneous melanoma of the left foot 4.1 mm with ulceration. WLE and SLNB showed no residual melanoma but 2 nodes positive. LND 0/12 nodes pos. What intervention has the best outcome:

A. Active surveillance
B. High dose interferon for one year
C. Ipi 3 mg/kg every 3 weeksX4 then every 3 months for up to 3 years
D. Ipi 10 mg/kg every 3 weeksX4 then every 3 months for up to 3 years
E. Nivolumab 240 mg every 2 weeks for one year
F. Ipi + Nivo 4 cycles followed by nivo every 2 weeks