Immunotherapy for the Treatment of Melanoma

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Society for Immunotherapy of Cancer
ACI – TX Program
Friday, June 19, 2015

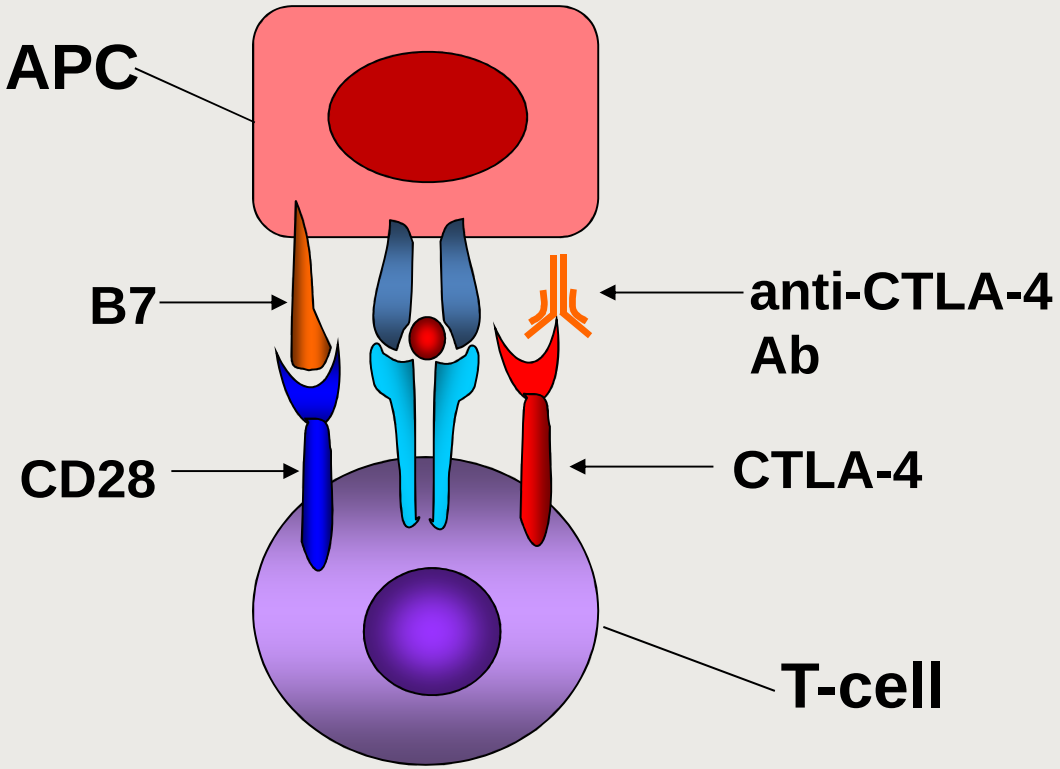
MD Anderson Cancer Center
Making Cancer History

More Recent Agents that have been FDA Approved for Metastatic Melanoma

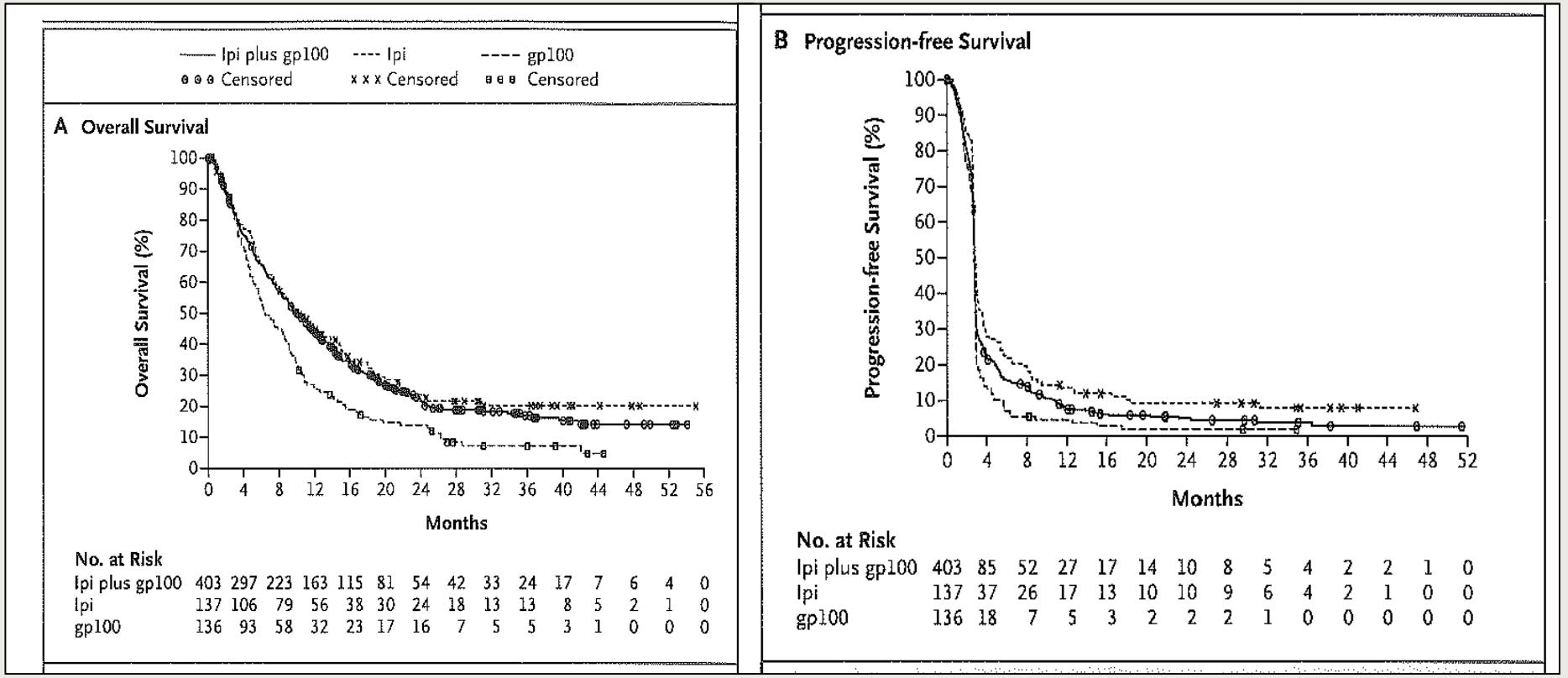
- **Vemurafenib (Zelboraf) for BRAF mutant late-stage melanoma - August 17, 2011.**
- **Ipilimumab (MDX-010/Yervoy) for late-stage melanoma that has spread or cannot be removed by surgery - March 2011.**
- **Dabrafenib (Talfinlar) for BRAF mutant metastatic melanoma that cannot be surgically removed – May 2013.**
- **Tremetinib (Mekinist) for metastatic melanoma that cannot be surgically removed – May 2013.**
- **Pembrolizumab (Keytruda) for advanced melanoma that no longer responds to other drugs - September 2014.**
- **Nivolumab (Opdivo) for advanced melanoma that no longer responds to other drugs – December 2014.**

anti-CTLA-4: Mechanism of Action

- **Blocks CTLA-4, an inhibitory receptor on T-cells.**
- **CTLA-4 is only expressed on the surface of T-cells after stimulation with antigen.**

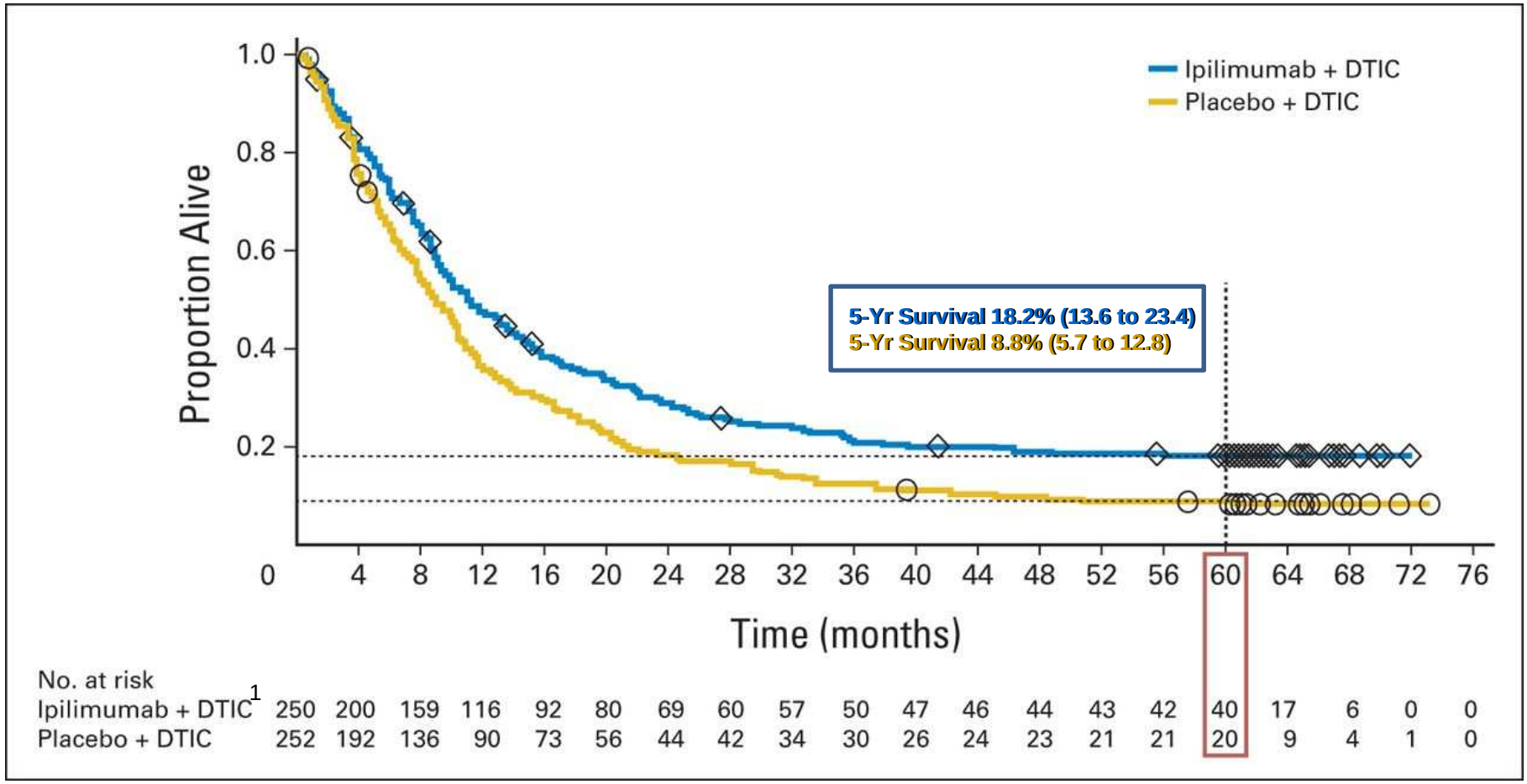


anti-CTLA-4 (Ipilimumab) Increases Progression Free Survival and Overall Survival Compared to Vaccine Alone for Patients with Metastatic Melanoma



Hodi et al. *N Engl J Med* 2010

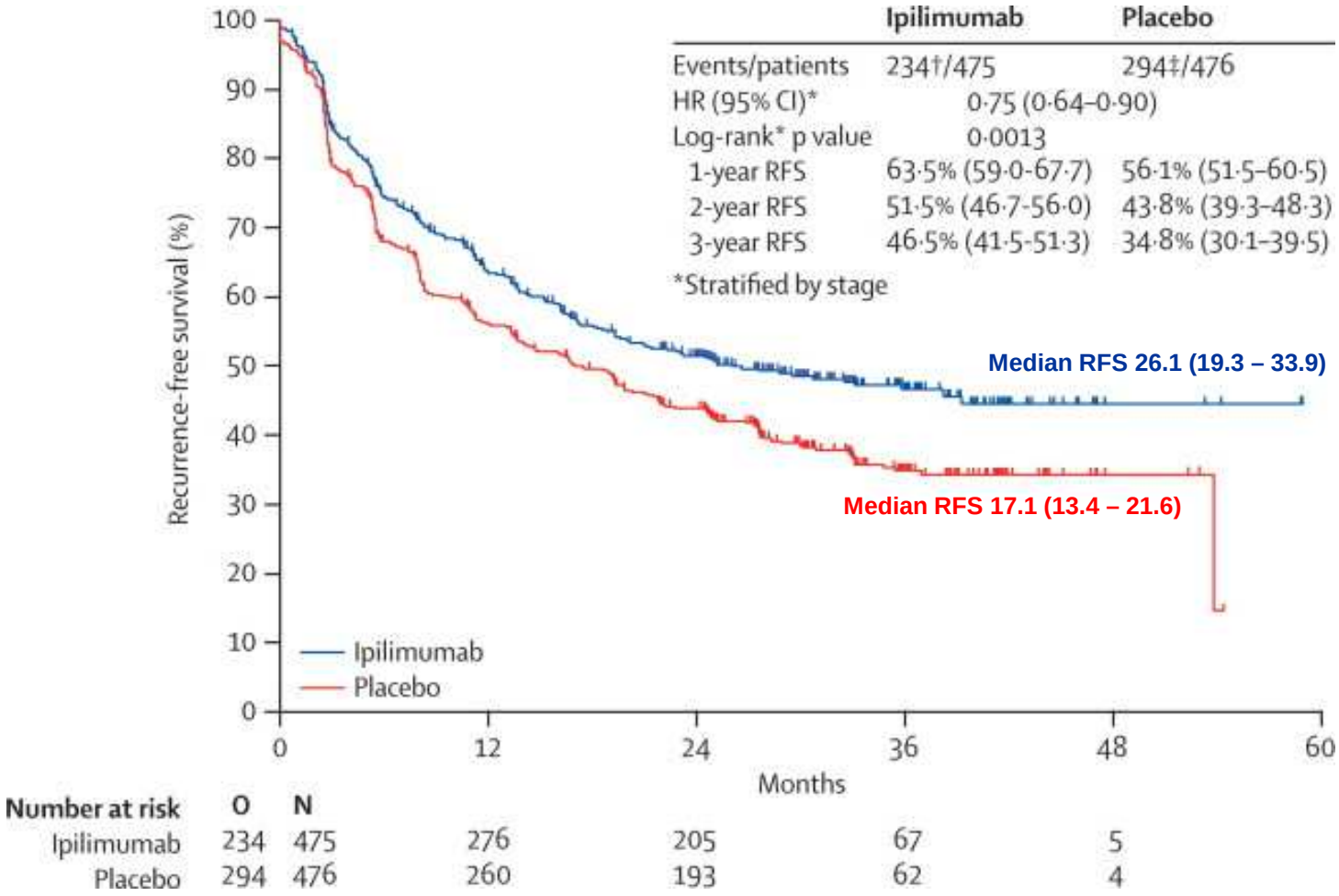
Kaplan-Meier Estimates of Overall Survival in Advanced Melanoma Patients Treated with Ipilimumab plus Dacarbazine (DTIC) or Placebo plus DTIC in Phase III CA184-024 study.



1. Ipilimumab dose 10 mg/kg

Maio M et al. *JCO* May 2015;33:1191-1196

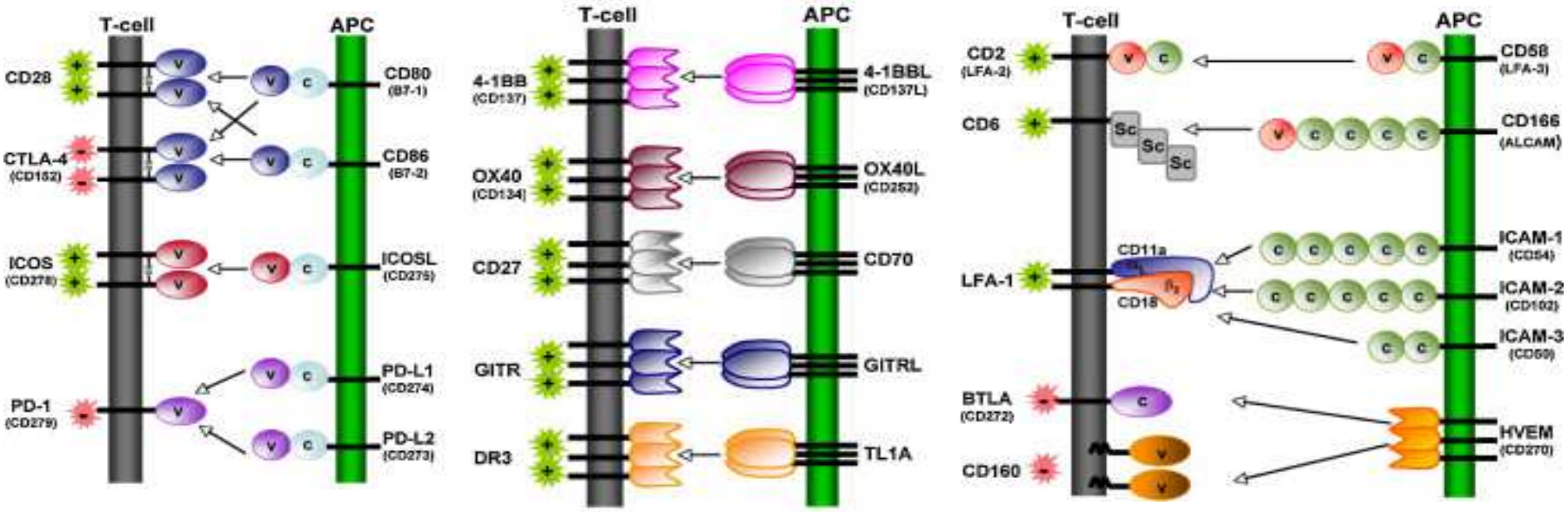
Adjuvant Ipilimumab vs. Placebo Recurrence-free Survival (RFS) in Resected High Risk Stage III Melanoma Patients



Eggermont AM et al. *Lancet* May 2015; 16:522-30, randomized double-blind phase 3 trial

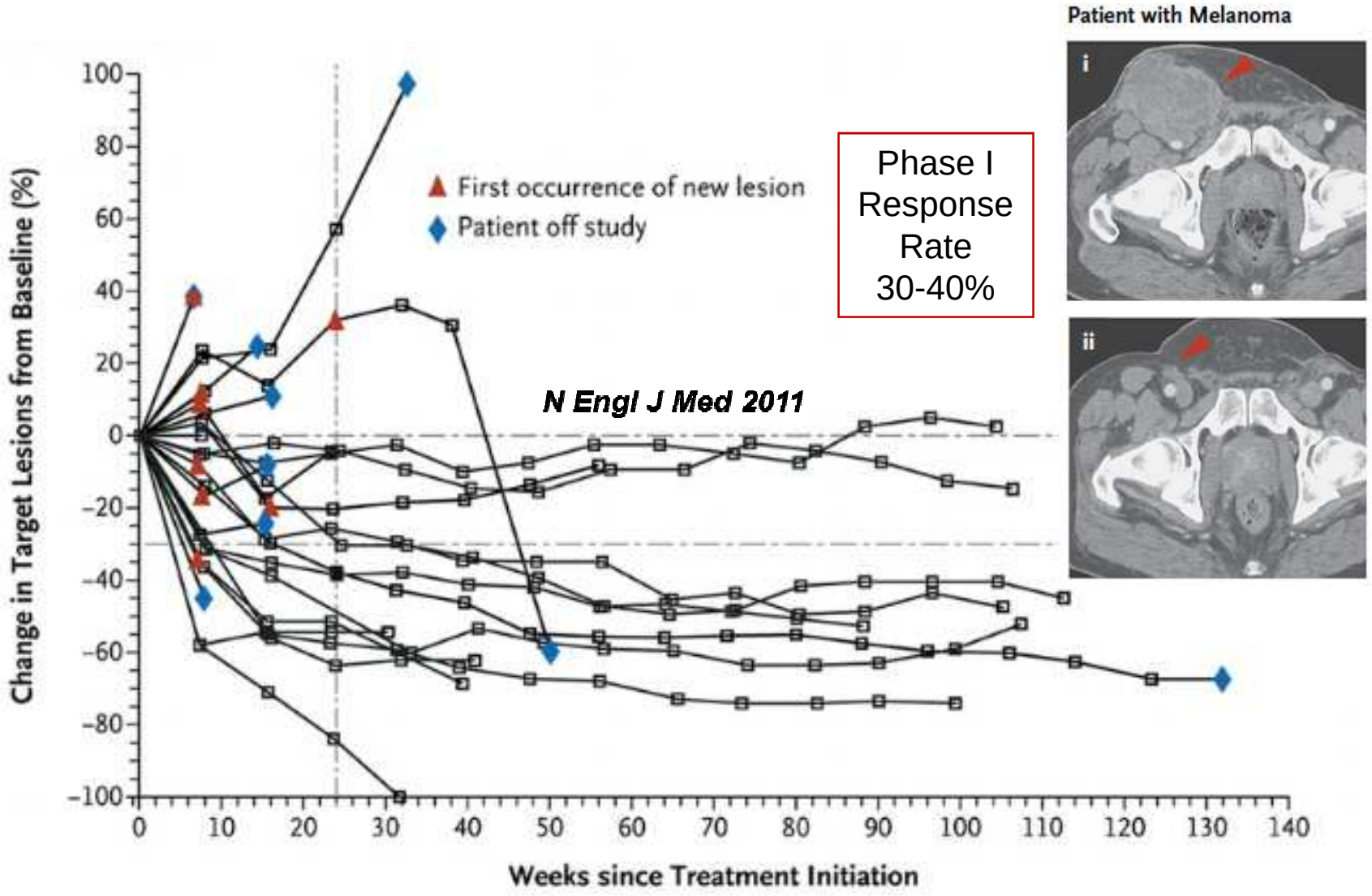
Receptor-ligand Pairs that Play a Role in Regulating T-cell Function

B7-CD28 family TNF-TNFR family Additional molecules



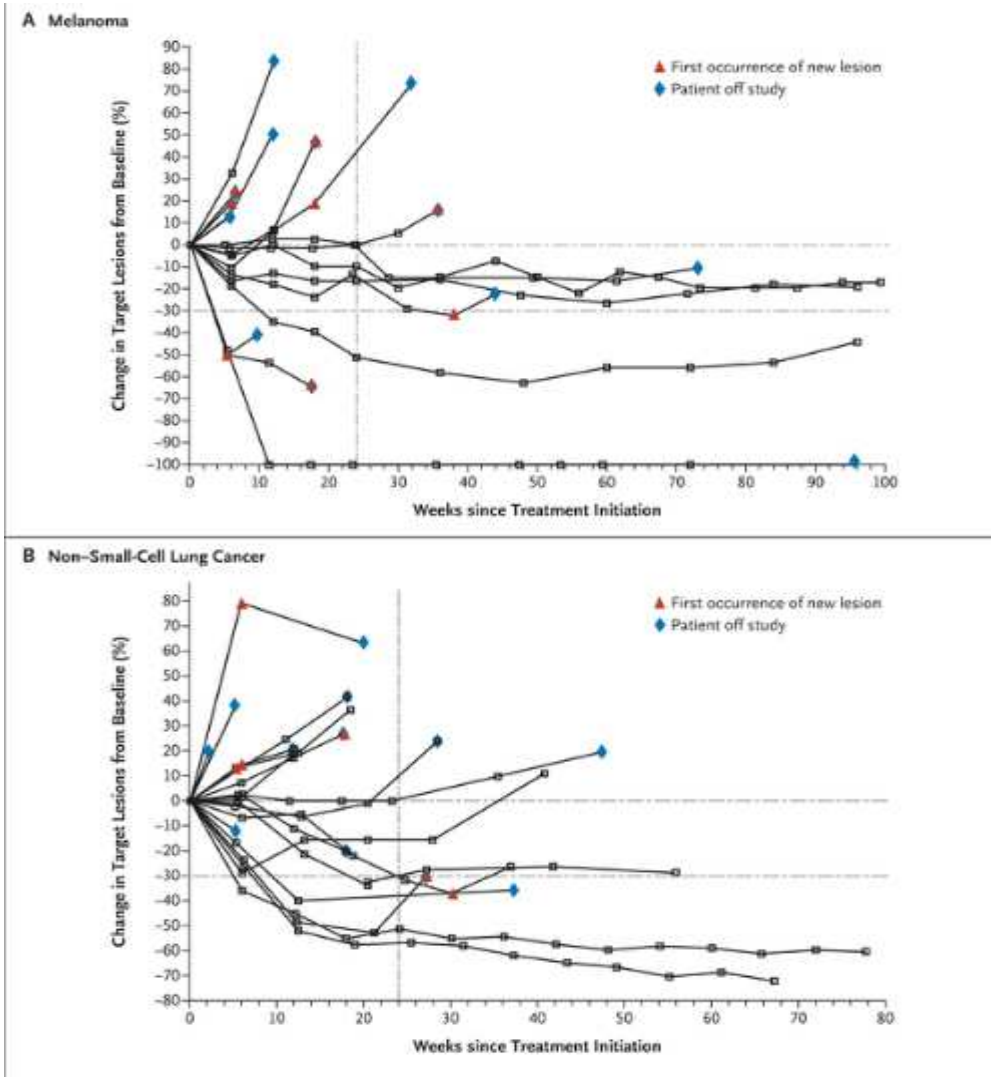
Adapted from *Immunology Letter* 128:89-97, 2011

Durable Responses are Seen in Patients with Metastatic Melanoma Treated with anti-PD-1 Antibody



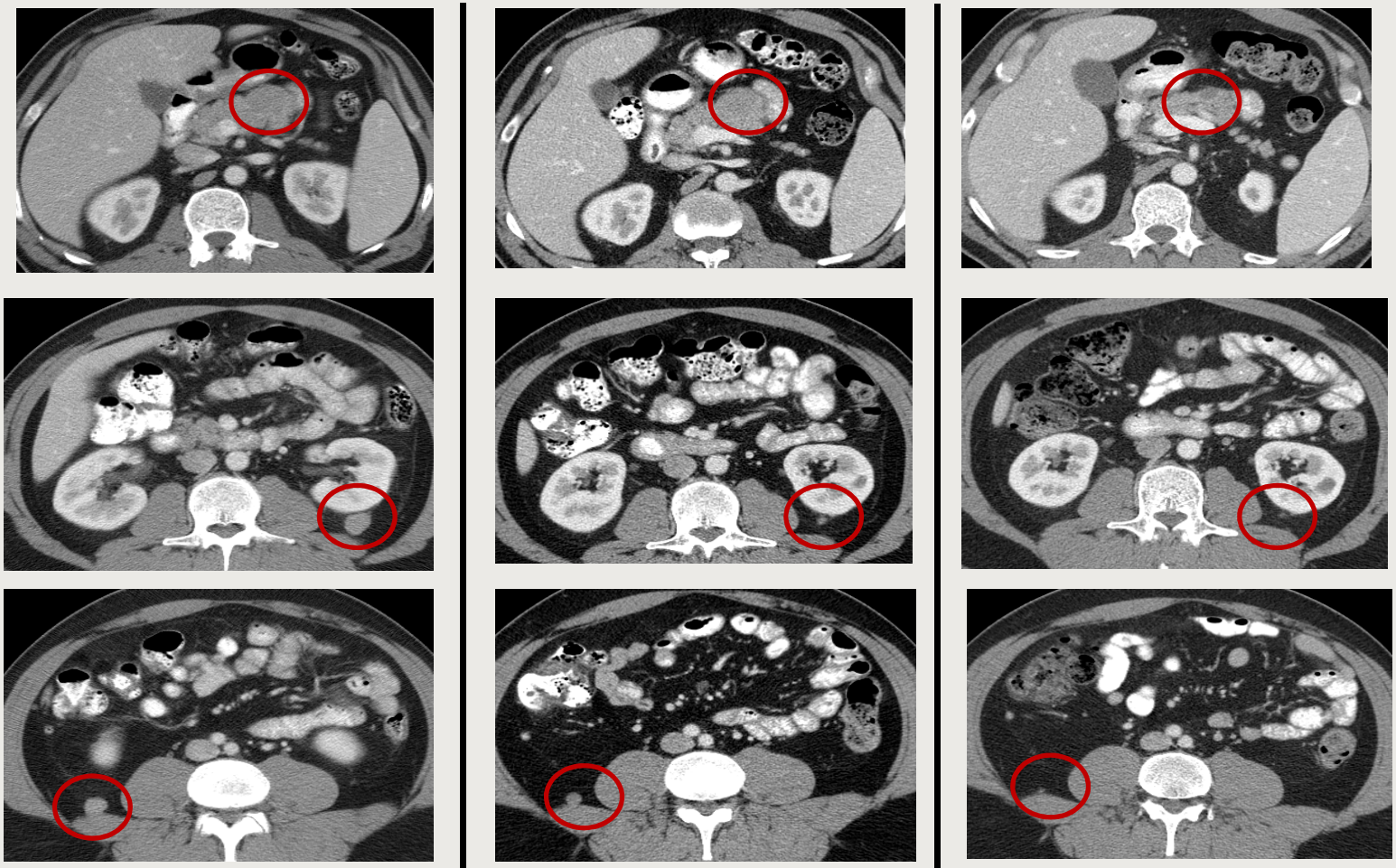
Topalian et al. *NEJM* 2012

Activity of anti-PD-L1 Antibody in Patients with Advanced Melanoma and Non-Small-Cell Lung Cancer



Brahmer et al. *NEJM* 2012

Clinical Response to anti-PDL-1 in a Patient with Metastatic Melanoma



Baseline | After 2 months | After 6 months

Brahmer et al. *NEJM* 2012

Anti-PD1 vs. Dacabazine in Patients with Previously Untreated Melanoma without BRAF Mutation

Table 2. Response to Treatment.*

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	
Time to objective response — mo		
Median	2.1	2.1
Range	1.2–7.6	1.8–3.6
Mean	2.6±1.3	2.5±0.7
Duration of response — mo§		
Median (95% CI)	Not reached	6.0 (3.0–not reached)
Range	0.0–12.5	1.1–10.0

* Plus–minus values are means ±SD.

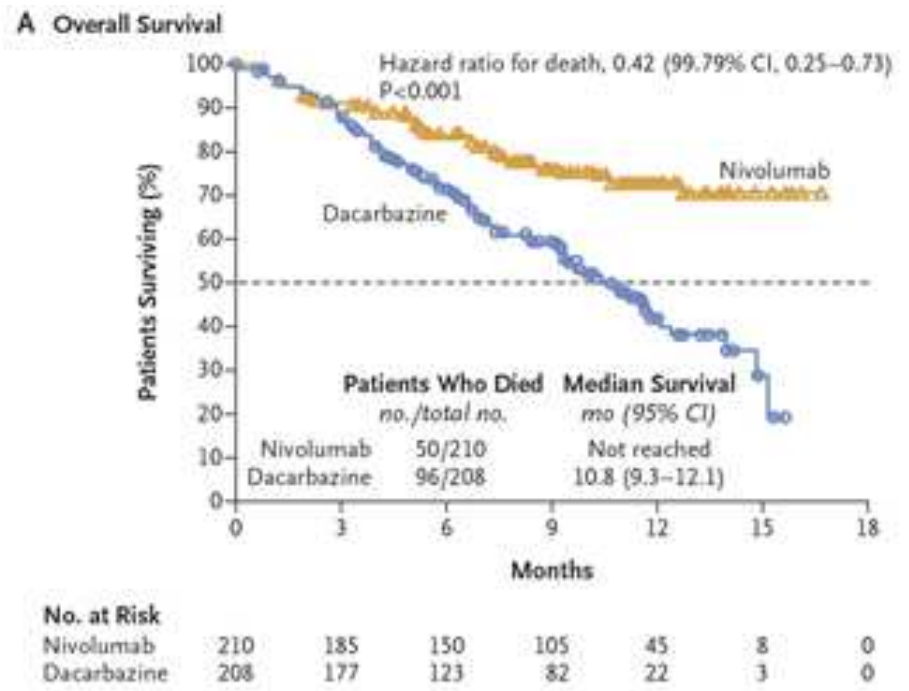
† The best overall response was assessed by the investigator with the use of the Response Evaluation Criteria in Solid Tumors, version 1.1.[19]

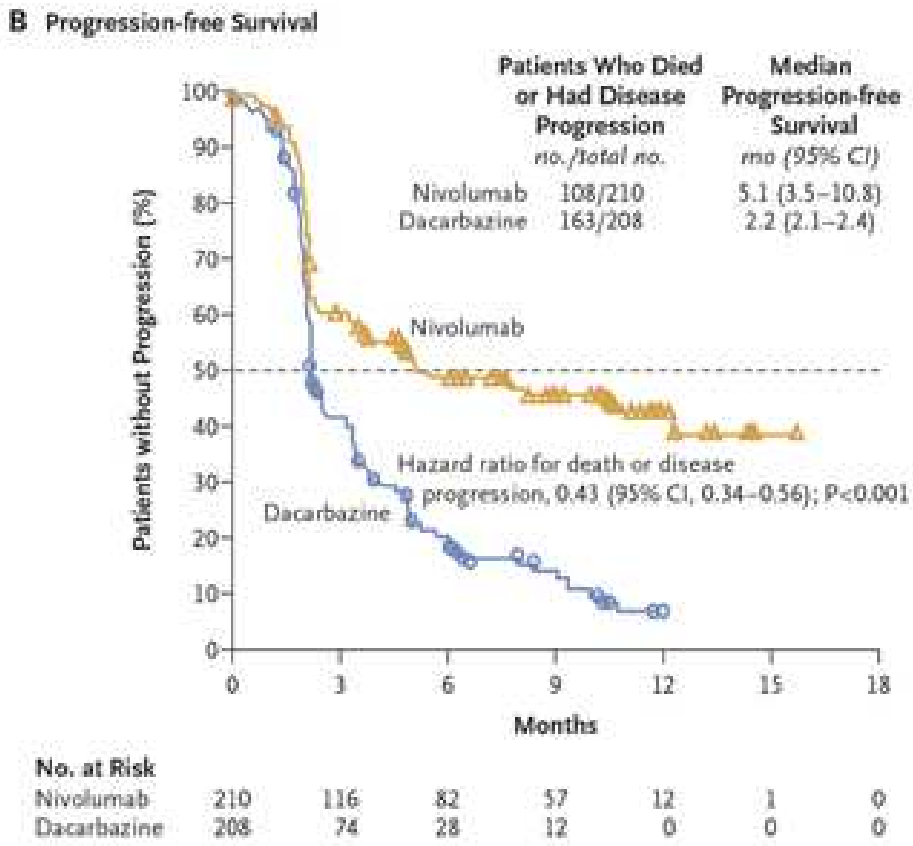
‡ Data include patients with a complete response and those with a partial response. The calculation of the confidence interval was based on the Clopper–Pearson method. The estimate of the difference (the rate in the nivolumab group minus the rate in the dacarbazine group) was based on the Cochran–Mantel–Haenszel method of weighting, with adjustment for PD-L1 status and metastasis stage as entered into the interactive voice-response system. The odds ratio and two-sided P value for an objective response with nivolumab as compared with dacarbazine were calculated with the use of a Cochran–Mantel–Haenszel test stratified according to PD-L1 status and metastasis stage.

§ The median was calculated with the use of the Kaplan–Meier method. Data were censored for the range values because the observations are ongoing. The cutoff date for clinical data was August 5, 2014, with a range of follow-up from 5.2 to 16.7 months.

Robert C et al. *N Engl J Med* Jan 2015;372:320-330.

Anti-PD1 Associated with Higher Response Rates Compared to Dacarbazine in Patients with Previously Untreated Melanoma without BRAF Mutation



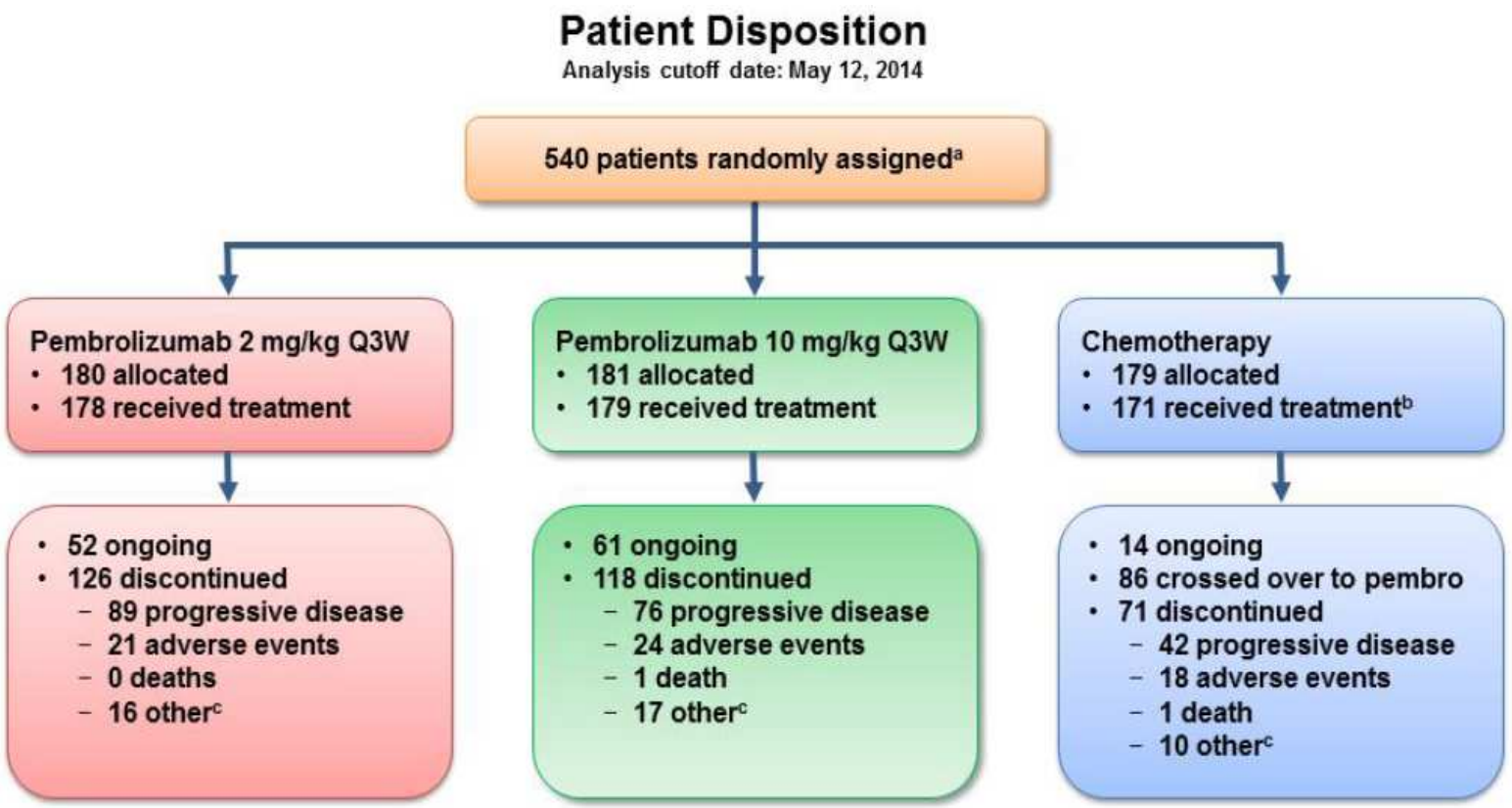


Panel A shows the Kaplan–Meier curves for overall survival. The median follow-up for overall survival was 8.9 months in the nivolumab group and 6.8 months in the dacarbazine group.

Panel B shows the Kaplan–Meier curves for progression-free survival.

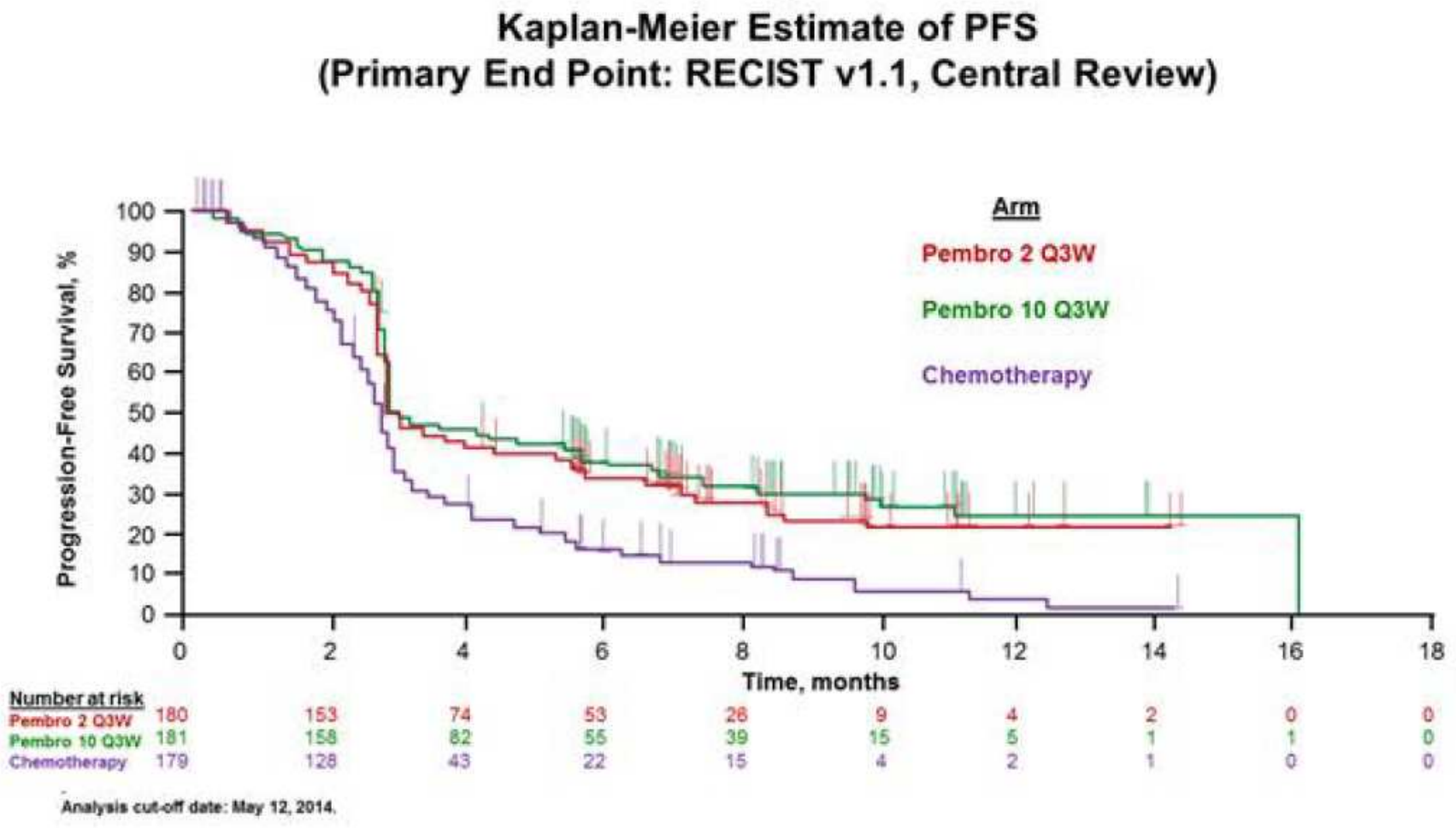
Robert C et al. *N Engl J Med* Jan 2015;372:320-330.

Randomized Study of anti-PD1 in Patients Who Have Progressed After anti-CTLA-4

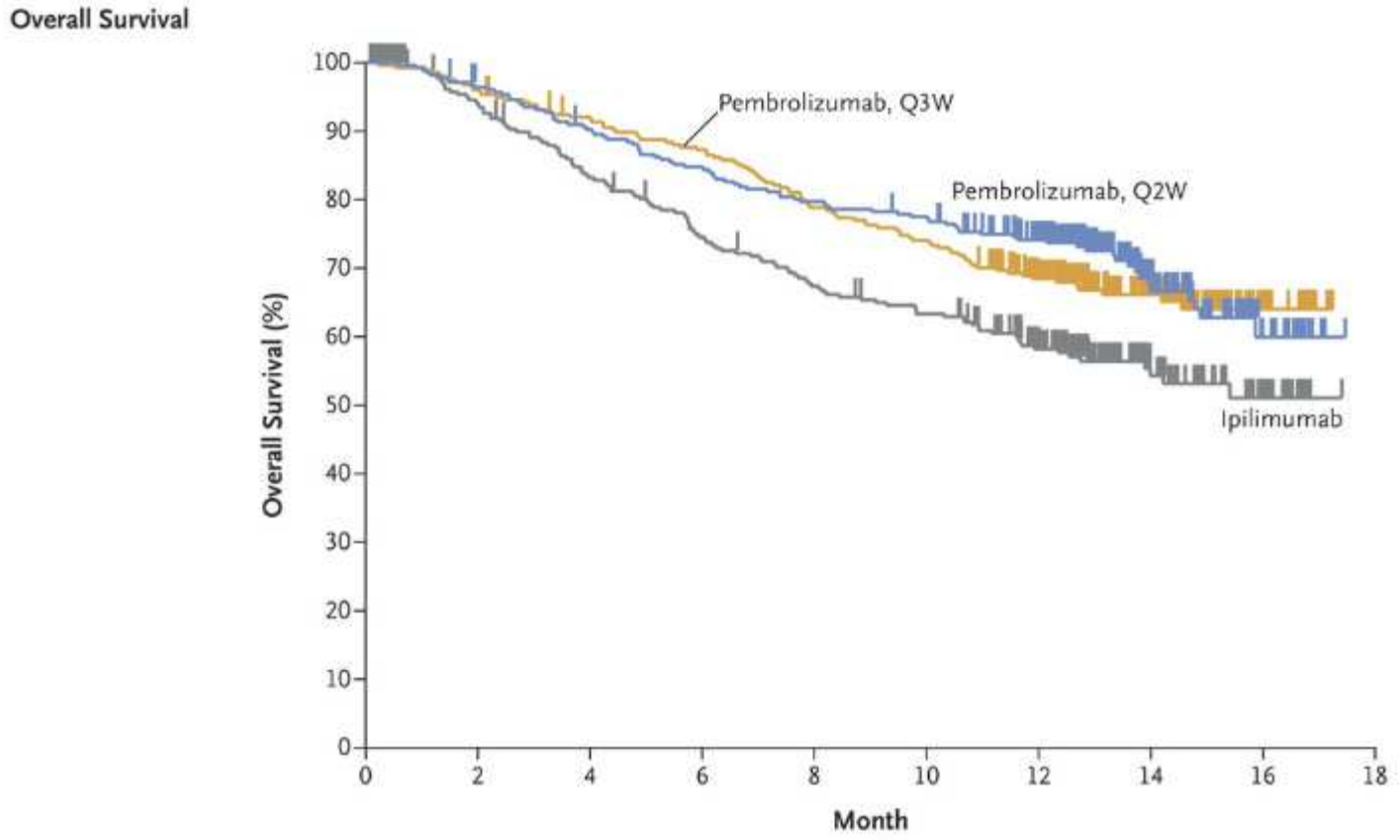


[a]Enrollment period: November 2012 to November 2013; Median follow-up duration: 10 months
[b]Dacarbazine, n = 45; temozolomide, n = 43; Paclitaxel + carboplatin, n = 42; paclitaxel, n = 28; carboplatin, n = 13.
[c]Includes physician decision, withdrawal by patient, and noncompliance with study drug.

Randomized Study of anti-PD-1 in Patients Who Have Progressed After anti-CTLA-4



Kaplan-Meier Estimates of Overall Survival Patients Treated with Pembrolizumab Every 2 or 3 Weeks vs Ipilimumab



No. at Risk										
Pembrolizumab (10mg/kg), Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab (10mg/kg), Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab (3 mg/kg)	278	242	212	188	169	157	117	51	17	0

Robert C et al. *N Engl J Med* 2015 Apr 19. [Epub ahead of print]

Comparison of Adverse Events in Patients Treated with Pembrolizumab Every 2 and 3 Weeks vs Ipilimumab

Table 2. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Every 2 Wk (N=278)		Pembrolizumab Every 3 Wk (N=277)		Ipilimumab (N=256)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)					
Related to treatment*						
Any	221 (79.5)	37 (13.3)	202 (72.9)	28 (10.1)	187 (73.0)	51 (19.9)
Occurring in ≥10% of patients in any study group						
Fatigue	58 (20.9)	0	53 (19.1)	1 (0.4)	39 (15.2)	3 (1.2)
Diarrhea	47 (16.9)	7 (2.5)	40 (14.4)	3 (1.1)	58 (22.7)	8 (3.1)
Rash	41 (14.7)	0	37 (13.4)	0	37 (14.5)	2 (0.8)
Pruritus	40 (14.4)	0	39 (14.1)	0	65 (25.4)	1 (0.4)
Asthenia	32 (11.5)	1 (0.4)	31 (11.2)	0	16 (6.3)	2 (0.8)
Nausea	28 (10.1)	0	31 (11.2)	1 (0.4)	22 (8.6)	1 (0.4)
Arthralgia	26 (9.4)	0	32 (11.6)	1 (0.4)	13 (5.1)	2 (0.8)
Vitiligo	25 (9.0)	0	31 (11.2)	0	4 (1.6)	0
Adverse event of special interest†						
Hypothyroidism	28 (10.1)	1 (0.4)	24 (8.7)	0	5 (2.0)	0
Hyperthyroidism	18 (6.5)	0	9 (3.2)	0	6 (2.3)	1 (0.4)
Colitis	5 (1.8)	4 (1.4)	10 (3.6)	7 (2.5)	21 (8.2)	18 (7.0)
Hepatitis	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)	3 (1.2)	1 (0.4)
Hypophysitis	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)	6 (2.3)	4 (1.6)
Pneumonitis	1 (0.4)	0	5 (1.8)	1 (0.4)	1 (0.4)	1 (0.4)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0	0
Uveitis	1 (0.4)	0	3 (1.1)	0	0	0
Myositis	0	0	2 (0.7)	0	1 (0.4)	0
Nephritis	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)

* The relationship between an adverse event and a study drug was attributed by the investigator. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks, except for hypothyroidism, hyperthyroidism, and colitis, which are reported as adverse events of special interest.

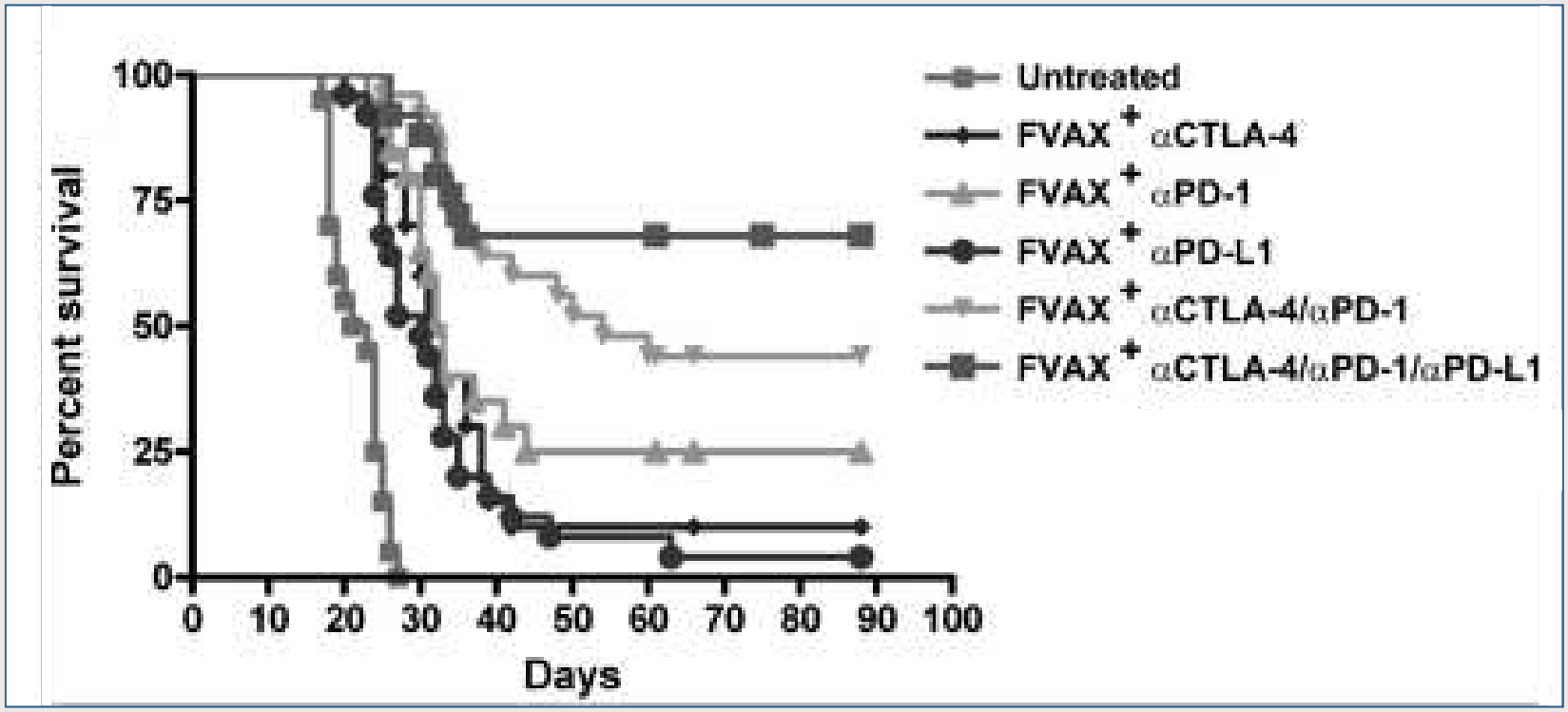
† The listed adverse events of special interest include related terms and are provided regardless of attribution to a study drug. Events are listed in order of descending frequency in the group receiving pembrolizumab every 2 weeks.

Robert C et al. *N Engl J Med* 2015 Apr 19. [Epub ahead of print]

Moving Beyond Single Agent Checkpoint Inhibition

- **Combination Immunotherapy**
  - **Antibody plus Antibody**
  - **Antibody plus T-cells**
- **Targeted Therapy and Immunotherapy**

Survival of B-16-bearing Mice Vaccinated with Fvax + Antibody

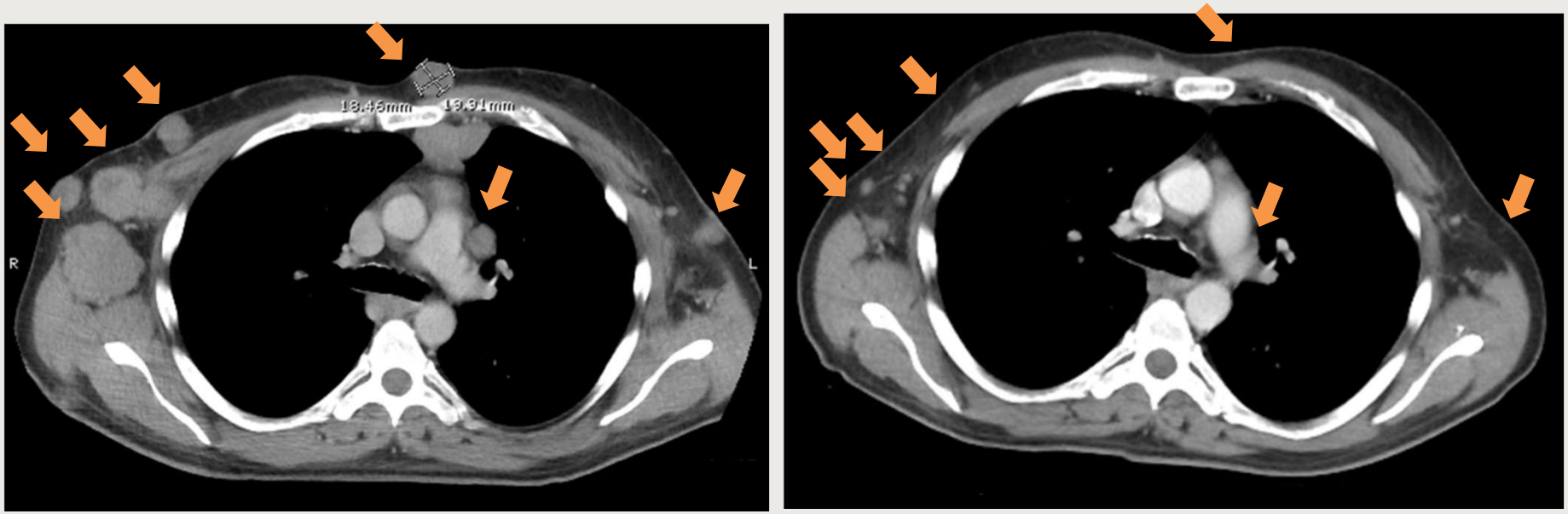


Curran … Allison. *PNAS* 2010

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

Pretreatment

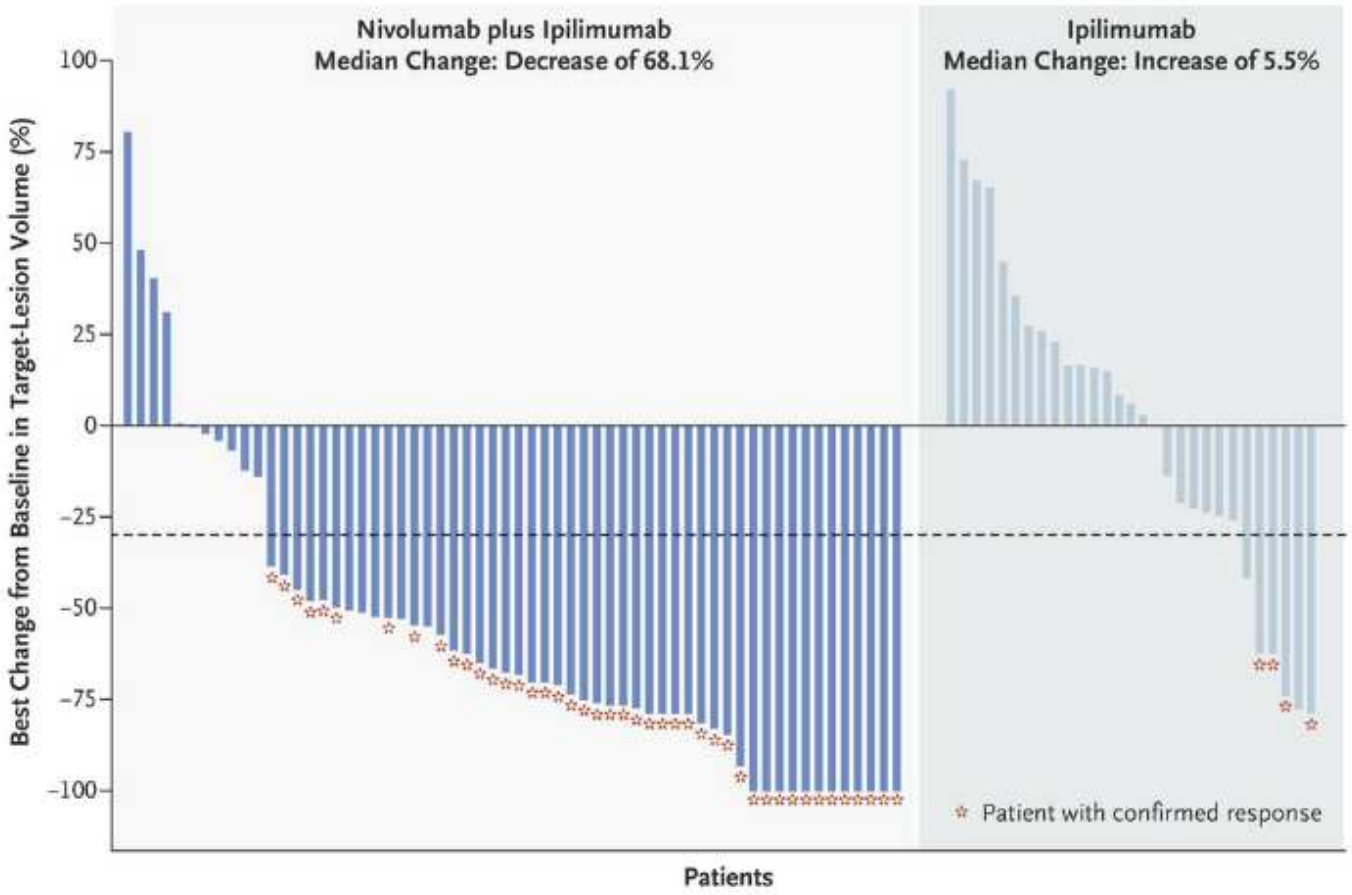
12 weeks



- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of Weeks since treatment initiation disease as shown

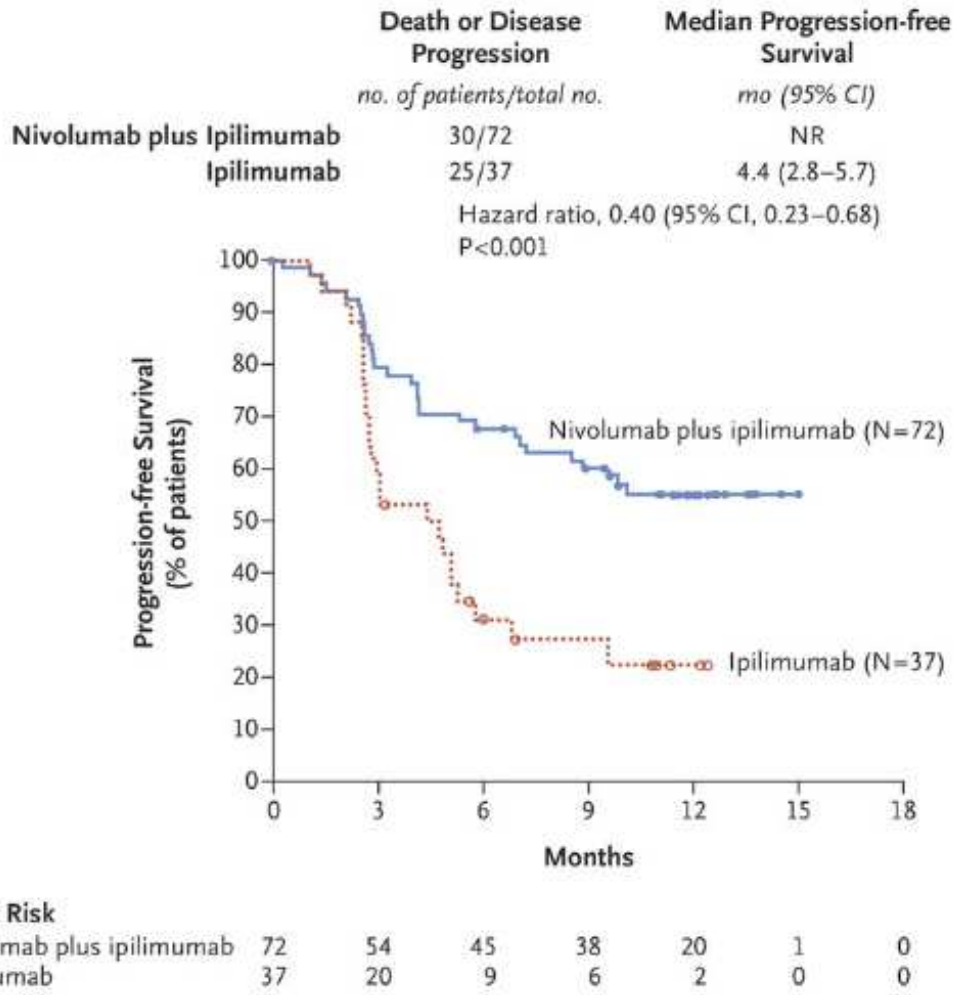
Wolchok, *NEJM*, 2013

anti-PD1 plus Ipilimumab vs Ipilimumab Alone in Previously Untreated Melanoma – Change in Tumor Burden per RECIST Guidelinesv



Postow MA et al. *NEJM* Apr 2015;372:320-30, [Epub ahead of print]

Progression-free Survival for Melanoma Patients with BRAF Wild-type Tumors Treated with anti-PD1 plus Ipilimumab vs Ipilimumab Alone



Postow MA et al. *NEJM* Apr 2015;372:320-30, [Epub ahead of print]

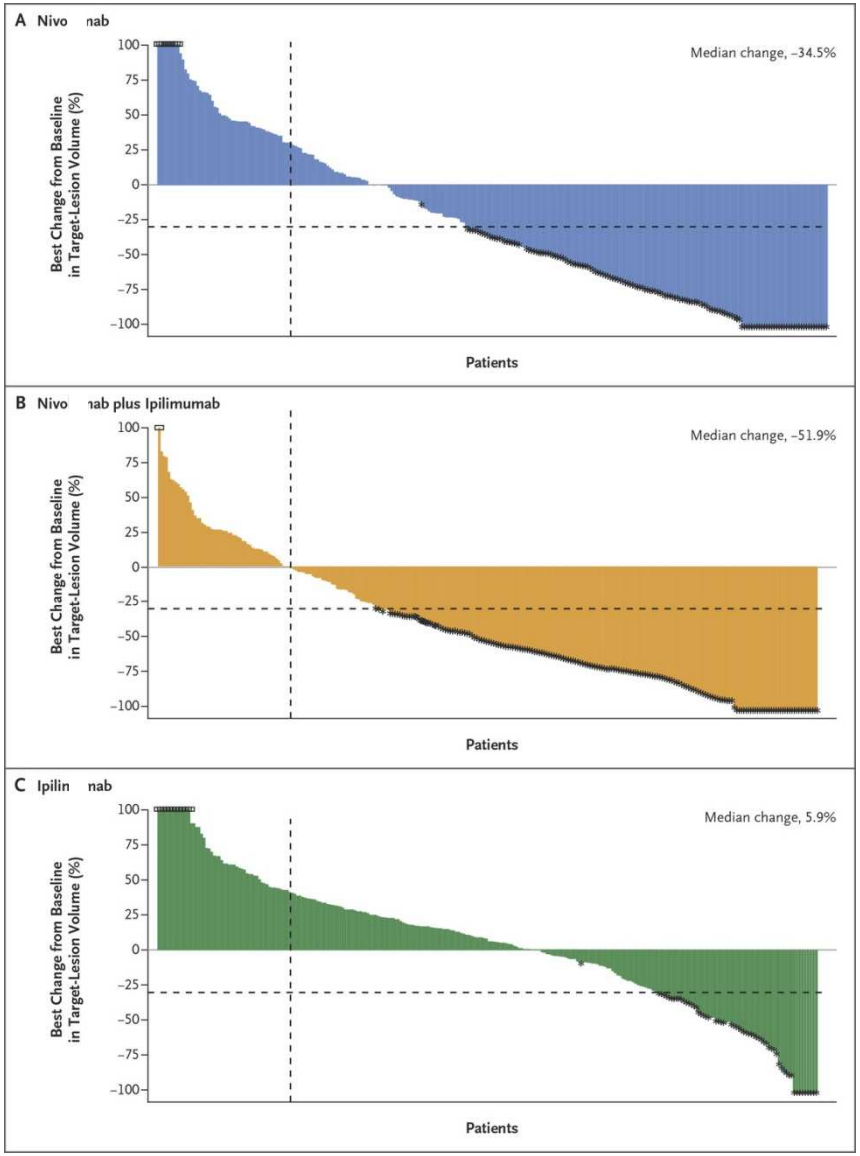
Treatment Related Adverse Events for Melanoma Patients Treated with anti-PD1 plus Ipilimumab vs Ipilimumab Alone

Table 3. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=94)		Ipilimumab (N=46)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any treatment-related adverse event	86 (91)	51 (54)	43 (93)	11 (24)
Most common treatment-related adverse events†				
Diarrhea‡	42 (45)	10 (11)	17 (37)	5 (11)
Rash	39 (41)	5 (5)	12 (26)	0
Fatigue	37 (39)	5 (5)	20 (43)	0
Pruritus	33 (35)	1 (1)	13 (28)	0
Colitis‡	22 (23)	16 (17)	6 (13)	3 (7)
Nausea	21 (22)	1 (1)	11 (24)	1 (2)
Elevated alanine aminotransferase	21 (22)	10 (11)	2 (4)	0
Elevated aspartate aminotransferase	20 (21)	7 (7)	2 (4)	0
Pyrexia	19 (20)	3 (3)	7 (15)	0
Maculopapular rash	15 (16)	3 (3)	8 (17)	0
Hypothyroidism	15 (16)	0	7 (15)	0
Decreased appetite	14 (15)	0	4 (9)	0
Headache	13 (14)	2 (2)	5 (11)	0
Vomiting	13 (14)	1 (1)	5 (11)	0
Increased lipase	12 (13)	8 (9)	2 (4)	1 (2)
Hypophysitis	11 (12)	2 (2)	3 (7)	2 (4)
Pneumonitis§	10 (11)	2 (2)	2 (4)	1 (2)
Arthralgia	10 (11)	0		
Chills	10 (11)	0		
Vitiligo	10 (11)			
Abdominal pain	10 (11)			

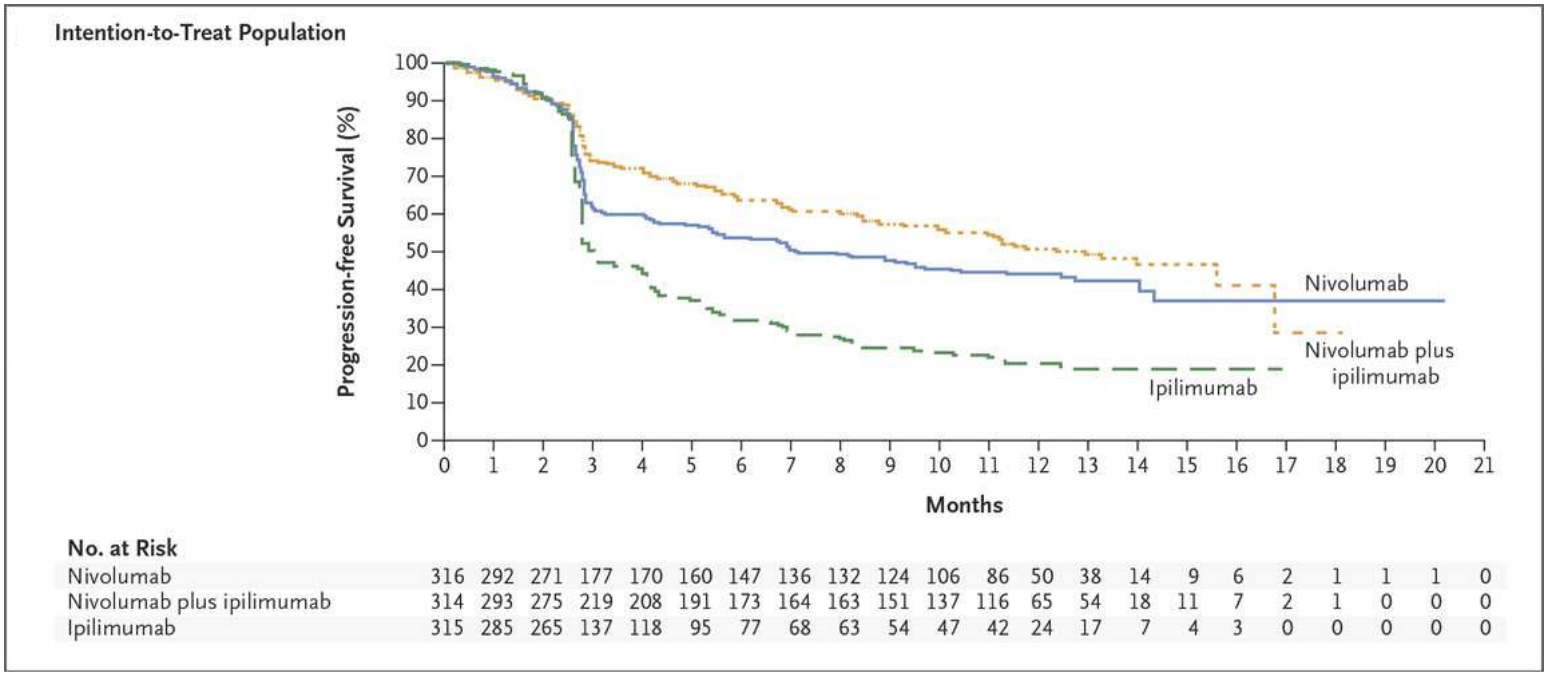
Postow MA et al. *NEJM* Apr 2015;372:320-30, [Epub ahead of print]

Change in Tumor Burden after Treatment with Combined Nivolumab and Ipilimumab or Monotherapy for Patients with Untreated Melanoma



Larkin J…Hodi FS, Wolchok JD *NEJM* May 31 [Epub ahead of print] DOI: 10.1056/NEJMoa1504030

Progression Free Survival for Patients with Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

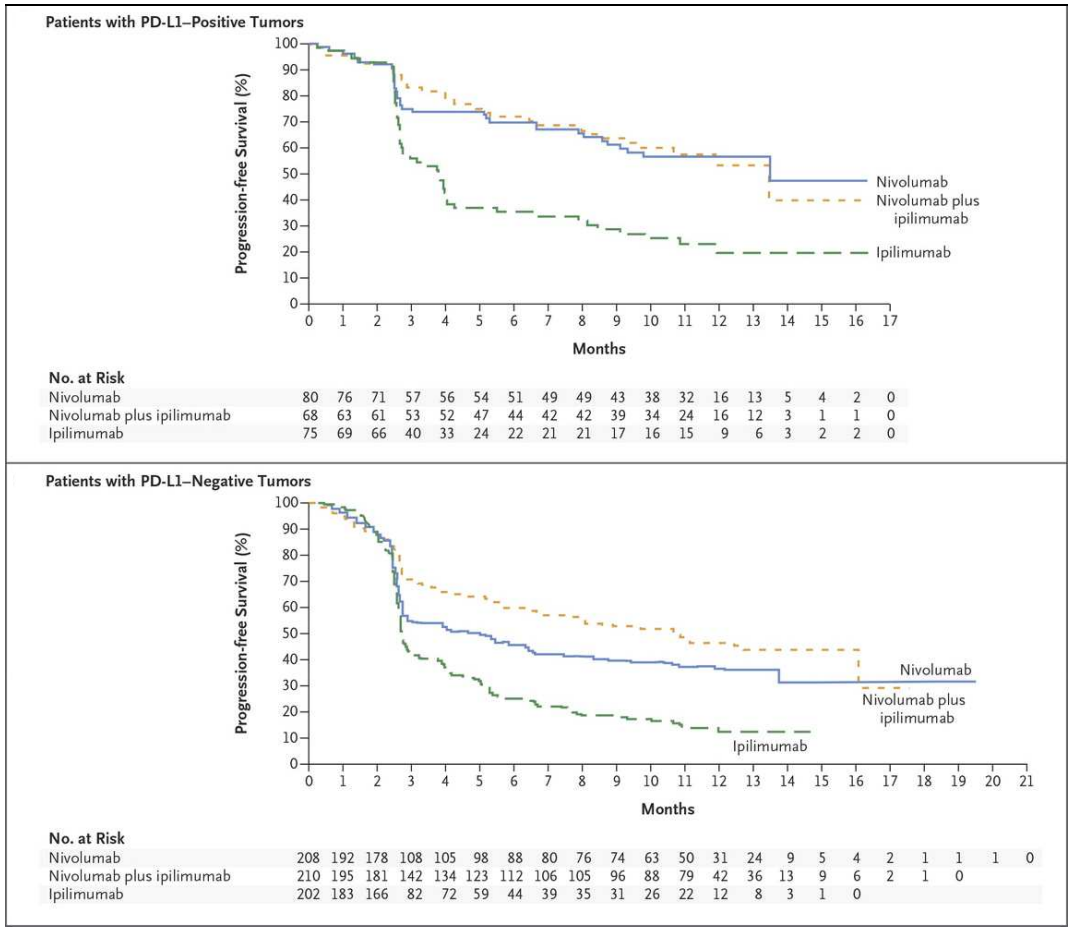


No. at Risk

Nivolumab	316	292	271	177	170	160	147	136	132	124	106	86	50	38	14	9	6	2	1	1	1	0
Nivolumab plus ipilimumab	314	293	275	219	208	191	173	164	163	151	137	116	65	54	18	11	7	2	1	0	0	0
Ipilimumab	315	285	265	137	118	95	77	68	63	54	47	42	24	17	7	4	3	0	0	0	0	0

Larkin J…Hodi FS, Wolchok JD *NEJM* May 31 [Epub ahead of print] DOI: 10.1056/NEJMoa1504030

The Influence of PDL1 Positivity on Progression Free Survival for Patients with Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

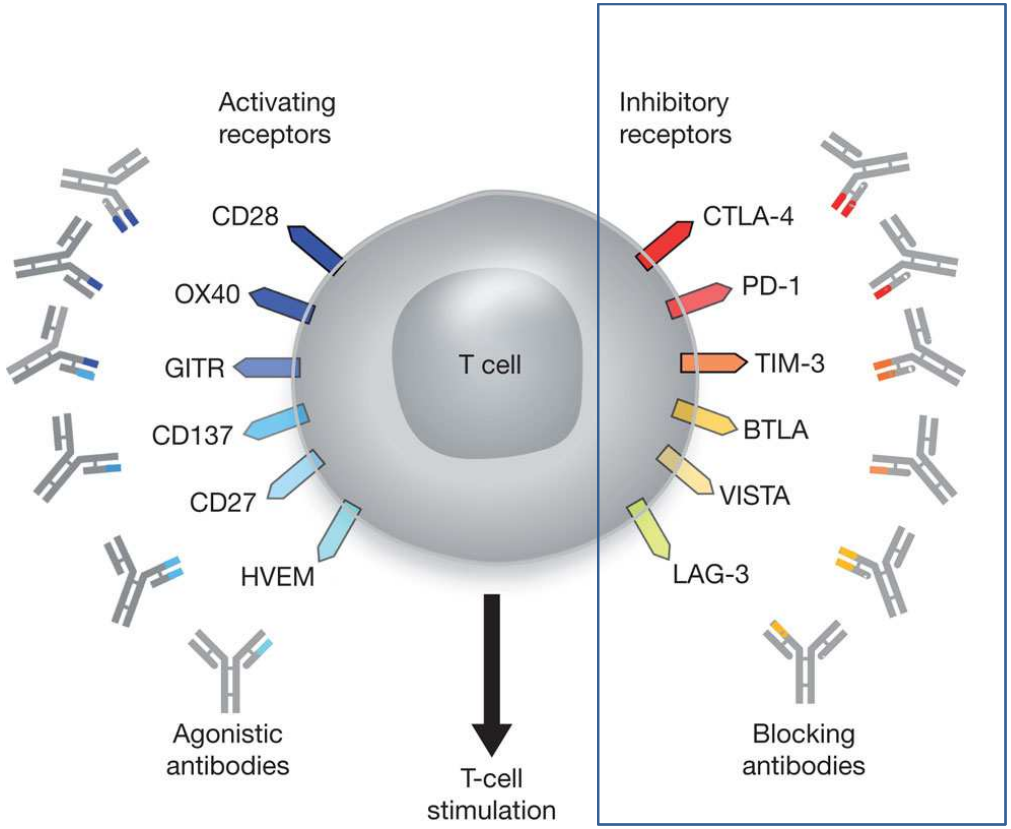


Larkin J…Hodi FS, Wolchok JD *NEJM* May 31 [Epub ahead of print] DOI: 10.1056/NEJMoa1504030

Moving Forward

Future Approaches

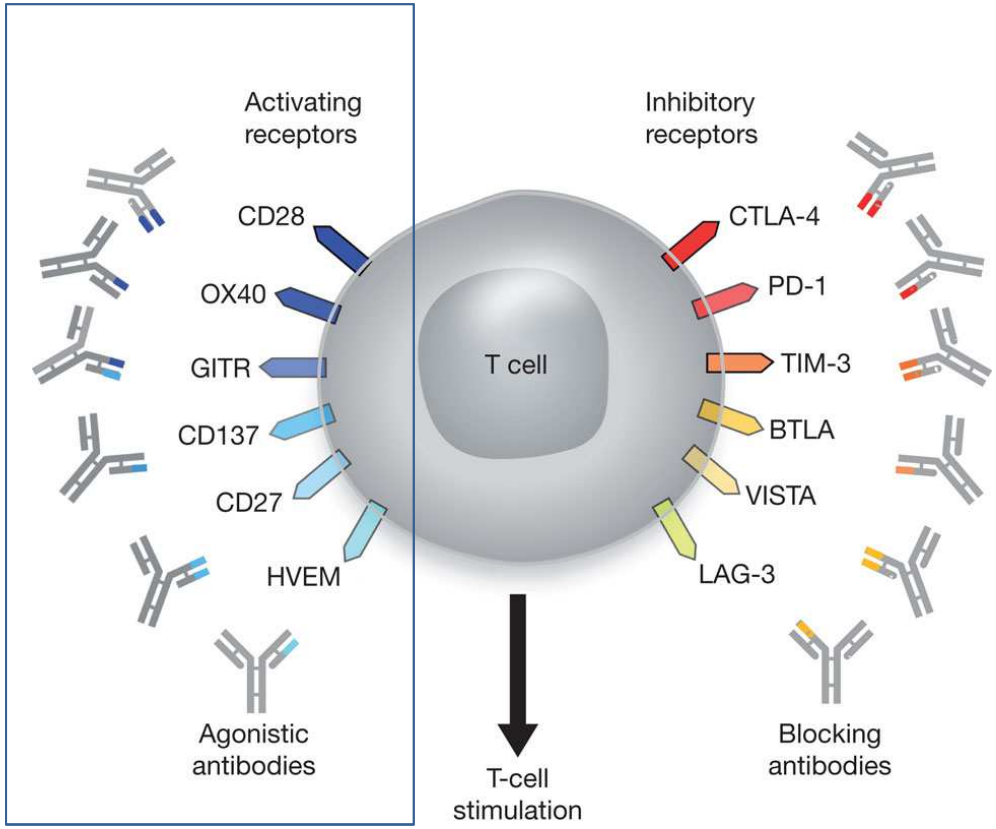
T-cell Targets for Immunoregulatory Antibody Therapy



I Mellman et al. *Nature* 480, 480-489 (2011) doi:10.1038/nature10673

nature

T-cell Targets for Immunoregulatory Antibody Therapy



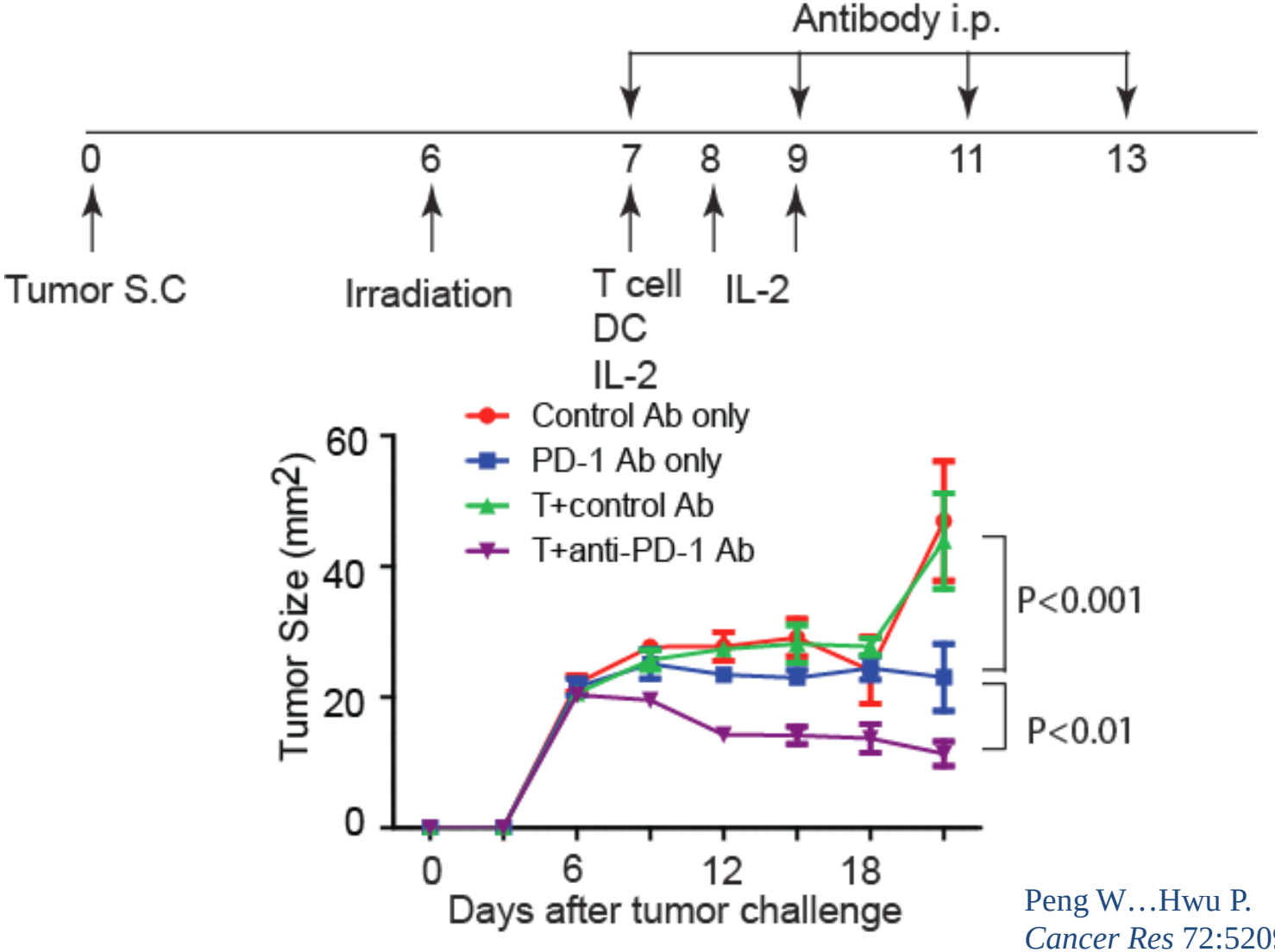
I Mellman et al. *Nature* 480, 480-489 (2011) doi:10.1038/nature10673

nature

Question?

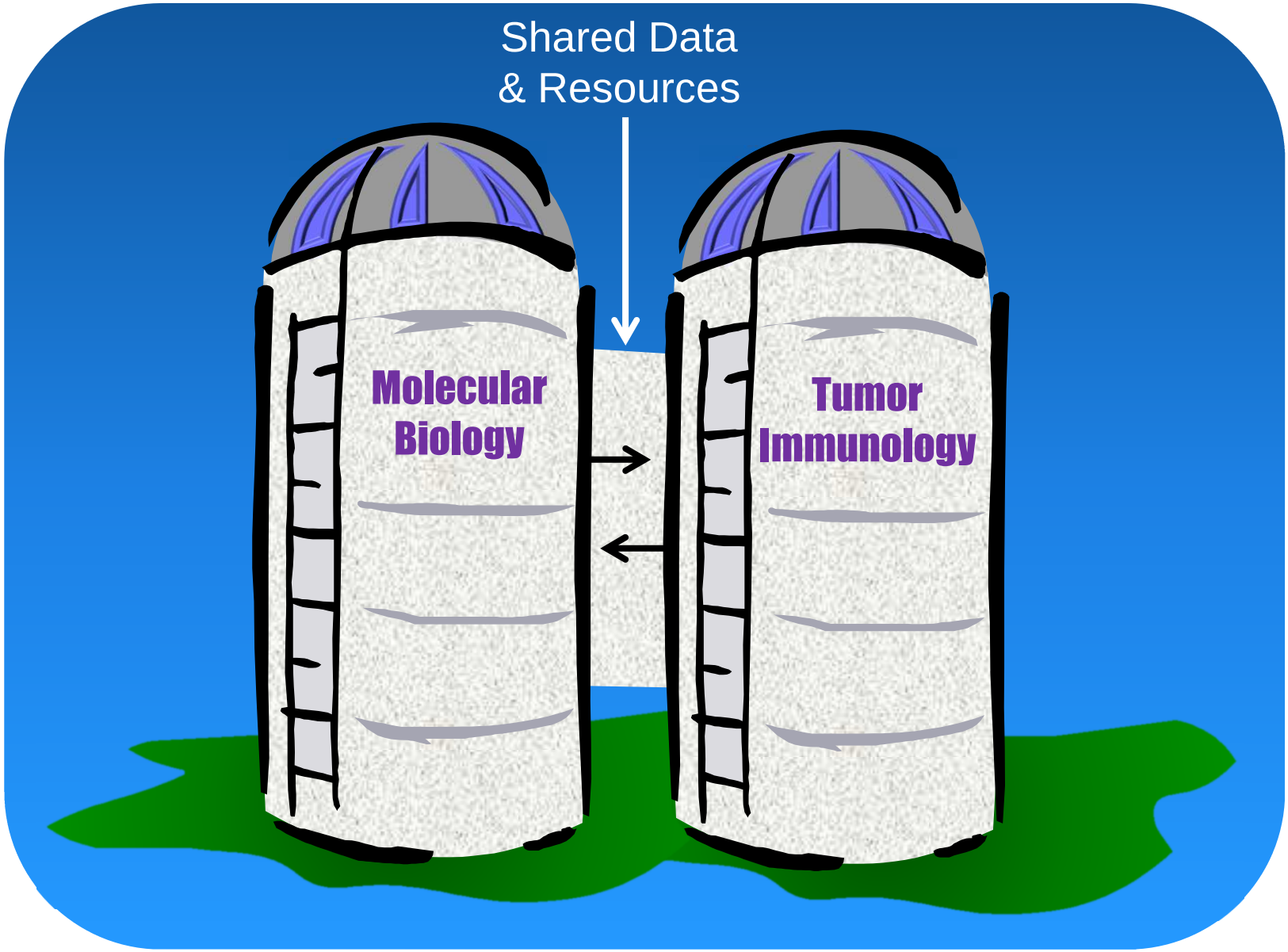
Does PD-1 inhibition enhance T-cell therapy?

Delayed Tumor Progression in Tumor-bearing Mice Receiving anti-PD-1 and ACT Treatment



Peng W…Hwu P.
Cancer Res 72:5209-18, 2012

Bringing Silos Together



Potential Combinations for Clinical Trials

Targeted Agents

- BRAFi
- MEKi
- CDK4i
- PI3Ki
- AKTi

Immune Agents

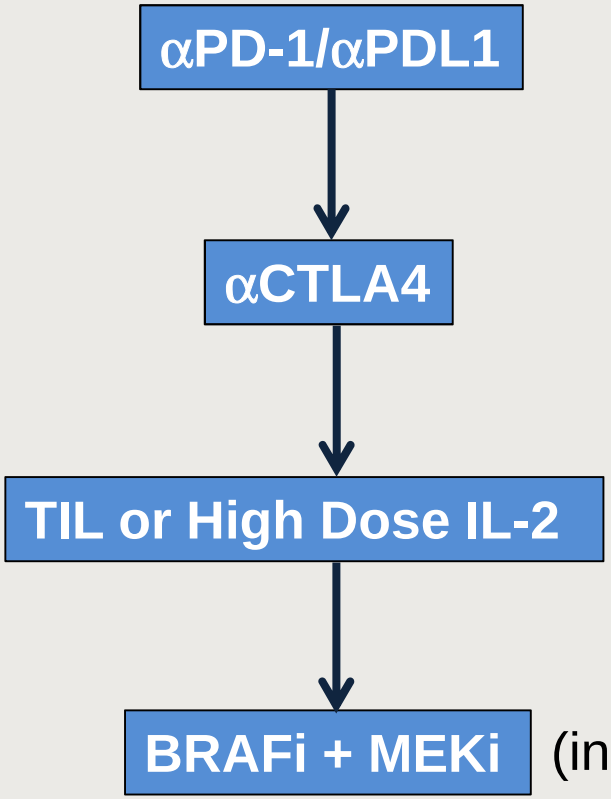
- anti-CTLA-4
- anti-PD-1
- anti-PDL1
- Anti-41BB
- Anti-KIR
- anti-CD4OL
- anti-OX4O
- Vaccines
- T-cells

Considerations when Selecting Therapies

Therapy	Response Rate	Rapidity of Response	Duration of Response	Availability	Toxicity
BRAFi	50%	Rapid	Low	High	Low
BRAFi + MEKi	75%	Rapid	Moderate	High	Low
αCTLA4	10%	Slow	High	High	Moderate
αPD-1/αPDL1	20-40%	Rapid	High	High	Low
TIL	40-50%	Slow*	High	Low	High
High Dose IL-2	10-15%	Slow	High	Moderate	High
Biochemotherapy	30-40%	Rapid	Moderate	Moderate	High
Surgery	100%	Rapid	Low	High	Variable
Chemotherapy	15%	Rapid	Low	High	Moderate

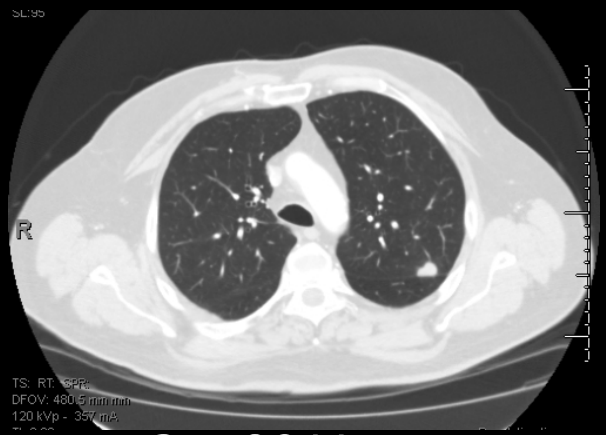
*Due to time required to generate cells

Patients with Slow to Moderate Growing Melanoma with Good Performance Status

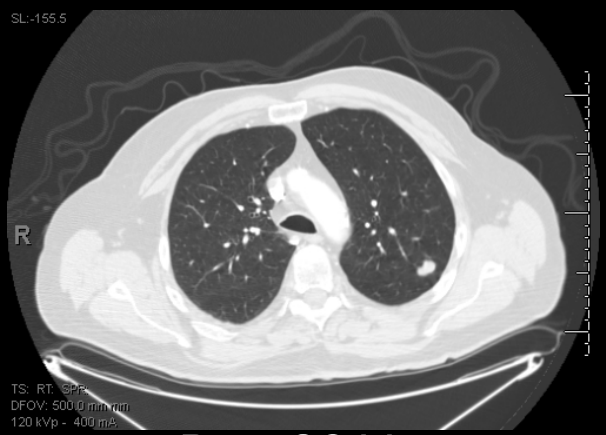


(in BRAF V600 mutants)

anti-PD1 Antibody Therapy



Oct 2011



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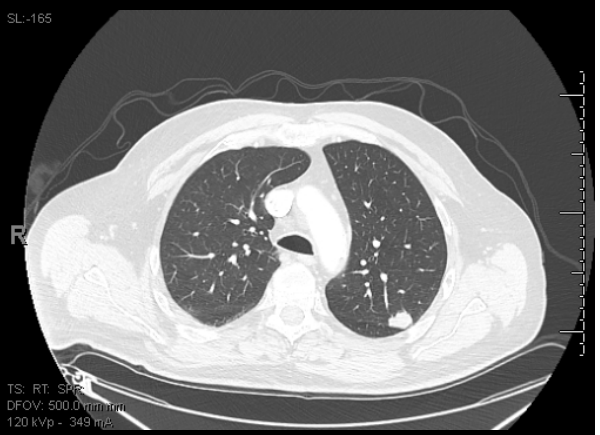
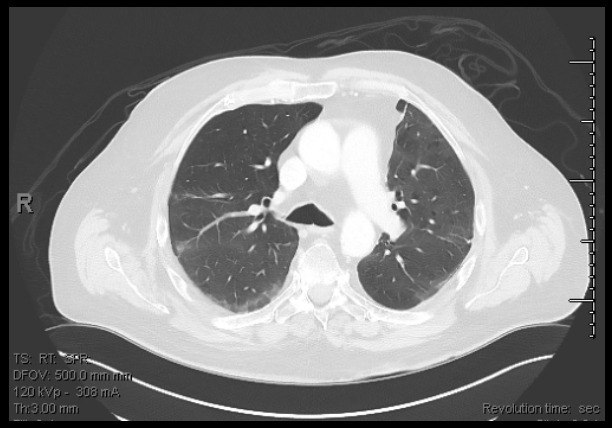


March 2012

75 year old with melanoma metastatic
to lungs (BRAF/NRAS WT).
Waited for anti-PD1 antibody trial
to open March 2012.
Now CR 18 months later.

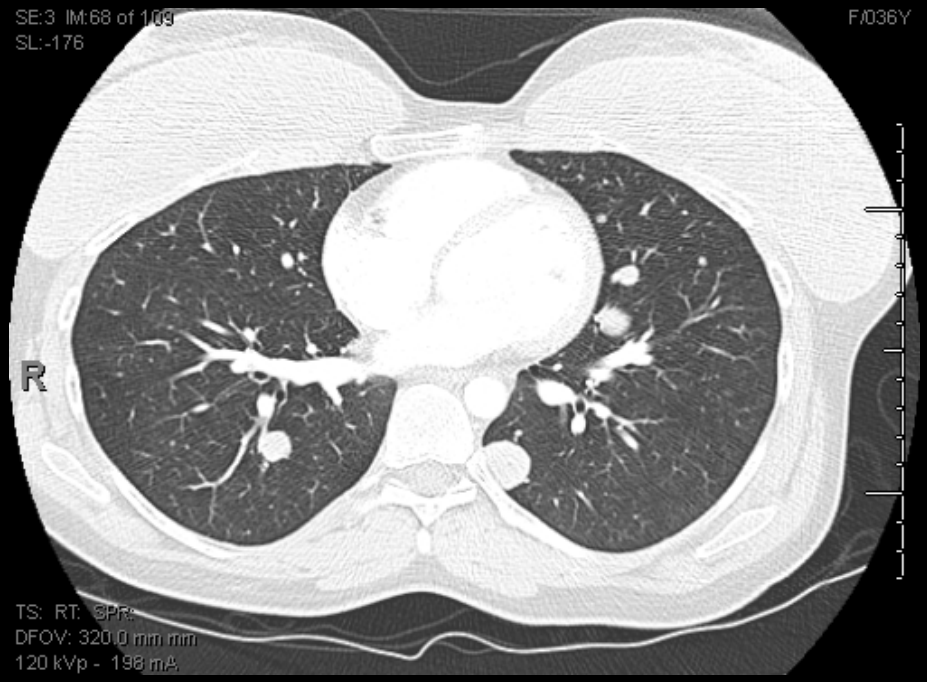


Aug 2013

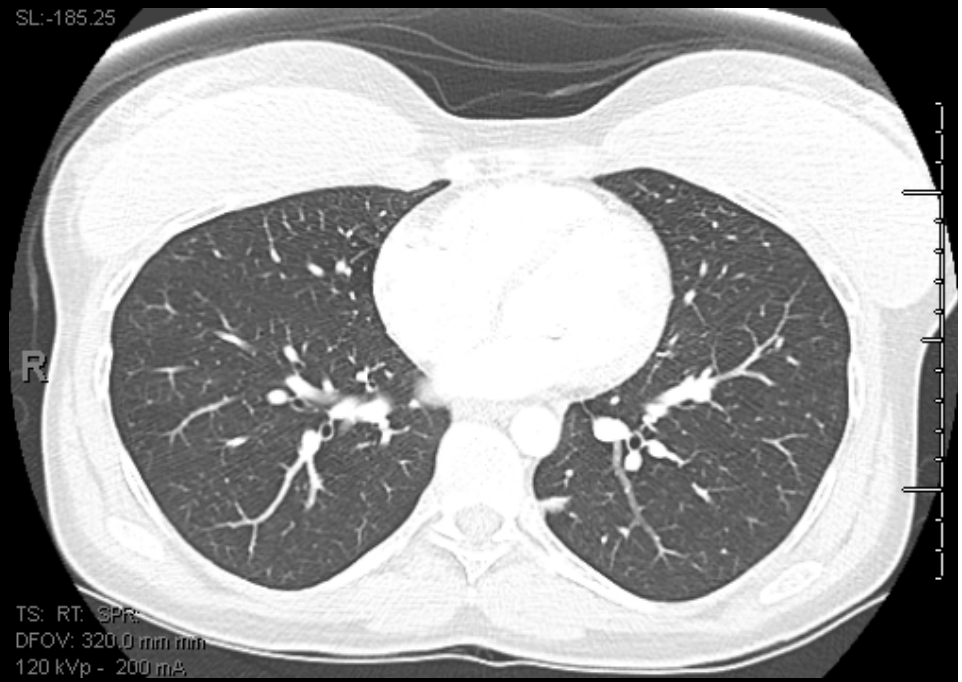
Melanoma Case Presentation

- **23 year old woman presents with a conjunctival pigmented lesion.**
- **Biopsy reveals melanoma, thickness of 0.5 mm. Resection and cryotherapy performed.**
- **8 years later, the patient presents with a breast mass; biopsy is positive for melanoma.**
- **PET-CT reveals bilateral lung metastases and multiple subcutaneous lesions.**
- **Molecular testing of primary and metastases reveals BRAF V600E mutation.**

anti-PD1 Antibody Therapy

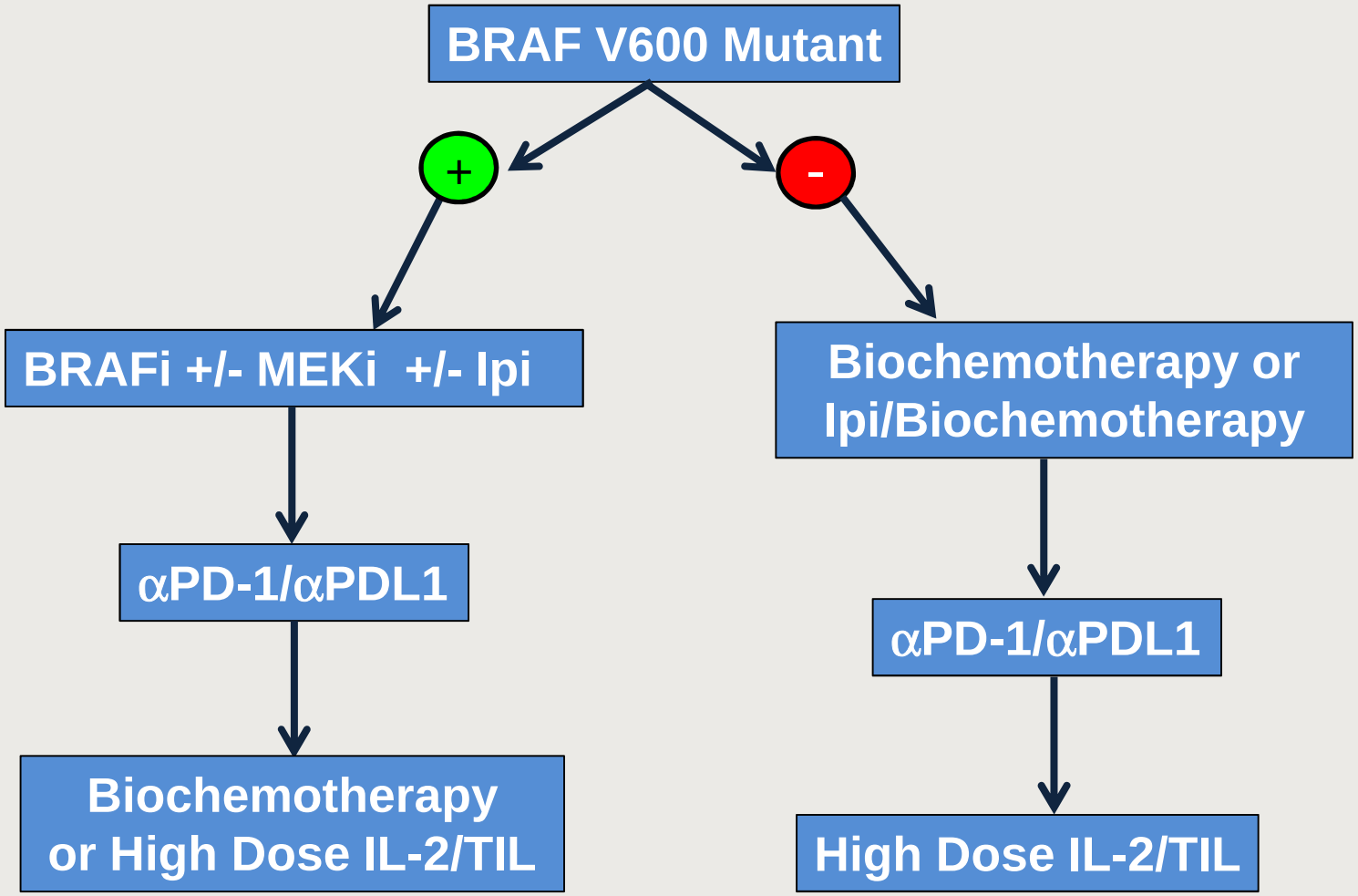


February 2013



August 2013

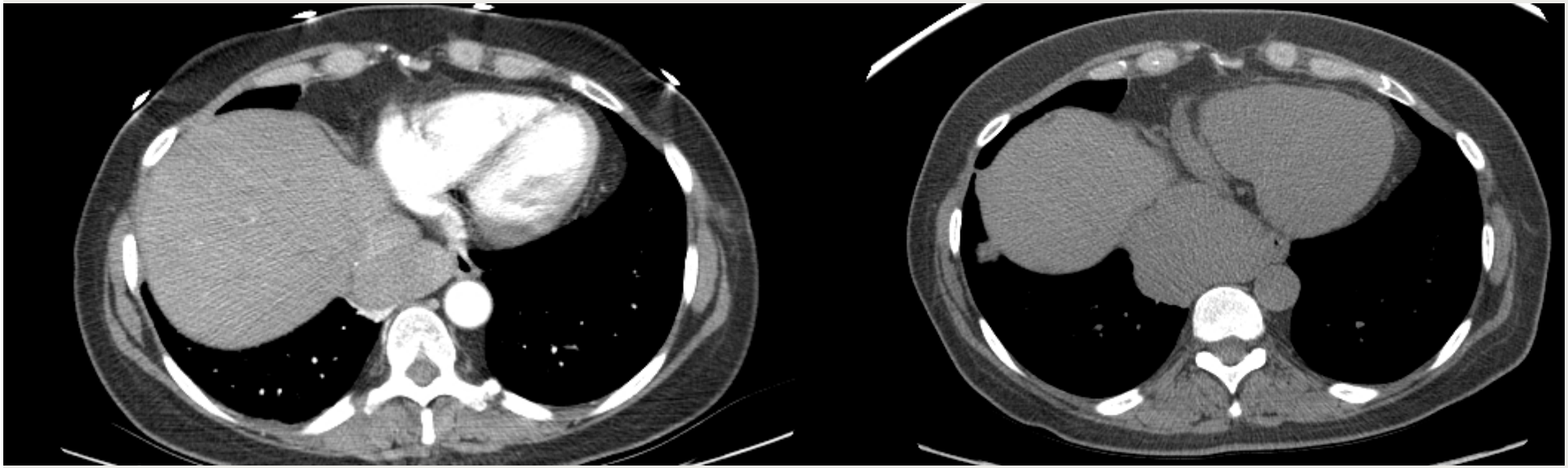
Patients with Rapidly Growing Melanoma with Good Performance Status



The Growing Importance of Surgery as Systemic Agents Improve

Before Anti-CTLA4

After Anti-CTLA4



Tumor was resected and patient is 4 years disease free (W. Hofstetter)

Considerations when Selecting Therapies

Therapy	Response Rate	Rapidity of Response	Duration of Response	Availability	Toxicity
BRAFi	50%	Rapid	Low	High	Low
BRAFi + MEKi	75%	Rapid	Moderate	High	Low
αCTLA4	10%	Slow	High	High	Moderate
αPD-1/αPDL1	20-40%	Rapid	High	High	Low
TIL	40-50%	Slow*	High	Low	High
High Dose IL-2	10-15%	Slow	High	Moderate	High
Biochemotherapy	30-40%	Rapid	Moderate	Moderate	High
Surgery	100%	Rapid	Low	High	Variable
Chemotherapy	15%	Rapid	Low	High	Moderate

*Due to time required to generate cells

Acknowledgements

Preclinical Data and Laboratory Endpoints

- Weiyi Peng
- Shruti Malu
- Rina Mbofung
- Jodi McKenzie
- Leila Williams
- Chengwen Liu
- Zhe Wang
- Donald Sakellariou-Thompson
- Krit Ritthipichai
- Jie Qing Chen
- Mike Davies
- Jen Wargo
- Zac Cooper
- Andy Futreal
- Tim Heffernan
- Cassian Yee
- Jungsun Park
- Willem Overwijk
- Scott Woodman
- Jason Roszik
- Chantale Bernatchez
  - Cara Haymaker
  - Caitlin Creasy
  - Rene Tavera
- Laszlo Radvanyi
- Luis Vence
- Gordon Mills
- Liz Grimm
- Waun Ki Hong

TIL Lab:

Marie Andre Forget

- OJ Fulbright
- Arly Wahl
- Esteban Flores
- Shawne Thorsen
- Rene Tavera
- Vanessa Jackson

Adelson Medical Research Foundation

NCI

MDACC Melanoma Moon Shot Program

Levi Garraway

Jim Allison

Clinical Research

Melanoma Medical Oncologists:

- Roda Amaria
- Wen Jen Hwu
- Adi Diab
- Isabella Glitza
- Sapna Patel

Surgeons:

- Jeff E. Lee
- Merrick Ross
- Jeff Gershenwald
- Richard Royal
- Anthony Lucci
- Janice Cormier

Pathologists:

- Victor Prieto
- Carlos Torres Cabala
- Michael Tetzlaff
- Doina Ivan

Research Nurses:

- Anna Vardeleon
- Suzanne Cain
- Vruti Patel
- Carol Vaughn

GMP Lab:

- EJ Shpall
- Enrique Alvarez

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