Anti-PD-1 and Anti-PD-L1 Therapy

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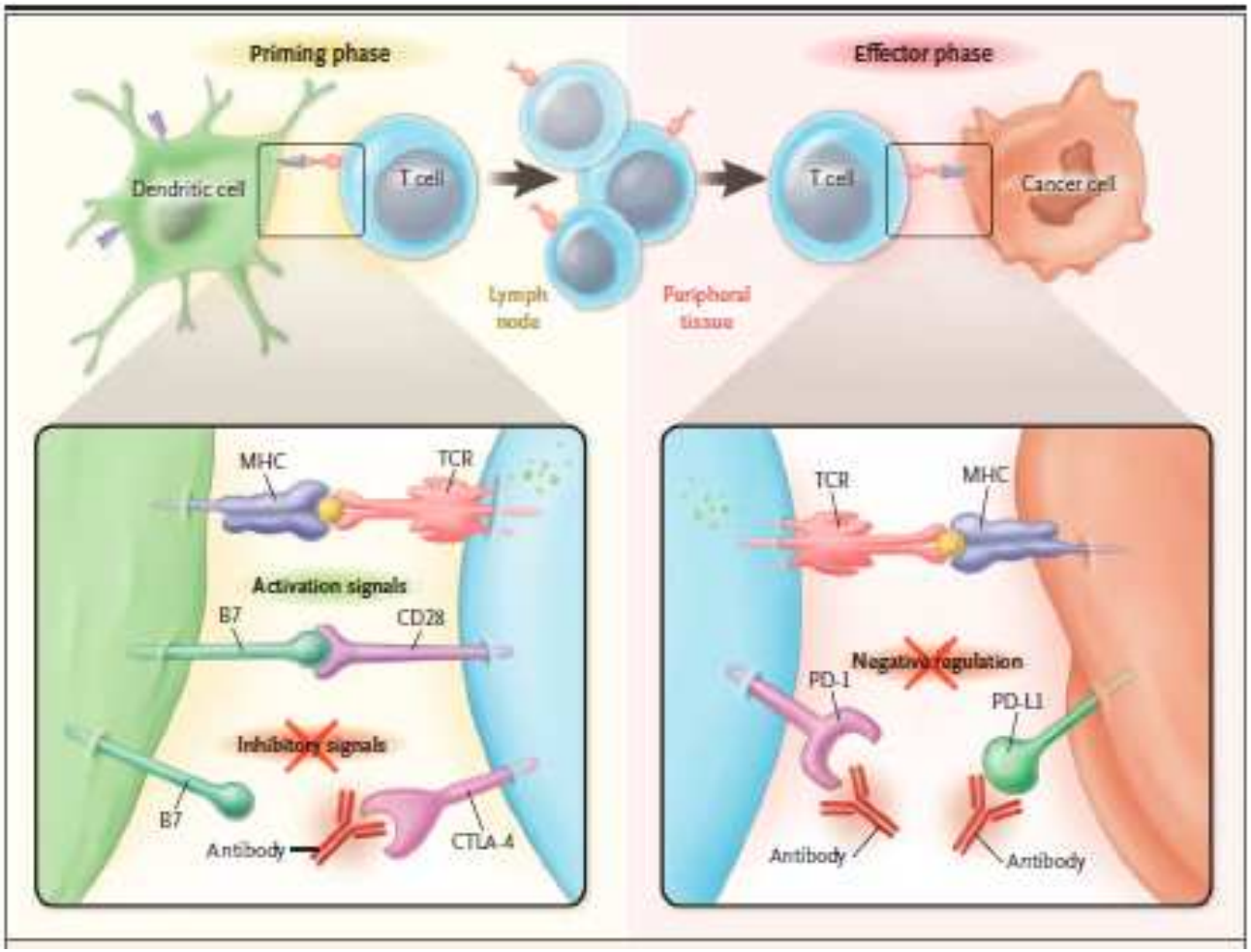
Chair, Melanoma Committee at SWOG

EDITORIAL

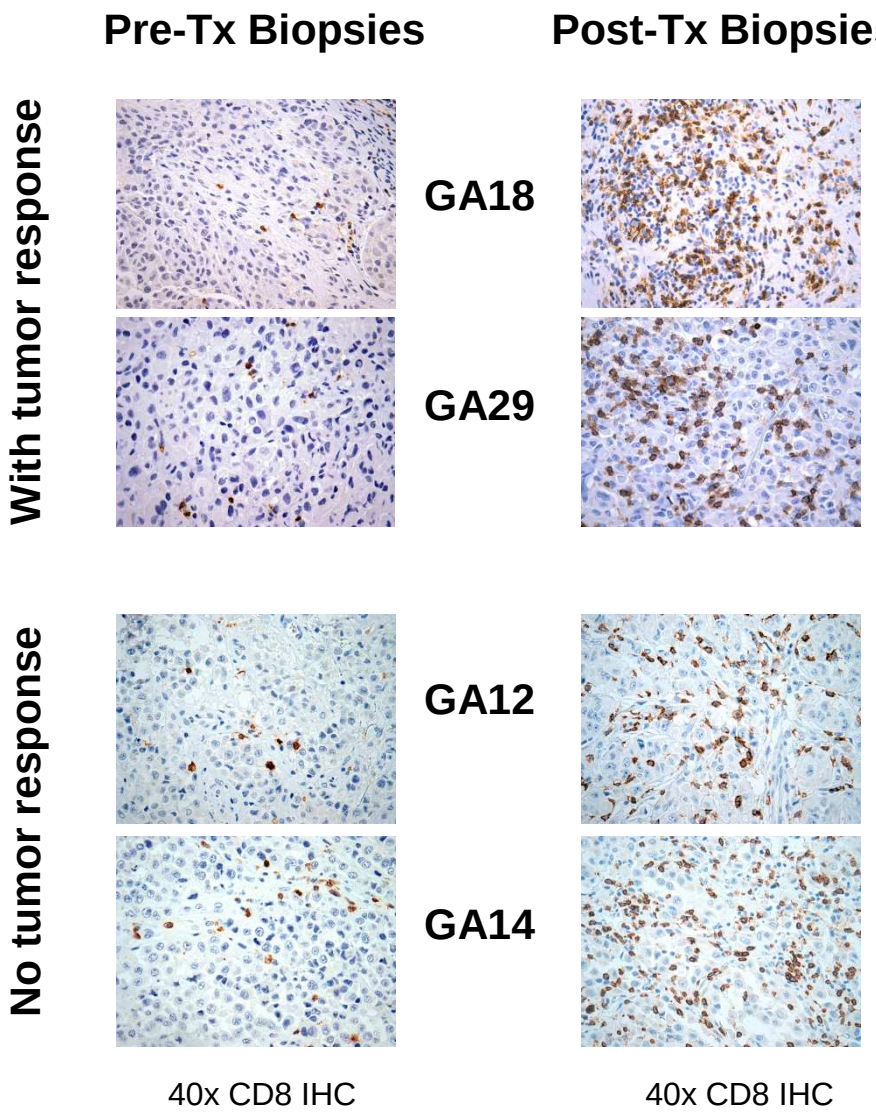
Tumor Immunotherapy Directed at PD-1

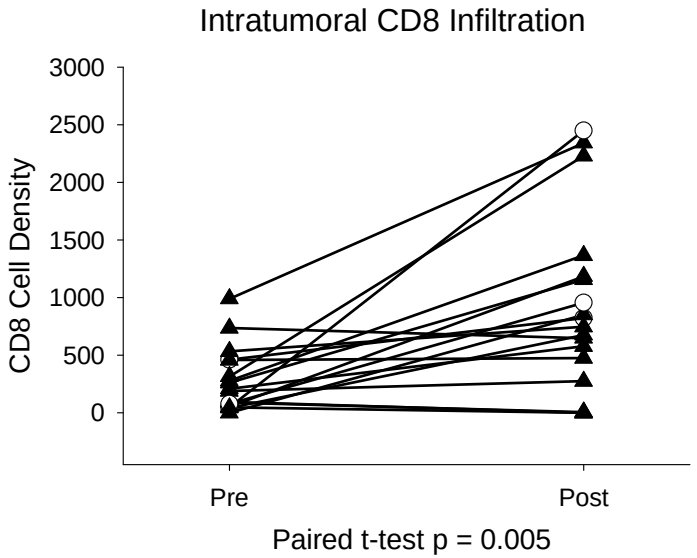
Antoni Ribas, M.D., Ph.D.



NEJM 2012; Jun 28; 366 (26): 2517-9

Increase in TIL in most patients treated with anti-CTLA4 (tremelimumab) regardless of tumor response





CTLA4 blockade brings T cells into tumors

Huang… Cochran, Ribas Clinical Cancer Research 2011

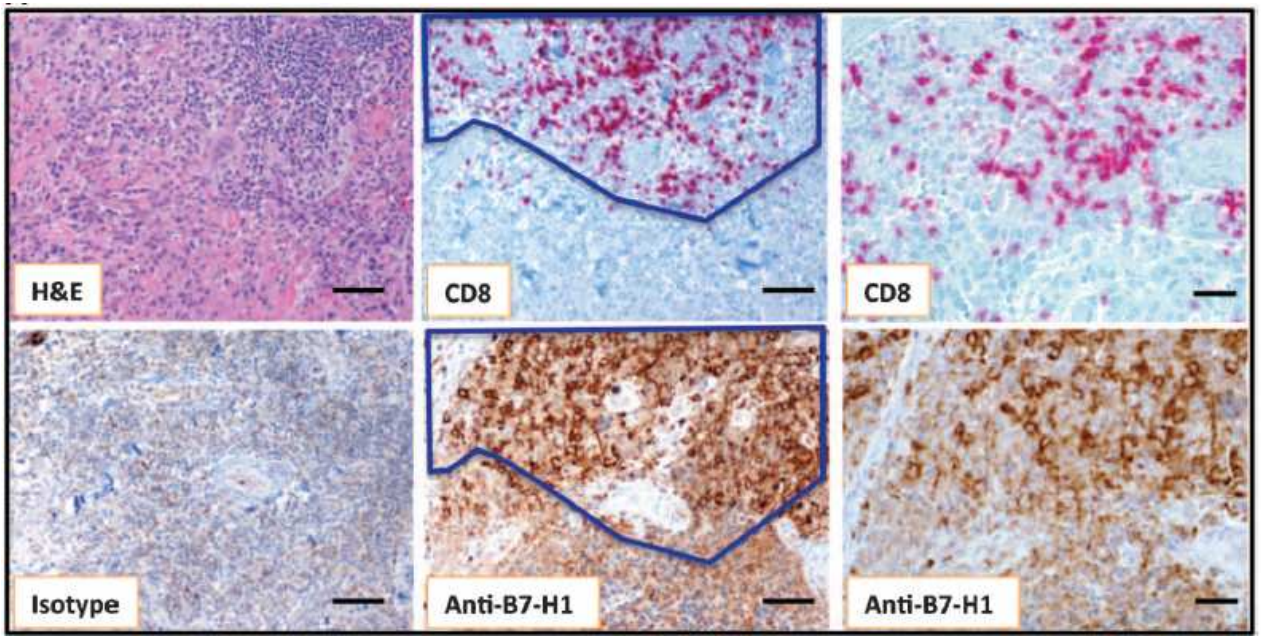
RESEARCH ARTICLE

CANCER

Colocalization of Inflammatory Response with B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape

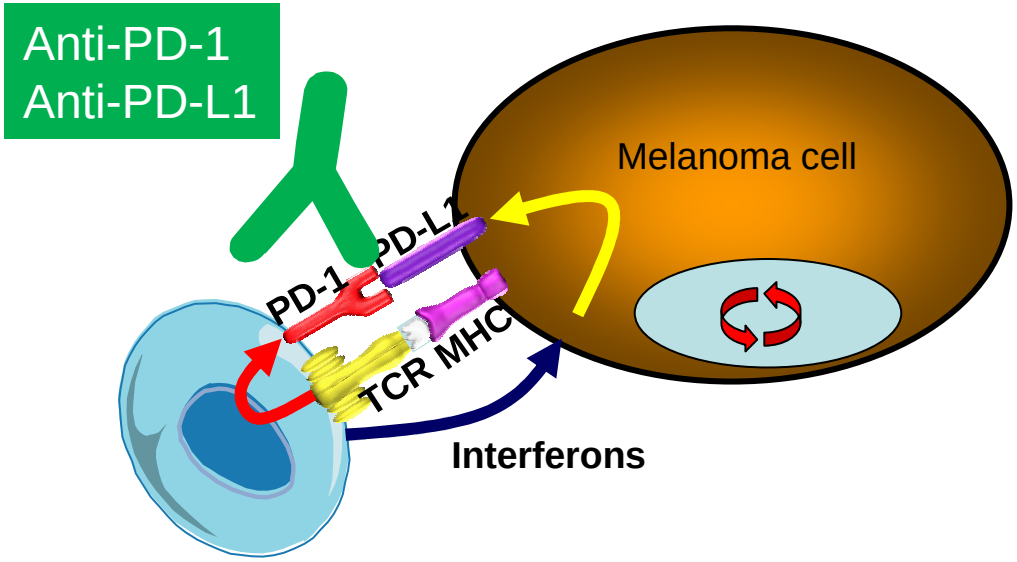
Janis M. Taube,[1,2]* Robert A. Anders,[2] Geoffrey D. Young,[3,4] Haiying Xu,[1] Rajni Sharma,[2] Tracee L. McMiller,[4] Shuming Chen,[4] Alison P. Klein,[2,5] Drew M. Pardoll,[5] Suzanne L. Topalian,[4]* Lieping Chen[1,5,6]*

www.ScienceTranslationalMedicine.org 28 March 2012 Vol 4 Issue 127 127ra37



Melanoma responds to T cell infiltration by expressing PD-L1 (adaptive immune resistance)

Adaptive resistance to immunotherapy



PD-1/PD-L1 inhibiting reagents in clinical development

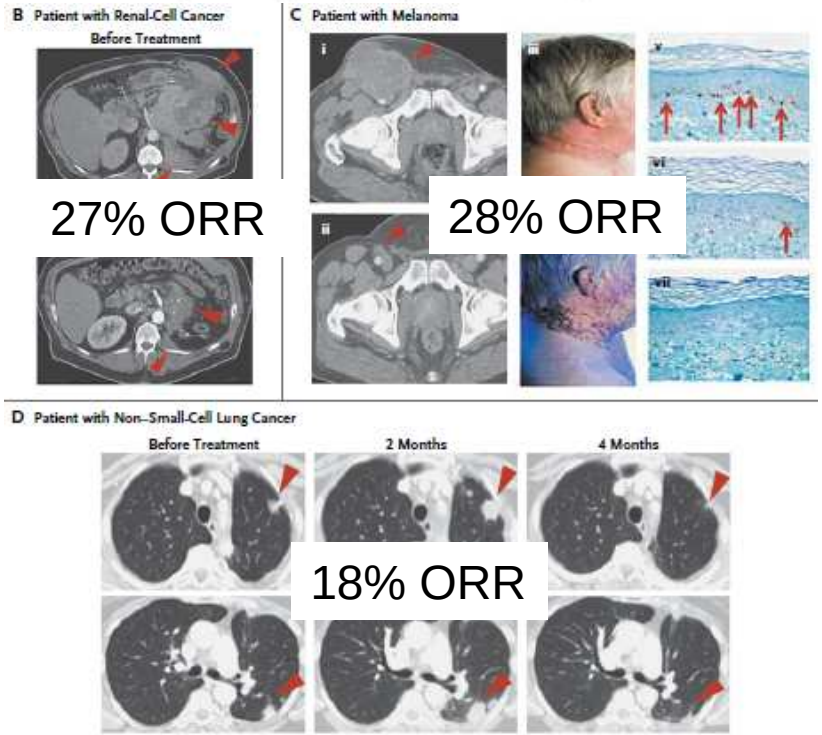
Target	Agent	Class	K_D
PD-1	Nivolumab (MDX1106, BMS936558, BMS-ONO)	IgG4 fully human antibody	3 nM
	MK-3475 (lambrolizumab, Merck)	IgG4 engineered humanized antibody	29 pM
	Pidilizumab (CT-011, CureTech-Teva)	IgG1 humanized antibody	-
	AMP-224 (Amplimmune-GSK)	Fc-PD-L2 fusion protein	-
PD-L1	BMS935559 (MDX-1105, BMS-ONO)	IgG4 fully human antibody	-
	MPDL3280A (Genentech)	IgG1 engineered fully human antibody	-
	MEDI4736 (MedImmune, AZ)	IgG1 engineered fully human antibody	-
	MSB0010718C (Merck-Serono)	NA	-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.



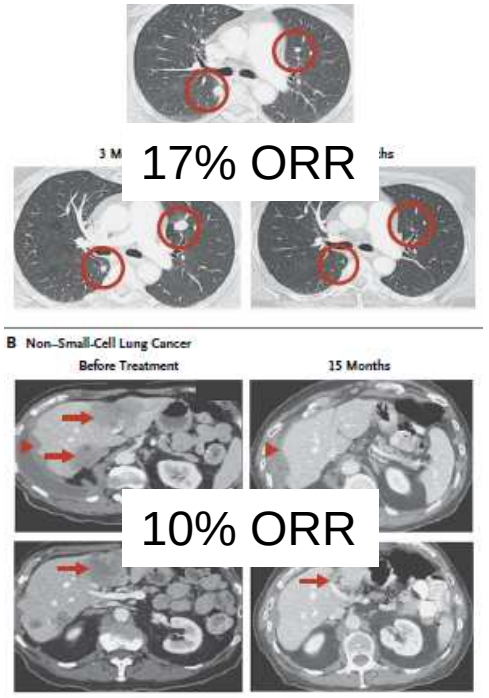
Nivolumab

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

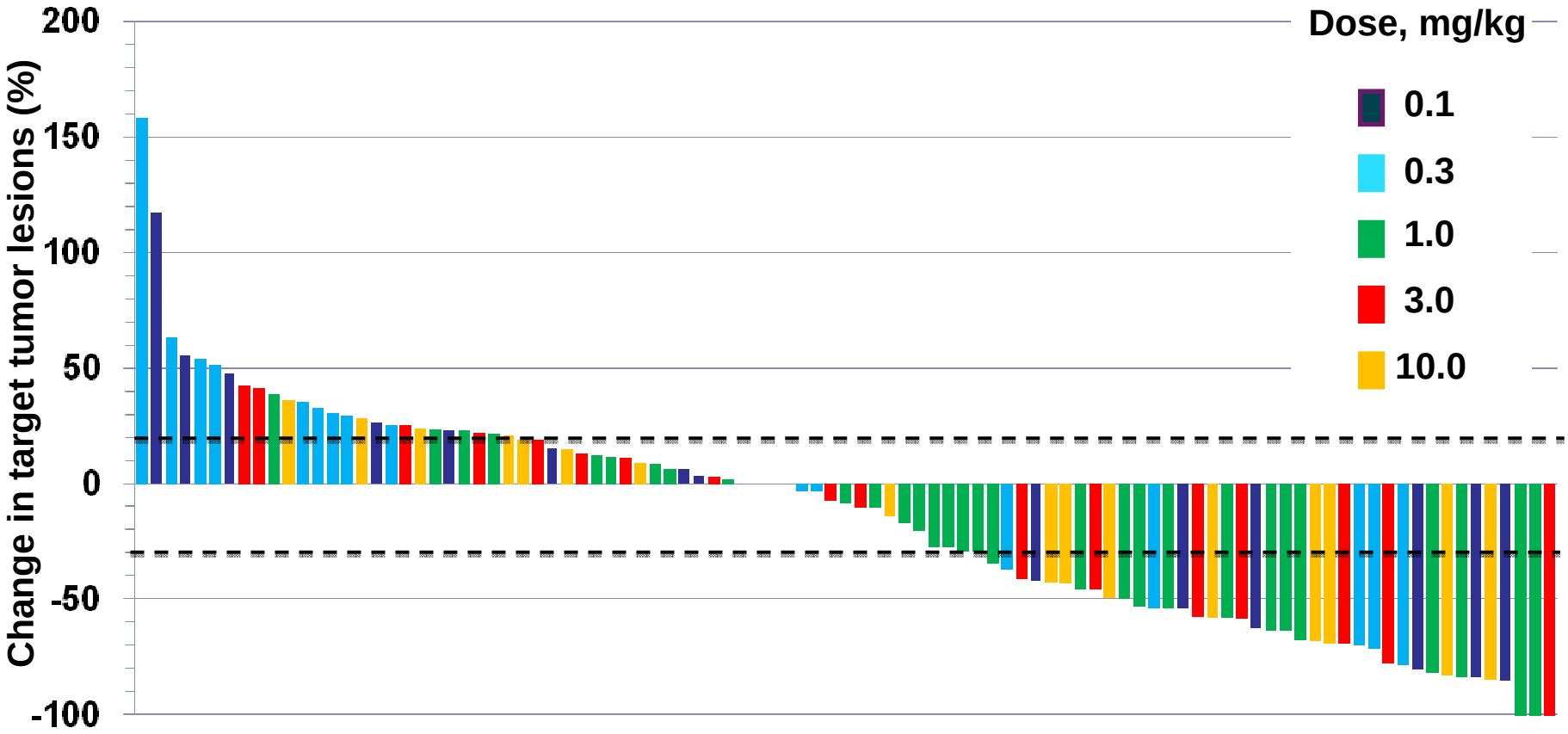
Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.



BMS935559

N Engl J Med 2012.

Nivolumab single agent therapy: Best Change In Target Lesions to First RECIST Progression

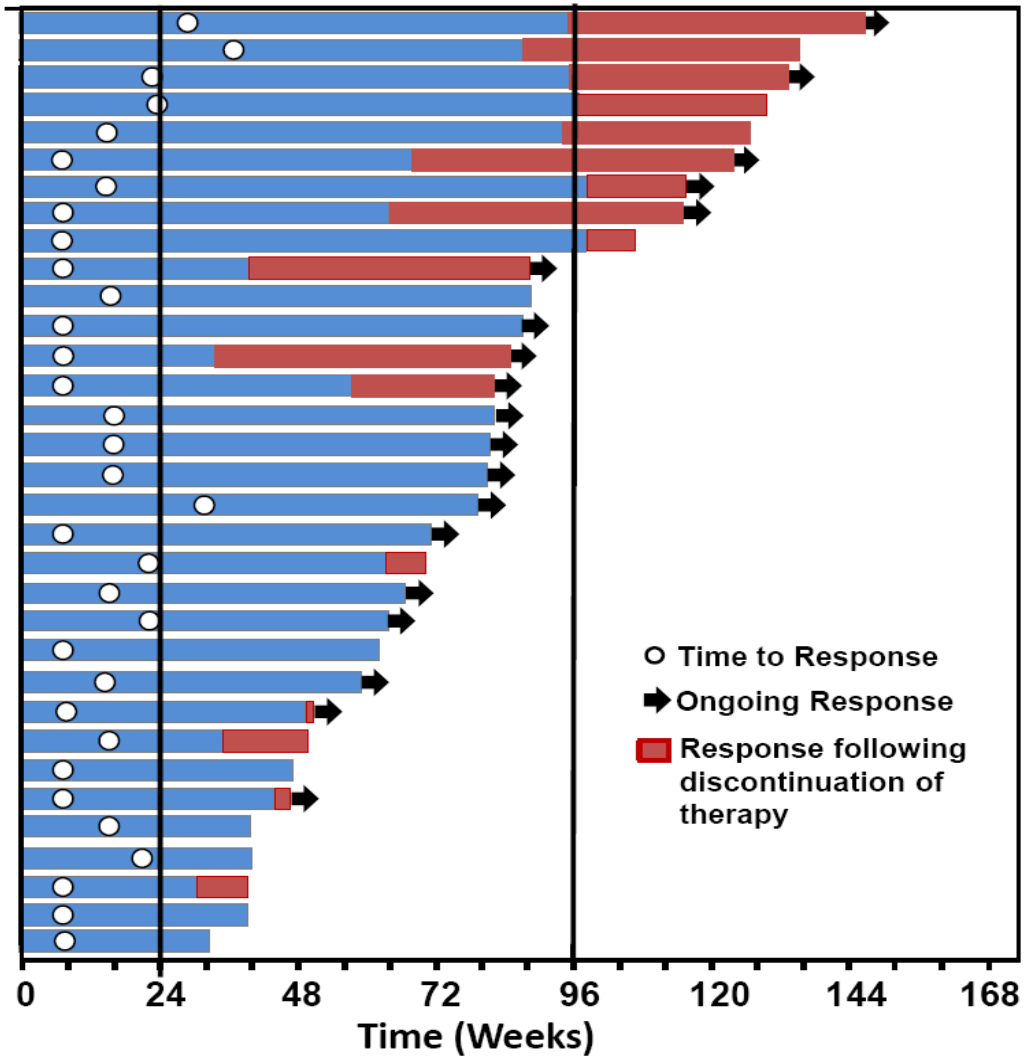


* Nonconventional responders

Horizontal line at −30% = threshold for defining objective response (partial tumor regression) in absence of new lesions or non-target disease according to RECIST. Horizontal line at +20% indicates the threshold for determination of progressive disease according to RECIST.

Sznol *et al*. ASCO 2013

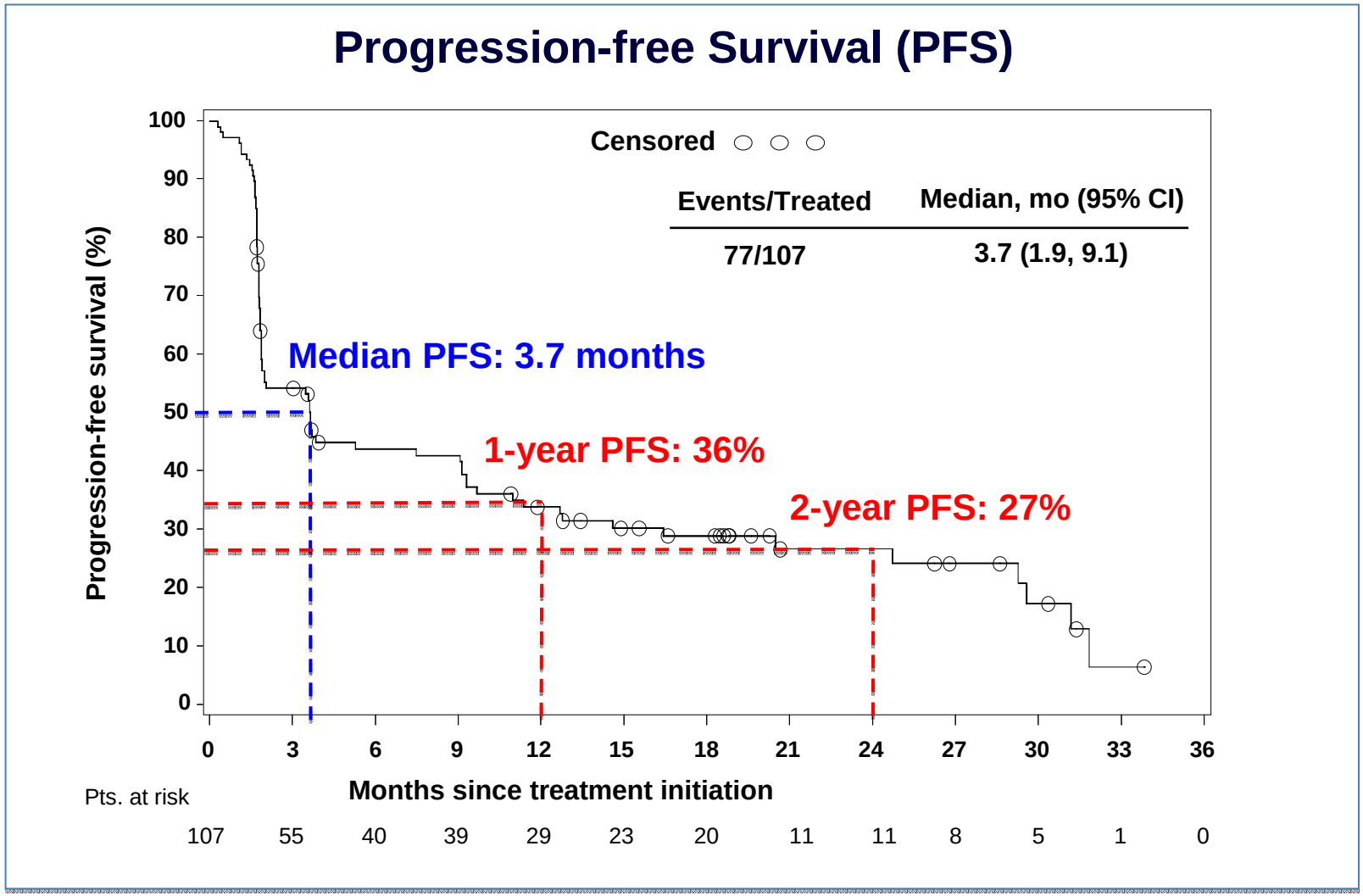
Response Characteristics in Patients with Melanoma Receiving Nivolumab



- For 17 responding patients who discontinued therapy for reasons other than disease progression, 71% (12/17) responded for ≥16 weeks since end of therapy
- 67% (8/12) remained in response from 16-56 weeks at time of data analysis

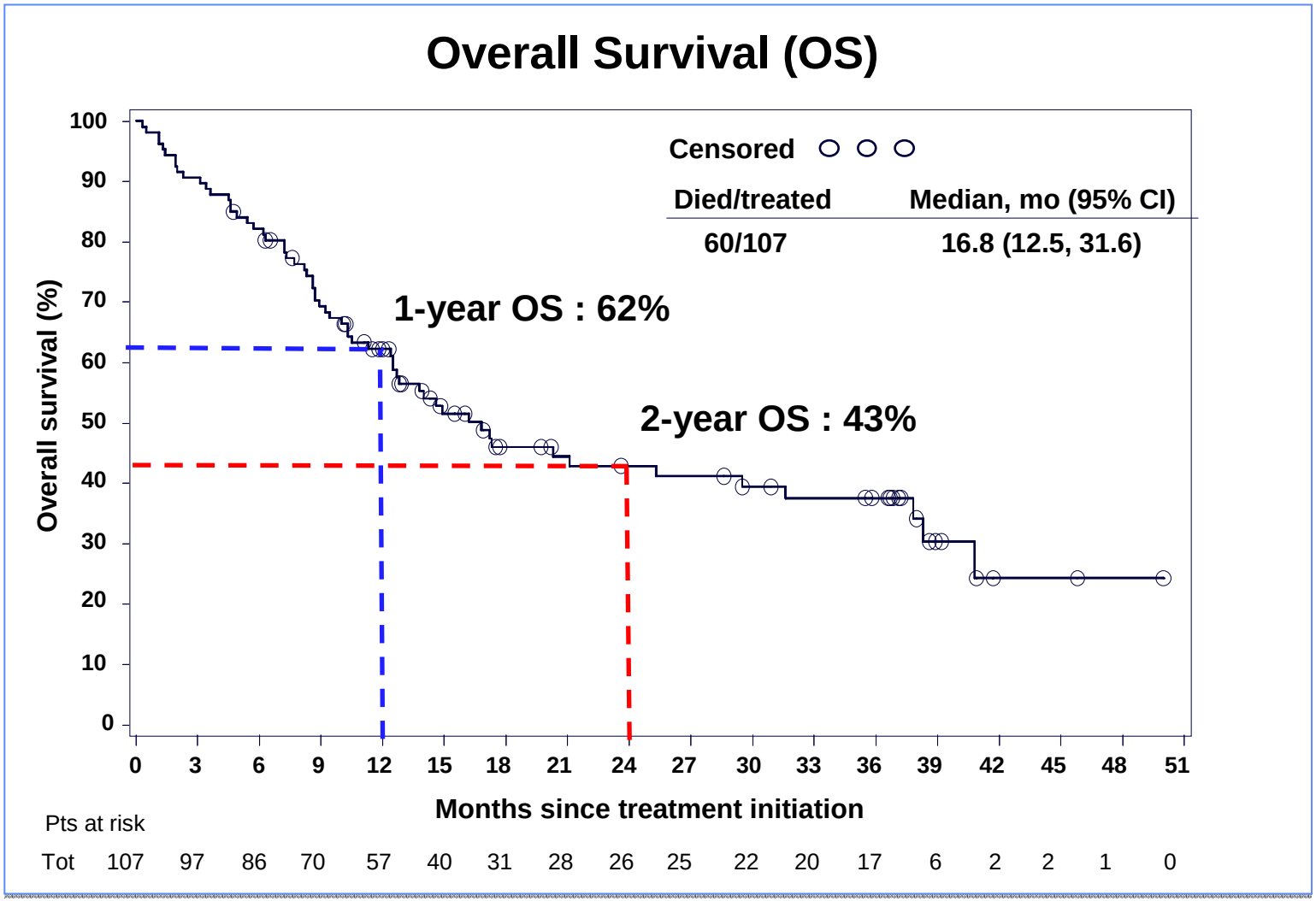
Presented by M. Sznol, ASCO 2013

Progression-free Survival for Patients with Melanoma Treated with Nivolumab



Presented by M. Sznol, ASCO 2013

Overall Survival for Patients with Melanoma Treated with Nivolumab



Median Survival = 16.8 months

Presented by M. Sznol, ASCO 2013

Select Drug-Related Adverse Events (≥1%) Occurring in Melanoma Patients Treated with Nivolumab

- Select AE: AE with potential immunologic etiologies that require more frequent monitoring and/or unique intervention
- All patients have ≥1 year of follow-up

Category	Any Grade % (n)	Grade 3-4 % (n)
Any select AE	54 (58)	5 (5)
Skin	36 (38)	2 (2)
Gastrointestinal	18 (19)	2 (2)
Endocrinopathies	13 (14)	2 (2)
Hepatic	7 (7)	1 (1)
Infusion reaction	6 (6)	0
Pulmonary	4 (4)	0
Renal	2 (2)	1 (1)

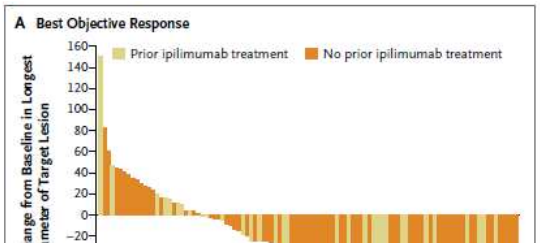
Presented by M. Sznol, ASCO 2013

The NEW ENGLAND JOURNAL of MEDICINE

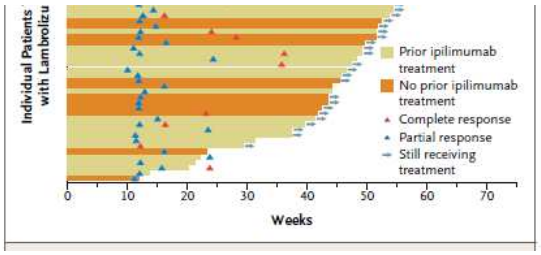
ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

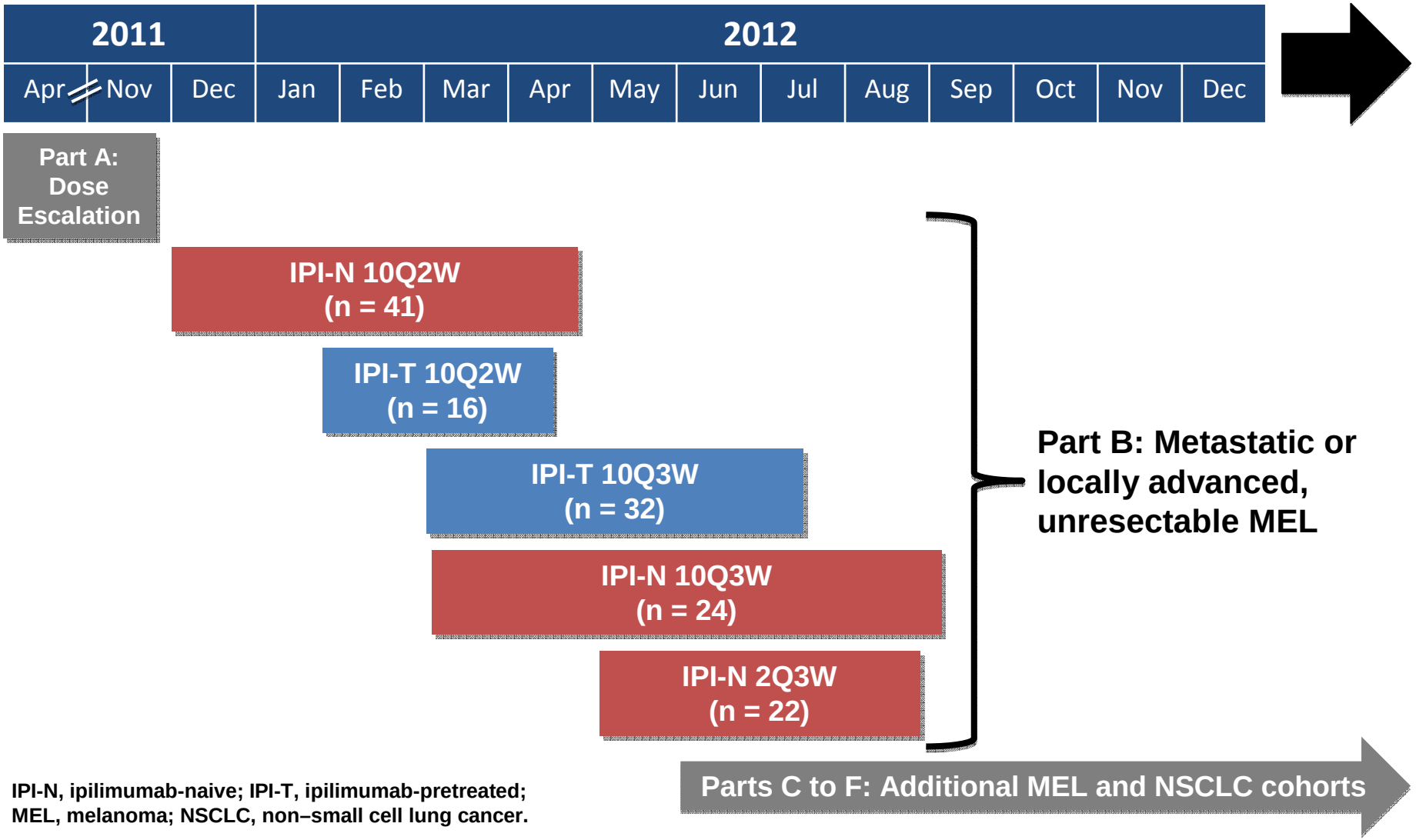


ORR: 38%
Highest dose ORR: 52%
(by RECIST 1.1 with confirmation assessed by ICR)



Lambrolizumab

Phase I Trial Design (NCT01295827)

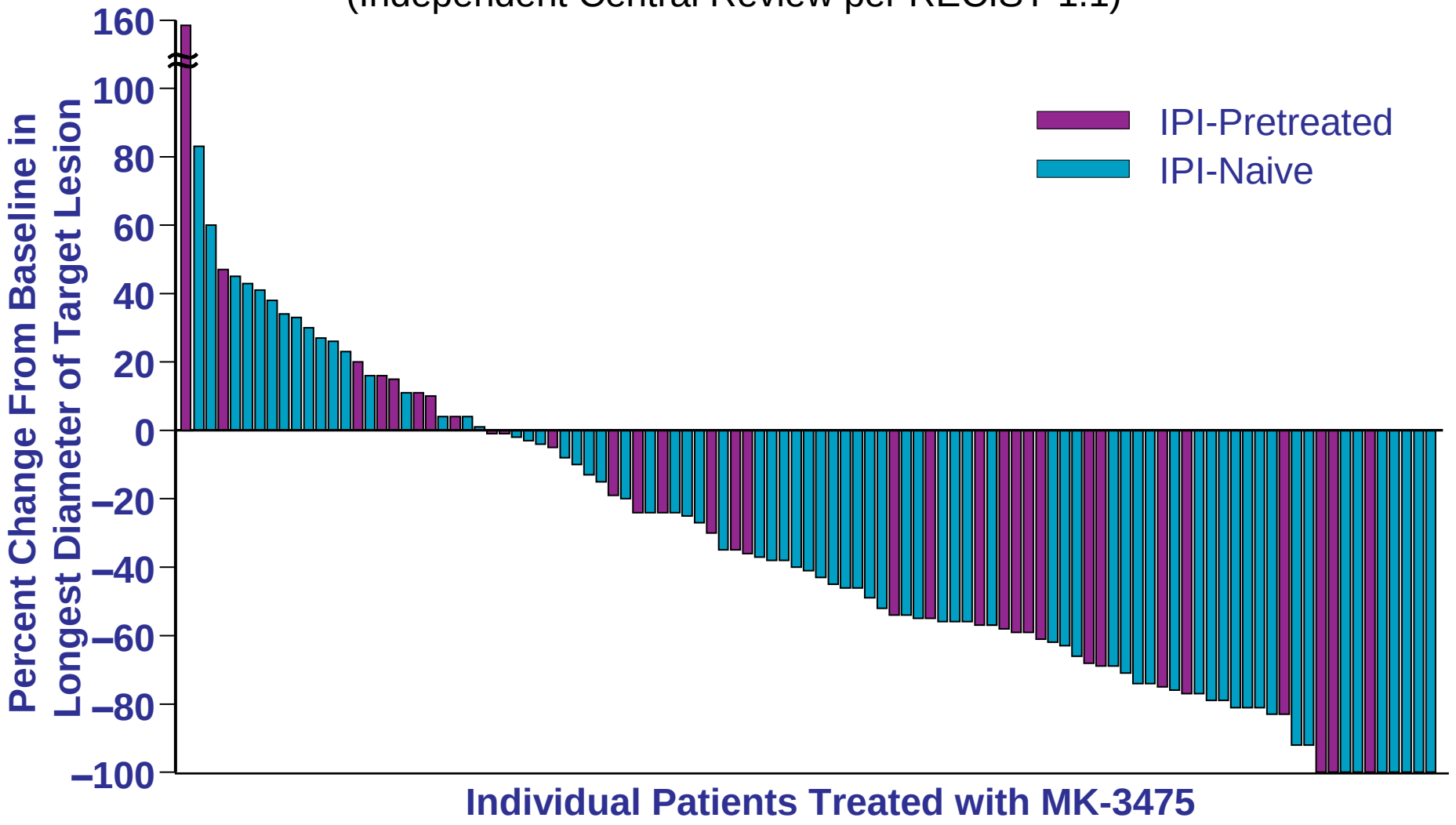


IPI-N, ipilimumab-naive; IPI-T, ipilimumab-pretreated; MEL, melanoma; NSCLC, non–small cell lung cancer.

Presented by A. Ribas, ASCO 2013

MK-3475 (lambrolizumab) single agent therapy: Maximum Change From Baseline in Tumor Size

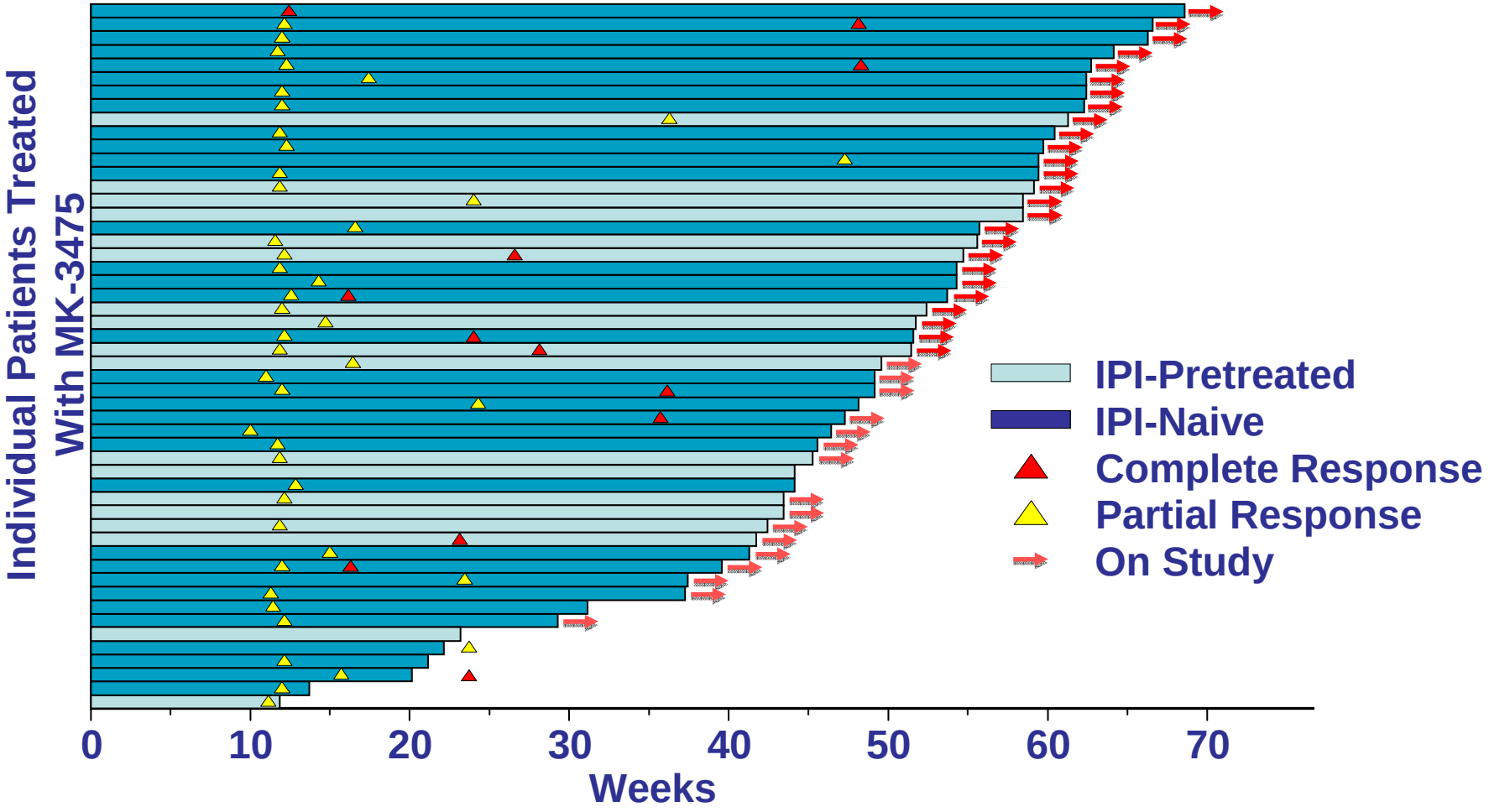
(Independent Central Review per RECIST 1.1)



Ribas *et al*. ASCO 2013

Time to Response and On-Study Duration

(Independent Central Review per RECIST 1.1)



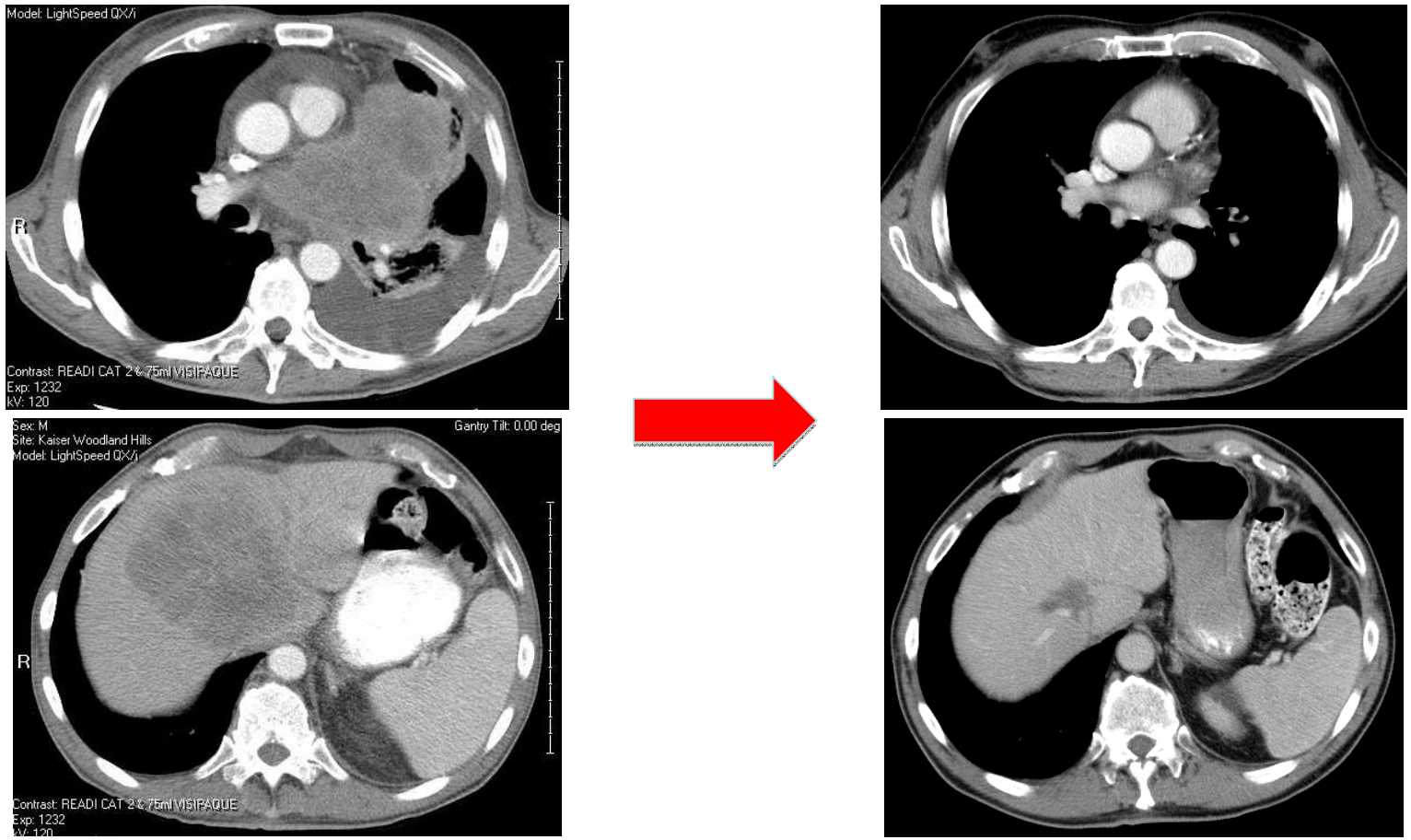
The median duration of response had not been reached at the time of analysis, with median follow-up time of 11 months.

Ribas *et al*. ASCO 2013

Clinical activity of MK-3475 in a patient progressing to 3 prior lines of therapy

Baseline: April 13, 2012

April 9, 2013



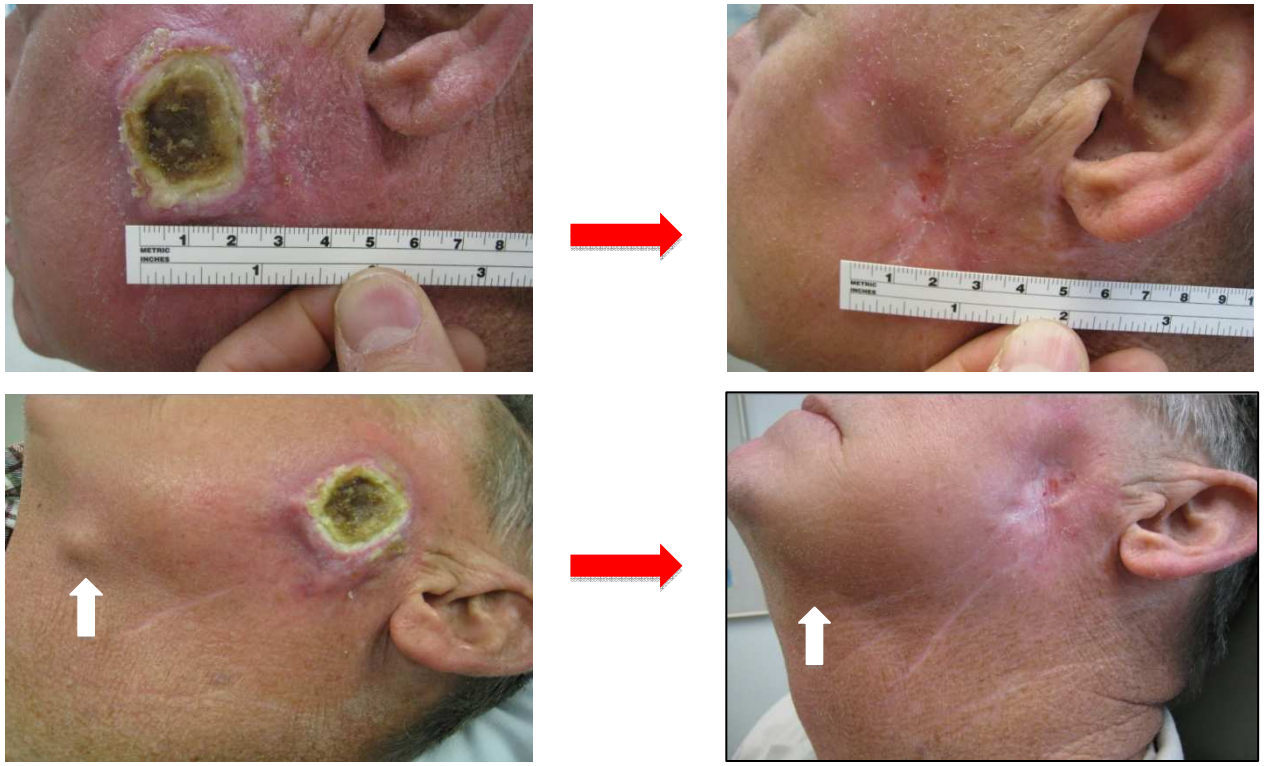
72-year-old male with symptomatic progression after bio-chemotherapy, HD IL-2, and ipilimumab

A. Ribas, ASCO 2013

Clinical activity in a patient with a metastatic desmoplastic melanoma

Baseline Jan/2012

Apr/2012



54 yrs old male with desmoplastic melanoma after progressing on ipilimumab

A. Ribas, ASCO 2013

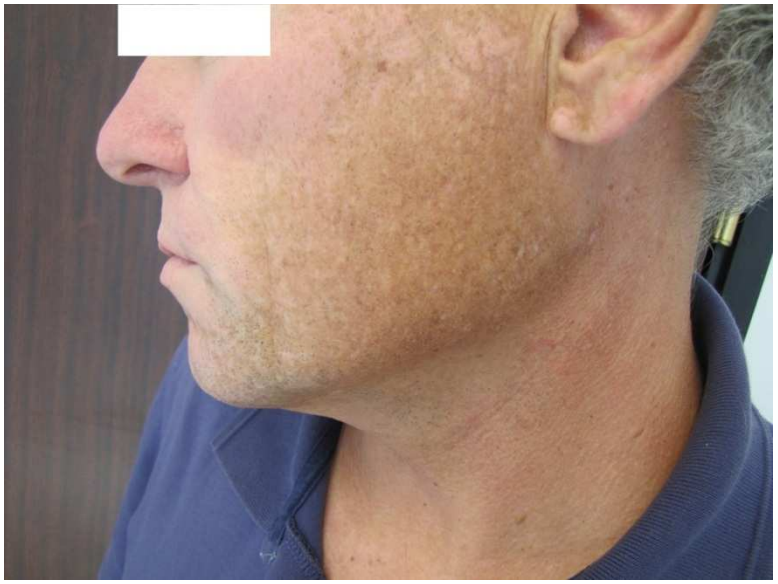
B. Chmielowski M.D., Ph.D.
Paul Tumeh M.D.

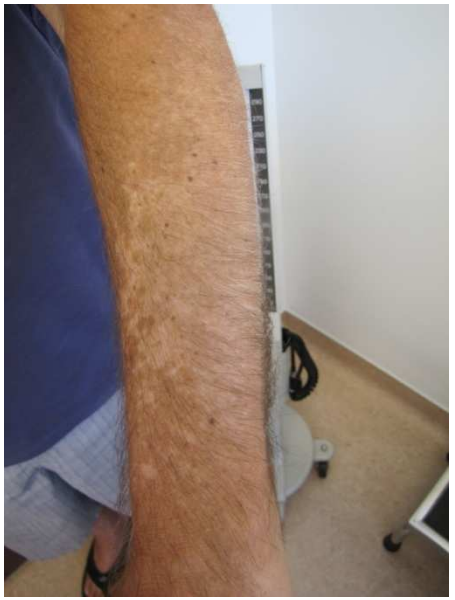
Drug-Related Adverse Events

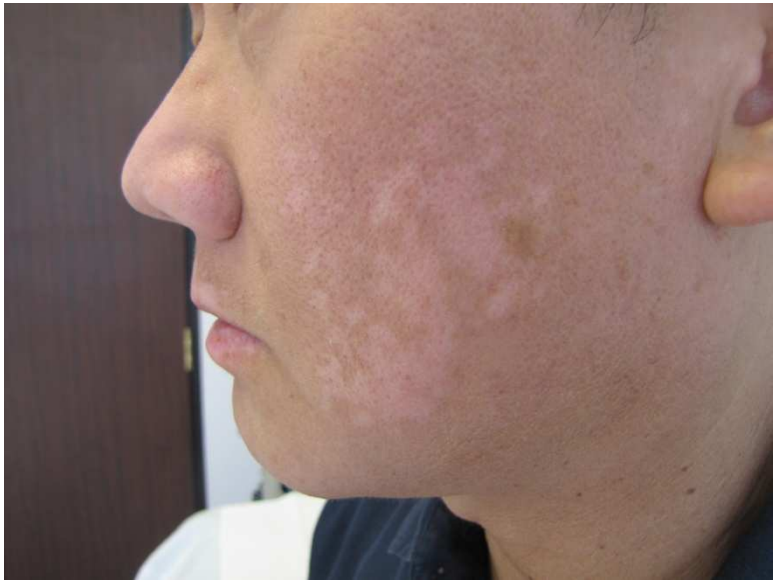
Observed in >5% of Patients (N = 135)

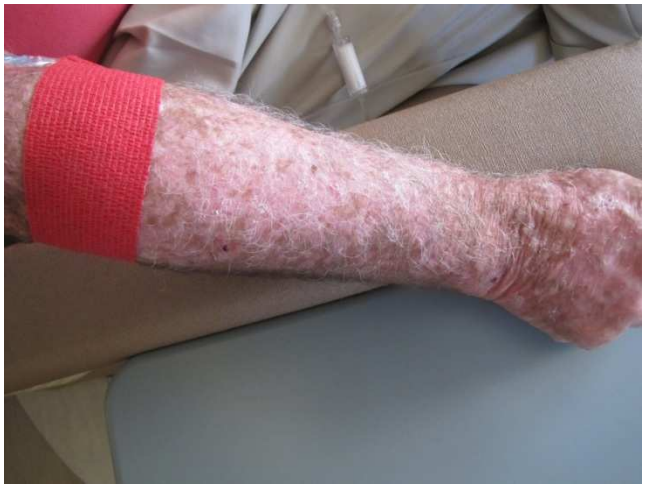
Adverse Event	All Grades, n (%)	Grade 3-4, n (%)
Any	107 (79.3)	17 (12.6)
Fatigue	41 (30.4)	2 (1.5)
Rash	28 (20.7)	3 (2.2)
Pruritus	28 (20.7)	1 (0.7)
Diarrhea	27 (20.0)	1 (0.7)
Myalgia	16 (11.9)	0
Headache	14 (10.4)	0
Increased AST	13 (9.6)	2 (1.5)
Asthenia	13 (9.6)	0
Nausea	13 (9.6)	0
Vitiligo	12 (8.9)	0
Hypothyroidism	11 (8.1)	1 (0.7)
Increased ALT	11 (8.1)	0
Cough	11 (8.1)	0
Pyrexia	10 (7.4)	0
Chills	9 (6.7)	0
Abdominal pain	7 (5.2)	1 (0.7)

Frequent development of vitiligo (skin depigmentation) in responding patients



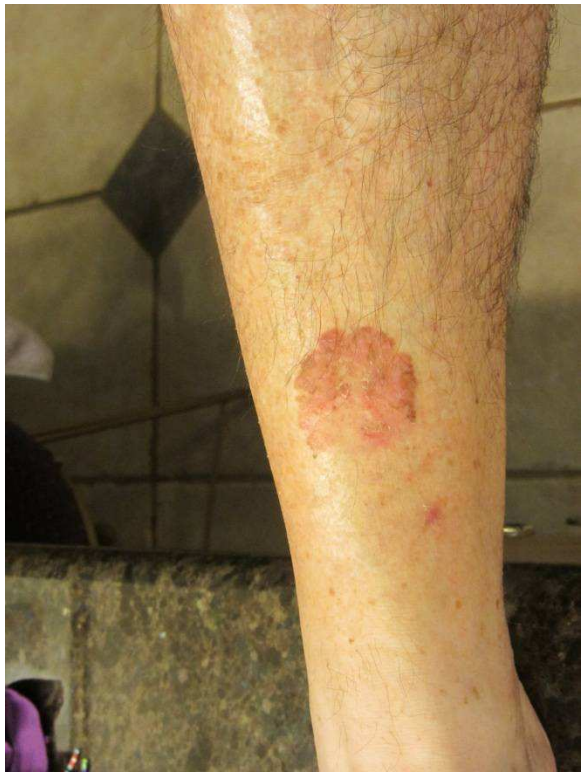




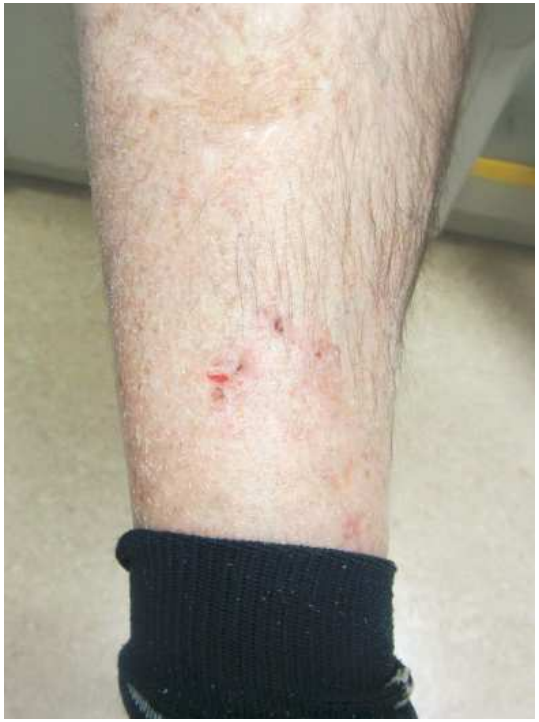


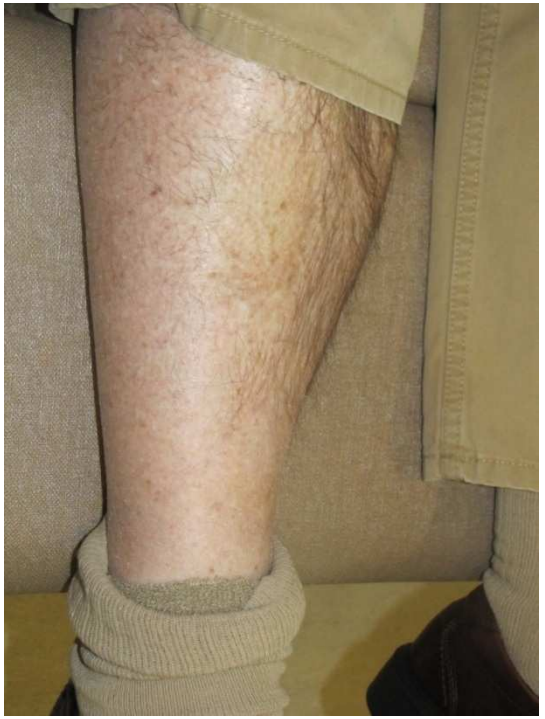
PD-1 blockade improving other skin conditions

Before



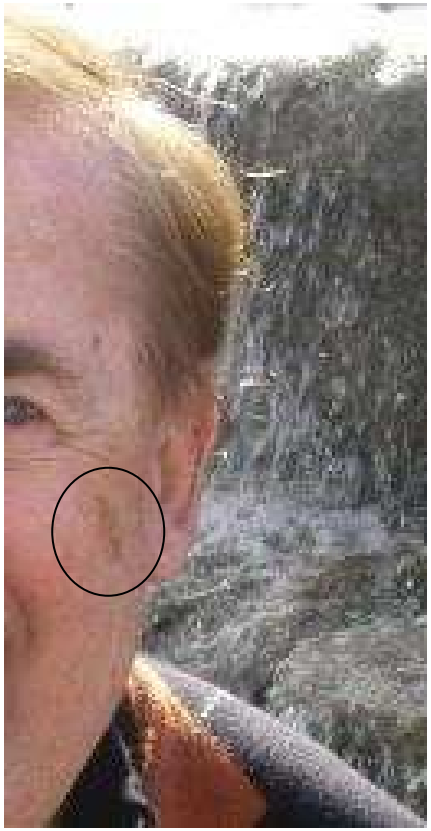
After



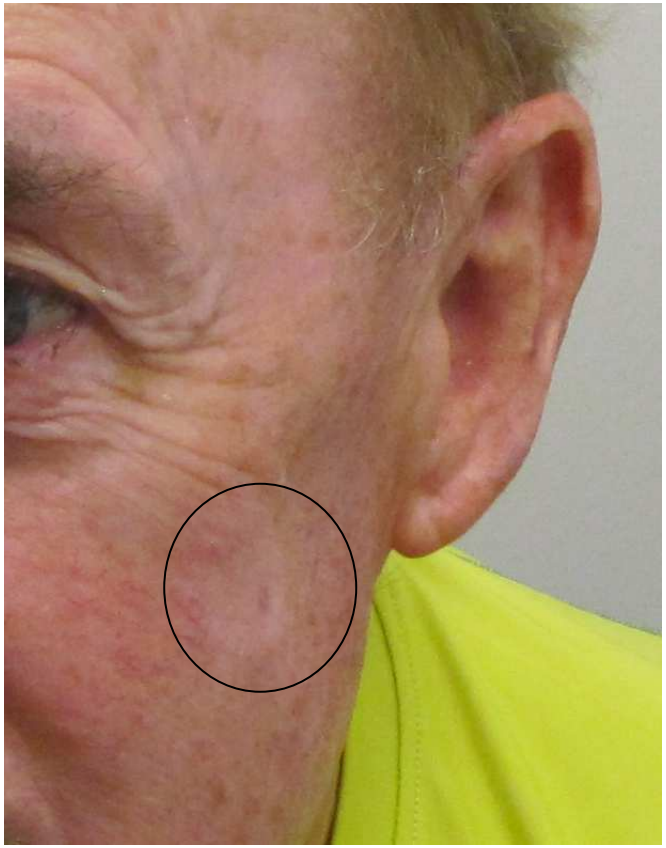


PD-1 blockade leading to the disappearance of a pigmented birth mark

Before



After



15th World Conference of Lung Cancer
Sydney, Australia, Oct 27-30, 2013

2416: PRELIMINARY CLINICAL SAFETY AND ACTIVITY OF MK-3475 MONOTHERAPY FOR THE TREATMENT OF PREVIOUSLY TREATED PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

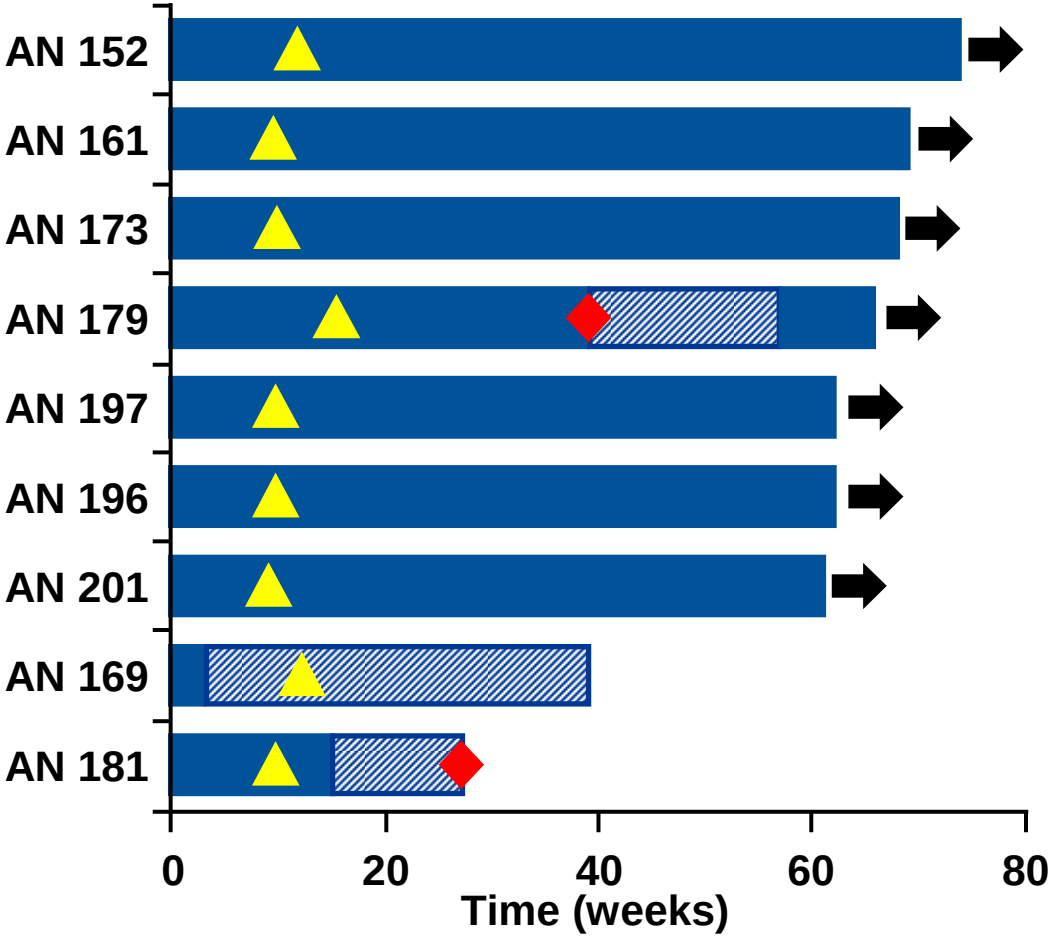
Edward B. Garon,[1] Ani Balmanoukian,[2] Omid Hamid,[2] Rina Hui,[3] Leena Gandhi,[4] Natasha Leighl,[5] Matthew Gubens,[6] Jonathan W. Goldman,[1] Gregory M. Lubiniecki,[7] Kenneth Emancipator,[7] Marisa Dolled-Filhart,[7] Jared Lunceford,[7] Kevin Gergich,[7] Naiyer Rizvi[8]

[1]David Geffen School of Medicine at UCLA, Los Angeles, USA; [2]The Angeles Clinic, Los Angeles, USA; [3]Crown Princess Mary Cancer Centre, Westmead, Australia; [4]Dana Farber Cancer Institute, Boston, USA; [5]Princess Margaret Hospital, Toronto, Canada; [6]University of California San Francisco, San Francisco, USA; [7]Merck and Co, Inc, Whitehouse Station, USA; [8]Memorial Sloan-Kettering Cancer Center, New York, USA

Subgroup	irRC, Investigator Review			RECIST v1.1, Independent Review			
	N	ORR, n (%) [95% CI]	Median PFS, wk (95% CI)	N	ORR,* (%), [95% CI]	Median PFS, wk (95% CI)	Median OS, wk (95% CI)
All	38	9 (24%) [11%, 40%]	9.1 (8.3, 17.4)	33	7 (21%) [9%, 39%]	9.7 (7.6, 17)	51 (14, NR)
Non-squamous	31	7 (23%) [10%, 41%]	9.1 (8.3, 17.0)	26	4 (16%) [4%, 35%]	10.3 (7.6, 17)	35 (14, NR)
Squamous	6	2 (33%) [4%, 78%]	23.5 (2.7, NR)	6	2 (33%) [4%, 78%]	15.2 (1.4, NR)	NR (2.7, NR)
Patients with measurable disease on baseline imaging and an evaluable tumor specimen for PD-L1							
Score ≥ potential cut point	9	6 (67%) [30%, 93%]	—	7	4 (57%) [18%, 90%]	—	—
Score < potential cut point	24	1 (4%) [0%, 21%]	—	22	2 (9%) [1%, 29%]	—	—

*Response rate per RECIST v1.1 is based on those patients who had ≥1 measurable lesion at baseline per central review. All responses were confirmed except for 2. One patient withdrew consent for treatment, unrelated to toxicity, after the first imaging assessment, and 1 patient had a confirmatory scan of PR at day 27.

MK-3475 Responders Have Prolonged Duration of Response



- 7/9 responders on treatment at time of analysis
- Median PFS of responders not reached at 62 weeks
- AN 179: stopped MK for local therapy to brain metastasis; MK resumed based on continued systemic response
- AN 169: after 1 dose, MK stopped for unrelated grade 4 hypercalcemia; response maintained without further treatment; per protocol, follow-up ceased at 39 weeks

On therapy
Confirmed response
Off therapy
Progression
Therapy continuing

Clinical Activity, Safety and Biomarkers of MPDL3280A, an Engineered PD-L1 Antibody in Patients With Metastatic Melanoma

Omid Hamid,[1] Jeff Sosman,[2] Donald Lawrence,[3] Ryan J Sullivan,[3] Nageatte Ibrahim,[4] Harriet Kluger,[5] Peter Boasberg,[1] Keith Flaherty,[3] Patrick Hwu,[6] Marcus Ballinger,[7] Ahmad Mokatrin,[7] Marcin Kowanetz,[7] Daniel S. Chen[7] and F. Stephen Hodi[4]

[1]*The Angeles Clinic and Research Institute,* [2]*Vanderbilt-Ingram Cancer Center,* [3]*Massachusetts General Hospital,* [4]*Dana-Farber Cancer Institute,* [5]*Yale University,* [6]*MD Anderson,* [7]*Genentech Inc.*

MPDL3280A Phase Ia: Efficacy Summary

Investigator Assessed

	ORR*	SD of 24 Weeks or Longer	24-Week PFS
Overall population (N = 140)	21%	16%	45%
Melanoma (n = 38)	**29%**	**5%**	**43%**
Cutaneous† (n = 27)	33%	7%	54%
Mucosal† (n = 4)	25%	0	25%
Ocular† (n = 4)	0	0	0

* ORR includes unconfirmed PR/CR and confirmed PR/CR.

† 3 patients had undetermined histology status.

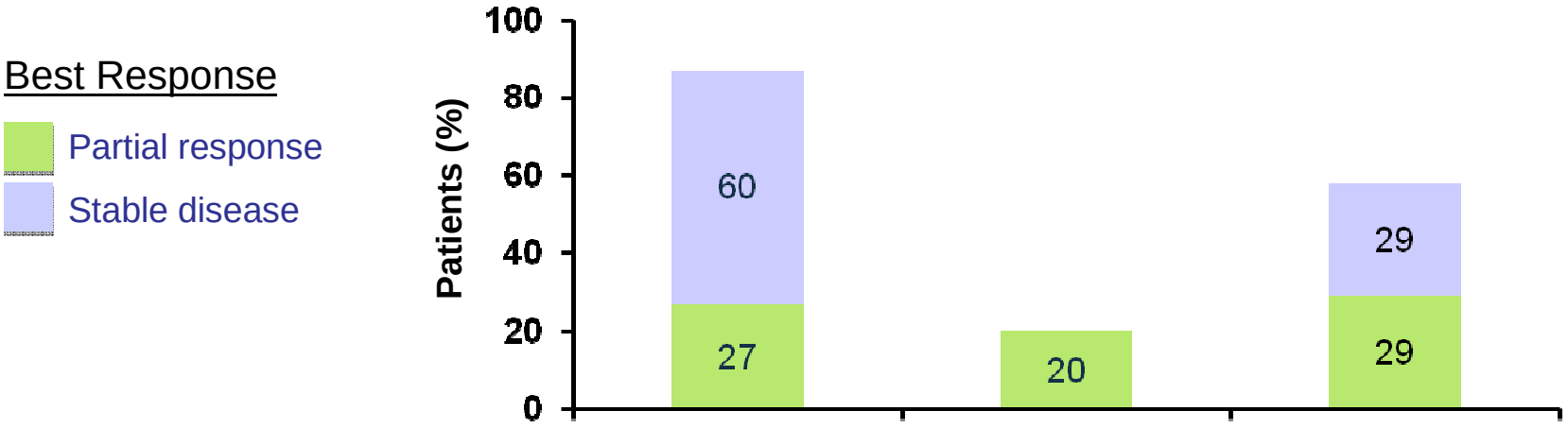
Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.

7 overall population patients and 1 melanoma patient who did not have a post-baseline scan were included as non-responders.

Presented by O. Hamid, ASCO 2013

MPDL3280A Phase Ia: Summary of Response by PD-L1 IHC Status

Investigator-Assessed Best Overall Response Rate (ORR), n/n (%)			
	PD-L1 Positive	**PD-L1 Negative**	**All†**
Overall population ORR (N = 140)	13/36 (36%)	9/67 (13%)	29/140 (21%)
Melanoma ORR (N = 38)	**4/15 (27%)**	**3/15 (20%)**	**11/38 (29%)**
Melanoma PR + SD (N = 38), %	**87%**	**20%**	**58%**

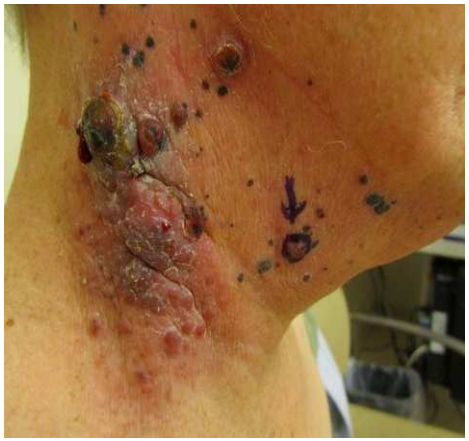


* ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1.
† All patients include PD-L1–positive, PD-L1–negative and patients with unknown tumor PD-L1 status.
Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.

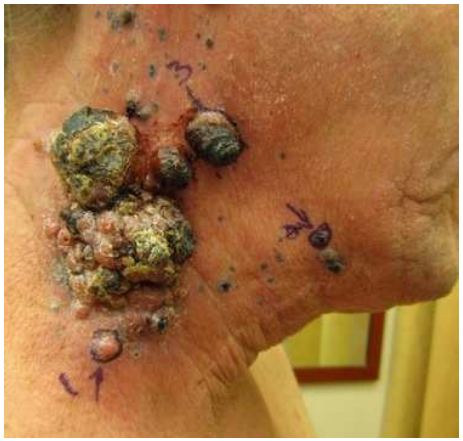
Presented by O. Hamid, ASCO 2013

Salvage of BRAF-Mutant Metastatic Melanoma Patient After Progression on Vemurafenib

Baseline

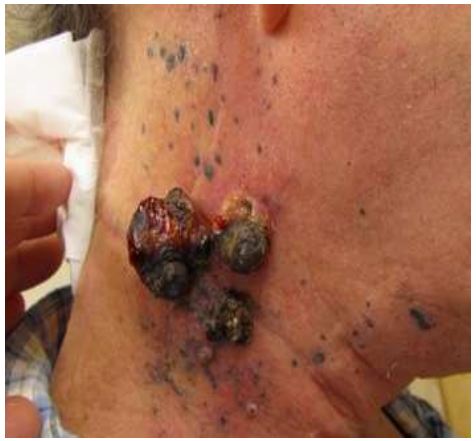


Week 6

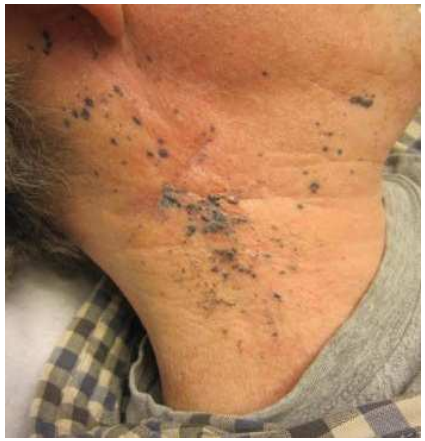


31% increase in target lesions **(RECIST PD)**

Week 12

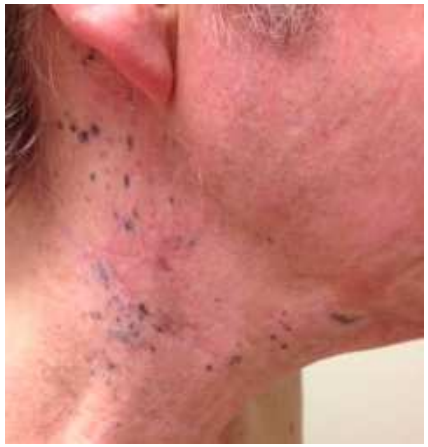


Week 18



Post-Resection

Week 46



Dx: Nov 2010 (cutaneous melanoma)
Prior treatment: cisplatin, vemurafenib

Images include data from after Feb 1, 2013.
Dana Farber Cancer Institute (Ibrahim/Hodi).

MPDL3280A Phase Ia

Comparison of key clinical data with anti-PD-1 or anti-PD-L1 antibodies in patients with advanced melanoma

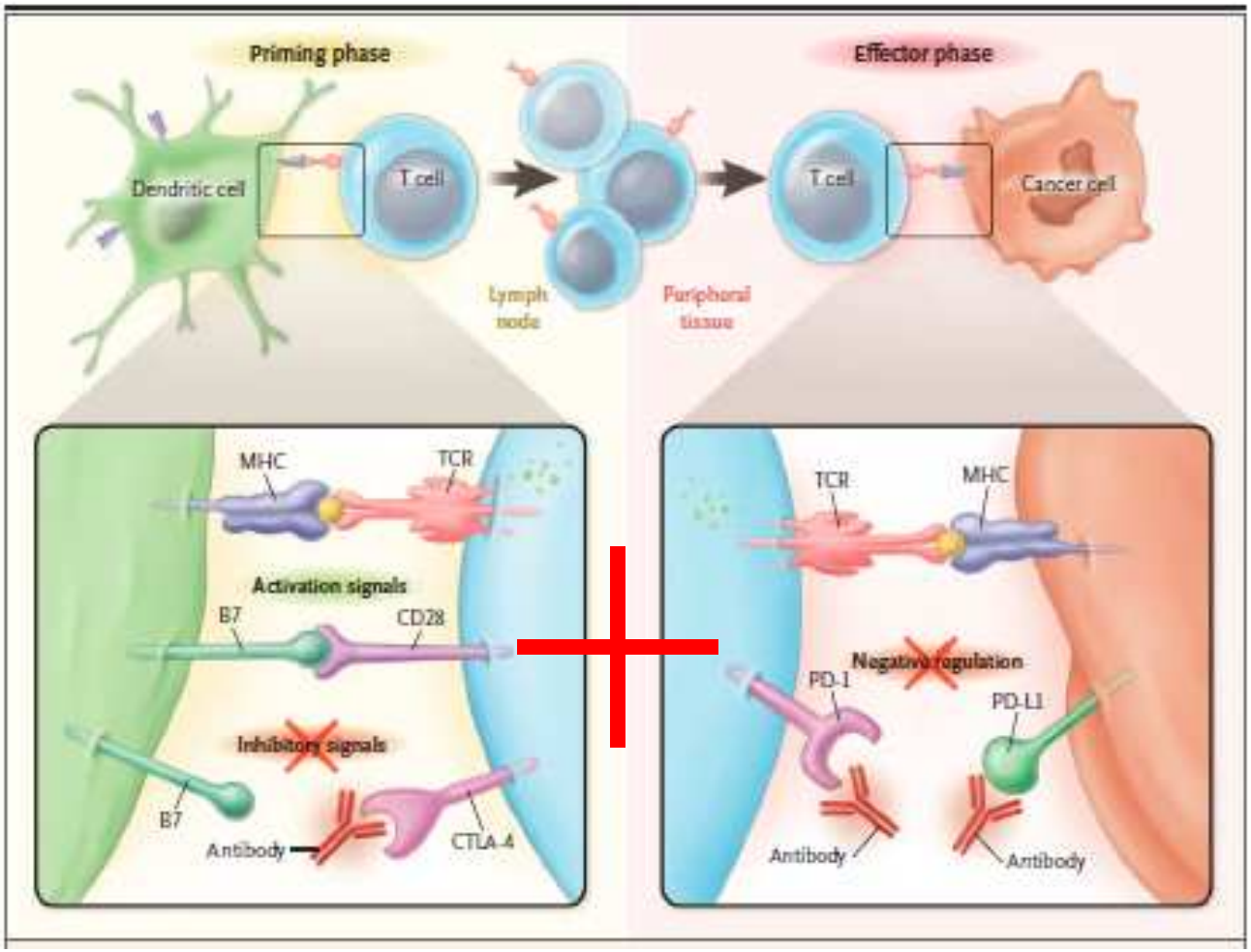
Antibody	# pts	ORR (at optimal dose)	Grade 3/4 related toxicities	6 mo PFS	12 mo PFS	Median PFS	1 yr OS	2 yr OS	Refs.
Nivolumab (anti-PD-1)	107	31% (41%)	14%	41%	36%	3.7 mo	62%	43%	Sznol ASCO 2013 Topalian NEJM 2012
MK-3475 (anti-PD-1)	117	38% (52%)	13%	NA	NA	>7 mo	NA	NA	Ribas ASCO 2013 Hamid NEJM 2013
Nivolumab + ipilimumab (anti-PD-1 + anti-CTLA4)	52	40% (53%)	53%	NA	NA	NA	82%	NA	Wolchok ASCO 2013, NEJM 2013
BMS559 (anti-PD-L1)	52	17%	5%	NA	NA	NA	NA	NA	Brahmer NEJM 2012
MPDL3280A (anti-PD-L1)	38	29%*	14%	43%	NA	NA	NA	NA	Hamid ASCO 2013

*Includes 4 patients with UM without a response

EDITORIAL

Tumor Immunotherapy Directed at PD-1

Antoni Ribas, M.D., Ph.D.



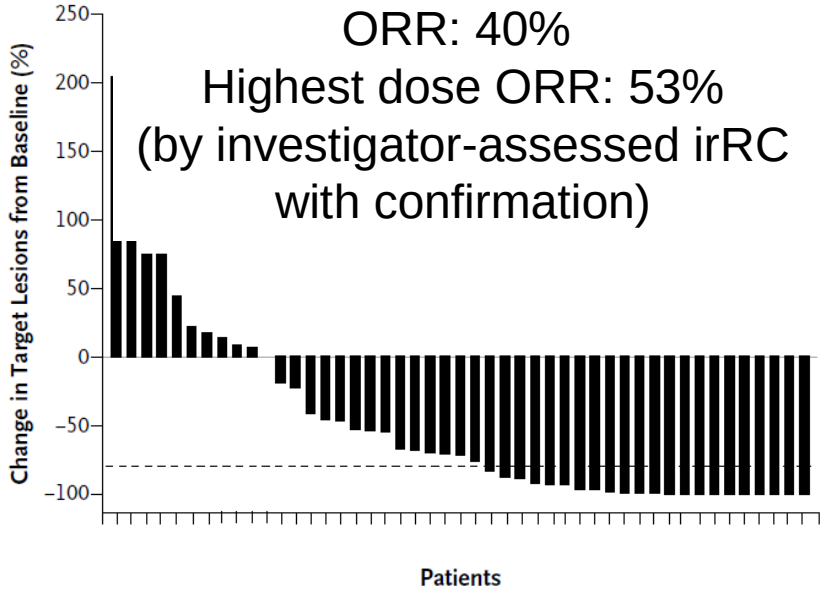
NEJM 2012; Jun 28; 366 (26): 2517-9

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Advanced Melanoma

Jedd D. Wolchok, M.D., Ph.D., Harriet Kluger, M.D., Margaret K. Callahan, M.D., Ph.D., Michael A. Postow, M.D., Naiyer A. Rizvi, M.D., Alexander M. Lesokhin, M.D., Neil H. Segal, M.D., Ph.D., Charlotte E. Ariyan, M.D., Ph.D., Ruth-Ann Gordon, B.S.N., Kathleen Reed, M.S., Matthew M. Burke, M.B.A., M.S.N., Anne Caldwell, B.S.N., Stephanie A. Kronenberg, B.A., Blessing U. Agunwamba, B.A., Xiaoling Zhang, Ph.D., Israel Lowy, M.D., Ph.D., Hector David Inzunza, M.D., William Feely, M.S., Christine E. Horak, Ph.D., Quan Hong, Ph.D., Alan J. Korman, Ph.D., Jon M. Wigginton, M.D., Ashok Gupta, M.D., Ph.D., and Mario Sznol, M.D.



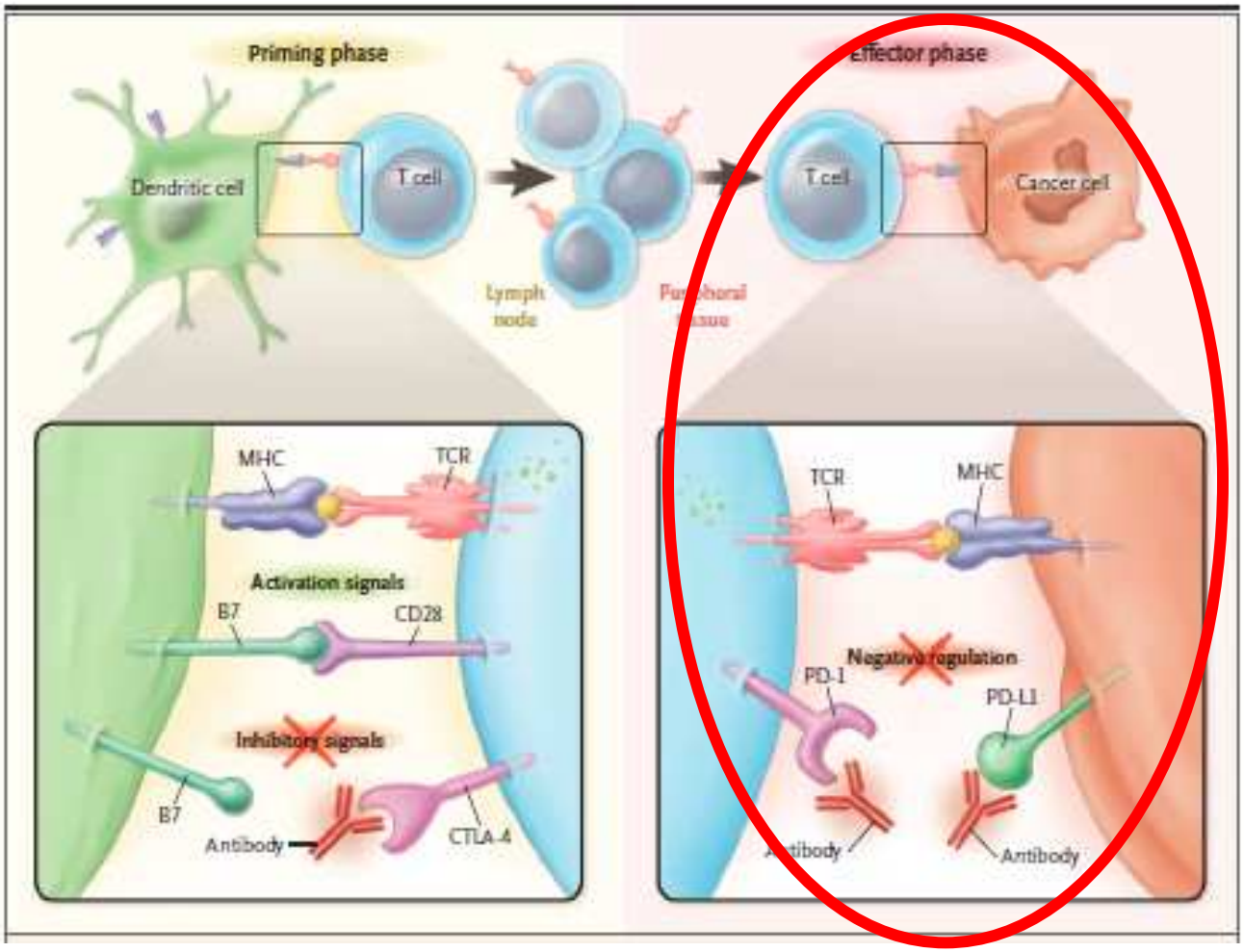
Objective responses were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22) (P>0.99).

EDITORIAL

What is the mechanism of action of PD-1 blockade?

Tumor Immunotherapy Directed at PD-1

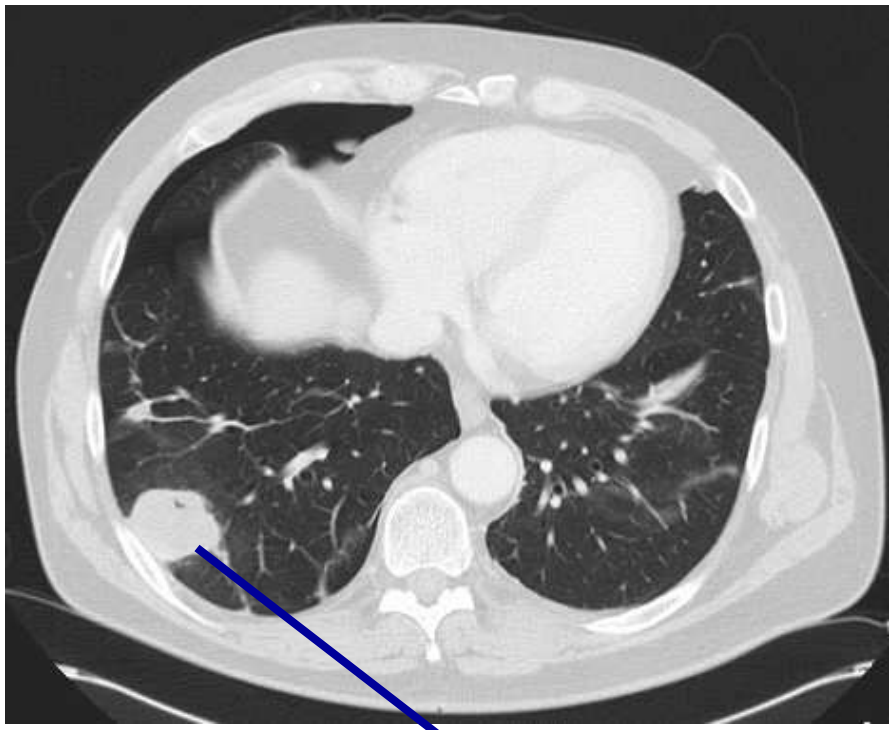
Antoni Ribas, M.D., Ph.D.

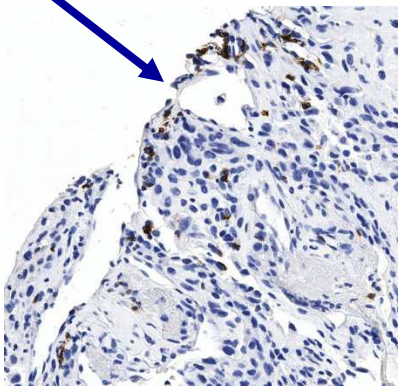


NEJM 2012; Jun 28; 366 (26): 2517-9

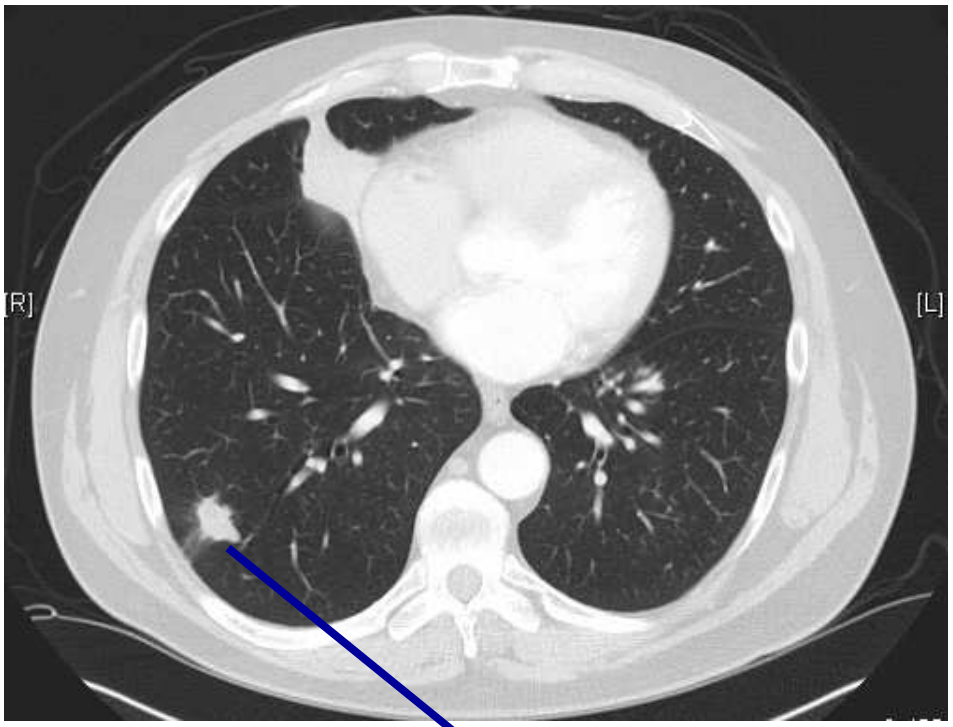
CD8+ CTL infiltrates in a regressing metastatic melanoma lesion

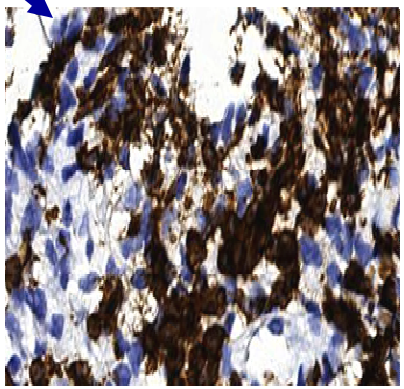
Baseline: 02/29/12





08/20/12





CD8+ IHC
Paul Tumeh, MD

A. Ribas, ASCO 2013

Conclusions

- PD-1/PD-L1 blocking immunotherapy agents are the most promising new agents in clinical development for the treatment of cancer
- PD-1 blockade works by:
  - Expanding an intratumoral infiltrate by effector T cells
- The full potential of PD-1/PD-L1 blocking antibodies is only starting to be realized:
  - Range of indications
  - Improved patient selection
  - Combination therapies