Immunotherapy for High-Risk and Metastatic Melanoma

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INSTITUTE FOR CLINICAL IMMUNO-ONCOLOGY

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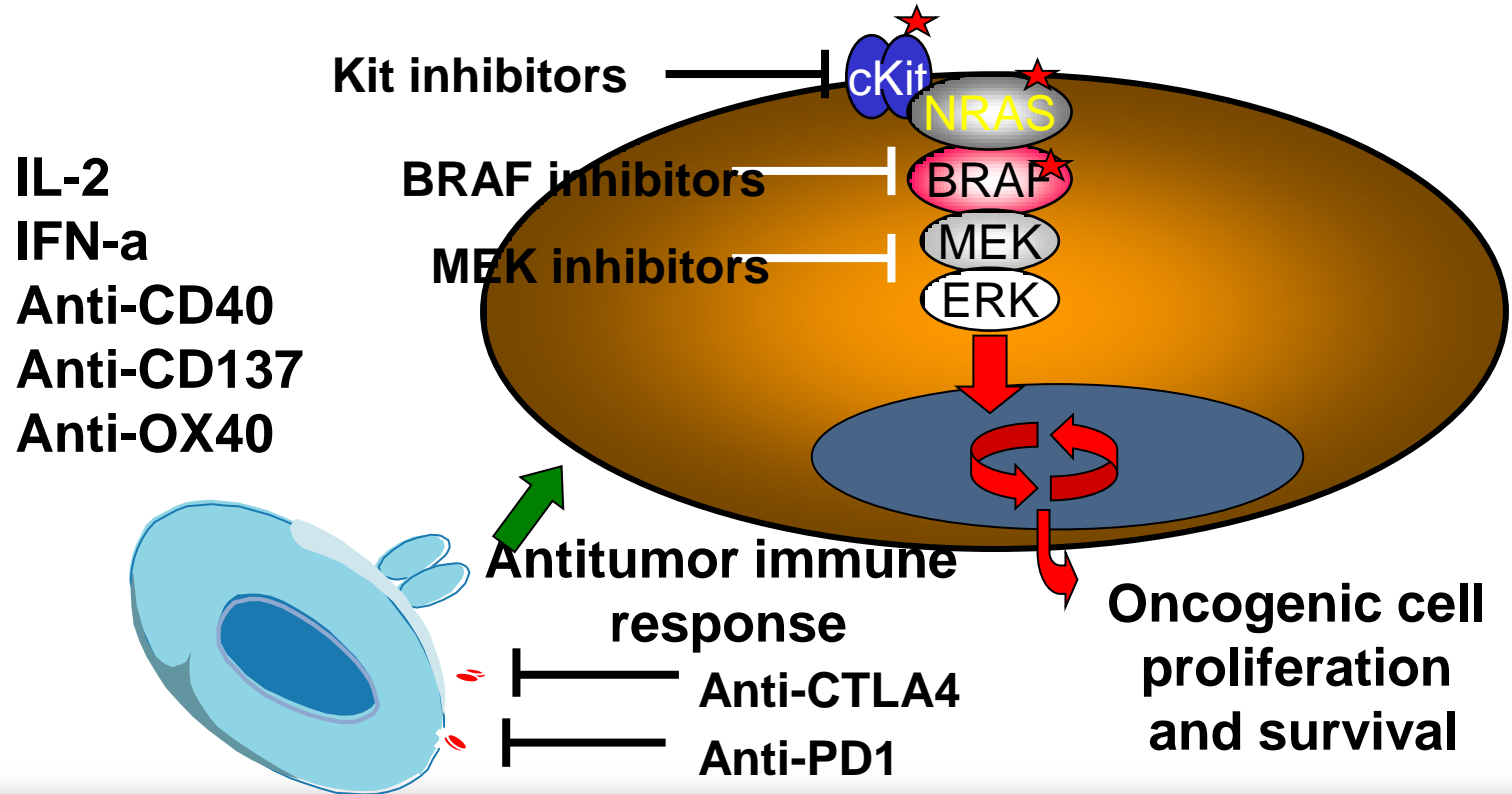Association of Community Cancer Centers

Financial Disclosures

- I currently have or have the following relevant financial relationships to disclose:
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    - Speakers Bureau: Genentech

Off-Label Use Disclosures

- I **<u>do intend</u>** to discuss off-label uses of products during this activity.

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Therapeutic Targets in Metastatic Melanoma

Kit inhibitors — cKit

IL-2
IFN-a
Anti-CD40
Anti-CD137
Anti-OX40

BRAF inhibitors — BRAF

MEK inhibitors — MEK

NRAS

ERK

Antitumor immune response

Anti-CTLA4

Anti-PD1

Oncogenic cell proliferation and survival

MEK = MAPK/ERK kinase; CTLA4 = cytotoxic T-lymphocyte antigen-4; PD1 = programmed death-1; IL-2 = interleukin-2; IFN-a = interferon alfa-2b.
Adapted from Fecher et al, 2007; Xing, 2010.

# Relevance of Immunotherapy for the Treatment of Melanoma

- **FDA-approved immunotherapies for melanoma**
  - **Adjuvant treatment**
    - High-dose IFN-a
    - Pegylated IFN-a
  - **Metastatic melanoma**
    - High-dose IL-2
    - Ipilimumab
    - Anti PD-1 antibodies (nivolumab or pembrolizumab)
- **Immunotherapy has been demonstrated to re-producibly result in long-term responses (not immediate) in (a minority of) patients with metastatic melanoma**

Yervoy™ prescribing information, 2012; Proleukin® prescribing information, 2012; Sylatron® prescribing information, 2012; Intron-A® prescribing information, 2012; NCCN, 2012.

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Select Ongoing Phase III Adjuvant Therapy Trials in Melanoma

Study	Author or Group	N	Data Expected
MM-ADJ-5 (standard HDI vs intermittent HDI)	Mohr	660	2012
MM-ADJ-8 (pegIFN vs LDI)	Garbe	880	2012/13
AVAST-M (bevacizumab vs observation, UK)	Lorigan	1320	2012/13
SWOG/ECOG 0008 (N2, N3) (CVD/IL-2/IFN vs HDI x 1 yr)	SWOG	410	2012
DERMA (MAGE-3 vs observation)	GSK	1300	2015
EORTC 18071 (ipilimumab vs observation)	EORTC	950	2015
ECOG 4697 (GM-CSF ± peptide vaccine vs placebo in HLA-A2 positive or negative patients)	ECOG	800	2015?
ECOG 1609 (ipilimumab vs HDI)	ECOG	1500	2015?
EORTC 18081 (pegIFN vs observation in ulcerated melanoma)	EORTC	1200	2017?

ClinicalTrials.gov

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Interleukin-2: Immunologic Background
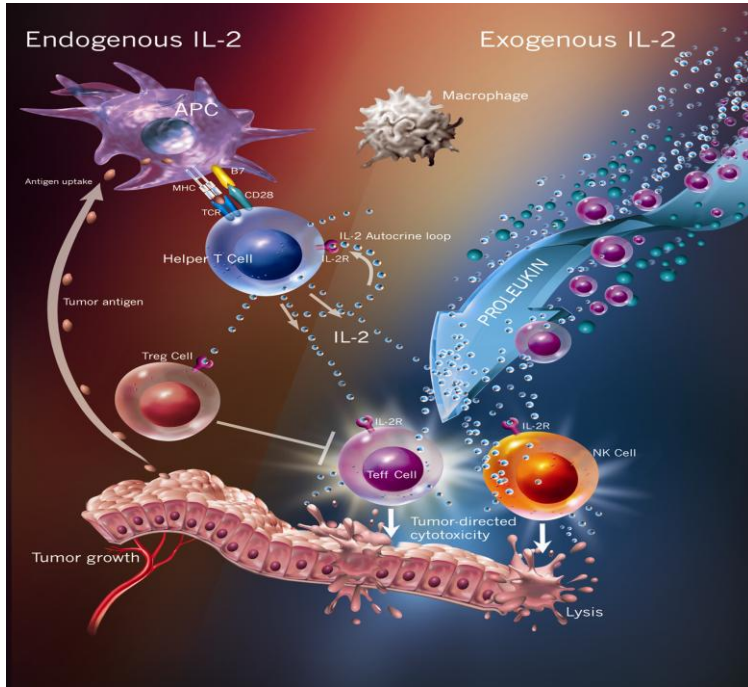
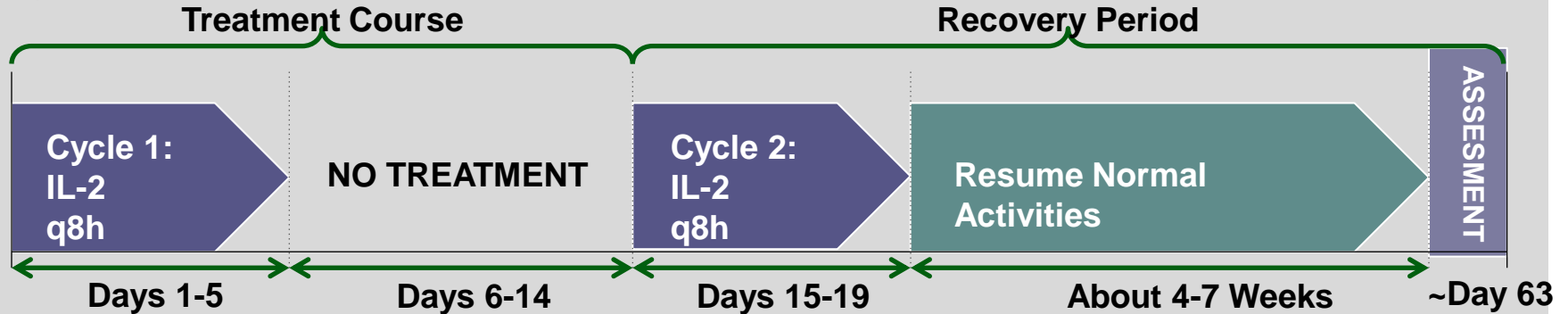Abbas AK and Lichtman AH. *Cellular and Molecular Immunology*. 2003

- Natural biologic immunomodulatory agent

- Autocrine T-cell growth factor
    – Produced exclusively by activated T cells
    – Predominantly CD-4+ (T-helper) lymphocytes

- Immunomodulatory actions:
    – Proliferation and activation of T cells
    – Immune response amplification
    – Enhanced antibody production by B cells
    – NK cell expansion and activation

- Stimulates T-cell secretion
    – Tumor necrosis factor (TNF)
    – Other cytokines (ie, IL-4, interferon-gamma)

- Stimulates proliferation and activation of:
    – All T cells, including cytotoxic
      T lymphocytes (CTLs) but also Regulatory T cells (Tregs)
    – Natural killer and Lymphokine-activated Killer (LAK) cells

Schedule for HD-Interleukin-2 Therapy

High-dose IL-2 (HD IL-2) has the potential to induce durable complete responses in a small number of patients

- 600,000 IU/kg (0.037 mg/kg) delivered by 15-min bolus i.v. infusion q8h for 14 doses

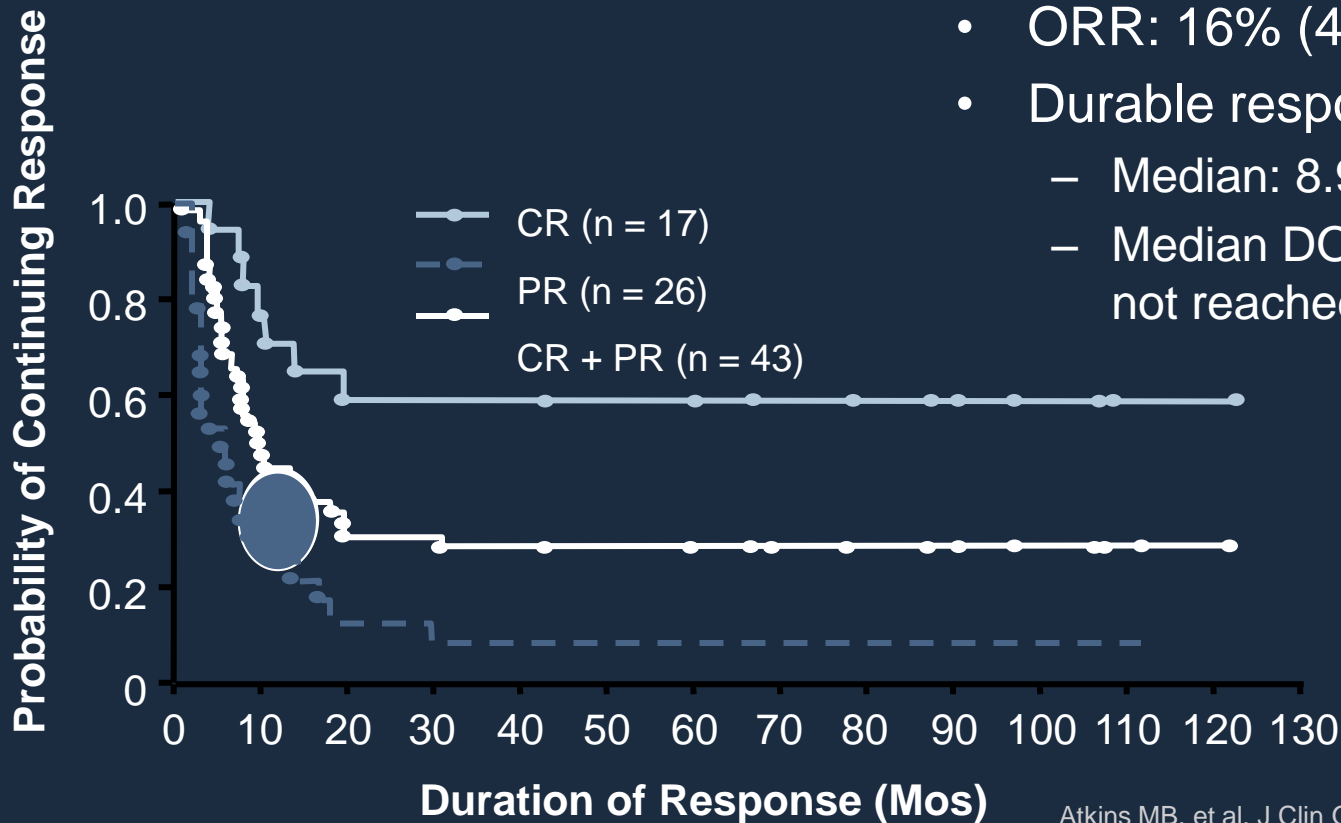- 720,000 IU/kg delivered by 15-min bolus i. v. infusion q8h for 12 doses

Typical Interleukin-2 Treatment Schedule

Treatment Course			Recovery Period	

Cycle 1: IL-2 q8h · NO TREATMENT · Cycle 2: IL-2 q8h · Resume Normal Activities · ASSESSMENT

Days 1-5 · Days 6-14 · Days 15-19 · About 4-7 Weeks · ~Day 63

- Additional courses of treatment are given if there is some shrinkage following the last course.

- Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge.

High-Dose IL-2 Therapy

- ORR: 16% (43/270)
- Durable responses
  - Median: 8.9 mos
  - Median DOR if CR achieved: not reached

Chart axes: Probability of Continuing Response (y-axis, 0 to 1.0) vs Duration of Response (Mos) (x-axis, 0 to 130)

Legend:
- CR (n = 17)
- PR (n = 26)
- CR + PR (n = 43)

Atkins MB, et al. J Clin Oncol. 1999;17:2105-2116.

Newer Immunotherapies for Advanced Melanoma: Checkpoint Blockade

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CTLA-4 and PD-1/L1 Checkpoint Blockade for Cancer Treatment
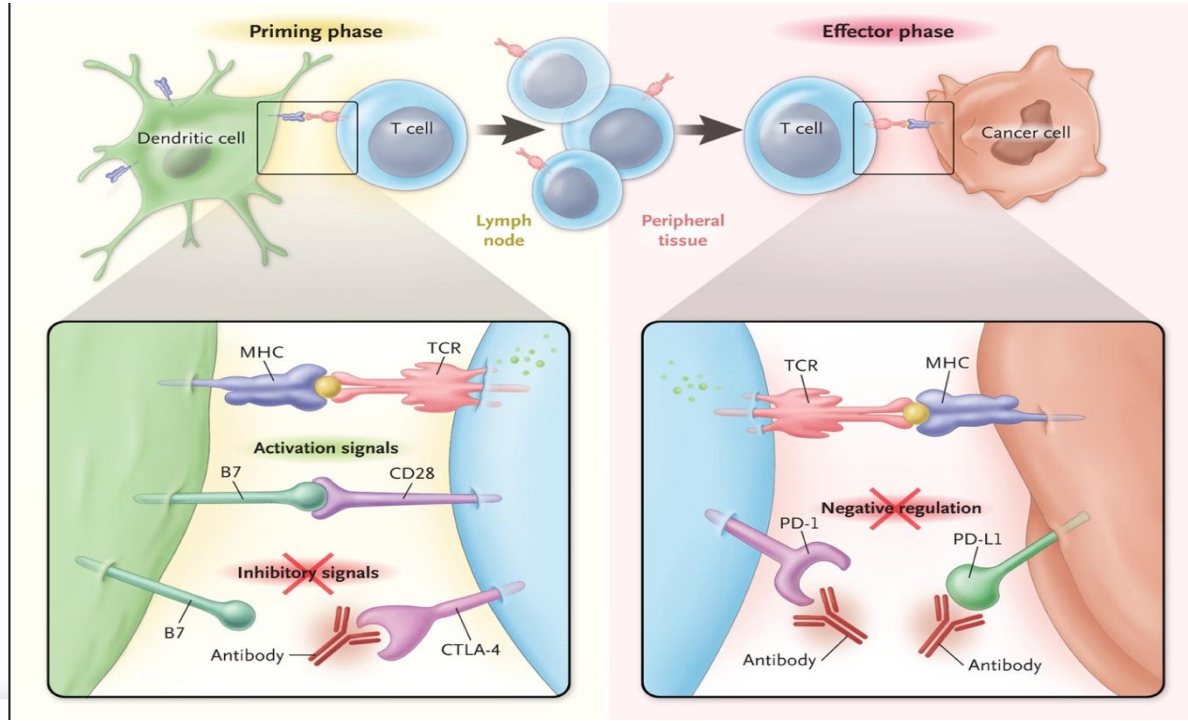
Ribas A. N Engl J Med. 2012;366:2517-2519. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Improved Survival With Ipilimumab
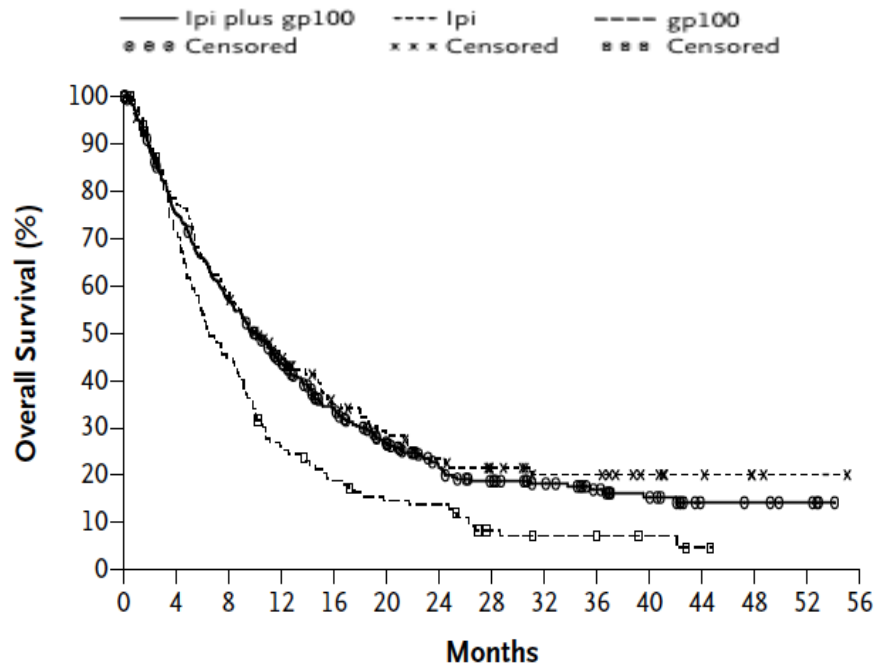
Standard dose:3 mg/kg x 4 doses q3wks with or without gp100
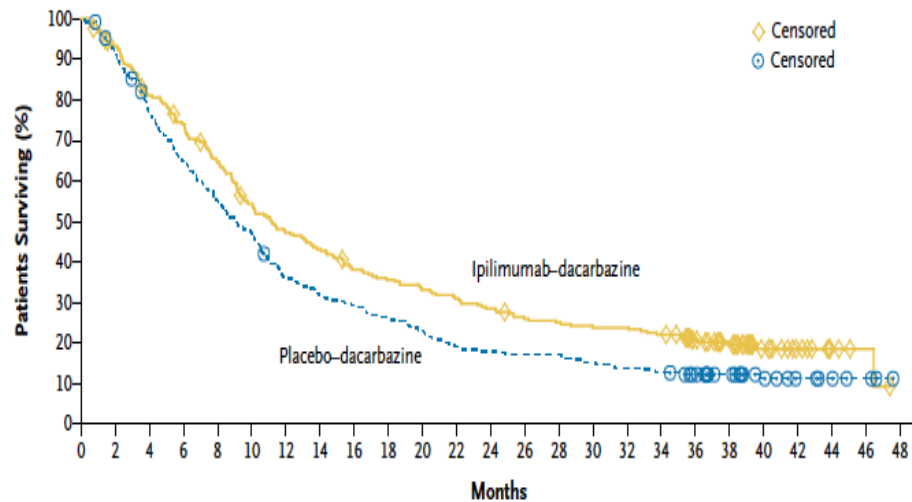
10 mg/kg x 4 doses q3wks, then q3mos + dacarbazine

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Future Directions in Immunotherapy:

Anti PD-1/PD-L1 antibodies
New Combinations

Induced Expression of PD-L1 (B7-H1) on Melanoma Cells by Infiltrating T Cells
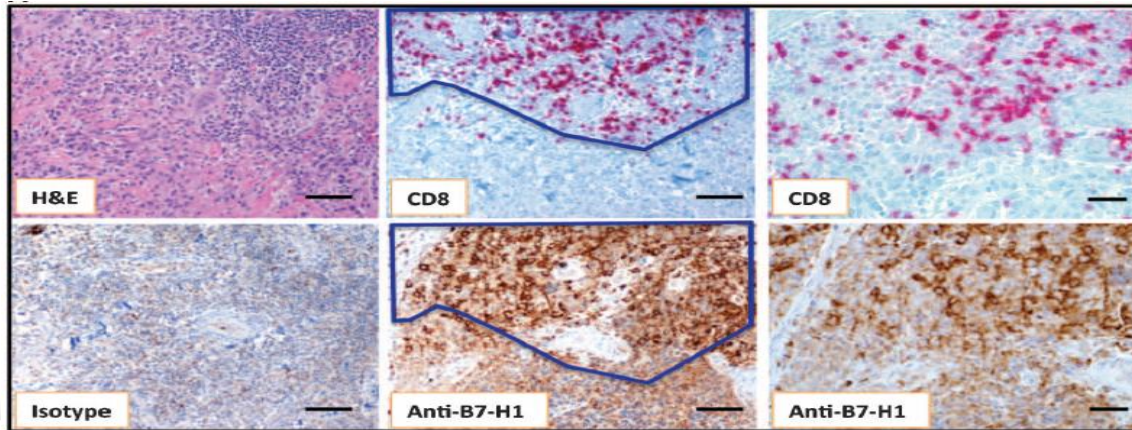
Induction of the B7-H1/PD-1 pathway may represent an adaptive immune resistance mechanism exerted by tumor cells in response to endogenous antitumor activity and may explain how melanomas escape immune destruction despite endogenous antitumor immune responses

Clinical Activity of MK-3475 in a Patient With Metastatic Desmoplastic Melanoma

54-yr-old male with desmoplastic melanoma after progressing on ipilimumab
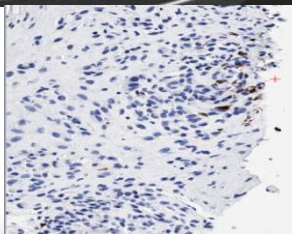
Baseline January 2012

April 2012

CTL Infiltrates in Regressing Metastatic Melanoma Lesion After MK-3475 Treatment
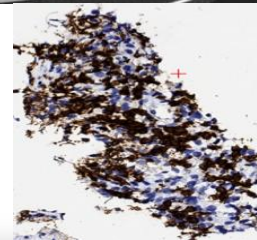
Baseline: February 29, 2012

August 20, 2012

CD8+ IHC

CD8+ IHC

Ribas A, et al. ASCO 2013. Abstract 9009.

Activity of Anti-PD-1/PD-L1 in Patients With Advanced Melanoma

Agent	Pts, n	ORR (at Optimal Dose), %	Grades 3/4 Tx-Related AEs, %	6-Mo PFS, %	12-Mo PFS, %	Median PFS, Mos	1-Yr OS, %	2-Yr OS, %
Nivolumab (anti-PD-1)[1-3]	104	31 (41)	22	41	36	3.7	62	43
MK-3475 (anti-PD-1)[4,5]	135	38 (52)	13	NA	NA	> 7	81	NA
BMS559 (anti-PD-L1)[6]	55	17	5	NA	NA	NA	NA	NA
MPDL3280A (anti-PD-L1)[7]	44	29*	36	43	NA	NA	NA	NA

*Includes 4 patients with UM without a response.

1. Topalian SL, et al. J Clin Oncol. 2014;32:1020-1030. 2. Sznol M, et al. ASCO 2013. Abstract 9006.
3. Topalian SL, et al. N Engl J Med. 2012;366:2443-2454. 4. Ribas A, et al. ASCO 2013. Abstract 9009.
5. Hamid O, et al. N Engl J Med. 2013;369:134-144. 6. Brahmer JR, et al. N Eng J Med. 2012. 366:2455-2465. 7. Hamid O, et al. ASCO 2013. Abstract 9010.

KEYNOTE-006 (NCT01866319):
International,[a] Randomized, Phase III Study

Patients

- **Unresectable, stage III or IV melanoma**
- **≤1 prior therapy, excluding anti– CTLA-4, PD-1, or PD-L1 agents**
- **Known *BRAF* status[b]**
- **ECOG PS 0-1**
- **No active brain metastases**
- **No serious autoimmune disease**

R 1:1:1

Pembrolizumab 10 mg/kg IV Q2W

Pembrolizumab 10 mg/kg IV Q3W

Ipilimumab 3 mg/kg IV Q3W x 4 doses

Stratification factors:
- **ECOG PS (0 vs 1)**
- **Line of therapy (first vs second)**
- **PD-L1 status (positive[c] vs negative)**

- **Primary end points: PFS and OS**
- **Secondary end points: ORR, duration of response, safety**

[a]Patients enrolled from 83 sites in 16 countries.
[b]Prior anti-BRAF targeted therapy was not required for patients with normal LDH levels and no clinically significant tumor-related symptoms or evidence of rapidly progressing disease.
[c]Defined as membranous PD-L1 expression in ≥1% of tumor cells as assessed by IHC using the 22C3 antibody.

Ribas_AACR 2015_19Apr15

Tumor Response at the First Interim Analysis (RECIST v1.1, Central Review)

	Pembrolizumab Q2W n = 279	Pembrolizumab Q3W n = 277	Ipilimumab n = 278
ORR (95% CI)	33.7% (28.2-39.6)	32.9% (27.4-38.7)	11.9% (8.3-16.3)
Best overall response			
Complete response (CR)	5.0%	6.1%	1.4%
Partial response	28.7%	26.7%	10.4%
Stable disease	13.3%	14.1%	16.5%
NonCR/nonPD[a]	4.7%	5.1%	3.6%
Progressive disease (PD)	38.0%	41.2%	48.9%
Not evaluable[b]	7.2%	5.4%	18.3%
No assessment[c]	3.2%	1.4%	0.7%
Ongoing responses	89.4%	96.7%	87.9%
Median duration of response (range), days	251 (42+ to 251)	NR (42+ to 246+)	NR (33+ to 239+)

[a]Patients without measurable disease per central review at baseline who did not experience complete response or disease progression.
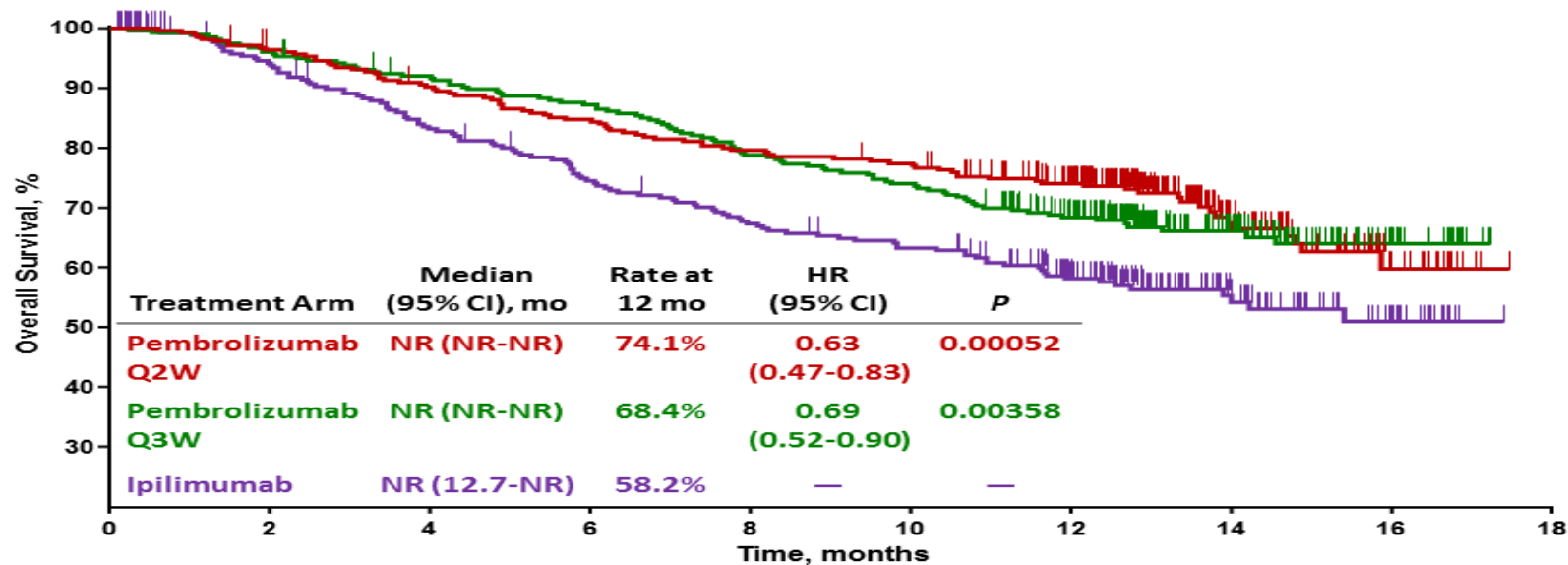[b]Target lesion not captured by postbaseline scans or for whom a target lesion was surgically removed.
[c]No postbaseline scan performed or were not able to be evaluated.
Analysis cut-off date: September 3, 2014.

Ribas_AACR 2015_19Apr15

OS at the Second Interim Analysis (IA2)

Treatment Arm	Median (95% CI), mo	Rate at 12 mo	HR (95% CI)	P
Pembrolizumab Q2W	NR (NR-NR)	74.1%	0.63 (0.47-0.83)	0.00052
Pembrolizumab Q3W	NR (NR-NR)	68.4%	0.69 (0.52-0.90)	0.00358
Ipilimumab	NR (12.7-NR)	58.2%	—	—

Overall Survival, %

Time, months

No. at risk

279	266	248	233	219	212	177	67	19	0
277	266	251	238	215	202	158	71	18	0
278	242	212	188	169	157	117	51	17	0

Analysis cut-off date: March 3, 2015.

Ribas_AACR 2015_19Apr15

Time to First Grade 3-5 Adverse Event[a] at IA1

Treatment Arm	Median (range), days	HR (95% CI)	P
Pembrolizumab Q2W	59.0 (4-357)	0.59 (0.43-0.80)	0.00037
Pembrolizumab Q3W	64.0 (4-283)	0.52 (0.38-0.72)	0.00003
Ipilimumab	39.5 (4-94)	—	—

No. at risk

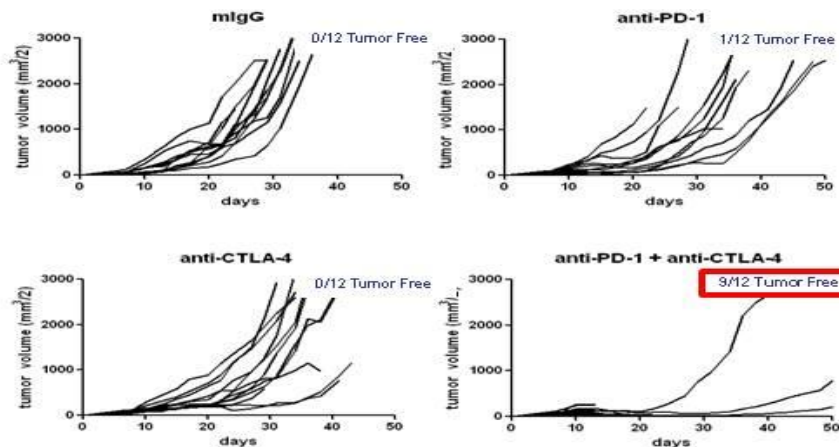|							
278	230	188	139	98	45	22	1
277	233	179	140	97	47	17	0
256	182	6	1	1	1	1	0
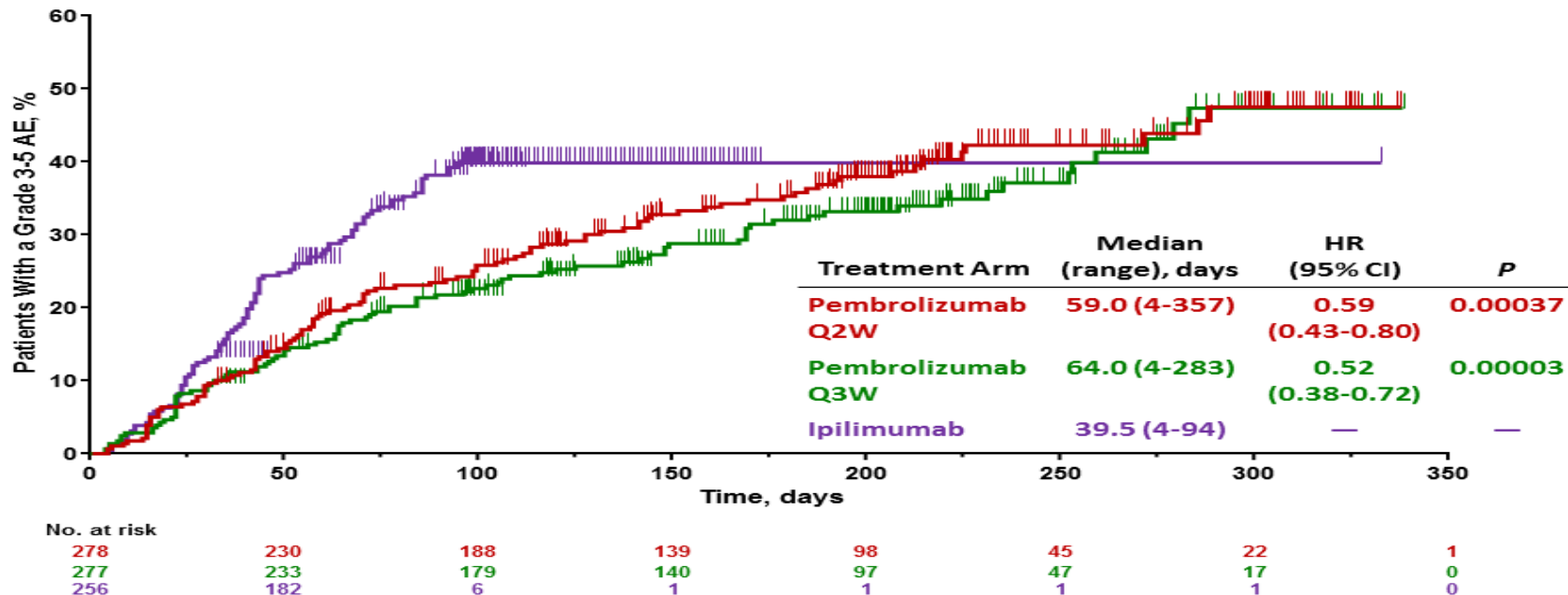
[a]Adverse events are presented regardless of causality.
Analysis cut-off date: September 3, 2014.
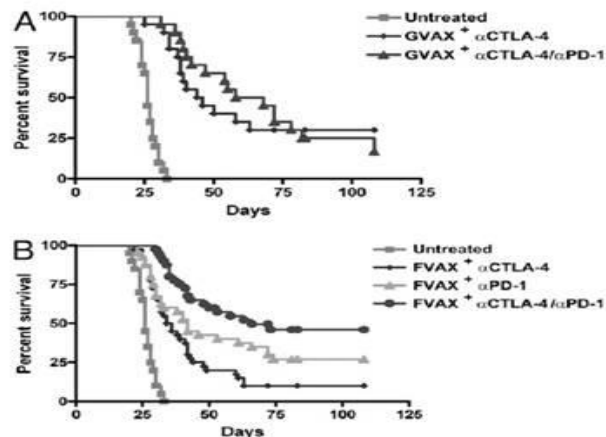
Ribas_AACR 2015_19Apr15

Antitumor Activity of Anti-CTLA-4 and Anti-PD-1 Antibodies in Murine Tumor Models

1. Korman et al. *J Immunol* 2007;178:48.37. 2. Selby et al. ASCO 2013, abs 3061. 3. Curran et al. *Proc Natl Acad Sci USA* 2010;107:4275-4280.

Presented By Jedd Wolchok at 2015 ASCO Annual Meeting

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Phase II CA209-069: Study Design

Eligible patients with unresectable stage III or IV melanoma
- **Treatment-naïve**
- **BRAF WT (N = 100) or MT (N = 50)**
- **Stratified by BRAF status**

R 2:1

NIVO 1 mg/kg + IPI 3 mg/kg → Q3Wx4 → **NIVO 3 mg/kg** → Q2W

Double-blind

Placebo + IPI 3 mg/kg → Q3Wx4 → **Placebo** → Q2W

Treat until: disease progression[a] or unacceptable toxicity
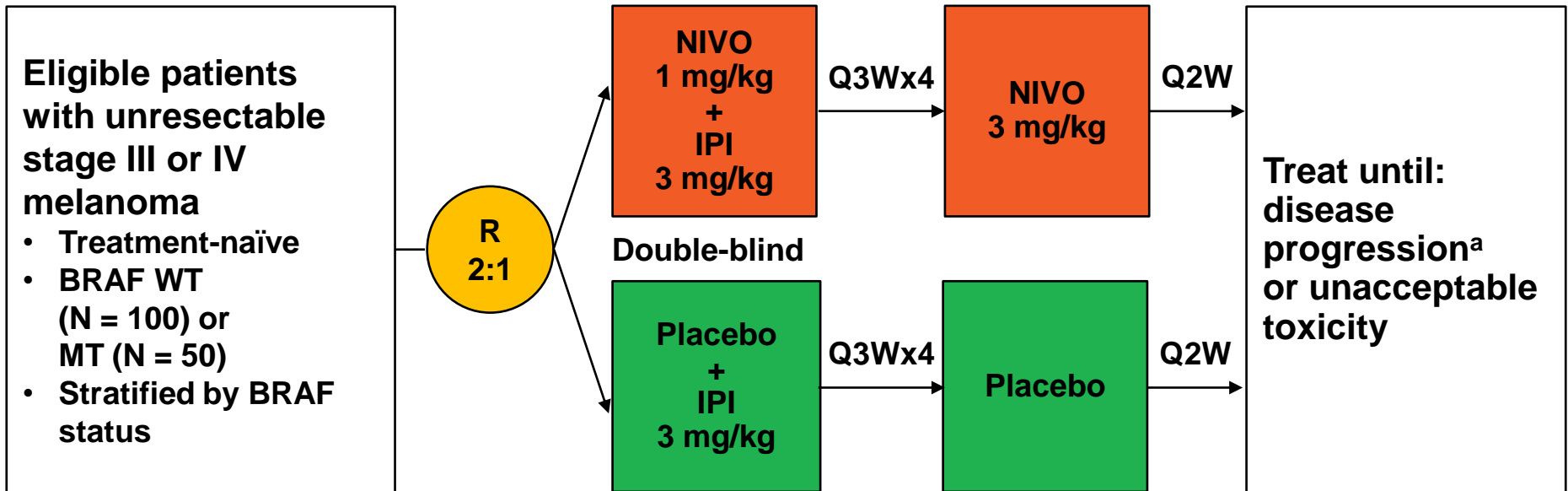
[a]Treatment beyond initial investigator-assessed RECIST v1.1- defined progression is permitted in patients experiencing clinical benefit and tolerating study therapy. IPI patients have an option to receive nivolumab monotherapy after progression. Upon confirmed progression and change of treatment, all patients are unblinded.

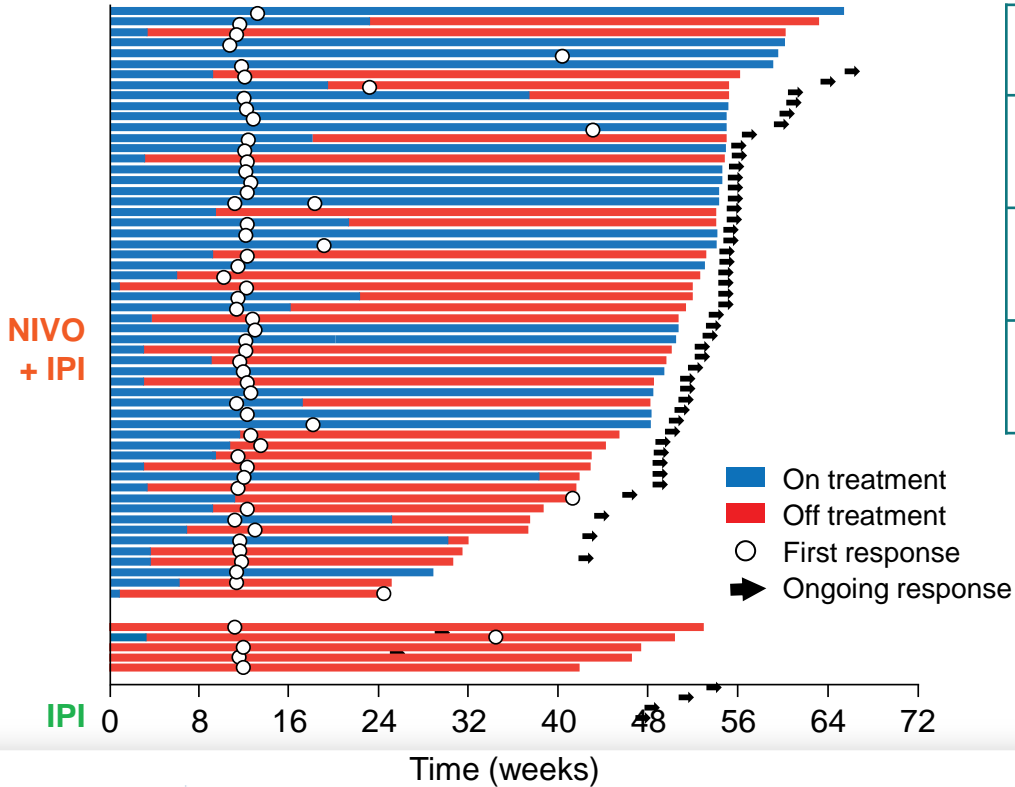MT = mutation; PFS = progression-free survival; Q3W = every 3 weeks; WT = wild type

Primary endpoint:
- ORR in BRAF WT patients

Secondary endpoints:
- PFS in BRAF WT patients
- ORR and PFS in BRAF MT pts
- Safety

Time to and Durability of Response(All Randomized Responders)

	NIVO + IPI (N = 95)	IPI (N = 47)
Median time to response, months (range)[a]	2.8 (2.3, 9.9)	2.7 (2.5, 7.9)
Median duration of response, months (range)[a]	NR (0–12.1)[b]	NR (3.5–9.8)[b]
Ongoing response among responders, n (%)[a]	46/56 (82)	4/5 (80)

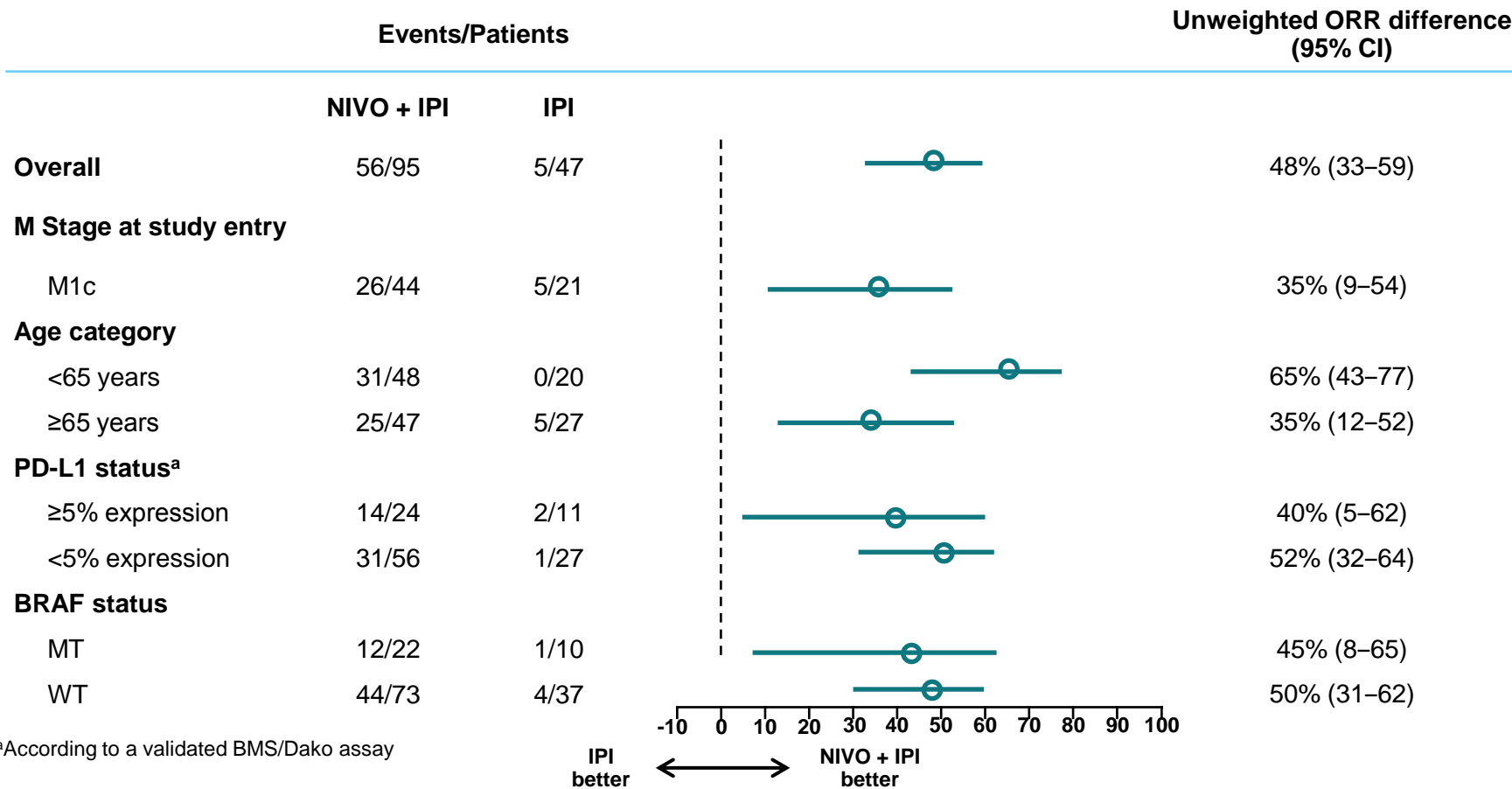[a]Minimum follow-up of 11 months from date of randomization
[b]Censored data (response ongoing)
NR = not reached

- 68% of patients (30/44) who discontinued the NIVO + IPI combination due to drug-related toxicity experienced a complete or partial response
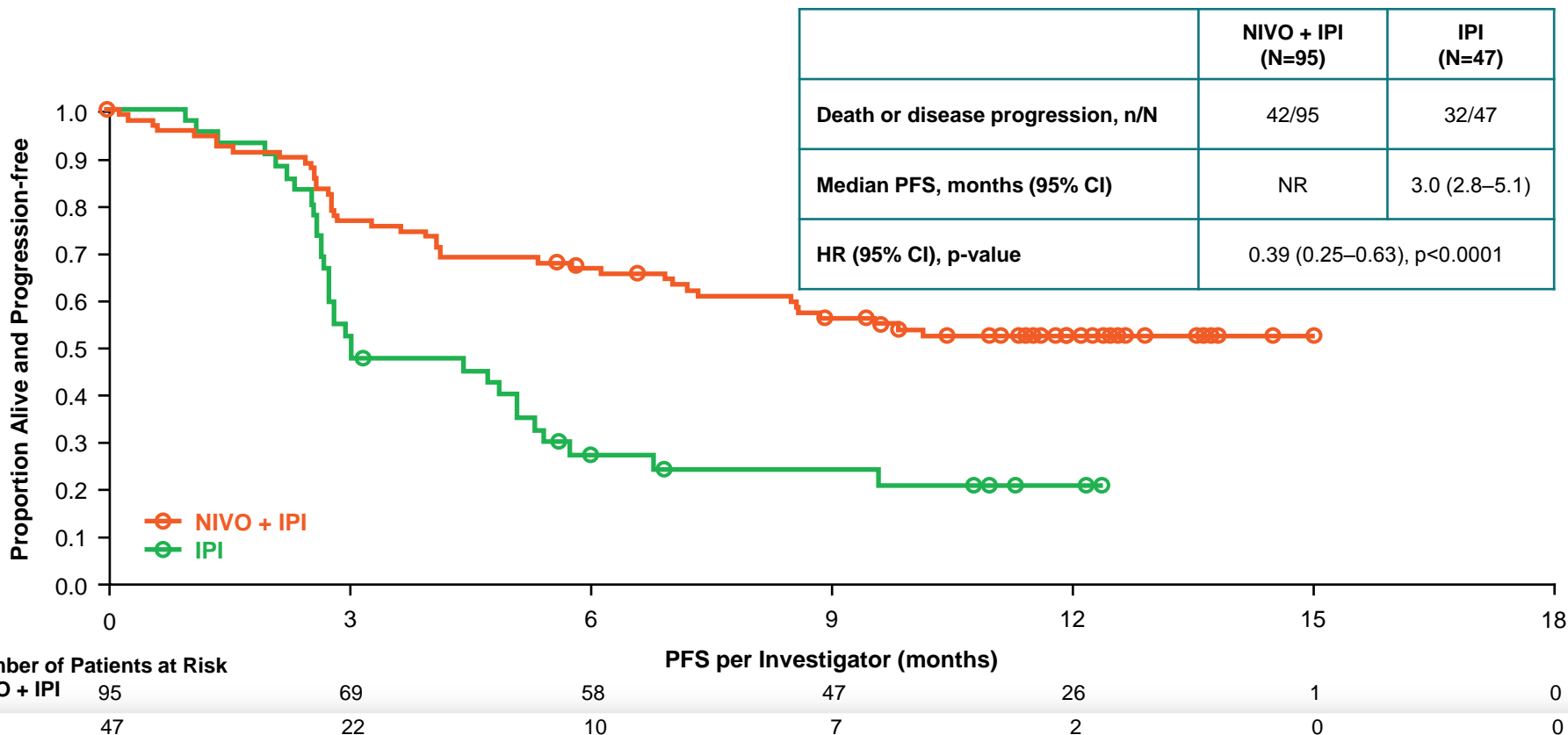
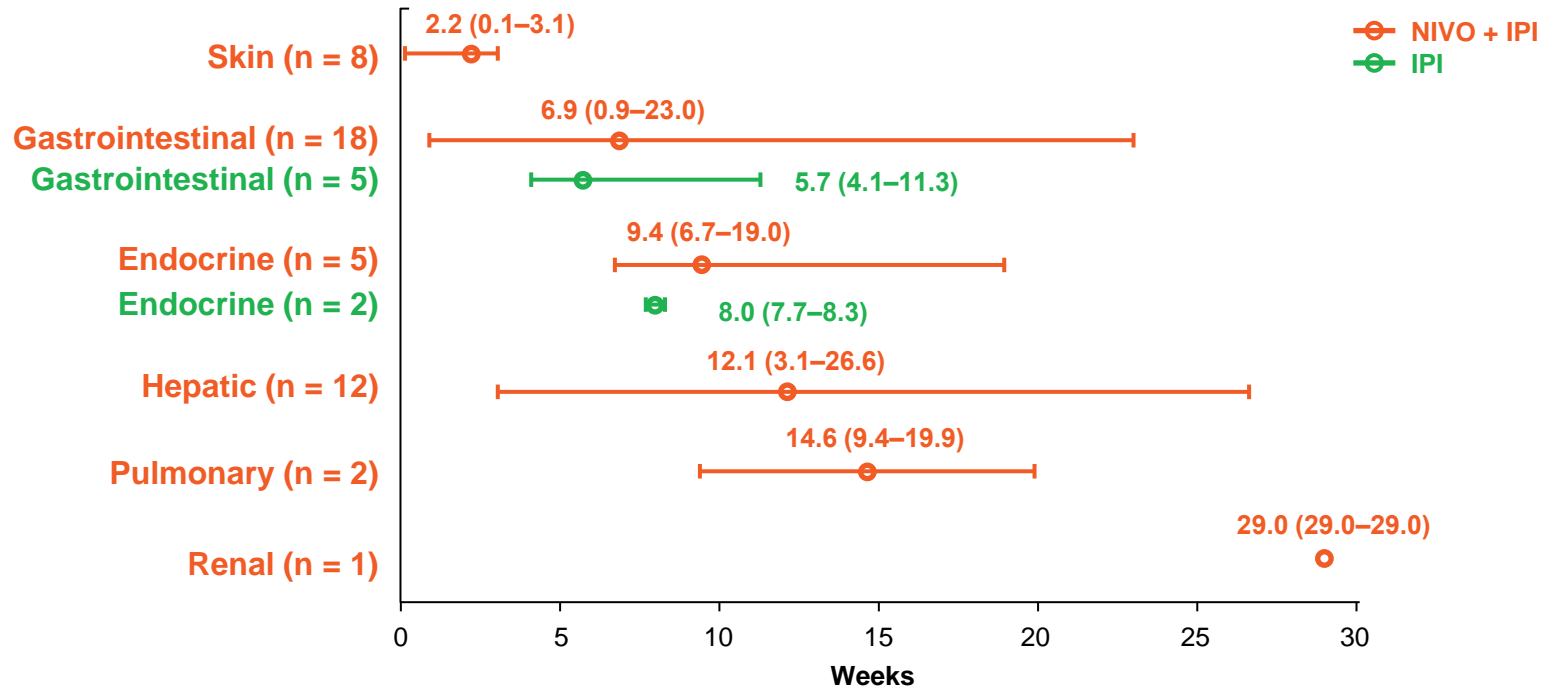Legend: On treatment / Off treatment / ○ First response / ➤ Ongoing response

X-axis: Time (weeks) — 0, 8, 16, 24, 32, 40, 48, 56, 64, 72

NIVO + IPI / IPI

ORR in Patient Subgroups

	Events/Patients			Unweighted ORR difference (95% CI)
	NIVO + IPI	**IPI**		
Overall	56/95	5/47		48% (33–59)
M Stage at study entry				
M1c	26/44	5/21		35% (9–54)
Age category				
<65 years	31/48	0/20		65% (43–77)
≥65 years	25/47	5/27		35% (12–52)
PD-L1 status[a]				
≥5% expression	14/24	2/11		40% (5–62)
<5% expression	31/56	1/27		52% (32–64)
BRAF status				
MT	12/22	1/10		45% (8–65)
WT	44/73	4/37		50% (31–62)

-10 0 10 20 30 40 50 60 70 80 90 100

IPI better ← → NIVO + IPI better

[a]According to a validated BMS/Dako assay

PFS in All Randomized Patients

	NIVO + IPI (N=95)	IPI (N=47)
Death or disease progression, n/N	42/95	32/47
Median PFS, months (95% CI)	NR	3.0 (2.8–5.1)
HR (95% CI), p-value	0.39 (0.25–0.63), p<0.0001	

Proportion Alive and Progression-free

PFS per Investigator (months)

Number of Patients at Risk

NIVO + IPI	95	69	58	47	26	1	0
IPI	47	22	10	7	2	0	0

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Time to Onset of Grade 3/4 Treatment-related Select AEs

Circles represent median; bars signify ranges

- Most grade 3/4 treatment-related select AEs occurred during the combination phase
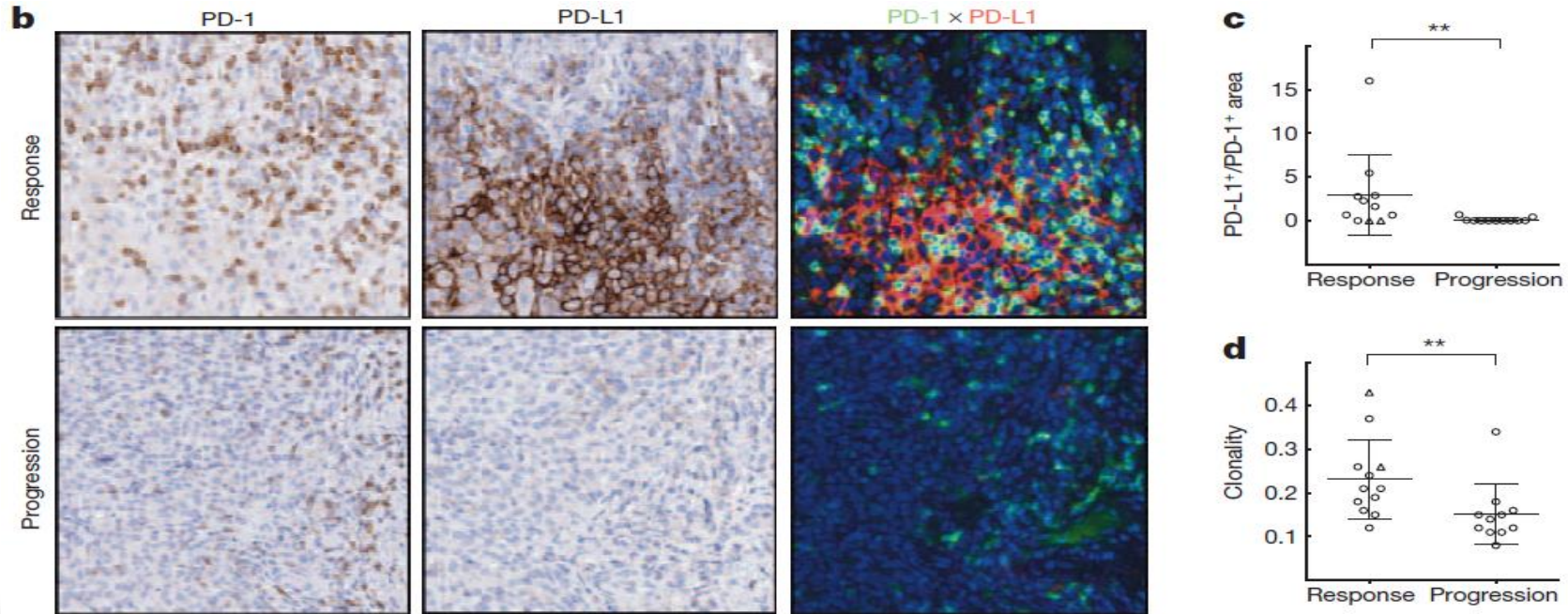
Is PD-L1 a valid Biomarker

- Assays are technically difficult and imperfect
    -No standard assay/each manufacturer has a
   proprietary antibody
   -Variable targets for "positive" (tumor vs immune cells)
    -Optimal specimen-paraffin embedded archive vs fresh vs met or primary

- In most studies, most responders are PDL-1 negative

- Threshold for declaring "positive" different in various studies (Nivo 067-27%
  PDL1+ vs Keynote 006 study-80% PDL-1+)

- And yet?????????

PD-L1, PD-1, and TIL are associated with response with response to anti-PD-1 therapy

- Tumor biopsies performed before and during pembrolizumab
- Performed quantitative IHC, quantitative multiplex immunofluorescence, and next generation sequencing for T-cell antigen receptors.

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Tumeh PC, et al., Nature Letter 2015
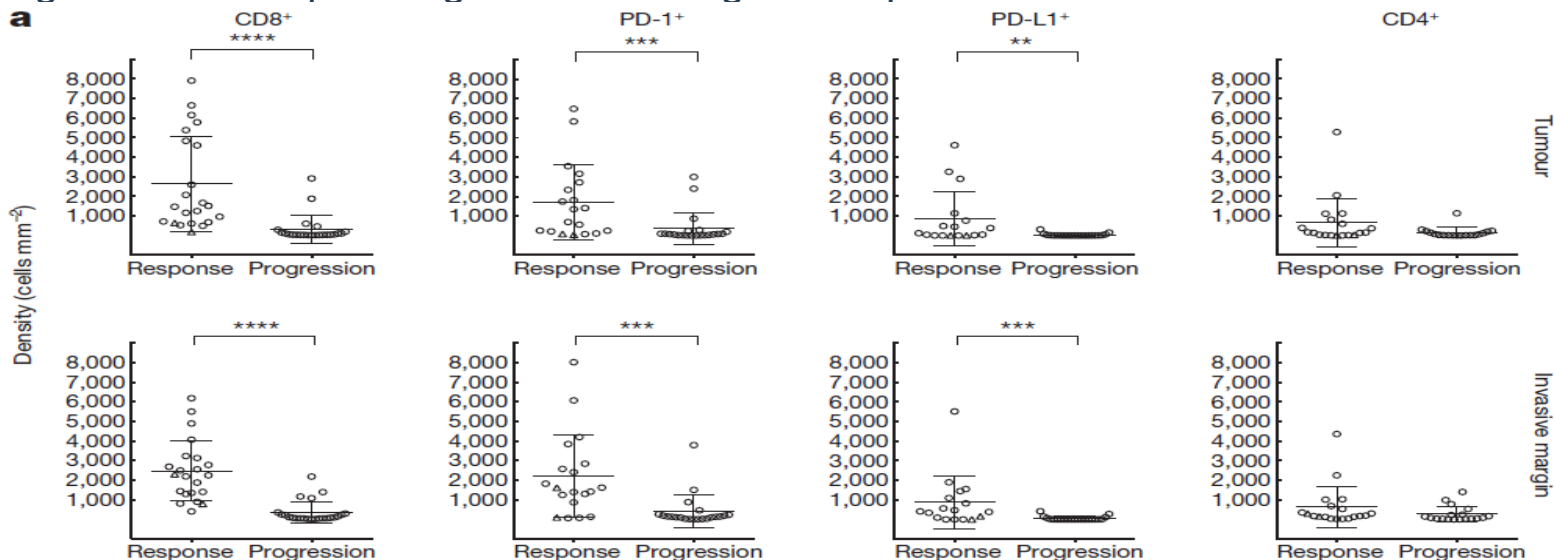
PD-1/PD-L1 interface and TCR clonality predict for anti-PD-1 response

Tumeh PC, et al., Nature Letter 2015

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Predictive model validated in separate panel of tumor biopsies for anti-PD-1 response

Extended Data Table 4 | Predictive model and validation

a

Variable	AUC (95% CI)*	P-value**
Tumour		
CD8+ Density	.91 (0.81, 1.00)	<0.001
PD-1+ Density	.80 (0.67, 0.94)	0.001
PD-L1+ Density	.71 (0.54, 0.88)	0.026
CD4+ Density	.66 (0.48, 0.84)	0.095
Invasive Margin		
CD8+ Density	.94 (0.88, 1.00)	<0.001
PD-1+ Density	.80 (0.66, 0.94)	0.001
PD-L1+ Density	.79 (0.64, 0.95)	0.002
CD4+ Density	.66 (0.48, 0.84)	0.095

- Accurately predicted 4/5 patients with progression and 9/9 patients with response to anti-PD-1 therapy.

b

Patient ID	CD8+ Density, Before Tx (Invasive Margin)	Predicted Probability of Response (Logistic Model)	Blinded Prediction	True Clinical Response (RECIST 1.1)
IGR - A	58	0.35	Progression	Progression
IGR - B	159	0.37	Progression	Progression
IGR - C	329	0.40	Progression	Progression
IGR - D	341	0.41	Progression	Progression
IGR - E	2120	0.75	Response	Stable
IGR - F	5466	0.98	Response	Progression
IGR - G	2211	0.76	Response	Response
IGR - H	3810	0.92	Response	Response
IGR - I	4294	0.95	Response	Response
IGR - J	4948	0.97	Response	Response
IGR - K	5565	0.98	Response	Response
IGR - L	6004	0.99	Response	Response
IGR - M	5951	0.99	Response	Complete Response
IGR - N	7230	0.99	Response	Complete Response
IGR - O	6320	0.99	Response	Complete Response

A Better Biomarker for Tumor Selection?

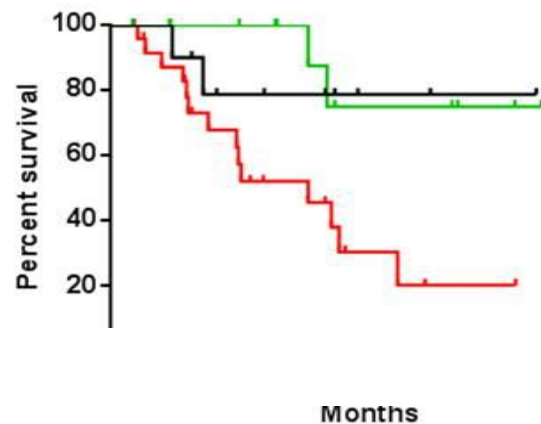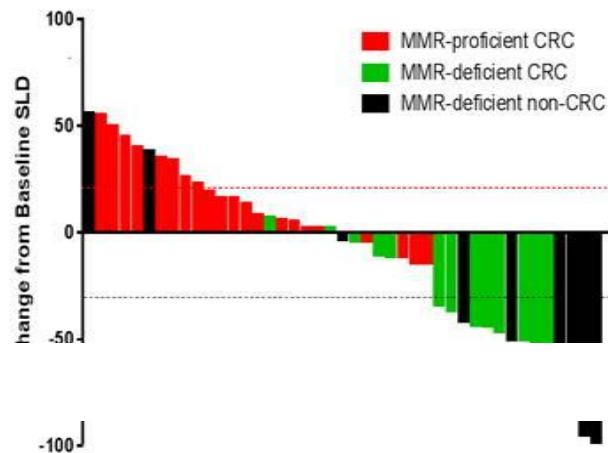Somatic mutation frequencies observed in exomes from 3,083 tumor–normal pairs.
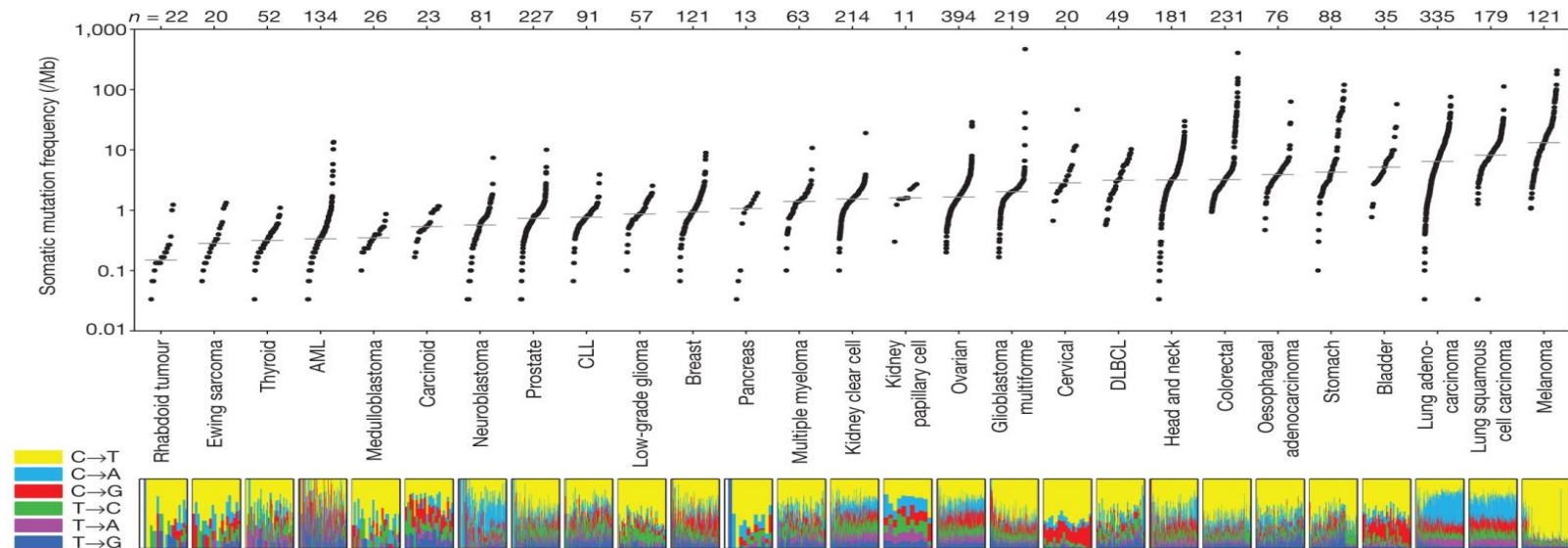
MS Lawrence *et al. Nature* **000**, 1-5 (2013) doi:10.1038/nature12213

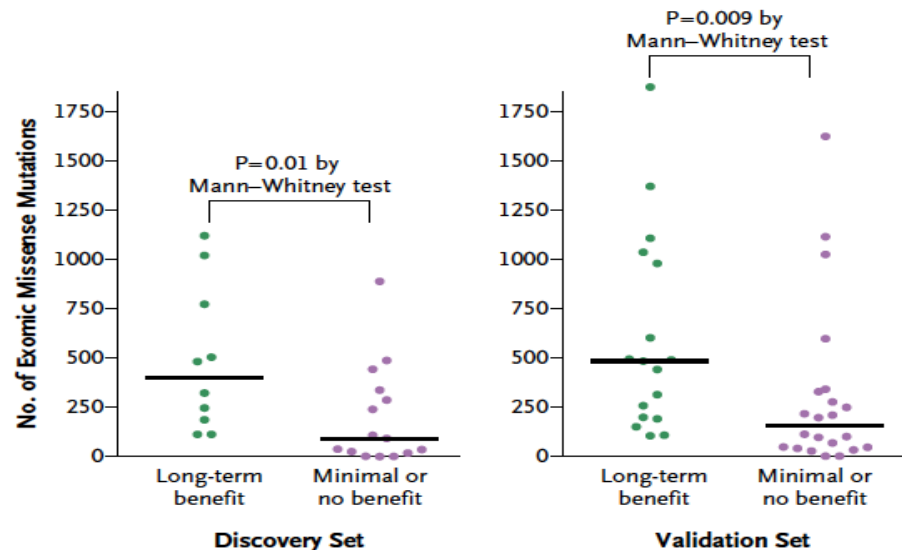# Genetic subsetting predicts response to anti-PD-1 therapy (Le, Diaz, et al., ASCO 2015)

	MMR-deficient CRC	MMR-proficient CRC	MMR-deficient non-CRC	
Objective Response Rate	62%	0%	60%	
Disease Control Rate	92%	16%	70%	

GI, GYN, prostate Ca

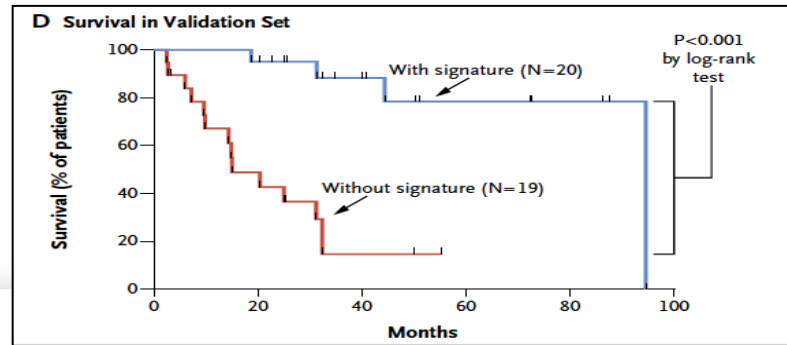# Association of Mutational Load with Clinical Benefit of anti-CTLA therapy in Melanoma Patients
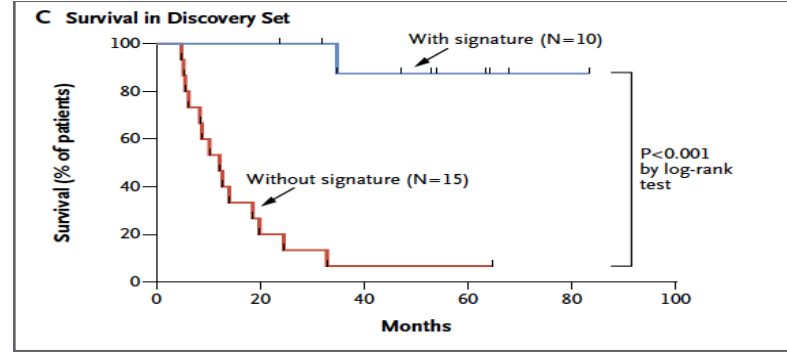

Snyder A, N Engl J Med, 2014
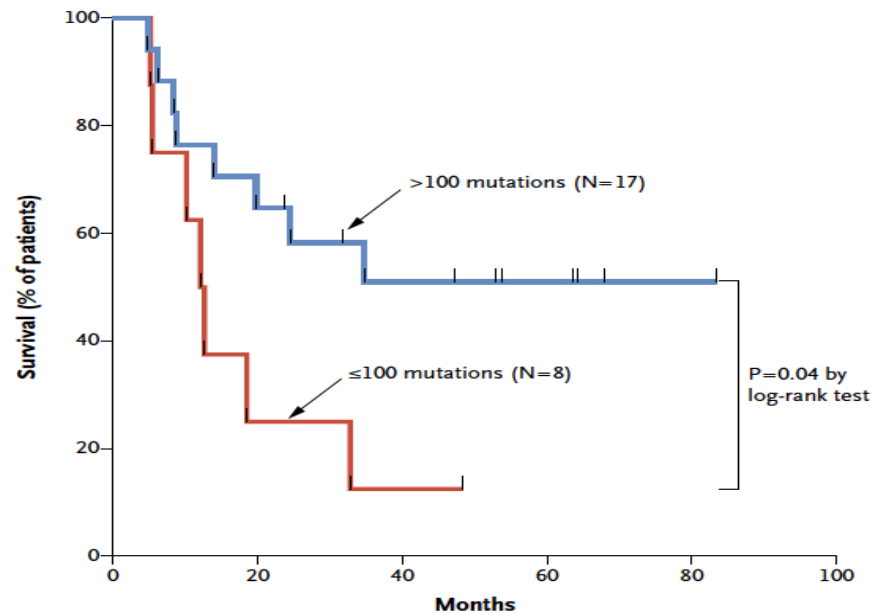
Association of Neoepitopes with Clinical Benefit of anti-CTLA4 therapy in Melanoma Patients

Snyder A, N Engl J Med, 2014
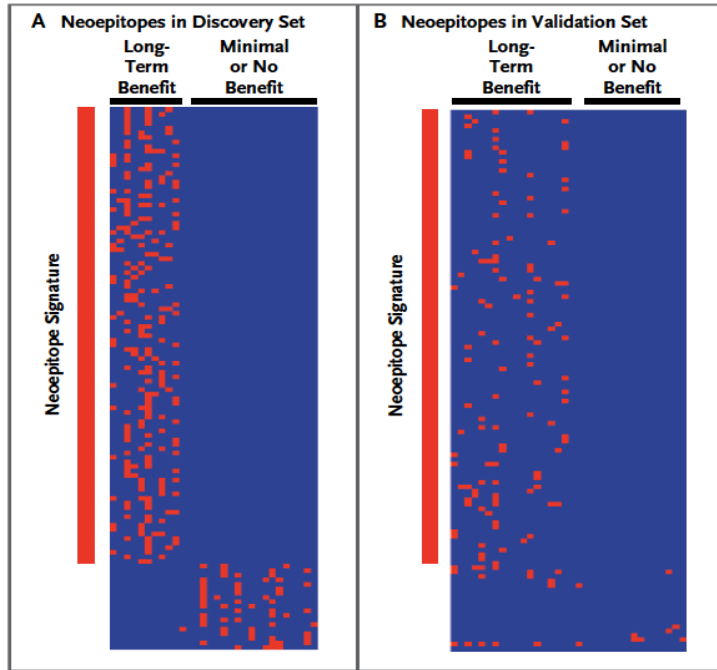
Conclusions

Nivo and Pembro and Nivo+Ipi all superior to Ipi.

These single agents (and possibly the combination should be standard first line therapy

Nivo +Ipi likely superior to Nivo alone (and Pembro?) but at a large financial and tolerability cost

Role for Biomarker of PD-L1 expression to help decide?

More trials needed

Audience Questions