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Immunotherapy for the Treatment of Melanoma

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Roswell Park Comprehensive Cancer Center

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Disclosures

- Consultant: Amgen, Roche, Nektar

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

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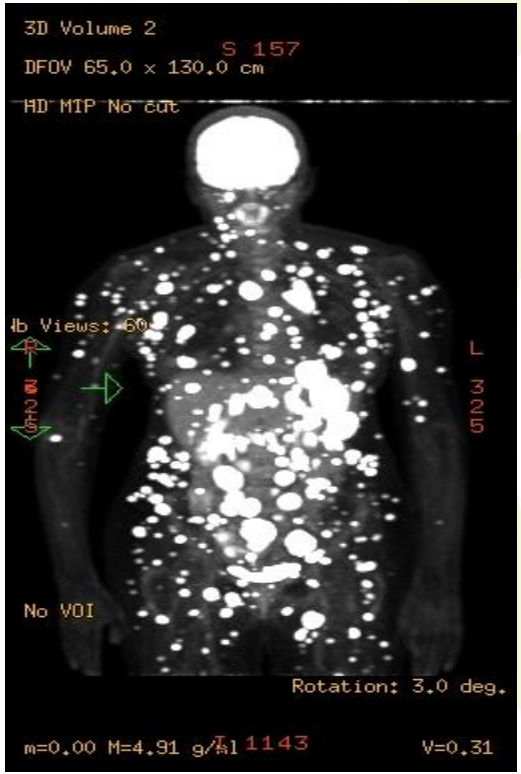
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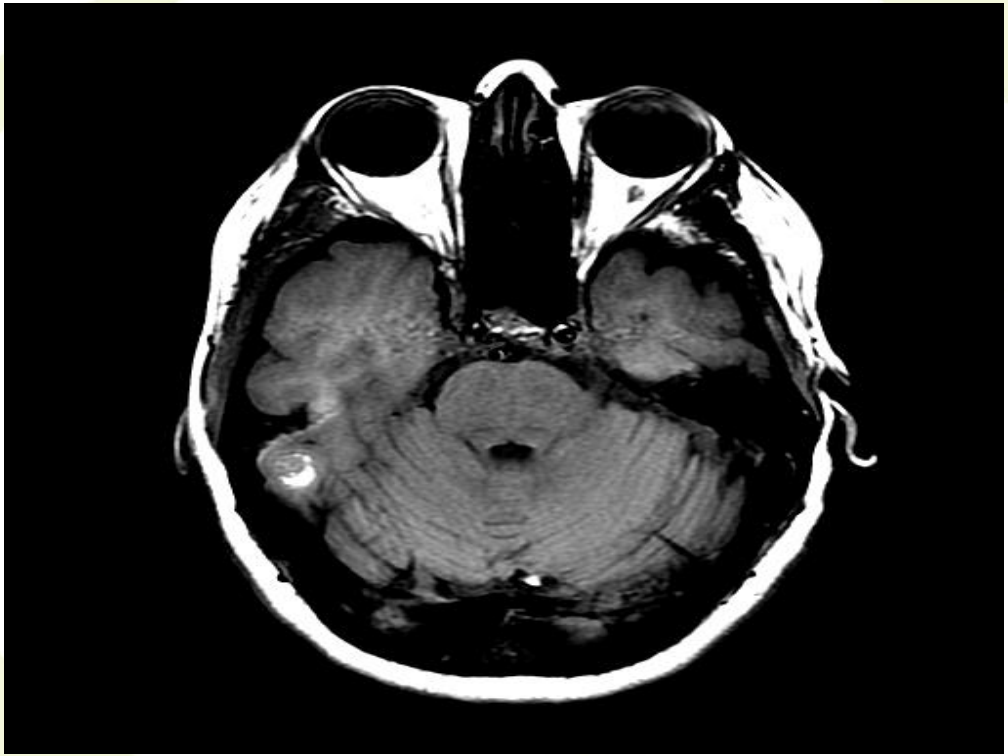

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Types of Immunotherapies for Melanoma

- Cytokines
  - Interferon-α 2b- Adjuvant therapy
  - Interleukin-2- Stage IV
- Oncolytic Virus
  - Modified Herpes Virus (Talimogene Laharparepvec; TVEC)
- Checkpoint antibodies
  - Anti-CTLA4 (ipilimumab)
  - Anti-PD1 (pembrolizumab, nivolumab)
    - (Avelumab for Merkel cell carcinoma – March 2017)

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Adjuvant Therapy

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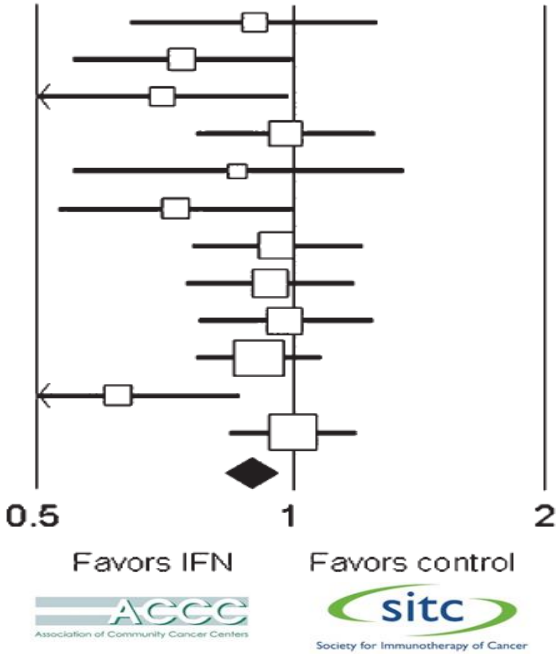
Adjuvant Treatment of High-Risk Melanoma

	HR	LL	UL	SE	Patients	Events (IFN/control)
NCCTG (Creagan, 1995)	0.90	0.64	1.25	0.17	264	68/72
E1684 (Kirkwood, 1996)	0.73	0.54	0.99	0.15	287	81/90
FCGM (Grob, 1998)	0.70	0.49	0.98	0.17	499	59/76
E1690 (Kirkwood, 2000)	0.98	0.76	1.24	0.12	642	194/186
SMG (Cameron, 2001)	0.86	0.54	1.35	0.23	96	31/36
E1694 (Kirkwood, 2001)	0.72	0.52	0.99	0.16	880	52/81
WHO (Cascinelli, 2001)	0.95	0.76	1.20	0.12	444	146/138
UKCCCR (Hancock, 2004)	0.94	0.74	1.17	0.12	674	151/156
EORTC18871 (Kleeberg, 2004)	0.98	0.77	1.23	0.12	484	137/202
EORTC18952 (Eggermont, 2005)	0.91	0.76	1.07	0.09	1388	534/292
DeCOG (Garbe, 2008)	0.62	0.44	0.86	0.17	296	65/88
EORTC18991 (Eggermont, 2008)	1.00	0.84	1.18	0.09	1256	256/257
	0.89	0.83	0.96	0.04		



Mocellin et al. JNCI. 2010

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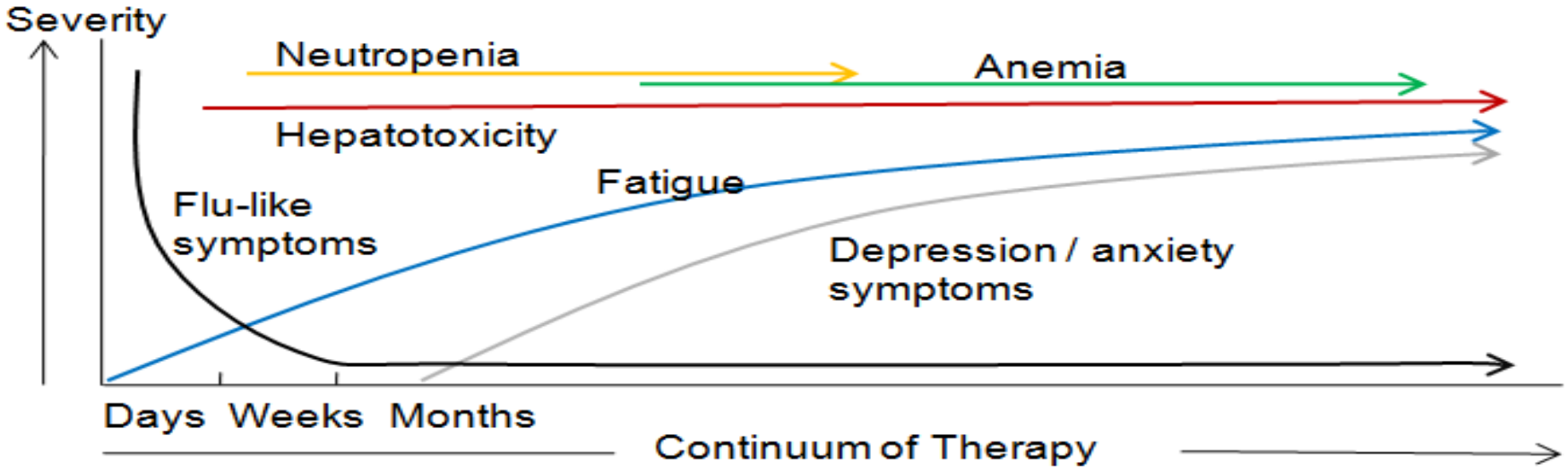
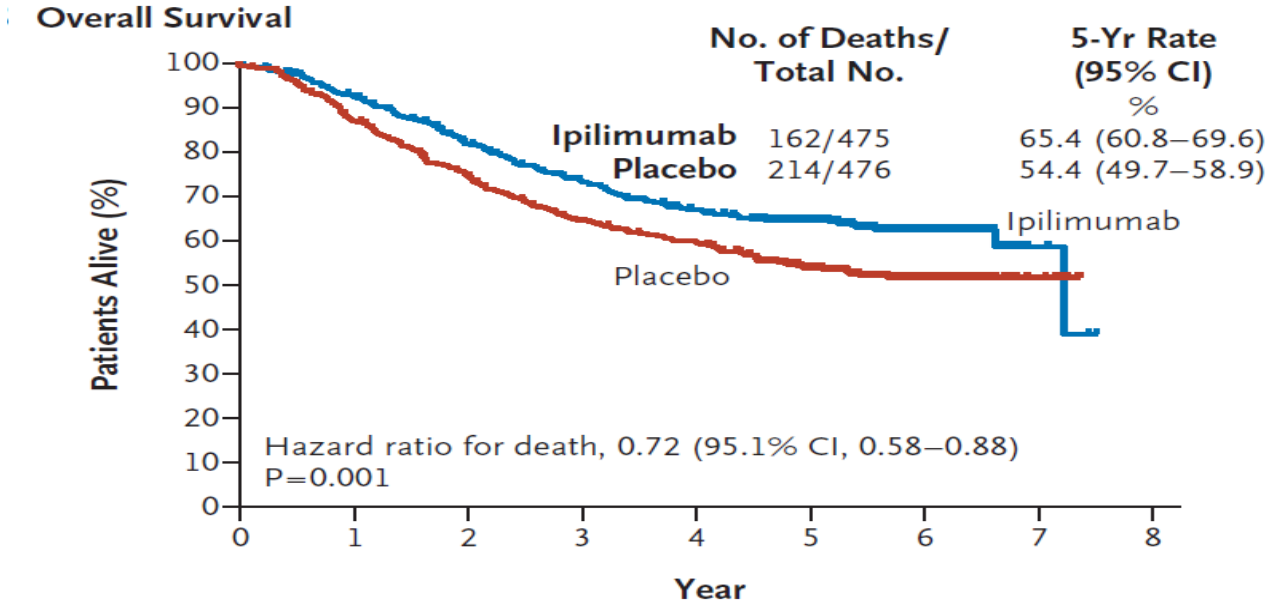
Toxicity of Adjuvant Interferon-α



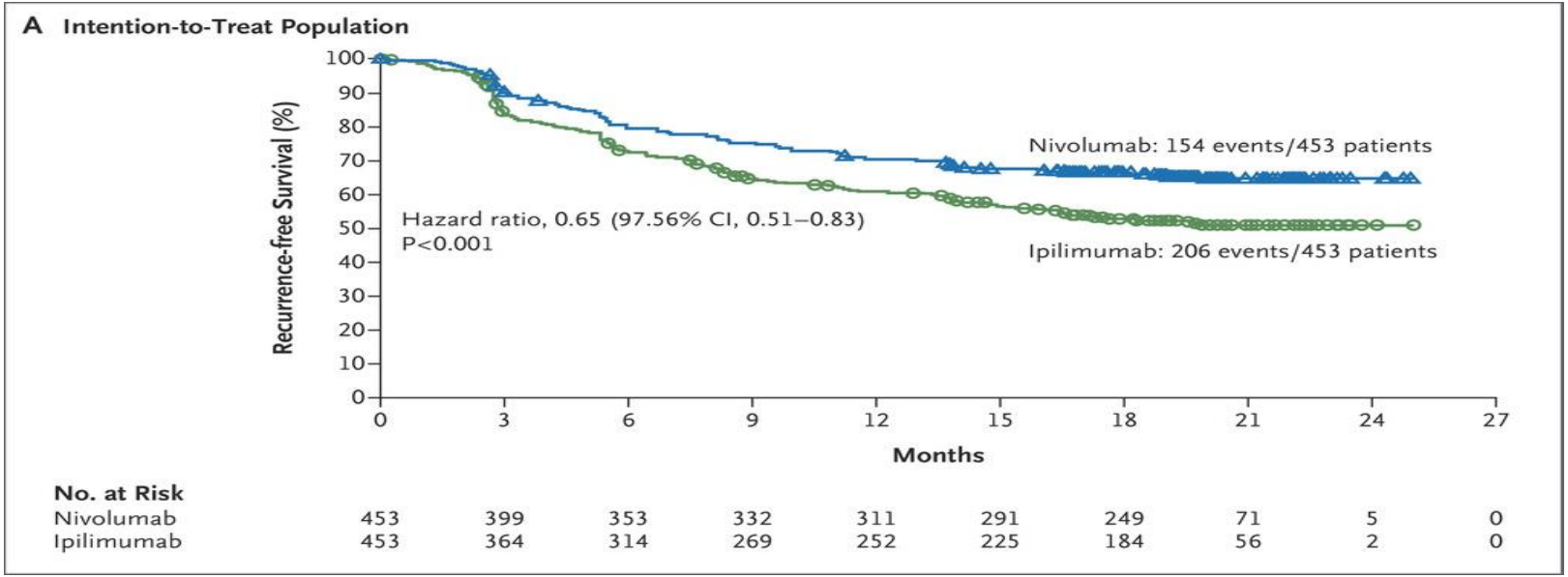
http://www.sinobiological.com/Interferon-Side-Effects-a-6085.html

Adjuvant Ipilimumab in High-Risk Melanoma



Eggermont *et al*. NEJM 2016

Adjuvant nivolumab vs ipilimumab in High-Risk Melanoma



Weber *et al*. NEJM 2017

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Systemic Therapy/Injectables

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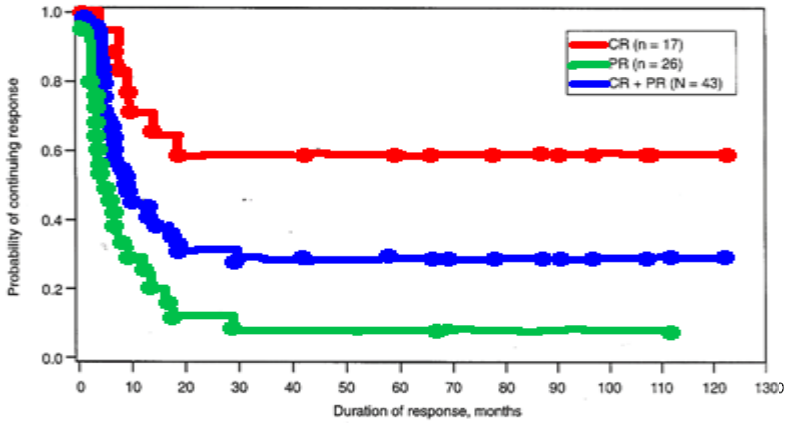
High Dose Interleukin-2 Therapy (HD IL-2) : Durable Responses

- HD IL-2 produces durable responses in 6%-10% of patients with advanced melanoma
- Few relapses in patients responding for over 2.5 years (cured?)
- FDA approval for melanoma in 1998
- High toxicity



Atkins et al. J Clin Oncol. 1999

Atkins et al. J Clin Oncol. 1999

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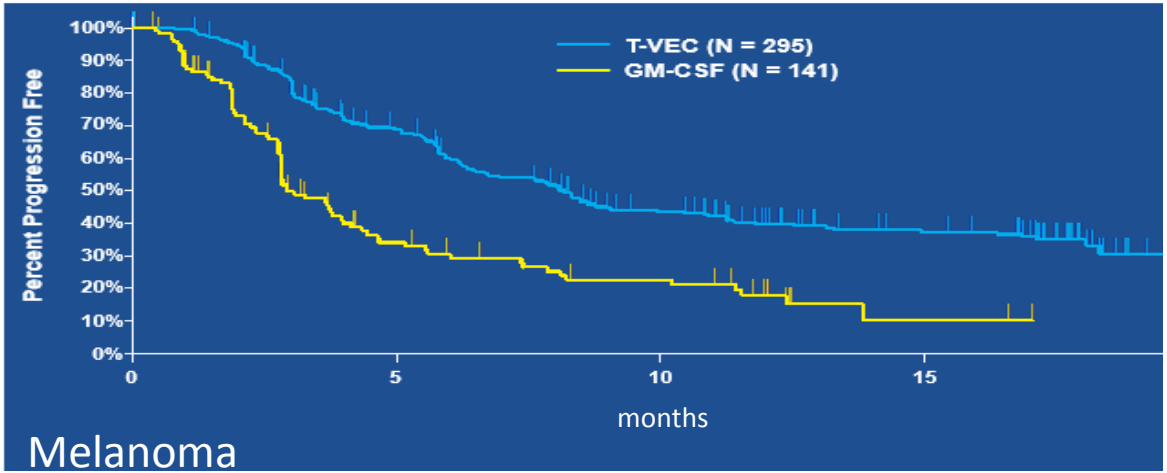
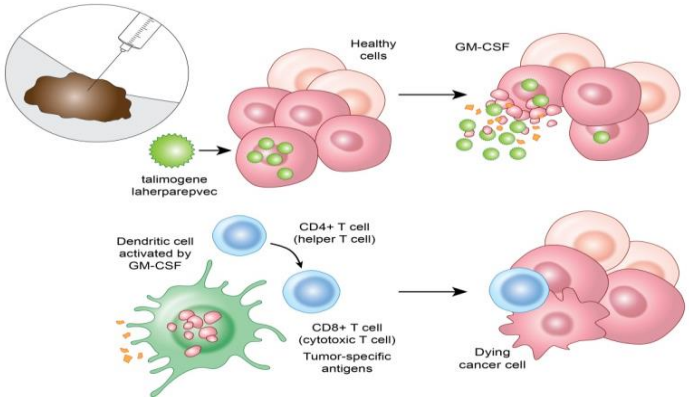
Phase III Trial of T-VEC vs GM-CSF PFS per Investigator



Melanoma



Andtbacks et al. ASCO 2013; LBA9008

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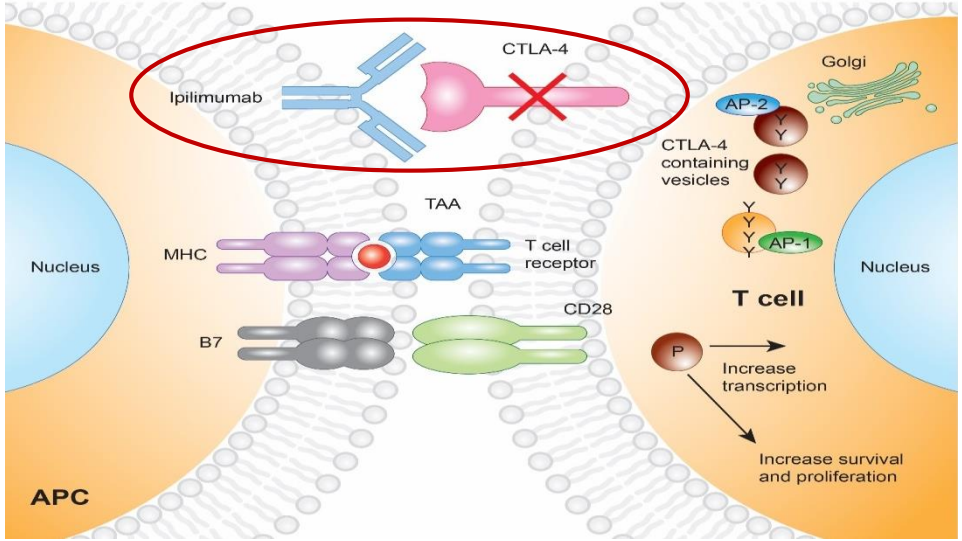
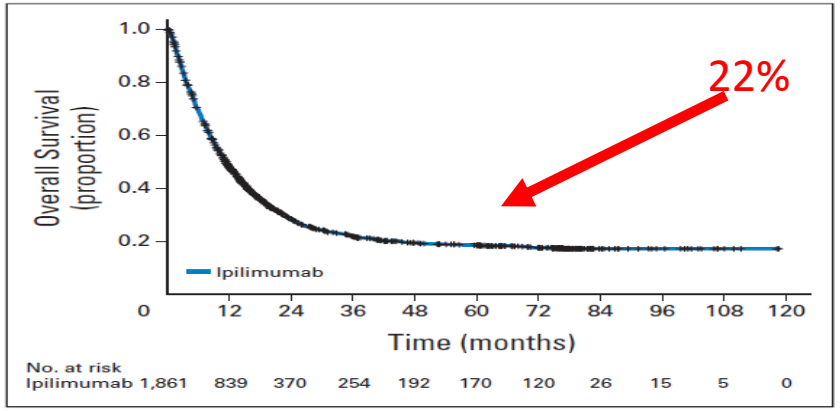
Ipilimumab & Immune Check-Point Blockade





Luke et al, Oncologist 2013
Schadendorf et al, J Clin Oncol 2015

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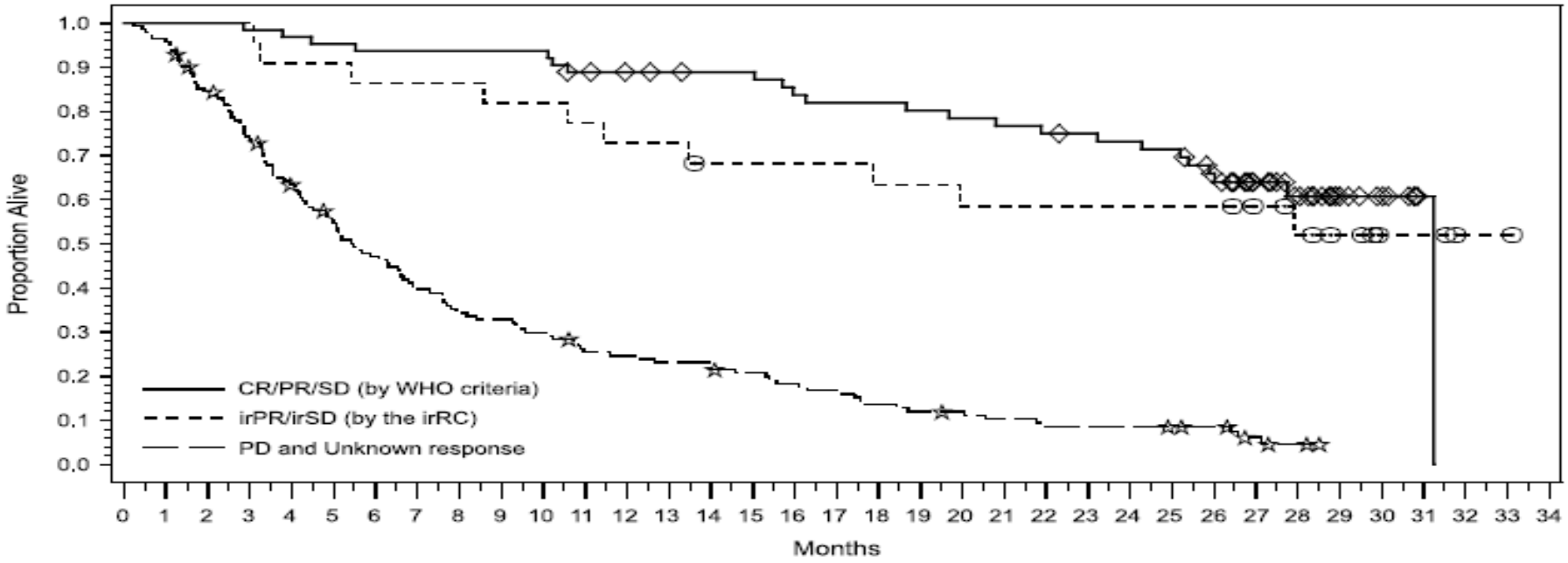
Immune Related Response Criteria



Wolchok et al. Clin Can Res 2009

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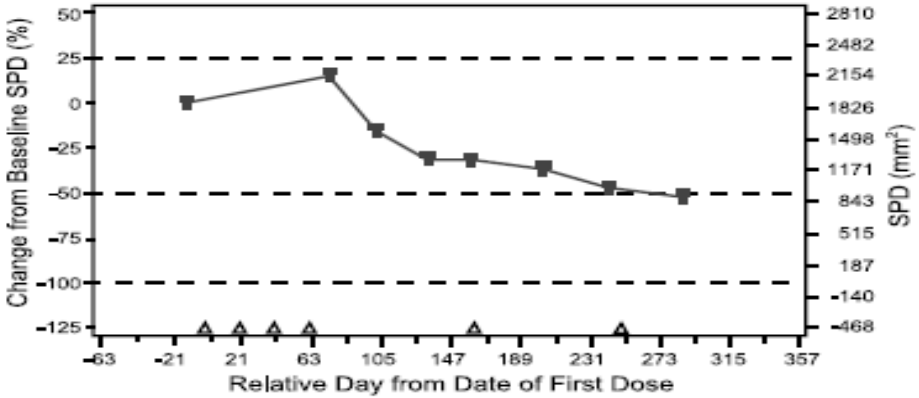
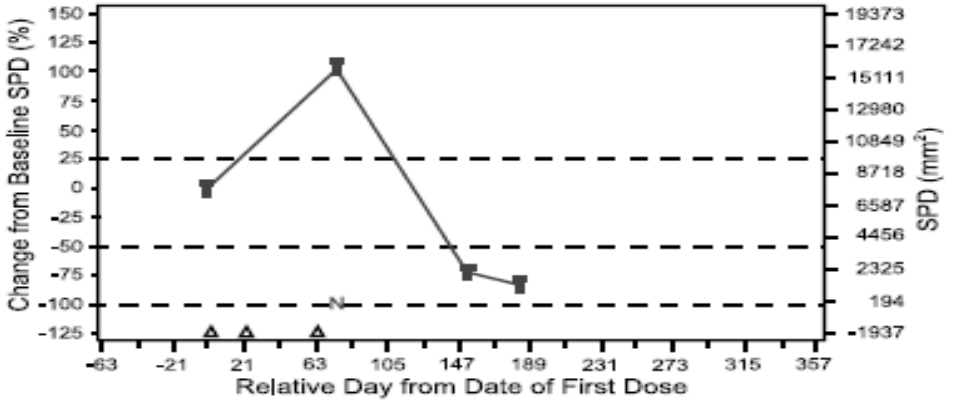
Immune Related Response Criteria

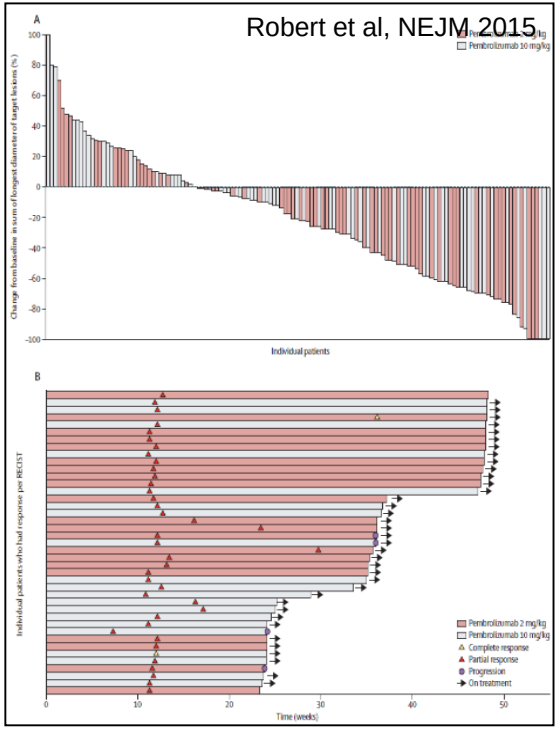




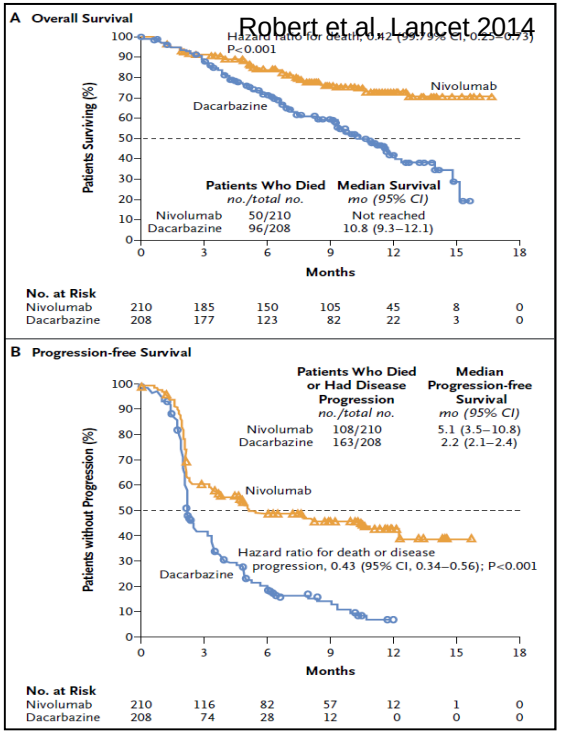
Wolchok et al. Clin Can Res 2009

Anti-PD1 in Melanoma

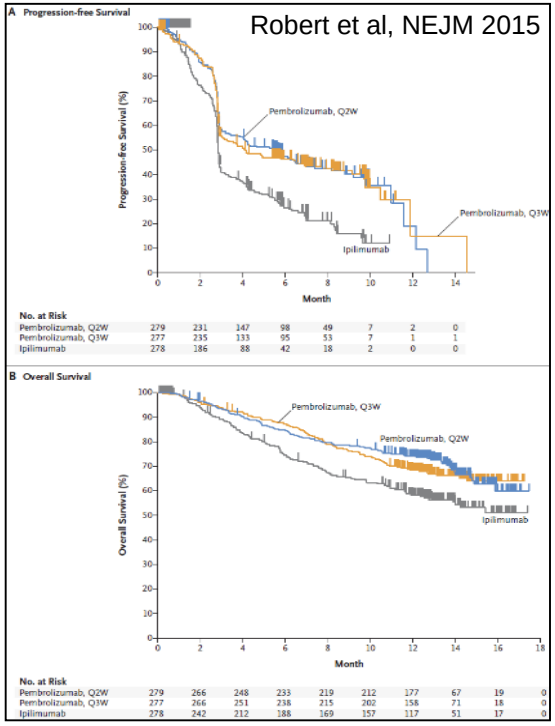
Anti-PD1 (pembrolizumab) *after* ipilimumab



Front-line anti-PD1 (nivolumab) vs. DTIC in Melanoma(BRAF WT)



Front-line anti-PD1 (pembrolizumab) vs. ipilimumab



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Case #1: stage III→stage IV-M1a

TL, male patient in 30s

- Therapeutic lymph node dissection of left inguinal node on 1/2017 revealed 3+ stage III melanoma of unknown primary origin
  - Randomized to pembrolizumab on SWOG-1404 adjuvant trial
  - 6 cycles: no significant irAEs
- Relapse in L neck and R back soft tissue

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Case #1: stage IV-M1a Oligometastatic M1a BRAFwt on adjuvant pembrolizumab

- Systemic therapy
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab 3 mg/kg x 4
  - Nivolumab plus Ipilimumab
  - Targeted Rx based on next-generation sequencing
  - High-dose IL-2
- Lesional therapy
  - Talimogene laherparepvec
  - Radiotherapy

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Best Therapies → Clinical Trials

- Tumor-infiltrating lymphocytes (TILs)
- Neoantigen vaccines
- Oncolytic virotherapy
- New/improved immune checkpoint blockers w/immunomodulators
  - of resistance (indoleamine dioxygenase inhibitors)
  - agonistic costimulatory antibodies (CD137, OX40)
  - hypofractionated or stereotactic radiotherapy
- Molecularly-focused treatment paradigms—all immunomodulatory
  - Metabolic reprogramming
  - Next generation sequencing→molecular drivers and/or modifiers

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Case #2: same as #1, but BRAF^{V600}

Additional decision needed: MAPK inhibitor timing and choice

How I treated patient:

- Resected, sent tumor for research studies of tumor microenvironment
- Margins + at muscle—did not send for resection
- Ipilimumab at “adjuvant” dose of 10mg/kg with maintenance

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Case #2: metastatic melanoma BRAFm from unknown primary

RN, male patient in 50s

- Presented 8/2015 with pleuropulmonary disease symptoms and large R adrenal $BRAF^{V600E}$ metastasis
- Initial Therapy:
  - Dabrafenib and trametinib
  - Near CR x 18 months
  - Tolerated therapy with minimal side effects—mainly peripheral edema

Progression in R adrenal but controlled in lung; new small asymptomatic brain metastasis

- Checkmate 209204
  - Nivolumab plus ipilimumab for metastatic melanoma to brain

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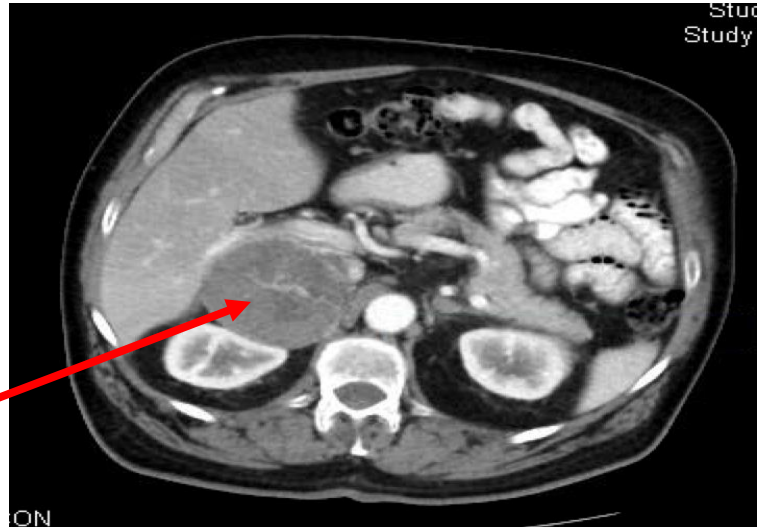
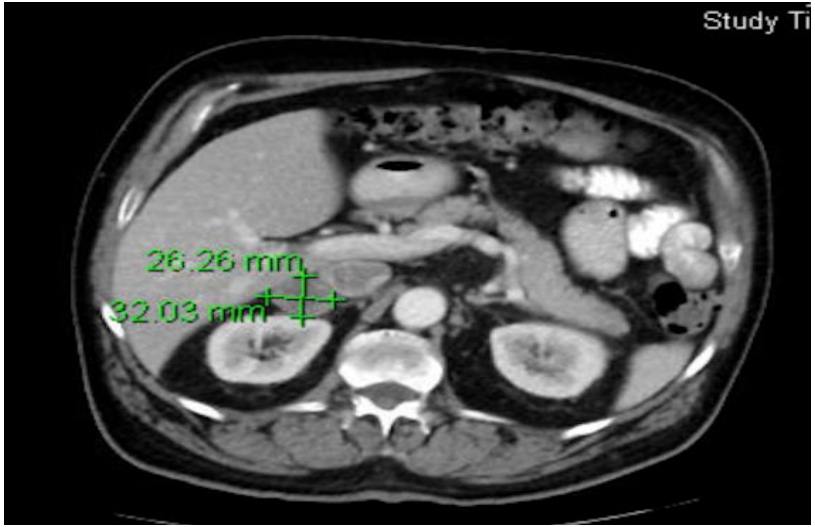
Therapeutic effect—representative images (also had small brain metastasis⟶ CR)

Adrenal metastasis





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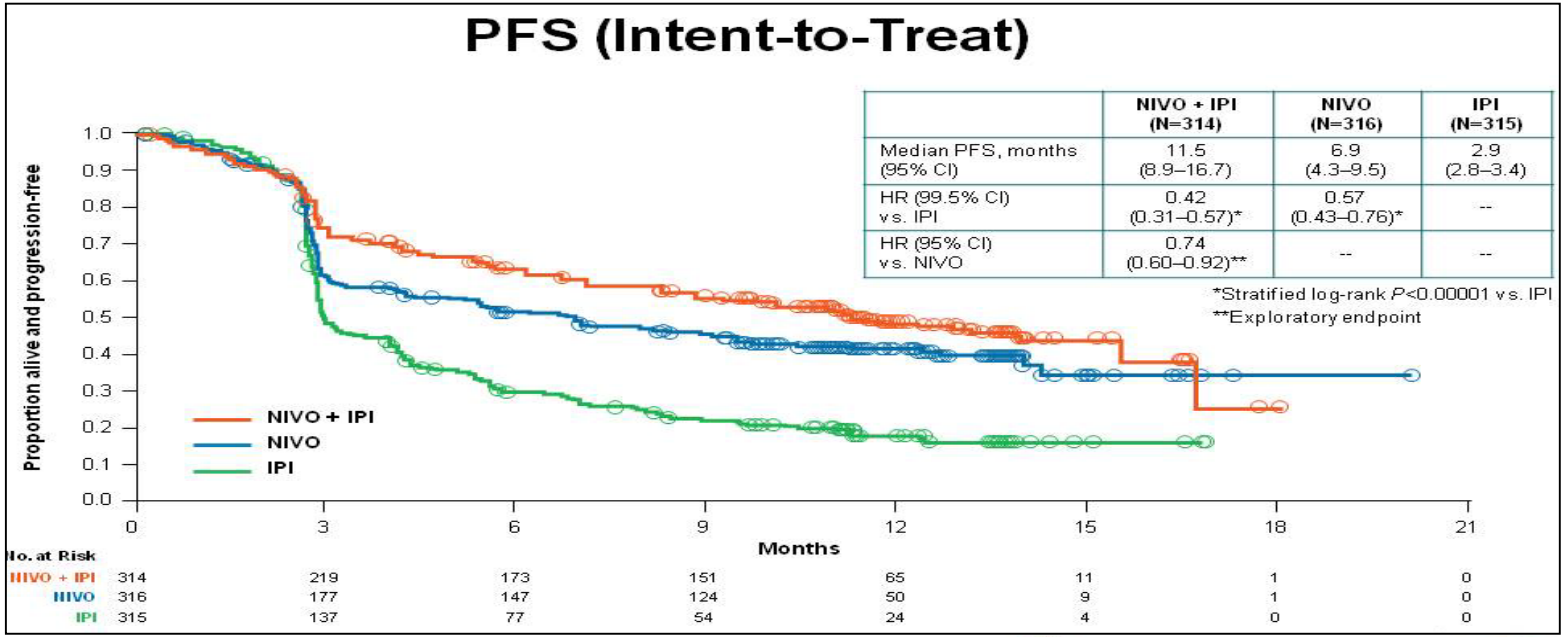
Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma



	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank $P<0.00001$ vs. IPI
**Exploratory endpoint

Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)

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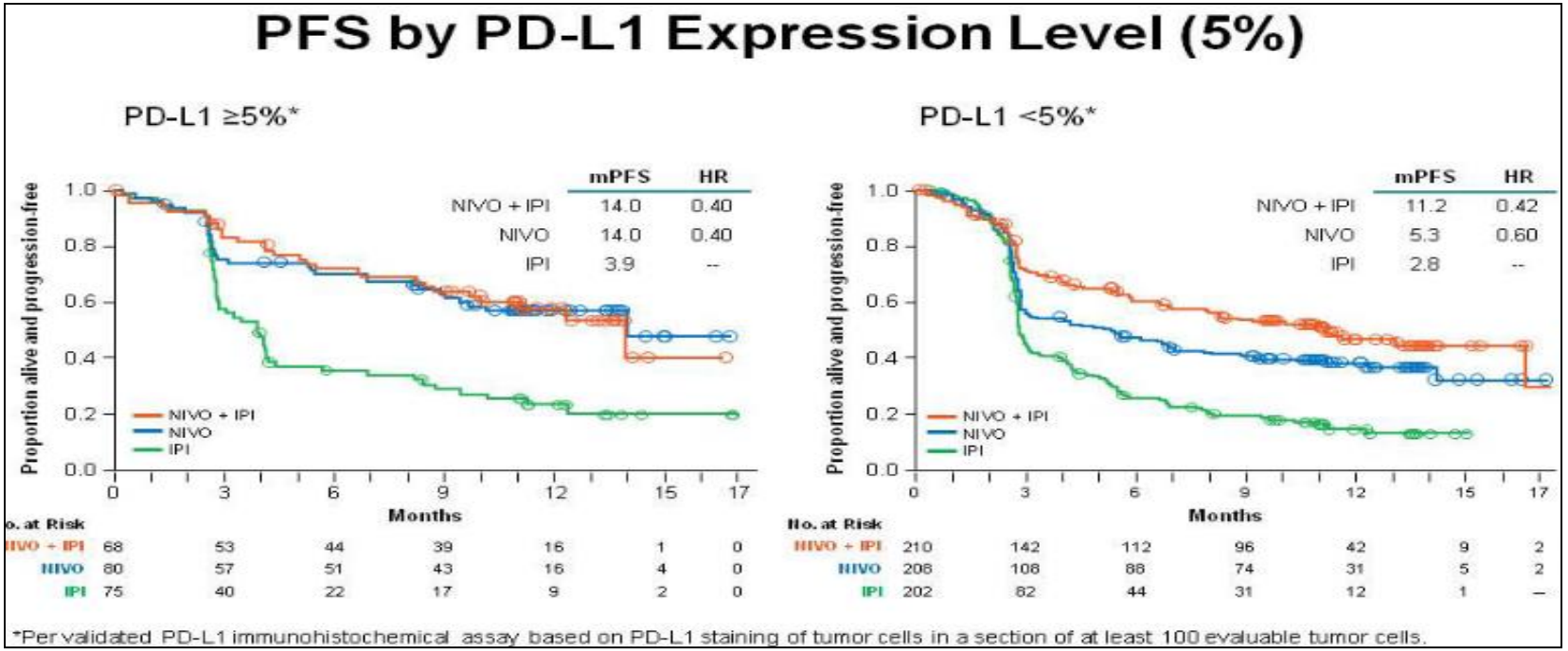
Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma



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Ipilumamab: CTLA-4

Nivolumab: PD-1

Ipi+Nivo vs. Ipi or Nivo vs. Ipi in Melanoma

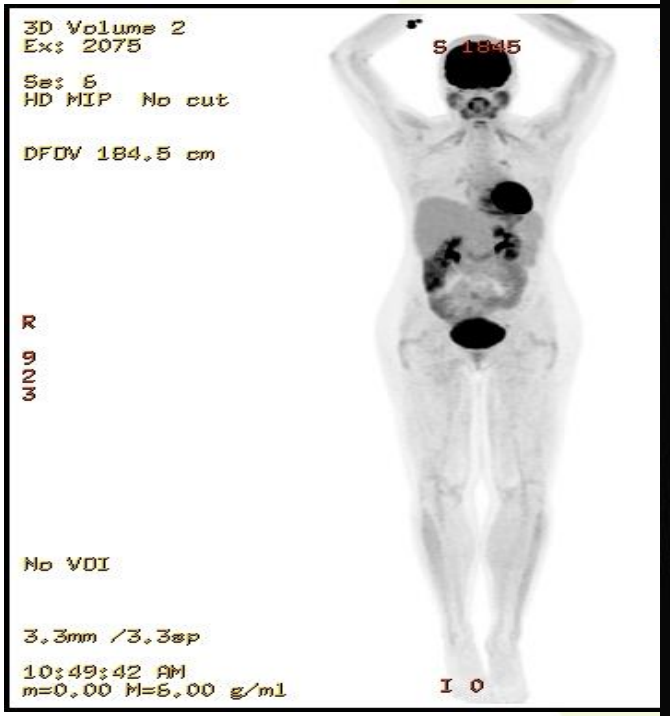
Safety Summary

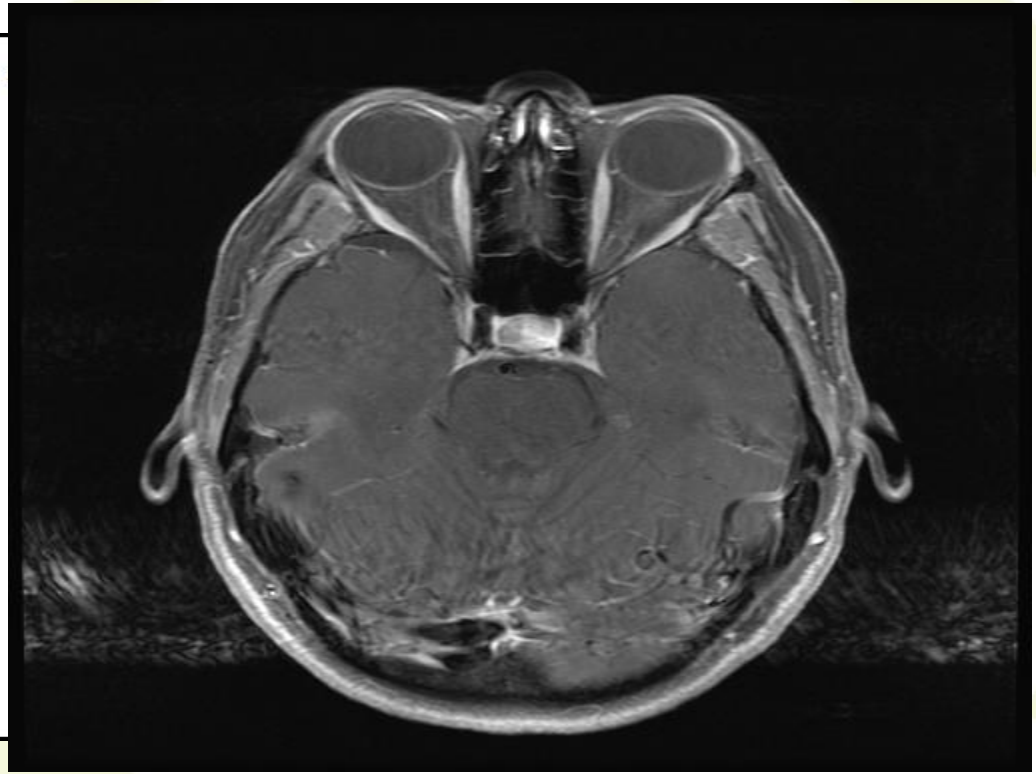
Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Presented by Jedd Wolchok at ASCO 2015 - Wolchok et al. J Clin Oncol 33, 2015 (suppl; abstr LBA1)


3D Volume 2
Ex: 2075
Se: 5
HD MIP No cut
DFOV 184.5 cm
R
9
2
3
No VOI
3.3mm /3.3sp
10:49:42 AM
m=0.00 M=5.00 g/ml
S 1845
I 0



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Case #2: Questions raised

1. Was it appropriate to start with MAPKi? Unknown
2. Should he have received combination with immunotherapy Unknown
3. Is it best to switch to immunotherapy early, or at best response to MAPKi? UNKNOWN
4. Why did he have such a sustained response to MAPKi? Immunomodulation?
5. Is nivolumab plus ipilimumab the optimal immunotherapy in June 2017? PROBABLY
6. Should PD-L1 expression have been checked? Maybe…but many issues remain
7. How long to continue Rx? UNKNOWN/1 yr?

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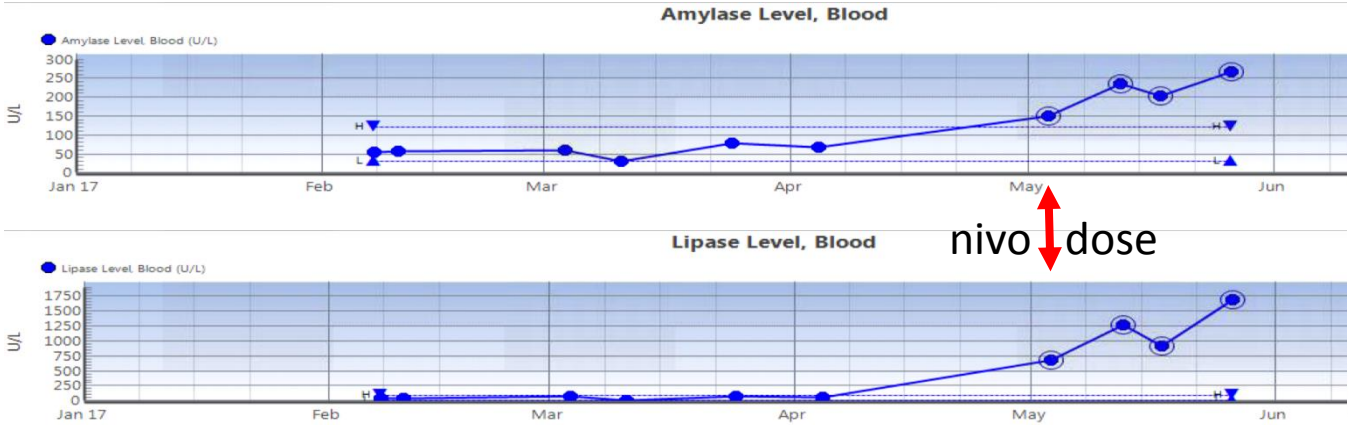
Toxicity management issues

Diarrhea from ipilimumab/nivolumab combination responded to steroid;
Ipilimumab dropped after 2 cycles, in part because pt was traveling to Poland (QoL)

Nivolumab dosed at 1 mg/kg in cycles 3 and 4—should it have been increased?

Pt developed chemical pancreatitis, initially without Sx, now with mild abdominal pain—enzymes rising despite skipping last dose nivolumab→steroid?
[US not diagnostic, CT is negative, pt continues to work, eat, perform ADLs normally



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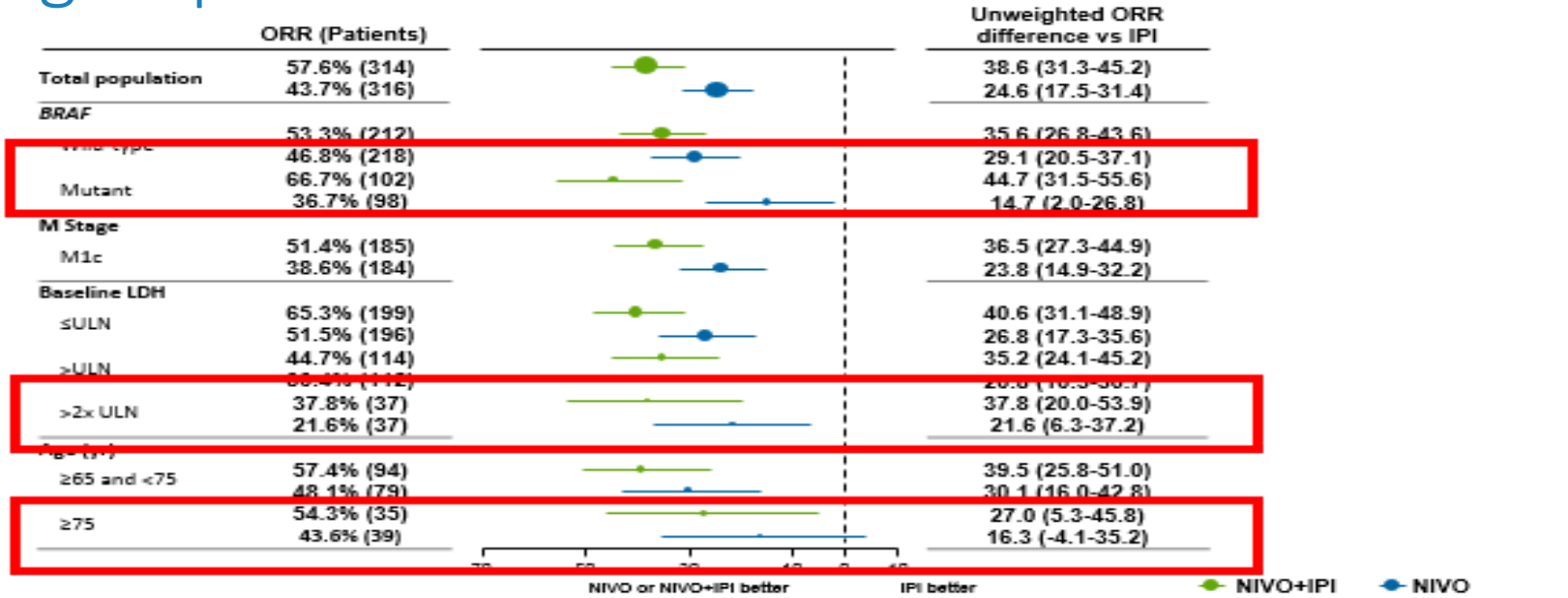
Ipi-Nivo vs Nivo Overall Response Rate in Patient Subgroups



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On-Going Phase III Trials in Melanoma

- BRAFi + MEKi + anti PD-(L)1
- MEKi + anti PD-(L)1
- Indolamine Dioxygenase inhibitors (IDOi) + anti PD-(L)1
- Talimogene laharparepvec (TVEC) + anti PD(L)1

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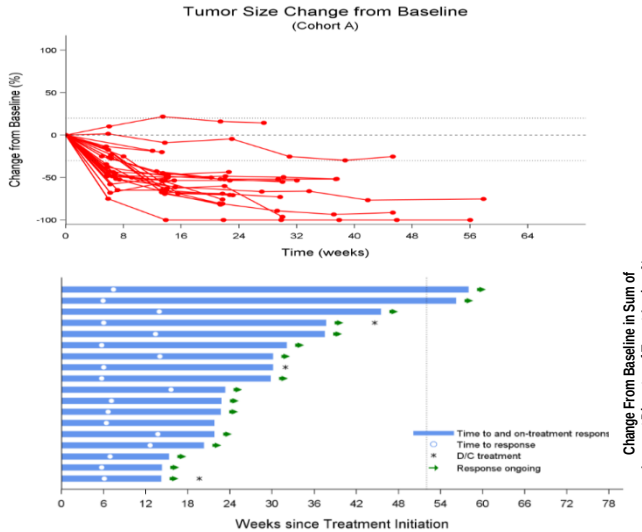
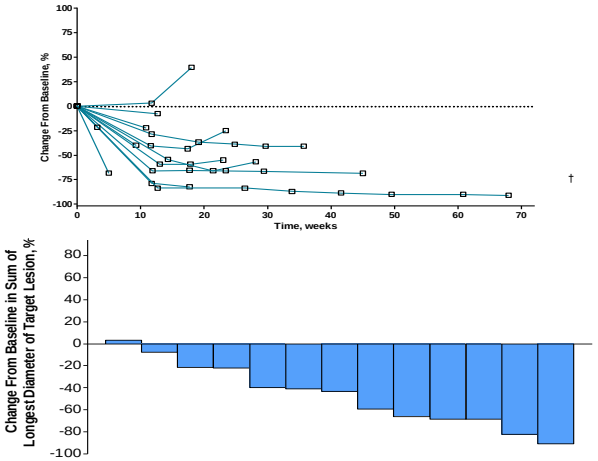
Target-Immuno Triplets: BRAF + MEK + PD1/L1

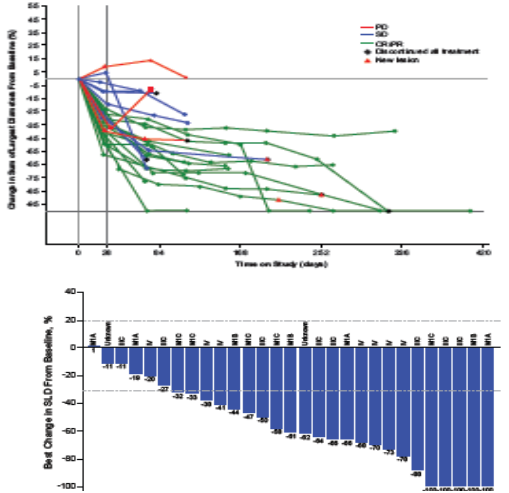
Dabrafenib+Trametinib+ Durvalumab



Dabrafenib+Trametinib+ Pembrolizumab



Vemurafenib+Cobimetinib+ Atezolizumab



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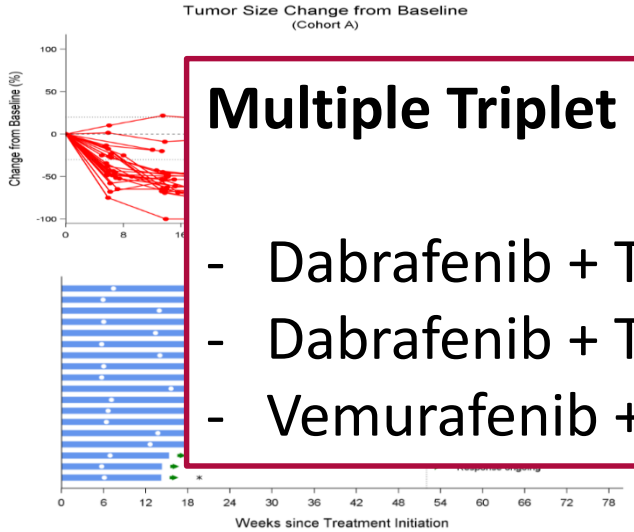
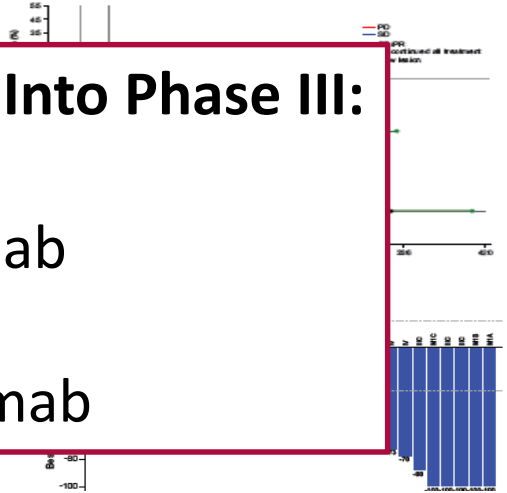
Target-Immuno Triplets: BRAF + MEK + PD1/L1

Dabrafenib+Trametinib+ Durvalumab

Dabrafenib+Trametinib+ Pembrolizumab

Vemurafenib+Cobimetinib+ Atezolizumab





Multiple Triplet Combinations Launching Into Phase III:

- Dabrafenib + Trametinib + Pembrolizumab
- Dabrafenib + Trametinib + PDR-001
- Vemurafenib + Cobimetinib + Atezolizumab

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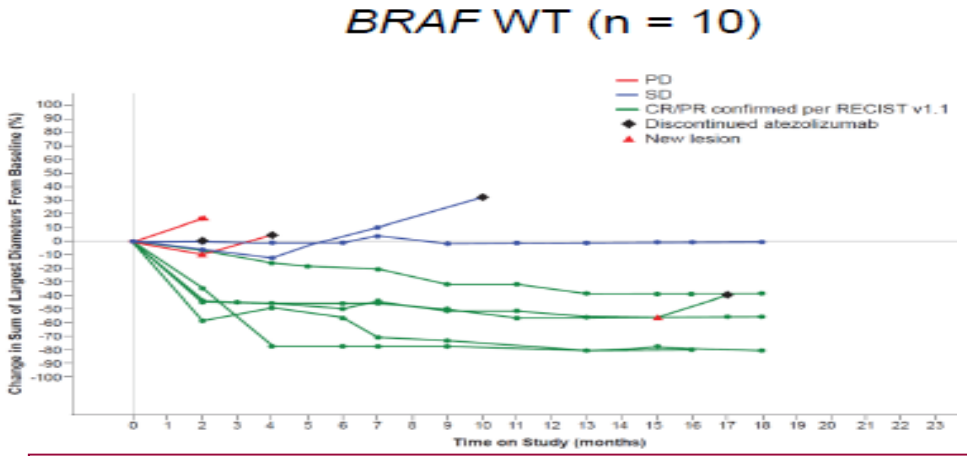
MEK inhibitor + PDL-1 for BRAFwt Melanoma Phase I Cobimetinib + Atezolizumab



	N = 22, n (%)
Median safety follow-up, mo (range)	14.0 mo (2.4-20.2)
All grade treatment-related AEs	22 (100%)
Grade 3-4 treatment-related AEs	13 (59%)
Grade 3-4 atezolizumab-related AEs	8 (36%)
Grade 3-4 cobimetinib-related AEs	10 (45%)
AEs leading to treatment dose modification/interruption	14 (64%)
Treatment-related SAEs[a]	4 (18%)
Treatment discontinuation[b]	3 (14%)
Cobimetinib discontinuation	3 (14%)
All treatment discontinuation	1 (5%)

Phase III Study of Cobimetinib + Atezolizumab versus Pembrolizumab in Patients with Untreated BRAFV600 Wild-Type Melanoma

PROTOCOL NUMBER: CO39722

Atezolizumab: PD-L1

Pembrolizumab : PD-1

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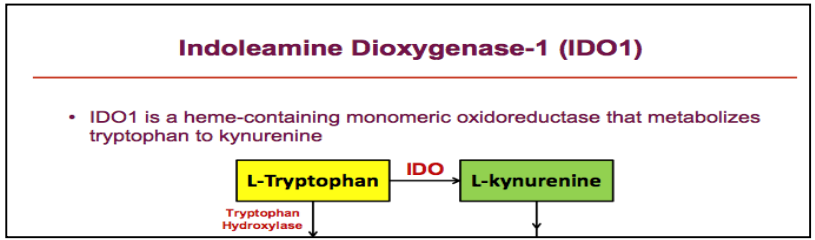
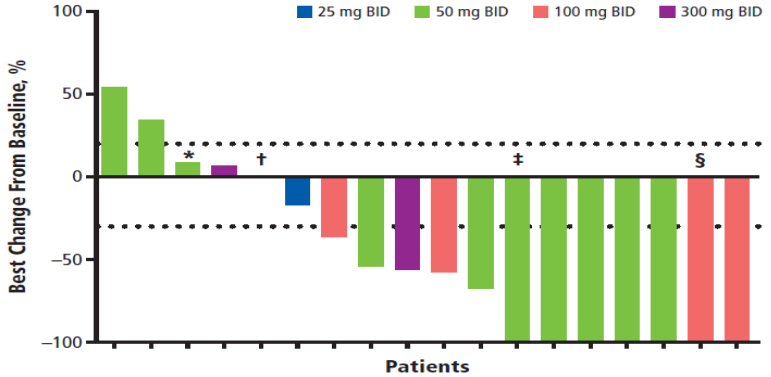
IDO inhibitor epacadostat + pembrolizumab



Phase 1/2 Study of **Epacadostat** (INCB024360) + **Pembrolizumab** in Patients With Melanoma



A Phase 3 Study of Pembrolizumab + Epacadostat or Placebo in Subjects With Unresectable or Metastatic Melanoma (Keynote-252 / ECHO-301)
ClinicalTrials.gov Identifier: NCT02752074

RECIST response = 58%, no increase in toxicity from pembrolizumab alone

Beatty et al. ASCO (2012) Abstract 2500^
Gangadhar *et al*. ESMO 2016

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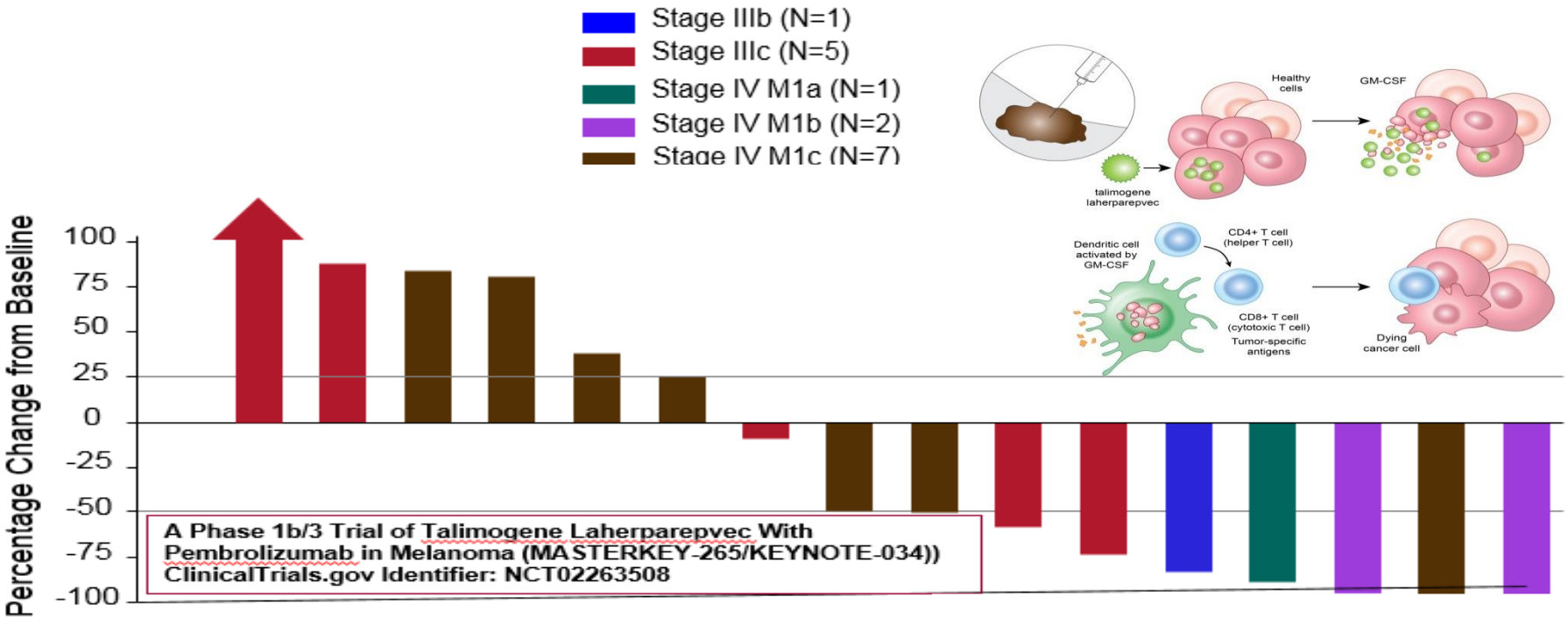
T-Vec + Pembrolizumab in Stage IIIB-IV Melanoma



RECIST response = 46%, no increase in toxicity from pembrolizumab alone

Long et al. SMR 2015

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Future Combinations

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SITC 2017

Pivot-02: Preliminary safety, efficacy and biomarker results from dose escalation of the Phase 1/2 study of CD-122-biased agonist NKTR-214 plus nivolumab in patients with locally advanced/metastatic melanoma, renal cell carcinoma and non-small cell lung cancer

ClinicalTrials.gov Identifier: NCT02983045

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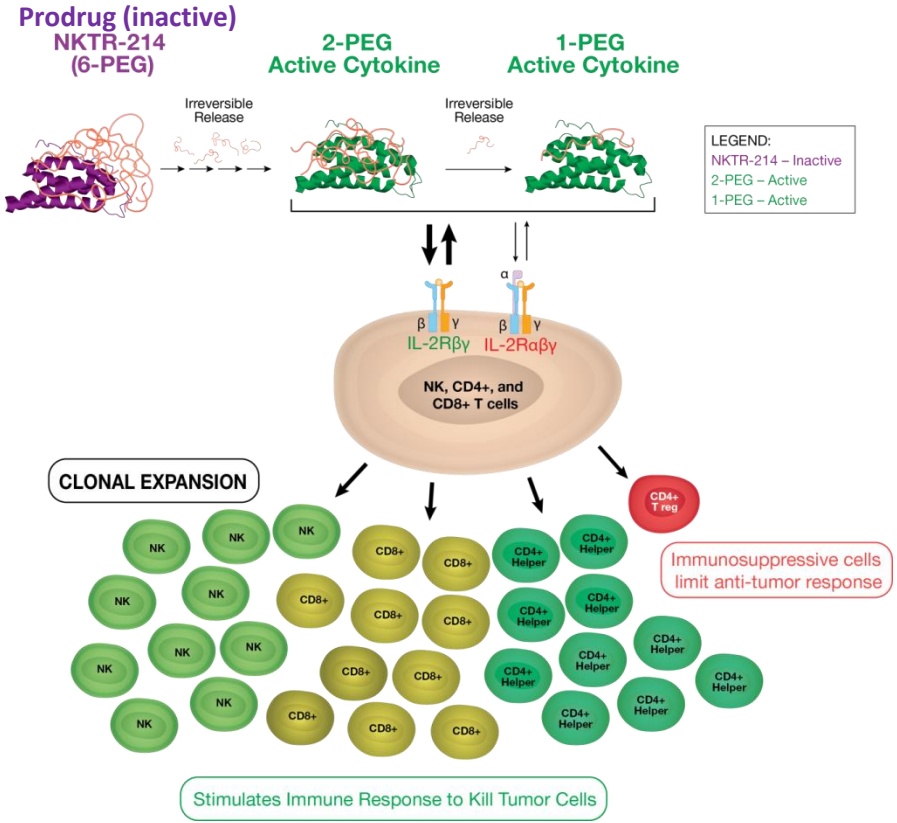
NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs

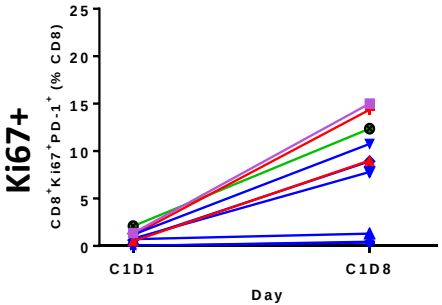


- NKTR-214 prodrug design with sustained signaling
- Q2W or Q3W Dosing
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- Increases proliferation of TILs and PD-1 expression on effector T cells in the tumor microenvironment

Clinical and Preclinical Rationale for Combination of NKTR-214 + Anti-PD-1

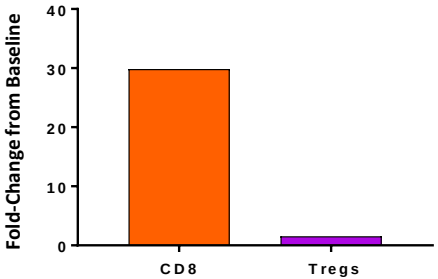
NKTR-214 Monotherapy Clinical Trial[2]

PD-1 Expression on CD8 T Cells in Blood



N=10 patients

CD8 / Treg Ratio in Tumor

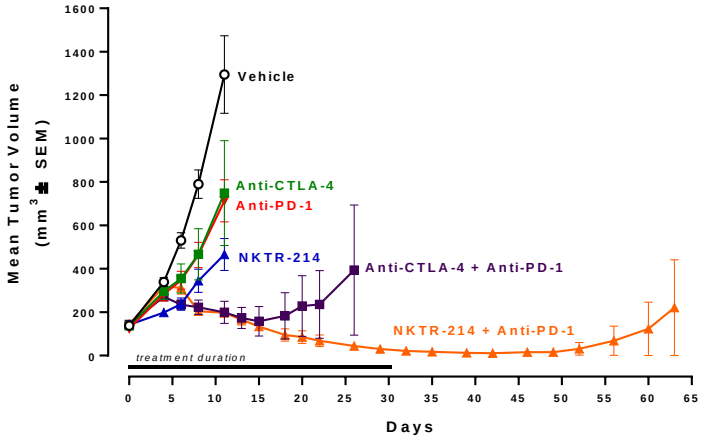


Fold change expressed as Week 3 / pre-dose
Shown are results from N=10 patients
Q3W dose schedules

- **Blood:** Increase in newly proliferating (Ki67+) PD-1+ CD8 T cells
- **Tumor**: Increase in total T cells, NK and CD8+ T cells with no increase in Tregs, increase in newly proliferating (Ki67+) PD-1+ CD8 T cells

NKTR-214 + Anti-PD-1 Preclinical Data[1]

CT26 Mouse Colon Tumor Model



NKTR-214 dosed 0.8 mg/kg q9dx3, anti-PD-1 or anti-CTLA-4 dosed 200ug or 100ug 2x/week respectively.

1. Abstract 11545 (169221): ASCO 2016; 2. Abstract No: 2545 (Board #37) ASCO 2017.

PIVOT-02 Dose Escalation

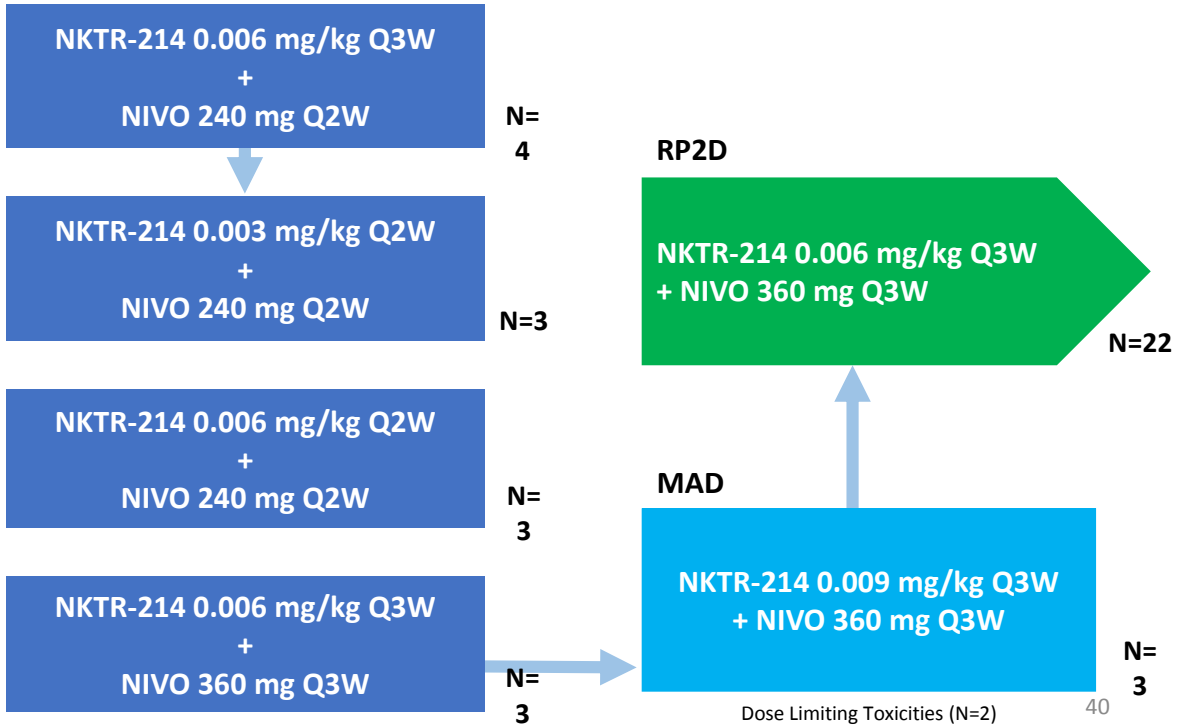
Phase 1b (N=38)

Patients

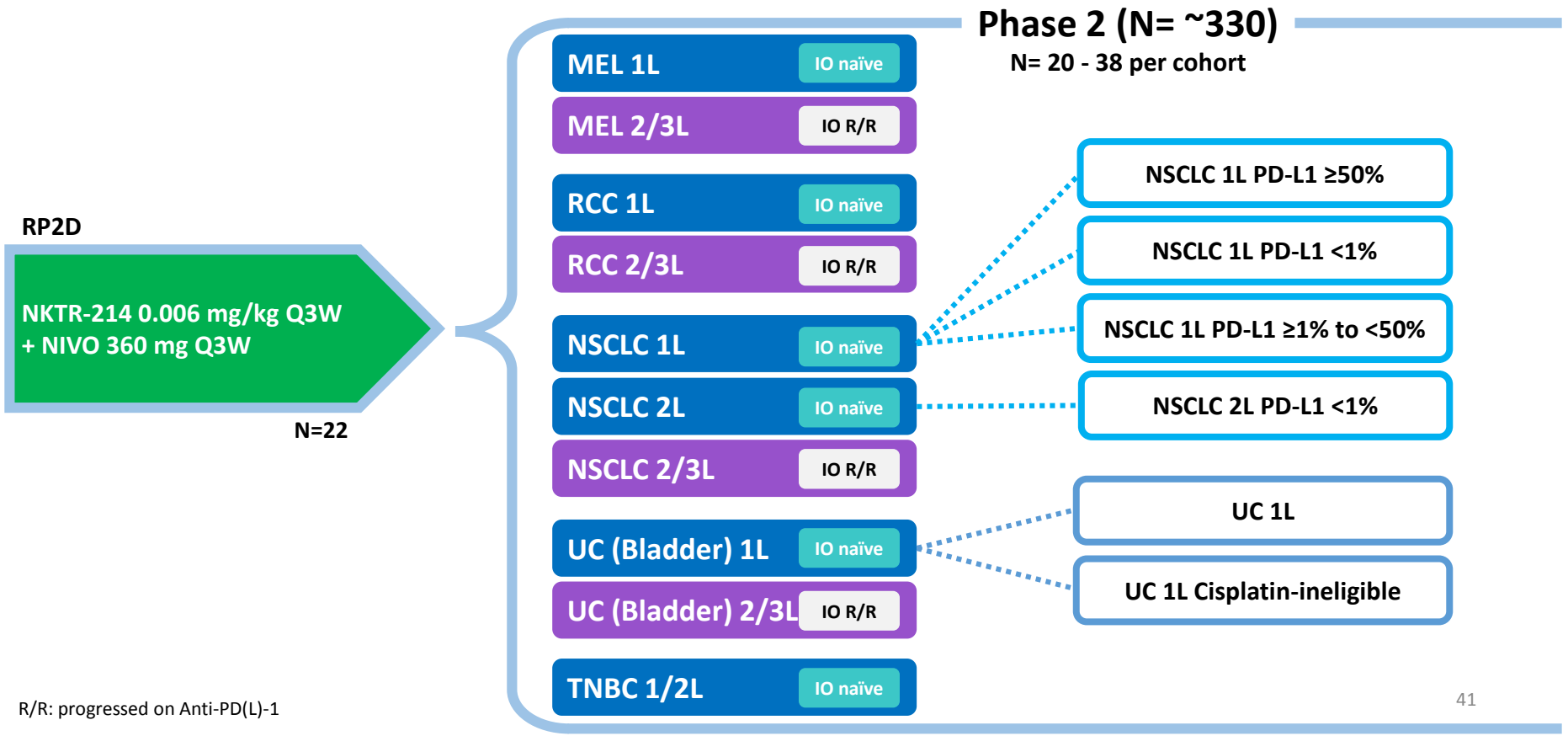
IO Treatment-Naïve

- MEL 1L (with known BRAF status) (N=11)
- RCC 1L, 2L (N=22)
- NSCLC 1L, 2L (EGFR & ALK WT) (N=5)

- Confirmed locally advanced or metastatic solid tumors
- Measurable disease per RECIST 1.1
- ECOG 0 or 1
- Adequate organ function
- Fresh biopsy and archival tissue

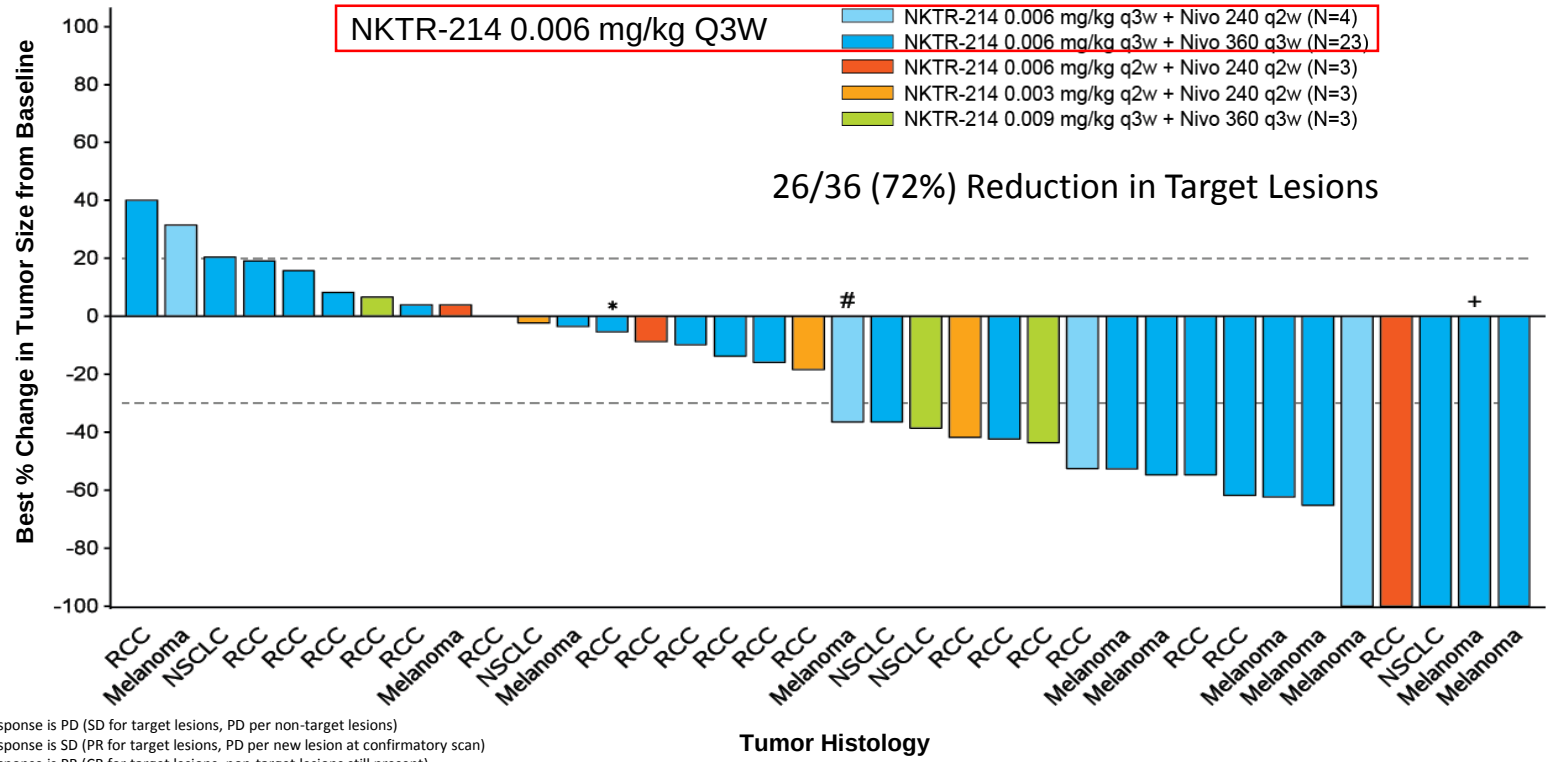


PIVOT-02 Dose Expansion Underway in 13 Cohorts



R/R: progressed on Anti-PD(L)-1

PIVOT-02: Best Percent Change in Target Lesions by Tumor Type and Dose (n=36)

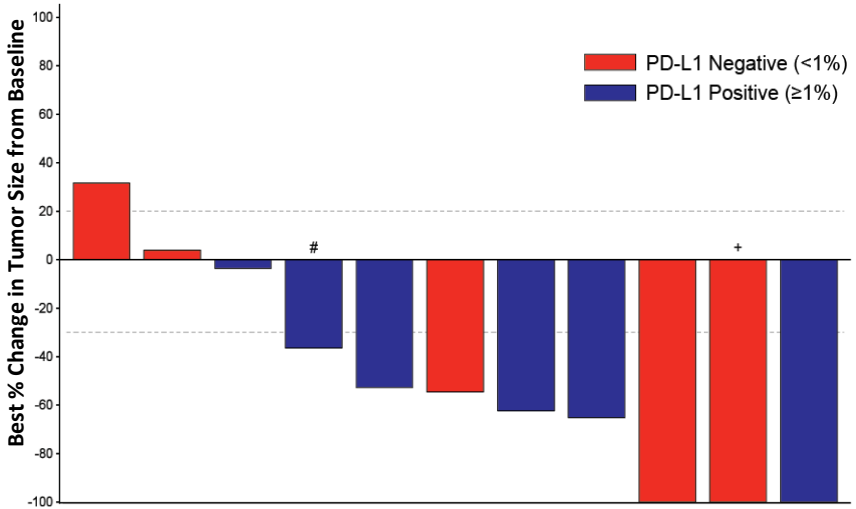


* Best overall response is PD (SD for target lesions, PD per non-target lesions)
\# Best overall response is SD (PR for target lesions, PD per new lesion at confirmatory scan)
\+ Best overall response is PR (CR for target lesions, non-target lesions still present)
Data are shown for patients with post-baseline scans that included assessment of target lesions.
Two patients not included in the figure: one patient discontinued from study due to clinical progression before the first post-baseline tumor assessment and one patient on treatment does not have a post-baseline scan.

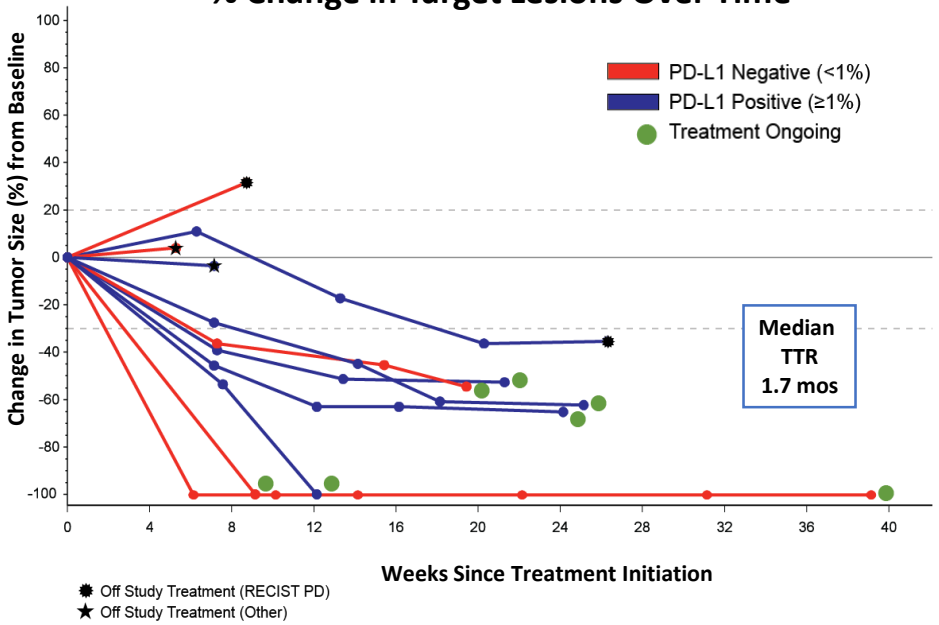
Stage IV Treatment-Naïve Melanoma Patients (N=11)

Best Overall Response by RECIST*: ORR=7/11 (64%); DCR=10/11 (91%)
Best Overall Response by irRECIST: ORR=8/11 (73%); DCR=10/11 (91%)

% Change From Baseline in Target Lesions



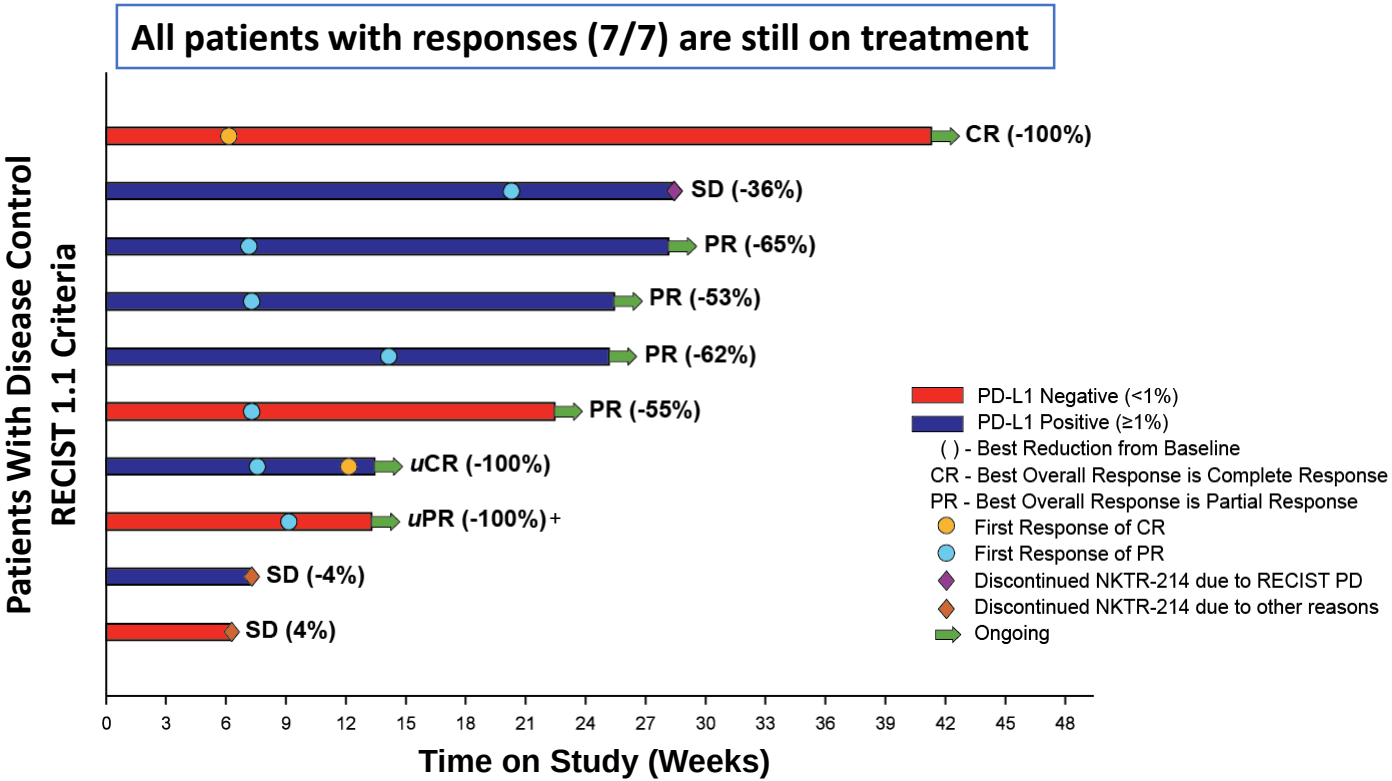
% Change in Target Lesions Over Time



Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. # Best Overall Response is SD (PR for target lesions, PD per new lesion on confirmatory scan) + Best Overall response is PR (CR for target lesions, non-target lesions still present)
*One patient in ORR calculation has unconfirmed PR.

Time to and Duration of Response

Stage IV Treatment-Naïve Melanoma



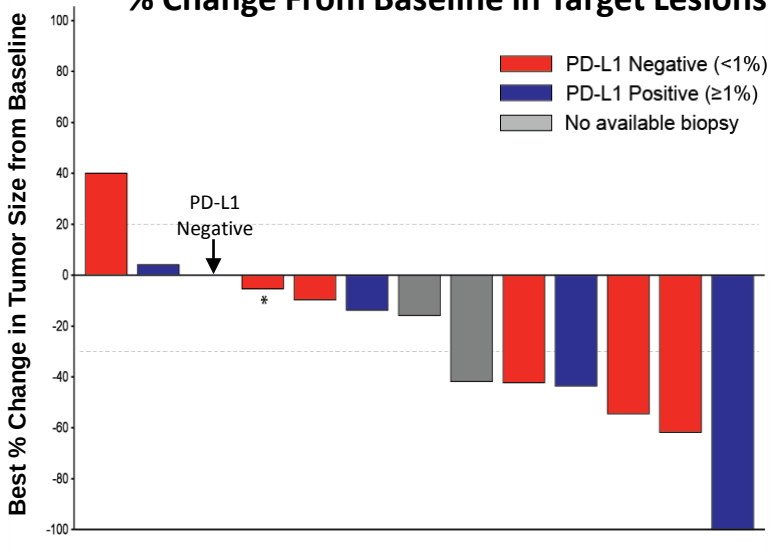
+ Best Overall response is PR (CR for target lesions, non-target lesions still present)

Stage IV Treatment-Naïve 1L Renal Cell Carcinoma (N=13)

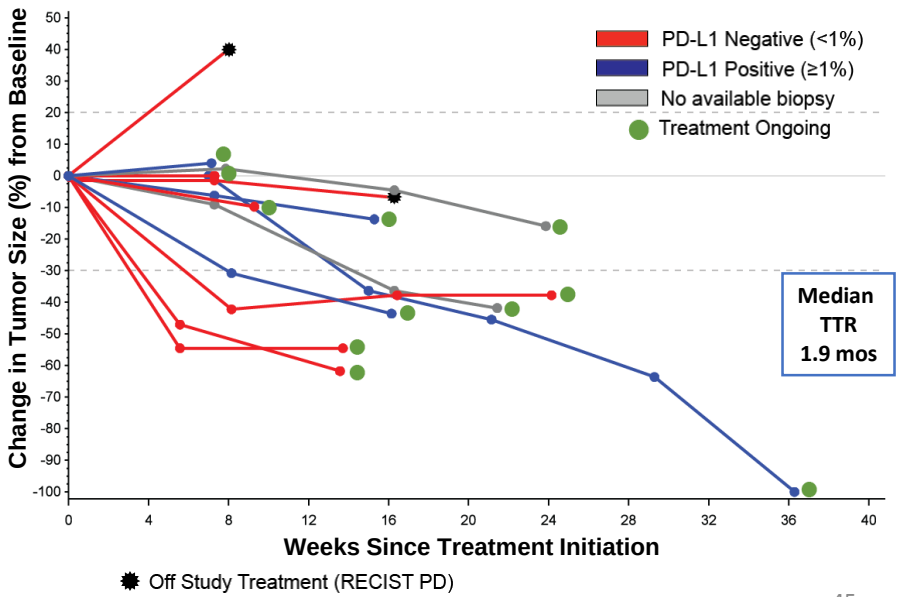
Efficacy-evaluable patients with ≥1 or ≥2 post baseline scans

Best ORR by RECIST ≥1 post baseline scan: ORR=6/13 (46%); DCR=11/13 (85%)

% Change From Baseline in Target Lesions



% Change in Target Lesions Over Time



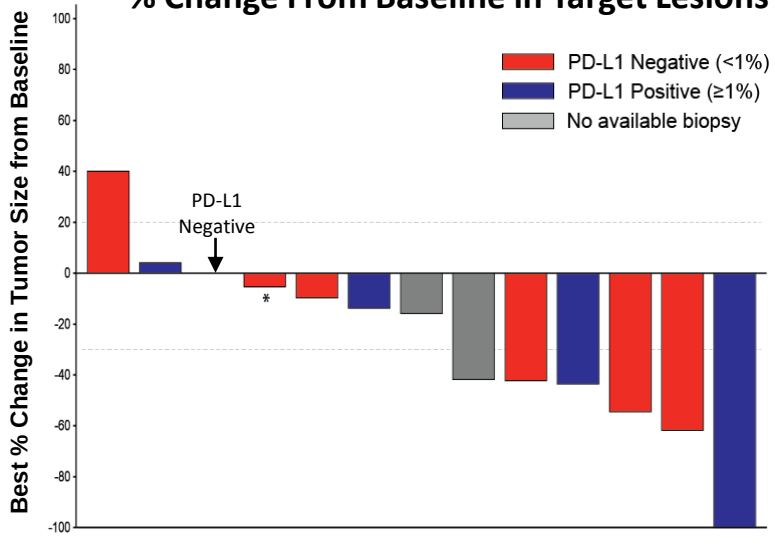
Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. * Best overall response is PD (SD for target lesions, PD per non-target lesions).

Stage IV Treatment-Naïve 1L Renal Cell Carcinoma (N=13)

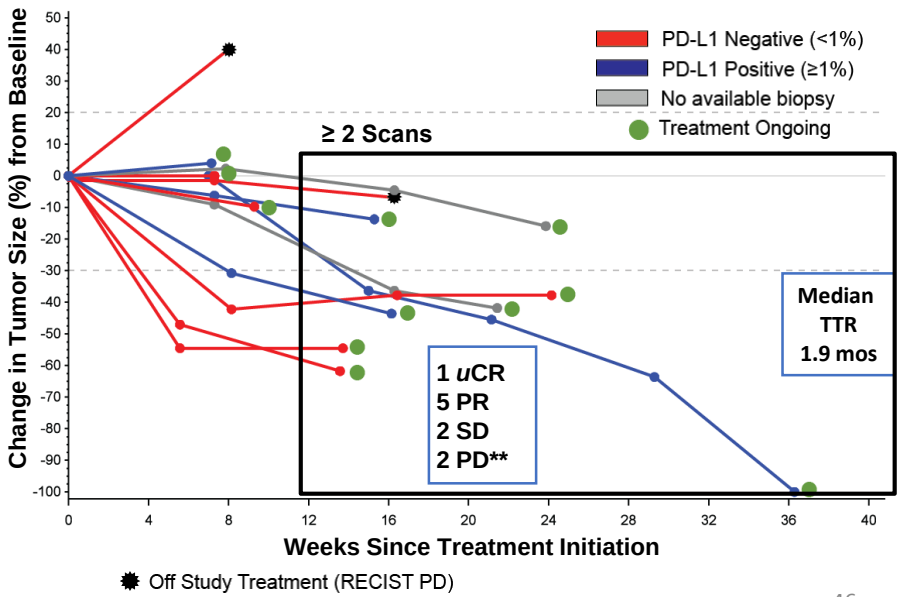
Efficacy-evaluable patients with ≥1 or ≥2 post baseline scans

Best ORR by RECIST ≥1 post baseline scan: ORR=6/13 (46%); DCR=11/13 (85%)
Best ORR by RECIST ≥2 post baseline scans: ORR=6/10 (60%); DCR=8/10 (80%)

% Change From Baseline in Target Lesions



% Change in Target Lesions Over Time

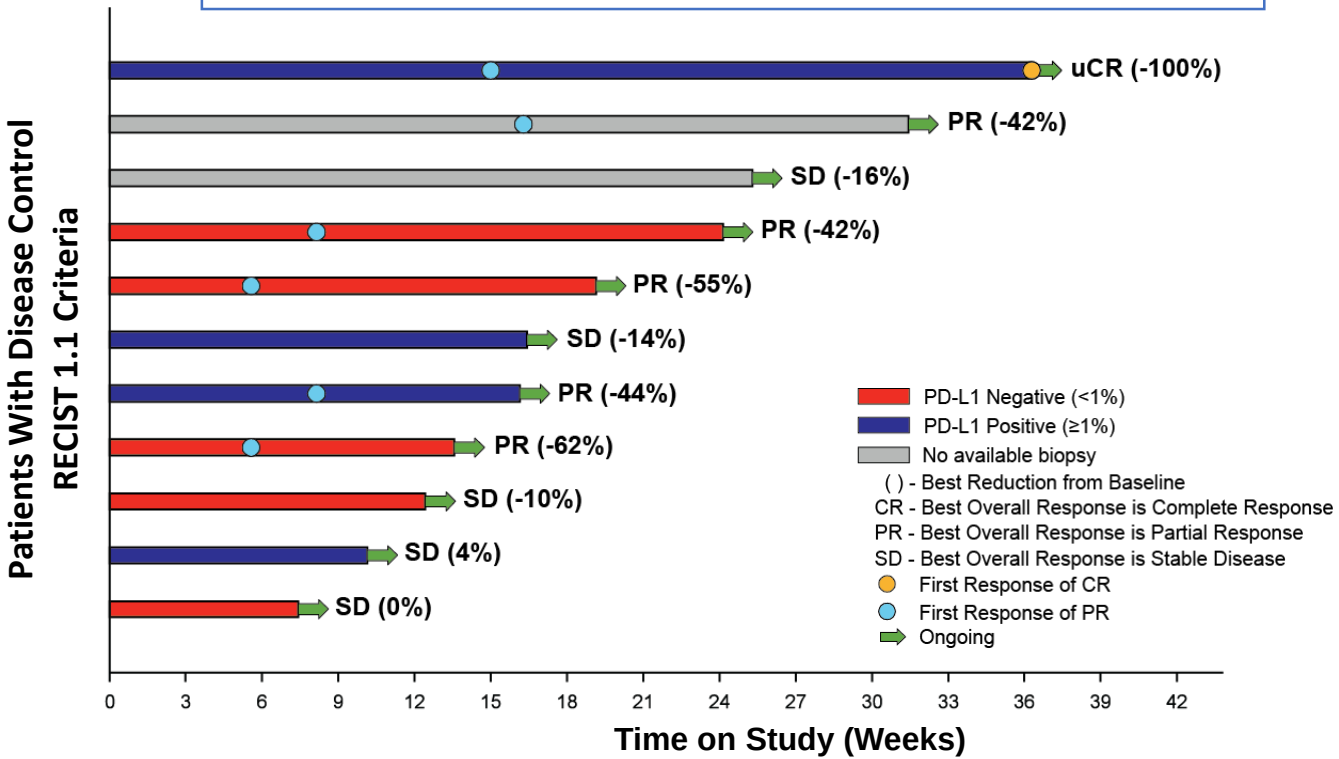


Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. * Best overall response is PD (SD for target lesions, PD per non-target lesions). **Includes PD with 1 post base-line scan

Time to and Duration of Response

Stage IV Treatment-Naïve Renal Cell Carcinoma 1L (CR, PR or SD)

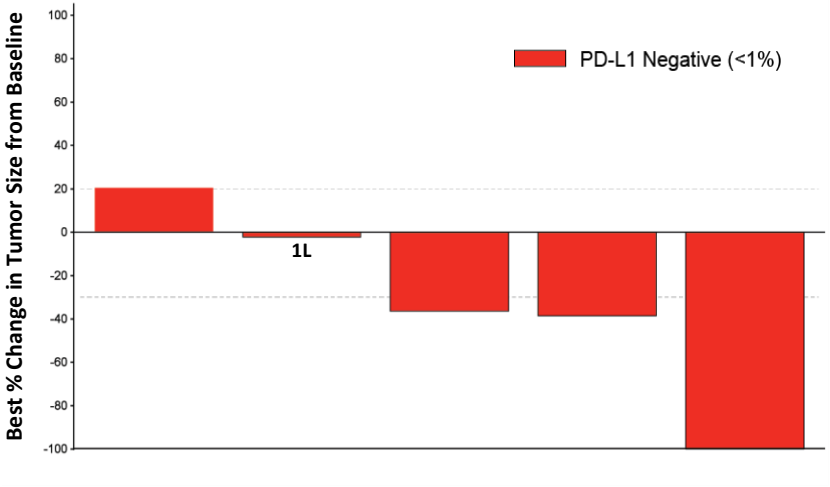
All patients with disease control (11/13) are still on treatment



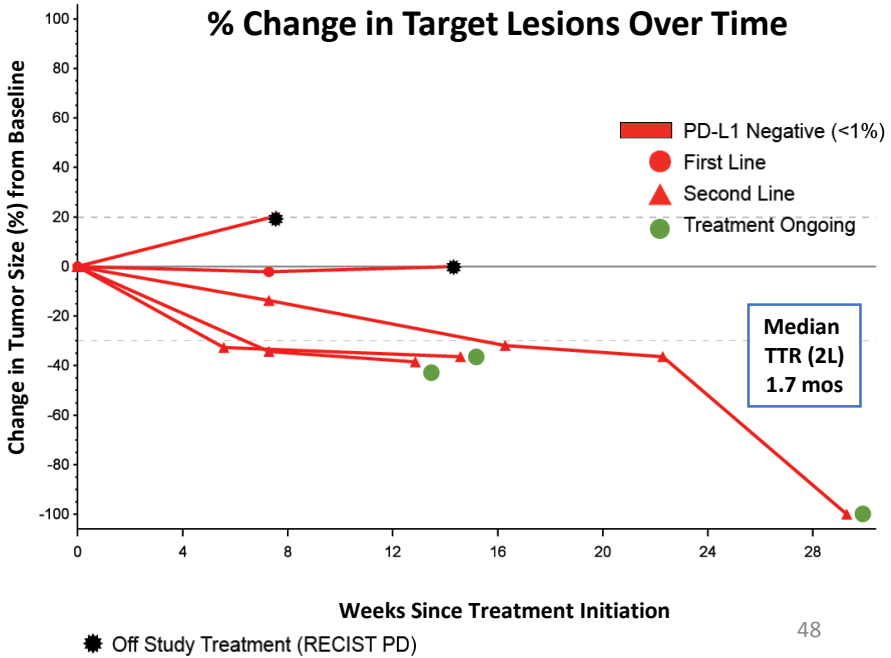
Stage IV IO-Naïve PD-L1 Negative NSCLC (1L and 2L)

Best Overall Response by RECIST (2L): ORR=3/4 (75%); DCR=3/4 (75%)
Best Overall Response by RECIST (1L and 2L): ORR=3/5 (60%); DCR=3/5 (60%)

% Change From Baseline in Target Lesions



% Change in Target Lesions Over Time



Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria.

Best Overall Response by RECIST 1.1 as of November 2, 2017

Patients	Stage IV Treatment-Naïve Melanoma (N=11)	Stage IV Treatment-Naïve 1L RCC (N=14)		2L RCC (N=8)	1L NSCLC (N=1)	2L NSCLC (N=4)
		Patients with at least one or more scans	Patients with at least two or more scans or PD**			
Total Evaluable	**11**	**13**	**10**	**7**	**1**	**4**
ORR (CR+PR)	**7 (64%) +**	**6 (46%)**	**6 (60%)**	**1 (14%)**	**0 (0)**	**3 (75%)**
CR	2 (18%)	1 (8%) #	1 (10%) #	0	0	1 (25%) #
PR	5 (45%)	5 (38%)	5 (50%)	1 (14%)	0	2 (50%)
SD	3 (27%)	5 (38%)	2 (20%)	6 (86%)	1 (100%)	0
DCR (CR+PR+SD)	**10 (91%)**	**11 (85%)**	**8 (80%)**	**7 (100%)**	**1 (100%)**	**3 (75%)**
PD	1	2	2	0	0	1

CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease
+ CR is waiting to be confirmed for 1 of 2 patients with CR; one patient in calculation has *u*PR.
# PR for patient confirmed. CR is waiting to be confirmed.
** Patients with at least 2 post-baseline scans or progressed on 1st post-baseline scan.

Treatment-Related AEs

Preferred Term[1]	Total (N=38)	NKTR-214 0.006 q3w + Nivo 360 (N=25)	NKTR-214 0.006 q3w + Nivo 240 (N=4)	NKTR -214 0.006 q2w + Nivo 240 (N=3)	NKTR-214 0.003 q2w + Nivo 240 (N=3)	NKTR-214 0.009 q3w + Nivo 360 (N=3)
Grade 3 or 4	**4 (10.5%)**	**1 (4.0%)**	**1 (25.0%)**	**0**	**0**	**2 (66.7%)**
Acidosis	1 (2.6%)	0	0	0	0	1 (33.3%)◊
Arthralgia	1 (2.6%)	0	1 (25.0%)	0	0	0
Diarrhea	1 (2.6%)	0	0	0	0	1 (33.3%)◊
Hyperglycemia	1 (2.6%)	0	0	0	0	1 (33.3%)◊
Hyperthyroidism	1 (2.6%)	0	0	0	0	1 (33.3%)◊
Hyponatraemia	1 (2.6%)	1 (4.0%)	0	0	0	0
Hypotension	1 (2.6%)	0	0	0	0	1 (33.3%)
Syncope	1 (2.6%)	1 (4.0%)	0	0	0	0
Grade 1&2 (>25%)						
Fatigue	28 (73.7%)	17 (68.0%)	4 (100.0%)	2 (66.7%)	3 (100.0%)	2 (66.7%)
Flu Like Symptoms**	26 (68.4%)	15 (60.0%)	3 (75.0%)	3 (100.0%)	2 (66.7%)	3 (100.0%)
Rash*	23 (60.5%)	13 (52.0%)	4 (100.0%)	1 (33.3%)	2 (66.7%)	3 (100.0%)
Pruritus	16 (42.1%)	8 (32.0%)	2 (50.0%)	2 (66.7%)	2 (66.7%)	2 (66.7%)
Headache	14 (36.8%)	8 (32.0%)	3 (75.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Nausea	14 (36.8%)	8 (32.0%)	3 (75.0%)	1 (33.3%)	0	2 (66.7%)
Diarrhea	12 (31.6%)	8 (32.0%)	2 (50.0%)	0	1 (33.3%)	1 (33.3%)
Arthralgia	11 (28.9%)	6 (24.0%)	3 (75.0%)	1 (33.3%)	0	1 (33.3%)
Decreased Appetite	10 (26.3%)	3 (12.0%)	3 (75.0%)	2 (66.7%)	0	2 (66.7%)

(1) Patients counted/grouped under each preferred term using highest grade

* Rash includes the following MedDRA preferred terms: Rash, rash erythematous, rash macular and rash maculo-popular; ** Flu-like symptoms includes the following MedDRA preferred terms: influenza-like illness, pyrexia, and chills.

◊ AEs occurred in same patient, patient was dose reduced to NKTR-214 0.003 mg/kg + nivo 360 mg q3w and patient continues on treatment with ongoing confirmed PR

- No study discontinuations due to TRAEs
- No treatment-related deaths
- No G3/4 immune-mediated AEs at RP2D and lower

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Conclusions

- Immunotherapy is standard of care in melanoma
- Likely first and second line in most patients
- Understanding mechanisms of action important
- Manage side effects, understand long-term benefit
- Immunotherapy combinations are likely the future for melanoma and likely all cancers!

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