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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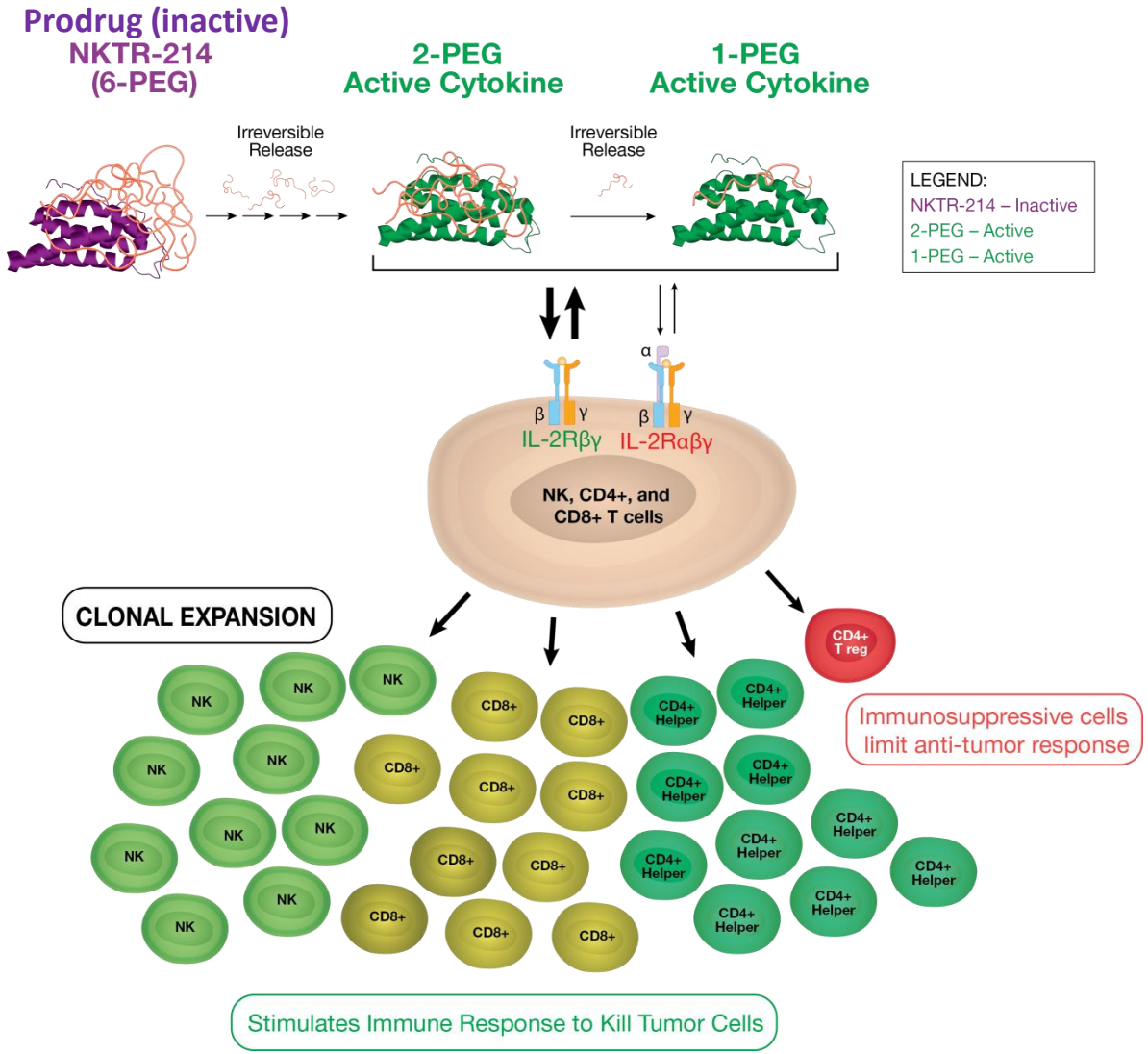
Presenter Disclosure Information

Dr. Adi Diab, MD Anderson Cancer Center

The following relationships exist related to this presentation:

Research funding (institution): Nektar Therapeutics and Bristol-Myers Squibb

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

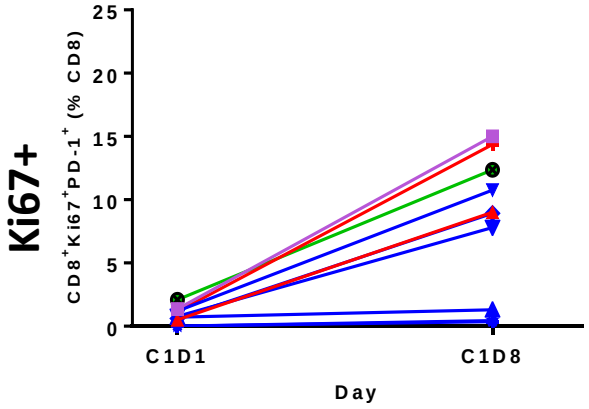


- NKTR-214 prodrug design with sustained signaling
- Q2W or Q3W Dosing
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- Increases proliferation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

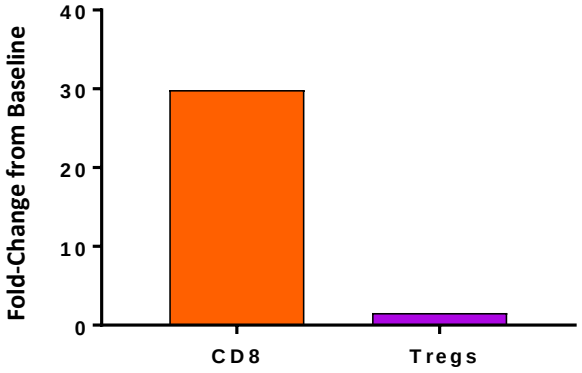
NKTR-214 Monotherapy Clinical Trial[1]

PD-1 Expression on CD8 T Cells in Blood



N=10 patients

CD8 / Treg Ratio in Tumor

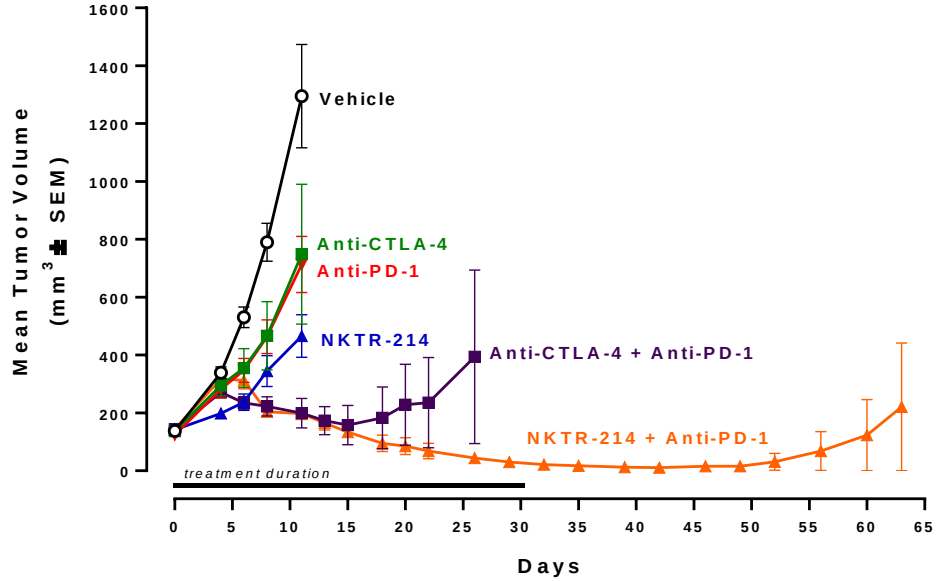


Fold change expressed as Week 3 / pre-dose
Shown are results from N=10 patients
Q3W dose schedules

- **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[2]

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

PIVOT-02 Dose Escalation

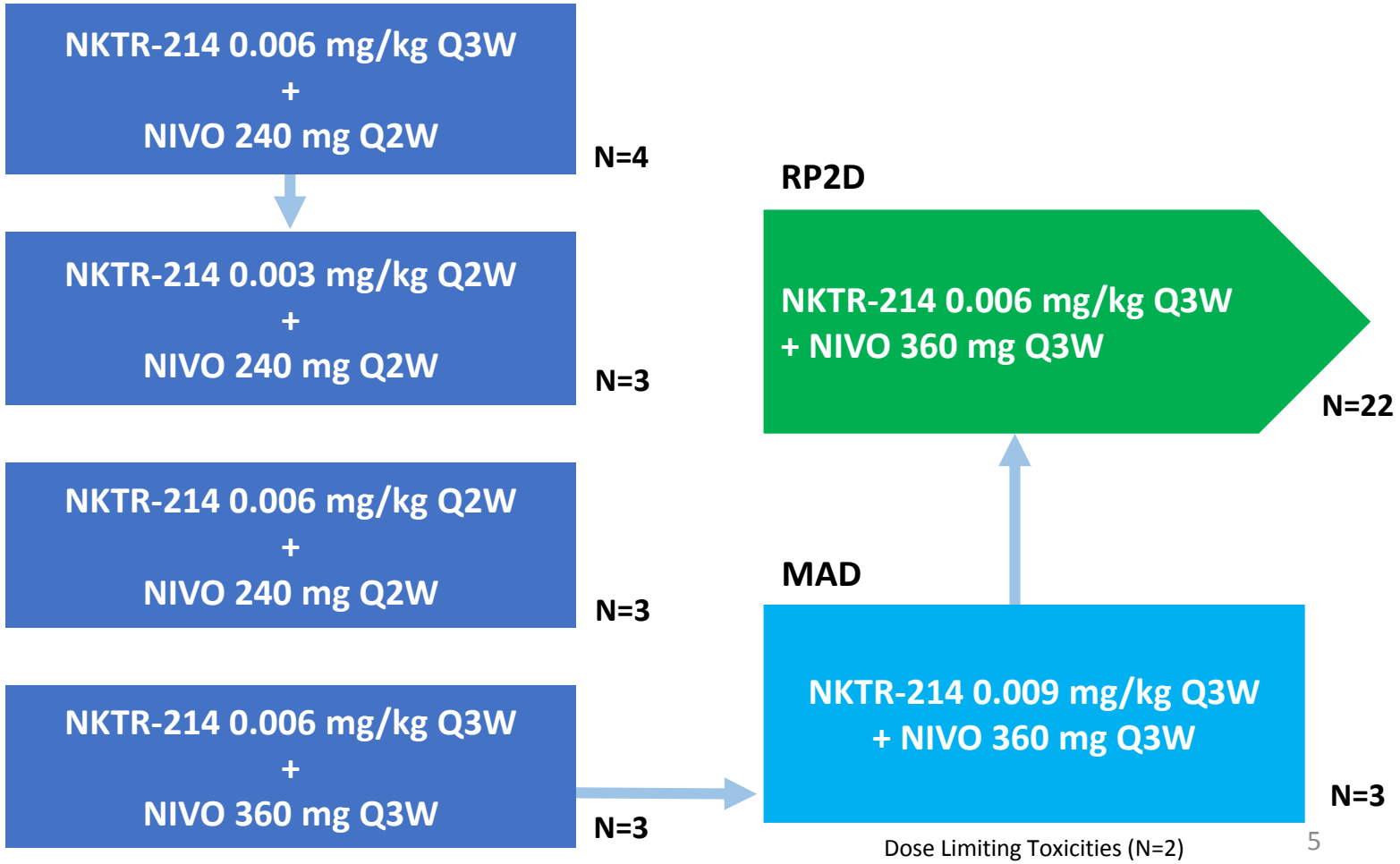
Phase 1b (N=38)

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

RP2D

NKTR-214 0.006 mg/kg Q3W + NIVO 360 mg Q3W

N=22

Phase 2 (N= ~330)

N= 20 - 38 per cohort

MEL 1L	IO naïve
MEL 2/3L	IO R/R
RCC 1L	IO naïve
RCC 2/3L	IO R/R
NSCLC 1L	IO naïve
NSCLC 2L	IO naïve
NSCLC 2/3L	IO R/R
UC (Bladder) 1L	IO naïve
UC (Bladder) 2/3L	IO R/R
TNBC 1/2L	IO naïve

- NSCLC 1L PD-L1 ≥50%
- NSCLC 1L PD-L1 <1%
- NSCLC 1L PD-L1 ≥1% to <50%
- NSCLC 2L PD-L1 <1%
- UC 1L
- UC 1L Cisplatin-ineligible

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

Study Assessments

- **Data cutoff:** November 2, 2017
- **Efficacy**
  - Response was assessed by investigator every 8 (+/- 1) weeks per RECIST v1.1 and immune-related RECIST (irRECIST)
  - Per protocol, efficacy-evaluable is defined as patients with ≥1 post baseline scan
- **Safety and tolerability**
  - Adverse events were assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03
  - Safety-evaluable includes ≥1 dose of study treatment
- **Biomarker exploratory analyses**
  - Baseline tumor PD-L1 status by tumor type
  - Longitudinal sampling of blood and tumor biopsies to be presented at a future conference

Dose Escalation: Patient Demographics and Disease Characteristics

	Total (N=38)	Melanoma (N=11)	RCC (N=22)	NSCLC (N=5)
Sex				
Male	30 (78.9%)	7 (63.6%)	19 (86.4%)	4 (80.0%)
Female	8 (21.1%)	4 (36.4%)	3 (13.6%)	1 (20.0%)
Age (years)				
Median (Range)	61 (22-72)	62 (22-70)	61 (45-72)	58 (53-72)
ECOG Performance Status				
0	25 (65.8%)	8 (72.7%)	15 (68.2%)	2 (40.0%)
1	13 (34.2%)	3 (27.3%)	7 (31.8%)	3 (60.0%)
Prior systemic therapy for metastatic disease				
0	26 (68.4%)	11 (100%)	14 (63.6%)	1 (20.0%)
1	12 (31.6%)	0	8 (36.4%)	4 (80.0%)

Dose Escalation: Disease Characteristics

Melanoma	(N=11)	%
BRAF status		
Mutant V600E	6	54.5
Wild-Type	5	45.5
LDH at baseline*		
High	4	36.4
Normal	7	63.6
PD-L1 status**		
Positive ≥1%	6	54.5
Negative <1%	5	45.5
Stage		
M1a	1	9.1
M1b	2	18.2
M1c	8	72.7
Liver metastases at baseline		
Yes	4	36.4
No	7	63.6

* Based on maximum value prior to dosing.

** Measured using either **28-8 or 22C3** assays on fresh or archival tumor with specific cutoffs.

RCC	(N=22)	%
1L IMDC Score	n=14	
Favorable	1	7.1
Intermediate	12	85.7
Poor	1	7.1
1L PD-L1 status **	n=14	
Positive ≥1%	4	28.6
Negative <1%	8	57.1
No available biopsy	2	14.3
2L PD-L1 status **	n=8	
Positive ≥1%	5	62.5
Negative <1%	3	37.5

NSCLC	(N=5)	%
Histologic Subtype		
Adenocarcinoma	4	80.0
Squamous	1	20.0
Smoker		
Yes	5	100.0
No	0	0
PD-L1 status **		
Positive ≥1%	0	0
Negative <1%	5	100.0

Dose Escalation: Disease Characteristics

Melanoma	(N=11)	%
BRAF status		
Mutant V600E	6	54.5
Wild-Type	5	45.5
LDH at baseline*		
High	4	36.4
Normal	7	63.6
PD-L1 status**		
Positive ≥1%	6	54.5
Negative <1%	5	45.5
Stage		
M1a	1	9.1
M1b	2	18.2
M1c	8	72.7
Liver metastases at baseline		
Yes	4	36.4
No	7	63.6

* Based on maximum value prior to dosing.

** Measured using either **28-8 or 22C3** assays on fresh or archival tumor with specific cutoffs.

RCC	(N=22)	%
1L IMDC Score	n=14	
Favorable	1	7.1
Intermediate	12	85.7
Poor	1	7.1
1L PD-L1 status **	n=14	
Positive ≥1%	4	28.6
Negative <1%	8	57.1
No available biopsy	2	14.3
2L PD-L1 status **	n=8	
Positive ≥1%	5	62.5
Negative <1%	3	37.5

NSCLC	(N=5)	%
Histologic Subtype		
Adenocarcinoma	4	80.0
Squamous	1	20.0
Smoker		
Yes	5	100.0
No	0	0
PD-L1 status **		
Positive ≥1%	0	0
Negative <1%	5	100.0

Dose Escalation: Disease Characteristics

Melanoma	(N=11)	%
BRAF status		
Mutant V600E	6	54.5
Wild-Type	5	45.5
LDH at baseline*		
High	4	36.4
Normal	7	63.6
PD-L1 status**		
Positive ≥1%	6	54.5
Negative <1%	5	45.5
Stage		
M1a	1	9.1
M1b	2	18.2
M1c	8	72.7
Liver metastases at baseline		
Yes	4	36.4
No	7	63.6

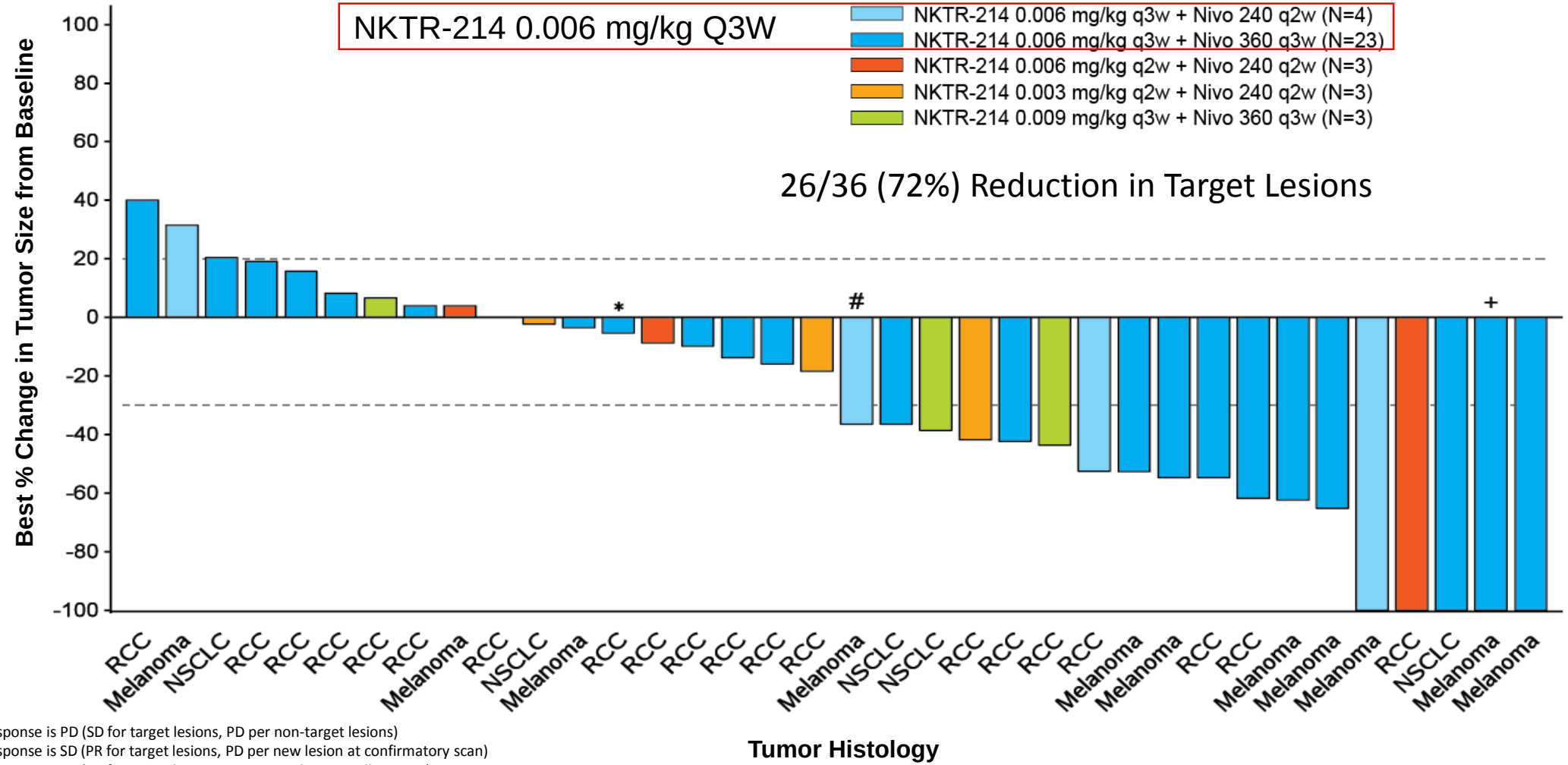
* Based on maximum value prior to dosing.

** Measured using either **28-8 or 22C3** assays on fresh or archival tumor with specific cutoffs.

RCC	(N=22)	%
1L IMDC Score	n=14	
Favorable	1	7.1
Intermediate	12	85.7
Poor	1	7.1
1L PD-L1 status **	n=14	
Positive ≥1%	4	28.6
Negative <1%	8	57.1
No available biopsy	2	14.3
2L PD-L1 status **	n=8	
Positive ≥1%	5	62.5
Negative <1%	3	37.5

NSCLC	(N=5)	%
Histologic Subtype		
Adenocarcinoma	4	80.0
Squamous	1	20.0
Smoker		
Yes	5	100.0
No	0	0
PD-L1 status **		
Positive ≥1%	0	0
Negative <1%	5	100.0

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

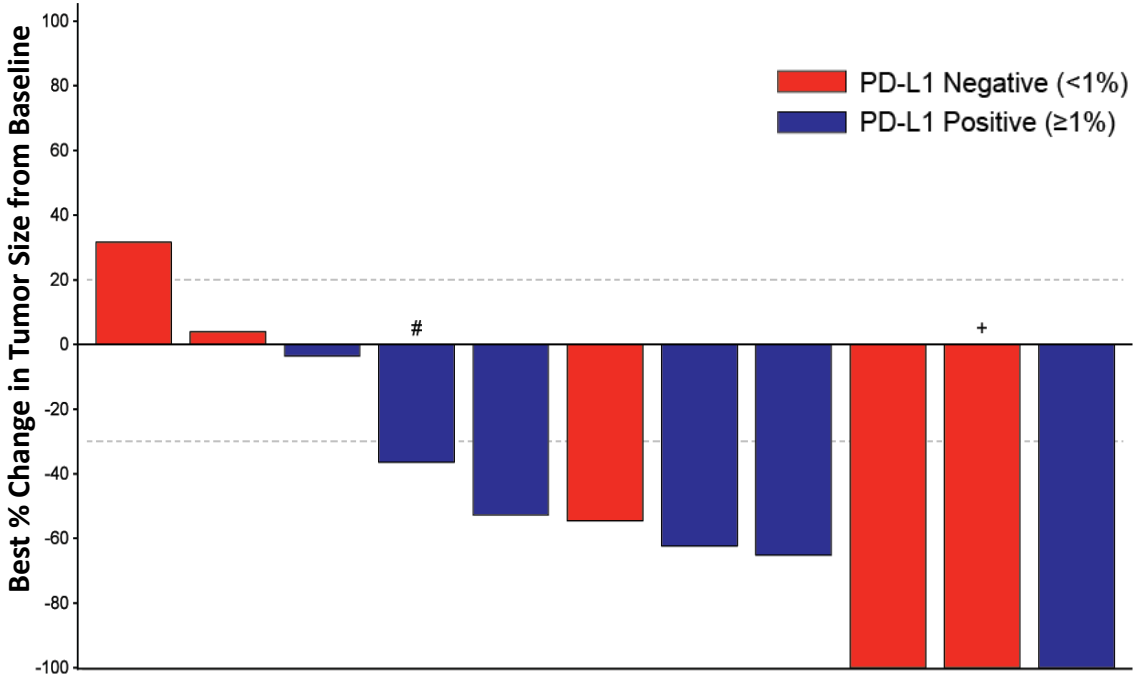


* Best overall response is PD (SD for target lesions, PD per non-target lesions)
\# Best overall response is SD (PR for target lesions, PD per new lesion at confirmatory scan)
\+ Best overall response is PR (CR for target lesions, non-target lesions still present)
Data are shown for patients with post-baseline 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.

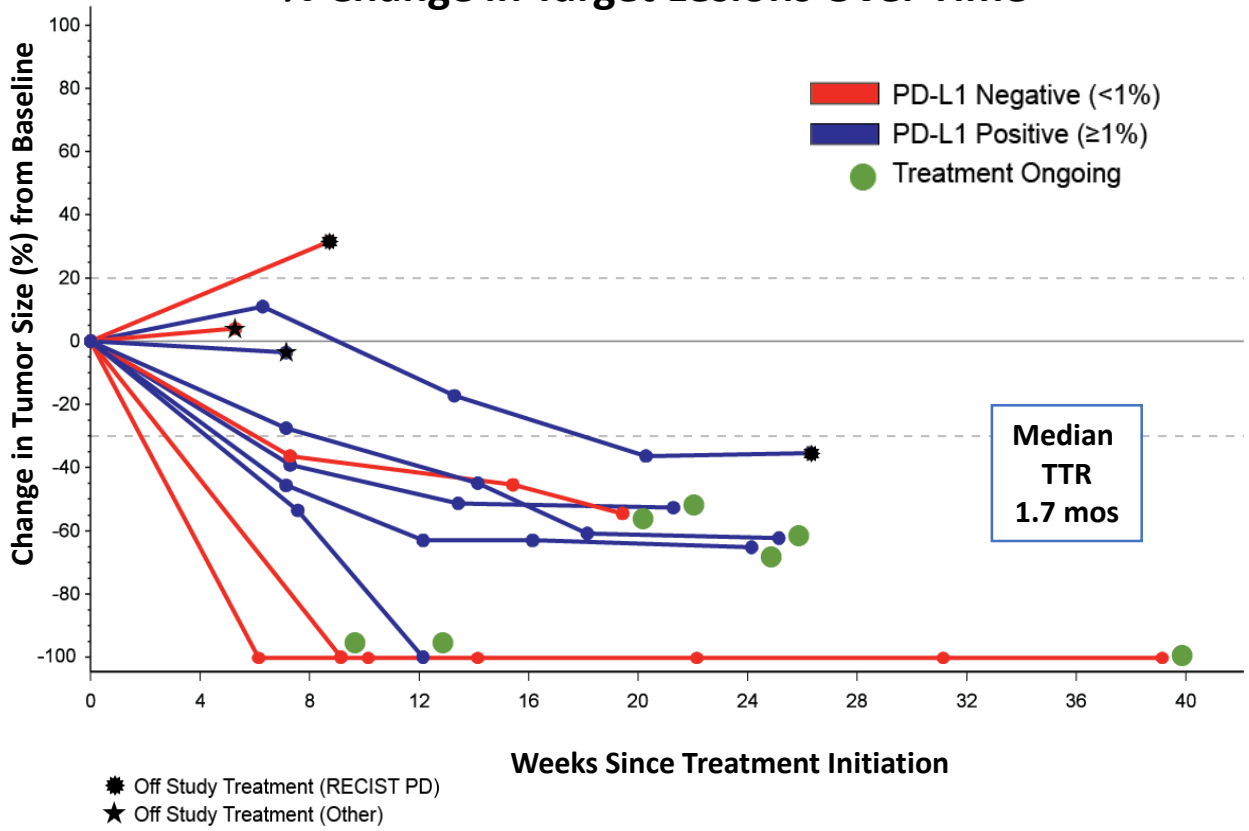
Stage IV Treatment-Naïve Melanoma Patients (N=11)

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

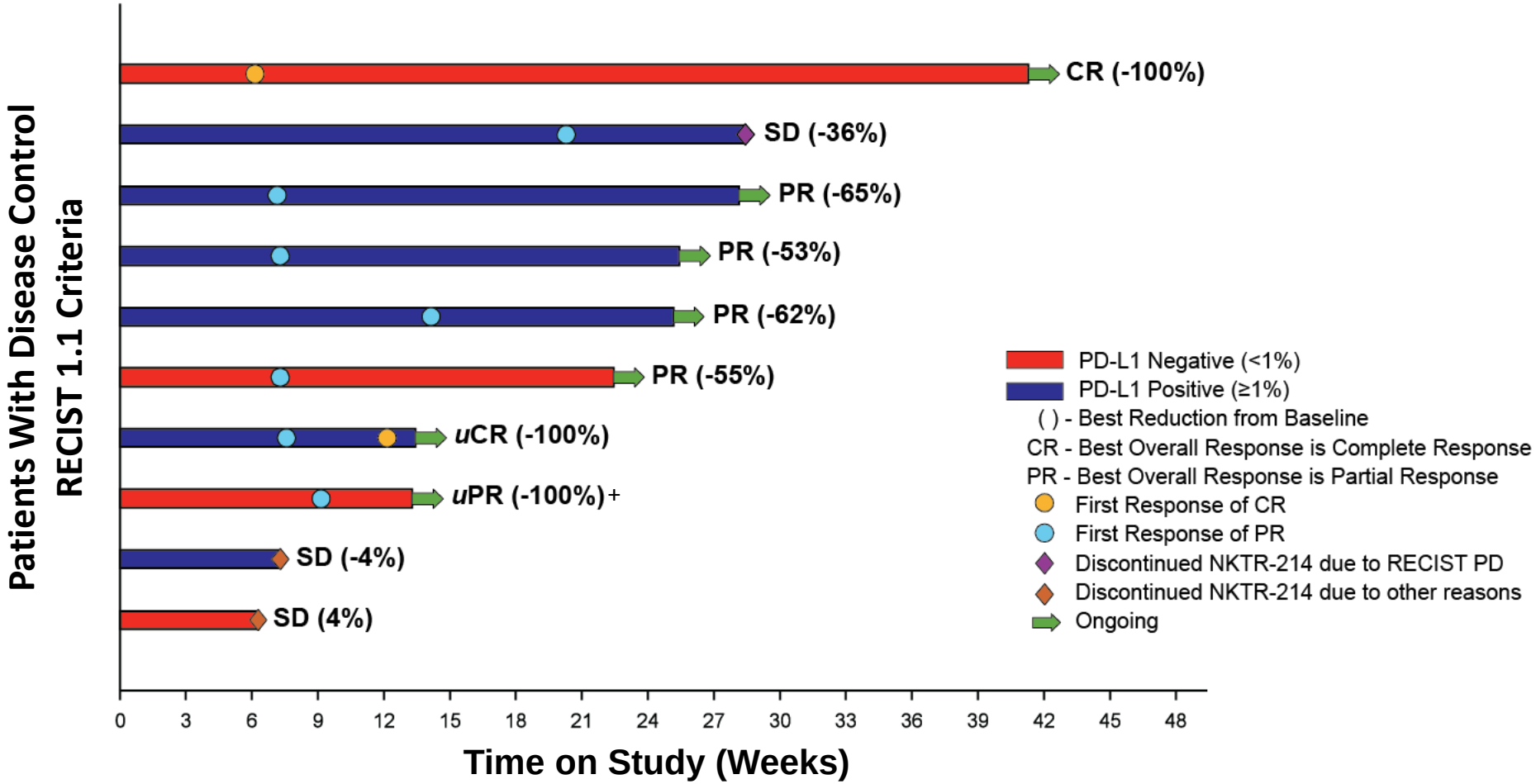


Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. # Best Overall Response is SD (PR for target lesions, PD per new lesion on confirmatory scan) + Best Overall response is PR (CR for target lesions, non-target lesions still present)
*One patient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

Time to and Duration of Response

Stage IV Treatment-Naïve Melanoma

All patients with responses (7/7) are still on treatment



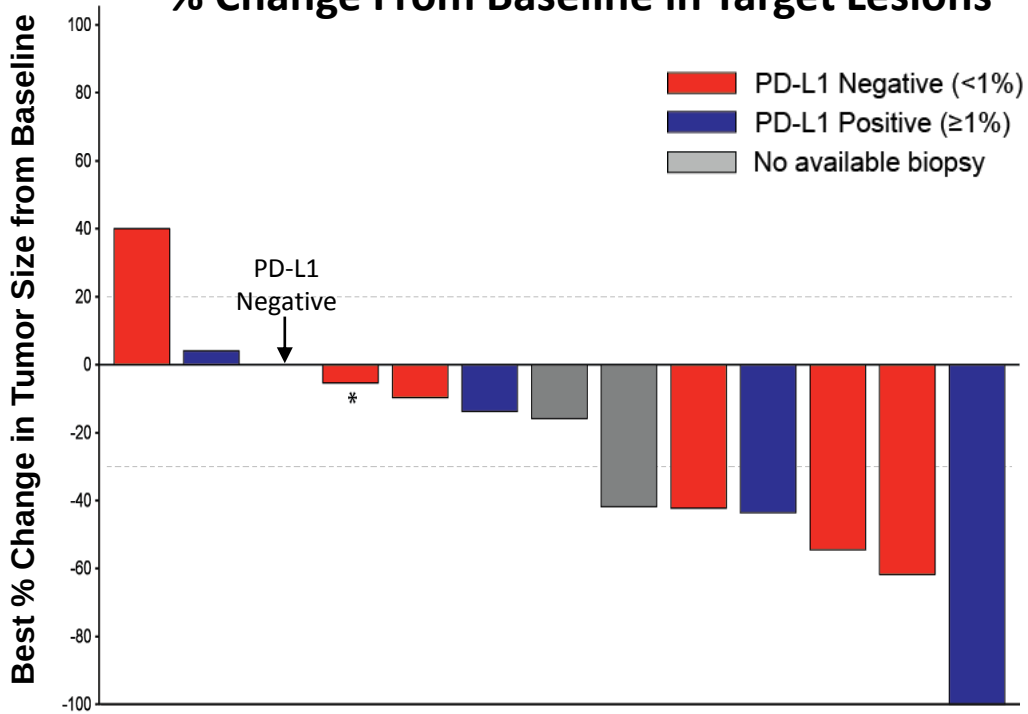
+ Best Overall response is PR (CR for target lesions, non-target lesions still present)

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

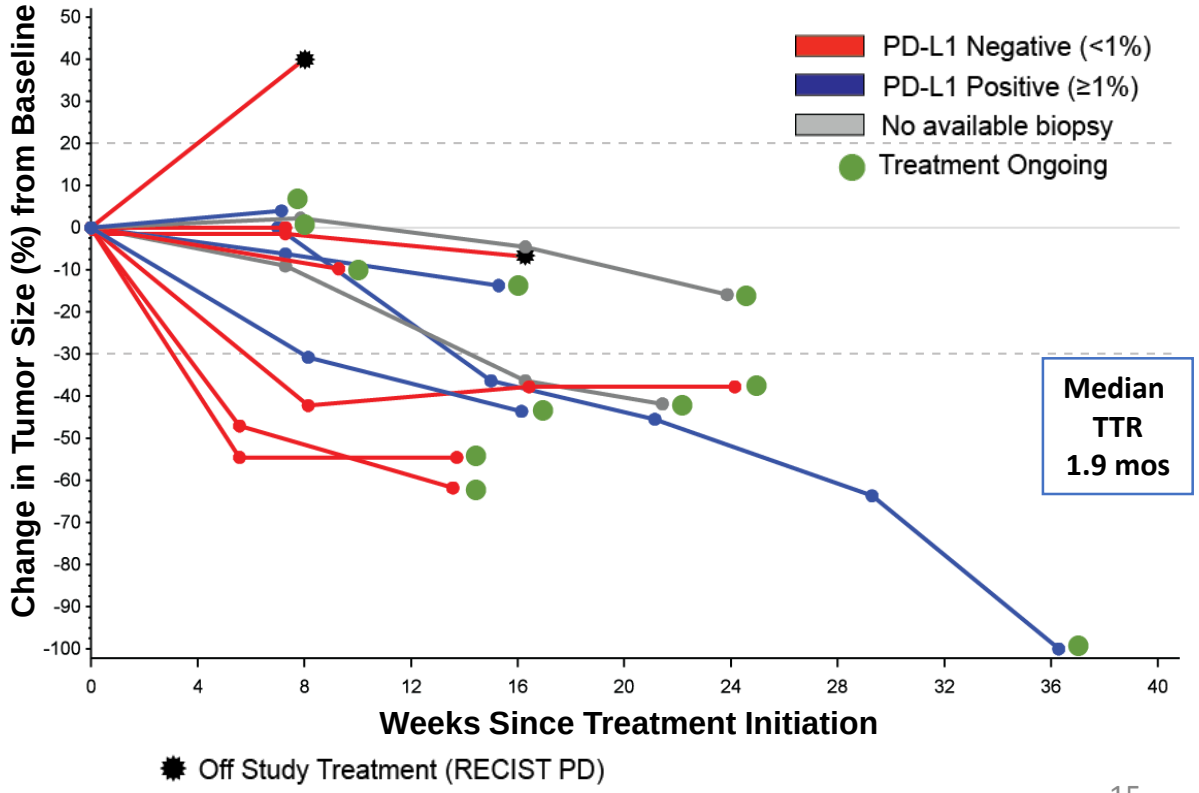
Efficacy-evaluable patients with ≥1 or ≥2 post baseline scans

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



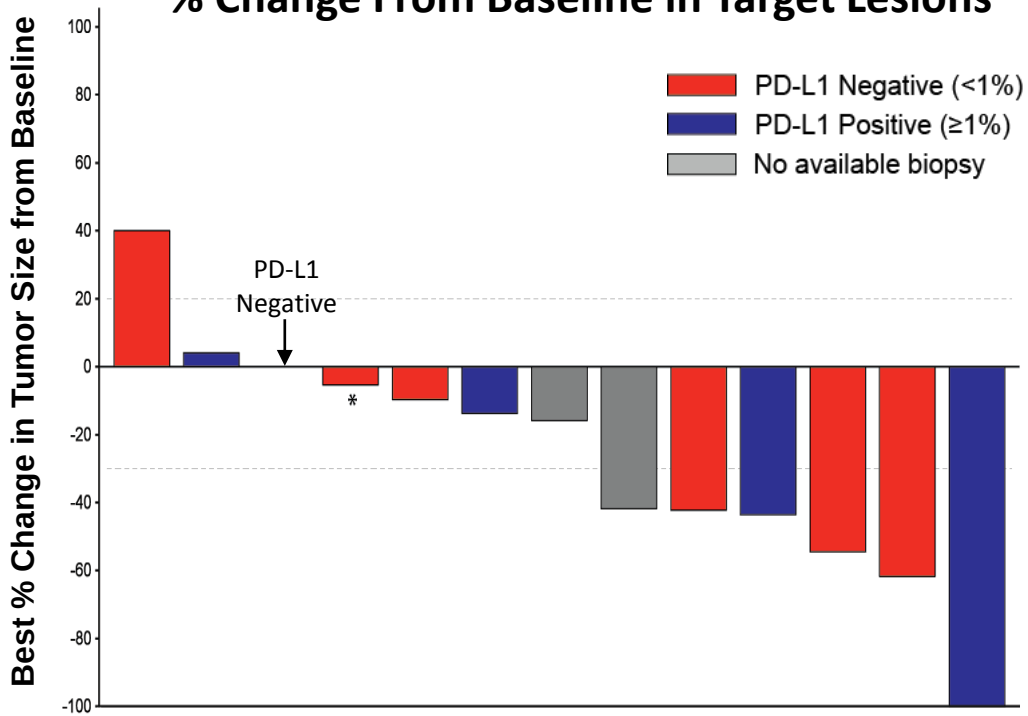
Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. * Best overall response is PD (SD for target lesions, PD per non-target lesions).

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

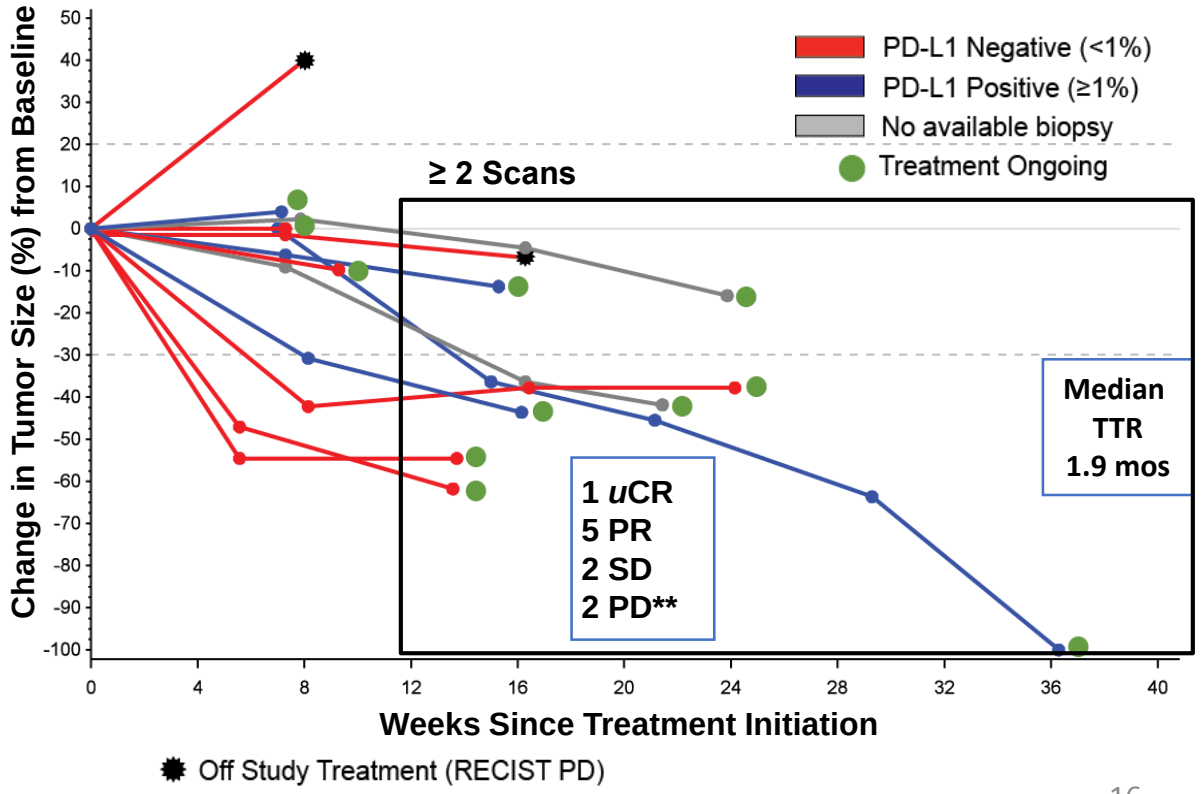
Efficacy-evaluable patients with ≥1 or ≥2 post baseline scans

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

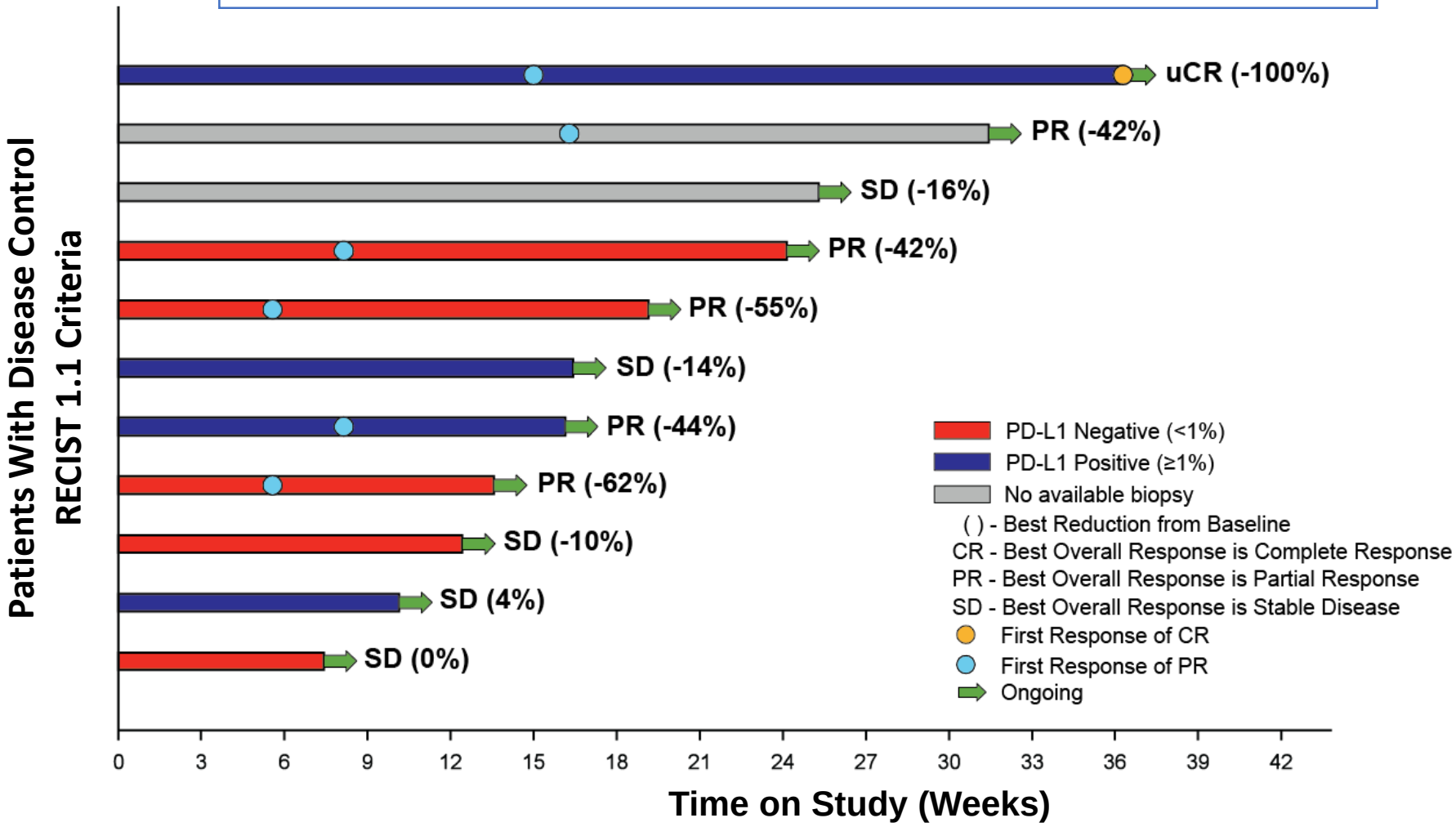


Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. * Best overall response is PD (SD for target lesions, PD per non-target lesions). **Includes PD with 1 post base-line scan

Time to and Duration of Response

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

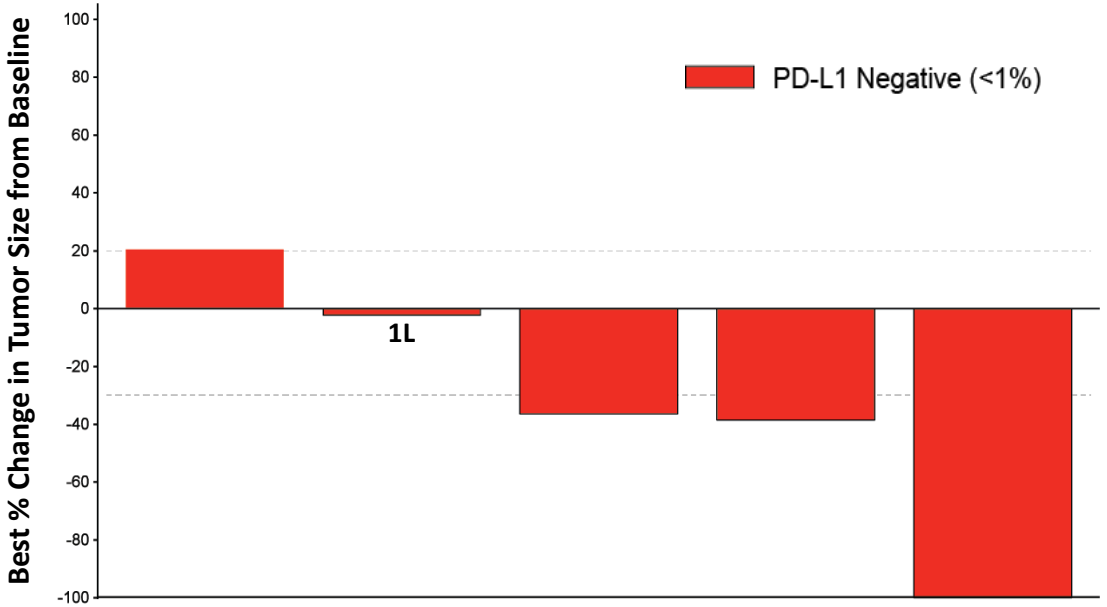
All patients with disease control (11/13) are still on treatment



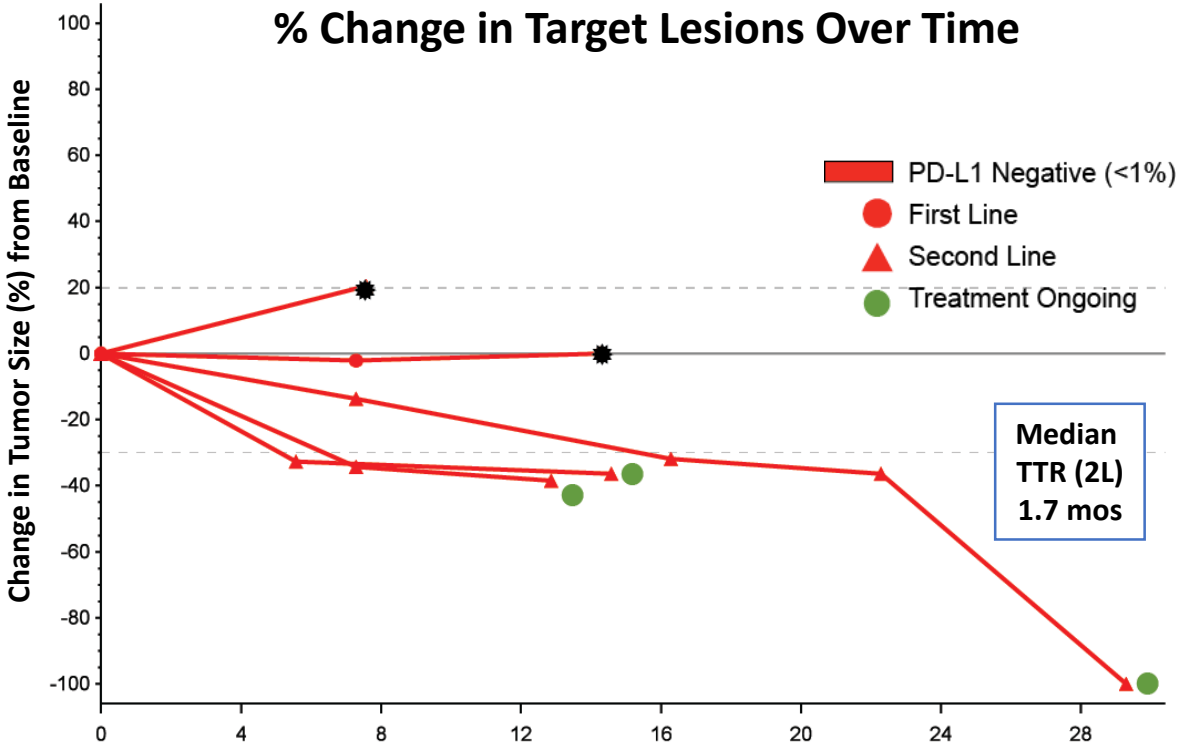
Stage IV IO-Naïve PD-L1 Negative NSCLC (1L and 2L)

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%)

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

(1) Patients are only counted once 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

Conclusions

- NKTR-214 plus nivolumab is a novel combination of immuno-oncology agents with differentiated, complementary and non-overlapping mechanisms of immune activation
- Efficacy results demonstrate important clinical activity in both PD-L1 negative and positive patients
  - All patients with responses continue on treatment
  - Few patients experienced rapid progression on treatment
  - Melanoma 1st line: ORR 64% (2 CR, 5 PR), DCR 91%, mTTR 1.7 mos
  - RCC 1st line: (≥ 1 scan) ORR 46% (1 CR, 5 PR), DCR 85%, mTTR 1.9 mos; (≥ 2 scans) ORR 60%, DCR 80%
  - NSCLC 2nd line (PD-L1 Negative): ORR 75% (1 CR, 2 PR), DCR 75%, mTTR 1.7 mos
- NKTR-214 plus nivolumab is safe and tolerable and can be administered as a convenient, outpatient regimen
  - No study discontinuations due to TRAEs and no treatment related deaths
  - NKTR-214 did not increase the risk for imAEs associated with nivolumab
  - RP2D established NKTR-214 0.006 mg/kg plus nivolumab 360 mg IV Q3W
- Enrollment to 13 expansion cohorts is underway (N=~330)

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A special thank you is extended to the patients, their families and all study staff who are participating and have participated in the PIVOT-02 dose-escalation study and PIVOT expansion study

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- Michael Hurwitz, MD
- Harriet Kluger, MD
- Scott Gettinger, MD

Providence Cancer Center
- Brendan Curti, MD

New York University
- Daniel Cho, MD

Roswell Park Cancer Institute
- Igor Puzanov, MD

Seattle Cancer Center
- Scott Tykodi, MD