

## **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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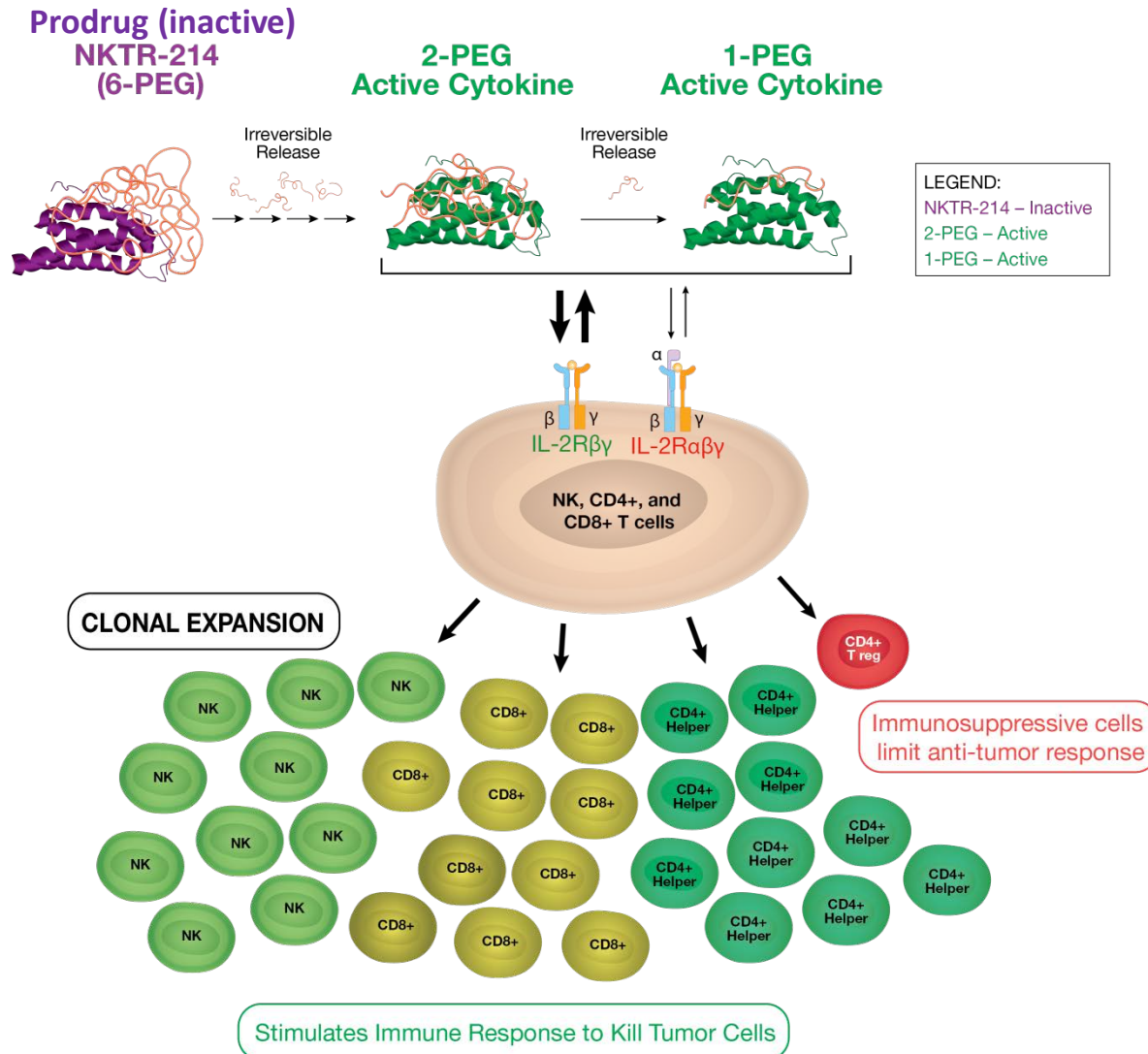
# Presenter Disclosure Information

*Dr. Adi Diab, MD Anderson Cancer Center*

*The following relationships exist related to this presentation:*

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

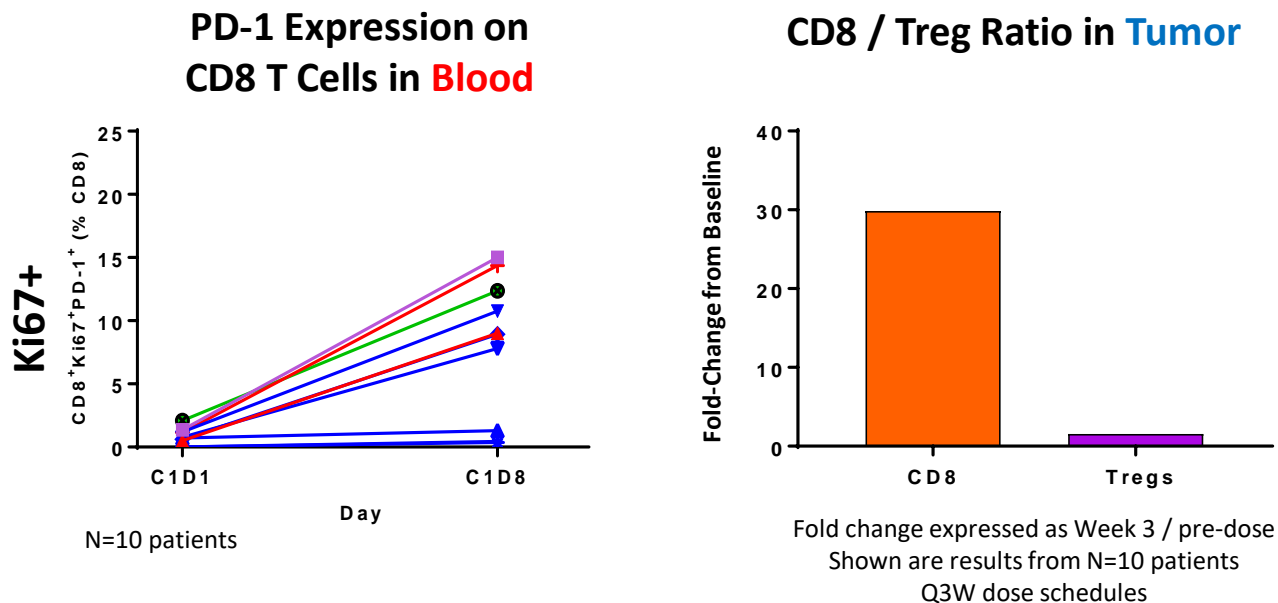
# NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



- 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

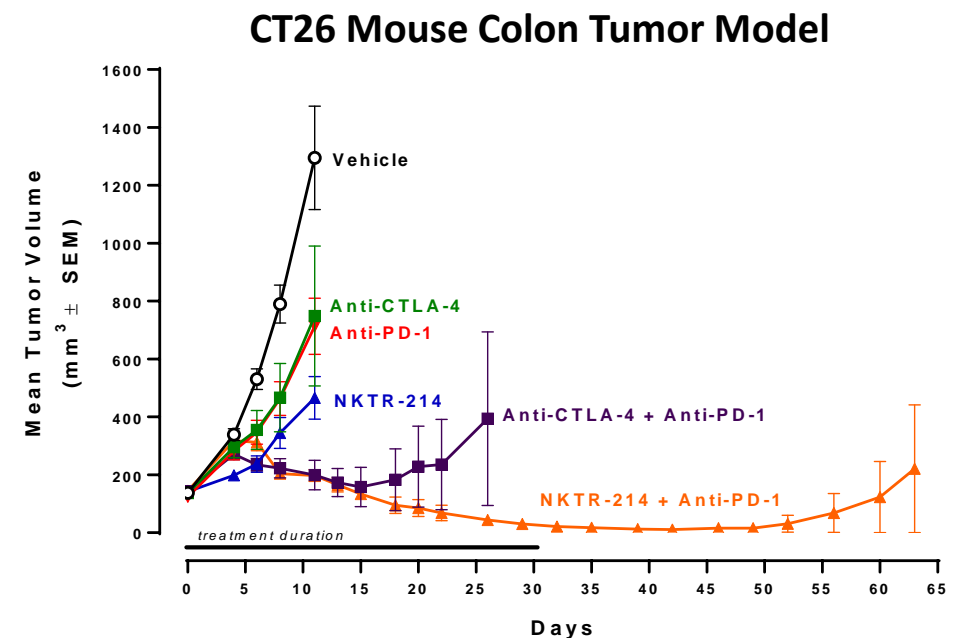
# Clinical and Preclinical Rationale for Combination of NKTR-214 + Anti-PD-1

## NKTR-214 Monotherapy Clinical Trial<sup>1</sup>



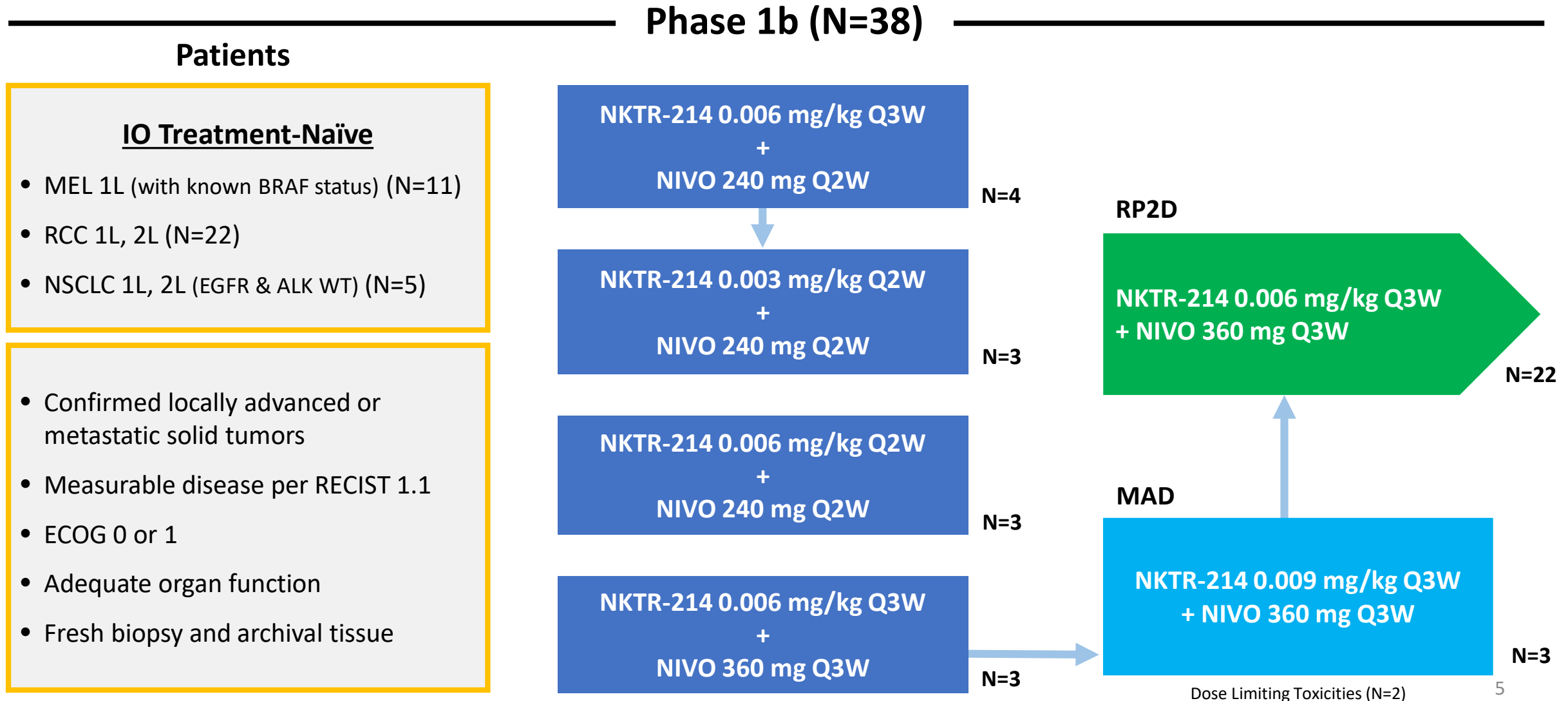
- Blood:** Increase in newly proliferating (Ki67+) PD-1+ CD8 T cells
- Tumor:** Increase in total T cells, NK and CD8+ T cells with no increase in Tregs, increase in newly proliferating (Ki67+) PD-1+ CD8 T cells

## NKTR-214 + Anti-PD-1 Preclinical Data<sup>2</sup>



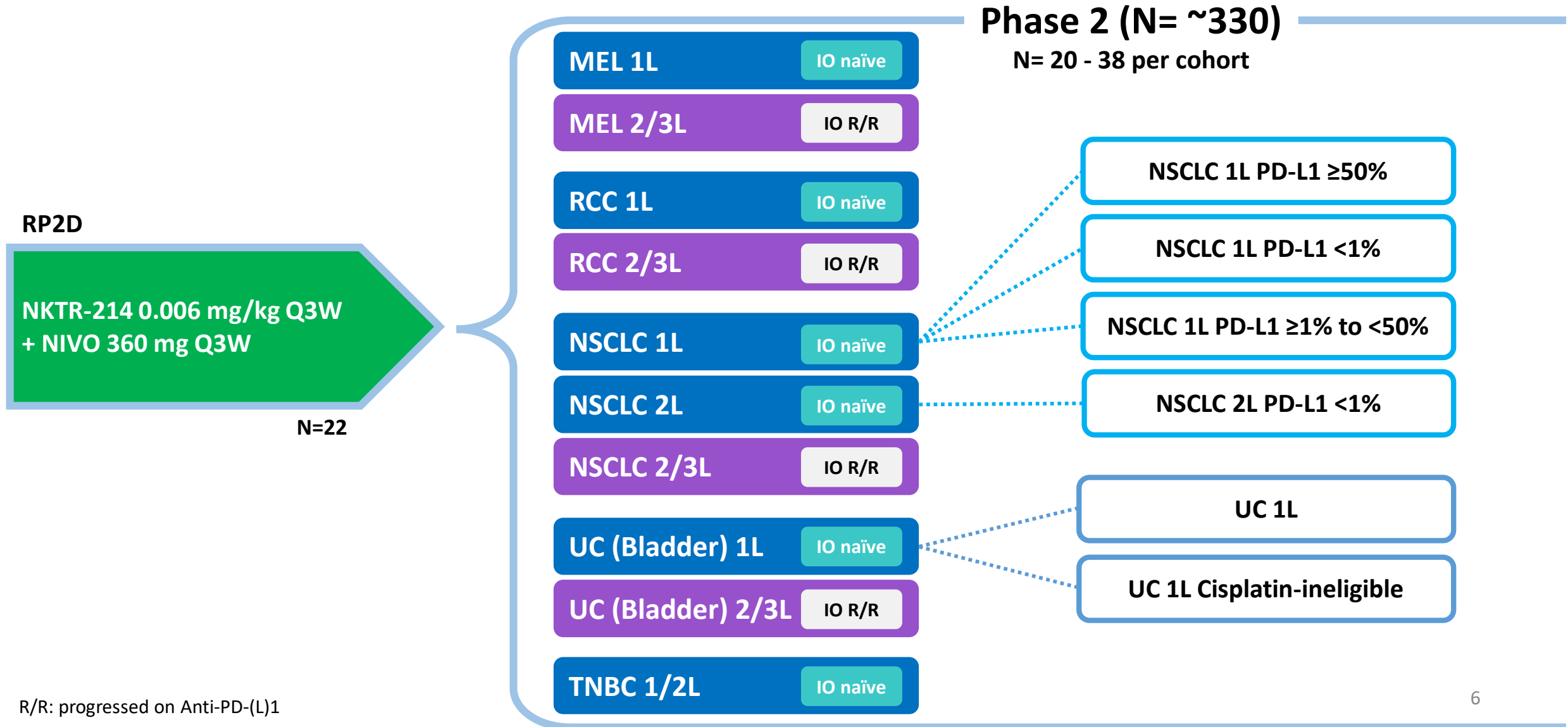
NKTR-214 dosed 0.8 mg/kg q9dx3, anti-PD-1 or anti-CTLA-4 dosed 200ug or 100ug 2x/week respectively.

# PIVOT-02 Dose Escalation





# PIVOT-02 Dose Expansion Underway in 13 Cohorts



# 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  $\geq 1$  post baseline scan
- **Safety and tolerability**
  - Adverse events were assessed by Common Terminology Criteria for Adverse Events (CTCAE) v4.03
  - Safety-evaluable includes  $\geq 1$  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)
<b>Sex</b>				
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%)
<b>Age (years)</b>				
Median (Range)	61 (22-72)	62 (22-70)	61 (45-72)	58 (53-72)
<b>ECOG Performance Status</b>				
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%)
<b>Prior systemic therapy for metastatic disease</b>				
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)	%
<b>BRAF status</b>		
Mutant V600E	6	54.5
Wild-Type	5	45.5
<b>LDH at baseline*</b>		
High	4	36.4
Normal	7	63.6
<b>PD-L1 status**</b>		
Positive ≥1%	6	54.5
Negative <1%	5	45.5
<b>Stage</b>		
M1a	1	9.1
M1b	2	18.2
M1c	8	72.7
<b>Liver metastases at baseline</b>		
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)	%
<b>1L IMDC Score</b>	n=14	
Favorable	1	7.1
Intermediate	12	85.7
Poor	1	7.1
<b>1L PD-L1 status **</b>	n=14	
Positive ≥1%	4	28.6
Negative <1%	8	57.1
No available biopsy	2	14.3
<b>2L PD-L1 status **</b>	n=8	
Positive ≥1%	5	62.5
Negative <1%	3	37.5
<b>NSCLC</b>	(N=5)	%
<b>Histologic Subtype</b>		
Adenocarcinoma	4	80.0
Squamous	1	20.0
<b>Smoker</b>		
Yes	5	100.0
No	0	0
<b>PD-L1 status **</b>		
Positive ≥1%	0	0
Negative <1%	5	100.0

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

## Dose Escalation: Disease Characteristics

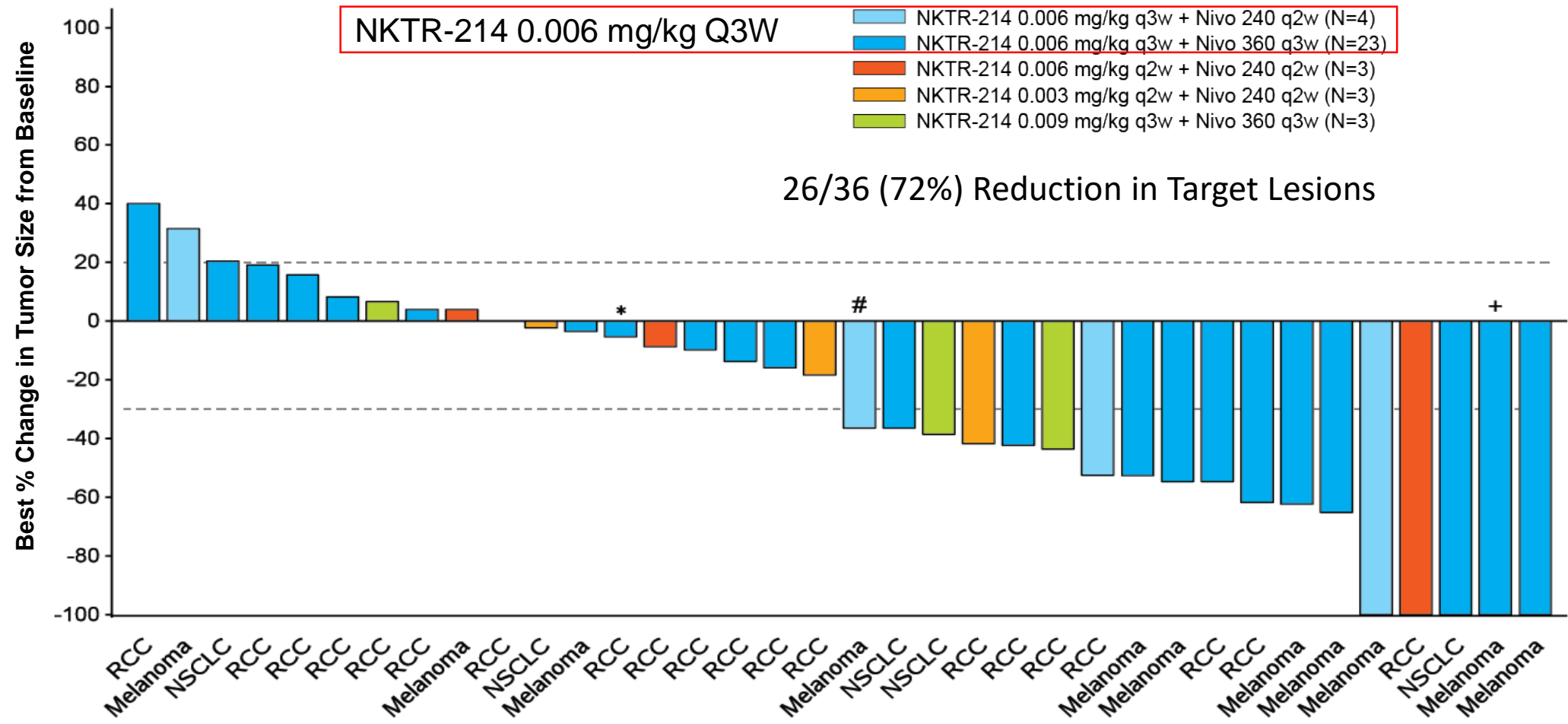
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Adenocarcinoma	4	80.0
Squamous	1	20.0
<b>Smoker</b>		
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No	0	0
<b>PD-L1 status **</b>		
Positive ≥1%	0	0
Negative <1%	5	100.0

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

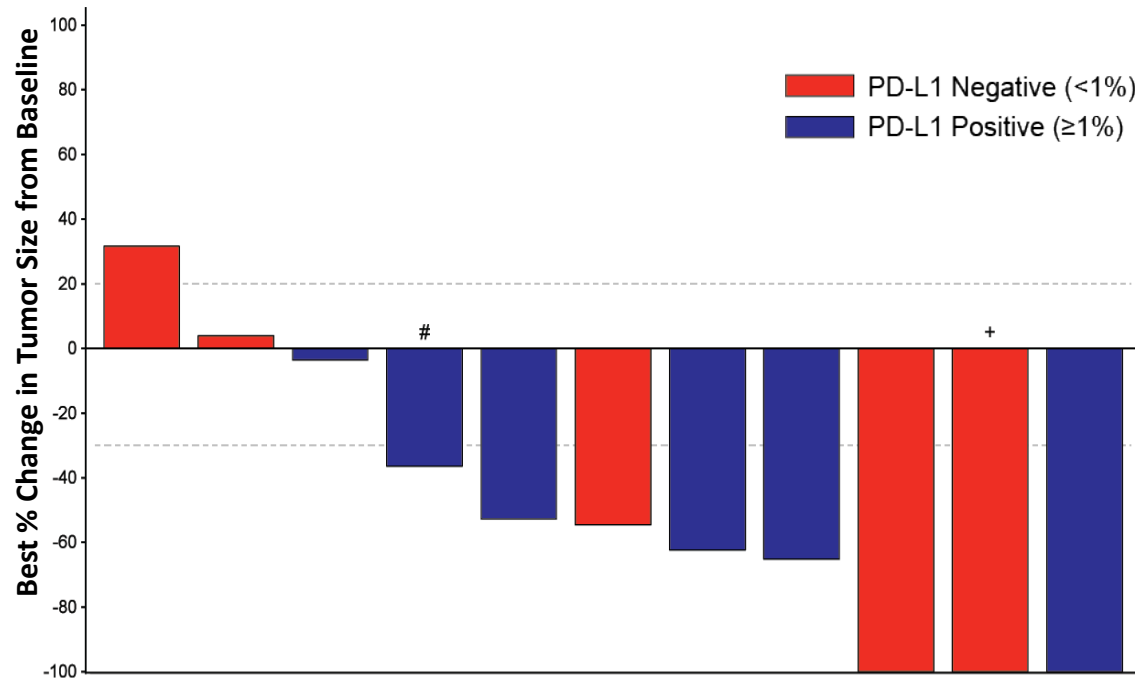


\* Best overall response is PD (SD for target lesions, PD per non-target lesions)  
# Best overall response is SD (PR for target lesions, PD per new lesion at confirmatory scan)  
+ Best overall response is PR (CR for target lesions, non-target lesions still present)  
Data are shown for patients with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

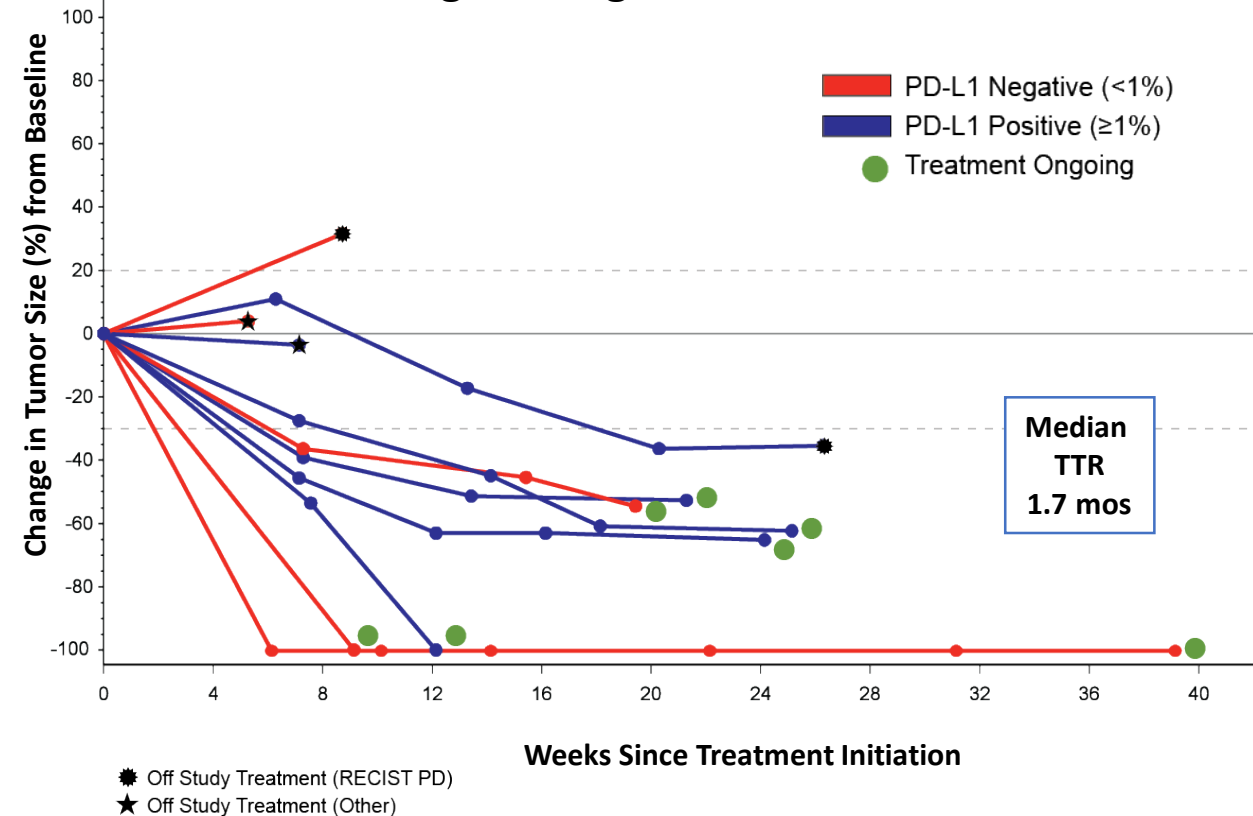
# Stage IV Treatment-Naïve Melanoma Patients (N=11)

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

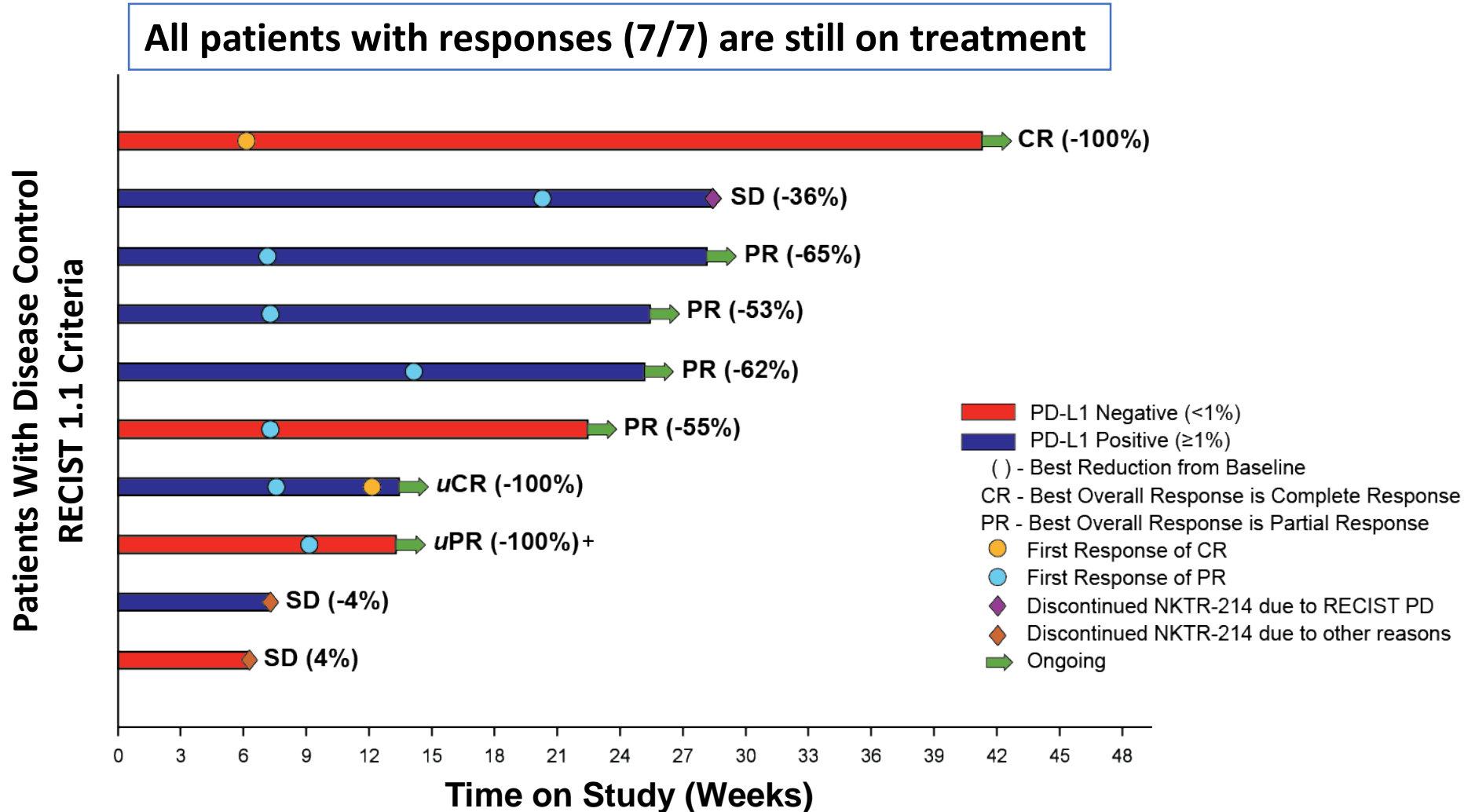


Horizontal dotted lines indicate the thresholds for PD and response according to RECIST (version 1.1) criteria. # Best Overall Response is SD (PR for target lesions, PD per new lesion on confirmatory scan) + Best Overall response is PR (CR for target lesions, non-target lesions still present)

\*One patient in ORR calculation has unconfirmed PR.

# Time to and Duration of Response

## Stage IV Treatment-Naïve Melanoma



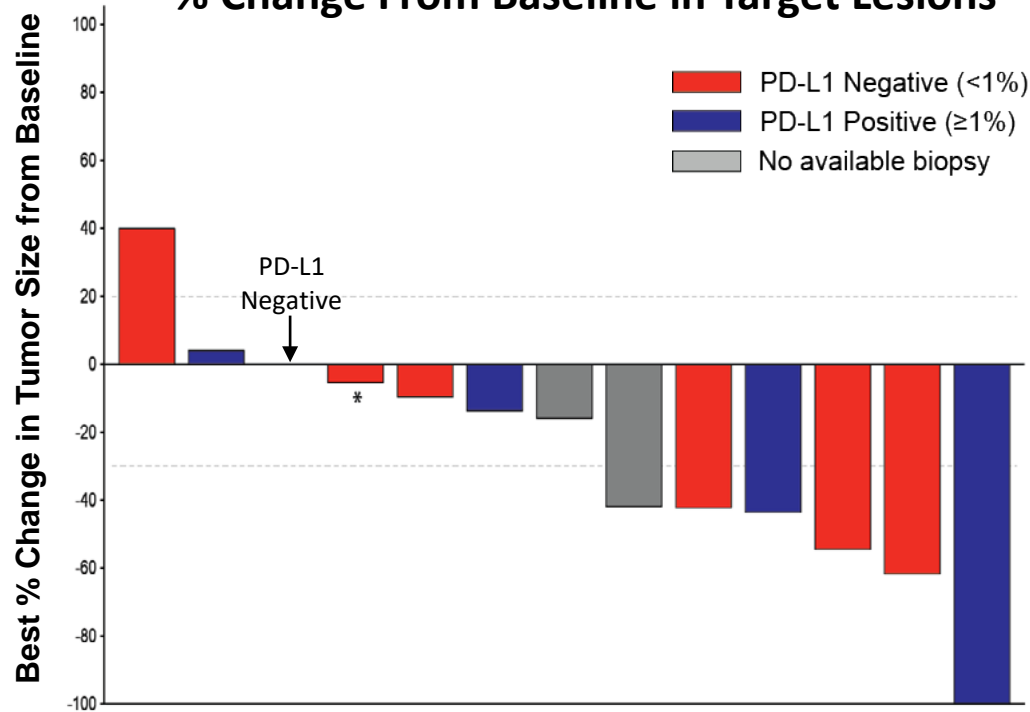


# Stage IV Treatment-Naïve 1L Renal Cell Carcinoma (N=13)

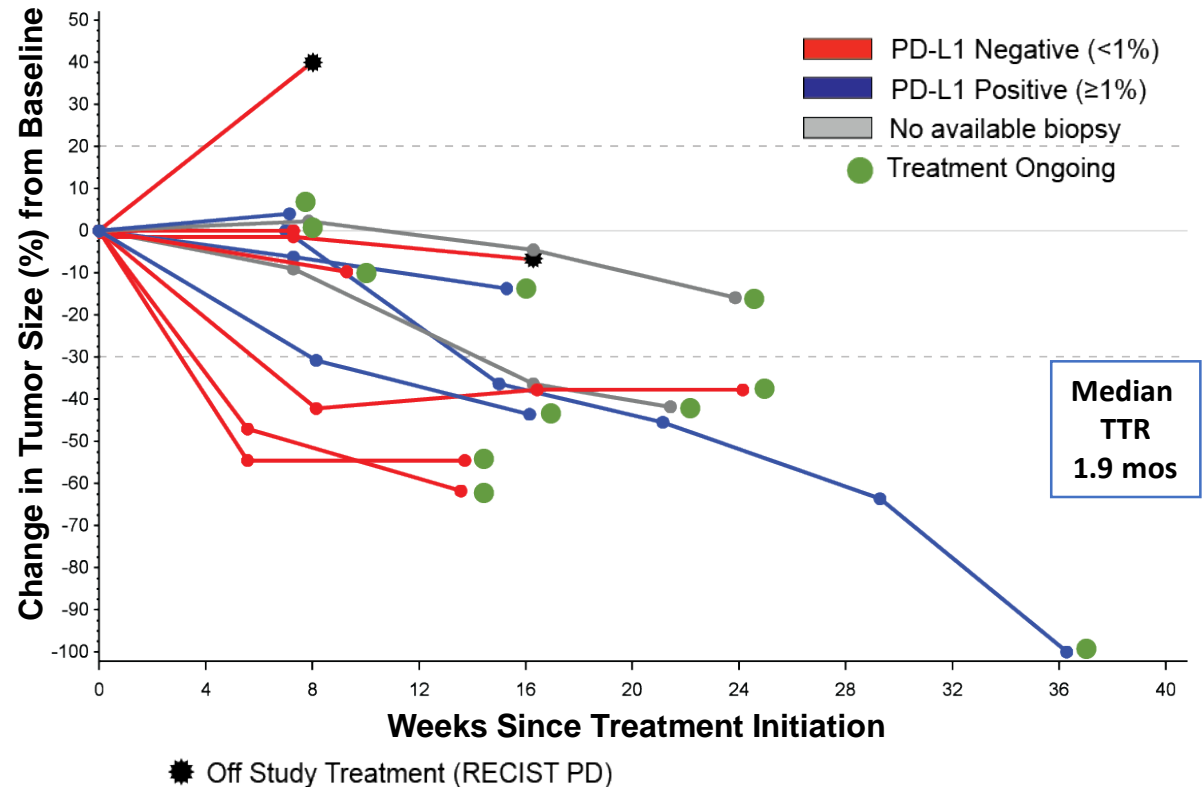
*Efficacy-evaluable patients with  $\geq 1$  or  $\geq 2$  post baseline scans*

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

% Change From Baseline in Target Lesions



% Change in Target Lesions Over Time

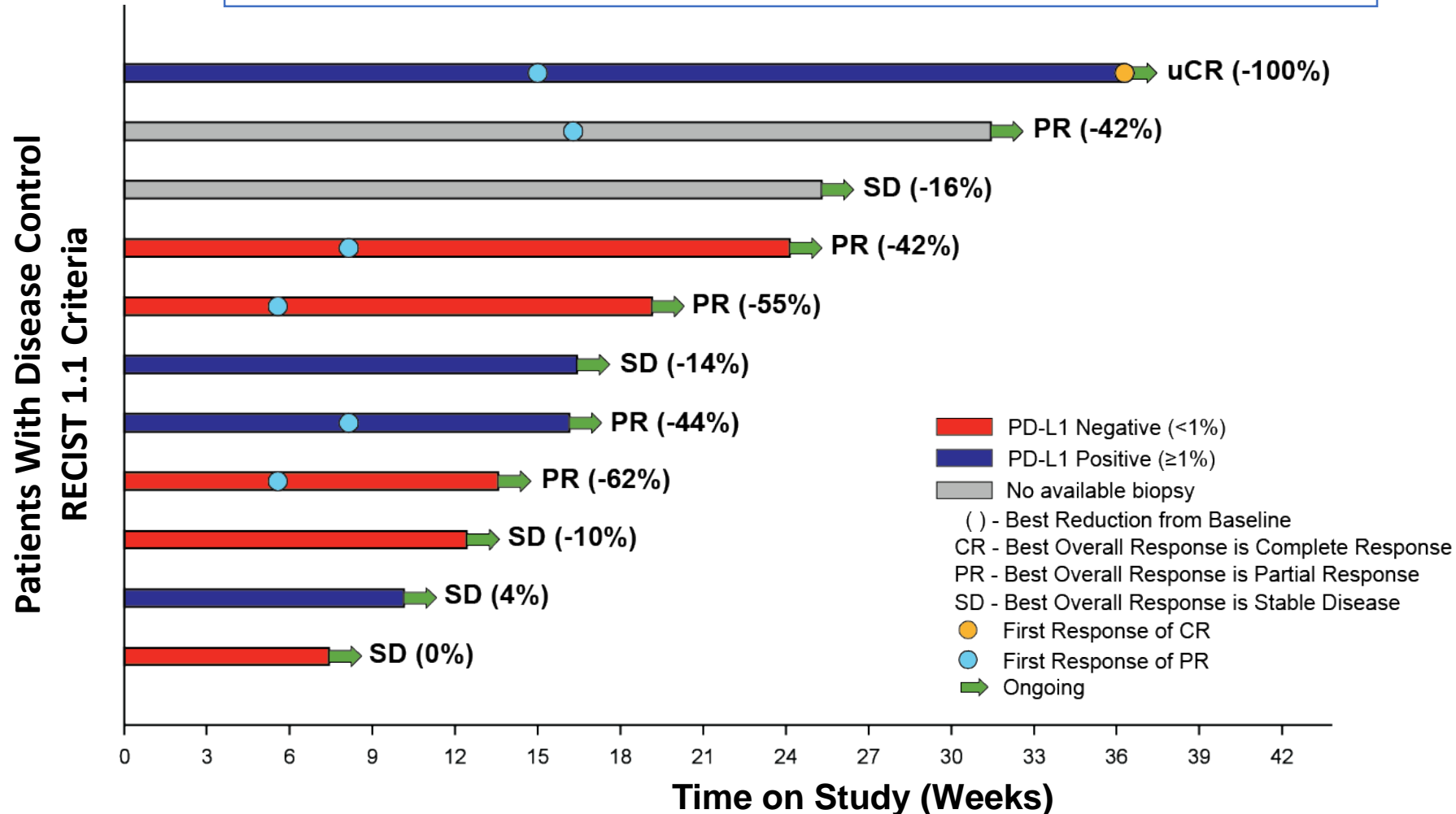




# Time to and Duration of Response

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

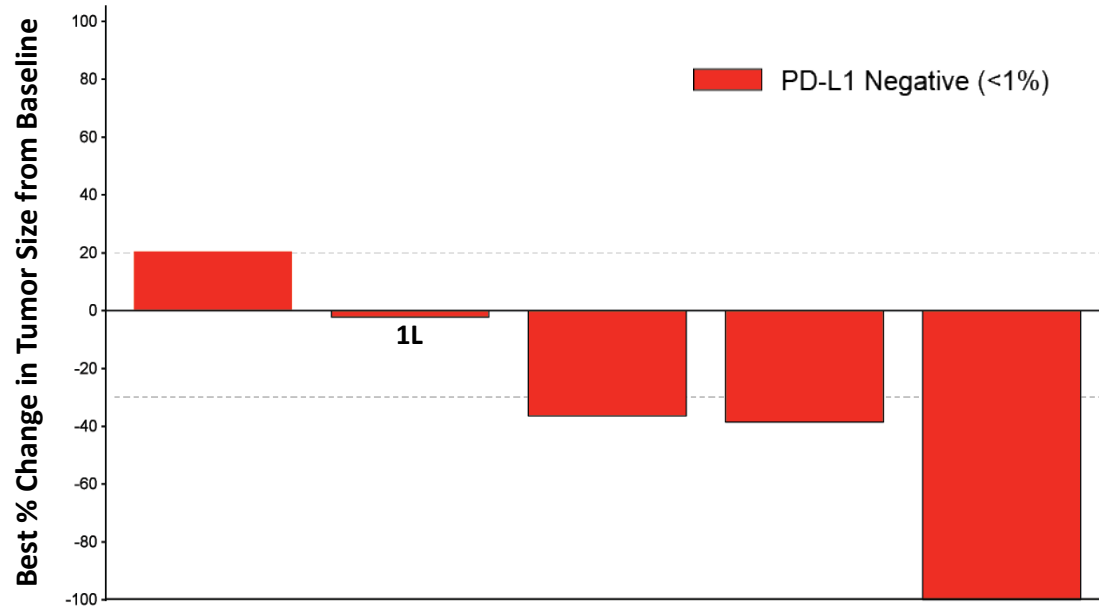
All patients with disease control (11/13) are still on treatment



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

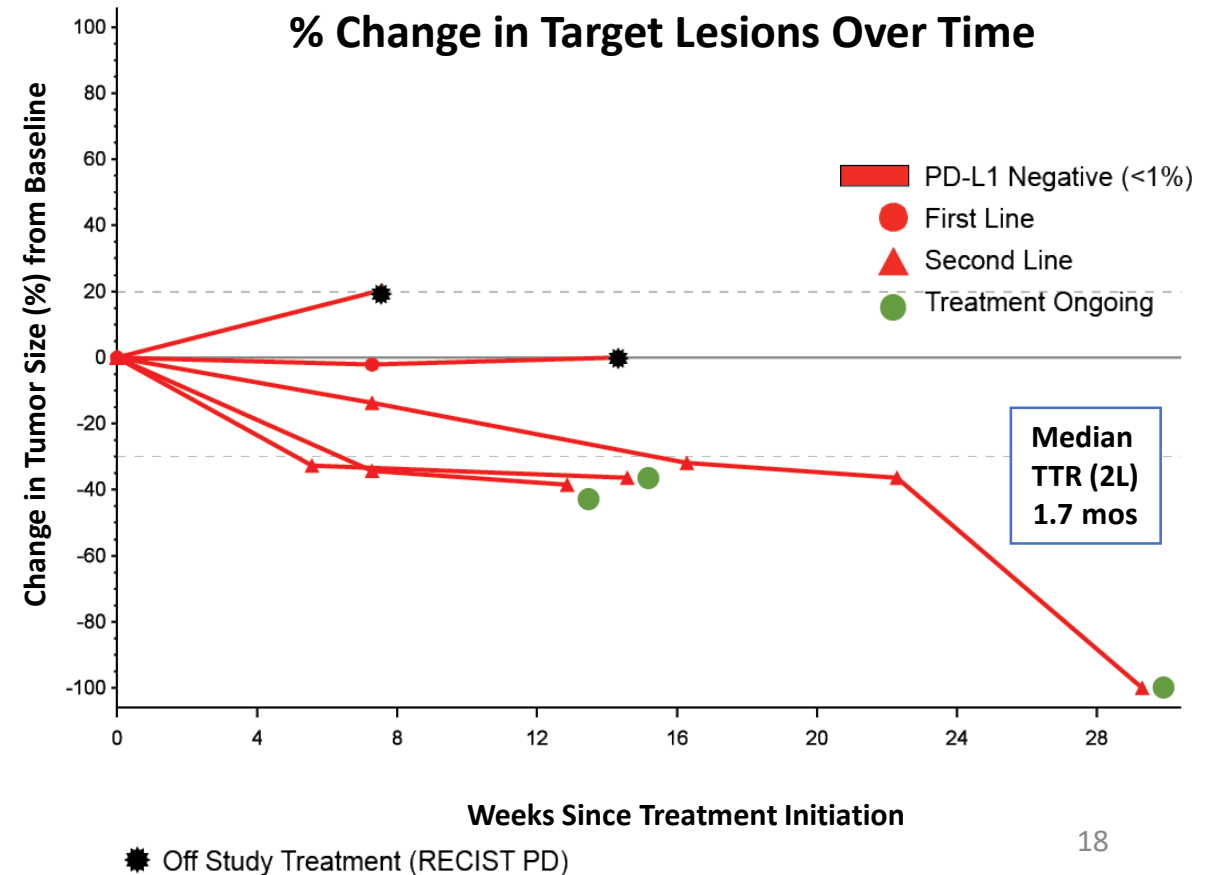
Best Overall Response by RECIST (2L): ORR=3/4 (75%); DCR=3/4 (75%)  
 Best Overall Response by RECIST (1L and 2L): ORR=3/5 (60%); DCR=3/5 (60%)

% Change From Baseline in Target Lesions



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

% Change in Target Lesions Over Time



# 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%) <sup>+</sup>	6 (46%)	6 (60%)	1 (14%)	0 (0)	3 (75%)
CR	2 (18%)	1 (8%) <sup>#</sup>	1 (10%) <sup>#</sup>	0	0	1 (25%) <sup>#</sup>
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

<sup>+</sup> CR is waiting to be confirmed for 1 of 2 patients with CR; one patient in calculation has uPR.

<sup>#</sup> PR for patient confirmed. CR is waiting to be confirmed.

<sup>\*\*</sup> Patients with at least 2 post-baseline scans or progressed on 1<sup>st</sup> post-baseline scan.

# Treatment-Related AEs

Preferred Term <sup>[1]</sup>	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)
<b>Grade 3 or 4</b>	<b>4 (10.5%)</b>	<b>1 (4.0%)</b>	<b>1 (25.0%)</b>	<b>0</b>	<b>0</b>	<b>2 (66.7%)</b>
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
<b>Grade 1&amp;2 (&gt;25%)</b>						
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 1<sup>st</sup> line: ORR 64% (2 CR, 5 PR), DCR 91%, mTTR 1.7 mos
  - RCC 1<sup>st</sup> line: ( $\geq 1$  scan) ORR 46% (1 CR, 5 PR), DCR 85%, mTTR 1.9 mos; ( $\geq 2$  scans) ORR 60%, DCR 80%
  - NSCLC 2<sup>nd</sup> 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= $\sim$ 330)

# Acknowledgments

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- Daniel Cho, MD

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- Igor Puzanov, MD

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