NKTR-214 (CD-122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT

ClinicalTrials.gov Identifier: NCT02983045

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Presenter Disclosure Information

Dr. Adi Diab, The University of Texas MD Anderson Cancer Center

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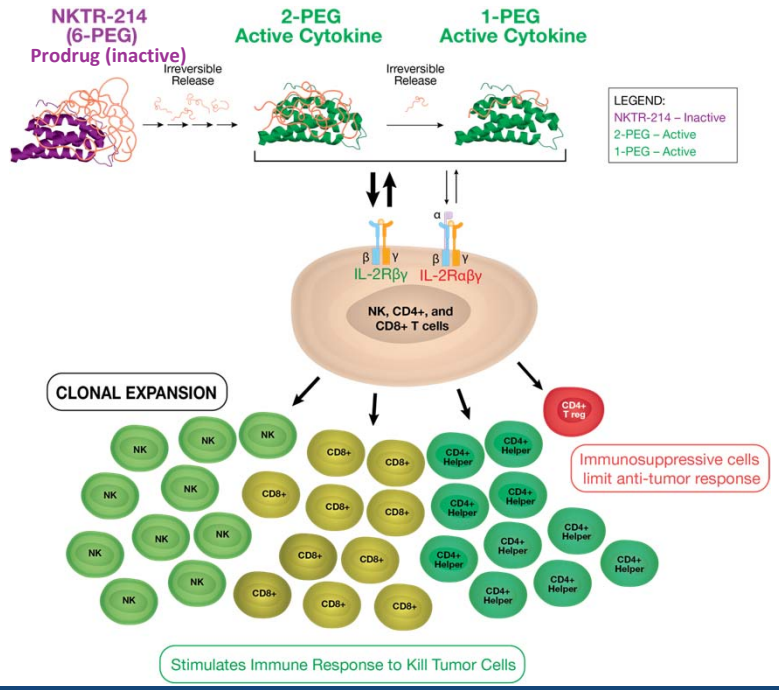
NKTR-214 Background: Harnessing the IL-2 Pathway to Increase TILs



- NKTR-214 prodrug design with sustained signaling
- Mitigation of rapid immune stimulation to achieve safe, outpatient regimen administered every 3 week IV dosing
- Biased signaling preferentially activates and expands effector T cells and NK cells over Tregs in the tumor microenvironment
- NKTR-214 increases proliferation of TILs and PD-1 expression on the surface of CD8+ T cells providing a mechanistic rationale for combining with nivolumab

PIVOT-02 Study Dose-Escalation in I-O Treatment-Naïve Patients: Enrollment Complete

Phase 1 (N=38) Enrollment Compete

I-O 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

NKTR-214 0.006 mg/kg Q3W + NIVO 240 mg Q2W

NKTR-214 0.003 mg/kg Q2W + NIVO 240 mg Q2W

NKTR-214 0.006 mg/kg Q2W + NIVO 240 mg Q2W

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

RP2D N=25

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

Maximum Administered Dose

NKTR-214 0.009 mg/kg Q3W + NIVO 360 mg Q3W

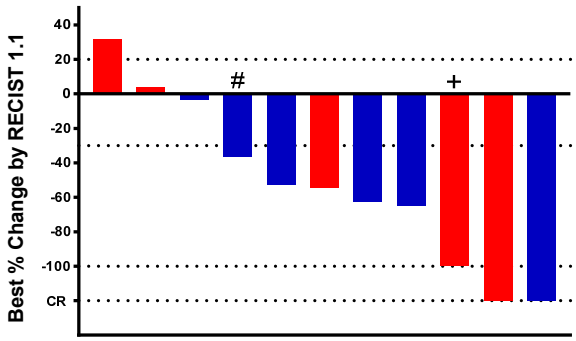
Dose Limiting Toxicities (N=2)

RP2D, recommended Phase 2 dosing

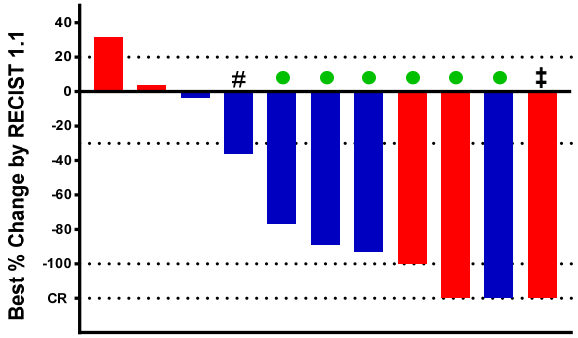
Stage IV IO-Naïve 1L Melanoma Dose Escalation Cohort (N=11) Deepening of Responses Over Time

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

SITC 2017 (Data Cut: Nov 2, 2017)



ASCO 2018 (Data Cut: May 29, 2018)



PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
Treatment Ongoing
‡ Off Study Treatment (maximal clinical benefit achieved)

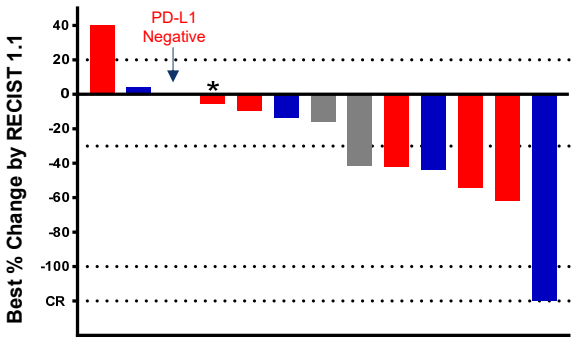
ORR PD-L1 (-) 3/5 (60%)
ORR PD-L1 (+) 4/6 (67%)

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. CR: Complete response, all target and non-target lesions cleared.# Best Overall Response is SD (PR for target lesions, PD per new lesion on confirmatory scan) + Best overall response is PR to (CR for target lesions, non-target lesions still present).. -100% is PR (CR for target lesions, non-target lesions still present) "u": Unconfirmed.

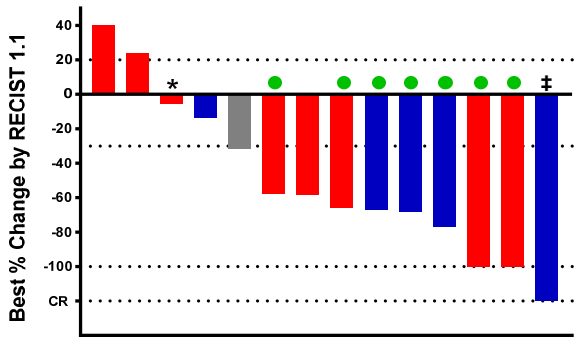
Stage IV IO-Naïve 1L RCC Dose Escalation Cohort (N=14)
Deepening of Responses Over Time

SITC 2017: ORR=6/13 (46%); DCR=11/13 (85%)
ASCO 2018: ORR=10/14 (71%); DCR=11/14 (79%)

SITC 2017 (Data Cut: Nov 2, 2017)



ASCO 2018 (Data Cut: May 29, 2018)



PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
Unknown
Treatment Ongoing
‡ Off Study Treatment (maximal clinical benefit achieved)

ORR PD-L1 (-) 5/8 (63%)
ORR PD-L1 (+) 4/5 (80%)
ORR PD-L1 Unknown 1/1

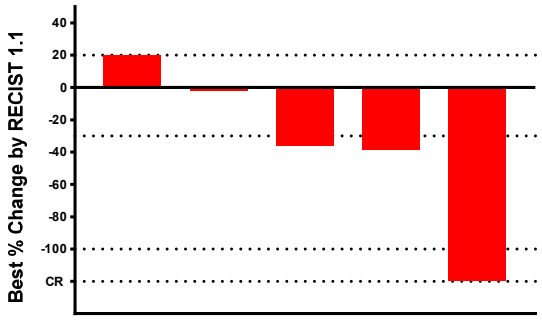
Increased ORR With Continued Treatment
Patients with Initial Stable Disease Convert to Responses Over Time

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

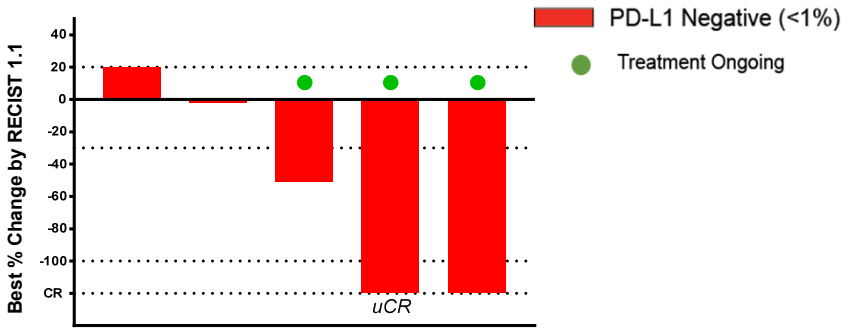
Stage IV IO-Naïve 1-2L NSCLC Dose Escalation Cohort (N=5)
Deepening of Responses Over Time in PD-L1 Negative Patients

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=4/5 (80%)

SITC 2017 (Data Cut: Nov 2, 2017)

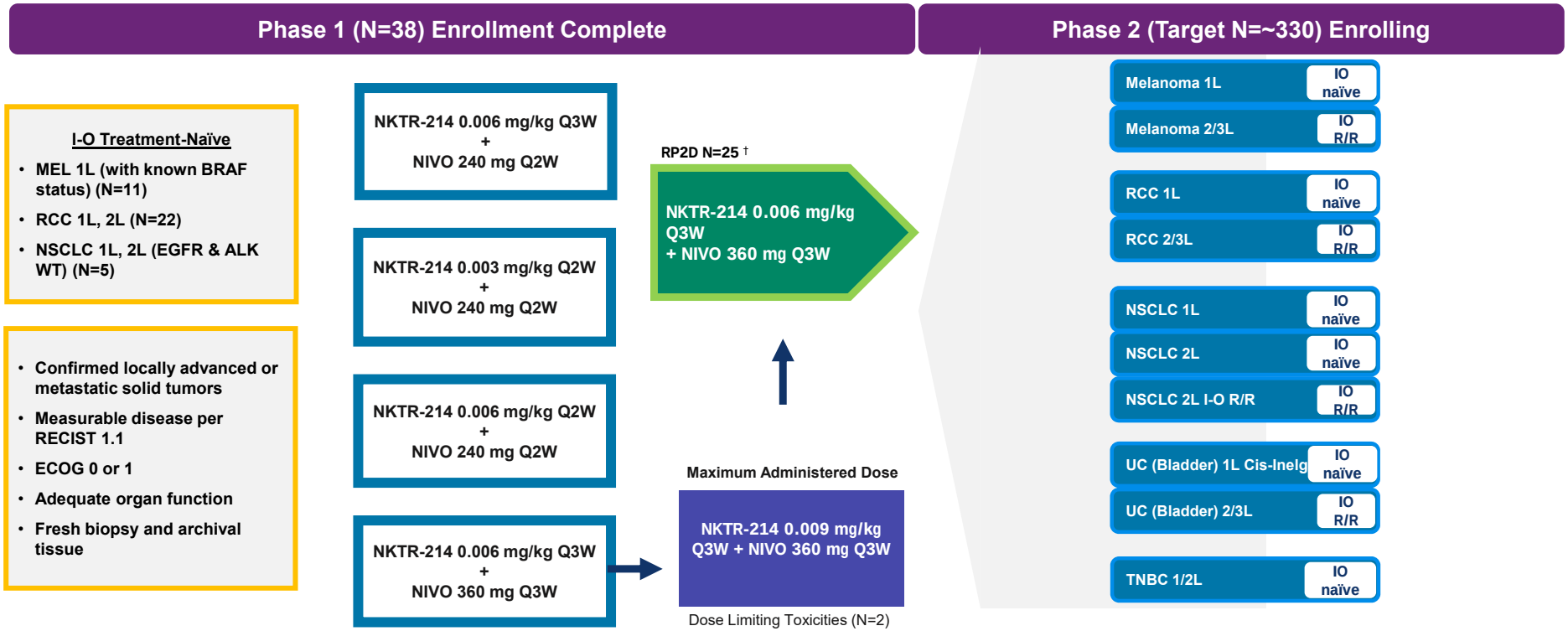


ASCO 2018 (Data Cut: May 29, 2018)



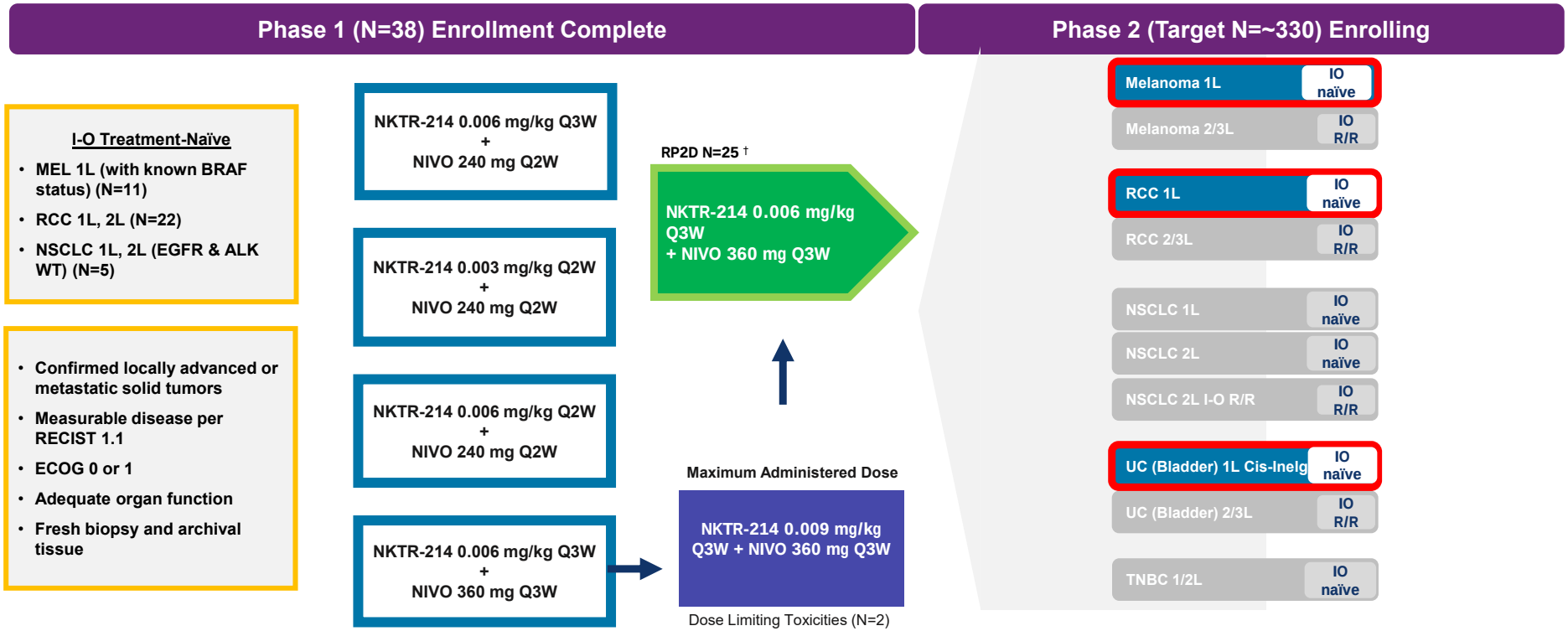
PDL1 positivity for this analysis was 1% or greater. Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria., CR: Complete response, all target and non-target lesions cleared,. "u": Unconfirmed

PIVOT-02 RP2D Dose Expansion Cohorts in 5 Tumor Types: Enrollment Ongoing



†7 patients from 1L melanoma dose escalation cohort, 11 patients from 1L RCC dose escalation cohort included in RP2D expansion cohorts
RP2D: recommended Phase 2 dosing

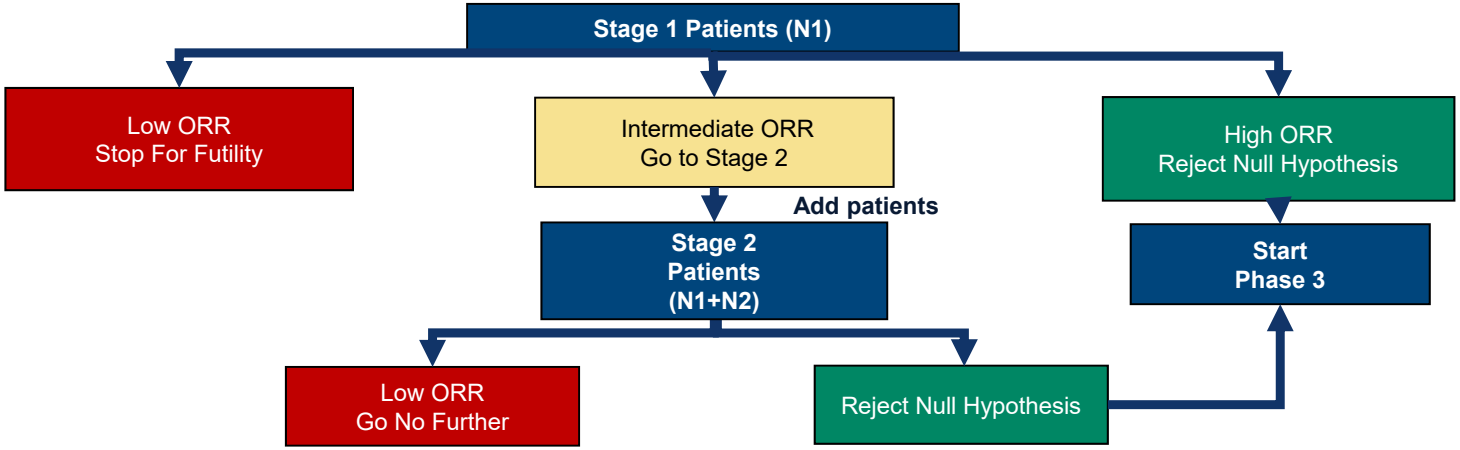
PIVOT-02 RP2D Dose Expansion Cohorts in 5 Tumor Types: Enrollment Ongoing



†7 patients from 1L melanoma dose escalation cohort, 11 patients from 1L RCC dose escalation cohort included in RP2D expansion cohorts
RP2D: recommended Phase 2 dosing

PIVOT-02 Fleming Two Stage Design

Criteria Based on Consecutive Patients Enrolled at RP2D



Indications That Met Fleming Efficacy Criteria To-Date	Objective Response Rate		Sample Sizes		Pre-Specified Efficacy Boundary for Responses	
	Historical* %	Target %	Stage 1 N1	Stage 2 N1+N2	Stage 1 N1	Stage 2 N1+N2
1L Melanoma	40[1]	65	**13**†	28	≥ 10	≥ 15
1L RCC	25[2,3]**	50	**11**†	26	≥ 6	≥ 10
1L Urothelial (Cis-ineligible)	16[4]	45	**10**	18	≥ 4	≥ 6

† 7 patients from 1L melanoma dose escalation cohort, 11 patients from 1L RCC dose escalation included in RP2D expansion cohorts

The Fleming two stage design: alpha 0.1 and power 90% designed to show superiority over single agent checkpoint Inhibitor.
*Historical rates are for single checkpoint inhibitors
1. Robert et al. N Engl J Med. 2015;372:320-30; 2.Topalian et al. N Engl J Med. 2012;366:2443-54; 3. Motzer et al. JCO 33(13): 1430-7;
4. Rosenberg et al., Lancet 2016; 387:1909-20; **RCC trials noted were 2+ line following VEGF therapy.

Enrollment to I-O Naïve Cohorts That Met Fleming Efficacy Criteria as of May 29, 2018

I-O Naïve Cohort	Eligible Per Protocol Treated at RP2D	Evaluable	Consecutive Enrollment Fleming Analysis N1	Consecutive Enrollment Fleming Analysis N1+N2
1L Melanoma	41†	37	13	28
1L RCC	48†	47	11	26
1L Urothelial (Cis-Ineligible)	16	10	10	Enrolling
Total	**105**	**94**		

All other patient cohorts in PIVOT are ongoing and/or enrolling and have not yet met Fleming futility or efficacy criteria to-date.

† 7 patients from 1L melanoma dose escalation cohort, 11 patients from 1L RCC dose escalation cohort included in RP2D expansion cohorts.

Patient Demographics and Disease Characteristics

	1L Melanoma (N=41)	1L RCC (N=48)	Urothelial (Cis-Ineligible) (N=16)
Sex			
Female	17 (41.5%)	10 (20.8%)	5 (31.3%)
Male	24 (58.5%)	38 (79.2%)	11 (68.8%)
Age (years)			
Median (Range)	63 (22-80)	61 (40-78)	70 (54-83)
ECOG Performance Status			
0	31 (75.6%)	29 (60.4%)	6 (37.5%)
1	9 (22.0%)	19 (39.6%)	10 (62.5%)
Not Done	1 (2.4%)		
PD-L1 status*			
Positive ≥1%	20 (48.8%)	14 (29.2%)	7 (43.8%)
Negative <1%	14 (34.1%)	30 (62.5%)	7 (43.8%)
Unknown	7 (17.1%)	4 (8.4%)	2 (12.6%)

*>95% measured using central lab (28-8 assays on fresh or archival tumor with specific cutoffs).

Disease Characteristics at Study Entry

1L Melanoma	(N=41)	%
BRAF status		
Mutant (V600E, V600K or other)	15	36.6
Wild-Type	25	61.0
Unknown	1	2.4
LDH*		
Normal	33	80.5
Elevated > ULN	8	19.5
Stage (7th edition AJCC)		
M0	0	0
M1a	6	14.6
M1b	18	43.9
M1c+**	17	41.4
Liver metastases		
Yes	11	26.8
No	30	73.2

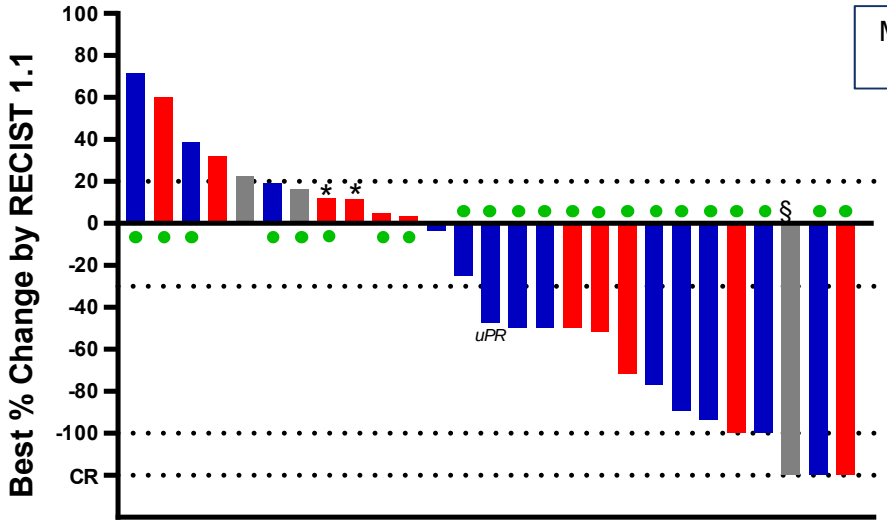
*Based on maximum value prior to dosing

1L RCC	(N=48)	%
IMDC score		
Favorable	5	10.4
Intermediate	34	70.8
Poor	9	18.8

1L Urothelial	(N=16)	%
Primary site		
Urinary Bladder	10	62.5
Renal Pelvis	5	31.3
Urethra	1	6.3
Liver metastases at baseline		
Yes	2	12.5
No	14	87.5
Prior neoadjuvant/adjuvant therapy		
Yes	6	37.5
No	10	62.5

Stage IV IO-Naïve 1L Melanoma Cohort at RP2D: Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 11/13 (85%)
Stage 2: Best Overall Response ORR=14/28 (50%); DCR=20/28 (71%)



Median Time on Study 4.6 Months (N=28)
As of May 29, 2018

PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
PD-L1 Unknown
Treatment Ongoing

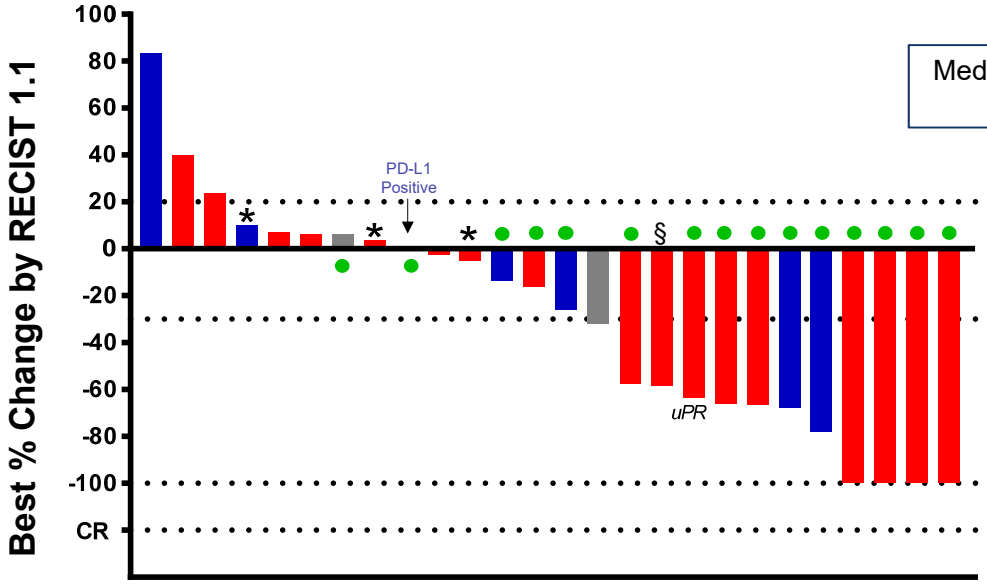
ORR PD-L1 (-) 5/12 (42%)
ORR PD-L1 (+) 8/13 (62%)
ORR PD-L1 Unknown 1/3 (33%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria. -100% is PR for complete clearance of target lesions. CR is a complete response. "u": Unconfirmed. *Best overall response is PD; SD for target lesions but PD due to a new lesion. §Off study treatment with confirmed CR due to patient decision.
One PD-L1(-) patient had PD due to non-target lesions and target lesions were not assessed, therefore 27/28 patients included in waterfall plot..

Stage IV IO-Naïve 1L RCC Cohort Achieved Pre-Specified Efficacy Criteria

Stage 1: ORR 7/11 (64%)
Stage 2: Best Overall Response ORR=12/26 (46%); DCR=20/26 (77%)



Median Time on Study 5.6 Months (N=26)
As of May 29, 2018

PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
PD-L1 Unknown
Treatment Ongoing

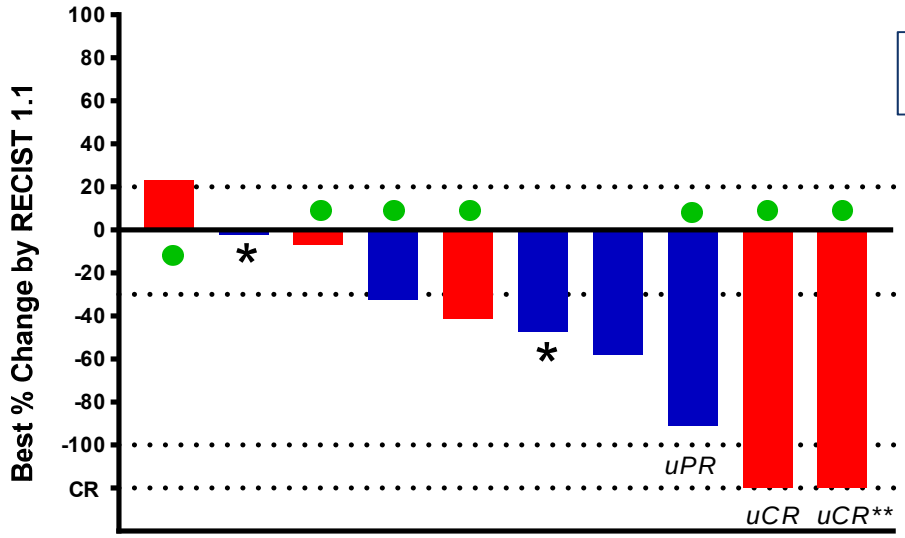
ORR PD-L1 (-) 9/17 (53%)
ORR PD-L1 (+) 2/7 (29%)
ORR PD-L1 Unknown 1/2 (50%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria; -100% is PR for complete clearance of target lesions. CR is a complete response, "u": Unconfirmed. *Best overall response is PD (SD for target lesions, PD for non-target lesions). §Off study treatment with confirmed PR due to patient decision.

Stage IV IO-Naïve 1L Urothelial Cohort (Cisplatin-Ineligible) Achieved Pre-Specified Efficacy Criteria

Stage 1: Best Overall Response ORR=6/10 (60%); DCR=7/10 (70%)



Median Time on Study 3.9 Months (N=10)
As of May 29, 2018

PD-L1 Negative (<1%)
PD-L1 Positive (≥1%)
Treatment Ongoing

ORR PD-L1(-) 3/5 (60%)
ORR PD-L1(+) 3/5 (60%)

Data cut: May 29, 2018

Horizontal dotted lines indicate the thresholds for PD, PR and CR response according to RECIST (version 1.1) criteria.
"u": Unconfirmed. -100% is PR for complete clearance of target lesions. CR is a complete response. *Best overall response is PD due to new lesion or non-target lesion progression. **uCR (confirmed PR by prior scan).

Treatment-Related Adverse Events (AEs) at RP2D

Preferred Term[1]	NKTR-214 0.006 q3w + Nivo 360 (N=283)
Treatment-Related Grade 3 or higher (≥1% listed below)	**40 (14.1%)**
Hypotension	5 (1.8%)
Syncope	5 (1.8%)
Increased Lipase	4 (1.4%)
Rash*	4 (1.4%)
Dehydration	3 (1.1%)
Treatment-Related Grade 1-2 in >15%	
Flu Like Symptoms**	166 (58.7%)
Rash*	126 (44.5%)
Fatigue	119 (42.0%)
Pruritus	89 (31.4%)
Nausea	62 (21.9%)
Decreased Appetite	54 (19.1%)
Diarrhea	43 (15.2%)
Patients who discontinued due to a TRAE	6 (2.1%)

Data cut: May 7, 2018 includes any AE deemed treatment-related by investigator and includes all available adjudicated safety data.
(1) Patients are only counted once under each preferred term using highest grade
*Rash includes the following MedDRA preferred terms: Rash, Rash Erythematous, Rash Maculo-papular, Rash Pruritic, Erythema, Rash Generalized, Rash Papular, Rash Pustular, Rash Macular
** Flu-like symptoms includes the following MedDRA preferred terms: Chills, Influenza, Influenza-like Illness, Pyrexia.

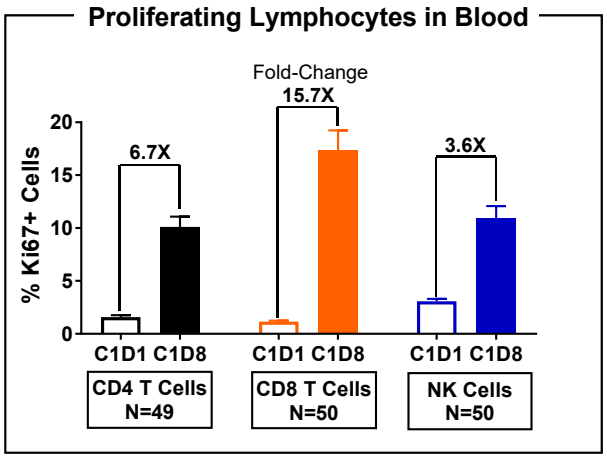
Immune-Mediated Grade ≥3 AEs at RP2D

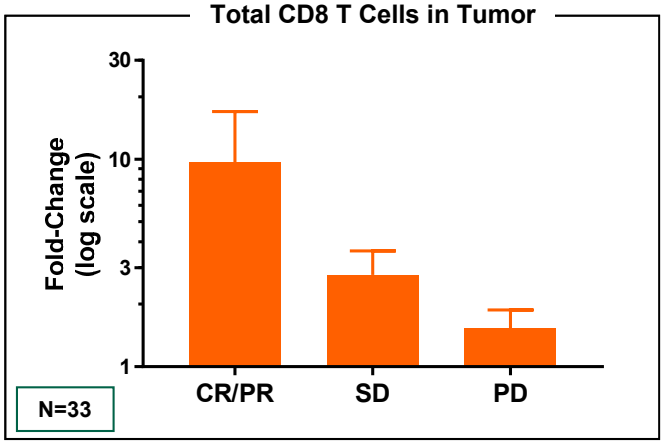
Immune-Mediated Adverse Events	NKTR-214 0.006 q3w + Nivo 360 (N=283)
Any imAE (Grade ≥3)	**10 (3.5%)**
Grade ≥3 imAE Treated with Steroid / Immuno-modulating Medication	**7 (2.5%)**
Pneumonitis*/dyspnea	2 (0.7%)
Skin adverse event	2 (0.7%)
Hepatitis	1 (0.4%)
Colitis	1 (0.4%)
Elevated Lipase	1 (0.4%)
Grade ≥3 Endocrinopathy	**3 (1.1%)**
Diabetes Mellitus Treated with Insulin	1 (0.4%)
Hyperglycemia Treated with Insulin	2 (0.7%)

- One treatment-related G5 pneumonitis related to nivolumab in patient with NSCLC pre-treated with carboplatin/pemetrexed and history of brain metastases

Data cut: May 7, 2018

NKTR-214 + Nivolumab Increased Lymphocyte Proliferation in Blood and CD8 T Cells in Tumor





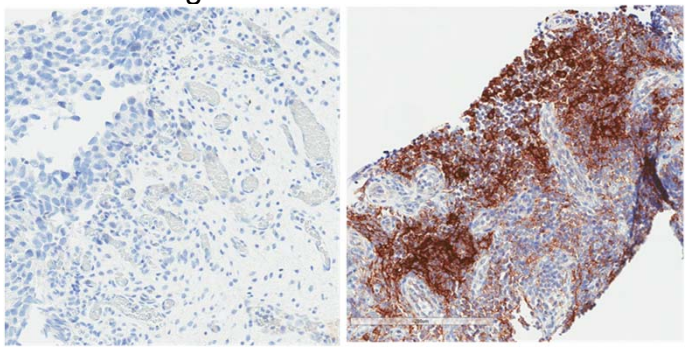
"Proliferating Lymphocytes in Blood" were measured using flow cytometry of fresh whole blood for all patients that the met inclusion criteria and had matched Cycle 1 Day 1 (C1D1) and Cycle 1 Day 8 (C1D8) blood collections. Data presented as mean ± standard error. Fold-change calculated for C1D8/C1D1. Ki67 is a marker of proliferation. "Total CD8 T Cells in Tumor" measured using immunohistochemistry using biopsy specimens collected at baseline and week 3. Cells/mm^2 were counted and fold-change calculated for week3/baseline, data presented as mean ± standard error.

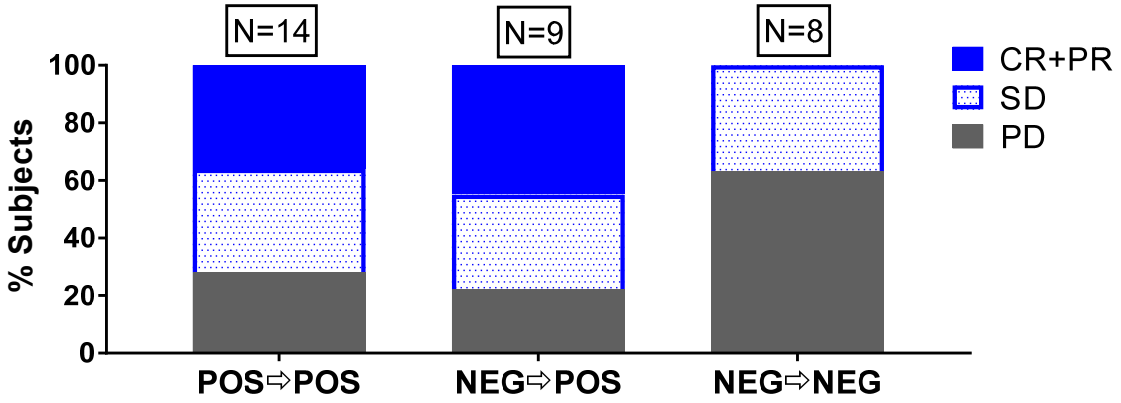
Conversion of PD-L1(-) to PD-L1(+) in Tumor Biopsies from Baseline to Week 3 is Associated with Clinical Benefit

Patient with Urothelial Carcinoma

Baseline:
PD-L1 Negative

Week 3:
PD-L1 Positive





- NKTR-214 + nivolumab can convert PD-L1(-) tumors to PD-L1(+)
  - PD-L1 negative to positive conversion in 9/17 (53%) of patients
- Patients that were PD-L1(+) at baseline, or converted to PD-L1(+) after start of treatment showed greatest clinical benefit

31 patients were available with matched baseline and week 3 results for PD-L1 status. Of these, 17 were PD-L1 negative at baseline. PD-L1 was assessed on tumor cells using a validated 28-8 method. Example image shown for UC patient at baseline and week 3, 20x magnification.

PIVOT-02 Preliminary Data Conclusions

- NKTR-214 in combination with nivolumab showed encouraging anti-tumor activity with notable ORR in PD-L1 negative patients (42% melanoma, 53% RCC, 60% urothelial).
- Pre-specified efficacy criteria were achieved in 1L melanoma, 1L renal cell carcinoma and 1L cisplatin-ineligible urothelial carcinoma which support the evaluation of NKTR-214 plus nivolumab in registrational trials.
- NKTR-214 in combination with nivolumab at the RP2D was well tolerated with a low rate of Gr3+ TRAEs including immune mediated AEs.
- Robust translational data confirm rationale for activation of the immune system in the tumor microenvironment with a conversion of PD-L1 negative tumors to PD-L1 positive on treatment.
- Ongoing enrollment in PIVOT-02 continuing for additional tumor types in I-O naïve and refractory settings.

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