Today's Outside Speakers and Panelists

Dr. Adi Diab

Assistant Professor of Melanoma Medical Oncology MD Anderson

Dr. Michael Hurwitz

Assistant Professor of Medicine, Medical Oncology Yale Cancer Center

Dr. Nizar M. Tannir

Professor of Genitourinary Medical Oncology & Deputy Department Chair of the Department of Genitourinary Medical Oncology MD Anderson

Dr. Antoni Ribas

Professor of Medicine, Professor of Surgery, and Professor of Molecular and Medical Pharmacology at the University of California Los Angeles (UCLA)

Dr. Patrick Hwu

Division Head, Division of Cancer Medicine, Medical Oncology MD Anderson

Dr. Mary Tagliaferri

Senior Vice President, Clinical Development Nektar Therapeutics

Dr. Jonathan Zalevsky

Senior Vice President, Biology & Preclinical Development Nektar Therapeutics

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Today's Agenda

- **Primary resistance to PD-1 blockade resultant from lack of pre-existing antitumor immunity**
  - *Dr. Antoni Ribas, UCLA*
- **NKTR-214 Development Program: PIVOT and Beyond**
  - *Dr. Mary Tagliaferri, Nektar*
- **Translational Biomarkers and Targeting the Innate and Adaptive Immune System with NKTR-262 and NKTR-214**
  - *Dr. Jonathan Zalevsky, Nektar*
- **NKTR-214 Future Pathways & Investigator Panel Discussion**
  - *Led by Dr. Mary Tagliaferri, Nektar*

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Primary resistance to PD-1 blockade resultant from lack of pre-existing antitumor immunity

Antoni Ribas, M.D., Ph.D.
Professor of Medicine, Surgery, Molecular and Medical Pharmacology
Director, Tumor Immunology Program, Jonsson Comprehensive Cancer Center (JCCC)
Director, Parker Institute for Cancer Immunotherapy (PICI) Center at UCLA
University of California Los Angeles (UCLA)
Chair, Melanoma Committee at SWOG

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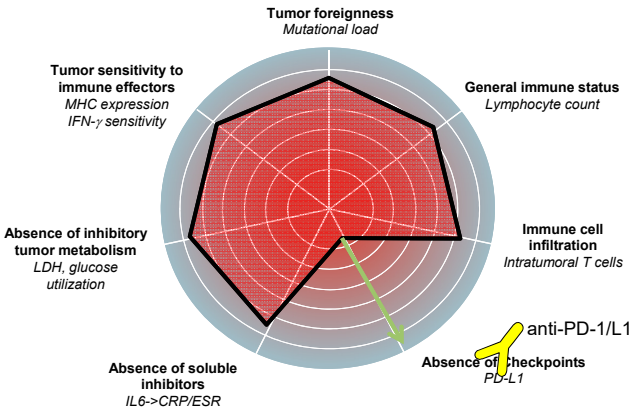
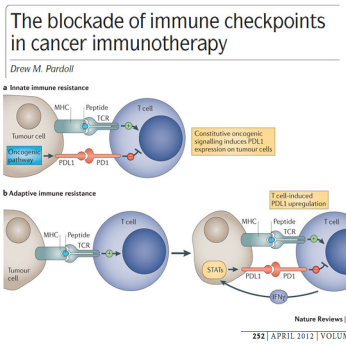
The Cancer Immunogram

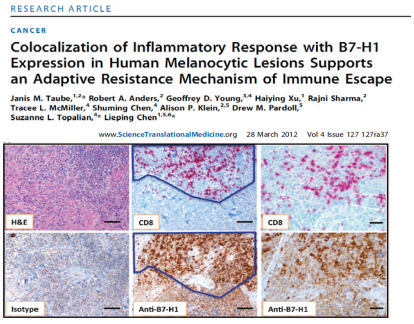


Blank, Haanen, Ribas, Schumacher. Science 2016

5

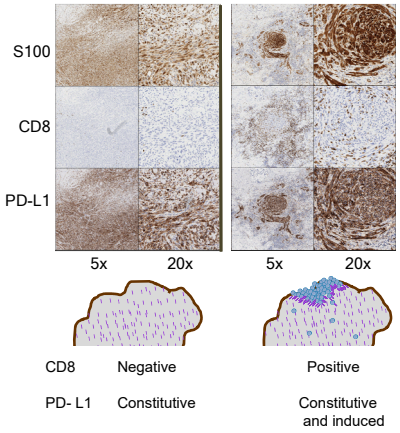
PD-1/L1-mediated adaptive immune resistance





6

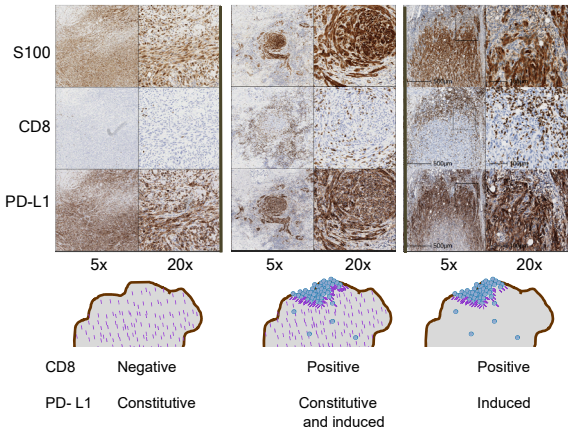
Mechanisms of PD-L1 Expression



Ribas and Hu-Lieskovan, JEM 2016

7

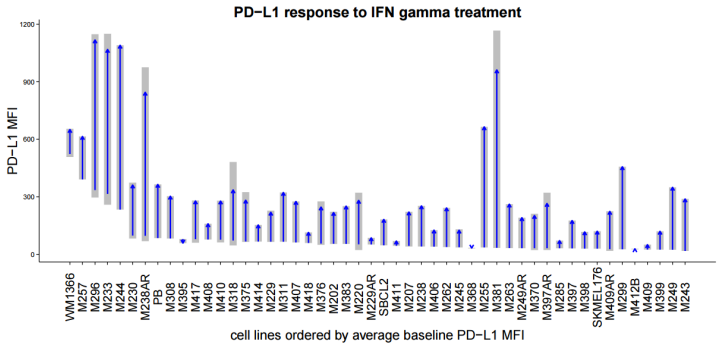
Mechanisms of PD-L1 Expression



Ribas and Hu-Lieskovan, JEM 2016

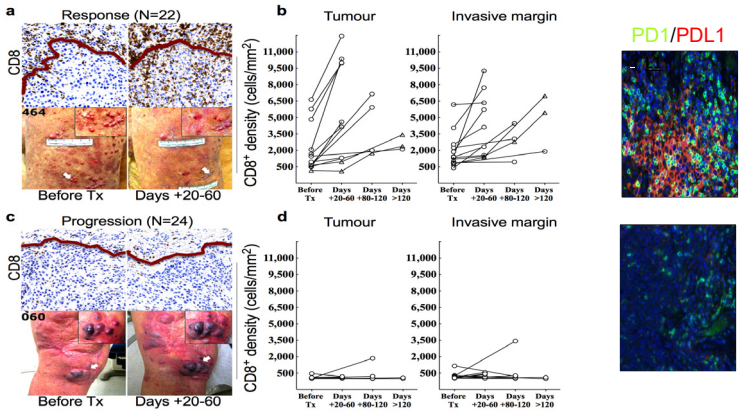
8

2 out of 48 melanoma cell lines had *JAK1/2* LOF mutations and did not respond to IFN-gamma by expressing PD-L1



Shin et al. Cancer Discovery 2017, 7, 188-201

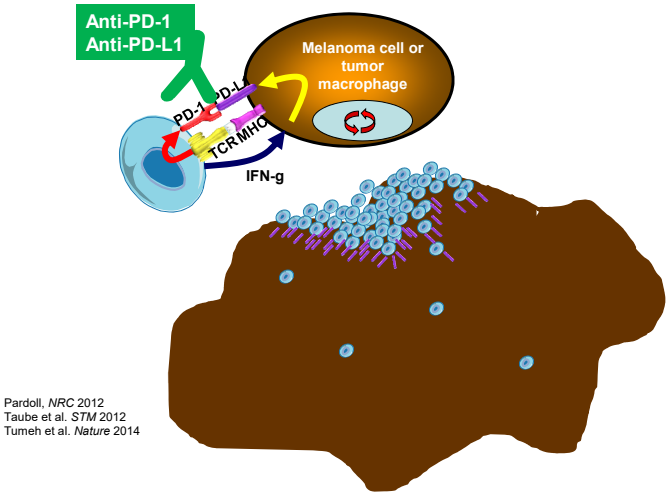
Melanoma response to PD-1 blockade is mediated by pre-existing infiltrates of CD8s inhibited by reactively expressed PD-L1



IHC Analysis of CD8+ T-cells in samples obtained before and during anti-PD1 treatment

Tumeh *et al*. Nature 2014

Inhibiting PD-1-mediated adaptive immune resistance



Pardoll, *NRC* 2012
Taube et al. *STM* 2012
Tumeh et al. *Nature* 2014

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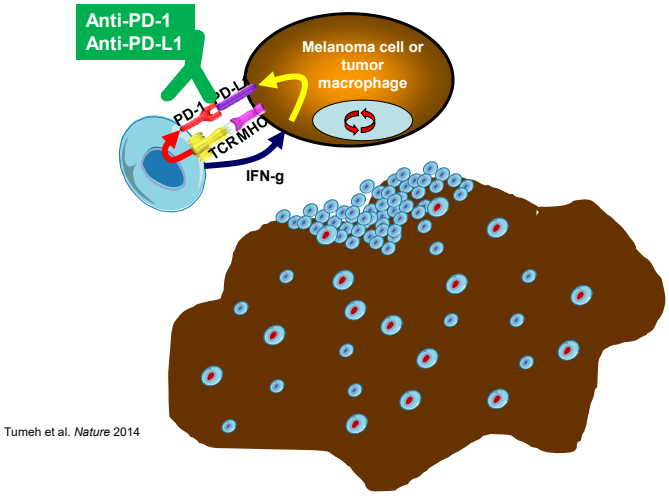
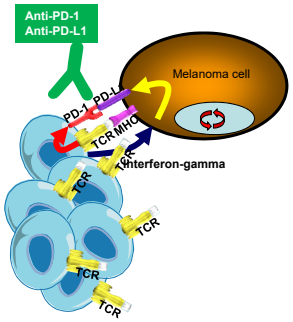
Inhibiting PD-1-mediated adaptive immune resistance

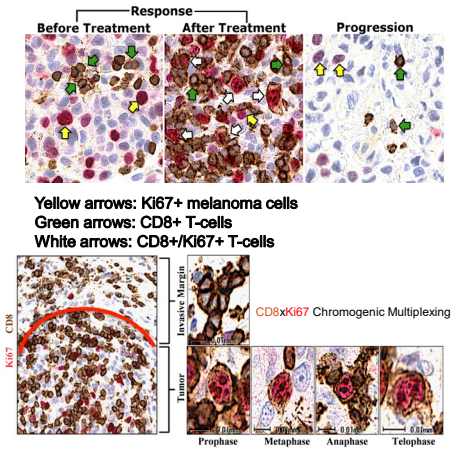


Tumeh et al. *Nature* 2014

12

Intratumoral T cell replication upon PD-1 blockade





Tumeh *et al*. Nature 2014

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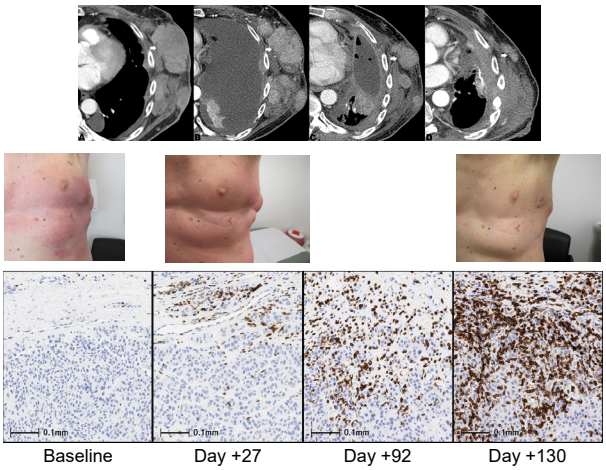
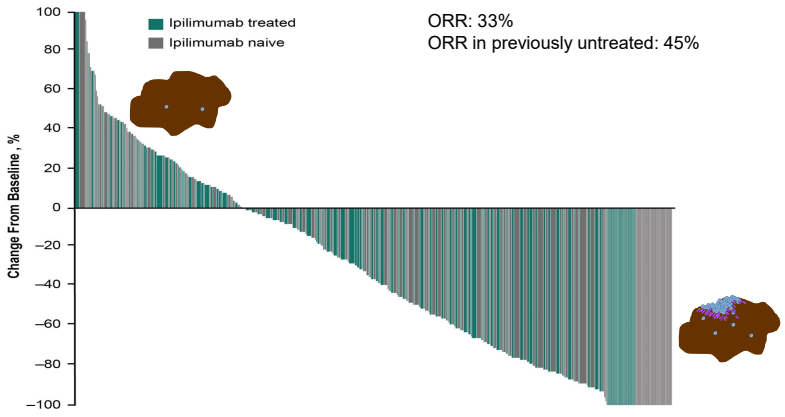
Delayed response to PD-1 blockade after transient progression



14

What differentiates anti-PD-1-responsive from non-responding melanomas?



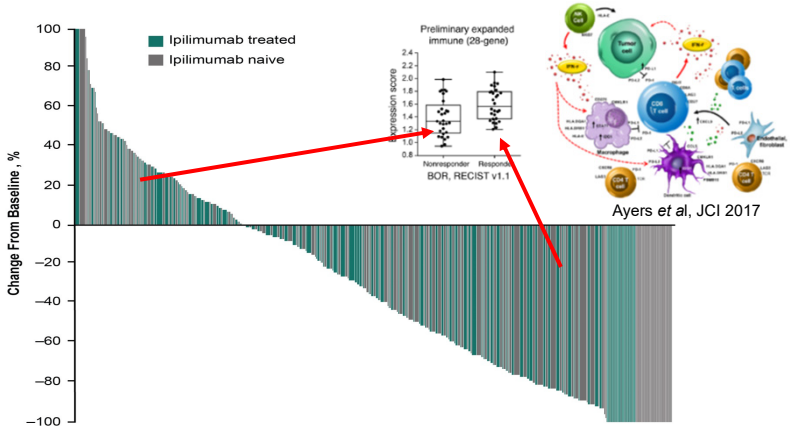
ORR: 33%
ORR in previously untreated: 45%

Pembrolizumab Keynote 001 trial. Central radiology review by RECIST v1.1

Ribas *et al.* JAMA 2016

15

What differentiates anti-PD-1-responsive from non-responding melanomas?



Ayers *et al*, JCI 2017

Pembrolizumab Keynote 001 trial. Central radiology review by RECIST v1.1

Ribas *et al.* JAMA 2016

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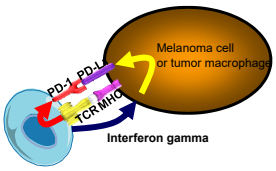
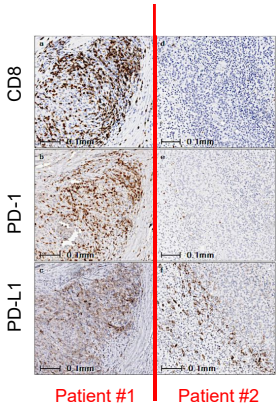
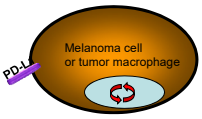
PD-1 blockade induces responses by inhibiting adaptive immune resistance



Hypothesis formulated based on quantitative IHC analyses of 46 cases from UCLA





Adapted from Tumeh *et al*. Nature 2014

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Conclusions

- Inhibiting adaptive immune resistance is the mechanistic basis of the antitumor activity of PD-1 blockade therapies
- Patients without a pre-existing tumor antigen-specific T cell infiltrate inducing reactive PD-L1 expression are unlikely to respond to PD-1 blockade therapy
- Inducing intratumoral infiltration by antigen-specific T cells is likely to potentiate the antitumor activity of PD-1 blockade therapy

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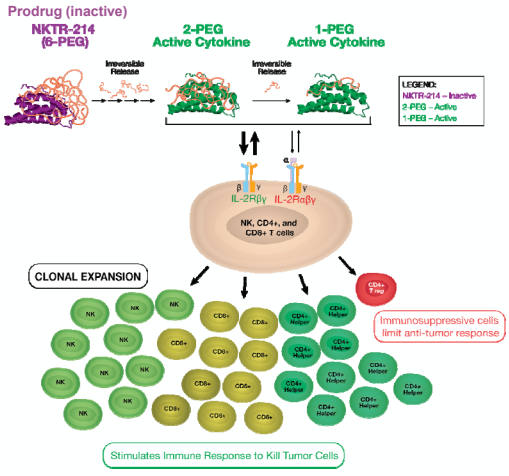
NKTR-214 Development Program PIVOT and Beyond

Dr. Mary Tagliaferri
Senior Vice President, Clinical Development Nektar Therapeutics

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 to preferentially activate and expand 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

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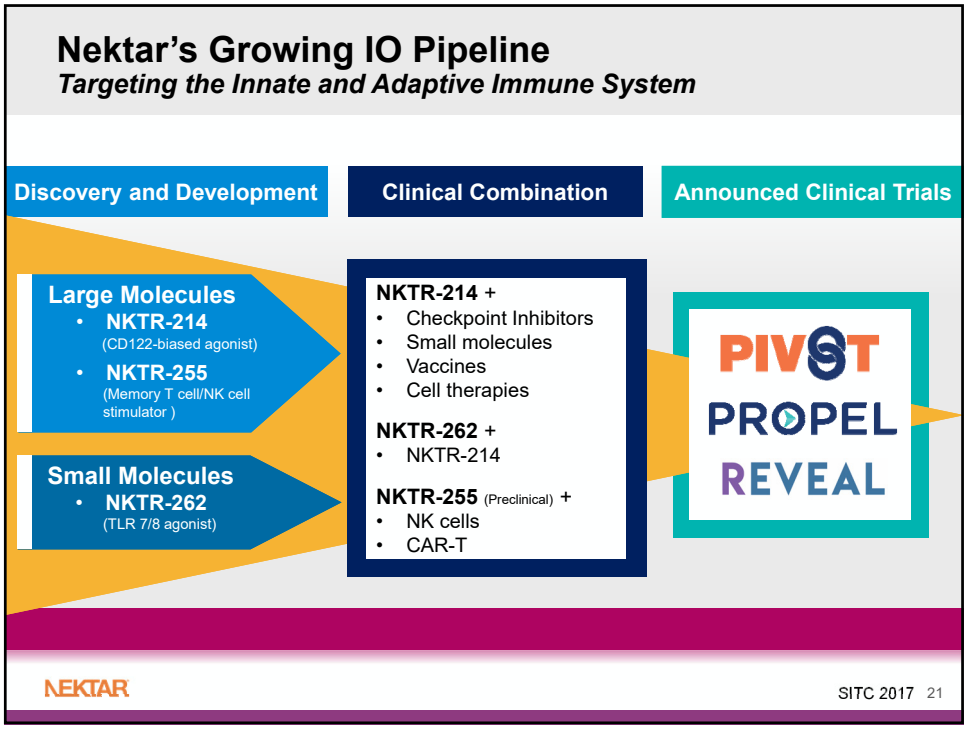
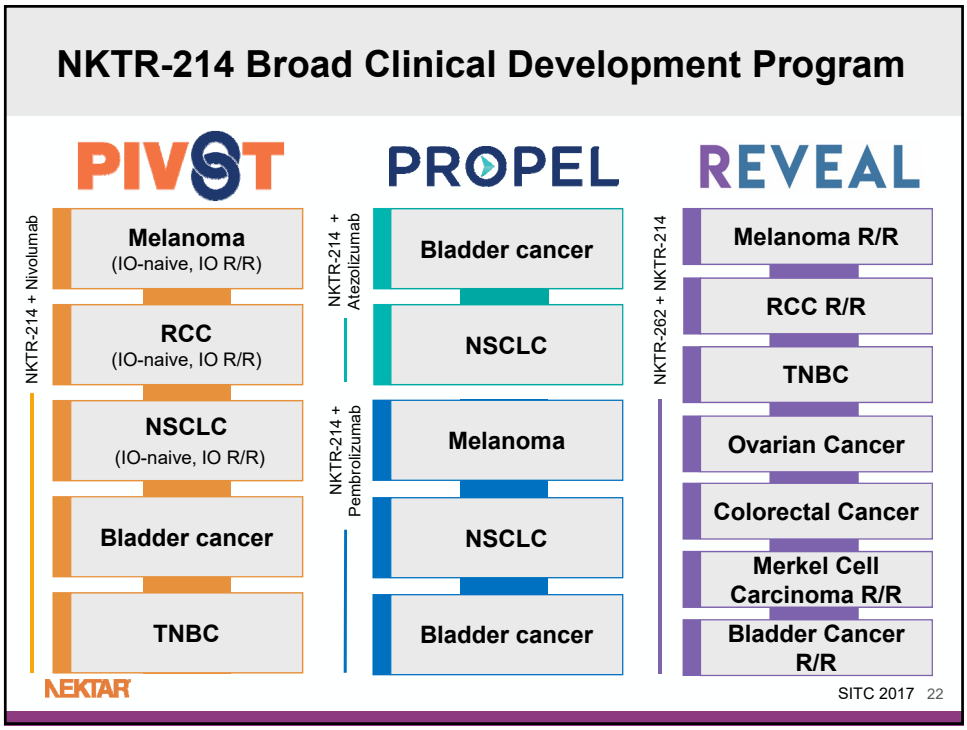

Nektar's Growing IO Pipeline
Targeting the Innate and Adaptive Immune System
Discovery and Development
Clinical Combination
Announced Clinical Trials
Large Molecules
• NKTR-214 (CD122-biased agonist)
• NKTR-255 (Memory T cell/NK cell stimulator)
Small Molecules
• NKTR-262 (TLR 7/8 agonist)
NKTR-214 +
• Checkpoint Inhibitors
• Small molecules
• Vaccines
• Cell therapies
NKTR-262 +
• NKTR-214
NKTR-255 (Preclinical) +
• NK cells
• CAR-T
PIVOT
PROPEL
REVEAL
NEKTAR
SITC 2017 21


NKTR-214 Broad Clinical Development Program
PIVOT
PROPEL
REVEAL
NKTR-214 + Nivolumab
Melanoma (IO-naive, IO R/R)
RCC (IO-naive, IO R/R)
NSCLC (IO-naive, IO R/R)
Bladder cancer
TNBC
NKTR-214 + Atezolizumab
Bladder cancer
NSCLC
NKTR-214 + Pembrolizumab
Melanoma
NSCLC
Bladder cancer
NKTR-262 + NKTR-214
Melanoma R/R
RCC R/R
TNBC
Ovarian Cancer
Colorectal Cancer
Merkel Cell Carcinoma R/R
Bladder Cancer R/R
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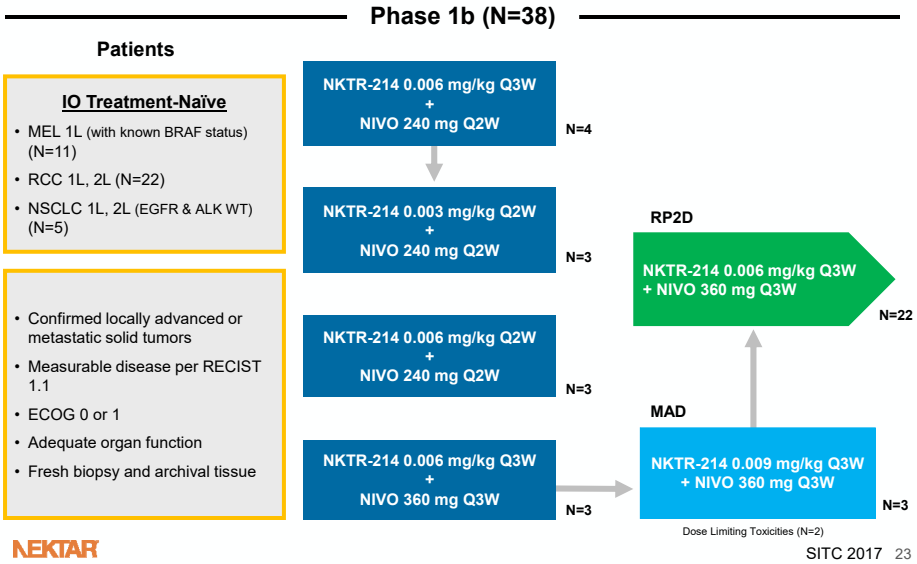
PIVOT-02 Dose Escalation



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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 PD-L1 status by tumor type
  - Longitudinal sampling of blood and tumor biopsies to be presented at a future conference

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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%)

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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

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

*Based on maximum value prior to dosing.
** Measured using either **28-8 or 22C3** assays on fresh or archival tumor with specific cutoffs.

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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

RCC	(N=22)	%
1L IMDC Score	n=14	
Favorable	1	7.1
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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

*Based on maximum value prior to dosing.
** Measured using either **28-8 or 22C3** assays on fresh or archival tumor with specific cutoffs.

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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

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

*Based on maximum value prior to dosing.
** Measured using either **28-8 or 22C3** assays on fresh or archival tumor with specific cutoffs.

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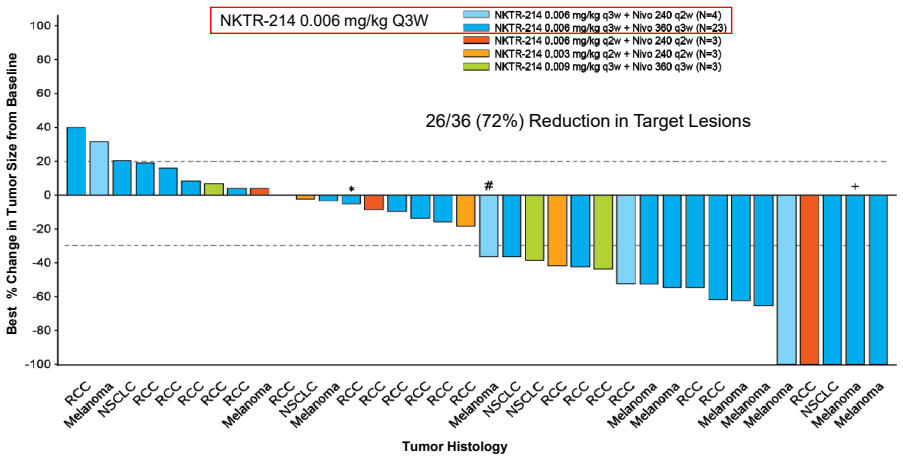
PIVOT-02: Best Percent Change in Target Lesions by Tumor Type and Dose (n=36)



* 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.

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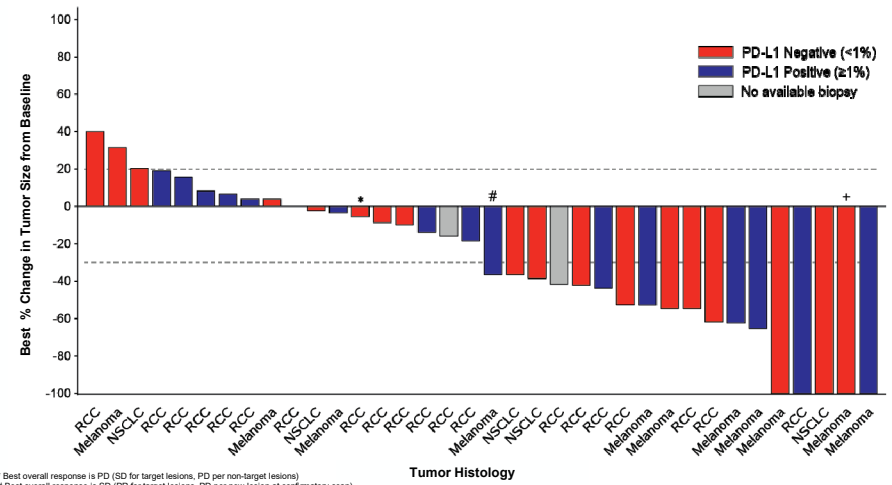
Best Percent Change of Target Lesions by Tumor Type and PD-L1 Status (n=36)



* 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.

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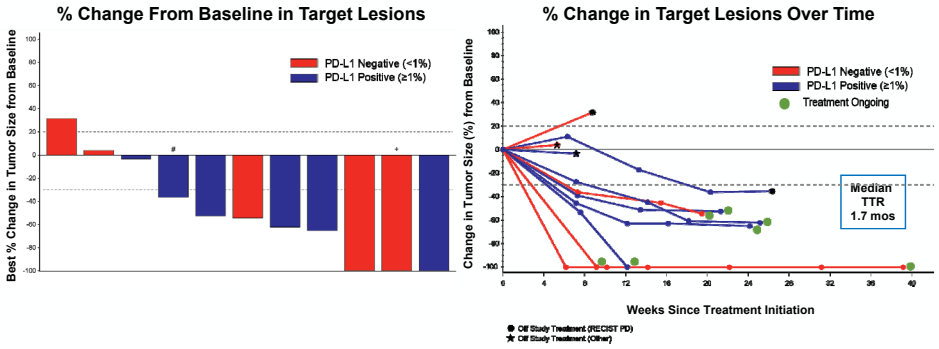
Stage IV Treatment-Naïve Melanoma Patients (N=11)

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%)



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.

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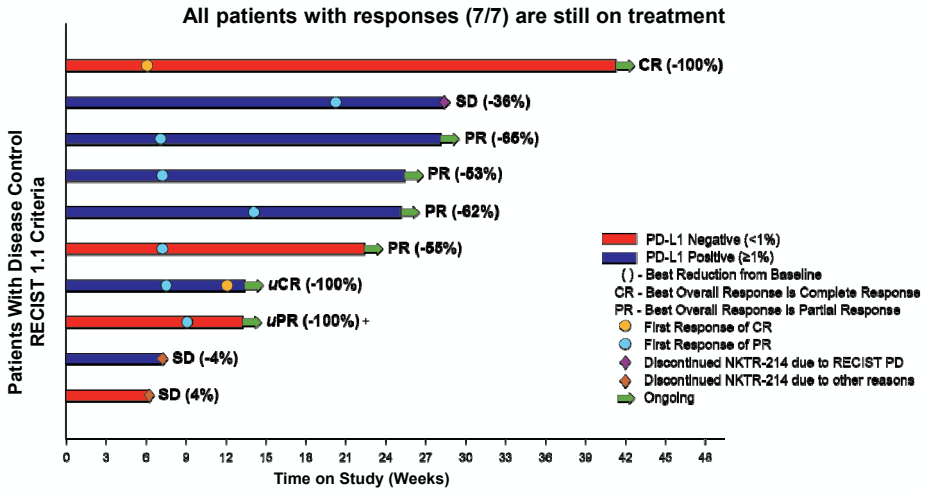
Time to and Duration of Response

Stage IV Treatment-Naïve Melanoma



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

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Treatment Naïve Melanoma ORR by PD-L1 Expression, N=11

PD-L1 Expression

Therapy	NKTR-214 + NIVO	
PD-L1 Expression	**Positive n=6 (55%)**	**Negative n=5 (45%)**
ORR, n (%)	**4 (67%)**	**3 (60%)**
BOR, n (%)		
CR	1 (20%)	1 (17%)
PR	3 (60%)	2 (33%)
SD	2 (33%)	1 (20%)
DCR, n (%)	6 (100%)	4 (80%)

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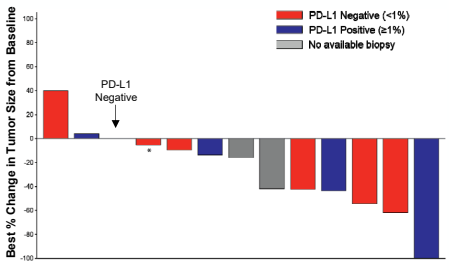
Stage IV Treatment-Naïve 1L Renal Cell Carcinoma (N=13)

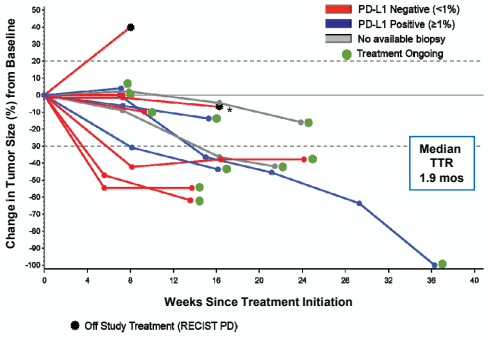
Efficacy-evaluable patients with ≥ 1 or ≥ 2 post baseline scans

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).

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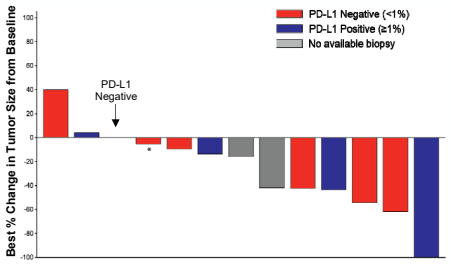
Stage IV Treatment-Naïve 1L Renal Cell Carcinoma (N=13)

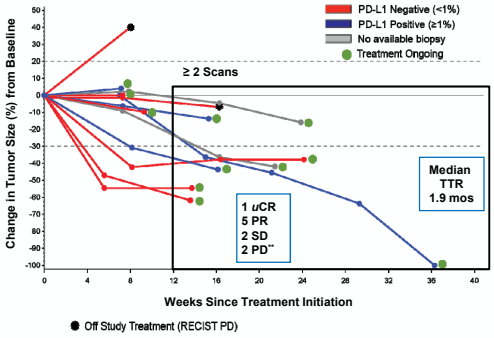
Efficacy-evaluable patients with ≥ 1 or ≥ 2 post baseline scans

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

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1L Renal Cell Carcinoma ORR by PD-L1 Expression

PD-L1 Expression

Therapy	NKTR-214 + NIVO					
Number of Scans	≥1 Scan (N=13)			≥2 Scans (N=10)		
PD-L1 Expression	Positive n=4 (31%)	Negative n=7 (54%)	Unknown n=2 (15%)	Positive n=3 (30%)	Negative n=5 (50%)	Unknown n=2 (20%)
ORR, n (%)	2 (50%)	3 (43%)	1 (50%)	2 (67%)	3 (60%)	1 (50%)
BOR, n (%)						
CR	1 (25%)	0	0	1 (33%)	0	0
PR	1 (25%)	3 (43%)	1 (50%)	1 (33%)	3 (60%)	1 (50%)
SD	2 (50%)	2 (29%)	1 (50%)	1 (33%)	0	1 (50%)
DCR, n (%)	4 (100%)	5 (71%)	2 (100%)	3 (100%)	3 (60%)	2 (100%)

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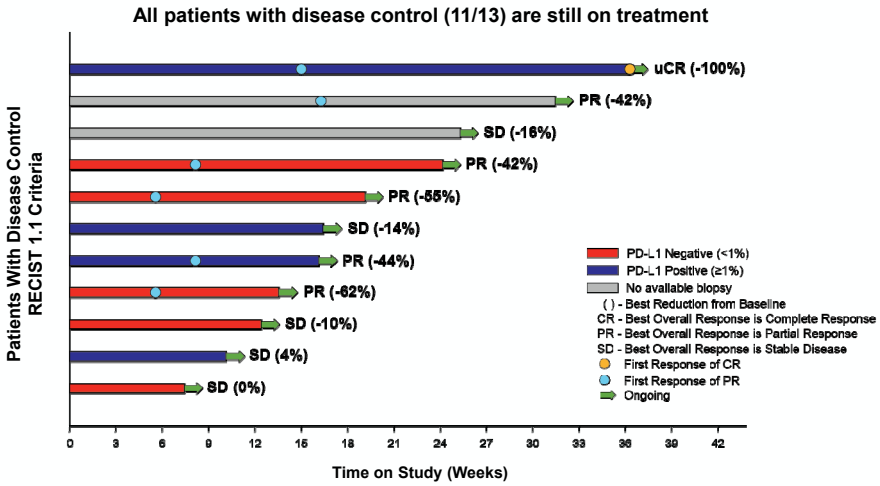
Time to and Duration of Response

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



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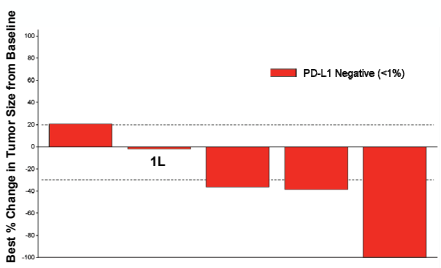
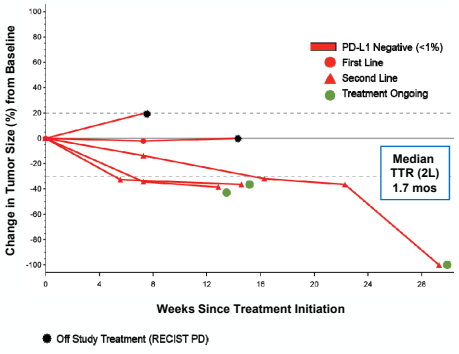
Stage IV IO-Naïve PD-L1 Negative NSCLC (1L and 2L)

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.

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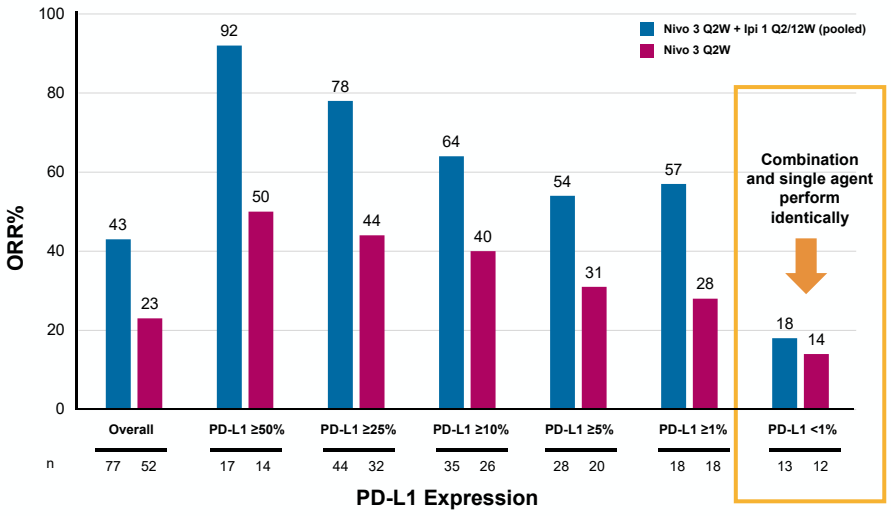
NSCLC: Minimal Clinical Benefit in Patients with PD-L1 <1%



NEKTAR Source: Checkmate-012; Presented By Matthew Hellmann at 2016 ASCO Annual Meeting

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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.

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Treatment-Related AEs

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

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 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

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Key Takeaways

Efficacy

- Compelling ORR and DCR in both PD-L1 negative and PD-L1 positive patients
- Majority of responses occurred within the first 2 months of treatment
- Complete responses were observed in every tumor type
- All patients with responses continue on treatment

Safety and Tolerability

- Convenient, outpatient dosing schedule once every 3 weeks
- No grade 3 or higher immune-related adverse events at recommended phase 2 dose and below
- No treatment study discontinuations from TRAEs
- No treatment related deaths
- Most common side effects were flu like symptoms that were predictable, short lived and easily managed

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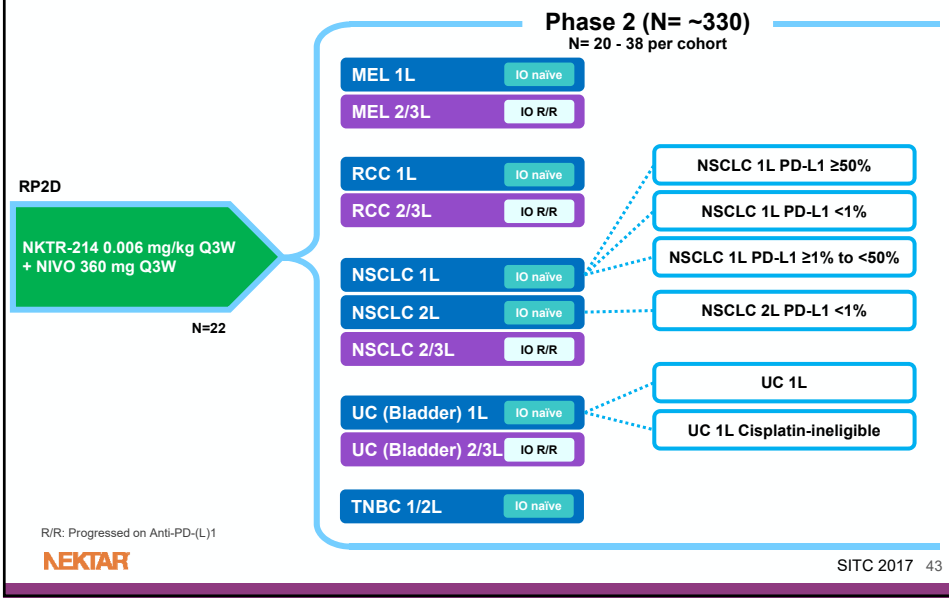
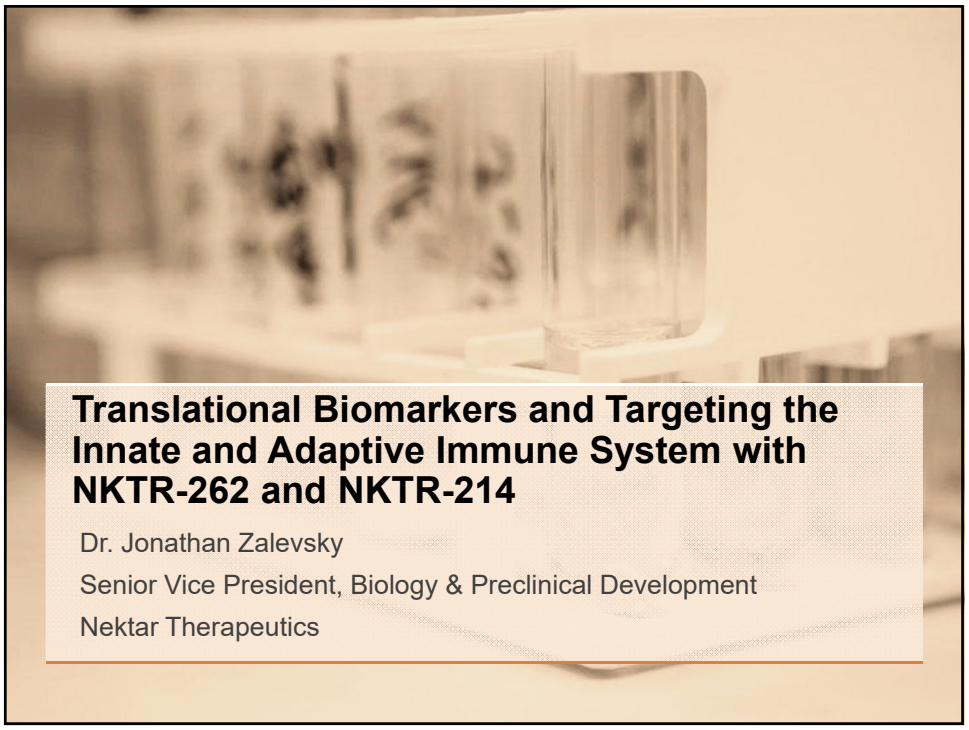
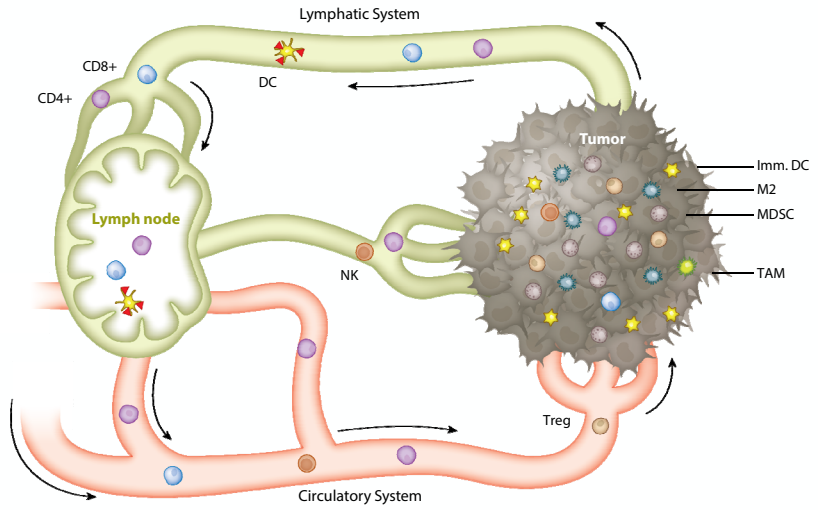
PIVOT-02 Dose Expansion Underway in 13 Cohorts





Before NKTR-214/Checkpoint Therapy



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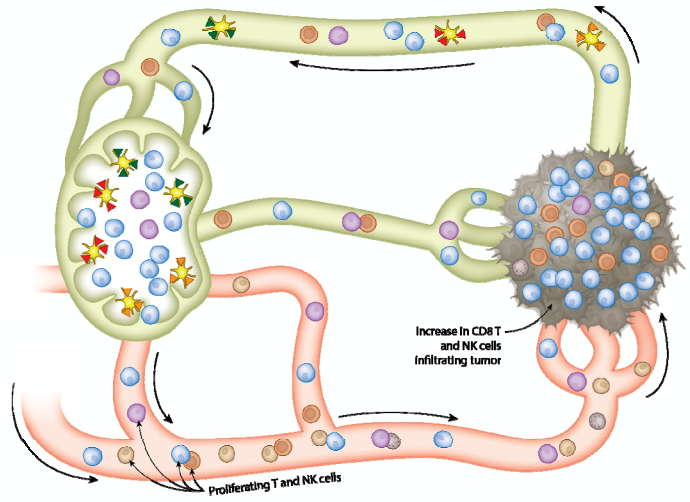
After NKTR-214/Checkpoint Therapy



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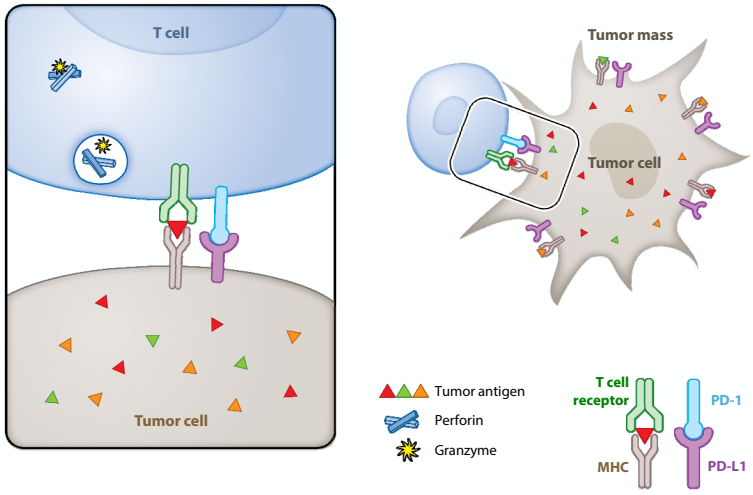
Detail of CD8+ Interaction with Tumor Cell (Before)



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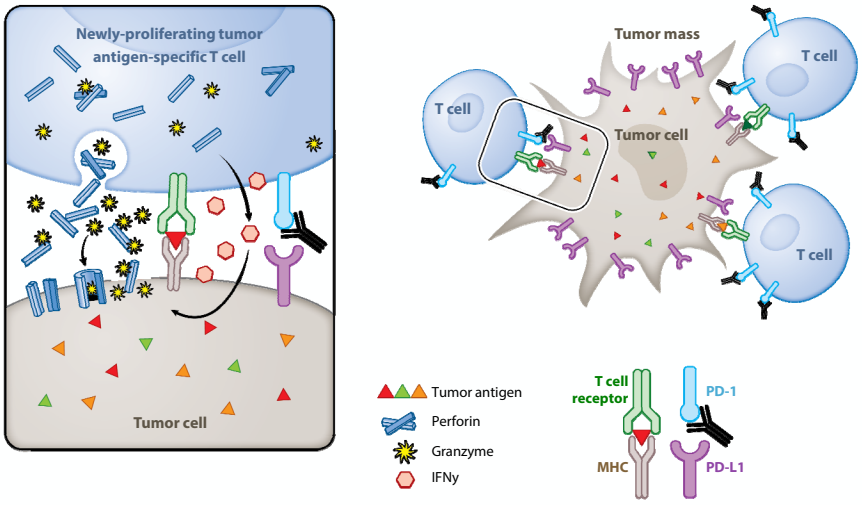
Detail of CD8+ Interaction with Tumor Cell (After)



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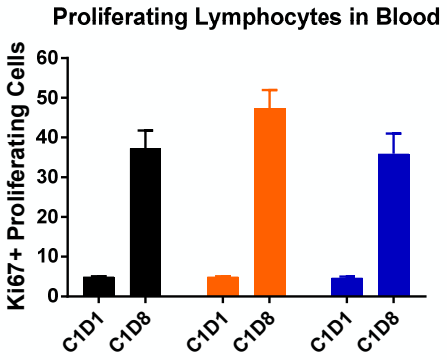
NKTR-214 + Nivolumab Increased Lymphocyte Proliferation in Blood



Method: Blood samples were collected on Predose (C1D1) or 7 Days after the start of therapy (C1D8). Blood was processed to PBMCs and stored frozen until analysis. Lymphocyte subsets were enumerated using flow cytometry gating on CD3+CD4+ (CD4), CD3+CD8+ (CD8), CD3-CD56+ (NK), and scored for Ki67 expression as a function of each respective parent population.
Data: Ki67 gate for each patient was set using a 5% Ki67+ value on the C1D1 sample (N=19, mean ± standard error)

- Proliferation observed in CD4, CD8, and NK Cells
- Average fold-increase:
  - CD4: 7.5X over baseline
  - CD8: 9.5X over baseline
  - NK: 7.6X over baseline

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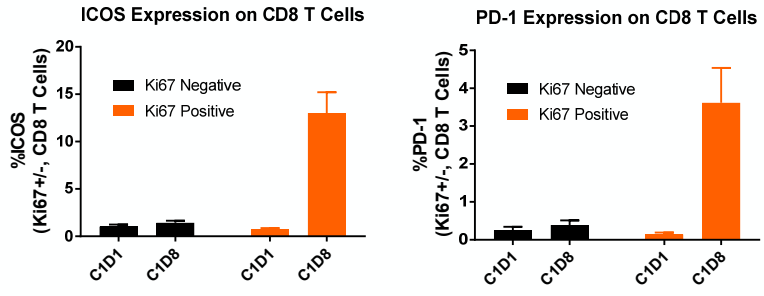
Treatment Induced PD-1 and ICOS Expression Only on Proliferating CD8 T Cells in Blood



Method: Blood samples were collected on Predose (C1D1) or 7 Days after the start of therapy (C1D8). Blood was processed to PBMCs and stored frozen until analysis. CD3-CD8+ T cells were enumerated using flow cytometry and then further stained for Ki67, PD-1, and ICOS (N=15, mean ± standard error).

- Treatment-induced proliferating CD8 T Cells express markers of T cell invigoration (PD-1) and activation (ICOS)
- Average fold-increase in Ki67+ CD8 T Cells:
  - PD-1: 26X over baseline
  - ICOS: 18X over baseline

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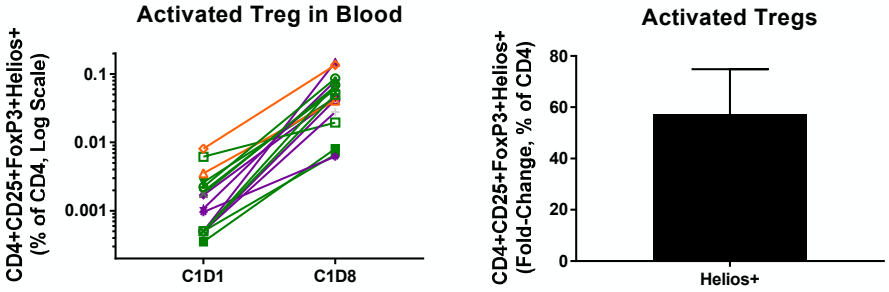
All Patients Treated with NKTR-214 + Nivolumab Had Increase in Activated Tregs in Blood

- >50X increase in activated (Helios+) Tregs in blood of all patients
- No change / decrease in Tregs in tumor



Legend: Orange – NSCLC, Green – Melanoma, Purple - RCC
Method: Blood samples were collected on Predose (C1D1) or 7 Days after the start of therapy (C1D8). Blood was processed to PBMCs and stored frozen until analysis. Activated Tregs were enumerated using flow cytometry gating on CD4+CD8-CD25+FoxP3+Helios+ (N=17).
Fold-Change: C1D8 value divided by C1D1, results shown are mean ± standard error.

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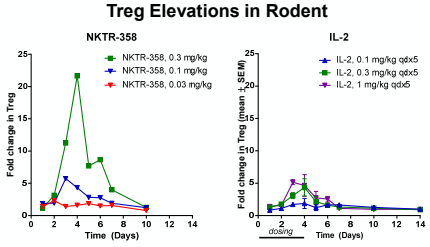
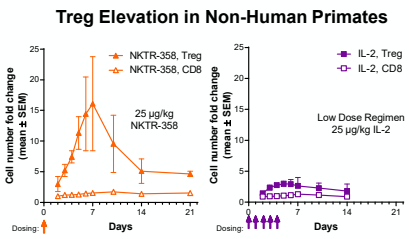
NKTR-358: Selective Treg Induction for the Treatment of Autoimmune and Chronic Inflammatory Diseases





- Low dose IL-2 can induce elevations in human Tregs
- Treg elevation a cutting-edge therapeutic hypothesis for autoimmune diseases
- NKTR-358 is a PEG-conjugated IL-2 designed to selectively elevate Tregs and not Teff for the treatment of autoimmune disease
- NKTR-358 currently in Phase 1A and partnered with Eli Lilly in 2017

NEKTAR Langowski, ACR 2017

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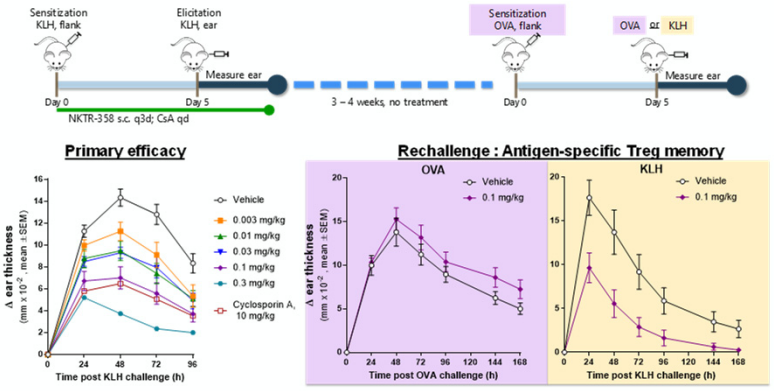
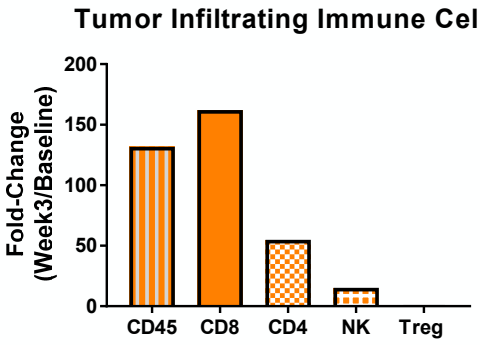
NKTR-358: Elevated Tregs Suppress Inflammation and Promote Antigen-Specific Treg Memory



- Drug induced & antigen-specific Tregs can suppress inflammation in the tissues with Treg memory after cessation of dosing
- Treg hypothesis could explain safety advantage of NKTR-214 + nivolumab combination

NEKTAR Langowski, ACR 2017

Increase in Tumor Infiltrating Immune Cells



Method: Fresh tumor biopsy was disaggregated to single cell suspension and processed using flow cytometry. Total intratumoral immune cells were identified using CD45 staining and expressed as % of live cells for CD45, or as %CD45 for CD3+CD8+ (CD8 T Cells), CD3+CD4+ (CD4 T Cells, and CD3-CD56+ (NK Cells). Only patients with identifiable tumor by IHC at Baseline & Week 3, and on Q3WK NKTR-214 regimen were included.
Fold-Change: Week 3 value divided by Baseline, results shown are mean of N=4 patients.

- Total immune infiltrate and CD8 T Cell increase > 100-fold over Baseline
- No increase / undetectable levels of intratumoral Tregs

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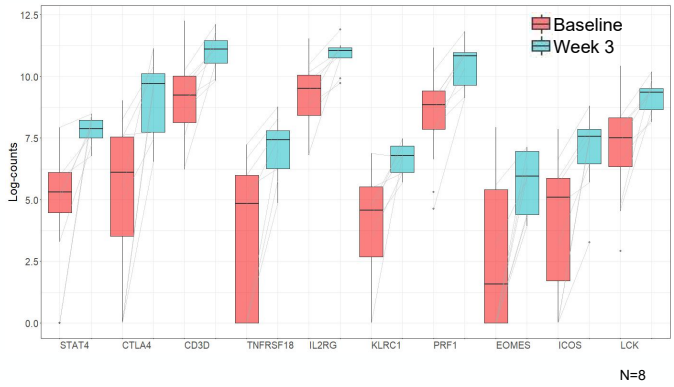
Treatment Induced Increased Expression in Lymphocyte Activation and Function Genes

Top 10 differentially-expressed genes of 770 profiled



N=8

Method: Fresh tumor biopsy from Baseline and Week 3 was processed to nucleic acid and analyzed using Nanostring . Gene expression data at each timepoint is presented on a Log Y-axis (N=8).

- STAT4: Transcription factor required for TH1 differentiation and IFNg production
- CTLA-4: Immune checkpoint
- CD3D: T cell surface glycoprotein delta
- TNFRSF18: GITR
- IL2RG: IL2 receptor gamma
- KLRC1: NKG2A
- PRF1: Perforin
- EOMES: T-box protein in tumor infiltrating CD8 T cells
- ICOS: Costimulatory molecule
- LCK: T cell tyrosine kinase

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Key Takeaways from Biomarker Summary

- Tumor infiltrating lymphocyte levels increase after the start of treatment with NKTR-214 + Nivolumab
- Gene expression changes between baseline and post-treatment tumor biopsies show clear and robust evidence of IL-2 receptor pathway activation by NKTR-214
- Proliferating lymphocytes increase in blood with elevated expression of PD-1 and ICOS on Ki67+ CD8 T cells
- NKTR-214 elevates and activates Tregs only in the periphery and not in the tumor
  - Peripheral Treg can control unwanted immune activitation outside the tumor and may explain the desirable safety profile of the NKTR-214 + Nivolumab combination

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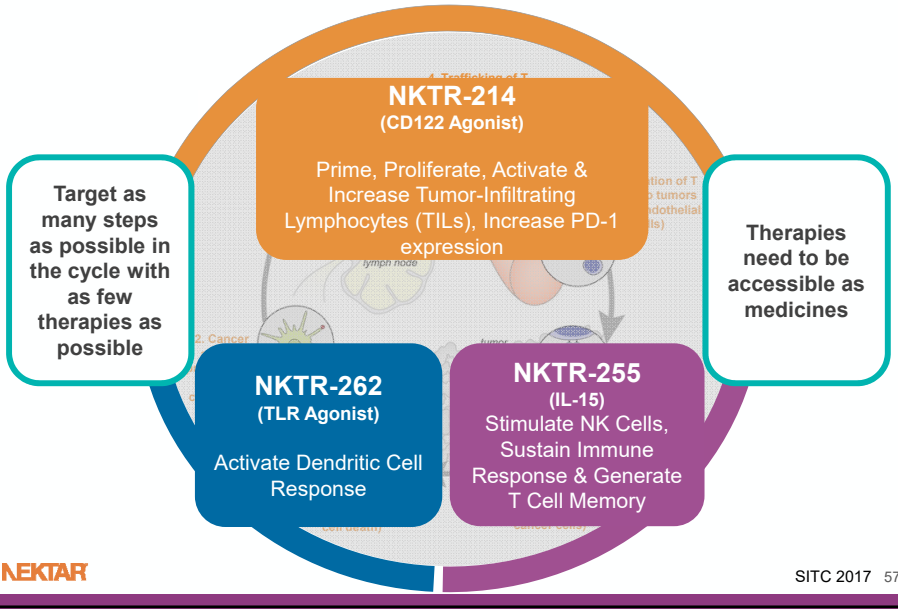
Nektar's Immuno-Oncology Strategy to Create Therapies that Cover the Immunity Cycle



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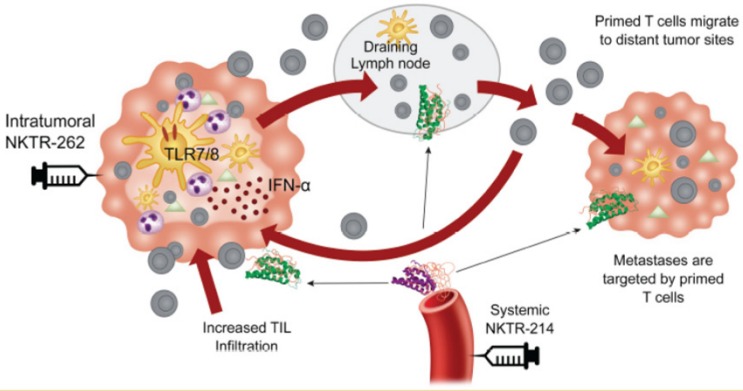
NKTR-262: Adding a Unique Intratumoral TLR Agonist to Nektar's Immuno-Oncology Portfolio



- TLR agonists activate innate immunity, myeloid cells and increase tumor antigen presentation
- NKTR-262 designed with Nektar technology to be highly synergistic with NKTR-214
- NKTR-262 with NKTR-214 represents a novel, wholly-owned combination regimen in IO

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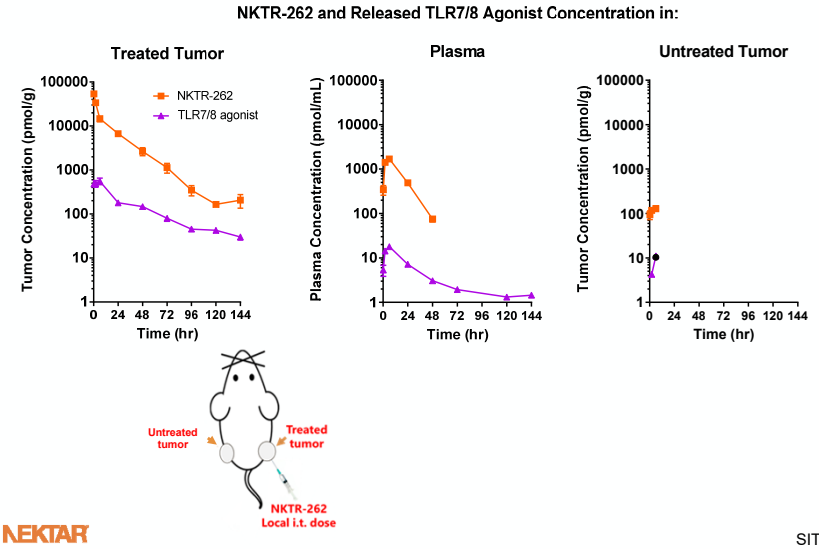
Nektar Technology Extends Exposure in the Injected Tumor With Minimal Systemic Exposure



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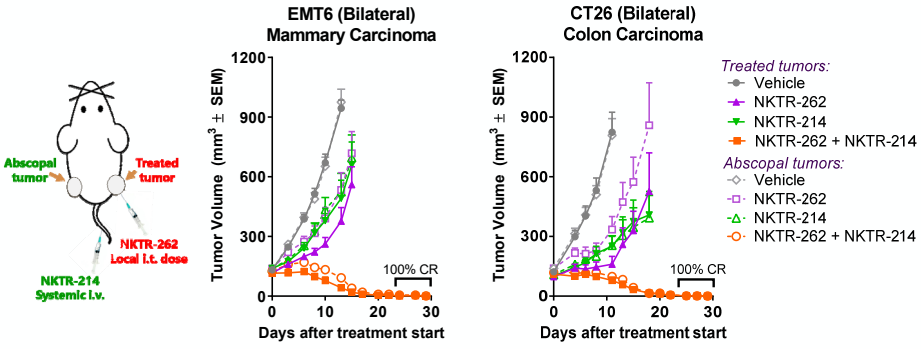
Tumor Regressions and Abscopal Effect from NKTR-262 + NKTR-214



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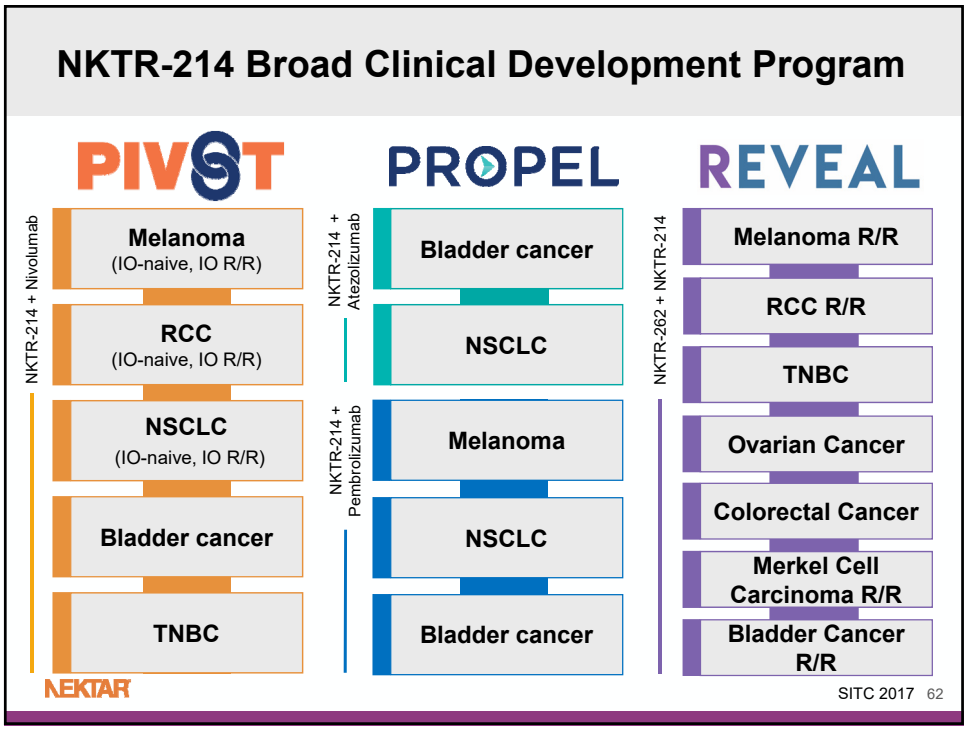
NKTR-214 Future Development Pathways
Dr. Mary Tagliaferri
Senior Vice President, Clinical Development
Nektar Therapeutics


NKTR-214 Broad Clinical Development Program
PIVOT
PROPEL
REVEAL
NKTR-214 + Nivolumab
Melanoma (IO-naive, IO R/R)
RCC (IO-naive, IO R/R)
NSCLC (IO-naive, IO R/R)
Bladder cancer
TNBC
NKTR-214 + Atezolizumab
Bladder cancer
NSCLC
NKTR-214 + Pembrolizumab
Melanoma
NSCLC
Bladder cancer
NKTR-262 + NKTR-214
Melanoma R/R
RCC R/R
TNBC
Ovarian Cancer
Colorectal Cancer
Merkel Cell Carcinoma R/R
Bladder Cancer R/R
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Investigator Initiated Study: Sarcoma
Co-Funded with Bristol-Myers Squibb

Phase 2 Study Proposed by Dr. Sandra D'Angelo (MSKCC) and Tony Conley (MD Anderson)
- Both investigators with proven track record of high enrollment to IO studies in sarcoma
- Initiate study with RP2D of NKTR-214 plus Opdivo
- Can amend proposal to evaluate triplet regimen

Eligibility: At least one prior line of systemic therapy

Basket Study: 2 Bone Sarcomas and 4 Soft Tissue Sarcomas

Endpoints
- Safety and tolerability
- PFS at 24 weeks, median PFS, OS at 12 months and median OS
- RECIST 1.1
- Radiographic scans every 8 weeks
- Measure biomarkers in blood and tumor

- **Osteosarcoma N=10**
- **Chondrosarcoma N=10**
- **Undifferentiated pleomorphic sarcoma/malignant fibrous histiosarcoma N=10**
- **Angiosarcoma N=10**
- **Dedifferentiated/ pleomorphic liposarcoma N=10**
- **Leiomyosarcoma N=10**

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PROPEL Program: NKTR-214 plus TECENTRIQ® or KEYTRUDA®

PROPEL

NKTR-214 + Atezolizumab
Phase 1 Dose Escalation
N= 20-30

- **NSCLC**
  2nd line metastatic disease with progression following platinum or targeted therapy
- **Urothelial Carcinoma**
  2nd line locally advanced or metastatic disease with progression following platinum

NKTR-214 + Pembrolizumab
Phase 1 Dose Escalation
N= 20-30

- **NSCLC**
  1st line metastatic disease (PD-L1 ≥50%)
  2nd line metastatic disease with progression following platinum or targeted therapy (PD-L1 ≥1%)
- **Melanoma**
  1st line advanced or metastatic disease
- **Urothelial Carcinoma**
  1st line cisplatin-ineligible
  2nd line locally advanced or metastatic disease with progression following platinum

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Takeda and Nektar Research Collaboration

- Takeda and Nektar collaborating on combining NKTR-214 with five Takeda oncology compounds
- Collaboration will explore five targeted mechanisms in Takeda's oncology portfolio including:
  - SYK-inhibitor
  - Proteasome inhibitor
- Combinations will be tested in preclinical models of lymphoma, melanoma and colorectal cancer
- Takeda and Nektar will share costs and each will maintain global commercial rights to respective drugs/candidates

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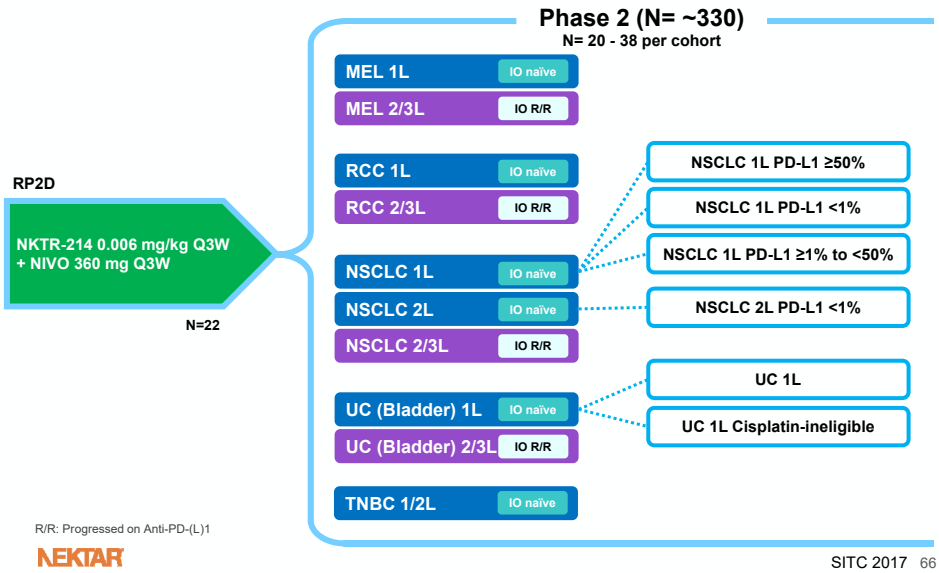
Exploring Potential Phase 3 Pathways



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Investigator Panel Discussion