SITC 2016

Nektar Therapeutics Investor Meeting

November 9, 2016

Today's Agenda

Welcome

- Howard W. Robin, President & CEO, Nektar

NKTR-214 Phase 1 Dose Escalation Study Clinical Data Presentation

- Dr. Adi Diab, MD Anderson Cancer Center, Assistant Professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
- Dr. Jonathan Zalevsky, Vice President of Biology and Preclinical Development, Nektar

NKTR-214 Clinical Development Program

- Dr. Mary Tagliaferri, Vice President of Clinical Development, Nektar

Panel Discussion with Q & A

Today's Speakers

Dr. Adi Diab
MD Anderson

Assistant Professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Dr. Mario Sznol
Yale Cancer Center

Professor of Medicine (Medical Oncology); Co-Director, Yale SPORE in Skin Cancer

President-elect SITC

Dr. Mary Tagliaferri
Nektar Therapeutics

Vice President, Clinical Development

Dr. Jonathan Zalevsky
Nektar Therapeutics

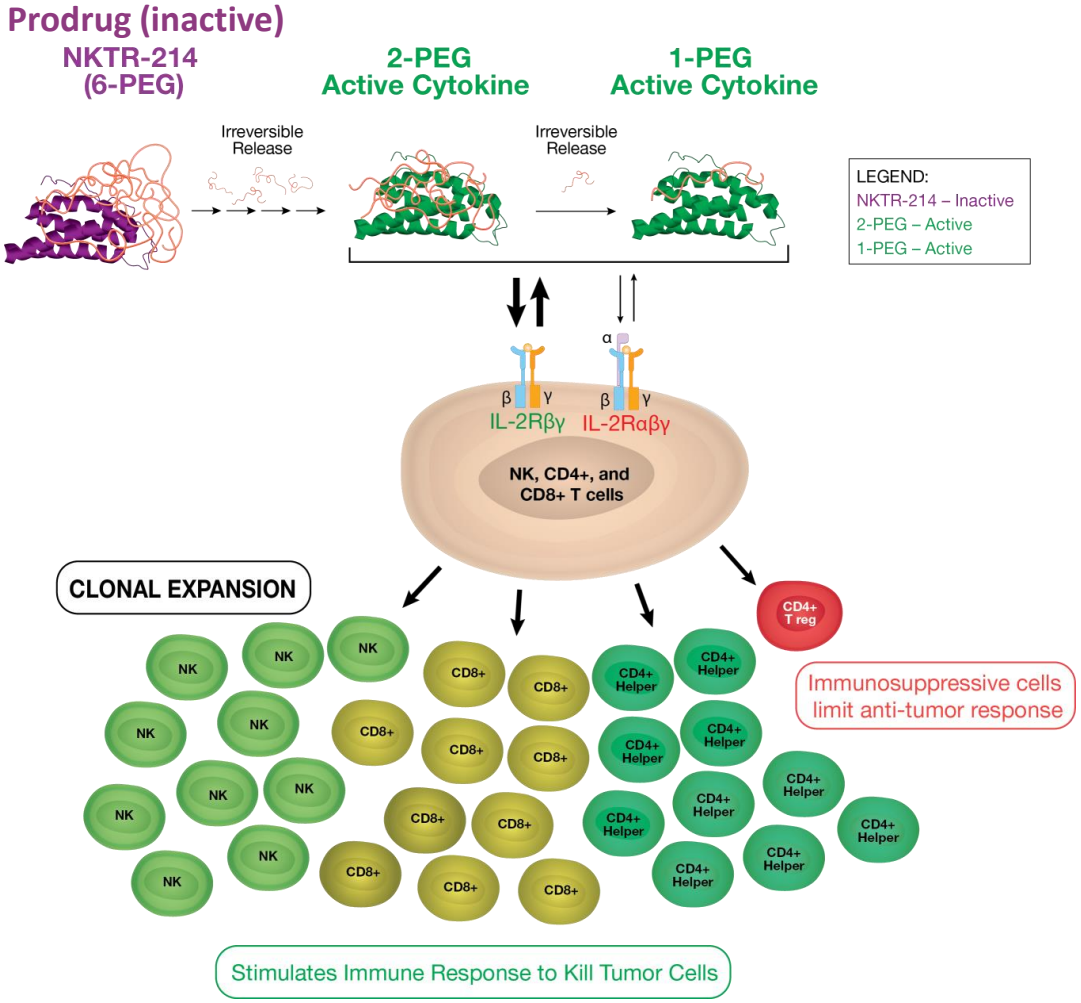
Vice President, Biology and Preclinical Development

NKTR-214 Phase 1 Dose Escalation Study Clinical Data Presentation

Dr. Adi Diab

Assistant Professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center, Houston, TX

Harnessing the IL-2 Pathway the Right Way to Increase TILs



- Prodrug design to enable safe, outpatient dosing Q2w or Q3w
- Active cytokine species bias signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ)
- Biased and sustained signaling to preferentially activate and expand effector CD8+ T and NK cells over Tregs in the tumor microenvironment

Trial Design

Study Design and Treatment

- Phase 1 dose escalation study evaluating the safety, tolerability and immune phenotyping of NKTR-214 in patients with advanced solid tumors
- NKTR-214 administered as a 15-minute IV infusion every 2-3 weeks
- The study is a standard 3+3 dose escalation design
- Tumor and blood samples collected
- Radiographic scans completed at baseline and every 8 weeks
- Patients continued on NKTR-214 monotherapy until they meet criteria for study discontinuation (withdrawal of consent, adverse event [AE], progressive disease [PD] or death)

Trial Design

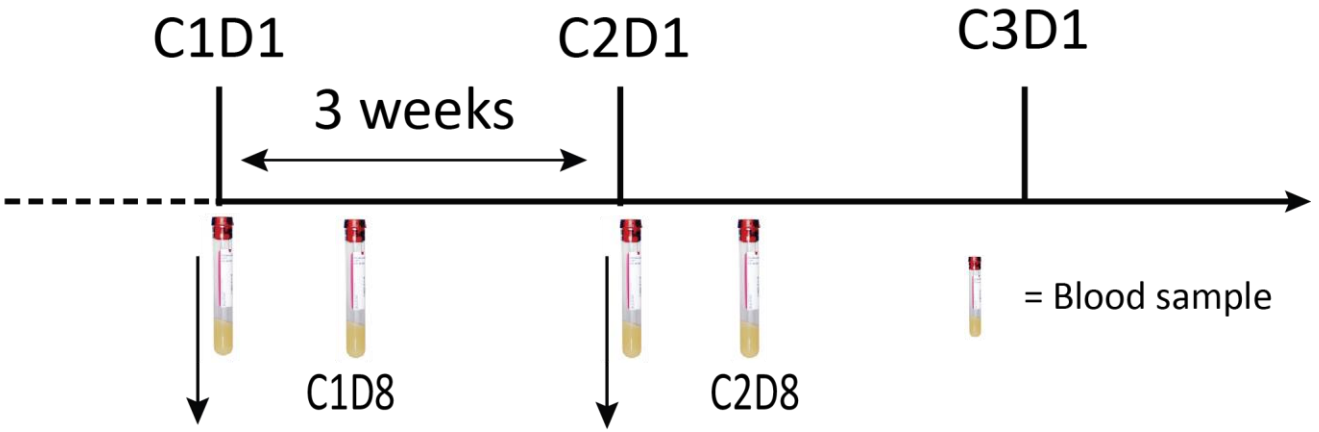
Patient Population

- Adults age 18 and older with histologically confirmed locally advanced or metastatic solid tumors

Study Objectives

- Safety and tolerability
- Define the maximum tolerated dose (MTD) of NKTR-214
- Objective response rate per RECIST 1.1
- Biomarkers of immune activation in the tumor and blood

PD and Biomarker Collection Scheme



Tumor Analysis

- ✓ **Fresh TIL analysis by flow cytometry**
- ✓ **IHC**
- ✓ **T cell receptor gene sequencing**
- ✓ **Gene expression analysis**

Blood Analysis

- ✓ **Flow cytometry**
- ✓ **Cytokines**
- ✓ **PK**
- ✓ **PD (sCD25, lymphocytes)**

Patient Characteristics

Characteristics	No. of Patients		%
Sex:	Male	16	64
	Female	9	36
Age (years):	Median	60	
	Range	34-77	
Tumor Histology:	Renal cell carcinoma	15	60
	Malignant melanoma	6	24
	Bladder cancer	1	4
	Chondrosarcoma	1	4
	Colorectal adenocarcinoma	1	4
	Leimyosarcoma	1	4
EGOG Performance Status:	0	15	60
	1	10	40
	Median	2	
	Range	1-12	
Prior Therapies	Chemotherapy	9	36
	Immune checkpoint inhibitor	15	60
	Targeted therapy	16	64

Abbreviations: ECOG, Eastern Cooperative Oncology Group

NKTR-214 Monotherapy Dose Escalation: Related Treatment Emergent AEs

	Grade 1-2					Grade 3				
Preferred Term	0.003 q3w (n=4)	0.006 q3w (n=9)	0.006 q2w (n=5)	0.009 q3w (n=6)	0.012 q3w (n=1)	0.003 q3w (n=4)	0.006 q3w (n=9)	0.006 q2w (n=5)	0.009 q3w (n=6)	0.012 q3w (n=1)
Hypotension	2	5	2	1			1		1	1†
Infusion reaction									1	
Syncope										1†
Fatigue	2	6	3	4	1					
Pruritus	2	6	2	3	1					
Cough		5	1	3	1					
Decreased appetite		5	2	3						
Pyrexia	2	3	2	3						
Chills	1	1	3	4						
Dizziness	1	3	1	1						
Nasal congestion	1	1	1	3						
Nausea	1	2	1	2						
Arthralgia		3	2							
Influenza like illness	1	2	1	1						
Myalgia		2	1	2						
Edema peripheral		3	1	1						
Rash maculo-papular			2	3						
Headache	2		1	1						
Rash erythematous	1	2		1						

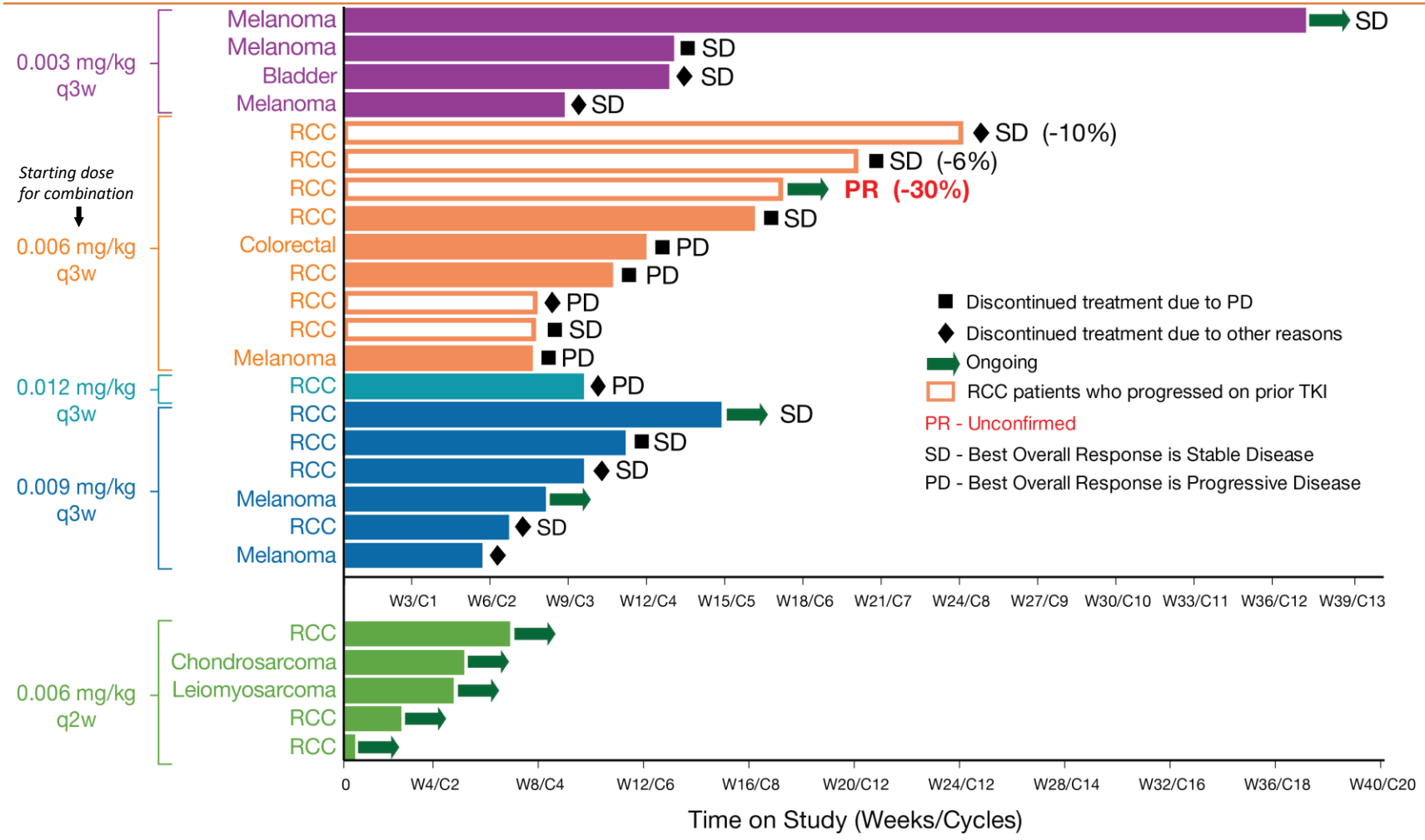
- 4/25 (16%) patients experienced a Grade 3 TEAE. G3 hypotension rapidly reversed with fluids and all patients continued on treatment.
- Hydration guidelines, including discontinuation of antihypertensive medications, implemented May 1, 2016 resulted in Grade 3 drug-related hypotension decreasing to only 1/20 (5%) patient

†Hypotension and syncope in the patient treated at 0.012 mg/kg occurred at the same time.

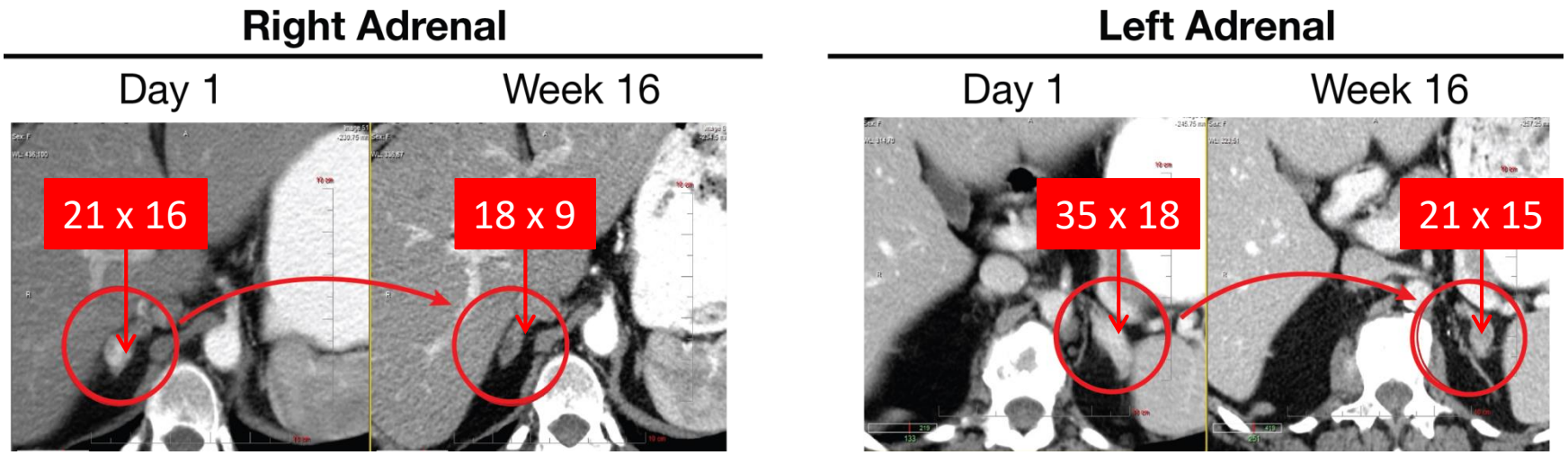
NKTR-214: Safety Summary

- NKTR-214 has a favorable safety and tolerability profile with convenient, outpatient 15 minute IV dosing regimen once every 2 or 3 weeks
- Most common grade 1-2 adverse events were fatigue, pruritis, cough, decreased appetite, pyrexia, and hypotension
- No immune-related AEs were observed (e.g. colitis, dermatitis, hepatitis, pneumonitis, adrenal insufficiency)
- No deaths or grade 4 AEs related to NKTR-214
- No capillary leak syndrome was observed at any dose
- One patient experienced a dose-limiting toxicity (DLT) of hypotension/syncope at 0.012 mg/kg q3w and continued on treatment at 0.006 mg/kg q3w
- There were 3 reports of grade 3 hypotension (of 25 patients treated in the study to-date), all of which were rapidly reversed with fluid administration and all patients continuing on treatment with NKTR-214

Time on Study and Best Overall Response



Case 1: 60-Year old female with RCC and uPR



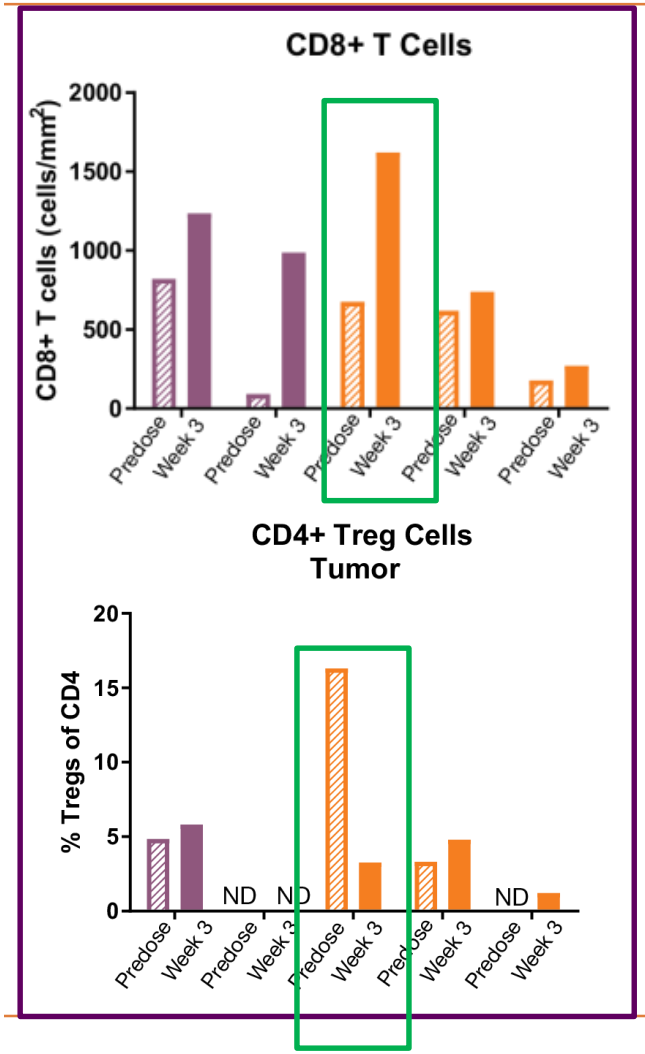
- 60 year old female with RCC and metastatic disease in the adrenal gland; patient previously progressed on a TKI

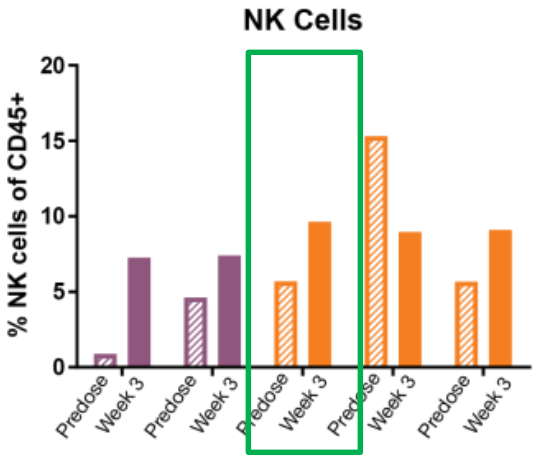
	16-week Scan
RECIST 1.1	-30%
Immune related response criteria (bi-dimensional)	-51%

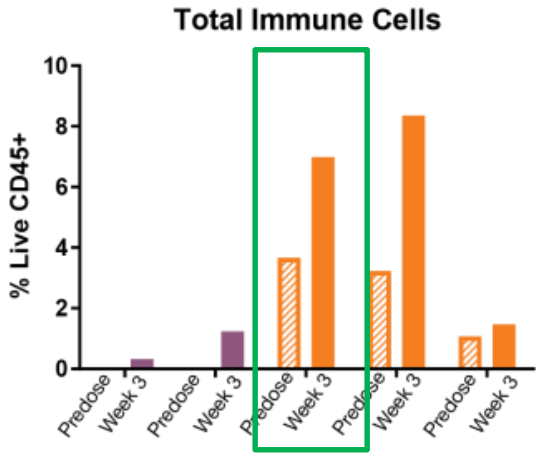
Encouraging Evidence of Clinical Activity

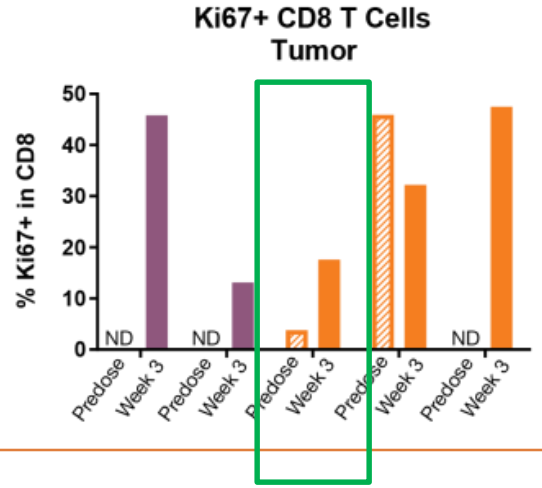
- 7/18 (39%) evaluable patients had radiographic reductions per RECIST 1.1
- 12/18 (72%) had SD at initial 8 week scan
- Patient on study the longest has received 13 cycles with stable disease for ~9 months (BRAF-positive melanoma)
- In the 18 evaluable patients, 5 had metastatic RCC and had progressed on 1 prior TKI
  - 3/5 experienced radiographic reductions at the 0.006 mg/kg q3w dose
  - 1/5 had an unconfirmed PR per RECIST 1.1
  - 2/5 had tumor reductions of 6% and 10% per RECIST 1.1

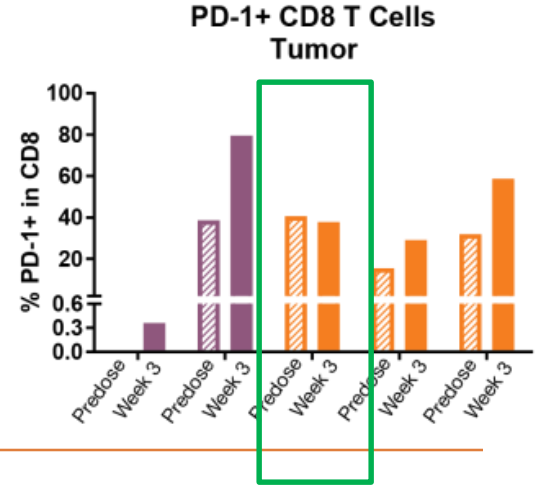
NKTR-214 Activates the Immune System in Tumor







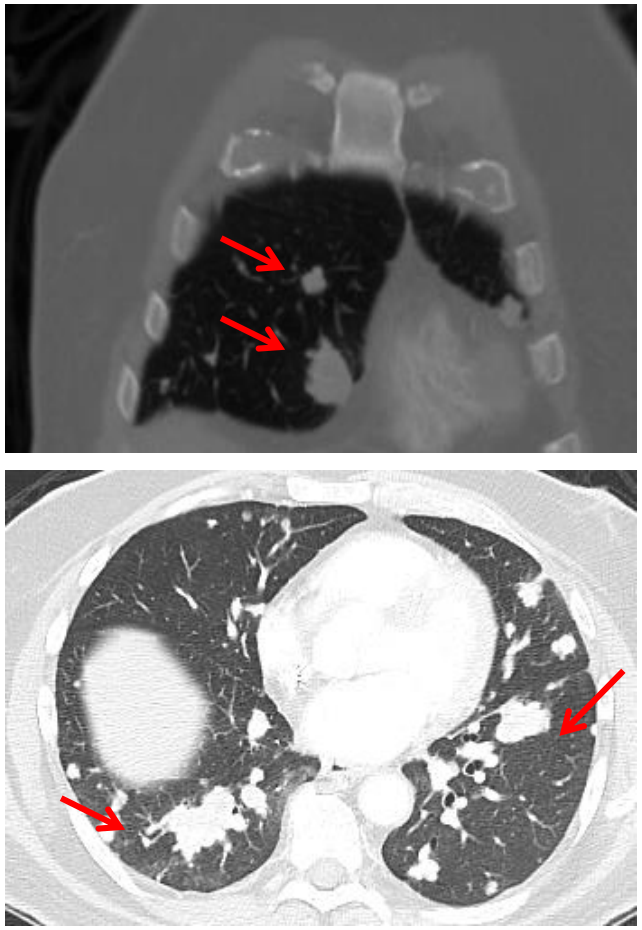




Case 2: 59 year old male with RCC who progressed on prior TKI

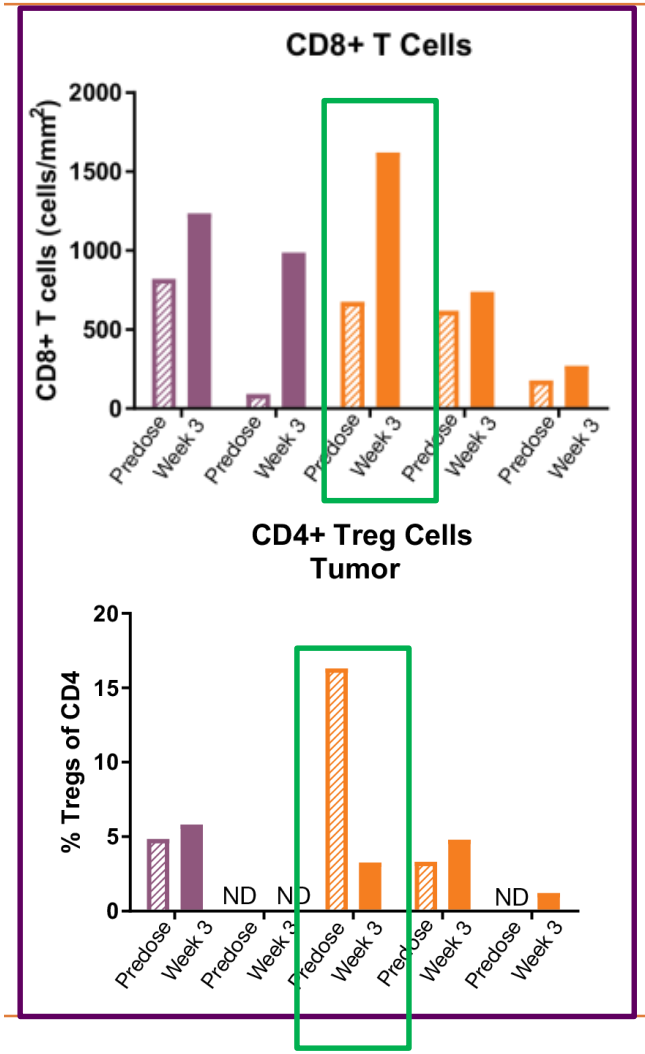
- Patient initiated NKTR-214 with large burden of disease on 3/14/2016
- Patient received 8 cycles (0.006 mg/kg q3w) for six months with stable disease and maximum radiographic reduction in tumor of 10%
- Week 3 tumor biopsy showed strong evidence of active immune infiltrate including an effector gene signature
- Patient discontinued from NKTR-214 and was started on nivolumab one week later
- At first 8-week scan after nivolumab, patient experienced remarkable treatment response with significant reduction in tumor burden of >50%
- Clinical case study demonstrating potential for synergy of NKTR-214 with anti-PD-1

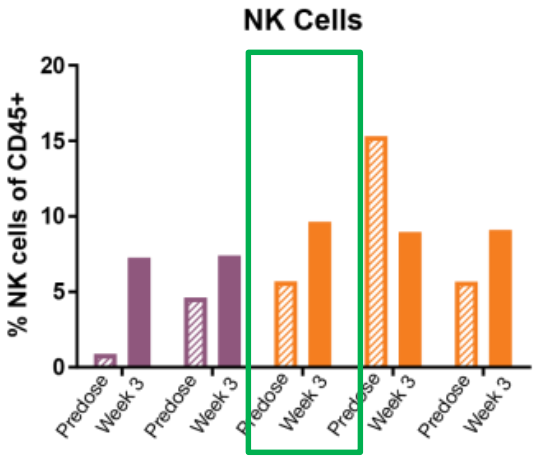
Case 2: 59 year old male with RCC who progressed on prior TKI

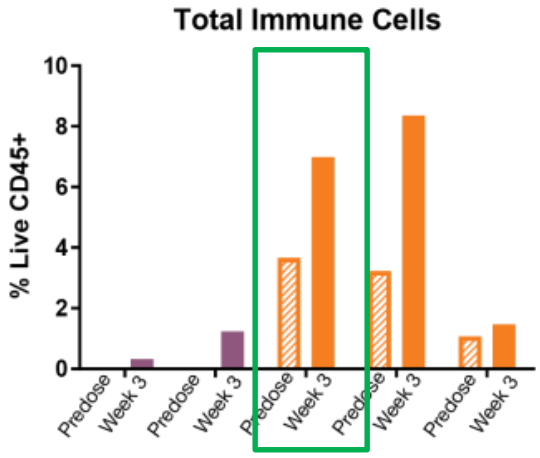


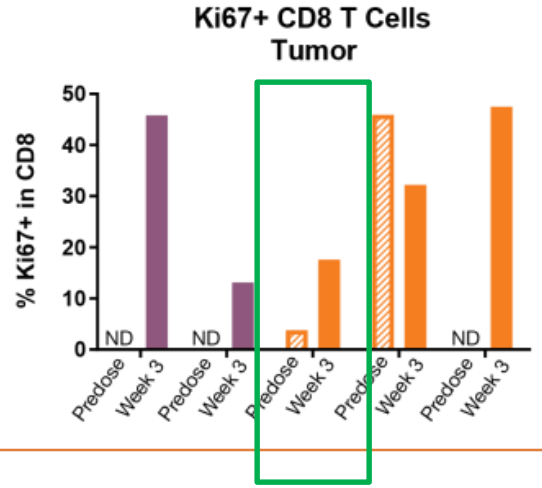
Scan post NKTR-214; Pre-nivolumab

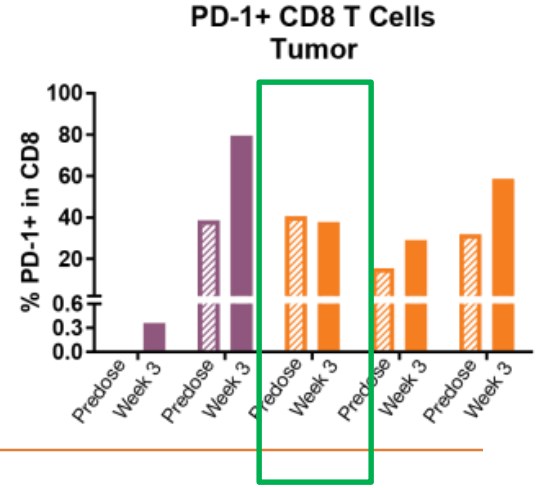
NKTR-214 Activates the Immune System in Tumor



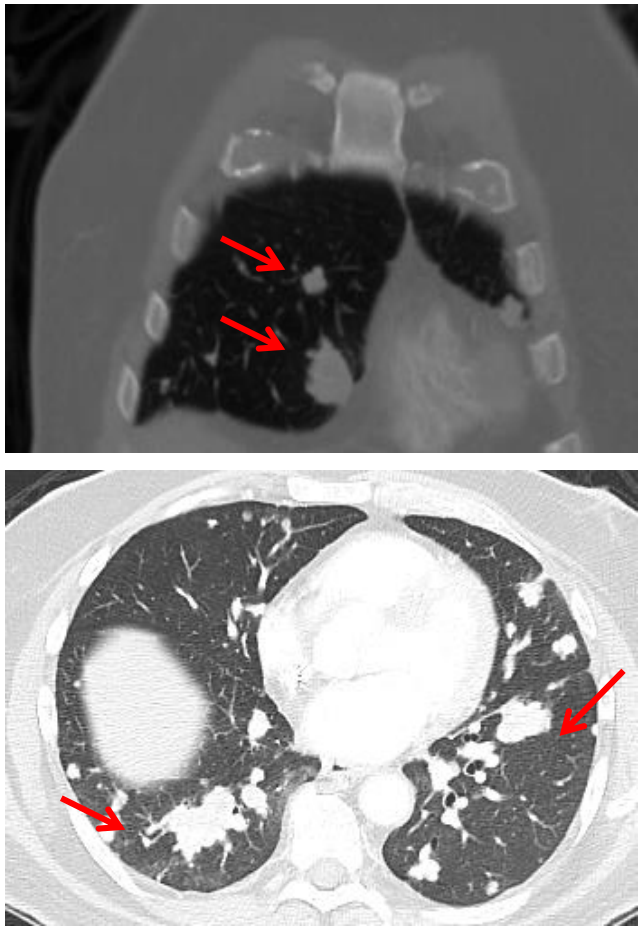




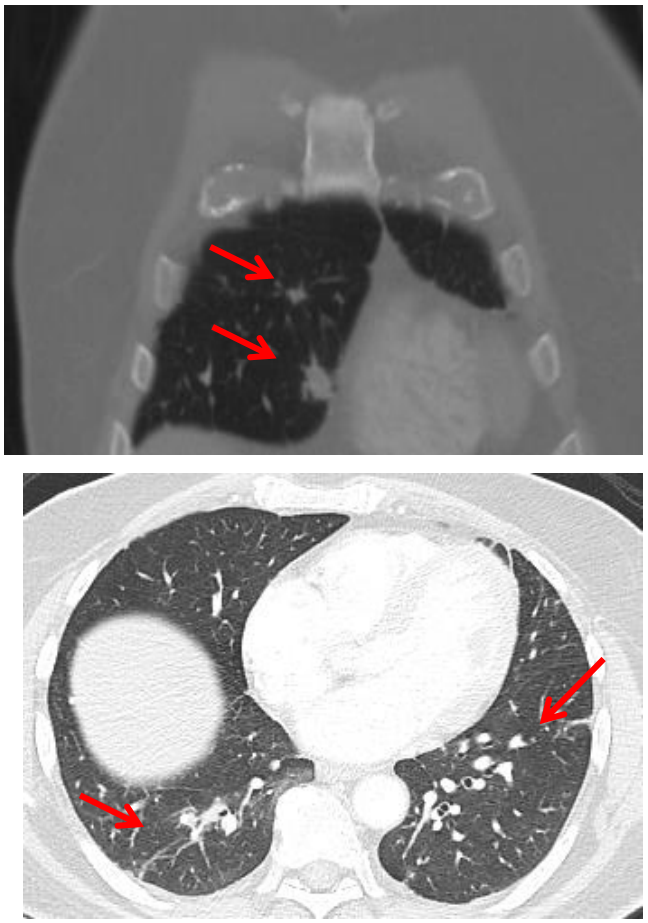




Case 2: 59 year old male with RCC who progressed on prior TKI

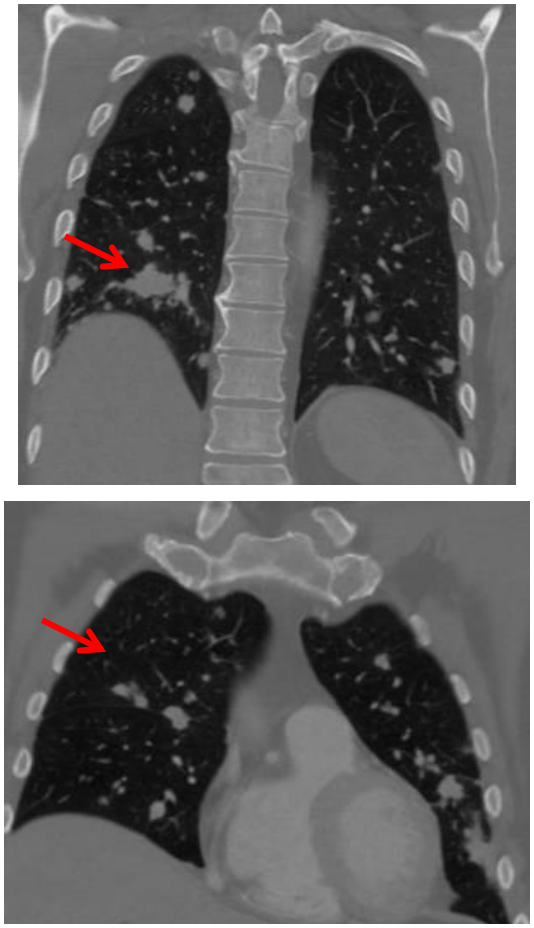


Scan post NKTR-214; Pre-nivolumab

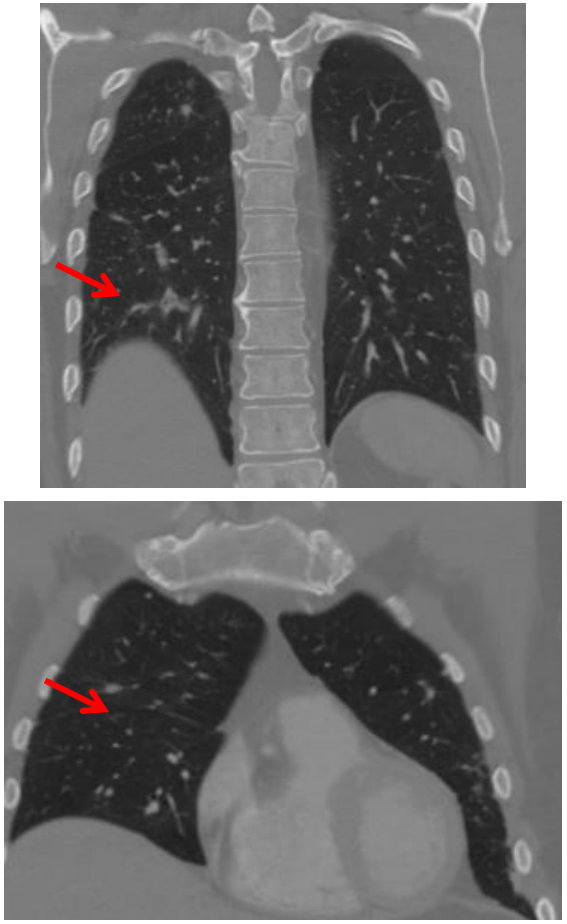


First 8-week scan post-nivolumab

Case 2: 59 year old male with RCC who progressed on prior TKI

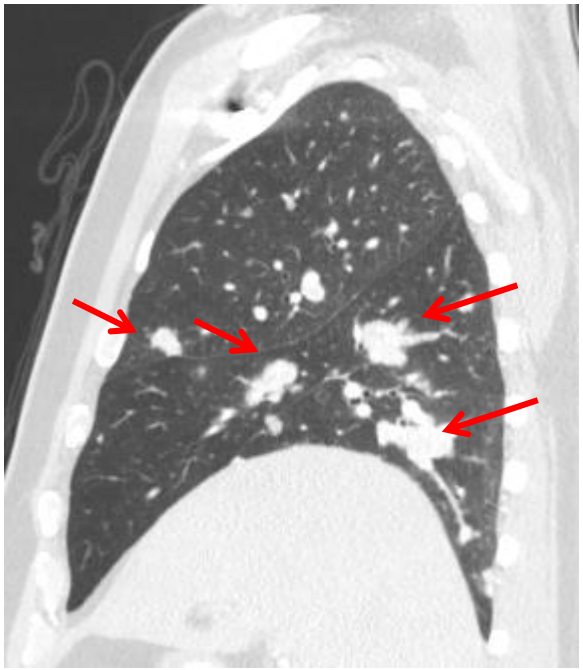


Scan post NKTR-214; Pre-nivolumab

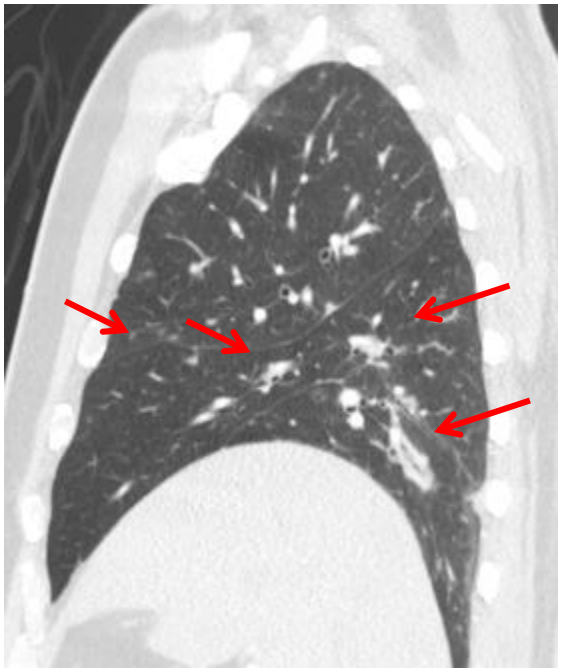


First 8-week scan post-nivolumab

Case 2: 59 year old male with RCC, prior treatment with TKI



Scan post NKTR-214; Pre-nivolumab



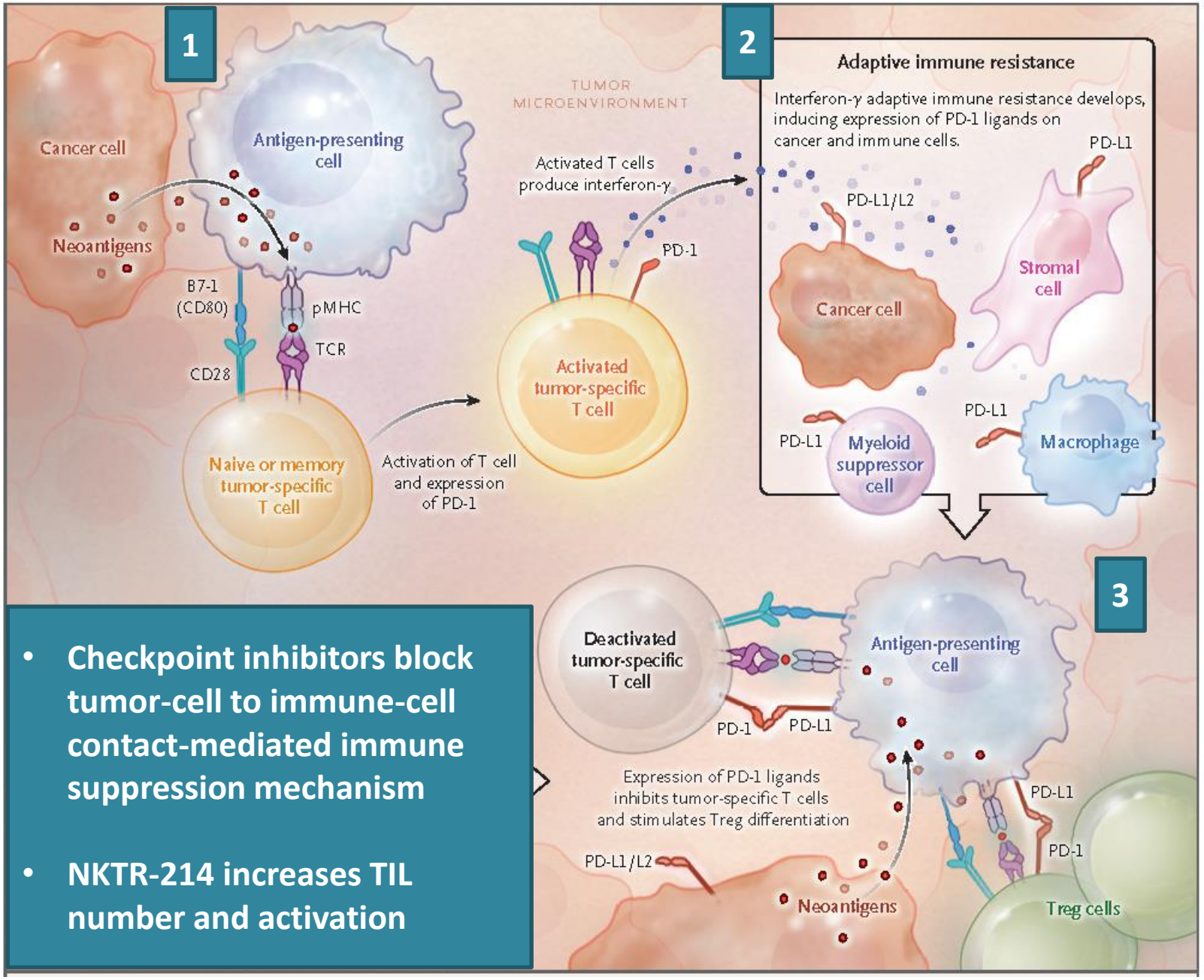
First 8-week scan post-nivolumab

Conclusions

- NKTR-214 has a favorable safety and tolerability profile with convenient, outpatient 15 minute IV dosing regimen once every 2 or 3 weeks
- Encouraging evidence of clinical activity in heavily pre-treated patient population
  - 7/18 evaluable patients had radiographic reductions per RECIST 1.1 on NKTR-214
  - In the 18 evaluable patients, 5 had metastatic RCC and had progressed on 1 prior TKI; 3/5 experienced radiographic reductions at the 0.006 mg/kg q3w dose
    - **1/5 had an unconfirmed partial response per RECIST 1.1**
    - **2/5 had tumor reductions of 6% and 10% per RECIST 1.1**
- NKTR-214 induces a robust immune-stimulatory response in the tumor and blood
- Tolerability, activity and pharmacokinetic profile supported evaluation of q2w dosing, which commenced in September 2016
- The ability of NKTR-214 to increase TILs and increase PD-1 expression on immune cells provides strong biologic rationale for combination with anti-PD1 checkpoint inhibitors

NKTR-214 Phase 1 Dose Escalation Study Clinical Data Presentation

Dr. Jonathan Zalevsky
Vice President of Biology and Preclinical Development
Nektar



- **Checkpoint inhibitors block tumor-cell to immune-cell contact-mediated immune suppression mechanism**
- **NKTR-214 increases TIL number and activation**

N Engl J Med 375;18

Clinical Program Includes In-Depth Immune Biomarker Program to Characterize the MOA of NKTR-214 in Cancer Patients

Comprehensive Immunological and Pharmacodynamic Monitoring

Pharmacokinetics and Pharmacodynamics

- AUC, Cmax, $T_{1/2,}$
- sCD25
- Lymphocytes
- Anti-drug antibodies

Tumor Biopsies

- T, B, NK cells
- PD-1 expression
- Mechanism of action
- Gene expression
- IHC
- T-cell receptor repertoire

Blood Samples

- Mechanism of action
- Gene expression
- T, B, NK cells
- T cell memory, function
- T-cell receptor repertoire

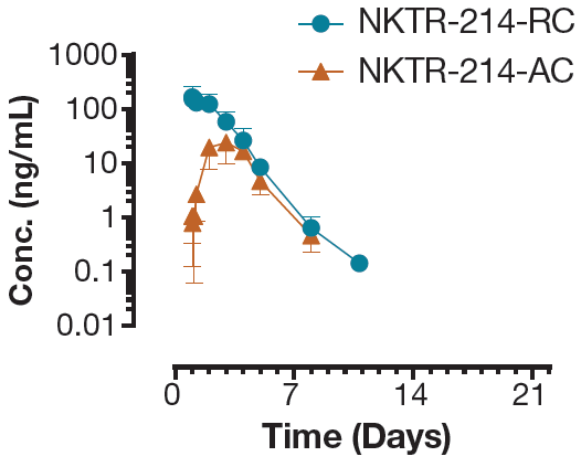
Establish RP2 dose, confirm MOA, evaluate signals of response

Questions the Biomarker Program is Designed to Help Answer

- What are the primary pharmacokinetics and pharmacodynamics of NKTR-214?
- Does NKTR-214 cause the expected increase in lymphocyte proliferation and systemic immune activation?
- Does NKTR-214 increase the abundance and activation of immune cells in the tumor microenvironment?
  - If yes, are these new or previously existing T cell clones?
- What is the biological evidence for dose-level and regimen?

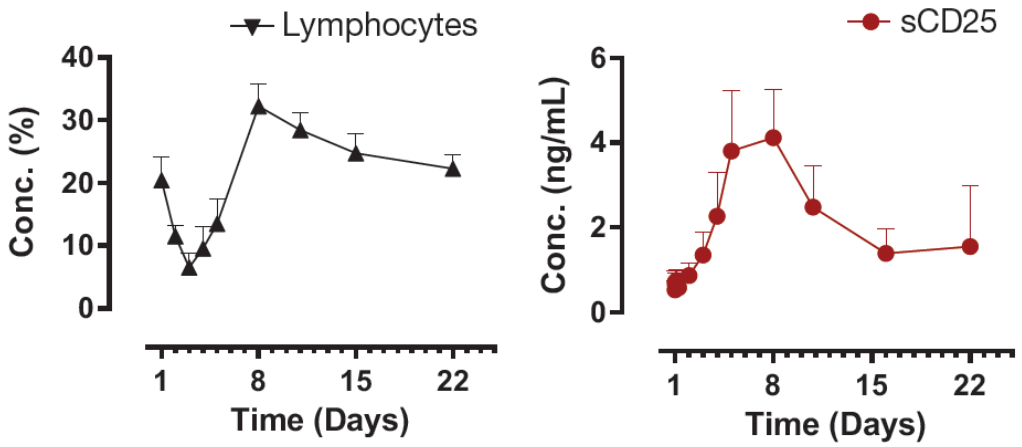
Sustained Exposure and Robust PD Changes After a Single Dose of NKTR-214

Pharmacokinetics (0.006 mg/kg, n=9)



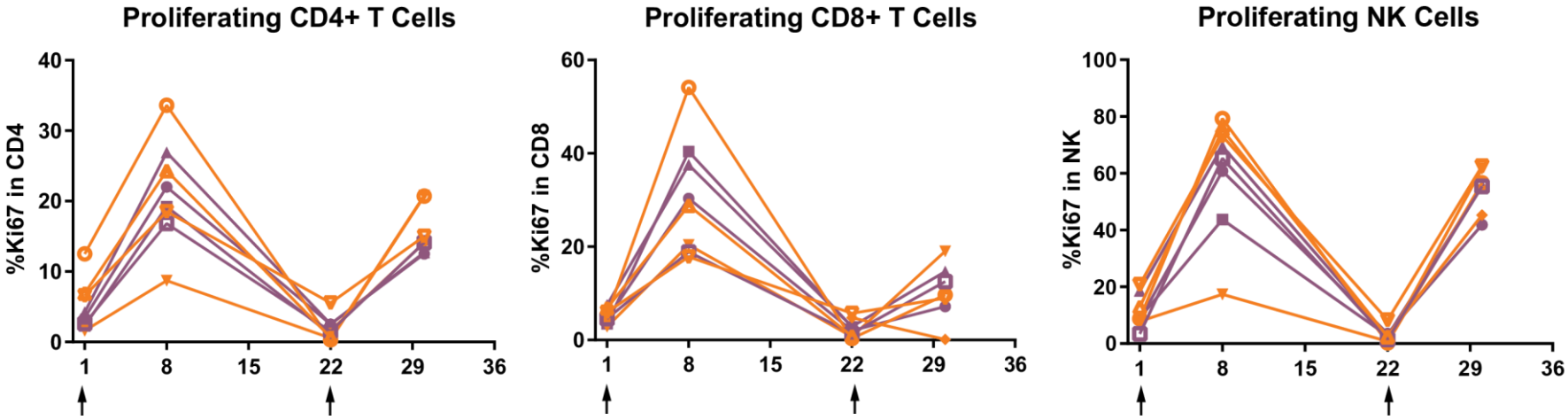
- Sustained exposure with half-life of ~20 hours
- Gradual increase in active cytokine species, reaching C_{max} 1-2 days post dose
- Exposure increases in proportion to dose

Pharmacodynamics (0.006 mg/kg, n=9)



- Transient decrease (Day 3) followed by increase (Day 9) in lymphocytes, consistent with observations after HD-IL-2
- Transient increase in soluble IL-2 receptor alpha (sCD25), shed from activated T cells
- PD effects return to baseline by 14 days post-dose on Day 15
- Similar PD effects observed across dose levels

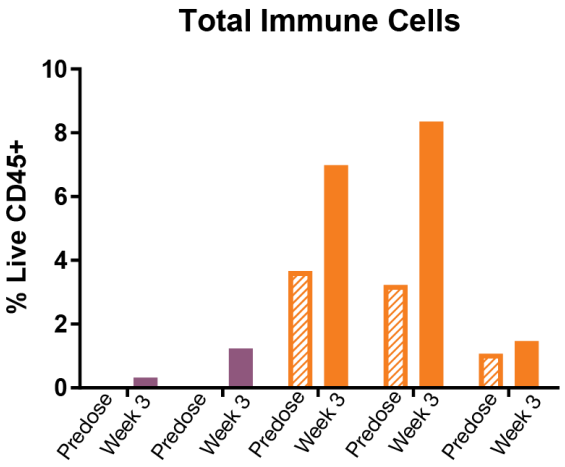
Peripheral Blood: NKTR-214 Promotes Proliferation of CD4, CD8, and NK Cells

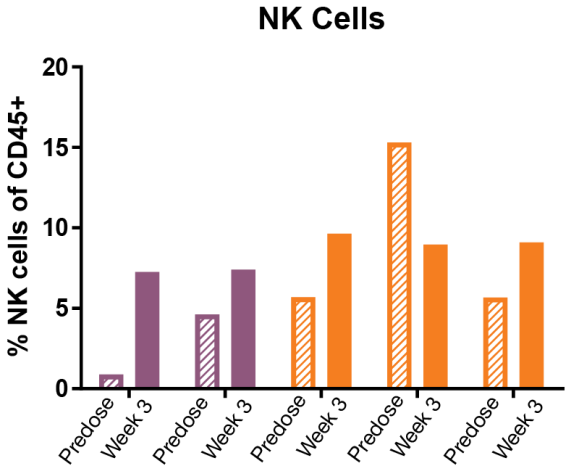


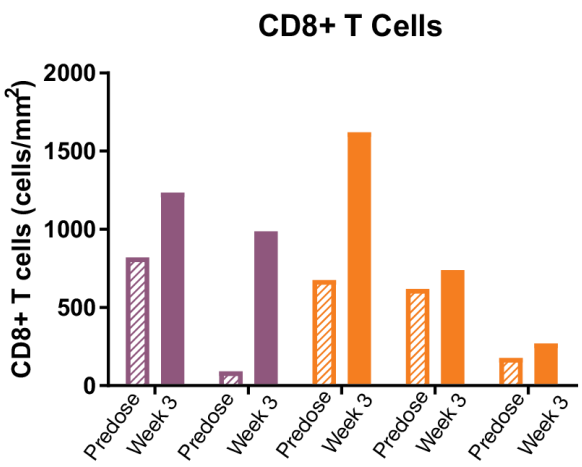
- Every patient evaluated had proliferating CD4+, CD8+ T cells & NK cells
- Effects reproduced with repeat administration
- Effects consistent with increases in total cell numbers
- CD4+ T cells expressed activation markers PD-1, ICOS, TIM-3, and CTLA-4

Purple: 0.003 mg/kg (n=4)
Orange: 0.006 mg/kg (n=5)
Dosing Day
Flow cytometry of PBMCs
Ki67 is a marker of cell proliferation

Tumor: NKTR-214 Increases Immune Cells Including CD8 and NK Cells



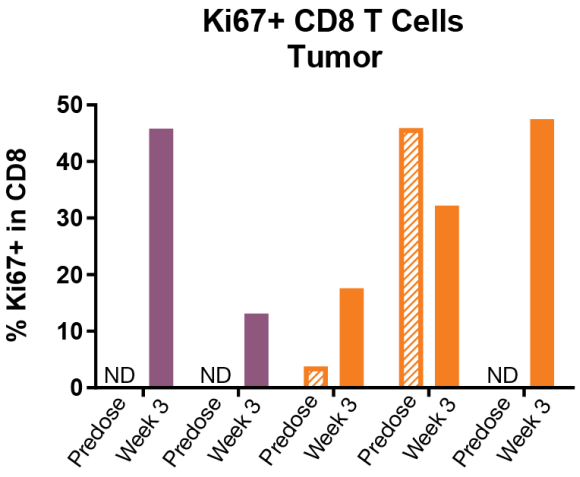


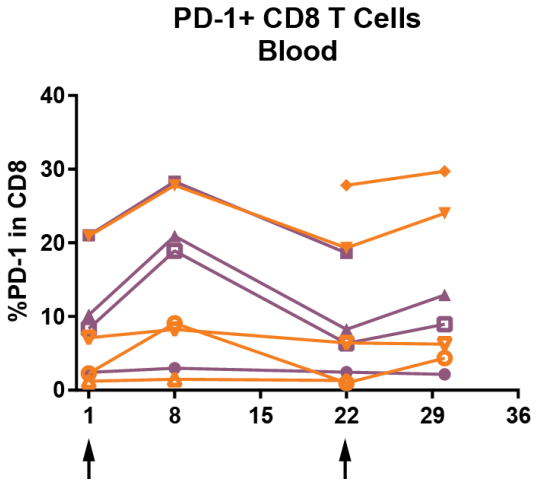


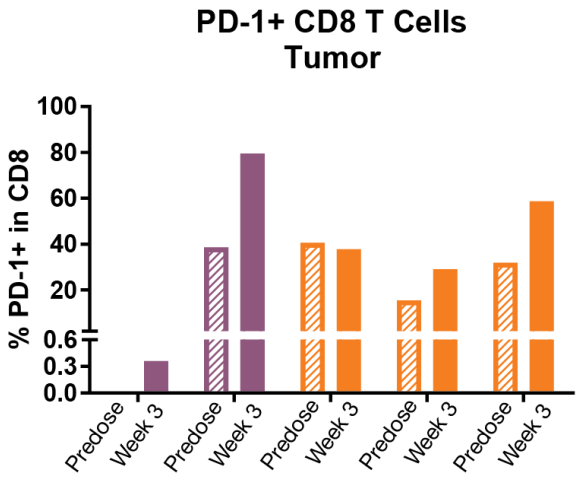
- Increases in immune cell populations observed in 5/5 patients
- The immune cell elevations (observed at Week 3) outlasted measurable plasma exposure to NKTR-214
- Good concordance between IHC and flow cytometry for cell analysis of tumor biopsies

Purple: 0.003 mg/kg (n=2)
Orange: 0.006 mg/kg (n=3)
Hatched bars are predose & solid bars are Week 3 biopsy samples
Total immune cells (CD45+) and NK cells (CD3-,CD19-,CD56+) obtained from fresh tissue flow cytometry; CD8 T cells from IHC

Peripheral Blood and Tumor: NKTR-214 Increases the Abundance of Proliferating CD8 and PD-1+ T Cells



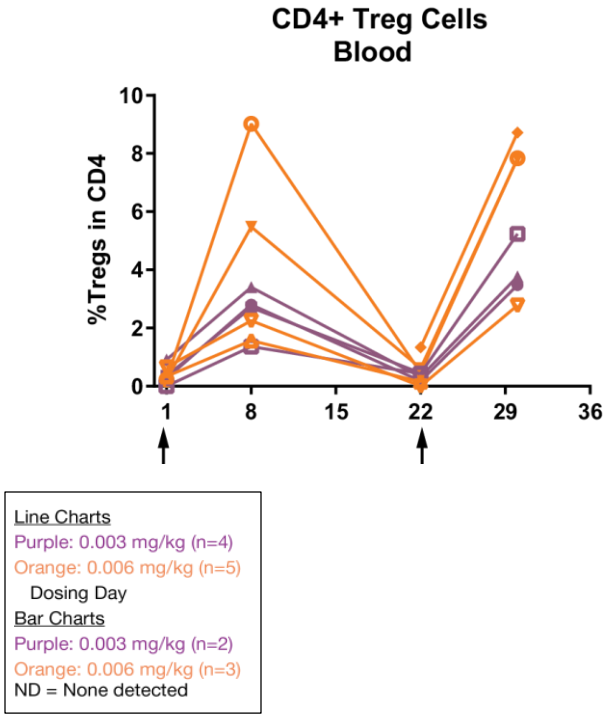


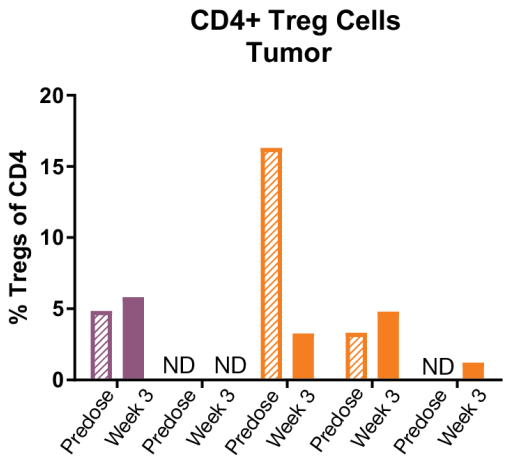


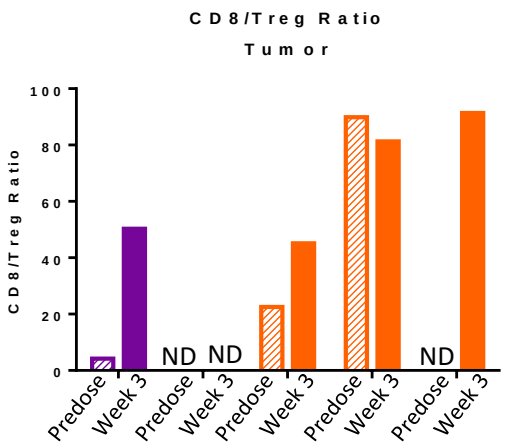
- Increase in proliferating CD8 T cells seen in 4/5 patients after NKTR-214
- PD-1+ CD8 T cells increase in blood and tumor

Line Charts
Purple: 0.003 mg/kg (n=4)
Orange: 0.006 mg/kg (n=5)
Dosing Day
Bar Charts
Purple: 0.003 mg/kg (n=2)
Orange: 0.006 mg/kg (n=3)
ND = None detected

NKTR-214 Transiently Increases Treg Cell Frequency in Blood but Not in Tumor

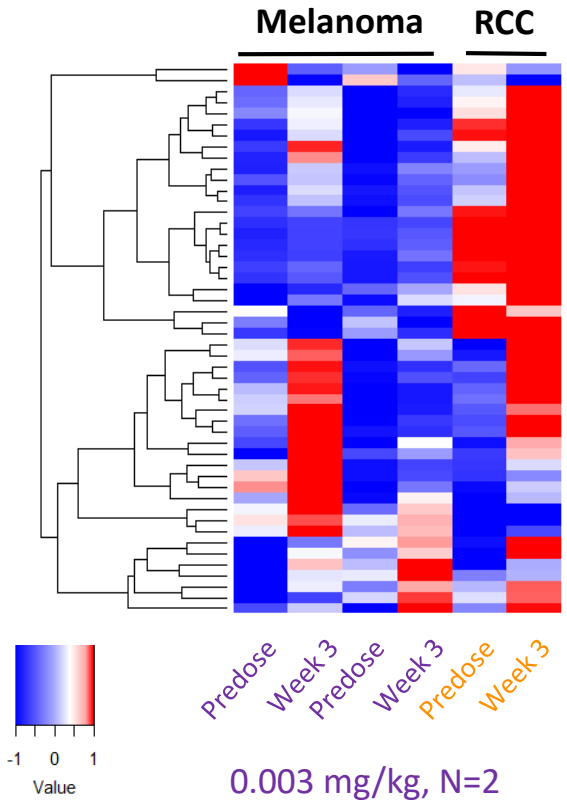






- Minimal Treg accumulation in the tumor
- Increase CD8/Treg ratio in tumor

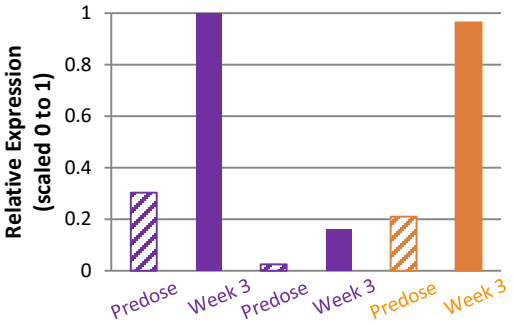
NKTR-214 Induces an Activation Gene Signature in the Tumor Microenvironment



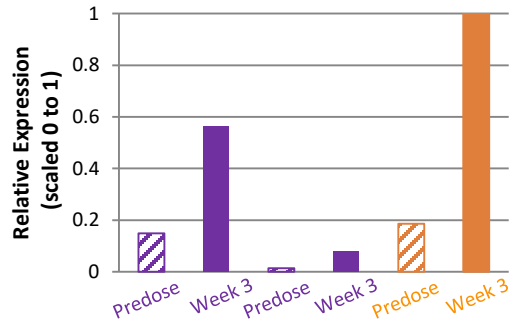
0.003 mg/kg, N=2
0.006 mg/kg, N=1

Top 50 most differentially expressed genes shown in the heat map

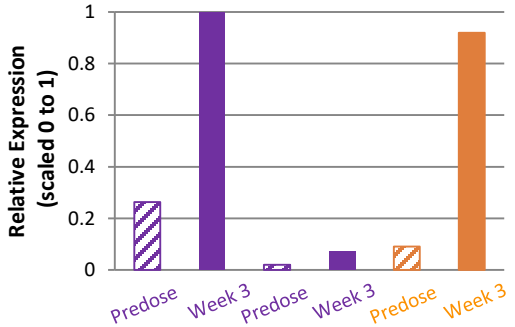
Interferon γ



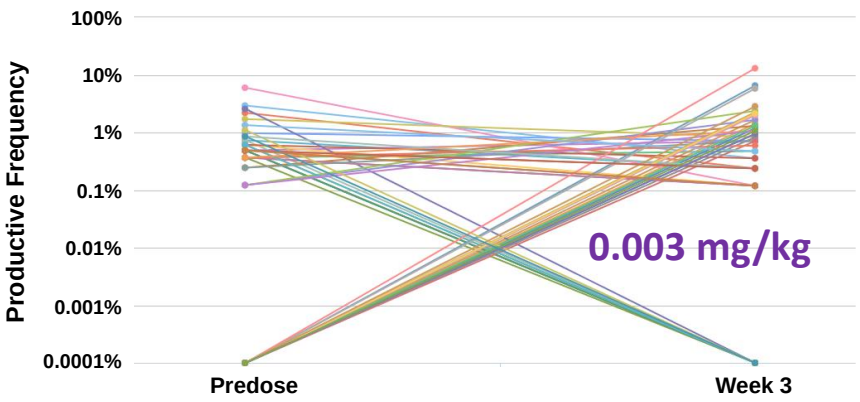
Perforin

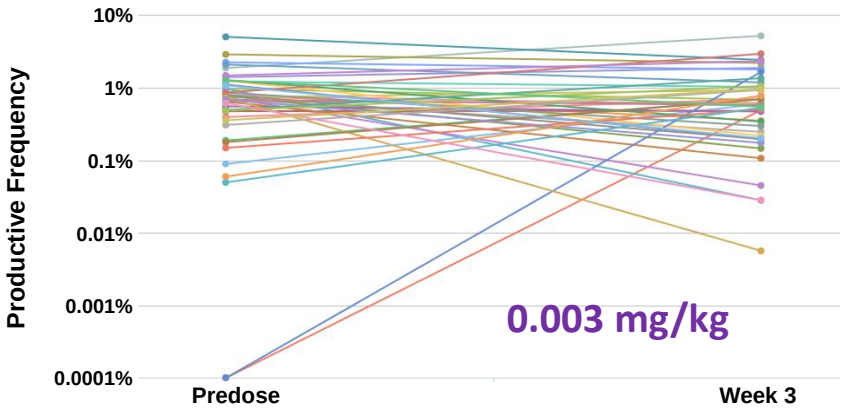


Granzyme B

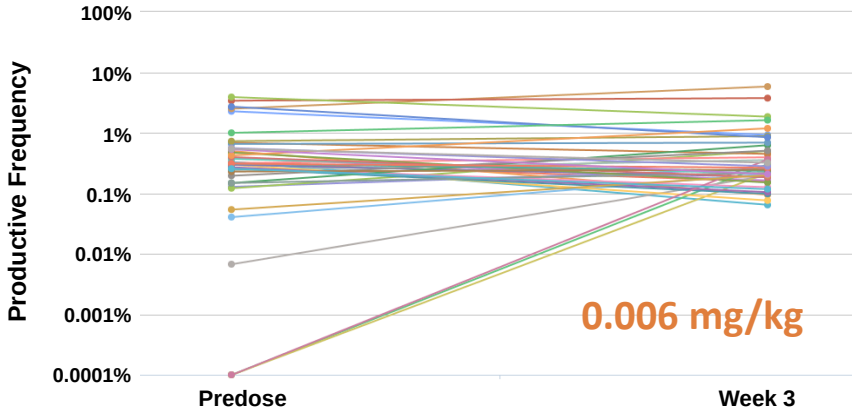


NKTR-214 Promotes a Change in T Cell Repertoire, a Measure of Clonality in the Tumor



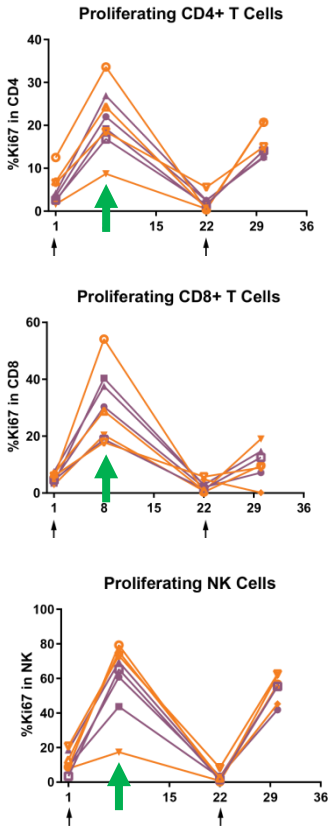


- Adaptive sequencing data shows change in TCR frequency and identity
- NKTR-214 promoted a change in frequency of specific TCR sequences detected among the top 30 most abundant TCR sequences between Predose and Week 3

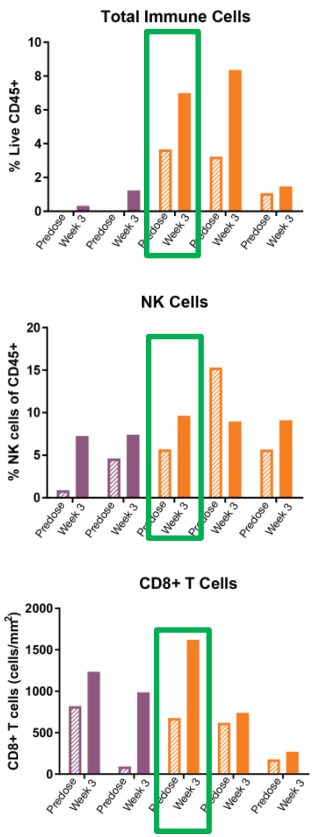


NKTR-214 Induced Multiple Measures of Immune Activation in Patient 0220-0004

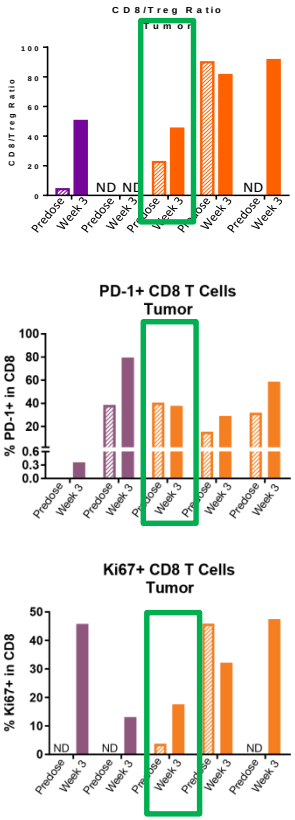
Increased proliferation in blood



Increased immune cells in tumor



Increased quality of immune response in the tumor

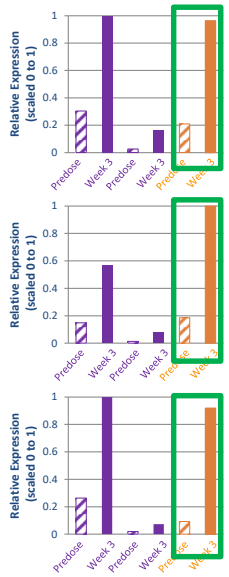


Increased immune activation and effector gene signature in the tumor

Interferon γ

Perforin

Granzyme B

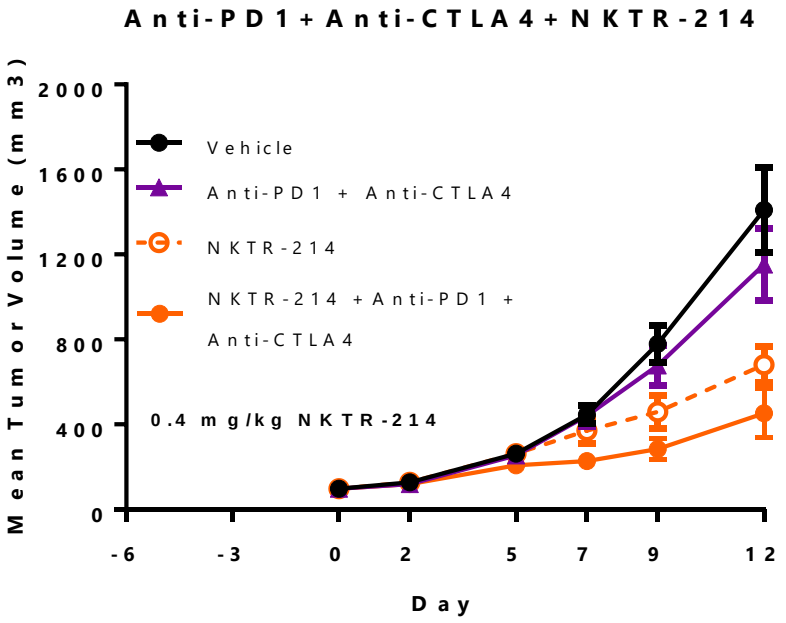


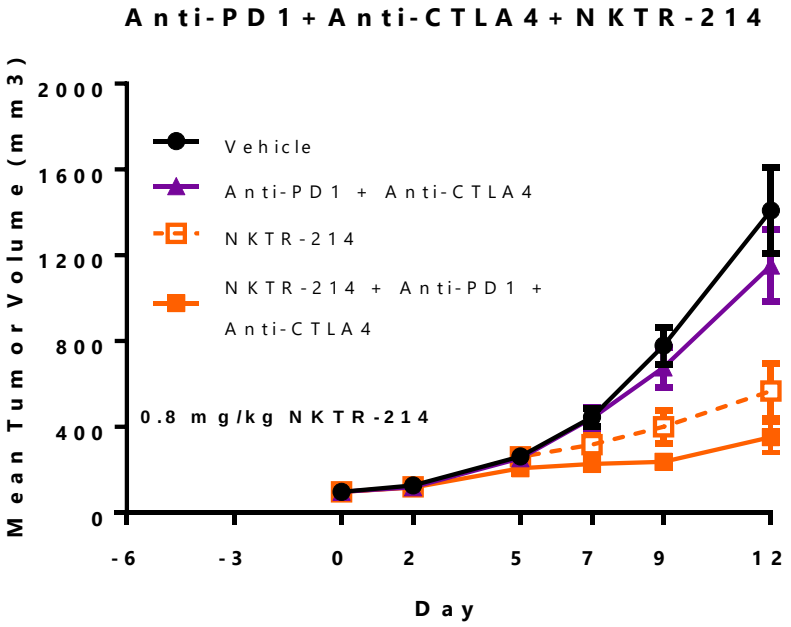
PD-L-1 expression (IHC) was negative predose and 5% positive cells at Week 3

NKTR-214 Human Clinical Biomarker Conclusions

- Treatment with NKTR-214 produced a robust elevation in immune cell frequency and activation, including:
  - Increase in total and newly proliferating (Ki67+) CD4+ T cells, CD8+ T cells, and Natural Killer (NK) cells in 9/9 patients with blood samples evaluated in the trial to-date, with increases of up to 30-fold observed
  - Increase in frequency of PD-1+ T cell subsets of up to 9-fold in the blood
  - Increase in CD8+ T cells and Natural Killer (NK) cells of up to 10-fold in the tumor micro-environment in patients with evaluable tumor biopsies (pre-dose and post-dose at week 3), with minimal changes to T regulatory cells
  - Increase in expression of cell-surface PD-1 on T cell subsets of up to 2-fold in the tumor micro-environment
  - Induction of an activation gene signature in the tumor micro-environment, including increases of 5-fold or more in expression of interferon γ, perforin and granzyme B genes
  - Changes in T cell repertoire (TCR), which is a measure of T cell clonality, in the tumor micro-environment

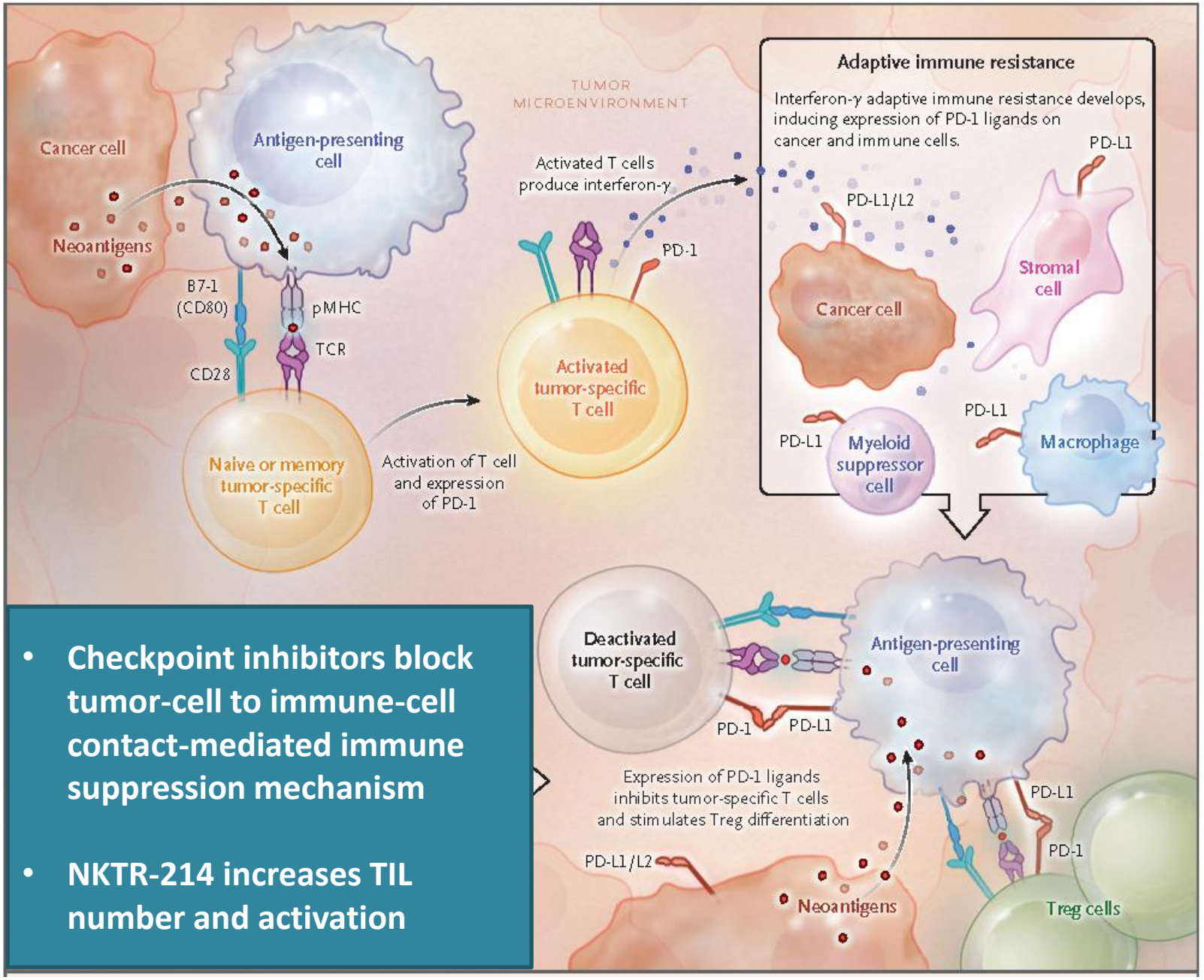
High Anti-Tumor Efficacy for Triple Combination of NKTR-214 + Anti-PD-1 + Anti-CTLA-4





- CT26 tumor model
- Treatment begun on established tumors (100-200 mm^3)
- 8.3 µg/mouse anti-PD-1, twice weekly
- 4.1 µg/mouse anti-CTLA-4, twice weekly
- 0.4 or 0.8 mg/kg NKTR-214, q9d

Study ongoing, showing data through Day 12



- **Checkpoint inhibitors block tumor-cell to immune-cell contact-mediated immune suppression mechanism**
- **NKTR-214 increases TIL number and activation**

N Engl J Med 375;18

NKTR-214 Clinical Development Program

Dr. Mary Tagliaferri

Vice President of Clinical Development

Nektar

Clinical Collaboration Terms

- Nektar retains all rights to NKTR-214
- Nektar and Bristol to split clinical costs of trials in at least seven different indications
- Prior to Sept. 2018, if Nektar chooses to partner NKTR-214, Bristol has right of first negotiation
- Nektar and Bristol to collaborate exclusively on anti-PD1 mechanism
- Nektar retains ability to conduct its own trials of NKTR-214 with any anti-PD1/PDL1 agents
- Nektar can collaborate to run trials with any other company outside of anti-PD1/PDL1 mechanisms

Clinical Development Program for NKTR-214 + Nivolumab

NKTR-214 + OPDIVO Combo (n=260)

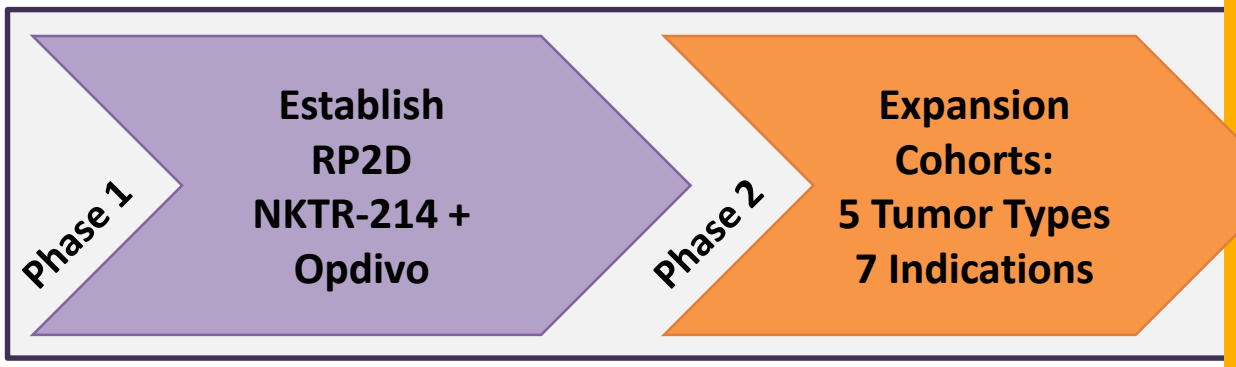
- Dose escalation for combination underway
- Melanoma: First line and relapsed on IO agent
- Renal cell carcinoma: Second line and relapsed on IO agent
- NSCLC: Second line, IO naïve
- Bladder cancer: First line
- Triple negative breast cancer: Second line, IO naïve
- Data from these trials anticipated over the course of the next 18 months

OPDIVO™ (nivolumab)
Bristol-Myers Squibb

NKTR-214 plus Opdivo
Phase 1/2 Program: Solid Tumor Indications

Phase 1 Dose Escalation

- Establish RP2D
- Safety and tolerability
- Objective response rate (ORR)
- Measure biomarkers in blood and tumor



2H2016

Cohort 1: 0.006 q3w NKTR-214 + 240 mg nivo
Cohort 2: 0.003 q2w NKTR-214 + 240 mg nivo
Cohort 3: 0.006 q2w NKTR-214 + 240 mg nivo

1H2017

Melanoma
Cohort 1: 1L
Cohort 2: Relapsed on IO

NSCLC
Cohort 3: 2L IO naïve

RCC
Cohort 4: 2L IO naïve
Cohort 5: Relapsed on IO

TNBC
Cohort 6: 2L IO naïve

Bladder
Cohort 7: 1L

One Protocol / Continuous Study

Possible Additional Collaborations for NKTR-214

Enter into collaborations where biologic rationale is strong:

Discussion and Q&A

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MD Anderson

Assistant Professor, Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Dr. Mario Sznol
Yale Cancer Center

Professor of Medicine (Medical Oncology); Co-Director, Yale SPORE in Skin Cancer

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Dr. Mary Tagliaferri
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Nektar Therapeutics

Vice President, Biology and Preclinical Development

SITC 2016

Nektar Therapeutics Investor Meeting

November 9, 2016