A CD122-biased agonist increases CD8+T cells and natural killer cells in the tumor microenvironment; making cold tumors hot with NKTR-214

Chantale Bernatchez[1], Cara Haymaker[1], Nizar M. Tannir, [1] Harriet Kluger, [2] Michael Tetzlaff, [1] Salah Eddine Bentebibel[1], Natalie Jackson[1], Ivan Gergel[3], Mary Tagliaferri[3], Jonathan Zalevsky[3], Ute Hoch[3], Patrick Hwu[1], Mario Sznol[2], Michael Hurwitz[2], Adi Diab[1]

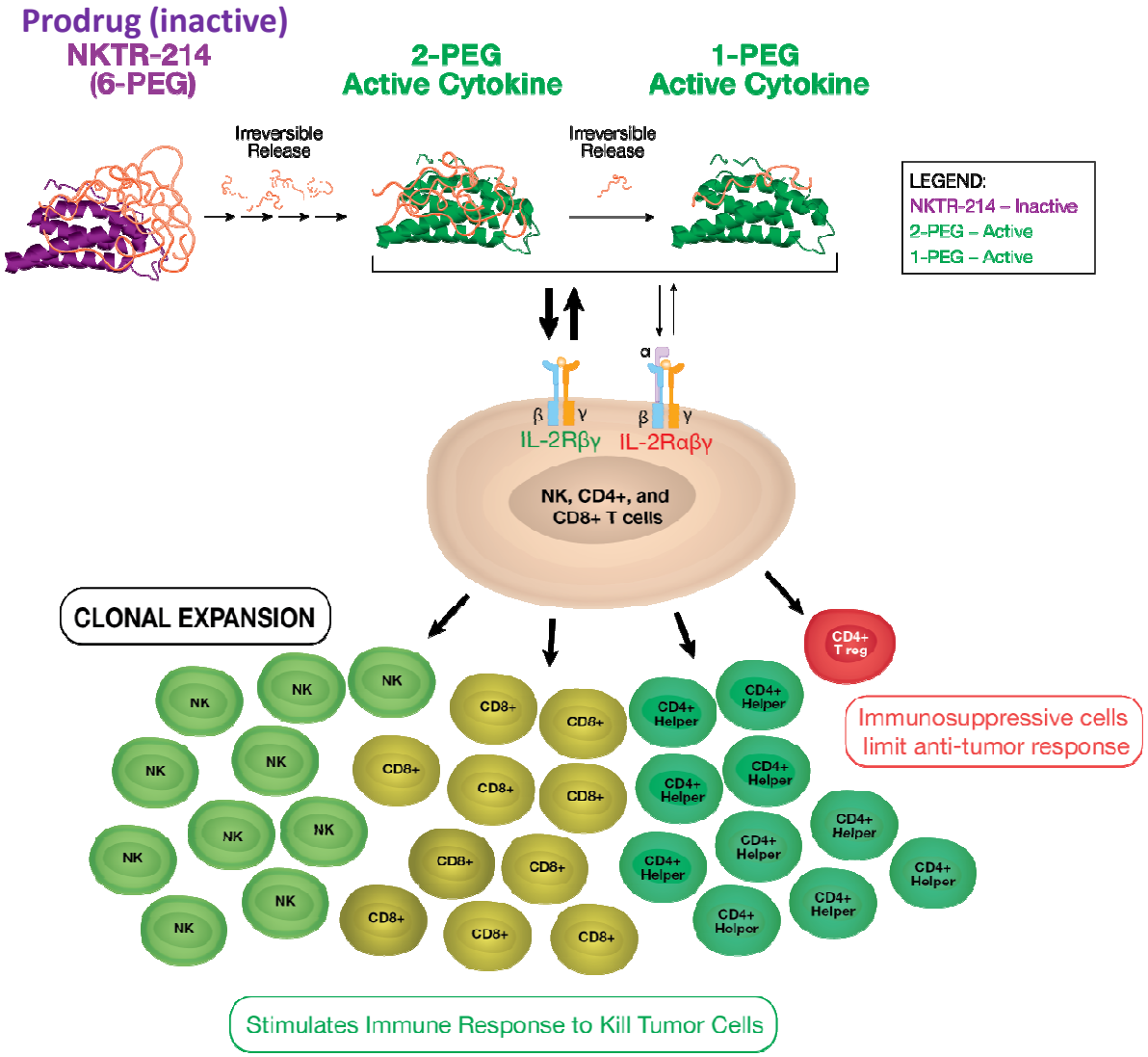
1. The University of Texas MD Anderson Cancer Center, Houston, TX; 2. Yale Medical Oncology, New Haven, CT; 3. Nektar Therapeutics, San Francisco, CA

NEKTAR®

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Yale University School of Medicine

Harnessing the IL-2 pathway the right way to increase TILs



- Prodrug design to enable safe, outpatient dosing Q2W or Q3W
- Active cytokine species with biased 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

Standard 3+3 P1 Trial Design with Robust Biomarker Analyses

- Heavily-pretreated patient population
- 60% of patients received prior IO therapies
- NKTR-214 administered as a 15-minute IV infusion every two to three weeks
- Radiographic scans at baseline and every 8 weeks
- Blood samples collected before and during treatment
- Tumor biopsies collected pre-dose and post-dose (week 3)

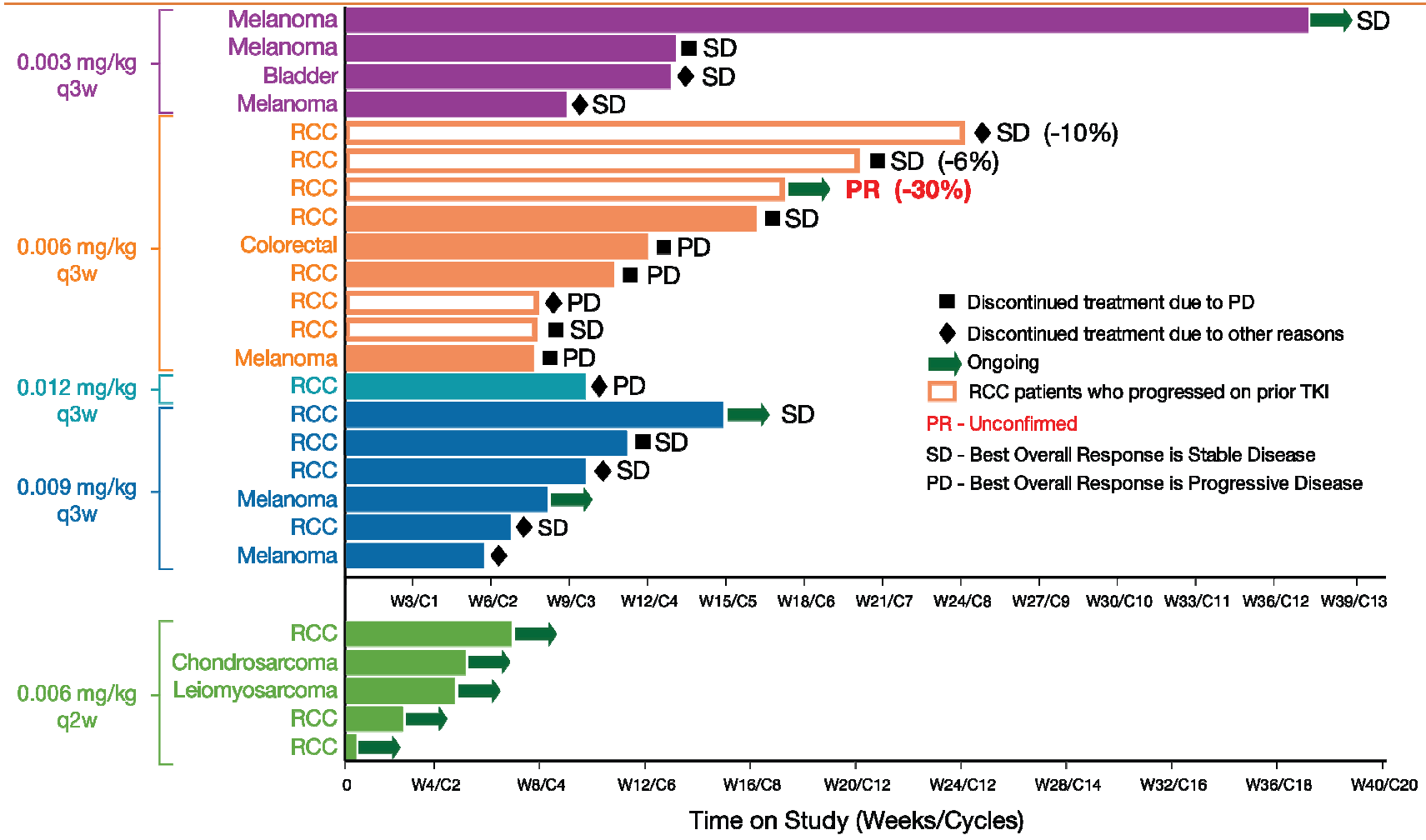
NKTR-214 Monotherapy Dose Escalation: Related Treatment Emergent AEs

	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.

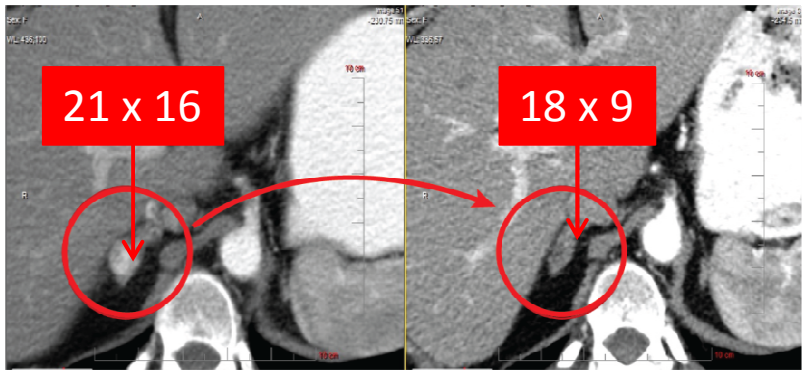
Time on Study and Best Overall Response



60-Year Old Female with RCC and uPR

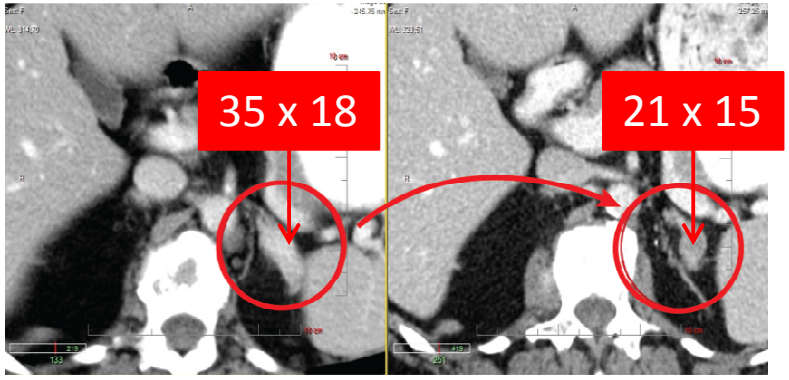
Right Adrenal

Day 1 | Week 16



Left Adrenal

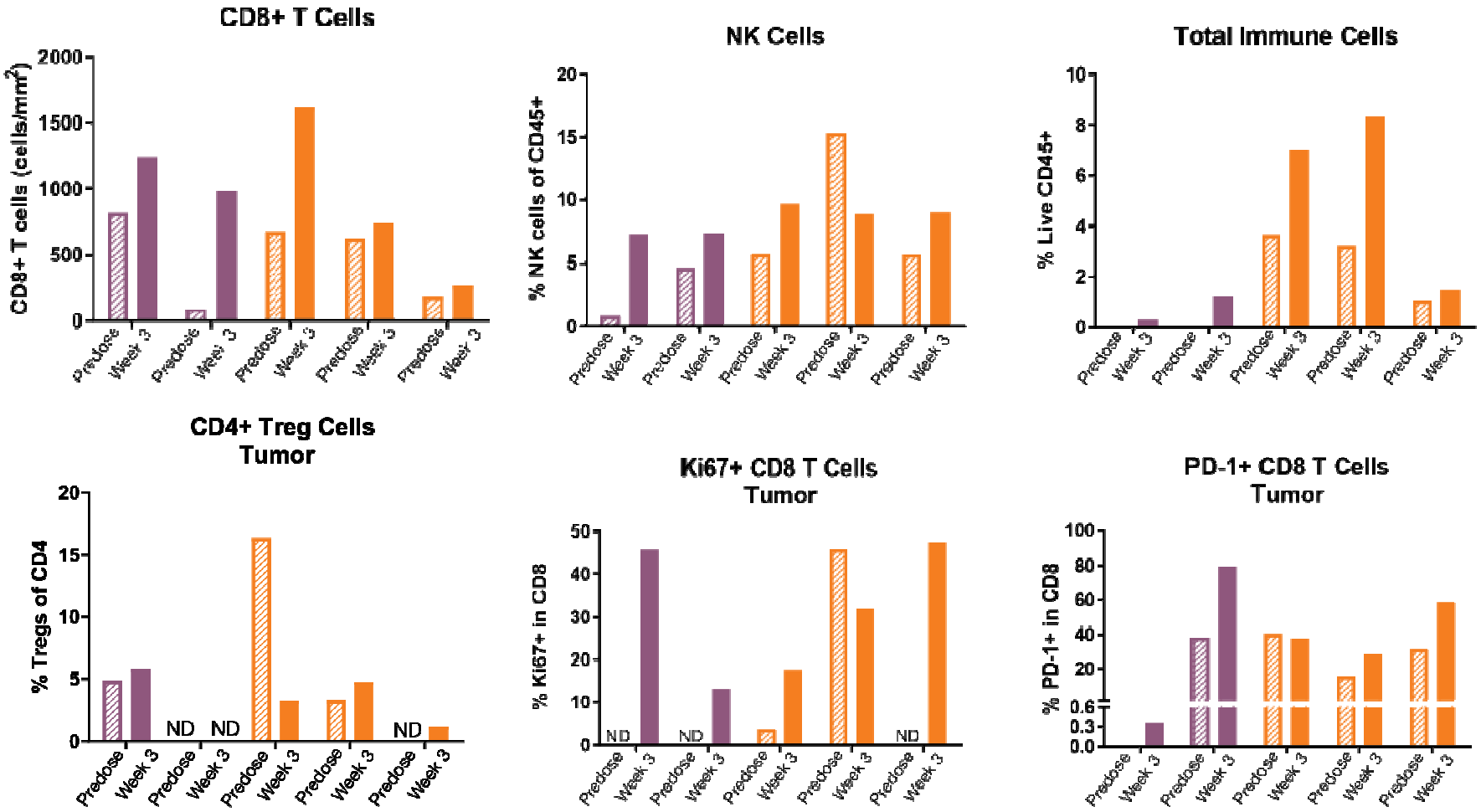
Day 1 | Week 16



- 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%

NKTR-214 Activates the Immune System in Tumor



Conclusions

- NKTR-214 has a favorable safety and tolerability profile with convenient, outpatient dosing regimen once every 2 or 3 weeks
- Encouraging evidence of clinical activity in heavily pre-treated patient population including one partial response
- 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 a sound biological basis for combination with anti-PD1 checkpoint inhibitors

Future Directions

- Combination of NKTR-214 and nivolumab is being evaluated in 5 tumor types and 7 indications:
  - Melanoma (1L, 2L relapse on I-O agent)
  - Renal cell carcinoma (2L IO-naïve and relapse on I-O agent)
  - NSCLC (2L IO-naïve)
  - Bladder (1L)
  - Triple negative breast cancer (2L IO-naïve)

Acknowledgements

The authors would like to acknowledge the contribution of patients and their families in participation of this clinical trial.

References:
1) Daud AI, Wolchok JD, Robert C, et al. *J Clin Oncol.* [Epub ahead of print] DOI:10.1200/JCO.2016.67.2477.
2) Daud AI, Loo K, Pauli ML, et al. *J Clin Invest*. 2016;126(9):3447-52.
3) Charych DH, Hoch U, Langowski JL, et al. *Clin Cancer Res*. 2016;22(3):680-90.