PROPEL: A Phase 1/2 Trial of NKTR-214 (CD122-Biased Agonist) Combined With Anti-PD-1 (Pembrolizumab) or Anti-PD-L1 (Atezolizumab) in Patients (Pts) With Advanced Solid Tumors

Daniel Cho[1], Daniel Vaena[2], Jorge M. Chaves[3], Nicholas J. Vogelzang[4], Marc Matrana[5], Matthew Riese[6], Mary Tagliaferri[7], Jonathan Zalevsky[7], Sunny Xie[7], Ute Hoch[7], Ahsan Rizwan[7], Margit Tagliaferri[7], Rabih Saab[7], Sandra Aung[7], Michael Imperiale[7], James K. Schwarz[8]

[1]New York University, New York City, NY, US; [2]West Cancer Center, Germantown, TN, US; [3]Northwest Medical Specialties, Tacoma, WA, US; [4]Comprehensive Care Centers of Nevada, Las Vegas, NV, US; [5]Ochsner Cancer Institute, New Orleans, LA; [6]Medical College of Wisconsin, Milwaukee, WI, US; [7]Nektar Therapeutics, San Francisco, CA, US; [8]University of Nebraska Medical Center, Omaha, NE, US

TPS3115

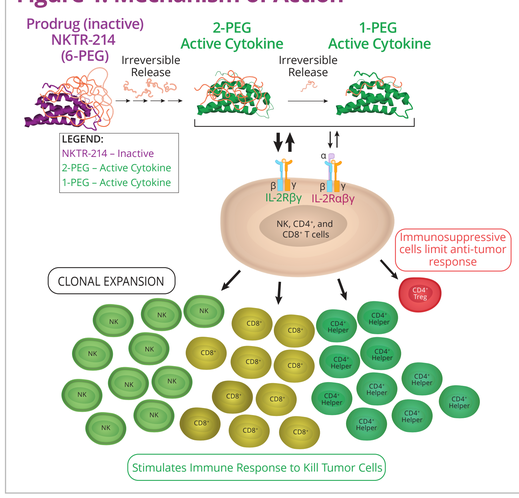
BACKGROUND

- Immune system activation with checkpoint inhibitors has proven to be an effective strategy for inhibiting tumor growth and prolonging survival[1-3]
- Anti-PD-1 and anti-PD-L1 therapies, such as pembrolizumab and atezolizumab, depend on pre-existing T cell infiltration within the tumors for optimal efficacy[4,5]
- Abundance and functional quality of tumor-infiltrating lymphocytes are positively linked with tumor response and improved survival with checkpoint inhibitors[1-5]

NKTR-214

- NKTR-214 is a CD122-biased cytokine agonist conjugated with multiple releasable chains of polyethylene glycol (PEG) designed to provide sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2R) to preferentially activate and expand effector CD8+ T and NK cells over Tregs[6] (**Figure 1**)

Figure 1. Mechanism of Action



EXCEL: NKTR-214 MONOTHERAPY (Study Completed)

- Outpatient regimen with convenient IV dosing regimen every 2 or 3 weeks
- Favorable safety and tolerability profile[7]
- No evidence of immune-mediated AEs or organ related inflammation (eg, colitis, pneumonitis, dermatitis, hepatitis, endocrinopathies)
- NKTR-214 substantially increases CD8+ T cells that were newly proliferative (Ki67+) (**Figure 2**)[8]

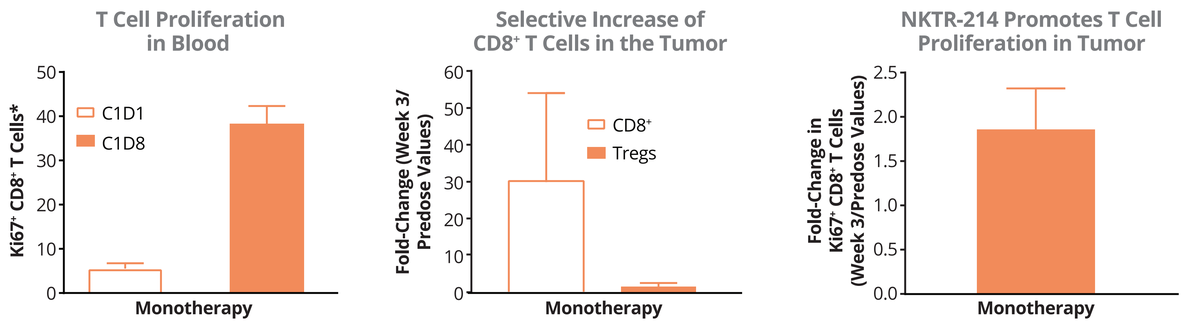
PIVOT-02: NKTR-214 PLUS NIVOLUMAB (Active and Enrolling)

- NKTR-214 plus nivolumab resulted in rapid tumor responses in patients with metastatic melanoma, non-small cell lung cancer, and renal cell carcinoma[9]
- NKTR-214 plus nivolumab is safe and tolerable and can be administered as a convenient, outpatient regimen[8]

PROPEL: NKTR-214 PLUS ATEZOLIZUMAB OR PEMBROLIZUMAB (Active and Enrolling)

- Given the early efficacy data and favorable safety profile of NKTR-214 plus nivolumab, PROPEL will evaluate the clinical benefit, safety and tolerability of NKTR-214 combined with pembrolizumab or atezolizumab

Figure 2. NKTR-214 Monotherapy Promotes T Cell Proliferation and Selectively Increases T Cells in the Tumor



*Data are expressed as %Ki67+ CD8+ T cells on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 8 (C1D8) plotted as Mean ± Standard Error

PROPEL STUDY

DESIGN

- In PROPEL (**Figure 3**), approximately 74 patients with stage III (unresectable) or stage IV melanoma, locally advanced or metastatic urothelial carcinoma (UC), or stage IV non-small cell lung cancer (NSCLC) will be enrolled
- Blood samples for PK analyses will be collected from all patients
- Systemic and tumor tissue-based pharmacodynamic effects of NKTR-214 in combination with pembrolizumab or atezolizumab will be examined
- Tumor measurements will be performed every 8 weeks ± 7 days
- Safety assessments will include AEs, clinical laboratory tests, vital signs, physical examinations, and ECGs

REFERENCES

1) Reck M, Rodríguez-Abreu D, Robinson AG, et al. *N Engl J Med.* 2016;375(19);1823-33.
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3) Rittmey A, Barlesi F, Waterkamp D, et al. *Lancet.* 2017;389(10066):255–265.
4) Daud AI, Wolchok JD, Robert C, et al. *J Clin Oncol.* 2016;67:2477.
5) Daud AI, Loo K, Pauli ML, et al. *J Clin Invest.* 2016;126(9):3447–52.
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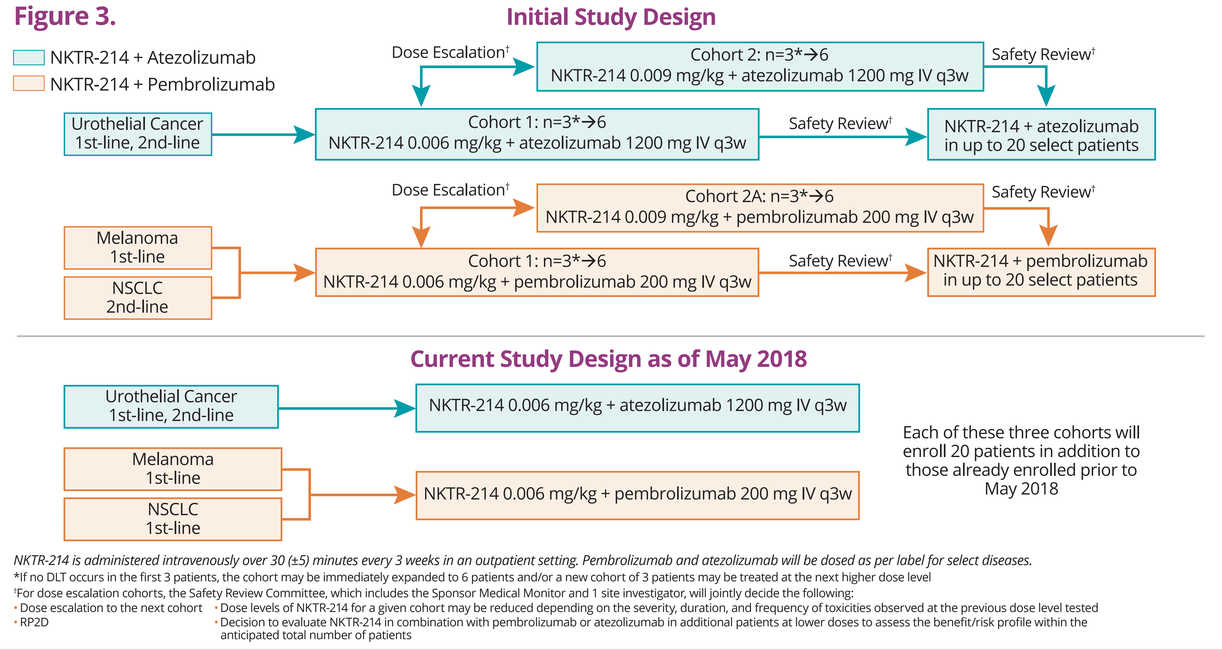
7) Bernatchez C, Bentebibel SE, Hurwitz ME, et al. Presented at ASCO 2017, Chicago, IL.
8) Nektar Therapeutics Analyst & Investor Event at 2017 ASCO Annual Meeting (2017). [online] Available at: http://ir.nektar.com/events-and-presentations/events
9) Diab A, Tannir N, Cho D, et al. Presented at SITC 2017, National Harbor, MD.

PROPEL STUDY *(continued)*

Figure 3.



NKTR-214 is administered intravenously over 30 (±5) minutes every 3 weeks in an outpatient setting. Pembrolizumab and atezolizumab will be dosed as per label for select diseases.

*If no DLT occurs in the first 3 patients, the cohort may be immediately expanded to 6 patients and/or a new cohort of 3 patients may be treated at the next higher dose level

†For dose escalation cohorts, the Safety Review Committee, which includes the Sponsor Medical Monitor and 1 site investigator, will jointly decide the following:
- Dose escalation to the next cohort
- RP2D
- Dose levels of NKTR-214 for a given cohort may be reduced depending on the severity, duration, and frequency of toxicities observed at the previous dose level tested
- Decision to evaluate NKTR-214 in combination with pembrolizumab or atezolizumab in additional patients at lower doses to assess the benefit/risk profile within the anticipated total number of patients

STUDY OBJECTIVES

Primary Outcome Measures:

- To evaluate the safety and tolerability, and define the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of NKTR-214 in combination with pembrolizumab or atezolizumab

Secondary Outcome Measures:

- To evaluate the preliminary anti-tumor activity of NKTR-214 in combination with pembrolizumab or atezolizumab by assessing the objective response rate (ORR) by RECIST 1.1
- To evaluate the preliminary efficacy of NKTR-214 in combination with pembrolizumab or atezolizumab by assessing overall survival (OS) and progression-free survival (PFS)

SELECTED ELIGIBILITY CRITERIA FOR ALL TUMOR TYPES

Key INCLUSION Criteria:

- Histologically confirmed stage III (unresectable) or stage IV melanoma (pembrolizumab only), stage IV NSCLC (pembrolizumab only), or locally advanced or metastatic urothelial carcinoma (atezolizumab only)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Measurable disease per RECIST 1.1
- Demonstrated adequate organ function within 28 days of treatment initiation
- Life expectancy > 12 weeks as determined by the Investigator
- Sample of fresh baseline tumor biopsies is required. Archival tumor tissue and may be used for PD-L1 status
- Palliative radiotherapy must have been completed > 14 days before administration of first dose of study drug(s)

Key EXCLUSION Criteria:

- Use of an investigational agent or device within 28 days before administration of first dose of study drug
- Prior interleukin-2 (IL-2) therapy
- Prior immune-oncology regimens
- Females who are currently pregnant or breastfeeding
- Active, known or suspected autoimmune disease
- Active malignancy not related to the current diagnosed malignancy
- Stable or active brain metastases
- Uveal melanoma
- History of organ transplant that requires use of immune suppressive agents
- Evidence of clinically significant interstitial lung disease or active noninfectious pneumonitis
- Prior surgery or radiotherapy within 14 days of initiating study drug
- > 2 antihypertensive medications for management of hypertension (including diuretics)

INCLUSION CRITERIA FOR DISEASE-SPECIFIC TUMOR TYPES

Tumor Type	Line of Treatment	PD-L1 Status	Atezolizumab*	Pembrolizumab*
Melanoma	1st	Any		X
NSCLC	1st	≥ 50%		X
Urothelial Carcinoma	1st	Any	X	
	2nd	Any	X	

Treatment is "on label"

STATUS

- Safety has been established at a NKTR-214 0.006 mg/kg dose for both cohorts
- Dose escalation is closed for both combinations. A maximal NKTR-214 dose of 0.006 mg/kg will be implemented for both cohorts based on the PIVOT study RP2D, to maintain consistency across the NKTR-214 and checkpoint inhibitor combination studies
- Patients are currently enrolling into two cohorts
  - NKTR-214 0.006 mg/kg + Atezolizumab 1200 mg
  - NKTR-214 0.006 mg/kg + Pembrolizumab 200 mg
- Sites are currently enrolling in the United States
- For participating trial sites, please visit https://clinicaltrials.gov, and search NCT03138889

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