Phase 1b: Preliminary clinical activity and immune activation for NKTR-262 [TLR 7/8 agonist] plus bempegaldesleukin (NKTR-214) [CD122-biased agonist] in patients (pts) with locally advanced or metastatic solid tumors (REVEAL phase 1b/2 trial)

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The University of Texas MD Anderson Cancer Center, Houston, TX; Nektar Therapeutics, San Francisco, CA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; University of Texas Southwestern Medical Center, Dallas, TX; Winship Cancer Institute of Emory University; University of Minnesota Masonic Cancer Center, Minneapolis, MN; Mayo Clinic, Rochester, MN; HonorHealth Research Institute, Scottsdale, AZ; Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR

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Presenter Disclosure Information

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

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NKTR-262 plus Bempegaldesleukin: Targeting the Innate and Adaptive Immune Response

- NKTR-262 is a novel small molecule agonist of toll-like receptors (TLRs) 7/8. NKTR-262 is given by intratumoral injection and designed to be retained in the tumor micro-environment and activate antigen-presenting cells (APC), such as dendritic cells, to prime new antigen-specific cytotoxic T cells
- Bempegaldesleukin (NKTR-214) is a CD122-preferential IL-2 pathway agonist that increases CD8+ T cells and NK cells in the tumor microenvironment[1]
- Combination of NKTR-262 and bempegaldesleukin led to synergistic activation of both the innate and adaptive anti-tumor immune response and resulted in abscopal responses in preclinical models[2]
- The Phase 1b/2 REVEAL study to evaluate NKTR-262 plus bempegaldesleukin is currently enrolling patients with metastatic solid tumors in its dose-escalation stage (NCT03435640)

1. Journal for ImmunoTherapy of Cancer 2017, 5(Suppl 2):P77; 2. Journal for ImmunoTherapy of Cancer 2017, 5(Suppl 2):P275

NKTR-262 plus Bempegaldesleukin: Targeting the Innate and Adaptive Immune Response

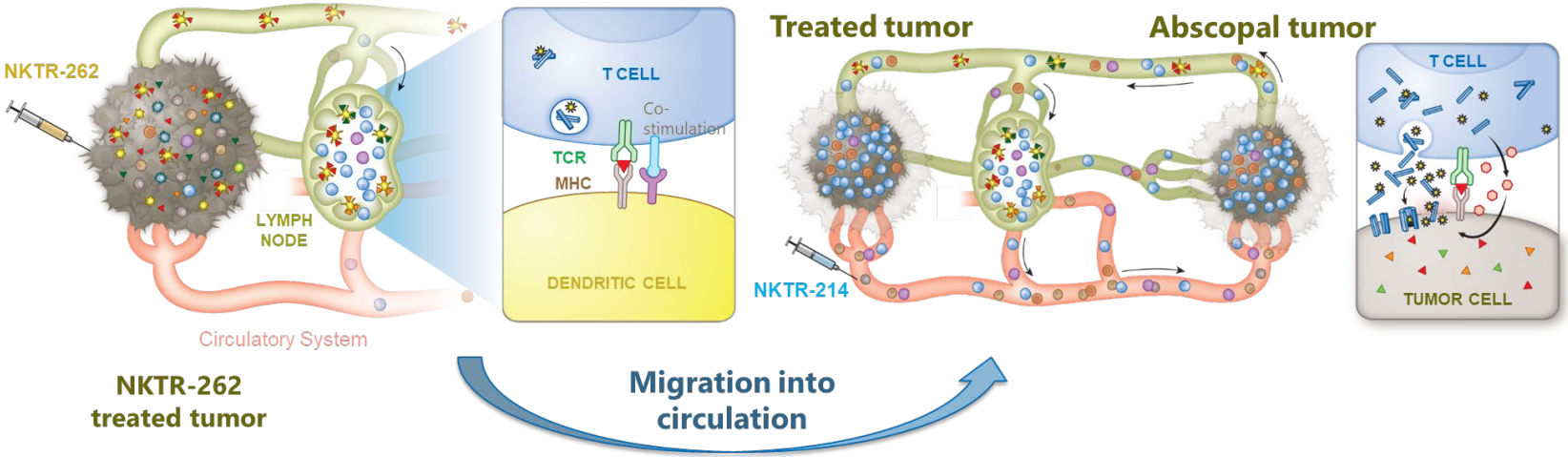
PRIMING
with NKTR-262

Enhanced antigen presentation and T cell priming in lymph node

BOOSTING
with bempegaldesleukin

Expansion of circulatory antitumor CD8 T cells and tumor infiltration

Tumor killing



REVEAL: NKTR-262 + Bempegaldesleukin Doublet Ongoing Dose-Escalation Portion of Study (Phase 1b)

Patient Eligibility Criteria for Dose Escalation (Phase 1b):

- Patients with locally advanced or metastatic solid tumors and **relapsed/refractory** to all therapies known to confer any clinical benefit to their disease

Objectives for Dose Escalation:

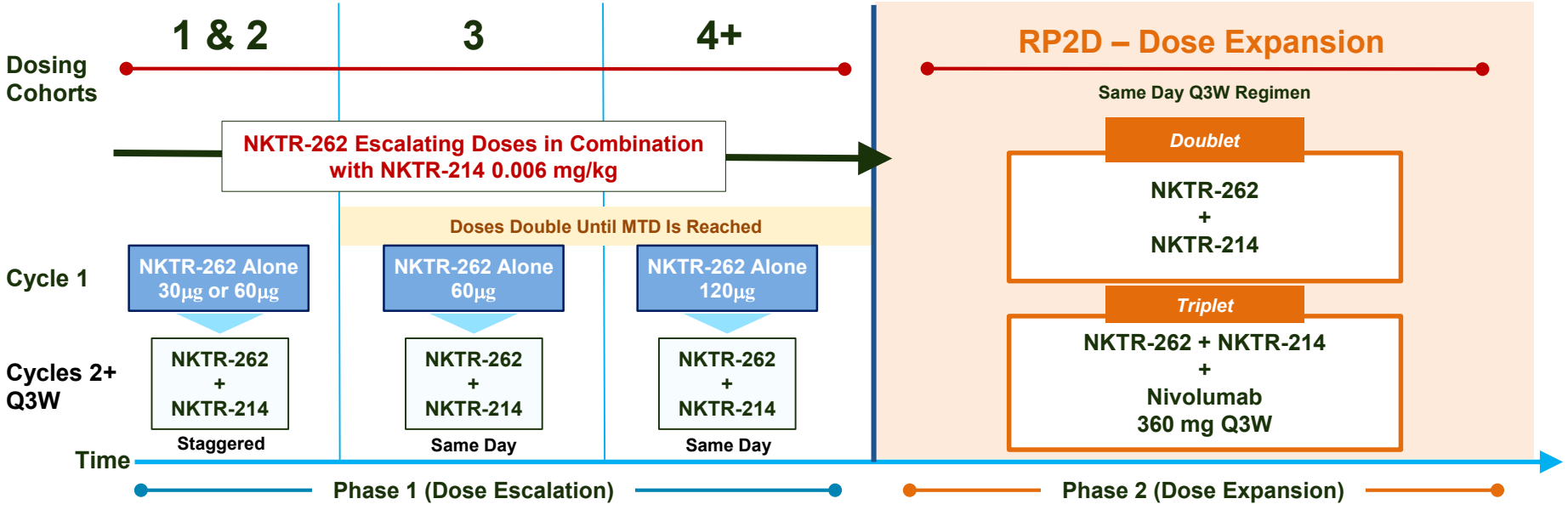
- Phase 1b: Evaluate safety and determine recommended Phase 2 dose (RP2D) of doublet of NKTR-262+NKTR-214
- Phase 1b: Evaluate correlative biomarkers for NKTR-262 and bempegaldesleukin
- Phase 1b/2: Assess anti-tumor activity and response by RECIST 1.1 (i.e., abscopal responses)

Administration of Doublet (Q3W Dose Regimen):

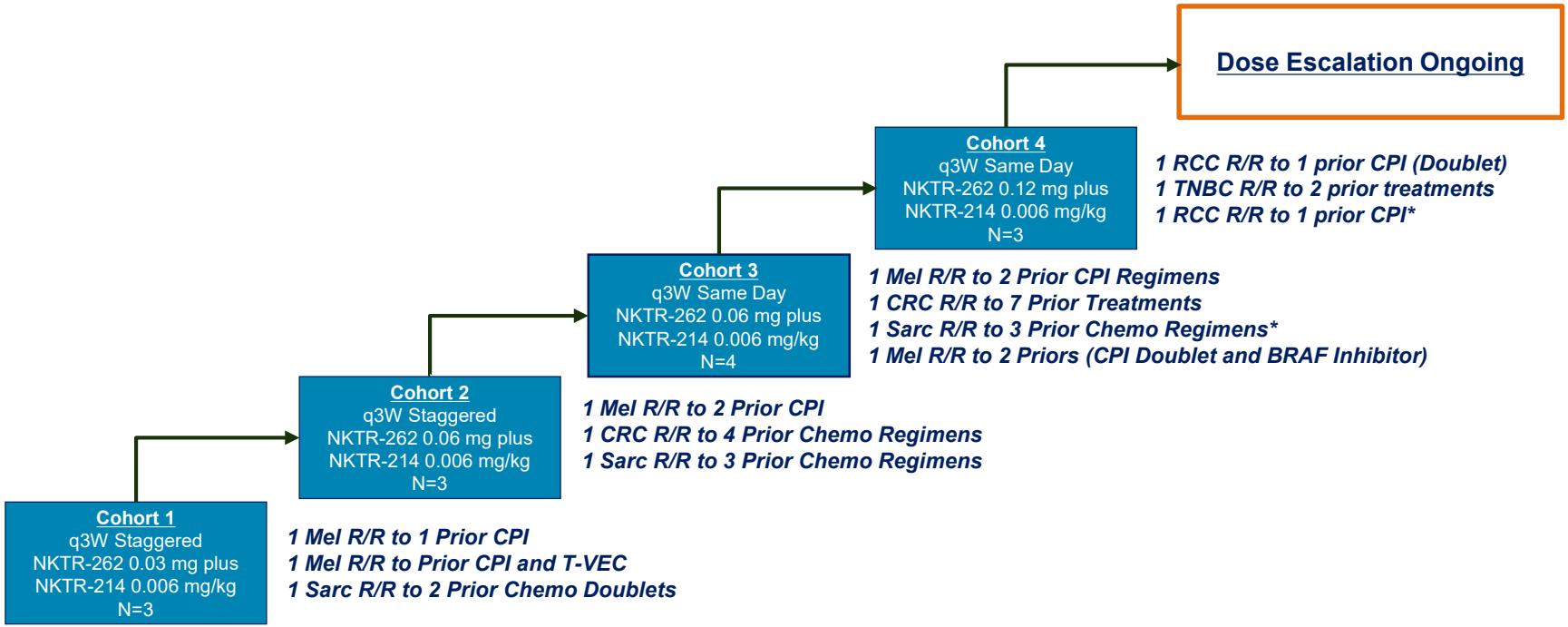
- Intratumoral (IT) NKTR-262 Q3W; starting dose 0.03 mg
- During dose escalation:
  - Cycle 1: NKTR-262 IT was administered in Cycle 1 to assess single agent safety
  - Cycle 2 and beyond: NKTR-214 fixed dose of 0.006 mg/kg IV Q3W is combined with NKTR-262 IT Q3W
- NKTR-262 injected lesions (up to two) must be between 20 mm and 90 mm in diameter for IT injection
- Target lesions chosen for RECIST response assessment must be lesions not injected with NKTR-262

REVEAL Phase 1/2 Study Design to Evaluate Combination of NKTR-262 Plus NKTR-214

Melanoma, Merkel Cell, Renal, Urothelial, Triple Negative Breast Cancer, Ovarian, Colorectal, Sarcoma



Dose Escalation: Patient Disease Characteristics (n=13) as of January 23, 2019



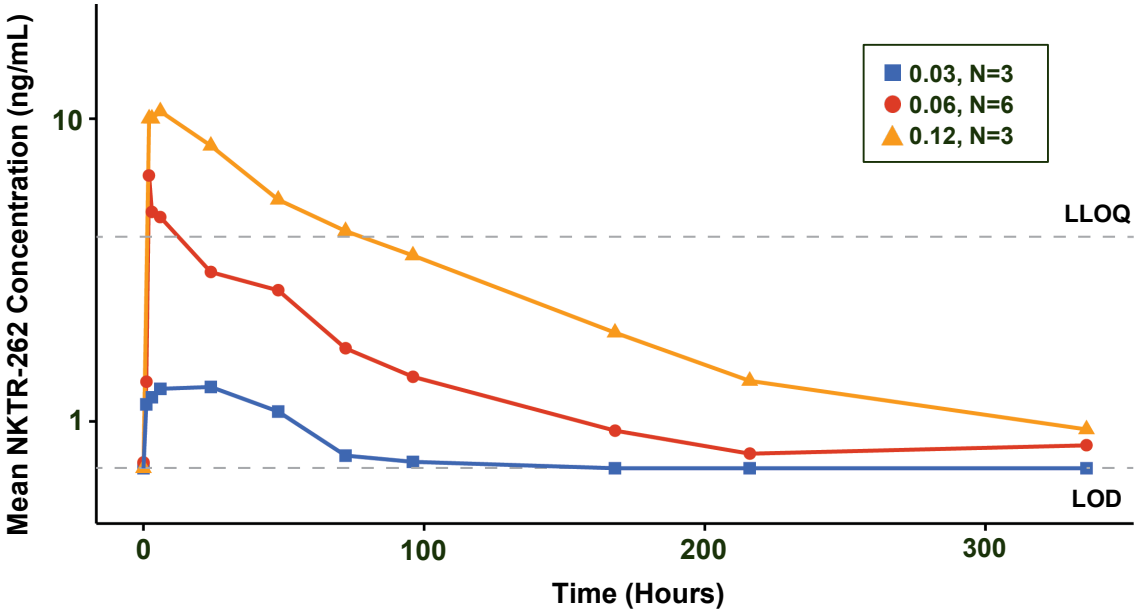
CPI: checkpoint inhibitor; CRC: colorectal cancer; Mel: melanoma; MCC: Merkel cell carcinoma; RCC: renal cell carcinoma; R/R relapsed/refractory; Sarc: sarcoma; TNBC: triple negative breast cancer
* Not efficacy evaluable. Efficacy evaluable defined per protocol as having one post baseline scan.

Safety Profile of NKTR-262 and Bempegaldesleukin as of January 23, 2019

- Most common treatment-related adverse events (TRAEs) G1-2 were transient flu-like symptoms (69.2%), rash (46.2%), fatigue (46.2%), pruritus (46.2%) and nausea (30.8%)
- One patient (7.7%) with Grade 3 TRAEs of maculopapular rash and leukocytosis*
- No Grade 4-5 TRAEs
- Most TRAEs are attributable to bempegaldesleukin
- No immune-mediated AEs
- No study discontinuations due to TRAEs

***One G3 TRAE of leukocytosis was later updated to unrelated status after January 23, 2019**

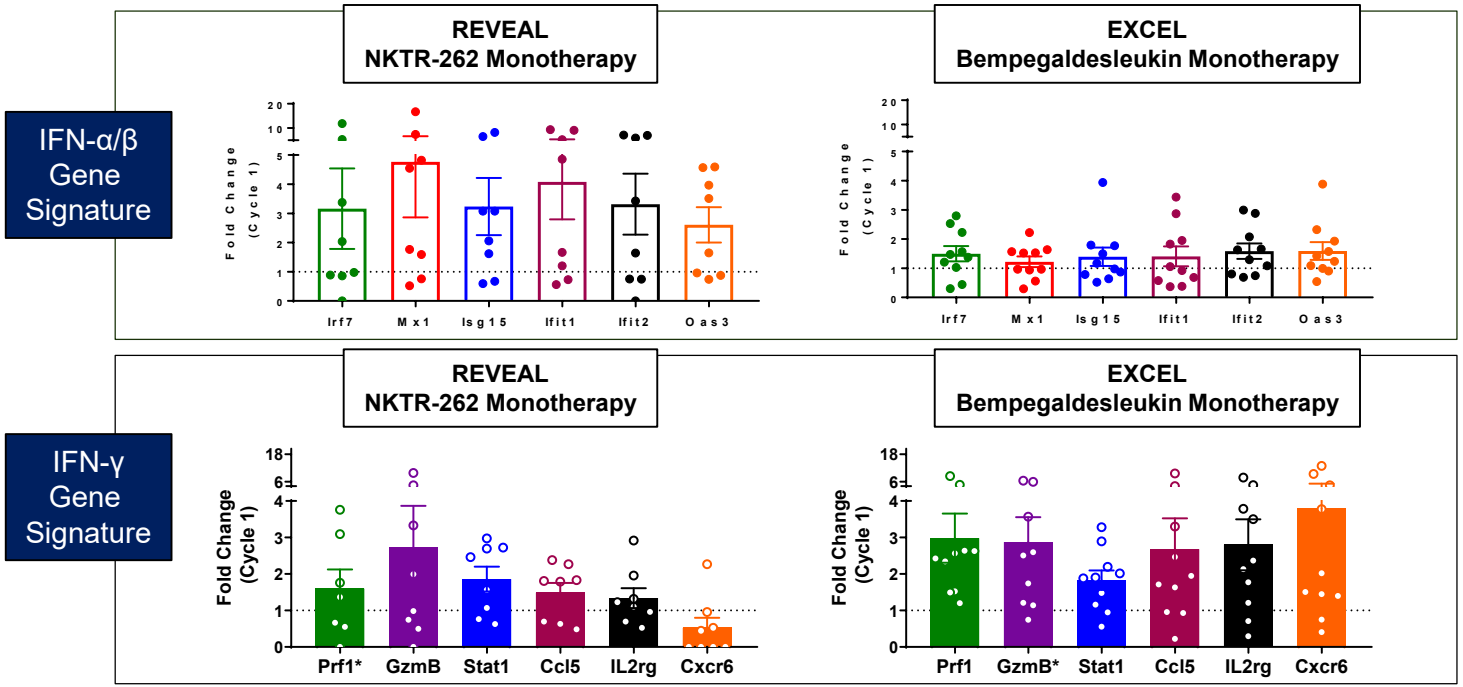
Plasma Pharmacokinetic Profile Across Escalating Dose Levels of NKTR-262



- Plasma levels of NKTR-262 increased with escalating doses
- Concentrations of TLR 7/8 agonist resiquimod (R848) released from NKTR-262 were below the limit of quantification at all dose levels

LOD: Limit of detection; LLOQ: Lower limit of quantification. N= 12, excludes one patient from 0.06 mg dose group, an outlier with 10-fold higher PK exposure. Mean R848 concentrations are below the limit of quantification for all dose levels. LLOQ for NKTR-262 is 4.2 ng/mL and LOD is 0.7 ng/mL. For NKTR-262, values below LOD are imputed to be LOD (0.7 ng/mL). For resiquimod (R848), LLOQ is 0.1 ng/mL and LOD is 0.007 ng/mL.

NKTR-262 and Bempegaldesleukin Promote Comprehensive Activation of the Immune System in the Tumor Microenvironment

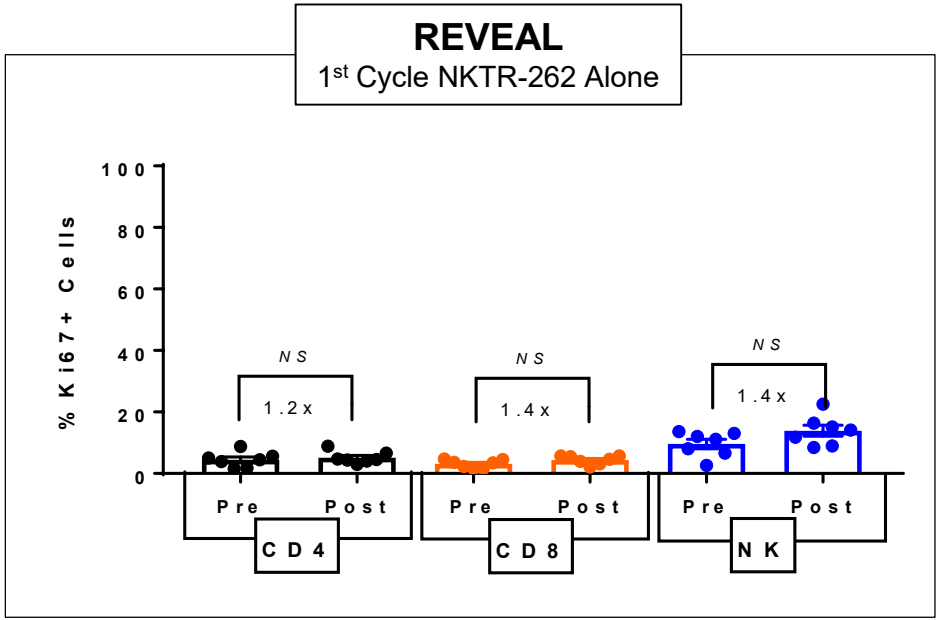


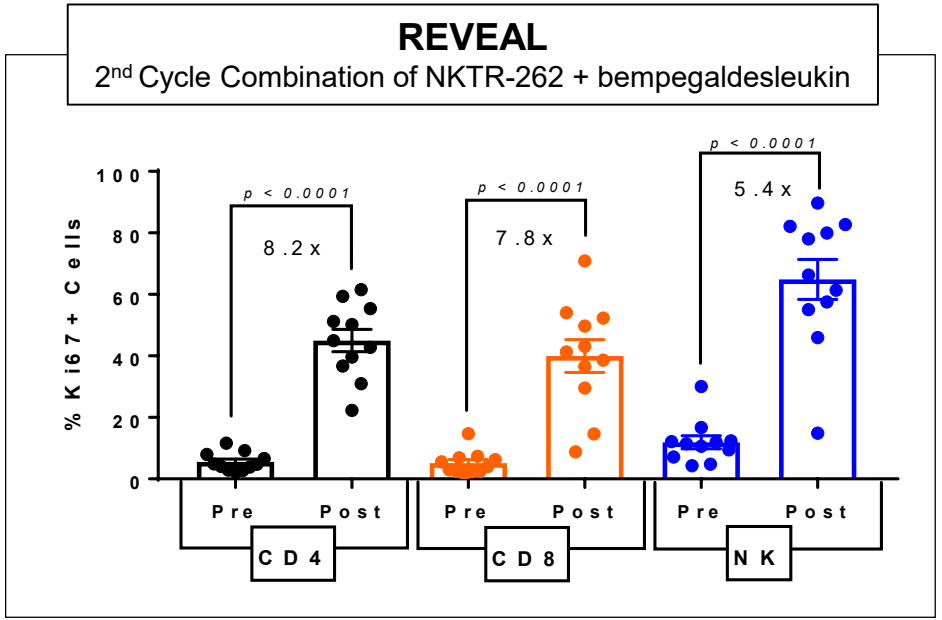
NKTR-262 promotes local activation of the innate immune system

Bempegaldesleukin promotes activation of the adaptive immune system

Intratumoral NKTR-262 (0.03mg – 0.12mg, N=8) gene expression was compared between pre-dose and 24 hrs post-dose tumors biopsies in Cycle 1 (NKTR-262 monotherapy, REVEAL Study). IV bempegaldesleukin (0.003 - 0.012 mg/kg, N=10) gene expression was compared between pre-dose and 3 wks post-dose tumor biopsies in Cycle 1 (bepegaldesleukin monotherapy, EXCEL Study). Genetic analysis conducted using the nCounter platform from Nanostring Technologies. *One patient excluded from analysis because baseline value is 0 and fold change cannot be calculated.

Bempegaldesleukin Drives Systemic Proliferation of Lymphocytes to Activate the Adaptive Immune System





Whole blood was collected pre and post-treatment (8-10 days) after the first cycle (NKTR-262 alone, N=7) and after the second cycle (NKTR-262 + bempegaldesleukin, N=11) of treatment in REVEAL. Lymphocytes were enumerated and stained for Ki67 using flow cytometry. Results presented as proportion (%) of each cell population and fold changes calculated based on pre-treatment values. T-test used to calculate p values.

Best Overall Response by RECIST 1.1 as of January 23, 2019 (Doublet Dose Escalation)

	Totals
Total Evaluable*	**11**
ORR (CR+PR)	**2**
CR	0
PR	2
SD	3
DCR (CR+PR+SD)	**5 (45.5%)**
PD	6 (55.5%)

- 2/5 Stage IV melanoma patients who progressed on prior CPI therapies experienced confirmed partial responses (-100%) and (-50%)
- 2/2 heavily pre-treated Stage IV leiomyosarcoma patients experienced stable disease as best response
- 1/1 heavily pre-treated TNBC patient experienced stable disease as best response

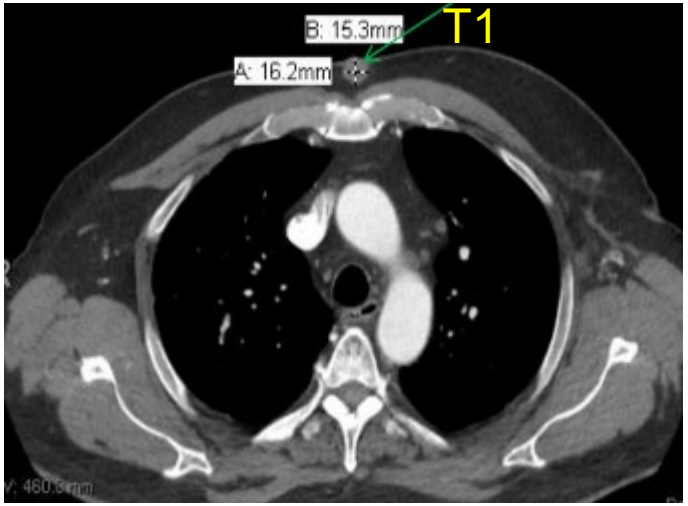
CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease
* Patients with at least 1 post-baseline scan.

Case 1: Stage IV Melanoma IO Refractory
Confirmed Partial Response (-100%)

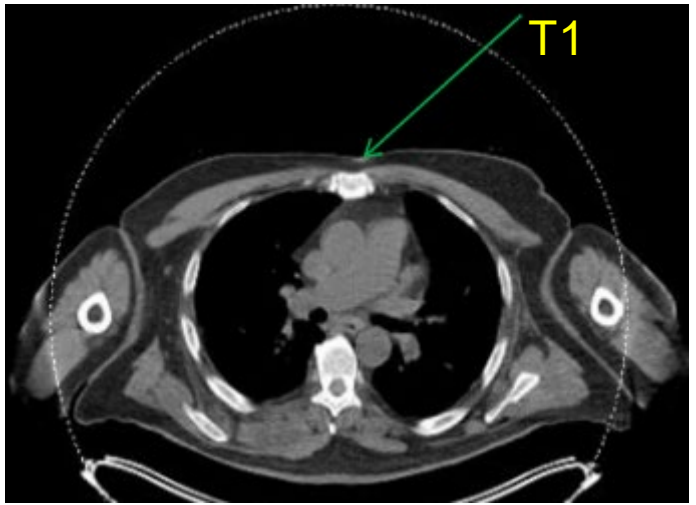
- 63-year-old male diagnosed with metastatic melanoma 2/25/17
- Metastatic disease to chest wall (multiple lesions), brain (M1d)
- BRAF wild type
- Best Response of PD to Prior Cancer Treatment
  - May 2017 - July 2017: Treated with pembrolizumab (AE disc.) with BOR: PD
  - Complications with pneumonitis limited further CPI treatment
  - January 2018 – March 2018: Treated with IMLYGIC™(T-VEC) with Radiation; BOR: PD
- NKTR-262 Intratumoral Injection Site: Right posterior chest wall (Injected non-target lesion 70 mm @ Baseline)
- Partial Response at scan 2 and confirmed at scan 3 (on study for 34 weeks)

Case 1: Stage IV Melanoma IO Refractory
Confirmed Partial Response (-100%)

Baseline

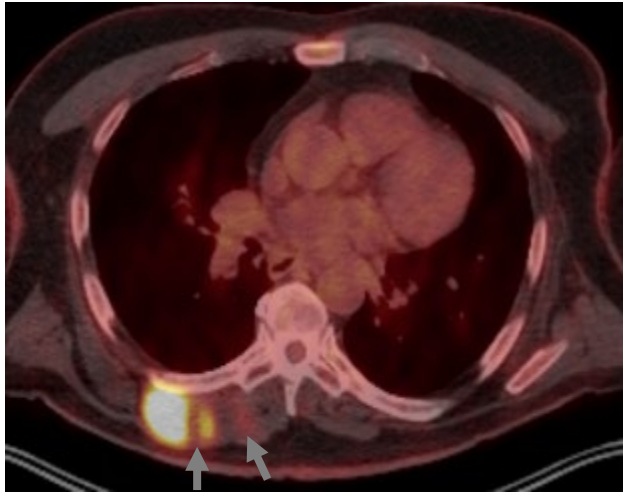


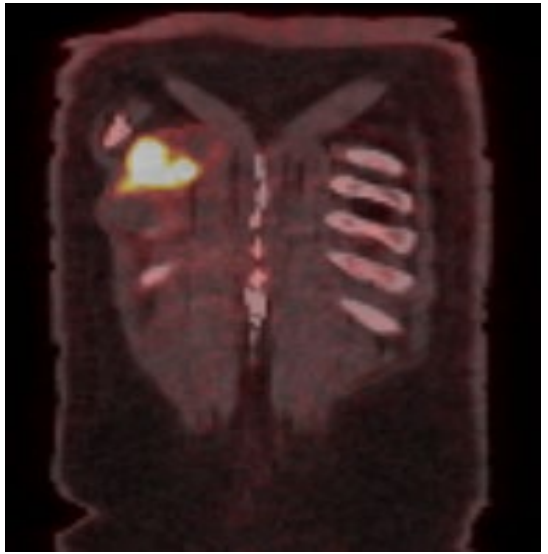
Scan 3



	Lesion Description	Baseline	Scan 1	Scan 2	Scan 3
Target Lesions	Exam/Scan Date	2018-04-13	2018-07-02	2018-09-12	2018-10-11
	T01: Chest Wall	16	18	11	0
	Sum of the diameters (% Change from Baseline)	16	18 (12.5)	11 (-31.3)	0 (-100.0)
Overall Response	RECIST 1.1 from Site		Stable Disease	Partial Response	Partial Response

Case 1: Stage IV Melanoma IO Refractory
Confirmed Partial Response (-100%)



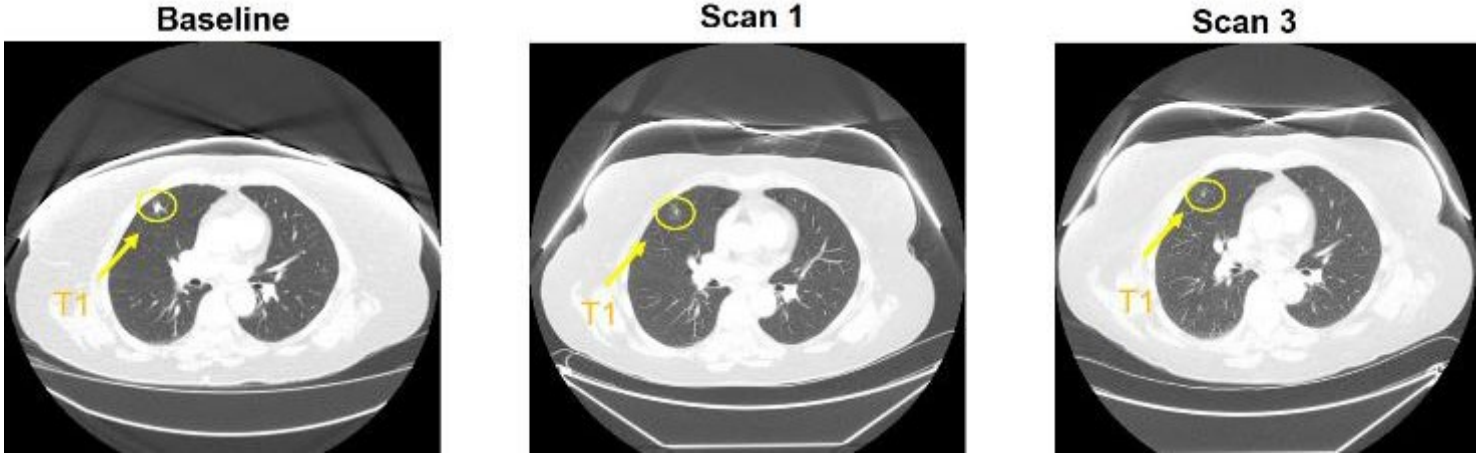


- Non-target injected lesions on PET scan showed multiple areas of fibrosis, necrosis and melanophages upon pathology analysis (October 18, 2018)

Case 2: Stage IV Melanoma IO Refractory Confirmed Partial Response (-50%)

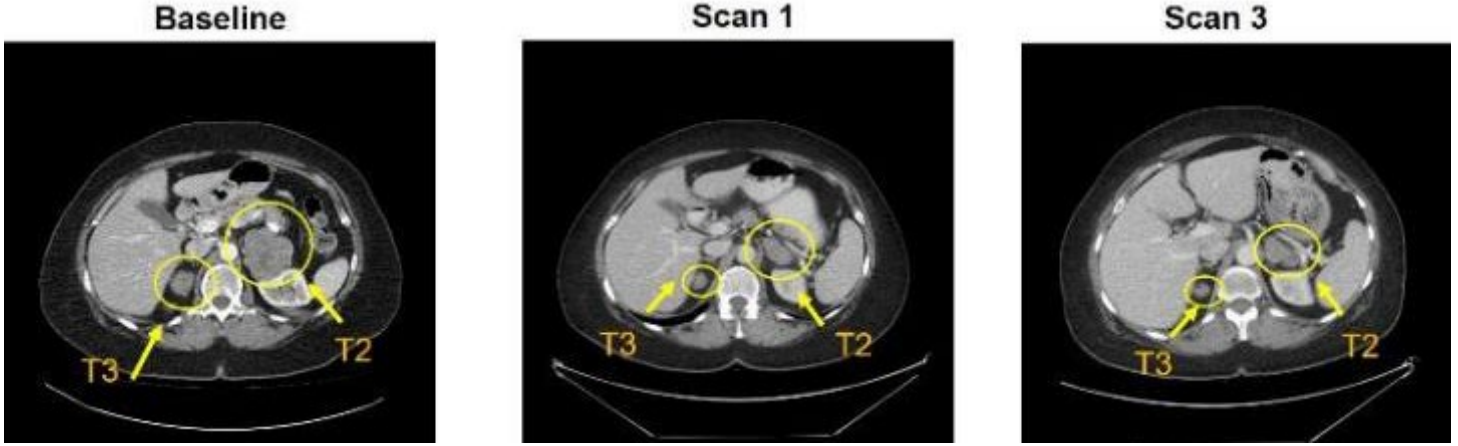
- 71-year-old female diagnosed with metastatic melanoma 2/15/18
- Metastatic disease (M1c) to the lung, adrenal glands, bone, lymph nodes and soft tissue
- LDH high, PD-L1 negative at baseline, BRAF wild type
- Best Response of PD on prior CPI Treatment Regimens:
  - March 2018 - May 2018: Treated with nivolumab with Best Response of PD
  - May 2018 - July 2018: Treated with ipilimumab + nivolumab with Best Response of PD
- Enrolled in REVEAL: received first NKTR-262 IT injection on September 1, 2018
- Non-injected target lesions had tumor reductions ranging between 36%-100%; now confirmed PR
- NKTR-262 IT Injection Site: Left Inguinal Lymph Node became too small to inject on Cycle 5 (Injected Non-Target Lesions 22 mm @ Baseline)
- Response and treatment ongoing with IV bempegaldesleukin (NKTR-214) monotherapy (on study for 18 weeks as of data cut-off)

Case 2: Stage IV Melanoma CPI-Refractory Patient Confirmed Partial Response (-50%) with Treatment Ongoing



	Lesion Description	Baseline	Scan 1	Scan 2	Scan 3
Target Lesions (Non Injected Lesions)	Exam/Scan Date	2018-08-29	2018-11-05	2018-12-10	2019-01-07
	Target Lesion 1 (T1): Right Anterior Lung	11	4	0	0
	Target Lesion 2 (T2): Left Adrenal Gland	55	35	37	39
	Target Lesion 3 (T3): Right Adrenal Gland	25	18	17	17
	Target Lesion 4 (T4): Right Lateral Intra-Abdominal	21	12	4	0
	Sum of the Diameters (% Change from Baseline)	112	69 (-38.3%)	58 (-48%)	56 (-50%)
Overall Response	RECIST 1.1		Partial Response	Partial Response	Partial Response

Case 2: Stage IV Melanoma CPI-Refractory Patient Confirmed Partial Response (-50%) with Treatment Ongoing



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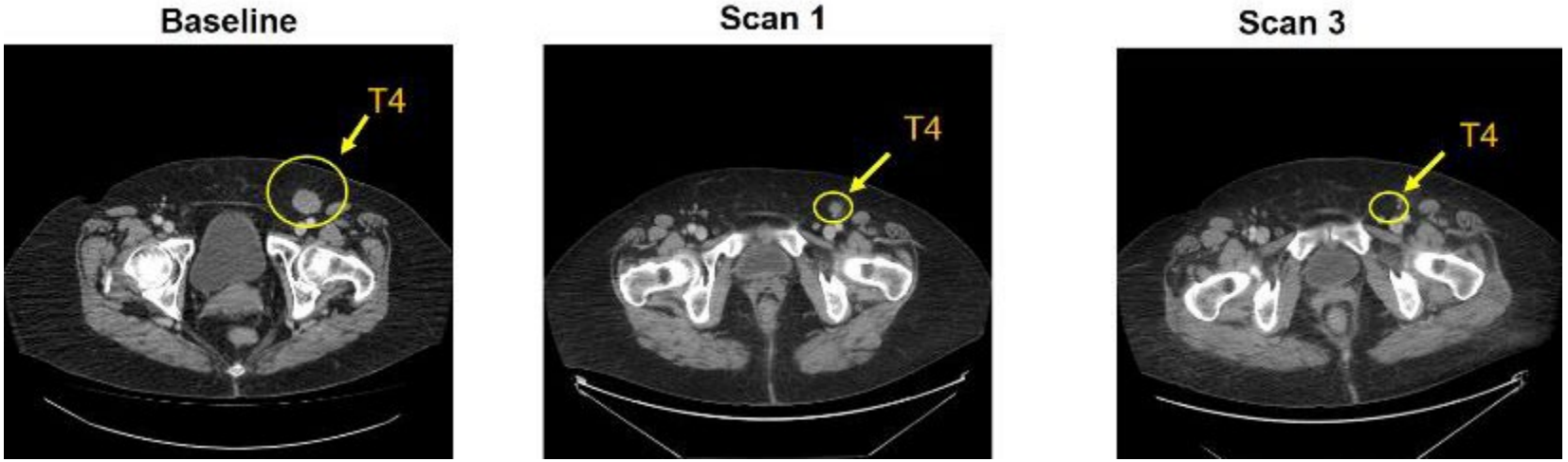

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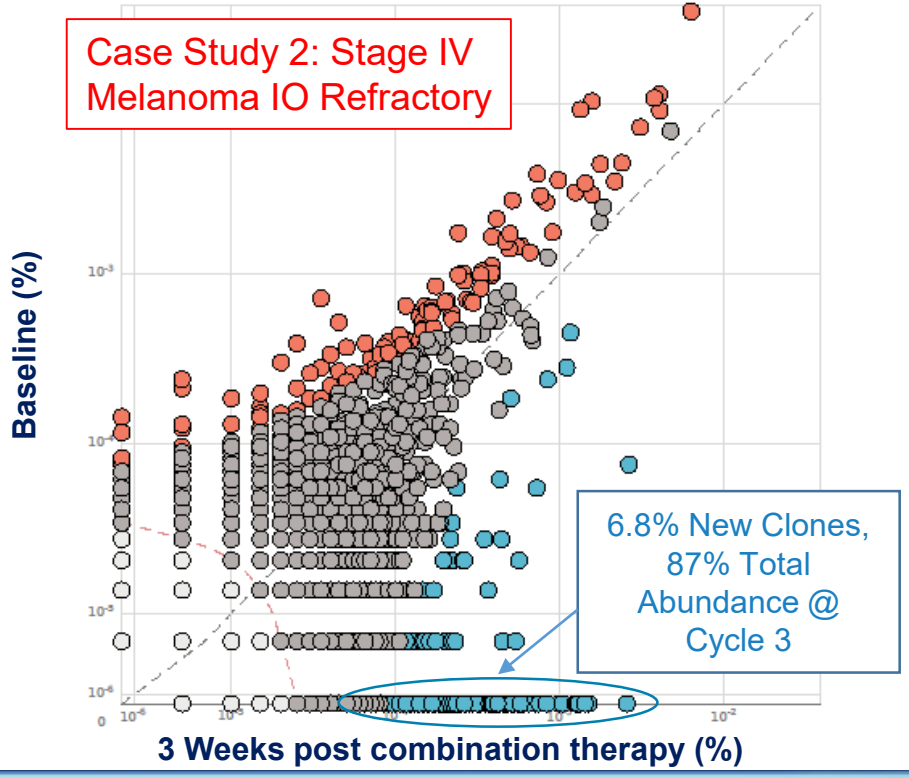
Overall Response	RECIST 1.1		Partial Response	Partial Response	Partial Response

The Combination of NKTR-262 and Bempegaldesleukin Promotes Rapid Clonal Expansion in Blood



- TCR Repertoire change after a single cycle (21 days) of combination treatment
  - 4/5 patients (80%) had higher clonal expansion
  - 4/5 patients (80%) had reduced Morisita-Horn Index value indicating TCR repertoire difference pre- and post-treatment

Baseline > Week 3 | Not statistically significant
Week 3 > Baseline | Excluded for low abundance

Whole blood was processed to extract nucleic acid and used for TCR repertoire analysis using immunoSEQ. Five patients with matched Baseline and 3 Weeks post therapy for the NKTR-262 + bempegaldesleukin combination were available as of 23Jan2019 and are included in the analysis. TCR Clones more abundant at Baseline are shown in red and clones more abundant at Week 3 are shown in blue. Dark grey dots are not significant between timepoints and light gray dots are excluded for low abundance. The gray dashed line lists frequency equality and the red dashed line identifies the population used for statistical comparison. New T Cell infiltrates are shown in the oval

REVEAL Preliminary Conclusions from Ongoing Dose-Escalation

Safety and Tolerability:

- NKTR-262 thus far combined with fixed dose of bempegaldesleukin (NKTR-214) was well tolerated
- No treatment-related SAEs or DLTs
- MTD not reached and dose escalation continuing
- NKTR-262 + bempegaldesleukin TRAEs were transient, characterized by Grade 1-2 flu-like symptoms that were manageable with over-the-counter medications
- No evidence of an increased incidence or severity of TRAEs over bempegaldesleukin monotherapy

Initial Pharmacokinetic, Biomarker and Efficacy:

- PK exposure increased with dose
- Systemic (adaptive) and local (innate) activation of the immune system with the combination of NKTR-262 + bempegaldesleukin
- TCR repertoire change detected in patients after a single cycle treatment with NKTR-262 + bempegaldesleukin
- Early evidence of clinical activity in first 11 patients evaluable for efficacy in the ongoing Phase 1 dose escalation in heavily pretreated patients

Acknowledgements

A special thank you is extended to the patients, their families and all study staff who are participating and have participated in the REVEAL study

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