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SMARTER MEDICINE™

# 2019 ASCO-SITC

Nektar Therapeutics  
Investor & Analyst Call

March 1, 2019

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# Today's Speakers



**Dr. Adi Diab**

Assistant Professor  
of Melanoma  
Medical Oncology  
MD Anderson



**Dr. Mary Tagliaferri**

Chief Medical Officer  
Nektar Therapeutics



**Dr. Jonathan Zalevsky**

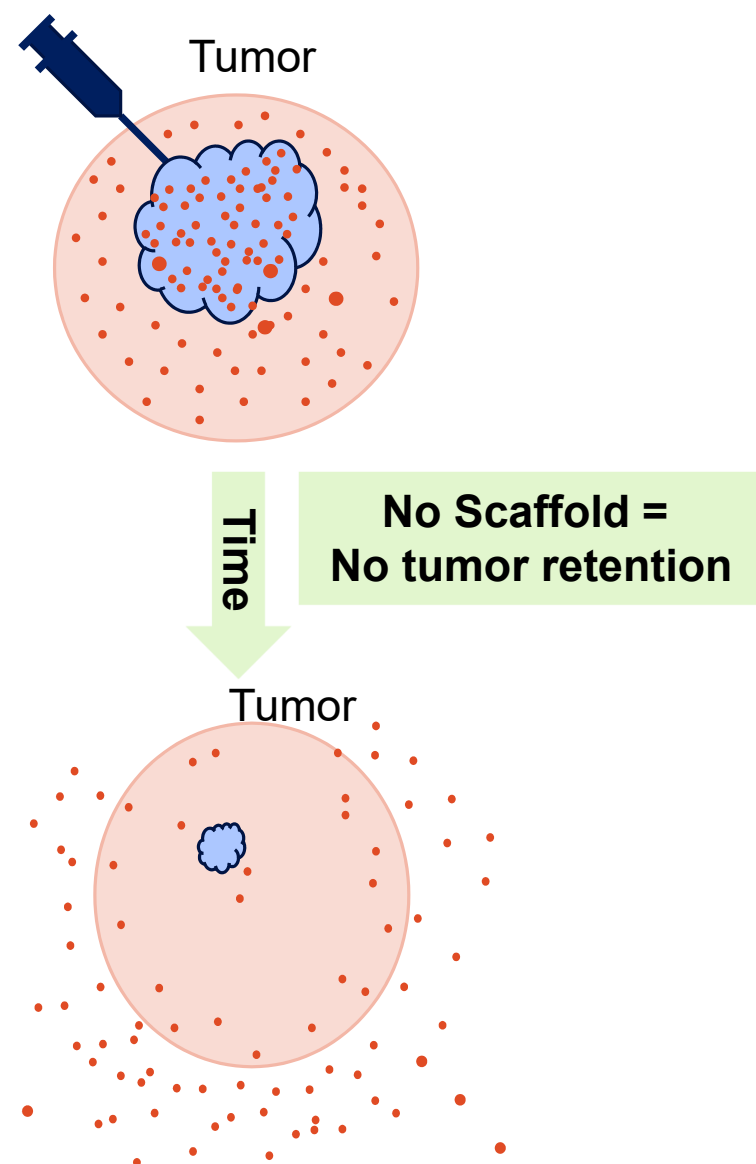
Chief Scientific Officer  
Nektar Therapeutics





# Today's Agenda

- Jonathan Zalevsky Ph.D., Nektar Therapeutics
  - Introduction to NKTR-262
  - Overview of the REVEAL Study of NKTR-262 plus bempeg
  - Biomarker and Translational Medicine from Ongoing Dose Escalation Stage of REVEAL Study
- Mary Tagliaferri M.D., Nektar Therapeutics
  - Clinical Safety from REVEAL
  - Clinical Activity from Ongoing Dose-escalation Stage of REVEAL Study
- Q&A Panel with Dr. Adi Diab, MD Anderson Cancer Center

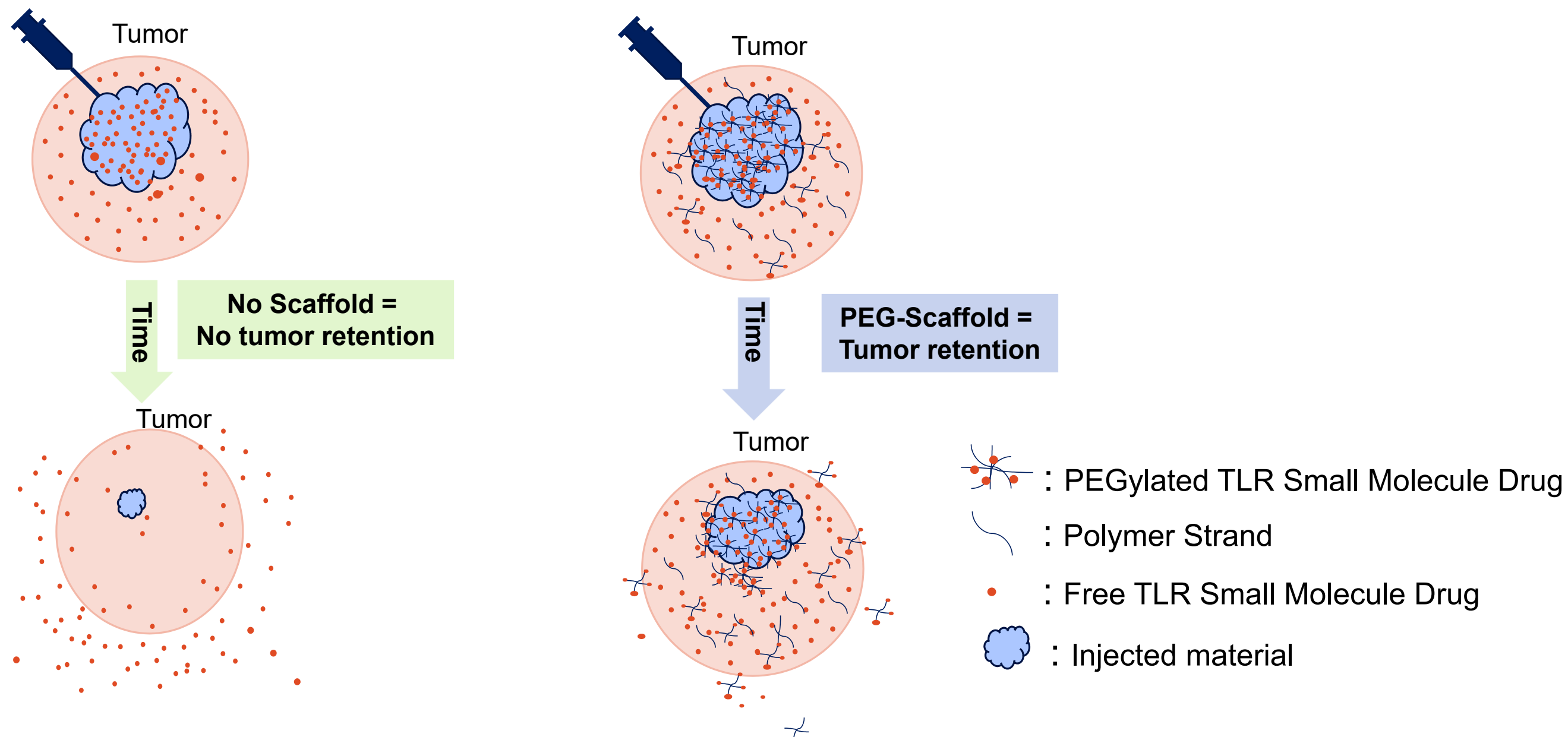


# NKTR-262 Design Strategy: PEGylation Will Keep Scaffold in Tumor And Reduces Systemic Exposure



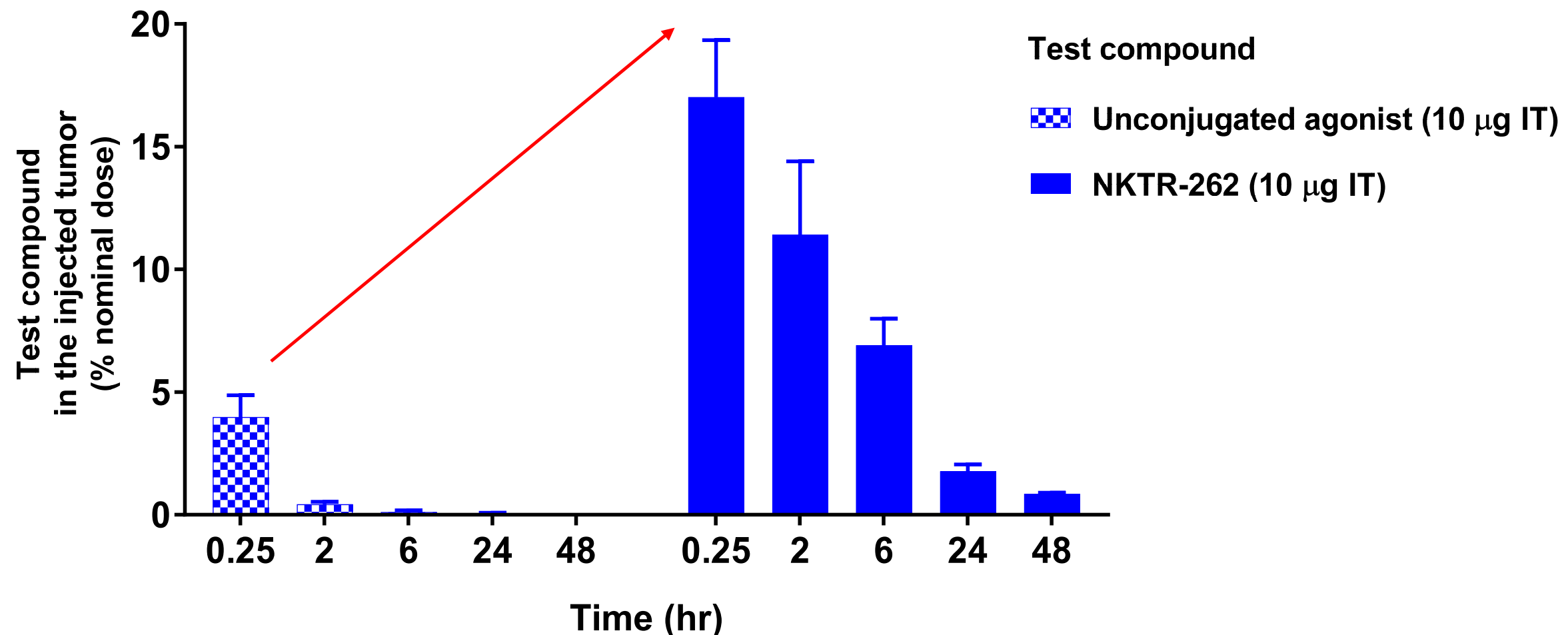
-  : PEGylated TLR Small Molecule Drug
-  : Polymer Strand
-  : Free TLR Small Molecule Drug
-  : Injected material

# NKTR-262 Design Strategy: PEGylation Will Keep Scaffold in Tumor And Reduces Systemic Exposure



# NKTR-262 is Retained More Effectively in Injected Tumors Compared to Unconjugated TLR7/8 Agonist

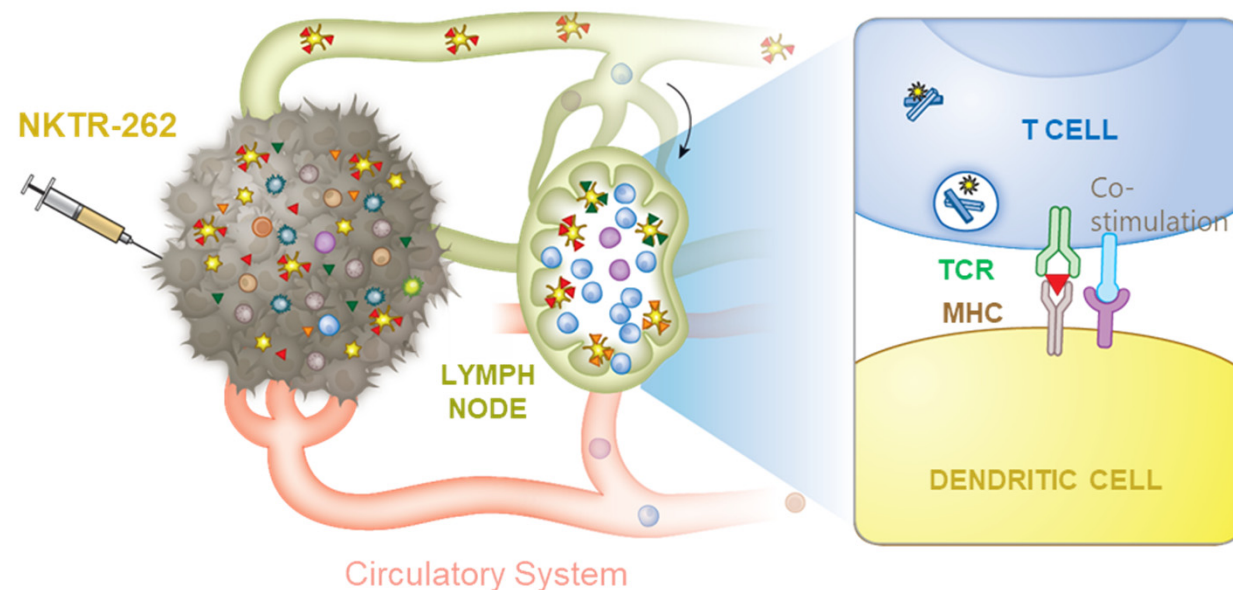
Intratumoral retention of unconjugated TLR7/8 agonist vs NKTR-262 in the injected tumor



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

## PRIMING with NKTR-262

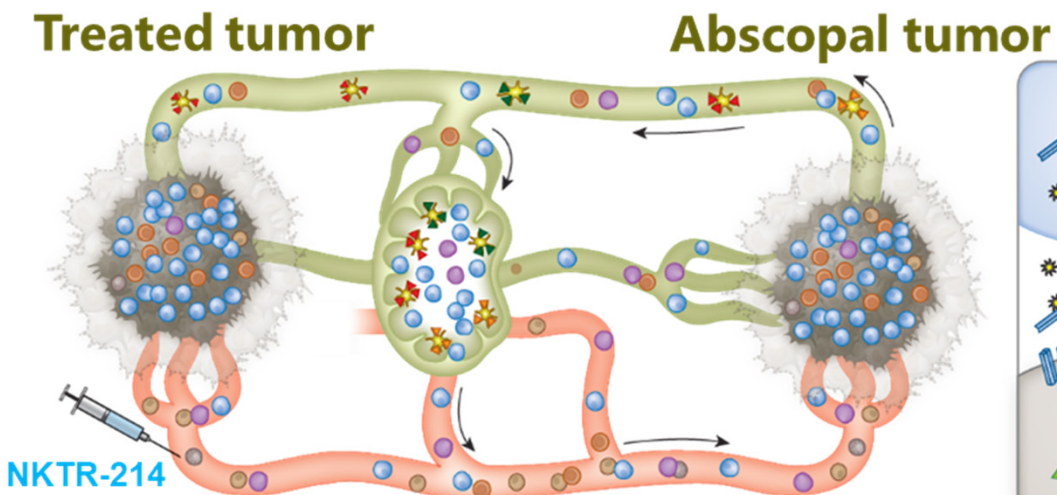
Enhanced antigen presentation  
and T cell priming in lymph node



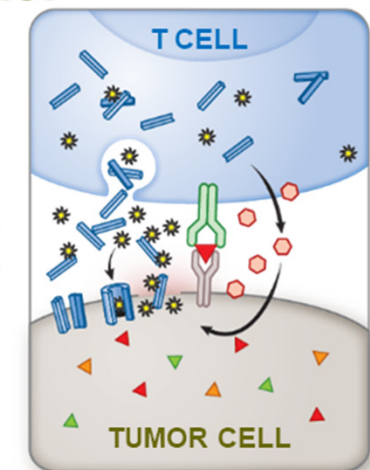
**NKTR-262  
treated tumor**

## BOOSTING with bempegaldesleukin

Expansion of circulatory antitumor  
CD8 T cells and tumor infiltration

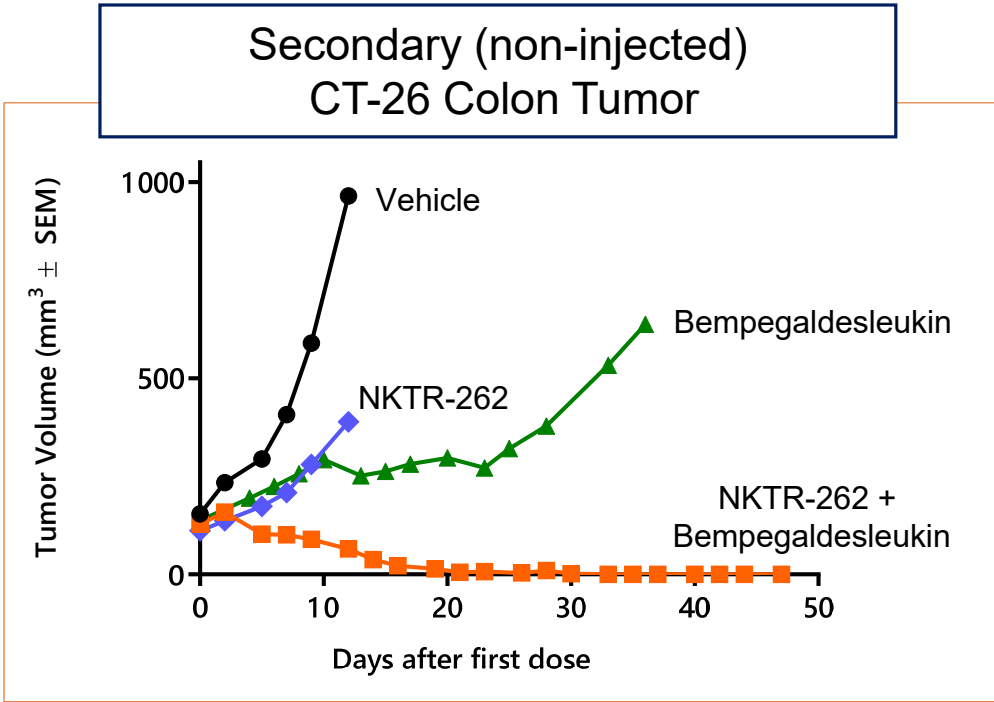
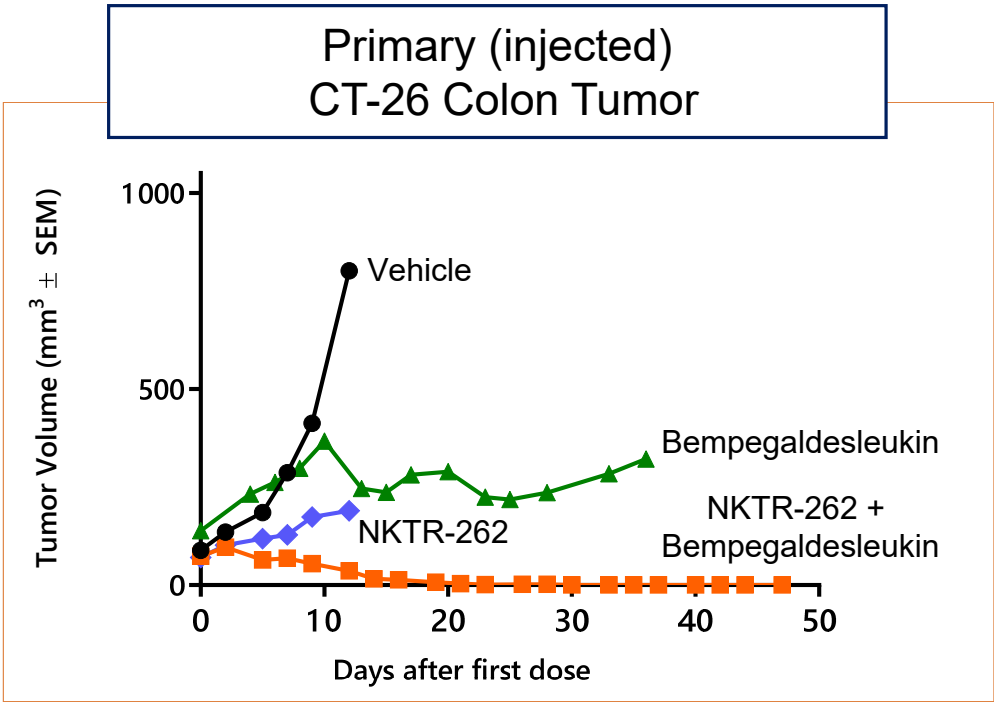
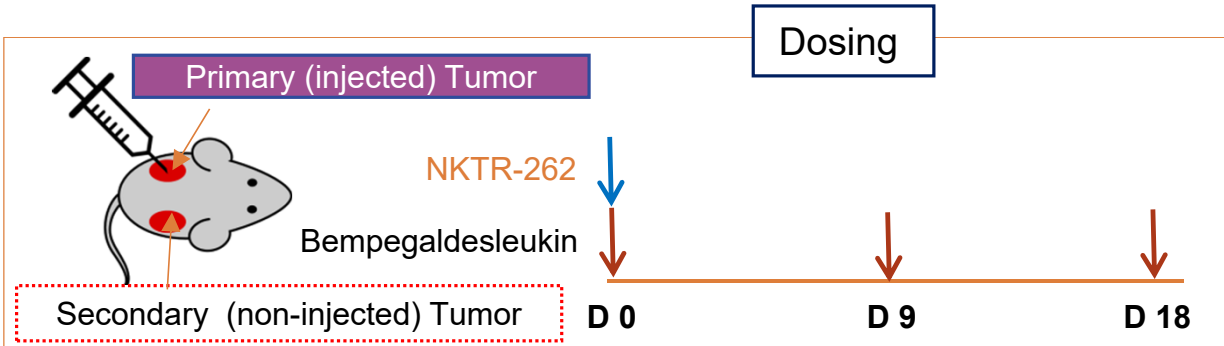


Tumor killing





# Complete Regression and Abscopal Effect with Combination of NKTR-262 and Bempegaldesleukin



NKTR-262 0.8 mg in 40 µL volume given in a single IT dose, bempegaldesleukin 0.8 mg/kg q9dx3 IV; N=10 per group



# REVEAL Study Design

# 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

## Administration of Doublet (Q3W Dose Regimen):

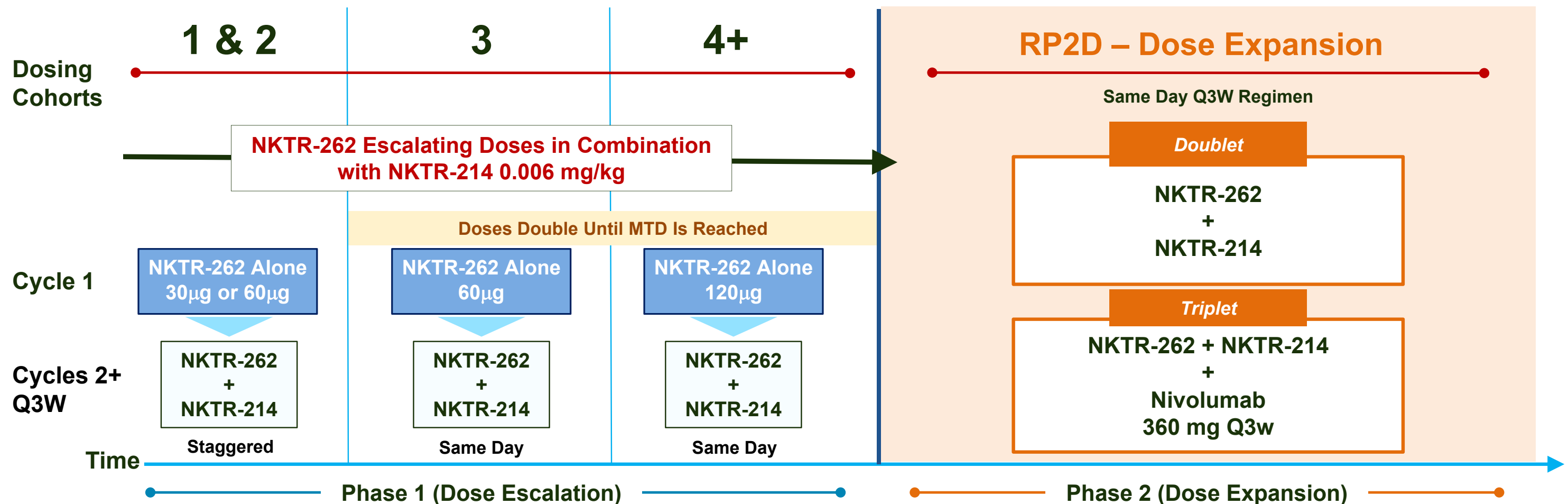
- Intra-tumoral (IT) NKTR-262 Q3W; starting dose 0.03 mg
- During dose escalation:
  - Cycle 1: NKTR-262 IT was administered in Cycle 1 to assess single agent safety
  - Cycle 2 and beyond: NKTR-214 fixed dose of 0.006 mg/kg IV Q3W is combined with NKTR-262 IT Q3W
- NKTR-262 injected lesions (up to two) 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

## Primary 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)

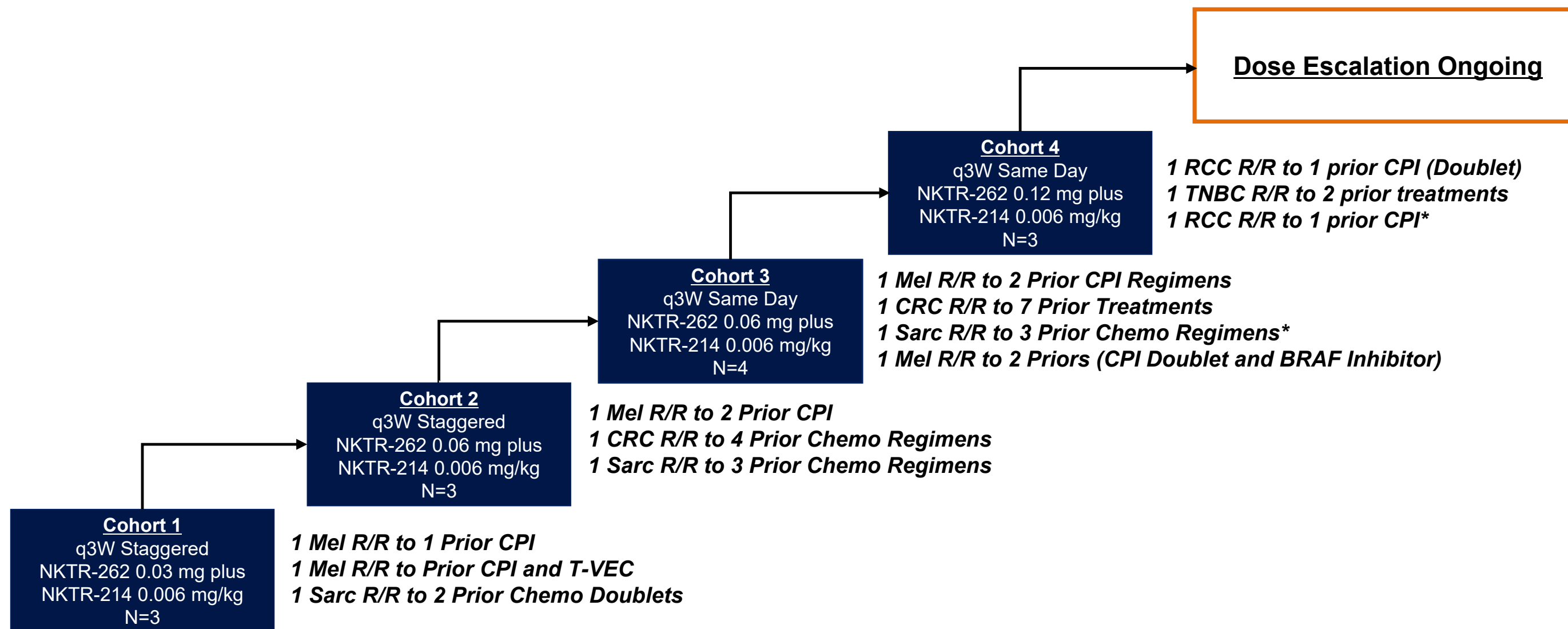
# REVEAL Phase 1/2 Study Design to Evaluate Combination of NKTR-262 Plus NKTR-214

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





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

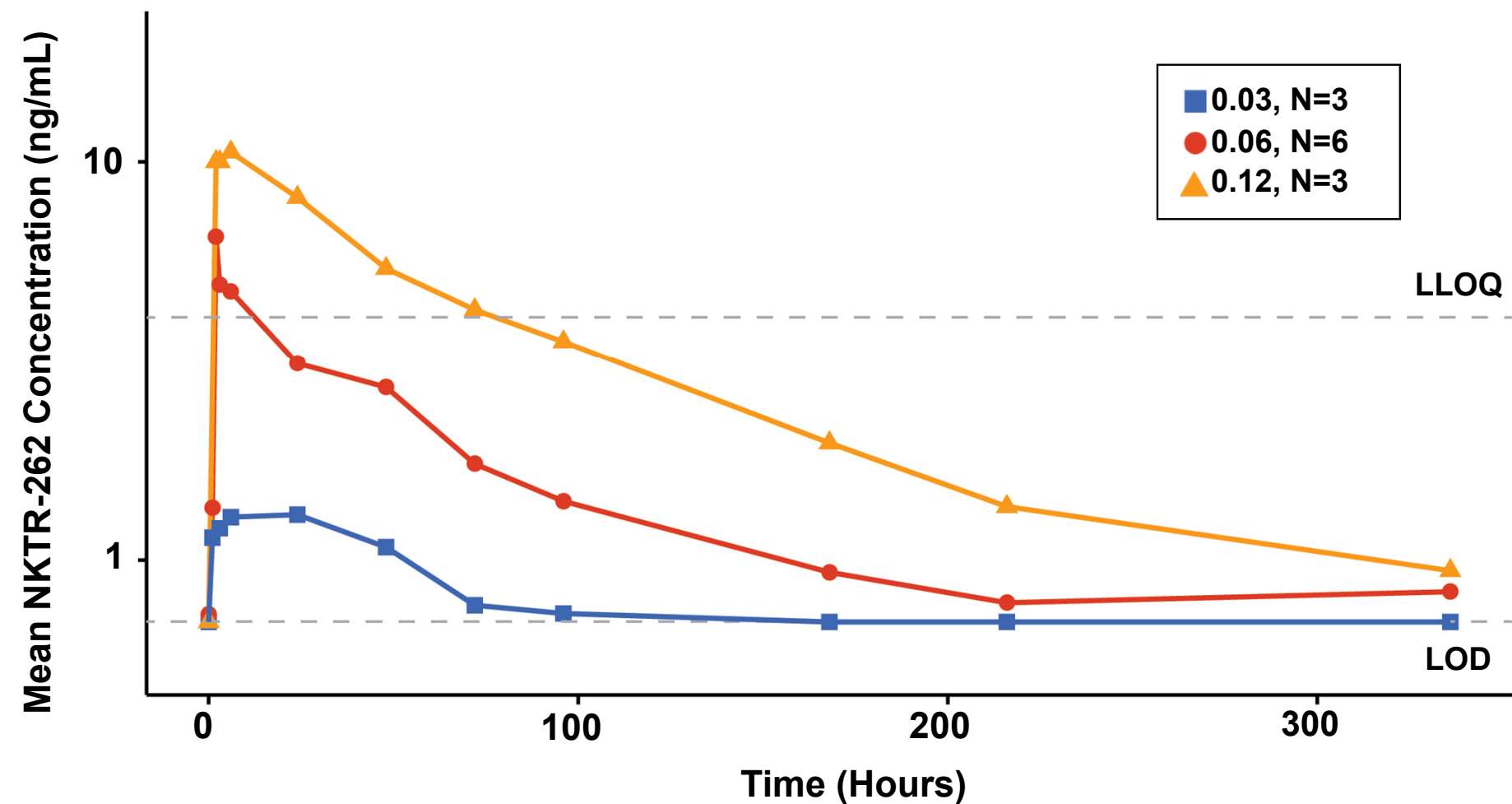






## **REVEAL Immune Activation Markers**

# Plasma Pharmacokinetic Profile Across Escalating Dose Levels of NKTR-262

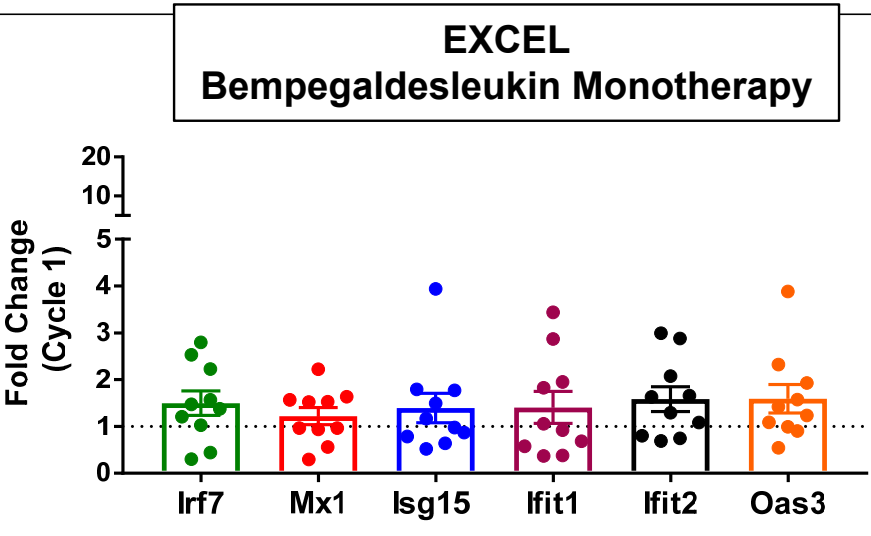
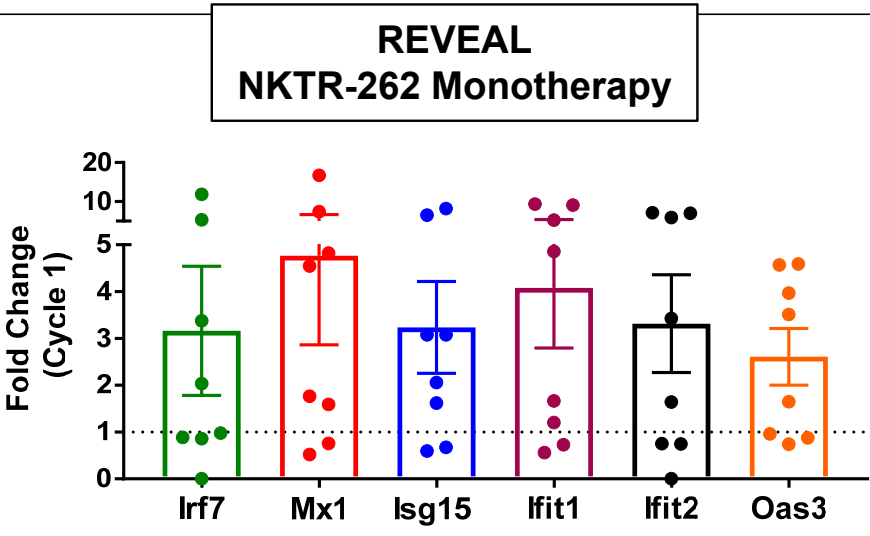


- Plasma levels of NKTR-262 increased with escalating doses
- Concentrations of TLR 7/8 agonist resiquimod (R848) released from NKTR-262 were below the limit of quantification at all dose levels

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.

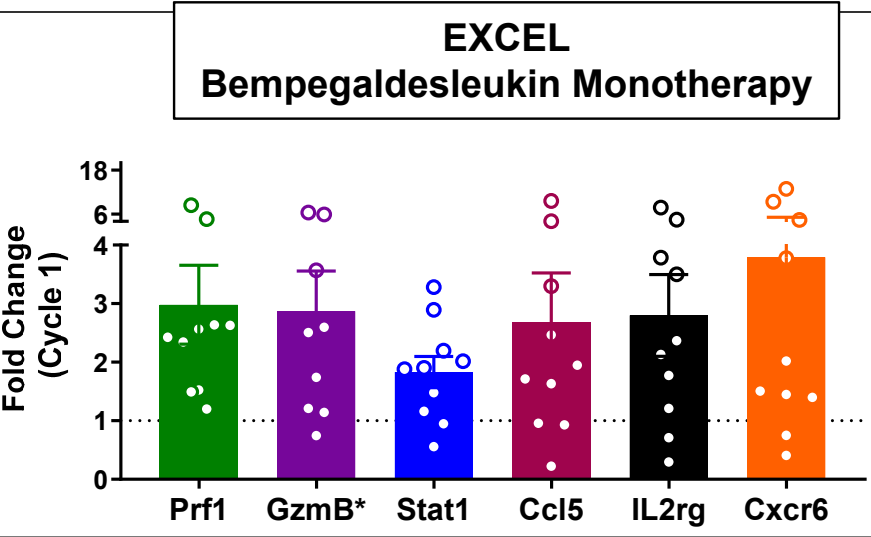
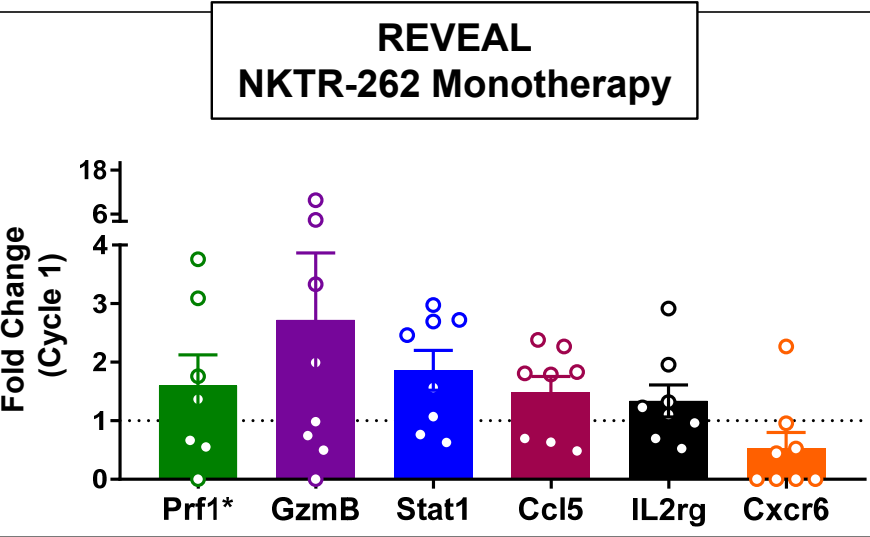
# NKTR-262 and Bempegaldesleukin Promote Comprehensive Activation of the Immune System in the Tumor Microenvironment

IFN- $\alpha/\beta$   
Gene  
Signature



NKTR-262  
promotes local  
activation of the  
innate immune  
system

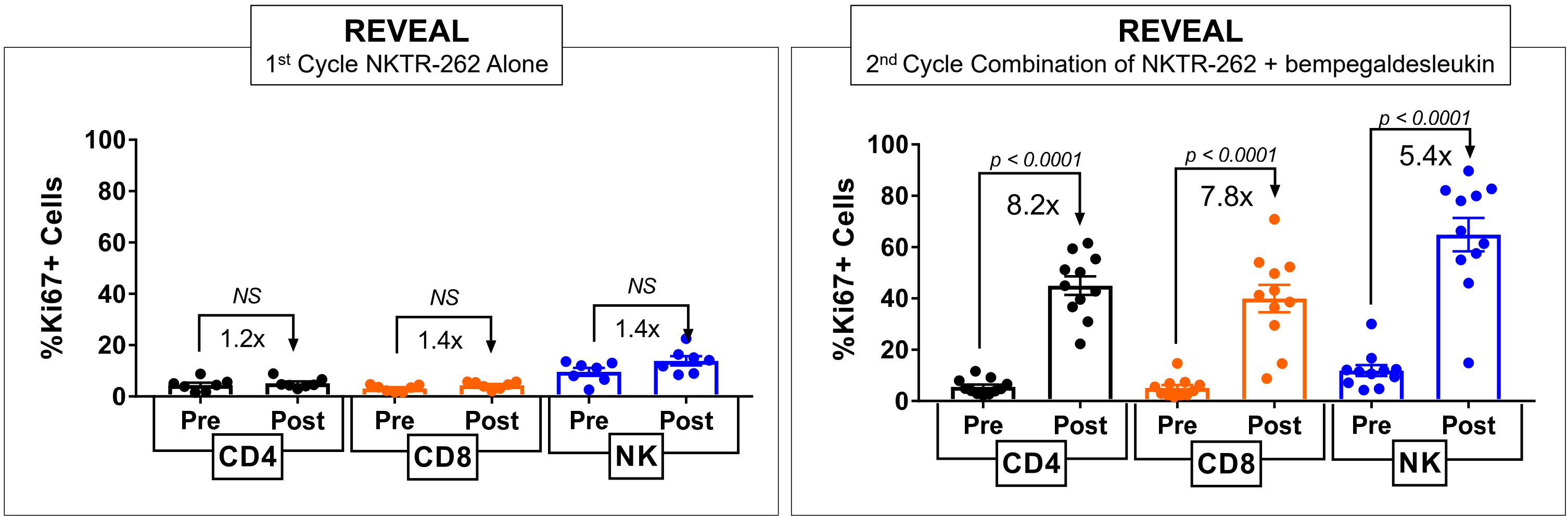
IFN- $\gamma$   
Gene  
Signature



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 (bempegaldesleukin 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







## **Safety and Clinical Data from REVEAL Dose Escalation**



# Safety Profile of NKTR-262 and Bempegaldesleukin as of January 23, 2019 (n=13)

- 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

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

	Totals
<b>Total Evaluable*</b>	<b>11</b>
<b>ORR (CR+PR)</b>	<b>2</b>
CR	0
PR	2
SD	3
<b>DCR (CR+PR+SD)</b>	<b>5 (45.5%)</b>
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

# Case 1: Stage IV Melanoma IO Refractory

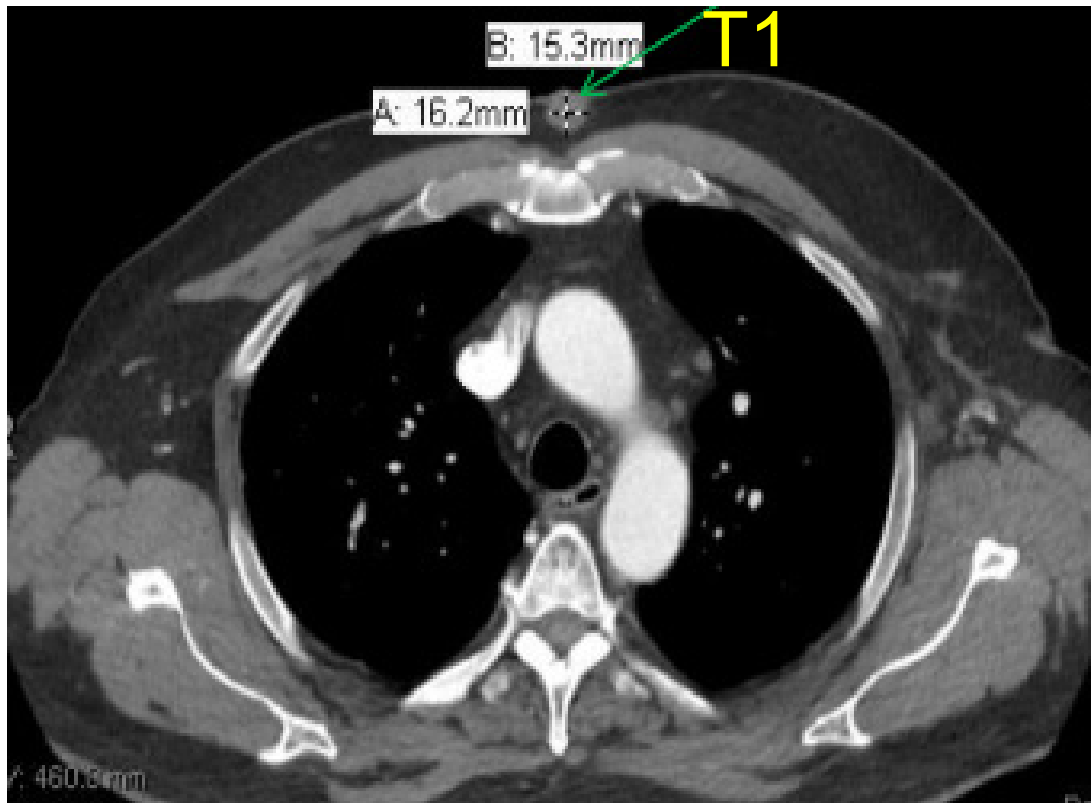
## Confirmed Partial Response (-100%)

- 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 of PD
  - Complications with pneumonitis limited further CPI treatment
  - January 2018 – March 2018: Treated with IMLYGIC™ (T-VEC) with Radiation; BOR of PD
- NKTR-262 Intratumoral Injection Site: Right posterior chest wall (Injected NTL 70mm @ Baseline)
- Partial Response at scan 2 and confirmed at scan 3 (on study for 34 weeks)

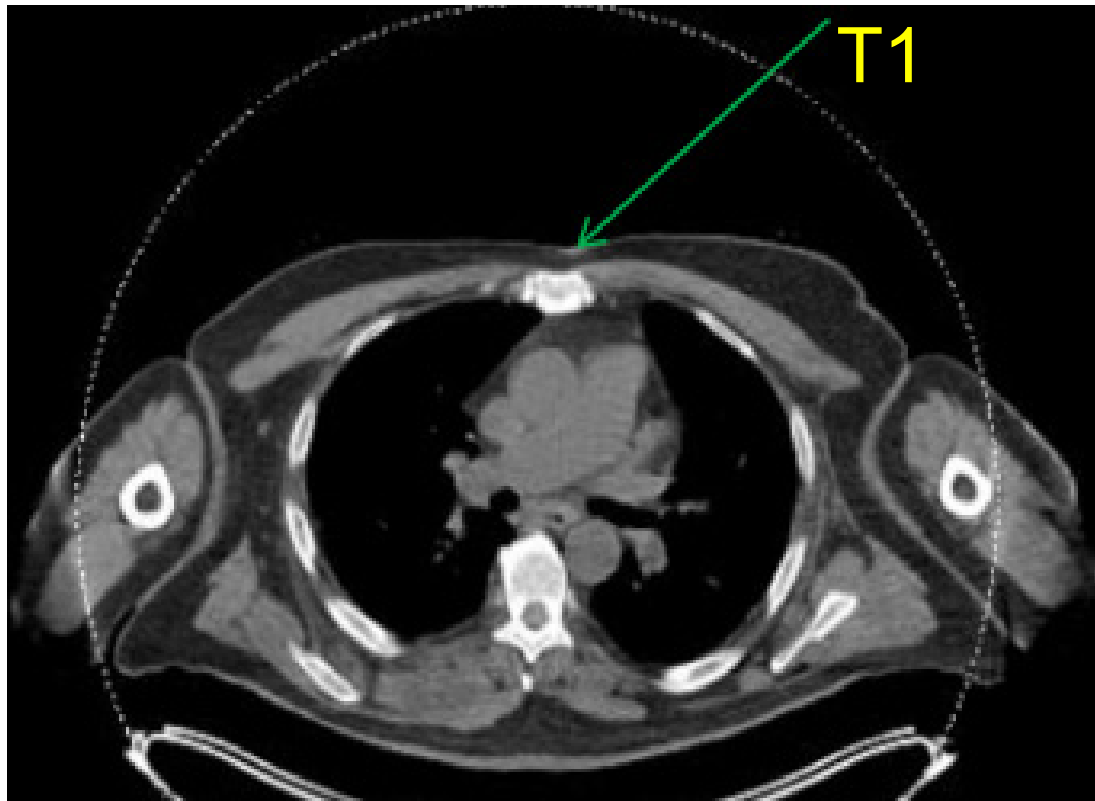
# Case 1: Stage IV Melanoma IO Refractory

## Confirmed Partial Response (-100%)

Baseline

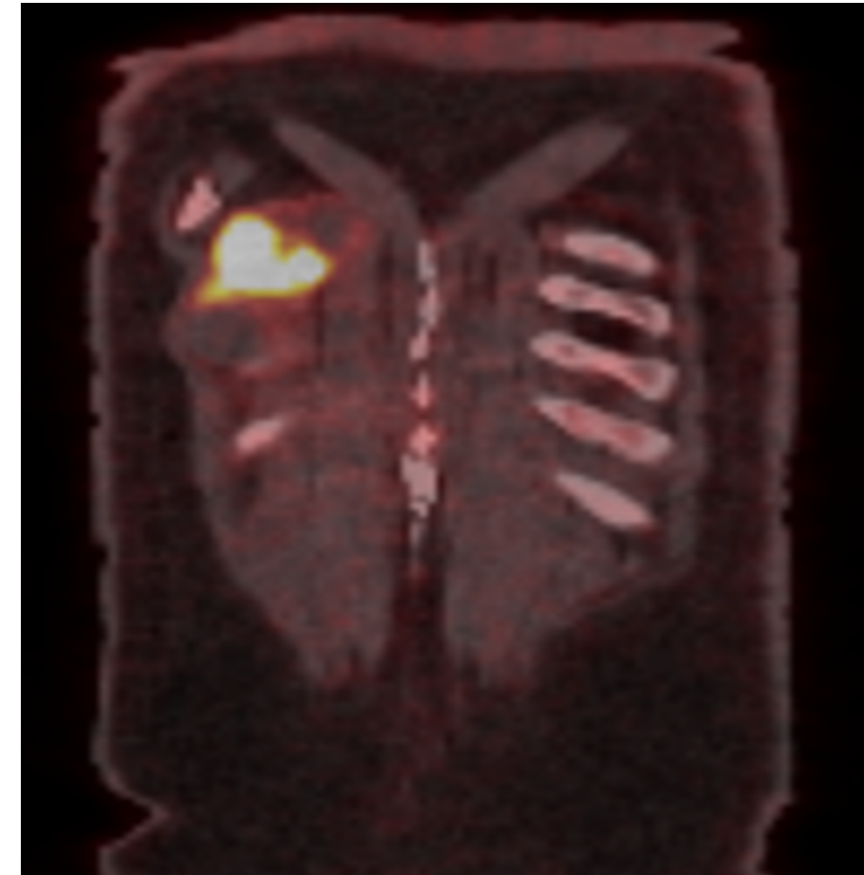
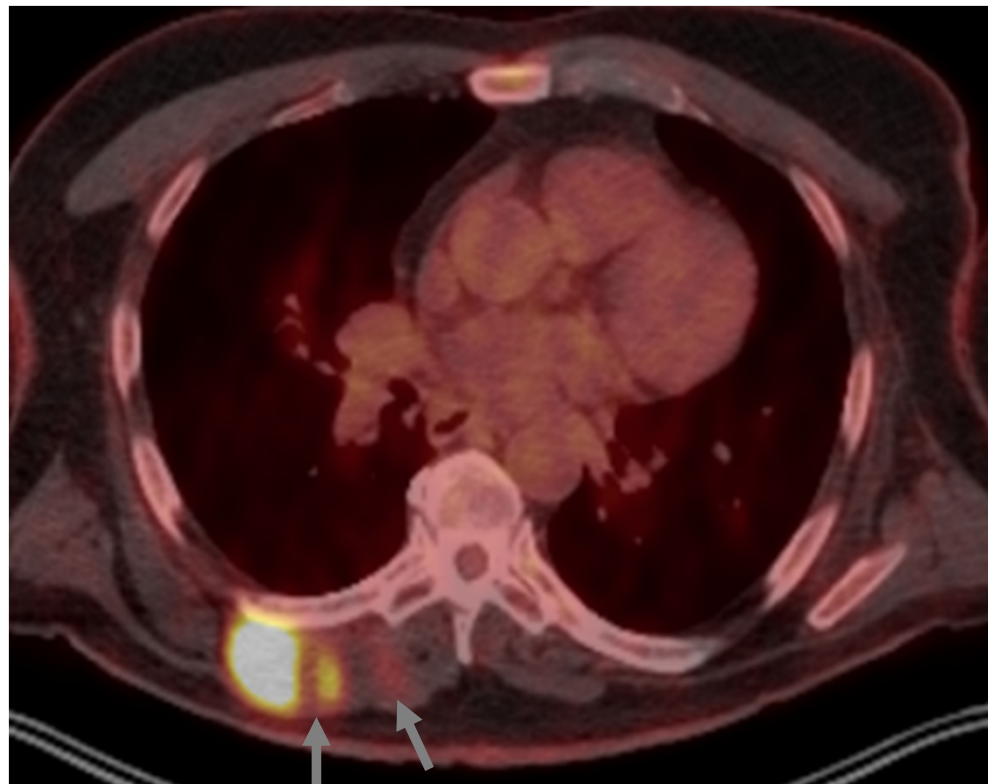


Scan 3



	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%)



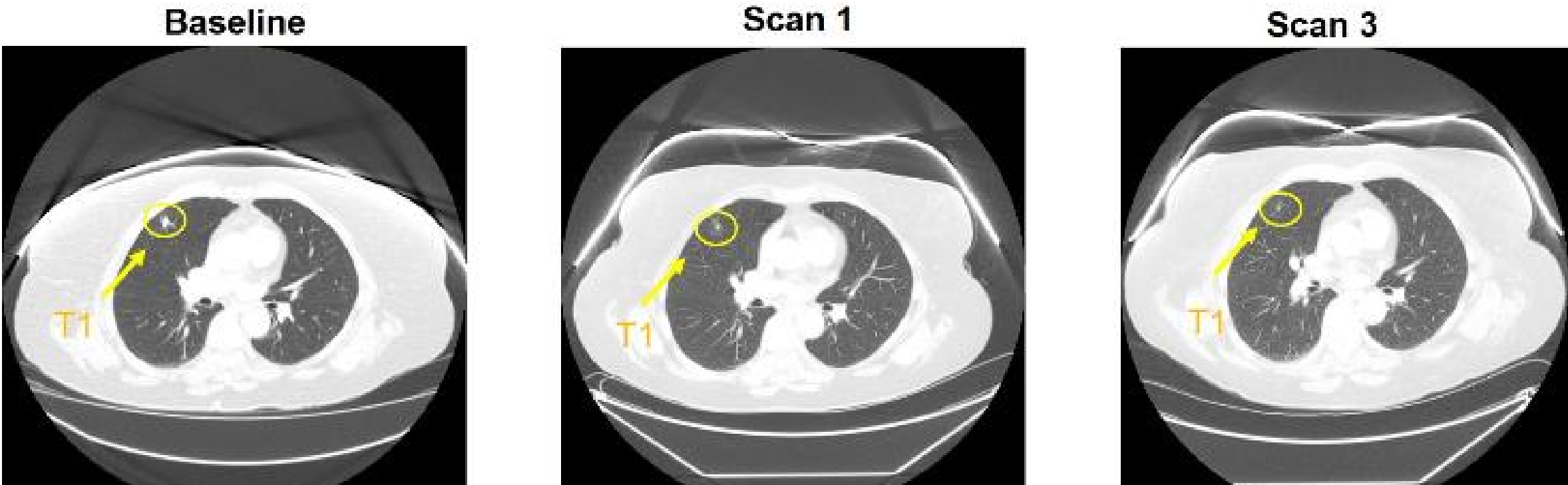
- Non-target injected lesions on PET scan showed multiple areas of fibrosis, necrosis and melanophages upon pathology analysis (October 18, 2018)



## 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 (NTL) 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

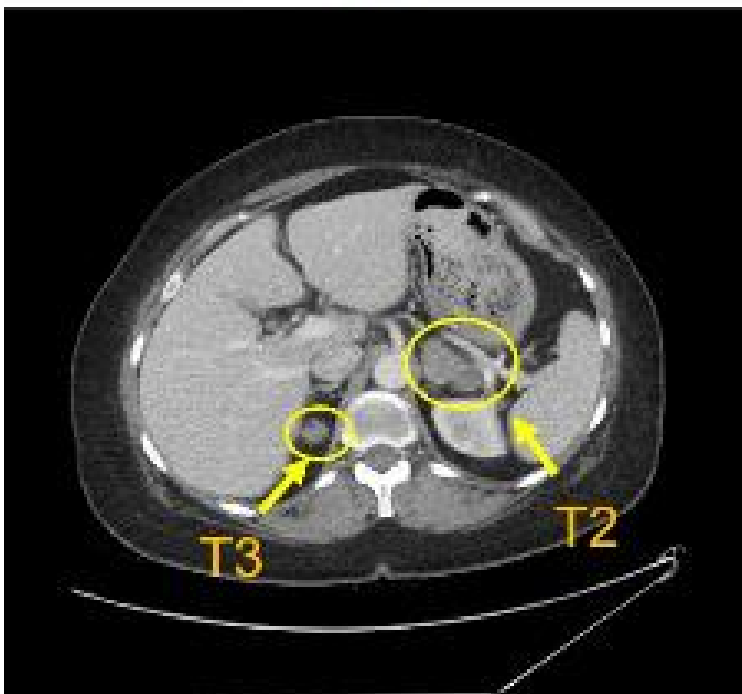
Baseline



Scan 1

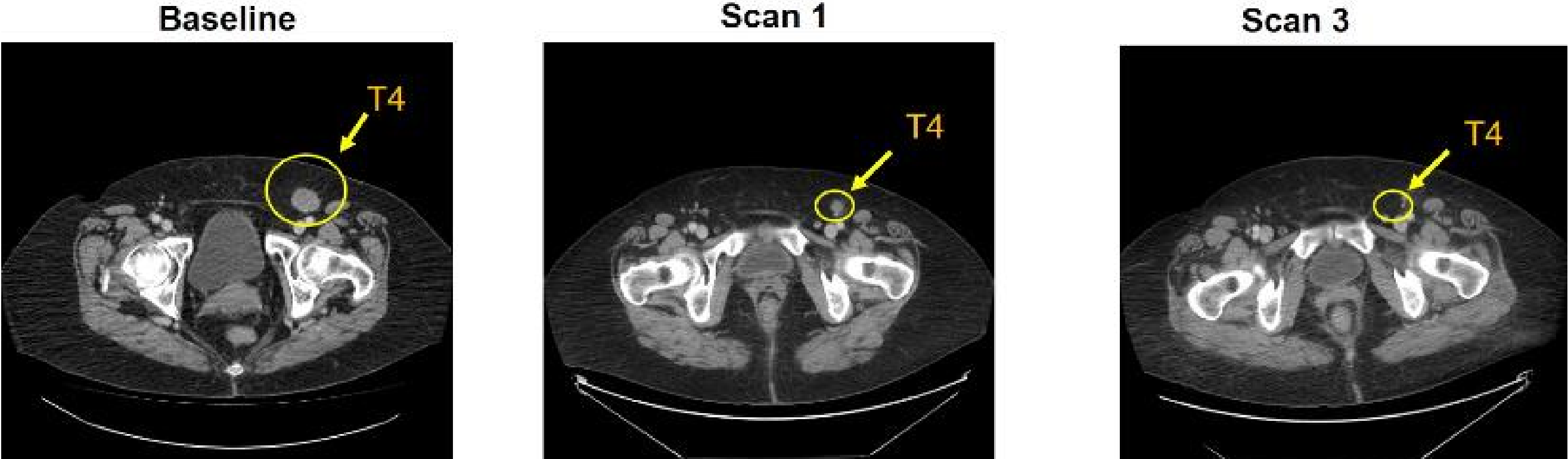


Scan 3



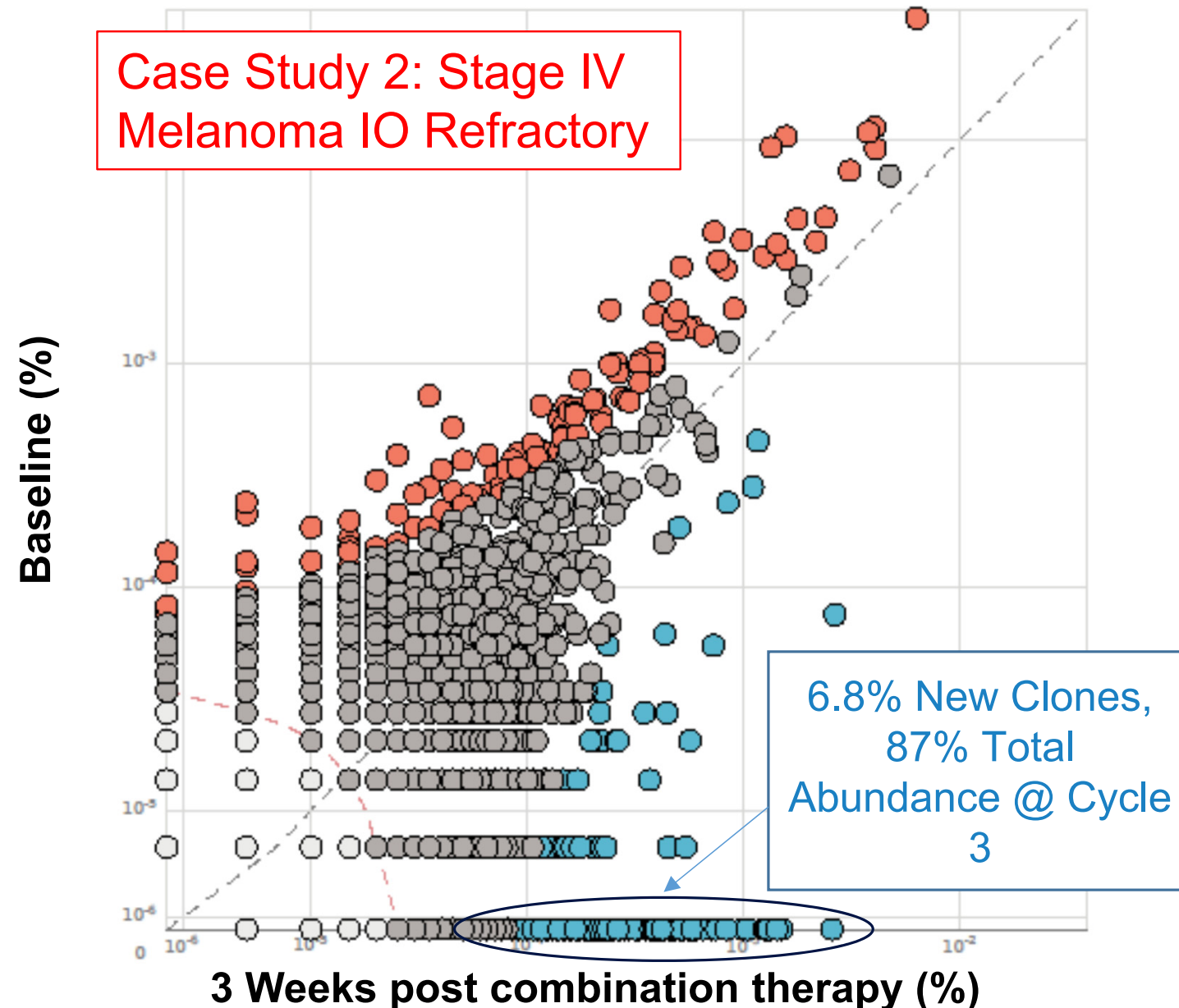
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	Sum of the Diameters (% Change from Baseline)	112	69 (-38.3%)	58 (-48%)	56 (-50%)
Overall Response	RECIST 1.1		Partial Response	Partial Response	Partial Response

# 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

# Q & A Panel



**Dr. Adi Diab**

Assistant Professor  
of Melanoma  
Medical Oncology  
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