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REVEAL: Phase 1 Dose-Escalation Study of NKTR-262, a Novel TLR7/8 Agonist, Plus Bempegaldesleukin: Local Innate Immune Activation and Systemic Adaptive Immune Expansion for Treating Solid Tumors

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Presenter Disclosure Information:

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

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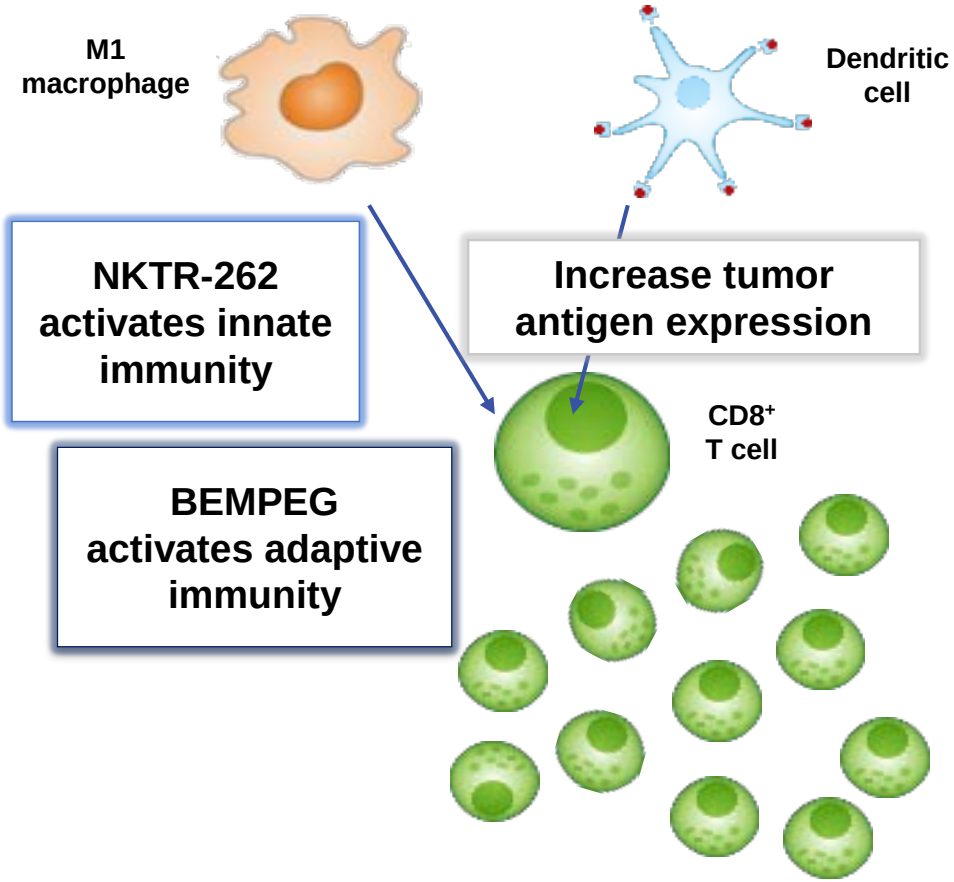
- Consulting or advisory role: Apexigen, Array, BMS, Celgene, CureVac, Dragonfly, Iovance, Nektar, Memgen
- Research funding (institution): Idera, Nektar, Pfizer, BMS , Apexigen

Bempegaldesleukin in combination with nivolumab is an investigational combination and is not currently approved by the FDA

MoA: Targeting the Innate and Adaptive Immune Response With NKTR-262 Plus BEMPEG

- NKTR-262 is an intratumorally delivered TLR7/8 agonist that activates APCs to prime new antigen-specific cytotoxic T cells
- Bempegaldesleukin (BEMPEG or NKTR-214) is an investigational, first-in-class, CD122-preferential, IL-2–pathway agonist
- In preclinical models, NKTR-262 plus BEMPEG combined innate immune signaling and enhanced antigen presentation with sustained T-cell activation, resulting in tumor growth inhibition of treated and abscopal lesions[1]
- High levels of TLR activation in the TME after NKTR-262 dose[1] allow us to understand PK/PD, and subsequently characterize the safety of NKTR-262



APC, antigen-presenting cell; IL, interleukin; MoA, mechanism of action; PD, pharmacodynamics; PK, pharmacokinetics; TLR, toll-like receptor; TME, tumor microenvironment.

1. Kivimae S, et al. *J Immunother Cancer* 2017;5(Suppl 2):P275.

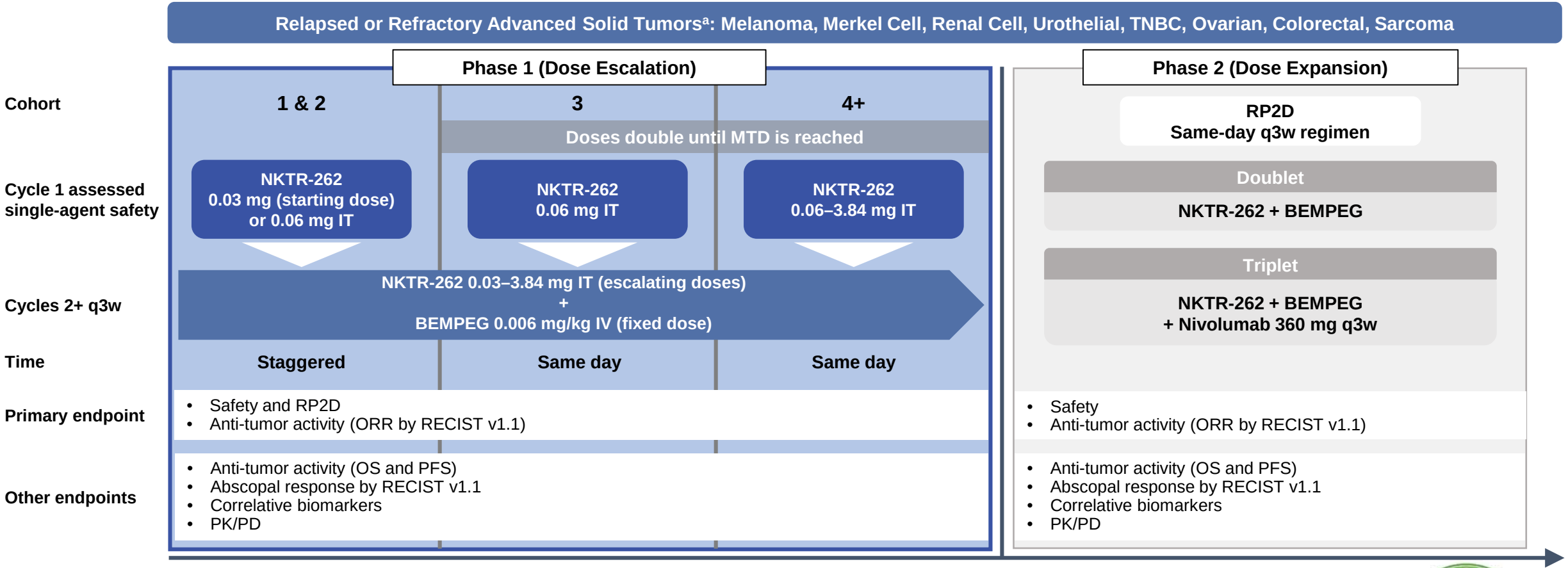
Previously Reported Clinical Results From the REVEAL Study

- Initial clinical results[a] were reported for 13 patients with relapsed or refractory advanced solid tumors enrolled across four cohorts
- NKTR-262 combined with fixed-dose BEMPEG was well tolerated[1]
  - Systemic (adaptive) and local (innate) activation of the immune system was observed
  - PK exposure increased with dose
  - TCR repertoire change was seen after a single cycle of treatment with NKTR-262 plus BEMPEG
    - Clonal expansion has been observed
  - Early evidence of clinical activity in the first, heavily pretreated, 11 patients evaluable for efficacy
    - In non-injected lesions, NKTR-262 plus BEMPEG resulted in abscopal responses

Here we present the factors (safety, PK, and biomarker data) that supported selection of the RP2D of NKTR-262 plus BEMPEG in the REVEAL study in advanced solid tumors

[a]Data from January 23, 2019.
PK, pharmacokinetic; RP2D, recommended Phase 2 dose; TCR, T-cell receptor.
1. Diab A, et al. ASCO-SITC Clinical Immuno-Oncology Symposium 2019: Abstract 28.

REVEAL: Phase 1/2 Study Schema



[a]Injected lesions 20–90 mm in diameter.
Cohorts 1 and 2 explored staggered administration of NKTR-262 and BEMPEG; cohort 3 onwards explored same-day administration of NKTR-262 and BEMPEG.
IT, intratumoral; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; q3w, every 3 weeks; RP2D, recommended Phase 2 dose; TNBC, triple-negative breast cancer.

Dose-Escalation Cohorts and the Clinical Activity of NKTR-262 Combined With BEMPEG

Dose Escalation	N=36	NKTR-262 (mg IT)	BEMPEG (mg/kg q3w IV)	Tumor Type
Cohort 1	3	0.03 (starting dose)	0.006	Melanoma, sarcoma
Cohort 2	7	0.06	0.006	Melanoma, sarcoma, CRC
Cohort 3				
Cohort 4	3	0.12	0.006	TNBC, RCC
Cohort 5	4	0.24	0.006	TNBC, RCC, CRC, Merkel cell
Cohort 6	4	0.48	0.006	Melanoma
Cohort 7	4	0.96	0.006	Melanoma
Cohort 8	3	1.92	0.006	Melanoma
Cohort 9 (RP2D)	**8**	**3.84**	**0.006**	**Melanoma**

- As of 1 Sept 2020, 36 patients with R/R metastatic solid tumors were enrolled across nine cohorts
  - Of the 28 patients in the efficacy-evaluable population, eight (29%) had regression in the injected lesions
- 2 of 22 efficacy-evaluable, heavily pretreated melanoma patients (9%) experienced an objective response
  - 1 had a 50% reduction in tumor burden and 1 had a 100% reduction in sum of diameters in the non-injected target lesions

Initial results of clinical activity; further assessments are ongoing.
CRC, colorectal cancer; IT, intratumoral; IV, intravenous; q3w, every 3 weeks; RCC, renal cell carcinoma; RP2D, recommended Phase 2 dose; R/R, relapsed or refractory; SD, stable disease; TNBC, triple-negative breast cancer.

Treatment-Related Adverse Events

Preferred Term, n (%)	Total (N=36)
Patients reporting ≥1 TRAE (NKTR-262 monotherapy) (≥10% listed below)	**17 (47.2)**
Flu-like symptoms[a]	8 (22.2)
Fatigue	4 (11.1)
Nausea	4 (11.1)
Patients reporting ≥1 TRAE (NKTR-262 + BEMPEG) (≥20% listed below)	**35 (97.2)**
Flu-like symptoms[a]	28 (77.8)
Fatigue	16 (44.4)
Nausea	15 (41.7)
Pruritus[b]	15 (41.7)
Rash[c]	13 (36.1)
Vomiting	9 (25.0)
Grade ≥3 TRAEs (NKTR-262 + BEMPEG) (≥5% listed below)	**11 (30.6)**
Elevated ALT	2 (5.6)
Hypotension	2 (5.6)
Leukocytosis	2 (5.6)
Rash[c]	2 (5.6)
Syncope	2 (5.6)

The safety profile of NKTR-262 + BEMPEG was favorable and tolerable, with few treatment discontinuations due to adverse events[d]

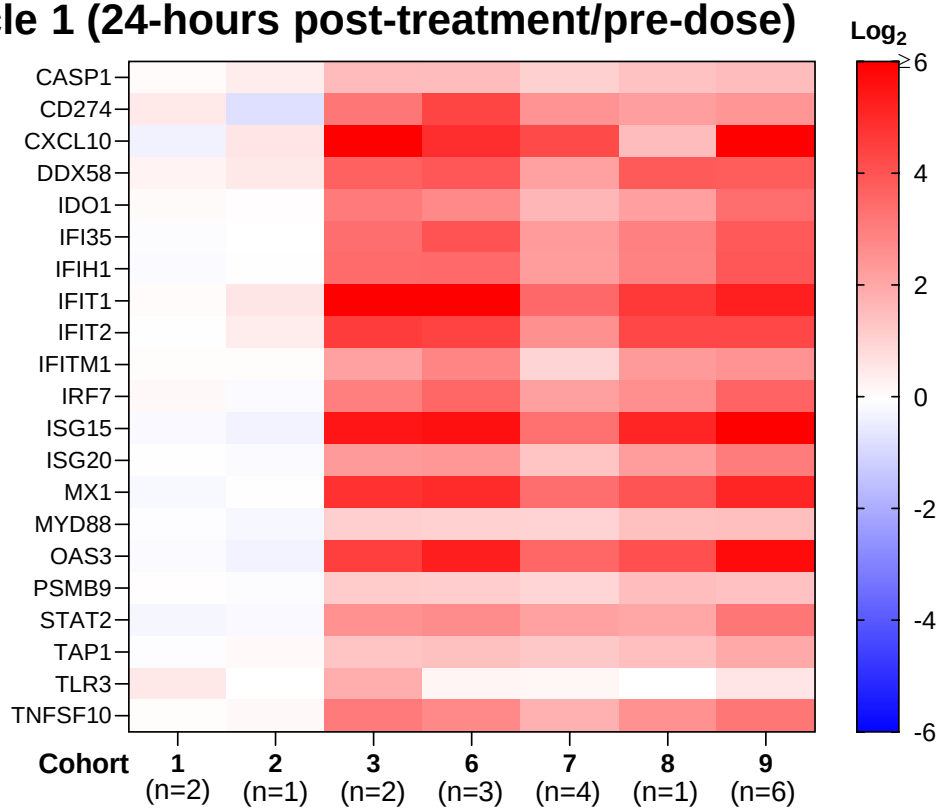
The MTD was not reached*

*One DLT of transient grade 3 elevated ALT and grade 4 elevated AST in the highest dose cohort

[a]Flu-like symptoms included the following preferred terms: influenza-like illness, influenza, pyrexia, chills. [b]Pruritus included the following preferred terms: pruritus, pruritus generalized. [c]Rash included the following preferred terms: erythema, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, rash generalized, rash macular. [d]Four patients discontinued treatment due to an adverse event. ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT; dose-limiting toxicity; MTD, maximum tolerated dose; TRAE, treatment-related adverse event.

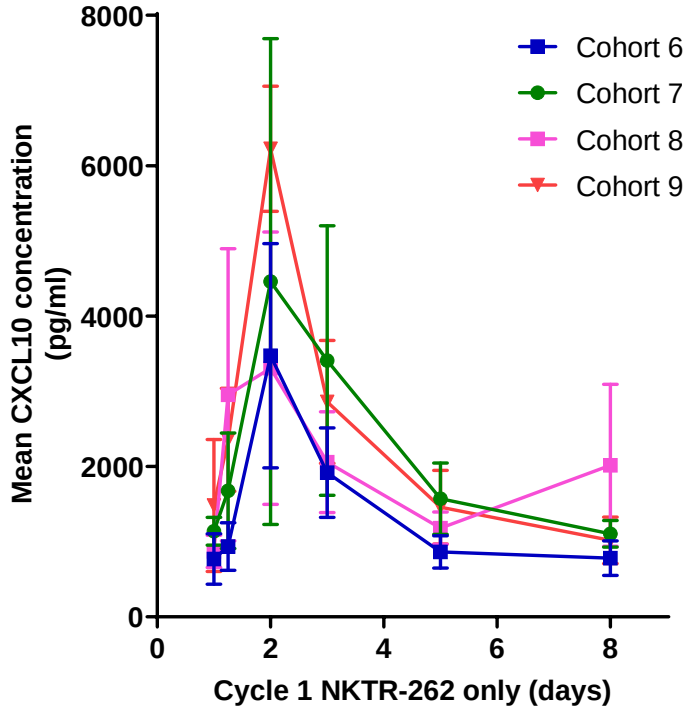
Dose-dependent Induction of Type 1 IFN Genes and CXCL10 Chemokine in Blood Consistent With TLR7/8 Target Engagement

Gene expression changes in peripheral blood, Cycle 1 (24-hours post-treatment/pre-dose)



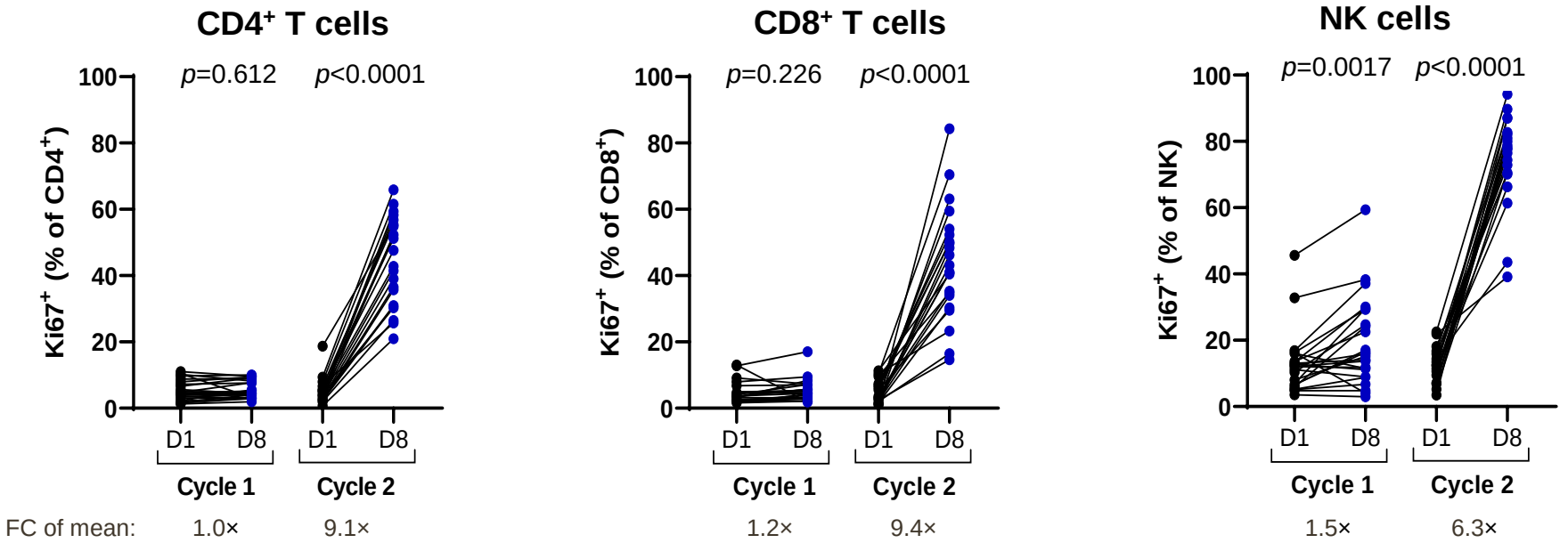
Median $\log_2$ fold change at 24-hours post-cycle 1 NKTR-262 monotherapy for each cohort

Induction of plasma CXCL10/IP10 in Cycle 1



Data shown are for patients with melanoma.

Increased Proliferation (%Ki67$^+$) of CD4$^+$, CD8$^+$, and NK Cells in Blood in Cycle 2 is Consistent With the MoA of BEMPEG*

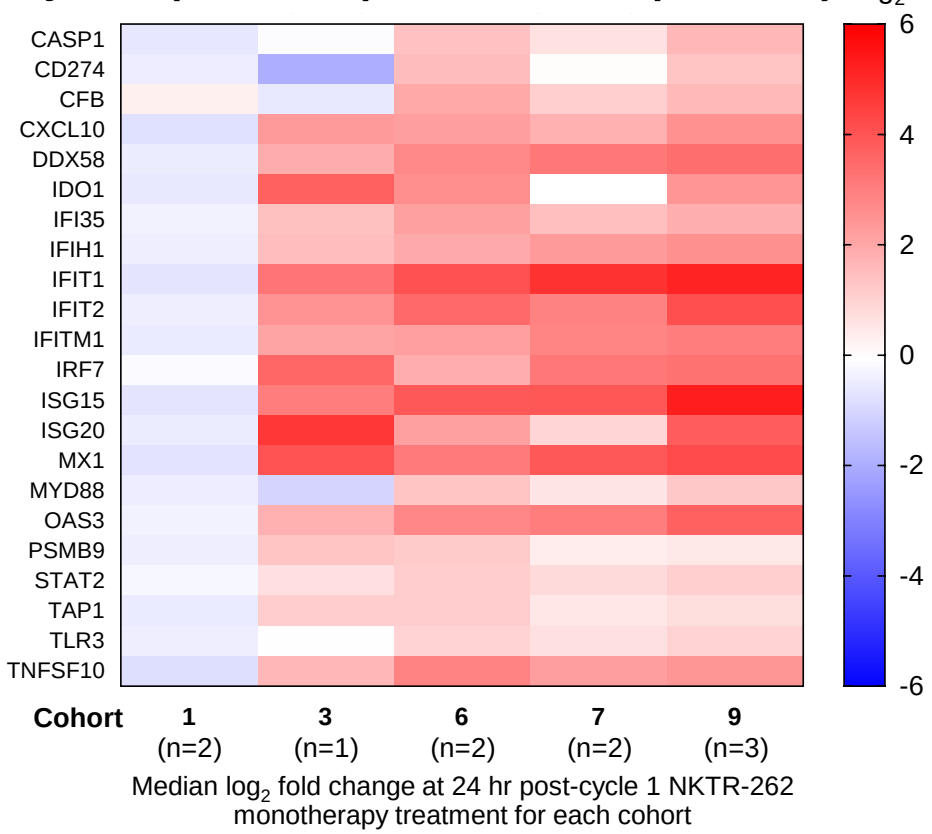


Minimal induction of proliferative immune cell subsets in Cycle 1 reflects retention of NKTR-262 in the TME following local delivery

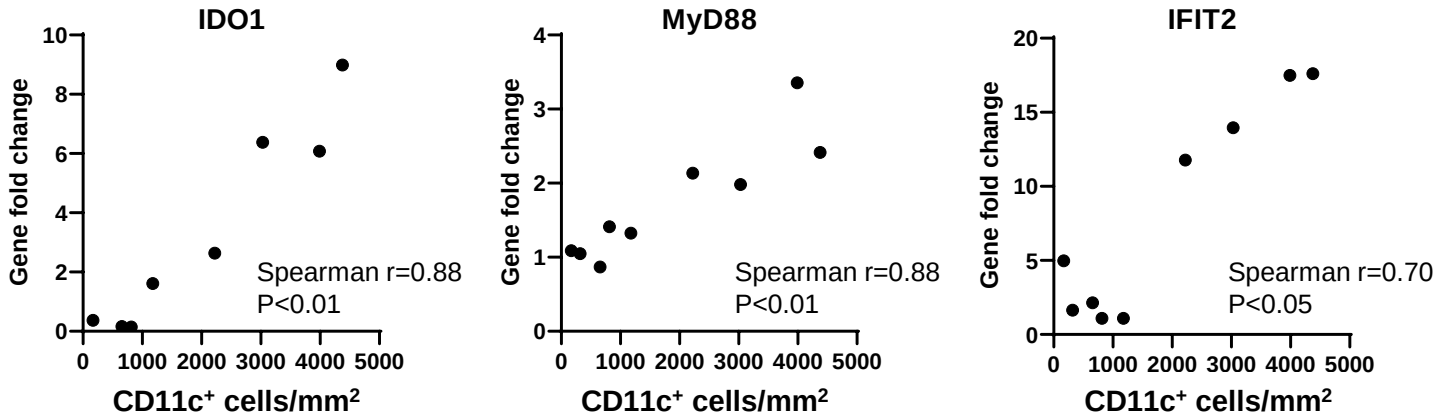
*Matched pairs only; n=24 in Cycle 1, n=22 in Cycle 2.
Cycle 1: NKTR-262 monotherapy; **Cycle 2:** first exposure to NKTR-262 + BEMPEG.
D, day; FC, fold change; MoA, mechanism of action; NK, natural killer; TME, tumor microenvironment.

Induction of Type 1 IFN Genes in Biopsies Correlates With Density of CD11c$^+$ NKTR-262–Targeted Cells

Gene expression changes in melanoma biopsies, Cycle 1 (24-hours post-treatment/pre-dose)



Representative correlations between select genes and CD11c$^+$ density[a]

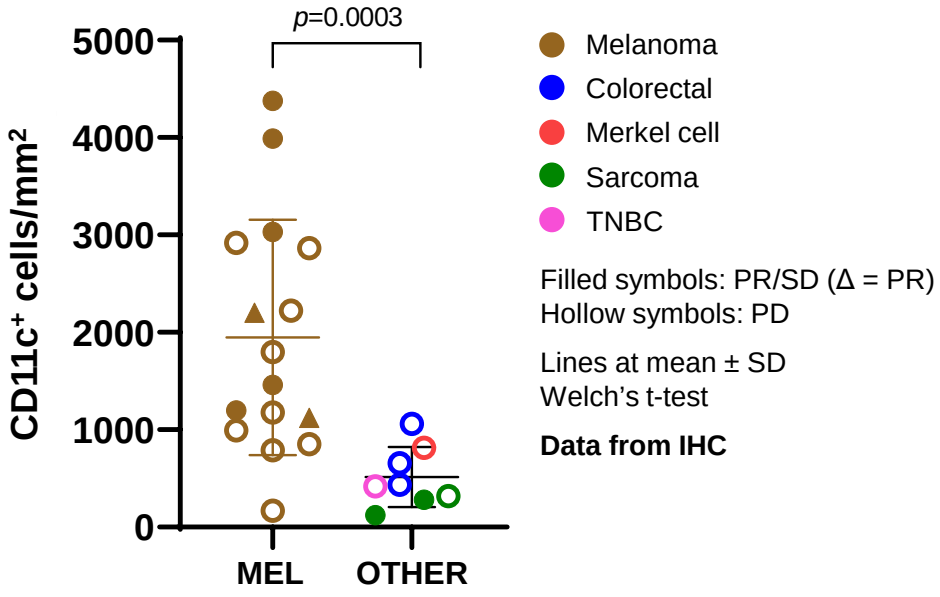


Dose- and CD11c$^+$-dependent induction of Type 1 IFN genes in melanoma biopsies consistent with TLR7/8 target engagement

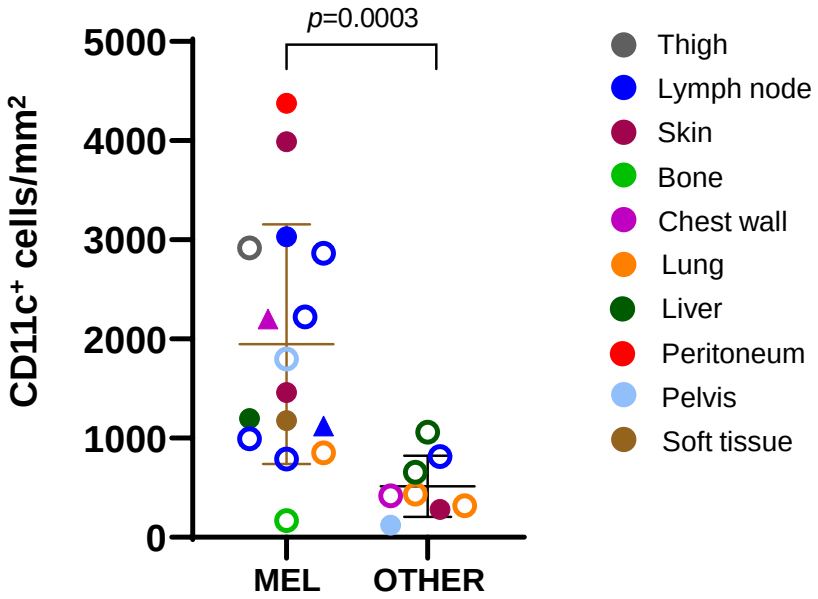
[a]Correlation between fold change of induction for each gene (at Day 2) and CD11c$^+$ density (by IHC) at baseline across samples where both datasets available (melanoma [6], sarcoma [1], Merkel cell [1], CRC [1]).
IFN, interferon; TLR, toll-like receptor.

Higher Density of CD11c$^+$ Target Cells in Melanoma Baseline Biopsies vs Other Tumor Types

Melanoma vs other indications



Location of biopsy



Preliminary data show a potential trend for a higher density of CD11c$^+$ cells with an anti-tumor effect in melanoma

Biopsies taken at 24 hours post-cycle 1 NKTR-262 monotherapy for each cohort.
IHC, immunohistochemistry; MEL, melanoma; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

Conclusions

- NKTR-262 IT, as monotherapy or in combination, showed early signs of clinical activity and an acceptable safety profile in this highly relapsed/refractory melanoma patient population
- MTD was not reached; the totality of the safety, PK/PD, and biomarker data supported selection of NKTR-262 3.84 mg IT plus BEMPEG 0.006 mg IV q3w as the RP2D
  - For NKTR-262, robust TLR7/8 engagement supported the MoA, and the minimal toxicity profile underscored the benefit of local delivery
  - NKTR-262 plus BEMPEG induced systemic activation of T and NK cells demonstrating engagement of the entire immune activation cascade required for systemic tumor clearance
  - $CD11c^+$ target cells were significantly more abundant in baseline melanoma biopsies vs other tumor types; induction of TLR7/8-responsive genes significantly correlated with $CD11c^+$ baseline density
- Our findings support the ongoing Phase 1b dose expansion of NKTR-262 plus BEMPEG, with or without nivolumab, in patients with relapsed/refractory melanoma

IT, intratumoral; IV, intravenous; MoA, mechanism of action; MTD, maximum tolerated dose; NK, natural killer; PD, pharmacodynamics; PK, pharmacokinetics; q3w, every 3 weeks; RP2D, recommended Phase 2 dose; TLR, toll-like receptor.

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