



NEKTAR[®]

NEW PATHWAYS TO
SMARTER MEDICINE™

Society for Immunotherapy of Cancer 2021 Annual Meeting

Investor & Analyst Call

November 12, 2021

This presentation includes forward-looking statements regarding Nektar's proprietary drug candidates, the timing of the start of and plans for ongoing or planned clinical trials with partners, the therapeutic potential of our drug candidates, the timing and outcome of regulatory decisions, and future availability of clinical trial data. Actual results could differ materially, and these statements are subject to important risks detailed in Nektar's filings with the SEC including the Form 10-Q filed on November 5, 2021. Nektar undertakes no obligation to update forward-looking statements as a result of new information or otherwise.

Today's speakers



Jonathan Zalevsky, PhD

Chief Research &
Development Officer at
Nektar Therapeutics



Dimitry Nuyten, MD, PhD

Chief Medical Officer at
Nektar Therapeutics



Mehmet Altan, MD

Assistant Professor in the
Department of Thoracic-Head
and Neck Medical Oncology,
Division of Cancer Medicine at
The University of Texas
MD Anderson Cancer Center



Alan Tan, MD

Assistant Professor
Department of Internal Medicine,
Division of Hematology,
Oncology and Cell Therapy at
Rush University Medical Center

Mehmet Altan, MD – MD Anderson Cancer Center



Mehmet Altan, MD, is an Assistant Professor in the Department of Thoracic-Head and Neck Medical Oncology, Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center. Dr. Altan is one of the lead investigators in the phase 1/2, dose-escalation and dose-expansion study of NKTR-255 in combination with cetuximab in patients with refractory 2nd and 3rd line metastatic colorectal cancer or metastatic head and neck cancer. His current research areas include identification of mechanisms for primary and secondary resistance to immunotherapies and predictive markers for immunotherapy toxicities. He also works on translational research projects for identification of spatiotemporal dynamics of the tumor microenvironment in response to immunotherapy to define potential therapeutic targets.

Alan Tan, MD – Rush University Medical Center

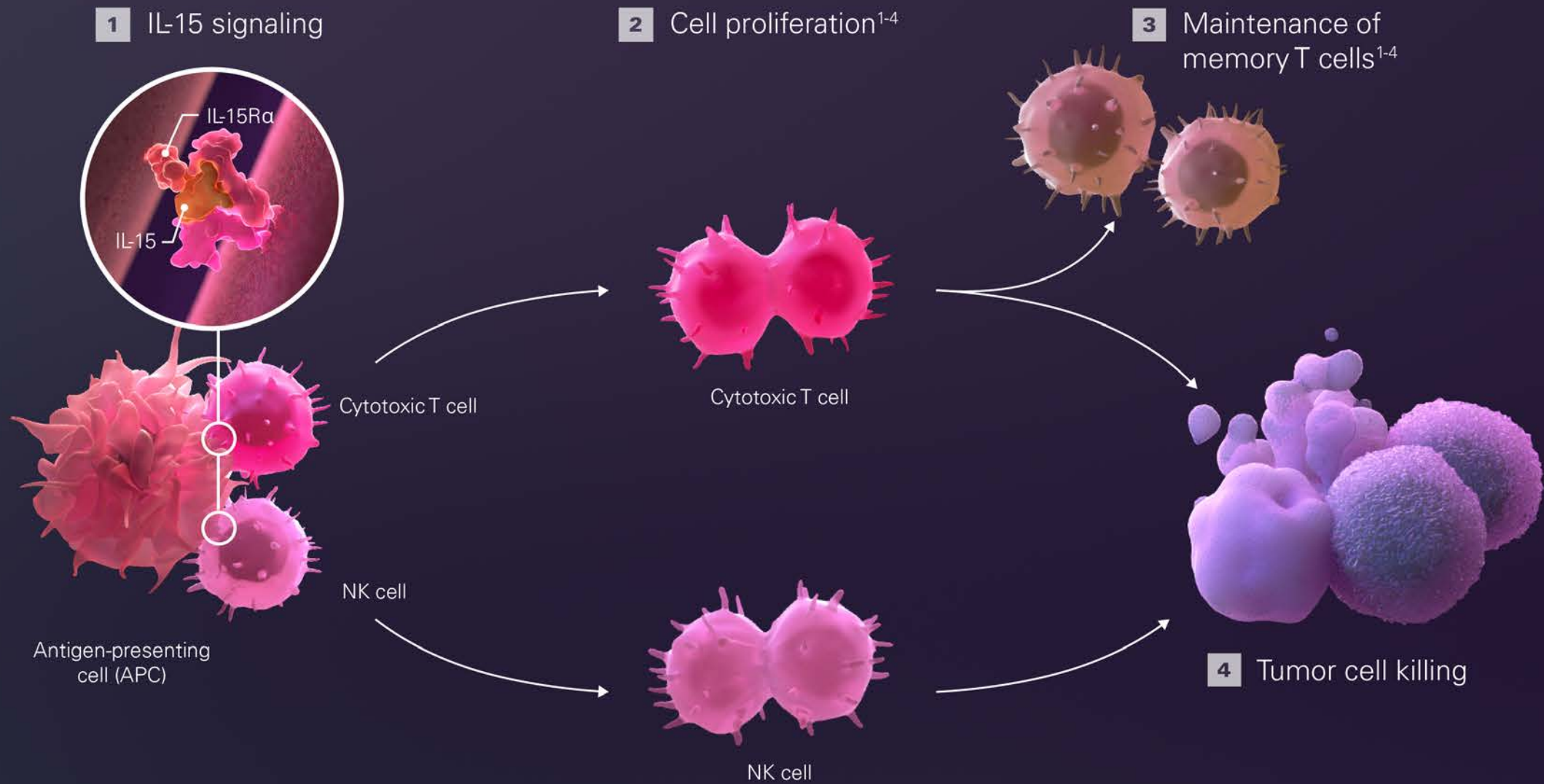


Alan Tan, MD, is a Director of GU Medical Oncology and an Assistant Professor in the Division of Hematology, Oncology and Cell Therapy at Rush University Medical Center. He specializes in kidney cancer, urothelial/bladder cancer, prostate cancer and melanoma. Dr. Tan has clinical research interest in designing and implementing clinical trials to test novel immunotherapies and targeted therapies in these cancers. He also leads the Rush University Precision Oncology and Genomics program. He is co-chair for the Hoosier Cancer Research Network (HCRN) Melanoma Working Group.

Agenda

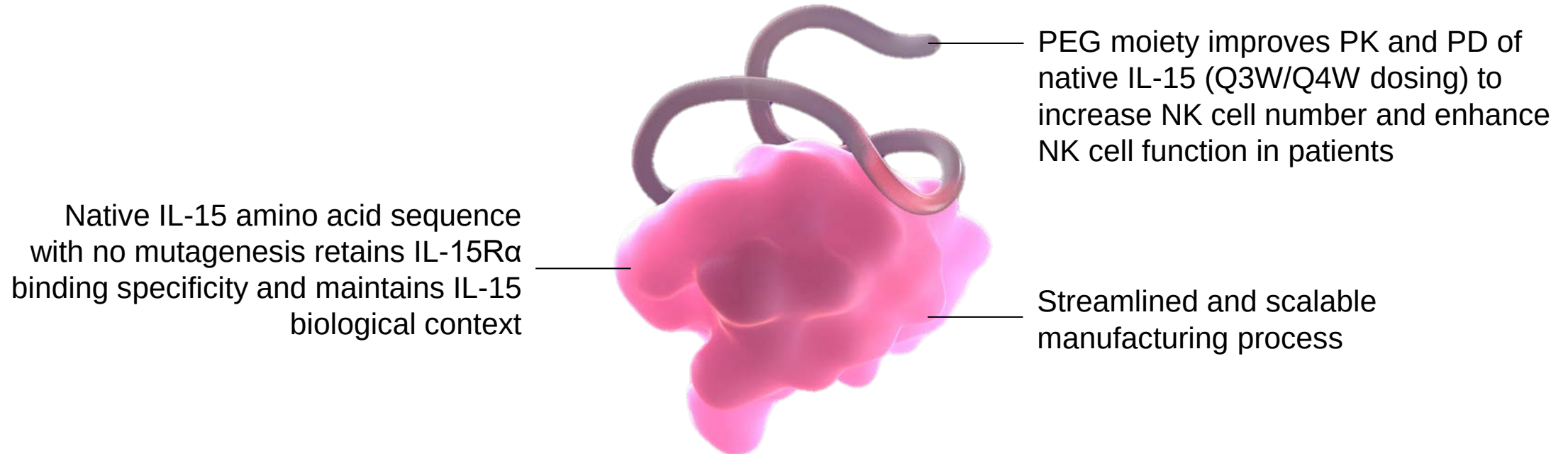
NKTR-255: an IL-15 pathway agonist

- **Overview of the NKTR-255 program and scientific rationale for combination with targeted tumor therapies**
 - Jonathan Zalevsky, Ph.D., Nektar Therapeutics
- **SITC 2021: "NKTR-255 + Cetuximab in Patients with Solid Tumors: Interim Safety and Efficacy Results from the Phase 1b Dose-escalation Study"**
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- **Discussion with Dr. Altan and Dr. Tan**
- **Q&A Session**



NKTR-255: IL-15 agonist designed to capture full receptor binding

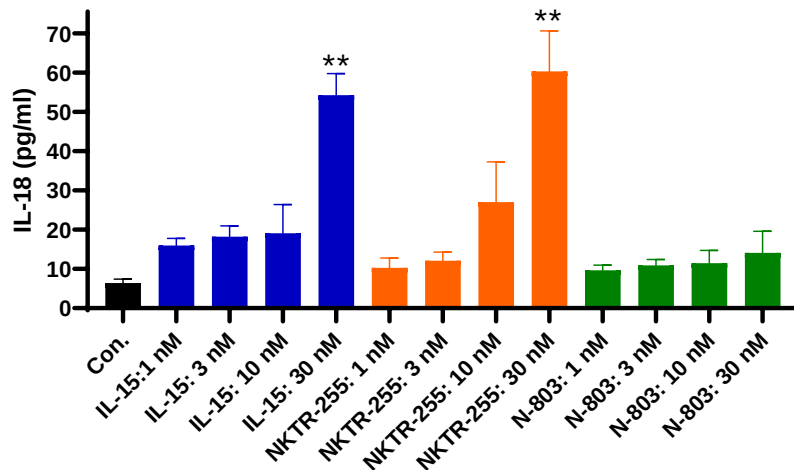
Nektar employed polymer conjugation technology to create NKTR-255



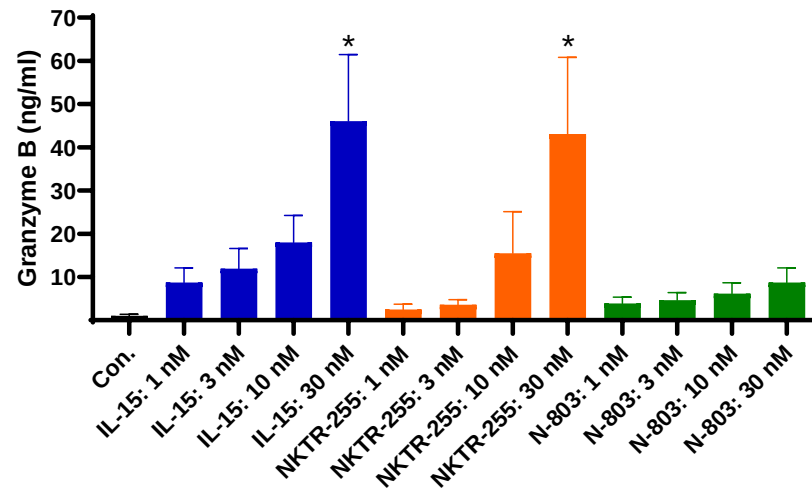
NKTR-255 engages the full spectrum of IL-15 biology to drive complete & functional immune response

Human PBMCs (3 or 4 healthy donors for IL-18 or Granzyme B, respectively)
overnight culture

IL-18



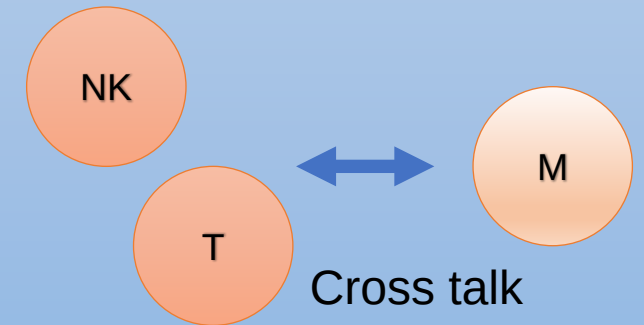
Granzyme B



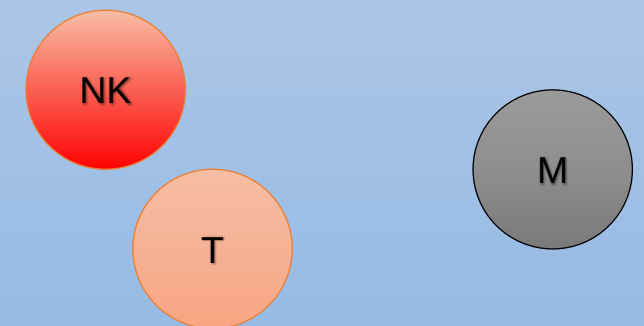
* : $P \leq 0.01$, **: $P \leq 0.0001$ (Dunnett's multiple comparisons test versus Con.)

NKTR-255 Induces Higher Maximal IL-18 and Granzyme B Secretion in Human PBMCs Compared to Precomplexed IL-15 Agonists

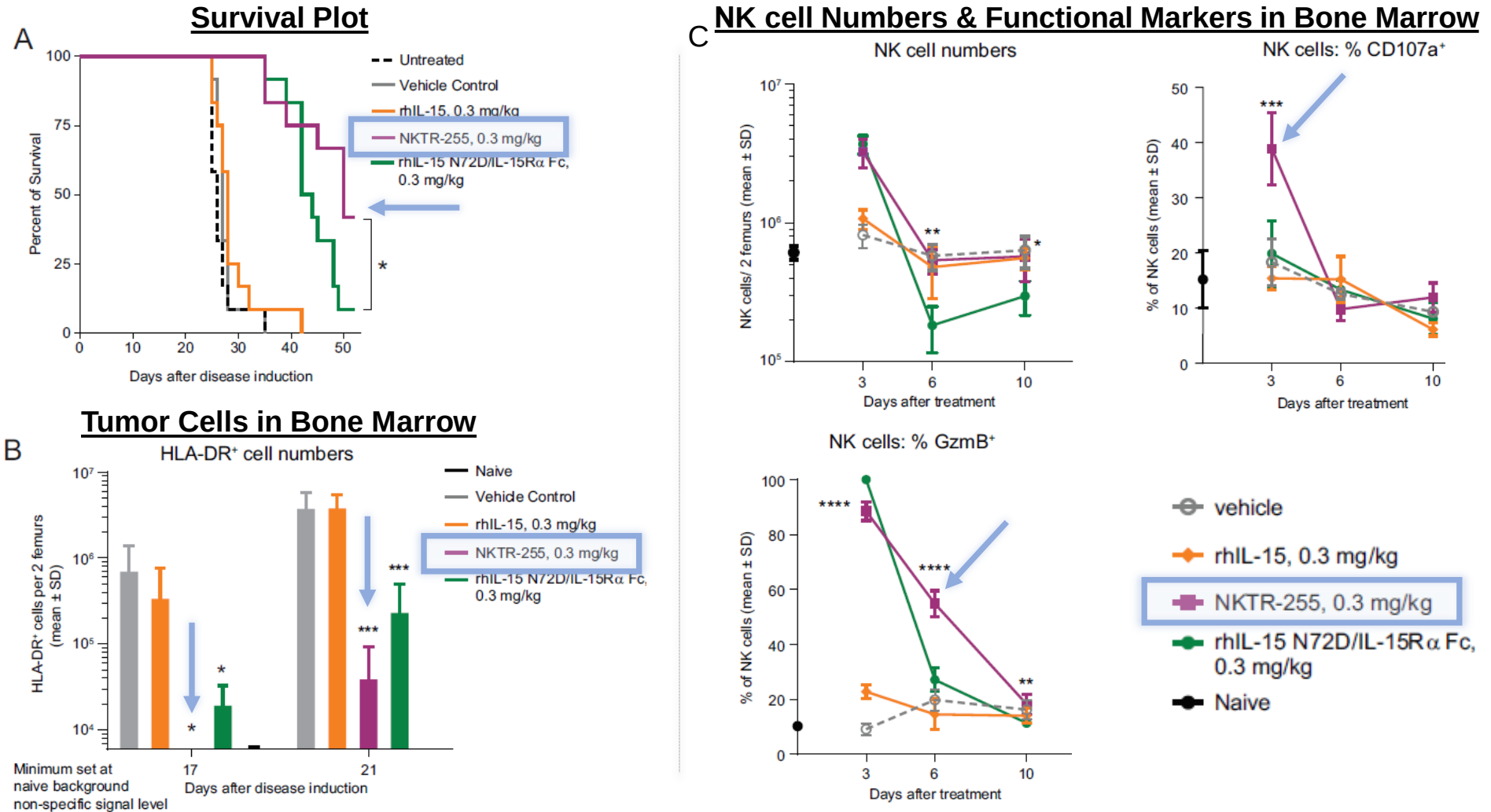
IL-15R α dependent ligands



IL-15R α independent ligands

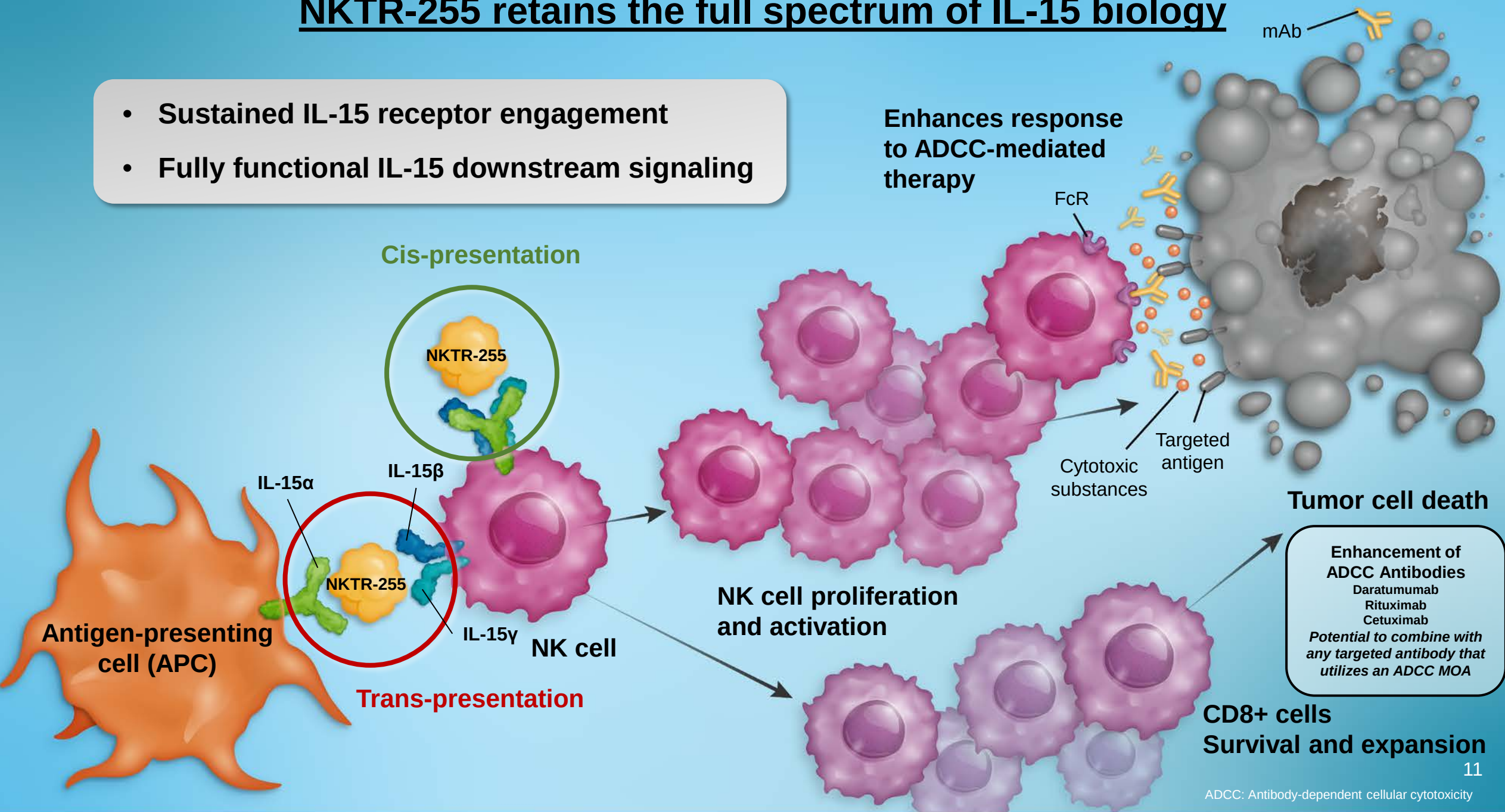


NKTR-255 has superior antitumor activity compared to precomplexed IL-15/IL-15R α in a Daudi lymphoma model

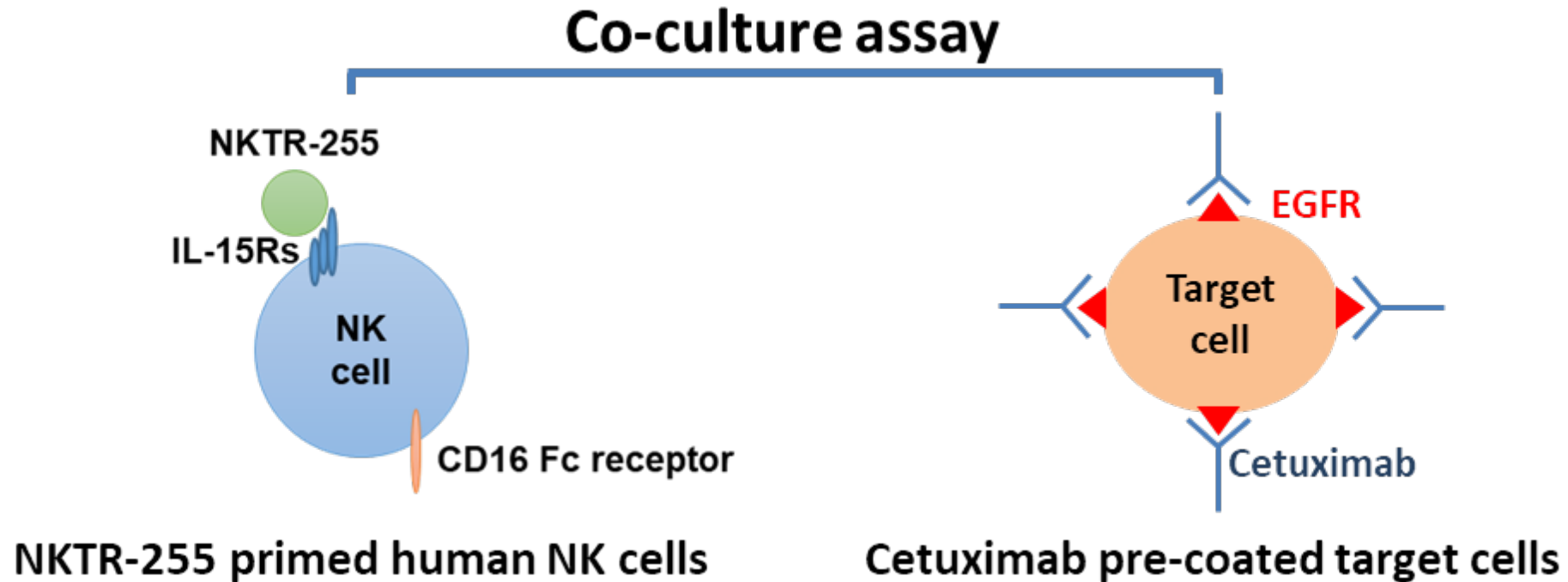


NKTR-255 retains the full spectrum of IL-15 biology

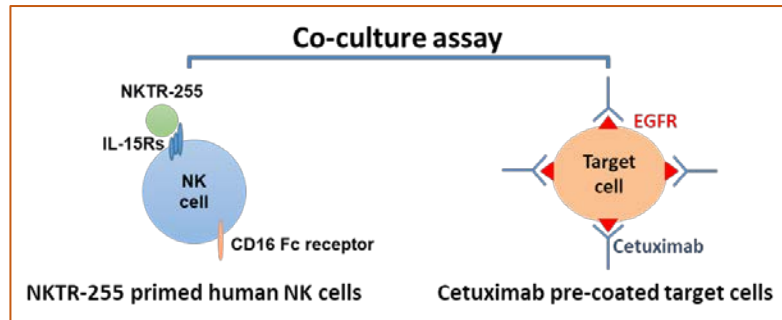
- Sustained IL-15 receptor engagement
- Fully functional IL-15 downstream signaling



NKTR-255 enhances cetuximab-mediated ADCC against HNSCC and CRC cell lines *in vitro*

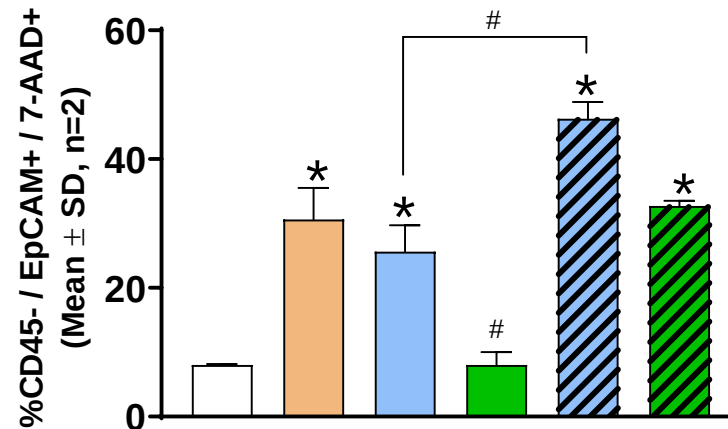


NKTR-255 enhances cetuximab-mediated ADCC against HNSCC and CRC cell lines *in vitro*



CRC

% HCT-116 Cell Death

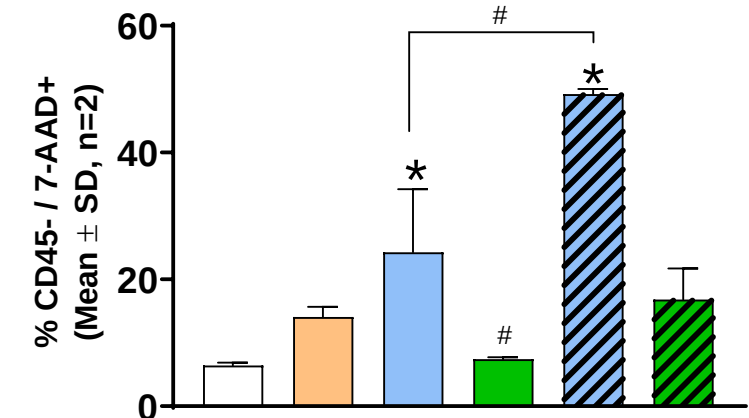


NKTR-255, ng/ml	-	300	-	-	300	300
Cetuximab, µg/ml	-	-	30	-	30	-
Isotype (IgG), µg/ml	-	-	-	30	-	30



HNSCC

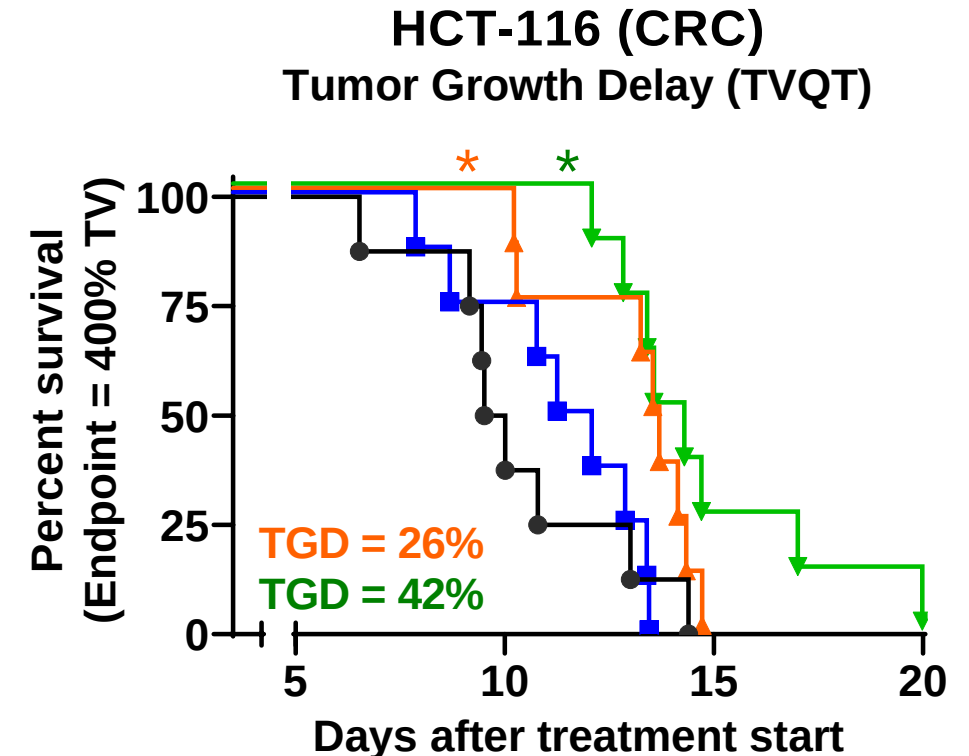
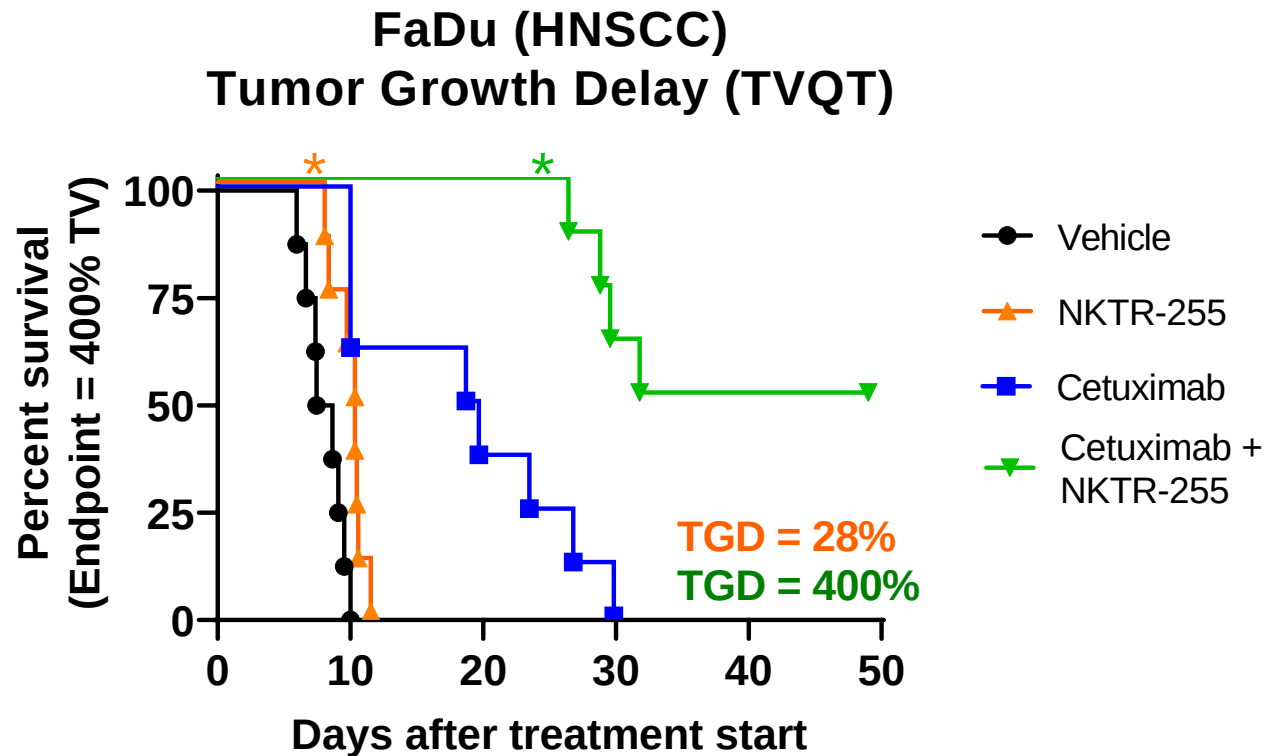
% FaDu Cell Death



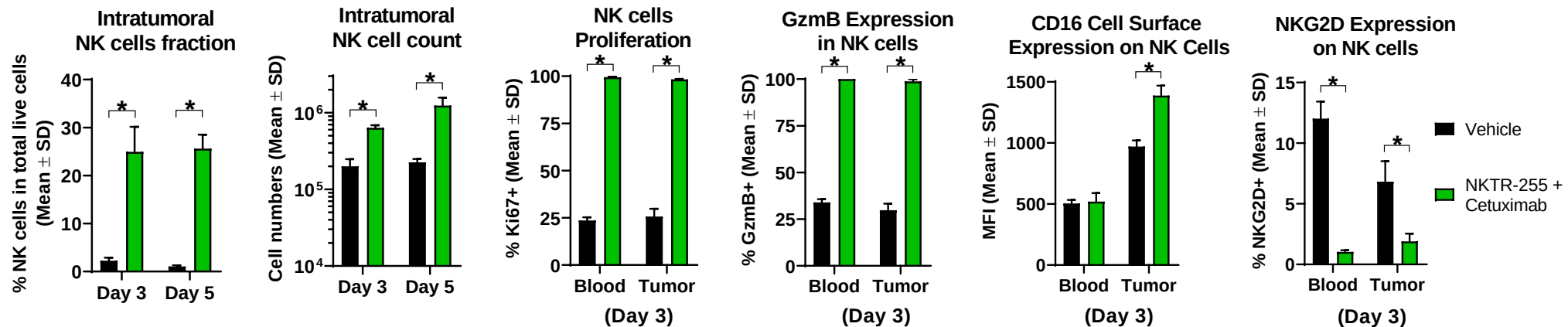
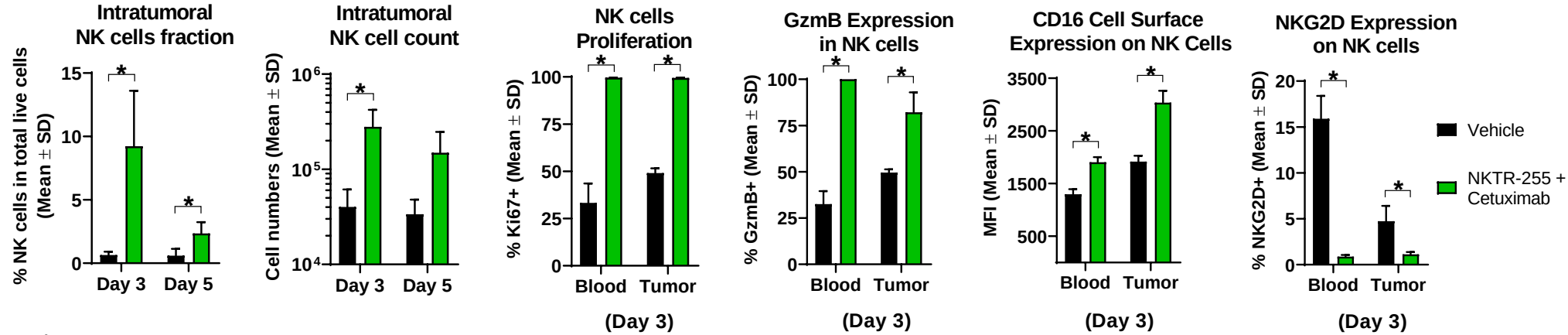
NKTR-255, ng/ml	-	300	-	-	300	300
Cetuximab, µg/ml	-	-	0.3	-	0.3	-
Isotype (IgG), µg/ml	-	-	-	0.3	-	0.3



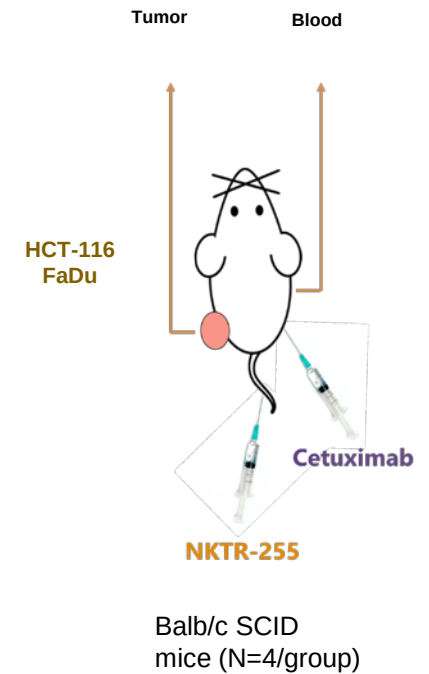
NKTR-255 combined with cetuximab produces tumor growth inhibition in cetuximab sensitive and resistant xenograft tumor models



NKTR-255 promotes NK cell infiltration and function in solid tumors

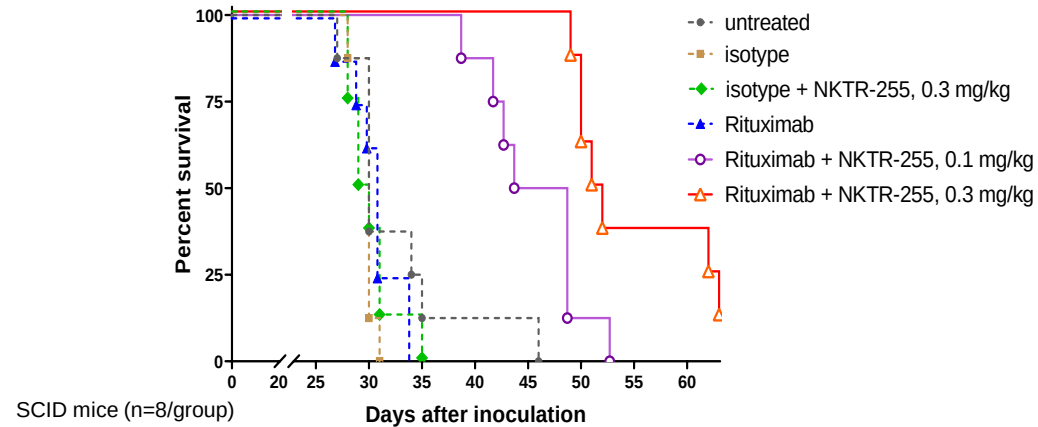


Flow cytometry analysis
(Day 3 and Day 5 after treatment)

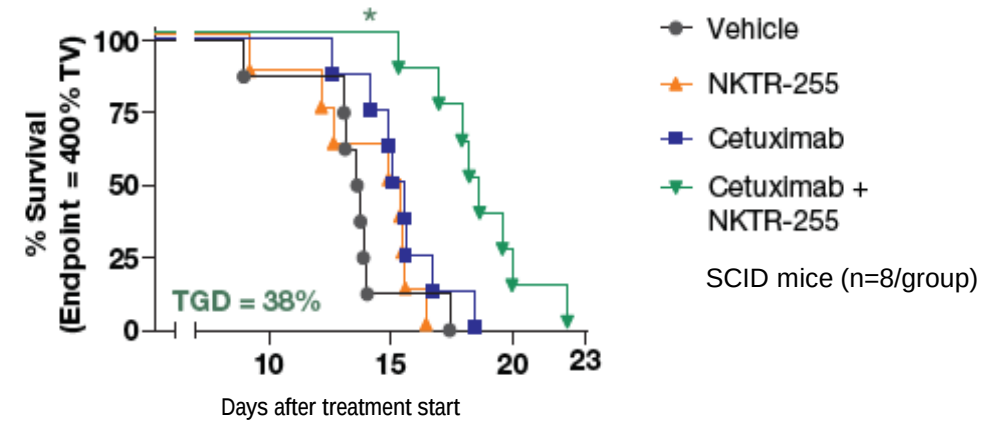


NKTR-255 enhances the ADCC efficacy of multiple liquid- and solid-tumor targeting antibodies

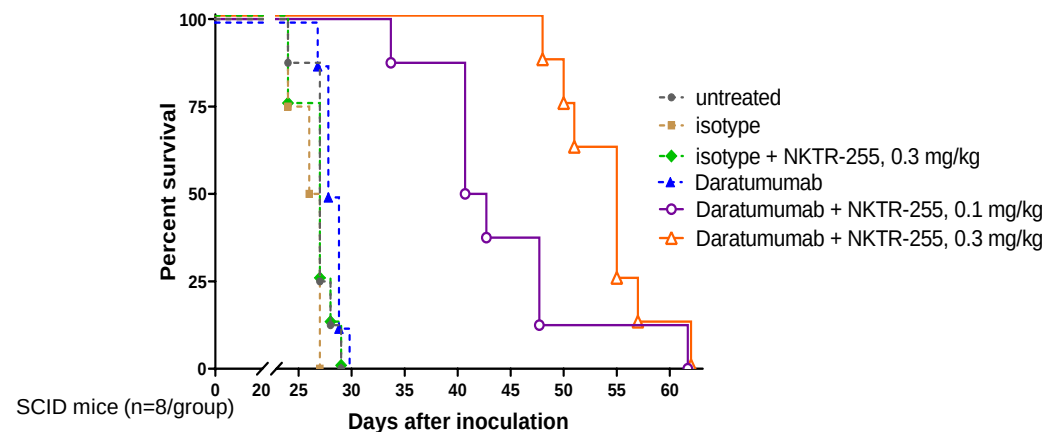
Rituximab-resistant Daudi Model



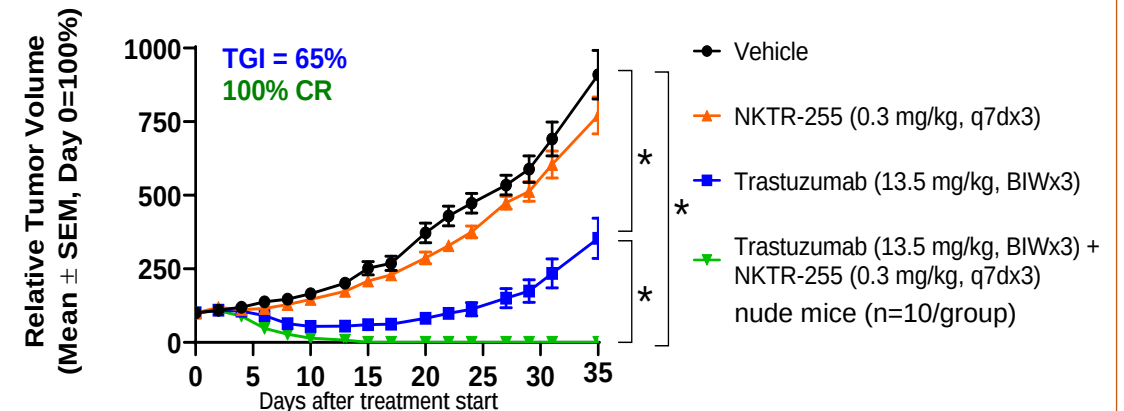
Cetuximab-resistant HT-29 Model



Daratumumab-resistant Daudi Model



Trastuzumab-sensitive SKOV-3 model



Key attributes of NKTR-255

- **NKTR-255 is a highly differentiated, potentially best-in-class IL-15 agonist**
 - Engages full spectrum of IL-15 biology to drive a complete & functional cellular immune response
 - Consistent NK and CD8 T cell expansion as well as NK cell activation
- **NKTR-255 can effectively engage NK cells and be paired with a wide range of therapeutics to treat both liquid and solid tumors**
- **Synergistic with antibodies that function via ADCC mechanisms (rituximab, daratumumab, trastuzumab, elotuzumab, and cetuximab)**

Phase 1/2 dose-escalation and dose-expansion study of NKTR-255 + cetuximab in patients with r/r HNSCC or CRC

POPULATION

- R/R HNSCC or CRC
- Life expectancy >12 weeks
- ECOG PS 0 or 1

PHASE 1: DOSE ESCALATION* Currently Enrolling

R/R HNSCC or CRC (n≤30)

Cetuximab
loading dose
400 mg/m² IV
(Week -1)

3 x 21-day cycles
NKTR-255 1.5–6 µg/kg IV per
cycle + cetuximab 250 mg/m² IV
weekly

Cohort 1 (closed)
NKTR-255 1.5 µg/kg + cetuximab

Cohort 2 (closed)
NKTR-255 3.0 µg/kg + cetuximab

Cohort 3 (enrolling)
NKTR-255 4.5 µg/kg + cetuximab

Cohort 4
NKTR-255 6.0 µg/kg + cetuximab

Dose escalation is ongoing

RP2D

PHASE 2: DOSE EXPANSION Pending RP2D (n≈48)

COHORT A: R/R HNSCC (n≈24)

Cetuximab
loading dose
400 mg/m² IV
(Week -1)

Every 21 days
NKTR-255 RP2D IV +
cetuximab IV

COHORT B: R/R CRC (n≈24)

Cetuximab
loading dose
400 mg/m² IV
(Week -1)

Every 21 days
NKTR-255 RP2D IV +
cetuximab IV

PRIMARY ENDPOINTS

- Safety and tolerability
- MTD or RP2D
- Objective response rate

SECONDARY ENDPOINTS

- Progression-free survival
- Overall survival
- PK/PD

NCT04616196. *Dose-escalation rules: Successive cohorts each receive escalating doses of NKTR-255 every 21 days plus a fixed dose of cetuximab weekly to determine the MTD/RP2D.

A two-parameter Bayesian logistic regression model was used to guide each dose level and determine the MTD. The MTD will be declared when at least 6 patients have been evaluated at a dose and the posterior probability of targeted toxicity is at least 60% for that dose. Patients who achieve an optimal response (PR or CR), will be given the option to continue NKTR-255 (every 28 days) as maintenance therapy. CR, complete response; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; IV, intravenous; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; RP2D, recommended phase 2 dose; R/R, relapsed/refractory.

Study procedures and assessments

Safety and Tolerability

- AEs were assessed by CTCAE v5.0
- The safety evaluable population includes all patients who received ≥ 1 dose of treatment
- Data cutoff: October 13, 2021

PK and PD

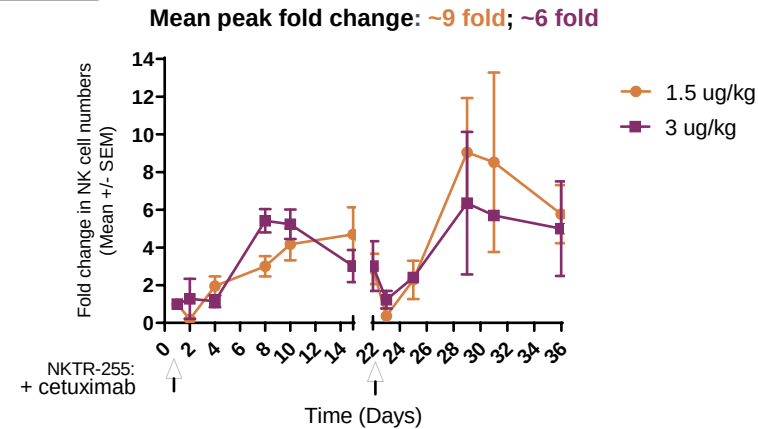
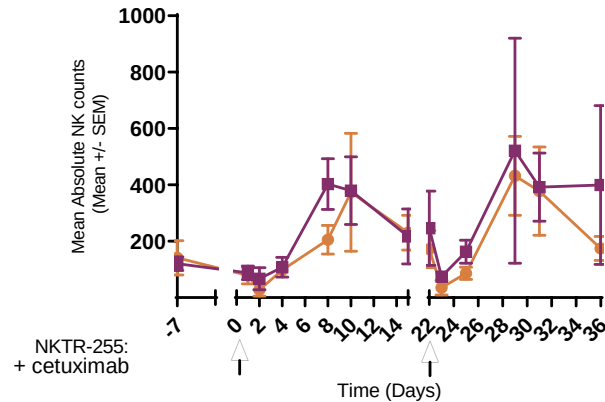
- PK with concentration–time profiles (data cutoff: June 8, 2021)
- PD (data cutoff: July 30, 2021)
 - Assessment of CD4⁺ T cells, CD8⁺ T cells, and NK Cells
 - Evaluation of inflammatory cytokines
 - Evaluation of T regs

Efficacy

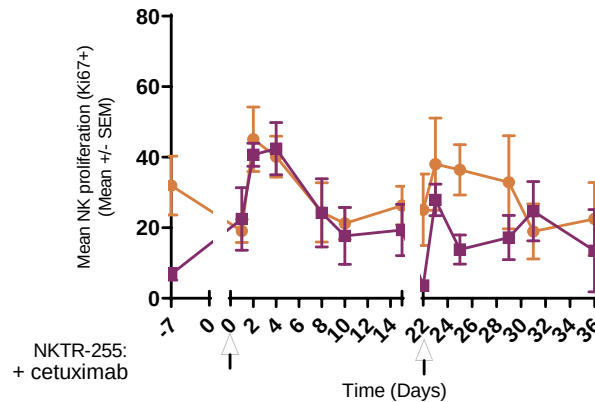
- Objective response: assessed by investigator every 9 weeks (± 1 week) per RECIST v1.1
- Per protocol, efficacy-evaluable population defined as patients with ≥ 1 post-baseline, on-treatment radiographic scan
- Data cutoff: October 13, 2021

NKTR-255 + cetuximab increased total expansion and proliferation of NK cells in blood

NK-cell expansion



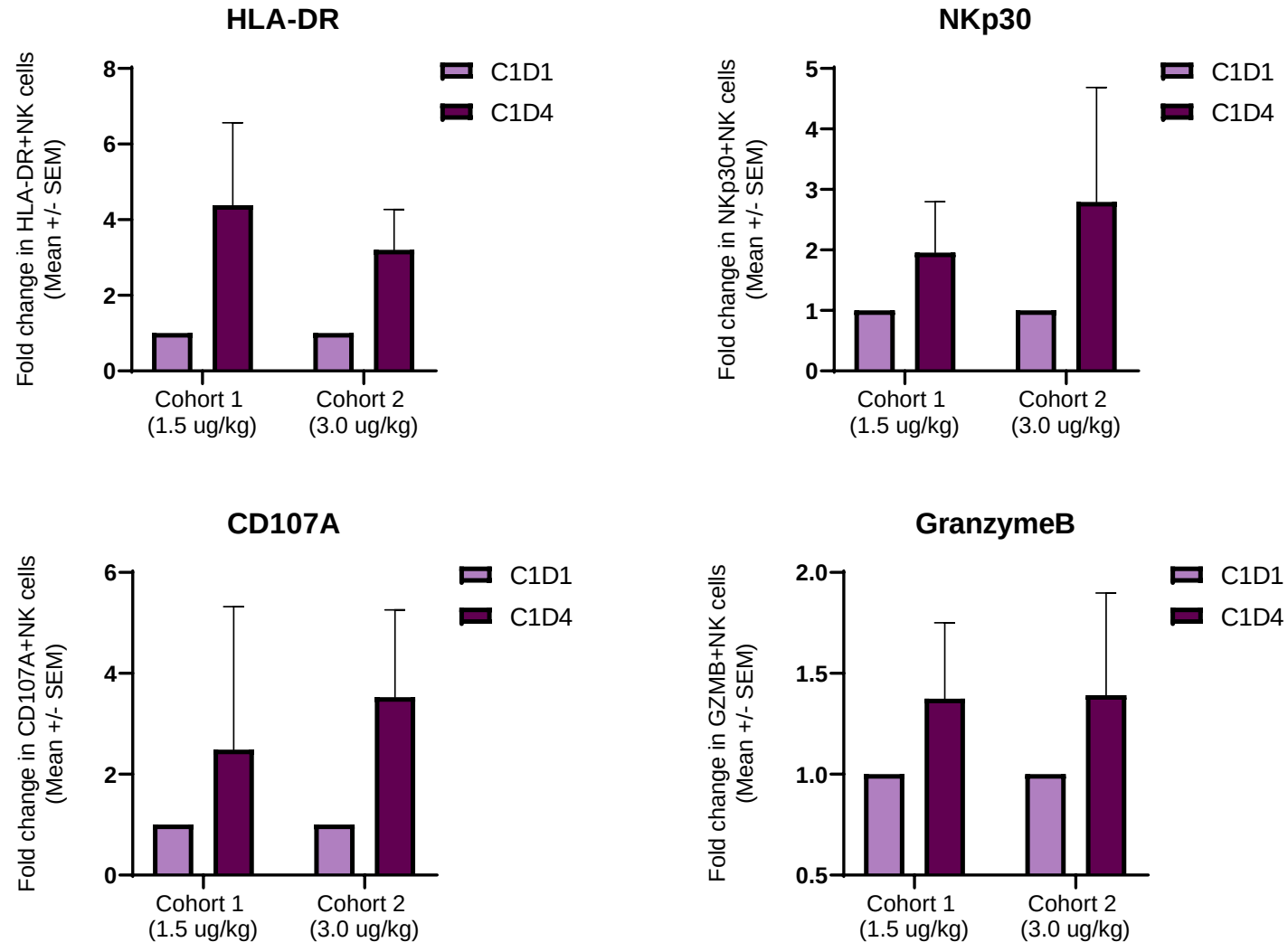
NK-cell proliferation



- Cetuximab administered with loading dose on Day -7 (not shown), and then weekly starting D1
- 1.5 ug/kg dose: N=7 for cycle 1, N= 5 for cycle 2;
3 ug/kg dose: N=7 for cycle 1, N=2 for cycle 2

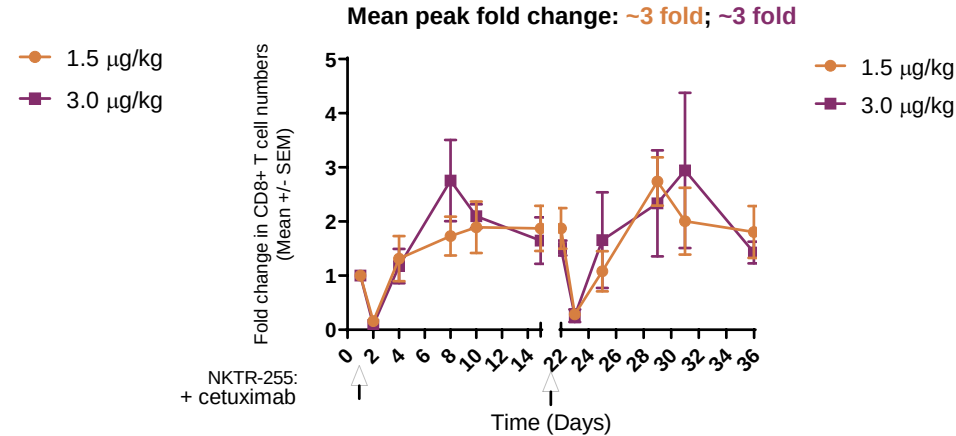
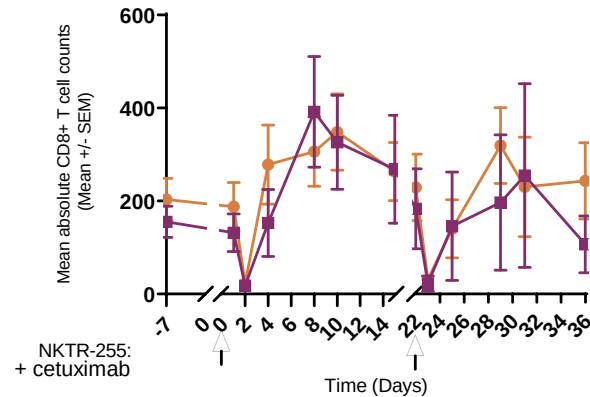
- NKTR-255 + cetuximab led to expansion and increased proliferative capacity (Ki67⁺) of NK cells in blood

Increased activation markers on NK cells after treatment with NKTR-255 + cetuximab

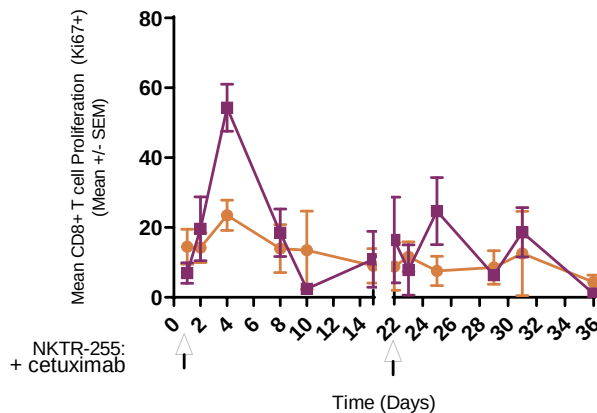


NKTR-255 + cetuximab increased total expansion and proliferation of CD8+ T Cells in blood

CD8⁺ T-cell expansion



CD8⁺ T-cell proliferation



- Cetuximab administered with loading dose on Day -7 (not shown), and then weekly starting D1
- 1.5 ug/kg dose: N=7 for cycle 1, N= 5 for cycle 2; 3 ug/kg dose: N=7 for cycle 1, N=2 for cycle 2

- NKTR-255 + cetuximab led to expansion and increased proliferative capacity (Ki67+) of CD8+ T cells in blood

Agenda

NKTR-255: an IL-15 pathway agonist

- **Overview of the NKTR-255 program and scientific rationale for combination with targeted tumor therapies**
 - Jonathan Zalevsky, Ph.D., Nektar Therapeutics
- **SITC 2021: "NKTR-255 + Cetuximab in Patients with Solid Tumors: Interim Safety and Efficacy Results from the Phase 1b Dose-escalation Study"**
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Patient demographics and disease characteristics: heavily pretreated population enrolled in the dose escalation phase

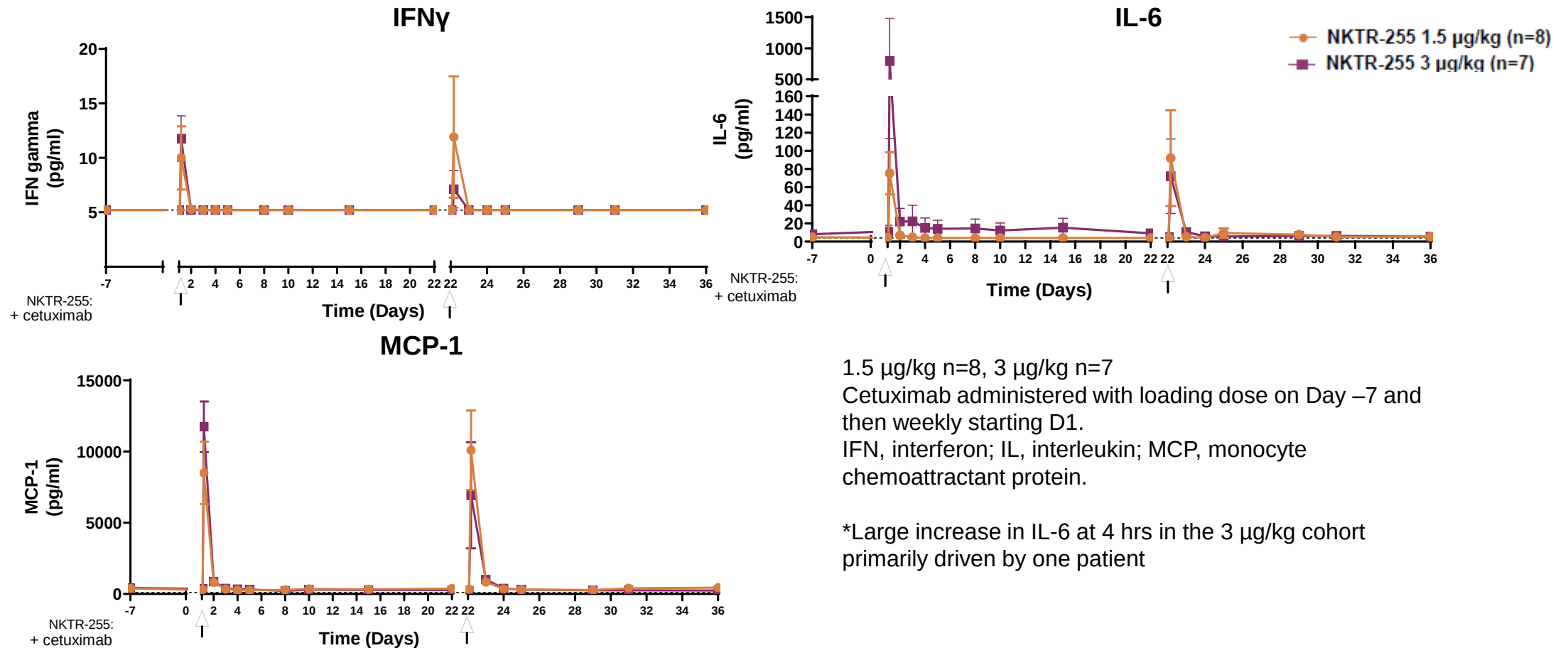
Patients with HNSCC		N=4
Median age, years		59.5
Sex, n (%)	Female	0
	Male	4 (100)
ECOG PS, n (%)	0	2 (50)
	1	2 (50)
Metastatic disease, n (%)		4 (100)
Median (range) number of prior therapies		4 (1–4)
Previous EGFR-targeted therapy, n (%)		1 (25)
Previous CPI, n (%)		3 (75)

Patients with CRC		N=10
Median age, years		59.5
Sex, n (%)	Female	2 (20)
	Male	8 (80)
ECOG PS, n (%)	0	4 (40)
	1	6 (60)
Mutational status, n (%)	<i>BRAF/RAS</i> all wild-type	5 (50)
	<i>KRAS</i> or <i>NRAS</i> mutation	4 (40)
	<i>RAS</i> wild-type <i>BRAF</i> missing	1 (10)
Median (range) number of prior therapies		3 (2–8)
Previous EGFR-targeted therapy, n (%)		4 (40)
Previous CPI, n (%)		3 (30)

NKTR-255 + cetuximab was well tolerated with no grade 4/5 TRAEs

Selected TRAEs; n (%)	NKTR-255 dose		Total (N=14)
	1.5 µg/kg (n=7)	3.0 µg/kg (n=7)	
Grade 1 or 2 (≥1 patient)			
Chills	1 (14.3)	1 (14.3)	2 (14.3)
Fatigue	1 (14.3)	2 (28.6)	3 (21.4)
Infusion-related reaction	2 (28.6)	6 (85.7)	8 (57.1)
Nausea	0	2 (28.6)	2 (14.3)
Grade 3 (all)			
Infusion-related reaction/hypoxia*	0	1 (14.3)	1 (7.1)

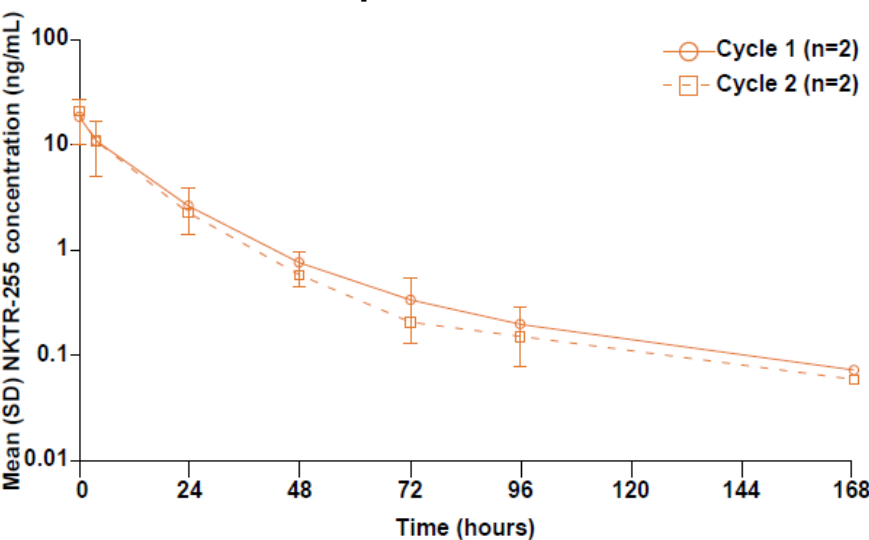
Transient increase and rapid reduction of cytokines back to baseline levels by 24 to 48 hours post dose



- NKTR-255 + cetuximab induced transient upregulation and rapid decline of inflammatory cytokines (IFN γ , MCP-1, and IL-6) by 24 to 48 hours post dose, with no further increases later in the cycle

NKTR-255 demonstrated a 27.8 hour half-life with minimal accumulation on a Q3W dosing regimen

Concentration–time profiles



Preliminary PK analyses

Dose	Cycle	T _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/mL)	T _{1/2} (hr)	CL (L/hr)
1.5 µg/kg	1 (N=2)	0.58	18.4	209	27.8	0.79
		(0.52, 0.65)	(8.90)	(50.1)	(33.2)	(69.9)
	2 (N=2)	0.53	21.5	204	20.2	0.70
		(0.52, 0.53)	(30.9)	(18.4)	(62.2)	(41.7)

PK parameters: Mean (coefficient of variance %).
All pre-dose NKTR-255 concentrations at Cycle 2+ were below the lower limit of quantification of 0.05 ng/mL.

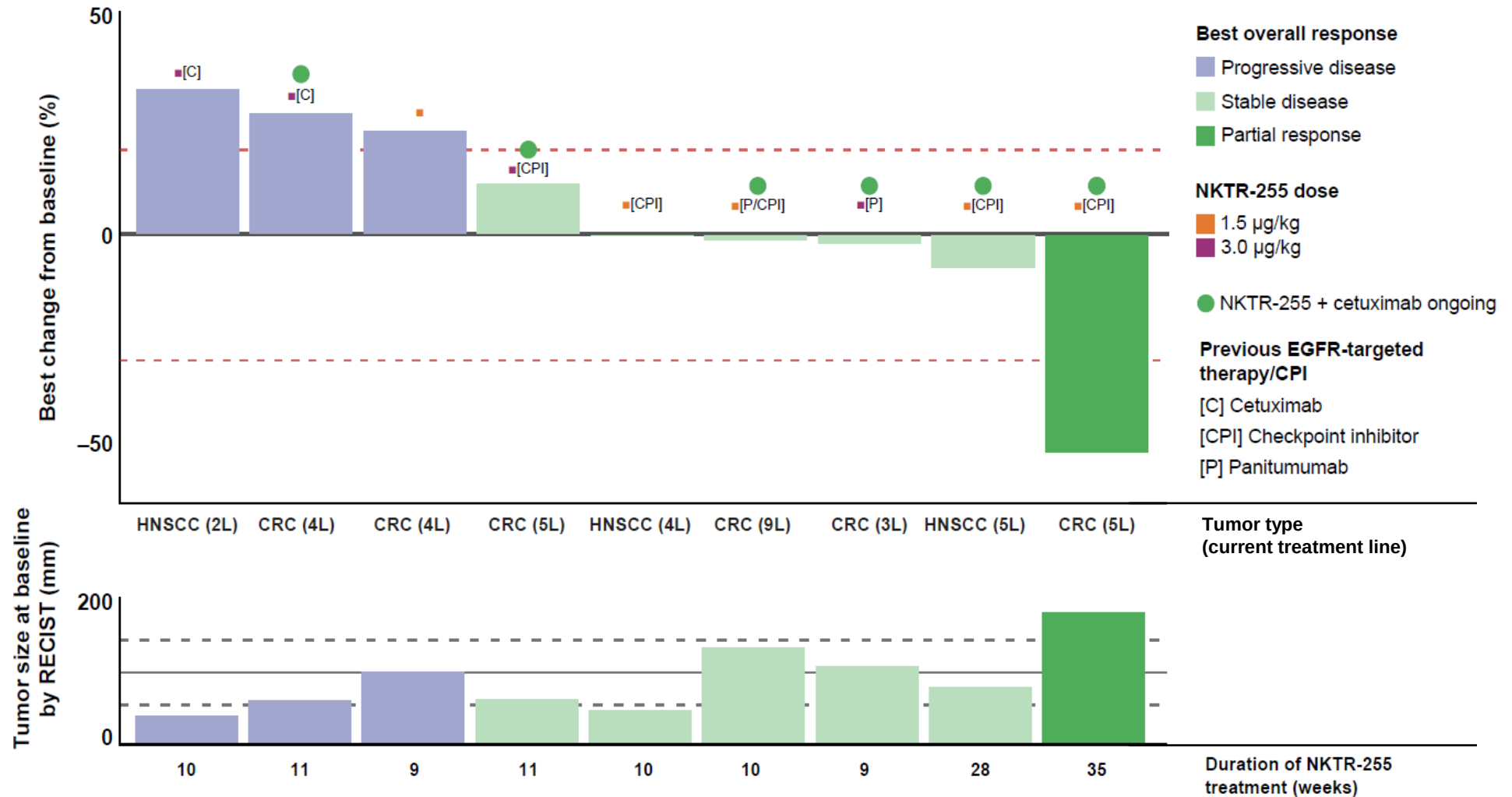
- The mean T_{1/2} of NKTR-255 (1.5 µg/kg) was 27.8 hours, which is ≈10-fold longer than that reported for rhIL-15,¹ with no or minimal accumulation following repeat dosing

NKTR-255 + cetuximab shows evidence of preliminary efficacy at initial doses in heavily pretreated patients

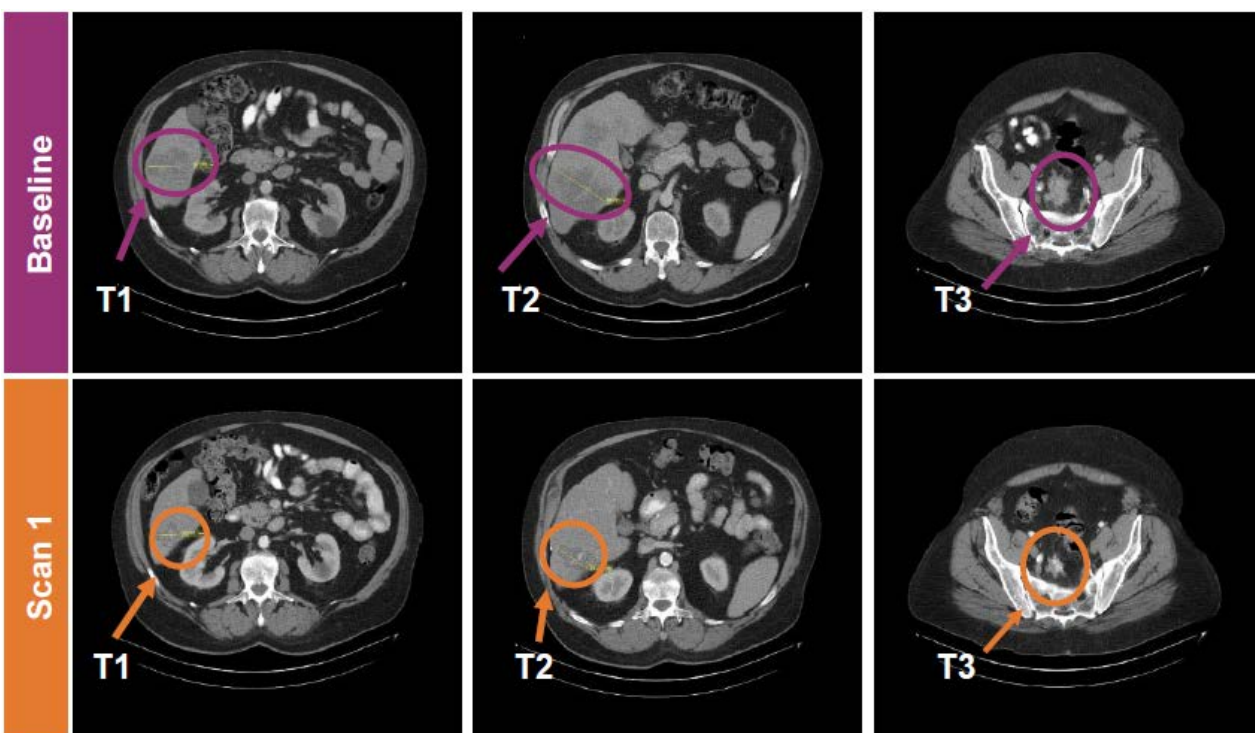
6 patients with CRC were efficacy evaluable (1 PR; 3 SD)

3 patients with HNSCC were efficacy evaluable (2 SD)

6 of 9 patients are ongoing treatment as of the October 13th data cut



Patient Vignette: 4L CRC patient achieved a confirmed PR (-51.5%) with NKTR-255 + cetuximab



	Tumor assessment	Lesion	Baseline	Scan 1 (Week 9)	Scan 2 (Week 18)
Target lesions measurements, mm	T1 – Liver	Right dome liver	61 x 51	38 x 34	24 x 14
	T2 – Liver	Interior right lobe liver	86 x 69	52 x 36	29 x 22
	T3 - Pelvis	Pelvis mass	47 x 42	32 x 25	46 x 23
Non-target lesions	NT01 - Lung	Lung nodule	Present	Present	Present
Sum of diameters, mm (% change from baseline)			194	122 (-37.5)	94 (-51.5)
Overall response (RECIST v1.1)				PR	PR

Prior treatments (best objective response):

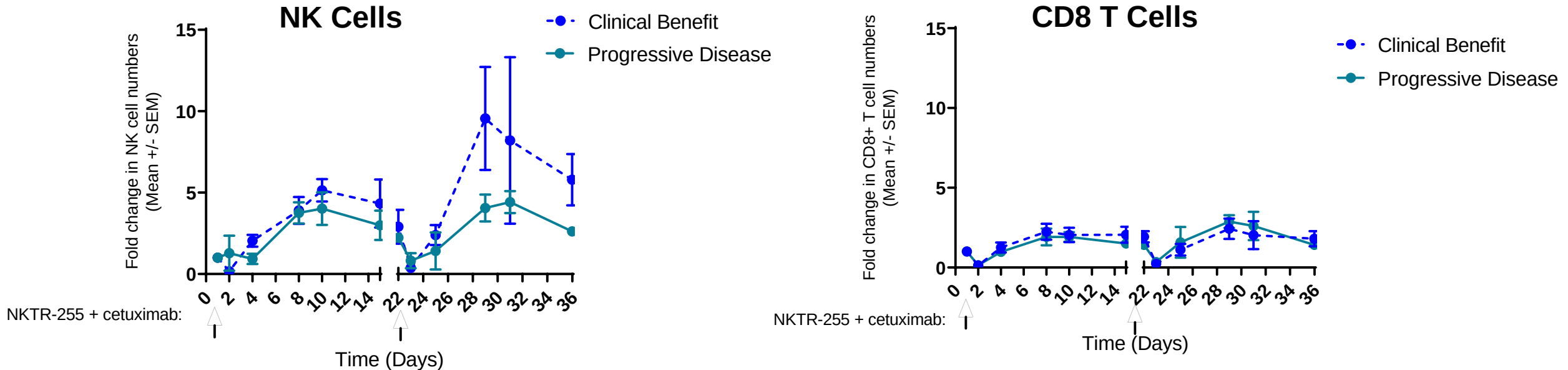
- 1) FOLFOX + nivolumab + bevacizumab (PR, Mar 19 to Nov 19)
- 2) Aflibercept + FOLFIRI (SD, Feb 2 to Mar 20)
- 3) Regorafenib (SD, Mar 20 to Jun 20)
- 4) Trifluridine/tipiracil (PD, Jul 20 to Oct 20)

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Evident differences in NK expansion in patients with clinical benefit as compared to progressive disease



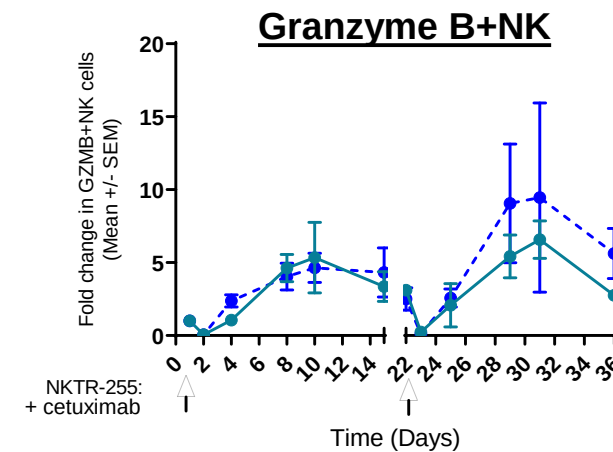
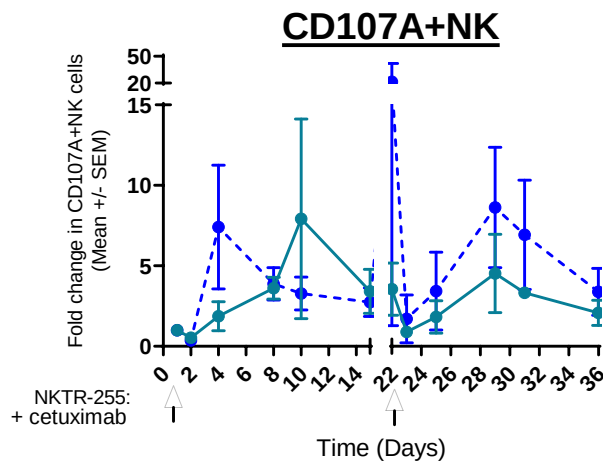
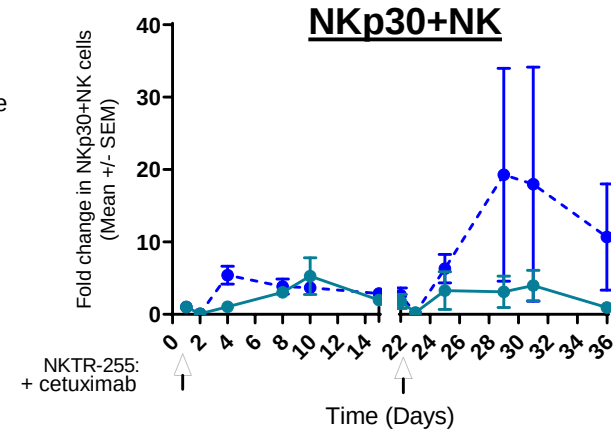
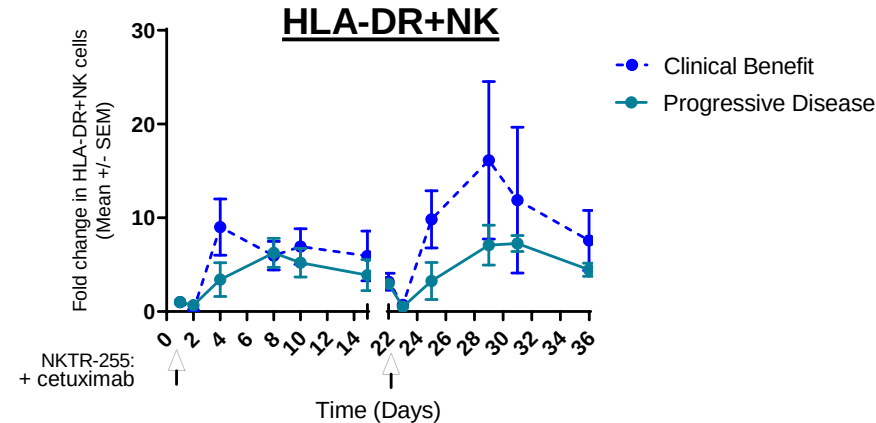
- Differences in NK expansion but not CD8 T cells expansion in patients with clinical benefit as compared to progressive disease

Patient Numbers: Clinical Benefit: Total 7 patients, Progressive Disease: Total 5 patients

*2 Pts missing C1D1-used baseline counts from Run-7 for this analysis

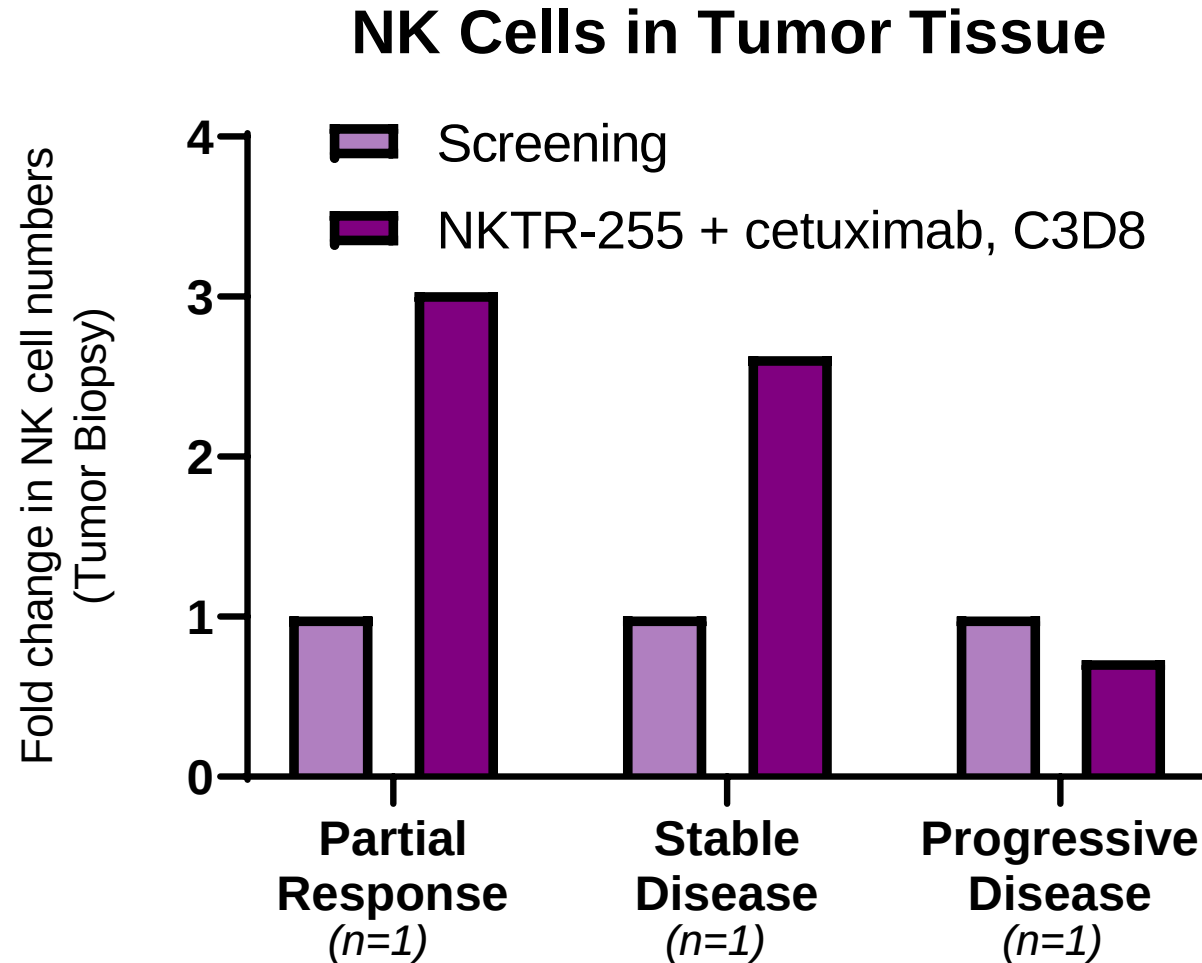
* Not all patients have data in cycle 2: 3 patients for clin benefit and 3 for PD

Evident differences in activation markers on NK cells in patients with clinical benefit as compared to progressive disease

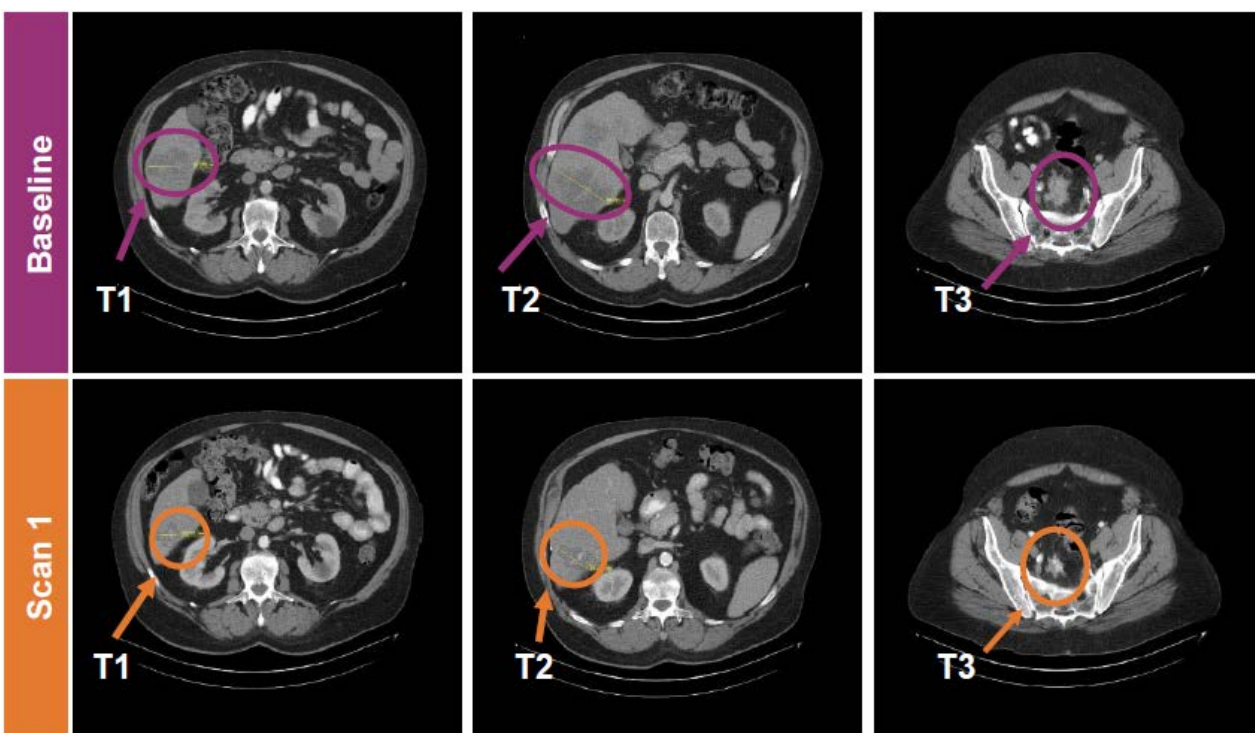


- NK activation marker activity demonstrates separation between patients with Clinical Benefit as compared to Progressive Disease

NK cell elevations in tumor biopsies from patients with clinical benefit after NKTR-255 + cetuximab



Patient Vignette: 4L CRC patient achieved a confirmed PR (-51.5%) with NKTR-255 + cetuximab

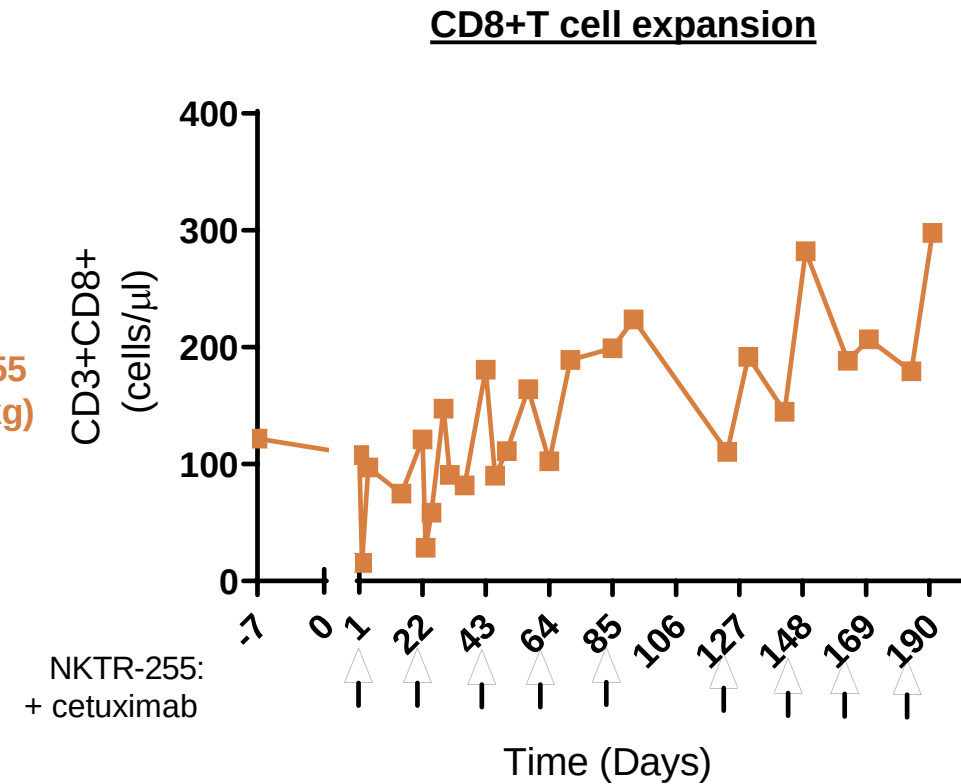
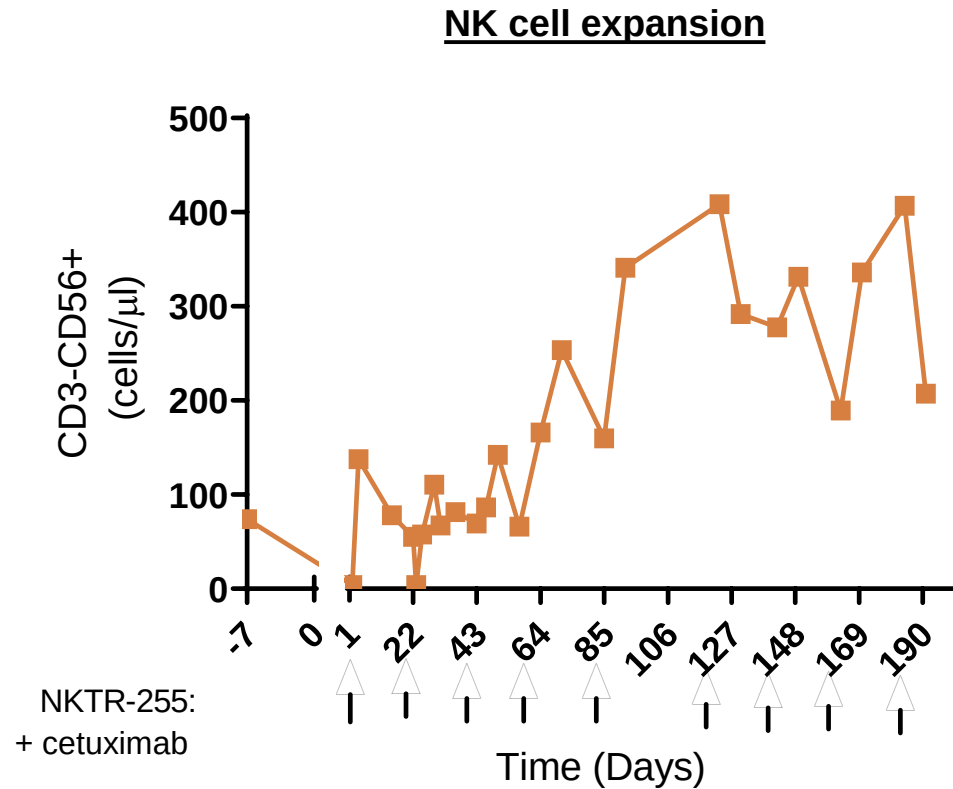


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Sum of diameters, mm (% change from baseline)			194	122 (-37.5)	94 (-51.5)
Overall response (RECIST v1.1)				PR	PR

Prior treatments (best objective response):

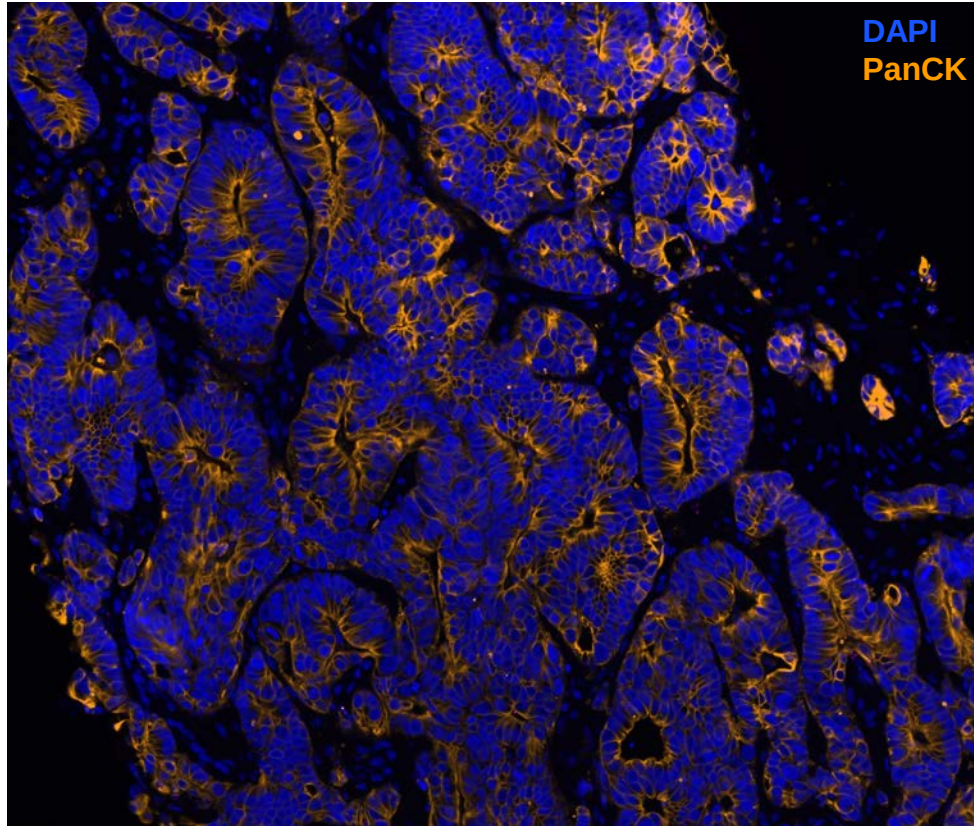
- 1) FOLFOX + nivolumab + bevacizumab (PR, Mar 19 to Nov 19)
- 2) Aflibercept + FOLFIRI (SD, Feb 2 to Mar 20)
- 3) Regorafenib (SD, Mar 20 to Jun 20)
- 4) Trifluridine/tipiracil (PD, Jul 20 to Oct 20)

Patient Vignette: NK and CD8+ T cells continue to expand over multiple cycles of NKTR-255 + cetuximab



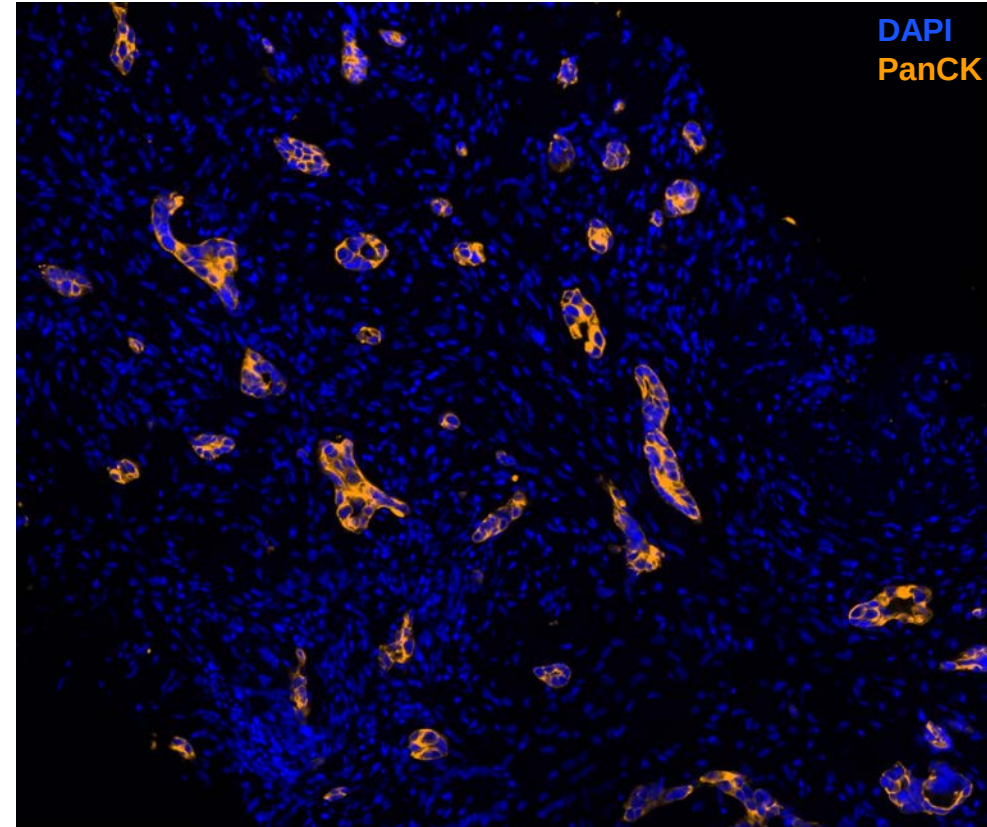
Elimination of tumor cells in a liver lesion after NKTR-255 + cetuximab treatment

Screening



Tumor cells per $\text{mm}^2 = 7475$

NKTR-255 + cetuximab, C3D8

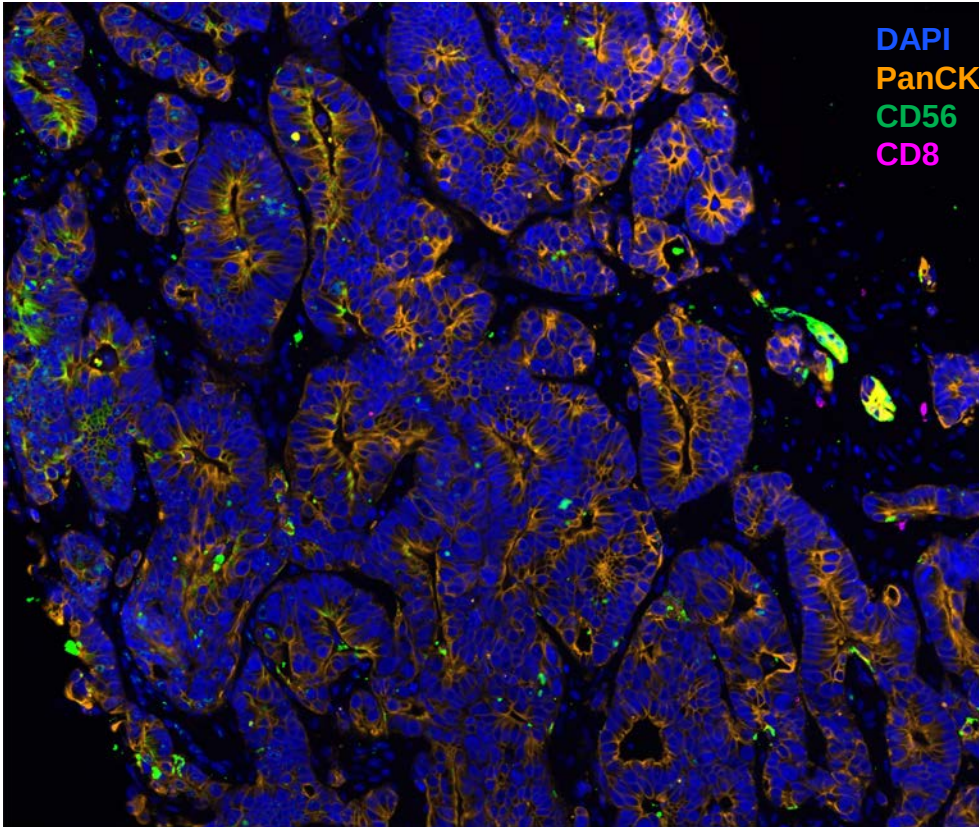


Tumor cells per $\text{mm}^2 = 737$

Liver lesion

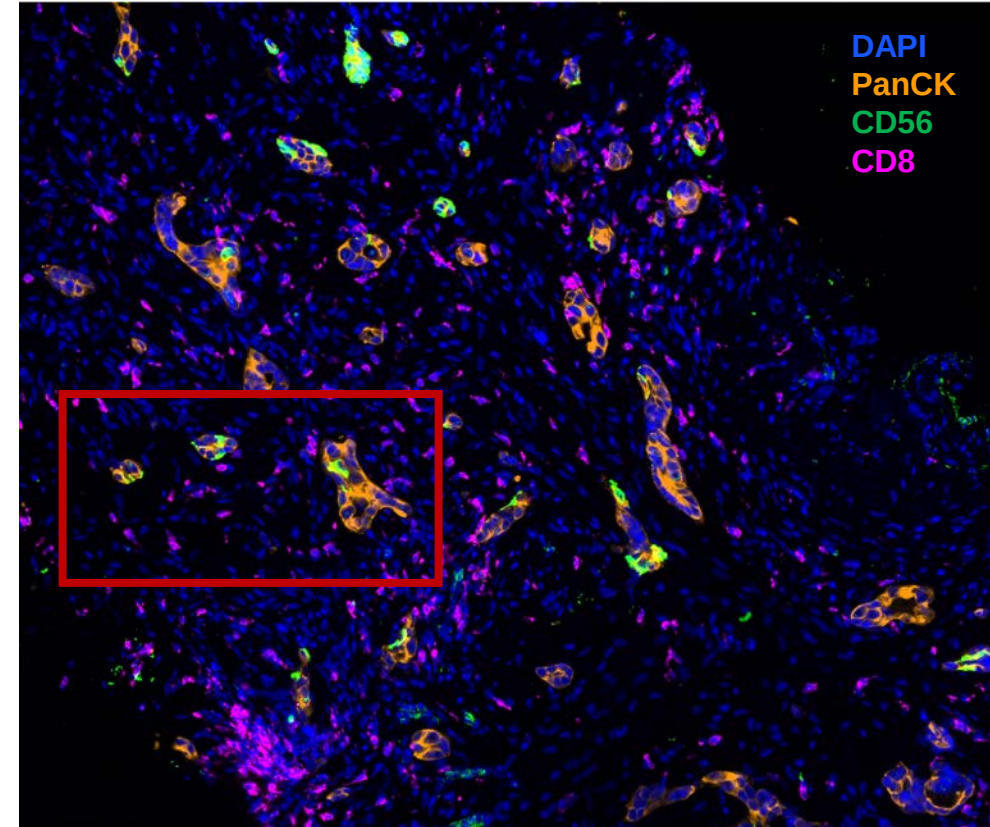
NKTR-255 + cetuximab treatment increases NK and CD8 T cells in the tumor microenvironment

Screening



CD56 (NK) cells per mm² = 31
CD8 T cells per mm² = 8

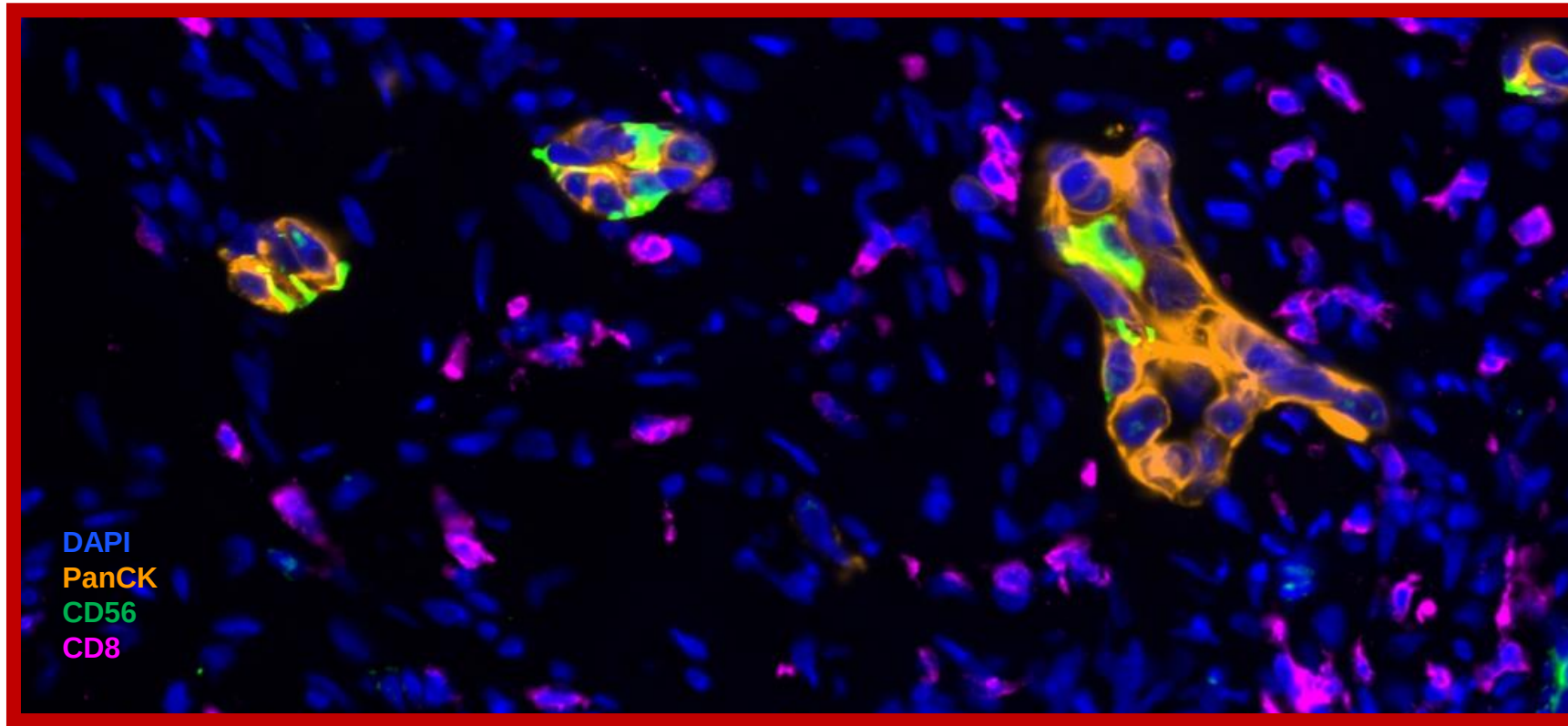
NKTR-255 + cetuximab, C3D8



Liver lesion

CD56 (NK) cells per mm² = 94
CD8 T cells per mm² = 691

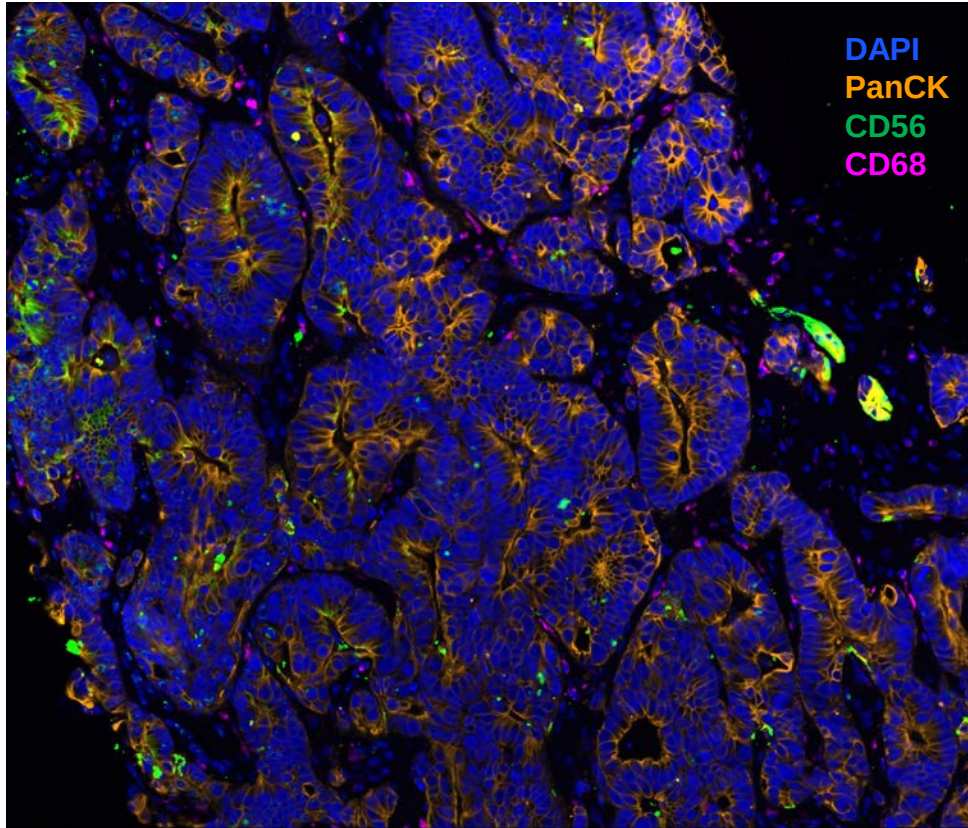
NKTR-255 + cetuximab treatment increases NK and CD8 T cells in the tumor microenvironment



Liver lesion

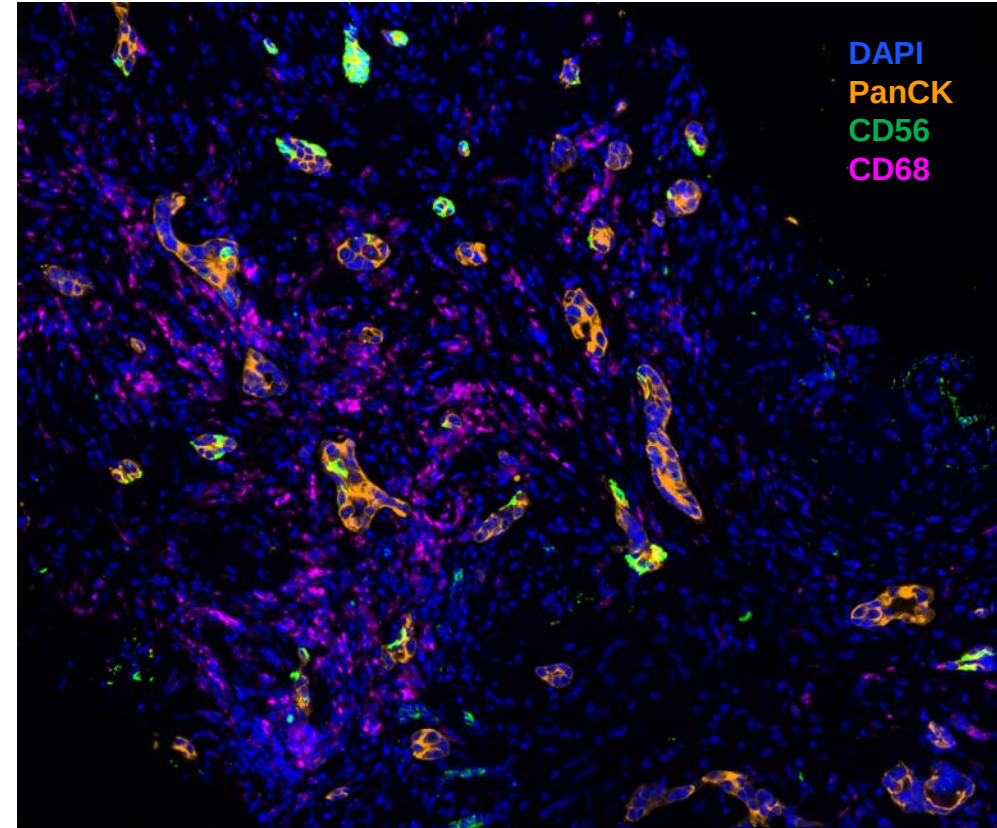
NKTR-255 + cetuximab treatment increases macrophages in the tumor microenvironment

Screening



CD56 (NK) cells per mm² = 31
CD68 (Mac) cells per mm² = 136

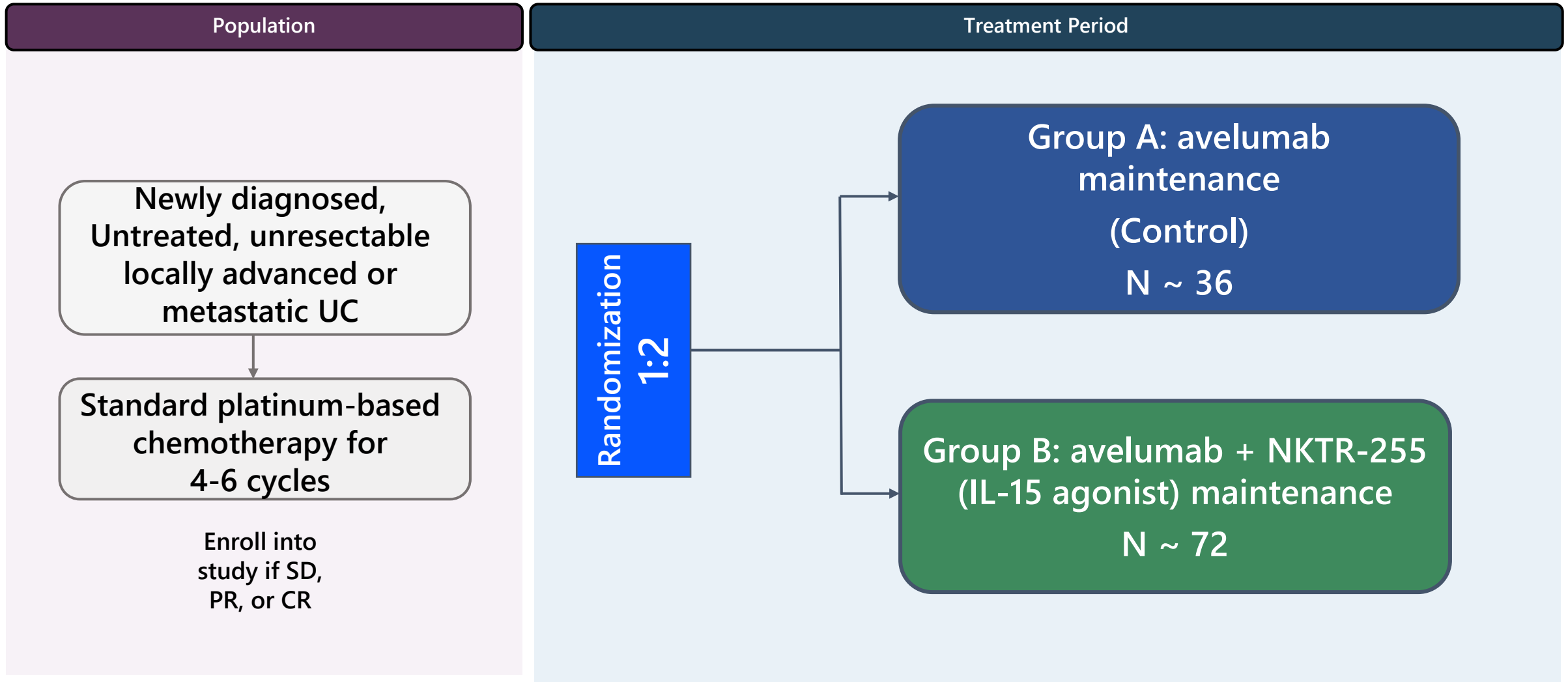
NKTR-255 + cetuximab, C3D8



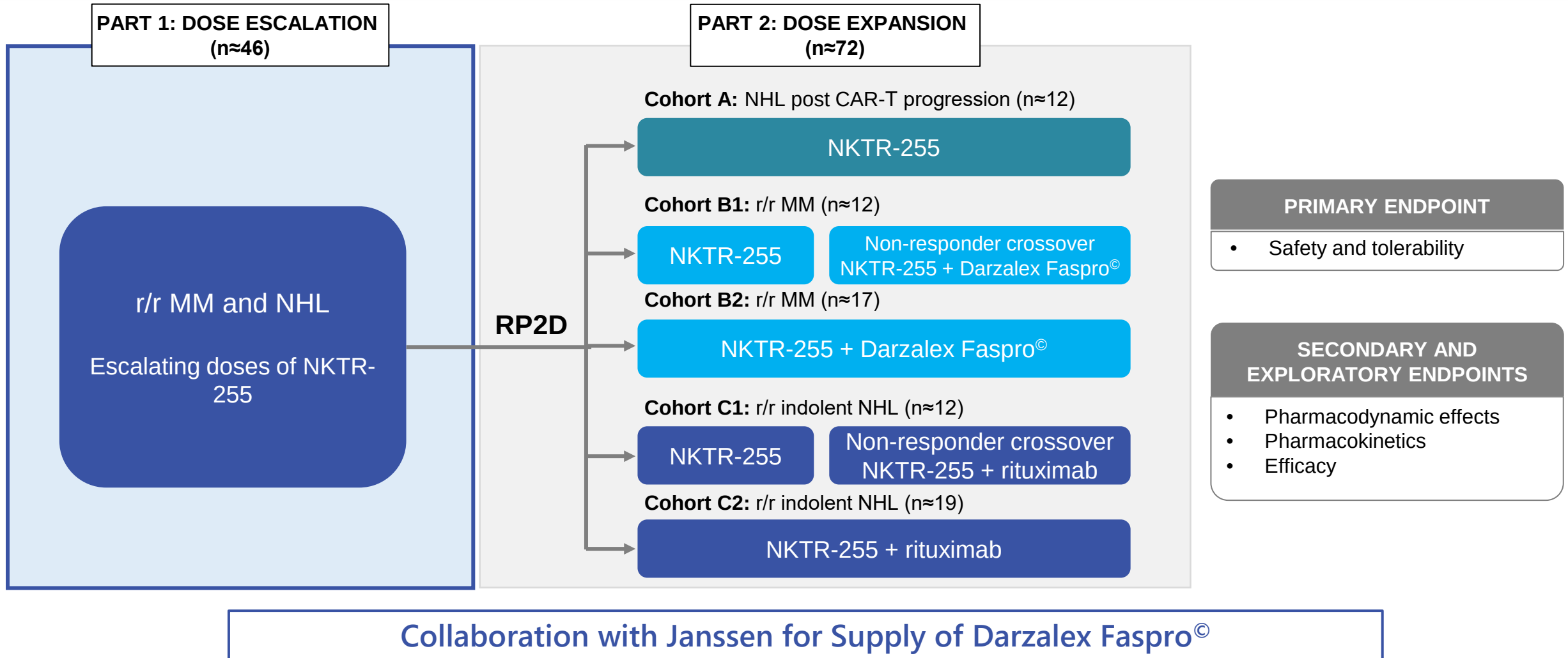
CD56 (NK) cells per mm² = 94
CD68 (Mac) cells per mm² = 979

Liver lesion

JAVELIN Bladder Medley Study: NKTR-255 plus avelumab arm to compare to avelumab alone



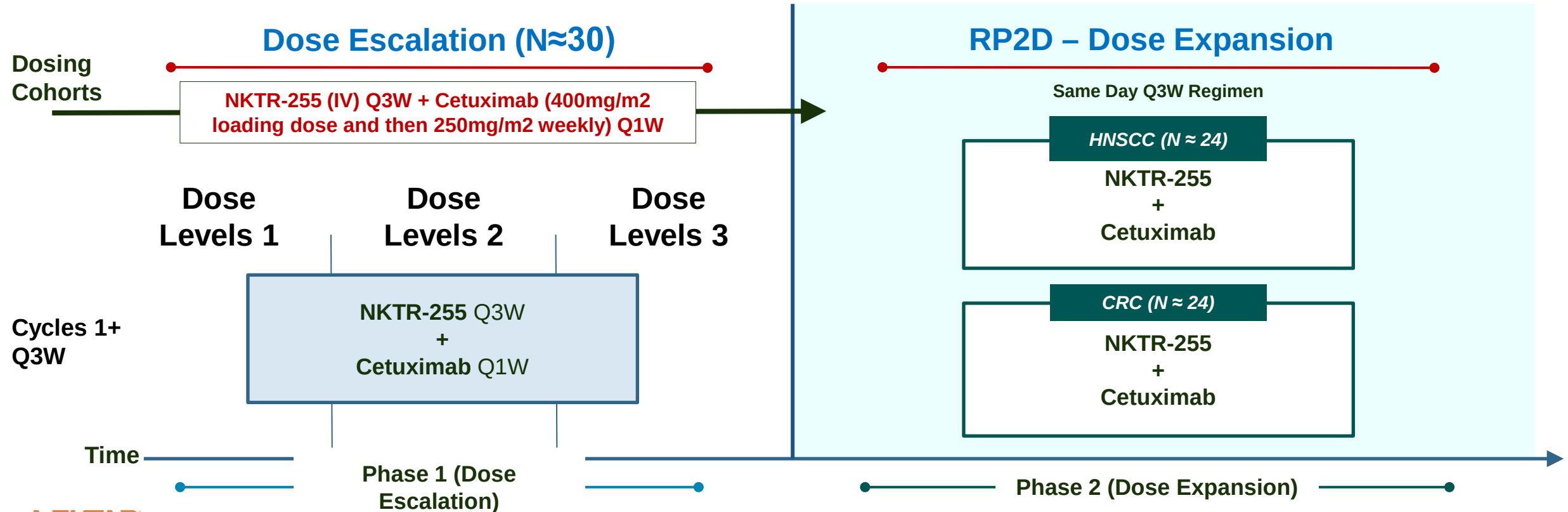
Phase 1, open-label, multicenter dose-escalation and dose-expansion study in patients with r/r MM or NHL



Phase 1 dose-escalation and dose-expansion study of NKTR-255 in patients with HNSCC and CRC

Locally advanced metastatic:

- **HNSCC:** Progression (or toxicity precluding additional treatment on any first or second line platinum-based chemotherapy AND anti-PD-(L)1 antibody
- **CRC:** Received or intolerant to 2 prior cancer therapy regimens administered for metastatic disease



Agenda

NKTR-255: an IL-15 pathway agonist

- **Overview of the NKTR-255 program and scientific rationale for combination with targeted tumor therapies**
 - Jonathan Zalevsky, Ph.D., Nektar Therapeutics
- **SITC 2021: "NKTR-255 + Cetuximab in Patients with Solid Tumors: Interim Safety and Efficacy Results from the Phase 1b Dose-escalation Study"**
 - **Study Design & Biomarker Data:** Jonathan Zalevsky, Ph.D., Nektar Therapeutics
 - **Clinical Safety & Efficacy:** Dimitry Nuyten, M.D., Ph.D., Nektar Therapeutics
 - **Translational Research:** Jonathan Zalevsky, Ph.D., Nektar Therapeutics
- **Discussion with Dr. Altan and Dr. Tan**
- **Q&A Session**

Q&A session



Jonathan Zalevsky, PhD

Chief Research &
Development Officer at
Nektar Therapeutics



Dimitry Nuyten, MD, PhD

Chief Medical Officer at
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