Novartis Biomedical Research

The role of exposure-response analyses in determination of RDE in a FIH Ph1/1b study

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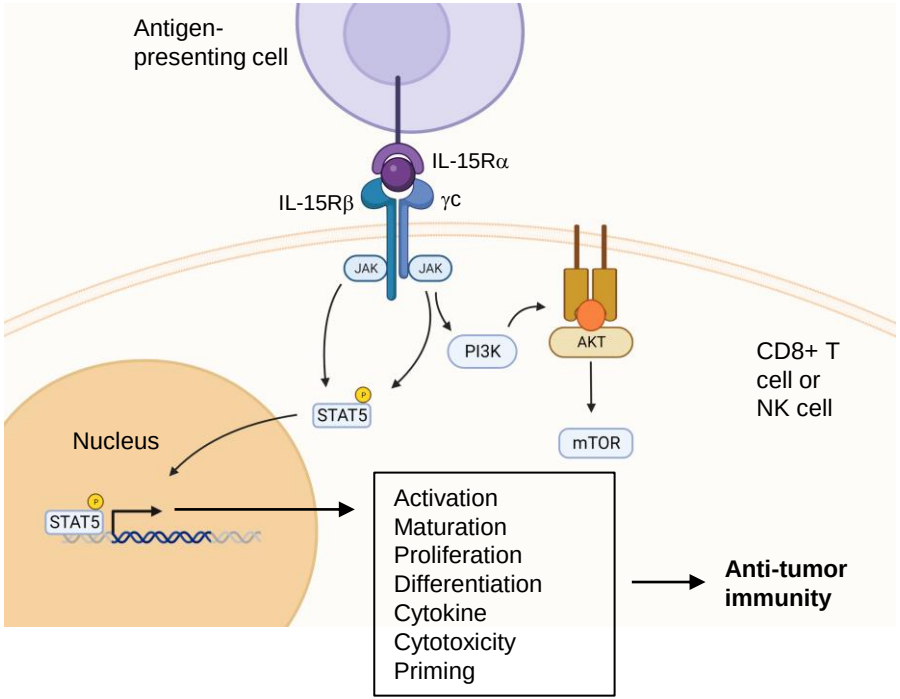
IL-15 as a strategic immuno-oncology therapeutic target

- IL-15 is a cytokine involved in the growth, mobilization and activation of NK, CD8 T cells, and NKT cells
- Contrary to IL-2, IL-15 does not have a strong effect on Tregs and minimizes activation-induced cell death
- Supporting the function of cytotoxic immune cells can be an effective cancer immunotherapy



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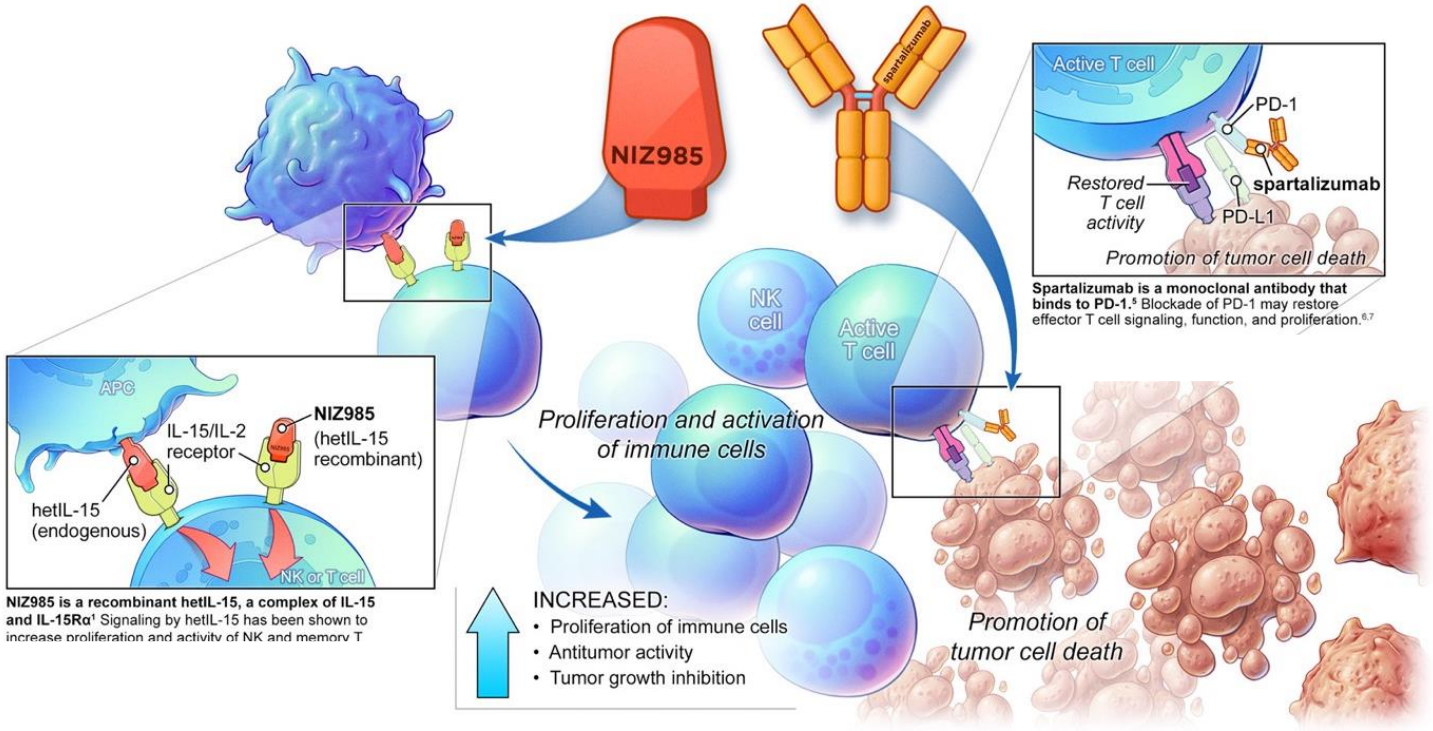
Proposed mechanism of action of NIZ985 + anti-PD1 (Spartalizumab)



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NIZ985B12101 clinical trial study design

Phase I/Ib, NCT02452268

Patients with metastatic/ unresectable solid tumors who have previously relapsed after CPI response

DOSE ESCALATION (SA then combo)

SA x 2 cycles; add spartalizumab (aPD1) after 1st disease evaluation
NIZ985 SC qw x 3 (4 wks/cycle)

2 mcg/kg | 4 mcg/kg | 8 mcg/kg | 16 mcg/kg | 12 mcg/kg

DOSE ESCALATION (Combo)

NIZ985 + spartalizumab
NIZ985 SC qw x 3
Spartalizumab IV q4w (4 wks/cycle)

2 mcg/kg | 4 mcg/kg | 8 mcg/kg | 16 mcg/kg | 12 mcg/kg

12 mcg/kg

RDE

DOSE EXPANSION (Combo)

NSCLC NIZ985 (RDE) + tislelizumab (aPD1) 300 mg IV q4w (4 wks/cycle)

Primary objectives	Secondary objectives	Exploratory objectives
• Safety • Tolerability	• Anti-tumor activity • PK • Immuno-genicity	• PD • Predictive biomarkers

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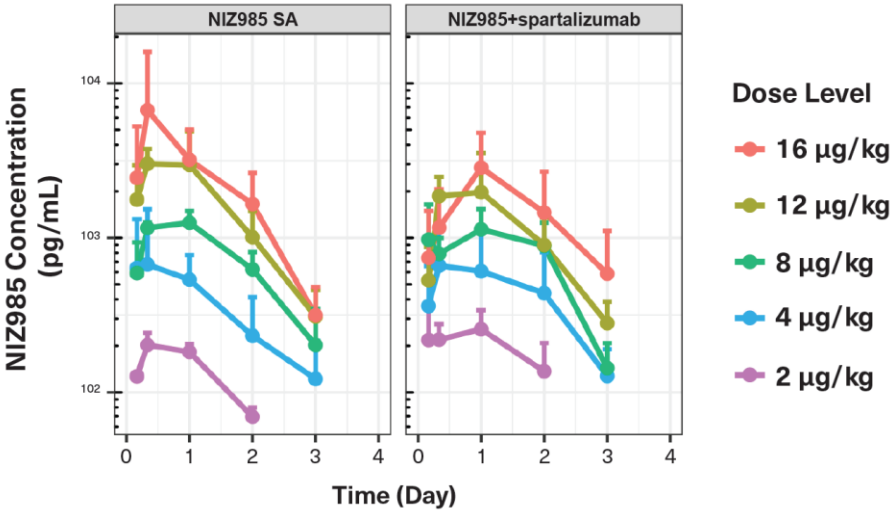
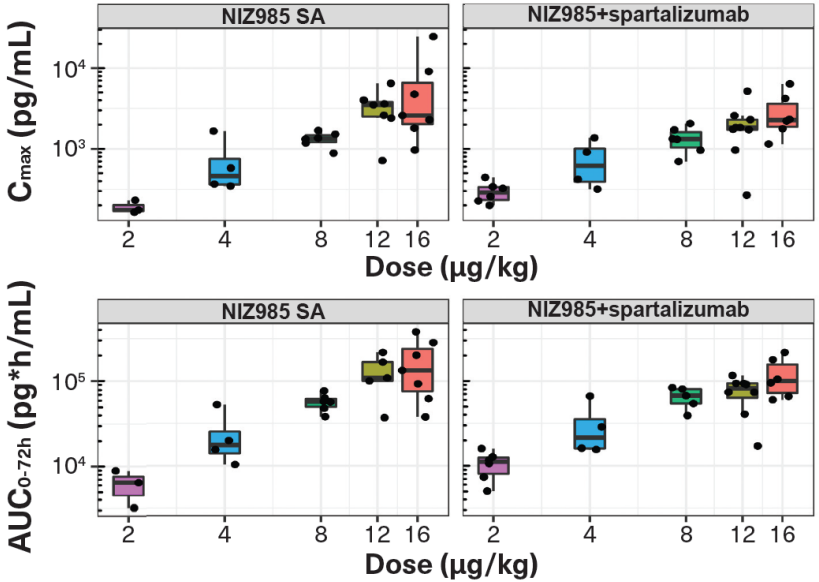
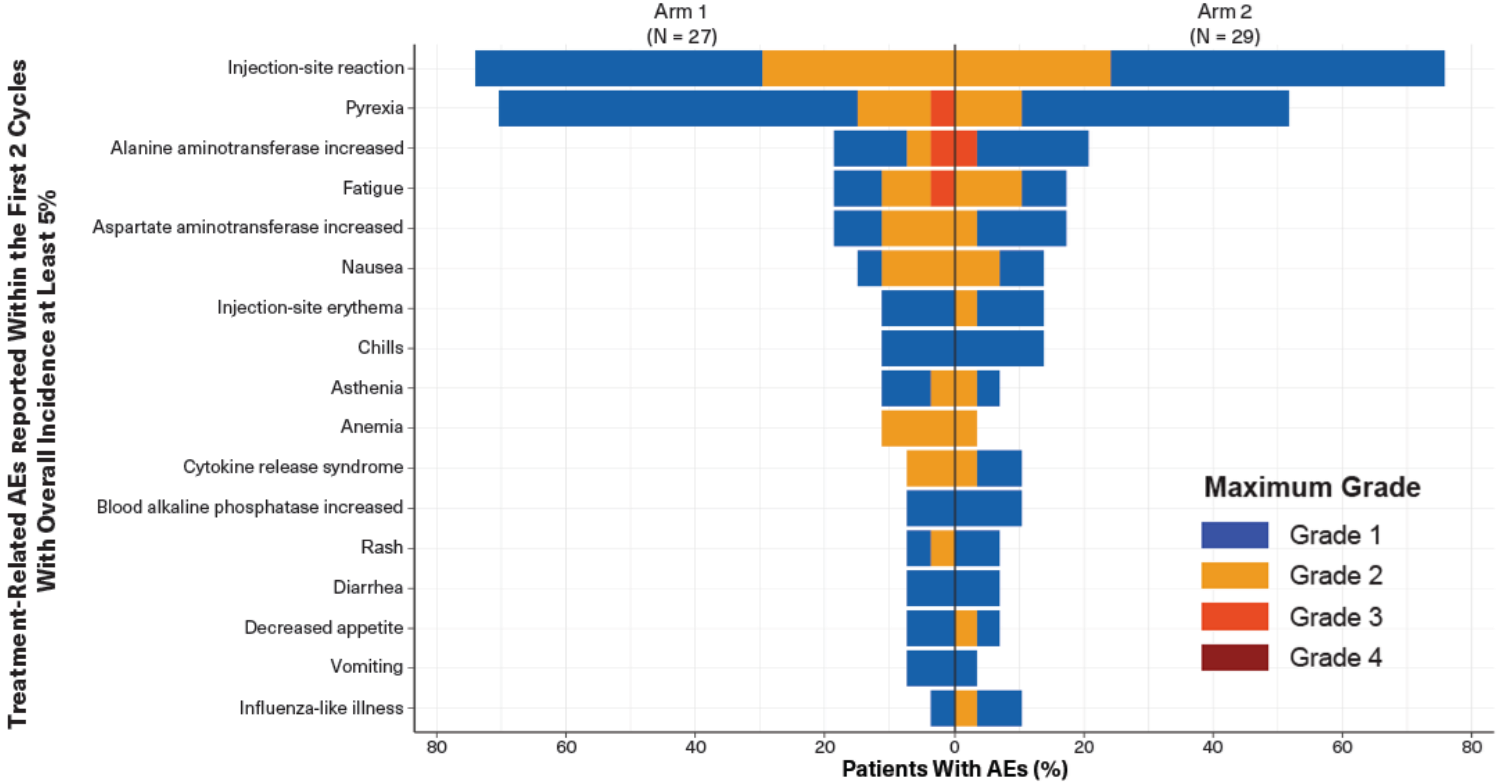
Plateau in PK exposure observed from 12 µg/kg





- NIZ985 PK was dose proportional up to 12 µg/kg, with a plateau in exposure between 12 and 16 µg/kg.
- Due to a short half-life, no accumulation of NIZ985 was observed following weekly dosing. PK exposure after the third dose (cycle 1 day 15) decreased by 20%-70%, with a large variability due to the increased target resulting from proliferation of NK cells and T cells.

NIZ985 is safe and well tolerated as single agent or in combination with spartalizumab



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16 µg/kg resulted in numerically highest incidence of dose interruption due to AEs (Cycle 1)

Arm 1 (SA)	NIZ985 2 µg/kg N=3	NIZ985 4 µg/kg N=4	NIZ985 8 µg/kg N=6	NIZ985 12 µg/kg N=7	NIZ985 16 µg/kg N=7	All Subjects N=27
Dose interruption - Number of subjects -n (%)						
With no dose interruption	3 (100)	4 (100)	6 (100)	4 (57.1)	2 (28.6)	19 (70.4)
With at least one dose interruption	0	0	0	3 (42.9)*	5 (71.4)*	8 (29.6)
Only one dose interruption	0	0	0	3 (42.9)*	5 (71.4)*	8 (29.6)

Arm 2 (Combo)	NIZ985 2 µg/kg Spartalizumab 400mg N=6	NIZ985 4 µg/kg Spartalizumab 400mg N=4	NIZ985 8 µg/kg Spartalizumab 400mg N=6	NIZ985 12 µg/kg Spartalizumab 400mg N=6	NIZ985 16 µg/kg Spartalizumab 400mg N=7	All Subjects N=29
Dose interruption - Number of subjects -n (%)						
With no dose interruption	6 (100)	4 (100)	3 (50.0)	5 (83.3)	3 (42.9)	21 (72.4)
With at least one dose interruption	0	0	3 (50.0)	1 (16.7)*	4 (57.1)	8 (27.6)
Only one dose interruption	0	0	2 (33.3)	1 (16.7)*	4 (57.1)	7 (24.1)
More than one dose interruption	0	0	1 (16.7)	0	0	1 (3.4)

*Includes 1 dose interruption due to study treatment un-related AEs.

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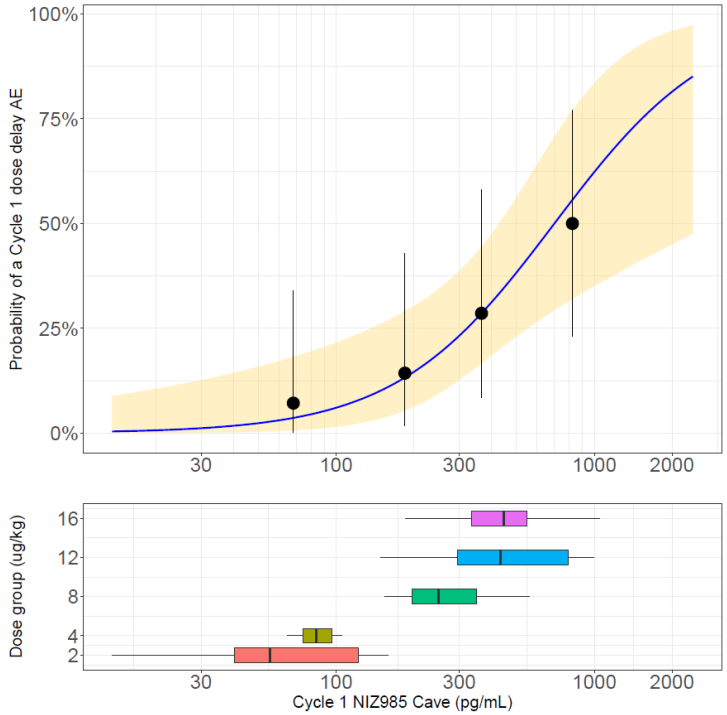
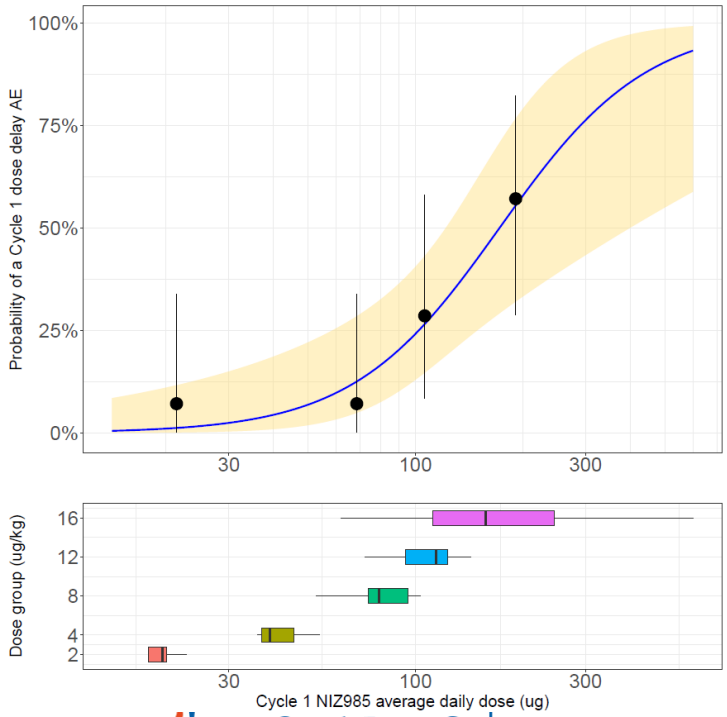
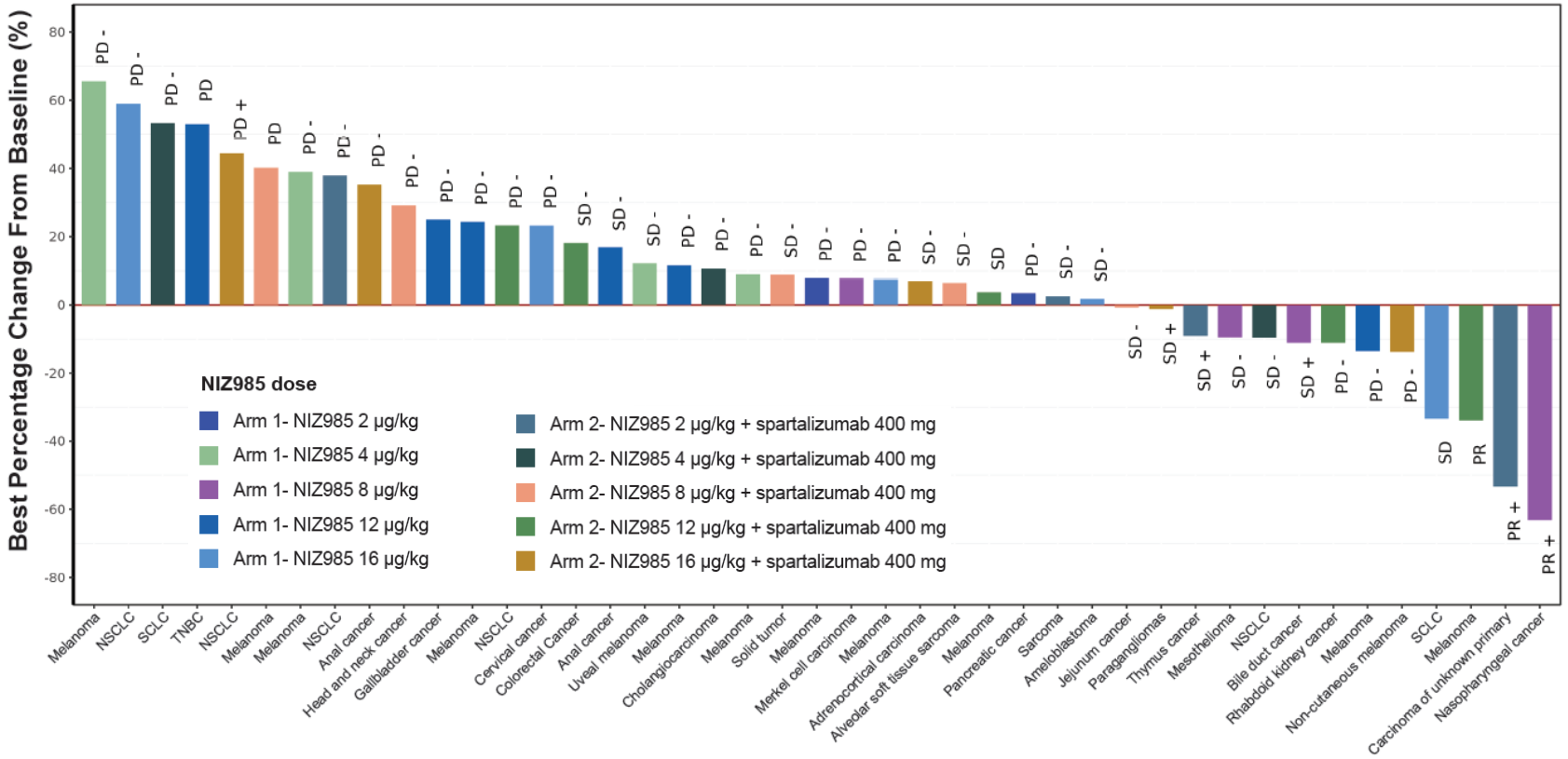
Data cut-off: Janurary 2023

Higher drug exposure leads to higher probability of dose interruption





No clear correlation between dose and efficacy



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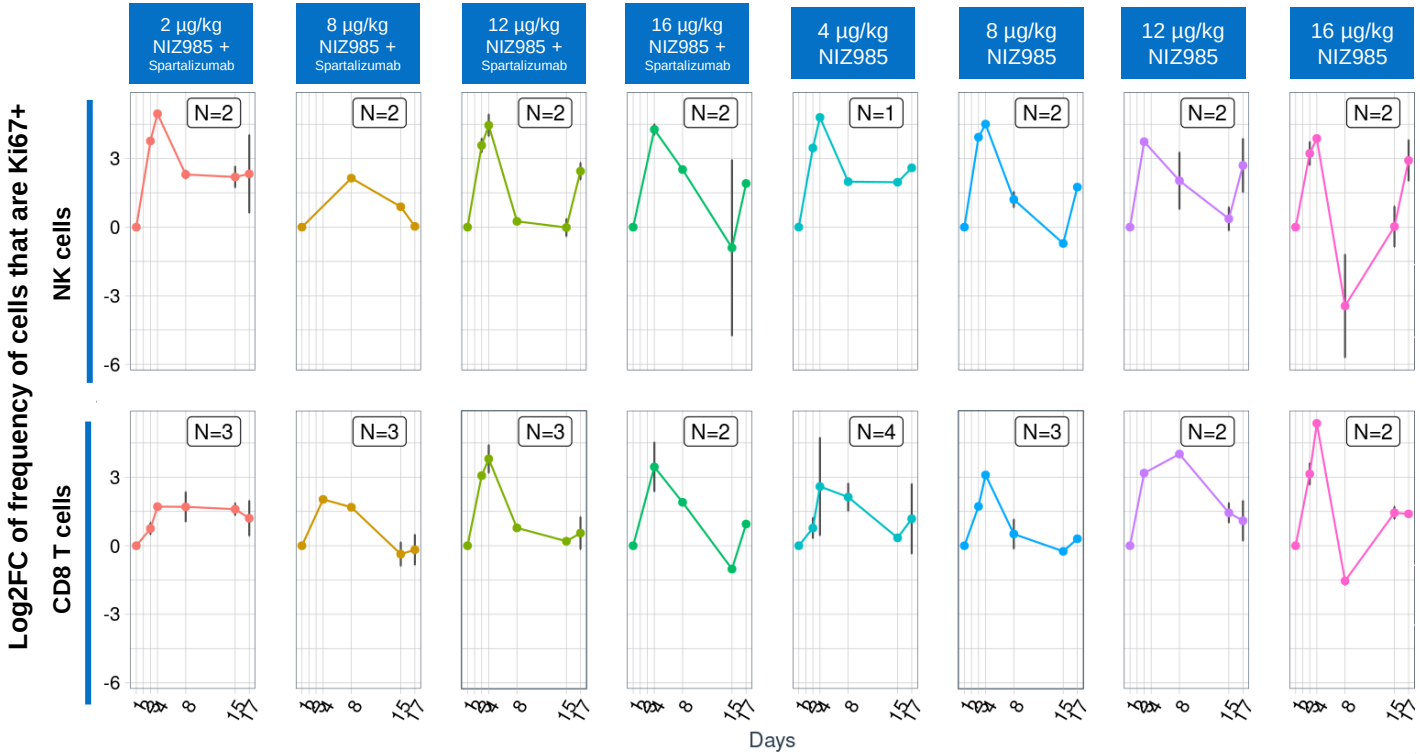
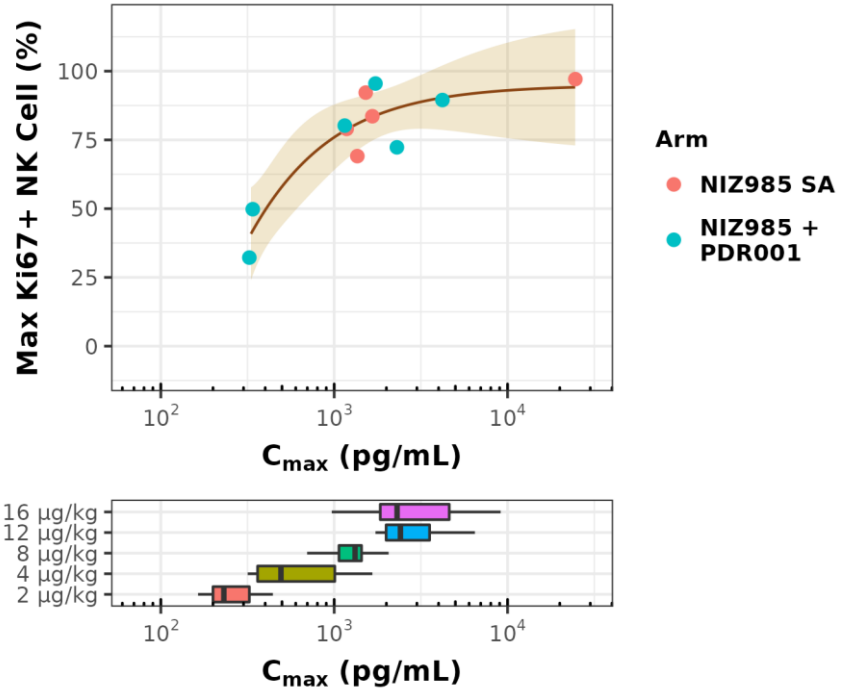
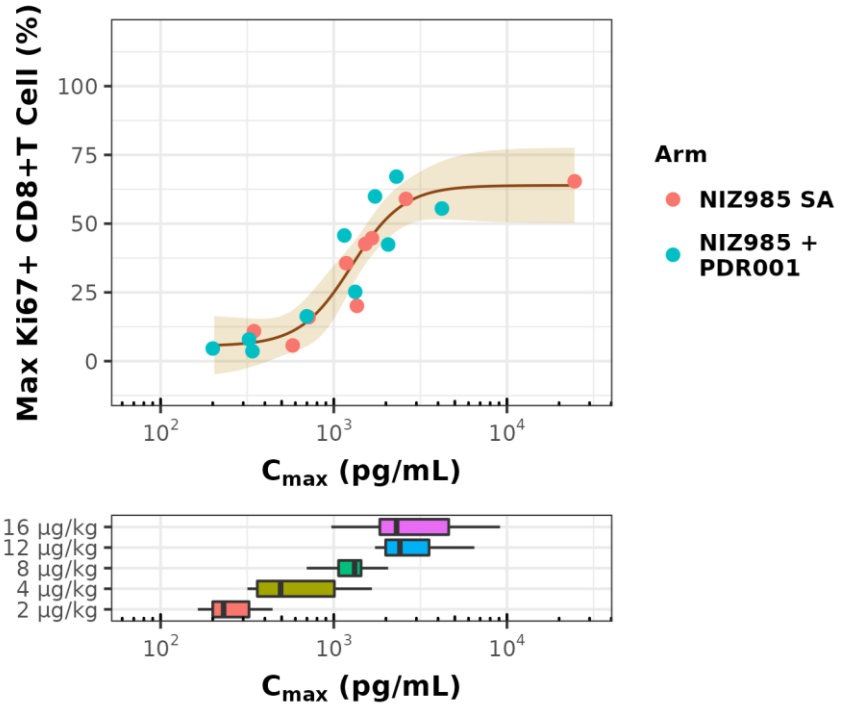
NIZ985 increases circulating Ki67+ NK and CD8 T cells

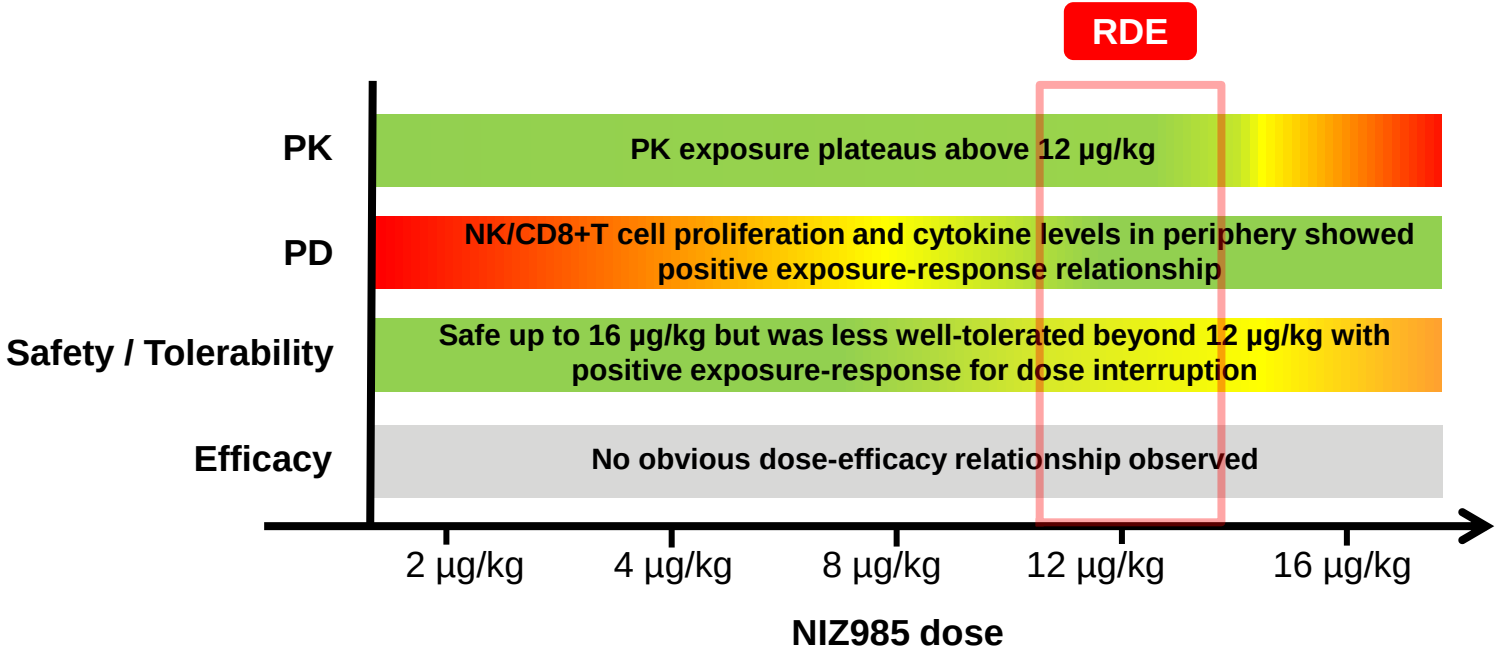


Exposure-response analysis shows positive correlation: 12 µg/kg is expected to show max effect





NIZ985 12 µg/kg alone or in combination with spartalizumab is a dose that appropriately balances safety, tolerability and pharmacological activity



Thank you

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