Phase I/Ib first-in-human study of NIZ985 (HetIL-15; IL-15/IL-15Rα) alone and in combination with spartalizumab, in adults with advanced and metastatic solid tumors

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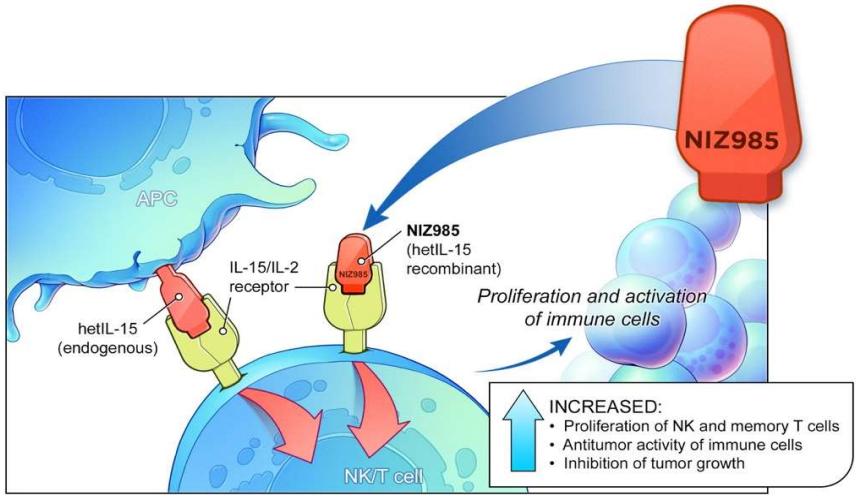
Introduction

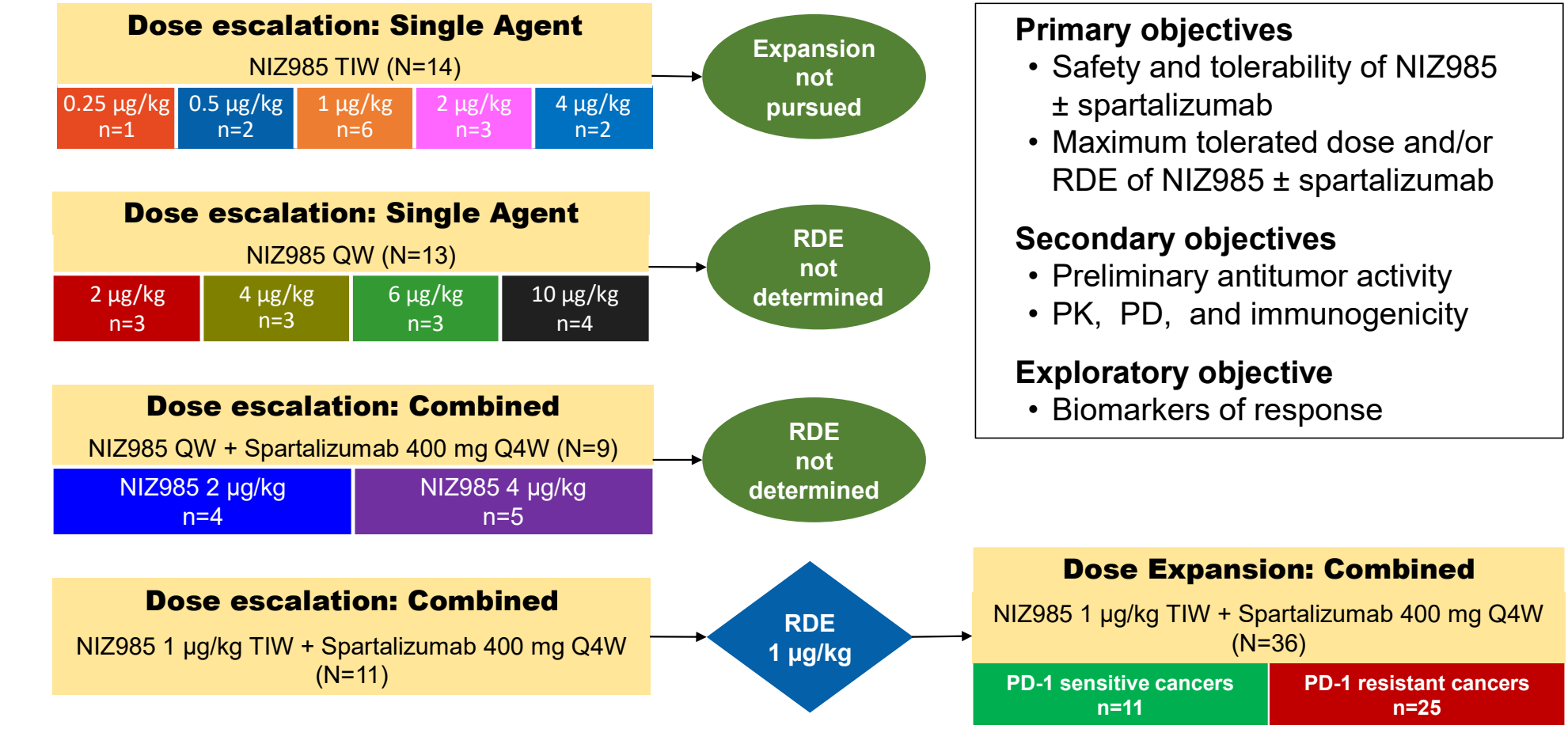
- NIZ985 is a recombinant heterodimer of IL-15 and IL-15Rα (hetIL-15)[1,2]
  - Promotes CD8+ T-cell and NK cell tumor infiltration and delays tumor growth in mouse models
- Spartalizumab is a humanized IgG4 monoclonal antibody that blocks binding of PD-1 to PD-L1/2[3,4]



- Combining IL-15 and anti–PD-L1 agents in a mouse colon cancer model resulted in enhanced antitumor immune response and increased survival compared with either agent alone[5]
- We present data from a Phase 1, first-in-human dose-escalation/expansion study evaluating the safety and efficacy of NIZ985 (HEK cell derived) ± spartalizumab in patients with metastatic or unresectable solid tumors

APC, antigen-presenting cell; HEK, human embryonic kidney; hetIL-15, IL-15/IL-15 receptor alpha heterodimer; IL, interleukin; NK, natural killer; PD-1, programmed cell death 1; PD-L1/2, programmed cell death ligand 1/2.

1. Dubois S *et al. J Immunol* 2008;180:2099–2106; 2. Ng SSM *et al. Clin Cancer Res* 2017;23:2817–2830; 3. Pardoll DM. *Nat Rev Cancer* 2012;12:252–264; 4. Naing A *et al. J Clin Oncol* 2016;34(15 Suppl):abst 3060; 5. Yu P *et al. Clin Cancer Res* 2010;16:6019–6028.



Primary objectives

- Safety and tolerability of NIZ985 ± spartalizumab
- Maximum tolerated dose and/or RDE of NIZ985 ± spartalizumab

Secondary objectives

- Preliminary antitumor activity
- PK, PD, and immunogenicity

Exploratory objective

- Biomarkers of response

NIZ985 administered subcutaneously and spartalizumab intravenously

TIW dosing: **2 weeks on/2 weeks off schedule;** ***QW dosing:*** **3 weeks on/1 week off schedule**

Key Inclusion Criteria

- Adults with metastatic/unresectable solid tumors
  - Progression on ≥1 prior therapy
  - Standard therapy or palliative measures not reasonably effective or do not exist
- Measurable disease (RECIST v1.1 or irRC)
- ECOG PS ≤1

Key Exclusion Criteria

- Prior IL-15 therapy
- Checkpoint inhibitors (e.g. anti–CTLA-4 or anti–PD-1/PD-L1) within 6 weeks of study start, or other anticancer treatment within 4 weeks
- Primary CNS tumor or CNS tumor involvement
- Impaired cardiac function or clinically significant cardiac disease
- Systemic steroid therapy (excluding replacement for adrenal insufficiency)
- Historical/current drug-induced interstitial lung disease or pneumonitis of Grade >1
- Prior anti–PD-1 therapy discontinued for anti–PD-1-related toxicity

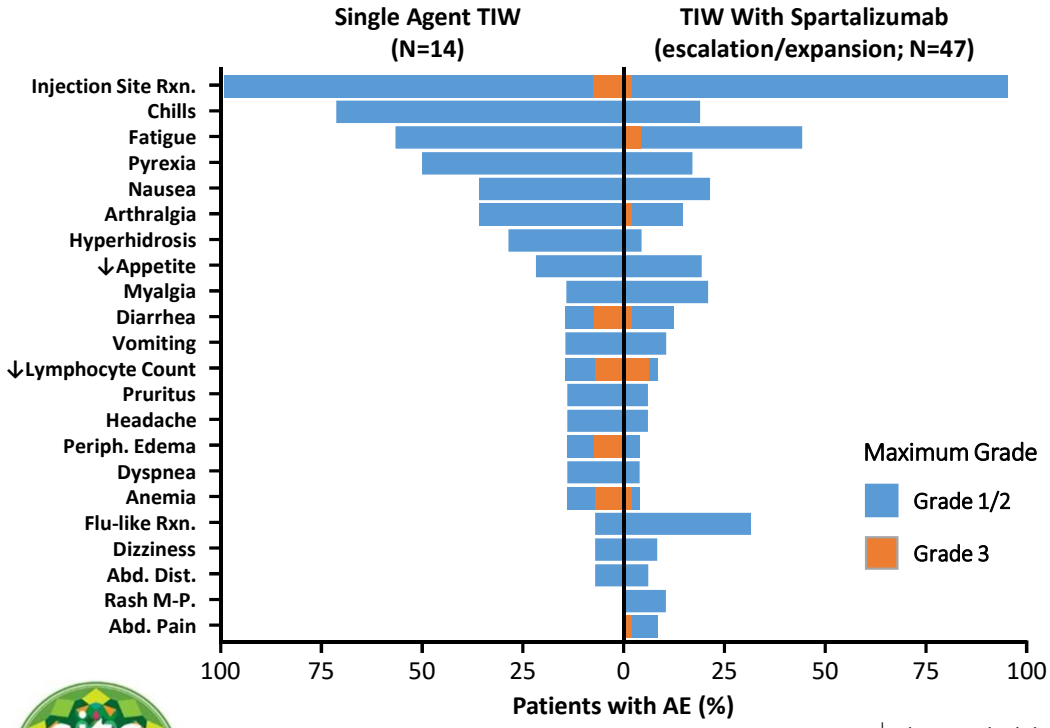
CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; IL, interleukin; irRC, immune-related response criteria; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors.

Patient Baseline Characteristics	NIZ985 Dose Escalation (TIW or QW, N=47)		NIZ985 TIW COMBO Dose Expansion (N=36)	
	SA (n=27)	COMBO (n=20)	PD-1–sensitive tumors (N=11)	PD-1–resistant tumors (N=25)
Median (range) age, yrs	60 (42–80)	61.5 (34–76)	66 (28–76)	64 (32–85)
Sex, n (%)				
Male	17 (63)	14 (70)	7 (64)	9 (36)
Female	10 (37)	6 (30)	4 (36)	16 (64)
Race, n (%)				
White	23 (85)	20 (100)	9 (82)	22 (88)
Black/African-American	1 (4)	0	1 (9)	1 (4)
Asian	1 (4)	0	1 (9)	2 (8)
Unknown/unreported	2 (7)	0	0	0
Prior therapy lines, n (%)				
1	3 (11)	2 (10)	0	1 (4)
2	8 (30)	3 (15)	2 (18)	7 (28)
≥3	16 (59)	15 (75)	9 (82)	16 (64.0)
Any prior IO treatment, n (%)	12 (44)	8 (40)	11 (100)	4 (16)
Disease diagnosis, n (%)				
Pancreatic	2 (7)	2 (10)	0	5 (20)
Colorectal	5 (19)	4 (20)	0	3 (12)
Renal	2 (7)	1 (5)	0	0
Breast	1 (4)	1 (5)	0	3 (12)
Prostate	1 (4)	1 (5)	0	2 (8)
Gastric	0	1 (5)	0	2 (8)
NSCLC	0	0	3 (27)	0
Melanoma	3 (11)	1 (5)	7 (64)	0
Cholangiocarcinoma	1 (4)	0	0	3 (12)
Other/unknown	12 (44)	9 (45)	1 (9)	7 (28)

COMBO, combination treatment with 400 mg spartalizumab every 4 weeks; IO, immuno-oncology; NSCLC, non-small cell lung carcinoma; PD-1, programmed cell death 1; QW, once weekly; SA, single agent; TIW, three times weekly.

NIZ985X2101J Safety Summary (TIW)

Treatment-related AEs in ≥5% of patients



- Most common AEs were low-grade ISRs, chills, fatigue, and pyrexia
- Similar AEs noted across both TIW (shown) and QW schedules in SA and combination treatment, including local ISRs (noted across all IL-15 compounds)

↓, decreased; Abd. Dist., abdominal distension; AE, adverse event; IL, interleukin; ISR, injection site reaction; M-P., maculo-papular; Periph., peripheral; QW, once weekly; Rxn., reaction; SA, single agent; TIW, three times weekly.

Safety and Tolerability

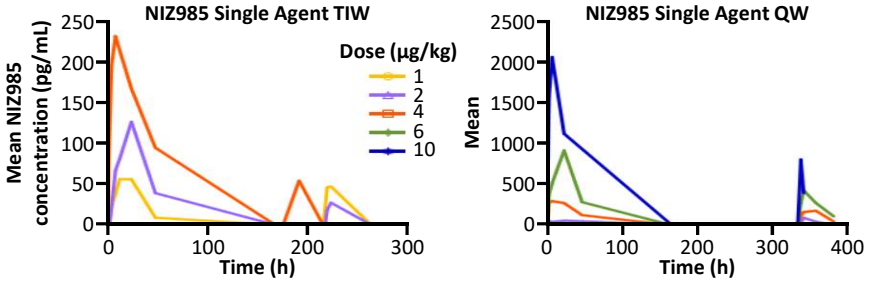
- No dose-limiting toxicities were observed*
- **Six patients with SAEs suspected to be treatment related**
  - IgA pemphigus (2 µg/kg); purpura (2 µg/kg); and thromboembolic event, acute kidney injury, and vasculitis (4 µg/kg) – all non-dose-limiting, occurred in cycle 2
  - Other related SAEs: fatigue (10 µg/kg QW SA), arthralgia (TIW + spartalizumab escalation), and pyrexia (TIW + spartalizumab expansion)
- Similar treatment-related systemic skin AEs were not seen at 1 µg/kg TIW ± spartalizumab, or QW at doses up to 10 µg/kg
- NIZ985 1 µg/kg TIW was therefore considered safe and tolerable
  - Due to limited SA efficacy, TIW SA expansion was not initiated
  - 1 µg/kg was set as the recommended dose for TIW spartalizumab expansion

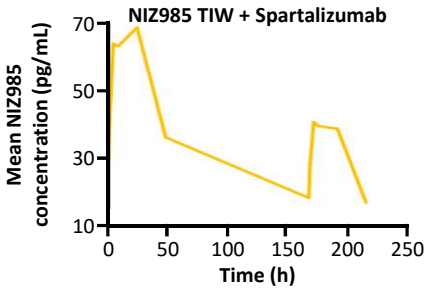
**Observation window for dose-limiting toxicity was during the first 28-day treatment cycle.*

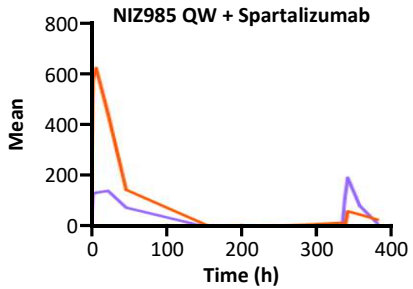
AE, adverse event; IgA, immunoglobulin A; QW, once weekly; SA, single agent; SAE, serious adverse event; TIW, three times weekly.

NIZ985 PK: Dose-Proportional and Time-Dependent

NIZ985 Concentration–Time Profiles

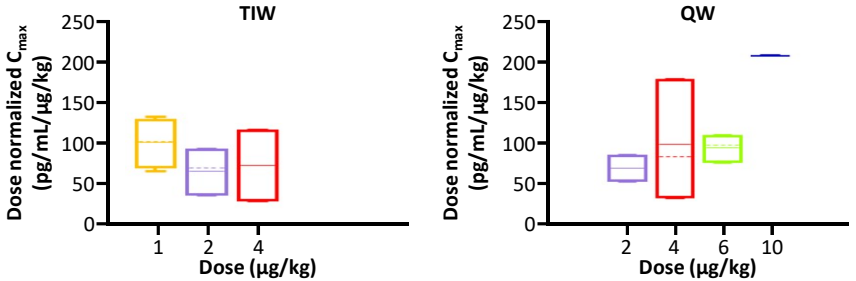




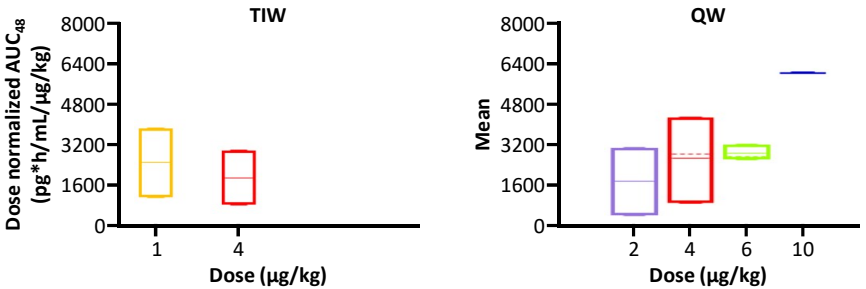


- Time-dependent PK, with lower serum levels over time & with repeat dosing
- No accumulation

Dose-Normalized NIZ985 C_{max} (Single Agent)



Dose-Normalized NIZ985 AUC_{48} (Single Agent)

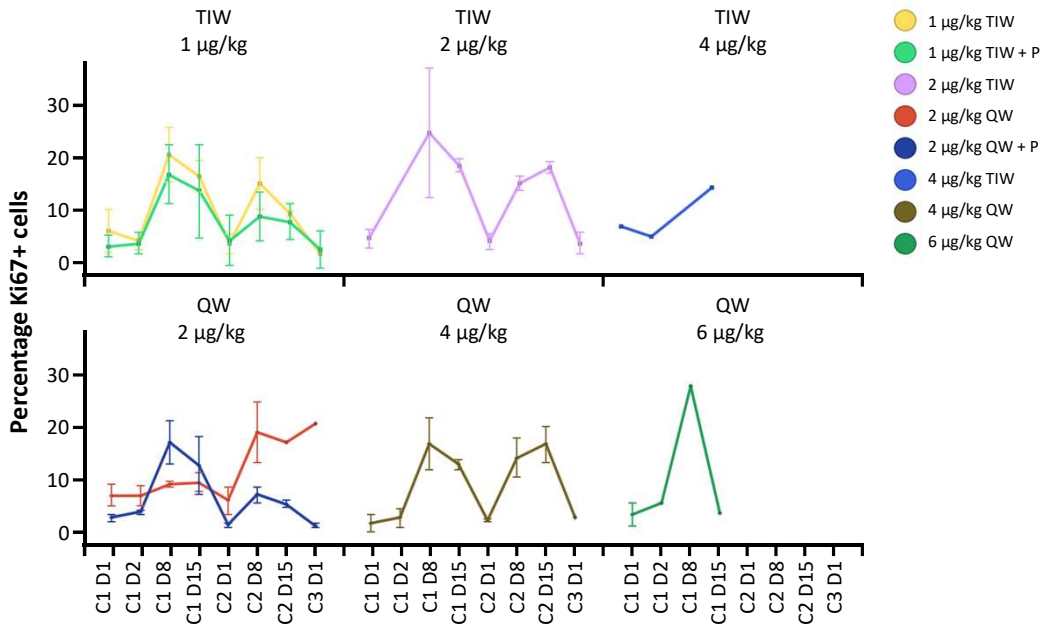


- Approximately dose proportional exposure from 1–6 µg/kg
- Greater than dose proportional exposure at 10 µg/kg

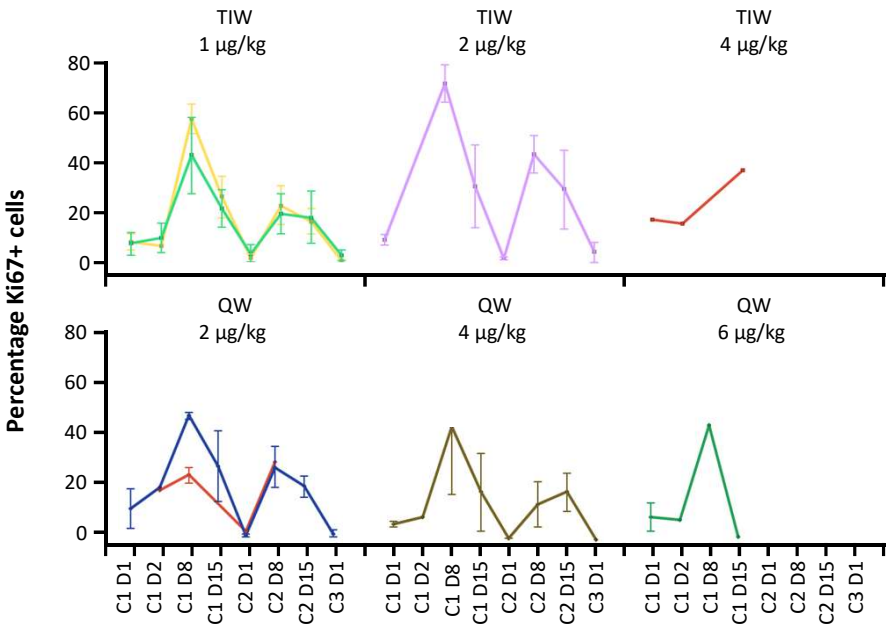
AUC_{48}, area under the NIZ985 concentration–time curve over 48 hours post-dose; C_{max}, maximum NIZ985 plasma concentration; PK, pharmacokinetics; QW, once weekly; TIW, three times weekly.

NIZ985 Induces Proliferation of Peripheral Lymphocytes

CD8+ T Cells



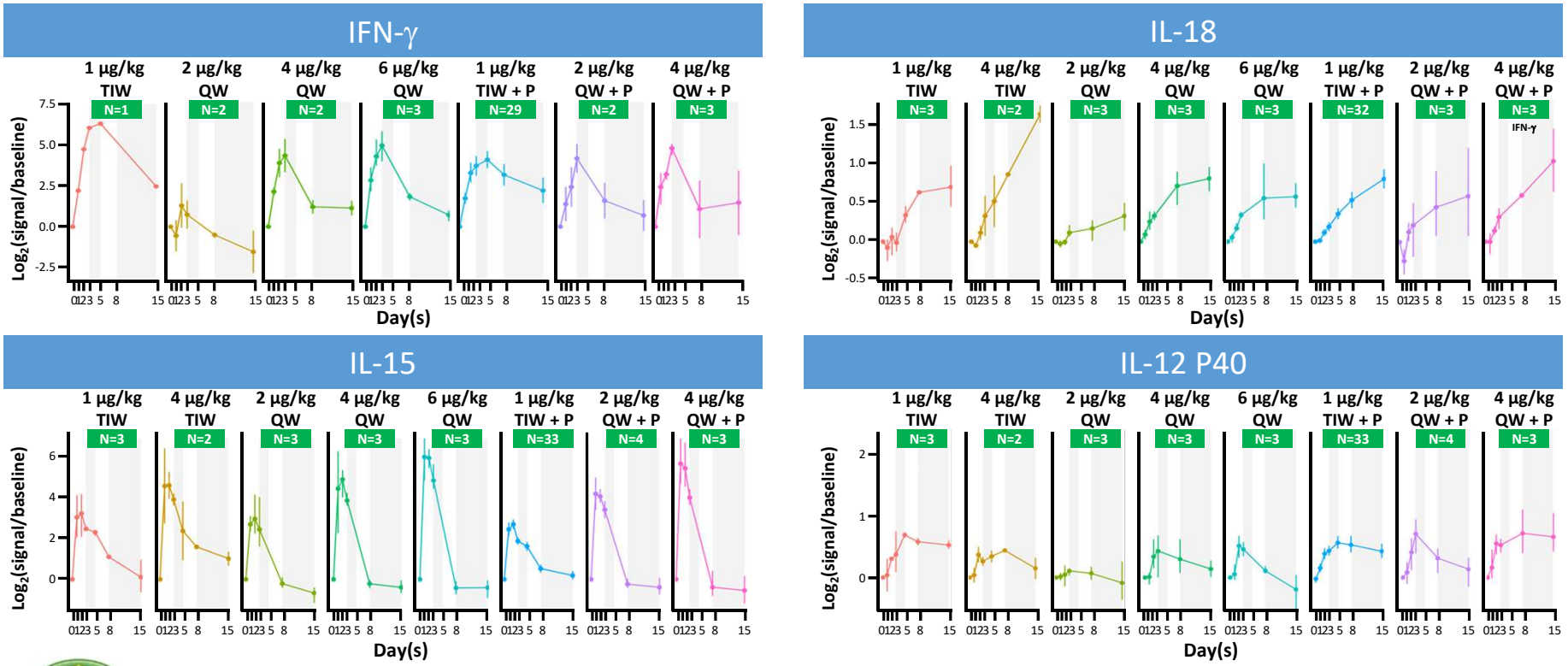
NK Cells



- Both TIW and QW dosing of NIZ985 induced CD8+ T cell and NK-cell proliferation at comparable rates
- No strong correlation between lymphocyte expansion and clinical response (data not shown)

C, Cycle; D, Day; NK, natural killer; P, spartalizumab (PDR001); QW, once weekly; TIW, three times weekly.

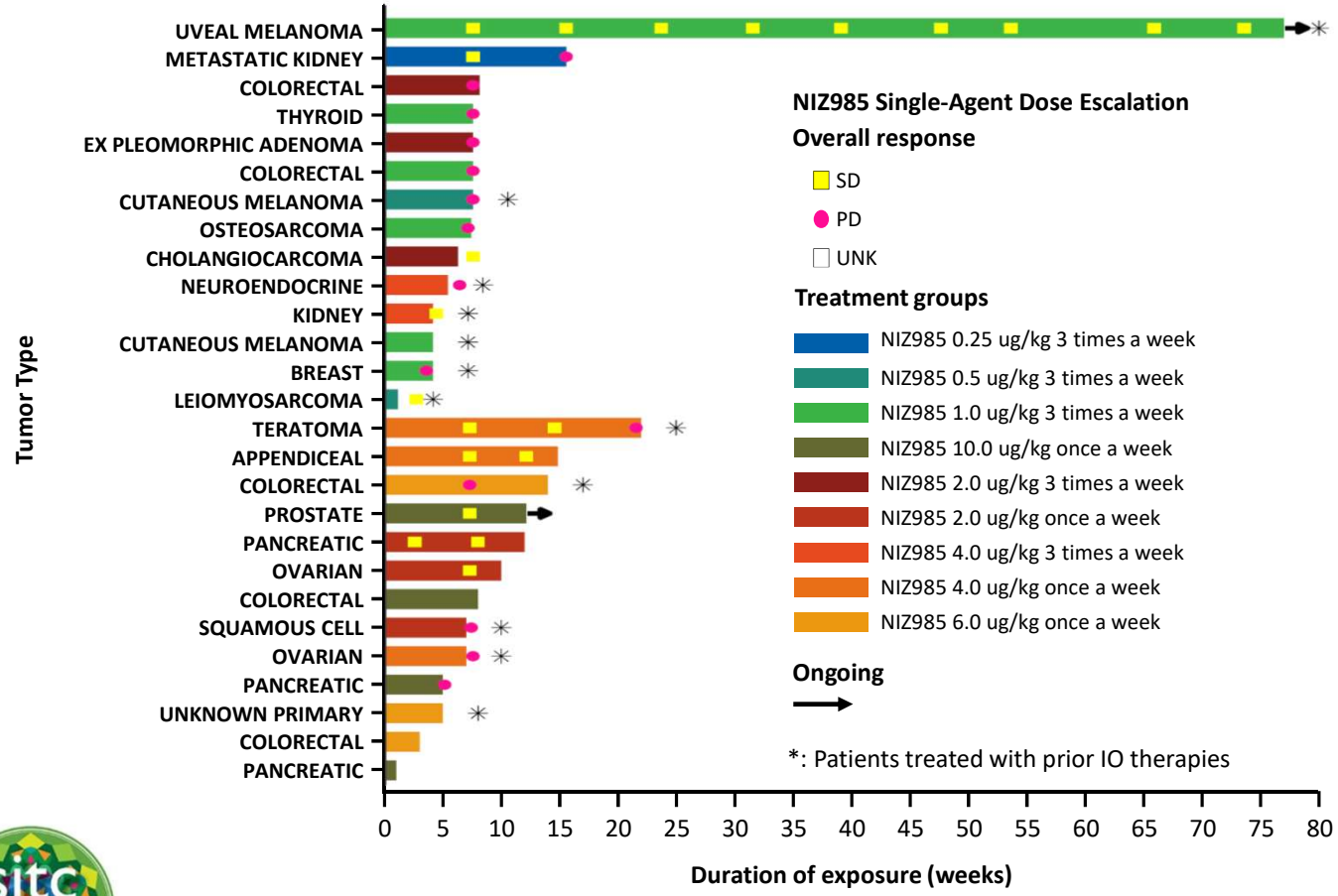
NIZ985 Increases Plasma Inflammatory Cytokines



- Kinetics of cytokine induction were similar for NIZ985 with or without spartalizumab
- Small sample sizes in the single-agent escalation cohorts did not allow robust assessment of dose dependency

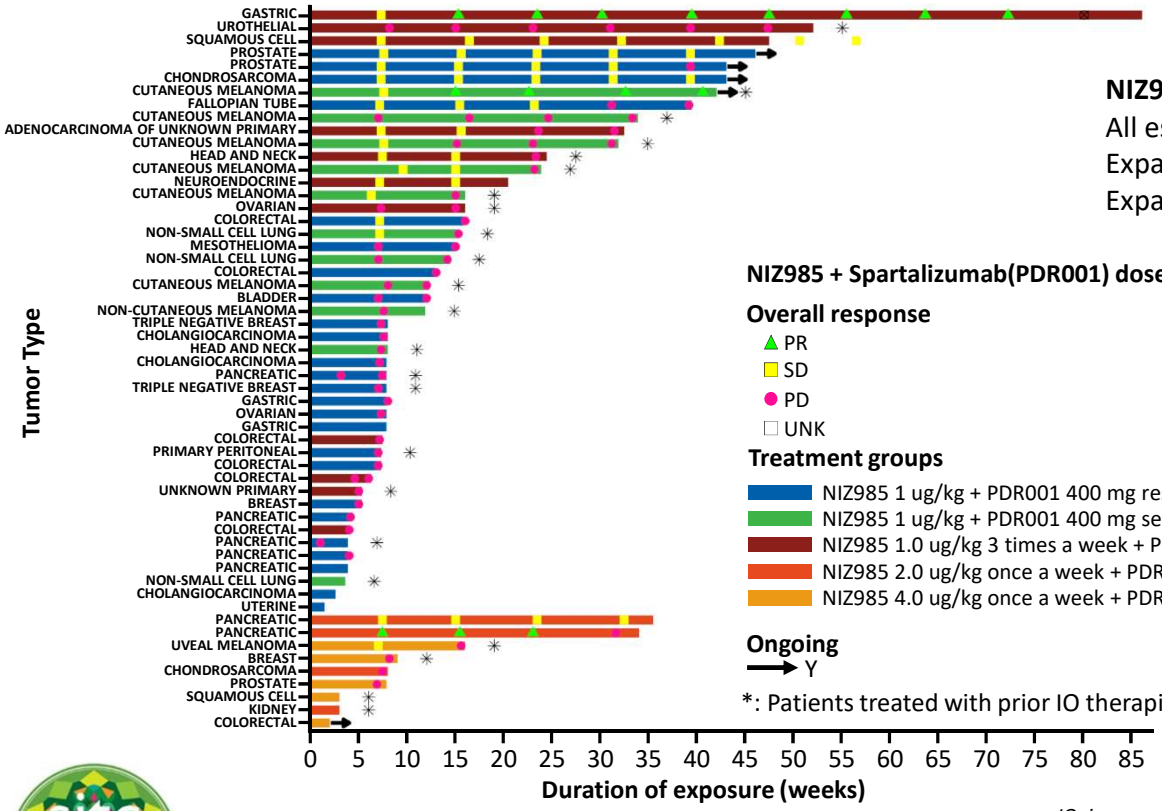
IFN, interferon; IL, interleukin; P, spartalizumab (PDR001); QW, once weekly; TIW, three times weekly.

NIZ985 Single Agent: Time on Treatment and Response



NIZ985 Single Agent, median (range)
7.6 (1.0–77.1) weeks

NIZ985 + Spartalizumab: Time on Treatment and Response Evaluation



NIZ985 + Spartalizumab 400 mg Q4W, median (range)
All escalation: 12.6 (2.1–86.1) weeks
Expansion – PD-1 sensitive: 15.4 (3.7–42.1) weeks
Expansion – PD-1 resistant: 8.0 (1.6–46.1) weeks

NIZ985 + Spartalizumab(PDR001) dose escalation/expansion

Overall response
- PR
- SD
- PD
- UNK

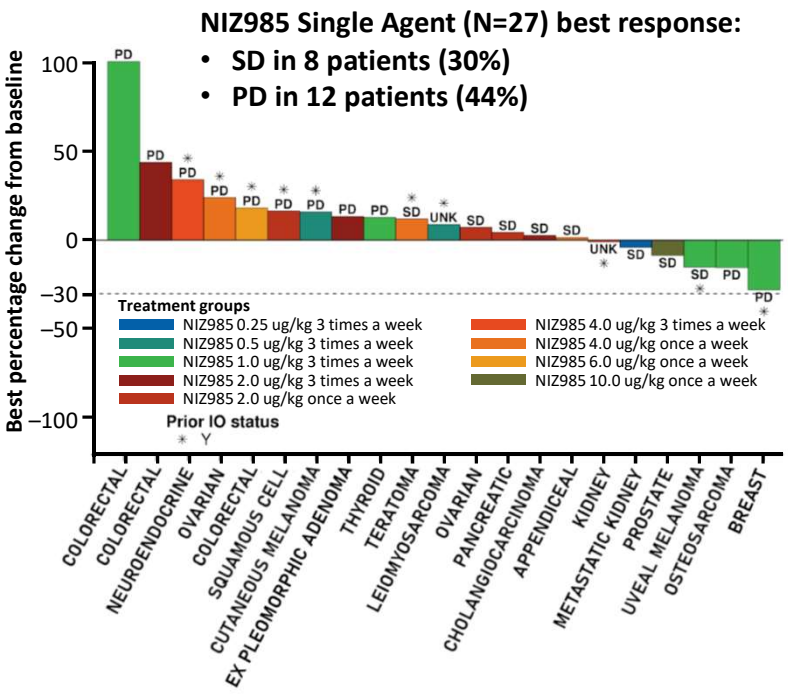
Treatment groups
- NIZ985 1 ug/kg + PDR001 400 mg resistant expansion
- NIZ985 1 ug/kg + PDR001 400 mg sensitive expansion
- NIZ985 1.0 ug/kg 3 times a week + PDR001 400 mg
- NIZ985 2.0 ug/kg once a week + PDR001 400 mg
- NIZ985 4.0 ug/kg once a week + PDR001 400 mg

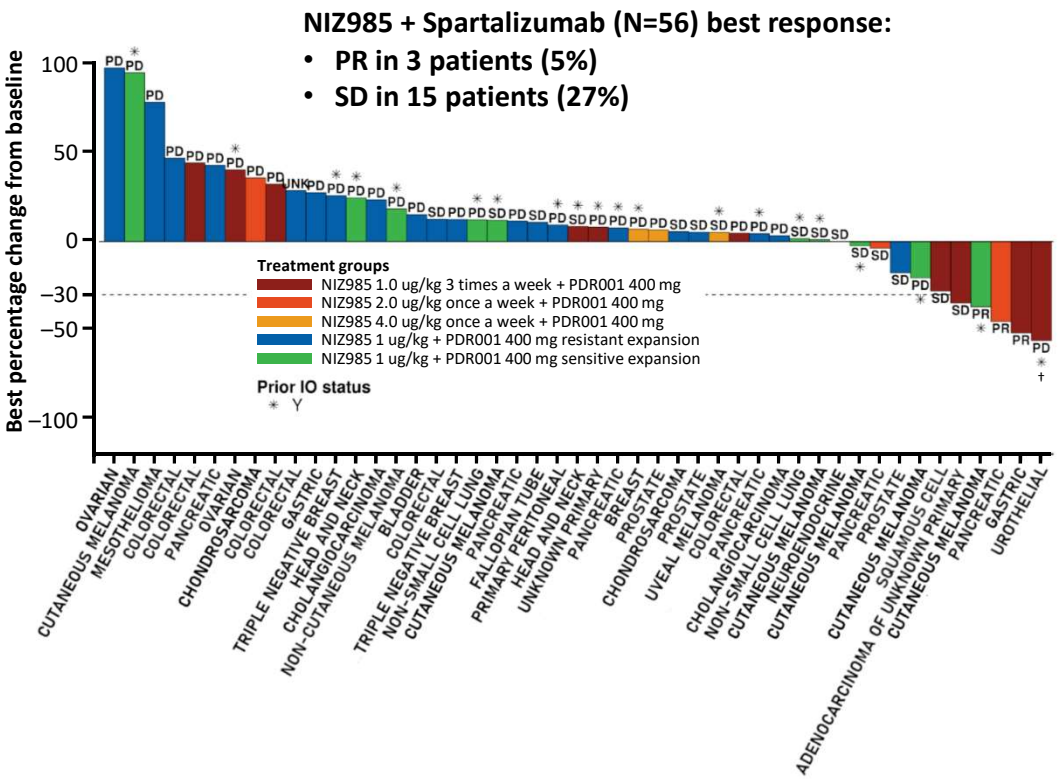
Ongoing
- → Y

*: Patients treated with prior IO therapies

IO, immuno-oncology; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; Q4W, every 4 weeks; SD, stable disease; UNK, unknown.

Best Percentage Change From Baseline in Target Lesions





†Urothelial cancer patient classified as PD per RECIST due to development of a new lesion (neck) not previously evaluated.

IO, immuno-oncology treatment; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown response status.

Conclusions

- NIZ985 demonstrates safety and tolerability at both TIW and QW dosing alone and with spartalizumab 400 mg every 4 weeks
- NIZ985 displays approximately dose-proportional, time-dependent PK, and a cytokine and proliferating lymphocyte response profile consistent with target engagement
- Antitumor activity was limited for NIZ985 as a single agent. However, preliminary responses were observed for combination treatment with spartalizumab in both IO–experienced and IO–naive patients warranting further investigation

IO, immuno-oncology treatment; PK, pharmacokinetics; QW, once weekly; TIW, three times weekly.

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