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First-in-human phase I/Ib study of NIZ985, a recombinant heterodimer of IL-15 and IL-15Rα, as a single agent and in combination with spartalizumab in patients with advanced and metastatic solid tumors

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ABSTRACT

Background Preclinically, interleukin-15 (IL-15) monotherapy promotes antitumor immune responses, which are enhanced when IL-15 is used in combination with immune checkpoint inhibitors (ICIs). This first-in-human study investigated NIZ985, a recombinant heterodimer comprising physiologically active IL-15 and IL-15 receptor α, as monotherapy and in combination with spartalizumab, an anti-programmed cell death protein-1 (anti-PD-1) monoclonal antibody, in patients with advanced solid tumors.

Methods This phase I/Ib study had two dose-escalation arms: single-agent NIZ985 administered subcutaneously thrice weekly (TIW, 2 weeks on/2 weeks off) or once weekly (QW, 3 weeks on/1 week off), and NIZ985 TIW or QW administered subcutaneously plus spartalizumab (400 mg intravenously every 4 weeks (Q4W)). The dose-expansion phase investigated NIZ985 1 µg/kg TIW/spartalizumab 400 mg Q4W in patients with anti-PD-1–sensitive or anti-PD-1–resistant tumor types stratified according to approved indications. The primary objectives were the safety, tolerability, and the maximum tolerated doses (MTDs) and/or recommended dose for expansion (RDE) of NIZ985 for the dose-expansion phase.

Results As of February 17, 2020, 83 patients (median age: 63 years; range: 28–85) were treated in dose escalation (N=47; single-agent NIZ985: n=27; NIZ985/spartalizumab n=20) and dose expansion (N=36). No dose-limiting toxicities occurred nor was the MTD identified. The most common treatment-related adverse event (TRAE) was injection site reaction (primarily grades 1–2; single-agent NIZ985: 85% (23/27)); NIZ985/spartalizumab: 89% [50/56]). The most common grade 3–4 TRAE was decreased lymphocyte count (single-agent NIZ985: 7% [2/27]; NIZ985/spartalizumab: 5% [3/56]). The

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Preclinical studies showed that interleukin-15 (IL-15) triggers an immune response against different tumor types, and the antitumor activity is enhanced when IL-15 is used in combination with immune checkpoint inhibitors (ICIs).

⇒ An earlier report of this first-in-human study of single-agent NIZ985, an IL-15 and IL-15 receptor α heterodimer, reported a favorable toxicity profile, with induction of cytotoxic lymphocyte proliferation and interferon-γ in patients with advanced cancer.

WHAT THIS STUDY ADDS

⇒ Here, we report final results for the first-in-human, 83-patient study that investigated NIZ985 as a single agent and in combination with spartalizumab, an anti-programmed cell death protein-1 (anti-PD-1) monoclonal antibody, in advanced solid tumors.

⇒ Both NIZ985 monotherapy and the combination of NIZ985 with spartalizumab were well tolerated.

⇒ The best overall response observed in the combination arm was partial response and in the single-agent arm, stable disease.

⇒ Preliminary antitumor activity of NIZ985 in combination with spartalizumab was observed in patients with melanoma, gastric cancer and pancreatic cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study warrant further investigation of NIZ985 in combination with ICIs for the treatment of patients with various types of malignancies, particularly anti-PD-1–resistant tumor types.

best overall response was stable disease in the single-agent arm (30% (8/27)) and partial response in the NIZ985/spartalizumab arm (5% [3/56]; melanoma, pancreatic cancer, gastric cancer). In dose expansion, the disease control rate was 45% (5/11) in the anti-PD-1–sensitive and 20% (5/25) in the anti-PD-1–resistant tumor type cohorts. Pharmacokinetic parameters were similar across arms. The transient increase in CD8+ T cell and natural killer cell proliferation and induction of several cytokines occurred in response to the single-agent and combination treatments.

Conclusions NIZ985 was well tolerated in the single-agent and NIZ985/spartalizumab regimens. The RDE was established at 1 µg/kg TIW. Antitumor activity of the combination was observed against tumor types known to have a poor response to ICIs.

Trial registration number NCT02452268.

INTRODUCTION

Activation of cytokine-driven T cells and natural killer (NK) cells enhance the antitumor potential of these effector cells and has been shown to be a viable therapeutic strategy for patients with advanced cancer.[1 2] Cytokines play a pivotal pleiotropic role in orchestrating the immune system by promoting the development of immune cells and regulating counterproductive autoimmune and inflammatory activity.[3 4]

IL-15 is a pleiotropic cytokine with important biological functions that overlap with those of IL-2 but without the undesirable effects of IL-2, such as Treg stimulation, severe capillary leak and activation-induced cell death.[5–9] The 12 kDa polypeptide of IL-15 is coproduced together with the IL-15 receptor α (IL-15Rα), forming a heterodimeric complex in the endoplasmic reticulum, that is transported to the surface of antigen-presenting and other cells, and transpresented to adjacent IL-2/IL-15βγ receptor expressing immune cells, such as cytotoxic CD8+T cells and NK cells. This leads to the initiation of downstream signaling and the activation of immune responses.[10–12] The membrane-associated extracellular heterodimeric IL-15/IL-15Rα complex is rapidly cleaved to generate a biologically active, stable and soluble IL-15 heterodimer (hetIL-15), which is the physiological form of circulating IL-15 in mouse and human plasma.[11–13] In the tumor microenvironment, IL-15 promotes the accumulation of CD8+T cells by mediating their infiltration and local proliferation.[14]

Preclinically, recombinant IL-15 showed antitumor activity that was associated with enhanced CD8+ T cell and NK cell activity,[13] resulting in a survival benefit in various murine cancer models.[13 15] In addition, hetIL-15 was shown to have rapid and indirect effects on different myeloid cells and recruit conventional type-1 dendritic cells to tumors (online supplemental figure 1).[13 16] The antitumor activity of IL-15 was explored further in combination with programmed cell death protein-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) antagonist therapies to bypass immunological checkpoints.[17 18] Compared with monotherapy, the combination of IL-15 with an anti-PD-1 antibody enhanced the antitumor immune response and prolonged survival of mice bearing colon carcinoma xenografts.[17] In non-human primates, daily administration of IL-15 had a minimal effect on Treg cells, led to the expansion of memory CD8+ and CD4+ T cells and NK cells in peripheral blood, persistently elevated plasma IL-15 levels, and resulted in only transient toxicity. Moreover, intermittent administration improved the IL-15 toxicity profile.[19]

Clinical manufacturing methods for recombinant IL-15 appear to impact the IL-15 toxicity profile. Administration of recombinant IL-15 expressed in *Escherichia coli* by an intravenous bolus or subcutaneous injection in patients with advanced cancers was poorly tolerated, with chills, fever and alterations in blood pressure reported within a few hours of administration. Moreover, this preparation had limited efficacy, achieving only stable disease (SD) as the best response,[20 21] which could be partially explained by the combined effect of rapid plasma clearance and activation of immunological checkpoint responses.[20 21] Several different formulations of recombinant IL-15 molecules have subsequently been developed, including recombinant hetIL-15 (NIZ985), which retains glycosylation and high homology to the physiologically active form of human plasma IL-15.[7 22] NIZ985 was shown to promote CD8+ T cell and NK cell infiltration into tumors and to delay tumor growth in preclinical models.[7 22] The safety and preliminary antitumor activity of single-agent NIZ985 administered subcutaneously thrice weekly (TIW; 2 weeks on/2 weeks off), were first reported as part of this phase I/Ib first-in-human study of NIZ985 in patients with metastatic or unresectable solid tumors.[23] This first report showed that subcutaneous administration of NIZ985 at a dose of 1 µg/kg using the TIW dosing schedule was generally well tolerated and led to immune responses, including the induction of interferon-γ (IFN-γ).[23]

Here, the final results of the previously reported NIZ985 TIW regimen[23] are presented, together with novel safety and efficacy data for a once weekly (QW) NIZ985 regimen, as single agent and in combination with spartalizumab, for patients with advanced malignancies.

METHODS

Study design

This open-label, phase I/Ib study investigated the safety and efficacy of single-agent NIZ985 and the combination of NIZ985 and spartalizumab (NIZ985/spartalizumab) in patients with metastatic or unresectable cancers. Two NIZ985 dose-escalation cohorts in the single-agent and the combination treatment arms were investigated: single-agent NIZ985 administered subcutaneously TIW on a 2 weeks on/2 weeks off schedule and QW administered subcutaneously on a 3 weeks on/1 week off schedule and each of the NIZ985 schedules in combination with spartalizumab 400 mg intravenously every 4 weeks (Q4W) (figure 1). The 3 weeks on/1 week off QW schedule was introduced to mitigate the risks associated with potential NIZ985 toxicity due to skin toxicities/vasculitis occurring beyond the dose-limiting toxicity (DLT) period in the TIW schedule in order to allow for further dose escalation.

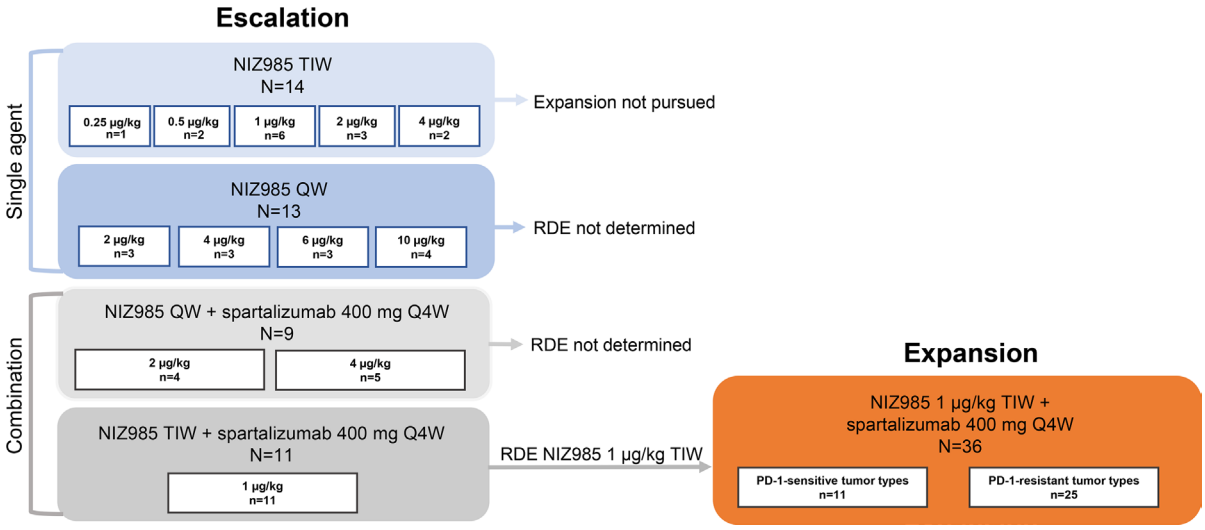

Figure 1 Study design. PD-1, programmed cell death protein-1; Q4W, every 4 weeks; QW, once a week; RDE, recommended dose for expansion; TIW, three times a week.

Initially, dose escalation in the single-agent NIZ985 TIW cohort followed an accelerated design with single patient cohorts until a grade 2 adverse event (AE) occurred, and then switched to a standard 3+3 dose-escalation design. Treatment was continued in the absence of DLT or other unacceptable AEs, disease progression defined by the immune-related Response Criteria (irRC), or patient withdrawal. The earlier publication reported results of single-agent NIZ985 administered TIW at 0.25, 0.5, 1, 2 and 4 µg/kg.[23] No DLTs during the cycle 1 evaluation period were observed; however, immune-related bullous pemphigoid and vasculitis occurred after cycle 1 in the 2 and 4 µg/kg groups, respectively,[23] which led to a protocol amendment allowing the introduction of the less dose-intense QW treatment schedule. Subsequent protocol amendments supported the administration of NIZ985/spartalizumab to establish whether NIZ985 and immune checkpoint inhibitors (ICIs) act in synergy. Recruitment to the NIZ985 QW/spartalizumab cohort was halted prior to identification of recommended dose for expansion (RDE) due to a decision to discontinue the NIZ985 formulation used in this study and not for reasons related to safety and tolerability.

In the dose-expansion phase, patients with various tumor types considered to be either sensitive or resistant to anti-PD-1 agents (PD-1-sensitive or PD-1-resistant, respectively), were evaluated for response to NIZ985 1 µg/kg TIW in combination with spartalizumab 400 mg Q4W. Tumor types were considered PD-1-sensitive if approved for anti-PD-1/-PD-L1 therapies by the US Food and Drug Administarion (FDA) and/or the European Medicines Agency (EMA) (eg, non-small cell lung cancer, melanoma and bladder cancer); PD-1-resistant tumor types were all other diagnoses without an approved indication by the FDA and/or EMA at the time of a patient's enrollment.

This study was performed in compliance with the Good Clinical Practice Guidelines in accordance with the principles of the Declaration of Helsinki and approved by the appropriate institutional review board and independent ethics committee of the respective study centers (online supplemental table 1). Written informed consent was obtained from patients prior to participating and before any study-specific procedures were initiated. This trial is registered with ClinicalTrials.gov (number NCT02452268).

Patients

Patient eligibility criteria have been previously described.[23] Briefly, eligible patients were aged ≥18 years with histologically confirmed advanced/metastatic solid tumors who had progressed on, or were intolerant of standard treatment, or for whom curative or palliative measures were non-existent or associated with minimal survival benefit. Patients had to have an Eastern Cooperative Oncology Group performance status of ≤1, and measurable disease as assessed by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and irRC. Patients were excluded if they had received either prior IL-15 therapy, ICIs within 6 weeks or other anticancer treatment within 4 weeks from the start of the study or had received prior anti-PD-1 therapy that was discontinued due to toxicity related to anti-PD-1 agents (online supplemental methods). Patients with untreated or progressive central nervous system metastases were also excluded (exceptions listed in online supplemental methods).

Study objectives

The primary objective was to assess the safety and tolerability of single-agent NIZ985 and NIZ985/spartalizumab and to establish the maximum tolerated doses (MTDs) and/or the recommended dose of NIZ985 in combination with spartalizumab for the phase Ib expansion. The secondary objectives were to evaluate preliminary antitumor activity, and pharmacokinetic (PK) and immunogenic profiles of NIZ985 administered as a single agent and in combination with spartalizumab. The exploratory

objectives were to investigate biomarkers of tumor immune response and to assess the effects of NIZ985 on modulation of immune cell markers in blood and tumor biopsies.

Definition of DLT

Any study treatment-related grade 3 and grade 4 AEs occurring during cycle 1 (the first 28 days) from the initiation of single-agent NIZ985 treatment or 56 days from the initiation of NIZ985/spartalizumab treatment were defined as DLTs, except for those listed in online supplemental methods. Some grade 2 AEs were defined as DLTs (online supplemental methods). Other DLT determination was made on a case-by-case basis based on discussion between the investigator and the Novartis medical monitor.

Treatment discontinuation and dose modification

For DLTs occurring during the DLT observation period, patients had to discontinue study treatment, with exceptions predefined by the protocol. Patients were allowed to resume the study treatment on the same dosing schedule at the same or a lower dose level following resolution of the AE to the extent stated in the protocol if there was no evidence of disease progression per irRC. For patients who experienced non-DLT AEs, dose adjustments were permitted for NIZ985 as outlined in the protocol for no more than two dose levels.

PK and immunogenicity analyses

Blood samples for immunogenicity analyses were collected before and after dosing at the beginning and end of the study, as well as at specified time points during the study. NIZ985 serum concentrations were measured using a validated electrochemiluminescent immunoassay specific for NIZ985, with a lower limit of quantification (LLOQ) of 50 pg/mL. PK parameters were determined using a noncompartmental method available in Phoenix WinNonlin V.6.2 (Certara USA, Princeton, New Jersey, USA). For the immunogenicity analysis, antidrug antibodies were assessed by homogenous bridging assays against NIZ985.

Pharmacodynamic assessments and biomarker analyses

Flow cytometry assessments for T and NK cell subsets and proliferation were performed at baseline and on-treatment to monitor changes in immune cell populations from cycle 1 to cycle 6. Peripheral blood mononuclear cells were collected prior to dosing, on day 2, day 8 and day 15 of cycle 1, and on day 1, day 8 and day 15 for each following cycle through to cycle 6. Availability of samples varied across different time points in each cycle. The expression of nuclear protein Ki67 was assessed in the CD8+ T cell and CD56+ NK cell populations as described in online supplemental methods.

Plasma samples were collected for systemic cytokine modulation analysis during cycle 1. Inflammatory cytokines were measured pretreatment and post-treatment in serum samples using the V-PLEX Chemokine Panel 1 Human Kit (MSD K15047D), the V-PLEX Cytokine Panel 1 Human Kit (MSD K15050D), the V-PLEX Proinflammatory Panel 1 Human Kit (MSD K15049D) and the Human IL-18 Kit (151MCD) comprising 31 analytes in total.

Tumor biopsies for the analysis of PD-L1 and CD8 protein expression by immunohistochemistry (IHC) staining were collected at baseline, on day 15 of cycle 2, and at the end of treatment. PD-L1 expression was measured using IHC staining for PD-L1 (clone 22C3, PharmDx SK006 kit, Dako Autostainer Link 4B) and scored for the percentage of cell membrane positivity. The proportions of PD-L1-positive tumor cells (tumor positivity score) were quantified for all indications except melanoma. For melanoma, the combined positivity score was quantified, where the percentage of positive cells—including tumor and immune cells—was analyzed. The combined positivity score provides a more accurate histological evaluation than tumor positivity score in melanoma tissue, where differentiation between the staining of melanoma cells and immune cells is challenging.[24] The IHC staining signal for CD8 was quantified as the percent marker area representing quantification of the CD8 IHC staining area (clone C8/144B, Ventana Benchmark XT).

Statistical analyses

The safety analyses included all patients who received at least one dose of study drug and had at least one valid postbaseline safety assessment (safety analysis set). The safety endpoints were the incidence and severity of treatment-related AEs (TRAEs); the incidence of serious AEs (SAEs); the incidence of DLTs; changes between baseline and worst postbaseline laboratory values; vital signs and ECG parameters; dose intensity; frequencies of dose reductions, interruptions or discontinuations; and the frequency of cytokine release syndrome. The AE data for the safety evaluation were coded according to the Medical Dictionary for Regulatory Activities version 20.1 for the escalation phase and version 25 for the expansion phase. Safety assessments included toxicities graded according to the Common Terminology Criteria for Adverse Events version 4.03. Descriptive statistics were used to report the safety endpoints.

The secondary endpoints were the best overall response (BOR), disease control rate (DCR), duration of response, overall response rate, progression-free survival (PFS) per RECIST v1.1 and irRC, serum concentrations and derived PK parameters for NIZ985 and spartalizumab, and detection and/or concentration of anti-NIZ985 and anti-spartalizumab antibodies. Efficacy endpoints were measured in all patients who received at least one dose of the study drug (full analysis set). Efficacy assessments were carried out from baseline up to the follow-up period. Response evaluation criteria for target lesions and the definitions of BOR are described in online supplemental methods. SD as the BOR was reported based on at least one SD assessment more than 6 weeks after start of treatment while not qualifying for complete response (CR) or partial response (PR). The DCR was defined as the proportion of patients with the BOR of CR, PR or SD.

The exploratory endpoints assessed post-treatment changes in biomarkers of immunological response to determine pharmacodynamic effects of different NIZ985 treatment schedules.

Statistical analyses for the secondary and exploratory endpoints and the sample size calculation for the expansion phase are detailed in online supplemental methods.

RESULTS

Patient population

Between July 13, 2015 and February 17, 2020 (the study completion date was March 7, 2022), 47 and 36 patients were enrolled and treated in the dose-escalation and dose-expansion phases, respectively. The number of patients treated in each cohort of the two treatment arms is shown in figure 1 and baseline characteristics are detailed in table 1 and online supplemental table 2. In the PD-1-sensitive arm, the primary sites of cancer were lung, rectum, skin, esophagus and melanoma (45% [5/11]), while in the PD-1-resistant arm, the most common primary sites of cancer were pancreas (16%) and breast (12%) (online supplemental table 3).

Safety

No DLTs were observed and the MTD was not reached in any of the dose groups of TIW and QW schedules in the single-agent and combination arms.

At least one dose interruption of NIZ985 was reported in 30% (8/27) of patients in the single-agent TIW and QW cohorts and 43% (24/56) of patients in the combination cohorts. All patients discontinued treatment in all cohorts (online supplemental table 4). The primary reason was progressive disease (PD). At least one NIZ985 dose reduction due to an AE occurred in two patients in the single-agent NIZ985 QW cohort and in two patients in the dose-escalation cohorts (NIZ985 TIW/spartalizumab and NIZ985 QW/spartalizumab) (online supplemental table 4). An evaluation of the combination treatment with NIZ985 and spartalizumab 400 mg Q4W identified a RDE of 1 µg/kg TIW for the expansion phase of this study.

Treatment-emergent AEs (TEAEs) resulting in dose modification or interruption for the single-agent and combination cohorts are shown in online supplemental tables 5 and 6. In the single-agent NIZ985 10 µg/kg QW cohort, one patient developed grade 2 fatigue and grade 2 peripheral edema resulting in a dose reduction on day 36, and another patient developed grade 3 fatigue and grade 2 decrease in weight, with the dose reduced on day 43 and again on day 141. In the combination cohorts, one patient treated with NIZ985 1 µg/kg TIW/spartalizumab developed grade 3 joint effusion, leading to a dose reduction on day 177; another patient treated with NIZ985 4 µg/kg QW/spartalizumab developed grade 3 anemia, leading to a dose reduction on day 37. Treatment discontinuation due to TEAEs occurred in 19% (5/27) of patients in the single-agent NIZ985 arm, with pulmonary embolism, bullous dermatitis and small intestinal obstruction occurring in patients treated with the TIW dosing schedule (each in 1 of 14 patients), and ischemic stroke and multiple organ dysfunction syndrome in patients treated with the QW schedule (each in 1 of 13 patients). In the combination arm, 7% (4/56) of patients discontinued treatment due to fatigue, large intestinal obstruction, seizure and tongue edema—each of these were reported in one of 56 patients (data on file).

The most common TRAE in the single-agent and the combination arms was injection site reaction (85% [23/27] and 89% [50/56], respectively). In the single-agent arm, low-grade fatigue (52%), chills (48%), nausea (41%), pyrexia (41%), arthralgia (30%), decreased appetite (19%) and decreased lymphocyte count (19%) were the most common TRAEs. In the combination arm, low-grade fatigue (43%), influenza-like illness (32%), nausea (25%), chills (23%), myalgia (21%) and decreased appetite (20%) were the most common TRAEs (figure 2A). The most common grade 3–4 TRAE was decreased lymphocyte count in the single-agent (7%) and combination (5%) arms (figure 2A). Grade 1–2 and grade 3–4 TEAEs in the single-agent and combination arms are shown in figure 2B and listed for each dose level in online supplemental table 7. The most common TEAE was injection site reaction in the single-agent (85%) and combination (89%) arms, followed by fatigue (67% and 55%, respectively) (figure 2B).

IHC staining of a representative injection site reaction tissue biopsy (online supplemental methods), obtained outside the study protocol through the clinical management pathway of patients with IL-15-mediated toxicity, showed perivascular localization of CD3+ and CD8+ lymphocytes near dermal blood vessels and accumulation of CD56+ lymphocytes between the dermal and epidermal layers (online supplemental figure 2).

Any-grade treatment-related SAEs were reported in 21% (3/14) of patients in the single-agent TIW and one patient in the QW dose-escalation cohorts (online supplemental table 8). Significant skin toxicities were not observed in patients on the QW schedule at doses of up to 10 µg/kg (online supplemental table 8). For the combination treatment, two patients reported grade 1–2 SAEs (pyrexia and arthralgia, respectively) leading to hospitalization in the NIZ985 1 µg/kg TIW/spartalizumab cohort (N=47).

AEs of special interest (AESIs) included IL-15-mediated skin toxicities (pruritus, vasculitis, vasculitic rash and bullous dermatitis), which were reported in patients on the single-agent NIZ985 TIW schedule at doses higher than 1 µg/kg (except pruritus) but not in those on the single-agent NIZ985 QW schedule (online supplemental table 9). In the NIZ985 1 µg/kg TIW/spartalizumab dose-escalation/dose-expansion cohorts, diarrhea (30% [14/47]), maculo-papular rash (15% [7/47]), and dry skin and pruritus (each 11% [5/47]) were the most frequently occurring AESIs of any grade, while grade ≥3 AESIs occurred in 13% (6/47) of patients (online supplemental table 10).

Table 1 Demographics and baseline characteristics

Parameter	NIZ985 TIW (escalation) n=14	NIZ985 QW (escalation) n=13	NIZ985 TIW 1 µg/kg+spartalizumab (escalation) n=11	NIZ985 QW+spartalizumab (escalation) n=9	NIZ985 1 µg/kg TIW+spartalizumab PD-1-sensitive tumor types (expansion) n=11	NIZ985 1 µg/kg TIW+spartalizumab PD-1-resistant tumor types (expansion) n=25	Total N=83
Age (years), median (range)	56.5 (42–73)	66.0 (57–80)	61.0 (34–75)	64.0 (50–76)	66.0 (28–76)	64.0 (32–85)	63.0 (28–85)
Sex, n (%)							
Male	8 (57.1)	9 (69.2)	7 (63.6)	7 (77.8)	7 (63.6)	9 (36.0)	47 (56.6)
Female	6 (42.9)	4 (30.8)	4 (36.4)	2 (22.2)	4 (36.4)	16 (64.0)	36 (43.4)
Race, n (%)							
White	12 (85.7)	11 (84.6)	11 (100)	9 (100)	9 (81.8)	22 (88.0)	74 (89.2)
Black/African American	1 (7.1)	0	0	0	1 (9.1)	1 (4.0)	3 (3.6)
Asian	0	1 (7.7)	0	0	1 (9.1)	2 (8.0)	4 (4.8)
Not reported	0	1 (7.7)	0	0	0	0	1 (1.2)
Unknown	1 (7.1)	0	0	0	0	0	1 (1.2)
ECOG performance status, n (%)							
0	7 (50.0)	6 (46.2)	5 (45.5)	4 (44.4)	4 (36.4)	8 (32.0)	34 (41.0)
1	7 (50.0)	7 (53.8)	5 (45.5)	5 (55.6)	7 (63.6)	17 (68.0)	48 (57.8)
2	0	0	1 (9.1)*	0	0	0	1 (1.2)*
Prior lines of therapy, n (%)							
1	3 (21.4)	0	1 (9.1)	1 (11.1)	0	1 (4.0)	6 (7.2)
2	4 (28.6)	4 (30.8)	2 (18.2)	1 (11.1)	2 (18.2)	7 (28.0)	20 (24.1)
≥3	7 (50.0)	9 (69.2)	8 (72.7)	6 (66.7)	9 (81.8)	16 (64.0)	55 (66.3)
Prior immunotherapy, n (%)	7 (50.0)	4 (30.8)	4 (36.4)	4 (44.4)	11 (100)	4 (16.0)	34 (41.0)
Anti-PD-1	6 (42.9)	2 (15.4)	2 (18.2)	2 (22.2)	4 (36.4)	11 (44.0)	27 (32.5)
Anti-PD-L1	1 (7.1)	1 (7.7)	2 (18.2)	1 (11.1)	0	0	5 (6.0)
Anti-CTLA-4	3 (21.4)	0	0	0	0	7 (28.0)	10 (12.0)
Type of last therapy,† n (%)							
Hormonal therapy	0	1 (7.7)	0	0	0	0	1 (1.2)
mTOR inhibitor	0	1 (7.7)	0	0	0	0	1 (1.2)
Monoclonal antibody	1 (7.1)	0	0	0	0	0	1 (1.2)
TKI	1 (7.1)	0	0	0	0	0	1 (1.2)
Targeted therapy	1 (7.1)	0	0	0	0	3 (12.0)	4 (4.8)
Chemotherapy	7 (50.0)	8 (61.5)	5 (45.5)	6 (66.7)	3 (27.3)	17 (68.0)	46 (55.4)
Immunotherapy	4 (28.6)	3 (23.1)	4 (36.4)	2 (22.2)	8 (72.7)	3 (12.0)	24 (28.9)

*The patient met eligibility criteria at screening and at baseline. At day 1 of cycle 1, there was a documented change in ECOG performance status due to tumor pain, which subsequently improved. ECOG performance status at day 1 of cycle one was documented as progressive disease.
†Selected therapies are shown.
ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin; PD-1, programmed cell death protein-1; QW, once a week; TIW, three times a week; TKI, tyrosine kinase inhibitor.

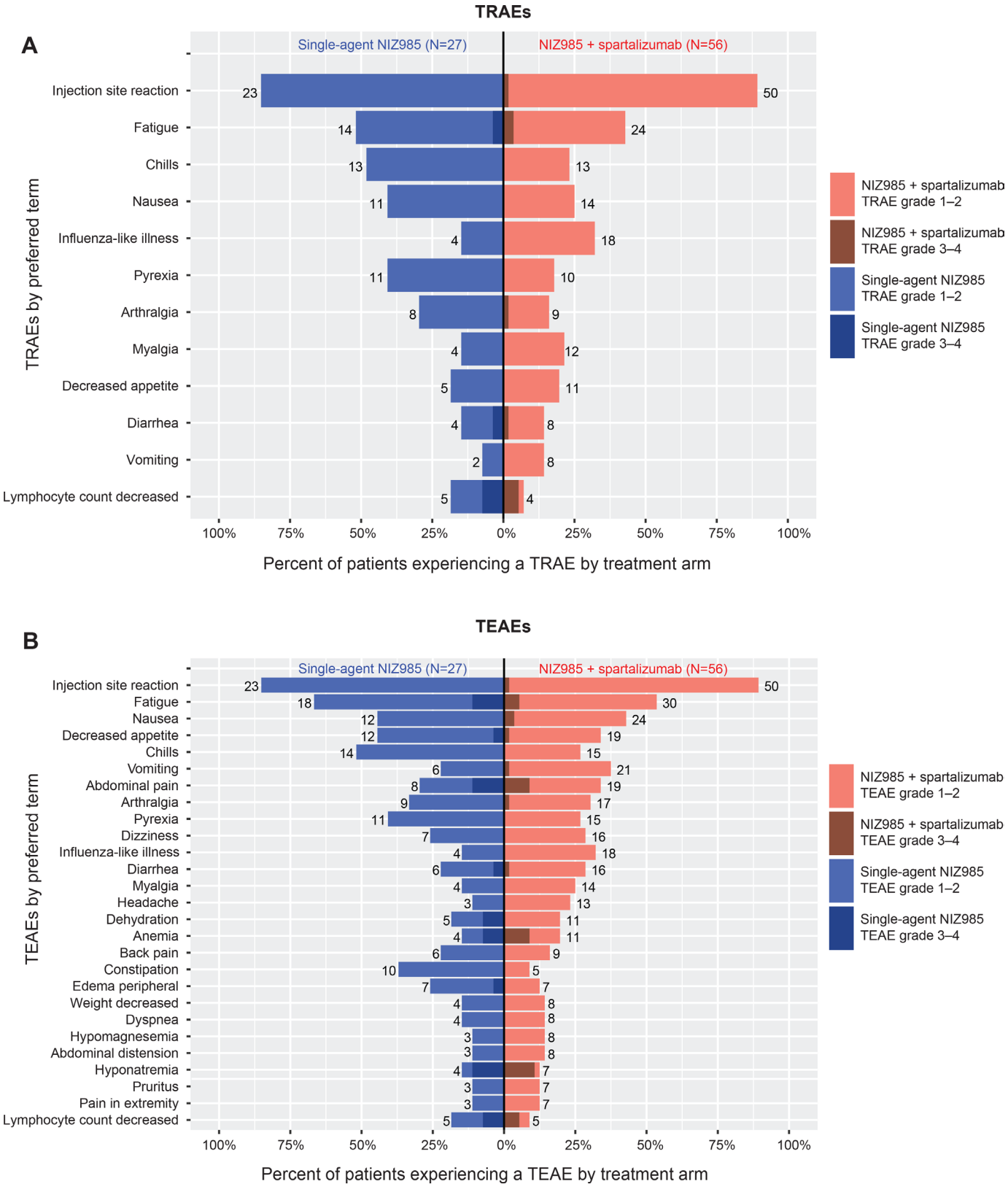

Figure 2 TRAEs and TEAEs occurring in at least 10% of patients treated with single-agent NIZ985 and the combination of NIZ985 with spartalizumab (safety analysis set). The number of patients experiencing a TRAE or a TEAE is shown beside each bar. TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

A total of 12 patients died in the on-treatment period (from the day of first treatment to 30 days after the last treatment). One patient died of underlying malignancy in the single-agent NIZ985 TIW cohort and six patients died in the single-agent NIZ985 QW cohort (five of underlying malignancy and one of ischemic stroke not related to the

Table 2 Best overall response, overall response rate and disease control rate based on local radiology assessment per RECIST v1.1 for single-agent NIZ985 and the combination of NIZ985 with spartalizumab cohorts (full analysis set)

Response	NIZ985 TIW (escalation) n=14	NIZ985 QW (escalation) n=13	NIZ985 TIW 1 µg/kg+spartalizumab (escalation) n=11	NIZ985 QW+spartalizumab (escalation) n=9	NIZ985 1 µg/kg TIW+spartalizumab PD-1-sensitive tumor types (expansion) n=11	NIZ985 1 µg/kg TIW+spartalizumab PD-1-resistant tumor types (expansion) n=25
Best overall response rate, n (%)						
Complete response	0	0	0	0	0	0
Partial response	0	0	1 (9.1)	1 (11.1)	1 (9.1)	0
Stable disease	3 (21.4)	5 (38.5)	4 (36.4)	3 (33.3)	4 (36.4)	5 (20.0)
Progressive disease	8 (57.1)	4 (30.8)	6 (54.5)	3 (33.3)	5 (45.5)	16 (64.0)
Unknown*	3 (21.4)	4 (30.8)	0	2 (22.2)	1 (9.1)	4 (16.0)
Overall response rate,† n (%) (95% CI)‡	0 (0 to 23.2)	0 (0 to 24.7)	1 (9.1) (0.2 to 41.3)	1 (11.1) (0.3 to 48.2)	1 (9.1) (0.2 to 41.3)	0 (0 to 13.7)
Disease control rate,§ n (%) (95% CI)	3 (21.4) (4.7 to 50.8)	5 (38.5) (13.9 to 68.4)	5 (45.5) (16.7 to 76.6)	4 (44.4) (13.7 to 78.8)	5 (45.5) (16.7 to 76.6)	5 (20.0) (6.8 to 40.7)

*Progression was not documented, and one or more target lesions were not assessed or were assessed using a different method than at baseline.
†The overall response rate includes a complete response and partial response.
‡95% CI for the overall response rate and the disease control rate were obtained using the Clopper-Pearson's method.
§The disease control rate includes a complete response, partial response and stable disease.
PD-1, programmed cell death protein-1; QW, once a week; RECIST, Response Evaluation Criteria in Solid Tumors; TIW, three times a week.

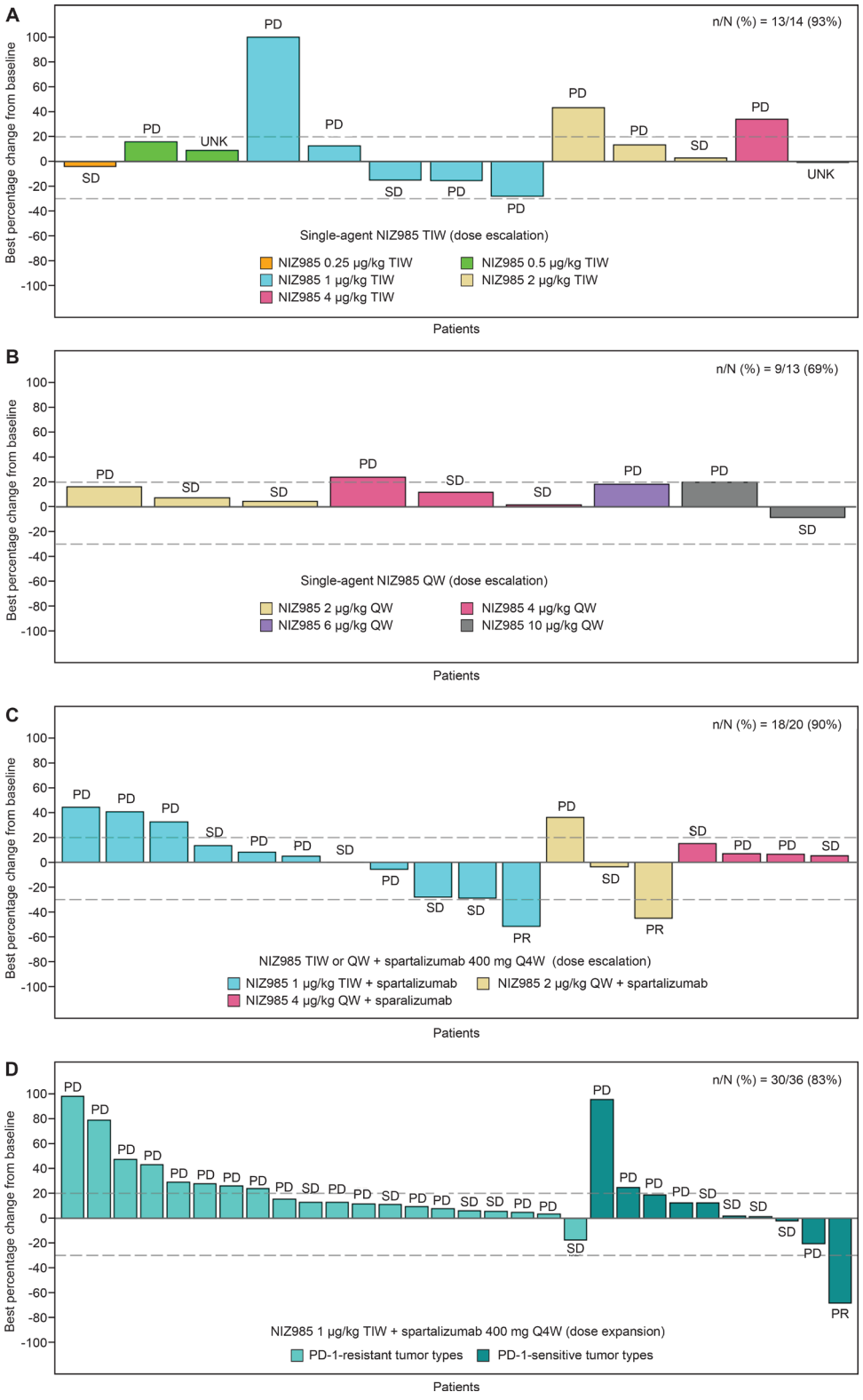

Figure 3 Best percentage change from baseline in target lesions in the single-agent NIZ985 and the combination with spartalizumab cohorts. Percentage changes from baseline >100% are set to 100%. PD, progressive disease; PD-1, programmed cell death protein-1; PR, partial response; Q4W, every 4 weeks; QW, once a week; SD, stable disease; TIW, three times a week; UNK, unknown response status.

study treatment). In the combination arm, five patients died: three of underlying malignancy and one of encephalopathy unrelated to study drugs (possible contributing factor was progression of underlying malignancy) in the NIZ985 1 µg/kg TIW/spartalizumab cohorts; and one of underlying malignancy in the NIZ985 2 µg/kg QW/spartalizumab cohort (data on file).

Figure 4 Duration of exposure to single-agent NIZ985 and NIZ985 in combination with spartalizumab by tumor type. Duration of exposure is shown for (A) the single-agent NIZ985 TIW dose-escalation cohort, (B) the single-agent NIZ985 QW dose-escalation cohort, (C) the combination of NIZ985 TIW or QW and spartalizumab dose-escalation cohort, and (D) the combination of NIZ985 TIW and spartalizumab dose-expansion cohort. *Patients treated with prior immuno-oncology therapies. CR, complete response; PD, progressive disease; PD-1, programmed cell death protein-1; PR, partial response; QW, once a week; SD, stable disease; TIW, three times a week.

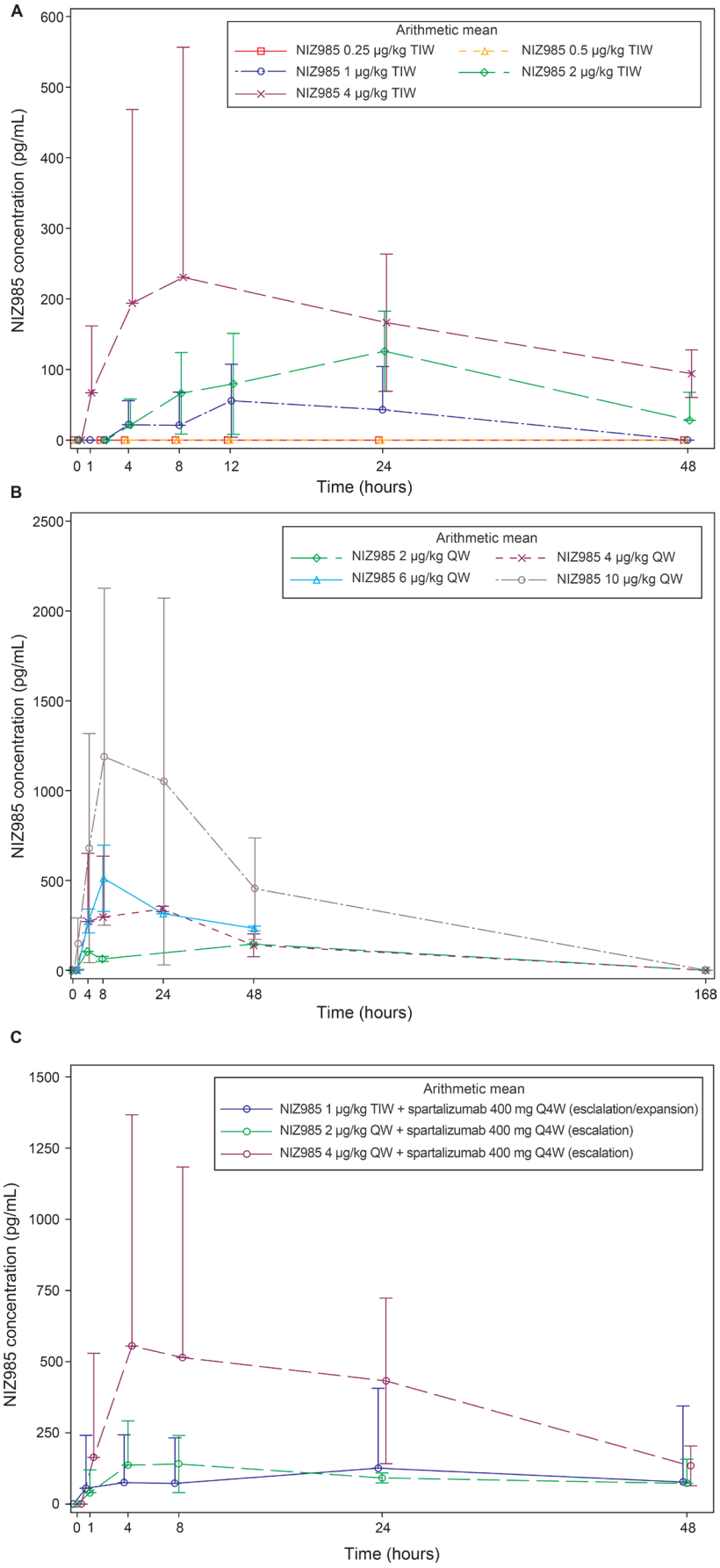

Figure 5 Serum NIZ985 concentration over time after the first dose of (A) single-agent NIZ985 TIW, (B) single-agent NIZ985 QW, and (C) the combination of NIZ985 with spartalizumab. Q4W, every 4 weeks; QW, once a week; TIW, three times a week.

Efficacy

Of the 27 evaluable patients by RECIST v1.1 in the single-agent NIZ985 arm, 30% (8/27) had SD (57–690 days), 44% (12/27) had PD (table 2) and none experienced PR. In the combination arm, 5% (3/56) of patients experienced a PR, 29% (16/56) had SD (51–420 days) and 54% (30/56) had PD by RECIST v1.1 (table 2). No CR was observed in any of the study cohorts. One case of PD by RECIST v1.1 in the combination arm was considered a PR when assessed by irRC, thus resulting in 7% (4/56) of patients with a PR (online supplemental table 11). By irRC, 32% (18/56) of patients had SD (online supplemental table 11). In the expansion phase, four patients achieved SD (51–124 days) and one patient achieved PR in the PD-1-sensitive cohort (n=11) and five patients achieved SD (61–344 days) and no patient achieved PR in the PD-1-resistant cohort (n=25), resulting in the DCR of 45% (95% CI 16.7% to 76.6%) and 20% (95% CI 6.8% to 40.7%), respectively, by RECIST v1.1 (table 2). The DCR by irRC increased to 55% (95% CI 23.4% to 83.3%) in the PD-1-sensitive cohort but remained unchanged in the PD-1-resistant cohort (table 2, online supplemental table 11). All patients with PR/SD in the PD-1-sensitive cohort had received prior anti-PD-1 therapy, while none of the patients with SD in the PD-1-resistant cohort had received prior anti-PD-1 therapy. At least three patients with SD in the PD-1-sensitive cohort (4 SD, 1 PR) had progressed on a prior anti-PD-1 therapy (data on file). Waterfall plots of the best percentage change from baseline in the size of target lesions are presented in figure 3. Twenty-seven percent (3/11) of patients in the PD-1-sensitive cohort and only one of 25 patients in the PD-1-resistant cohort showed a decrease in target lesion measurements from baseline.

The duration of exposure in the single-agent NIZ985 dose-escalation cohorts and the NIZ985/spartalizumab dose-escalation/dose-expansion cohorts is shown by tumor type in figure 4. Two patients achieved PR, one in the NIZ985 1 µg/kg TIW/spartalizumb group and one in the 2 µg/kg QW/spartalizumab dose-escalation group, occurring in patients with gastric cancer and pancreatic cancer, which are considered poorly responsive to anti-PD-1 therapies (figure 4C). In dose expansion, a PR was observed in a patient with cutaneous melanoma (figure 4D), who had received a prior anti-PD-1 therapy. One patient with uveal melanoma in the single-agent NIZ985 TIW cohort had prolonged SD lasting for approximately 22 months (figure 4A). This patient was treated with nivolumab as the last ICI prior to the study and achieved SD as the best response.

The median PFS was 1.9 months (95% CI 1.6 to 3.5) in the PD-1-sensitive cohort and 1.6 months (95% CI 1.4 to 1.8) in the PD-1-resistant cohort (online supplemental figure 3).

PK and immunogenicity

PK parameters for patients treated with single-agent NIZ985 TIW or QW and in combination with spartalizumab in the dose-escalation/dose-expansion cohorts are summarized in online supplemental table 12. The PK profiles of NIZ985 are shown in figure 5. Exposure to NIZ985 after the first dose increased in an approximately dose-proportional manner over the dose range of 1–4 µg/kg with the TIW schedule, and over the dose range of 2–10 µg/kg with the QW schedule, although the data showed large variability. The median T_{max} of NIZ985 after the first dose was approximately 8–28 hours. No accumulation of NIZ985 following multiple doses was observed. The elimination half-life was not estimable in most patients (online supplemental table 12). Exposure of NIZ985 did not appear to be affected by co-administration of spartalizumab. Treatment-induced anti-NIZ985 antibodies were detected in 1 of 12 patients in the single-agent NIZ985 1 µg/kg TIW cohort, 36% (4/11) of patients in the single-agent NIZ985 QW cohort and 28% (15/53) of patients in the combination cohorts (online supplemental table 13).

Pharmacodynamics and biomarkers

The flow cytometric evaluation of lymphocyte cell subsets showed transient increases in the expression of the proliferation marker Ki67 in CD8+ T cells and NK cells following treatment with single-agent NIZ985 and with the combination at different dose levels (online supplemental figure 4). NIZ985 treatment was associated with the transient induction of several cytokines, including C-X-C motif chemokine ligand 10 (CXCL10), IFN-γ, IL-15, IL-12p40, IL-18, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)-1α, MIP-1β and tumor necrosis factor (TNF)α (online supplemental figure 5). Dose-dependent modulation of CXCL10, IFN-γ, MCP-1, MIP-1α, MIP-1β and TNFα levels in serum occurred in response to single-agent NIZ985 in the QW schedule cohort.

IHC staining of tumor biopsy tissue at baseline and on-treatment showed that two out of two evaluable patients with a PR had an increase in tumor CD8+ cell infiltration following treatment with the combination of NIZ985 TIW or QW and spartalizumab (online supplemental figure 6). No association was evident between the CD8+ cell infiltration and SD. The limited availability of baseline and on-treatment biopsy samples precluded a meaningful investigation of CD8+ T cell infiltration into tumors.

DISCUSSION

This first-in-human study reports the safety, PK/pharmacodynamics, preliminary antitumor activity and biomarker data for two schedules of NIZ985 administered with or without spartalizumab in heavily pretreated patients with advanced solid tumors. Overall, NIZ985 was well tolerated in the single-agent and combination regimens. The combination treatment showed antitumor activity against tumor types known to have a poor response to ICIs.

Preclinical studies investigated different types of recombinant IL-15 constructs, with or without IL-15Rα, and have provided essential evidence for IL-15 antitumor activity, leading to tumor regression in experimental murine models, reduced metastatic spread and prolonged survival,[15 25 26] with the antitumor activity enhanced on combination of IL-15 with anti-PD-1/anti-PD-L1 agents.[17 18] Despite promising preclinical data, IL-15 monotherapy has not demonstrated significant clinical activity in first-in-human phase I studies to date.[21 27] Moreover, IL-15 has been shown to induce the expression of PD-1 and PD-L1 on T cells,[28 29] potentially limiting its effectiveness as a single agent and prompting investigation of combinations with PD-1/PD-L1 blocking agents. ALT-803, a heterodimer of the recombinant IL-15 mutant (N72D) and an IL-15Rα fragment fused to an immunoglobulin G Fc domain with a prolonged retention in serum and improved tolerability,[30 31] showed promising activity in combination with nivolumab in patients with relapsed/refractory lung cancer.[32] ALT-803 (N803) in combination with intravesical Bacillus Calmette-Guérin (BCG), standard of care for non-muscle-invasive bladder cancer (NMIBC), is currently under review by the FDA for the treatment of patients with BCG-unresponsive NMIBC carcinoma in situ with or without Ta (papillary noninvasive carcinomas) or T1 (tumors infiltrating the lamina propria) disease.[33] The combination of ALT-803 with BCG suppressed disease progression in this clinical setting.[33]

A preliminary report of the current study showed that subcutaneous administration of NIZ985 in the TIW dosing schedule was generally well tolerated and triggered an immune response that induced proliferation of cytotoxic lymphocytes and the secretion of IFN-γ.[23] However, IL-15-mediated skin toxicities (bullous dermatitis or pemphigoid, and vasculitis) were observed in cycle 2 in the 2 µg/kg TIW and 4 µg/kg TIW dosing groups, suggesting that patients may benefit from a less frequent, weekly NIZ985 dosing schedule. The PK data from this early report[23] and a previous study of hetIL-15 PK/pharmacodynamics and retention in plasma of rhesus macaques[19] led to the investigation of the QW schedule in the current study.

Treatment with different schedules of single-agent NIZ985, or NIZ985/spartalizumab, was well tolerated by the majority of patients in this study, with a sample size considerably larger (N=83) than typical phase I datasets (N=15–30).[34] The QW dosing schedule showed a marginally better safety profile than the TIW schedule at doses higher than 1 µg/kg due to reduced systemic skin toxicities. No DLTs were reported during escalation and the MTD was not reached. The most common TRAE in the single-agent and combination arms was a low-grade injection site reaction, and the spectrum and incidence of low-grade TRAEs were largely similar across all cohorts. This is in agreement with the previously published safety data for other single-agent IL-15 formulations, where the most frequent TRAEs were a low-grade injection site reaction, fatigue, vomiting, nausea, chills and transient clinically inconsequential decrease in lymphocyte count in patients with advanced solid tumors.[21 27] Of grade 3–4 toxicities, decreased lymphocyte count and fatigue were the most common TRAEs in both the single-agent and combination arms of this study. Decreased lymphocyte count reflects the exit of lymphocytes from the blood and relocation to the tissues, and this process is reversible.[20]

Three patients experienced a PR by RECIST v1.1 (gastric cancer and pancreatic cancer in the combination escalation cohort, and melanoma in the combination expansion cohort) and one additional patient had a PR per irRC (urothelial cancer in the combination escalation cohort). The antitumor activity observed in the two patients with pancreatic and gastric cancer who were naïve to treatment with anti-PD-1/anti-PD-L1 agents is encouraging, considering that currently no strong clinical evidence exists for the antitumor effects of a PD-1/PD-L1 blockade in pancreatic ductal adenocarcinoma.[35] The patient with melanoma who reported a PR had achieved SD as the best response to prior anti-PD-1 therapy, while the patient with urothelial cancer who experienced a PR per irRC progressed on a prior anti-PD-L1 therapy. Several patients in the dose-expansion cohort experienced reduction of target lesions from baseline, but the total reduction did not reach the threshold of a PR. A third of patients in the PD-1-sensitive cohort and one-fifth of patients in the PD-1-resistant cohort achieved SD as the best response, resulting in DCR of 45% and 20%, respectively. Overall, the efficacy of NIZ985 in combination with spartalizumab might have been limited by mechanisms of immune resistance in this population of heavily pretreated patients, 41% of which had received prior ICI therapy.

PK parameters between the single-agent and combination arms did not substantially differ, indicating that no significant drug–drug interactions appear to occur between NIZ985 and spartalizumab. Due to the small sample sizes in the single-agent NIZ985 dose-escalation cohorts, a robust assessment of dose dependency was not performed. Accumulation of NIZ985 following administration of multiple doses was not observed due to the rapid elimination of NIZ985 from the body. In fact, the values of exposure parameters (area under the curve and C_{max}) following the administration of multiple doses were lower than those after the first dose in most patients. Reasons for this phenomenon may be related to the proliferation of NK and T cells, known to result in enhanced target-mediated drug disposition (TMDD),[19 36] which would lead to increased clearance of NIZ985. Other circulating IL-15 agonists are known to behave in a similar manner.[36] The variability of PK parameters was high in this study, potentially due to small sizes of cohorts (except for the expansion phase), NIZ985 concentrations below the LLOQ, rapid elimination of NIZ985 and TMDD.

Proliferation of peripheral CD8+ and NK lymphocytes, and increased levels of circulating inflammatory cytokines were observed in response to the single-agent NIZ985 and combination NIZ985/spartalizumab, indicating that NIZ985 treatment induces systemic immune activation.

Moreover, a systemic inflammatory cytokine analysis performed at baseline and during cycle 1 of treatment with single-agent NIZ985 in the QW schedule cohort revealed dose-dependent modulation of CXCL10, IFN-γ, MCP-1, MIP-1α, MIP-1β and TNFα levels in serum. Tumor tissue staining for CD8 showed markedly increased CD8+ cell infiltration in tumors in two patients with a PR treated with the combination therapy.

Different IL-15 therapeutic preparations have proven ineffective as single agents in patients with solid tumors, despite the success in improving the stability of IL-15 and its PK profile, and the ability of therapeutic IL-15 to induce a robust proliferation of NK cells and CD8+ T cells in preclinical models and the clinical setting.[37] A number of immunoregulation mechanisms counteracting the immunostimulatory effects of IL-15 have been identified and suggested to play a role in deactivation of NK cells and CD8+ T cells in the tumor microenvironment.[37] It has been argued that systemic administration of IL-15 formulation may not be sufficient to overcome the negative effects of tumor microenvironment, whereas local delivery achieves higher concentrations of cytokine and better therapeutic results.[26] One mechanism contributing to suppressive tumor microenvironment is based on the induction of checkpoint molecules, including PD-1, on CD8+ T cells.[37] Therefore, various clinical trials have been initiated to investigate the safety and efficacy of IL-15-based combinations with different ICIs are currently being investigated in several phase I clinical trials.[38] A phase I/Ib study of weekly NIZ985 alone and in combination with a PD-1 inhibitor has been initiated in patients with advanced solid tumors and lymphoma who have progressed following a previous response to an ICI (NCT04261439).[39] Another phase I trial is recruiting patients with metastatic solid tumors and treatment-refractory tumors for investigation of IL-15 therapy in combination with nivolumab (anti-PD-1 agent) and ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4) (NCT03388632).[40] Two phase I studies have completed patient enrollment for the evaluation of the combination of IL-15 with avelumab (anti-PD-L1) in relapsed/refractory T cell malignancies (NCT03905135)[41] and with alemtuzumab (humanized monoclonal antibody against CD52) in refractory/relapsed chronic and acute adult T cell leukemia (NCT02689453).[42] In addition, ALT-803 is currently being investigated in combination with nivolumab (NCT02523469)[43] or pembrolizumab (NCT05096663)[44] in patients with non-small cell lung cancer.

In conclusion, the NIZ985 TIW (1 µg/kg and lower dose levels) and QW regimens were well tolerated either as monotherapy or in combination with spartalizumab. The effects of NIZ985 on CD8+ T cell and NK cell proliferation and cytokine levels suggested engagement of the target immune cells. Preliminary antitumor activity of NIZ985 used in combination with spartalizumab was detected in several patients with tumors considered to be unresponsive to anti-PD-1 therapy or with sensitive tumors that had progressed on prior anti-PD-1 therapy. Further investigation of combinations of NIZ985 with ICIs, not only in patients with solid tumors but also in those with hematological malignancies, is warranted to determine whether NIZ985 can help overcome acquired resistance to ICIs. Novel potential indications have recently emerged from preclinical testing of hetIL-15, including a significant antimetastatic potential of hetIL-15 with or without chemotherapy in the neoadjuvant setting, preventing the dissemination of metastatic cells in murine cancer models.[45] Therefore, the therapeutic value of IL-15 formulations may prove highest at early disease stages. Blocking or eliminating metastatic disease is an important parameter of treatment. Ongoing phase I studies and future biomarker studies may elucidate novel mechanisms of resistance and facilitate the selection of combinatorial therapies—other than ICIs—with IL-15 agents.

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