First-in-human trial to evaluate safety, PK/PD and initial clinical activity of NM21-1480, an affinity-balanced PD-L1x4-1BBxHSA trispecific antibody: Results of Phase 1 dose escalation

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Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy, inducing durable responses in cancer patients diagnosed with various tumor types.[1] Despite the clinical success of Programmed Death (Ligand) 1 (PD-L1/PD-1) inhibitors, the majority of malignancies—even those expressing high levels of PD-L1—exhibit inadequate responses to these agents, *i.e.,* are primary or secondary resistant to PD-L1/PD-1 blockade.[2] The co-stimulatory receptor 4–1BB expressed on tumor-infiltrating T cells is a compelling target for overcoming resistance to ICIs, but initial clinical studies of 4–1BB agonistic mAbs have been hampered due to severe liver toxicity.[3-6] Combination of PD-1/PD-L1 blockade and potent 4-1BB agonism has demonstrated pronounced activity in preclinical models and promising signals in early clinical studies.[7-10]

Mechanism of action and preclinical data: NM21-1480 is a next generation ICI. The molecule is a tri-specific Fc-lacking antibody engineered to block PD-L1/PD-1 signaling and selectively co-stimulate 4–1BB in the tumor microenvironment only. The molecule lacks an Fc part (to avoid Fc receptor-mediated cross-link) but contains an anti-human serum albumin domain resulting in clinically favorable pharmacokinetics. NM21-1480 contains an ultra-potent PD-L1 blocking moiety and an affinity-balanced 4-1BB binding moiety to assure maximal tumor-targeted activity on both pathways over a broad dose range (Figure 1). NM21-1480 exhibited high efficacy for co-activation of pre-stimulated T cells *in vitro*. In xenograft models in humanized mice, NM21-1480 induced tumor regression and tumor infiltration of T cells without causing systemic T-cell activation. A GLP toxicology study revealed no evidence of liver toxicity at doses up to 140 mg/kg, the maximum assessed dose in animals.[11] Here we report the results of the Phase 1 dose-escalation part (Part A) of the ongoing First-in-Human Phase 1/2a clinical trial with NM21-1480.

NM21-1480: PD-L1×4-1BBxHSA antibody mechanism of action

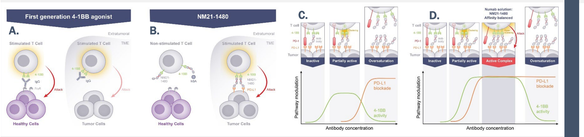

Figure 1. Affinity balancing unlocks full potential of a PD-L1x4-1BB bispecific molecule: Maximal 4-1BB activity maintained at concentrations that completely block PD-L1[11] **A.** Systemic stimulation of T cells through 4-1BB dimerization and interaction with FcγR. **B.** Restriction of T cell stimulation to TME due to: (1) required anchoring to PD-L1 for cross-linking 4-1BB signals; (2) lack of Fc domain; and (3) monovalent design. **C.** Affinity to PD-L1 = 4-1BB. Unbalanced target affinities lead to loss of 4-1BB activation at full PD-L1 blockade and vice versa. **D.** Affinity to PD-L1 >>> 4-1BB. Affinity-Balance results in overlapping activity and active complex formation.

Objectives:

- The primary objectives of this dose escalation part of the trial were the characterization of the safety and tolerability profile of NM21-1480, the determination of its maximum tolerated dose (MTD) and the determination of dose level(s) for further evaluation of pharmacodynamics and clinical activity in expansion cohorts.
- The secondary objectives were the establishment of a pharmacokinetic profile and the evaluation of immunogenicity.
- Exploratory objectives comprised the assessment of anti-tumoral activity of NM21-1480, based on RECIST 1.1., the characterization of the pharmacodynamic profile of the compound, and the exploration of potential biomarkers of clinical response.

Methods:

- This is a first-in-human, multicenter, open-label, phase 1/2a trial of NM21-1480 in advanced solid tumors (NCT04442126) (Figure 2).
- The trial consists of two consecutive parts: dose escalation (phase 1 – Part A) and expansion (phase 2 – Part B).
- The dose-limiting toxicity (DLT) monitoring period was 28 days, comprising two full dosing intervals.

Dose escalation trial design

Treatment:

- Dose escalation started with an accelerated phase consisting of single-patient cohorts followed by cohorts of n≥3 patients upon occurrence of a first treatment-related AE (TRAE) of CTCAEv5.0 Grade 2, as guided by a Bayesian Optimal Interval (BOIN) design.
- Efficacy was assessed by on-treatment CT or MRI at Week 8 and every 8 weeks thereafter until disease progression or another discontinuation criterion was met (unless the investigator elected to treat beyond progression as per protocol-defined criteria).

Inclusion criteria

- ✓ 18 years of age or above
- ✓ Patients with metastatic/ unresectable solid tumors confirmed by pathology/fresh biopsy, with progressing disease since last therapy and for whom there is no available standard of care
- ✓ Measurable disease according to RECIST 1.1
- ✓ ECOG PS 0–1
- ✓ Adequate renal, liver, and hematologic function

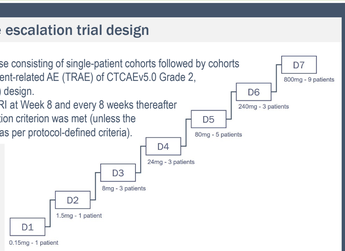

Figure 2. Dose escalation trial design. NM21-1480 administered as intravenous flat dose every 2 weeks until disease progression or unacceptable toxicity during dose escalation. Data cut-off date: 19 September 2022. ECOG PS, Eastern Cooperative Oncology Group Performance Status; RECIST, Response Evaluation Criteria in Solid Tumors.

Results:

Patient characteristics and disposition

- 26 patients were enrolled in the dose escalation part of the trial (Table 1).
- Patients were heavily pretreated, with median (range) of 3.5 (1–10) prior lines of treatment; 61.5% of patients received prior PD-(L)1 immunotherapy.
- As of data cut-off date (19SEP2022), treatment ongoing in 1 (3.8%) patient (Table 2).
- MTD was not reached.
- Patients discontinued treatment due to the following AEs: Infusion related reaction (n=3; all events Grade 2) and ALT increased (n=1; Grade 4).
- There was a single on-treatment death which was due to rapid disease progression and unrelated to treatment.

Median (range) age, years	63 (27-76)
Age groups, n (%) <65 years ≥65 years	 16 (61.5) 10 (38.5)
Female	11 (42.3)
Cancer type, n (%) NSCLC Colorectal HNSCC Pancreatic Appendiceal Other*	 4 (15.4) 4 (15.4) 3 (11.5) 3 (11.5) 3 (11.5) 9 (34.6)
ECOG performance status, n (%) 0 1	 7 (26.9) 19 (73.1)
Median (range) number of prior therapies	3.5 (1-10)
Prior PD-(L)1 inhibitor treatment, n(%)	16 (61.5)

Table 1. Baseline demographics and clinical characteristics NCT04442126, Part A (Dose Escalation). All patients N=26. Data cut-off: 19 September 2022; *Cancer types occurring in less than 10% of enrolled patients were categorized as «Other»; NSCLC: Non-Small Cell Lung Cancer; HNSCC: Head and Neck Squamous Cell Carcinoma

Median (range) on treatment, including FU, in weeks	23.4 (2.7-86.4)
Treatment ongoing, n (%)	1 (3.8)
Reason for treatment discontinuation, n (%) Progressive disease AE	 21 (80.8) 4 (15.4)
Median (range) number of NM21-1480 dose infusions	4 (1-21)
Median (range) duration of exposure, in weeks	9.1 (2.1-42.3)

Table 2. Patient disposition and exposure NCT04442126, Part A (Dose Escalation). All patients N=26. Data cut-off: 19 September 2022; AE: Adverse events; FU: follow-up

Safety

Treatment-emergent AEs (TEAEs) occurred in 25 (96.2%) patients. Most AEs were Grade 1-2 (Figure 3).

- The most common (≥10%) TEAEs were back pain, infusion-related reaction, and fatigue.
- Grade 3-4 TEAEs were reported for 8 (30.8%) patients.
- Treatment-emergent transaminase elevations (AST and/or ALT increased) occurred in 19.2% of patients (Grade 3-4: 7.7%).

Treatment-related AEs (TRAEs) occurred in 19 (73.1%) patients (Table 3).

- Grade 3-4 TRAEs reported for 2 (7.7%) patients. No Grade 5 TRAE occurred.
- Treatment-related AST and/or ALT increases occurred in ≥3 (11.5%) patients (Grade ≥3, 3.8%); No patient had treatment-related bilirubin elevation.

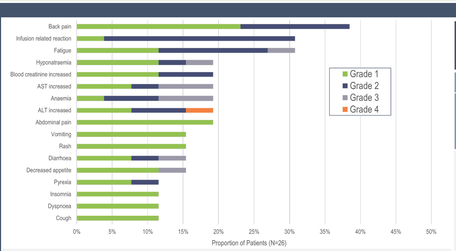

Figure 3. TEAEs occurring in ≥10% of patients. Data cutoff: 19 September 2022; Adverse events graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)v.5.0; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

	All patients (N=26)		
	All grades, n (%)	Grade 3, n (%)	Grade 4, n %
Any TRAE	19 (73.1)	1 (3.8)	1 (3.8)
TRAE in ≥10% of patients by preferred term			
Infusion-related reaction	8 (30.8)	0 (0.0)	0 (0.0)
AST/ALT elevation	3 (11.5)	0 (0.0)	1 (3.8)*
Fatigue	3 (11.5)	0 (0.0)	0 (0.0)

Table 3. TRAEs occurring in ≥10% of patients. Data cut-off: 19 September 2022; AEs graded according to NCI CTCAEv.5.0; *One patient presented with clinically silent Grade 3 AST/ALT elevation after 2 months on treatment and 15 days after receiving final dose (patient was stable with -3% decrease from baseline sum of diameters [SoD] at Week 8 scans). Liver biopsy confirmed likely non-viral hepatitis. Patient was discontinued and rapidly improved to Grade 1 with budenoside treatment. Patient developed a rebound to clinically silent Grade 4 transaminase elevation 57 days after receiving final dose of NM21-1480. Event again rapidly improved to Grade 1 with treatment; patient is doing well as per September 2022 and has since entered another clinical trial. Concomitant alcohol consumption and lack of compliance with steroid treatment was reported during the entire period. Due to liver biopsy result, the Grade 4 event was assessed as possibly related to study drug and thus represents a delayed DLT.

Dose level	Patients, n	Patients with DLTs, n	DLT
0.15 mg	1	0	None
1.5 mg	1	0	None
8 mg	3	0	None
24 mg	3	0	None
80 mg	5[a]	1	Grade 2 Infusion-Related Reaction[b]
240 mg	3	0	None
800 mg	9	0	None

Table 4. Summary of DLTs. Data cut-off: 19 Sept 2022. [a] One patient died due to rapid disease progression on study Day 20 and was therefore not evaluable for the DLT rate calculation for this dose level; [b] Patient developed a Grade 2 IRR during second infusion. Infusion was stopped and completion of dosing following pre-medication attempted the next day. However, the patient again reported subjective symptoms and infusion was not completed. As the patient could not tolerate two full doses of the assigned dose level, the event was considered a DLT as per protocol. Except for patients described under a. and b., all patients received at least two full doses of their assigned dose and completed the full 28-day DLT evaluation period including all safety examinations.

Pharmacokinetics

- Peak concentrations observed shortly after infusion (Figure 4).
- Mean terminal half-life after first dose ranged from 6 to 16 days (across doses of 24mg to 800mg).
- PK for doses below 24mg affected by target-mediated drug disposition (TMDD).
- Occurrence of IRRs were typically associated with development of treatment-emergent anti-drug antibodies (ADAs), generally observed after 2-6 months on treatment.
- In some patients treated at 24mg to 240mg that developed ADAs, exposure was negatively impacted.
- Exposure was generally maintained at 800mg despite development of ADAs in some patients.

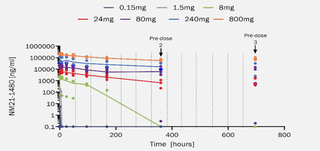

Figure 4. NM21-1480 pharmacokinetics for the first two dosing events, occurring every 2 weeks. Mean PK values per dose level are shown. Data cutoff: 24 Aug 2022.

Receptor Occupancy

- Receptor occupancy was measured on circulating CD3-positive T cells and is reflective of drug binding to 4-1BB and/or PD-L1 (Figure 5).
- 100% receptor occupancy is maintained for the full dosing interval at doses of 24mg and greater.

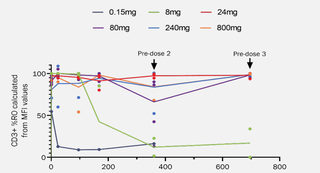

Figure 5. NNM21-1480 receptor occupancy on CD3-positive cells for the first two dosing events, occurring every 2 weeks. Data cutoff: 24 Aug 2022.

Pharmacodynamics (PD)

- Significant increase in various PD markers *vs.* baseline observed starting with 24mg dose.
- Full PD activity maintained over broad dose range between 24mg and 800mg flat doses.
- PD data strongly suggestive that affinity balancing built into NM21-1480 by design permits for a broad optimal dose range at which strong 4-1BB agonism is maintained at full PD-L1 blockade.
- Soluble 4-1BB (s4-1BB) may be the most predictive and quantitative peripheral PD biomarker dynamically reflecting 4-1BB agonistic activity of therapeutic intervention.[12]
- With NM21-1480 treatment, peripheral s4-1BB continues to increase over time, *i.e.,* from visit to visit.
- Pronounced increase of s4-1BB observed starting with the 24mg dose of NM21-1480 and is fully maintained up to 800mg, the highest dose assessed in the study.
- Data suggests that, at 800mg dose, NM21-1480 is highly active as a 4-1BB agonist.
- 800mg of NM21-1480 is suggested to provide complete blockade of PD-L1.[13]

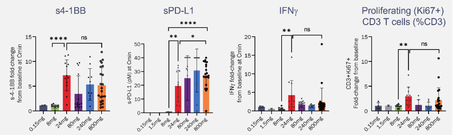

Figure 6. Peripheral pharmacodynamic effects induced by NM21-1480. * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001, Student t-test.

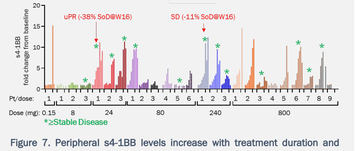

Figure 7. Peripheral s4-1BB levels increase with treatment duration and correlate with signs of clinical activity. uPR: unconfirmed partial response; SD: stable disease; SoD: Sum of Diameters (Target Lesions); W: Week

Efficacy Of 26 patients enrolled, 23 were evaluable for efficacy. Disease control occurred in 12/21 (57%) of patients treated in the clinically relevant dose range of 24-800mg flat dose. Unconfirmed partial response (uPR) was achieved in one patient with colorectal cancer at study Week 16.

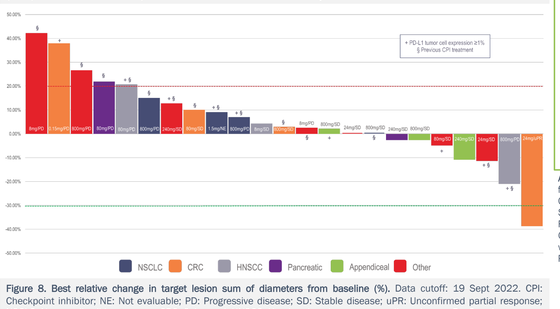

Figure 8. Best relative change in target lesion sum of diameters from baseline (%). Data cutoff: 19 Sept 2022. CPI: Checkpoint inhibitor; NE: Not evaluable; PD: Progressive disease; SD: Stable disease; uPR: Unconfirmed partial response; NSCLC: Non-small-cell lung cancer; CRC: Colorectal; HNSCC: Head and neck squamous cell carcinoma; For 3 patients no on-treatment scans are available.

Conclusions:

- NM21-1480 is a next generation immune stimulator that blocks the immune-suppressive PD-L1 axis and simultaneously signals through the immune-stimulatory receptor 4-1BB, locally restricted to the TME.
- In the dose escalation phase of this phase 1/2a study, NM21-1480 demonstrated a well-manageable safety profile and preliminary clinical activity in a heavily pretreated population with advanced solid tumors, the vast majority of which were resistant to earlier checkpoint inhibition therapy, and/or suffered from tumors typically not responding to ICIs.
- Most TRAEs were mild-to-moderate with only two Grade 3-4 TRAEs occurring in the study.
- The most frequent TRAEs were IRRs which were typically associated with development of treatment-emergent ADAs that negatively impacted drug exposure at dose levels between 24mg-240mg, typically after patients were on treatment for 2-6 months.
- In patients dosed at 800mg, exposure to study drug was maintained despite occurrence of treatment-emergent ADAs in some patients.
- MTD was not reached.
- Clinical benefit was observed in the majority of patients dosed at 24-800mg flat dose; one patient demonstrated uPR, overall DCR at Week 8 was 57% for patients dosed at 24-800mg.
- PD data strongly suggests that full 4-1BB agonism is observed at doses providing complete inhibition of PD-L1, *i.e.,* up to 800mg of NM21-1480, thus, clinically validating the concept of affinity-balancing built into the design of the molecule.
- In order to explore exposure to NM21-1480 for prolonged treatment periods and to ensure full blockade of PD-L1, the 800mg dose of NM21-1480 is currently further studied in the phase 2a (Part B) part of the trial, for which enrollment is ongoing (NCT04442126).

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