FIRST-IN-HUMAN TRIAL TO EVALUATE SAFETY, PK/PD AND INITIAL CLINICAL ACTIVITY OF NM21-1480, AN AFFINITY-BALANCED PD-L1X4-1BBXHS4 TRISPECIFIC ANTIBODY: RESULTS OF PHASE 1 DOSE ESCALATION


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Background NM21-1480 is a tri-specific Fc-lacking antibody that agonizes 4-1BB and blocks PD-L1/PD-1 signaling, designed to restrict activation of the 4-1BB pathway to the tumor microenvironment. NM21-1480 contains an ultra-potent PD-L1 blocking moiety and an affinity-balanced 4-1BB binding moiety to assure maximal activity on both pathways over a broad dose range. Here we report the results of the Phase 1 dose-escalation part of the ongoing First-in-Human Phase 1/2a clinical trial with NM21-1480.

Methods Patients with metastatic or unresectable solid tumors not eligible for standard therapy received flat-dose NM21-1480 (0.15–800mg) intravenously every 2 weeks until disease progression or unacceptable toxicity. Primary endpoints were dose-limiting toxicities (DLTs) and adverse events (AEs). Secondary endpoints included pharmacokinetic (PK) parameters and anti-drug antibody (ADA) assessments. Pharmacodynamic (PD) biomarkers and antitumor activity (RECIST1.1) were assessed as exploratory endpoints.

Results 26 patients with various primary solid tumors were enrolled (median age: 63 years). Patients had previously received a median (range) of 3.5 (1–10) treatments; 62% of whom had prior anti-PD-(L)1 immunotherapy. As per 14 July 2022 patients received a median (range) of 4 (1–19) biweekly NM21-1480 infusions. Full peripheral receptor occupancy at trough level was observed at the dose of 24mg or above. Maximum tolerated dose was not reached; 1 patient experienced a DLT. The most common (≥10%) of patients treatment-related AEs (all grades; Grades 3–4) were infusion-related reactions (27% [11% at 800mg dose]; 0%), fatigue (12%; 0%) and transaminase elevations (12%; 4%) according to CTCAEv.5.0. One patient each experienced treatment-related Grade-3 transaminase elevations and adrenal insufficiency, respectively; no treatment-related adverse event higher than Grade 3 occurred. In the 24/mg-800mg dose range, disease control, i.e., at least stable disease at first assessment at 8 weeks, occurred in 12/21 patients (57%). One patient demonstrated an unconfirmed partial response at Week 16. PD activity on PD-L1 blockade as well as 4-1BB signaling was observed and remained stable at a broad dose range (24–800mg). Based on the totality of the data derived from safety/immunogenicity, PK/PD and clinical activity, the 800mg flat dose of NM21-1480 has been selected for further clinical evaluation.

Conclusions NM21-1480 demonstrated biological activity associated with a manageable safety profile. Encouraging early clinical activity across different dose levels was observed in a heavily pretreated population with advanced solid tumors, including those resistant to prior immunotherapy or typically less sensitive to ICIs. Enrollment into expansion cohorts will start in the second half of 2022.

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Trial Registration ClinicalTrials.gov; trial number: NCT044442126.

REFERENCE

Ethics Approval This trial is undertaken following full approval of the final protocol, amendments, informed consent form, applicable recruiting materials, and subject compensation programs by the Independent Ethics Committee/Institutional Review Board.

Consent Written informed consent, in accordance with principles that originated in the Declaration of Helsinki 2013, current ICH guidelines including ICH-GCP E6(R2), applicable regulatory requirements, and sponsor policy, was provided by the patients.