A Phase 1/2 Study of NM21-1480 (Anti-PDL-1/Anti-4-1BB/Anti-HSA Tri-Specific Antibody) in Adult Patients with Advanced Solid Tumors.

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Part BPrimary:• To determine the anti-tumor activity of NM21 1480 according to RECIST 1.1• To assess the safety and tolerability of NM21 1480 in patients with selected advanced cancers treated at or around the recommended Phase 2 dose (RP2D)• To...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52041

Source
ToetsingOnline

Brief title
NB-ND021 (NM21-1480)-101 [ICON 5013/0001]

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced solid tumors, cancer

Research involving
Human

Sponsors and support

Primary sponsor: Numab Therapeutics
Source(s) of monetary or material Support: Numab Therapeutics

Intervention

Keyword: Advanced Solid Tumors, NM21-1480

Outcome measures

Primary outcome

Part B

• BOR (Primary endpoint for Cohort B1-4, 6-7)

• ORR (Primary endpoint for Cohort B5)

• Incidence and severity of TEAEs with specific focus on incidence and severity of irAEs

• Characterization of exposure-dependent PD markers of target and pathway engagement. Potential PD markers are included in the below list of exploratory markers applicable to all Parts A, A-2 and B

Secondary outcome

• Disease Control Rate (DCR)

• DOR

• PFS

• OS

• BOR, DCR, ORR, DOR, PFS as per iRECIST

• PK parameters

o AUCtau

o AUC (0-infinity) (first dose only)

o Cmax

o Cmin

o t*

o Tmax

o *z

o CL

o Vd

• Frequency of specific anti-drug antibodies to NM21 1480

Study description

Background summary

NM21-1480 is a protein that binds to 3 molecules called PD-L1, 4-1BB and human serum.
With this action, NM21-1480 is expected to help the subject's immune system to fight against cancer.

Study objective

Part B
Primary:
• To determine the anti-tumor activity of NM21 1480 according to RECIST 1.1
• To assess the safety and tolerability of NM21 1480 in patients with selected advanced cancers treated at or around the recommended Phase 2 dose (RP2D)
• To determine the RP2D
• To determine the safety and efficacy of NM21 1480 in combination with standard-of-care anti-PD1 therapy in patients with head and neck squamous cell cancer (Cohort B5)

Secondary:
• To further evaluate the preliminary anti-tumor activity of NM21-1480
• To characterize the PK profile of NM21-1480
• To evaluate the immunogenicity of NM21-1480

Study design

This is a first-in-human (FIH), open label, multi-center, Phase 1/2, dose-escalation study with dose expansion cohorts in specific tumor types to evaluate NM21 1480 for safety and immunogenicity, to determine the MTD and Recommended Phase 2 Dose (RP2D), define the PK, to explore the pharmacodynamics (PD), and to obtain preliminary evidence of the clinical activity in adult patients with selected advanced solid tumors.

NM21-1480 is a recombinant protein consisting of 3 stabilized antibody Fv fragments directed against the molecular targets Programmed death-ligand 1 (PD-L1), 4-1BB, and serum albumin (SA). It is designed for avoidance of systemic 4-1BB activation and preferential 4-1BB activation in the TME to avoid the dose-limiting toxicities (DLT) of systemically active 4-1BB agonists.

This is an open-label study and includes an ascending-dose cohort component (Part A) to be optionally followed by an additional cohort (optional Part A-2) to further characterize the exposure/PD response relationship of the compound to support optimal dose range selection for further evaluation in dose expansion cohorts in specific tumor types in Part B. Depending on Part A data, Part B may be initiated without the conduct of the optional A2 Cohort. For patients in all cohorts, the study will consist of 3 periods: Screening (up to 28 days), treatment (until confirmed progression or meeting any other reason for discontinuation specified by the protocol), and Follow-up (up to 12 weeks).In Part A (and optional Part A-2) of the study, NM21-1480 will be administered as a single intravenous (IV) infusion approximately every 14 days for a total of 2 infusions per treatment cycle. A treatment cycle is thus defined as 28 days (4 weeks). In Part A (and optional Part A-2), response assessments are done every 8 weeks, thus one assessment cycle is defined as 8 weeks. Any dose level to be studied in Part B (or optionally in Part A-2) will be below or at the MTD determined upon decision by the Safety Monitoring Committee (SMC) once all patients enrolled to Part A have completed their 28-day DLT evaluation period. In Part B of the study, NM21-1480 will be administered as a single IV infusion either approximately every 14 or 21 days, dependent on the respective dose level. Selection of dose level(s) and corresponding dosing interval(s) for Part B will be based on Sponsor proposal and SMC decision after formal conclusion on the Part A 28-day DLT evaluation period data and resulting determination of the MTD, once all patients enrolled to Part A have completed their 28-day/end of DLT period assessments. If the optional Part A-2 of the study is conducted, the SMC may also consider its resulting data for dose selection for Part B. Any dose level to be selected for Part B by the SMC must not exceed the MTD determined in Part A. In Part B, a treatment cycle, dependent on the dosing interval selected by the SMC for a given dose level (i.e., 2-week or 3-week dosing interval), is thus defined as 28 days (4 weeks) or 42 days (6 weeks), respectively. Response assessments in Part B will be done every 6 weeks during the first 24 weeks patients are on

treatment and every 8 weeks beyond 24 weeks on treatment.

Intervention

In Part A (and optional Part A-2) of the study, NM21-1480 will be administered as a single intravenous (IV) infusion approximately every 14 days for a total of 2 infusions per treatment cycle. A treatment cycle is thus defined as 28 days (4 weeks). In Part A (and optional Part A-2), response assessments are done every 8 weeks, thus one assessment cycle is defined as 8 weeks. Any dose level to be studied in Part B (or optionally in Part A-2) will be below or at the MTD determined upon decision by the Safety Monitoring Committee (SMC) once all patients enrolled to Part A have completed their 28-day DLT evaluation period. In Part B of the study, NM21-1480 will be administered as a single IV infusion either approximately every 14 or 21 days, dependent on the respective dose level. Selection of dose level(s) and corresponding dosing interval(s) for Part B will be based on Sponsor proposal and SMC decision after formal conclusion on the Part A 28-day DLT evaluation period data and resulting determination of the MTD, once all patients enrolled to Part A have completed their 28-day/end of DLT period assessments. If the optional Part A-2 of the study is conducted, the SMC may also consider its resulting data for dose selection for Part B. Any dose level to be selected for Part B by the SMC must not exceed the MTD determined in Part A. In Part B, a treatment cycle, dependent on the dosing interval selected by the SMC for a given dose level (i.e., 2-week or 3-week dosing interval), is thus defined as 28 days (4 weeks) or 42 days (6 weeks), respectively. Response assessments in Part B will be done every 6 weeks during the first 24 weeks patients are on treatment and every 8 weeks beyond 24 weeks on treatment.

Study burden and risks

NM21-1480 has not yet been tested in humans, and therefore its side effects in humans are unknown. However, NM21-1480 has been studied in animals, and other drugs, such as avelumab and atezolizumab (so-called *anti-PD-L1 antibodies*), are similar to NM21-1480 and have been studied in humans,
Based on human studies with other *PD-L1 antibodies*, serious side effects may include lung problems (pneumonitis), liver problems (hepatitis), intestinal problems (colitis), problems in hormone glands (for example thyroid problems or diabetes), heart, nervous system, and other organs.
More about the side effects and risks from study procedures is listed in appendix D of the SIS-ICF.

Contacts

Public

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Parts A and A-2 are not conducted in EU/EEA and, therefore, specific inclusion criteria are not described.

Part B (all cohorts): Patients with locally advanced or metastatic, non-resectable disease.

• Cohorts B1 and B7
o Patients with NSCLC

• Cohort B2
o Patients with HPV-associated (i.e. HPV+ tumor) SCC of the anus, cervix, vulva, vagina, penis or oropharynx

• Cohort B4
o Patients with recurrent, persistent or metastatic ovarian, primary peritoneal or fallopian tumor carcinoma

• Cohort B5
o Patients with head and neck squamous cell cancer

• Cohort B6
o Patients with TNBC according to current ASCO/CAP guidelines that is measurable according to RECIST1.1 criteria

Part B:
For Cohorts B1, B2, B6 (subgroup with required previous checkpoint inhibitor therapy) and B7: Last dose of therapy with anti-PD-1 antibody must have been received at least 2 weeks prior to the administration of the first dose of the study drug. All cohorts (while not applicable to Cohort B5): Prior chemotherapy must have been completed at least 4 weeks prior to the administration of the first dose of study drug. Exceptions: Hormone replacement therapy.

Exclusion criteria

Key Exclusion Criteria:

Patient previously had known immediate or delayed hypersensitivity reaction or idiosyncrasy to the excipients of investigational product (IP) or has experienced >= Grade 3 irAEs with previous checkpoint inhibitor therapy.

Part B:
• Cohort B1 and B7:
o Treatment with PD-1 antibody within 2 weeks.
o Patients who, for the treatment of the current cancer, has received any other treatment than anti PD 1 and/or chemotherapy prior to initiation of the study drug or who has not recovered to CTCAE V5.0 Grade 1 or better from the AE due to anti-PD-1 administered earlier; in addition, patients with any ongoing Grade 1 or higher AE of colitis, hepatitis, nephritis, or pneumonitis considered to be related to previous anti-PD-1 therapy is exclusionary. However, sensory neuropathy <=Grade 2, alopecia and endocrine disorder treated with hormone replacement are acceptable.

• Cohort B2:
o Patients who, for the treatment of the current cancer, has received any treatment other than anti PD 1 or a platinum-based chemotherapy regimen recommended as first-line or second-line treatment by current National Comprehensive Cancer Network (NCCN) treatment guidelines or who has not recovered to CTCAE V5.0 Grade 1 or better from the AE due first- or second-line treatment; in addition, patients with any ongoing Grade 1 or higher AE of colitis, hepatitis, nephritis or pneumonitis considered to be related to previous anti-PD-1 therapy is exclusionary. However, sensory neuropathy <=Grade

2, alopecia and endocrine disorders treated with hormone replacement are acceptable.

• Cohort B4:
o Patients who have had prior therapy with anti-PD-1, anti-PD-L, anti-4-1-BB or anti-CTLA-4 antibodies or any other antibody or drug specifically targeting T-cell co-stimulation or immune check point pathways.
o Patients who have received prior chemotherapy for any abdominal or pelvic tumor other than for treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last 3 years; patients may have received prior adjuvant chemotherapy and radiotherapy for localized breast cancer, provided that it was completed more than 2 years prior to consenting to this study, and the patient remains free of recurrent or metastatic disease and hormonal therapy has been discontinued; patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis or thoracic cavity within the last 3 years are excluded; prior radiation for localized cancer of the head and neck or skin is permitted, provided that it was completed more than 3 years prior to consenting to this study, and the patient remains free of recurrent or metastatic disease.

• Cohort B5
o Patients who have previously received systemic drug therapy for their disease.

• Cohort B6
o For patients in the subgroup in which previous therapy with a checkpoint inhibitor is required:
* Treatment with PD-1 antibody within 2 weeks prior to the first dose of study drug
* Treatment with PD-L1 antibody within 5 half-lives prior to first dose of study drug
* Patient who has not recovered to CTCAE V5.0 Grade 1 or better from the AE due to anti-PD-1 or anti-PD-1 antibody administered earlier; in addition, patient with any ongoing Grade 1 or higher AE of colitis, hepatitis, nephritis, or pneumonitis considered to be related to previous anti-PD1 or anti-PD-L1 therapy is exclusionary. However, sensory neuropathy <=Grade 2, alopecia and endocrine disorder treated with hormone replacement are acceptable
* Previous treatment with anti-CTLA-4 or anti-4-1BB antibody or drug specifically targeting T cell co-stimulation or immune checkpoint pathways other than the PD-1/PD-L1 pathway
o For patients in the subgroup in which previous therapy with a checkpoint inhibitor is prohibited
* Patients who had prior therapy with anti-PD-1, anti-PD-L1, anti-4-1BB or anti CTLA 4 antibodies or any other antibody or drug specifically targeting T-cell co-stimulation or immune check point pathways.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NM21-1480
Generic name:	NM21-1480

Ethics review

Approved WMO Date:	27-05-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	04-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-000441-41-NL
ClinicalTrials.gov	NCT04442126
CCMO	NL77592.056.21