TITLE PAGE

CLINICAL STUDY PROTOCOL TITLE:

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

Protocol Number:	NB-ND021 (NM21-1480)-101
Test Product:	NM21-1480
Indication:	Advanced solid tumors
Development Phase:	Phase 1/2
Sponsor:	Numab Therapeutics AG
Legal Registered Address:	Bachtobelstrasse 5, CH-8810 Horgen Switzerland
Approval Date:	17 Nov 2022 (Version 9.0)
Previous Version(s):	11 Jul 2022 (Version 8.0) 28 Feb 2022 (Version 7.0) 29 Oct 2021 (Version 6.0) 01 Sep 2021 (Version 5.0) 17 May 2021 (Version 4.0) 15 Jan 2021 (Version 3.0) 04 Jun 2020 (Version 2.0) 27 Apr 2020 (Version 1.2) 20 Apr 2020 (Version 1.1) 07 Feb 2020 (Version 1.0)

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SPONSOR SIGNATURE PAGE

DECLARATION OF SPONSOR

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

PROTOCOL NUMBER: NB-ND021 (NM21-1480)-101

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements. Essential study documents will be archived in accordance with applicable regulations.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the International Council for Harmonization (ICH) guidelines on GCP.

Numab Therapeutics AG

[redacted]

17 November 2022
Date (day/month/year)

1 GENERAL INFORMATION

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

Protocol Number:	NB-ND021 (NM21-1480)-101
Approval Date:	17 Nov 2022
Sponsor:	Numab Therapeutics AG Bachtobelstrasse 5, CH-8810 Horgen, Switzerland
Sponsor Signatory:	[redacted]
Clinical Research Organization:	
Medpace Medical Monitor:	
Serious Adverse Event Reporting:	

2 STUDY SYNOPSIS

Name of Sponsor/Company:
Numab Therapeutics AG

Name of Product:
NM21-1480

Title of Study:
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.

Study Center(s):
Part A of the study has been conducted at 7 sites in the United States (US) and Taiwan. Part A was formally completed on 23 May 2022 by a Meeting of the Safety Monitoring Committee (SMC) at which the SMC determined that Part A of the study did not technically identify a maximum tolerated dose (MTD) as the highest dose assessed (800mg flat dose) was considered a tolerable dose. An optional Part A-2 of the study may now be conducted at Part A sites and additional selected Part B sites in the US, Spain, the United Kingdom (UK), Germany, and/or the Netherlands given formal conclusion on the 28-day dose-limiting toxicity (DLT) assessment period data, and resulting determination of a presumptive Recommended Phase 2 Dose (RP2D) based on Part A data has occurred. Part A-2 may be conducted to further explore different dose levels and/or dosing intervals *in parallel to* Part B to complement the pharmacokinetics (PK), immunogenicity and PD data to be provided by Part B. Additional sites will be added for Part B of the study; Part B will be conducted as up to 8 separate cohorts: B1-B8. Cohorts B1, B2, and B7 will be conducted in up to 86 sites in the US, Spain, UK, the Netherlands, Germany, and Taiwan. Cohort B3 will be conducted in up to 30 sites in Turkey, Georgia, Ukraine, and Taiwan. Cohort B4 will be conducted in up to 92 sites in the US, Spain, UK, the Netherlands, Germany, Taiwan, Turkey, Georgia, and Ukraine. Cohorts B5 and B6 will be conducted in up to 75 sites in the US, Spain, UK, the Netherlands, and Taiwan. Cohort B8 will be conducted in up to 83 sites in the US, Spain, UK, the Netherlands and Germany.

Development Phase:
Phase 1/2

Disclosure Statement:
With the exception of Cohort B5 (i.e., Part A, optional Part A-2, and Cohorts B1-B4 and B6-B8), this is a single arm study with different cohorts. Cohort B5 is a randomized, open-label, active-control study cohort comparing NM21-1480 plus standard-of-care vs. standard-of-care alone.

Objectives and Endpoints

	Objectives	Endpoints
Part A		
Primary	• To assess the safety and tolerability of NM21-1480 • To determine the MTD of NM21-1480 • To determine up to four (4) safe dose levels for further evaluation of PD and clinical activity in the optional Part A-2 and Part B of the study	• Incidence and nature of dose-limiting toxicities (DLTs) • Incidence and severity of treatment-emergent adverse events (TEAEs) with specific focus on incidence and severity of immune-related adverse events (irAEs)
Secondary	• To characterize the pharmacokinetic (PK) profile of NM21-1480	• PK parameters o AUCtau o AUC (0-infinity) (first dose only) o Cmax o Cmin o t½ o Tmax

		○ λz ○ CL ○ Vd
	• To evaluate the immunogenicity of NM21-1480	• Frequency of specific anti-drug antibodies to NM21-1480
Exploratory	• To determine the anti-tumor activity of NM21-1480 according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • To determine safe dose levels associated with meaningful PD response to inform dose selection for optional Part A-2 and Part B. This is in support of nominating up to four (4) safe dose levels to be further studied in Part B of the study	• Best overall response (BOR) • Objective response rate (ORR) • Time-to-response (TTR) • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Characterization of exposure-dependent PD markers of target and pathway engagement. Potential PD markers are summarized in detail in the below list of exploratory markers applicable to all Parts A, A-2 and B
Part A-2 (OPTIONAL)		
Primary	• To assess the safety and tolerability of NM21-1480 at a dose level beyond what has been assessed in Part A (i.e. at 1400mg) • To further explore drug-exposure/PK/PD relationships in order to complement respective Part B data when conducted in parallel to Part B	• 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	• To characterize the PK profile of NM21-1480 • To evaluate the immunogenicity of NM21-1480	• PK parameters: ○ AUCtau ○ AUC (0-infinity) (first dose only) ○ Cmax ○ Cmin ○ t½ ○ Tmax ○ λz ○ CL ○ Vd • Frequency of specific anti-drug antibodies to NM21-1480
Exploratory	• To determine the anti-tumor activity of NM21-1480 according to RECIST1.1	• BOR • ORR • TTR • DOR • PFS • OS
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 (including the MTD) 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)	• BOR (Primary endpoint for Cohort B1-4, 6-8) • 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	• To further evaluate the preliminary anti-tumor activity of NM21-1480	• Disease Control Rate (DCR) • DOR • TTR • PFS • OS • BOR, DCR, ORR, DOR, PFS as per iRECIST
	• To characterize the PK profile of NM21-1480	• PK parameters o AUCtau o AUC (0-infinity) (first dose only) o Cmax o Cmin o t½ o Tmax o λz o CL o Vd
	• To evaluate the immunogenicity of NM21-1480	• Frequency of specific anti-drug antibodies to NM21-1480
Part A, Part A-2 (OPTIONAL), and Part B		
Exploratory	• To characterize the PD profile of NM21-1480	Change from baseline in the following biomarkers/PD parameters: • Change from baseline in levels of cytokines/chemokines including interleukin (IL)-1b, IL-6, tumor necrosis factor (TNF)α interferon gamma (IFN_γ), IL2, IL8, CXCL9, CXCL10, CXCL11, IL18, and other selected markers; soluble PD-L1 (Programmed death-ligand 1); soluble 4-1BB • Phenotypic characterization of peripheral blood cells (cellular populations include resting and activated B-cells, T-cell subpopulations [T-helper cells {Th}, cytotoxic T lymphocytes {CTLs}, regulatory T-cells {Treg}], natural

		killer cells {NK cells}, and natural killer T-cells {NKT cells}), and cellular receptor occupancy (PD-L1; 4-1BB)[a] • In cohort B8: Carcinoembryonic Antigen (CEA); circulating tumor DNA (ctDNA)
	• To evaluate biomarkers potentially capable of predicting a clinical response to NM21-1480	• Change in RNA expression from baseline and after-treatment in tumor tissues • Change in PD-L1 expression and presence of PD1/CD8/4-1BB triple positive T-cells in baseline and after-treatment tumor tissues • Change in level of inflammatory infiltrate (e.g., CD3 and CD8 density; CD8/Treg ratio; CD8/CD4 ratio) in baseline and after-treatment tumor tissue • Assessment of tumor mutational burden (TMB) and microsatellite instability – high/deficient mismatch repair (MSI-H/dMMR) status in baseline tumor tissues • Correlation of PD-L1 expression status in the tumor microenvironment (TME) with PD and clinical activity • Assessment of T-cell Receptor clonality in tumor tissue • In cohort B8: MHC-I expression on tumor cells; specific mutational analysis including *e.g.,* BRAF, KRAS, NRAS, POLE, PIK3CA, PTEN. APC, p53

[a] Pending availability of validated assay

Abbreviations: APC = Adenomatous Polyposis Coli; AUC = Area under the serum concentration-time curve, AUC(0-infinity) = Area under the serum concentration-time curve extrapolated from the last quantifiable concentration to infinity; AUCtau = area under the serum concentration-time curve over dosing interval, B-cells = B lymphocytes; BRAF = B-raf proto-oncogene; CD3 = Cluster of differentiation 3; CD4 = Cluster of differentiation 4; CD8 = Cluster of differentiation 8; CEA = Carcinoembryonic Antigen; CL = Clearance, Cmax = The maximum observed serum concentration determined by direct inspection of the concentration versus time data, Cmin = The minimum observed serum concentration determined by direct inspection of the concentration versus time data; CTL = Cytotoxic T lymphocytes, CXCL = Chemokine (C-X-C motif) ligand, λz = Terminal phase (apparent elimination) rate constant; KRAS = Kirsten Rat Sarcoma oncogene; MHC-I = Major Histocompatibility Complex – I; Microsatellite instability-high (MIS-H), NK cells = Natural killer cells, NKT = Natural killer T-cells; NRAS = Neuroblastoma ras viral oncogene homolog; PD-1 = Programmed cell death protein-1, PD-L1 = Programmed death-ligand 1; PIK3CA = Phosphaytidylinositol 3-kinase CA; POLE = Polymerase Epsilon Catalytic Subunit; PTEN = Phosphatase and Tensin Homologue; RNA = Ribonucleic acid, t½ = Elimination half-life, Tmax = The time from dosing at which Cmax is apparent determined by direct inspection of the concentration versus time data, Vd = Volume of distribution

Methodology:

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 explore different dose levels and/or dosing intervals *in parallel* to Part B to complement the PK, immunogenicity and PD data to be provided by Part B. Part B may be initiated without the conduct of the optional A-2 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 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, 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 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. Part A was formally completed on 23 May 2022 by a Meeting of the SMC which determined that Part A of the study did not technically identify an MTD as the highest dose assessed (800mg flat dose) was considered a tolerable dose. In Part B of the study, NM21-1480 will thus be administered as a single IV infusion approximately every 14 days at the 800mg flat dose, based on Part A PK data which do not indicate substantial NM21-1480 accumulation over time with this dosing interval; the 800mg dose of NM21-1480 thus represents the presumptive RP2D to be further studied in Part B (Cohorts B1- B8) with the aim to confirm this dose as the R2PD for the compound. Based on Part A identifying the 800mg dose of NM21-1480 to represent a tolerable and fully active dose, optional Part A-2 of the study will explore one additional higher dose level (1400mg flat dose with approximately 14-day dosing interval) than was studied in Part A. Such 1400mg dose level is explored in Part A-2 applying strict stopping criteria and respecting a 28-day DLT evaluation period before more than 6 subjects are exposed to it. PK data for this 1400mg dose level in Part A-2 will be closely followed and in case of observation of relevant drug accumulation over time, the dosing interval for this dose may be adjusted to approximately 21 days. The Sponsor, together with the SMC will determine whether further exploration of this 1400mg dose in Part B may be clinically meaningful once data are available. The optional Part A-2 of the study is conducted in parallel to Part B, and its resulting exposure/PK/PD data will be used to complement Part B data to guide later stage clinical development. Any dose level to be assessed in Part B as by SMC recommendation must not exceed the MTD determined in Part A (or Part A-2 when applicable). In optional Part A-2 and Part B, a treatment cycle, dependent on the dosing interval selected by the SMC for a given dose level (i.e., 2-week dosing interval for the 800mg dose and 2-week or eventually 3-week dosing interval for the 1400mg dose in Part A-2), is thus defined as 28 days (4 weeks) or 42 days (6 weeks), respectively. Response assessments in the optional Part A-2 and 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.

Part A

In Part A, a Bayesian optimal interval (BOIN) design was used to assess the safety and tolerability of NM21-1480. This part of the study consists of 7 planned escalating flat dose levels; 0.15 mg (dose level 1), 1.5 mg (dose level 2), 8 mg (dose level 3), 24 mg (dose level 4), 80 mg (dose level 5), 240 mg (dose level 6), and 800 mg (dose level 7).

Enrollment of patients into dose level 1 took place first and subsequent dose levels were only opened after the previous dose level was deemed tolerable. The first dose level was to enroll a minimum of one patient at 0.15 mg (corresponding to approximately 0.002 mg/kg). Following the detailed rules described in Section 10.3.1 of this protocol, as soon as a Grade 2 or higher, treatment-related adverse event (TRAE) was observed during the 28-day DLT evaluation period, or when dose level 5 (80 mg dose corresponding to approximately 1 mg/kg) was reached, a minimum of 3 patients were to be enrolled at the current dose level as well as at potential additional dose levels planned in accordance with the BOIN design dosing rules.

Part A of the study was formally completed on 23 May 2022 by a Meeting of the SMC at which the SMC determined that Part A of the study did not technically identify a MTD as the highest dose assessed (800mg flat dose) was considered a tolerable dose. Part A dose-escalation was based on the number of DLTs experienced during the DLT evaluation interval as determined by the Investigators, Medical Monitor, and Sponsor. The DLT evaluation interval begins on the first day of treatment and continues for 28 days. Patients who received at least one dose of investigational product in Cycle 1 (i.e., one of the 2 doses intended to be administered in Cycle 1), and either meet the minimum exposure criterion and have sufficient safety evaluations or discontinued due to DLT, were considered evaluable for DLT determination. Dose-escalation continued until the stopping rules of the BOIN design were reached.

The MTD was defined as the highest dose associated with DLTs in ≤30% of patients receiving NM21-1480 administered during the DLT period. This was the highest dose to be potentially recommended for further evaluation in the subsequent part(s) of the study. At the end of Part A, the SMC concluded on 23 May 2022 that none of the 7

dose levels, including the highest dose (800mg flat) dose assessed in Part A was to be considered intolerable and thus Part A did not technically identify a MTD. Due to the specific pharmacological mechanism of action of NM21-1480, the SMC, supported by the Sponsor, besides determining the MTD, was also to consider the selection of additional (lower) dose levels to be further studied in Part A-2 (optional) and/or Part B, based on review of Part A safety, PK, and PD (as far as available) data. This was based on the assumption that indeed, it may only be possible to determine an optimal RP2D in Part B of the study, as binding of NM21-1480 to PD-L1 is a pre-requisite for activation of the 4-1BB pathway by the compound. This is likely only possible in a tumor patient population with well-documented PD-L1 expression in the TME. In addition, in a situation with substantial excess of NM21-1480 over PD-L1 and 4-1BB on target cells in the tumor tissue, a decline in 4-1BB activity (due to a bell-shaped dose response curve for the 4-1BB agonistic activity of the compound) cannot be formally excluded to occur within the dose range explored in Part A of the study. Such bell-shaped dose response may occur because in such situation of substantial excess of NM21-1480, molecules over available PD-L1 and 4-1BB binding sites, an immediate saturation of PD-L1 and 4-1BB binding sites by different NM21-1480 molecules may occur. As such, concomitant binding of a single NM21-1480 molecule to both antigens may no longer be possible and consequently the immunological synapse between tumor cells and immune cells that is required to trigger 4-1BB signaling, could no longer be established. This important aspect of dose finding was considered based on thorough review of the entirety of non-clinical and clinical data available at the end of the 28-day DLT evaluation period of the last patient enrolled to Part A (i.e. at the 23 May 2022 SMC meeting). At this point, the SMC, together with the Sponsor, considered the nomination of up to 4 different dose levels of NM21-1480 and determined the optimal dosing interval (i.e., dosing approximately every 14 or 21 days) for administration of a given NM21-1480 dose for Part B with the goal to determine a final RP2D and dosing interval with an optimized activity and safety profile for future development within Part B. Part A study data discussed with SMC on 23 May 2022 demonstrated the development of treatment-emergent anti-drug-antibodies (ADAs) in a relevant fraction of patients dosed at 24mg-240mg. These ADAs were typically associated with rapid elimination of NM21-1480 from the circulation and loss of exposure. However, PK, PD, receptor occupancy and clinical activity data available for the 800mg dose level indicated that at this higher dose level, no relevant loss of exposure was observed and full pharmacodynamic activity of the compound was preserved, a phenomenon described for other checkpoint inhibitors (i.e. atezolizumab) at higher doses as well. As such, the SMC agreed with the Sponsor to consider the 800mg to represent the presumptive RP2D and further study this dose, applying a biweekly dosing interval in Part B of the study. The SMC, together with the Sponsor, also considered at this point (i.e., at the end of the 28-day DLT evaluation period of the last patient enrolled to Part A) to enroll additional patients into an optional additional Cohort A-2*in parallel* to Part B to complement the PK, immunogenicity and PD data to be provided by Part B. The Sponsor, following formal completion of Part A on 23 May 2022, is therefore exploring within this optional Part A-2 and under continuous review of emerging safety data by the SMC, the safety, PK/PD and clinical activity profile of one higher dose level of NM21-1480 (1400mg flat dose) in up to 10 patients to complement Part B data and thus further inform development of NM21-1480 beyond initial Part B. As this dose level to be studied in in Cohort A-2 is above the maximum dose level characterized in Part A, exploration of this 1400mg dose level will be conducted under the continuous safety data review and guidance by the SMC, applying similar rules as in Part A.

In summary, Part A was considered completed on 23 May 2022, when the maximal number of patients to be treated overall, as per BOIN design rules, was reached, and the SMC, upon documented review of all clinical safety, PK, and clinical activity data up to and including the 4-week visit from all patients dosed in Part A determined that even the highest dose assessed in Part A (800mg flat) was considered a tolerable dose. For nomination of dose levels to be further evaluated in Part B (and/or optional Cohort A-2), the SMC, together with the Sponsor, considered all available non-clinical and clinical data and information (i.e., including all available clinical data beyond 28 days of treatment with NM21-1480) at the time the final patient enrolled into Part A according to the BOIN design had 28-day data available. The 800mg flat dose was nominated as presumptive RP2D to be studied in Part B and a dose of 1400mg was nominated for additional exploration within optional Part A-2 by the Sponsor.

Part A-2 (OPTIONAL)

Part A-2 is an optional part of the study. It might be initiated after determination of the MTD based on Part A data. On 23 May 2022 the SMC determined that Part A did not technically identify a MTD and the highest dose level assessed (800mg flat) was considered a tolerated dose. The rationale behind the potential conduction of Part A-2 was to cover situations in which the SMC, together with the Sponsor, upon comprehensive review of all available data at the time of MTD determination (i.e. at the formal end of Part A on 23 May 2022), came to the conclusion that either additional exposure-dependent PD data at dose levels at or below the MTD were needed to allow for selection of up to 4 dose levels to be further studied in Part B, or it may be desirable to explore different dose levels and/or dosing intervals in parallel to Part B to complement the PK, immunogenicity and PD data to be provided by Part B to inform development of NM21-1480 beyond Part B. Indeed, based on the finding that some patients dosed at 24-240mg in Part A developed treatment-emergent ADAs leading to loss of exposure, while this was not observed at

the 800mg dose level, a decision was taken to explore one additional higher dose level (1400mg flat dose) in up to 10 patients within Part A-2 in parallel to studying the 800mg dose level in Part B. The primary intention of exploring this 1400mg dose level in Part A-2 is to further study the overall PK/PD relationship of NM21-1480 over a broad range of doses. Further dose levels or dosing intervals may in the future be studied within Part A-2 as well if emerging data from the ongoing study provides a rationale to do so. Patients to be enrolled into this optional cohort will need to fulfill Part A eligibility criteria but in addition will need to have documented minimal PD-L1 expression on at least 1% of tumor and/or immune cells in the TME, as detected by local testing with a Food and Drug Administration (FDA)-cleared or any PD-L1 assay approved for use by local competent authority. As the 1400mg flat dose level to be explored in Part A-2 is above the maximum dose level characterized in in Part A, exploration of this 1400mg dose level will be conducted under the continuous safety data review and guidance by the SMC.

In this setting in which Part A-2 will be conducted in parallel to Part B, its resulting data will be used to complement Part B data in regards of getting to a comprehensive understanding on the PK/PD relationship of different dosing regimens for NM21-1480 before engaging into subsequent clinical development steps beyond Part B.

Part B

To further characterize the safety and clinical activity of NM21-1480, Part B, Cohorts B1-B4 and B6-B8 will employ a Bayesian Optimal Phase II (BOP2) design to enroll patients with selected advanced solid tumors with locally advanced or metastatic, non-resectable disease, which has progressed despite treatment with standard first-line, or first- *and* second-line, a maximum of 3 previous cytotoxic treatment regimens, or a defined set of previous standard-of-care therapies for Cohorts B1-B4 and B6-B8, as described per specific cohort. Based on the results of Part A of the study and as per SMC recommendation, patients in these cohorts will be dosed at the 800mg flat dose level, considered the presumptive RP2D of NM21-1480, applying a biweekly dosing interval. Cohort B5 will be a randomized, open-label, active-control, Bayesian study cohort in which the combination of NM21-1480 plus standard-of-care anti-PD1 therapy will be compared to standard-of-care anti-PD1 monotherapy in patients with head and neck squamous cell cancer. For Cohort B5, patients randomized to the NM21-1480/PD1 checkpoint inhibitor arm will be treated with 800mg NM21-1480, administered in a biweekly dosing interval. However, a safety run-in for this dose in Cohort B5 will be applied: an enrollment stop will be made once 6 patients have been enrolled to the NM21-1480 plus standard of care arm with remaining patients only to be enrolled once the SMC has reviewed the 28-day safety data for all these 6 patients in comparison to the anti-PD1 treatment arm and has confirmed the tolerability of the 800mg dose in this combination therapy setting. If the 800mg dose of NM21-1480 was not considered to represent a tolerable dose in this combination setting as per SMC decision, the Sponsor may either stop Cohort B5 or together with the SMC or select a lower dose level for continued exploration within Cohort B5. In this latter case a safety run-in with 6 patients would be applied again at such lower dose before remaining patients were to be enrolled to the combination therapy arm. Once an MTD for NM21-1480 in this Cohort B5 combination setting has been determined by the SMC, remaining patients may only be assigned to NM21-1480 dose levels at or below this combination therapy MTD for NM21-1480.

Enrollment in Part B (Cohorts B1 through B8) may begin when the SMC has completed its review of the Part A data and has recommended the dose levels to be initially studied in Part B. Part A was formally completed on 23 May 2022 and the SMC determined that the 800mg flat dose level was a tolerable dose to be further studied as the presumptive RP2D in Part B of the study.

Cohort B1: This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, **Germany,** and **Taiwan**. Cohort B1 will include non-small cell lung cancer (NSCLC) patients with documented previous (i.e., prior to initiation of first-line therapy) PD-L1 expression on ≥50% of tumor cells who have progressed after first-line treatment with either anti-PD-(L)1 monotherapy, anti-PD-(L)1/chemotherapy or chemotherapy regimen, or who have progressed after-treatment with up to 3 previous lines of therapy, including at least one line of anti-PD-(L)1 checkpoint inhibitor therapy. It should be noted that, **specifically for patients to be enrolled to Cohort B1 in Germany,** they must have previously received anti-PD-(L)1 therapy and a platinum-based chemotherapy (i.e., at least 2 prior lines of treatment) in order to be eligible for enrollment into this cohort.

Cohort B2: This cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, **Germany,** and **Taiwan**. Cohort B2 will include patients with human papillomavirus positive (HPV+) squamous cell carcinoma (SCC) of the anus, cervix, vulva, vagina, penis, or oropharynx, who have progressed on a first-line standard-of-care anti-PD1 monotherapy, anti-PD-1/chemotherapy, or chemotherapy regimen. Inclusion of patients, who have progressed after receiving 2 previous lines of therapy, e.g., one line of anti-PD-1 checkpoint inhibitor therapy and one line of chemotherapy regimen is also acceptable; patients must have documented PD-L1 expression in the TME with PD-L1

	expressed on at least 1% of tumor and/or immune cells, as detected by local testing with an FDA-cleared or any PD-L1 assay approved for use by local competent authority.
Cohort B3:	This Cohort will be conducted in **Turkey, Georgia, Ukraine,** and **Taiwan**. Cohort B3 will include patients with NSCLC with PD-L1 expression on ≥50% of tumor cells who have progressed on first-line local standard-of-care chemotherapy.
Cohort B4:	This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, **Germany**, **Taiwan, Turkey, Georgia,** and **Ukraine**. Cohort B4 will include patients with recurrent or persistent ovarian, primary peritoneal, or fallopian tumor carcinoma of all histologic types except mucinous adenocarcinoma and carcinosarcoma with a history of primary platinum-based chemotherapy with a maximum of 3 prior cytotoxic regimens with at least one regimen for recurrent disease containing a platinum or a taxane for those with 3 prior regimens: last platinum-free interval must be maximally 12 months.
Cohort B5:	This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, and **Taiwan**. Cohort B5 will include patients to be treated in-label with an approved PD-1 checkpoint inhibitor (pembrolizumab) as a single agent for the first-line treatment of metastatic or unresectable, recurrent head and neck squamous cell cancer whose tumors express PD-L1 (Combined Positive Score (CPS)≥1) as standard-of-care treatment with doses not to exceed those approved in local product labels. Patients fulfilling this criterion will be randomized 2:1 to either such standard-of-care PD-1 checkpoint inhibitor plus NM21-1480 or the standard-of-care PD-1 checkpoint inhibitor therapy only.
Cohort B6:	This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, and **Taiwan**. Cohort B6 will include patients with metastatic or unresectable, locally advanced triple-negative breast cancer (TNBC) that is measurable according to RECIST1.1 criteria. Tumors need to be Estrogen receptor (ER), Progesterone receptor (PR) and HER2 negative as per current American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) Guidelines and patients need to have progressed on at least one but no more than 3 previous lines of cytotoxic chemotherapy. Two subgroups of 20 patients each will be enrolled and analysed, based on having received a prior line of checkpoint inhibitor therapy or not.
Cohort B7:	This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, **Germany,** and **Taiwan**. Cohort B7 will include NSCLC patients with documented previous (i.e., prior to initiation of previous-line therapies) PD-L1 expression on ≥1%-49% of tumor cells who have progressed after first-line treatment with either anti-PD-(L)1 monotherapy, anti-PD-(L)1/chemotherapy or chemotherapy regimen, or who have progressed after-treatment with up to 3 previous lines of therapy, at least one including an anti-PD-(L)1 checkpoint inhibitor. It should be noted that, **specifically for patients to be enrolled to Cohort B7 in Germany,** they must have previously received anti-PD-(L)1 therapy and a platinum-based chemotherapy (i.e., at least 2 prior lines of treatment) in order to be eligible for enrollment into this cohort.
Cohort B8:	This Cohort will be conducted in the **US, Spain, UK, the Netherlands, and Germany.** Cohort B8 will include patients with metastatic colorectal cancer (mCRC) that are MSS or MSI low and who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and if RAS wild-type, an anti-EGFR therapy, if eligible. Patients previously treated with an additional anti-VEGF biological therapy are also eligible. Patients must have documented PD-L1 expression in the TME with PD-L1 expressed on at least 1% of tumor and/or immune cells, as detected by local testing with an FDA-cleared or any PD-L1 assay approved for use by local competent authority.
Stratification factors will be applied for Part B Cohort enrollment.	

Number of Patients:

Part A: As guided by the BOIN design, patient recruitment in Part A occurs until a maximum sample size of 25 is reached. Stop Part A if the number of patients treated at the current dose reaches 12. The optional Part A-2 will potentially enroll up to 40 patients. Part A was formally completed on 23 May 2022 by means of a formal SMC meeting, and based on availability of all required data for 25 patients evaluable for safety evaluation according to the

BOIN rules. The 800mg flat dose level was determined by the SMC to represent a tolerable dose to be further studied as presumptive RP2D in Part B of the trial.

Part B (Cohorts B1 through B8): As guided by the BOP2 design, up to 40 patients per cohort will be enrolled initially into Cohorts B1-B4 and B6-B8. In Cohorts B1-B4 and B6-B8, patients will be treated with 800mg NM21-1480 to be administered approximately every 14 days. For Cohort B5, initial patients randomized to the NM21-1480/PD1 checkpoint inhibitor (pembrolizumab) arm will be administered the 800mg flat dose of NM21-1480 approximately every 14 days. There will be an enrolment stop after 6 patients have been enrolled to the NM21-1480/anti-PD1 combination arm. Only upon safety data review and clearance of this NM21-1480 dose level as a tolerable dose in the combination therapy setting by the SMC, the remaining patients are to be enrolled to Cohort B5. Once an MTD has been determined for NM21-1480 in this Cohort B5 combination setting, remaining patients may only be assigned to NM21-1480 dose levels at or below this combination therapy MTD for NM21-1480.

For the primary goal of assessing clinical response in Part B, depending on recruitment and availability of primary efficacy data, an interim futility analysis will be conducted for each cohort after 25 patients have response data following completion of 2 assessment cycles (i.e., 12 weeks). No such interim analysis will be done for Cohort B5 though. Dose groups may be pooled within cohorts for analysis if the response is deemed independent of dose from a PD/clinical perspective.

For Cohort B5, a total of approximately 200 patients with head and neck squamous cell cancer may ultimately be randomized 2:1 to either NM21-1480 plus a PD-1 standard-of-care first-line checkpoint inhibitor or to the standard-of-care PD-1 checkpoint inhibitor monotherapy. Randomization will be stratified by combined positive score (CPS ≥1; CPS ≥20), as determined by an FDA-cleared or any PD-L1 test approved for use by local competent authority. An interim analysis will be performed after 60 patients (40 patients in the NM21-1480 arm) have been enrolled. At this point, recruitment will be paused, the accumulated data analysed and regulatory authorities consulted. As with the other cohorts, decisions at this interim point will be taken based on clinical and regulatory input and not formal statistical testing.

Key Inclusion Criteria:

1. **Parts A & A-2**: Patients with any previously treated solid tumor-type other than hepatocellular carcinoma or intrahepatic cholangiocarcinoma, confirmed by available pathology records and/or current biopsy, that is advanced (non-resectable or metastatic), or recurrent and progressing since last anti-tumor therapy, and for which no alternative, standard therapy exists.
2. **Part B (all cohorts)**:
   - Cohorts B1 and B7
     - Patients with locally advanced or metastatic, non-resectable NSCLC and documented PD-L1 expression on ≥50% of tumor cells[#] (Cohort B1) or documented PD-L1 expression on ≥1%-49% of tumor cells [#] (Cohort B7)
     - Cohort B1 and B7 will be conducted in the US, Spain, UK, the Netherlands, Germany, and Taiwan. Patients must have received at least 1, and a maximum of 3, previous lines of therapy, including at least 1 previous line containing a PD-(L)1 checkpoint inhibitor. **For patients enrolled to Cohorts B1 and B7 in Germany, they must have received *both* an anti-PD-(L)1 therapy and a platinum-based chemotherapy (i.e., at least 2 prior lines of treatment) to be eligible for study entry.**
     - Patients must have disease that is resistant (i.e., primary resistant[&]) or refractory (i.e., secondary resistant[&]) to anti-PD-(L)1 therapy as defined by:
       a) Has received at least 2 doses of an approved anti-PD-(L)1 monoclonal antibody.
       b) Has demonstrated progressive disease after anti-PD-(L)1 therapy as defined by RECIST 1.1, which was subsequently confirmed by a second assessment no less than 4 weeks from the date of the first documented progressive disease to rule out pseudo-progression, if the latter could not be excluded by the investigator based on the initial imaging demonstrating disease progression.

     [#] Prospective testing is not done for Cohort B1 and B7, i.e., inclusion relies on documented previous testing leading to initiation of anti-PD-(L)1 therapy.

     [&] Primary vs. secondary resistance will be determined based on documented progression of patients following less than or at least 24 weeks on previous anti-PD-(L)1 therapy.
   - Cohort B2
     - Patients with locally advanced or metastatic, non-resectable HPV-associated (i.e., HPV+ tumor) SCC of the anus, cervix, vulva, vagina, penis or oropharynx with documented PD-L1 expression on at least 1% of tumor and/or immune cells in the TME, as detected by a locally-assayed, FDA-cleared PD-L1 test or any PD-L1 test approved for use by local competent authority

- Cohort B2 will be conducted in the US, Spain, UK, the Netherlands, Germany, and Taiwan. For Cohort B2, disease progression must have been documented following a first-line standard-of-care anti-PD-1 monotherapy, anti-PD-1/chemotherapy or chemotherapy regimen. Inclusion of patients with progression on or after 2 previous lines of therapy, including one line of anti-PD-1 checkpoint inhibitor therapy and one line of chemotherapy is also acceptable. Patients must:
  a) Either have documented previous testing results indicating HPV positivity for the current tumor or, in absence of a positive previous HPV test result, the current tumor must be tested positive for HPV applying the local standard testing approach.
  b) Have demonstrated progressive disease after standard first-line, or first- *and* second-line, therapy as defined by RECIST 1.1 or in the view of the Investigator be ineligible or unwilling to be treated with standard first- or second-line therapy.

  NOTE: A maximum of 10 patients with oropharyngeal SCC and a minimum of 15 patients with cervical SCC and 15 patients with anal SCC, respectively, will be enrolled within the total of 40 patients in the cohort.

- Cohort B3
  - Patients with locally advanced or metastatic, non-resectable NSCLC and documented PD-L1 expression on ≥50% of tumor cells
  - Cohort B3 will be conducted in Turkey, Georgia, Ukraine, and Taiwan. For Cohort B3, standard-of-care first-line treatment is defined as: standard local first-line chemotherapy. Patients must have demonstrated progressive disease after standard-of-care local first-line therapy as defined by RECIST 1.1. PD-L1 expression on tumor cells is determined centrally by a Sponsor-approved PD-L1 assay.
- Cohort B4
  - Patients with recurrent, persistent or metastatic ovarian, primary peritoneal or fallopian tumor carcinoma of all histologic types, except mucinous adenocarcinoma and carcinosarcoma, with documented disease progression (disease not amenable to curative therapy) and a history of primary platinum-based chemotherapy
  - Cohort B4 will be conducted in the US, Spain, UK, the Netherlands, Germany, Taiwan, Turkey, Georgia, and Ukraine. For Cohort B4, patients must have a history of primary platinum-based chemotherapy with a maximum of 3 prior cytotoxic regimens and with at least one regimen for recurrent disease containing a platinum or a taxane for those with 3 prior regimens; the last platinum-free interval must be ≤12 months. Histologic confirmation of the original primary tumor is required via the pathology report. NOTE: Patients with mucinous or carcinosarcoma histology are not eligible.
  - Patients are allowed to have received up to 3 prior cytotoxic regimens for treatment of their epithelial ovarian, fallopian tube, or primary peritoneal cancer;
    - they must have had one prior platinum-based chemotherapeutic regimen for management of primary disease, possibly including intra-peritoneal therapy, consolidation, biologic/targeted (non-cytotoxic) agents or extended therapy (maintenance/consolidation) administered after surgical or non-surgical assessment;
    - patients are allowed to have received, but are not required to have received, one to 2 cytotoxic regimens for management of recurrent or persistent disease;
    - poly-adenosine diphosphate (ADP) ribose polymerase (PARP) inhibitors given for recurrent or progressive disease will be considered cytotoxic;
    - PARP inhibitors given as maintenance therapy in continuation with management of primary disease will not be considered as separate cytotoxic regimen;
    - if 2 cytotoxic regimens had been received for management of recurrent or persistent disease, one of these regimens would have had to contain either a platinum or a taxane agent
  - Platinum-free interval (PFI) – patients must have progressed ≤12 months after completion of their last platinum-based chemotherapy; the date (PFI) should be calculated from the last administered dose of platinum therapy to documentation of progression
- Cohort B5
  - Patients with head and neck squamous cell cancer with documented CPS ≥1 in the TME and as determined by an FDA-cleared* or any PD-L1 test approved for use by competent authority
  - Cohort B5 will be conducted in the US, Spain, UK, the Netherlands, and Taiwan. For Cohort B5, patients must have metastatic or unresectable, recurrent disease considered incurable by local therapies

. Patients must qualify for in-label first-line, single agent treatment with an approved anti-PD-1 checkpoint inhibitor and as per investigator judgement would also be put on such treatment as part of standard-of-care, i.e., irrespective of clinical trial participation, at doses not exceeding those approved in local product labels

**FDA-cleared tests include: PD-L1 IHC 22C3 (Dako; preferred assay), VENTANAPD-L1 (SP142; Ventana/Roche), and PD-L1 IHC 28-8 (Dako, VENTANA PD-L1 (SP263; Ventana/Roche), or any other companion /complementary diagnostic PD-L1 assay that may receive FDA approval during the conduct of this study.*

- Cohort B6
  - Patients with TNBC according to current ASCO/CAP guidelines that is measurable according to RECIST1.1 criteria
  - Cohort B6 will be conducted in the US, Spain, UK, the Netherlands, and Taiwan. For Cohort B6, patients must have metastatic disease or locally advanced breast cancer (beyond curative management)
  - TNBC must be characterized as having ≤1% cellular expression of ER and PR as determined by immunohistochemistry (IHC) and having HER2 expression of 0 to 2+ by IHC as per current ASCO/CAP Guidelines. If IHC 2+, a negative in situ hybridization test (preferably fluorescence in situ hybridization (FISH); chromogenic or silver-enhanced in situ hybridization (CISH; SISH) acceptable) is required by local laboratory testing
  - Patients must have received at least one line of previous systemic therapy for advanced breast cancer (chemotherapy or targeted therapy allowed); however, patients must not have received more than 3 previous lines of cytotoxic chemotherapy (*i.e.,* targeted agents not counting as previous line in this context)
  - 20 patients in the cohort must have received prior therapy with an immune checkpoint inhibitor (i.e., an approved PD-1 or PD-L1 antibody), while the other 20 patients must not have received prior therapy with an immune checkpoint inhibitor (as per stratification)
- Cohort B8
  - Cohort B8 will be conducted in the US, Spain, UK, the Netherlands, and Germany. Patients with metastatic, non-resectable colorectal cancer (mCRC) that is MSS or MSI low*, previously treated with all of the following:
    - fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy,
    - and, if RAS wild-type, an anti-EGFR therapy, if eligible.
    - Patients previously treated with an additional anti-VEGF biological therapy are also eligible
  - Patient agrees to paired biopsies and is judged by the Investigator as safe for paired biopsies.
  - Patients must have documented PD-L1 expression in the TME with PD-L1 expressed on at least 1% of tumor and/or immune cells, as detected by local testing with an FDA-cleared or any PD-L1 assay approved for use by local competent authority*.

    *Eligibility determination can be done based on documented previous testing results. If no previous testing result is available eligibility determination will be done based on archival tissue or fresh biopsy taken during screening

3. **Parts A & A-2**: Prior chemotherapy or systemic radiotherapy (for immunotherapy see exclusion criteria) must have been completed at least 4 weeks prior to the administration of the first dose of study drug, and patient has recovered to Common Terminology Criteria for Adverse Events (CTCAE) V5.0 Grade 1 or better from all AEs associated with prior therapy or surgery (however, sensory neuropathy ≤Grade 2, alopecia and endocrine disorder treated with hormone replacement is acceptable).
4. **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 (e.g., thyroid hormone) replacement therapy.
5. **Part A-2:** Documented minimal PD-L1 expression on at least 1% of tumor and/or immune cells in the TME, as detected by local testing with an FDA-cleared or any PD-L1assay approved for use by local competent authority.

Key Exclusion Criteria:

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

1. **Parts A & A-2:** Treatment with any antibody targeting PD-1, CTLA-4, 4-1BB or PD-L1 or other investigational biological drugs within 5 half-lives of that antibody prior to the administration of the first dose of study drug (or within 8 weeks if the half-life is not known). **Part B:**
   - Cohorts B1 and B7 – NSCLC and documented PD-L1 expression on ≥50% of tumor cells (Cohort B1) or documented PD-L1 expression on ≥1%-49% of tumor cells (Cohort B7):
     - Treatment with PD-1 antibody within 2 weeks prior to first dose of study drug
     - Treatment with any PD-L1-directed therapy within 5 (five) half-lives of the respective drug; if the half-life of the respective PD-L1 antibody is unknown, treatment with such a PD-L1 antibody within 12 weeks prior to the first dose of study drug is exclusionary
     - Previous treatment with a PD-(L)1x4-1BB bispecific antibody or any other treatment targeting 4-1BB
     - Patients who, for the treatment of the current cancer, has received any other treatment than anti-PD-(L)1 or chemotherapy within 28 days 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-(L)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-(L)1 therapy is exclusionary. However, sensory neuropathy ≤Grade 2, alopecia and endocrine disorder treated with hormone replacement are acceptable
   - Cohort B2 – HPV-associated (i.e. HPV+ tumor) SCCs:
     - 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
     - Treatment with PD-1 antibody within 2 weeks prior to first dose of study drug
   - Cohort B3 – NSCLC and documented PD-L1 expression on ≥50% of tumor cells:
     - Patients who, for the treatment of the current cancer, has received any treatment other than a local standard-of-care first-line chemotherapy regimen or who has not recovered to CTCAE V5.0 Grade 1 or better from the AE due first-line treatment. However, sensory neuropathy ≤ Grade 2, alopecia and endocrine disorders treated with hormone replacement are acceptable
     - Patient has received a PD-1, PD-L1, 4-1BB or CTLA-4 antibody or any other investigational biological drugs for treatment of the current cancer
     - Patients with epithelial growth factor receptor (EGFR) tyrosine kinase activating mutations or anaplastic lymphoma kinase (ALK) gene rearrangements. Patients with EGFR inactivating mutations (e.g., exon 20) may be eligible
   - Cohort B4 – ovarian, primary peritoneal or fallopian tumor carcinoma:
     - Patients who have 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
     - 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 – head and neck squamous cell cancer with documented CPS ≥1:
     - Patients who have previously received a checkpoint inhibitor for their disease
   - Cohort B6 – TNBC:
     - 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. If the half-life of a previously used anti-PD-L1 antibody is unknown, the Medical Monitor must be contacted.
- 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

  - 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

- Cohort B8 – mCRC:
  - Patients who have previously been treated with trifluridine/tipiracil or regorafenib
  - Patients who have previously been treated with T-cell bispecifics, 4-1BB agonists, or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD1 and anti-PD-L1 unless discussed with the Medical Monitor and agreed by the Sponsor
  - Patients who have received treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5-half lives, whatever is longer, prior to initiation of NM21-1480 treatment
  - Patients who have received treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNFalpha medications) within 2 weeks prior to initiation of NM21-1480 treatment, or anticipation of need for systemic immunosuppressive medication during NM21-1480 treatment
  - Presence of ascites that required two or more therapeutic paracenteses in the last 30 days

2. **Parts A & A-2:** Use of other biological investigational drugs (drugs not marketed for any indication), including use of investigational antibodies targeting CD137/4-1BB, PD-1 or PD-L1 within at least 5 half-lives (or within 8 weeks if half-life of that investigational drug is not known) prior to the administration of the first dose of study drug.
3. Patient has an active autoimmune disease or a documented history of autoimmune disease. Patients with vitiligo, autoimmune thyroiditis, or psoriasis (not requiring systemic treatment within the past 2 years), type I diabetes on stable insulin therapy or – in the view of the Investigator – resolved childhood asthma/atopy would be an exception to this rule. Patients that require intermittent use of bronchodilators, inhaled steroids or local steroid injections including intra-articular injections will not be excluded from the study. Patients with hypothyroidism stable on hormone replacement will not be excluded from the study. Patients with celiac disease adequately controlled by diet alone will not be excluded from the study.

Duration of Treatment:

There is no pre-specified maximal treatment duration. Treatment for a given patient shall be continued until there is confirmed disease progression by the Investigator or the patient meets any of the pre-specified conditions for discontinuation.

Statistical Methods:

Sample Size Determination

No formal group size calculation has been applied as the sample size during dose-escalation cannot be precisely determined but depends on the observed toxicity.

For Part A dose-escalation, a BOIN design with a pre-specified maximal patient number of 25 will be applied. For Part A-2 (OPTIONAL), a maximum number of 40 patients will be treated to provide additional PD data in support of dose selection for Part B, or in order to complement the PK, immunogenicity, and PD data provided by Part B. The sample size is based on clinical rather than statistical considerations.

For Part B dose expansion (Cohorts B1 through B4 and B6-B8), a BOP2 design will be applied with a maximum of 40 patients per cohort. An interim futility analysis will be conducted for each Part B cohort (other than Cohort B5) after 25 patients have response data following completion of 2 assessment cycles (i.e., 12 weeks). For Cohort B8, the Sponsor will hold enrollment to the Cohort after 25 patients have received at least one dose of NM21-1480

treatment until all relevant safety, efficacy, PK, immunogenicity and most prominently all relevant PD data that has accrued until then has been reviewed by the SMC and the Sponsor. After this interim review, the Sponsor may decide to stop the cohort, to continue with full enrollment of the cohort or revise eligibility criteria before the remaining 15 patients in the cohort are enrolled. Patients in Part B will be treated at the 800mg flat dose of NM21-1480; for Cohort B5, patients in the combination treatment arm will be administered the 800mg flat dose of NM21-1480 approximately every 14 days. There will be an enrolment stop after 6 patients have been enrolled to the NM21-1480/anti-PD1 combination arm. Only upon safety data review and clearance of this NM21-1480 dose level as a tolerable dose in the combination therapy setting by the SMC, the remaining patients are to be enrolled to Cohort B5. For any of the Part B cohorts, PD data may be analysed during Part B and used to drop dose groups within cohorts based on review by the SMC and the Sponsor. Decisions will be based on clinical considerations, not formal statistical arguments. For final response assessment, dose groups may be pooled within cohorts for analyses if the response is deemed to be independent of dose from a clinical perspective.

For Cohort B5, a total of approximately 200 patients with head and neck squamous cell cancer will be randomized 2:1 to either NM21-1480 plus a PD-1 standard-of-care first-line checkpoint inhibitor or to the standard-of-care PD1 checkpoint inhibitor monotherapy. Based on 10,000 trial simulations performed in R, a sample size of 180 patients in a 2:1 randomization provides approximately 90% power to detect a difference of 15% between the treatment groups with an estimated two-sided Type 1 error rate <0.05 of 0.0391. Allowing for 10% losses to follow-up, at least 200 subjects will be randomized in Cohort B5. An interim analysis will be performed after a minimum of 60 patients (40 patients in the NM21-1480 arm) have been enrolled. At this point recruitment will be paused, the accumulated data analyzed and regulatory authorities consulted. Cohort B5 will be regarded as futile (non-binding) if the probability of observing a difference in estimated effects between control and treatment of at least 15% is less than 0.1. However, as with the other cohorts, decisions at the interim point will be taken based on clinical and regulatory input and not formal statistical testing.

Safety Analyses

All recorded TEAEs will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of Aes will be tabulated. A separate listing and summary of all irAEs will be provided. Adverse events will be summarized for all reported data and by study part as well as study period, i.e., up to and including 70 days post last dose of study treatment. Safety data for Part B may be pooled across dose groups to mirror the efficacy analysis decisions to facilitate an appropriate risk benefit assessment per cohort.

Efficacy Analyses

Summary statistics will be presented for data collected during Part A and Part A-2, and separately for Part B within cohorts and pooled across dose groups as appropriate. If sufficient data are available for the selected dose levels, the PD/dose response relationship may be formally modelled.

In order to perform preliminary evaluation of anti-tumor activity, best overall response (BOR) outcomes, objective response rate (ORR) and Disease Control Rate (DCR) according to RECIST 1.1 will be tabulated by frequency distribution overall, and 6 weeks and 12 weeks following the start of study treatment in Part A-2 (if applicable) and Part B. For Part B only, these clinical activity assessments will also be done according to iRECIST criteria. Similar exploratory analyses will be done for Part A (if applicable) overall and 8 and 16 weeks following Day 1, in accordance with the respective imaging visit frequency. Median time-to-response (TTR) and duration of response (DOR) will be summarized for those patients with responses, using the Kaplan-Meier method, i.e., by generation of Kaplan-Meier curves for time-to-event variables; PFS and OS will be similarly summarized. Exploratory clinical anti-tumor analysis to assess the overall survival (OS) will be provided by Kaplan-Meier method. Dose groups may be pooled within cohorts for interim and final analyses in Part B if the response is deemed to be independent of dose from a clinical perspective.

For Cohort B5, the primary efficacy endpoint will be ORR. The primary analysis will be performed in the Efficacy Analysis Set using a Bayesian logistic regression model with treatment and (CPS ≥1; CPS ≥20) as covariates:

$$Logit\,(p_i) = \beta_0 + \beta_1 \times treatment + \beta_2 \times CPS20$$

The following prior distributions have been assumed:

$\beta_0 \sim N(-1.45, 0.16^2)$, equivalent to a control response rate of 20 (±4)% observed in the KEYNOTE-048 study with pembrolizumab;

β_1 ~ N (0,1), vague prior on treatment equivalent to expected treatment difference of 0% (95% confidence interval: -16% to +43%, which corresponds to a N(0,1) prior on logistic scale)

β_2 ~ N (0, 0.1^2), vague prior on CPS effect, based on KEYNOTE-048 study with pembrolizumab, where a 0%-3% difference in response was observed across CPS levels.

The Bernoulli likelihood is not conjugate to the normal priors on the regression coefficients and so the posterior distribution of regression coefficients is not known. Let $\beta = (\beta_0, \beta_1, \beta_2)$.

$$\pi(\beta|data) \propto \pi(data|\beta)\pi(\beta)$$

In order to avoid the use of Monte Carlo methods for inference on parameters (and the requirement of large simulations to estimate posteriors with sufficient precision) we fit Laplace approximations to posterior distributions. We approximate $\pi(\beta|data) \approx N\ (\beta', Var(\beta'))$ where β' is the mode of the posterior distribution of $\pi(\beta|data)$ with $Var(\beta')$ the posterior covariance matrix estimated at this mode.

At the interim analysis, Cohort B5 will be regarded as futile (non-binding) if the probability of observing a difference in estimated effects between control and treatment of at least 15% is less than 0.1. However, as with the other cohorts, decisions at the interim point will be taken based on clinical and regulatory input and not formal statistical testing. Statistical superiority of the treatment in the final analysis will be concluded if $Pr(\beta_1 > 0 \mid data)$ is > 0.95.Analysis of Pharmacokinetics Endpoints and Anti-Drug Antibody

Pharmacokinetics parameters such as the maximum observed serum concentration (Cmax), the minimum observed serum concentration (Cmin), the time from dosing at which Cmax is apparent (Tmax), terminal phase (apparent elimination) rate constant (λz), elimination half-life (t½), area under the serum concentration-time curve extrapolated from the last quantifiable concentration to infinity (AUC[0-infinity]), area under serum concentration-time curve over dosing interval (AUCtau), clearance (CL), apparent volume of distribution (Vd), and accumulation index will be derived from serum concentration versus time data for patients with serial PK samples. Data obtained from patients with serial sampling and limited sampling will eventually be combined with data from other studies for population PK analysis but reported separately.

A listing will be generated of all available immunogenicity data, comprising all numeric titer values. Additionally, a listing of immunogenicity data from those patients with at least 1 positive anti-drug antibody (ADA) assessment (titer value greater than 2-fold of baseline titer) at any time point will be provided by dose regimen. The frequency of patients with at least 1 positive ADA assessment (titer value greater than 2-fold of baseline titer), and frequency of patients who develop ADA after a negative baseline assessment (i.e., titer value equal to 1), and frequency of patients who develop ADA after a baseline titer assessment greater than 1, will be provided by dose. In addition, the frequency of patients who do not develop ADAs after treatment following either a negative baseline assessment (i.e., titer value equal to 1), or a baseline titer greater than 1 will be provided by dose. Treatment-induced, treatment-enhanced and treatment-unaffected ADA patients will be summarized. In addition, to examine the potential relationship between immunogenicity and safety, the frequency and type of AEs may be examined by overall immunogenicity status.

Pharmacodynamic Characteristics and Exploratory Biomarkers

Key PD parameters for determination of dose levels to be selected for Part B will comprise all exposure-dependent PD markers of target and pathway engagement including but not limited to characterization of peripheral PD (IFNɣ; CXCL10; soluble 4-1BB; proliferating CD8+ and effector memory CD8+ cells) and receptor occupancy: this may be supplemented by other exploratory biomarker data, for example assessment of T-cell receptor clonality in tumor tissue. Summary statistics for blood- and tissue-based PD markers, including but not limited to flow cytometry outcomes, cytokines, and their changes (or fold changes) from baseline will be tabulated by cycle, visit, and dose to assess PD effects and potential association with PK exposure. Associations of status of exploratory biomarkers (baseline value or change from baseline) with clinical outcome (e.g., tumor response) may be explored based on data availability, using response-evaluable patients, to explore potential predictive markers (e.g., PD-L1) expression in tumors. Additional tissue biopsy-based exploratory analysis for biomarkers may be applied for mCRC patients possibly enrolled to Cohort B8, given there is a mandatory requirement to provide matched fresh biopsies for this cohort.

Administrative interim analyses on safety and clinical activity or on PK, immunogenicity, and selected biomarkers may be provided at several times prior to completion of the study in order to facilitate program decisions and to support study presentations or publications.

Date of the protocol: 17 Nov 2022

3 TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTH	Adrenocorticotrophic hormone
ADA	Anti-drug antibody
ADP	Adenosine Disphosphate
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
APC	Adenomatous Polyposis Coli
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC(0-infinity)	Area under the serum concentration-time curve extrapolated from the last quantifiable concentration to infinity
AUCtau	Area under serum concentration-time curve over dosing interval
AT	Aminotransferase
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal phase II
BOR	Best overall response
BRAF	B-raf protooncogene
CAP	College of American Pathologists
CBD	Cannabidiol
CEA	Carcinembryonic Antigen
CEC	Central Ethics Committee
Cmax	The maximum observed serum concentration determined by direct inspection of the concentration versus time data
Cmin	The minimum observed serum concentration determined by direct inspection of the concentration versus time data
CL	Clearance
CPI	Checkpoint inhibitor
CPS	Combined Positive Score
CR	Complete response
CSF	Colony-stimulating factor
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumor Deoxyribonucleic Acid
CTLA	Cytotoxic T-lymphocyte associated protein
CTL	Cytotoxic T-lymphocyte
CYP	Cytochrome P (450)
DCR	Disease Control Rate

DLT	Dose-limiting toxicity
DMC	Data monitoring committee
dMMR	Deficient mismatch repair
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epithelial growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen Receptor
FDA	Food and drug administration
FIH	First-in-human
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GGT	Gamma glutamyl transferase
HCV	Hepatitis C virus
HER2	Human Epithelial Growth Factor Receptor-2
HIV	Human immunodeficiency viruses
HPV(+)	Human papillomavirus (positive)
HSA	Human serum albumin
IB	Investigator's brochure
ICF	Informed consent form
ICH	International council for harmonization
iCPD	iRECIST Confirmed Progressive Disease
IEC	Independent ethics committee
IFNϒ	Interferon gamma
IHC	Immuno-Histochemistry
IL	Interleukin
IND	Investigational new drug
IP	Investigational product
IRAE	Immune-related adverse event
IRB	Institutional review board
IV	Intravenous
KRAS	Kirsten rat sarcoma oncogene
mCRC	Metastatic colorectal cancer
MedDRA	Medical dictionary for regulatory activities
MHC	Major Histocompatibility complex

MRI	Magnetic resonance imaging
MSI-H	Microsatellite instability-high
MTD	Maximal tolerated dose
NCCN	National Comprehensive Cancer Network
NK	Natural Killer cells
NKT	Natural killer T cells
NRAS	Neuroblastoma rat viral oncogene homolog
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
PARP	Poly-Adenosine Disphosphate (ADP) Ribose Polymerase
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFI	Platinum-Free Interval
PFS	Progression-free survival
PIK3CA	Phosphatidyl 3-kinase CA
PK	Pharmacokinetics
POLE	Polymerase Epsilon Catalytic subunit
PR	Progesterone Receptor
PT	Prothrombin time
PTEN	Phosphatase and Tensin homolog
PTT	Partial thromboplastin time
RT	Radiotherapy
RECIST 1.1	Response evaluation criteria in solid tumors version 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SA	Serum albumin
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SMC	Safety monitoring committee
SMP	Safety management plan
SOP	Standard operating procedure
SS	Safety set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin level
Th	T-helper cells
TEAE	Treatment-emergent adverse event
TIL	Tumor-Infiltrating Lymphocyes
TNBC	Triple-Negative Breast Cancer
Treg	Regulatory T-cells

TRAE	Treatment-related adverse event
Tmax	The time from dosing at which Cmax is apparent determined by direct inspection of the concentration vs time data
TME	Tumor microenvironment
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTR	Time-to-response
T½	Elimination half-life
UK	United Kingdom
ULN	Upper limit of normal
US	United States
Vd	Volume of distribution
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cell
WOCBP	Women of child-bearing potential
λz	Terminal phase (apparent elimination) rate constant

5 INTRODUCTION

5.1 Background

Immune checkpoint blockade has revolutionized cancer treatment. Monoclonal antibodies targeting programmed cell death protein 1 (PD-1) and its major ligand Programmed death-ligand 1 (PD-L1) have demonstrated sustained clinical benefit in diverse cancer types including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, bladder cancer, head and neck squamous cell carcinoma, microsatellite instability-high (MSI-H) colorectal carcinoma, Merkel cell carcinoma, and Hodgkin lymphoma, where they have quickly changed the practice of medical oncology (Bartkowiak and Curran, 2015; Chester, et al. 2018). Most recently, approval was even granted for a tumor-type agnostic indication, based on presence of certain tumor deoxyribonucleic acid (DNA) biomarkers (MSI-H/DNA mismatch repair deficiency). However, anti-PD-1/PD-L1 therapy exhibits an almost dichotomous initial response pattern: some patients experience rapid and durable tumor regression (typically 10-30% of patients), while a majority of patients derive minimal or no appreciable benefit (i.e., patients with innate/primary resistance). Furthermore, with longer follow-up of patients, a third population of patients has emerged, namely those that respond initially but eventually develop disease progression (i.e., patients with acquired/secondary resistance) (Jenkins, et al. 2018). Specifically in melanoma treatment, combination immunotherapy or dual immune-checkpoint blockade [anti-PD-1+ anti-cytotoxic T-lymphocyte-associated protein (anti-cytotoxic T-lymphocyte associated protein [CTLA]-4] has recently shown dramatic response rates in patients with metastatic melanoma (response rate [RR]: 58% [Jenkins, et al. 2018]); however, half of patients experienced significant toxicity from the treatment regimen and furthermore an efficacy advantage of this immune-checkpoint inhibitor (CPI) combination in other tumor types remains to be demonstrated at this point. From a mechanistic point of view, there are 3 major reasons for failure of immune-checkpoint blockade (Jenkins, et al. 2018):

- Insufficient tumor T-cell generation, due to low mutational burden and/or low/insufficient neo-antigen formation, presentation, and/or processing, resulting in primary resistance.
- Inadequate tumor T-cell effector function due to functional exhaustion of CD8+ T-cells, similarly resulting in primary resistance.
- Impaired formation of T-cell memory, resulting in secondary resistance.

Thus, the next wave of immunomodulatory approaches in oncology aims at increasing the fraction of patients that respond and continue to respond to anti-PD-1/PD-L1 immunotherapy, however combined with a substantially better tolerability profile than typically observed with the anti-PD-1/CTLA-4 combination approach. A main therapeutic strategy to achieve that goal is to agonistically act on immuno-stimulatory receptors to induce immune cell activation. Such “co-stim” strategies have provided the mechanistic foundation for multiple agents in clinical development, including antibodies targeting OX40, CD27, CD40, GITR, and 4-1BB (Mahoney, et al. 2015; Chester, et al. 2018).

4-1BB (CD137), a surface glycoprotein and member of the tumor necrosis factor receptor superfamily 9, is a uniquely compelling therapeutic target in this context. Indeed, 4-1BB possesses an unequaled capacity for both activation and pro-inflammatory polarization of anti-tumor lymphocytes (Chester, et al. 2018). While functional studies of 4-1BB have focused on its prominent role in augmenting cytotoxic CD8 T-cells, 4-1BB can also modulate the activity of cluster of differentiation 4 T-cells (CD4 T-cells), B-cells, natural killer cells, monocytes, macrophages, and dendritic cells. 4-1BB's expression on both T-cells and antigen presenting cells, coupled with its capacity to promote survival, expansion, and enhanced effector function of activated T-cells, has made it an alluring target for tumor immunotherapy.

As such, based on the biological mechanism of action following stimulation of 4-1BB signaling, an efficient co-stimulatory activation of this receptor is suggested to play an important role in T-cell activation, persistence, and T-cell memory.

Based on the biological rationale for targeting of 4-1BB to activate the immune system in cancer patients, 2 anti-4-1BB therapeutic antibodies have entered clinical development. The agonistic anti-human 4-1BB human immunoglobulin G4 (IgG4) antibody (anti–hu4-1BB huIgG4) urelumab (BMS-663513) caused dose-dependent hepatitis in patients, most likely due to 4-1BB cross-linking via FcγRIIb-expressing liver-resident cells such as hepatic myeloid and sinusoidal endothelial cells (Bartkowiak, et al. 2018; Chester, et al. 2018). Subsequent studies revealed that urelumab could be administered at a safe dose of 0.1 mg/kg, however at this dose it only mediated limited efficacy (Chester, et al. 2018). A second anti-4-1BB antibody, anti-hu4-1BB huIgG2 utomilumab (PF-05082566), displayed a better safety profile but lower agonistic potency than urelumab (Chester, et al. 2018). These early clinical data show promise for the approach of targeting 4-1BB, however the safety to efficacy balance is not optimal in these initial therapeutic molecules.

Taken together these data indicate that a therapeutic approach which can safely but effectively stimulate 4-1BB signaling, in addition to inhibition of the PD-L1/PD-1 axis, has major potential to address at least 2 of the major resistance mechanisms for CPIs, i.e., overcoming severe T-cell exhaustion and improving T-cell memory. Furthermore, there is further potential of the approach for boosting antigen presentation, while this may require combinations with chemotherapy, radiation therapy, or tumor vaccination.

Overall, there are a number of differences between urelumab and utomilumab (i.e., the known differences between the monoclonal antibodies (mAbs) including: intrinsic agonistic activity, immunoglobulin subclass, Fc receptor binding profile, targeted epitope on 4-1BB, and 4-1BBL blockade capacity) (Chin, et al. 2018; Chester, et al. 2018). While the impact of these individual factors on the respective benefit-to-risk profile of the 2 mAbs is not entirely clear, the following conclusion on their clinical impact seems to be justified for standard (bivalent) mAbs targeting 4-1BB:

Conventional monoclonal antibodies, due to their bivalent binding mode to 41BB, lead to clustering of 4-1BB on the surface of the target cell, and consequently activation of 4-1BB

signaling, based on simple bivalent binding to the target – if an optimally active epitope is targeted by the antibody (i.e., urelumab)

Targeting of epitopes that allow for optimal activation of 4-1BB signaling (and thus full exploitation of the beneficial co-stimulatory activity of the receptor) by bivalent antibodies will necessarily be associated with systemic toxicity.

It is possible to reduce the toxicity potential of 4-1BB agonistic, bivalently binding antibodies by targeting a different epitope on 4-1BB (i.e., using an epitope that competes with binding of the natural 4-1BB ligand, such as in the case of utomilumab). However, this will lead to reduced potency, i.e., reduced activation of 4-1BB signaling and thus reduced to absent clinical efficacy. As a consequence, less systemic activity/toxicity but also less activity in the tumor microenvironment (TME) is observed with utomilumab in comparison to urelumab.

Numab has designed ND021 (NM21-1480), in order to resolve the 4-1BB-targeting dilemma, i.e., in order to maximize the benefit to-risk profile of targeting this co-stimulatory receptor in combination with inhibiting the PD-L1/PD-1 pathway.

5.1.1 NM21-1480

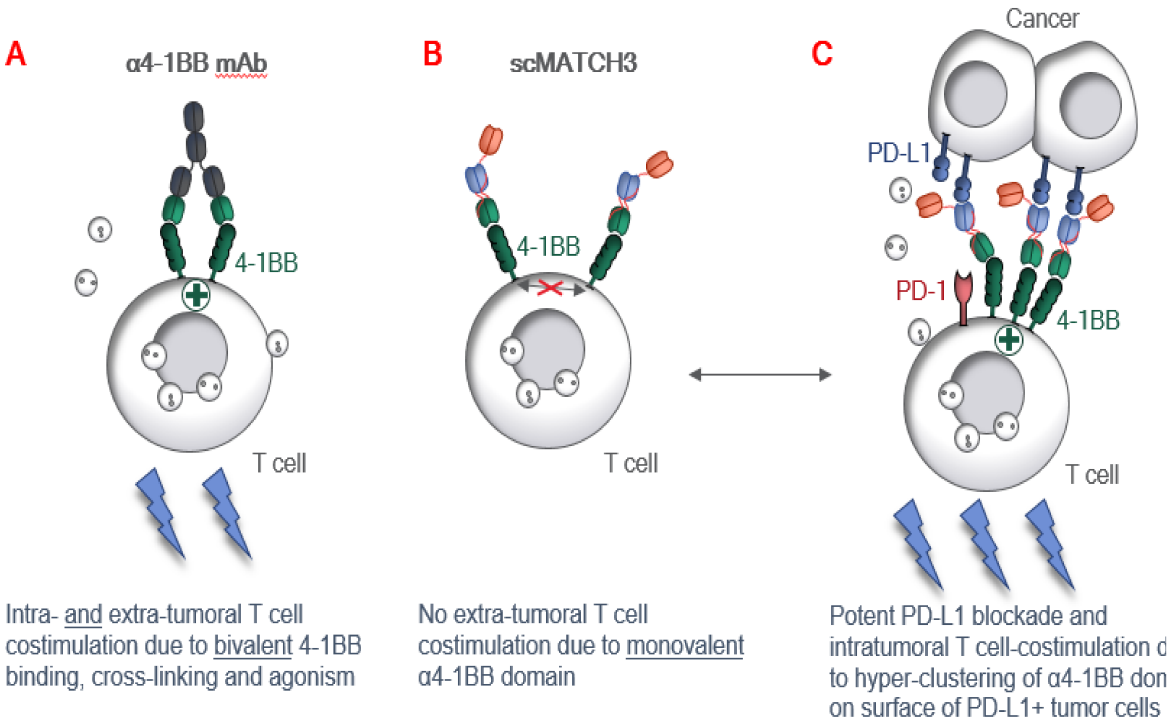
NM21-1480 is a recombinant protein consisting of 3 stabilized antibody Fv fragments directed against the molecular targets PD-L1, 4-1BB, and serum albumin (SA). It is designed for avoidance of systemic 4-1BB activation and preferential 4-1BB activation in the TME to avoid the dose-limiting toxicities (DLTs) of systemically active 4-1BB agonists. NM21-1480 is a tri-specific antibody targeting the clinically validated inhibition of immunosuppressive PD-L1 combined with co-stimulation of cancer-specific T-cells via the co-stimulatory receptor 4-1BB. This dual action provides the perspective of broader and more sustained treatment response in tumor indications known to be responsive to inhibition of the PD1-PD-L1 axis. Importantly, the molecule has been designed to vastly restrict its activities to the TME only, thus avoiding the type of DLTs observed with antibodies providing systemic 4-1BB agonism, such as urelumab.

One essential component of the design of a molecule to achieve this goal is to generate an antibody (i.e., binding domains within the multi-specific antibody) that binds in a monovalent manner to its molecular targets. Conventional antibodies (such as, e.g., urelumab) bind to 4-1BB in a bivalent manner and activate the 4-1BB signaling pathway by simple binding on 4-1BB expressing cells. In contrast, the monovalent binding of ND021 (NM21-1480) to 4-1BB-expressing cells does not trigger activation of the 4-1BB signaling pathway as no clustering of 4-1BB is triggered on the surface of these cells. Instead, for ND021 (NM21-1480) to induce 4-1BB signaling upon target binding, additional binding to PD-L1 on cancer cells is necessary. Only upon concomitant binding of ND021 (NM21-1480) to 4-1BB on immune cells and PD-L1 on tumor cells, an immunological synapse is formed which triggers hyperclustering of 4-1BB on T-cells in the proximity of tumor cells.

Numab has designed a PD-L1/4-1BB/human serum albumin (HSA) tri-specific scMATCH™ 3 immunomodulatory drug candidate (NM21-1480) that agonizes 4-1BB conditionally upon

PD-L1-binding and associated PD-L1/PD-1 antagonism. NM21-1480 is initially being developed for the treatment of tumors for whom anti-PD-L1 antibodies are approved but demonstrate primary or secondary resistance to anti-PD1 or anti-PD-L1 therapy. Upon demonstration of clinical benefit in such patients, NM21-1480 may also be developed as a first-line CPI treatment including but not restricted to tumor indications for which PD1 and/or PD-L1 antibodies are approved (see Figure 5–1).

Figure 5–1 NM21-1480 (scMATCH™ 3) Tumor-Localized Agonism of 4-1BB



Abbreviations: mAb = Monoclonal antibodies; PD-L1 = Programmed death-ligand 1

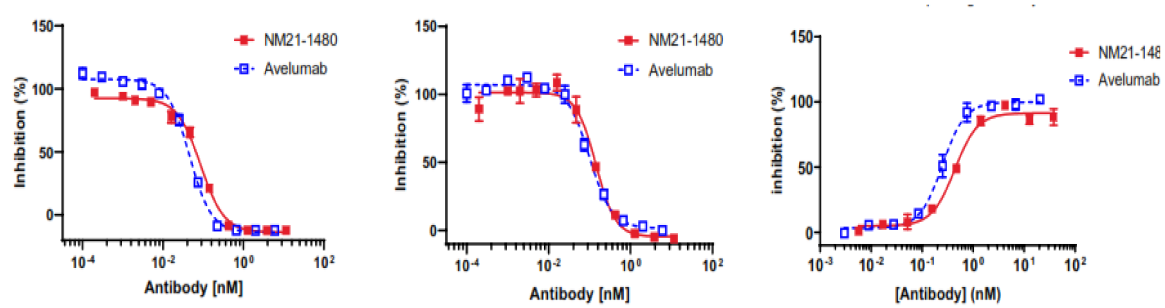
The proposed indications for NM21-1480 (non-comprehensively) include melanoma, non-small cell lung cancer, head and neck and other types of squamous cell carcinoma (SCC), urothelial carcinoma, renal cell carcinoma, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma and MSI-H/deficient mismatch repair (dMMR) cancer. Additional indications for which efficacy of anti-PD1 antibodies has been suggested more recently, e.g., certain forms of sarcomas, may also be considered for clinical development.

5.1.2 Non-Clinical Summary

The affinity of NM21-1480 to human PD-L1, human 4-1BB and SA has been determined by surface plasmon resonance to be 4.38E-12 ± 1.65E-12 M, 4.49E-10 ± 0.51E-10 M, and 6.73E-10 ±3.21E-10 M, respectively. All 3 domains of NM21-1480 show nearly identical binding affinity to all 3 cynomolgus monkey proteins as compared to their human counterpart.

NM21-1480 blocks the interaction between PD-L1 and PD-1 with a similar potency to the market-approved PD-L1 blocking antibody avelumab, as shown in a cell-based nuclear factor of activated T-cells reporter gene assay (see Figure 5–2).

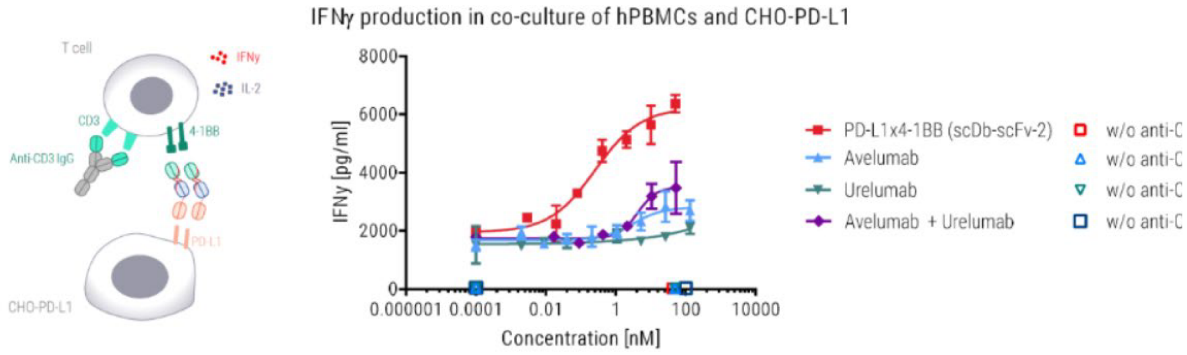
Figure 5–2 NM21-1480 Potency to Block A) The PD-L1/PD-1 Interaction, B) The PD-L1/B7.1 Interaction in a Competition ELISA, and C) The Potency of PD-L1/PD-1 Signaling Blockade in a Transgenic NFAT-Luciferase Reporter Jurkat Cell-Line



Abbreviations: ELISA = Enzyme-linked immunosorbent assay, PD-1 = Programmed cell death protein 1, PD-L1 = Programmed cell death-ligand 1

NM21-1480 activates 4-1BB signaling in human NFκB-luciferase reporter Jurkat T-cells, exclusively upon binding to PD-L1 expressing (tumor) cells. NM21-1480 in a dose-dependent manner enhanced IL-2 secretion by human peripheral blood mononuclear cells (PBMCs) with an EC50 of 362.5 pM. The induction of IL-2 production mediated by NM21-1480 is conditional to the preceding stimulation of PBMCs, for example by the staphylococcus enterotoxin. In this assay, NM21-1480 shows up to 2-fold lower EC50 (i.e., higher potency) to co-stimulate 4-1BB+ cells than the combination of the clinical stage anti-PD-L1 and 4-1BB antibody combinations avelumab/urelumab and nivolumab/urelumab, while the maximum IL-2 release is a factor of 2- to 3-fold higher, respectively. The synergistic effects of concomitant inhibition of PD-L1 and 4-1BB were further analysed in an alternative setup. In this assay, T-cells were activated by co-stimulation with anti-CD3 antibodies, as 4-1BB is essentially only expressed on activated T-cells. NM21-1480 potently induced IL-2 and interferon gamma (IFNγ) secretion only in presence of anti-CD3 antibodies confirming that T-cell receptor (TCR) signaling or CD3 engagement is required for productive 4-1BB signaling (see Figure 5–3).

Figure 5–3 ND021 (NM21-1480) Provides Stronger T-cell Activation than Benchmark Combo Therapies –IFNγ

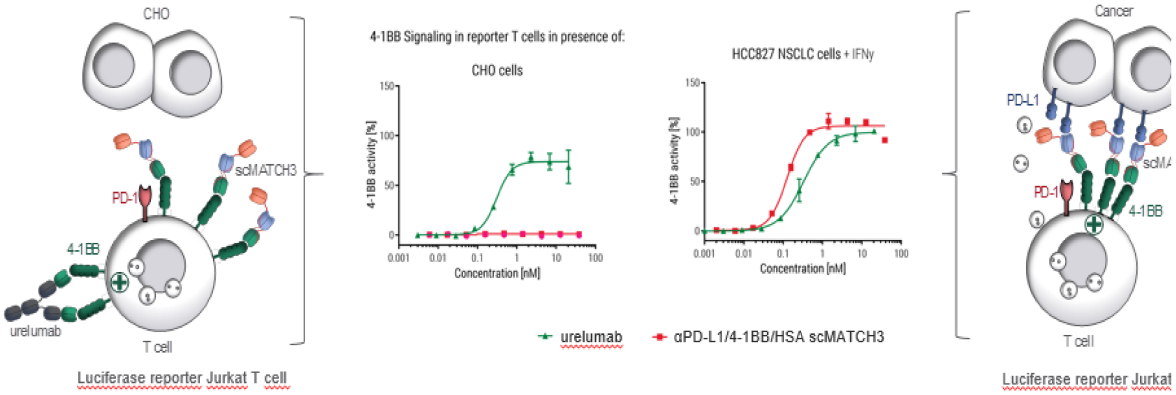


Abbreviations: CHO-PD-L1 =CHO Programmed death-ligand-1; hPBMCs = human peripheral blood mononuclear cells; IFNγ = Interferon gamma.

Human PBMCs from healthy donors were incubated for 3 days in presence of an agonistic anti-CD3 antibody. Human PD-L1 expressing CHO cells and serial dilutions of avelumab, urelumab. Avelumab/urelumab combination or PD-L1×4-1BB scDb-scFv-2 were added to the culture. IFNγ secretion was assessed by ELISA. The PD-L1×4-1BB scDb-scFv-2 more potently induced IL-2 (not shown) and IFNγ production than avelumab, the urelumab, or the combination of the 2. In absence of anti-CD3 antibodies, IL-2 and IFNγ levels were comparable to basal cytokine secretion at all concentrations tested, confirming that TCR signaling or CD3 engagement is required for productive 4-1BB signaling.

Figure 5–4 summarizes the mechanism of action of ND021 (NM21-1480) in comparison to conventional agonistic antibodies targeting 4-1BB.

Figure 5–4 NM21-1480 *In Vitro* Proof-of-Mechanism



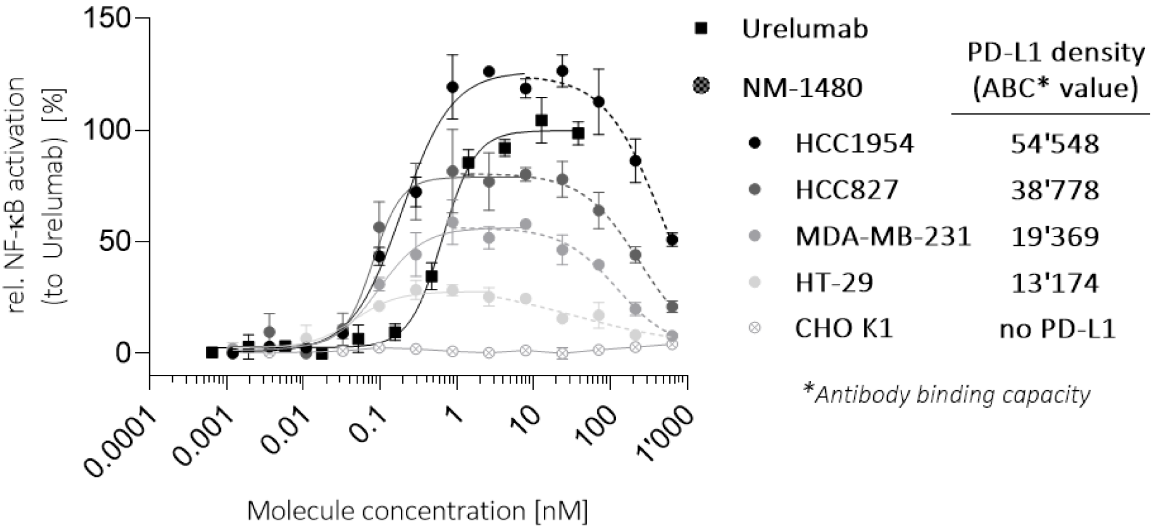
4-1BB signaling in luciferase reported Jurkat T-cells by scMATCH3 molecules in presence or absence of PD-L1+ cells. PD-L1+ HCC827 NSCLC cells (stimulated with IFNγ) or CHO control cells were cultivated together with reporter Jurkat T-cells that express luciferase upon 4-1BB signaling. scMATCH3 molecules were added in increasing concentrations and in presence of 25 mg/mL HSA. After 24 hours of incubation, 4-1BB signaling activity in Jurkat cells was assessed by measurement of luciferase activity. In presence of PL-L1+ HCC827 tri-specific scMATCH3 molecules induce luciferase activity more efficiently than urelumab, whereas, in the absence of PD-L1 (CHO cells), only urelumab induced luciferase expression. Thus, in contrast to urelumab, the monovalent, tri-specific scMATCH3 triggers 4-1BB signaling exclusively in the proximity of PL-L1+ cells.

Due to the lack of affinity of NM21-1480 to murine PD-L1, 4-1BB, and SA, pharmacology studies were conducted in humanized mouse xenograft models using surrogate molecules with a mouse cross-reactive SA binding domain. Immunodeficient NOD/Shi-scid/IL-2Rγ^{null} (NOG)

mice engrafted with human umbilical cord blood HUCB-derived CD34+ stem cells – efficiently reconstituting the human T-cell repertoire in the mice, were injected with HCC827 NSCLC cells (a PD-L1 expressing human cancer cell-line). NM21-1480 surrogate therapy resulted in stronger reduction of tumor growth than therapy with PD-L1 immunoglobulin G (IgG) s, 4-1BB IgGs, or the combination thereof. This correlated with higher frequency of cytotoxic T-cells in the TME. Further, NM21-1480 therapy led to higher response rates (shrinking tumors/complete response [CR]) in mice and was generally better tolerated than single-agent PD-L1 IgG and combination therapies with PD-L1 IgG and 4-1BB IgGs. In a second model, NOG mice were engrafted with human PBMCs after implantation of PD-L1+ HCC827 cells. Similar to the first model, the NM21-1480 surrogate therapy resulted in stronger reduction of tumor growth and led to higher response rates (details are provided in the Investigator's Brochure (IB)). This clinical response pattern correlated with higher frequency of cytotoxic T-cells in the tumor tissue.

Pre-clinical assessment of the activity of NM21-1480 has demonstrated that the stimulation of T-cells via the 4-1BB pathway following PD-L1 dependent clustering results in a bell-shaped dose response (see Figure 5–5). The decrease in activity seen for 4-1BB stimulation at high concentrations is most likely driven by the saturation of PD-L1 on tumors cells and the concomitant saturation of 4-1BB on T-cells, thus leading to a loss in synapse formation across these 2 cell types. Of note is the lack of bell-shaped dose response for PD-L1 antagonism (see Figure 5–2). Since antagonism of PD-L1 is solely dependent on PD-L1 saturation, the activity of this mechanism by NM21-1480 reaches maximal inhibition and maintains this maximum despite increasing concentrations of drug. Therefore, a careful assessment is required of the dose of NM21-1480 needed to achieve maximal 4-1BB stimulation and concomitant maximal PD-L1 stimulation, without overdosing and a resultant decrease in 4-1BB stimulation. Importantly, it has also been demonstrated that the concentration required to achieve 50% 4-1BB stimulation is independent of the level of PD-L1 expression on tumor cells, therefore an optimal dose level is predicted to be similar across patients, independent of the level of PD-L1 tumor expression. The maximal level of 4-1BB stimulation does however increase with increasing PD-L1 expression on tumor cells, with no stimulation seen in the absence of PD-L1.

Figure 5–5 4-1BB Activation by NM21-1480 in NF-κB Reporter Gene Assay in Presence of PD L1 Expressing Cancer Cells



The graph shows a representative concentration-dependent activation curve of NF-κB signaling in Jurkat reporter cells by NM21-1480-mediated clustering of 4-1BB in the presence of IFNγ stimulated cancer cells. 4-1BB activation is represented as relative NF-κB activation by normalization to reference antibody urelumab that was taken along on each test plate. Curves with circle symbols represent NM21-1480 responses, the black curve with square symbols depicts a representative curve of urelumab co-cultivated with HCC827 cells. PD-L1 density on co-cultivated cancer cells is represented as the average of antibody binding capacity of each cell-line and was quantified by flow cytometry prior the execution of NF-κB reporter gene assay. NM21-1480 induces a concentration-dependent response in Jurkat reporter gene cells and the maximum NF-κB activation was affected by the different PD-L1 expression levels in co-cultivated cancer cells showing a direct correlation between 4-1BB signal activity and PD-L1 abundancy.

The tolerability profile and pharmacokinetics (PK) of NM21-1480 have been studied in cynomolgus monkeys (details are provided in the IB). The initial single-dose non-GLP PK/Tolerability study conducted in cynomolgus monkeys confirmed that NM21-1480, administered at single doses of 0.2, 2, and 20 mg/kg, was well tolerated, and later repeat-dose studies confirmed this finding. Further, no signs of hepatotoxicity were observed even at the highest applied dose (20 mg/kg) in the single-dose studies as demonstrated by the lack of any clinically relevant increase of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT). Similarly, there was no impact on neutrophil or thrombocyte counts – another frequent adverse effect observed with the 4-1BB agonist urelumab. Results from the repeat-dose cynomolgus study entirely confirmed this data and can be found in more detail in the IB. As such, none of the most prominent adverse drug reactions clinically observed under urelumab treatment was seen in the single-dose or repeat-dose monkey studies with NM21-1480 even at the highest dose applied (140 mg/kg). The single-dose PK profile of NM211480 assessed in this monkey study resulted in a half-life of approximately 5 days, corresponding to a predicted half-life in humans of about 2 weeks. The lack of systemic 4-1BB activity of NM21-1480 was further confirmed by the observation that

in the blood of these monkeys no significant expansion of proliferating effector memory and central memory cytotoxic T-cells could be detected – a cell population that has been reported to expand following non-TME restricted stimulation of 4-1BB signaling, e.g., by agonistic IgGs.

5.1.3 Clinical

Part A of the study has been formally completed as per discussion of all enrolled patient's data up to and including at least completion of the 28-day DLT evaluation period for all patients enrolled to Part A with the SMC on 23 May 2022. At this SMC meeting, the SMC determined that Part A of the study did not technically identify a MTD and that the highest dose assessed in Part A (800mg) is considered a tolerable dose of NM21-1480. Upon comprehensive review of safety, clinical activity, PK, RO and PD data from Part A, the SMC supported further assessment of safety and efficacy of the 800mg dose of NM21-1480 as presumptive RP2D in Part B of the study. Part A has been conducted at 7 active sites in the US and Taiwan and as of November 2022, all enrolled patients have completed treatment in Part A. A summary of Part A study results can be found in below sections and the IB (Version 3.0, 15 June 2022), to which reference is made for more details (Luke, et al. 2022. SITC poster #732). Based on the results of Part A of the study, as supported by the SMC, the Sponsor will study the 800mg dose of NM21-1480 in Part B of the study with the aim to confirm this dose as the RP2D for the compound. Selection of this dose level for Part B is primarily based on the fact that some patients dosed at 24-240mg in Part A experienced the development of treatment-emergent ADAs that were associated with loss of exposure to the study drug, while such phenomenon was not observed at the 800mg dose level. Full pharmacodynamic activity of NM21-1480 was preserved at the 800mg dose in Part A. The Sponsor thus further decided to explore one more higher dose level (1400mg flat dose with approximately 14-day dosing interval) in up to 10 patients within the optional Part A-2 of the study in order to further study the PK/PD relationship over a broad range of doses. Exploration of this 1400mg dose within Part A-2 will be conducted in parallel to Part B and under application of strict stopping criteria respecting a 28-day DLT evaluation period before more than 6 patients are exposed to this dose level. PK data for this dose level in Part A-2 will be closely followed and in case of observation of relevant drug accumulation over time, the dosing interval for this dose may be adjusted to approximately 21 days.

5.2 Study Rationale

The combined immunomodulation of PD-L1/PD-1 blockade and 4-1BB activation is considered a promising strategy to increase response rates among cancer patients who are eligible to receive PD-L1/PD-1 inhibitors. Unfortunately, encouraging pre-clinical results achieved with such regimens have not yet translated into durable clinical success; due to co-administration of 4-1BB-agonistic antibodies targeting different epitopes on 4-1BB being either intolerable at effective doses or ineffective at all evaluated doses. To eliminate this safety/efficacy trade off, Numab has designed a PD-L1/4-1BB/HSA tri-specific scMATCH™

3 immuno-modulatory drug candidate (NM21-1480) that agonizes 4-1BB conditionally upon PD-L1-binding/-blockade.

This study will evaluate the safety, tolerability, PK and pharmacodynamic (PD) profile of NM21-1480 as well as explore the clinical activity of NM21-1480 in selected tumor types. Through analysis of safety, PK and PD, the maximal tolerated dose (MTD) for NM21-1480 in adults with selected advanced solid tumors will be determined in Part A of the study. If conducted, the optional Part A-2, in addition to providing additional safety and PK data, will aim at further exploring different dose levels and/or dosing intervals in parallel to Part B to complement the PK, immunogenicity, and PD data to be provided by Part B to inform later clinical development of NM21-1480. Part B of the study aims at assessing the clinical activity of the 800mg dose of the compound as presumptive RP2D. Binding of NM21-1480 to PD-L1 in the TME is a pre-requisite for not only blocking the PD1/PD-L1 axis but also for additional activation of the co-stimulatory 4-1BB pathway by the compound. Thus, a minimal PD-L1 expression in the TME of Part B patients is needed from a mechanistic point of view to explore the therapeutic potential of NM21-1480 in patients that have the highest likelihood to benefit from treatment. A clinically meaningful benefit for patients with NSCLC and PD-L1 expression on ≥50% and ≥1%-49% of tumor cells is suggested based on the fact that clinical response of NSCLC patients to conventional checkpoint inhibitors correlates with PD-L1 expression, animal NSCLC models suggesting added benefit of NM21-1480 (see IB for details) and another bispecific anti-PD-L1x4-1BB antibody (GEN1046) has recently demonstrated clinically relevant response rates in NSCLC patients resistant to PD1/PD-L1 antibodies (Garralda, et al. 2020. SITC poster #412). A clinically meaningful benefit for patients with HPV+ SCC of different origin and documented PD-L1 expression in the TME is suggested by modest clinical activity of conventional checkpoint inhibitors in these tumors, increased PD-L1 expression in HPV+ tumors (Hong, et al. 2019) and most interestingly, a proposed unique therapeutic potential of activating the 4-1BB pathway in HPV+ tumors (Bartkowiak, et al. 2015). A clinically meaningful benefit for patients with recurrent or persistent ovarian, primary peritoneal or fallopian tumor carcinoma is suggested by recent clinical data demonstrating that the combination of PD1/PD-1 pathway inhibitors with additional immune-modulatory agents substantially increased ORRs over single-agent checkpoint inhibitors (Zamarin, et al. 2020). Most importantly, the combination of PD1/PD-L1 pathway inhibition with agonistic 4-1BB antibodies is highly effective in animal models of ovarian cancer (Wei, et al. 2013). In addition, 4-1BB expressing tumor-infiltrating lympohocytes (TILs) in primary and metastatic sites of ovarian cancer patients appear to be tumor-specific and 4-1BB-agonistic antibodies further enhances anti-PD1-mediated reinvigoration of exhausted CD8+ TILs at both sites (Leem, et al. 2020). Finally, administration of another bispecific anti-PD-L1x4-1BB antibody (GEN1046) resulted in a clinical response in a heavily pretreated ovarian cancer patient (Garralda, et al. 2020. SITC poster #412). Similar to ovarian cancer, clinically meaningful benefit for patients is also suggested for patients with metastatic or advanced local TNBC. Recent data demonstrate specific expansion and activation of TILs from human tumors by an agonistic 4-1BB antibody (Harao, et al. 2017) and superior efficacy of combination therapy including 4-1BB-agonistic antibodies over PD-1 inhibition alone in mouse TNBC models

(Dushyanthen, et al. 2017). Finally, early clinical data combining PD-L1 blockade and activation of the 4-1BB pathway from 2 independent programs resulted in clinical responses of patients with heavily pretreated TNBC (Garralda, et al. 2020. SITC poster #412; Melero, et al. 2020. ESMO abstract #1025MO). Monotherapy with anti-PD1 antibodies in patients expressing PD-L1 in at least 1% of tumor and/or immune cells has become the standard-of-care first-line treatment in patients with metastatic or unresectable, recurrent head and neck squamous cell carcinoma (Keytruda Prescribing Information 2021). However, while patients responding to anti-PD1 monotherapy benefit from a substantially longer duration of response compared to alternative therapy, the ORR observed with anti-PD1 monotherapy remains modest in this setting. The combination of anti-PD1 standard-of-care with an anti-PD-L1 antibody as well as with an agonistic 4-1BB antibody provide the perspective of addressing this shortcoming of current therapy. This approach is anticipated to allow for broader anti-tumoral activity, as proposed by recent scientific and clinical data suggesting differential (additive) effects of PD-L1 vs. PD1 blockade and additional benefit by activation of the 4-1BB pathway (Bar, et al. 2020; Srivastava, et al. 2017). Based on the clinical data from Part A of this clinical study it is suggested that NM21-1480 may provide substantial clinical benefit to MSS mCRC patients, a population that demonstrates notoriously poor response to conventional anti-PD1/PD-L1 checkpoint inhibitors (Ciardiello, et al. 2019). In fact, all 3 CRC patients enrolled to dose levels 4-7 (i.e., 24mg, 80mg and 800mg) in Part A of the current trial have demonstrated at least stabilization of disease with one patient even demonstrating unconfirmed partial response at study week 16, associated with reduction of liver metastases diameters in the range of 50% or more. Unfortunately, after being on treatment for 4 months at the 24mg dose, this patient developed treatment-emergent ADAs that were associated with loss of exposure to study drug and subsequent progression of disease at study week 24 (month 6). Interestingly, early clinical data with GEN1046 also showed stabilization of mCRC in the majority of patients treated in the respective Phase 1 dose escalation of that compound (Garralda, et al. 2020. SITC poster #412), suggesting that activation of the 4-1BB pathway may have a clinically relevant role in MSS mCRC. As such, this clinical trial will further explore the effect of a NM21-1480 treatment in MSS mCRC.

5.2.1 Rationale for the NM21-1480 Starting Dose

NM21-1480 targets immune-modulating receptors (i.e., PD-L1 and 4-1BB, respectively) that have already been targeted in patients with various approved and clinical stage monoclonal antibodies. Also, the mechanism of action of NM21-1480, whereby T-cells are activated via 4-1BB agonism in a tumor-restricted manner, has precedence for testing in clinical stage multi-specific antibodies.

Nevertheless, with a novel molecule for clinical investigation, we have used state-of-the-art methods for determining a suitable starting dose for NM21-1480. The starting dose is based upon a modelling approach taking into consideration the available pre-clinical data describing the PK and PD properties of the molecule. Through the understanding of the pharmacology of the molecule in cell-based assays using primary human T-cells and tumor-derived cell lines expressing varying levels of PD-L1, we can derive a concentration to which a minimal

pharmacological effect level can be seen for NM21-1480. By combining these data with an understanding of the PK of the molecule in the blood of mice and cynomolgus monkeys, as well as the bio-distribution of the molecule in mice bearing PD-L1-positive human tumors, we have made conservative predictions to a first-in-human (FIH) dose. Numab is of the opinion that this dose provides a highly reasonable compromise between remaining (theoretical) safety concerns on the molecule's systemic 4-1BB activation capacity and yet still retaining a dosing level from which there is a potential to provide clinical benefit to enrolled patients.

5.3 Benefit – Risk Assessment

5.3.1 Benefit Assessment

In various *in vitro* and *in-vivo* experiments, Numab has demonstrated that in contrast to bivalently binding urelumab, ND021 (NM21-1480) only triggers 4-1BB activation on T-cells in the presence of PD-L1 expressing tumor cells. In addition, ND021 (NM21-1480) when assessed for its T-cell activation potential in cellular assays, was demonstrated to be more potent (as measured by interleukin (IL)-2 and IFNγ release) in the tumor cell proximity in comparison to any combination of PD-1/PD-L1 and 4-1BB monoclonal antibodies evaluated in clinical trials.

Efficacy and tolerability of ND021 (NM21-1480) was studied in *in-vivo* mouse tumor models. These studies demonstrated superior efficacy over CPI standard-of-care and even over the combination of anti-PD-L1 (avelumab) and anti 4-1BB (urelumab) in suitable PD-L1 inhibitor-sensitive mouse models. Animal studies also confirmed the superior safety profile of ND021 (NM21-1480) versus avelumab and urelumab in (multiple-dose) mouse and (single- and repeat-dose) non-human primate studies (for details see IB).

The PK profile of ND021 (NM21-1480) assessed in a single-dose non-GLP PK/tolerability study conducted in cynomolgus monkeys, resulted in a half-life of approximately 5 days, which when applying standard allometric scaling predicts a half-life of ND021 (NM21-1480) of approximately 2 weeks in man. Thus, ND021 (NM21-1480) is expected to allow for a clinically convenient 2-week dosing interval in the clinical setting. As per July 2022, Part A of the ongoing FiH study has formally been completed by means of an SMC meeting that determined that Part A did not technically identify a MTD and the highest dose assessed (800mg) was considered a tolerable dose. Clear evidence of pharmacodynamic activity correlating with early signs of clinical activity has been observed in this part of the study. In the dose range considered relevant based on exposure, peripheral receptor occupancy and pharmacodynamic data (24mg-800mg range), a disease control rate of 62% was observed. Within those patients in whom disease control has been observed, 62% had previously been treated with and were progressive on such checkpoint inhibitor therapy. In one patient suffering from MSS metastatic colorectal cancer, a type of cancer notoriously unresponsive to standard checkpoint inhibitor therapy, an unconfirmed partial response associated with pronounced reduction of liver metastases diameters was observed. These promising early clinical data in a heavily pre-treated patient population suggest NM21-1480 to provide therapeutic benefit

aligned with the initial development hypothesis of the compound that warrants further clinical investigation. For details, reference is made to the IB, Version 3.0 dated 15 June 2022.

5.3.2 Risk Assessment

The tolerability profile and PK of NM21-1480 have been studied in a single-dose, non-GLP PK/tolerability study and a formal repeat-dose toxicology study conducted in cynomolgus monkeys. The single-dose study confirmed that NM21-1480 administered at single doses of 0.2, 2, and 20 mg/kg was well tolerated. Further, no signs of hepatotoxicity were observed even at the highest applied dose (20 mg/kg) as demonstrated by the lack of any clinically relevant increase of ALT, AST, and GGT. Similarly, there was no impact on neutrophil or thrombocyte counts, another frequent adverse effect observed with the 4-1BB agonist urelumab. As such, none of the most prominent adverse drug reactions clinically observed under urelumab treatment were seen in this monkey study with NM21-1480 even at the highest dose applied. Similar data was generated from the formal repeat-dose toxicology study in which NM21-1480 was well tolerated at doses of 20, 60 and 140 mg/kg given over a weekly dosing schedule for 5 doses. NM21-1480 may impact Cytochrome P (CYP) enzyme production and activity via cytokine modulation. For this reason, there may be a risk of drug interactions and concomitant medications that are narrow therapeutic index substrates for CYP enzymes should be used with caution and appropriate monitoring. As per July 2022, Part A (the dose escalation part) of the NM21-1480 FiH study has been completed with at least 28-day safety data available for all of the 26 patients exposed in this part of the study by 23 May 2022. Patients received between 1 and 19 infusions of NM21-1480 at one of the 7 dose levels to be assessed in Part A of the protocol (0.15 mg, 1.5 mg, 8 mg, 24 mg, 80 mg, 240mg, 800mg). Only two Grade 3 TRAEs (one event of hyponatremia/adrenal insufficiency and one event of transaminase elevation, according to CTCAE V5.0) were observed and no TRAE was assessed as higher than Grade 3 by investigators. Most importantly, only a single TRAE of Grade 3 transaminase elevation was reported during this study which compares very well to other compounds with a similar mechanism of action (Garralda, et al. 2020. SITC poster #412). The most frequently observed TRAEs, were Grade 2 infusion-related reactions which in some instances have led to discontinuation of patients as despite pre-medication and reduction of infusion rate, it was not possible to fully prevent re-occurrence of the IRR. Development of these IRRs was typically observed in patients who developed treatment-emergent ADAs and was typically associated with loss of exposure to study drug over time in affected patientsFor details, reference is made to the IB, Version 3.0 dated 15 June 2022.

5.3.3 Overall Benefit Risk Assessment

ND021 (NM21-1480) was designed to overcome the clinical limitations of standard CPIs targeting the PD-L1/PD-1 axis. Indeed, based on currently available data, Numab perceives ND021 (NM21-1480) to have the potential to become the preferred (i.e., first-line) treatment option for various tumors for which PD-1/PD-L1 CPIs (i.e., nivolumab, pembrolizumab, avelumab, and durvalumab, etc.) are approved due to its concomitant immune cell activation provided by the molecule's 4-1BB pathway activation in the TME. ND021 (NM21-1480)

requires (possibly minimal) expression of PD-L1 on target tumor cells in order to ignite its anti-tumoral effects and its therapeutic effects may possibly increase over time due generation of a "positive feedback loop" in the TME, induced by activation of the 4-1BB pathway in immune cells, leading, e.g., to IFNγ release resulting in additional subsequent IFNγ-induced PD-L1 expression on tumor cells. Based on the available pre-clinical data, it is suggested that ND021 (NM21-1480) may thus demonstrate a substantially higher overall response rate and prolonged overall mean survival time as compared to standard-of-care treatment in various tumor types in the clinic. As such, the basic clinical target product profile for ND021 (NM21-1480) aims at clinical demonstration of superior efficacy combined with a non-inferior safety profile (and thus an improved overall benefit-to-risk profile) as compared with single anti-PD-L1 or PD-1 CPIs in suitable patient populations. For this reason, in principle, all tumor types for which PD-L1/PD-1-inhibitors are approved and/or for which clinical efficacy has been demonstrated, represent target indications for ND021 (NM21-1480). In addition, based on its mechanism of action, ND021 (NM21-1480) may be able to demonstrate substantial incremental clinical benefit in tumor types in which conventional CPIs demonstrate comparably poor efficacy (i.e., PD-L1 "negative" tumors). With Part A of the FiH study for NM21-1480 completed, the overall benefit-to-risk assessment remains positive at this point of time when considering the totality of available clinical safety, activity, pharmacokinetic and pharmacodynamic data and further clinical assessment of NM21-1480 in selected cancer population as remains warranted. Full maintenance of exposure combined with fully maintained pharmacodynamic and clinical activity was observed at the 800mg dose level which has also been determined to represent a tolerable dose by the study SMC. However, careful continued evaluation of the impact of treatment-emergent ADAs on patient's long-term exposure to NM21-1480 during further development is warranted. For details, reference is made to the IB, Version 3.0 dated 15 June 2022.

6 STUDY OBJECTIVES AND ENDPOINTS

	Objectives	Endpoints
Part A		
Primary	• To assess the safety and tolerability of NM21-1480 • To determine the MTD of NM21-1480 • To determine up to four (4) safe dose levels for further evaluation of PD and clinical activity in the optional Part A-2 and Part B of the study	• Incidence and nature of dose-limiting toxicities (DLTs) • Incidence and severity of treatment-emergent adverse events (TEAEs) with specific focus on incidence and severity of immune-related adverse events (irAEs)
Secondary	• To characterize the PK profile of NM21-1480 • To evaluate the immunogenicity of NM21-1480	• PK parameters o AUCtau o AUC (0-infinity) (first dose only) o Cmax o Cmin o t½ o Tmax o λz o CL o Vd • Frequency of specific anti-drug antibodies to NM21-1480
Exploratory	• To determine the anti-tumor activity of NM21-1480 according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • To determine safe dose levels associated with meaningful PD response to inform dose selection for optional Part A-2 and Part B. This is in support of nominating up to four (4) safe dose levels to be further studied in Part B of the study	• Best overall response (BOR) • Objective response rate (ORR) • Time-to-response (TTR) • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Characterization of exposure-dependent PD markers of target and pathway engagement. Potential PD markers are summarized in detail in the below list of exploratory markers applicable to all Parts A, A-2 and B
Part A-2 (OPTIONAL)		
Primary	• To assess the safety and tolerability of NM21-1480 at a dose level beyond what has been assessed in Part A (i.e. at 1400mg) • To further explore PK/PD relationships in order to complement respective Part B data when conducted in parallel to Part B	• Incidence and severity of treatment-emergent adverse events (TEAEs) with specific focus on incidence and severity of immune-related adverse events (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	• To characterize the PK profile of NM21-1480	• PK parameters: o AUCtau

	Objectives	Endpoints
	• To evaluate the immunogenicity of NM21-1480	○ AUC (0-infinity) (first dose only) ○ Cmax ○ Cmin ○ t½ ○ Tmax ○ Λz ○ CL ○ Vd • Frequency of specific anti-drug antibodies to NM21-1480
Exploratory	• To determine the anti-tumor activity of NM21-1480 according to RECIST 1.1	• BOR • ORR • TTR • DOR • PFS • OS
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 • To determine the RP2D • To determine the safety (including the MTD) 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)	• 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	• To further evaluate the preliminary anti-tumor activity of NM21-1480	• Disease Control Rate (DCR) • DOR • TTR • PFS • OS • BOR, DCR, ORR, DOR, PFS as per iRECIST
	• To characterize the PK profile of NM21-1480	• PK parameters ○ AUCtau ○ AUC (0-infinity) (first dose only) ○ Cmax ○ Cmin ○ t½ ○ Tmax ○ λz

	Objectives	Endpoints
		○ CL ○ Vd
	• To evaluate the immunogenicity of NM21-1480	• Frequency of specific anti-drug antibodies to NM21-1480
Part A, Part A-2 (OPTIONAL), and Part B		
Exploratory	• To characterize the pharmacodynamic (PD) profile of NM21-1480	Change from baseline in the following biomarkers/PD parameters: • Change from baseline in levels of cytokines/chemokines including interleukin (IL)-1b, IL-6, tumor necrosis factor (TNF)α interferon gamma (IFN_{γ}), IL2, IL8, CXCL9, CXCL10, CXCL11, IL18, and other selected markers; soluble PD-L1 (Programmed death-ligand 1); soluble 4-1BB • Phenotypic characterization of peripheral blood cells (cellular populations include resting and activated B-cells, T-cell subpopulations [T-helper cells {Th}, cytotoxic T lymphocytes {CTLs}, regulatory T-cells {Treg}], NK cells, and NKT cells), and cellular receptor occupancy (PD-L1; 4-1BB)[a] • In Cohort B8: Carcinoembryonic Antigen (CEA); circulating tumor DNA (ctDNA)
	• To evaluate biomarkers potentially capable of predicting a clinical response to NM21-1480	• Change in RNA expression from baseline and after-treatment in tumor tissues • Change in PD-L1 expression and presence of PD1/CD8/4-1BB triple positive T-cells in baseline and after-treatment tumor tissues • Change in level of inflammatory infiltrate (e.g., CD3 and CD8 density; CD8/Treg ratio; CD8/CD4 ratio) in baseline and after-treatment tumor tissue • Assessment of tumor mutational burden (TMB) and microsatellite instability – high/deficient mismatch repair (MSI-H/dMMR) status in baseline tumor tissues • Correlation of PD-L1 expression status in the TME with PD and clinical activity • Assessment of T-cell Receptor clonality in tumor tissue • In Cohort B8: MHC-I expression on tumor cells; specific mutational analysis including e.g., BRAF, KRAS, NRAS, POLE, PIK3CA, PTEN, APC, p53

	Objectives	Endpoints

[a] Pending availability of validated assay

Abbreviations: APC = Adenomatous Polyposis Coli; AUC = Area under the serum concentration-time curve; AUC(0-infinity) = Area under the serum concentration-time curve extrapolated from the last quantifiable concentration to infinity; AUCtau = Area under the serum concentration-time curve over dosing interval; B-cells = B lymphocytes; BRAF = B-raf proto-oncogene; CD3 = Cluster of differentiation 3; CD4 = Cluster of differentiation 4; CD8 = Cluster of differentiation 8; CEA = Carcinoembryonic Antigen; CL = Clearance; Cmax = The maximum observed serum concentration determined by direct inspection of the concentration versus time data; Cmin = The minimum observed serum concentration determined by direct inspection of the concentration versus time data; CTL = Cytotoxic T lymphocytes; CXCL = Chemokine (C-X-C motif) ligand; KRAS = Kirsten rat sarcoma oncogene; λz = Terminal phase (apparent elimination) rate constant; NK cells = Natural killer cells; NKT = Natural killer T-cells; NRAS = Neuroblastoma ras viral oncogene homolog; PD-1 = Programmed cell death protein-1; PD-L1 = Programmed death-ligand 1; PIK3CA = Phosphatidylinositol 3-kinase CA; POLE = Polymerase Epsilon Catalytic Subunit; PTEN = Phosphatase and Tensin Homolog; RNA = Ribonucleic acid; t½ = Elimination half-life; Tmax = Time to maximum concentration; Vd = Volume of distribution

7 OVERALL STUDY DESIGN AND PLAN

7.1 Study Design Description

This is a 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 RP2D, define the PK, to explore the PD, and to obtain preliminary evidence of the clinical activity in adult patients with selected advanced solid tumors.

This is an open-label study and includes an ascending-dose cohort component (Part A) to be optionally followed by an additional cohort (optional Cohort A-2) to further explore different dose levels and/or dosing intervals *in parallel* to Part B to complement the PK, immunogenicity, and PD data to be provided by Part B. Part B may be initiated without the conduct of the optional Part A-2 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 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, 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 will be below or at the MTD determined upon decision by the SMC once all patients enrolled to Part A have completed their 28-day DLT evaluation period. Part A was formally completed on 23 May 2022 by a meeting of the SMC which determined that this part of the study did not technically identify a MTD as the highest dose assessed (800mg) was considered a tolerable dose. In Part B of the study, NM21-1480 will be thus be administered as a single IV infusion approximately every 14 days at the 800mg flat dose, based on Part A PK data which do not indicate substantial drug accumulation over time with this dosing interval while full pharmacodynamic activity of NM21-1480 is maintained.The 800mg dose of NM21-1480 thus represents the presumptive RP2D to be further studied in Part B with the aim to confirm this dose as the RP2D for the compound. Optional Part A-2 of the study will explore one more higher dose level (1400mg flat dose with approximately 14-day dosing interval) than was studied in Part A. Such 1400mg dose level will be explored in order to further study the PK/PD relationship over a broad range of doses, applying strict stopping criteria and respecting a 28-day DLT evaluation period before more than 6 subjects are exposed. PK data for this 1400mg dose level in Part A-2 will be closely followed and in case of observation of relevant drug accumulation over time, the dosing interval for this dose may be adjusted to approximately 21 days. The optional Part A-2 of the study is conducted in parallel to Part B, and its resulting exposure/PK/PD data will be used to complement Part B data to guide later stage clinical development. Any dose level to be assessed in Part B as by the SMC recommendation must not exceed the MTD determined in Part A (or Part A-2 if applicable). In optional Part A-2 and Part B, a treatment cycle, dependent on the dosing interval selected by the SMC for a given dose level (i.e., 2-week dosing interval for the 800mg dose and 2-weekor 3-week dosing interval for the 1400mg dose in Part A-2), is thus defined as 28 days (4 weeks) or 42 days (6 weeks), respectively. Response assessments in the optional Part A-2 and 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. Sections 7.1.6 and 7.1.7 provide separate tables summarizing schedule of assessments and blood sampling schedules, respectively, for 14-day and 21-day dosing intervals which may apply for given dose levels in the optional Part A-2 and Part B.

Part A

Part A followed a Bayesian optimal interval (BOIN) design. This part of the study consisted of 7 planned escalating flat dose levels; 0.15 mg (dose level 1), 1.5 mg (dose level 2), 8 mg (dose level 3), 24 mg (dose level 4), 80 mg (dose level 5), 240 mg (dose level 6), and 800 mg (dose level 7). Enrollment of patients into dose level 1 took place first and subsequent dose levels were only to be opened if the previous dose level was deemed tolerable. The first dose level enrolled a minimum of one patient at 0.15 mg (corresponding to approximately 0.002 mg/kg). Following the detailed rules described in Section 10.3.1 of this protocol, as soon as a Grade 2 or higher treatment-related adverse event (TRAE) is observed during the 28-day DLT evaluation period or when dose level 5 (80 mg dose corresponding to approximately 1 mg/kg) is reached, a minimum of 3 patients were to be enrolled at the current dose level as well as at potential additional dose levels in accordance with the BOIN design dosing rules.

In the event a DLT was observed in the first patient treated at dose level 1 (0.15 mg), the study was to be halted and the SMC must be consulted. Upon thorough evaluation of all available data, the SMC was to determine to terminate the study or recommend that 2 more patients were to be enrolled at this dose level. In the latter case, if after completion of the DLT evaluation period of this total of 3 patients enrolled at the starting dose level, the BOIN design would demand de-escalation of the dose level from the starting dose, the study was to be terminated.

Part A of the study was formally completed on 23 May 2022 by a Meeting of the SMC at which the SMC determined that Part A of the study did not technically identify a MTD as the highest dose assessed (800mg flat dose) was considered a tolerable dose. Dose-escalation was based on the number of DLTs experienced during the DLT evaluation interval as determined by the Investigators, Medical Monitor, and Sponsor. The DLT evaluation interval begins on the first day of treatment and continues for 28 days. Patients who received at least one dose of investigational product in Cycle 1 (i.e., one of the 2 doses intended to be administered in Cycle 1), and either meet the minimum exposure criterion and have sufficient safety evaluations, or discontinued due to DLT, were considered evaluable for DLT determination. Dose-escalation continued until the stopping rules of the BOIN design were reached. The MTD was defined as the highest dose associated with DLTs in ≤30% of patients receiving NM21-1480 administered during the DLT period. This was the highest dose to be potentially recommended for further evaluation in the subsequent part(s) of the study. At the end of Part A, a formal SMC meeting on 23 May 2022 concluded that none of the 7 dose levels, including the highest dose (800mg flat) dose assessed in Part A was to be considered intolerable and thus Part A did not technically identify a MTD. Due to the specific pharmacological mechanism of action of NM21-1480, the SMC, supported by the Sponsor, besides determining the MTD, was also to consider selection of additional (lower) dose levels to be further studied in Part A-2 (optional) and/or Part B, based on review of Part A safety, PK, and PD (as far as available) data. This was based on the

assumption that indeed, it may only be possible to determine an optimal RP2D in Part B of the study, as binding of NM21-1480 to PD-L1 is a pre-requisite for activation of the 4-1BB pathway by the compound. This is likely only possible in a tumor patient population with well-documented PD-L1 expression in the TME and since PD-L1 positivity was not an inclusion criterion for Part A, the likelihood of PD activity of the drug in Part A is reduced compared to Part B. In addition, in a situation with substantial excess of NM21-1480 over PD-L1 and 4-1BB on target cells in the tumor tissue, a decline in 4-1BB activity (due to a bell-shaped dose response curve for the 4-1BB agonistic activity of the compound) cannot be formally excluded to occur within the dose range explored in Part A of the study. Such bell-shaped dose response curve may occur because in such situation of substantial excess of NM21-1480, molecules over available PD-L1 and 4-1BB binding sites, an immediate saturation of PD-L1 and 4-1BB binding sites by different NM21-1480 molecules may occur. As such, concomitant binding of a single NM21-1480 molecule to both antigens may no longer be possible and consequently the immunological synapse between tumor cells and immune cells that is required to trigger 4-1BB signaling could no longer be established. This important aspect of dose finding was considered based on thorough review of the entirety of non-clinical and clinical data available at the end of the 28-day DLT evaluation period of the last patient enrolled to Part A. At this point (at the end of Part A SMC meeting on 23 May 2022), the SMC, together with the Sponsor, considered the nomination of up to 4 different dose levels of NM21-1480 and determine the optimal dosing interval (i.e., dosing approximately every 14 or 21 days) for administration of a given NM21-1480 dose for the optional Part A-2 and Part B with the goal to determine a final RP2D and dosing interval with an optimized activity and safety profile for future development within Part B. Part A study data discussed with SMC on 23 May 2022 demonstrated the development of treatment-emergent anti-drug-antibodies (ADAs) in a relevant fraction of patients dosed at 24mg-240mg. These ADAs were typically associated with rapid elimination of NM21-1480 from the circulation and loss of exposure. However, PK, PD, receptor occupancy and clinical activity data available for the 800mg dose level indicated that at this dose, the issue of loss of exposure was no longer present while full pharmacodynamic activity was maintained, a phenomenon described for other checkpoint inhibitors (i.e. atezolizumab) at higher doses as well. As such, the SMC agreed with the Sponsor to consider the 800mg dose to represent the presumptive RP2D and further study this dose, applying a biweekly dosing interval in Part B of the study. The SMC, together with the Sponsor, also considered at this point (i.e., at the end of the 28-day DLT evaluation period of the last patient enrolled to Part A) to enroll additional patients into an optional additional Cohort A-2 in parallel to Part B to complement the PK, immunogenicity and PD data to be provided by Part B. The Sponsor, following formal completion of Part A on 23 May 2022 is therefore exploring within this optional Cohort A-2 and under continuous review of emerging safety data by the SMC the safety, PK/PD and clinical activity profile of one higher dose level of NM21-1480 (1400mg flat dose) in up to 10 patients to complement Part B data and thus further inform development of NM21-1480 beyond initial Part B. As this dose level to be studied in Cohort A-2 is above the maximal dose level characterized in Part A, exploration of the 1400mg dose will be

conducted under the continuous safety data review and guidance by the SMC, applying similar rules as in Part A.

A DLT is defined as a treatment-emergent adverse event (TEAE) occurring during the first 28 days of dosing that meets the DLT criteria specified in Section 7.2.5.1 of the protocol.

In summary, Part A was considered completed on 23 May 2022, when the maximal number of patients to be treated per overall as per BOIN design rules was reached, and the SMC, upon documented review of all clinical safety, PK, and clinical activity data up to and including the 4-week visit from all patients dosed in Part A determined that even the highest dose assessed in Part A (800mg flat) was considered a tolerable dose. For nomination of dose levels to be further evaluated in Part B (or optionally in Cohort A-2), the SMC, together with the Sponsor, considered all available non-clinical and clinical data and information (i.e., including all available clinical data beyond 28 days of treatment with NM21-1480) at the time the final patient enrolled into Part A according to BOIN design had 28-day data available. The 800mg flat dose was nominated as the dose level to be studied as presumptive RP2D in Part B and a dose of 1400mg was nominated for further exploration within optional Part A-2).

Part A-2 (OPTIONAL)

Part A-2 is an optional part of the study. It might be initiated after determination of the MTD based on Part A data. On 23 May 2022, the SMC determined that Part A did not technically identify a MTD and the highest dose level assessed (800mg) was considered a tolerated dose. The rationale behind the potential conduction of Part A-2 was to cover situations in which the SMC, together with the Sponsor, upon comprehensive review of all available data at the time of MTD determination (i.e. at the formal end of Part A on 23 May 2022), came to the conclusion that either additional exposure-dependent PD data at dose levels at or below the MTD were needed to allow for selection of the up to 4 dose levels to be further studied in Part B, or it may be desirable to explore different dose levels and/or dosing intervals in parallel to Part B to complement the PK, immunogenicity, and PD data to be provided by Part B to inform development of NM21-1480 beyond Part B. Based on the finding that some patients dosed at 24-240mg in Part A developed treatment-emergent ADAs leading to loss of exposure, while this was not observed at the 800mg dose level, a decision was taken to explore one additional higher dose level (1400mg flat dose) in up to 10 patients within Part A-2 in parallel to studying the 800mg dose level in Part B. The primary intention of exploring this 1400mg dose level in Part A-2 is to further characterize the overall PK/PD relationship of NM21-1480 over a broad range of doses. Further dose levels or dosing intervals may in the future be studied within Part A-2 as well if emerging data from the ongoing study provide a rationale to do so. Patients to be enrolled into this optional cohort will need to fulfill Part A eligibility criteria but in addition will need to have documented minimal PD-L1 expression on at least 1% of tumor and/or immune cells in the TME, as detected by local testing with a Food and Drug Administration (FDA)-cleared or any PD-L1 assay approved for use by local competent authority. As the 1400mg flat dose level to be explored in Part A-2 is above the maximal dose level characterized in Part A, exploration of the 1400mg dose level will be conducted under the continuous safety data review and guidance by the SMC. In this setting in which Part A-2 will be conducted in

parallel to Part B, its resulting data will be used to complement Part B data in regards of getting to a comprehensive understanding on the PK/PD relationship of different dosing regimens for NM21-1480 before engaging into subsequent clinical development steps beyond Part B.

Part B

To further characterize the safety and clinical activity of NM21-1480, Part B will employ a Bayesian Optimal Phase II (BOP2) design (Cohorts B1-B4 and B6-B8) or a randomized, open-label, active-control Bayesian design (Cohort B5) to enroll patients in up to 8 expansion cohorts (Cohorts B1 through B8) with selected advanced solid tumors. Enrollment in Part B will begin when the SMC has completed its review of the Part A data and has recommended dose levels to be initially studied in Part B. Part A of the study was formally completed on 23 May 2022 and the SMC determined that the 800mg flat dose level was a tolerable dose to be further studied as the presumptive RP2D in Part B of the study.

Cohort B1: This Cohort will be conducted in the **US, Spain, United Kingdom (UK)**, **the Netherlands**, **Germany,** and **Taiwan**. Cohort B1 will include NSCLC patients with documented previous (i.e., prior to initiation of first-line therapy) PD-L1 expression on ≥50% of tumor cells who have progressed after first-line treatment with either anti-PD-(L)1 monotherapy, anti-PD-(L)1/chemotherapy or chemotherapy regimen or who have progressed after-treatment with up to 3 previous lines of therapy including at least one line of anti-PD-(L)1 checkpoint inhibitor therapy and one or more lines of a chemotherapy regimen. It should be noted that, **specifically for patients to be enrolled to Cohort B1 in Germany,** they must have previously received, anti-PD-(L)1 therapy and a platinum-based chemotherapy (i.e., at least 2 prior lines of treatment) in order to be eligible for enrollment into this cohort.

Cohort B2: This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, **Germany,** and **Taiwan**. Cohort B2 will include patients with HPV+ SCC of the anus, cervix, vulva, vagina, penis, or oropharynx, who have progressed on a first-line standard-of-care anti-PD-1 monotherapy, anti-PD-1/chemotherapy or chemotherapy regimen. Inclusion of patients who have progressed after receiving 2 previous lines of therapy, e.g., one line of anti-PD-1 checkpoint inhibitor therapy and one line of chemotherapy regimen is also acceptable; patients must have documented PD-L1 expression in the TME with PD-L1 expressed on at least 1% of tumor and/or immune cells, as detected by local testing with an FDA-cleared or any PD-L1 assay approved for use by local competent authority.

Cohort B3: This Cohort will be conducted in **Turkey, Georgia, Ukraine,** and **Taiwan**. Cohort B3 will include patients with NSCLC with PD-L1 expression on ≥50% of tumor cells who have progressed on first-line local standard-of-care chemotherapy.

Cohort B4: This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, **Germany, Taiwan, Turkey. Georgia,** and **Ukraine**. Cohort B4 will include patients with recurrent or persistent ovarian, primary peritoneal, or fallopian tumor carcinoma of all histologic types except mucinous adenocarcinoma and carcinosarcoma with a history of primary platinum-based chemotherapy with a maximum of 3 prior cytotoxic regimens with at least one regimen for recurrent disease containing a platinum or a taxane for those with 3 prior regimens: last platinum-free interval must be maximally 12 months.

Cohort B5: This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, and **Taiwan**. Cohort B5 will include patients to be treated in-label with an approved PD-1 checkpoint inhibitor (pembrolizumab) as a single agent for the first-line treatment of metastatic or unresectable, recurrent head and neck squamous cell cancer whose tumors express PD-L1 (CPS≥1) as standard-of-care treatment with doses not to exceed those approved in local product labels. Patients fulfilling this criterion will be randomized 2:1 to either such standard-of-care PD-1 checkpoint inhibitor plus NM21-1480 or the standard-of-care PD-1 checkpoint inhibitor therapy only.

Cohort B6: This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, and **Taiwan**. Cohort B6 will include patients with metastatic or unresectable, locally advanced TNBC that is measurable according to RECIST1.1 criteria. Tumors need to be ER, PR and HER2 negative as per current ASCO/CAP Guidelines and patients need to have progressed on at least one but no more than 3 previous lines of cytotoxic chemotherapy. Two subgroups of 20 patients each will be enrolled and analysed, based on having received a prior line of checkpoint inhibitor therapy or not.

Cohort B7: This Cohort will be conducted in the **US, Spain, UK**, **the Netherlands**, **Germany,** and **Taiwan**. Cohort B7 will include NSCLC patients with documented previous (i.e., prior to initiation of previous-line therapies) PD-L1 expression on ≥1% - 49% of tumor cells who have progressed after first-line treatment with either anti-PD-(L)1 monotherapy, anti-PD-(L)1/chemotherapy or chemotherapy regimen or who have progressed after-treatment with up to 3 previous lines of therapy, at least one including an anti-PD-(L)1 checkpoint inhibitor. It should be noted that, **specifically for patients to be enrolled to Cohort B7 in Germany,** they must have previously received, as per established treatment guidelines of the AWMF, anti-PD-(L)1 therapy and a platinum-based chemotherapy (i.e., at least 2 prior lines of treatment) in order to be eligible for enrollment into this cohort.

Cohort B8: This Cohort will be conducted in the **US, Spain, UK, the Netherlands, and Germany**. Cohort B8 will include patients with metastatic colorectal cancer (mCRC) that are MSS or MSI low and who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and if RAS

wild-type, an anti-EGFR therapy, if eligible Patients previously treated with an anti-VEGF biological therapy are also eligible. Patients must have documented PD-L1 expression in the TME with PD-L1 expressed on at least 1% of tumor and/or immune cells, as detected by local testing with an FDA-cleared or an PD-L1 assay approved for use by local competent authority.

Stratification factors will be applied for Part B enrollment (see Section 10.4.4 for details).

Intra-patient dose-escalation is generally not allowed; upon discussion between Investigators, Medical Monitor and Sponsor, exceptions to this rule may be granted for Part B Cohort patients.

In Part A, NM21-1480 (dose levels 1 through 7 in the escalation phase) will be administered as a single IV infusion every 14 days for a total of 2 infusions per treatment cycle (4 weeks). Each treatment cycle comprises 2 doses of study drug administered on Days 1 and 15. Treatment for the second cycle is administered on Days 29 and 43, with a response assessment between Days 52 and 56 after the first dose of every other treatment cycle in Part A (i.e., every 8 weeks at the "8-Week Assessment", see Table 7-1 for details). In Part A, response assessment between Days 52 and 56 and between Days 108 and 112, respectively, is conducted for all patients still in the study, independent of the number of study drug administrations received during the previous 8-week/2-treatment cycles. Following each treatment cycle, the decision to treat a patient with additional cycles of NM21-1480 will be based on tolerability of the study drug and tumor response evaluation performed every 8 weeks i.e., in the week prior to administration of NM21-1480 in all odd number treatment cycles (e.g., Cycles 3, 5, 7, etc.). For optional Part A-2 and Part B, depending on SMC decision on dose levels and dosing intervals to be chosen for this expansion cohort phase, treatment cycles and dosing intervals may remain the same as described above for Part A (i.e., dosing intervals of approximately 14 days). In Part B of the study, NM21-1480 will thus be administered as a single IV infusion approximately every 14 days at the 800mg flat dose, based on Part A PK data which do not indicate substantial accumulation over time with this dosing interval; the 800mg dose of NM21-1480 thus represents presumptive RP2D to be further studied in Part B Optional Part A-2 of the study will explore one more higher dose level (1400mg flat dose with approximately 14-day dosing interval) than was studied in Part A. Such 1400mg dose level will be explored applying strict stopping criteria and respecting a 28-day DLT evaluation period before more than 6 subjects are exposed. PK data for this 1400mg dose level in Part A-2 will be closely followed and in case of observation of relevant drug accumulation over time, the dosing interval for this dose may be adjusted to approximately every 21 days, resulting in treatment cycles of 6 weeks in such case. In optional Part A-2 and Part B of the study, response assessment is done every 6 weeks for the first 24 weeks patients are on active treatment, before switching to a response assessment every 8 weeks thereafter. Following each response assessment in optional Part A-2 and Part B, the decision to treat a patient with additional dose administrations of NM21-1480 will be based on tolerability of the study drug, perceived clinical benefit and tumor response evaluation performed every 6 weeks (first 24 weeks) or 8

weeks (beyond 24 weeks) as per discontinuation criteria described in Section 7.2.9. Unless the patient develops a treatment-related adverse event (TRAE) qualifying for permanent discontinuation and precluding further treatment, patients will be treated until progressive disease is confirmed by the Investigator (for details on study drug discontinuation see Section 7.2.9). Sections 7.1.6 and 7.1.7 provide separate tables summarizing schedule of assessments and blood sampling schedules, respectively, for 14-day and 21-day dosing intervals which may apply for given dose levels in optional Part A-2 and Part B. Prior to enrollment of the first patient to optional Part A-2 and/or Part B, sites will receive a written notification of the SMC decision on the selection of dose levels and dosing intervals for Part B by means of a letter of amendment, to be followed by a full protocol amendment.

All patients will be followed for survival until death after discontinuation of the Treatment and/or completion of Follow-up periods (Section 7.2.12).

Part A of the study is planned to be conducted at up to 8 sites in the **United States (US)** and **Taiwan**; optional Part A-2 may be conducted at Part A sites and additional selected Part B sites in the US, Spain, the UK, Germany, and/or the Netherlands. Part B will be conducted as up to 8 separate cohorts B1-B8. Cohort B1, B2 and B7 will be conducted in the **US, Spain, UK, the Netherlands, Germany,** and **Taiwan**. Cohort B3 will be conducted in **Turkey, Georgia, Ukraine,** and **Taiwan**. Cohort B4 will be conducted in the **US, Spain, UK, the Netherlands, Germany, Taiwan, Turkey, Georgia,** and **Ukraine**. Cohorts B5 and B6 will be conducted in the **US, Spain, UK, the Netherlands,** and **Taiwan.** Cohort B8 will be conducted in the **US, Spain, UK, the Netherlands** and **Germany.**

A SMC (consisting of study Investigators and an independent clinical expert as Chairperson, with Medical Monitor and Sponsor attending SMC meetings as observers) has been established to review cumulative and emerging safety data during study conduct (Part A and B). The Safety Monitoring Committee's major responsibilities comprise evaluation of DLTs, dose-escalation decisions and continuous safety monitoring in Part A. Safety monitoring committee meetings will also be held according to the SMC charter to evaluate the safety data emerging in (optional) Part A-2 and Part B (expansion cohorts). Finally, the SMC has an additional major responsibility for DLT evaluation and dose escalation decision in the evaluation of NM21-1480 safety data in the combinatorial treatment approach with a PD1 checkpoint inhibitor in Cohort B5. The SMC, based on Part A data, has also supported the Sponsor in the determination of dose levels and dosing intervals to be evaluated in Part B. Part A of the study was formally completed on 23 May 2022 as a per a regular SMC meeting.

7.1.1 Estimated Number of Enrolled Patients

7.1.1.1 Part A (Dose-Escalation)

The number of patients is guided by the BOIN design. The design recommends recruitment in Part A until a maximum sample size of 25 is reached. Stop Part A if the number of patients treated at the current dose reaches 12.

7.1.1.2 Part A-2 (Optional)

The optional Cohort A-2 will enroll up to 40 patients.

7.1.1.3 Part B (Dose Expansion)

For Cohorts B1-B4 and B6-B8, up to 40 patients per Part B cohort will be enrolled. A BOP2 design will be applied. Up to 40 patients per cohort will be enrolled initially. An interim analysis for futility will be conducted after enrollment and treatment of 25 patients per cohort according to the BOP2 design in order to stop cohorts for futility and limit exposure of additional patients in that cohort in case of lack sufficient clinical activity is observed. This futility analysis will be conducted based on availability of response data following completion of 2 assessment cycles (i.e., 12 weeks) for the 25 patients (See Section 10.2). For Cohort B8, the Sponsor will hold enrollment to the cohort after 25 patients have received at least one dose of NM21-1480 treatment until all relevant safety, efficacy, PK, immunogenicity and most prominently all relevant PD data that has accrued until then has been reviewed by the Sponsor in consultation with the SMC. After this interim review, the Sponsor may decide to stop the cohort, to continue with full enrollment of the cohort or revise eligibility criteria before the remaining 15 patients in that cohort are enrolled.

For Cohort B5, a total of approximately 200 patients with head and neck squamous cell cancer may ultimately be randomized 2:1 to either NM21-1480 plus a PD-1 standard-of-care first-line checkpoint inhibitor or to the standard-of-care PD1 checkpoint inhibitor monotherapy. Randomization will be stratified by combined positive score (CPS ≥1; CPS ≥20), as determined by a FDA-cleared or any PD-L1 test approved for use by local competent authority. An interim analysis will be performed after a minimum of 60 patients (40 patients in the NM21-1480 arm) have been enrolled. At this point recruitment will be paused, the accumulated data analysed and regulatory authorities consulted. As with the other cohorts, decisions at the interim point will be taken based on clinical and regulatory input and not formal statistical testing.

7.1.2 Estimated Number of Screened Patients

Approximately 42 patients for Part A, up to approximately 67 patients for the optional Part A-2 and approximately 560 patients for Part B (assuming full enrollment of all Part B Cohorts B1 through B8) based on an assumed screen-failure rate of 40% for Cohort A, 40% for Cohort A-2, 25% for Cohorts B1-B2, and B4-B8, and screen-failure rate of 75% for Cohort B3. Patients who received <80% of both of the total intended Cycle 1 doses for reasons other than DLT and patients who may require discontinuation of NM21-1480 before the end of the DLT evaluation period for reasons other than the occurrence of a DLT, can be replaced.

7.1.3 Duration of Participation

All patients may continue to receive NM21-1480 until precluded by toxicity, non-compliance, withdrawal of consent, Investigator's decision, progressive disease, death, or closure of the study by the Sponsor (see Sections 7.2.9 and 7.2.11).

Patients with documented progression in tumor burden or the appearance of new lesions in the absence of significant clinical deterioration (decline in performance status and/or laboratory values), suspected by the Investigator as pseudo-progression, are permitted to continue with treatment until confirmation of disease progression with repeat imaging at least 4 weeks later, while the next imaging to confirm disease progression must not exceed 12 weeks from initial documentation of disease progression. Patients continuing on therapy despite suspected pseudo-progression need to fulfill the following criteria:

- Investigator-assessed clinical benefit, such as absence of clinical symptoms and signs of disease progression (including worsening laboratory values)
- Tolerance of study treatment
- Stable Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) that necessitates urgent alternative medical intervention

Following completion of the Treatment and Follow-up periods, all patients will be followed for survival.

7.1.4 Treatment Beyond Disease Progression

In Part A and optional Part A-2 of the study, patients treated with NM21-1480 will be permitted to continue NM21-1480 treatment beyond initial Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) defined progressive disease until the maximum of 12 months from the first treatment, assessed by the Investigator, as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Tolerance of study drug
- Continues to meet relevant eligibility criteria and criteria for administration of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases)
- Patient provides written informed consent prior to receiving additional NM21-1480 treatment. All other elements of the main consent including description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply

The decision to continue treatment beyond initial Investigator-assessed progression should be discussed with the study Medical Monitor (or designee) and documented in the study records. A radiographic assessment/scan should be performed at the next scheduled imaging evaluation 6 weeks (during the first 24 weeks of optional Part A-2 and Part B) or 8 weeks (but no less than 4 weeks) later to determine whether there has been a decrease in the tumor size or continued

progressive disease. The assessment of clinical benefit should be balanced by clinical judgement as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment with NM21-1480.

If the Investigator believes the patient would continue to receive clinical benefit by continuing NM21-1480 treatment after scans showing disease progression from continued treatment, the patient may continue to receive NM21-1480 treatment, remain on the study, and continue to receive monitoring according to the Schedule of Assessments in Section 7.1.6, Table 7-1 and Table 7-2.

For patients who continue NM21-1480 therapy beyond initial RECIST 1.1-defined disease progression, further progression is defined as an additional 10% increase in tumor burden from the time of the initial progressive disease assessment. This includes an increase in the sum of diameters of all target lesions and/or the diameters of new measurable lesions compared to the initial progressive disease evaluation. NM21-1480 treatment should be discontinued permanently upon determination of further progression. Study therapy should be discontinued in any patient for whom these criteria are met and should be documented.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

While for Part B of the study the criteria for treatment beyond progression described above shall be considered, decisions related to potential treatment beyond progression shall follow the principles of iRECIST (Seymour, et al. 2017). Any patient that has confirmed iCPD should be discontinued.

7.1.5 Duration of Treatment

There is no pre-specified maximal treatment duration. Treatment for a given patient shall be continued until there is confirmed disease progression by the Investigator or the patient meets any of the pre-specified conditions for discontinuation (see Section 7.2.9).

7.1.6 Schedule of Assessments

Table 7-1 Schedule of Assessments (2-week Dosing Interval; APPLIES TO ALL PARTS [A, A-2 AND B] OF THE STUDY)

Period	Screening Period*		Treatment Period[d] **(2-week Dosing Interval/4-Week Treatment Cycles)**				Follow-up Period[a]	Survival Follow-up[b]
Visit Name	Pre-Screen (Cohorts B2, B3, B5 and B8 *only)*[bb,dd,ee]	Screening	Cycle Day 1 Treatment Visit[e]	Cycle Day 15 Treatment Visit[e]	Cycle 1 Day 21± 3[gg] (Biopsy Visit)	Imaging and Treatment Response Assessment Visits[c]	Follow-up (FU) 1, FU2, and FU3 Visits	
Time point (Day / Week)	Day -42 to -29	Day -28 to -1	C1: Day 1 / Week 1 C2: Day 29 ± 2 / Week 5 C3: Day 57 ± 3 / Week 9 C4: Day 85 ± 3 / Week 13 C5: Day 113 ± 3 / Week 17 C6: Day 141 ± 3 / Week 21 C7: Day 169 ± 3 / Week 25 C8: Day 197 ± 3 / Week 29	C1: Day 15 ± 2 / Week 3 C2: Day 43 ± 2 / Week 7 C3: Day 71 ± 3 / Week 11 C4: Day 99 ± 3 / Week 15 C5: Day 127 ± 3 / Week 19 C6: Day 155 ± 3 / Week 23 C7: Day 183 ± 3 / Week 27 C8: Day 211 ± 3 / Week 31[e]		Day 39-43 / Week 6 (Pt A-2 and B *only*) Day 52-56 / Week 8 (Pt A *only*) Day 79-85 / Week 12 (Pt A-2 and B *only*) Day 108-112 / Week 16 (Pt A *only*) Day 120-127 / Week 18 (Pt A-2 and B *only*) Day 164-168 / Week 24 (Pts A, A-2 **and** B) Day 220-224 / Week 32 (Pts A, A-2 **and** B)[e]	FU1: 0 to 30 days post discontinuation FU2: 60 days ± 7 post discontinuation FU3: 90 days ± 7 post discontinuation	Every 3 months ± 7 days
ICF/ HIPAA[f]	x[bb]	x						
Eligibility Criteria		x						
Demographics & medical history[g,h]		x						
Diagnosis & confirmation stage		x						
Tumor-specific therapy history[ff]		x						
Hepatitis B and C, & HIV testing[i]		x						
CD4 T-cell count[j]		x						
Covid-19 vaccination confirmation or negative Covid-19 polymerase chain reaction (PCR) test		x						
NM21-1480 infusion[e]			x	x				
Vital signs[k]		x	x	x			x	
Height		x						
Weight		x	x (Odd-numbered cycles *only*)				x (FU1 *only*)	
Physical exam[l]		x	x	x			x	
Oxygen saturation[m]			x	x				
ECOG performance		x	x	x			x	

Period	Screening Period*		Treatment Period[d] **(2-week Dosing Interval/4-Week Treatment Cycles)**				Follow-up Period[a]	Survival Follow-up[b]
Visit Name	Pre-Screen (Cohorts B2, B3, B5 and B8 *only*)[bb,dd,ee]	Screening	Cycle Day 1 Treatment Visit[e]	Cycle Day 15 Treatment Visit[e]	Cycle 1 Day 21± 3[gg] (Biopsy Visit)	Imaging and Treatment Response Assessment Visits[c]	Follow-up (FU) 1, FU2, and FU3 Visits	
Time point (Day / Week)	Day -42 to -29	Day -28 to -1	C1: Day 1 / Week 1 C2: Day 29 ± 2 / Week 5 C3: Day 57 ± 3 / Week 9 C4: Day 85 ± 3 / Week 13 C5: Day 113 ± 3 / Week 17 C6: Day 141 ± 3 / Week 21 C7: Day 169 ± 3 / Week 25 C8: Day 197 ± 3 / Week 29	C1: Day 15 ± 2 / Week 3 C2: Day 43 ± 2 / Week 7 C3: Day 71 ± 3 / Week 11 C4: Day 99 ± 3 / Week 15 C5: Day 127 ± 3 / Week 19 C6: Day 155 ± 3 / Week 23 C7: Day 183 ± 3 / Week 27 C8: Day 211 ± 3 / Week 31[e]		Day 39-43 / Week 6 (Pt A-2 and B *only*) Day 52-56 / Week 8 (Pt A *only*) Day 79-85 / Week 12 (Pt A-2 and B *only*) Day 108-112 / Week 16 (Pt A *only*) Day 120-127 / Week 18 (Pt A-2 and B *only*) Day 164-168 / Week 24 (Pts A, A-2 **and** B) Day 220-224 / Week 32 (Pts A, A-2 **and** B)[e]	FU1: 0 to 30 days post discontinuation FU2: 60 days ± 7 post discontinuation FU3: 90 days ± 7 post discontinuation	Every 3 months ± 7 days
Hematology, Serum Chemistry, and Coagulation Parameters[n]		x	x	x			x	
Urinalysis[n]		x	x (Odd-numbered cycles *only*)				x	
Thyroid function[n]		x	x (Odd-numbered cycles *only*)				x	
Pregnancy test and FSH[o]		x	x (Odd-numbered cycles *only*)				x	
CEA[hh]		x[hh]	x[hh]	x[hh]			x	
ECG (12-lead)		x[p]	x[q] (Odd-numbered cycles *only*)				x (FU1 *only*)	
Serum sample for PK[ii]			See PK serum collection schedule in Table 7-3				x (FU1 *only*)	
Serum sample for immunogenicity assessment[ii]			See ADA serum collection schedule in Table 7-3				x (FU1 *only*)	
Blood for PD analysis			See PD blood sample collection schedule in Table 7-3					
ctDNA[hh]		x[hh]	x[hh]	x[hh]			x[hh]	
HPV Testing	x[dd]							
Tumor or other biopsy[r] (regular)	x[bb,ee]	x	x[r]	x[r]				
Fresh tumor biopsy (Cohort B8)[gg]		x[gg]			x[gg]			
CTI or MRI brain[s, t]		x[p]				x[c,u]	x[u,v]	
CTI or MRI (chest, abdomen, pelvis)[t]		x[p]				x[c]	x[v]	
Bone scan[w]		x				x[c]	x[v]	
Tumor-specific blood tests[n,x]		x	x (Odd-numbered cycles *only*)				x[v]	
Tumor response assessment						x[c,y]	x[v]	
Concomitant medications		x	x	x			x	
Adverse events[z]		x[h]	x	x[cc]	x		x[aa]	
Survival status								x

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; BRCA1 = Breast cancer type 1; C = cycle; CA = Carbohydrate antigen; CEA = Carcinoembryonic antigen; CD4 T-cell = cluster of differentiation 4 T-cell; CRF = Case report form; ctDNA = circulating tumor DNA; CTI = Computed tomography imaging; dMMR = Deficient mismatch repair; DLT = Dose-limiting toxicity; ECG = Electrocardiogram; ECOG = Eastern cooperative oncology group; FFPE = Formalin-fixed paraffin-embedded; FSH = Follicule-stimulating hormone; FU = Follow-up; HCG = Human chorionic gonadotropin; HCV = Hepatitis C virus; HIPAA = Health insurance portability and accountability act of 1996; HIV = Human immunodeficiency virus; HPV = Human papillomavirus; ICF = Informed consent form; irAE = Immune-related adverse event; MRI = Magnetic resonance imaging; MSI-H = Microsatellite instability-high; PD = Pharmacodynamics; PK = Pharmacokinetics; PD-L1 = Programmed death-ligand 1; RNA = Ribonucleic acid; SAE = Serious adverse event; T4 = Free thyroxine; TMB = Tumor mutational burden; TRAE = Treatment-related adverse event; TSH = Thyroid stimulating hormone.

[*] Screening assessments will be used for determination of study eligibility.

a. When a patient will discontinue study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single PK sample taken at applicable visits), and the patient should enter the Follow-up period. When a patient will be withdrawn from the study (during the treatment or Follow-up period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.

b. Following completion or discontinuation of the Treatment and/or Follow-up phases of the study, all patients will be followed (by phone) every 3 months to assess their survival status until patient death.

c. These visits are NOT clinic visits. The purpose of these visits are for radiologic assessment and subsequent evaluation of results by the Investigator (tumor response assessment). However, should radiologic and clinic visit (comprising a study drug dosing event) be scheduled for the same day, the radiologic procedures and assessments shall occur BEFORE the clinic visit/administration of study drug.

d. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed, and subsequent visits will follow every 2 weeks (the infusion at the original scheduled visit will be considered a missed dose). Patients with infusion delays >35 days (i.e., 2 missed doses + 7 days) should normally discontinue treatment and enter the Follow-up period with the exception of delays related to prophylactic vaccinations in special cases needed after specific consultation and agreement between the Investigator, and the Medical Monitor or in settings where benefit/risk may justify continued study therapy (e.g., patient deriving clinical benefit who requires prolonged steroid taper for management of non-DLT irAEs; again upon agreement with the Medical Monitor).

e. Treatment and imaging/tumor assessments will continue until discontinuation criteria have been met.

f. ICF and HIPAA – or any locally applicable – authorization are to be provided before initiation of any Screening assessments and may be obtained before Day 28.

g. To include collection of prior medication and prior/concurrent medical conditions. Also to include collecting prior local test results on tumor genetic alterations such as MSI-H, dMMR, *BRCA1*, *Kras*, PD-L1 status, TMB, etc. (if available).

h. Aes occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded as Aes (though non-treatment-emergent).

i. Hepatitis B surface antigen (HBVs Ag), Anti-Hepatitis B surface antibody (HBVs Ab), Anti-Hepatitis B core antibody (HBVc Ab), a Hepatitis B panel, and anti-hepatitis C antibody (HCV ab) (with reflex viral load assessment by quantitative polymerase chain reaction (PCR) hepatitis C RNA if antibody test is positive) testing. To be done by local site laboratory or its contract laboratory.

j. CD4 T-cell count should only be performed if a patient is HIV positive at Screening.

k. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained pre-infusion, every 15 minutes during the infusion, at the end of the infusion, and 15, 30, and 60 minutes after completion of the infusion. When slowing or re-starting an infusion due to an infusion

reaction/AE, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15, 30, and 60 minutes after completion of the infusion and/or until the patient is stabilized. Vital signs should be collected ± 5 minutes from the scheduled times noted above.

l. Complete physical exam to be performed at Screening, Follow-up 1, and on Day 1 of all odd-numbered cycles from Cycle 3 onward. Limited physical exam to be performed at all other clinic visits. Ideally, physical examinations should be performed prior to dose administration on days when both procedures are scheduled to occur. Complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. Limited physical examination includes assessment of the lungs, heart, abdomen, and skin. All abnormal findings noted at the Screening and pre-treatment physical examinations should be recorded on the medical history CRF. Abnormal findings of clinical significance that occur after the Cycle 1/Day 1 evaluation (or new AEs) should be explicitly documented on the AE CRF.

m. To be done at rest and after mild exertion. On treatment days, to be completed prior to infusion.

n. During the study Treatment Period, hematology, coagulation parameters (as per inclusion criterion 14, Section 7.2.1), serum chemistries, urinalysis, thyroid function (free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) [See Section 18.7, Appendix VII for full list of required laboratory tests]. If FT3 and FT4 tests are not available, total T3/T4 is acceptable), pregnancy tests and tumor-specific blood tests (if applicable, see footnote x) will be evaluated only by local study site or its contract laboratory at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** If practicable, laboratory samples may be drawn up to 72 hours prior to infusions for pre-infusion safety review; in such case it is not necessary to repeat tests on the day of dosing. Any new ≥Grade 3 laboratory abnormality or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medical Monitor should be contacted.

o. Serum β-HCG pregnancy test to be performed at Screening (in case of a positive serum pregnancy test, the site is allowed to apply standard site procedures to rule out false positive test results; enrollment of the patient may be considered only in case false positivity of the serum pregnancy test has been confirmed). Urine pregnancy test to be performed at all other time points for women of child-bearing potential. Urine pregnancy tests on days of study drug administration must be performed at the visits indicated and negative before study drug administration. FSH to be tested at Screening only, and only if applicable, i.e., if needed to confirm non-childbearing potential in accordance with inclusion criterion 15.

p. Baseline imaging and 12-lead ECG done as part of the patient's previous routine care before signing the ICF and completed within 28 days before the administration of ND021 (NM21-1480) need not be repeated. Whenever possible, baseline imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the patient's participation in the study.

q. Not required at Cycle 1 Day 1 visit.

r. Patient must provide baseline tumor tissues at Screening (archival or freshly acquired) for exploratory biomarker analysis. Archival tumor tissue can be FFPE blocks or slides. Whenever clinically feasible, additional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at other times but preferably at or around the time of the first dose administration in Treatment Cycle 2 or Treatment Cycle 3 (i.e., approximately 4 and 8 weeks following treatment initiation). Part A (and optional Part A-2): Additional tumor or other biopsy requires specific agreement by the patient in the informed consent. Part B: **Whenever considered clinically feasible by the investigator,** one additional post-treatment tumor biopsy is mandatory for patients presenting with at least stable disease (i.e., stable disease, partial response or complete response) according to RECIST1.1 or suspected pseudo-progression at the Week 6 imaging.

s. Brain scan (MRI preferred) required only if applicable (see inclusion criterion 10, Section 7.2.1)

t. The same technique (CTI/MRI) used at baseline should be utilized throughout the study for a given patient. CTI is the imaging modality of choice for chest/abdomen/pelvis.

u. Brain scans during Treatment and Follow-up periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain CTI scans/MRI should be repeated at each Imaging and Treatment Response Assessment Visit, and at Follow-up Visits in accordance with footnote "v".

v. Only if applicable and only needed for patients who were taken off NM21-1480 therapy due to AE, i.e., without progressive disease or patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time. Only a single scan during the follow-up period is to be performed (i.e., at Follow-up Visit 2 or 3) and should only be performed if at least 4 weeks have passed since the most recent prior assessment.

w. Bone scans at baseline or subsequent visits will be performed only if clinically indicated. If required, subsequent bone scans should ONLY be repeated every other assessment cycle (i.e., at Weeks 16, 32, etc., in Part A; and at Weeks 12, 24, 40, etc., for Part B) and a single scan at Follow-up Visit in accordance with footnote "v" unless the investigator suspects progression of disease in bone or in case complete response is identified in target disease.

x. Blood tests are to be tumor-specific (e.g., CEA and CA 19-9 for colorectal and pancreatic cancer, respectively). In case of uncertainty, use of a blood test should be discussed with the Medical Monitor.

y. Tumor response status will be assessed by the Investigators using RECIST 1.1 *only* (Parts A and A-2), or RECIST1.1 and iRECIST (Part B). Response assessments must be performed by the Investigator every 8 weeks (Parts A), or every 6 weeks during the first 24 weeks the patient is on treatment and every 8 weeks thereafter (Part A-2 and Part B), to document eligibility to remain on treatment with study drug (see also footnote c).

z. All patients who discontinue from the study within 70 days after the administration of the last dose of study drug should be followed until resolution and/or stabilization of any study TRAE and of those AE(s) that led to the discontinuation, and should be monitored for 70 days following the last dose of NM21-1480 for the occurrence of study TRAE. These patients should complete Follow-up Visits 1 and 2 unless the patient begins a new therapy.

aa. For all Follow-up periods beyond 70 days from the last dose of study drug, only study treatment-related SAEs or late-occurring irAEs should be reported.

bb. For Cohort B3 only: The screening process is to be conducted in 2 subsequent steps. Following signature of the ICF, PD-L1 expression scoring on tumor cells needs to be conducted either based on archival or fresh biopsy material from the TME and conducted centrally using a Sponsor-approved PD-L1 assay prior to entering the formal 28-day screening period. Only upon determination of a PD-L1 tumor cell expression score qualifying for study inclusion, the remaining eligibility criteria will be assessed.

cc. For Part A (Cycle 1 *only*), the site is encouraged to call the patient approximately one week after the Day 15 / Week 3 dosing event in order to learn about any AEs that may have occurred.

dd. For Cohort B2 and Cohort B5 only: Pre-screening visit only required if HPV positivity has not previously been determined for the current tumor (or if criteria described in footnote ee are met). In case HPV positivity has previously been confirmed, no new HPV testing is required for eligibility. If HPV status is unknown, HPV positivity must be confirmed for eligibility by local testing, applying the standard local testing approach for the given tumor, while use of the CINtec p16 histology assay, another p16 immunohistochemistry assay, or a locally established RT-PCR or PCR test is recommended.

ee. For Cohort B2, Cohort B5, and Cohort B8 only: Pre-screening visit only required if PD-L1 expression status has not previously been determined for the current tumor (or if criteria described in footnote dd are met). In case PD-L1 expression in at least 1% of tumor and/or immune cells has previously been confirmed, no new PD-L1 testing is required for eligibility. If PD-L1 expression status is unknown, PD-L1 expression in at least 1% of tumor and/or immune cells must be confirmed for eligibility by local testing, using any PD-L1 test approved or cleared for use by the local competent authority.

ff. Sites are requested to attempt gathering and submitting the last pre-baseline scans for a patient as part of the tumor-specific therapy history; unavailability of these pre-baseline scans do not, however, make a patient ineligible for the study.

gg. Mandatory fresh, paired biopsy to be taken during screening period and at Day 21±3. **This only applies to patients with mCRC enrolled to Cohort B8**. The on-treatment biopsy can be delayed to the next clinically feasible day closest to Day 21 in situations in which as per investigator judgement taking the biopsy is not clinically feasible at the scheduled day. In any case, on-treatment biopsies should not be taken at days of dosing with NM21-1480. Both baseline as well as matched on-treatment biopsies. Fresh biopsies can be taken from primary tumor or metastases. At least 3 biopsy cores, but preferably more if considered safe by the radiologist, shall be taken at each biopsy event and touch preparation as per site standard approach shall be applied to ensure specimen adequacy (i.e., confirm tumor content). Further details are described in the laboratory manual. In addition to these

fresh biopsies, for patients for whom there is archival primary tumor tissue available, this archival tissue, as per inclusion criterion 3 requirements shall also be provided for biomarker analysis.

hh. Only applicable for mCRC patients enrolled to Cohort B8.

ii. Not applicable to patients in Cohort B5 randomized to standard-of-care anti-PD1 therapy only.

Table 7-2 Backup Schedule of Assessments (3-week Dosing Interval; APPLIES TO PART A-2 AND B ONLY IN CASE OF A POTENTIAL FUTURE SMC DECISION TO PROLONG DOSING INTERVAL#)

Period	Screening Period*		Treatment Period[d] **(3-week Dosing Interval/6-Week Treatment Cycles)**				Follow-up Period[a]	Survival Follow-up[b]
Visit Name	Pre-Screen (Cohorts B2, B3, B5 and B8 *only)* [bb,cc,dd]	Screening	Cycle Day 1 Treatment Visit[e]	Cycle Day 22 Treatment Visit[e]	Cycle 1 Day 28± 3[ff] (Biopsy Visit)	Imaging and Treatment Response Assessment Visits[c]	Follow-up (FU) 1, FU2, and FU3 Visits	
Time point (Day / Week)	Day -42 to -29	Day -28 to -1	C1: Day 1 / Week 1 C2: Day 43 ± 2 / Week 7 C3: Day 85 ± 3 / Week 13 C4: Day 127 ± 3 / Week 19 C5: Day 169 ± 3 / Week 25 C6: Day 211 ± 3 / Week 31	C1: Day 22 ± 2 / Week 4 C2: Day 64 ± 2 / Week 10 C3: Day 106 ± 3 / Week 16 C4: Day 148 ± 3 / Week 22 C5: Day 190 ± 3 / Week 28 C6: Day 232 ± 3 / Week 34[e]		Day 39-43 / Week 6 Day 79-85 / Week 12 Day 120-127 / Week 18 Day 164-168 / Week 24 Day 220-224 / Week 32 Day 256-260 / Week 40[e]	FU1: 0 to 30 days post discontinuation FU2: 60 days ± 7 post discontinuation FU3: 90 days ± 7 post discontinuation	Every 3 months ± 7 days
ICF/ HIPAA[f]	x[bb]	x						
Eligibility Criteria		x						
Demographics & medical history[g,h]		x						
Diagnosis & confirmation stage		x						
Tumor-specific therapy history[ee]		x						
Hepatitis B and C, & HIV testing[i]		x						
CD4 T-cell count[j]		x						
Covid-19 vaccination confirmation or negative Covid-19 PCR test		x						
NM21-1480 infusion[e]			x	x				
Vital signs[k]		x	x	x			x	
Height		x						
Weight		x	x (Odd-numbered cycles *only*)				x (FU1 *only*)	
Physical exam[l]		x	x	x			x	
Oxygen saturation[m]			x	x				
ECOG performance		x	x	x			x	
Hematology, Serum Chemistry, and Coagulation Parameters[n]		x	x	x			x	
Urinalysis[n]		x	x (Odd-numbered cycles *only*)				x	
Thyroid function[n]		x	x (Odd-numbered cycles *only*)				x	
Pregnancy test and FSH[o]		x	x (Odd-numbered cycles *only*)				x	
CEA[gg]		x	x	x			x	
ECG (12-lead)		x[p]	x[q] (Odd-numbered cycles *only*)				x (FU1 *only*)	

Period	Screening Period*		Treatment Period[d] **(3-week Dosing Interval/6-Week Treatment Cycles)**				Follow-up Period[a]	Survival Follow-up[b]
Visit Name	Pre-Screen (Cohorts B2, B3, B5 and B8 *only)* [bb,cc,dd]	Screening	Cycle Day 1 Treatment Visit[e]	Cycle Day 22 Treatment Visit[e]	Cycle 1 Day 28± 3[ff] (Biopsy Visit)	Imaging and Treatment Response Assessment Visits[c]	Follow-up (FU) 1, FU2, and FU3 Visits	
Time point (Day / Week)	Day -42 to -29	Day -28 to -1	C1: Day 1 / Week 1 C2: Day 43 ± 2 / Week 7 C3: Day 85 ± 3 / Week 13 C4: Day 127 ± 3 / Week 19 C5: Day 169 ± 3 / Week 25 C6: Day 211 ± 3 / Week 31	C1: Day 22 ± 2 / Week 4 C2: Day 64 ± 2 / Week 10 C3: Day 106 ± 3 / Week 16 C4: Day 148 ± 3 / Week 22 C5: Day 190 ± 3 / Week 28 C6: Day 232 ± 3 / Week 34[e]		Day 39-43 / Week 6 Day 79-85 / Week 12 Day 120-127 / Week 18 Day 164-168 / Week 24 Day 220-224 / Week 32 Day 256-260 / Week 40[e]	FU1: 0 to 30 days post discontinuation FU2: 60 days ± 7 post discontinuation FU3: 90 days ± 7 post discontinuation	Every 3 months ± 7 days
Serum sample for PK[hh]			See PK serum collection schedule in Table 7-4				x (FU1 *only*)	
Serum sample for immunogenicity assessment[hh]			See ADA serum collection schedule in Table 7-4				x (FU1 *only*)	
Blood for PD analysis			See PD blood sample collection schedule in Table 7-4					
ctDNA[gg]		x[gg]	x[gg]	x[gg]			x[gg]	
HPV Testing	x[cc]							
Tumor or other biopsy[r] (regular)	x[bb,dd]	x	x[r]	x[r]				
Fresh tumor biopsy (Cohort B8)[ff]		x[ff]			x[ff]			
CTI or MRI brain[s, t]		x[p]				x[c,u]	x[u,v]	
CTI or MRI (chest, abdomen, pelvis)[t]		x[p]				x[c]	x[v]	
Bone scan[w]		x				x[c]	x[v]	
Tumor-specific blood tests[n,x]		x	x (Odd-numbered cycles *only*)				x[v]	
Tumor response assessment						x[c,y]	x[v]	
Concomitant medications		x	x	x			x	
Adverse events[z]		x[h]	x	x	x		x[aa]	
Survival status								x

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; BRCA1 = Breast cancer type 1; C = cycle; CA = Carbohydrate antigen; CEA = Carcinoembryonic antigen; CD4 T-cell = cluster of differentiation 4 T-cell; CRF = Case report form; CTI = Computed tomography imaging; dMMR = Deficient mismatch repair; DLT = Dose-limiting toxicity; ECG = Electrocardiogram; ECOG = Eastern cooperative oncology group; FFPE = Formalin-fixed paraffin-embedded; FSH = Follicule-stimulating hormone; FU = Follow-up; HCG = Human chorionic gonadotropin; HCV = Hepatitis C virus; HIPAA = Health insurance portability and accountability act of 1996; HIV = Human immunodeficiency virus; HPV = Human papillomavirus; ICF = Informed consent form; irAE = Immune-related adverse event; MRI = Magnetic resonance imaging; MSI-H = Microsatellite instability-high; PD = Pharmacodynamics; PK = Pharmacokinetics; PDL1 = Programmed death-ligand 1; RNA = Ribonucleic acid; SAE = Serious adverse event; T4 = Free thyroxine; TMB = Tumor mutational burden; TRAE = Treatment-related adverse event; TSH = Thyroid stimulating hormone.

[#] **As per 23 May 2022 SMC call, the 800mg flat dose level shall be further studied in Part B by infusion approximately every 14 days (i.e. following Table 7-1 Schedule of Assessments), based on Part A PK data which do not indicate substantial accumulation at this dose level over time with this dosing interval. Optional Part A-2 of the study will explore one more higher dose level (1400mg flat dose with approximately 14-day dosing interval, i.e. following Table 7-1 Schedule of Assessments) than was studied in**

Part A. Such 1400mg dose level will be explored applying strict stopping criteria and respecting a 28-day DLT evaluation period before more than 6 subjects are exposed. PK data for this 1400mg dose level in Part A-2 will be closely followed and in case of observation of relevant drug accumulation over time, the dosing interval for this dose may be adjusted to approximately every 21 days, in which case Table 7-2 Schedule of Assessments applies. Such change from a 2-week to a 3-week dosing interval would only be applicable if communicated separately to sites by a written notification of the SMC decision on such change of dosing interval by means of a letter of amendment, to be followed by a full protocol amendment.

[*] Screening assessments will be used for determination of study eligibility.

a. When a patient will discontinue study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single PK sample taken at applicable visits), and the patient should enter the Follow-up period. When a patient will be withdrawn from the study (during the treatment or Follow-up period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF.
b. Following completion or discontinuation of the Treatment and/or Follow-up phases of the study, all patients will be followed (by phone) every 3 months to assess their survival status until patient death.
c. These visits are NOT clinic visits. The purpose of these visits are for radiologic assessment and subsequent evaluation of results by the Investigator (tumor response assessment). However, should radiologic and clinic visit (comprising a study drug dosing event) be scheduled for the same day, the radiologic procedures and assessments shall occur BEFORE the clinic visit/administration of study drug.
d. In the case that an infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed. If the delay is more than 7 days, the procedures at the next visit should be performed, and subsequent visits will follow every 3 weeks (the infusion at the original scheduled visit will be considered a missed dose). Patients with infusion delays >49 days (i.e., 2 missed doses + 7 days) should normally discontinue treatment and enter the Follow-up period with the exception of delays related to prophylactic vaccinations in special cases needed after specific consultation and agreement between the Investigator, and the Medical Monitor or in settings where benefit/risk may justify continued study therapy (e.g., patient deriving clinical benefit who requires prolonged steroid taper for management of non-DLT irAEs; again upon agreement with the Medical Monitor).
e. Treatment and imaging/tumor assessments will continue until discontinuation criteria have been met.
f. ICF and HIPAA - or any locally applicable - authorization are to be provided before initiation of any Screening assessments and may be obtained before Day 28.
g. To include collection of prior medication and prior/concurrent medical conditions. Also to include collecting prior local test results on tumor genetic alterations such as MSI-H, dMMR, *BRCA1*, *Kras*, PD-L1 status, TMB, etc. (if available).
h. AEs occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded as AEs (though non-treatment-emergent).
i. Hepatitis B surface antigen (HBVs Ag), Anti-Hepatitis B surface antibody (HBVs Ab), Anti-Hepatitis B core antibody (HBVc Ab), a Hepatitis B panel, and anti-hepatitis C antibody (HCV ab) (with reflex viral load assessment by quantitative polymerase chain reaction (PCR) hepatitis C RNA if antibody test is positive) testing. To be done by local site laboratory or its contract laboratory.
j. CD4 T-cell count should only be performed if a patient is HIV positive at Screening.
k. Vital sign measurements to include temperature, pulse, and resting systolic and diastolic blood pressure. On the day of each infusion, vital signs will be obtained pre-infusion, every 15 minutes during the infusion, at the end of the infusion, and 15, 30, and 60 minutes after completion of the infusion. When slowing or re-starting an infusion due to an infusion reaction/AE, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15, 30, and 60 minutes after completion of the infusion and/or until the patient is stabilized. Vital signs should be collected ± 5 minutes from the scheduled times noted above.

l. Complete physical exam to be performed at Screening, Follow-up 1, and on Day 1 of all odd-numbered cycles from Cycle 3 onward. Limited physical exam to be performed at all other clinic visits. Ideally, physical examinations should be performed prior to dose administration on days when both procedures are scheduled to occur. Complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. Limited physical examination includes assessment of the lungs, heart, abdomen, and skin. All abnormal findings noted at the Screening and pre-treatment physical examinations should be recorded on the medical history CRF. Abnormal findings of clinical significance that occur after the Cycle 1/Day 1 evaluation (or new AEs) should be explicitly documented on the AE CRF.

m. To be done at rest and after mild exertion. On treatment days, to be completed prior to infusion.

n. During the study Treatment Period, hematology, coagulation parameters (as per inclusion criterion 14, Section 7.2.1), serum chemistries, urinalysis, thyroid function (free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) [See Section 18.7, Appendix VII for full list of required laboratory tests]. If FT3 and FT4 tests are not available, total T3/T4 is acceptable), pregnancy tests and tumor-specific blood tests (if applicable, see footnote x) will be evaluated only by local study site or its contract laboratory at these time points. The hematology and clinical chemistry laboratories **must be performed and reviewed before dosing.** If practicable, laboratory samples may be drawn up to 72 hours prior to infusions for pre-infusion safety review; in such case it is not necessary to repeat tests on the day of dosing. Any new ≥Grade 3 laboratory abnormality or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medical Monitor should be contacted.

o. Serum β-HCG pregnancy test to be performed at Screening (in case of a positive serum pregnancy test, the site is allowed to apply standard site procedures to rule out false positive test results; enrollment of the patient may be considered only in case false positivity of the serum pregnancy test has been confirmed). Urine pregnancy test to be performed at all other time points for women of child-bearing potential. Urine pregnancy tests on days of study drug administration must be performed at the visits indicated and negative before study drug administration. FSH to be tested at Screening only, and only if applicable, i.e., if needed to confirm non-childbearing potential in accordance with inclusion criterion 15.

p. Baseline imaging and 12-lead ECG done as part of the patient's previous routine care before signing the ICF and completed within 28 days before the administration of ND021 (NM21-1480) need not be repeated. Whenever possible, baseline imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the patient's participation in the study.

q. Not required at Cycle 1 Day 1 visit.

r. Patient must provide baseline tumor tissues at Screening (archival or freshly acquired) for exploratory biomarker analysis. Archival tumor tissue can be FFPE blocks or slides. Whenever clinically feasible, additional tumor or other biopsies (e.g., inflamed tissue at anatomical sites that are readily accessible without the need for general anesthesia) may be performed at other times but preferably at or around the time of the first dose administration in Treatment Cycle 2 or Treatment Cycle 3 (i.e., approximately 6 and 12 weeks following treatment initiation). **Whenever considered clinically feasible by the investigator,** an additional tumor biopsy is mandatory for patients presenting with at least stable disease (i.e., stable disease, partial response or complete response) according to RECIST1.1 or suspected pseudo-progression at the Week 6 imaging.

s. Brain scan (MRI preferred) required only if applicable (see inclusion criterion 10, Section 7.2.1)

t. The same technique (CTI/MRI) used at baseline should be utilized throughout the study for a given patient. CTI is the imaging modality of choice for chest/abdomen/pelvis.

u. Brain scans during Treatment and Follow-up periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain CTI scans/MRI should be repeated at each Imaging and Treatment Response Assessment Visit, and at Follow-up Visits in accordance with footnote "v".

v. Only if applicable and only needed for patients who were taken off NM21-1480 therapy due to AE, i.e., without progressive disease or patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time. Only a single scan during the follow-up period is to be performed (i.e., at Follow-up Visit 2 or 3) and should only be performed if at least 4 weeks have passed since the most recent prior assessment.

w. Bone scans at baseline or subsequent visits will be performed only if clinically indicated. If required, subsequent bone scans should ONLY be repeated every other assessment cycle (i.e., at Weeks 12, 24, 40, etc.) and a single scan at Follow-up Visits in accordance with footnote "v" unless the investigator suspects progression of disease in bone or in case complete response is identified in target disease.

x. Blood tests are to be tumor-specific (e.g., CEA and CA 19-9 for colorectal and pancreatic cancer, respectively). In case of uncertainty, use of a blood test should be discussed with the Medical Monitor.

y. Tumor response status will be assessed by the Investigators using RECIST 1.1 (Part A-2) and RECIST1.1 *and* iRECIST (Part B). Response assessments must be performed by the Investigator every 6 weeks during the first 24 weeks the patient is on treatment and every 8 weeks thereafter (Part A-2 and B) to document eligibility to remain on treatment with study drug (see also footnote c).

z. All patients who discontinue from the study within 70 days after the administration of the last dose of study drug should be followed until resolution and/or stabilization of any study TRAE and of those AE(s) that led to the discontinuation, and should be monitored for 70 days following the last dose of NM21-1480 for the occurrence of study TRAE. These patients should complete Follow-up Visits 1 and 2 unless the patient begins a new therapy.

aa. For all Follow-up periods beyond 70 days from the last dose of study drug, only study treatment-related SAEs or late-occurring irAEs should be reported.

bb. For Cohort B3 only: The screening process is to be conducted in 2 subsequent steps. Following signature of the ICF, PD-L1 expression scoring on tumor cells needs to be conducted either based on archival or fresh biopsy material from the TME and conducted centrally using a Sponsor-approved PD-L1 assay prior to entering the formal 28-day screening period. Only upon determination of a PD-L1 tumor cell expression score qualifying for study inclusion, the remaining eligibility criteria will be assessed.

cc. For Cohort B2 and Cohort B5 only: Pre-screening visit only required if HPV positivity has not previously been determined for the current tumor (or if criteria described in footnote dd are met). In case HPV positivity has previously been confirmed, no new HPV testing is required for eligibility. If HPV status is unknown, HPV positivity must be confirmed for eligibility by local testing, applying the standard local testing approach for the given tumor, while use of the CINtec p16 histology assay, another p16 immunohistochemistry assay, or a locally established RT-PCR or PCR test is recommended.

dd. For Cohort B2, Cohort B5, and Cohort B8 only: Pre-screening visit only required if PD-L1 expression status has not previously been determined for the current tumor (or if criteria described in footnote cc are met). In case PD-L1 expression in at least 1% of tumor and/or immune cells has previously been confirmed, no new PD-L1 testing is required for eligibility. If PD-L1 expression status is unknown, PD-L1 expression in at least 1% of tumor and/or immune cells must be confirmed for eligibility by local testing, using any PD-L1 test approved or cleared for use by the local competent authority.

ee. Sites are requested to attempt gathering and submitting the last pre-baseline scans for a patient as part of the tumor-specific therapy history; unavailability of these pre-baseline scans do not, however, make a patient ineligible for the study.

ff. Mandatory fresh, paired biopsy to be taken during screening period and at Day 28±3. **This only applies to patients with mCRC enrolled to Cohort B8**. The on-treatment biopsy can be delayed to the next clinically feasible day closest to Day 28 in situations in which as per investigator judgement taking the biopsy is not clinically feasible at the scheduled day. In any case, on-treatment biopsies should not be taken at days of dosing with NM21-1480. Both baseline as well as matched on-treatment biopsies. Fresh biopsies can be taken from primary tumor or metastases. At least 3 biopsy cores, but preferably more if considered safe by the radiologist, shall be taken at each biopsy event and touch preparation as per site standard approach shall be applied to ensure specimen adequacy (i.e., confirm tumor content). Further details are described in the laboratory manual. In addition to these fresh biopsies, for patients for whom there is archival primary tumor tissue available, this archival tissue, as per inclusion criterion 3 requirements shall also be provided for biomarker analysis.

gg. Only applicable for mCRC patients enrolled to Cohort B8.

hh. Not applicable to patients in Cohort B5 randomized to standard-of-care anti-PD1 therapy only.

7.1.7 Blood Sampling Schedule (APPLIES TO ALL PARTS [A, A-2 AND B] OF THE STUDY)

Table 7-3 Pharmacokinetics, Anti-Drug Antibody, and Pharmacodynamic Blood Sampling Schedule (2-week Dosing Interval)

		PK[a,b,j]	ADA[j]	IPT	sPD-L1/ sCD137	Cytokines	RO	ctDNA[k]	PD-L1 IHC	TMB, TCRseq, & MSI by DNA Analysis	mRNA/ IF	DNA, mRNA, IHC[h]
Visit name / Study day	**Time Point**	**Serum**	**Serum**	**Whole Blood**	**Serum**	**Serum**	**Whole Blood**	**Whole Blood**	**Biopsy (FFPE)**	**Biopsy (FFPE)**	**Biopsy (FFPE)[c]**	**Mandatory Biopsy[h]**
Screening / Day -28 to -1	--							x[k]	x	x	x	x
Cycle 1, Day 1 / Study Day 1	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]				
	EOI[f] ± 5 min	x[g]			x[g]	x[g]	x[g]					
	4 h ± 10 min	x[d]										
	8 h ± 1 h	x[d]										
Cycle 1, Day 2 / Study Day 2	24 h ± 2 h	x[d]			x[d]	x[d]	x[d]					
Cycle 1, Day 3 / Study Day 3	48 h ± 4 h	x[d]										
Cycle 1, Day 5 / Study Day 5	96 h ± 12 h	x[d]			x[d]		x[d]					
Cycle 1, Day 8 / Study Day 8	168 h ± 24 h	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]					
Cycle 1, Day 15 / Study Day 15 ± 2	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]				
Cycle 1, Day 21 / Study Day 21 ± 3	--											x[i]

		PK[a,b,j]	ADA[j]	IPT	sPD-L1/ sCD137	Cytokines	RO	ctDNA[k]	PD-L1 IHC	TMB, TCRseq, & MSI by DNA Analysis	mRNA/ IF	DNA, mRNA, IHC[h]
Visit name / Study day	**Time Point**	**Serum**	**Serum**	**Whole Blood**	**Serum**	**Serum**	**Whole Blood**	**Whole Blood**	**Biopsy (FFPE)**	**Biopsy (FFPE)**	**Biopsy (FFPE)[c]**	**Mandatory Biopsy[h]**
Cycle 2, Day 1 / Study Day 29 ± 2	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]			x	
Cycle 2, Day 8 / Study Day 36 ± 2	168 h ± 48 h	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]					
Cycle 2, Day 15 / Study Day 43 ± 2	Pre-dose	x[g]	x[g]		x[g]	x[g]		x[k]				
Cycle 3, Day 1 / Study Day 57 ± 3	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]			x	
	EOI[f] ± 5 min	x[g]										
	4 h ± 10 min	x[d]										
	8 h ± 1 h	x[d]										
Cycle 3, Day 2 / Study Day 58	24 h ± 2 h	x[d]				x[d]						
Cycle 3, Day 3 / Study Day 59	48 h ± 4 h	x[d]										
Cycle 3, Day 5 / Study Day 61	96 h ± 12 h	x[d]										
Cycle 3, Day 8 / Study Day 64	168 h ± 24 h	x[g]				x[g]						
Cycle 3, Day 15 / Study Day 71 ± 3	336 h ± 48 h	x[d]						x[k]				

		PK[a,b,j]	ADA[j]	IPT	sPD-L1/ sCD137	Cytokines	RO	ctDNA[k]	PD-L1 IHC	TMB, TCRseq, & MSI by DNA Analysis	mRNA/ IF	DNA, mRNA, IHC[h]
Visit name / Study day	**Time Point**	**Serum**	**Serum**	**Whole Blood**	**Serum**	**Serum**	**Whole Blood**	**Whole Blood**	**Biopsy (FFPE)**	**Biopsy (FFPE)**	**Biopsy (FFPE)[c]**	**Mandatory Biopsy[h]**
All subsequent even-numbered cycles, Days 1 and 15 / Study Days e.g., 85 ± 3, 99 ± 3, 141 ± 3, 155 ± 3, etc.								x[k]				
All subsequent even-numbered cycles,Day 8 / Study Days e.g., 92 ± 3, 148 ± 3, 204 ± 3, etc.	168 h ± 48 h	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]					
All subsequent odd-numbered cycles, Day 1 / Study Days 113 ± 3, 169 ± 3, etc.	Pre-dose	x[g]	x[g]	x[d]	x[d]	x[d]	x[d]	x[k]			x	
All subsequent odd-numbered cycles, Day 15 / Study Days e.g., 127 ± 3, 183 ± 3, etc.								x[k]				
Follow-up Period	--	x (FU1 *only*)	x (FU1 *only*)					x[k] (FU1, FU2, and FU3)				

Abbreviations: ADA = Anti-drug antibodies; D = Dose (study drug administration); DNA = Deoxyribonucleic acid; EOI = End of infusion; FFPE = Formalin-fixed paraffin-embedded; h = Hour; IHC = Immunohistochemistry; IPT = Immunophenotyping; TMB = Tumor mutational burden; MSI = Microsatellite instability; IF = Immunofluorescence;

PK = Pharmacokinetics; PD-L1 = Programmed death-ligand 1; mRNA = Messenger Ribonucleic acid; RO = Receptor occupancy; TCRseq = T-cell receptor sequencing; TMB = Tumor mutational burden

*Assessment of IPT, sPD-L1, sCD137, cytokine panel, RO, PD-L1 IHC, TMB, TCRseq, MSI and mRNA/IF may be adjusted for Part B, following availability of Part A data; conduct of RO assay (for Part A and B) will be dependent on availability of a suitable assay.

a. Serial PK samples will be collected from all the patients enrolled in Part A and A-2. For the patients in Part B serial PK is optional except for the mandatory pre-dose, EOI and 168 ± 24 h sampling timepoints (see footnote "g").
b. If a patient permanently discontinues study drug treatment, or is not receiving an infusion at a given visit, a single PK sample will be taken at that visit.
c. Optional biopsy material for patients enrolled in Part A and A-2 from as many cycles as possible, and Follow-up period. For patients in Part B, a single post treatment biopsy material collection is considered mandatory per footnote "r" in Table 7-1, i.e., for patients presenting with at least stable disease during treatment with NM21-1480.
d. Optional sampling point for Part B. Sites are not required to collect these optional PK samples in Part B. These sampling timepoints are however mandatory in Part A and Part A-2. For sampling timepoints considered mandatory in Part B at all sites, see also footnote "g".
e. EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion from the counter arm of the site of injection. All subsequent timepoints indicated for PK blood draws refer to hours *after* EOI.
f. For FU visits: PK and ADA sample will be taken at Follow-up Visit 1 only.
g. Mandatory sample for all patients in Part A, Part A-2 and Part B (unless drawing is not considered clinically feasible due to the condition of the patient).
h. Only applicable for mCRC patients enrolled to CohortB8. For specifics on sample acquisition please refer to specialty lab manual.
i. Reference is made to footnote gg in Table 7-1 for timing of these mandatory on-treatment biopsies for mCRC patients enrolled to Cohort B8.
j. Not applicable to patients in Cohort B5 randomized to standard-of-care anti-PD1 therapy only.
k. Only applicable for mCRC patients enrolled to Cohort B8.

Table 7-4 Backup Pharmacokinetics, Anti-Drug Antibody, and Pharmacodynamic Blood Sampling Schedule (3-week Dosing Interval: APPLICABLE TO PART A-2 AND B ONLY IN CASE OF A POTENTIAL FUTURE SMC DECISION TO PROLONG DOSING INTERVAL#)

		PK[a,b,j]	ADA[j]	IPT	sPD-L1/ sCD137	Cytokines	RO	ctDNA[k]	PD-L1 IHC	TMB, TCRseq, & MSI by DNA Analysis	mRNA/IF	DNA, mRNA, IHC[h]
Visit name / Study day	**Time Point**	**Serum**	**Serum**	**Whole Blood**	**Serum**	**Serum**	**Whole Blood**	**Whole Blood**	**Biopsy (FFPE)**	**Biopsy (FFPE)**	**Biopsy (FFPE)[c]**	**Mandatory Biopsy[h]**
Screening / Day -28 to -1	--							x[k]	x	x	x	x
Cycle 1, Day 1 / Study Day 1	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]				
	EOI[f] ± 5 min	x[g]			x[g]	x[g]	x[g]					
	4 h ± 10 min	x[d]										
	8 h ± 1 h	x[d]										
Cycle 1, Day 2 / Study Day 2	24 h ± 2 h	x[d]			x[d]	x[d]	x[d]					
Cycle 1, Day 3 / Study Day 3	48 h ± 4 h	x[d]										
Cycle 1, Day 5 / Study Day 5	96 h ± 12 h	x[d]			x[d]		x[d]					
Cycle 1, Day 8 / Study Day 8	168 h ± 24 h	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]					
Cycle 1, Day 22 / Study Day 22 ± 2	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]				

		PK[a,b,j]	ADA[j]	IPT	sPD-L1/ sCD137	Cytokines	RO	ctDNA[k]	PD-L1 IHC	TMB, TCRseq, & MSI by DNA Analysis	mRNA/IF	DNA, mRNA, IHC[h]
Visit name / Study day	**Time Point**	**Serum**	**Serum**	**Whole Blood**	**Serum**	**Serum**	**Whole Blood**	**Whole Blood**	**Biopsy (FFPE)**	**Biopsy (FFPE)**	**Biopsy (FFPE)[c]**	**Mandatory Biopsy[h]**
Cycle 1, Day 28 / Study Day 28 ± 3	--											x[i]
Cycle 2, Day 1 / Study Day 43 ± 2	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]			x	
Cycle 2, Day 8 Study Day 50 ± 2	168 h ± 48 h	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]					
Cycle 2, Day 22 / Study Day 64 ± 2	Pre-dose	x[g]	x[g]		x[g]	x[g]		x[k]				
Cycle 3, Day 1 / Study Day 85 ± 3	Pre-dose	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]	x[k]			x	
	EOI[f] ± 5 min	x[g]										
	4 h ± 10 min	x[d]										
	8 h ± 1 h	x[d]										
Cycle 3, Day 2 / Study Day 86	24 h ± 2 h	x[d]				x[d]						
Cycle 3, Day 3 / Study Day 87	48 h ± 4 h	x[d]										
Cycle 3, Day 5 / Study Day 89	96 h ± 12 h	x[d]										
Cycle 3, Day 8 / Study Day 92	168 h ± 24 h	x[g]				x[g]						

		PK[a,b,j]	ADA[j]	IPT	sPD-L1/ sCD137	Cytokines	RO	ctDNA[k]	PD-L1 IHC	TMB, TCRseq, & MSI by DNA Analysis	mRNA/IF	DNA, mRNA, IHC[h]
Visit name / Study day	**Time Point**	**Serum**	**Serum**	**Whole Blood**	**Serum**	**Serum**	**Whole Blood**	**Whole Blood**	**Biopsy (FFPE)**	**Biopsy (FFPE)**	**Biopsy (FFPE)[c]**	**Mandatory Biopsy[h]**
All subsequent even-numbered cycles, Days 1 and 22 / Study Days e.g., 127 ± 3, 148 ± 3, etc.								x[k]				
All subsequent even-numbered cycles Day 8 / Study Days, e.g., 134 ± 3, 218 ± 3 etc.	168 h ± 48 h	x[g]	x[g]	x[g]	x[g]	x[g]	x[g]					
All subsequent odd-numbered cycles, Day 1 / Study Day 169 ± 3, etc.	Pre-dose	x[g]	x[g]	x[d]	x[d]	x[d]	x[d]	x[k]			x	
All subsequent odd-numbered cycles, Day 22 / Study Days e.g., 190 ± 3, etc.								x[k]				
Follow-up Period	--	x (FU1 *only*)	x (FU1 *only*)					x[k] (FU1, FU2, and FU3)				

Abbreviations: ADA = Anti-drug antibodies; D = Dose (study drug administration); DNA = Deoxyribonucleic acid; EOI = End of infusion; FFPE = Formalin-fixed paraffin-embedded; h = Hour; IHC = Immunohistochemistry; IPT = Immunophenotyping; TMB = Tumor mutational burden; MSI = Microsatellite instability; IF = Immunofluorescence; PK = Pharmacokinetics; PD-L1 = Programmed death-ligand 1; mRNA = Messenger Ribonucleic acid; RO = Receptor occupancy; TCRseq = T-cell receptor sequencing; TMB = Tumor mutational burden

*Assessment of IPT, sPD-L1, sCD137, cytokine panel, RO, PD-L1 IHC, TMB, TCRseq, MSI and mRNA/IF may be adjusted for Part B, following availability of Part A data; conduct of RO assay will be dependent on availability of a suitable assay.

[#] **As per 23 May 2022 SMC call, the 800mg flat dose level shall be further studied in Part B by infusion approximately every 14 days (i.e. following Table 7-1 Schedule of Assessments and applying Table 7-3 for PK, ADA and PD sampling), based on Part A PK data which do not indicate substantial accumulation at this dose level over time with this dosing interval. Optional Part A-2 of the study may explore one more higher dose level (1400mg flat dose with approximately 14-day dosing interval , i.e. following Table 7-1 Schedule of Assessments and applying Table 7-3 for PK, ADA and PD sampling) than was studied in Part A. Such 1400mg dose level will be explored applying strict stopping criteria and respecting a 28-day DLT evaluation period before more than 6 subjects are exposed. PK data for this 1400mg dose level in Part A-2 will be closely followed and in case of observation of relevant drug accumulation over time, the dosing interval for this dose may be adjusted to approximately every 21 days, in which case Table 7-2 Schedule of Assessments applies and consequently Table 7-4 would become applicable for PK, ADA and PD sampling. Such change from a 2-week to a 3-week dosing interval would only be applicable if communicated separately to sites by a written notification of the SMC decision on such change of dosing interval by means of a letter of amendment, to be followed by a full protocol amendment.**

a. Serial PK is optional except for the mandatory pre-dose, EOI and 168 ± 24 h sampling timepoints (see footnote "g").
b. If a patient permanently discontinues study drug treatment, or is not receiving an infusion at a given visit, a single PK sample will be taken at that visit.
c. Optional biopsy material for patients enrolled in Part A and A-2 from as many cycles as possible, and Follow-up period. For patients in Part B a single post treatment biopsy material collection is considered mandatory per footnote "r" in Table 7-2, i.e., for patients presenting with at least stable disease during treatment with NM21-1480.
d. Optional sampling point for Part B. Sites are not required to collect these optional PK samples in Part B. These sampling timepoints are, however, mandatory in Part A and Part A-2. For sampling timepoints considered mandatory in Part B at all sites, see also footnote "g".
e. EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion from the counter arm of the site of injection. All subsequent timepoints indicated for PK blood draws refer to hours *after* EOI.
f. For FU visits: PK and ADA sample will be taken at Follow-up Visit 1 only.
g. Mandatory sample for all patients in Part B (unless drawing is not considered clinically feasible due to the condition of the patient).
h. Only applicable for mCRC patients enrolled to Cohort B8. For specifics on sample acquisition please refer to specialty lab manual.
i. Reference is made to footnote ff in Table 7-2 for timing of these mandatory on-treatment biopsies for mCRC patients enrolled to Cohort B8.
j. Not applicable to patients in Cohort B5 randomized to standard-of-care anti-PD1 therapy only.
k. Only applicable for mCRC patients enrolled to Cohort B8.

7.2 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

7.2.1 Inclusion Criteria (Part A and Part B)

Patients are eligible to be included in this study only if all of the following criteria apply:

1. Patients aged 18 years or older or above minimum legal age to attend a clinical study on the day written informed consent is given.
2. **In Part A & A-2**: Patients with any previously treated solid tumor-type other than hepatocellular carcinoma or intrahepatic cholangiocarcinoma, confirmed by available pathology records and/or current biopsy, that is advanced (non-resectable or metastatic), or recurrent and progressing since last anti-tumor therapy, and for which no alternative, standard therapy exists.

   In Part B (all cohorts):

   - Cohorts B1 and B7:
     - Patients with locally advanced or metastatic, non-resectable NSCLC and documented PD-L1 expression on ≥50% of tumor cells[#] (Cohort B1), or documented PD-L1 expression on ≥1%-49% of tumor cells[#] (Cohort B7)
     - Cohort B1 and B7 will be conducted in the US, Spain, UK, the Netherlands, Germany, and Taiwan. Patients must have received at least 1, and a maximum of 3, previous lines of therapy, including at least 1 previous line containing a PD-(L)1 checkpoint inhibitor. **For patients enrolled to Cohorts B1 and B7 in Germany, they must have received both an anti-PD-(L)1 therapy and a platinum-based chemotherapy (i.e., at least 2 prior lines of treatment) to be eligible for study entry.**
     - Patients must have disease that is resistant (i.e., primary resistant[&]) or refractory (i.e., secondary resistant[&]) to anti-PD-(L)1 therapy as defined by:
       a) Has received at least 2 doses of an approved anti-PD-(L)1 monoclonal antibody.
       b) Has demonstrated progressive disease after anti-PD-(L)1 therapy as defined by RECIST 1.1, which was subsequently confirmed by a second assessment no less than 4 weeks from the date of the first documented progressive disease to rule out pseudo-progression, if the latter could not be excluded by the investigator based on the initial imaging demonstrating disease progression.

[#] *Prospective testing is not done for Cohort B1 and B7, i.e., inclusion relies on documented previous testing leading to initiation of anti-PD-(L)1 therapy.*

[&] *Primary vs. secondary resistance will be determined based on documented progression of patients following less than or at least 24 weeks on previous anti-PD-(L)1 therapy.*

- Cohort B2:
    - Patients with locally advanced or metastatic, non-resectable HPV-associated (i.e., HPV+ tumor) SCC of the anus, cervix, vulva, vagina, penis or oropharynx with documented PD-L1 expression on at least 1% of tumor and/or immune cells in the TME, as detected by a locally-assayed, FDA-cleared PD-L1 test or any PD-L1 test approved for use by local competent authority
    - Cohort B2 will be conducted in the US, Spain, UK, the Netherlands, Germany, and Taiwan. For Cohort B2, disease progression must have been documented following a first-line standard-of-care anti-PD-1 monotherapy, anti-PD-1/chemotherapy or chemotherapy regimen or 2 previous lines of therapy including one line of anti-PD-1 checkpoint inhibitor therapy and one line of chemotherapy. Patients must:
        a) Either have documented previous testing results indicating HPV positivity for the current tumor or, in absence of a positive previous HPV test result, the current tumor must be tested positive for HPV applying the local standard testing approach.
        b) Have demonstrated progressive disease after standard first-line, or first-*and* second-line therapy, as defined by RECIST 1.1, or in the view of the Investigator be ineligible or unwilling to be treated with standard first- or second-line therapy.

      NOTE: A maximum of 10 patients with oropharyngeal SCC and a minimum of 15 patients with cervical SCC and 15 patients with anal SCC, respectively, will be enrolled within the total of 40 patients in this cohort.
- Cohort B3:
    - Patients with locally advanced or metastatic, non-resectable NSCLC and documented PD-L1 expression on ≥50% of tumor cells
    - Cohort B3: will be conducted in Turkey, Georgia, Ukraine, and Taiwan. For Cohort B3, standard-of-care first-line treatment is defined as: standard local first-line chemotherapy. Patients must have demonstrated progressive disease after standard-of-care local first-line therapy, as defined by RECIST 1.1. PD-

L1 expression on tumor cells is determined centrally by a Sponsor-approved PD-L1 assay

- Cohort B4:
    - Patients with recurrent, persistent or metastatic ovarian, primary peritoneal or fallopian tumor carcinoma of all histologic types, except mucinous adenocarcinoma and carcinosarcoma, with documented disease progression (disease not amenable to curative therapy) and a history of primary platinum-based chemotherapy
    - Cohort B4 will be conducted in the US, Spain, UK, the Netherlands, Germany, Taiwan, Turkey, Georgia, and Ukraine. For Cohort B4, patients must have a history of primary platinum-based chemotherapy with a maximum of 3 prior cytotoxic regimens and with at least one regimen for recurrent disease containing a platinum or a taxane for those with 3 prior regimens; the last platinum-free interval must be ≤12 months. Histologic confirmation of the original primary tumor is required via the pathology report. NOTE: Patients with mucinous or carcinosarcoma history are not eligible.
    - Patients are allowed to have received up to 3 prior cytotoxic regimens for treatment of their epithelial ovarian, fallopian tube, or primary peritoneal cancer;
        - they must have had one prior platinum-based chemotherapeutic regimen for management of primary disease, which could include intra-peritoneal therapy, consolidation, biological/targeted (non-cytotoxic) agents or extended therapy (maintenance/consolidation) administered after surgical or non-surgical assessment;
        - patients are allowed to have received, but are not required to have received, one to 2 cytotoxic regimens for management of recurrent or persistent disease;
        - PARP inhibitors given for recurrent or progressive disease will be considered cytotoxic;
        - PARP inhibitors given as maintenance therapy in continuation with management of primary disease will not be considered as separate cytotoxic regimen;
        - if 2 cytotoxic regimens had been received for management of recurrent or persistent disease, one of these regimens would have had to contain either a platinum or a taxane agent

- Platinum-free interval (PFI) – patients must have progressed ≤12 months after completion of their last platinum-based chemotherapy; the date (PFI) should be calculated from the last administered dose of platinum therapy to documentation of progression

- Cohort B5:
  - Patients with head and neck squamous cell cancer with documented CPS ≥1 in the TME and as determined by an FDA-cleared* or any PD-L1 test approved for use by competent authority
  - Cohort B5 will be conducted in the US, Spain, UK, the Netherlands, and Taiwan. For Cohort B5, patients must have metastatic or unresectable, recurrent disease considered incurable by local therapies. Patients must qualify for in-label first-line, single-agent treatment with an approved anti-PD1 checkpoint inhibitor and as per investigator judgement would also be put on such treatment as part of standard-of-care, i.e., irrespective of clinical trial participation, at doses not exceeding those approved in local product labels.

    * *FDA-cleared tests include: PD-L1 IHC 22C3 (Dako; preferred assay), VENTANAPD-L1 (SP142; Ventana/Roche), and PD-L1 IHC 28-8 (Dako, VENTANA PD-L1 (SP263; Ventana/Roche), or any other companion /complementary diagnostic PD-L1 assay that may receive FDA approval during the conduct of this study.*

- Cohort B6:
  - Patients with TNBC according to current ASCO/CAP guidelines that is measurable according to RECIST1.1 criteria
  - Cohort B6 will be conducted in the US, Spain, UK, the Netherlands, and Taiwan. For Cohort B6, patients must have metastatic disease or locally advanced breast cancer (beyond curative management).
  - TNBC must be characterized as having ≤1% cellular expression of ER and PR as determined by IHC and having HER2 expression of 0 to 2+ by IHC as per current ASCO/CAP Guidelines. If IHC 2+, a negative in situ hybridization test (preferably FISH; CISH or SISH acceptable) is required by local laboratory testing
  - Patients must have received at least one line of previous systemic therapy for advanced breast cancer (chemotherapy or targeted therapy allowed); however, patients must not have received mor than 3 previous lines of cytotoxic chemotherapy (*i.e.,* targeted agents not counting as previous line in this context)

- 20 patients in the cohort must have received prior therapy with an immune checkpoint inhibitor (i.e., an approved PD-1 or PD-L1 antibody), while the other 20 patients must not have received prior therapy with an immune checkpoint inhibitor (as per stratification)

- Cohort B8:
  - Cohort B8 will be conducted in the US, Spain, UK, the Netherlands, and Germany. Patients with metastatic, non-resectable colorectal cancer (mCRC) that is MSS or MSI low*, previously treated with all of the following:
    - fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy,
    - and, if RAS wild-type, an anti-EGFR therapy, if eligible
    - Patients previously treated with an additional anti-VEGF biological therapy are also eligible
  - Patient agrees to paired biopsies and is judged by the investigator as safe for paired biopsies
  - Patients must have documented PD-L1 expression in the TME with PD-L1 expressed on at least 1% of tumor and/or immune cells, as detected by local testing with an FDA-cleared or any PD-L1 assay approved for use by local competent authority*.

    *Eligibility determination can be done based on documented previous testing results. If no previous testing result is available eligibility determination will be done based on archival tissue or fresh biopsy taken during screening

3. Patients must provide tumor tissue (archival or fresh acquisition) at Screening for biomarker and PD evaluation. Archival tissue sample can be formalin-fixed paraffin-embedded (FFPE) tissue block(s) obtained within 5 years (for B cohorts: 2 years) before Screening (preferably within 12 months) or (at least 20) freshly sectioned unstained slides with tumor tissue present as per pathologist confirmation. Availability of tissue blocks is preferred over slides. Acceptable tissue sample include core needle punctured, resected or incisional biopsy, or surgical sample. (Note, fine needle aspirate (FNA) sample and tumor tissue from bone metastasis are not acceptable). Fresh biopsy should not be obtained from RECIST-defined target lesions if possible. Consult the Medical Monitor when no other lesions are suitable for biopsy, or in cases where archival tissue was obtained outside the above-specified timeframes, as exceptions may be approved on a case-by-case basis.
4. **Cohort B8**: For biomarker and PD evaluation, MSS or MSI low mCRC patients enrolled must mandatorily provide freshly acquired tumor tissue (primary tumor or metastases) at Screening and – whenever considered clinically feasible as per investigator judgement – at least once

while on treatment. Acceptable tissue sample include core needle punctured, resected or incisional biopsy, or surgical sample. (Note, FNA sample and tumor tissue from bone metastasis are not acceptable). Fresh biopsy should not be obtained from RECIST-defined target lesions if possible. Consult the Medical Monitor when no other lesions are suitable for biopsy. At least 3 biopsy cores, but preferably more if considered safe by the radiologist, shall be taken at each biopsy event and touch preparation as per site standard approach shall be applied to ensure specimen adequacy (i.e., confirm tumor content). In addition to these fresh biopsies, for patients for whom there is archival primary tumor tissue available, this archival tissue, as per inclusion criterion #3 requirements, shall also be provided for biomarker analysis.

5. **Part A:** Patients with liver metastases may be enrolled provided that less than 50% of the liver is involved according to the judgement of the Investigator.
6. ECOG performance status 0 or 1.
7. Life expectancy ≥12 weeks.
8. Must have at least 1 measurable lesion per RECIST 1.1 that is progressing or new since last anti-tumor therapy. The measurable lesion(s) can be inside the field of prior radiotherapy (RT) provided that the lesion has documented progression post RT as per RECIST 1.1.
9. **Part A & A-2**: Prior chemotherapy or systemic radiotherapy (for immunotherapy see exclusion criteria) must have been completed at least 4 weeks prior to the administration of the first dose of study drug, and patient has recovered to Common Terminology Criteria for Adverse Events (CTCAE) V5.0 Grade 1 or better from all AEs associated with prior therapy or surgery (however, sensory neuropathy, alopecia and endocrine disorder treated with hormone replacement ≤Grade 2 is acceptable).

   Part B: *For Cohort B1, B2, B6 (subgroup with required previous checkpoint inhibitor therapy) and B7:* Last dose of therapy with anti-PD-1 monotherapy must have been received at least 2 weeks prior to the administration of the first dose of the study drug. *All Part B 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 (e.g., thyroid hormone) replacement therapy.
10. Prior treated brain or meningeal metastases must be without magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks and off immunosuppressive doses of systemic steroids (>10 mg/day prednisone or equivalent) for at least 2 weeks prior to the administration of the first dose of study drug; patients must be without neurologic dysfunction that would confound the evaluation of neurologic and other AEs (patients with a history of carcinomatous meningitis are not eligible).

11. **Part A & A-2:** Breast cancer patients who are receiving adjuvant hormonal therapy are eligible.
12. Prior systemic RT must have been completed at least 4 weeks prior to the administration of the first dose of study drug. Prior focal radiotherapy must have been completed at least 2 weeks before first study drug administration. No radiopharmaceuticals (strontium, samarium) must have been used within 8 weeks prior to the administration of the first dose of study drug.
13. Immunosuppressive medication including immunosuppressive doses of systemic steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent) must be discontinued at least 2 weeks prior to the administration of the first dose of study drug.
14. Prior major surgery that required general anesthesia must be completed at least 2 weeks prior to the administration of the first dose of study drug; minor surgical procedures (such as e.g. laparoscopy, endoscopy, port insertion etc.) conducted under general anesthesia or surgery requiring regional/epidural anesthesia must be completed at least 72 hours prior to the administration of the first dose of study drug and patients should be recovered. Cutaneous biopsies with only local anesthesia should be completed at least 1 hour prior to the administration of the first dose of study drug.
15. Screening laboratory values must meet the following criteria:
    - Hematological:
        - White blood cell (WBC) $\geq 2.0\times10^9$/L
        - Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L
        - Lymphocyte count $\geq 0.5\times10^9$/L
        - Platelets $\geq 100\times10^9$/L
        - Hemoglobin ≥9 g/dL
    - Renal: serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated using the Cockcroft-Gault formula or measured creatinine clearance >50 mL/min.

$$Female\ creatinine\ clearance = \frac{(140 - age\ in\ years) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine in mg}/dL}$$

$$Male\ creatinine\ clearance = \frac{(140 - age\ in\ years) \times \text{weight (kg)} \times 1.00}{72 \times \text{serum creatinine in mg}/dL}$$

    - Hepatic:

- Total bilirubin ≤1.5×ULN (except patients with Gilbert's syndrome, who must have total bilirubin ≤3.0×ULN)
- AST and ALT ≤2.0×ULN
- **Cohort B8:**
  - Serum albumin ≥30 g/L (3.0 g/dL)
  - Lactate dehydrogenase ≤2.5xULN

- Coagulation:
  - International Normalized Ratio or Prothrombin time (PT) ≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or Partial Thromboplastin Time (PTT) is within therapeutic range of intended use of anticoagulants based on the institutional standard-of-care
  - Activated Partial Thromboplastin Time ≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants based on the institutional standard-of-care
- Thyroid stimulating hormone (TSH) is required to be within normal limits at baseline; however, if TSH is not within normal limits at baseline, the patient may still be eligible if total triiodothyronine (T3) or free T3 and free thyroxine (T4) are within the normal limits.

16. Female patients must have a negative serum pregnancy test within 72 hours prior to the administration of the first dose of study drug if of child-bearing potential or be of non-child-bearing potential. In case of a positive serum pregnancy test, the site is allowed to apply standard site procedures to rule out false positive test results; enrollment of the patient may be considered only in case of false positivity of the serum pregnancy test has been confirmed. A urine pregnancy test is to be done prior to dosing at all other time points and must be negative prior to the administration of the first dose of study drug.

    If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible for continued treatment with the study medication. Non-child-bearing potential is defined as (by other than medical reasons):

    - ≥45 years of age with continuous amenorrhea for >2 years and a follicle stimulating hormone (FSH) of >40 IU/L upon pre-study (Screening) evaluation.
    - Women who were surgically sterilized, i.e., had a hysterectomy and bilateral oophorectomy, or have a documented permanent female sterilization procedure including tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation

must be confirmed with medical records of the actual procedure otherwise the patient must be willing to utilize a reliable form of contraception (either medication – oral, implant or injection – or a barrier method). In general, the decision for appropriate methods to prevent pregnancy should be determined by discussions between the Investigator and the study patient. A FSH level can be used to confirm post-menopausal status in amenorrheic patients not on hormonal therapy.

- Women of child-bearing potential (WOCBP) must agree to use a highly effective method of contraception (i.e. pregnancy rate of less than 1% per year) during the study Treatment Period and for 180 days following the last dose of study drug.

17. Men who have female partners of child-bearing potential must agree to the use of contraception during the study Treatment Period and for at least 180 days after the last dose of study drug (see Appendix V, Section 18.5).
18. No active bleeding.
19. Able to understand and give written informed consent and comply with study procedures.
20. **Part A-2:** Documented minimal PD-L1 expression on at least 1% of tumor and/or immune cells in the TME, as detected by a local testing with an FDA-cleared or any PD-L1 assay approved for use by local competent authority.
21. **Part B:** Must have received complete Covid-19 vaccination within the timeframe considered to provide protection at the time of study enrollment according to current local guidelines, or must have a negative Covid-19 test polymerase chain reaction (PCR) test result.

7.2.2 Exclusion Criteria (Part A and Part B)

Patients are excluded from the study if any of the following criteria apply:

1. Patient previously had known immediate or delayed hypersensitivity reaction or idiosyncrasy to the excipients (refer to Appendix I, Section 18.1) of IP or has experienced ≥Grade 3 immune-related adverse events (irAEs) with previous CPI therapy.
2. Prior (other) malignancy active within the previous 2 years (any prior malignancy for which there were detectable lesions [solid tumors] or for which the patient was not considered to be in complete remission [liquid tumors] or for which there was ongoing curative treatment) except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast.
3. **In Part A & A-2**: Treatment with any antibody targeting PD-1, CTLA-4, 4-1BB or PD-L1 or other investigational biological drugs within 5 half-lives of that antibody prior to the administration of the first dose of study drug (or within 8 weeks if the half-life is not known).

   In Part B:

   - Cohorts B1 and B7 – NSCLC and documented PD-L1 expression on ≥50% of tumor cells (Cohort B1) or documented PD-L1 expression on ≥1%-49% of tumor cells (Cohort B7):
     - Treatment with any PD-1 antibody within 2 weeks prior to first dose of study drug
     - Treatment with any PD-L1-directed therapy within 5 (five) half-lives of the respective drug; if the half-life of the respective PD-L1 antibody is unknown, treatment with such a PD-L1 antibody within 12 weeks prior to the first dose of study drug is exclusionary.
     - Previous treatment with a PD-(L1)x4-1BB specific antibody or any other treatment targeting 4-1BB
     - Patient who for the treatment of the current cancer has received any other treatment than anti-PD-(L)1 or chemotherapy within 28 days 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-(L)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-(L)1 therapy is exclusionary. However, sensory neuropathy ≤Grade 2, alopecia and endocrine disorder treated with hormone replacement is acceptable.
   - Cohort B2 – HPV-associated (i.e. HPV+ tumor) SCCs:
     - 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-line or second-line treatment; in addition, patients with 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 hormonal replacement are acceptable.

  - Treatment with PD-1 antibody within 2 weeks prior to first dose of study drug

- Cohort B3 – NSCLC and documented PD-L1 expression on ≥50% of tumor cells:
  - Patients who, for the treatment of the current cancer, has received any treatment other than a local standard-of-care first-line chemotherapy regimen or who has not recovered to CTCAE V5.0 Grade 1 or better from the AE due first-line treatment. However, sensory neuropathy ≤Grade 2, alopecia and endocrine disorders treated with hormonal replacement are acceptable.
  - Patient has received a PD-1, PD-L1, 4-1BB or CTLA-4 antibody or any other investigational biological drugs for treatment of the current cancer.
  - Patients with epithelial growth factor receptor (EGFR) tyrosine kinase activating mutations or anaplastic lymphoma kinase (ALK) rearrangements. Patients with EGFR inactivating mutations (e.g., exon 20) may be eligible.
- Cohort B4 – ovarian, primary peritoneal or fallopian tumor carcinoma:
  - Patients who have had prior therapy with anti-PD1, 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 checkpoint pathways.
  - 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, 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 recurrence or metastatic disease.
- Cohort B5 – head and neck squamous cell cancer with documented CPS≥1:
  - Patients who have previously received a checkpoint inhibitor for their disease
- Cohort B6 – TNBC:

- 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 the study drug. If the half-life of a previously used anti-PD-L1 antibody is unknown, the Medical Monitor must be contacted.
    - Patient who has not recovered to CTCAE V5.0 Grade 1 or better from the AE due to anti-PD-1 or anti-PD-L1 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-PD-1 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
- 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 checkpoint pathways

- Cohort B8 – mCRC:
    - Patients who have previously been treated with trifluridine/tipiracil or regorafenib
    - Patients who have previously been treated with T-cell bispecifics, 4-1BB agonists, or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD1 and anti-PD-L1 unless discussed with the Medical Monitor and agreed by the Sponsor
    - Patients who have received treatment with systemic immunostimulatory agents (including, but not limited to, interferon and IL-2) within 4 weeks or 5-half lives, whatever is longer, prior to initiation of NM21-1480 treatment
    - Patients who have received treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNFalpha medications) within 2 weeks prior to initiation of NM21-1480 treatment, or anticipation of need for systemic immunosuppressive medication* during NM21-1480 treatment

- Presence of ascites that required two or more therapeutic paracenteses in the last 30 days

4. Patient is currently participating in a study of an investigational agent or using an investigational device within 4 weeks prior to the administration of the first dose of study drug (see further specification in exclusion criterion 5 and 6).
5. Use of small molecule-based therapy within at least 5 half-lives based on last dose of the small molecule therapy or 4 weeks (if half-life of the small molecule drug is not known) prior to the administration of the first dose of study drug.
6. **In Part A & A-2:** Use of other biological investigational drugs (drugs not marketed for any indication), including use of investigational drugs targeting CD137/4-1BB, PD-1 or PD-L1 within at least 5 half-lives (or within 8 weeks, if half-life of that investigational drug is not known) prior to the administration of the first dose of study drug.
7. Patient is expected to require any other form of systemic or localized antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative RT, or standard or investigational agents for treatment of malignancy) while on study.
8. Concurrent medical condition requiring the use of systemic immunosuppressive medications.
9. Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally (also refer to exclusion criterion 23).
10. Patient has an active autoimmune disease or a documented history of autoimmune disease that required systemic therapy within 5 years prior to screening. Patients with documented history of autoimmune disease who required therapies other than dietary modification for disease control within 5 years prior to screening must be discussed with the Medical Monitor to determine eligibility status, except for the following cases which are not exclusionary: a) Patients with vitiligo, autoimmune thyroiditis, or psoriasis (not requiring systemic treatment within the past 2 years); b) Type I diabetes controlled with stable insulin therapy; c) Childhood asthma/atopy which, in the view of the investigator, has resolved; d) Patients that require intermittent use of bronchodilators, inhaled steroids or local steroid injections including intra-articular injections; e) Patients with hypothyroidism stable on hormone replacement.
11. **In Part A & A-2**: Patients with active or known history of hepatitis (viral or non-viral) or liver cirrhosis, colitis, non-infectious pneumonitis or interstitial lung disease; patient with hepatocellular carcinoma or intrahepatic cholangiocarcinoma.

In Part B: Patients with active or known history of hepatitis (viral or non-viral) or liver cirrhosis, colitis, non-infectious pneumonitis or interstitial lung disease. Patients who have received curative anti-viral treatment for hepatitis C may be eligible but must be discussed with and approved by the Medical Monitor prior to inclusion into the study.

12. Patient with an active infection requiring systemic therapy (antibiotics, antivirals or antifungals) or for whom based on screening results initiation of systemic anti-infective therapy is indicated in the opinion of the Investigator.
13. Patient who are seropositive for human immunodeficiency viruses (HIV) and have CD4 T-cell counts below 350 cells/mcL or with a history of AIDS-defining opportunistic infections.
14. Patients who have a known history of or are seropositive for hepatitis B or hepatitis C. Patients who have received curative anti-viral treatment for hepatitis C may be eligible but must be discussed with and approved by the Medical Monitor prior to inclusion into the study.
15. Patient with active or known latent tuberculosis.
16. At time of Screening, patient has an uncontrolled cardiovascular, liver or lung disease, myelodysplastic syndrome, neurologic or psychiatric disorder, laboratory abnormality, acute infectious disease, or other systemic disease, which the Investigator determines will make the administration of study drug hazardous or obscure the interpretation of toxicities or AEs.
17. Grade >1 QTc prolongation at baseline (>480 msec by Bazett formula) confirmed by a repeat electrocardiogram (ECG).
18. Patients with a history of venous thrombosis within the past 6 months prior to the administration of the first dose of study drug.
19. Patients with a diagnosis of acute coronary syndrome including myocardial infarction or unstable angina pectoris, other arterial thrombotic event including cerebrovascular accident or transient ischemic attack or stroke within the past 12 months prior to the administration of the first dose of study drug.
20. Patients with congestive heart failure with New York Heart Association Class II or greater diagnosis, serious cardiac arrhythmia requiring medication, or uncontrolled hypertension (≥160 mmHg systolic and/or ≥100 mmHg diastolic, despite appropriate antihypertensive medication).
21. Patients with a history of hypertensive crisis/hypertensive encephalopathy within the past 12 months prior to the administration of the first dose of study drug.
22. Patient has known psychiatric or substance (including alcohol) abuse disorders that would interfere with cooperation with the requirements of the study per the determination of the Investigator.

23. Patient is not willing to refrain from or cannot discontinue concomitant intake of medications or substances known to cause elevation of liver enzymes, including e.g., acetaminophen (a daily dose of up to 2 g/day is allowed to manage acute pain), or systemically active cannabidiol (CBD); topical CBD is allowed.
24. Patient is pregnant or breast feeding or expecting to conceive or father children within the projected duration of the study or for 180 days after discontinuing study drug.
25. Patient has received a live vaccine within 30 days prior to the administration of the first dose of study drug.
26. Receipt of an allogeneic stem cell transplantation or organ allograft.
27. **In Part B**: Treatment with systemically active antibiotics within 14 days prior to the administration of the first dose of study drug.

7.2.3 Strategies for Recruitment and Retention

All recruitment material will be approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) prior to implementation.

Regular study monitoring will enable identification of any potential issues related to participant retention.

7.2.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who do not subsequently receive a minimum of one dose of study drug. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any serious adverse event (SAE).

7.2.5 Stopping Rules and Decision-Making Procedure

A BOIN design is applied in Part A. The DLT evaluation period consists of one full treatment cycle, i.e., ends 28 days following the first dose administration. The target toxicity rate for the MTD for the BOIN design applied is $\phi = 0.3$ and the maximum sample size is 25. The design is described as follows:

1. Perform accelerated titration as follows: treat the first patient at dose level 1. If no ≥Grade 2 toxicity (as assessed by the Investigator to be related, probably related, or possibly related to the drug at any dose level) is observed, escalate the dose to the next higher level. Continue this 1-patient-per-dose dose-escalation process until the first ≥Grade 2 toxicity during the DLT evaluation period is observed or dose level 5 (80 mg dose level) is reached. Treat an additional

2 patients at the dose at which the first ≥Grade 2 toxicity is observed. Hereafter, patients are treated in cohorts of 3 as described in steps 2 and 3.

2. To assign a dose to the next cohort of patients, conduct dose-escalation/de-escalation according to the BOIN rule, which minimizes the probability of incorrect dose assignment. Please note the following:
   a. "Eliminate" means eliminate the current and higher doses from the study to prevent treating any future patients at these doses because they are overly toxic.
   b. When a dose is eliminated, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the study for safety. In this case, no dose should be selected as the MTD.
   c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.
   d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the study for safety.
   e. If the current dose is the highest dose and the rule indicates dose-escalation, treat the new patients at the highest dose.
3. Repeat step 2 until the maximum sample size of 25 is reached or stop Part A of the study if the number of patients treated at the current dose reaches 12.

The first patient treated with each dose level will be observed for 48 hours after dosing for the occurrence of DLT before treatment of potential additional patients at this dose level can occur.

Part A of the study was formally completed on 23 May 2022 at which occasion, based on availability of at least 28-day safety data for all 25 patients evaluable for BOIN in Part A, the SMC determined that Part A did not technically identify a MTD and that even the highest dose level assessed in Part A (800mg flat dose) was considered a tolerated dose. However, based on the finding that some patients dosed at 24-240mg in Part A developed treatment-emergent ADAs leading to loss of exposure, while this was not observed at the 800mg dose level, a decision was taken to explore one higher dose level (1400mg flat dose) in up to 10 patients within Part A-2 in parallel to studying the 800mg dose level in Part B. For safety evaluation of this single additional dose level, the target toxicity rate applied for BOIN in Part A ($\phi = 0.3$) will be applied. Initially, 6 patients will be dosed with 1400mg of NM21-1480 in Part A-2 and upon completion of the 28-day DLT evaluation period for these six patients, as per SMC call, an additional up to 4 patients may be enrolled at this dose level (to end up with a maximum of 10 patients to be exposed to 1400mg in Part A-2), applying the decision rules defined for BOIN as detailed in Table 10-2. Whenever after 6 patients have completed the 28-day DLT evaluation period at the 1400mg dose level, according to the BOIN decision rules, de-escalation from the 1400mg dose or elimination of

the 1400mg dose would be required, further enrollment into the dose level will be stopped. In such situation, ongoing patients who are tolerating the dose level may be continued at 1400mg flat dose unless the safety review mandates dose reduction in which case the dose may be reduced to 800mg or the patient may be discontinued from treatment based on discussion between the investigator and the Medical Monitor. If tolerability of the 1400mg dose allows for completion of the 28-day DLT evaluation period for 6-10 patients, the SMC will determine based on the BOIN decision rule guidance provided in Table 10-2 whether:

- The 1400mg dose level is considered a tolerable dose and technically not considered to represent the MTD because BOIN would recommend further dose escalation at this point (i.e. $\phi \leq 0.236$)
- The 1400mg dose level is considered a tolerable dose and to represent the MTD if $\phi > 0.236$ and $\phi \leq 0.3$
- The 1400mg dose level is not considered a tolerable dose (i.e. $\phi > 0.3$)

However, the SMC is free to apply a more stringent definition of the MTD for ruling of the 1400mg dose level if deemed necessary.

7.2.5.1 Dose-Limiting Toxicity

A DLT is defined as a TEAE (using CTCAE V5.0) occurring during the first 28 days of dosing, as follows:

- Any death not clearly due to the underlying disease or extraneous causes
- Hematologic AEs:
    - Febrile neutropenia, defined as ANC <1000 mm^3 with a single temperature of ≥38.3°C or a sustained temperature of; ≥38°C for more than 1 hour;
    - Neutropenia, Grade 4 that does not resolve to Grade 1 with granulocyte macrophage-colony-stimulating factor (CSF) or granulocyte-CSF treatment within 7 days;
    - Neutropenia or thrombocytopenia Grade 4 or higher present for >7 days, neutropenic infection, Grade 3;
    - Thrombocytopenia with clinically significant bleeding, Grade 3;
    - (Life-threatening) anemia, Grade 4.
- Non-hematologic AEs:
    - Any Grade ≥3 toxicities including maximally treated (with adequate antiemetic and other supportive care) Grade ≥3 nausea, vomiting, or diarrhea of >72 hours duration;
        - Grade ≥3 increased AST or ALT, or satisfying Hy's Law (i.e., AST/ALT >3× ULN with concomitant total bilirubin >2× ULN with no evidence of hemolysis and

alkaline phosphatase (ALP) >2 × ULN or not available), for patients with hepatic metastases: AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 days;

- Grade ≥3 non-hematologic laboratory abnormality requiring medical treatment or hospitalization, Grade ≥3 fatigue present for ≥1 week;
- Grade ≥3 electrolyte abnormality that lasts for >72 hours, unless the patient has clinical symptoms, in which case all Grade 3+ electrolyte abnormality regardless of duration counts as a DLT;
- Grade 4 laboratory abnormalities irrespective of duration;
- Grade 3+ irAEs except for those listed below.

In addition, any grade drug-related toxicity (with the exception of infusion-related reactions) which in the judgement of the Investigator or Sponsor requires removal of the patient from the study.

Patients who received <80% of both of the total intended Cycle 1 doses for reasons other than DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and can be replaced.

Resumption of NM21-1480 administration for patients experiencing DLTs may be permitted according to the criteria described under Section "Dose Resumption", if clinically appropriate, contingent on the return of the DLT to ≤Grade 0-1 severity or to baseline, and interruption or delay of treatment for no more than 35 days (i.e., 2 missed doses + 7 days) from the scheduled dosing and upon discussion with and approval by the Medical Monitor.

The following events shall not be regarded as a DLT:

- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) present for less than 7 continuous days
- Grade 3 Infusion-related reaction resolving within 6 hours and controlled with medical management
- Transient (≤6 hours) Grade 3 influenza-like symptoms or pyrexia controlled with medical management
- Grade 3 local reaction or headache that resolves to a maximal severity of Grade 1 within 24 hours
- Grade 3 skin toxicity, or increase liver enzyme (AST, ALT) that resolves to a maximum severity of Grade 1 within 7 days after initiation of medical management (e.g., immunosuppressant treatment)
- Grade 3 skin toxicity that improves to Grade 0 to 2 within 3 days

- Grade 3+ amylase or lipase elevation not associated with symptoms or clinical manifestations of pancreatitis does not represent a DLT
- Grade 3 treatment-related endocrinopathy AEs, such as adrenal insufficiency, adrenocorticotrophic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively
- Grade 3 laboratory abnormalities that improve to ≤Grade 2 within 3 days only if asymptomatic and if medical intervention was not required

Elevations of ALT/AST that are >3-fold above baseline are to be considered adverse events of special interest (AESI) and to be reported with SAE timelines. The details on how to handle this situation are described in Appendix VI, Section "Hepatitis". In case of Grade 3+ hepatotoxicity, an initial ultrasound or image needs to be done to visualize the biliary tree and to rule out disease progression or occurrence of gall stones.

DLTs must be confirmed by a SMC (consisting of study Investigators, Medical Monitor, and Sponsor observers) as related or relevant to treatment with NM21-1480. Patients with occurrence (with the exception of those listed above) of any Grade 3 or worse AE as defined above should be permanently discontinued from the study. All AEs (with the exception of those listed above) of the specified grades should count as DLTs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

A DLT will be considered related to study drug unless there is a clear, well-documented, alternative explanation for the toxicity.

All AEs that meet DLT criteria, as well as any Grade 3 or 4 infusion reactions whether or not the event is a DLT, must be reported as AESI within 24 hours using rapid notification procedures.

7.2.5.2 Stopping Rules for Delayed AEs During Dose-Escalation

Delayed AEs fulling criteria of DLTs (i.e., occurring after the 4-week DLT evaluation period) will be evaluated on a case-by-case basis. Delayed DLTs will not be used to estimate the MTD for dose-escalation. However, if 2 or more delayed DLTs are noted within a dose-escalation cohort, further accrual in that cohort will be held pending safety analysis of the AEs.

7.2.5.3 Safety Stopping Rules in the Expansion Cohorts

Safety Monitoring Committee (SMC) meetings will be held according to the SMC charter to evaluate the safety data in Part A-2 (optional) and Part B. Within Part A-2, the SMC will meet and evaluate the DLT rate and re-consider dosing/dosing intervals whenever a patient experiences a DLT as well as when six patients have completed the 28-day DLT evaluation period for patients dosed at 1400mg flat dose in the optional Part A-2. The SMC will also meet and evaluate the DLT rate within Part B, whenever in a given Part B dose expansion cohort (Part B; expansion cohorts

B1-B4 and B6-B8) two patients have experienced a DLT and when a minimum of 20 patients have been dosed across all Part B expansion cohorts and the DLT evaluation period for all these dose expansion patients has been completed. If the incidence of DLT in Cycle 1 in any Part B cohort is greater than 30%, the SMC may pause enrollment of that or all cohorts and re-assess the dose/regimen of the study drug. For Cohort B5, the SMC will also follow the same DLT evaluation approach for patients enrolled to the combinatorial treatment arm of Cohort B5 as described for Cohort A-2 above: The SMC will meet and evaluate the DLT rate and re-consider dosing/dosing intervals whenever a patient experiences a DLT as well as when six patients have completed the 28-day DLT evaluation period for patients dosed at the 800mg NM21-1480 flat dose in the NM21-1480/PD-1 checkpoint inhibitor arm.

Enrollment into Part B may be held either if the rate of DLTs is ≥30% across all the expansion cohorts or if the rate of DLTs is ≥30% for a specific expansion cohort with more than 6 patients enrolled. New enrollment should be held in the dose level where a ≥30% DLT rate occurs (in such cases, however, lower dose level expansion may continue). Patients who are tolerating a study drug dose level that is being reviewed due to DLTs that occurred in other patients will not be automatically precluded from continued dosing during this safety review, and will be allowed to continue dosing for as long as it is tolerated unless the safety review mandates dose reduction. After safety analysis by the Investigators and the Sponsor, a decision will be made by the SMC whether to resume enrollment into Part B cohorts and continue dosing at the current dose or continue the expansion cohort at a lower NM21-1480 dose. The SMC will also periodically (at least every 6 months, with details described in the SMC charter) review delayed DLTs, while enrollment will be held and/or restarted using the same rules as that for DLTs (i.e., based on a ≥30% DLT rate).

For expansion Cohort B5, patients randomized to the NM21-1480/PD-1 checkpoint inhibitor arm will be treated with the 800mg flat dose of NM21-1480. Once 6 patients have been enrolled to the combination treatment arm, enrollment to the cohort will be put on hold until the safety data for the 28-day DLT evaluation period for these six patients have been reviewed by the SMC. At this point, the SMC will determine whether the 800mg NM21-1480 represents a tolerable dose in the combinatorial setting applied in Cohort B5, following the below guiding BOIN principles provided in Table 10-2:

- The 800mg dose level is considered a tolerable dose and technically not considered to represent the MTD in this combinatorial setting because BOIN would recommend further dose escalation at this point (i.e. $\phi \leq 0.236$)
- The 800mg dose level is considered a tolerable dose and to represent the MTD in this combinatorial setting if $\phi > 0.236$ and $\phi \leq 0.3$
- The 800mg dose level is not considered a tolerable dose (i.e. $\phi > 0.3$)

However, the SMC is free to apply a more stringent definition of the MTD for ruling of the 800mg dose level of NM21-1480 in the combinatorial setting applied in Cohort B5 if deemed necessary. Should the SMC, upon review of the 28-day safety data for the first six patients enrolled to the combinatorial arm of Cohort B5 conclude that the 800mg dose is not considered tolerable in this setting, Cohort B5 will be stopped. However, if the SMC concludes at this point that the 800mg dose of NM21-1480 represents a tolerable dose, enrollment into Cohort B5 may be resumed.

Following SMC review of the 28-day safety data for the first six patients enrolled to the combinatorial arm of Cohort B5, the same safety stopping rules will apply as described for Cohorts B1-B4 and B6-B8 above.

7.2.5.4 Stopping Rules for Futility in the Expansion Cohorts

A BOP2 design is applied for Part B, Cohorts B1 through B4, and B6 through B8 which includes an interim futility analysis conducted after 25 patients have been enrolled and treated in the respective cohort(s). This futility analysis will be conducted based on availability of response data following completion of the first 2 RECIST 1.1 and iRECIST assessments (i.e., when 12 weeks of imaging data is available) for the 25 patients. The Sponsor in consultation with the SMC will determine at this point whether the cohort shall be stopped or continued. Go/no-go criteria based on posterior probability will be applied as specified in Table 10-6. For Cohort B8, the Sponsor will hold enrollment to the Cohort after 25 patients have received at least one dose of NM21-1480 treatment until all relevant safety, efficacy, PK, immunogenicity and most prominently all relevant PD data that has accrued until then has been reviewed by the Sponsor and the SMC. After this interim review, the Sponsor may decide to stop the cohort, to continue with full enrollment of the cohort or revise eligibility criteria before the remaining 15 patients in the cohort are enrolled.

The go/no-go criteria of the BOP2 are non-binding though, in particular as an ORR of 10% in the patient population assessed may already be considered a clinically meaningful result by the Sponsor e.g., based on clinical subgroup and/or biomarker data. Futility analyses will be done based on availability of 12 weeks data. The data monitoring committee (DMC), consisting of Sponsor representatives will determine whether a cohort shall be stopped or continued after the interim analysis.

In case (a) cohort is not stopped for futility after the interim analysis, enrollment continues until 40 patients per cohort have been enrolled and treated. A final analysis will then be conducted after initial response data (i.e., based on availability of 12-week data) for the total (maximum) of 40 patients for a given cohort is available. Part A study data discussed with SMC on 23 May 2022 demonstrated the development of treatment-emergent anti-drug-antibodies (ADAs) in a relevant fraction of patients dosed at 24mg-240mg. These ADAs were typically associated with rapid elimination of NM21-1480 from the circulation and loss of exposure. However, PK, PD, receptor occupancy and clinical activity data available for the 800mg dose level indicated that at this dose, the issue of loss of exposure was no longer present while full pharmacodynamic activity was

maintained, a phenomenon described for other checkpoint inhibitors (i.e. atezolizumab) at higher doses as well. As such, the SMC agreed with the Sponsor to further study the 800mg dose level as the presumptive RP2D, applying a biweekly dosing interval in Part B of the study.

For Cohort B5, an interim analysis will be performed after a minimum of 60 patients have been enrolled. At this point recruitment will be paused, the accumulated data analysed and regulatory authorities consulted. At the interim analysis the cohort will be regarded as futile (non-binding) if the probability of observing a difference in estimated effects between control and treatment of at least 15% is less than 0.1. However, as with the other cohorts, decisions at the interim point will be taken based on clinical and regulatory input and not formal statistical testing.

7.2.6 Withdrawal of Participants

Participants may voluntarily withdraw consent to participate in the study for any reason at any time or may be withdrawn at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

Withdrawal of consent occurs when a participant does not want to participate in the study anymore and does not want to attend any further visits or assessments, have further study-related contact, or allow analysis of already obtained biologic material. If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

If a patient is withdrawn from the study (during the Treatment or Follow-up period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the electronic case report form (eCRF). For patients that are withdrawn while in the treatment period for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging at FU2 or FU3 or until (1) the start of new anticancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first. If a participant withdraws consent, the Investigator must make every effort to determine the primary reason for this decision, should obtain written notice of the decision from the patient, if possible, should document the decision in source and additionally record this information on the treatment disposition eCRF page. If the participant decides to completely withdraw from the study (refuses any further study participation or contact), all study participation for that participant will cease and data to be collected at subsequent visits will be considered missing. Investigational treatments must be discontinued and no further assessments conducted. Further attempts to contact the participant are not allowed unless safety findings require communication or follow-up.

However, for safety reasons, visit should be conducted as far as possible if the withdrawn participant is willing to undergo the assessments.

The Investigator must also contact the interactive web response system service to register the participant's discontinuation from investigational treatment.

7.2.7 Lost to Follow-up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant. Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, faxes or emails (not performed on the same day), as well as a lack of response by the participant to one registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death and as much other information as can be obtained, including post-mortem reports.

Data to be collected at subsequent visits will be considered missing.

7.2.8 End of Study Definition

A patient will have completed the study if the patient dies while on Treatment or in Follow-up. The cause of death will be documented in the eCRF.

Patients no longer required to be followed for survival are considered as having completed the study if 1 of the following events occurs: disease progression or death. Following the completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow-up all patients for their survival status until patient death or termination by the Sponsor.

The end of the study is defined as the date once all patients have completed the Follow-up period (i.e., 12 weeks after discontinuation).

7.2.9 Discontinuation of Study Drug

When a patient will discontinue study drug treatment, the date and reason for study drug discontinuation should be documented on the CRF, all remaining visits of that treatment cycle should be completed (without infusions and with only a single PK sample taken at applicable visits), and the patient should enter the Follow-up period. When a patient will be withdrawn from the study (during the Treatment or Follow-up period), all evaluations associated with that study visit should be performed and the date and reason for study discontinuation should be documented on the CRF. In addition, if more than 4 weeks since the last imaging-based response assessment have passed at the time of discontinuation, a final response assessment shall be done if feasible.

Following completion or discontinuation of the Treatment and/or Follow-up phases of the study, all patients will be followed (by phone) every 3 months to assess their survival status until patient death.

Continued treatment should occur for patients with a best overall response (BOR) of CR (patients with confirmed CR may be discontinued from treatment upon discussion between the Investigator, Medical Monitor, and Sponsor), partial response (PR), or stable disease until the first occurrence of either:

- Documented progressive disease by RECIST 1.1 – while reference is made to Section 7.1.4 for treatment beyond progression considering the principles of iRECIST (Seymour et al., 2017)
- Clinical deterioration suggesting that no further benefit from treatment is likely
- Patient meets permanent discontinuation criteria for study therapy due to meeting respective tolerability criteria
- Other intolerability to therapy requiring discontinuation according to the Investigator's opinion
- Requirement for another form of antineoplastic therapy as determined by the Investigator or
- Discontinuation resulting from protocol violation, withdrawal of consent, or lost to follow-up
- Termination of the study by the Sponsor
- Pregnancy
- Need for prohibited medication
- Lack of compliance with the study and/or study procedures (e.g., administration instructions, study visits)
- Patient is lost to follow-up

If any of the above situations apply, the patient is withdrawn from treatment and enters the Follow-up period. Consequently, the reason for discontinuation of NM21-1480 will be recorded in the eCRF. These reasons include:

- Radiographic disease progression
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any significant AE that compromises the patient's ability to participate in the study
- Patient's decision to discontinue the study treatment (A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments)

- The Investigator or Sponsor determines it is in the best interest of the patient
- Death

7.2.10 Discontinuation of Study Sites

Study site participation may be discontinued if Sponsor or designee, the Investigator or IEC/IRB of the study site judges it necessary for medical or safety reasons consistent with applicable laws, regulations and GCP.

7.2.11 Discontinuation of Study

The study will be discontinued if Sponsor or designee, including through SMC recommendation, judges it necessary for medical, safety, or business reasons consistent with applicable laws, regulation and GCP.

7.2.12 Follow-up

All patients will be followed for survival until death after discontinuation of the Treatment and/or completion of Follow-up periods.

- Follow-up 1 to be scheduled within 30 days of the last visit.
- Safety Follow-up Visit 2 and Visit 3 are to be scheduled 60 days and 90 days after discontinuation, respectively after discontinuation.
- Following completion or discontinuation of the Treatment and/or Follow-up phases of the study, all patients will be followed (by phone) every 3 months to assess their survival status until patient death.

8 STUDY TREATMENT

Study treatment is defined as the investigational intervention intended to be administered to the study participant according to the study protocol.

8.1 Administration of Study Treatment(s)

Part A (Dose-Escalation)

NM21-1480 will generally be administered over approximately 60-90 minutes as a single IV infusion every 14 days for a total of 2 infusions per treatment cycle (4 weeks). Details on study drug administration can be found in the study Pharmacy Manual. The following escalating flat dose levels will be administered according to the BOIN design:

IV Administration of NM21-1480

Dose 1: 0.15 mg

Dose 2: 1.5 mg

Dose 3: 8 mg

Dose 4: 24 mg

Dose 5: 80 mg

Dose 6: 240 mg

Dose 7: 800 mg

Radiological (response) assessments are done every 8 weeks, i.e., 1 assessment cycle (at 8-Week Assessment, see Table 7-1).

Part A-2 (optional)

Part A of the study was formally completed on 23 May 2022 at which occasion, based on availability of at least 28-day safety data for all 25 patients evaluable for BOIN in Part A, the SMC determined that Part A did not technically identify a MTD and that even the highest dose level assessed in Part A (800mg flat dose) was considered a tolerated dose. However, based on the finding that some patients dosed at 24-240mg in Part A developed treatment-emergent ADAs leading to loss of exposure, while this was not observed at the 800mg dose level, a decision was taken to explore one higher dose level (1400mg flat dose, applying an approximately 14-day dosing interval) in up to 10 patients within Part A-2 in parallel to studying the 800mg dose level in Part B. The SMC, together with the Sponsor, may also choose to evaluate different (i.e., longer than 2-week) dosing intervals if supported by emerging Part A-2 data. Additional dose levels (i.e. doses other than 1400mg) or dosing intervals (i.e. other than biweekly) may in the future be studied within Part A-2 as well if emerging data from the ongoing study provide a rationale to do so.

Part B (Dose Expansion):

Based on the comprehensive review of Part A data on 23 May 2022, the SMC determined that the 800mg flat dose of NM21-1480 shall be further studied as the presumptive RP2D in Part B of the study. As such, this dose level will be assessed in Part B, Cohorts B1-B4 and B6-B8 in order to confirm the RP2D for NM21-1480 monotherapy. For Cohort B5, the SMC will initially evaluate the tolerability of the 800mg NM21-1480 doe in the combinatorial treatment setting with a PD-1 antibody in six patients enrolled to this treatment arm (see Section 7.2.5.3 for detailed decision rules). As no relevant accumulation of NM21-1480 was observed in Part A, the 800mg dose of NM21-1480 to be administered in all Part B cohorts will be administered as a single IV infusion approximately every 14 days for a total of 2 infusions per treatment cycle (4 weeks). However, PK data will be closely followed and in case of observation of relevant drug accumulation over time, the dosing interval for may be adjusted to approximately every 21 days, for a total of 2 infusions per treatment cycle (or 6 weeks). Radiological (response) assessments are done every 6 weeks during the first 24 weeks on treatment and every 8 weeks, i.e., at 8-Week Assessments thereafter, see Table 7-1 and Table 7-2.

Tumor response will be evaluated by the Investigator using RECIST 1.1 and iRECIST. Tumor response assessments should be completed as instructed in Table 7-1 and Table 7-2 footnotes c and v, respectively.

8.1.1 Duration of Treatment with Study Drug

There is no pre-specified maximal treatment duration. Treatment for a given patient shall be continued until there is confirmed disease progression by the Investigator or the patient meets any of the pre-specified conditions for discontinuation.

8.1.2 8-Week Assessment

In Part A, radiological assessments are conducted every 8 weeks, this period defines 1 assessment cycle (i.e., in the week prior to administration of NM21-1480 in all odd number treatment cycles [e.g., Cycles 3, 5, 7]). In the optional Part A-2 and in Part B, radiological assessments are conducted every 6 weeks for the first 24 weeks on treatment and every 8 weeks thereafter.

8.1.3 Radiological Assessment in the Follow-up Period

All patients who discontinue study treatment without radiologically documented disease progression will continue to receive radiological assessments until disease progression, patient withdraws informed consent, initiation of new anti-cancer treatment, lost to follow-up, death, or end of this study, whichever occurs first.

8.1.4 Re-initiation of Study Therapy for Patients in Follow-up Period

Patients that have been discontinued from treatment will not be allowed to be re-initiated with the IP. The only exceptions are treatment re-initiations in patients who were discontinued due to confirmed CR and thereafter recurrence or in patients following elective surgery provided that patients still meet the eligibility criteria. Re-initiation of treatment in this situation may be allowed following discussion between Investigator, Medical Monitor and Sponsor.

8.1.5 Dose Modification

In the case that an infusion cannot be administered at a scheduled visit, every attempt should be made to administer the infusion as soon as possible. Patients with infusion delays >35 days (i.e., 2 missed doses + 7 days in settings with intended biweekly dosing events) or >49 days (i.e., 2 missed doses + 7 days in settings with intended dosing events every three weeks) from the scheduled dosing should normally discontinue treatment and enter the Follow-up period with the exception of delays related to prophylactic vaccinations or after specific consultation and agreement between the Investigator and the Medical Monitor in settings where benefit/risk may justify continued study therapy (e.g., patient deriving clinical benefit who requires prolonged steroid taper for management of non-DLT irAEs). For more details of dose modification relevant to irAEs, please refer to Appendix VI, (irAE management guidance for Investigators).

8.1.5.1 Dose Reduction

In Part A, dose may be reduced to the next lower pre-specified dose level of the BOIN design due to toxicity if deemed necessary by the Investigator after consultation with the Medical Monitor, specifically after occurrence of a DLT.

Only one dose reduction is allowed.

In general, tolerability issues in both Part A and Part B are to be addressed by dose withholding; however, dose reduction may be considered upon discussion with the Medical Monitor if deemed necessary as per the Investigator's assessment.

8.1.5.2 Dose Withheld

NM21-1480 will be withheld for any of the following treatment-emergent adverse events (TEAEs):

- Any Grade ≥2 TRAE, with the following exceptions:
  - Grade 2 TRAE fatigue, alopecia, skin rash or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, TRAE
- Any Grade 3 TRAE laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:

  - Grade 3 lymphopenia does not require dose delay
  - If a patient has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for treatment-related Grade ≥2 toxicity
  - If a patient has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for treatment-related Grade ≥3 toxicity
  - Any Grade ≥3 treatment-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Medical Monitor should be consulted for such Grade ≥3 amylase or lipase abnormalities

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgement of the Investigator, warrants delaying the dose of study medication.
- Grade 2 TRAEs that recur shall be managed by dose modifications (changes in the infusion rate) and dose delays, and those that do not resolve to Grade 1 or less by the end of the next treatment cycle shall lead to permanent discontinuation of NM21-1480. Pre-planned dose level reductions are not allowed; however, interruptions in delivering the planned dose that results in an actual dose that is less than 90% of the planned dose is defined as dose reduction.

8.1.6 Dose Resumption

Patients may resume treatment with NM21-1480 when the TRAEs resolve(s) to Grade ≤1 or baseline within 35 days (i.e., 2 missed doses + 7 days in settings with intended biweekly dosing events) or within 49 days (i.e., 2 missed doses + 7 days in settings with intended dosing events every three weeks) from the scheduled dosing, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue, alopecia, skin rash.
- Patients who have not experienced a Grade 3 treatment-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 1 AST/ALT or total bilirubin.
- Patients with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Treatment-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for re-treatment if discussed with and approved by the Medical Monitor.

- Treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

Two dosing delays due to toxicity will be permitted.

In the event of a third occurrence of a toxicity which would require dosing delay, study therapy may be discontinued permanently after consultation with the Sponsor monitor.

8.1.7 Management of Infusion-Related Reactions

Infusion-related reactions may occur during or after administration of NM21-1480. Dose reductions, other than a decrease in the infusion rate, are not allowed. Management guidelines for infusion reactions are displayed in Table 8-1.

Table 8-1 Management of Infusion-related Reactions

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the symptoms have resolved. The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event.	Patient may be pre-medicated at the discretion of the Investigator as per institutional norm or consider premedication 1.5 hours (± 30 minutes) prior to infusion of NM21-1480 with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine) • Acetaminophen (Paracetamol) 500-1000 mg orally (or equivalent dose of antipyretic)
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics. Increase monitoring of vital signs as medically indicated until the symptoms have resolved. If symptoms resolve within 1 hour of stopping IP infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 to 50 mL/hour). Otherwise, dosing will be held until symptoms resolve and the participant should be pre-medicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further IP administration.	Patient should be pre-medicated as per institutional norm or consider premedication 1.5 hours (± 30 minutes) prior to infusion of NM21-1480 with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine) • Acetaminophen (Paracetamol) 500-1000 mg orally (or equivalent dose of antipyretic)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop infusion immediately. Begin an IV infusion of normal saline and treat the patient as per institutional norms or consider treating the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Additional appropriate medical therapy may include but is not limited to: IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, pressors, corticosteroids, and epinephrine. Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. Participant is permanently discontinued from further IP administration.	Permanently discontinue dosing

Abbreviations: IP = Investigational product; IV = Intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, NSAID = Nonsteroidal anti-inflammatory drug

8.2 Study Treatment Packaging and Labelling

8.2.1 Packaging

Prior to addition of the IP, 0.02% poloxamer 188 will be added to the diluent sodium chloride for injection, USP (0.45% or 0.9% dependent on the dose level). Ten (10) mL of the product will be filled into 20R type I glass vials from which the required dose volume will be injected into suitable infusion bags or administered by perfusion syringes, dependent on dose level. The intended clinical dosing frequency is once every other week, or every third week (if applicable) in optional Part A-2 and Part B, over 60-90 minutes through an IV line containing a sterile, non-pyrogenic, low protein-binding inline filter (pore size of 0.2 micron). Additional details can be found in the study Pharmacy Manual.

8.2.2 Storage

All IP supplies for this study must be stored under refrigerated conditions (2°C to 8°C) per storage conditions stated on the IP label. Until dispensed for administration to patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only. Details can be found in the study Pharmacy Manual.

8.3 Patient Compliance

The dosage, timing and mode of administration of study medication may not be changed. Any departures from the intended regimen must be recorded in the eCRF. Study medication accountability and patient compliance will be documented throughout the study/treatment periods using study-specific medication administration record forms. If a participant does not receive the scheduled dose, every effort should be made to administer the dose as soon as possible. Deviations from the intended regimen include:

- receiving unscheduled dose of study drug
- missing a dose
- receiving the incorrect dose

8.4 Study Treatment Accountability

Records shall be maintained of the delivery of study treatment(s) to the study site(s), the inventory at the study site(s), the use of each participant and the return to the Sponsor.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study medication and to the study participants.

The Investigator shall be responsible for ensuring that the records adequately document that the participants were provided the doses specified in the protocol and that all study medication received from the Sponsor is reconciled.

8.5 Concomitant Therapy

8.5.1 Permitted Medications

Patients are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Steroid doses <10 mg daily prednisone or equivalent (e.g. for adrenal replacement) are permitted. A course of corticosteroids for prophylaxis for contrast dye allergy is allowed.

Bone modifying agents, including bisphosphonates and denosumab, should be used in accordance with label indications as appropriate for patients with bone metastases.

Colony stimulating factors (G-CSF, GM-CSF, erythropoietin stimulating agents, etc.) should not be administered prophylactically. Interventional use of these agents is permitted for the treatment of adverse events.

Palliative and supportive care measures should be administered at the discretion of the Investigator in accord with standards of care.

NM21-1480 may impact CYP enzyme production and activity via cytokine modulation. For this reason, there may be a risk of drug interactions and concomitant medications that are narrow therapeutic index substrates for CYP enzymes should be used with caution and appropriate monitoring.

8.5.2 Prohibited Medications

The following medications and therapies are not permitted during the study from signature of informed consent:

- Other investigational agents or investigational device.
- Any other systemic or localized antineoplastic therapy. Palliative radiation therapy may be permitted for pain or severe symptom control (i.e., radiation for pain control of bony metastases) after discussion with the study Medical Monitor. Radiation will be limited to non-target lesions only.
- Any botanical preparation (e.g., herbal supplements or traditional Chinese medicines) intended to treat the disease under study or provide supportive care. Use of marijuana and its derivatives for treatment of symptoms related to cancer or cancer treatment are permitted if obtained by medical prescription or if its use (even without a medical prescription) has been legalized locally
- Medications or substances known to cause elevation of liver enzymes, including e.g., acetaminophen (a daily dose of up to 2 g/day is allowed to manage acute pain), or systemically active cannabidiol (CBD); topical CBD is allowed
- Immunosuppressive medication including immunosuppressive doses of systemic steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent). However, continued treatment with NM21-1480 of a patient on doses ≤10 mg/day prednisone or equivalent that were initiated for treatment of an AE/irAE within the study is allowable if that AE/irAE has improved to ≤ Grade 1 in severity or baseline and continued NM21-1480 treatment is considered in the best interest of the patient as per investigator judgement and following consultation with the Medical Monitor.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Clinical Activity Assessments

9.1.1 Tumor Response

Tumor response will be evaluated by the Investigator according to RECIST 1.1 using measurement such as computed tomography (CTI) scan (with IV contrast, chest, abdomen, and pelvis) or MRI in case of IV contrast contraindication. In Part B, tumor response will also be evaluated by the investigator according to iRECIST and response assessment for RECIST1.1 and iRECIST will be independently determined by central reading of images, while decisions on continuation of treatment will be based on the investigator's RECIST1.1 and iRECIST assessment. Response assessments will be performed by the Investigators at the end of each assessment cycle to document eligibility for entry into the next treatment cycle. Also, if applicable (see Table 7-1 and Table 7-2, footnote v.), response assessment will be performed at Follow-up Visit 1 (0 to 30 days after discontinuation), Visit 2 (60±7 days after discontinuation), and/or Visit 3 (90±7 days after discontinuation).

Copies of scans will be collected and stored at Medpace in Part A and optional Part A-2. In part B, copies of scans will also be sent to Medpace for independent determination of RECIST1.1 and iRECIST assessments. A detailed description of the central read process can be found in the imaging charter.

Sites are also requested to attempt gathering and submitting the last pre-baseline scans for a patient as part of the tumor-specific therapy history; inavailability of these pre-baseline scans do however not make a patient ineligible for the study.

The same technique (CTI/MRI) used at baseline will be utilized throughout the study for a given patient. Computed tomography is the imaging modality of choice for chest/abdomen/pelvis. Brain scans during Treatment and Follow-up periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated. If required, subsequent brain CTI scans/MRI should be repeated at assessment cycles 1, 2, etc., and at Follow-up Visit 2. Bone scans at baseline or subsequent visits will be performed only if clinically indicated. If required, subsequent bone scans should be repeated every other assessment cycle (end of assessment cycles 2, 4, 6, etc.) and a single scan at Follow-up Visit 2 or 3.

The timing and frequency of clinical activity assessments are described in Table 7-1 and Table 7-2.

Additional assessments of overall survival (OS) and progression-free survival (PFS) will be assessed by the Kaplan-Meier method (described in Section 10.6.2).

While conducting the study, tumor response assessment will be done locally, CTI/MRI scans will also be stored centrally. During the study, i.e., on an ongoing basis while enrollment into Part B is ongoing and/or at the end of Part B, the Sponsor will re-confirm response assessment by a central

reader blinded to assigned NM21-1480 dose levels (all B cohorts) and treatment assignment (Cohort B5).

9.2 Safety Assessments

At Screening, a medical history will be obtained to capture relevant underlying conditions and prior medications will be collected. The Screening examinations will include hepatitis B and C test, HIV tests, CD4 T-cell count (only for patients who are HIV positive at Screening), and height within 28 days prior to the administration of the first dose of study drug.

Safety assessments including weight, ECOG performance status, ECG (12-lead), vital signs, complete physical examination, limited physical examination, oxygen saturation, concomitant medications, AEs, hematology, serum chemistry, urinalysis, TSH and T4, and pregnancy tests, will be performed as noted in the Schedule of Assessments.

The timing and frequency of safety assessments are described in Table 7-1 and Table 7-2.

9.2.1 Definitions

The definition of AEs, TEAEs, and SAEs is given below. The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of and AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that causes the participant to discontinue the study drug/study.

9.2.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a participant, or clinical investigation participant administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

9.2.1.2 Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

9.2.1.3 Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2.1.4 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that:

- Results in death. The cause of death is the AE, death is an outcome.
- Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires in-patient hospitalization or prolongs existing hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that

occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event. Important medical events that my not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgement, they may jeopardize the participant or the participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Patients will be required to permanently discontinue NM21-1480 for the following TRAEs:
    - Any Grade 2 TRAE uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
    - Any Grade 3 non-skin, TRAE lasting >7 days, with the following exceptions:
        1. Grade 3 TRAE uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
        2. Grade 3 TRAE endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
        3. Grade 3 TRAE laboratory abnormalities not requiring medical treatment or hospitalization do not require treatment discontinuation except:
            a. Grade 3 TRAE thrombocytopenia >7 days or associated with clinically significant bleeding requires discontinuation.
            b. Any TRAE liver function test abnormality that meets the following criteria requires discontinuation:
                i. AST or ALT >5-10 × ULN for >2 weeks or AST or ALT >10 × ULN.

ii. Total bilirubin >5 × ULN.

iii. Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN without initial finding of cholestasis (elevation of alkaline phosphatase [ALP]).

iv. For patients with hepatic metastases: AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 days.

- Any patient experiencing a Grade 4 toxicity or laboratory abnormality must be permanently discontinued.
- Any event that leads to delay in dosing lasting >35 days (i.e., 2 missed doses + 7 days in settings with intended biweekly dosing events) or >49 days (i.e., 2 missed doses + 7 days in settings with intended dosing events every three weeks) from the scheduled dosing requires discontinuation, with the following exceptions:

  1. Dosing delays to allow for prolonged steroid tapers to manage TRAEs may be allowed if approved by the Medical Monitor. Prior to re-initiating treatment in a patient with a dosing delay lasting >35 days (i.e., 2 missed doses + 7 days in settings with intended biweekly dosing events) or >49 days (i.e., 2 missed doses + 7 days in settings with intended dosing events every three weeks) from the scheduled dosing, the Medical Monitor must be consulted. Tumor assessments should continue as per-protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 2 weeks or more frequently if clinically indicated during such dosing delays.
  2. Dosing delays lasting >35 days (i.e., 2 missed doses + 7 days in settings with intended biweekly dosing events) or >49 days (i.e., 2 missed doses + 7 days in settings with intended dosing events every three weeks) from the scheduled dosing that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor. Prior to re-initiating treatment in a patient with a dosing delay lasting 35 days (i.e., 2 missed doses + 7 days in settings with intended biweekly dosing events) or 49 days (i.e., 2 missed doses + 7 days in settings with intended dosing events every three weeks), the Medical Monitor must be consulted. Tumor assessments should continue as per-protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 2 weeks or more frequently if clinically indicated during such dosing delays.

Patients who meet toxicity related discontinuation criteria discussed above or presented in Appendix VI, (management of irAEs) may be permitted to remain on therapy if the benefits are

considered to outweigh the risks of continued treatment after discussion between the Sponsor and Investigator and between the Investigator and the patient.

In case of development of a ≥Grade 3 (CTCAE V5.0) intolerability or AE related to NM21-1480 that precludes further treatment with the study drug, but patient does not have worsening progression: Patients will complete the remaining visits of their current treatment cycle (without infusions) if possible. Patients will then enter the Follow-up period.

9.2.1.5 Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the first dose of study drug.

9.2.1.6 Adverse Event of Special Interest

An AESI must be reported as if it were an SAE (Section 9.2.6).

Elevations of ALT/AST that are >3-fold above baseline are to be considered AESI and to be reported with SAE timelines. The details on how to handle such situations are provided in Appendix VI, "Hepatitis"). In case of Grade 3+ hepatotoxicity, an initial ultrasound or image needs to be done to visualize the biliary tree and to rule out disease progression or occurrence of gall stones.

The following types of AESIs will be examined:

- AEs falling under the system order class (SOC) of hepatobiliary disorders (i.e., to cover any potential liver toxicity) Grade 3 or higher
- SOC of immune system disorders (i.e., to cover cytokine release syndrome and irAEs) Grade 3 or higher
- Any AE of CTCAE V5.0 Grade 3 or higher
- Any CTCAE V5.0 Grade 3 or 4 infusion reaction whether or not the event is a DLT or delayed DLT
- Any AE considered by the Investigator to represent a DLT or delayed DLT

9.2.1.7 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the participant has been withdrawn from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be

handled as SAEs, but should be reported as a follow-up report for the pregnancy. All outcomes of pregnancy must be reported to the Sponsor on a Pregnancy Outcomes Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in the study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Pregnancies must be reported to Arriello within 24 hours of awareness, using the reporting details provided in Section 9.2.6.

9.2.2 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded as AEs (though unrelated to study drug). All AEs will be collected at the time points specified in the Schedule of Assessments (Table 7-1 and Table 7-2). All patients who intend to discontinue the study within 70 days after the administration of the last dose of study drug should be followed until resolution and/or stabilization of any study TRAEs and AEs that led to the discontinuation, and should be monitored for 70 days following the last dose of ND021 (NM21-1480) for the occurrence of study TRAEs. These patients should complete Follow-up visits 1 and 2 unless the patient begins a new therapy.

For all Follow-up periods beyond 70 days from the last dose of study drug, only study treatment-related SAEs or late-occurring irAEs should be reported.

At any time after completion of the Follow-up visit, if an Investigator learns of an SAE that can be reasonably related to study drug, they should promptly notify the Sponsor.

9.2.3 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to enquire about AE occurrences.

9.2.4 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE information in the eCRF. It is not acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page. There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity (refer to Section 9.2.4.1), seriousness (Section 9.2.1.4), causality rating (Section 9.2.4.2), whether or not the AE caused the participant to discontinue (Section 9.2.4.3), any other action (Section 9.2.4.4), and the outcome (Section 9.2.4.5). A new AE must be recorded if the severity of the AE changes.

Should an SAE have an outcome of death, the report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

9.2.4.1 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon NCI CTCAE Version 5.0. It is important to distinguish between serious and severe AEs. Severity is a measure of intensity and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least one of the criteria listed in Section 9.2.1.4.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

9.2.4.2 Assessment of Causality

The Investigator must assess the relationship between study drug and each occurrence of each AE/SAE using their clinical judgement. A reasonable possibility of a causal relationship requires that there are facts, evidence, and/or arguments to suggest a relationship, rather than that a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as a temporal relationship of the event to study drug administration will be considered and investigated. The Investigator will also consult the IB and/or Product Information (for marketed products) as part of their assessment.

For each AE/SAE, the Investigator must document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data. The Investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements (Table 9-1).

Table 9-1 Assessment of Causality

Term	Definition	Clarification
Unrelated	Those AEs, which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)	
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.	1. It does not follow a reasonable temporal sequence (improbable temporal relationship) from study drug administration. 2. It could also be explained by participant's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions.
Possibly	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.	1. It follows a reasonable temporal sequence from study drug administration. 2. It could also be explained by participant's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals (including food-drug interactions). 3. There is no information or uncertainty with regard to what has happened after stopping the drug.
At least possibly	A TEAE is an AE with onset after administration of first study dose and is independent of any assessment of causality. Any TEAE that is considered at least possibly related to study drug is considered a TRAE.	
Probably	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.	1. It follows a reasonable temporal sequence from study drug administration. 2. It could not be readily explained (unlikely) by the participant's concurrent disease, environmental factors, medical history and other concomitant drugs or chemicals including food-drug interactions. 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. 4. No re-challenge information is available or possible.
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to administration of study drug, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a	1. It follows a plausible time sequence to drug intake; this means that there is a positive argument in sufficient detail to support the view that the drug is causally involved, pharmacologically or pathologically e.g., PK and type of reaction. 2. It could not be explained by the participant's concurrent disease, environmental factors, medical history and other

Term	Definition	Clarification
	satisfactory re-challenge procedure if necessary.	concomitant drugs or chemicals including food-drug interactions (i.e., no alternative causes). 3. It disappears or decreases in severity on cessation or reduction in dose or on administration of a specific antagonist wherever possible. 4. It is an objective and specific medical disorder or a recognized pharmacological phenomenon for instance 'grey baby syndrome' and chloramphenicol or anaphylaxis immediately after the administration of a drug that had been given previously. This means that any other event is automatically excluded and can never qualify for 'Certain' (even in the case of a positive re-challenge observation). 5. It reappears on re-administration of the drug (only if ethically correct i.e., in case of non-serious, and easily treatable AEs).

Abbreviations: AE = Adverse event; PK = pharmacokinetics; TEAE = Treatment-emergent adverse event; TRAE = Treatment-related adverse event.

When conducting the causality assessment of an AE, the Investigator should consider the following factors:

- Time relationship between study drug intake and event's onset
- De-challenge
- Re-challenge
- Medical history
- Study treatment
- Mechanism of action of study drug
- Class effect
- Concomitant treatments in use
- Withdrawal of study treatment
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study medication or concomitant medication
- Protocol-related process.

9.2.4.3 Action Taken with Study Drug Due to AE

The action taken with study drug should be recorded using one of the following:

- None
- Study drug temporarily discontinued
- Study drug permanently discontinued
- Unknown/not applicable

9.2.4.4 Other Action Taken

Details of any other actions taken should be specified:

- Specific therapy/medication
- Surgical medical procedure
- Prolonged hospitalization

9.2.4.5 AE Outcome

Each AE should be rated according to one of the following outcomes:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown

9.2.5 Follow-up of AEs/SAEs

All patients who intend to discontinue the study within 70 days after the administration of the last dose of study drug should be followed until resolution and/or stabilization of any study TRAEs and AEs that lead to the discontinuation, and should be monitored for 70 days following the last dose of ND021 (NM21-1480) for the occurrence of study TRAEs. These patients should complete Follow-up Visits 1 and 2 unless the patient begins a new therapy.

For all Follow-up periods beyond 70 days from the last dose of study drug, only fatal SAEs, study treatment-related SAEs or late-occurring irAEs should be reported to Sponsor/designee and Arriello initially, and then followed by report to Arriello according to the Safety Management Plan (SMP) for the study according to Section 9.2.6.

9.2.6 Reporting of SAEs

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. Investigators and other site personnel must inform Arriello of any SAE that occurs during the course of the study (from the time of informed consent until 70 days after the end of study visit), whether or not it is causally related to study drug or procedures, and within 24 hours of when they become aware of the event. An SAE with an onset greater than 70 days for the end of study visit will be recorded only for fatal SAEs, late-occurring irAEs, and those deemed by the Investigator to be treatment-related. The Investigator should make every effort to obtain follow-up information on the outcome until the event is considered resolved, chronic and/or stable.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to Arriello within 24 hours as described above. The start date of the SAE is not the AE start date, but the date when the AE becomes serious; analogously, the stop date is the date when any seriousness criterion is no longer applicable, not the date when the AE is resolved.

All SAEs will also be recorded in the eCRF. The Investigator is responsible for informing the Ethics Committee of the SAE as per local requirements. An SAE Report Form should be completed at the site and emailed within 24 hours of awareness of the event to the Central Receipt mailbox:

[redacted]

The SAE Report Form should be attached to the email; a notification email of the event describing it in the email text is not sufficient. There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial SAE Report Form. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE report form. Minimum criteria are identifiable participant (number), a suspect product (i.e., study drug or concomitant medication), an identifiable reporting source (Investigator/study site identification), and an event or outcome that can be identified as serious. Follow-up information on SAEs must also be reported by the Investigator within the same time frames.

9.2.6.1 Safety Reporting to Sponsor

Arriello will forward the SAE and Pregnancy reports to the Sponsor's safety representative(s) at [redacted] within 1 business day or 3 calendar days (whichever is earlier) of becoming aware of it.

9.2.6.2 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators

Arriello (Sponsor designee) will notify the Numab of any SAE and will perform follow-up activities with the concerned site. Arriello and Medpace will be responsible for expedited and

periodic reporting, as delineated in the SMP, to specified Health Authorities according to national requirements and to applicable Central Ethics Committees (CECs). Procedure and timelines for safety reporting are provided in the SMP as agreed by Arriello, Medpace, and the Sponsor. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths and suspected unexpected serious adverse reactions [SUSARs]) to the IEC/IRB that approved the study. Investigators should provide written documentation of IEC/IRB notification for each report to Arriello. In addition, all SAEs will be reported through the yearly Development Safety Update Report (DSUR).

In accordance with ICH GCP, Arriello will inform the Investigators of findings that could adversely affect the safety of participant, impact the conduct of the study, or alter the IEC's/IRB's approval/favorable opinion to continue the study, as assessed by the Sponsor. In particular, and in line with respective regulations, Arriello will inform the Investigators of SUSARs. The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regards to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, Arriello or Medpace (as specified in the SMP) will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by Arriello and of filing copies of all related correspondence in the Investigator Site File.

9.2.7 Laboratory Assessments

The Screening examinations will include hepatitis B and C, HIV, CD4 T-cell count (only for patients who are HIV positive at Screening), hematology, serum chemistries, urinalysis, TSH&T4, and pregnancy.

During the study hematology, serum chemistries, urinalysis, thyroid function and pregnancy tests will be evaluated only by local study site or its contract laboratory at the time points detailed in the Schedule of Assessments (Table 7-1 and Table 7-2). The hematology and clinical chemistry laboratories must be performed and reviewed before dosing. If practicable, laboratory samples may be drawn up to 72 hours prior to infusions for pre-infusion safety review; in such case it is not necessary to repeat tests on the day of dosing. Any new ≥Grade 3 laboratory abnormality or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continued dosing. In the event of uncertainty, the Medical Monitor should be contacted.

A full list of required laboratory tests is included in Section 18.7, Appendix VII.

9.2.7.1 Potential Hy's Law and Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN without evidence of intra- or extra-hepatic bilirubin obstruction (elevated at least ALP) or Gilbert's syndrome will need to be reported as SAEs. Please refer to Appendix II, Section 18.2 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

9.2.8 Electrocardiogram Assessments

Computerized 12-lead ECG recordings will be obtained at scheduled study visits (as specified in the Schedule of Assessments [Table 7-1 and Table 7-2]) after the participant has rested for at least 5 minutes in the supine position. The Investigator will document the occurrence of any clinically significant 12-lead ECG abnormalities within the eCRF based on correlation between the Investigator reading and clinical findings. Repeat measurements will be performed if needed.

The following ECG parameters will be obtained directly from the computerized 12-lead ECG recordings: rhythm, ventricular rate, P-R interval (the portion of the ECG between the onset of the P wave and the QRS complex), QRS duration and QT/QTcF where, according to the Fridericia formula, (QTcF) is the observed QT interval (the time from the beginning of the Q wave to the end of the T wave) divided by the cubed root of the R-R interval (interval from the peak of 1 QRS complex to the peak of the next) in seconds:

$$QTcF = \frac{QT}{3\sqrt{RR}}$$

QTcB (QTc corrected according to Bazett's formula) will also be recorded, where:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

Baseline imaging and 12-lead ECG done as part of the patient's previous routine care before signing the informed consent form (ICF) and completed within 28 days before the administration of ND021 (NM21-1480) need not be repeated. Whenever possible, baseline imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the patient's participation in the study.

9.2.9 Physical Examination

A standard complete physical examination will be performed at the weeks specified in the Schedule of Assessments (Table 7-1 and Table 7-2). Complete physical examination includes assessment of the skin, head, eyes, nose, throat, neck, joints, lungs, heart, abdomen (including liver and spleen), lymph nodes, and extremities. A brief neurological examination should also be performed. All abnormal findings noted at the Screening physical examination should be recorded

on the medical history CRF, and any new or worsening signs or symptoms are to be recorded on the AE CRF.

Limited physical examination includes assessment of the lungs, heart, abdomen, and skin. All abnormal findings noted at the Cycle 1/Day 1 evaluation should be recorded on the medical history CRF. Abnormal findings of clinical significance that occur after the Cycle 1/Day 1 evaluation (or new AEs) should be explicitly documented on the AE CRF.

9.2.10 Vital Signs

Body temperature, resting systolic and diastolic blood pressure, and pulse will be recorded according to the Schedule of Assessments (Table 7-1 and Table 7-2). Automatic or manual devices may be used, but the same device will be used for any given participant throughout the study. The same arm will be used for all blood pressure measurements. All devices must hold valid calibration documentation at the time of use.

On the day of each infusion, vital signs will be obtained pre-infusion, every 15 minutes during the infusion, at the end of the infusion, and 15, 30, and 60 minutes after completion of the infusion. When slowing or re-starting an infusion due to an infusion reaction/AE, vital signs should be monitored every 15 minutes or as directed by the Investigator until the infusion is completed, and 15, 30, and 60 minutes after completion of the infusion and/or until the patient is stabilized. Vital signs should be collected ± 5 minutes from the scheduled times noted in the Schedule of Assessments (Table 7-1 and Table 7-2).

9.3 Pharmacokinetics and Immunogenicity Assessments

Pharmacokinetic (PK) parameters such as the maximum observed serum concentration determined by direct inspection of the concentration versus time data (Cmax), the minimum observed serum concentration determined by direct inspection of the concentration versus time data (Cmin), the time from dosing at which Cmax is apparent determined by direct inspection of the concentration versus time data (Tmax), terminal phase (apparent elimination) rate constant (λz), elimination half-life (t½), area under the serum concentration-time curve extrapolated from the last quantifiable concentration to infinity (AUC[0-infinity]), area under serum concentration-time curve over dosing interval (AUCtau), clearance (CL), volume of distribution (Vd), and accumulation index will be derived from serum concentration versus time data for patients with serial PK samples.

Serum samples will be collected to assess the ADAs to NM21-1480. Pharmacokinetics and immunogenicity sampling time points are detailed in the Blood Sampling Schedule (Table 7-3 and Table 7-4).

9.4 Pharmacodynamic Assessments and Biomarker Analysis

Whole blood samples will be drawn and biopsy material will be collected for assessment of PD and biomarker analysis at the time points indicated in the Blood Sampling Schedule (Table 7-3 and Table 7-4). Blood samples will be processed to collect serum.

Assessment of immunophenotyping, soluble PD-L1, soluble 4-1BB, cytokine efficacy panel, receptor occupancy (RO), PD-L1 immunohistochemistry (IHC), tumor mutational burden (TMB), TCR clonality sequencing, microsatellite instability (MSI) and mRNA/IF may be adjusted for Part B, following availability of Part A data. Conduct of RO assay (for Part A and B) will be dependent on availability of a suitable assay.

Characterization of exposure-dependent PD markers of target and pathway engagement assessed in Part A and the optional Part A-2 (if applicable) will be core elements of selecting up to 4 dose levels of NM21-1480 that are at or below the MTD for determination of the RP2D in Part B. In mCRC patients enrolled to Cohort B8, additional biomarker/PD marker, including, e.g., assessment of ctDNA levels, determination of MHC-I expression on tumor cells; or specific mutational analysis including *e.g.,* BRAF, KRAS, NRAS, POLE, PIK3CA, PTEN. APC, p53 may be conducted.

10 STATISTICAL METHOD AND SAMPLE SIZE CALCULATION

10.1 General Considerations

A detailed statistical analysis plan (SAP) will be prepared by the Sponsor or designee. This plan may modify the statistical methods outlined in the protocol; however, any major modifications of the primary endpoint definition or analysis will also be described in a protocol amendment.

10.2 Sample Size Estimate Calculation

No formal group size calculation has been applied as the sample size during dose-escalation cannot be precisely determined but depends on the observed toxicity.

For Part A, dose-escalation cohorts, a BOIN design with a pre-specified maximal patient number of 25 will be applied.

The optional Part A-2 may only be initiated after Part A is complete (i.e., the MTD for Part A has been determined). Up to 40 patients across dose levels may be enrolled to further study the exposure-dependent PD response relationship for NM21-1480 to further explore different dose levels and/or dosing intervals in parallel to Part B to complement the PK, immunogenicity and PD data to be provided by Part B.

For Part B, Cohorts B1 through B4 and B6 through B8 a BOP2 design will be applied (see Section 10.3.2) and a maximum of 40 patients will be enrolled to each cohort to assess clinical response. For Part B, Cohorts B1 through B4 and B6 through B8, an interim analysis for futility

is planned, depending on recruitment and availability of data. The interim analysis is planned after enrollment and treatment of 25 patients in a given cohort according to the BOP2 design. This futility analysis will be conducted based on availability of response data following completion of the first 2 RECIST 1.1 (and iRECIST) assessments (i.e., after 12 weeks) for the 25 patients. The 800mg flat dose of NM21-1480 will be further studied as sole dose level in Part B based on results of Part A and as per recommendation by the SMC. The Sponsor in consultation with the SMC will determine at this point of futility analysis whether the cohort shall be stopped or continued. If (a) cohort will not be stopped due to futility after the interim analysis, the study will continue with an estimated total of 40 patients to be enrolled by cohort; a final futility/clinical activity analysis based on pre-specified criteria will be conducted at this point and the Sponsor will consider continued development of NM21-1480 in a given indication. For Cohort B8, the Sponsor will hold enrollment to the cohort after 25 patients have received at least one dose of NM21-1480 treatment until all relevant safety, efficacy, PK, immunogenicity and most prominently all relevant PD data that has accrued until then has been reviewed by the Sponsor and the SMC. After this interim review, the Sponsor may decide to stop the cohort, to continue with full enrollment of the cohort or revise eligibility criteria before the remaining 15 patients in that cohort are enrolled.

For Cohort B5, a total of approximately 200 patients with head and neck squamous cell cancer may ultimately be randomized 2:1 to either NM21-1480 plus a PD-1 standard-of-care first-line checkpoint inhibitor or to the standard-of-care PD1 checkpoint inhibitor monotherapy. Based on 10,000 trial simulations performed in R, a sample size of 180 patients in a 2:1 randomization provides approximately 90% power to detect a difference of 15% between the treatment groups with an estimated two-sided Type 1 error rate <0.05 of 0.0391 (Table 10-1). Based on 10,000 simulations, the margin of error is approximately ±0.4% for the Type 1 error calculations. Allowing for 10% losses to follow-up, at least 200 subjects will be randomized in Cohort B5.

Table 10-1 Sample size, power and Type 1 error

Sample Size	Power	Type 1 error
60	72.16%	5.3%
72	77.96%	5.42%
84	82.01%	5.14%
96	84.33%	4.84%
108	86.27%	4.78%
120	87.57%	4.68%
132	88.06%	4.38%
144	88.58%	4.2%
156	89.46%	4.38%
168	89.72%	4.07%
180	90.07%	3.91%
192	90.36%	3.62%
204	90.43%	3.69%

An interim analysis will be performed after a minimum of 60 patients (40 patients in the NM21-1480 arm) have been enrolled. At this point recruitment will be paused, the accumulated data analysed and regulatory authorities consulted. Cohort B5 will be regarded as futile (non-binding) if the probability of observing a difference in estimated effects between control and treatment of at least 15% is less than 0.1. However, as with the other cohorts, decisions at the interim point will be taken based on clinical and regulatory input and not formal statistical testing.

10.3 Statistical Design

10.3.1 Part A - Determining MTD Using Bayesian Optimal Interval Design

For dose-escalation, the BOIN design (Liu and Yuan, 2015; Yuan et al, 2016) is employed to find the MTD. The BOIN design is implemented in a simple way similar to the traditional 3+3 design,

but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou et al, 2018).

The target toxicity rate for the MTD is $\phi = 0.3$ and the maximum sample size is 25 (below steps describe the process in detail). To guide dose-escalation decisions, if the observed DLT rate at the current dose is ≤0.236, the next cohort of patients will be treated at the next higher dose level; if it is ≥0.359, the next cohort of patients will be treated at the next lower dose level. For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.3 \mid \text{data}) > 0.95$, where p_j is the true DLT rate of dose level $j, j = 1, 8$. When the lowest dose is eliminated, stop the study for safety.

The study design is illustrated in Figure 10–1 below and described through the following 3 steps:

a) Perform accelerated titration as follows: treat the first patient at dose level 1. If no ≥Grade 2 toxicity (as assessed by the Investigator to be related, probably related, or possibly related to the drug at any dose level) is observed, escalate the dose to the next higher level. Continue this 1-patient-per-dose dose-escalation process until the first ≥Grade 2 toxicity is observed or dose level 5 (80 mg dose level) is reached. Treat an additional 2 patients at the dose at which the first ≥Grade 2 toxicity is observed. Hereafter, patients are treated in cohorts of 3 as described in steps 2 and 3.

b) To assign a dose to the next cohort of patients, conduct dose-escalation/de-escalation according to the rule displayed in Table 10-2. When using Table 10-2, please note the following:

    c) "Eliminate" means that we eliminate the current and higher doses from the study to prevent treating any future patients at these doses because they are overly toxic.

    d) When dose is eliminated, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the study for safety. In this case, no dose should be selected as the MTD.

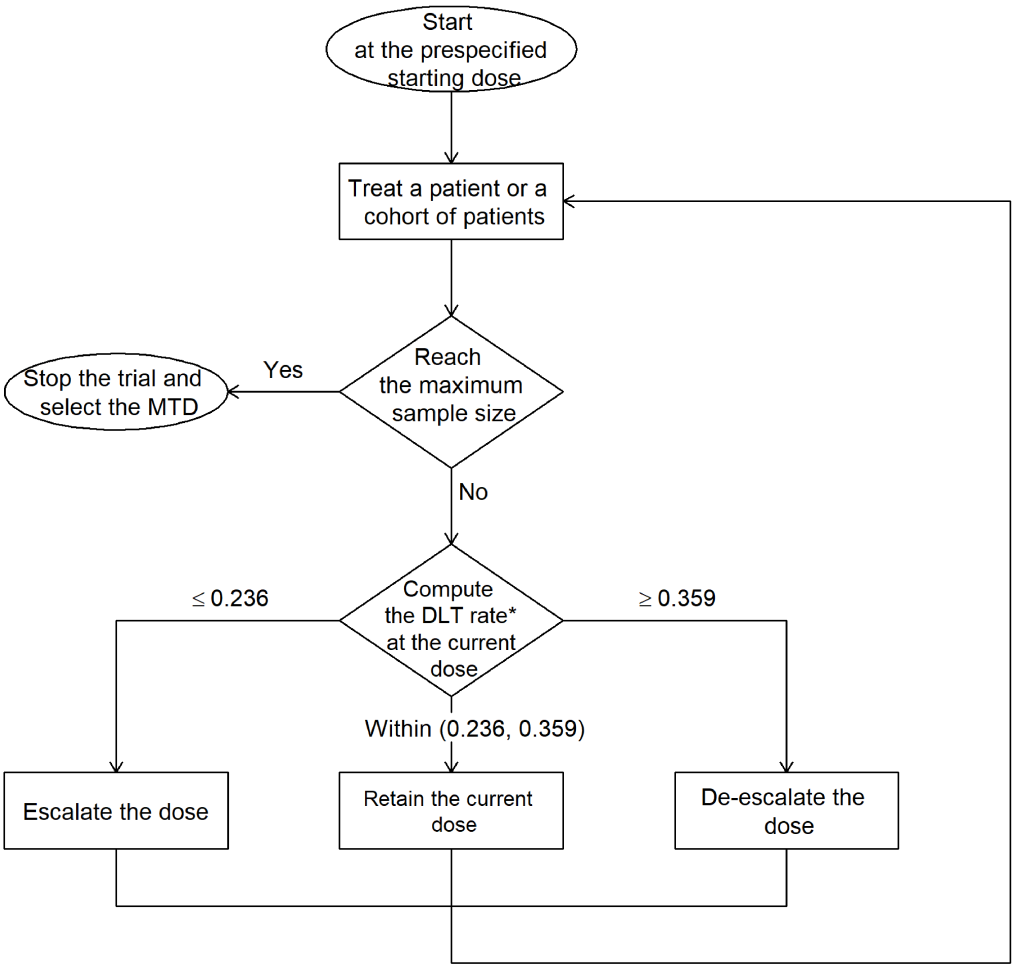
    e) If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.

    f) If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the study for safety.

    g) If the current dose is the highest dose and the rule indicates dose-escalation, treat the new patients at the highest dose.

h) Repeat step 2 until the maximum sample size of 25 is reached or stop Part A of the study if the number of patients treated at the current dose reaches 12.

Figure 10–1 BOIN Design



Abbreviations: DLT = Dose-limiting toxicity; MTD = Maximal tolerated dose

After the study is completed, the MTD based on isotonic regression as specified in Liu and Yuan, 2015 is selected (the MTD for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, the higher dose level is selected when the isotonic estimate is lower than the target toxicity rate and the lower dose level is selected when the isotonic estimate is greater than or equal to the target toxicity rate). Table 10-2 below provides the decision rules to be utilized during the dose-escalation period.

Table 10-2 Dose-Escalation/De-Escalation Decision Rules for the BOIN Design

Actions	The number of patients treated at the current dose											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Escalate if number of DLT ≤0.236	0	0	0	0	1	1	1	1	2	2	2	2
De-escalate if number of DLT ≥0.359	1	1	2	2	2	3	3	3	4	4	4	5
Eliminate if number of DLT	NA	NA	3	3	4	4	5	5	5	6	6	7

Abbreviations: BOIN = Bayesian optimal interval; DLT = Dose-limiting toxicity; NA = Not applicable

As of October 29, 2021, 13 evaluable patients have been treated at DL1 to DL5, as shown in Table 10-3 below. PK and PD data show that DL5 has reached the range of therapeutically effective dose. To reduce the chance of exposing patients to higher doses that may yield no additional benefit, amendment is made in Protocol V6.0 to remove DL8 from dose escalation. Accordingly, the maximum sample size in the BOIN is adjusted from 27 to 25.

Table 10-3 Observed Data as of October 29, 2021.

Dose level (DL)	DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8
Number of evaluable patients	1	1	3	3	5	0	0	0
Number of patients with DLT	0	0	0	0	1	0	0	0

Table 10-4 below shows the updated operating characteristics of the study design based on 1000 simulations, given the observed data (Table 10-3). The results show that the amended design (i.e., reducing the number of dose levels to be assessed in Part A from previously 8 to 7 in Protocol V6.0) yields higher probabilities of identifying the MTD than the original design. Of note, Table 10-4 does not consider the scenarios with the MTD lower than DL5 because the observed data show that is unlikely, and Scenarios 1 to 3 correspond to Scenarios 2-4 in operating characteristics of the original design with 8 dose levels.

Table 10-4 Operating Characteristics of the BOIN Design

Scenarios	DL1	DL2	DL3	DL4	DL5	DL6	DL7	Number of Patients	% Early Stopping
Scenario 1									
True DLT rate	**0.04**	**0.08**	**0.12**	**0.16**	**0.3**	**0.47**	**0.54**		
Selection %	**0**	**0**	**0**	**3.4**	**62.6**	**26.8**	**7.2**		**0**
Number of patients treated	**1**	**1**	**3**	**3.6**	**9.1**	**6.1**	**1.3**	**25**	
Scenario 2									
True DLT rate	**0.04**	**0.07**	**0.1**	**0.12**	**0.15**	**0.3**	**0.48**		
Selection %	**0**	**0**	**0**	**0.3**	**23.0**	**52.2**	**24.5**		**0**
Number of patients treated	**1**	**1**	**3**	**3.1**	**6.7**	**7.1**	**3.2**	**25**	
Scenario 3									
True DLT rate	**0.02**	**0.04**	**0.06**	**0.08**	**0.1**	**0.12**	**0.3**		
Selection %	**0**	**0**	**0**	**0**	**1.9**	**22.9**	**75.2**		**0**
Number of patients treated	**1**	**1**	**3**	**3**	**5.2**	**5.1**	**6.7**	**25**	

Abbreviations: BOIN = Bayesian optimal interval; DL = Dose Level; DLT = Dose-limiting toxicity

On 16 May 2022 the final (25th BOIN-evaluable) patient, dosed at dose level 7 (800mg), completed the 28-day DLT evaluation period. Consequently, a formal SMC meeting was held on 23 May 2022 to review all Part A clinical data with a primary focus on DLT rate and safety data. The below DLT data were observed in Part A (Table 10-5) and consequently the SMC determined that Part A of the study did not technically identify a MTD and the highest dose assessed (800mg) was considered a tolerable dose.

Table 10-5 Observed Data as of May 23, 2022.

Dose level (DL)	DL1	DL2	DL3	DL4	DL5	DL6	DL7
Dose (mg)	0.15mg	1.5mg	8mg	24mg	80mg	240mg	800mg
Number of evaluable patients	1	1	3	3	5	3	9
Number of patients with DLT	0	0	0	0	1	0	0

10.3.2 Part A-2 (Optional): PD Expansion

The primary objective of the optional Part A-2 is to better understand the exposure-dependent PD/dose response relationship. PD data will be combined across Part A and Part A-2 and summarized using descriptive statistics. If appropriate, the PD/dose relationship may be modelled. The shape of the dose response curve will be identified after plotting the data.

10.3.3 Part B - Clinical Activity Monitoring Using BOP2 Design

The efficacy endpoint is monitored using the BOP2 design (Zhou et al., 2017) in all Part B cohorts except for Cohort B5 (Section 10.6.2.1). Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the probability of clinical activity (response rate) and define the null hypothesis $H_0: p_{eff} \leq 0.05$, representing that the treatment is inefficacious. The patient enrollment will be stopped and claimed that the treatment is not promising if:

$$Pr(p_{eff} > 0.05|data) < \lambda(\frac{n}{N})^{\alpha}$$

Where λ=0.87 and α=0.62 are design parameters optimized to minimize the chance of incorrectly claiming that an efficacious treatment is not promising (i.e., type II error) under the alternative hypothesis $H_1: p_{eff} = 0.2$, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a β(0.05, 0.95) prior distribution for p_{eff}, and a maximum of 40 patients per cohort, the above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.9152 under H_1:

Table 10-6 Optimized Stopping Boundaries for BOP2 Design

Number of patients treated	Stop if # ORR ≤
25	1
40	4

Abbreviations: BOP2 = Bayesian optimal phase II; ORR = Objective response rate.

The interim analysis will be performed when the number of enrolled patients reaches 25. In this situation, the null hypothesis will be rejected if the number of responses is greater than 1; otherwise it is concluded that the treatment is not promising (Table 10-6). The go/no-go criteria are non-binding though, in particular as an ORR of 10% in the patient population assessed may already be considered a clinically meaningful result by the Sponsor. Futility analyses will be done based on availability of 12 weeks data. The data monitoring committee (DMC), consisting of Sponsor representatives will determine whether a cohort shall be stopped or continued after the interim analysis.

The operating characteristics of the design based on 10,000 simulations using shiny app "BOP2" published by MD Anderson Software are presented in Table 10-7.

Stratification factors will be applied to Part B enrollment.

Table 10-7 Operating Characteristics

Response rate	Early stopping (%)	Claim promising (%)	Sample size
0.01	97.42	0	25.4
0.05	64.24	4.50	30.4
0.10	27.12	35.90	35.9
0.15	9.31	72.22	36.6
0.20	2.74	91.52	39.6
0.25	0.7	99.03	39.9
0.30	0.16	99.64	40
0.35	0.03	99.94	40
0.40	0.01	99.99	40
0.45	0	100	40

10.4 Statistical Analyses Sets

10.4.1 Safety Set

The safety set (SS) consists of all patients who receive at least 1 dose of study drug. Unless otherwise specified, the SS will be the default analysis set used for all analyses.

10.4.2 Dose-Determining Set

The dose-determining set includes all Safety Run-in patients from the SS of Part A who either completed the minimum exposure requirement and have sufficient safety evaluations or experienced a DLT. Patients will be considered to have met the minimum exposure requirement if they received at least 80% of either originally-assigned dose within the first cycle of dosing (i.e., 80% of either the dose administered for Cycle 1/Day 1 [C1D1] or Cycle 1/Day 15 [C1D15]). The length of the DLT evaluation period is 28 days.

Patients who do not experience a DLT during the first cycle will be considered to have sufficient safety evaluations if they have been observed for ≥28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

10.4.3 Pharmacokinetic Set

The PK set will consist of all patients who receive at least 1 dose of NM21-1480 and have at least 1 post-dose PK blood collection with associated bioanalytical results. The PK set will be used for summaries and listings of PK data.

10.4.4 Efficacy Analysis Set

Consists of all patients who received at least one dose of study drug and have measurable baseline disease. The Efficacy Analysis Set will be the primary analysis set for efficacy in this study.

For Part B, patients who are still on treatment at the time of data cut-off, but have not yet reached the first post-baseline tumor assessment, will be excluded.

10.5 Stratification Factors

Stratification factors are applied for Part B cohorts as follows:

1. Primary vs. secondary resistance (Cohorts B1 and B7)
2. Number of previous lines of therapy; one vs. 2 lines (Cohort B2)
3. Duration of last platinum-free interval: ≤6 months vs. >6 months to ≤12 months (Cohort B4)
4. CPS of ≥1 to<20 vs. ≥20 (Cohort B5)
5. Checkpoint inhibitor naïve vs. Checkpoint inhibitor pretreated (Cohort B6)

No stratification factor is applied for Cohort B3 and for Cohort B8.

10.6 Statistical Analyses and Methods

10.6.1 Patient Characteristics

The following baseline patient characteristics will be summarized descriptively: demographics (age, gender, and race); prior anticancer agents (chemotherapy, biologics, targeted small molecules); best response and best response duration to prior anticancer therapy; prior RT, prior surgery; primary site of disease; medical history; ECOG performance status; concomitant medication usage.

10.6.2 Efficacy Analyses

In order to perform preliminary evaluation of anti-tumor activity, BOR outcomes, ORR, and disease control rate (DCR) according to RECIST 1.1 and iRECIST will be tabulated by frequency distribution overall, and 6 and 12 weeks following the start of study treatment for Part B cohorts as determined by central and institutional reads. Similar exploratory analyses as determined by institutional reads (but for RECIST1.1 only) will be done for Part A and A-2 (if applicable) overall, and 8 and 16 weeks following Day 1, in accordance with the respective imaging visit frequency.

Median TTR and duration of response (DOR) will be summarized for those patients with responses, using the Kaplan-Meier method, i.e., by generation of Kaplan-Meier curves for time-to-event variables; PFS and OS will be similarly summarized. Individual tumor measurements, tumor burden and % changes in tumor burden will be listed. Changes in tumor burden will be presented graphically for each tumor-type. All primary clinical activity analyses will be based on the Efficacy Analysis Set, ongoing patients who have not reached the first post-baseline tumor assessment will be excluded from response analyses. Exploratory analysis to assess the OS will be provided by a Kaplan-Meier method. Summary statistics and plots of measures of tumor-specific antigen levels may be provided if applicable.

Efficacy data will be presented in tabular and/or graphical format and summarized descriptively by dose level in Part A, Part A-2 and Part A/A-2 combined, and by cohort in Part B. Dose groups in Part B may be pooled within cohorts for final analyses if the response is deemed to be independent of dose from a clinical perspective.

10.6.2.1 Primary Efficacy Analysis, Cohort B5

For Cohort B5, the primary efficacy endpoint will be central RECIST 1.1 read of ORR. The primary analysis will be performed in the Efficacy Analysis Set using a Bayesian logistic regression model with treatment and (CPS ≥1; CPS ≥20) as a covariates:

$$Logit\,(p_i) = \beta_0 + \beta_1 \times treatment + \beta_2 \times CPS20$$

The following prior distributions have been assumed:

$\beta_0 \sim N(-1.45, 0.16^2)$, equivalent to a control response rate of 20 (±4)% observed in the KEYNOTE-048 study with pembrolizumab;

$\beta_1 \sim N(0,1)$, vague prior on treatment equivalent to expected treatment difference of 0% (95% confidence interval: -16% to +43%, which corresponds to a N(0,1) prior on logistic scale)

$\beta_2 \sim N(0, 0.1^2)$, vague prior on CPS effect, based on KEYNOTE-048 study with pembrolizumab, where a 0%-3% difference in response was observed across CPS levels.

The Bernoulli likelihood is not conjugate to the normal priors on the regression coefficients and so the posterior distribution of regression coefficients is not known. Let $\beta = (\beta_0, \beta_1, \beta_2)$.

$$\pi(\beta|data) \propto \pi(data|\beta)\pi(\beta)$$

In order to avoid the use of Monte Carlo methods for inference on parameters (and the requirement of large simulations to estimate posteriors with sufficient precision) we fit Laplace approximations to posterior distributions. We approximate $\pi(\beta|data) \approx N(\beta', Var(\beta'))$ where β' is the mode of the posterior distribution of $\pi(\beta|data)$ with $Var(\beta')$ the posterior covariance matrix estimated at this mode.

At the interim analysis, Cohort B5 will be regarded as futile (non-binding) if the probability of observing a difference in estimated effects between control and treatment of at least 15% is less

than 0.1. However, as with the other cohorts, decisions at the interim point will be taken based on clinical and regulatory input and not formal statistical testing. Statistical superiority of the treatment in the final analysis will be concluded if $Pr(\beta_1 > 0 \mid data)$ is > 0.95.

10.6.2.2 Best Overall Response

Best overall response (BOR) is defined as the best response obtained among all tumor assessment visits after the date of first dose of study drug until documented disease progression, taking into account the rules as detailed below. The tumor response will be determined according to RECIST 1.1 and also according to iRECIST in Part B. Only tumor assessments performed before the start of any subsequent anticancer therapies and not later than 30 days after last dose will be considered in the assessment of BOR. Clinical deterioration or clinical progression noted on the completion eCRF will not be considered as documented disease progression.

Two sets of BOR will be summarized in a single table by treatment phase, 1 for confirmed and 1 for confirmed + unconfirmed responses. Best overall response is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least 2 determinations of CR at least 4 weeks apart before disease progression, where confirmation required, or 1 determination of CR prior to disease progression, where confirmation is not required.
- PR = at least 2 determinations of PR or better at least 4 weeks apart before disease progression (and not qualifying for a CR), where confirmation required, or 1 determination of PR prior to disease progression, where confirmation is not required.
- Stable Disease (applicable only to patient with measurable disease at baseline) = at least 1 stable disease assessment (or better) ≥6 weeks after start of treatment (and not qualifying for CR or PR).
- Non-CR/non-progressive disease (applicable only to patients with non-measurable disease at baseline) = at least 1 non-CR/non-progressive disease assessment (or better) after start of treatment and before progression (and not qualifying for CR or PR).
- Progressive Disease = disease progression ≤12 weeks after first dose of study drug (and not qualifying for CR, PR, or stable disease).
- Not Evaluable = all other cases (i.e., not qualifying for CR or PR and without stable disease after at least 6 weeks or early progression within the first 12 weeks).

Patients with BOR 'Not Evaluable' will be summarized by reason for having unknown status. The following reasons will be used:

- No baseline assessment
- No adequate post-baseline assessment

- All post-baseline assessments have overall response of "NE"
- New anticancer therapy started before first post-baseline assessment
- Stable disease occurred <6 weeks after date of first dose of study drug
- Progression >12 weeks after date of first dose of study drug.

Special (and rare) cases where BOR is 'Not evaluable' due to both stable disease occurring <6 weeks after first dose of study drug and progression >12 weeks after first dose of study drug will be classified as "stable disease occurred <6 weeks after first dose of study drug".

10.6.2.3 Objective Response Rate

Objective response rate (ORR) is defined as the number of patients achieving an overall best response of CR or PR divided by the total number of patients. Two sets of ORR will be summarized, 1 for confirmed and 1 for confirmed + unconfirmed responses. A 2-sided exact 95% confidence interval based on the Clopper-Pearson method will be provided for ORR (Clopper and Pearson, 1934).

10.6.2.4 Duration of Response

Duration of response is defined as the time from first radiographic evidence of response to the earliest documented disease progression or death and is calculated for responders only. Responders who do not have a disease progression or death date by the data cut-off date will be censored for DOR at their last adequate radiological assessment (i.e., at the date of last tumor assessment of CR, PR, or stable disease) prior to cut-off date or date a subsequent anticancer therapy is started. Duration of response will be summarized using the Kaplan-Meier method.

10.6.2.5 Overall Survival

Overall survival is defined as the time from start of study treatment to death due to any cause. The survival follow-up (as defined in Table 7-1 and Table 7-2) is for up to 1 year following treatment discontinuation. Patients alive at the data cut-off date will be censored for survival at their last contact date. One-year survival rate will be estimated using the Kaplan-Meier method.

10.6.2.6 Progression-Free Survival

Progression-free survival is defined as the time from start of study treatment to the earliest documented date of disease progression, per RECIST 1.1 (and iRECIST in Part B) and as determined by Investigator, or death due to any cause. Progression-free survival will be calculated for all patients and summarized using the Kaplan-Meier method. Progressive disease and death (from any cause) will be considered as events. If death or disease progression is not observed, the PFS will be censored at the date of last adequate tumor assessment (i.e., at the date of last tumor assessment of CR, PR, or stable disease) prior to cut-off date or date a subsequent anticancer therapy is started (e.g., systemic therapy, non-palliative RT). However, if a PFS event is observed

after more than 1 missing or inadequate tumor assessment, PFS will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used.

When a patient discontinues treatment for "disease progression" but without documentation of radiological and/or pathological evidence of progression based on RECIST it will not be counted as a PFS event. The patient will continue to be followed for PFS until disease progression, withdrawal of consent/assent, initiation of subsequent anticancer therapy, the patient is lost to follow-up or until death. If a PFS event occurs during this follow-up, the date of the event will be included in the analysis. If the patient does not have a PFS event during this time, the patient will be censored at the last assessment date.

Handling of missing assessments and censoring rules for PFS are summarized in the SAP.

10.6.3 Safety Analyses

All recorded TEAEs will be listed and tabulated by system organ class, preferred term, and dose and coded according to the most current version of Medical Dictionary for Regulatory Affairs (MedDRA). Besides TEAEs, TRAEs (i.e., assessed as at least possibly related to study drug by the Investigator) will be separately listed and tabulated. The incidence of AEs will be tabulated. Vital signs and clinical laboratory test results will be listed and summarized by dose level. Any significant physical examination findings and results of clinical laboratory tests will be listed. ECG listings will be evaluated by the Investigator and abnormalities, if present, will be listed. A separate listing and summary of all irAEs will be provided. Adverse events will be summarized for all reported data and by study part as well as study period, i.e., up to and including 70 days post last dose of study treatment.

Safety data will be presented in tabular and/or graphical format and summarized descriptively by dose cohort and study day, where appropriate. Safety data for Part B may be pooled across dose groups to mirror the efficacy analysis decisions to facilitate an appropriate risk benefit assessment per cohort.

10.6.4 Study Drug Exposure

Duration of study treatment exposure, actual cumulative dose and relative dose intensity will be summarized. The number of patients with dose modifications/interruptions will be presented, along with reasons for the dose modification. The actual daily doses and reasons for dose modification will be listed.

10.6.5 Concomitant Medications

Concomitant medications will be listed and summarized by Anatomical Therapeutic Chemical Classification System term, preferred term. These summaries will include medications starting on

or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

10.6.6 Adverse Events

Adverse events will be coded using the most current version of the MedDRA. Incidence tables will be presented for all AEs by maximum grade according to CTCAE v5.0. Adverse events, SAEs, TEAEs, TRAEs (i.e., assessed as at least possibly related to study drug by the Investigator), and AEs resulting in dose reduction, interruption, or discontinuation of study drug will be tabulated, as well as AEs leading to additional therapy. Dose-limiting toxicity will also be tabulated. Summaries for deaths on study will be provided by system organ class and preferred term. Adverse event of special interest for NM21-1480 will be identified according to the most recent case retrieval strategy prior to database lock. Such categories consist of 1 or more well defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment. For each specific category, number and percentage of patients with at least 1 event will be reported. Additional analyses (including time to onset and duration) may also be performed for these events.

Adverse event of special interest do not require expedited reporting to the Sponsor unless the event(s) meets SAE reporting criteria (Section 9.2.6).

10.6.7 Laboratory Parameters

Hematology and chemistry laboratory parameters will be presented in shift tables of baseline grade versus maximum grade on study as per CTCAE v5.0. For laboratory parameters that are not gradable by CTCAE, shift tables of normal-abnormal will be provided. Laboratory measurements will be summarized descriptively, and plots of measurements over time will be generated for selected parameters (liver toxicity parameters, and WBC subpopulation cell counts). Calcium phosphate product values will be calculated using measurement of plasma total calcium and serum ionized calcium and will be summarized descriptively.

10.6.8 Electrocardiograms

Electrocardiogram values will be summarized descriptively and/or with shift tables.

10.6.9 Other Safety Data

Vital signs, body weight, and ECOG performance status data will be summarized descriptively by visit and/or with shift tables. Summaries of clinically notable measurements may also be provided. Definitions of “clinically notable” will be provided in the SAP.

A more detailed description of study analyses will be presented in the SAP.

10.6.10 Analysis of Pharmacokinetics Endpoints and Anti-Drug Antibody

Pharmacokinetic parameters such as Cmax, Cmin, Tmax, λz, t½, Tmax, AUCtau, CL, apparent Vd, and accumulation index will be derived from serum concentration versus time data for patients with serial PK samples. Data obtained from patients with serial sampling and limited sampling will eventually be combined with data from other studies for population PK analysis but reported separately.

A listing will be generated of all available immunogenicity data, comprising all numeric titer values. Additionally, a listing of immunogenicity data from those patients with at least 1 positive ADA assessment (titer value greater than 2-fold of baseline titer) at any time point will be provided by dose regimen. The frequency of patients with at least 1 positive ADA assessment (titer value greater than 2-fold of baseline titer), and frequency of patients who develop ADA after a negative baseline assessment (i.e., titer value equal to 1), and frequency of patients who develop ADAs after a baseline titer assessment greater than 1, will be provided by dose. In addition, the frequency of patients who do not develop ADAs after treatment following either a negative baseline assessment (i.e., titer value equal to 1), or a baseline titer greater than 1 will be provided by dose. Treatment-induced, treatment-enhanced and treatment-unaffected ADA patients will be summarized. In addition, to examine the potential relationship between immunogenicity and safety, the frequency and type of AEs may be examined by overall immunogenicity status.

Serum concentrations of NM21-1480 will be determined using validated bioanalytical methods. Serum concentration-time profiles for NM21-1480 will be generated. Descriptive summaries for NM21-1480 concentrations will be presented by dose and formulation.

10.6.11 Pharmacodynamic Characteristics and Exploratory Biomarkers

Summary statistics for blood- and tissue-based PD markers, including but not limited to flow cytometry outcomes, cytokines, and their changes (or percent changes) from baseline will be tabulated by cycle, visit, and dose to assess PD effects and potential association with PK exposure. Associations of status of exploratory biomarkers (baseline value or change from baseline) with clinical outcome (e.g., tumor response) may be explored based on data availability, using response-evaluable patients, to explore potential predictive markers (e.g., PD-L1) expression in tumors.

Administrative interim analyses on safety and clinical activity or on PK, immunogenicity, and selected biomarkers may be provided at several times prior to completion of the study in order to facilitate program decisions and to support study presentations or publications.

10.7 Safety Monitoring and Data Monitoring Committee

A Safety Monitoring Committee (SMC) (consisting of study Investigators, Medical Monitor and Sponsor observers) is formed that will review cumulative and emerging safety data during study conduct (Part A, optional Part A-2, and B). The SMC's major responsibilities comprise evaluation of DLTs, dose-escalation decisions and continuous safety monitoring in Part A. SMC meetings

will also be held according to the SMC charter to evaluate the safety data emerging in Part A-2 and Part B (expansion cohorts). For Part B, a separate Data Monitoring Committee (DMC), consisting of Sponsor representatives, will be established to review PD data and the interim clinical activity results. Based on continuous clinical activity reviews and the results of the Part B interim analyses, the DMC will determine whether expansion cohorts are to be continued until the full sample size of 40 patients per B cohort is reached or stopped early for futility. The Investigators will only be informed by the Sponsor in case of stopping the study or specific expansion cohorts for futility.

A DMC charter outlines DMC membership, the data that will be reviewed, and the timing and frequency of reviews.

11 ETHICS

11.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH GCP and local requirements as applicable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, participant recruitment procedures (e.g., advertisements), written information to be provided to the participants, IB, available safety information, information about payment and compensation available to participants, the Investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

11.2 Written Informed Consent

The nature and purpose of the study shall be fully explained to each participant (or their legally responsible guardian). They must be informed that participation is voluntary.

Written informed consent must be obtained from each participant (or authorized representative) prior to any study procedures being performed. The process of obtaining informed consent must be documented in the participant's source documents. The authorized person obtaining the informed consent must also sign the ICF, and a copy of the ICF must be provided to the participant or the participant's legally authorized representative. Participants must be re-consented to the most current version of the ICF during their participation in the study.

The consent documents to be used for the study shall include all the elements of informed consent as outlined in accordance with FDA, ICH GCP and local requirements as applicable and be reviewed and approved by the appropriate IEC/IRB prior to use.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Conduct of the Study

The Sponsor shall implement and maintain quality control and quality assurance procedures with written standard operating procedure (SOP) to ensure that the study is conducted, and data are generated, documented and reported, in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013), FDA (CFR, Sections 312.50 and 312.56), EU (536/2014) and UK regulations (The Medicines for Human Use [Clinical Trials] Regulations 2004 [no.1031]), and with ICH GCP (CPMP 135/95). The study also will be carried out in compliance with local legal requirements.

The Investigator will be responsible for the following:

1. Providing written summaries of the status of the study to the IEC/IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC/IRB
2. Notifying the IEC/IRB of SAEs or other significant safety findings as required by IEC/IRB procedures

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the participant or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the participant having to be withdrawn from the study and render that participant non-evaluable.

The identification and reporting of serious breaches of ICH GCP or the protocol to the Regulatory Authorities and Ethics Committees will be conducted according to local SOPs and regulations.

12.2 Study Monitoring

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. The Investigator shall permit the Sponsor Site monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The Investigator shall access medical records for the monitor in order that entries in the eCRF may be verified. The Investigator, as part of his/her responsibilities, is expected to co-operate with Medpace in ensuring that the study adheres to GCP requirements.

The Investigator may not recruit participants into the study until such time that a visit, or with the agreement of the Sponsor, attendance at an Investigator meeting, has been made by a Sponsor/Medpace monitor to conduct a detailed review of the protocol and CRF.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study monitoring plan.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms/Source Data Handling

All required study data must be entered in the eCRF created for the study. This data collection tool is a validated electronic data capture (EDC) system that contains a system generated audit trail. Data required according to this protocol are recorded by investigational site personnel via data entry into the internet-based EDC software system. The Investigator shall ensure that all data from participant visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded. All internal Medpace and external investigational site personnel seeking access to the eCRF are supported by a Service Desk (if applicable). At the end of the study all data captured electronically will be provided to the Investigator on CD-ROM for archiving at the investigational site.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analysed at that laboratory.

The Investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the participant's file.

The Investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review and regulatory inspection.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

13.2 Data Protection

Participants will be assigned a unique identifier by clinical research organization. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the

participant. The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC/IRB members, and by inspectors from regulatory authorities.

13.3 Dissemination of Clinical Study Data

The study will be registered and post-study results will be posted in accordance with the applicable laws and regulations. The results of this study may be published or presented at conferences/in journals.

13.4 Retention of Essential Documents

The Investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

14 PUBLICATION POLICY

The Sponsor shall retain the ownership of all data. When the study is complete Medpace shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. The Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship agreements. All proposed publications based on this study must be participant to the Sponsor's approval requirements.

The Sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

15 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the Sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

16 SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

((Type name and job title))	Date (day/month/year)

17 REFERENCE LIST

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18 APPENDICES

18.1 Appendix I: List of NM21-1480 Formulation Excipients

- Water for injection

18.2 Appendix II: Liver Safety Monitoring and Assessment

Introduction

The purpose of this appendix is to provide guidance for the monitoring of drug-induced liver injury (DILI) during the course of the study. It should be noted that this section does not specify the end of study analyses of liver enzymes. The end of study liver enzymes analyses will be described in the SAP. Any patient enrolled in a study with active drug therapy and who reveals an increase of serum aminotransferases (AT) to >3 × ULN (to >5 × ULN in patients with liver metastases) or total bilirubin level (TBL) >2 × ULN should undergo detailed testing for liver enzymes (including at least ALP, ALT, AST and TBL). Testing should be repeated within 72 hours of notification of the test results. Patients should be asked if they have any symptoms.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN is as shown in below table:

	ALT or AST		Total Bilirubin
Moderate	>3 × ULN (in patients without liver metastases), >5 × ULN (in patients with liver metastases)	or	>2 × ULN
Severe	>3 × ULN	and*	>2 × ULN

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal
*Samples taken simultaneously or within a maximum of 24 hours.

In addition, the patient should be considered to have severe hepatic abnormalities for any of the following:

- AST or ALT >5-10 × ULN for >2 weeks or AST or ALT >10 × ULN
- Total bilirubin >5 × ULN
- Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN without initial finding of cholestasis (elevation of ALP)
- For patients with hepatic metastases: AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 daysThe Investigator may determine that abnormal liver function results, other than those described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and clinical laboratory tests. The study site personnel are to complete the eCRF. Patients with confirmed abnormal liver function tests (LFT) should be followed as described below:

Confirmed moderately or severely abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the IP has been discontinued and the patient is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as an SAE. The Sponsor should be contacted and informed of all patients for whom severe hepatic liver function abnormalities possibly attributable to IP are observed.

To further assess abnormal hepatic laboratory findings, the Investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases are to be recorded as "AEs" in the eCRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic patients and may be associated with fluctuating AT levels. The Investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function;
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, including dose, are to be entered in the eCRF. Information on alcohol, other substance use and diet should be entered on the eCRF or an appropriate document;
- Obtain a history of exposure to environmental chemical agents;
- Based on the patient's history, other testing may be appropriate including:
  - Acute viral hepatitis (A, B, C, D, E or other infectious agents)
  - Ultrasound or other imaging to assess biliary tract disease
  - Other clinical laboratory tests including international normalized ratio and direct bilirubin;
- Consider gastroenterology or hepatology consultations; and
- Submit results for any additional testing and possible etiology on the eCRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased LFTs, such as viral hepatitis, pre-existing or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the patient may be discontinued from study treatment. The Investigator may determine that it is not in the patient's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

- AST or ALT >5-10 × ULN for >2 weeks or AST or ALT >10 × ULN
- Total bilirubin >5 × ULN
- Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN without initial finding of cholestasis (elevation of ALP)
- For patients with hepatic metastases: AST or ALT >8 × ULN or AST or ALT >5 × ULN for ≥14 days

* Samples taken simultaneously or within a maximum of 24 hours.

In addition, if close monitoring for a patient with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

Hy's Law Definition

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 × AT elevations over the ULN (2 × elevations are too common in treated and untreated patients to be discriminating).
2. Cases of increased bilirubin (to at least 2 × ULN) in people with concomitant AT elevation to at least 3 × ULN (but it is almost invariably higher) and no evidence of intra-or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Reference: Temple R. Hy's Law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf.2006; 15(4):241-3].

FDA Guidance for Industry titled "DILI: Premarketing Clinical Evaluation" issued by the FDA on July 2009.

FDA Guidance for Industry:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among patients showing such AT elevations, often with AT levels much greater than 3 × ULN, 1 or more also show elevation of serum TBL to >2 × ULN, without initial findings of cholestasis (elevated serum ALP).

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral Hepatitis A, B or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

18.3 Appendix III: Response Evaluation Criteria in Solid Tumors Version 1.1

Tumor lesions will be categorized as follows:

- **Measurable Lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
  - 10 mm caliper measurement by clinical examination (when superficial)
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm)
- **Non-measurable Lesions:** Non-measurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis). Lesions considered truly non-measurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- **Target Lesions:** At baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions:** It is possible to record multiple non-target lesions involving the same organ as a single item (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).
- **New Lesions**: Though only certain new lesion measurements will be included in the tumor burden, all new lesions that can be accurately measured should be recorded. Up to 5 additional target lesions (maximum of 2 additional lesions per organ) may be added to the tumor burden at each post-baseline assessment to facilitate the exploratory RECIST analysis. Other new lesions will be included into the non-tumor burden.

RECIST 1.1 Response Criteria

Evaluation of Target Lesions

- **CR** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (the sum may not be "0" if there are target nodes).
- **PR** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease** - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered disease progression.)
- **Stable Disease** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **CR** - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-progressive disease** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of stable disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see Section 7.2.9). In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase would be required to declare disease progression for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered disease progression according to RECIST 1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions can nonetheless derive clinical benefit.

Evaluation of Overall Response

For the overall response based on RECIST 1.1, confirmation of CR and PR is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. If a patient discontinues the study due to disease progression and begins another treatment, a confirmatory scan is not required.

Below table provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Evaluation of Overall Response Using RECIST 1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion [a]	Complete response	No	Complete response
Complete response	Not evaluable [b]	No	Partial response
Complete response	Non-complete response/ non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Non-complete response/ non-progressive disease	No	Non-complete response/ non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

RECIST 1.1 = Response Evaluated Criteria in Solid Tumors version 1.1.

a Defined as no target lesion at baseline.

b Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

Reference: Eisenhauer, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1), European Journal of Cancer, 2009, Vol. 45, p 228-247

18.4 Appendix IV: Eastern Cooperative Oncology Group Performance Status Scale

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, (e.g., light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Reference: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

18.5 Appendix V: Women of Child-Bearing Potential Definitions and Methods of Contraception

Definitions

Woman of Child-bearing Potential (WOCBP): A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  1. Documented hysterectomy
  2. Documented bilateral salpingectomy
  3. Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Post-menopausal female: A post-menopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum FSH level >40 mIU/mL to confirm menopause.

Contraception Guidance for Female Participants of Child-Bearing Potential

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 180 days after the end of study treatment (local laws and regulations may require use of alternative and/or additional contraception methods).

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly.[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 7.1.6. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the investigational medicinal product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone-releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus) • Spermicide only • Lactation amenorrhea method (LAM)

*Local laws and regulations may require use of alternative and/or additional contraception methods.

Contraception Guidance for Male Participants with Partner(s) of Child-Bearing Potential

Male participants with female partners of child-bearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 180 days after the end of study treatment.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 6 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 6 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 6 months after the end of study treatment.

18.6 Appendix VI Immune-Related Adverse Event Management Guidance for Investigators

Identification, Diagnosis, Management and Dose Modification for irAEs

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Pneumonitis	Symptomatic: dyspnea, cough, pleuritic chest pain, hypoxia Asymptomatic: lung infiltrates that mimic severe bacterial pneumonia	Radiographic imaging of chest Tissue and lavage samples from bronchoscopy to rule out infectious pathogens and pathologic evaluation	Grade 2: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold NM21-1480 until resolved to ≤Grade 1
			≥Grade 3: high-dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; in-patient hospitalization; consultation with a respiratory physician; additional immunosuppression with infliximab can be considered	Permanent discontinuation from the study
Colitis	Watery diarrhea, mucus or blood in stool, abdominal pain, nausea/vomiting, dehydration, peritoneal signs, bowel perforation	Stool cultures Endoscopy or colonoscopy to rule out infection Biopsy to rule out alternative etiology	≤Grade 2 diarrhea: antidiarrheal medication, oral hydration, electrolyte supplement	Continue dosing
			Persistent Grade 2 diarrhea: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold NM21-1480 until resolved to ≤Grade 1

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			Grade 3 diarrhea: high-dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; infliximab can be considered for steroid refractory diarrhea	Withhold NM21-1480 until resolved to ≤Grade 1
			Recurrent Grade 3 or Grade 4: high-dose corticosteroids (2-4 mg/kg/day IV methylprednisolone) along with antibiotics; infliximab can be considered for steroid refractory diarrhea; in-patient hospitalization	Permanent discontinuation from the study
			If bowel perforation is suspected, steroid should be withheld and surgical opinion should be explored; in-patient hospitalization; Infliximab should not be administered	Permanent discontinuation from the study
Hepatitis	Symptomatic: fever, fatigue, nausea, abdominal pain, jaundice, hepatomegaly, Asymptomatic: elevation of LFT (hepatic transaminases, bilirubin)	Chemistry: elevated levels of hepatic transaminases Serologic testing: should be performed to rule out viral hepatitis (including hepatitis A and B), cytomegalovirus, and Epstein-Barr virus Ultrasonograms of the liver Biopsy or radiologic imaging to distinguish from	Grade 2: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents For patients with liver metastasis (note: patients with HCC are excluded from this study) who entered the study with Grade 2 elevation of AST/ALT, NM21-	Withhold NM21-1480 until resolved to ≤Grade 1

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
		other etiologies of hepatic injury, such as neoplastic disease progression in the liver, infections, and effects of other medications or alcohol intake	1480 will be withheld if AST/ALT increase ≥50% relative to baseline	
			≥Grade 3: administration of high-dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); if not improved after 48-72 hours, alternative immunosuppression agents (mycophenolate mofetil) should be considered; in-patient hospitalization; consultation with a hepatologist For patients with liver metastasis or HCC (note: patients with HCC are excluded from this study) who entered the study with Grade 2 elevation of AST/ALT, NM21-1480 will be permanently discontinued if AST/ALT increase ≥50% relative to baseline and lasting ≥1 week	Permanent discontinuation from the study

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
			Total serum bilirubin >3 times upper limit of normal	
Hypophysitis	Headache refractory to nonsteroidal anti-inflammatory drugs or other analgesics; weakness; fatigue, weight gain or weight loss; changes in mood or behavior; hypotension; electrolyte disturbances; abdominal pain; loss of libido; adrenal crisis; hypogonadism	Clinical chemistry tests Endocrinologic laboratory test, ACTH, thyroid function test, MRI of the brain: enlargement of the pituitary with variable contrast enhancement characteristics	Grade 2 without adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); initiate appropriate hormone replacement therapy; consultation with an endocrinologist	Withhold NM21-1480 until resolved to ≤Grade 1
			≥Grade 3 or adrenal crisis: high-dose corticosteroids (methylprednisolone 1 to 2 mg/kg/day or the equivalent); consultation with an endocrinologist	Permanent discontinuation from the study
Nephritis	Hematuria, peripheral edema, elevated serum creatinine	Clinical chemistry tests Urine test Biopsy if necessary	Grade 2: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold NM21-1480 until resolved to ≤Grade 1
			≥Grade 3: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Permanent discontinuation from the study

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Hypothyroidism/ hyperthyroidism	Typically asymptomatic and is identified by lab tests	T3, T4, TSH test results	Asymptomatic ≤Grade 2 hypothyroidism: thyroxine replacement therapy	Continue dosing
			Asymptomatic ≤Grade 2 hyperthyroidism: consider beta blockade	Continue dosing
			≥Grade 3 hypothyroidism: replacement therapy	Withhold NM21-1480 until resolved to ≤Grade 1 or baseline
			Grade 3 hyperthyroidism lasting ≥6 weeks despite active management via administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold NM21-1480 until resolved to ≤Grade 1
			Grade 4 hyperthyroidism	Permanent discontinuation from the study

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
Dermatitis	Maculopapular rash or erythroderma, pruritus, skin ulceration, bullous dermatitis, Stevens-Johnson syndrome	Unless an alternative etiology is identified, it should be considered immune-related Pathologic evaluation of skin biopsy can be performed to rule out alternative etiology	≤Grade 2 (up to 30% of body surface area): topical corticosteroids and oral over-the-counter antihistamines and systemic corticosteroids if no improvement within 7 days	Continue dosing
			Grade 3 (>30% of body surface area): administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold NM21-1480 until resolved to ≤Grade 2
			Grade 4 (Stevens-Johnson syndrome, toxic epidermal necrosis, full-thickness dermal ulceration, necrosis or hemorrhage): high-dose corticosteroids (2-4 mg/kg/day IV methylprednisolone); in-patient hospitalization; consultation with a dermatologist	Permanent discontinuation from the study
Neuromuscular toxicity	Peripheral sensory neuropathy, muscle weakness, Guillain-Barre syndrome, transverse myelitis, myasthenia gravis	Physical exam of sensory change, loss of deep-tendon reflexes Neuroimaging, nerve conduction exam,	≤Grade 2: administration of corticosteroids at a dose of 1-2 mg/kg/day prednisone equivalents	Withhold NM21-1480 until resolved to ≤Grade 1

irAE	Potential signs and symptoms	Diagnosis and differential diagnosis	Recommended management	Dose modification
		Nerve/muscle biopsy	≥Grade 3: high-dose corticosteroids (2-4 mg/kg/day IV methylprednisolone)	Permanent discontinuation from the study
Ocular toxicity	Photosensitivity, pain or dryness of the eyes, blurred vision, uveitis, iritis, episcleritis	ophthalmic exam	≤Grade 2: topical steroids (1% prednisolone)	Withhold NM21-1480 until resolved to ≤Grade 1; if not resolved ≤Grade 1 within 14 days with topical steroids or initiation of systemic treatment, permanent discontinuation from the study
			≥Grade 3: high-dose systemic corticosteroids (2-4 mg/kg/day IV methylprednisolone)	Permanent discontinuation from the study
Other irAEs, such as arthritis, pancreatitis, hemolytic anemia, adrenal insufficiency, myasthenic syndrome, and rhabdomyolysis			Grade 2	Withhold NM21-1480 until resolved to ≤Grade 1
			≥Grade 3	Permanent discontinuation from the study

Abbreviations: ACTH = Adrenocorticotrophic hormone; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; HCC = Hepatocellular carcinoma; irAE = immune-related adverse event; IV = intravenous; LFT = Liver function tests; MRI = Magnetic resonance imaging; T4 = Free thyroxine; TSH = Thyroid stimulating hormone.

18.7 Appendix VII Required Laboratory Assessments by Panel

Chemistry	Hematology	Coagulation	Thyroid	Urinalysis	Hepatitis B, Hepatitis C, and HIV	Other

• AST
• ALT
• Alkaline Phosphatase
• Amylase
• Lipase
• Creatinine
• Creatinine Clearance
• Total Bilirubin
• Direct Bilirubin
• Albumin
• Calcium
• Glucose
• LDH
• Total Protein
• BUN
• Uric Acid
• Sodium
• Phosphorus
• Potassium
• Chloride
• Bicarbonate
• CRP (if indicated)
	• Hemoglobin
	• Erythrocytes/Red Blood Cells (RBC)
	• Hematocrit
	• WBC
	• Platelets (direct platelet count)
	• Complete Blood Count with Differential: Neutrophils, Lymphocyte, Eosinophils, Basophils, Monocytes
	• CD4+ lymphocyte count (if applicable)
		• PT
		• INR
		• PTT
		• Activated PTT (if applicable)
			• TSH
			• T4 (free)
			• T3 (total and free)
				• Gross examination including specific gravity, protein, glucose, and blood
				• Microscopic examination including WBC/HPF, RBC/HPF, and any additional findings
					• Hepatitis B Surface Ag
					• Hepatitis B Surface Ab
					• Hepatitis B core Ab
					• Hepatitis C Ab
					• HCV RNA (Reflex)
					• HIV
					• CD4, Absolute and Percentage (if patient is HIV positive at screening)
						• Pregnancy (Serum/Urine)
						• FSH
						• Local test results on tumor genetic alterations such as MSI-H, dMMR, BRCA1, Kras, PD-L1 status, TMB, etc. (if available at medical history)
						• Tumor-specific blood tests (as applicable), e.g.:
						  ○ CEA for colorectal cancero
						  ○ CA 19-9 for pancreatic cancer
						  ○ PSA for prostate cancer
						  ○ CA145 for ovarian cancer