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STATISTICAL ANALYSIS PLAN

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
Protocol Version/Date:	Version 9.0, 17 Nov 2022
Investigational Product:	NM21-1480
Sponsor:	Numab Therapeutics AG Bachtobelstrasse 5, CH-8810 Horgen Switzerland
SAP Version/Date:	3.0 / 01 Nov 2023

SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature	**Date**
[redacted]	

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VERSION HISTORY

Version	Version Date	Description
1.0	01 Jul 2020	Prepared by ICON: Original signed version
2.0	29 Oct 2021	Prepared by ICON: - Updated according to protocol V6.0 - Updated tumor tissue CD8 to Ki67_CD3 as per the data availability
3.0	01 Nov 2023	Prepared by Medpace: Original signed version

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1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number NB-ND021 (NM21-1480)-101. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives – Part A

2.1.1 Primary Objectives

- 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

2.1.2 Secondary Objectives

- To characterize the pharmacokinetic (PK) profile of NM21-1480
- To evaluate the immunogenicity of NM21-1480

2.1.3 Exploratory Objectives

- 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

2.2 Study Objectives – Part A-2

2.2.1 Primary Objectives

- 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

2.2.2 Secondary Objectives

- To characterize the PK profile of NM21-1480
- To evaluate the immunogenicity of NM21-1480

2.2.3 Exploratory Objectives

- To determine the anti-tumor activity of NM21-1480 according to RECIST1.1

2.3 Study Objectives – Part B

2.3.1 Primary Objectives

- 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)

2.3.2 Secondary Objectives

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

2.4 Study Objectives – Part A, Part A-2 and Part B

2.4.1 Exploratory Objectives

- To characterize the PD profile of NM21-1480
- To evaluate biomarkers potentially capable of predicting a clinical response to NM21-1480

2.5 Study Design

2.5.1 Overview

NB-ND021 (NM21-1480)-101 is a first-in-human (FIH), open-label, multi-center, Phase 1/2, dose-escalation study with dose expansion cohorts in specific tumor types designed to:

- evaluate NM21-1480 for safety and immunogenicity
- determine the MTD and Recommended Phase 2 Dose (RP2D)
- define the PK response
- explore the pharmacodynamics (PD)
- 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

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 the 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.

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. The Sponsor, following

formal completion of Part A on 23 May 2022 is exploring within the 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. 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 was an optional part of the study. It was 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 was to further characterize the overall PK/PD relationship of NM21-1480 over a broad range of doses. Patients enrolled into this optional cohort needed to fulfill Part A eligibility criteria but in addition will needed 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 explored in Part A-2 was above the maximal dose level characterized in Part A, exploration of the 1400mg dose level was conducted under the continuous safety data review and guidance by the SMC. In this setting in which Part A-2 was conducted in parallel to Part B, its resulting data was 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 planned to 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. But due to the limited patients enrolled onto the study, Part B only had Cohorts B1, B7 and B8. Enrollment in Part B began when the SMC had completed its review of the Part A data and had 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 was only conducted in Spain. Cohort B1 included NSCLC patients with documented previous (i.e., prior to initiation of first-line therapy) PD-L1 expression on ≥50% of tumor cells who had progressed after first-line treatment with either anti-PD-(L)1 monotherapy, anti-PD-(L)1/chemotherapy or chemotherapy regimen or who had 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.

Cohort B7: This Cohort was conducted in the US and Spain. Cohort B7 included NSCLC patients with documented previous (i.e., prior to initiation of previous-line therapies) PD-L1 expression on ≥1% - 49% of tumor cells who had progressed after first-line treatment with either anti-PD-(L)1 monotherapy, anti-PD-(L)1/chemotherapy or chemotherapy regimen or who had progressed after-treatment with up to 3 previous lines of therapy, at least one including an anti-PD-(L)1 checkpoint inhibitor.

Cohort B8: This Cohort was conducted in the US and Spain. Cohort B8 included patients with metastatic colorectal cancer (mCRC) that were MSS or MSI low and who had 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 were 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.

2.5.2 Randomization and Blinding

This study was an open-label study. No randomization and blinding will be applied.

2.5.3 Study Drug

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.

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. The anti-HSA subdomain confers serum half-life (t½) prolongation upon binding to HSA.

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.

2.5.4 Sample Size Determination

For Part A dose-escalation, a BOIN design with a pre-specified maximal patient number of 25 was applied. For Part A-2 (OPTIONAL), a maximum number of 40 patients was planned to 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 was based on clinical rather than statistical considerations.

For Part B dose expansion (Cohorts B1 through B4 and B6-B8), a BOP2 design was planned to be applied with a maximum of 40 patients per cohort.

2.6 Study Endpoints – Part A

2.6.1 Primary Endpoints

- 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)

2.6.2 Secondary Endpoints

- PK parameters
  - AUC_{tau}
  - $AUC_{0\text{-}inf}$ (first dose only)
  - $AUC_{0\text{-}t}$
  - C_{max}
  - C_{min}
  - t½
  - T_{max}
  - λz
  - CL
  - CL_{ss}

  - Vd
  - Vd_{ss}
- Frequency of specific anti-drug antibodies to NM21-1480

2.6.3 Exploratory Endpoints

- 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

2.7 Study Endpoints – Part A-2

2.7.1 Primary Endpoints

- 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

2.7.2 Secondary Endpoints

- PK parameters
  - AUC_{tau}
  - $AUC_{0\text{-}inf}$ (first dose only)
  - $AUC_{0\text{-}t}$
  - C_{max}
  - C_{min}
  - t½
  - T_{max}
  - λz
  - CL
  - CL_{ss}
  - Vd
  - Vd_{ss}
- Frequency of specific anti-drug antibodies to NM21-1480

2.7.3 Exploratory Endpoints

- BOR
- ORR
- TTR
- DOR
- PFS
- OS

2.8 Study Endpoints – Part B

2.8.1 Primary Endpoints

- 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

2.8.2 Secondary Endpoints

- Disease Control Rate (DCR)
- DOR
- TTR
- PFS
- OS
- BOR, DCR, ORR, DOR, PFS as per iRECIST
- PK parameters
  - AUC_{tau}
  - $AUC_{0\text{-}inf}$ (first dose only)
  - $AUC_{0\text{-}t}$
  - C_{max}
  - C_{min}
  - t½
  - T_{max}
  - λz
  - CL
  - CL_{ss}
  - Vd
  - Vd_{ss}
- Frequency of specific anti-drug antibodies to NM21-1480

2.9 Study Endpoints – Part A, Part A-2 and Part B

2.9.1 Exploratory Endpoints (Applicable to Part A, Part A-2, and Part B)

- 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)
  - In cohort B8: Carcinoembryonic Antigen (CEA); circulating tumor DNA (ctDNA)

- 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

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Groupings

Unless specified otherwise, analyses for Part A will be presented by dose level and in total, analysis for Part A-2 will be presented in total, and analysis for Part B will be presented by cohort and in total. Additionally, for the analysis of demographic, safety, PK, and immunogenicity data, a total for all patients across Part A and Part A-2 will be presented, as will a total for all Part B patients who received NM21-1480, and a total for all patients in any part who received NM21-1480 at the 800 mg dose level.

3.1.2 Analysis Day

Analysis day will be calculated from the date of first dose of study treatment. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.3 Definition of Baseline

Baseline is defined as the last measurement prior to the start of study treatment.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.5 Hypothesis Testing

No hypothesis testing will be provided.

3.1.6 Evaluation of Site Effect

Site effect will not be analyzed.

3.1.7 Handling of Missing Data

Unrecorded data values will be recorded as missing. Only recorded (i.e. complete) data values will be used for statistical analyses. In general, invalid or missing values will not be imputed unless stated otherwise.

- For BOR and ORR, patients in the Efficacy Analysis Set who do not have sufficient on-study tumor assessments to characterize response will be included in the denominator when calculating BOR percent and ORR, and will thus be treated as non-responders. Further details are found in section 3.4.1.1.
- In cases of missing or incomplete dates (e.g. AEs and concomitant medications or procedures), the missing component(s) will be assumed as the most conservative value possible. For the detailed missing/partial data handling conventions for treatment-emergent adverse events see Table 2 in Appendix A. The actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.
- To be conservative in the case of missing causality assessment for treatment-emergent AEs after data querying, AEs will be assumed to be related to NM21-1480 for all patients who received NM21-1480.
- Unless otherwise specified, for laboratory values that are reported using a non-numeric qualifier (e.g., less than [<] or greater than [>] sign), the reported numeric values will be used for summary or analysis without the qualifier.
- In some cases, when the White Blood Cells (WBC) count is too low, the WBC differentials may be difficult to detect and thus not reported by the lab. If the reported WBC count is <0.5*10^9/L, then the differentials such as absolute neutrophils value will be imputed as zero for both the lab value summary and the CTCAE v5.0 grading. For example, absolute neutrophils value imputed as 0 would be considered as grade 4.

3.2 Analysis Populations

3.2.1 Safety Set

The Safety Set (SS) consists of all patients who receive at least 1 dose of study drug (NM21-1480). Unless otherwise specified, the SS will be the default analysis set used for all analyses.

3.2.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) consists of all patients who received at least one dose of study drug (NM21-1480) and have measurable baseline disease. The Efficacy Analysis Set will be the primary analysis set for efficacy.

. The final analysis will not be performed before all patients have either reached the first post-baseline tumor assessment or discontinued clinical response evaluation.

3.2.3 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.

3.2.4 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.

3.3 Subject Data and Study Conduct

Unless specified otherwise, analyses for Part A will be presented by dose level and in total, analysis for Part A-2 will be presented in total, and analysis for Part B will be presented by cohort and in total. Additionally, a total for all patients across Part A and Part A-2 will be presented, as will a total for all Part B patients who received NM21-1480, and a total for all patients in any part who received NM21-1480 at the 800 mg dose level.

3.3.1 Subject Disposition

Counts and percentages of subjects who were pre-screened and screened (signed informed consent for pre-screening and main study, respectively), failure screening, and enrolled in the study will be summarized with denominator based on all screened subjects. Reasons for screen failure will be summarized.

Counts and percentages of patients who discontinued from the study treatment, and who completed or discontinued from the study will be summarized with denominator based on all enrolled patients. Reasons for treatment discontinuation and for study discontinuation will be summarized.

All disposition data will be listed by patient.

3.3.2 Protocol Deviations

Counts and percentages of patients with protocol deviations by deviation category will be summarized for all enrolled patients. All CSR reportable protocol deviations will be listed.

3.3.3 Analysis Populations

Counts and percentages of subjects in each analysis population will be summarized with denominator based on all enrolled patients.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Childbearing potential
- Race
- Ethnicity

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate for patients in the safety set, efficacy analysis set, and pharmacokinetic set. If two sets are identical, only one version of the table will be presented.

All demographics and baseline characteristics will be listed by patient.

3.3.5 Cancer History

The primary cancer type/diagnosis, stage at initial diagnosis, histological/cytological diagnosis, grade, stage at study entry, time from initial diagnosis until informed consent, time from last progression until informed consent, PD-L1 status, MSI-H status (Cohort B8), d-MMR status (Cohort B8), Oncotype Dx Score, and Tumor Mutational Burden (TMB) will be summarized. For time from initial diagnosis and time from last progression, if the day of diagnosis/progression is missing, the day will be imputed as the 15th of the month, and if the month of diagnosis/progression is missing, the month and day will be imputed as July 1 for the purpose of the duration computation.

The number of patients who have mutations vs wild type will be summarized along with the assessment method for the following mutations: BCRA1, KRAS, EGFR, ALK, ROS1, BRAF, HER2, AKT1, MEK1, NRAS, PIK3A, RET, STK11, PTEN, and NTRK.

Patients' prior anti-cancer treatment will be summarized, to include the number of prior lines of therapy, the treatment setting (adjuvant, maintenance, etc), the best response to the most recent prior regimen, and the numbers of patients who received prior checkpoint inhibitors, radiotherapy, and cancer surgery will be summarized. The number of patients who had any irAEs and grade ≥3 irAEs during prior anti-cancer therapy will be summarized.

All primary cancer history, mutation assessment, prior cancer therapy, radiotherapy and surgery, and all irAEs during prior cancer therapy will be listed by patient.

3.3.6 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. All medical history will be listed by patient.

3.3.7 Concomitant Medications and Procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary (WHODrug Global B3, Version March 2022). Medications or procedures will be considered prior medications/procedures if they stopped prior to the first dose of study drug and concomitant medications/procedures if they were taken at any time after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication or procedure has incomplete start or stop dates, dates will be imputed to determine whether a medication/procedure should be considered prior or concomitant. If a medication/procedure start date is incomplete, the first day of the month will be imputed for

missing day and January will be imputed for missing month. If a medication/procedure stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

All prior and concomitant medications and procedures will be listed by patient.

3.3.8 Study Drug Exposure and Compliance

The number of patients who received NM21-1480 at each planned time point (Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, etc.) as well as the total number of NM21-1480 infusions per patient will be summarized. The number of patients with infusion interruptions will be summarized, along with the reason for interruption, and duration of interruptions. The planned and total infusion volume will be summarized, as will the total dose administered (mg). The number of patients whose IV rate was reduced will be summarized, along with the reason for rate reduction. Summaries of exposure will be presented for both the Safety Set and the Efficacy Analysis Set. If the two sets are identical, only one version will be presented.

The planned and actual dose administered (mg) will be summarized. The number of patients whose infusion was interrupted or who did not receive all volume will be summarized along with the reason.

All NM21-1480 administration data will be listed by patient.

3.4 Efficacy Assessment

Efficacy data will be summarized based on the Efficacy Analysis Set. The final analysis will not be performed before all patients have either reached the first post-baseline tumor assessment or discontinued clinical response evaluation.

Unless specified otherwise, analyses for Part A will be presented by dose level and in total, analysis for Part A-2 will be presented in total, and analysis for Part B will be presented by cohort and in total.

For any parameters involving RECIST v1.1 or iRECIST response assessments, the assessment date will be based on the date of the imaging scans rather than the date of the clinical evaluation. In the event that an evaluation is made based on scans coming from multiple days, the earliest scan date will be used for PD, iUPD, and CPD assessments and the latest scan date will be used for CR, iCR, PR, iPR, SD, iSD, and NE assessments.

3.4.1 Definition of Efficacy Endpoints

3.4.1.1 Best Overall Response (BOR)

Only tumor assessments performed before the start of any subsequent anticancer therapies and no later than 30 days after last dose will be considered in the assessment of BOR. Clinical deterioration or clinical progression noted on the end of treatment or end of study eCRFs will not be considered as documented progressive disease. BOR will be derived overall, and by 6 weeks, by 9 weeks, by 12 weeks, and by 15 weeks following the start of study treatment. As the Week 6 and Week 12 tumor response assessments have protocol-specified windows of day 39-43 and day 79-85 respectively, assessments on day 43 (6 weeks + 1 day) and day 85 (12 weeks + 1 day) will be counted toward BOR for their respective weeks. BOR will be derived for the following combinations of conditions:

- Based on investigator RECIST v1.1 assessment, requiring CR/PR confirmation,
- Based on investigator RECIST v1.1 assessment, without CR/PR confirmation,
- Based on central RECIST v1.1 assessment, requiring CR/PR confirmation (part B only),
- Based on central RECIST v1.1 assessment, without CR/PR confirmation (part B only),
- Based on investigator iRECIST assessment, requiring iCR/iPR confirmation (part B only),
- Based on investigator iRECIST assessment, without iCR/iPR confirmation (part B only),
- Based on central iRECIST assessment, requiring iCR/iPR confirmation (part B only),
- Based on central iRECIST assessment, without iCR/iPR confirmation (part B only).

Precedence for best overall response according to RECIST v1.1 is determined as follows, in descending order:

- CR – When confirmation of CR is required, at least 2 assessments of CR at least 4 weeks apart and before any progressive disease (PD). If CR is not confirmed by a subsequent CR, then for the purpose of BOR determination it will instead be considered SD if it fell ≥39 days after the start of treatment or NE if it fell <39 days weeks after start of treatment. When confirmation of CR is not required, at least 1 assessment of CR before any progressive disease (PD).
- PR – When confirmation of PR is required, at least 2 assessments of PR or better at least 4 weeks apart weeks apart any before any progressive disease (PD). If an initial PR is followed by a CR assessment ≥4 weeks later, then the PR is considered confirmed. If PR is not confirmed by a subsequent PR or CR, then for the purpose of BOR determination it will instead be considered SD if it fell ≥39 days after the start of treatment or NE if it fell <39 days weeks after start of treatment. If an initial CR is followed by a PR assessment, the PR assessment would generally be considered as PD due to the (re)appearance of new lesions following CR. When confirmation of PR is not required, at least 1 assessment of PR before any progressive disease (PD).
- SD (applicable only to patient with measurable disease at baseline) – At least 1 stable disease assessment (or better) ≥39 days after start of treatment and before any progressive disease (PD). For the version of best overall response requiring confirmation for CR/PR, an unconfirmed CR or PR will generally be considered as SD as long as it occurs ≥39 days after start of treatment.
- PD – Progressive disease ≤12 weeks after first dose of study drug (and not qualifying for CR, PR, or stable disease). PD assessments on Day 85 will be counted as falling within 12 weeks, as the protocol-specified window for the Week 12 tumor response assessment is 79-85 days.
- Not Evaluable – All other cases (i.e., not qualifying for CR or PR and without stable disease after at least 39 days or early progression within the first 12 weeks).

Precedence for best overall response according to iRECIST is determined as follows:

- iCR – When confirmation of iCR is required, at least 2 assessments of iCR at least 4 weeks apart before any confirmed progressive disease (iCPD). If iCR is not confirmed by a subsequent iCR, then for the purpose of BOR determination it will instead be considered iSD if it fell ≥39 days after the start of treatment or NE if it fell <39 days weeks after start of treatment. When confirmation of iCR is not required, at least 1 assessment of iCR before any confirmed progressive disease (iCPD).

- iPR – When confirmation of iPR is required, at least 2 assessments of iPR or better at least 4 weeks apart weeks apart before any confirmed progressive disease (iCPD). If an initial iPR is followed by an iCR assessment ≥4 weeks later, then the iPR is considered confirmed. If iPR is not confirmed by a subsequent iPR or iCR, then for the purpose of BOR determination it will instead be considered iSD if it fell ≥39 days after the start of treatment or NE if it fell <39 days weeks after start of treatment. If an initial iCR is followed by an iPR assessment, this would generally be considered as progressive disease (iUPD or iCPD) due to the reappearance of new lesions following iCR. When confirmation of iPR is not required, at least 1 assessment of iPR before any confirmed progressive disease (iCPD).
- SD (applicable only to patient with measurable disease at baseline) – At least 1 stable disease assessment (or better) ≥39 days after start of treatment and before any confirmed progressive disease (iCPD). For the version of best overall response requiring confirmation for iCR/iPR, an unconfirmed iCR or iPR will generally be considered as iSD as long as it occurs ≥39 days weeks after start of treatment.
- iUPD – Unconfirmed progressive disease ≤12 weeks after first dose of study drug (and not qualifying for iCR, iPR, or iSD). iUPD assessments on Day 85 will be counted as falling within 12 weeks, as the protocol-specified window for the Week 12 tumor response assessment is 79-85 days.~~.~~ If iUPD is followed by only NE and/or iUPD assessments then it will be considered iUPD for the purpose of best overall determination. If an iUPD assessment is followed by an iCPD assessment, then it will be considered iCPD for the purpose of best overall response determination.
- iCPD – Confirmed progressive disease ≤12 weeks after first dose of study drug (and not qualifying for iCR, iPR, or iSD). iCPD assessments at the nominal “Week 12” visit will be counted, even if are more than 12 weeks after the first dose of study drug based on date. If the first response assessment is iUPD that is later confirmed by an iCPD assessment, then the best overall assessment will be considered to be iCPD.
- Not Evaluable – All other cases (i.e., not qualifying for iCR or iPR and without iSD after at least 39 days or early progression within the first 12 weeks).

3.4.1.2 Objective Response Rate (ORR)

Objective response rate according to RECIST v1.1 (or iRECIST for Part B only) is defined as the percentage of patients with a best overall response of CR or PR (or iCR or iPR) out of all patients in the efficacy analysis set for the given group (dose level, cohort, or arm).

Overall ORR and ORR by 6 weeks, by 9 weeks, by 12 weeks, and by 15 weeks post start of study treatment will be derived. As the Week 6 and Week 12 tumor response assessments have protocol-specified windows of day 39-43 and day 79-85 respectively, assessments on day 43 (6 weeks + 1 day) and day 85 (12 weeks + 1 day) will be counted toward ORR for their respective weeks. ORR will be derived for the following combinations of conditions:

- Based on investigator RECIST v1.1 assessment, requiring CR/PR confirmation,
- Based on investigator RECIST v1.1 assessment, without CR/PR confirmation,
- Based on central RECIST v1.1 assessment, requiring CR/PR confirmation (part B only),
- Based on central RECIST v1.1 assessment, without CR/PR confirmation (part B only),
- Based on investigator iRECIST assessment, requiring iCR/iPR confirmation (part B only),
- Based on investigator iRECIST assessment, without iCR/iPR confirmation (part B only),

- Based on central iRECIST assessment, requiring iCR/iPR confirmation (part B only),
- Based on central iRECIST assessment, without iCR/iPR confirmation (part B only).

3.4.1.3 Progression-Free Survival (PFS)

Progression-free survival will be defined as the time from the start of study treatment until the earliest documented date of disease progression (PD) or death for all patients in the Efficacy Analysis Set. Clinical deterioration or clinical progression noted on the end of treatment or end of study eCRFs will not be considered as documented progressive disease.

The event and censoring rules for PFS are summarized as follows:

Table 1 Date of Event or Censoring for PFS

Situation	Date of event or censoring	Outcome
Death	Date of death	Event
Progressive disease	Date of PD Assessment	Event
Initiation of subsequent anticancer treatment prior to relapse or death	Date of last evaluable disease assessment prior to start of subsequent anticancer treatment	Censored
Missing (or NE at) two or more consecutively scheduled disease assessments directly preceding a PD	Date of last evaluable disease assessment before the first missed (or NE) visit	Censored
Withdrawal from Study	Date of last evaluable disease assessment before study withdrawal	Censored
Alive without relapse and without initiation of subsequent anticancer treatment	Date of last evaluable disease assessment	Censored

If a patient has no evaluable (non-NE) post-baseline disease assessments or starts a subsequent anti-cancer therapy before having any evaluable post-baseline disease assessments, then they will be censored at start of study treatment. SD assessments, unconfirmed PR assessments, and unconfirmed CR assessments that falls within <39 days after the start of study treatment are considered evaluable post-baseline assessments for the purpose of PFS derivation (though they are counted as NE for BOR and ORR derivation).

PFS will be derived for the following combinations of conditions:

- Based on investigator RECIST v1.1 assessment,
- Based on central RECIST v1.1 assessment (part B only).

3.4.1.4 Overall Survival (OS)

Overall survival will be defined as the time from the start of study treatment until death due to any cause. Patients alive at the data cut-off date will be censored for survival at their last contact date. The date of last contact date will be the latest complete date among but not limited to the following:

- Date last known to be alive collected on the eCRF form “Survival Status” (only to be used if status is “Alive”),

- All patient assessment dates (e.g., laboratory blood draws, vital signs, performance status, ECGs, physical examination, tumor response assessment, and other study procedure dates),
- Start and end dates of concomitant medication and/or subsequent anti-cancer therapies,
- Study treatment start and end dates,
- AE start and end dates,
- Other available clinical data which can confirm patient's survival status,
- Date of discontinuation from End of Study eCRF forms (not to be used if reason for discontinuation is lost to follow-up).

3.4.2 Analysis of Efficacy Endpoints

3.4.2.1 Best Overall Response (BOR)

The number and percent of patients with each best overall response for each given group (dose level, cohort, or arm) in the Efficacy Analysis Set will be summarized separately for RECIST v1.1 and iRECIST for each combination of conditions described in section 3.4.1.1. The summaries of BOR using confirmed vs unconfirmed CR/PR (or iCR/iPR) and for overall, by 6 weeks, by 9 weeks, by 12 weeks, and by 15 weeks after the start of study treatment will all be presented in a single table.

For patients with BOR of Not Evaluable, the reason for non-evaluability will be summarized:

- 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
- Only post-baseline assessment was stable disease <39 days after the start of study treatment
- First evaluable post-baseline assessment was progressive disease >12 weeks after start of study treatment.

The investigator assessed RECIST v1.1 responses will be summarized for each of the planned response assessment timepoints with percentage based on the number of patients with available response assessments for the respective timepoint. For Part B, the iRECIST response assessments by timepoint will be likewise summarized.

All tumor measurements, sums of diameters, investigator and central response assessments according to RECIST v1.1 and iRECIST, and all derived BORs (overall, by 6 weeks, by 9 weeks, by 12 weeks, and by 15 weeks post start of study treatment) will be listed by patient.

3.4.2.2 Objective Response Rate (ORR)

The objective response rate for each given group (dose level, cohort, or arm) in the Efficacy Analysis Set will be summarized according to RECIST v1.1 (and according to iRECIST), accompanied by a 2-sided exact 95% Clopper-Pearson confidence interval. ORR will be presented separately for each combination of conditions described in section 3.4.1.2. The summaries of ORR using confirmed vs unconfirmed CR/PR (or iCR/iPR) and for overall, by 6 weeks, by 9 weeks, by 12 weeks, and by 15 weeks after the start of study treatment will all be presented in a single table.

3.4.2.3 Progression-Free Survival (PFS)

PFS will be summarized by dose level and in total for Part A, in total for Part A-2, and by cohort and in total for Part B in the Efficacy Analysis Set for each combination of conditions described in section 3.4.1.3. For each combination, Kaplan-Meier estimates for the first quartile, median, and third quartile PFS will be presented along with a 95% confidence interval based on the Brookmeyer-Crowley method. Kaplan-Meier estimates of the PFS at 3 months, 6 months, 9 months, and 12 months will be presented along with associated 95% Greenwood confidence intervals.

3.4.2.4 Overall Survival (OS)

OS will be summarized by dose level and in total for Part A, in total for Part A-2, and by cohort and in total for Part B in the Efficacy Analysis Set. Kaplan-Meier estimates for the first quartile, median, and third quartile OS will be presented along with a 95% confidence interval based on the Brookmeyer-Crowley method. Kaplan-Meier estimates of the OS rate at 6 months, 12 months, 18 months, and 24 months will be presented along with associated 95% Greenwood confidence intervals.

Kaplan-Meier curves will be presented for OS.

Survival status assessments and death details will be listed by patient.

3.5 Pharmacokinetic Assessment

Pharmacokinetic analysis will be performed for patients in the Pharmacokinetic Set.

3.5.1 Sample Collections for Pharmacokinetic Analysis

Pharmacokinetic blood sampling timepoints for determination of serum concentrations of NM21-1480 (2-week Dosing Interval) during Part A, Part A-2 and Part B of the study

VISIT	DAY	PK SAMPLING TIME
Cycle 1	1	(Pre-dose) 0 EOI ± 5 min[#] 4 h ± 10 min[*] 8 h ± 1 h[*]
	2	24 h ± 2 h[*]
	3	48 h ± 4 h[*]
	5	96 h ± 12 h[*]
	8	168 h ± 24 h
	15 ± 2	(Pre-dose) 0
Cycle 2	1 ± 2	(Pre-dose) 0
	8 ± 2	168 h ± 48 h
	15 ± 2	(Pre-dose) 0
Cycle 3	1 ± 3	(Pre-dose) 0 EOI ± 5 min[#] 4 h ± 10 min[*]

		8 h ± 1 h*
	2	24 h ± 2 h*
	3	48 h ± 4 h*
	5	96 h ± 12 h*
	8	168 h ± 24 h
	15 ± 3	336 h ± 48 h*
Every subsequent even cycle	8 ± 3	168 h ± 48 h
Every subsequent odd cycle	1 ± 3	(Pre-dose) 0
First follow up visit		Anytime

EOI: End of Infusion sample is 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

* 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-2

3.5.2 Handling Missing or Below the Lower Limit of Quantification Data

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the scheduled nominal time point may be used for the calculation of PK parameters.

In cases of missing pre-dose concentrations prior to the first dose of Cycle 1, the missing concentration value may be imputed as zero. If missing pre-dose concentrations of Cycle 3, the pre-dose of Cycle 4 (or any cycle after Cycle 3) may be used as pre-dose concentration values. For the other cases, the missing data will not be imputed.

For the individual concentration and PK parameter calculation for Part A and A-2 by dose level and cycle and Part B by cohort and cycle, the following rules will be applied:

- If one or more below the limit of quantitation (BLQ) values occur before the first measurable concentration, they will be assigned a value of zero.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be omitted (set to missing).
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).

For the concentration summary of NM21-1480 and mean (±SD) concentration plot preparation for Part A and A-2 by dose level and cycle and Part B by cohort and cycle, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the patients have valid values (i.e. quantifiable and not missing) at this time point for each dose level, cohort and cycle.
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to missing.
- BLQ values will be set to zero.
- The value of zero will be excluded from the calculation of GM and GM CV%

3.5.3 Pharmacokinetics Concentrations

Individual serum concentrations of NM21-1480 will be summarized by dose level and cycle (combined for Part A and A-2) and Part B by cohort and cycle at each nominal time point for the PK set descriptively. Individual serum concentrations will also be listed for the PK set.

Individual serum concentration (ie., Spaghetti plots) will be plotted by dose level, cohort and cycle for Cycle 1 and Cycle 3 on a linear and semi-logarithmic scale against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by dose level, cohort and cycle, when available for Part A, Part A-2, and Part B. LLOQ will be plotted as a reference line in both instances.

Mean (±SD) and Spaghetti plots for NM21-1480 serum concentrations at C_{168h} and C_{trough} will be plotted for Part A and A-2 by dose level and cycle and Part B by cohort and cycle.

Actual sampling times that are outside the sampling time windows may be excluded at the discretion of the clinical pharmacologist from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting.

The following descriptive statistics will be used for all summary data: n, arithmetic mean, geometric mean, standard deviation, geometric standard deviation, coefficient of variation (CV%), geometric CV% (calculated as: gCV% = SQRT(e^{s^2}-1)*100; where s is the standard deviation of the log-transformed values), minimum, maximum and median.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- Source data shall be used in all derived PK concentrations without prior rounding.
- The mean, standard deviation (SD), geometric mean and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.
- Geometric coefficient of variation (%CV) and coefficient of variation (%CV) will be presented to one decimal place.

3.5.4 Pharmacokinetics Parameters

The following serum PK parameters of NM21-1480 will be determined using WinNonlin v8.3 non-compartmental methods as appropriate for all parts (A, A-2 and B) for all patients for whom parameters can be calculated:

Parameters	**Description and Calculation**	**Cycle**
C_{max}	Maximum serum concentration; determined directly from the concentration time profile; if the maximum serum concentration occurs at more than one time point, C_{max} is defined as the first maximum value	Cycle 1, Cycle 3

C_{min}	Minimum serum concentration over the dosing interval	Cycle 1, Cycle 3
T_{max}	Time to C_{max}; If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value	Cycle 1, Cycle 3
Λz	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the serum concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using points in the terminal log-linear phase.	Cycle 1, Cycle 3
$t_{½}$	Apparent first-order terminal elimination half-life; calculated as ln(2)/λz	Cycle 1, Cycle 3
AUC_{0-t}	Area under the serum concentration vs time curve (AUC) from predose (time 0) to the last quantifiable serum concentration (C_{last})	Cycle 1, Cycle 3
AUC_{tau}	AUC over the dosing interval	Cycle 1, Cycle 3
AUC_{0-inf}	AUC from time 0 to infinity; calculated as $(AUC_{0-t} + C_{last}/\lambda z)$	Cycle 1
$AUC_{\%extrap}$	Percent of AUC_{0-inf} extrapolated, represented as $(1 - AUC_{0-t}/AUC_{inf})*100$	Cycle 1, Cycle 3
CL	Total serum clearance after IV administration; calculated as $Dose/AUC_{inf}$	Cycle 1
CL_{ss}	Total serum clearance after IV administration; calculated as $Dose/AUC_{tau}$	Cycle 3
Vd	Volume of distribution during terminal elimination phase after IV administration; calculated as $Dose/[\lambda z*AUC_{inf}]$	Cycle 1
Vd_{ss}	Volume of distribution during terminal elimination phase after IV administration; calculated as $Dose/[\lambda z*AUC_{tau}]$	Cycle 3
Accumulation Index (AR_{Cmax})	Accumulation ratios assessment of C_{max}; calculated as C_{max} in Cycle 3 divided by C_{max} in Cycle 1	Cycle 3

Accumulation Index (AR_{Cmin})	Accumulation ratios assessment of C_{min}; calculated as C_{min} in Cycle 3 divided by C_{min} in Cycle 1	Cycle 3
Accumulation Index (AR_{AUC})	Accumulation ratios assessment of AUC; calculated as AUC_{tau} in Cycle 3 divided by AUC_{tau} in Cycle 1	Cycle 3

Actual collection times will be used in PK parameter calculations. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values. In order to estimate the apparent first-order terminal elimination constant, λz, linear regression of concentration in logarithm scale vs. time will be performed using at least 3 data points post C_{max}. Uniform weighting will be selected to perform the regression analysis to estimate λz. The constant λz will not be assigned if one of the following occurs:

1. The terminal elimination phase is not linear (as it appears on a semi-logarithmic scale).
2. The terminal elimination rate constant indicates a positive slope (λz > 0).
3. T_{max} is one of the three last data points.

The constant λz and its derived parameters will be flagged and included in the statistical analysis if one of the following occurs:

1. The adjusted regression coefficient (R^2) is less than 0.8.
2. The $AUC_{\%extrap}$ exceeds 20%.

No value for λz, $AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, CL, CLss, Vz, Vzss or $t_{½}$ will be reported for cases that do not exhibit an acceptable terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for patients with 2 or fewer detectable concentrations in their PK profile.

PK parameters will be listed per patient and summarized by dose level and cycle (combined for Part A and A-2) and by cohort and cycle (Part B). The summaries of PK parameters will use following descriptive statistics: n, arithmetic mean, standard deviation, geometric mean, geometric standard deviation, 95% CI geometric mean, coefficient of variation (CV%), geometric CV% (calculated as: gCV% =SQRT(e^{s^2}-1)*100; where s is the standard deviation of the log-transformed values), minimum, maximum and median. Tmax will include median, minimum and maximum. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable.

3.5.5 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD relationship analysis will be provided.

3.5.6 Pharmacodynamic Assessment

No pharmacodynamic analysis will be performed.

3.5.7 Immunogenicity Assessment

Immunogenicity analysis for Part A will be presented by dose level and in total, analysis for Part A-2 will be presented in total, and analysis for Part B will be presented by cohort and in total. A total for all patients across Part A and Part A-2 will be presented, as will a total for all Part B patients who received NM21-1480, and a total for all patients in any part who received NM21-1480 at the 800 mg dose level.

Immunogenicity status will be summarized for patients in the Safety Set by scheduled time point and overall. For the overall post-baseline summary, a patient will be considered positive for ADAs if they are positive at any scheduled or unscheduled post-baseline assessment. The following immunogenicity categories will be presented:

- Patients with positive post-baseline ADA assessment
  - After missing baseline titer assessment
  - After negative baseline (titer value = 1)
  - After positive baseline titer value > 1
  - After positive baseline titer value > 1 AND increased from baseline
- Patients negative for ADAs at post-baseline
  - After missing baseline titer assessment
  - After negative baseline (titer value = 1)
  - After positive baseline titer value > 1

It will be noted in the analysis whether any patients have a reduced ADA titer value at post-baseline compared with baseline.

Among patients who have a positive post-baseline ADA assessment, descriptive statistics will be presented for the first positive post-baseline titer value and the maximum post-baseline titer value, and the duration from the start of treatment until the first positive ADA assessment will be summarized. A spider plot may be used to present the titer value trajectories over time for patients with positive post-baseline ADA assessment.

To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs may be compared between ADA positive and negative patients.

Neutralizing antibody status will be summarized.

Immunogenicity assessments including ADA titer values, ADA status by timepoint and overall post-baseline, and neutralizing antibody status will be listed by patient.

3.6 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Population.

For the safety analysis, unless specified otherwise, Part A will be presented by dose level and in total, Part A-2 will be presented in total, and Part B will be presented by cohort and in total.

3.6.1 Dose-Limiting Toxicities (DLTs)

For Parts A, A-2, and B, DLTs are defined in section 7.2.5.1 of the protocol. DLT's will be identified by the investigator and recorded in the eCRF. The number of patients with DLTs will be summarized, and all DLTs will be listed by patient.

3.6.2 Adverse Events (AEs)

AEs will be captured from signing informed consent/HIPAA authorization, through 70 days after the last dose of study drug, as specified in section 9.2.4 of the protocol. Beyond 70 days from the last dose of study drug, only study treatment-related SAEs or late-occurring irAEs should be reported. All AEs will be coded to system organ class and preferred term using MedDRA version 25.0 or later.

Treatment-emergent adverse events (TEAEs) are defined as AEs that occur or worsen on or after the first dose of study drug.

Adverse events of special interest (AESIs) are defined in section 9.2.1.6 of the protocol as:

- Elevations of ALT/AST that are >3-fold above baseline,
- 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.

AESI's will be identified by the investigator and recorded in the eCRF.

Immune-related AEs (irAEs) will be identified by the investigator and recorded in the eCRF.

An overview of AEs will be provided including counts and percentages of subjects (and event counts) with the following types of AEs:

- Any TEAEs (overall, by maximum severity, and grade ≥3)
- Any NM21-1480-related TEAEs (overall, by maximum severity, and and grade ≥3)
- Any TEAEs of special interest (overall, by maximum severity, and grade ≥3)
- Treatment-emergent irAEs
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESAEs)
- Any NM21-1480-related TESAEs
- Any TEAEs leading to temporary or permanent discontinuation of NM21-1480
- Any AEs leading to death

The number and percentage of patients with AEs will be summarized by system organ class (SOC) and preferred term (PT) for the following types of AEs:

- TEAEs
- Grade >=3 TEAEs

- NM21-1480-related TEAEs
- Grade >=3 NM21-1480-related TEAEs
- TEAEs of special interest
- Treatment-emergent irAEs
- TESAEs
- NM21-1480-related TESAEs

The number and percentage of patients with AEs will be summarized by SOC, PT, and highest CTCAE grade for the following types of AEs:

- TEAEs
- NM21-1480-related TEAEs

All adverse event data will be listed by patient. Additional listings will present SAEs, AESIs, irAEs, TEAEs leading to temporary or permanent discontinuation of NM21-1480, TEAEs leading to discontinuation of study, and AEs leading to death.

3.6.3 Clinical Laboratory Tests

The number and percentage of patients with the following abnormalities will be presented:

- ALT ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- AST ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN
- Total bilirubin ≥2xULN
- Potential Hy's Law cases: ALT or AST >3 xULN, total bilirubin ≥2xULN, and ALP < 2xULN at the same visit

Selected clinical laboratory evaluations (i.e., chemistry and hematology) may be summarized using descriptive statistics or CTCAE grade shift tables as appropriate.

All local laboratory assessments, including chemistry, coagulation, hematology, thyroid function will be listed by patient. Applicable chemistry (Alanine Aminotransferase, Albumin, Alkaline Phosphatase, Amylase, Aspartate Aminotransferase, Bilirubin, Creatinine, Glucose, Lactate Dehydrogenase, Lipase, Potassium, Sodium), and hematology (Eosinophils, Hemoglobin, Leukocytes, Lymphocytes, Neutrophils, Platelets) parameters will be graded according CTCAE v5.0. For some laboratory tests, the CTCAE criteria may include qualifying definitions (e.g., clinical AE and/or requirement for concomitant medication) in addition to the specific laboratory value used for the definition of the toxicity grades. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades.

3.6.4 Vital Signs

Descriptive statistics will be provided for vital signs measurements (systolic and diastolic blood pressure, heart rate, body temperature, and weight) and oxygen saturation measurements, in which absolute values and changes from baseline for the minimum, maximum, and last post-baseline values will be presented. Both scheduled and unscheduled post-treatment values will be considered for summaries of the minimum, maximum, and last post-baseline values.

The number and proportion of subjects with potentially clinically significant changes in vital signs will be presented based on the following thresholds:

- Systolic blood pressure ≥ 160 mmHg and increase ≥ 20 mmHg from baseline
- Systolic blood pressure ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline
- Diastolic blood pressure ≥ 100 mmHg and increase ≥ 15 mmHg from baseline
- Systolic blood pressure ≤ 50 mmHg and decrease ≥ 15 mmHg from baseline
- Heart rate ≥ 120 bpm with increase ≥ 15 bpm from baseline
- Heart rate ≤ 50 bpm with decrease ≥ 15 bpm from baseline

All vital signs data will be listed by patient.

3.6.5 Electrocardiograms

All ECG data will be listed by patient.

3.6.6 Performance Status

A shift table from baseline ECOG performance status to worst post-baseline status will be presented.

All ECOG performance status data will be listed by subject.

3.6.7 Other Safety Assessments

The following safety assessments will be listed by patient:

- All clinically significant (by investigator assessment) physical examinations,
- All clinically significant (by investigator assessment) neurological examinations,
- All positive COVID-19 tests,

4 SAFETY MONITORING COMMITTEE AND DATA MONITORING COMMITTEE

A Safety Monitoring Committee (SMC) monitored and reviewed accumulating data to detect potential risks to enrolled patients. The SMC evaluated delayed DLTs, reviewed ad-hoc safety issues, and supported the Sponsor in MTD determination. They were also planned to support the interim futility decisions for the Part B cohorts. The SMC consisted of an independent (i.e. not an investigator in the study) Chair and site investigators. Full details on SMC membership responsibilities are found in the SMC charter.

The SMC together with the Sponsor selected the dose levels and dosing intervals for Part B of the trial. A Data Monitoring Committee (DMC) was planned to review the accumulating clinical activity, PK/PD, ADA, and RO data, but was not needed due to early closure of the trial.

5 ANALYSIS TIMING

5.1 Interim Analysis

No interim analysis will be provided.

5.2 Pre-Final Analysis

After the database is locked, the pre-final analysis will be generated. Pre-final TFLs will be provided approximately 4 weeks after database lock.

5.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSIS

Only limited patients were enrolled onto the study under Cohort B1 (5 patients), Cohort B7 (5 patients) and Cohort B8 (10 patients) in Part B. Cohort A-2 only enrolled 5 patients. There are no patients enrolled under Cohort B2, Cohort B3, Cohort B4, Cohort B5 and Cohort B6 in Part B. Therefore, due to the limited data, only related TFLs will be generated and no interim analyses were performed.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 or higher. Phoenix WinNonlin version 8.1 or higher will be used in the determination of the PK terminal phase and the calculation of PK parameters. All the PK parameters will also be calculated via SAS® and verified with the Phoenix WinNonlin results. Detailed Programming Specifications for the final analysis will be provided in a separate document.

APPENDIX A: PARTIAL DATE CONVENTIONS

Table 2 Algorithm for Treatment-Emergent Adverse Events

AE Start Date	AE Stop Date	Action
Known	Known	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
	Missing or Unknown	If start date < study drug start date, then not TEAE If start date ≥ study drug start date, then TEAE
Partial, but the known date components show that it cannot be on or after study drug start date	Known	Not TEAE
	Partial	Not TEAE
	Missing or Unknown	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day is unknown or 31-Dec if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing or Unknown	Assumed TEAE
Missing or Unknown	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day is unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing or Unknown	Assumed TEAE

TEAE = treatment-emergent AE