Clinical trial results:
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

Summary

EudraCT number	2021-000441-41
Trial protocol	NL ES DE
Global end of trial date	06 February 2024

Results information

Result version number	v1 (current)
This version publication date	21 February 2025
First version publication date	21 February 2025

Trial information

Trial identification

Sponsor protocol code	NB-ND021(NM21-1480)-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04442126
WHO universal trial number (UTN)	-
Other trial identifiers	MDACC Protocol ID: 2020-0355

Notes:

Sponsors

Sponsor organisation name	Numab Therapeutics AG
Sponsor organisation address	Bachtobelstrasse 5, 8810 Horgen, Zurich, Switzerland, 8810
Public contact	Clinical Trial Information Desk, Numab Therapeutics AG, clinicaltrials@numab.com
Scientific contact	Clinical Trial Information Desk, Numab Therapeutics AG, clinicaltrials@numab.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2024
Global end of trial reached?	Yes
Global end of trial date	06 February 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part A (not conducted in EU):
• To assess the safety and tolerability of NM21-1480
• To determine the maximum tolerated dose (MTD) of NM21-1480
• To determine up to four (4) safe dose levels for further evaluation of pharmacodynamics (PD) and clinical activity in the optional Part A-2 and Part B of the study

Part A-2 (OPTIONAL - not conducted in EU):
• To assess the safety and tolerability of NM21-1480
• To further characterize PD response at or below the MTD in support of selection of up to four (4) safe dose levels to be further studied in Part B

Part B:
• 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 recommended Phase 2 dose (RP2D)

Protection of trial subjects:

The study was conducted in accordance with the declaration of Helsinki, good clinical practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	52
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	23
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 52 patients were enrolled onto the NB-ND021 study and 52 patients discontinued the study.

Pre-assignment

Screening details:

A total of 92 patients were screened onto the NB-ND021 study.

Period 1

Period 1 title	Enrollment (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A Dose Level 1 NM21-1480-Q2W 0.15mg

Arm description:

Part A Dose Level 1 NM21-1480-Q2W 0.15mg

Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

NM21-1480 0.15mg administered as a single IV infusion approximately every 14 days.

Arm title	Part A Dose Level 2 NM21-1480-Q2W 1.5mg

Arm description:

Part A Dose Level 2 NM21-1480-Q2W 1.5mg

Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

NM21-1480 1.5mg administered as a single IV infusion approximately every 14 days.

Arm title	Part A Dose Level 3 NM21-1480-Q2W 8mg

Arm description:

Part A Dose Level 3 NM21-1480-Q2W 8mg

Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

NM21-1480 8mg administered as a single IV infusion approximately every 14 days.

Arm title	Part A Dose Level 4 NM21-1480-Q2W 24mg
Arm description: Part A Dose Level 4 NM21-1480-Q2W 24mg	
Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: NM21-1480 24mg administered as a single IV infusion approximately every 14 days.	
Arm title	Part A Dose Level 5 NM21-1480-Q2W 80mg
Arm description: Part A Dose Level 5 NM21-1480-Q2W 80mg	
Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: NM21-1480 80mg administered as a single IV infusion approximately every 14 days.	
Arm title	Part A Dose Level 6 NM21-1480-Q2W 240mg
Arm description: Part A Dose Level 6 NM21-1480-Q2W 240mg	
Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: NM21-1480 240mg administered as a single IV infusion approximately every 14 days.	
Arm title	Part A Dose Level 7 NM21-1480-Q2W 800mg
Arm description: Part A Dose Level 7 NM21-1480-Q2W 800mg	
Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: NM21-1480 800mg administered as a single IV infusion approximately every 14 days.	
Arm title	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

NM21-1480 1400mg administered as a single IV infusion approximately every 14 days.

Arm title	Part B NM21-1480-Q2W 800mg

Arm description:

This part of the study consisted of a 800mg flat dose across three cohorts.

Arm type	Experimental
Investigational medicinal product name	NM21-1480
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

NM21-1480 800mg administered as a single IV infusion approximately every 14 days.

Number of subjects in period 1	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg
Started	1	1	3
Completed	0	0	0
Not completed	1	1	3
Consent withdrawn by subject	-	-	-
Death	1	-	-
Progressive Disease	-	1	3
Unknown	-	-	-
Study terminated by sponsor	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Part A Dose Level 4 NM21-1480-Q2W 24mg	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg
Started	3	6	3
Completed	0	0	0
Not completed	3	6	3
Consent withdrawn by subject	2	1	-
Death	1	2	2
Progressive Disease	-	3	-
Unknown	-	-	-
Study terminated by sponsor	-	-	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg	Part B NM21-1480-Q2W 800mg
Started	9	5	21
Completed	0	0	0
Not completed	9	5	21
Consent withdrawn by subject	1	1	3
Death	4	1	5
Progressive Disease	-	-	-
Unknown	-	-	1
Study terminated by sponsor	4	2	10
Lost to follow-up	-	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Enrollment

Reporting group description: -

Reporting group values	Enrollment	Total	
Number of subjects	52	52	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	23	23	
85 years and over	0	0	
Age continuous Units: years			
median	61.9		
standard deviation	± 10.26	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	32	32	

End points

End points reporting groups

Reporting group title	Part A Dose Level 1 NM21-1480-Q2W 0.15mg
Reporting group description: Part A Dose Level 1 NM21-1480-Q2W 0.15mg	
Reporting group title	Part A Dose Level 2 NM21-1480-Q2W 1.5mg
Reporting group description: Part A Dose Level 2 NM21-1480-Q2W 1.5mg	
Reporting group title	Part A Dose Level 3 NM21-1480-Q2W 8mg
Reporting group description: Part A Dose Level 3 NM21-1480-Q2W 8mg	
Reporting group title	Part A Dose Level 4 NM21-1480-Q2W 24mg
Reporting group description: Part A Dose Level 4 NM21-1480-Q2W 24mg	
Reporting group title	Part A Dose Level 5 NM21-1480-Q2W 80mg
Reporting group description: Part A Dose Level 5 NM21-1480-Q2W 80mg	
Reporting group title	Part A Dose Level 6 NM21-1480-Q2W 240mg
Reporting group description: Part A Dose Level 6 NM21-1480-Q2W 240mg	
Reporting group title	Part A Dose Level 7 NM21-1480-Q2W 800mg
Reporting group description: Part A Dose Level 7 NM21-1480-Q2W 800mg	
Reporting group title	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Reporting group description: -	
Reporting group title	Part B NM21-1480-Q2W 800mg
Reporting group description: This part of the study consisted of a 800mg flat dose across three cohorts.	

Primary: Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v5.0

End point title	Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v5.0[1]
End point description:	
End point type	Primary
End point timeframe: Up to 3 years	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: Participants				
number (not applicable)	1	1	3	3

End point values	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	9	2
Units: Participants				
number (not applicable)	5	3	9	5

End point values	Part B NM21-1480-Q2W 800mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Participants				
number (not applicable)	16			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose (MTD) of NM21-1480

End point title	Maximum Tolerated Dose (MTD) of NM21-1480[2][3]

End point description:

End point type	Primary

End point timeframe:

Up to 3 years.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: End point data is entered as per cohort.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: mg				
number (not applicable)	800	800	800	800

End point values	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	9	5
Units: mg				
number (not applicable)	800	800	800	1400

Statistical analyses

No statistical analyses for this end point

Primary: Determination of Phase 2 Dose of NM21-1480

End point title	Determination of Phase 2 Dose of NM21-1480[4][5]

End point description:

End point type	Primary

End point timeframe:

Up to 3 years.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: End point data is entered as per cohort.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: mg				
number (not applicable)	800	800	800	800

End point values	Part A Dose Level 5 NM21-	Part A Dose Level 6 NM21-	Part A Dose Level 7 NM21-	Part A2 Dose Level 1 NM21-

	1480-Q2W 80mg	1480-Q2W 240mg	1480-Q2W 800mg	1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	9	5
Units: mg				
number (not applicable)	800	800	800	800

Statistical analyses

No statistical analyses for this end point

Primary: To Determine the Anti-tumor Activity (Best Overall Response) of NM21-1480 According to RECIST 1.1

End point title	To Determine the Anti-tumor Activity (Best Overall Response) of NM21-1480 According to RECIST 1.1[6]

End point description:

End point type	Primary

End point timeframe:

Up to 3 years.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: 1	0	0	0	1

End point values	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	9	5
Units: 1	0	0	0	0

End point values	Part B NM21-1480-Q2W 800mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: 1	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Maximum Observed Serum Concentration Determined by Direct Inspection of the Concentration Versus Time Data (Cmax)

End point title	Assessment of the Maximum Observed Serum Concentration Determined by Direct Inspection of the Concentration Versus Time Data (Cmax)

End point description:

Cmax determined at C1 for all dose levels with the exception of Part A Dose Level 1 which was BLQ. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL.

End point type	Secondary

End point timeframe:

Up to 3 years.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: ng/ml				
arithmetic mean (standard deviation)	0 (± 0)	184.3 (± 184.3)	1604 (± 1101)	6334 (± 2331)

End point values	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	8	4
Units: ng/ml				
arithmetic mean (standard deviation)	19800 (± 5576)	66890 (± 43340)	204700 (± 32070)	420300 (± 12040)

End point values	Part B NM21-1480-Q2W 800mg			
Subject group type	Reporting group			
Number of subjects analysed	9			

Units: ng/ml				
arithmetic mean (standard deviation)	258500 (± 65390)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the the Minimum Observed Serum Concentration Determined by Direct Inspection of the Concentration Versus Time Data (Cmin)

End point title	Assessment of the the Minimum Observed Serum Concentration Determined by Direct Inspection of the Concentration Versus Time Data (Cmin)

End point description:

Cmin determined at C1 for all dose levels with the exception of Part A Dose Level 1 and Part which was BLQ. Note: Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL.

End point type	Secondary

End point timeframe:

Up to 3 years.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: ng/ml				
arithmetic mean (standard deviation)	0 (± 0)	0 (± 0)	201.7 (± 227.5)	658.2 (± 451.7)

End point values	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	8	4
Units: ng/ml				
arithmetic mean (standard deviation)	4203 (± 1340)	15880 (± 14540)	48670 (± 17090)	166000 (± 41730)

End point values	Part B NM21-1480-Q2W 800mg			
Subject group type	Reporting group			
Number of subjects analysed	9			

Units: ng/ml				
arithmetic mean (standard deviation)	54270 (± 22000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Terminal Phase (Apparent Elimination) Rate Constant (λz)

End point title	Assessment of the Terminal Phase (Apparent Elimination) Rate Constant (λz)[7]

End point description:

Lambda z determined at C1 for all dose levels with the exception of Part A Dose Level 1,2 and 3. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL. The constant Lambda z and its derived parameters meet one of the following conditions: theadjusted regression coefficient is less than 0.8 or the AUC%extrap exceeds 20%. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 4 NM21-1480-Q2W 24mg	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	3	8
Units: 1/h				
arithmetic mean (standard deviation)	0.007163 (± 0.002300)	0.005417 (± 0.002940)	0.003352 (± 0.001460)	0.003522 (± 0.0007292)

End point values	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg	Part B NM21-1480-Q2W 800mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: 1/h				
arithmetic mean (standard deviation)	0.002923 (± 0.001239)	0.002840 (± 0.0006234)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Elimination Half-life (t½)

End point title	Assessment of the Elimination Half-life (t½)[8]

End point description:

Assessment of the elimination half-life (t½) determined at C1 for all dose levels with the exception of Part A Dose Level 1, Part A Dose Level 2 and Part A Dose Level 3. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL. No descriptive statisticsdetermined when fewer than three individual PK parameters are available.

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 4 NM21-1480-Q2W 24mg	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	3	8
Units: h				
arithmetic mean (standard deviation)	102.824 (± 28.4100)	165.179 (± 90.7037)	230.048 (± 80.2781)	203.241 (± 36.4457)

End point values	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg	Part B NM21-1480-Q2W 800mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: h				
arithmetic mean (standard deviation)	272.095 (± 116.9242)	253.230 (± 56.1072)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Time From Dosing at Which Cmax is Apparent Determined by Direct Inspection of the Concentration Versus Time Data (Tmax)

End point title	Assessment of the Time From Dosing at Which Cmax is Apparent Determined by Direct Inspection of the Concentration Versus Time Data (Tmax)

End point description:

Tmax determined at C1 for all dose levels with the exception of Part A Dose Level 1 and Part A Dose Level 2. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL.

End point type	Secondary

End point timeframe:

Up to 3 years.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: h				
arithmetic mean (full range (min-max))	0 (0 to 0)	1 (1 to 1)	26.533 (1 to 77.58)	6.407 (4.92 to 8.03)

End point values	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	8	4
Units: h				
arithmetic mean (full range (min-max))	5.778 (0.97 to 25.37)	2.340 (0.95 to 5.05)	8.720 (1.50 to 48.60)	3.13 (1.53 to 8.58)

End point values	Part B NM21-1480-Q2W 800mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: h				
arithmetic mean (full range (min-max))	1.587 (1.53 to 1.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Area Under the Serum Concentration-time Curve Extrapolated From the Last Quantifiable Concentration to Infinity Quantifiable Concentration to Infinity (AUC[0-infinity])

End point title	Assessment of the Area Under the Serum Concentration-time Curve Extrapolated From the Last Quantifiable Concentration to Infinity Quantifiable Concentration to Infinity (AUC[0-infinity])[9]

End point description:

AUC0-t determined at C1 for all dose levels with the exception of Part A Dose Level 1 and Part A Dose Level 2. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL.

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	6	3
Units: h*ng/mL				
arithmetic mean (standard deviation)	81570 (± 59740)	802200 (± 339000)	2602000 (± 1177000)	9442000 (± 6364000)

End point values	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg	Part B NM21-1480-Q2W 800mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	4	9	
Units: h*ng/mL				
arithmetic mean (standard deviation)	32630000 (± 3717000)	57570000 (± 12480000)	39560000 (± 12150000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Area Under Serum Concentration-time Curve Over Dosing Interval (AUCtau)

End point title	Assessment of the Area Under Serum Concentration-time Curve Over Dosing Interval (AUCtau)[10]

End point description:

AUCtau determined at C1 for all dose levels with the exception of Part A Dose Level 1, Part A Dose Level 2 and Part A Dose Level 3. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL.

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 4 NM21-1480-Q2W 24mg	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	3	8
Units: h*ng/mL				
arithmetic mean (standard deviation)	803200 (± 340000)	2662000 (± 1022000)	9648000 (± 6863000)	32420000 (± 3342000)

End point values	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg	Part B NM21-1480-Q2W 800mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: h*ng/mL				
arithmetic mean (standard deviation)	69890000 (± 3413000)	36810000 (± 11890000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Clearance (CL)

End point title	Assessment of the Clearance (CL)[11]

End point description:

Assessment of the clearance (CL) determined at C1 for all dose levels with the exception of Part A Dose Levels 1, 2 and 3. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL.

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 4 NM21-1480-Q2W 24mg	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	3	8
Units: L/h				
arithmetic mean (standard deviation)	0.03037 (± 0.01332)	0.03034 (± 0.01764)	0.02257 (± 0.01329)	0.01717 (± 0.002606)

End point values	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg	Part B NM21-1480-Q2W 800mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: L/h				
arithmetic mean (standard deviation)	0.01218 (± 0.002768)	0.01596 (± 0.004527)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Volume of Distribution (Vd)

End point title	Assessment of the Volume of Distribution (Vd)[12]

End point description:

Assessment of the volume of distribution (Vd) determined at C1 for all dose levels with the exception of Part A Dose Level 1,2 and 3. Lower limit of quantification (LLOQ) of NM21-1480 = 5 ng/mL.

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 4 NM21-1480-Q2W 24mg	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	3	8
Units: L				
arithmetic mean (standard deviation)	4.155 (± 0.9071)	5.882 (± 2.263)	6.674 (± 3.379)	4.952 (± 0.6848)

End point values	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg	Part B NM21-1480-Q2W 800mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: L				
arithmetic mean (standard deviation)	4.454 (± 0.9507)	5.930 (± 2.472)		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Frequency of Specific Anti-drug Antibodies to NM21-1480

End point title	Assessment of the Frequency of Specific Anti-drug Antibodies to NM21-1480

End point description:

A patient is considered positive if they are positive at any scheduled or unscheduled post-baseline assessment.

End point type	Secondary

End point timeframe:

Up to 3 years.

End point values	Part A Dose Level 1 NM21-1480-Q2W 0.15mg	Part A Dose Level 2 NM21-1480-Q2W 1.5mg	Part A Dose Level 3 NM21-1480-Q2W 8mg	Part A Dose Level 4 NM21-1480-Q2W 24mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	3	3
Units: Participants	1	1	2	3

End point values	Part A Dose Level 5 NM21-1480-Q2W 80mg	Part A Dose Level 6 NM21-1480-Q2W 240mg	Part A Dose Level 7 NM21-1480-Q2W 800mg	Part A2 Dose Level 1 NM21-1480-Q2W 1400mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	9	5
Units: Participants	5	3	6	1

End point values	Part B NM21-1480-Q2W 800mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Participants	14			

Statistical analyses

No statistical analyses for this end point

Secondary: To Determine the Anti-tumor Activity (Duration of Response) of NM21-1480 According to RECIST 1.1

End point title	To Determine the Anti-tumor Activity (Duration of Response) of

	NM21-1480 According to RECIST 1.1[13]

End point description:

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 4 NM21-1480-Q2W 24mg			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Months				
number (not applicable)	1.84			

Statistical analyses

No statistical analyses for this end point

Secondary: To Determine the Anti-tumor Activity (Time-to-response) of NM21-1480 According to RECIST 1.1

End point title	To Determine the Anti-tumor Activity (Time-to-response) of NM21-1480 According to RECIST 1.1[14]

End point description:

End point type	Secondary

End point timeframe:

Up to 3 years.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point data is entered as per cohort.

End point values	Part A Dose Level 4 NM21-1480-Q2W 24mg			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: day				
number (not applicable)	110			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Aes occurring after signing informed consent/HIPAA authorization, but before study drug administration are to be recorded as Aes (though non-treatment-emergent).	
Adverse event reporting additional description:	
Treatment emergent AEs are captured within the below reporting group/s.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups	
Reporting group title	NM21-1480- Treatment arm
Reporting group description:	
Treatment emergent AEs across all NM21-1480 treatment arms.	

Serious adverse events	NM21-1480- Treatment arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 52 (32.69%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorder			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adrenal insufficiency			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			

subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestine Obstruction				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic failure				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary retention				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cholangitis infective			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	NM21-1480-Treatment arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 52 (88.46%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Blood creatinine increased			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Weight decreased			

subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	10 / 52 (19.23%)		
occurrences (all)	10		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Asthenia			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 52 (13.46%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	8 / 52 (15.38%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	5 / 52 (9.62%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		

Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 7 / 52 (13.46%) 7 6 / 52 (11.54%) 6		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 4 / 52 (7.69%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 7 / 52 (13.46%) 7		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 5 / 52 (9.62%) 5		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 12 / 52 (23.08%) 12		
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	 4 / 52 (7.69%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 6 / 52 (11.54%) 6 5 / 52 (9.62%) 5 3 / 52 (5.77%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2020	Protocol v 1.1 (Amendment 1) was dated 20 April 2020 and amended to incorporate FDA feedback on Protocol v 1.0, the changes in Administrative Letter #1, and other minor or administrative changes. Protocol v 1.1 was not executed, and no patients were enrolled under this version. The other key changes in Protocol v 1.1 included the following: Clarified that the SMC should utilize all available clinical data and information to determine the RP2D, not only the information from the first 4 weeks of treatment for each patient; and Provided guidance based on the potential that NM21-1480 might impact cytochrome P enzyme production and activity via cytokine modulation.
27 April 2020	Protocol v 1.2 (Amendment 2) was dated 27 April 2020 and amended to incorporate FDA feedback on Protocol v 1.1 and other minor or administrative changes. Protocol v 1.2 was executed as the final version and patients were enrolled. The key changes in Protocol v 1.2 included the following: Modified the definition of a DLT; and Provided guidance that any patient who experienced Grade 4 toxicity must have been permanently discontinued.

04 June 2020	Protocol v 2.0 (Amendment 3) was dated 04 June 2020 and amended to incorporate the following key changes and other minor or administrative changes: • Updated wording regarding definition of criteria to be fulfilled by patients to qualify as DLT-evaluable patients; • Provided more detailed specification of washout periods for different types of previous therapies in the eligibility criteria; • Introduced a new patient population (EAS) for statistical analyses of efficacy parameters; • Increased tolerated time windows for clinical visits; • Revised wording of Inclusion Criterion 1 to allow enrollment of patients aged 20 years and above in Taiwan, in accordance with local regulations; • Revised wording of Inclusion Criterion 3 to provide clarity on requirements for baseline biopsy; • Revised Inclusion Criteria 8 and 11 to provide clarity in regard of washout periods following previous systemic vs. focal RT; • Revised Inclusion Criterion 15 on WOCBP; • Revised wording of Exclusion Criteria 3 to 6 to provide more detailed guidance on necessary washout periods for different types of previous pharmaceutical treatments; • Revised Exclusion Criterion 23 to clarify use of systemically active versus topical CBD; Removed Exclusion Criterion 26 due to redundancy with other eligibility criteria; • Revised wording on study procedures following occurrence of repeated delayed DLTs; • Revised wording for continued treatment of patients with clinical benefit from treatment who had infusion delays of >35 days; and • Included DLTs and infusion reactions of any grade in the definition of AESIs. Administrative Letter #2 dated 08 July 2020 for Protocol v 2.0 was released to update the required duration for the use of a reliable contraception from 7 months to 6 months after the end of study treatment.

15 January 2021	Protocol v 3.0 (Amendment 4) was dated 15 January 2021 and amended to incorporate the changes in Administrative Letter #2, the following key changes, and other minor or administrative changes: • Clarified the number of study sites and geographical location of study sites in Part A and Part B; • Introduced the option to conduct a small intermediate dose-expansion cohort (Cohort A-2) between Part A and Part B to further characterize the dose/PD relationship in support of dose selection for Part B; • Revised to determine final RP2D in Part B rather than in Part A, by studying up to 4 different dose levels based on Part A data for which full PD-L1 target occupancy on peripheral T cells during the dosing interval had been demonstrated; • Replaced description of duration of DLT evaluation period from weeks to number of days; • Clarified definition of criteria to be fulfilled by patients to qualify as DLT-evaluable patients in some instances; • Revised response assessment intervals for the first 24 weeks in Part B of the study from every 8 weeks to every 6 weeks; • Revised Part B study design and patient eligibility criteria (ie, Inclusion Criteria 2 and 8 and Exclusion Criteria 3 and 6; all only applicable for Part B) for Cohorts B1 through B3; • Introduced additional Inclusion Criterion 19 (for optional Cohort A-2 only); • Clarified countries in which respective Part B Cohorts were conducted; • Increased the maximum number of patients treated in Part B cohorts from 25 to 40 and adjusted the BOP2 interim analysis approach accordingly; • Introduced a 2-step screening process for Cohort B3; • Provided more flexibility for timing of PK sampling; • Revised Exclusion Criterion 10 to allow patients with controlled psoriasis not requiring systemic therapy to be enrolled; • Clarified the preferred timepoints for post-treatment initiation biopsies; Clarified that for patients who withdraw early from the study for reasons other than disease progression, e
17 May 2021	Protocol v 4.0 (Amendment 5) was dated 17 May 2021 and amended to incorporate the changes in Protocol Clarification Memorandum #1, the following key changes, and other minor or administrative changes: • Updated Inclusion Criterion 3 to incorporate recent guidance from Protocol Clarification Memorandum #1 distributed to study sites (18 March 2021); • Clarified DLT classification criteria pertaining to toxicities leading to study/treatment discontinuation and infusion related reactions (IRRs); and • Clarified AESI reporting guidance for IRRs.

01 September 2021	Protocol v 5.0 (Amendment 6) was dated 01 September 2021 and amended to incorporate the changes in Administrative Letter #3, Administrative Letter #4, the following key changes, and other minor or administrative changes: • Increased the number of expansion cohorts from 3 cohorts to 7 cohorts (Cohorts B1 through B7) and increased the number of study sites in Part B to accommodate for enrollment in all of the Part B expanded cohorts; • Added details to Inclusion Criteria 2 and 8 and Exclusion Criterion 3 to describe the new tumor specific Cohorts B4-B7; • Revised the wording of the Inclusion Criteria 3 to provide clarity on requirements for baseline archival tissue; • Revised Inclusion Criterion 13 to clarify the waiting period for minor surgical procedures conducted prior to dosing of NM21-1480; • Added new Inclusion Criterion 20 to ensure patients were at low risk to develop symptoms of COVID-19 infection while on study; • Revised Exclusion Criterion 10 to provide granularity on potential eligibility of patients who had a history of autoimmune disease; • Revised Exclusion Criteria 11 and 14 to allow for inclusion of patients who had been cured from previous Hepatitis C infection; Revised statistical analysis text to include Cohort B5 evaluation; • Included an initial 3+3 dose-escalation design to determine optimal safe dose levels of NM21-1480 in the combinatorial setting (Cohort B5); • Added the determination of disease control rate (DCR) as per RECIST 1.1 and BOR, DCR, ORR, Duration of Response, and PFS as per iRECIST as secondary endpoints in Part B; • Included analysis of T-cell receptor clonality in tumor tissue samples; • Introduced the option for the SMC to assign a longer dosing interval (approximately 3 weeks) to given dose levels selected for Part B than previously defined in the Protocol for Part A (approximately 2 weeks); • Updated the Schedule of Assessments (Table 7-1 to Table 7-1a) and Blood Sampling Schedule (Table 7-2 to
29 October 2021	Protocol v 6.0 (Amendment 7) was dated 29 October 2021 and amended to incorporate the following key changes and other minor or administrative changes: • Removed Dose Level 8, 1400 mg flat dose from Part A and updated corresponding statistical section and operational characteristics of the BOIN design as applicable; • Removed full PK blood draw requirements for Part B patients in Taiwan; and • Provided additional details on analysis of ADA assessments. Protocol Letter of Amendment dated 13 December 2021 for Protocol v 6.0 was released to update PK/PD parameter sampling time points for Part A and optional Part A-2.

28 February 2022	Protocol v 7.0 (Amendment 8) was dated 28 February 2022 and amended to incorporate the following key changes and other minor or administrative changes: • Updated Contract Research Organization information for overall project oversight and safety processing and reporting; • Expanded optional Part A-2 to allow up to 40 patients to enroll in a broader range of countries/sites than originally planned, with possibility to dose NM21-1480 either bi-weekly or every 3 weekRevised to allow for possible parallel conduct of Part A-2 with Part B; • Added Cohort B8 (mCRC) to Part B; • Added time to response to exploratory endpoints in Part A and Part A-2 and secondary anti-tumor endpoints in Part B; and • Updated Section 8.5.1, Permitted Medications and added a new Section 8.5.2, Prohibited Medications. Administrative Letter #5 dated 24 May 2022 for Protocol v 7.0 was released to update telephone contact for SAE reporting. Protocol Letter of Amendment dated 11 July 2022 for Protocol v 7.0 was released to include the following: • Updated to include completion of enrollment into Part A and SMC determination of the MTD from Part A; • Updated dose level to be initially evaluated in Part B; and • Revised to study the 1400 mg flat dose in up to 10 patients under Part A-2.s;
11 July 2022	Protocol v 8.0 (Amendment 9) was dated 11 July 2022 and amended to incorporate the changes described above in Administrative Letter #5 dated 24 May 2022, Protocol Letter of Amendment dated 11 July 2022, the following key changes, and other minor or administrative changes: • Updated countries in which Part B8 may be conducted; • Updated primary objectives of Part A-2; • Updated dose level to be initially evaluated in Part B; • Updated safety run-in design for Cohort B5; • Updated eligibility criteria for Cohort B8; • Updated permitted and prohibited medications; • Updated Schedule of Assessments, Tables 7-1 to 7-4; • Updated Follow-up Procedures for patients with abnormal liver function tests; and • Updated list of required laboratory assessments by panel.
17 November 2022	Protocol v 9.0 (Amendment 10) was dated 17 November 2022 and amended to incorporate the following key changes and other minor or administrative changes: • Updated Sponsor address; • Updated status of Part A; • Updated countries in which Cohorts B5 and B6 may be conducted; • Updated eligibility criteria for Cohorts B1, B7, and B8; and • Clarified requirements for scans during Follow-up period. Protocol Letter of Amendment dated 12 January 2023 for Protocol v 9.0 was released to allow archival tissue utilization to satisfy Cohort B8 patient eligibility and screening requirements. Protocol Clarification Letter dated 09 August 2023 for Protocol v 9.0 was released to provide clarification on the events to be classified as an AESI under hepatobiliary disorders.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported