Clinical trial results:
A Randomized Phase 2 Trial to Evaluate Three Daratumumab Dose Schedules in Smoldering Multiple Myeloma

Summary

EudraCT number	2014-005139-14
Trial protocol	GB DE FR CZ IT
Global end of trial date	03 June 2024

Results information

Result version number	v1 (current)
This version publication date	18 June 2025
First version publication date	18 June 2025

Trial information

Trial identification

Sponsor protocol code	54767414SMM2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02316106
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.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	02 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate If daratumumab can effectively decrease Myeloma (M) protein in subjects with intermediate or high-risk smoldering multiple myeloma (SMM) as assessed by complete response (CR) rate, and to determine if daratumumab reduced the progression or death rate in subjects with intermediate or high-risk SMM.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Türkiye: 9
Country: Number of subjects enrolled	United States: 38
Worldwide total number of subjects	123
EEA total number of subjects	27

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)	71
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total of 123 subjects were enrolled and randomised, out of which 122 were treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Long Intense)

Arm description:

Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as intravenous (IV) infusion once every week (Q1W) (Days 1, 8, 15, 22, 29, 36, 43 & 50) in Cycle 1, every other week (Q2W) (Days 1, 15, 29 and 43) in Cycle 2 and 3, every 4 weeks (Q4W) (Days 1 and 29) in Cycle 4 to 7, and on Day 1 from Cycle 8 to 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent withdrawal/study end, whichever occurred first (up to 7.89 years).

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	JNJ-54767414
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects in EP received daratumumab 1800 mg SC dose Q8W up to maximum of 91.6 months.

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	JNJ-54767414
Other name	
Pharmaceutical forms	Injection
Routes of administration	Infusion

Dosage and administration details:

Daratumumab 16 mg/kg was administered as IV infusion Q1W in Cycle 1 , Q2W in Cycle 2 and Cycle 3, Q4W in Cycle 4 to Cycle 7, and on Day 1 from Cycle 8 to Cycle 20. In extension phase, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, then completed end of treatment visit 4 weeks after last dose.

Arm title	Arm B (Intermediate)

Arm description:

Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1, and then on Day 1 of each cycle from Cycle 2 to Cycle 20, and Q8W after Cycle 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent

withdrawal/study end, whichever occurred first (up to 7.89 years).

Arm type	Experimental
Investigational medicinal product name	daratumumab
Investigational medicinal product code	JNJ-54767414
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects in EP received daratumumab 1800 mg SC dose Q8W up to maximum of 91.6 months.

Investigational medicinal product name	Daratumumab
Investigational medicinal product code	JNJ-54767414
Other name	
Pharmaceutical forms	Injection
Routes of administration	Infusion

Dosage and administration details:

Daratumumab 16 mg/kg was administered as IV infusion Q1W in Cycle 1 , Q2W in Cycle 2 and Cycle 3, Q4W in Cycle 4 to Cycle 7, and on Day 1 from Cycle 8 to Cycle 20. In extension phase, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, then completed end of treatment visit 4 weeks after last dose.

Arm title	Arm C (Short Intense)

Arm description:

Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1 alone. Treatment cycle was of 8 weeks. After Cycle 1, subjects completed the end of treatment visit 4 weeks after last dose and were followed up for safety until death, lost to follow up, consent withdrawal, or study end, whichever occured first (up to 7.89 years).

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	JNJ-54767414
Other name	
Pharmaceutical forms	Injection
Routes of administration	Infusion

Dosage and administration details:

Daratumumab 16 mg/kg was administered as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1 alone.

Number of subjects in period 1	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)
Started	41	41	41
Subjects who entered extension phase	21	15	0
Subjects switched: Daratumumab IV to SC	16	10	0
Treated	41	41	40
Completed	1	0	0
Not completed	40	41	41
Adverse event, serious fatal	7	5	4
Consent withdrawn by subject	3	4	9
Unspecified	30	32	28

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Long Intense)
Reporting group description:	
Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as intravenous (IV) infusion once every week (Q1W) (Days 1, 8, 15, 22, 29, 36, 43 & 50) in Cycle 1, every other week (Q2W) (Days 1, 15, 29 and 43) in Cycle 2 and 3, every 4 weeks (Q4W) (Days 1 and 29) in Cycle 4 to 7, and on Day 1 from Cycle 8 to 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent withdrawal/study end, whichever occurred first (up to 7.89 years).	
Reporting group title	Arm B (Intermediate)
Reporting group description:	
Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1, and then on Day 1 of each cycle from Cycle 2 to Cycle 20, and Q8W after Cycle 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent withdrawal/study end, whichever occurred first (up to 7.89 years).	
Reporting group title	Arm C (Short Intense)
Reporting group description:	
Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1 alone. Treatment cycle was of 8 weeks. After Cycle 1, subjects completed the end of treatment visit 4 weeks after last dose and were followed up for safety until death, lost to follow up, consent withdrawal, or study end, whichever occured first (up to 7.89 years).	

Reporting group values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)
Number of subjects	41	41	41
Age categorical Units: Subjects			
In Utero	0	0	0
Preterm newborn infants (gestional age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days - 23 months)	0	0	0
Children (2 - 11 years)	0	0	0
12 - 17 years	0	0	0
Adults (18 - 64 years)	20	24	27
From 65 - 84 years	21	17	14
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.4	61.5	59.0
standard deviation	± 9.86	± 8.76	± 10.55
Gender categorical Units: Subjects			
Male	17	17	21

Female	24	24	20

Reporting group values	Total		
Number of subjects	123		
Age categorical Units: Subjects			
In Utero	0		
Preterm newborn infants (gestional age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days - 23 months)	0		
Children (2 - 11 years)	0		
12 - 17 years	0		
Adults (18 - 64 years)	71		
From 65 - 84 years	52		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Male	55		
Female	68		

End points

End points reporting groups

Reporting group title	Arm A (Long Intense)

Reporting group description:

Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as intravenous (IV) infusion once every week (Q1W) (Days 1, 8, 15, 22, 29, 36, 43 & 50) in Cycle 1, every other week (Q2W) (Days 1, 15, 29 and 43) in Cycle 2 and 3, every 4 weeks (Q4W) (Days 1 and 29) in Cycle 4 to 7, and on Day 1 from Cycle 8 to 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent withdrawal/study end, whichever occurred first (up to 7.89 years).

Reporting group title	Arm B (Intermediate)

Reporting group description:

Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1, and then on Day 1 of each cycle from Cycle 2 to Cycle 20, and Q8W after Cycle 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent withdrawal/study end, whichever occurred first (up to 7.89 years).

Reporting group title	Arm C (Short Intense)

Reporting group description:

Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1 alone. Treatment cycle was of 8 weeks. After Cycle 1, subjects completed the end of treatment visit 4 weeks after last dose and were followed up for safety until death, lost to follow up, consent withdrawal, or study end, whichever occured first (up to 7.89 years).

Primary: Percentage of Subjects who Achieved a Complete Response (CR) by International Myeloma Working Group (IMWG) Criteria

End point title	Percentage of Subjects who Achieved a Complete Response (CR) by International Myeloma Working Group (IMWG) Criteria[1]

End point description:

Percentage of subjects who achieved a CR by IMWG Criteria were reported. CR was defined as CR plus sCR by IMWG criteria. Per IMWG criteria, CR response was defined as a negative immunofixation on the serum and urine, and less than (<) 5 percentage (%) plasma cells (PCs) in bone marrow; Stringent complete Response (sCR) was defined as CR plus normal free light chain (FLC) ratio, and absence of clonal plasma cells (PCs) by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry. Response evaluable analysis set included subjects who had measurable disease at baseline as per IMWG criteria (serum and urine, serum only, urine only, FLC) and received at least 1 dose of daratumumab treatment and had at least 1 post-baseline disease assessment.

End point type	Primary

End point timeframe:

From Cycle 1 Day 1 up to 6 months post randomisation of the last subject (up to 1.58 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: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	41	40	
Units: percentage of subjects				
number (not applicable)	4.9	12.2	0	

Statistical analyses

No statistical analyses for this end point

Primary: Progressive Disease Per Death (PD/Death) Rate

End point title	Progressive Disease Per Death (PD/Death) Rate [2]

End point description:

Progressive Disease per Death (PD/Death) rate were reported. PD/Death rate per patient-year was defined as number of events (PD or death) per total progression-free survival for all subjects. Intent-to-treat (ITT) analysis set was defined as subjects who have been randomly assigned to one of the 3 daratumumab schedules based on interactive web response system (IWRS).

End point type	Primary

End point timeframe:

From Cycle 1 Day 1 up to 12 months post randomisation of the last subject (up to 2.07 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: No inferential statistics was done. Only descriptive statistics was performed.

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	41	41	
Units: events per patient-years				
number (not applicable)	0.096	0.102	0.109	

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease (MRD) Negative Rate

End point title	Minimal Residual Disease (MRD) Negative Rate

End point description:

MRD negative rate were reported. The MRD negativity rate was defined as the percentage of subjects with a CR or better response who had negative MRD (10^-4 and 10^-5) assessment at any timepoint after the first dose of study drugs by evaluation of bone marrow aspirates at any time after the randomisation and prior to progressive disease, subsequent therapy. Intent-to-treat (ITT) analysis set was defined as subjects who have been randomly assigned to one of the 3 daratumumab schedules based on interactive web response system (IWRS).

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to 91.6 months

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	41	41	
Units: percentage of subjects				
number (not applicable)				
MRD (10^-4)	2.4	7.3	0	
MRD (10^-5)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Treatment (TNT) for Active Myeloma

End point title	Time to Next Treatment (TNT) for Active Myeloma

End point description:

Time to next treatment (TNT) for active myeloma were reported. Time to next treatment was defined as the time from the date of randomization to the date of the first subsequent multiple myeloma treatment. Kaplan-Meier estimate was used. Intent-to-treat (ITT) analysis set was defined as subjects who have been randomly assigned to one of the 3 daratumumab schedules based on interactive web response system (IWRS). Here "N" (overall number of subjects analysed) signifies the subjects that were evaluable for this endpoint. Here, 99999 signifies that median and 90% CI were not estimable due to low number of subjects with events.

End point type	Secondary

End point timeframe:

From randomisation (Day -5) up to the date of first subsequent antimyeloma treatment (up to 7.89 years)

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	17	23	
Units: months				
median (confidence interval 90%)	99999 (99999 to 99999)	99999 (59.9 to 99999)	76.3 (40.4 to 80.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Achieved Partial Response or Better Response (Stringent Complete Response [sCR] Plus Complete Response [CR] Plus Very Good Partial Response [VGPR] or a Partial Response [PR])

End point title	Percentage of Subjects who Achieved Partial Response or Better Response (Stringent Complete Response [sCR] Plus Complete Response [CR] Plus Very Good Partial Response [VGPR] or a Partial Response [PR])

End point description:

Per IMWG criteria, CR: was defined as a negative immunofixation on serum & urine, & <5 % PCs in bone marrow; sCR: CR plus normal FLC ratio, & absence of clonal PCs by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry. VGPR: Serum & urine M-protein detectable by immunofixation but not on electrophoresis or >=90% reduction in serum M-protein plus urine M-protein level < 100mg/24 hours; PR: >=50 % reduction of serum M-protein & reduction in 24 hour urinary M-protein by >= 90% or to <200 mg/24 hours; if serum & urine M-protein are not measurable, a decrease of >=50% in difference between involved & uninvolved FLC levels was required instead of M-protein criteria. If serum and urine M-protein are not measurable and serum free light assay was also not measurable, >=50% reduction in bone marrow PCs was required in place of M-protein, provided baseline bone marrow PC percentage was >=30%. Response evaluable analysis set was used.

End point type	Secondary

End point timeframe:

From start of the treatment (Cycle 1 Day 1) until confirmed PD, death, start of new anticancer therapy, withdrawal of consent, lost to follow-up, or end of the study, whichever occurred first (up to 7.89 years)

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	41	40	
Units: percentage of subjects				
number (confidence interval 90%)	56.1 (42.1 to 69.4)	56.1 (42.1 to 69.4)	37.5 (24.7 to 51.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS: time from dates of randomization to initial documented PD per Sixty, BMPC, Light chains, focal lesions per MRI, elevated Calcium, Renal failure, Anemia, Bone lesions (SLiM-CRAB) criteria, or date of death, whichever was first. SLiM-CRAB criteria: clonal BM PCs % >=60%, Involved: uninvolved serum free LC ratio >=100, >1 focal lesion on MRI studies, calcium:>0.25 millimole/liter (mmol/L)(>1 mg/dL) higher than upper limit of normal or >2.75 mmol/L (>11 mg/dL); creatinine clearance <40 mL/min or serum creatinine >177 micromole/liter (>2 mg/dL); hemoglobin <10 g/dL(<6.5 mmol/L) or >2 g/dL(>1.25 mmol/L) lower than lower limit of normal;>1 osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT). Kaplan-Meier estimate was used. ITT analysis set was used. Here, "N" (overall number of subjects analysed) signifies subjects evaluable & 99999 signifies upper limit of 90% CI were not estimable due to low number of subjects with events.

End point type	Secondary

End point timeframe:

From randomisation (Day -5) until disease progression or death whichever occurred first (up to 7.89 years)

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	18	16	
Units: months				
median (confidence interval 90%)	81.12 (58.02 to 99999)	84.44 (44.02 to 99999)	81.35 (51.45 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Symptomatic Multiple Myeloma With Adverse Prognostic Features

End point title	Percentage of Subjects With Symptomatic Multiple Myeloma With Adverse Prognostic Features

End point description:

Percentage of subjects with symptomatic multiple myeloma with adverse prognostic features were reported. The International Staging System (ISS) for multiple myeloma (MM) was based on serum beta-2 microglobulin (S beta-2M) and serum albumin; that is, subjects progressed to symptomatic multiple myeloma (SymT MM) with stage III (S beta2M>= 5.5 mg/L) of ISS, Subjects progressed to SymT MM with adverse cytogenetic characteristics (ACC), Subjects progressed to SymT MM with stage III of ISS or adverse cytogenetic characteristics. Adverse cytogenetic characteristics included Fluorescence in situ hybridization (FISH) findings of del(17p13), t(14;16), t(4;14), amp(1q21) or karyotype findings of t(4;14), del(17p) or a combination of these. ITT analysis set was used.

End point type	Secondary

End point timeframe:

From start of treatment (Cycle 1 Day 1) until PD or prior to any subsequent anti-Multiple myeloma therapy (up to 7.89 years)

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	41	41	
Units: percentage of subjects				
number (not applicable)				
Subjects with stage III of ISS	2.4	0	0	
Subjects with ACC	19.5	12.2	9.8	
Subjects with stage III of ISS staging or ACC	22.0	12.2	9.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) was defined as the time from the date of randomization to the date of death. Median OS was estimated by using the Kaplan-Meier method. Intent-to-treat (ITT) analysis set was defined as subjects who have been randomly assigned to one of the 3 daratumumab schedules based on interactive web response system (IWRS). Here, 99999 signifies that median and 90% CI were not estimable due to low number of subjects with events.

End point type	Secondary

End point timeframe:

From randomisation (Day -5) till death (up to 7.89 years)

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	5	4	
Units: months				
median (confidence interval 90%)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Response to First Subsequent Multiple Myeloma Treatment

End point title	Number of Subjects with Response to First Subsequent Multiple Myeloma Treatment

End point description:

Response (IMWG Criteria) to first subsequent MM treatment: sCR: CR + normal FLC ratio & absence of clonal PCs by immunohistochemistry, immunofluorescence or 2- to 4-color flow cytometry; CR:a negative immunofixation on serum & urine, & <5% PCs in BM; VGPR: Serum & urine M-protein (SMP & UMP) detectable by immunofixation but not on electrophoresis or >=90% reduction in SMP + UMP level <100mg/24 hours; PR:>=50% reduction of SMP & >=90% reduction in UMP in 24 hour or to <200 mg/24 hours; if SMP & UMP are not measurable, a decrease of >=50% difference between involved & uninvolved FLC levels was required instead of M-protein criteria. If SMP & UMP & serum free light assay was also not measurable, >=50% reduction in BM PCs was required instead of M-protein, provided baseline BM PC percentage was >=30%. ITT analysis set was used. Here "N" (overall number of subjects analysed) signifies subjects evaluable for this endpoint. Only those who received first line of therapy were analysed.

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to 7.89 years

End point values	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	17	23	
Units: subjects	6	12	15	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Cause Mortality: From randomisation (Day -5) up to 7.89 years; Serious Adverse Events and Other Adverse Events: From Cycle 1 Day 1 up to 7.89 years

Adverse event reporting additional description:

Safety analysis set included subjects who had received at least 1 administration of daratumumab (partial or complete).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Arm A (Long Intense)

Reporting group description:

Subjects received daratumumab 16 milligrams per kilogram (mg/kg) as intravenous (IV) infusion once every week (Q1W) (Days 1, 8, 15, 22, 29, 36, 43 & 50) in Cycle 1, every other week (Q2W) (Days 1, 15, 29 and 43) in Cycle 2 and 3, every 4 weeks (Q4W) (Days 1 and 29) in Cycle 4 to 7, and on Day 1 from Cycle 8 to 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent withdrawal/study end, whichever occurred first (up to 7.89 years).

Reporting group title	Arm B (Intermediate)

Reporting group description:

Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1, and then on Day 1 of each cycle from Cycle 2 to Cycle 20, and Q8W after Cycle 20. Each treatment cycle was of 8 weeks. After Cycle 20, per investigator's discretion, subjects either entered into extension phase (EP) or completed end of treatment visit 4 weeks after last dose. In EP, subjects continued to receive daratumumab IV (Q8W) after end of Cycle 20 up to 91.6 months, and then completed end of treatment visit 4 weeks after last dose. After protocol amendment 5, subjects in EP optionally switched to daratumumab 1800 mg subcutaneous (SC) Q8W per investigator's discretion. After end of treatment, subjects were followed up for safety until death, lost to follow up, consent withdrawal/study end, whichever occurred first (up to 7.89 years).

Reporting group title	Arm C (Short Intense)

Reporting group description:

Subjects received daratumumab 16 mg/kg as IV infusion Q1W (Day 1, 8, 15, 22, 29, 36, 43 and 50) in Cycle 1 alone. Treatment cycle was of 8 weeks. After Cycle 1, subjects completed the end of treatment visit 4 weeks after last dose and were followed up for safety until death, lost to follow up, consent withdrawal, or study end, whichever occured first (up to 7.89 years).

Serious adverse events	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 41 (48.78%)	14 / 41 (34.15%)	4 / 40 (10.00%)
number of deaths (all causes)	7	5	4
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Breast cancer			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioblastoma			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Prepuce redundant			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress fracture			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			

subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hemiplegia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical radiculopathy			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Spinal stenosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 41 (9.76%)	1 / 41 (2.44%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Babesiosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Streptococcal sepsis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A (Long Intense)	Arm B (Intermediate)	Arm C (Short Intense)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 41 (92.68%)	41 / 41 (100.00%)	32 / 40 (80.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 41 (14.63%)	1 / 41 (2.44%)	1 / 40 (2.50%)
occurrences (all)	8	1	1
Hypertension			
subjects affected / exposed	11 / 41 (26.83%)	4 / 41 (9.76%)	2 / 40 (5.00%)
occurrences (all)	24	4	2
Hot flush			

subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	1 / 40 (2.50%)
occurrences (all)	3	1	1
Flushing			
subjects affected / exposed	5 / 41 (12.20%)	5 / 41 (12.20%)	1 / 40 (2.50%)
occurrences (all)	14	5	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 41 (19.51%)	4 / 41 (9.76%)	3 / 40 (7.50%)
occurrences (all)	11	8	5
Oedema peripheral			
subjects affected / exposed	6 / 41 (14.63%)	4 / 41 (9.76%)	1 / 40 (2.50%)
occurrences (all)	7	6	1
Non-cardiac chest pain			
subjects affected / exposed	2 / 41 (4.88%)	2 / 41 (4.88%)	2 / 40 (5.00%)
occurrences (all)	2	3	3
Malaise			
subjects affected / exposed	4 / 41 (9.76%)	2 / 41 (4.88%)	2 / 40 (5.00%)
occurrences (all)	5	2	2
Influenza like illness			
subjects affected / exposed	10 / 41 (24.39%)	4 / 41 (9.76%)	1 / 40 (2.50%)
occurrences (all)	15	4	1
Fatigue			
subjects affected / exposed	19 / 41 (46.34%)	25 / 41 (60.98%)	9 / 40 (22.50%)
occurrences (all)	26	29	11
Chills			
subjects affected / exposed	3 / 41 (7.32%)	6 / 41 (14.63%)	3 / 40 (7.50%)
occurrences (all)	4	6	3
Chest discomfort			
subjects affected / exposed	4 / 41 (9.76%)	3 / 41 (7.32%)	4 / 40 (10.00%)
occurrences (all)	5	4	4
Asthenia			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	4 / 40 (10.00%)
occurrences (all)	1	2	4
Respiratory, thoracic and mediastinal disorders			

Wheezing			
subjects affected / exposed	4 / 41 (9.76%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	5	2	0
Throat tightness			
subjects affected / exposed	4 / 41 (9.76%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	5	1	0
Throat irritation			
subjects affected / exposed	3 / 41 (7.32%)	4 / 41 (9.76%)	2 / 40 (5.00%)
occurrences (all)	5	4	2
Sneezing			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Rhinorrhoea			
subjects affected / exposed	3 / 41 (7.32%)	5 / 41 (12.20%)	2 / 40 (5.00%)
occurrences (all)	5	5	2
Rhinitis allergic			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	3 / 40 (7.50%)
occurrences (all)	3	3	8
Productive cough			
subjects affected / exposed	2 / 41 (4.88%)	5 / 41 (12.20%)	0 / 40 (0.00%)
occurrences (all)	2	5	0
Oropharyngeal pain			
subjects affected / exposed	6 / 41 (14.63%)	10 / 41 (24.39%)	4 / 40 (10.00%)
occurrences (all)	7	13	5
Nasal congestion			
subjects affected / exposed	9 / 41 (21.95%)	4 / 41 (9.76%)	6 / 40 (15.00%)
occurrences (all)	12	5	6
Dyspnoea			
subjects affected / exposed	12 / 41 (29.27%)	8 / 41 (19.51%)	3 / 40 (7.50%)
occurrences (all)	20	15	4
Cough			
subjects affected / exposed	18 / 41 (43.90%)	15 / 41 (36.59%)	11 / 40 (27.50%)
occurrences (all)	34	28	12
Dysphonia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	5 / 40 (12.50%)
occurrences (all)	0	1	5

Psychiatric disorders			
Depression			
subjects affected / exposed	4 / 41 (9.76%)	2 / 41 (4.88%)	1 / 40 (2.50%)
occurrences (all)	4	2	1
Anxiety			
subjects affected / exposed	5 / 41 (12.20%)	4 / 41 (9.76%)	1 / 40 (2.50%)
occurrences (all)	6	6	1
Insomnia			
subjects affected / exposed	13 / 41 (31.71%)	14 / 41 (34.15%)	5 / 40 (12.50%)
occurrences (all)	15	21	5
Restlessness			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 41 (7.32%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	3	3	0
Weight decreased			
subjects affected / exposed	5 / 41 (12.20%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	10	4	0
Weight increased			
subjects affected / exposed	7 / 41 (17.07%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	7	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 41 (4.88%)	4 / 41 (9.76%)	0 / 40 (0.00%)
occurrences (all)	8	4	0
Fall			
subjects affected / exposed	2 / 41 (4.88%)	6 / 41 (14.63%)	0 / 40 (0.00%)
occurrences (all)	2	8	0
Procedural pain			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Skin laceration			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0

Thermal burn			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	5	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	3 / 40 (7.50%)
occurrences (all)	3	1	3
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	3 / 41 (7.32%)	6 / 41 (14.63%)	2 / 40 (5.00%)
occurrences (all)	4	7	4
Dizziness			
subjects affected / exposed	6 / 41 (14.63%)	6 / 41 (14.63%)	1 / 40 (2.50%)
occurrences (all)	10	6	1
Headache			
subjects affected / exposed	13 / 41 (31.71%)	10 / 41 (24.39%)	13 / 40 (32.50%)
occurrences (all)	18	14	14
Hyperaesthesia			
subjects affected / exposed	2 / 41 (4.88%)	1 / 41 (2.44%)	2 / 40 (5.00%)
occurrences (all)	2	1	2
Hypoaesthesia			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	2	3	0
Memory impairment			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	1 / 40 (2.50%)
occurrences (all)	0	3	1
Tremor			
subjects affected / exposed	0 / 41 (0.00%)	4 / 41 (9.76%)	0 / 40 (0.00%)
occurrences (all)	0	9	0
Taste disorder			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	0	3	0
Somnolence			
subjects affected / exposed	6 / 41 (14.63%)	4 / 41 (9.76%)	0 / 40 (0.00%)
occurrences (all)	7	4	0
Peripheral sensory neuropathy			

subjects affected / exposed	3 / 41 (7.32%)	3 / 41 (7.32%)	2 / 40 (5.00%)
occurrences (all)	3	3	2
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	2 / 40 (5.00%)
occurrences (all)	4	3	2
Anaemia			
subjects affected / exposed	3 / 41 (7.32%)	5 / 41 (12.20%)	0 / 40 (0.00%)
occurrences (all)	4	7	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 41 (4.88%)	2 / 41 (4.88%)	2 / 40 (5.00%)
occurrences (all)	3	2	2
Vertigo			
subjects affected / exposed	4 / 41 (9.76%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	5	3	0
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Vision blurred			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	3 / 40 (7.50%)
occurrences (all)	2	3	3
Lacrimation increased			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	3 / 40 (7.50%)
occurrences (all)	1	1	7
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 41 (9.76%)	4 / 41 (9.76%)	1 / 40 (2.50%)
occurrences (all)	5	4	2
Abdominal pain			
subjects affected / exposed	4 / 41 (9.76%)	5 / 41 (12.20%)	3 / 40 (7.50%)
occurrences (all)	6	6	3
Constipation			
subjects affected / exposed	8 / 41 (19.51%)	6 / 41 (14.63%)	2 / 40 (5.00%)
occurrences (all)	10	7	2
Diarrhoea			

subjects affected / exposed	14 / 41 (34.15%)	13 / 41 (31.71%)	4 / 40 (10.00%)
occurrences (all)	22	23	6
Dry mouth			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Dyspepsia			
subjects affected / exposed	2 / 41 (4.88%)	4 / 41 (9.76%)	0 / 40 (0.00%)
occurrences (all)	3	6	0
Flatulence			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	10 / 41 (24.39%)	11 / 41 (26.83%)	3 / 40 (7.50%)
occurrences (all)	17	20	3
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 41 (4.88%)	5 / 41 (12.20%)	2 / 40 (5.00%)
occurrences (all)	2	5	2
Vomiting			
subjects affected / exposed	9 / 41 (21.95%)	5 / 41 (12.20%)	1 / 40 (2.50%)
occurrences (all)	13	6	1
Paraesthesia oral			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Oral pruritus			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	5 / 41 (12.20%)	5 / 41 (12.20%)	2 / 40 (5.00%)
occurrences (all)	6	6	2
Skin burning sensation			
subjects affected / exposed	0 / 41 (0.00%)	0 / 41 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	10 / 41 (24.39%)	3 / 41 (7.32%)	2 / 40 (5.00%)
occurrences (all)	16	4	2

Pruritus			
subjects affected / exposed	2 / 41 (4.88%)	5 / 41 (12.20%)	2 / 40 (5.00%)
occurrences (all)	5	5	4
Hyperhidrosis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	4	1	0
Alopecia			
subjects affected / exposed	3 / 41 (7.32%)	2 / 41 (4.88%)	1 / 40 (2.50%)
occurrences (all)	5	2	1
Erythema			
subjects affected / exposed	1 / 41 (2.44%)	0 / 41 (0.00%)	3 / 40 (7.50%)
occurrences (all)	1	0	3
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	6 / 41 (14.63%)	4 / 41 (9.76%)	2 / 40 (5.00%)
occurrences (all)	8	5	2
Bone pain			
subjects affected / exposed	3 / 41 (7.32%)	3 / 41 (7.32%)	3 / 40 (7.50%)
occurrences (all)	3	4	4
Back pain			
subjects affected / exposed	10 / 41 (24.39%)	12 / 41 (29.27%)	4 / 40 (10.00%)
occurrences (all)	15	14	4
Arthritis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Arthralgia			
subjects affected / exposed	14 / 41 (34.15%)	19 / 41 (46.34%)	1 / 40 (2.50%)
occurrences (all)	34	30	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 41 (4.88%)	7 / 41 (17.07%)	4 / 40 (10.00%)
occurrences (all)	2	8	4
Myalgia			
subjects affected / exposed	8 / 41 (19.51%)	4 / 41 (9.76%)	2 / 40 (5.00%)
occurrences (all)	10	12	2
Neck pain			

subjects affected / exposed	4 / 41 (9.76%)	2 / 41 (4.88%)	0 / 40 (0.00%)
occurrences (all)	4	2	0
Osteoarthritis			
subjects affected / exposed	1 / 41 (2.44%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	1	3	0
Pain in extremity			
subjects affected / exposed	10 / 41 (24.39%)	10 / 41 (24.39%)	2 / 40 (5.00%)
occurrences (all)	14	11	2
Bursitis			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 41 (7.32%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	4	3	0
Eye infection			
subjects affected / exposed	3 / 41 (7.32%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Conjunctivitis			
subjects affected / exposed	4 / 41 (9.76%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	4	1	0
COVID-19			
subjects affected / exposed	5 / 41 (12.20%)	6 / 41 (14.63%)	0 / 40 (0.00%)
occurrences (all)	5	7	0
Bronchitis			
subjects affected / exposed	5 / 41 (12.20%)	5 / 41 (12.20%)	1 / 40 (2.50%)
occurrences (all)	5	5	1
Herpes zoster			
subjects affected / exposed	4 / 41 (9.76%)	1 / 41 (2.44%)	0 / 40 (0.00%)
occurrences (all)	5	1	0
Influenza			
subjects affected / exposed	4 / 41 (9.76%)	5 / 41 (12.20%)	0 / 40 (0.00%)
occurrences (all)	5	5	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	3	3	0

Nasopharyngitis			
subjects affected / exposed	11 / 41 (26.83%)	8 / 41 (19.51%)	2 / 40 (5.00%)
occurrences (all)	16	9	2
Oral herpes			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	3	5	0
Pneumonia			
subjects affected / exposed	6 / 41 (14.63%)	0 / 41 (0.00%)	0 / 40 (0.00%)
occurrences (all)	6	0	0
Rhinitis			
subjects affected / exposed	2 / 41 (4.88%)	6 / 41 (14.63%)	0 / 40 (0.00%)
occurrences (all)	7	7	0
Sinusitis			
subjects affected / exposed	8 / 41 (19.51%)	4 / 41 (9.76%)	1 / 40 (2.50%)
occurrences (all)	8	5	1
Upper respiratory tract infection			
subjects affected / exposed	20 / 41 (48.78%)	15 / 41 (36.59%)	4 / 40 (10.00%)
occurrences (all)	40	31	4
Urinary tract infection			
subjects affected / exposed	5 / 41 (12.20%)	6 / 41 (14.63%)	1 / 40 (2.50%)
occurrences (all)	7	16	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 41 (0.00%)	3 / 41 (7.32%)	0 / 40 (0.00%)
occurrences (all)	0	5	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 41 (4.88%)	4 / 41 (9.76%)	0 / 40 (0.00%)
occurrences (all)	4	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2015	The purpose of the amendment 1 was to add administration of steroids for 2 days post infusion, as a safety precaution and in line with other single agent studies of daratumumab.
27 July 2015	The purpose of the amendment 2 was to address feedback from health authorities and investigators and to include the clarification of requirements for radiologic assessment to reduce exposure, addition of a disease evaluation to capture early response, adjustment of the entry criteria and visit windows, as well as other minor edits throughout the protocol.
20 June 2017	The purpose of the amendment 3 was to incorporate changes from practical experience with implementing study evaluations and to address feedback from investigators and the steering committee and to include the clarification that a subject with disease progression, assessed by serum FLC only, may continue to receive study treatment if the subject continues to show clinical benefit per investigator assessment and if agreed upon by the sponsor.
28 January 2019	The purpose of the amendment 4 was to allow extended treatment with IV daratumumab (Q8W) after 20 treatment cycles in long intense (Arm A) and intermediate arm (Arm B) if, as per investigator discretion, there is a positive benefit/risk ratio, absence of Grade >=3 treatment related toxicity, and at least stable disease has been achieved. In the case of subjects who already completed end of treatment and the end of Cycle 20 occurred <6 months, these subjects can continue receiving IV daratumumab administrations every 8 weeks.
01 April 2020	The purpose of the amendment 5 was 1) to extend the study duration and 2) to provide flexibility for study investigators as it relates to the global coronavirus (COVID-19) pandemic.
29 March 2021	The purpose of the amendment 6 was to extend the study duration up to a maximum of 7 years following Last Patient First Dose (LPFD) by redefining the End of Study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported