Clinical trial results:
Efficacy of Daratumumab in Patients with Relapsed/Refractory Myeloma with Renal Impairment

Summary

EudraCT number	2017-003950-18
Trial protocol	GR IT
Global end of trial date	22 March 2021

Results information

Result version number	v1 (current)
This version publication date	01 November 2022
First version publication date	01 November 2022

Trial information

Trial identification

Sponsor protocol code	EAE-2017/MM02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03450057
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Society of Hematology
Sponsor organisation address	27 Kifisias Ave, Athens, Greece, 11523
Public contact	Prof. Panayiotidis Panayiotis, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece, 0030 2107211806, infohaema@eae.gr
Scientific contact	Health Data Specialists Ireland, Health Data Specialists Ireland Limited, 0035 3906480600, info@heads-research.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	17 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate progression free survival (PFS) in subjects with relapsed or refractory multiple myeloma (RRMM) and renal impairment (RI) treated with daratumumab and dexamethasone (DaraD).

Protection of trial subjects:

This study was conducted in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	13 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 34
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	10

From 65 to 84 years	26
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

38 patients were enrolled and initiated study treatment across 5 centers in Greece and 2 centers in Italy.

Pre-assignment

Screening details:

Patients who did not meet all the inclusion criteria or met any of the exclusion criteria were considered screening failures.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	1st Arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	Dara, Darzalex
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Daratumumab was given at a dose of 16 mg/kg and administered as an intravenous (IV) infusion at weekly intervals (QW) for 8 weeks, then every 2 weeks (Q2W) for an additional 16 weeks, then every 4 weeks (Q4W) thereafter. Dexamethasone was administered according to standard clinical practice. The recommended dose of dexamethasone was 40 mg (20 mg for patients 75 years of age) orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Number of subjects in period 1	1st Arm
Started	38
Completed	15
Not completed	23
Consent withdrawn by subject	4
Death	17
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	38	38	
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)	10	10	
From 65-84 years	26	26	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	69.6		
standard deviation	± 11.2	-	
Gender categorical Units: Subjects			
Female	29	29	
Male	9	9	
Race/Ethnicity, Customized Units: Subjects			
Greek	32	32	
Other European	4	4	
Other	2	2	
Region of Enrollment Units: Subjects			
General Hospital of Athens "ALEXANDRA"	26	26	
University Hospital of Patras	4	4	
S. Orsola Malpighi	3	3	
Evangelismos Hospital	2	2	
Theagenio" Anticancer Hospital of Thesaloniki	1	1	
AUSL Santa Maria Nuova - IRCCS - Ematologia	1	1	
LAIKO General Hospital of Athens	1	1	

Subject analysis sets	
Subject analysis set title	Intra-group
Subject analysis set type	Per protocol

Subject analysis set description:

Baseline control group.

Reporting group values	Intra-group		
Number of subjects	38		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	10		
From 65-84 years	26		
85 years and over	2		
Age continuous Units: years			
arithmetic mean	69.6		
standard deviation	± 11.2		
Gender categorical Units: Subjects			
Female	29		
Male	9		
Race/Ethnicity, Customized Units: Subjects			
Greek	32		
Other European	4		
Other	2		
Region of Enrollment Units: Subjects			
General Hospital of Athens "ALEXANDRA"	26		
University Hospital of Patras	4		
S. Orsola Malpighi	3		
Evangelismos Hospital	2		
Theagenio" Anticancer Hospital of Thesaloniki	1		
AUSL Santa Maria Nuova - IRCCS - Ematologia	1		
LAIKO General Hospital of Athens	1		

End points

End points reporting groups

Reporting group title	1st Arm
Reporting group description: -	
Subject analysis set title	Intra-group
Subject analysis set type	Per protocol
Subject analysis set description:	
Baseline control group.	

Primary: The Evaluation of Progression Free Survival (PFS) in Subjects With Relapsed or Refractory Multiple Myeloma and Renal Impairment Treated With Daratumumab and Dexamethasone.

End point title	The Evaluation of Progression Free Survival (PFS) in Subjects With Relapsed or Refractory Multiple Myeloma and Renal Impairment Treated With Daratumumab and Dexamethasone.
End point description:	
Progression free survival was defined as the time, in months, from treatment initiation (C1D1) to the date of the first documented disease progression or death due to any cause, whichever came first. Clinical deterioration was not considered progression. For patients who neither progressed nor died, the survival time was censored at the date of their last disease assessment. For patients who started a new anti-tumor treatment, survival time was censored at the date of the start of the new treatment.	
End point type	Primary
End point timeframe:	
Duration from first daratumumab administration until death or last assessment, months.	

End point values	1st Arm	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	38[1]		
Units: Months				
median (confidence interval 95%)	11.8 (2.8 to 20.8)	0 (0 to 0)		

Notes:

[1] - Intra-group used for baseline statistical analysis.

Statistical analyses

Statistical analysis title	Kaplan-Meier product-limit method
Statistical analysis description:	
All statistical analyses and generation of tables and patient data listings were performed using SAS® statistical analysis software (v. 9.4). Summary statistics based on frequency tables were used for categorical variables. For continuous variables, descriptive statistics (mean, median, standard deviation, Q1, Q3, min, and max values) were used. The Kaplan-Meier method was applied for all time-to-event analyses.	

Comparison groups	1st Arm v Intra-group

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Kaplan-Meier product-limit
Point estimate	11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	20.8

Notes:

[2] - The PFS function was estimated using the Kaplan-Meier product-limit method. Median and two-sided confidence intervals (CIs) for PFS were computed and Kaplan-Meier plots of PFS were developed.

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

Overall response rate was defined as the proportion of subjects who achieve a best response of PR or better using modified IMWG criteria as their best overall response.

End point type	Secondary

End point timeframe:

From first dose of Daratumumab until end of treatment, PD or death (approximately up to 30 months)

End point values	1st Arm	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	38[3]		
Units: percent				
number (confidence interval 95%)				
Overall Response Rate (ORR)	47.4 (31.5 to 63.2)	0 (0 to 0)		

Notes:

[3] - Intra-group used for baseline statistical analysis.

Statistical analyses

Statistical analysis title	Kaplan-Meier product-limit method

Statistical analysis description:

All statistical analyses and generation of tables and patient data listings were performed using SAS® statistical analysis software (v. 9.4). Summary statistics based on frequency tables were used for categorical variables. For continuous variables, descriptive statistics (mean, median, standard deviation, Q1, Q3, min, and max values) were used. The Kaplan-Meier method was applied for all time-to-event analyses.

Comparison groups	1st Arm v Intra-group
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Kaplan-Meier product-limit
Point estimate	47.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	31.5
upper limit	63.2

Secondary: Renal Response Rate (RRR)

End point title	Renal Response Rate (RRR)

End point description:

Renal response rate was defined as the proportion of enrolled subjects who achieve a best response of renal partial response (PRRenal) or better using the IMWG criteria.

End point type	Secondary

End point timeframe:

From first dose of Daratumumab until end of treatment, PD or death (approximately up to 30 months).

End point values	1st Arm	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	38[4]		
Units: percent				
number (confidence interval 95%)				
Renal Response Rate (RR)	18.4 (7.7 to 34.3)	0 (0 to 0)		

Notes:

[4] - Intra-group used for baseline statistical analysis.

Statistical analyses

Statistical analysis title	Kaplan-Meier product-limit method

Statistical analysis description:

All statistical analyses and generation of tables and patient data listings were performed using SAS® statistical analysis software (v. 9.4). Summary statistics based on frequency tables were used for categorical variables. For continuous variables, descriptive statistics (mean, median, standard deviation, Q1, Q3, min, and max values) were used. The Kaplan-Meier method was applied for all time-to-event analyses.

Comparison groups	1st Arm v Intra-group
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Kaplan-Meier product-limit
Point estimate	18.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	34.3

Secondary: Duration of Response in Patients With RI

End point title	Duration of Response in Patients With RI

End point description:

Duration of response was restricted to the subjects that achieve a best objective response of PR or better. It was measured from the time, in months, that the criteria for objective response were first met until the date of a progression event (according to the primary definition of PFS).

End point type	Secondary

End point timeframe:

Assessed monthly from first dose of Daratumumab until PD or death from any cause (approximately up to 30 months).

End point values	1st Arm	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18[5]	18[6]		
Units: Months				
median (confidence interval 95%)				
Duration of Response in Patient with RI	28.4 (15.1 to 100)	0 (0 to 0)		

Notes:

[5] - Upper limit not reached; please ignore value of '100', as it is only for platform validation purpose

[6] - Intra-group used for baseline statistical analysis.

Statistical analyses

Statistical analysis title	Kaplan-Meier product-limit method

Statistical analysis description:

All statistical analyses and generation of tables and patient data listings were performed using SAS® statistical analysis software (v. 9.4). Summary statistics based on frequency tables were used for categorical variables. For continuous variables, descriptive statistics (mean, median, standard deviation, Q1, Q3, min, and max values) were used. The Kaplan-Meier method was applied for all time-to-event analyses.

Comparison groups	1st Arm v Intra-group
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Kaplan-Meier product-limit
Point estimate	28.4
Confidence interval	
level	95 %
sides	1-sided
lower limit	15.1

Secondary: Time to Next Therapy

End point title	Time to Next Therapy

End point description:

Time to next therapy was defined as the time, in months, from Cycle 1 Day 1 to the date to next anti-neoplastic therapy or death from any cause, whichever comes first.

End point type	Secondary

End point timeframe:

From first dose until the date to next anti-neoplastic therapy or death from any cause, whichever comes first (approximately up to 30 months).

End point values	1st Arm	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38[7]	38[8]		
Units: Months				
median (confidence interval 95%)				
Time to Next Therapy	18.0 (5.5 to 100)	0 (0 to 0)		

Notes:

[7] - Upper limit not reached; please ignore value of '100', as it is only for platform validation purpose

[8] - Intra-group used for baseline statistical analysis.

Statistical analyses

Statistical analysis title	Kaplan-Meier product-limit method

Statistical analysis description:

All statistical analyses and generation of tables and patient data listings were performed using SAS® statistical analysis software (v. 9.4). Summary statistics based on frequency tables were used for categorical variables. For continuous variables, descriptive statistics (mean, median, standard deviation, Q1, Q3, min, and max values) were used. The Kaplan-Meier method was applied for all time-to-event analyses.

Comparison groups	1st Arm v Intra-group
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Kaplan-Meier product-limit
Point estimate	18
Confidence interval	
level	95 %
sides	1-sided
lower limit	5.5

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time, in months, from the first dose of therapy to the date of death from any cause.

End point type	Secondary

End point timeframe:

Time from first dose of study treatment to death (approximately up to 30 months).

End point values	1st Arm	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38[9]	38[10]		
Units: month				
median (confidence interval 95%)				
Overall Survival	24.5 (5.5 to 100)	0 (0 to 0)		

Notes:

[9] - Upper limit not reached; please ignore value of '100', as it is only for platform validation purpose

[10] - Intra-group used for baseline statistical analysis.

Statistical analyses

Statistical analysis title	Kaplan-Meier product-limit method

Statistical analysis description:

All statistical analyses and generation of tables and patient data listings were performed using SAS® statistical analysis software (v. 9.4). Summary statistics based on frequency tables were used for categorical variables. For continuous variables, descriptive statistics (mean, median, standard deviation, Q1, Q3, min, and max values) were used. The Kaplan-Meier method was applied for all time-to-event analyses.

Comparison groups	1st Arm v Intra-group
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Kaplan-Meier product-limit
Point estimate	24.5
Confidence interval	
level	95 %
sides	1-sided
lower limit	5.5

Secondary: To assess the safety and tolerability of daratumumab with dexamethasone in patients with refractory and relapsed multiple myeloma (RRMM) and renal impairment (RI)

End point title	To assess the safety and tolerability of daratumumab with dexamethasone in patients with refractory and relapsed multiple myeloma (RRMM) and renal impairment (RI)

End point description:

The incidence of Adverse Events and Treatment Emergent Adverse Events in patients with refractory and relapsed multiple myeloma and renal impairment treated with daratumumab with dexamethasone was assessed according to the common Terminology Criteria for Adverse Events.

End point type	Secondary

End point timeframe:

Continuously throughout the study, starting from informed consent until 30 days after last study treatment (approximately up to 30 months).

End point values	1st Arm	Intra-group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	38	38[11]		
Units: Participants				
number (not applicable)				
Any (N)SAE	34	0		
Any NSAE	32	0		
Any SAE	11	0		
Any (N)SADR related to daratumumab	7	0		
Any NSADR related to daratumumab	7	0		
Any SADR related to daratumumab	1	0		
Any (N)SAE of Grade >=3	24	0		
Any (N)SAE of Grade 3 or 4	19	0		
Any fatal SAE	7	0		

Notes:

[11] - Intra-group used for baseline statistical analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years.

Adverse event reporting additional description:

All patients who received at least one dose of study treatment were considered for data analysis. The incidence of adverse events (AEs) was tabulated by MedDRA System Organ Class (SOC) and Preferred Term (PT), overall and by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 38 (28.95%)		
number of deaths (all causes)	17		
number of deaths resulting from adverse events	7		
Investigations			
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Peritonitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 3		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 38 (84.21%)		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Surgical and medical procedures			
Carpal tunnel decompression			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	9		
Influenza like illness			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Swelling			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Oropharyngeal pain			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Psychiatric disorders			
Dysphoria			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Tension			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 2		
Atrial tachycardia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Bradycardia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Somnolence subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	11 / 38 (28.95%) 16		
Haemolytic uraemic syndrome subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Leukocytosis subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Pancytopenia subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2		
Thrombotic thrombocytopenic purpura			

subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
External ear inflammation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Gastritis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		

Bone pain			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Groin pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	2		
Hypercalcaemia			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	9		
Hyperkalaemia			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	4		
Hyperuricaemia			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	7 / 38 (18.42%)		
occurrences (all)	12		
Hypokalaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2018	To clarify the below listed sections of the protocol and align it with other protocols of daratumumab studies.
13 July 2018	To update the protocol based on Italian health authority recommendations.
09 July 2019	To update the protocol based on new guidelines regarding the risk of HBV reactivation, give clarifications regarding the subject population, and provide additional recommendations on handling daratumumab delays and toxicities.
08 June 2020	To update the protocol regarding the overall duration of the study, from 30 to 37 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: