Clinical trial results:
MEDI4736-MM-005 (FUSION MM-005): A Multicenter, Single-arm, Phase 2 Study to Determine the Efficacy of the Combination of Daratumumab (DARA) Plus Durvalumab (DURVA) (D2) in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) who have Progressed on DARA While on a DARA-containing Regimen as the Most Recent MM Therapy.

Summary

EudraCT number	2016-003801-32
Trial protocol	DE SE ES GR NL AT IT
Global end of trial date	04 December 2017

Results information

Result version number	v1 (current)
This version publication date	23 November 2018
First version publication date	23 November 2018

Trial information

Trial identification

Sponsor protocol code	MEDI4736-MM-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03000452
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 8882601599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Steven Novick, MD, Celgene Corporation, 01 (908) 6084596, snovick@celgene.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	04 December 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of daratumumab plus durvalumab (DURVA) in subjects with relapsed and refractory multiple myeloma who have progressed on daratumumab while on a daratumumab-containing regimen as the most multiple myeloma recent treatment.

Protection of trial subjects:

The study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents and informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	18
EEA total number of subjects	12

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)	9
From 65 to 84 years	9

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 sites in 4 countries including Greece, Spain, Sweden and the United States, from 03 March 2017 to 04 December 2017

Pre-assignment

Screening details:

Eligible participants included those with relapsed and refractory multiple myeloma (RRMM) who progressed on daratumumab (DARA) while on a DARA-containing regimen as the most recent multiple myeloma (MM) therapy. Participants had to have received at least 3 prior anti-myeloma therapies.

Period 1

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

Arms

Arm title	Daratumumab and Durvalumab

Arm description:

Participants received intravenous daratumumab at 16 mg/kg on the same dosing schedule (weekly, every 2 weeks, or every 4 weeks of each 28-day treatment cycle) on their last prior therapy containing daratumumab regimen. The dosing schedule for daratumumab could be adjusted during the course of the study, provided the participant had a response of stable disease or better. Participants also received IV durvalumab at 1500 mg on Day 2 of Cycle 1 and then on Day 1 of Cycles ≥ 2 of each 28-day treatment cycle. Participants could continue on study treatment until progressive disease or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Daratumumab
Investigational medicinal product code	
Other name	Darzalex
Pharmaceutical forms	Dental gel, Blood fraction modifier, Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Daratumumab by intravenous (IV) administration at 16 mg/kg on the same dosing schedule (weekly, every 2 weeks, or every 4 weeks of each 28-day treatment cycle) on their last prior therapy containing daratumumab regimen.

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	Imfinzi
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Durvalumab 1500 mg by intravenous administration on Day 2 of Cycle 1 and then on Day 1 of Cycles ≥ 2 of each 28-day treatment cycle.

Number of subjects in period 1	Daratumumab and Durvalumab
Started	18
Completed	0
Not completed	18
Adverse event, serious fatal	1
Physician decision	1
Progressive Disease (PD)	14
Miscellaneous	2

Baseline characteristics

Reporting groups	
Reporting group title	Daratumumab and Durvalumab

Reporting group description:

Participants received intravenous daratumumab at 16 mg/kg on the same dosing schedule (weekly, every 2 weeks, or every 4 weeks of each 28-day treatment cycle) on their last prior therapy containing daratumumab regimen. The dosing schedule for daratumumab could be adjusted during the course of the study, provided the participant had a response of stable disease or better. Participants also received IV durvalumab at 1500 mg on Day 2 of Cycle 1 and then on Day 1 of Cycles ≥ 2 of each 28-day treatment cycle. Participants could continue on study treatment until progressive disease or unacceptable toxicity.

Reporting group values	Daratumumab and Durvalumab	Total	
Number of subjects	18	18	
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)	9	9	
From 65-84 years	9	9	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	62.8		
standard deviation	± 11.41	-	
Sex: Female, Male Units: Subjects			
Female	11	11	
Male	7	7	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	1	1	
White	15	15	
Not Collected or Reported	2	2	
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
ECOG PS is used by physicians and researchers to assess how a subject's disease is progressing, and how the disease affects the daily living activities and determine appropriate treatment and prognosis. 0 = Fully Active, able to carry on all pre-disease performance without restriction; 1 = Restricted, in physically strenuous activity but ambulatory; 2 = Ambulatory and capable of all self-care; unable to carry out work activities. 3 = Capable of only limited self-care, confined to bed or chair >50% of waking hours 4 = Completely Disabled, cannot carry on any self-care 5 = Dead			
Units: Subjects			

0 = Fully Active	12	12	
1 = Restrictive but ambulatory	5	5	
2 = Ambulatory but unable to work	1	1	
3 = Limited Self-Care	0	0	
International Staging System Multiple Myeloma Stage at Entry			
The International Staging System divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels. Stage I: Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L); Stage II: Neither stage I or III, meaning that either: # The beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), OR # The albumin is below 3.5 while the beta-2 microglobulin is less than 3.5 Stage III: Serum beta-2 microglobulin is greater than 5.5.			
Units: Subjects			
Stage I	5	5	
Stage II	4	4	
Stage III	9	9	
Missing	0	0	
Number of Prior Regimens			
Units: Regimens			
median	4.5		
full range (min-max)	3 to 16	-	

End points

End points reporting groups

Reporting group title	Daratumumab and Durvalumab

Reporting group description:

Participants received intravenous daratumumab at 16 mg/kg on the same dosing schedule (weekly, every 2 weeks, or every 4 weeks of each 28-day treatment cycle) on their last prior therapy containing daratumumab regimen. The dosing schedule for daratumumab could be adjusted during the course of the study, provided the participant had a response of stable disease or better. Participants also received IV durvalumab at 1500 mg on Day 2 of Cycle 1 and then on Day 1 of Cycles ≥ 2 of each 28-day treatment cycle. Participants could continue on study treatment until progressive disease or unacceptable toxicity.

Primary: Numberof Participants With an Objective Response According to International Myeloma Working Group (IMWG) Uniform Response Criteria

End point title	Numberof Participants With an Objective Response According to International Myeloma Working Group (IMWG) Uniform Response Criteria[1]

End point description:

Objective response is defined as a best overall response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) based on the investigator assessment: sCR: CR and normal free light chain (FLC) ratio and no clonal cells in bone marrow; CR: Negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein and urine M-protein level < 100 mg/24 hours; PR: ≥ 50% reduction of serum M-Protein and reduction in urinary M-protein by ≥ 90% or to < 200 mg/24 hours. In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required. The population analyzed included the full analysis set (FAS), meaning all participants who enrolled in the study.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 17 April 2018. The median duration of treatment for durvalumab and daratumumab was 7.9 weeks and 8.0 weeks respectively.

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 statistical analysis was performed as no subject achieved a best response better than stable disease of the study. Following the DMC review of the data from Part 1 Stage 1 and prior to the first formal interim analysis, the sponsor decided based on DMC recommendation, to close the study as the number of responses was not reached.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Number of participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Response (TTR)

End point title	Time-to-Response (TTR)

End point description:

TTR was defined as the time from treatment initiation to the first documentation of response (PR or greater) based on IMWG criteria. sCR: CR and normal free light chain (FLC) ratio and no clonal cells in bone marrow (BM); CR: Negative serum and urine on immunofixation (IFX), disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in BM; VGPR: Serum and urine M-protein detectable by IFX but not on electrophoresis or ≥90% reduction in serum and urine M-protein levels <100 mg/24 hours; PR: ≥50% reduction of serum M-Protein and reduction in urinary M-protein by ≥90% or to <200 mg/24 hours. A ≥50% decrease in the difference between involved and uninvolved FLC levels in place of the M-protein basis or a ≥50% reduction in plasma cells in place of M-protein if baseline was ≥30%. If present at baseline a ≥50% reduction in size of soft tissue plasmacytomas. Analyses was not conducted for TTR due to no subject achieving a response better than stable disease in Stage 1 of the study.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 17 April 2018. The median duration of treatment for durvalumab and daratumumab was 7.9 weeks and 8.0 weeks respectively.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: weeks				
median (full range (min-max))	(to)			

Notes:

[2] - No subject achievied a response better than SD

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response was defined as time from the first documentation of response (PR or greater) to the first documentation of PD or death, whichever is earlier, based on the investigator assessments according to the IMWG Uniform Response Criteria. Analyses was not conducted for duration of response due to no subject achieving a response better than stable disease in Stage 1 of the study.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 17 April 2018. The median duration of treatment for durvalumab and daratumumab was 7.9 weeks and 8.0 weeks respectively.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: weeks				
median (full range (min-max))	(to)			

Notes:

[3] - No subject achieving a response better than stable disease

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression free survival was defined as the time from treatment initiation to the first documentation of PD or death from any cause during study, whichever occurred earlier. Time to event analysis for PFS and was not analyzed due to insufficient follow up time because of early termination of the trial.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 17 April 2018. The median duration of treatment for durvalumab and daratumumab was 7.9 weeks and 8.0 weeks respectively.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: weeks				
median (full range (min-max))	(to)			

Notes:

[4] - Time to event analysis for PFS and was not analyzed due to early termination

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival was defined as the time from treatment initiation to death due to any cause. Time to event analysis for overall survival was not analyzed due to insufficient follow up time because of early termination of the trial.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 17 April 2018. The median duration of treatment for durvalumab and daratumumab was 7.9 weeks and 8.0 weeks respectively.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: weeks				
median (full range (min-max))	(to)			

Notes:

[5] - Time to event analysis for overall survival was not analyzed due to early termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve from Time 0 to the Time of the Last Quantifiable Concentration Of Durvalumab

End point title	Area Under the Plasma Concentration-time Curve from Time 0 to the Time of the Last Quantifiable Concentration Of Durvalumab

End point description:

Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration, calculated by linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing. The pharmacokinetic population included participants who received at least 1 dose of study medication and had evaluable plasma PK durvalumab profiles.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were drawn on Cycle 1 on Day 2 (C1D2) pre-dose, at the end of the infusion, on Day 8 at 144 hour post dose, on Day 15 at 312 hours post dose and on Day 22 at 480 hours post C1D2 infusion.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: day*µg/L				
geometric mean (geometric coefficient of variation)	3145469.40 (± 43.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve from Time 0 to Extrapolated to Infinity (AUC-inf) of Durvalumab

End point title	Area Under the Plasma Concentration-time Curve from Time 0 to Extrapolated to Infinity (AUC-inf) of Durvalumab

End point description:

Area under the plasma concentration-time curve from time 0 extrapolated to infinity, calculated as [AUCt + Ct/ λz]. Ct is the last quantifiable concentration. No AUC extrapolation was performed with

unreliable λz. If AUC %Extrap was ≥25%, AUC inf was not reported. The pharmacokinetic population included participants who received at least 1 dose of study medication and had evaluable plasma PK durvalumab profiles.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were drawn on Cycle 1 on Day 2 (C1D2) pre-dose, at the end of the infusion, on Day 8 at 144 hour post dose, on Day 15 at 312 hours post dose and on Day 22 at 480 hours post C1D2 infusion.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: day*µg/L				
geometric mean (geometric coefficient of variation)	5634957.81 (± 86.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) Of Durvalumab

End point title	Maximum Observed Concentration (Cmax) Of Durvalumab

End point description:

Maximum observed plasma concentration, obtained directly from the observed concentration versus time data. The pharmacokinetic population included participants who received at least 1 dose of study medication and had evaluable plasma PK durvalumab profiles.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were drawn on Cycle 1 on Day 2 (C1D2) pre-dose, at the end of the infusion, on Day 8 at 144 hour post dose, on Day 15 at 312 hours post dose and on Day 22 at 480 hours post C1D2 infusion.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: µg/L				
geometric mean (geometric coefficient of variation)	349391.46 (± 32.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Concentration (Tmax) of Durvalumab

End point title	Time to Reach Maximum Concentration (Tmax) of Durvalumab

End point description:

Time to Cmax, obtained directly from the observed concentration versus time data. The pharmacokinetic population included participants who received at least 1 dose of study medication and had evaluable plasma PK durvalumab profiles.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were drawn on Cycle 1 on Day 2 (C1D2) pre-dose, at the end of the infusion, on Day 8 at 144 hour post dose, on Day 15 at 312 hours post dose and on Day 22 at 480 hours post C1D2 infusion.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: days				
median (full range (min-max))	0.0476 (0.003 to 0.058)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half-Life (T1/2) of of Durvalumab

End point title	Terminal Half-Life (T1/2) of of Durvalumab

End point description:

Terminal phase half-life in plasma, calculated as [(ln 2)/λz]. t1/2 was only calculated when a reliable estimate for λz could be obtained. The pharmacokinetic population included participants who received at least 1 dose of study medication and had evaluable plasma PK Durvalumab profiles.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were drawn on Cycle 1 on Day 2 (C1D2) pre-dose, at the end of the infusion, on Day 8 at 144 hour post dose, on Day 15 at 312 hours post dose and on Day 22 at 480 hours post C1D2 infusion.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: days				
geometric mean (geometric coefficient of variation)	15.71 (± 75.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Clearance (CL/F) of of Durvalumab

End point title	Apparent Total Clearance (CL/F) of of Durvalumab

End point description:

Apparent total clearance, calculated as [Dose/AUCinf]. The pharmacokinetic population included participants who received at least 1 dose of study medication and had evaluable plasma PK Durvalumab profiles.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were drawn on Cycle 1 on Day 2 (C1D2) pre-dose, at the end of the infusion, on Day 8 at 144 hour post dose, on Day 15 at 312 hours post dose and on Day 22 at 480 hours post C1D2 infusion.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: L/day				
geometric mean (geometric coefficient of variation)	0.27 (± 86.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F) of Durvalumab

End point title	Apparent Volume of Distribution (Vz/F) of Durvalumab

End point description:

Apparent volume of distribution, calculated as [(CL/F)/λz]. The pharmacokinetic population included participants who received at least 1 dose of study medication and had evaluable plasma PK Durvalumab profiles.

End point type	Secondary

End point timeframe:

Pharmacokinetic samples were drawn on Cycle 1 on Day 2 (C1D2) pre-dose, at the end of the infusion, on Day 8 at 144 hour post dose, on Day 15 at 312 hours post dose and on Day 22 at 480 hours post C1D2 infusion.

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Liters				
geometric mean (geometric coefficient of variation)	5.48 (± 25.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Participants with Treatment-Emergent Adverse Events (TEAEs)

End point description:

TEAEs include AEs between the earliest of the first dose date of either study drug and 90 days after the last dose of either study drug. In addition, an AE that occurred beyond the timeframe and was assessed by the doctor as possibly related to IP was considered to be treatment-emergent. Severity was assessed using National Cancer Institute Common Toxicity Terminology Criteria for AEs (NCI CTCAE) version 4.03, where 1= Mild; 2= Moderate; 3= Severe; 4= Life-threatening; 5= Death related to AE. Serious AEs resulted in death, were life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability/incapacity, congenital anomaly, or resulted in a medical event that may have jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes above. The safety population consisted of all participants who received at least one dose of Durvalumab (Durva) or Daratumumab (Dara

End point type	Secondary

End point timeframe:

From the date of the first dose of study drug until 90 days after the last dose of durvalumab or daratumumab , whichever is later. Maximum overall time on treatment was 16 weeks for daratumumab and durvalumab

End point values	Daratumumab and Durvalumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: participants				
TEAE|	18			
TEAE Related to Durva|	1			
TEAE Related to Dara|	4			
TEAE Related to Durva or Dara|	4			
TEAE with CTCAE Grade (Gr) 3-4|	11			
TEAE with CTCAE Grade 3-4 Related to Durva|	1			
TEAE with CTCAE Grade 3-4 Related to Dara|	2			

TEAE with CTCAE Gr 3-4 Related to Durva or Dara|	2			
TEAE with CTCAE Grade 5|	4			
TEAE with CTCAE Grade 5 Related to Durva|	0			
TEAE with CTCAE Grade 5 Related to Dara|	0			
TEAE with CTCAE Gr 5 Related to Durva or Dara|	0			
Serious AE|	7			
Serious AE Related to Durva|	0			
Serious AE Related to Dara|	0			
Serious AE Related to Durva or Dara|	0			
TEAE leading to Interruption of Durva|	1			
TEAE leading to Interruption of Dara|	1			
TEAE leading to Interruption of Durva or Dara|	1			
TEAE interruption of Durva-without infusion delay|	1			
TEAE interruption of Dara-without infusion delay|	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of the first dose of study drug until 90 days after the last dose of durvalumab or daratumumab , whichever is later. Maximum overall time on treatment was 16 weeks for daratumumab and durvalumab

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	V20.0

Reporting groups

Reporting group title	Daratumab and Durvalumab

Reporting group description:

Participants received intravenous daratumumab at 16 mg/kg on the same dosing schedule (weekly, every 2 weeks, or every 4 weeks of each 28-day treatment cycle) on their last prior therapy containing daratumumab regimen. The dosing schedule for daratumumab could be adjusted during the course of the study, provided the participant had a response of stable disease or better. Participants also received IV durvalumab at 1500 mg on Day 2 of Cycle 1 and then on Day 1 of Cycles ≥ 2 of each 28-day treatment cycle. Participants could continue on study treatment until progressive disease or unacceptable toxicity.

Serious adverse events	Daratumab and Durvalumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 18 (38.89%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	4 / 18 (22.22%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 4		
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 18 (5.56%)		
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 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)		
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	Daratumab and Durvalumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

Fatigue subjects affected / exposed occurrences (all)	9 / 18 (50.00%) 13		
General physical health deterioration subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Localised oedema subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Pyrexia subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3		
Respiratory, thoracic and mediastinal disorders			
Catarrh subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Cough subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3		
Dyspnoea exertional subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Epistaxis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Psychiatric disorders			

Depression			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Disorientation			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Amylase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood fibrinogen decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	6 / 18 (33.33%)		
occurrences (all)	8		
Lipase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Nervous system disorders			

Neuralgia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Tremor subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Somnolence subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	12 / 18 (66.67%) 28		
Lymphopenia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Neutropenia subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 6		
Thrombocytopenia subjects affected / exposed occurrences (all)	7 / 18 (38.89%) 12		
Eye disorders Cataract subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 2		
Constipation subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nausea subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Vomiting			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Acute kidney injury			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	5		
Muscle spasms			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Pathological fracture			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Infections and infestations			

Herpes zoster			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	3		
Hypercalcaemia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Hyperuricaemia			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 September 2017	Study MEDI4736-MM-005 was placed on Partial Clinical Hold. As a result of the Partial Clinical Hold no further enrollment into the study was allowed and only subjects who were receiving clinical benefit, based on the discretion of the Investigator, could remain on study treatment after being re-consented.	-

Notes:

Limitations and caveats

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

An independent DMC reviewed data from Part 1 Stage 1 of the study on 26 Oct 2017; based on their recommendations, Celgene decided to close the study due to unfavorable efficacy results (number of responses to move to Stage 2 was not reached).

Notes: