Clinical trial results:
A Phase II Open-Label, Multi-Center Study of MEDI4736 Evaluated as Single Agent or in Combination with Tremelimumab in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

Summary

EudraCT number	2015-002001-11
Trial protocol	NL DE
Global end of trial date	15 June 2017

Results information

Result version number	v1 (current)
This version publication date	13 June 2018
First version publication date	13 June 2018

Trial information

Trial identification

Sponsor protocol code	D4198C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02558894
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One Medimmune Way, Gaithersburg, United States, MD 20878
Public contact	Global Clinical Lead, AstraZeneca, 1 3013980000, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, 1 3013980000, ClinicalTrialTransparency@astrazeneca.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	15 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2017
Global end of trial reached?	Yes
Global end of trial date	15 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of durvalumab (MEDI4736) monotherapy and durvalumab (MEDI4736) + tremelimumab combination therapy in terms of Objective Response Rate (ORR).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Korea, Republic of: 24
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	65
EEA total number of subjects	17

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)	40
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 16 Nov 2015; Part A data cut-off: 26 May 2017. The study contained a Part B which was not opened; only Part A was conducted.
Study performed at 21 sites in 6 countries.

Pre-assignment

Screening details:

95 patients were enrolled (signed informed consent), 65 were randomised to receive investigational product (IP), of whom 64 received treatment.

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	Durvalumab (MEDI4736) plus tremelimumab

Arm description:

Patients in the durvalumab (MEDI4736) plus tremelimumab combination therapy arm received 1.5 grams (g) durvalumab and 75 milligrams (mg) tremelimumab via intravenous (IV) infusion every 4 weeks (q4w) over a 16-week treatment period. Patients then continued with durvalumab monotherapy at 1.5 g q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy, up to a total of 9 additional doses, with the final dose at Week 48.

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	MEDI4736
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 1.5 g durvalumab via IV infusion q4w (up to 13 doses) administered as a 50 mg per millilitre (mg/mL) solution.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 75 mg tremelimumab via IV infusion q4w (up to 4 doses) administered as a 20 mg/mL solution.

Arm title	Durvalumab (MEDI4736) monotherapy

Arm description:

Patients in the durvalumab (MEDI4736) monotherapy arm received 1.5 g durvalumab via IV infusion q4w over a 48-week treatment period (up to 13 doses).

Arm type	Experimental

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	MEDI4736
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received 1.5 g durvalumab via IV infusion q4w (up to 13 doses) administered as a 50 mg/mL solution.

Number of subjects in period 1	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy
Started	32	33
Completed	0	0
Not completed	32	33
Consent withdrawn by subject	2	1
Death	28	31
Closure of Part A	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Durvalumab (MEDI4736) plus tremelimumab
Reporting group description:	
Patients in the durvalumab (MEDI4736) plus tremelimumab combination therapy arm received 1.5 grams (g) durvalumab and 75 milligrams (mg) tremelimumab via intravenous (IV) infusion every 4 weeks (q4w) over a 16-week treatment period. Patients then continued with durvalumab monotherapy at 1.5 g q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy, up to a total of 9 additional doses, with the final dose at Week 48.	
Reporting group title	Durvalumab (MEDI4736) monotherapy
Reporting group description:	
Patients in the durvalumab (MEDI4736) monotherapy arm received 1.5 g durvalumab via IV infusion q4w over a 48-week treatment period (up to 13 doses).	

Reporting group values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy	Total
Number of subjects	32	33	65
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational 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
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	21	19	40
From 65-84 years	11	14	25
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	61.3	61.6	
standard deviation	± 9.60	± 9.54	-
Sex: Female, Male Units: Subjects			
Female	17	14	31
Male	15	19	34
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	15	10	25
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	17	22	39
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	2	0	2
Not Hispanic or Latino	30	33	63
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Durvalumab (MEDI4736) plus tremelimumab

Reporting group description:

Patients in the durvalumab (MEDI4736) plus tremelimumab combination therapy arm received 1.5 grams (g) durvalumab and 75 milligrams (mg) tremelimumab via intravenous (IV) infusion every 4 weeks (q4w) over a 16-week treatment period. Patients then continued with durvalumab monotherapy at 1.5 g q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy, up to a total of 9 additional doses, with the final dose at Week 48.

Reporting group title	Durvalumab (MEDI4736) monotherapy

Reporting group description:

Patients in the durvalumab (MEDI4736) monotherapy arm received 1.5 g durvalumab via IV infusion q4w over a 48-week treatment period (up to 13 doses).

Primary: Objective Response Rate (ORR) in all patients using Investigator assessments according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

End point title	Objective Response Rate (ORR) in all patients using Investigator assessments according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)[1]

End point description:

ORR was defined as percentage of patients with at least 1 visit response of confirmed complete response (CR) or partial response (PR). CR defined as disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have had reduction in short axis to <10 millimeters (mm). PR defined as at least a 30% decrease in sum of diameters of TLs, taking as reference the baseline sum of diameters. A confirmed response meant a response of CR/PR recorded at 1 visit and confirmed by repeat imaging, preferably at next regularly scheduled imaging visit and not less than 4 weeks after visit when response was first observed with no evidence of progression between initial and CR/PR confirmation visits. Results reported as percentage of patients with confirmed response and percentage of patients with confirmed or unconfirmed responses (i.e., including single visit responses). Analysis performed on full analysis set (FAS), comprising all randomised patients.

End point type	Primary

End point timeframe:

From date of first infusion until confirmed disease progression or death (up to approximately 18 months for the data analysis cut-off)

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: Only descriptive analysis was planned and performed for analysis of the primary end point

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Percentage of participants				
number (confidence interval 95%)				
Confirmed responses only	3.1 (0.08 to 16.22)	0 (0 to 10.58)		
Confirmed and unconfirmed responses	3.1 (0.08 to 16.22)	6.1 (0.74 to 20.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) using Investigator assessments according to RECIST 1.1

End point title	Progression-free survival (PFS) using Investigator assessments according to RECIST 1.1

End point description:

PFS was defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient had withdrawn from randomised therapy or had received another anti-cancer therapy prior to progression. Results reported as median time from randomisation to PFS, calculated using the Kaplan-Meier technique. Analysis performed on FAS, comprising all randomised patients.

End point type	Secondary

End point timeframe:

From date of first infusion until confirmed disease progression or death (up to approximately 18 months for the data analysis cut-off)

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Months				
median (confidence interval 95%)	1.5 (1.2 to 1.5)	1.5 (1.3 to 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS rate at 3 months and at 6 months

End point title	PFS rate at 3 months and at 6 months

End point description:

PFS was defined as the time from the date of randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient had withdrawn from randomised therapy or had received another anti-cancer therapy prior to progression. PFS rates were calculated using Kaplan-Meier estimates of the cumulative probability of PFS. The PFS rate at 3 months and 6 months was equivalent to the percentage of patients with PFS after 3 months and 6 months, respectively. Analysis performed on FAS, comprising all randomised patients.

End point type	Secondary

End point timeframe:

From date of first infusion until confirmed disease progression or death (up to 3 months and 6 months)

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Percentage of participants				
number (confidence interval 95%)				
PFS rate at 3 months	9.4 (2.4 to 22.3)	10.9 (3.0 to 24.7)		
PFS rate at 6 months	9.4 (2.4 to 22.3)	3.6 (0.3 to 15.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomisation until death due to any cause. Results reported as median OS, calculated using the Kaplan-Meier technique. Analysis performed on FAS, comprising all randomised patients.

End point type	Secondary

End point timeframe:

From date of first infusion until death (up to approximately 18 months for the data analysis cut-off)

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Months				
median (confidence interval 95%)	3.1 (2.2 to 6.1)	3.6 (2.7 to 6.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Survival status, presented as OS rate, at 6 months and at 12 months

End point title	Survival status, presented as OS rate, at 6 months and at 12 months

End point description:

OS was defined as the time from the date of randomisation until death due to any cause. OS rates were calculated using Kaplan-Meier estimates of the cumulative probability of survival at each indicated time period. The OS rate at 6 months and 12 months was equivalent to the percentage of patients with OS after 6 months and 12 months, respectively. Analysis performed on FAS, comprising all randomised patients.

End point type	Secondary

End point timeframe:

From date of first infusion until death (up to 6 months and 12 months)

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Percentage of participants				
number (confidence interval 95%)				
Survival rate at 6 months	36.2 (20.0 to 52.7)	34.9 (19.2 to 51.1)		
Survival rate at 12 months	8.8 (1.8 to 22.8)	6.3 (1.1 to 18.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Objective Response (BoR) using Investigator assessments according to RECIST 1.1

End point title	Best Objective Response (BoR) using Investigator assessments according to RECIST 1.1

End point description:

BoR was based on the overall visit responses from each RECIST assessment. It was best response a patient had following date of first dosing but prior to starting any subsequent cancer therapy and prior to RECIST progression or last evaluable assessment in absence of RECIST progression. Categorisation of BoR was based on RECIST using the following response categories: CR and PR for status of 'Response'; Stable Disease (SD) ≥6 weeks, Progressive Disease (PD) and Not Evaluable (NE) for status of 'Non-response'. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. PD was defined as at least 20% increase in sum of diameters of TLs taking as reference the smallest sum on study. NE was only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Results reported as number of patients with BoR for each of indicated categories. Analysis performed on FAS, comprising all randomised patients.

End point type	Secondary

End point timeframe:

From date of first infusion until confirmed disease progression or death (up to approximately 18 months for the data analysis cut-off)

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Participants				
Response: Total	1	0		
Response: CR	0	0		
Response: PR	1	0		
Non-response: Total	31	33		
Non-response: Stable disease ≥6 weeks	5	7		
Non-response: Progression of disease	26	25		
Non-response: Not evaluable	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) using Investigator assessments according to RECIST 1.1

End point title	Disease control rate (DCR) using Investigator assessments according to RECIST 1.1

End point description:

DCR at 3 months was defined as the percentage of patients who have a BoR of CR or PR in the first 3 months or who have demonstrated SD for a minimum interval of 13 weeks following the start of treatment. DCR at 6 months was defined as the percentage of patients who have a BoR of CR or PR in the first 6 months or who have demonstrated SD for a minimum interval of 26 weeks following the start of treatment. DCR at 12 months was defined as the percentage of patients who have a BoR of CR or PR in the first 12 months or who have demonstrated SD for a minimum interval of 52 weeks following the start of treatment. Results reported as the percentage of patients with disease control for each of the indicated categories. Analysis performed on FAS, comprising all randomised patients.

End point type	Secondary

End point timeframe:

From date of first infusion until confirmed disease progression or death (up to 3 months, 6 months and 12 months)

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: Percentage of participants				
number (confidence interval 95%)				
At 3 months	9.4 (1.98 to 25.02)	6.1 (0.74 to 20.23)		
At 6 months	6.3 (0.77 to 20.81)	0 (0.00 to 10.58)		
At 12 months	3.1 (0.08 to 16.22)	0 (0.00 to 10.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of durvalumab (MEDI4736)

End point title	Pharmacokinetics (PK) of durvalumab (MEDI4736)

End point description:

To evaluate PK, blood samples were collected pre- and post-dose and durvalumab (MEDI4736) concentrations in serum were determined. On Day 1 of Cycles 1, 4 and 7 (Weeks 0, 12 and 24), PK samples were collected pre-dose (within 60 minutes prior to treatment with any IP) and post-dose at end of infusion (within 10 minutes of end of infusion of durvalumab and within 10 minutes of end of infusion of tremelimumab [for patients receiving durvalumab + tremelimumab]). On Day 1 of Cycle 2 (Week 4), PK samples were collected pre-dose (within 60 minutes prior to treatment with any IP) only. The 3-month follow-up sample for durvalumab was relative to the respective last dose. Results reported as mean pre- and post-dose durvalumab concentrations as indicated by the individual categories (1 cycle=4 weeks). Samples below lower limit of quantification were treated as missing in the analyses. The PK analysis set included all patients receiving at least 1 dose of IP who had evaluable PK data post-dose.

End point type	Secondary

End point timeframe:

Blood samples were collected pre-dose on Day 1 (Week 0), Week 4, Week 12 and Week 24, post-dose on Day 1, Week 12 and Week 24, and additionally at 3 months after the last dose (follow-up).

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32[2]	32[3]		
Units: Micrograms per mL (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1, Day 1, pre-infusion (Day 1) (n=3, 0)	217.338 (± 345.4913)	99999999 (± 99999999)		
Cycle 1, Day 1, post-infusion (Day 1) (n=31,31)	566.078 (± 151.4199)	562.218 (± 152.3811)		
Cycle 2, Day 1, pre-infusion (Day 29) (n=22, 21)	100.417 (± 39.7229)	98.668 (± 36.5072)		
Cycle 4, Day 1, pre-infusion (Day 85) (n=6, 6)	236.205 (± 98.8964)	228.450 (± 36.8395)		
Cycle 4, Day 1, post-infusion (Day 85) (n=5,6)	825.818 (± 322.8247)	760.456 (± 100.6974)		
Cycle 7, Day 1, pre-infusion (Day 169) (n=3, 1)	166.736 (± 47.3872)	152.706 (± 99999999)		
Cycle 7, Day 1, post-infusion (Day169) (n=3, 1)	918.270 (± 98.4286)	825.578 (± 99999999)		
3-month follow-up (n=1, 4)	38.456 (± 99999999)	19.684 (± 20.2664)		

Notes:

[2] - 99999999 denotes that the value was not calculable.

[3] - 99999999 denotes that the value was not calculable.

Statistical analyses

No statistical analyses for this end point

Secondary: PK of tremelimumab

End point title	PK of tremelimumab[4]

End point description:

To evaluate PK, blood samples were collected pre- and post-dose and tremelimumab concentrations in serum were determined. On Day 1 of Cycles 1 and 4 (Weeks 0 and 12), PK samples were collected pre-dose (within 60 minutes prior to treatment with any IP) and post-dose at the end of infusion (within 10 minutes of end of infusion of tremelimumab). On Day 1 of Cycle 2 (Week 4), PK samples were collected pre-dose (within 60 minutes prior to treatment with any IP) only. Results are reported as mean pre- and post-dose tremelimumab concentrations as indicated by the individual categories (1 cycle=4 weeks). Samples below lower limit of quantification were treated as missing in the analyses. The PK analysis set included all patients receiving at least 1 dose of IP who had evaluable PK data post-dose.

End point type	Secondary

End point timeframe:

Blood samples were collected pre-dose on Day 1 (Week 0), Week 4 and Week 12, post-dose on Day 1 and Week 12, and additionally at 3 months after the last dose (follow-up).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point is reporting PK data for tremelimumab and therefore reporting results for the durvalumab (MEDI4736) monotherapy arm is not applicable

End point values	Durvalumab (MEDI4736) plus tremelimumab			
Subject group type	Reporting group			
Number of subjects analysed	32[5]			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1, Day 1, pre-infusion (Day 1) (n=2)	13.114 (± 11.7182)			
Cycle 1, Day 1, post-infusion (Day 1) (n=30)	24.477 (± 6.3516)			
Cycle 2, Day 1, pre-infusion (Day 29) (n=23)	4.880 (± 2.2623)			
Cycle 4, Day 1, pre-infusion (Day 85) (n=6)	8.753 (± 4.9962)			
Cycle 4, Day 1, post-infusion (Day 85) (n=6)	21.150 (± 5.8997)			
3-month follow-up (n=0)	99999999 (± 99999999)			

Notes:

[5] - 99999999 denotes that the value was not calculable.

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of antidrug antibodies (ADAs) for durvalumab (MEDI4736)

End point title	Presence of antidrug antibodies (ADAs) for durvalumab (MEDI4736)

End point description:

ADA prevalence was the proportion of the ADA evaluable set who had an ADA positive result at any point in time, baseline or post-baseline. ADA incidence (treatment-emergent ADA) was the sum of both treatment-induced (post-baseline ADA positive only) and treatment-boosted ADA positive patients as a proportion of the evaluable patient population. Treatment-boosted ADA was defined as baseline positive ADA titre boosted to a 4-fold or higher level following IP administration. Persistently positive was defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment. Transiently positive was defined as at least 1 post-baseline ADA positive assessment and not fulfilling the conditions of persistently positive. Results reported as number of patients with detectable anti-durvalumab antibodies satisfying each of the indicated categories. Note: 'positive' is denoted by 'pos' in some category titles.

End point type	Secondary

End point timeframe:

Immunogenicity samples were collected on Day 1 (Week 0), Week 4, Week 12 and Week 24, and additionally at 3 months and 6 months after the last dose (follow-up).

End point values	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: Participants				
ADA prevalence	1	5		
ADA incidence	0	3		
ADA pos post-baseline & pos at baseline	0	0		
ADA pos post-baseline & not detected at baseline	0	3		
ADA not detected post-baseline & pos at baseline	1	2		
Treatment-boosted ADA	0	0		
Persistent positive	0	3		
Transient positive	0	0		
Never positive	24	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of ADAs for tremelimumab

End point title	Presence of ADAs for tremelimumab[6]

End point description:

ADA prevalence was the proportion of the ADA evaluable set who had an ADA positive result at any point in time, baseline or post-baseline. ADA incidence (treatment-emergent ADA) was the sum of both treatment-induced (post-baseline ADA positive only) and treatment-boosted ADA positive patients as a proportion of the evaluable patient population. Treatment-boosted ADA was defined as baseline positive

ADA titre boosted to a 4-fold or higher level following IP administration. Persistently positive was defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment. Transiently positive was defined as at least 1 post-baseline ADA positive assessment and not fulfilling the conditions of persistently positive. Results reported as number of patients with detectable anti- tremelimumab antibodies satisfying each of the indicated categories. Note: 'positive' is denoted by 'pos' in some category titles.

End point type	Secondary

End point timeframe:

Immunogenicity samples were collected on Day 1 (Week 0), Week 4 and Week 12, and additionally at 3 months and 6 months after the last dose (follow-up).

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point is reporting immunogenicty data for tremelimumab and therefore reporting results for the durvalumab (MEDI4736) monotherapy arm is not applicable

End point values	Durvalumab (MEDI4736) plus tremelimumab			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
ADA prevalence	2			
ADA incidence	0			
ADA pos post-baseline & pos at baseline	1			
ADA pos post-baseline & not detected at baseline	0			
ADA not detected post-baseline & pos at baseline	1			
Treatment-boosted ADA	0			
Persistent positive	0			
Transient positive	1			
Never positive	23			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event (AE) data is reported for the treatment period (up to 12 months) + follow-up (up to 90 days). Overall timeframe: up to approximately 15 months.

Adverse event reporting additional description:

Treatment-emergent AEs were defined with an onset date on or after date of first dose or pre-treatment AEs that increased in severity on or after date of first dose up to and including 90 days following date of last dose of study treatment or up to and including date of initiation of the first subsequent therapy (whichever occurred first).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Durvalumab (MEDI4736) plus tremelimumab

Reporting group description:

Patients in the durvalumab (MEDI4736) plus tremelimumab combination therapy arm received 1.5 g durvalumab and 75 mg tremelimumab via IV infusion q4w over a 16-week treatment period. Patients then continued with durvalumab monotherapy at 1.5 g q4w, beginning at Week 16, 4 weeks after the last dose of combination therapy, up to a total of 9 additional doses, with the final dose at Week 48.

Reporting group title	Durvalumab (MEDI4736) monotherapy

Reporting group description:

Patients in the durvalumab (MEDI4736) monotherapy arm received 1.5 g durvalumab via IV infusion q4w over a 48-week treatment period (up to 13 doses).

Serious adverse events	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 32 (34.38%)	9 / 32 (28.13%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematochezia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Durvalumab (MEDI4736) plus tremelimumab	Durvalumab (MEDI4736) monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 32 (81.25%)	26 / 32 (81.25%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	3 / 32 (9.38%)	3 / 32 (9.38%)	
occurrences (all)	5	6	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 32 (9.38%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Hypotension			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 32 (9.38%)	4 / 32 (12.50%)	
occurrences (all)	3	4	
Fatigue			
subjects affected / exposed	6 / 32 (18.75%)	9 / 32 (28.13%)	
occurrences (all)	6	10	
Feeling cold			
subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	2 / 32 (6.25%)	3 / 32 (9.38%)	
occurrences (all)	2	3	
Pyrexia			

subjects affected / exposed	6 / 32 (18.75%)	2 / 32 (6.25%)	
occurrences (all)	10	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 32 (9.38%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	3 / 32 (9.38%)	4 / 32 (12.50%)	
occurrences (all)	3	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Confusional state			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	2 / 32 (6.25%)	3 / 32 (9.38%)	
occurrences (all)	2	3	
Investigations			
Weight decreased			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 32 (9.38%)	2 / 32 (6.25%)	
occurrences (all)	4	2	
Ascites			

subjects affected / exposed	0 / 32 (0.00%)	3 / 32 (9.38%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	5 / 32 (15.63%)	7 / 32 (21.88%)	
occurrences (all)	5	7	
Diarrhoea			
subjects affected / exposed	4 / 32 (12.50%)	5 / 32 (15.63%)	
occurrences (all)	6	7	
Dry mouth			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	6 / 32 (18.75%)	2 / 32 (6.25%)	
occurrences (all)	6	2	
Flatulence			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	4 / 32 (12.50%)	5 / 32 (15.63%)	
occurrences (all)	5	6	
Vomiting			
subjects affected / exposed	5 / 32 (15.63%)	5 / 32 (15.63%)	
occurrences (all)	6	7	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 32 (3.13%)	2 / 32 (6.25%)	
occurrences (all)	1	2	
Nail ridging			

subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	4 / 32 (12.50%)	3 / 32 (9.38%)	
occurrences (all)	4	4	
Rash			
subjects affected / exposed	1 / 32 (3.13%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Rash maculo-papular			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 32 (12.50%)	0 / 32 (0.00%)	
occurrences (all)	4	0	
Thyroiditis			
subjects affected / exposed	2 / 32 (6.25%)	0 / 32 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 32 (6.25%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Myalgia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Infections and infestations			
Gingivitis			
subjects affected / exposed	2 / 32 (6.25%)	2 / 32 (6.25%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 32 (25.00%)	8 / 32 (25.00%)	
occurrences (all)	8	9	

Hypophagia subjects affected / exposed occurrences (all)	3 / 32 (9.38%) 3	0 / 32 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2015	• Following comments received from the US Food and Drug Administration, Substudies 1 and 2 were removed from the Clinical Study Protocol; the inclusion criterion that allows patients with Gilbert syndrome to enrol in the study was clarified; and it was clarified that a protocol amendment was be submitted once Part B of the study had been established. • Pregnancy testing was added to the schedule of assessments to require a pregnancy test before first dose of IP was administered. • The exclusion criteria were updated to add a weight criterion and clarify the criteria about tuberculosis and allergy or hypersensitivities to IP formulations or to other human monoclonal antibodies. • A definition of adverse event of special interest was added. • The list of prohibited medications/class of drug was updated.

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.

Study consisted of Part A Lead-in and 2 possible options for Part B: non-randomised expansion or randomised controlled trial. Criteria to open either option for Part B were not met and study was closed prematurely. Only Part A was conducted.

Notes: