



Clinical trial results:

A Phase Ib and II Open-Label, Multi-Center Study of MEDI4736 Evaluated in Different Combinations in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

Summary

EudraCT number	2015-003639-37
Trial protocol	GB
Global end of trial date	09 July 2018

Results information

Result version number	v1 (current)
This version publication date	30 May 2019
First version publication date	30 May 2019

Trial information

Trial identification

Sponsor protocol code	D4198C00003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02583477
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	35 Gatehouse Drive, Waltham, Massachusetts, United States, 02451
Public contact	Global Clinical Lead, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 302 885 1180, 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	09 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Cohort 1: To assess the safety and tolerability of MEDI4736 in combination with nab-paclitaxel + gemcitabine.

Cohort 2: To assess the safety, tolerability and objective response rate (ORR) for MEDI4736 + AZD5069 in combination.

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 Conference on 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	25 March 2016
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	United Kingdom: 24
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	27
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	7

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

This study consisted of 2 independent cohorts, each of which ran at separate times between 25 March 2016 and 09 July 2018. In Cohort 1, participants were recruited from 1 center in the United States; in Cohort 2, participants were recruited from 6 centers in the United Kingdom.

Pre-assignment

Screening details:

Participants underwent screening evaluations to determine eligibility within 4 weeks (28 days) prior to first administration of the Investigational Product (IP). A total of 27 participants (3 participants in Cohort 1 and 24 participants in Cohort 2) were enrolled into the study, of which 23 participants received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)

Arm description:

Participants with metastatic pancreatic ductal adenocarcinoma (PDAC) who were treatment naive received MEDI4736 1.5 gram (g) intravenous (IV) infusion on Day 1 of each 28-day cycle (q4w). Participants also received nab-paclitaxel 125 milligram per meter square (mg/m²) IV infusion followed by gemcitabine 1000 mg/m² IV infusion on Days 1, 8, and 15 of each 28-day cycle. Treatment continued until either confirmed progressive disease (PD) unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

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

Dosage and administration details:

MEDI4736 1.5 g IV infusion on Day 1 of each 28-day cycle.

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

Dosage and administration details:

Nab-paclitaxel 125 mg/m² IV infusion over 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

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

Dosage and administration details:

Gemcitabine 1000 mg/m² IV infusion over 30 minutes immediately after the completion of nab-paclitaxel administration on Days 1, 8, and 15 of each 28-day cycle.

Arm title	Cohort 2 (MEDI4736 + AZD5069)
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Arm description:

Participants with metastatic PDAC with progression on the indicated types of chemotherapy received MEDI4736 1.5 g IV infusion q4w. Participants also received AZD5069 orally twice daily (bid). The starting dose of 80 mg orally bid (with dose reductions to 40 mg or 20 mg for toxicity allowable). Treatment continued until either confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Arm type	Experimental
Investigational medicinal product name	AZD5069
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A starting dose of 80 mg orally bid (with dose reductions to 40 mg bid or 20 mg bid for toxicity allowable) in the morning and evening. AZD5069 was provided as 40 mg and 10 mg tablets.

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

Dosage and administration details:

MEDI4736 1.5 g IV infusion on Day 1 of each 28-day cycle.

Number of subjects in period 1	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)	Cohort 2 (MEDI4736 + AZD5069)
Started	3	24
Received treatment	3	20
Completed treatment	0	0
Completed	0	0
Not completed	3	24
Study terminated	2	2
Adverse event, non-fatal	-	2
Death	1	16
Did not receive treatment	-	4

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)
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Reporting group description:

Participants with metastatic pancreatic ductal adenocarcinoma (PDAC) who were treatment naive received MEDI4736 1.5 gram (g) intravenous (IV) infusion on Day 1 of each 28-day cycle (q4w). Participants also received nab-paclitaxel 125 milligram per meter square (mg/m²) IV infusion followed by gemcitabine 1000 mg/m² IV infusion on Days 1, 8, and 15 of each 28-day cycle. Treatment continued until either confirmed progressive disease (PD) unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Reporting group title	Cohort 2 (MEDI4736 + AZD5069)
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Reporting group description:

Participants with metastatic PDAC with progression on the indicated types of chemotherapy received MEDI4736 1.5 g IV infusion q4w. Participants also received AZD5069 orally twice daily (bid). The starting dose of 80 mg orally bid (with dose reductions to 40 mg or 20 mg for toxicity allowable). Treatment continued until either confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Reporting group values	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)	Cohort 2 (MEDI4736 + AZD5069)	Total
Number of subjects	3	24	27
Age, Customized Units: Subjects			
<50 years	0	4	4
>=50 - <65 years	1	15	16
>=65 - <75 years	2	5	7
Sex: Female, Male Units: Subjects			
Female	2	10	12
Male	1	14	15
Race/Ethnicity, Customized Units: Subjects			
Asian	0	2	2
White	3	21	24
Other	0	1	1

End points

End points reporting groups

Reporting group title	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)
Reporting group description: Participants with metastatic pancreatic ductal adenocarcinoma (PDAC) who were treatment naive received MEDI4736 1.5 gram (g) intravenous (IV) infusion on Day 1 of each 28-day cycle (q4w). Participants also received nab-paclitaxel 125 milligram per meter square (mg/m ²) IV infusion followed by gemcitabine 1000 mg/m ² IV infusion on Days 1, 8, and 15 of each 28-day cycle. Treatment continued until either confirmed progressive disease (PD) unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.	
Reporting group title	Cohort 2 (MEDI4736 + AZD5069)
Reporting group description: Participants with metastatic PDAC with progression on the indicated types of chemotherapy received MEDI4736 1.5 g IV infusion q4w. Participants also received AZD5069 orally twice daily (bid). The starting dose of 80 mg orally bid (with dose reductions to 40 mg or 20 mg for toxicity allowable). Treatment continued until either confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.	

Primary: Number of Participants With Dose-Limiting Toxicities (DLT)

End point title	Number of Participants With Dose-Limiting Toxicities (DLT) ^[1]
End point description:	
DLT period was defined as first treatment cycle for Cohort 1, and first dose of AZD5069 and MEDI4736 to end of Cycle 1 or until a participant experienced a DLT, whichever occurs first for Cohort 2. A DLT was any of below listed laboratory abnormalities or adverse events (AE) related to MEDI4736 during DLT period. •Liver transaminase elevation $\geq 5\times$ but $\leq 8\times$ upper limit of normal (ULN) that doesn't resolve to Grade 2 within 5 days •Transaminase elevation $> 8\times$ ULN or total bilirubin $> 5\times$ ULN •Any Grade 4 immune-related AE (irAE) not attributed to local tumor response, Grade ≥ 3 colitis, Grade ≥ 2 pneumonitis that doesn't resolve to \leq Grade 1 within 7 days, Grade 3 irAE, that doesn't resolve to Grade ≤ 1 or baseline status within 14 days •Any Grade ≥ 3 non-irAE toxicity that doesn't resolve to Grade ≤ 1 or baseline status within 14 days. A DLT was any Grade 3 or worse AE related to AZD5069 that occurs from first dose of AZD5069 up to end of DLT period. The DLT evaluable set analysed.	
End point type	Primary
End point timeframe:	
Cohort 1: From time of first dose of MEDI4736 on Day 1 up to Day 28 of Cycle 1 and Cohort 2: From time of first dose of AZD5069 and MEDI4736 on Day 1 up to Day 28 of Cycle 1 or until a participant experiences a DLT, whichever occurs first.	
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: Descriptive statistical analysis was performed for the outcome measure.	

End point values	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)	Cohort 2 (MEDI4736 + AZD5069)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: participants	0	4		

Statistical analyses

Primary: Number of Participants With AEs

End point title	Number of Participants With AEs ^[2]
End point description:	
An AE is development of an undesirable medical condition or deterioration of a pre-existing medical condition following or during exposure to study treatment, whether or not considered causally related to study treatment. An undesirable medical condition can be symptoms, signs or abnormal results of an investigation. A serious AE (SAE) is an AE that fulfills one or more following criteria: death, life-threatening, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or substantial disruption of ability to conduct normal life functions, congenital abnormality or birth defect, and an important medical event that may jeopardize participant or may require medical intervention to prevent one of outcomes listed above. AEs leading discontinuation of study treatment were those with action taken was 'Drug Permanently Discontinued' for any study treatment. Only treatment emergent AEs presented. The safety analysis set analysed.	
End point type	Primary
End point timeframe:	
From first dose of study treatment administration (Day 1) until 90 days after the last dose of IP or initiation of the first subsequent anticancer therapy (whichever occurred first), approximately 30 months.	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistical analysis was performed for the outcome measure.

End point values	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)	Cohort 2 (MEDI4736 + AZD5069)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	20		
Units: participants				
Any AE	3	20		
Any AE causally related to treatment (CRT)	3	14		
Any AE of CTCAE Grade 3 or higher	3	18		
Any AE of CTCAE Grade 3 or higher CRT	3	10		
Any AE leading discontinuation of study treatment	2	3		
Any AE with outcome of death	1	4		
Any AE with outcome of death CRT	1	0		
Any SAE	1	16		
Any SAE CRT	1	8		

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate in Cohort 2

End point title	Objective Response Rate in Cohort 2 ^{[3][4]}
End point description:	
ORR is defined as the percentage of participants with a confirmed overall response of complete response (CR) or partial response (PR). A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging, preferably at the next regularly scheduled imaging	

visit and not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. CR is defined as disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 millimeters (mm). PR is defined as at least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD were not met. ORR was determined using Investigator assessments according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). The efficacy analysis set analysed.

End point type	Primary
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End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 6 weeks +/-7 days for first 48 weeks, then every 12 weeks +/-7 days thereafter until confirmed objective disease progression. Up to approximately 30 months.

Notes:

[3] - 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: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

[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: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 80%)	5.6 (0.58 to 19.95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) in Cohort 2

End point title	Duration of Response (DoR) in Cohort 2 ^[5]
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End point description:

DoR was defined as the time from the first documentation of CR/PR (which is subsequently confirmed) until the date of progression/death, or the last evaluable RECIST assessment for participants that did not progress or did progress after 2 missed visits of the last evaluable assessment (or first dose). PD was defined as at least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. DoR was determined using Investigator assessments according to RECIST v1.1 and was calculated using the Kaplan-Meier technique. The efficacy analysis set included all participants who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 6 weeks +/-7 days for first 48 weeks, then every 12 weeks +/-7 days thereafter until confirmed objective disease progression. Up to approximately 30 months.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: weeks				
median (inter-quartile range (Q1-Q3))	18.29 (18.29 to 18.29)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) in Cohort 2

End point title	Disease Control Rate (DCR) in Cohort 2 ^[6]
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End point description:

DCR at 6 months is defined as the percentage of participants who had a best objective response (BoR) of CR or PR in the first 6 months (i.e. 24+1=25 weeks to allow for a late assessment within the assessment window) or who had demonstrated stable disease (SD) for a minimum interval of 24 weeks (minus 1 week to allow for an early assessment within the assessment window, i.e. 161 days) following the start of treatment. DCR at 12 months is defined as the percentage of participants who had a BoR of CR or PR in the first 12 months (i.e. 48+1=49 weeks to allow for a late assessment within the assessment window) or who had demonstrated SD for a minimum interval of 48 weeks (minus 1 week to allow for an early assessment within the assessment window, i.e. 329 days) following the start of treatment. DCR was determined using Investigator assessments according to RECIST v1.1. The efficacy analysis set analysed.

End point type	Secondary
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End point timeframe:

RECIST assessments were performed at baseline (within 28 days before start of study treatment) and every 6 weeks +/- 7 days for first 48 weeks up to 6 months and 12 months

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: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (not applicable)				
At 6 months	11.1			
At 12 months	5.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression-Free Survival (PFS) in Cohort 2

End point title	Median Progression-Free Survival (PFS) in Cohort 2 ^[7]
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End point description:

PFS is defined as the time from the date of first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdraws from allocated therapy or receives another anticancer therapy prior to progression. PFS was determined using Investigator assessments according to RECIST v1.1 and calculated using the Kaplan-Meier technique. The efficacy analysis set included all participants who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 6 weeks +/- 7 days for first 48 weeks, then every 12 weeks +/- 7 days thereafter until confirmed objective disease progression. Up to approximately 30 months.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
number (not applicable)	1.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival Rate at 6 Months (PFS6) in Cohort 2

End point title	Progression-Free Survival Rate at 6 Months (PFS6) in Cohort
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End point description:

The PFS6 was defined as percentage of participants alive and progression-free after 6 months. The PFS6 was calculated using Kaplan-Meier estimates. Tumor progression was determined based on Investigator assessment and RECIST v1.1. The efficacy analysis set included all participants who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation.

End point type	Secondary
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End point timeframe:

RECIST assessments were performed at baseline (within 28 days before start of study treatment) and every 6 weeks +/- 7 days up to 6 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 80%)	11.1 (3.91 to 22.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival Rate at 3 Months (PFS3) in Cohort 2

End point title	Progression-Free Survival Rate at 3 Months (PFS3) in Cohort
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End point description:

The PFS rate was defined as percentage of participants alive and progression-free after 3 months. The PFS3 was calculated using Kaplan-Meier estimates. Tumor progression was determined based on Investigator assessment and RECIST v1.1. The efficacy analysis set included all participants who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation.

End point type	Secondary
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End point timeframe:

RECIST assessments were performed at baseline (within 28 days before start of study treatment) and every 6 weeks +/- 7 days up to 3 months

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 80%)	11.1 (3.91 to 22.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival (OS) in Cohort 2

End point title	Median Overall Survival (OS) in Cohort 2 ^[10]
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End point description:

OS is defined as the time from the date of first dose until death due to any cause (i.e. date of death or censoring – date of first dose + 1). OS was calculated using the Kaplan-Meier technique. Any participant not known to have died at the time of analysis was censored based on the last recorded date on which the participant was known to be alive (censored at end of study). The efficacy analysis set included all participants who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation.

End point type	Secondary
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End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 6

weeks +/-7 days for first 48 weeks, then every 12 weeks +/-7 days thereafter until confirmed objective disease progression. Up to approximately 30 months.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: months				
number (not applicable)	2.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 6 Months (OS6) in Cohort 2

End point title	Overall Survival at 6 Months (OS6) in Cohort 2 ^[11]
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End point description:

OS6 is defined as percentage of participants alive at 6 months from first dose of study treatment. OS6 was calculated using the Kaplan-Meier estimate of OS at 6 months. The efficacy analysis set included all participants who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation.

End point type	Secondary
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End point timeframe:

From first dose of study treatment (Day 1) up to 6 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 80%)	22.2 (11.19 to 35.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 12 Months (OS12) in Cohort 2

End point title	Overall Survival at 12 Months (OS12) in Cohort 2 ^[12]
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End point description:

OS12 is defined as percentage of participants alive at 12 months from first dose of study treatment. OS12 was calculated using the Kaplan-Meier estimate of OS at 12 months. The efficacy analysis set included all participants who received at least 1 dose of IP and with no important protocol deviation that could impact the efficacy evaluation.

End point type	Secondary
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End point timeframe:

From first dose of study treatment (Day 1) up to 12 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: percentage of participants				
number (confidence interval 80%)	14.8 (5.74 to 27.92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Anti-Drug Antibody (ADAs) for MEDI4736 in Cohort 2

End point title	Number of Participants With Anti-Drug Antibody (ADAs) for MEDI4736 in Cohort 2 ^[13]
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End point description:

Samples were measured for the presence of ADAs and ADA-neutralizing antibodies for MEDI4736 using validated assays. Persistently positive is defined as positive at ≥ 2 post-baseline assessments or positive at the last post-baseline assessment. Transiently positive is defined as having at least one post-baseline ADA positive assessment and not fulfilling the conditions of persistently positive. The safety analysis set included all participants who received at least 1 dose of IP and for whom any post-dose data were available. NAB = neutralizing antibody.

End point type	Secondary
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End point timeframe:

On Day 1 of Cycles 1, 2, 3, 4, and 7; At months 3 and 6 after last dose

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants				
Positive at any visit	3			
Both baseline and post-baseline positive	0			
Only post-baseline positive	1			
Only baseline positive	2			
ADA persistently positive	0			
ADA transiently positive	1			
ADA positive participants who are NAB positive	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Plasma Concentrations of MEDI4736 in Cohort 2

End point title	Mean Plasma Concentrations of MEDI4736 in Cohort 2 ^[14]
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End point description:

Mean peak and trough plasma concentrations of MEDI4736 are presented. The Pharmacokinetic (PK) analysis set included all participants who received at least 1 dose of IP per protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses. 99999 denotes "standard deviation cannot be calculated when only one participant analyzed". Here, 'n' is number of participants analysed at each specific time point.

End point type	Secondary
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End point timeframe:

Predose (within 60 minutes prior to treatment with any IP) on Day 1 of Cycles 1, 2, 3, 4, and 7; and post infusion (within 10 minutes after end of MEDI4736 infusion) on Day 1 of Cycles 1 and 7

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: nanograms per milliliter				
arithmetic mean (standard deviation)				
Cycle 1 Day 1: Predose (n=2)	1444.730 (± 1010.7667)			
Cycle 1 Day 1: Post infusion (n=20)	339342.229 (± 95923.6405)			
Cycle 2 Day 1: Predose (n=11)	56773.555 (± 17716.8788)			
Cycle 3 Day 1: Predose (n=6)	63655.840 (± 26425.8402)			
Cycle 4 Day 1: Predose (n=4)	69325.233 (± 22750.3387)			

Cycle 7 Day 1: Predose (n=1)	79687.820 (\pm 99999)			
Cycle 7 Day 1: Post infusion (n=1)	435297.610 (\pm 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Plasma Concentrations of AZD5069 in Cohort 2

End point title	Mean Plasma Concentrations of AZD5069 in Cohort 2 ^[15]
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End point description:

Mean peak and trough plasma concentration of AZD5069 are presented. Concentration of AZD5069 was calculated by plasma concentration-time profile. The PK analysis set included all participants who received at least 1 dose of IP per protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses. 99999 denotes "standard deviation cannot be calculated when only one participant analyzed". Here, 'n' is number of participants analysed at each specific time point.

End point type	Secondary
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End point timeframe:

Predose (within 60 minutes prior to treatment with any IP) on Day 1 of Cycles 1, 2, 3, 4, and 7; and postdose (within 10 minutes after end of MEDI4736 infusion) on Day 1 of Cycles 1, 2, and 7

Notes:

[15] - 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: Due to a programmatic decision, enrolment of additional participants to cohort 1 was not pursued. Therefore, efficacy analysis was performed on Cohort 2 only.

End point values	Cohort 2 (MEDI4736 + AZD5069)			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: nanomoles per liter				
arithmetic mean (standard deviation)				
Cycle 1 Day 1: Predose (n=20)	10.60 (\pm 42.933)			
Cycle 1 Day 1: Postdose (n=19)	2236.29 (\pm 1678.496)			
Cycle 2 Day 1: Predose (n=11)	1829.36 (\pm 1473.533)			
Cycle 2 Day 1: Postdose (n=1)	24.40 (\pm 99999)			
Cycle 3 Day 1: Predose (n=5)	502.48 (\pm 601.914)			
Cycle 4 Day 1: Predose (n=4)	1345.00 (\pm 1068.666)			
Cycle 7 Day 1: Predose (n=1)	1200.00 (\pm 99999)			
Cycle 7 Day 1: Postdose (n=1)	7540.00 (\pm 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From initial IP administration (Day 1) until 90 days after the last dose of IP or initiation of the first subsequent anticancer therapy (whichever occurred first), approximately 30 months.

Adverse event reporting additional description:

The safety analysis set included all participants who received at least 1 dose of IP and for whom any post-dose data were available.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)
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Reporting group description:

Participants with metastatic PDAC who were treatment naive received MEDI4736 1.5 g IV infusion q4w. Participants also received nab-paclitaxel 125 mg/m² IV infusion followed by gemcitabine 1000 mg/m² IV infusion on Days 1, 8, and 15 of each 28-day cycle. Treatment continued until either confirmed PD unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Reporting group title	Cohort 2 (MEDI4736 + AZD5069)
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Reporting group description:

Participants with metastatic PDAC with progression on the indicated types of chemotherapy received MEDI4736 1.5 g IV infusion q4w. Participants also received AZD5069 orally bid. The starting dose of 80 mg orally bid (with dose reductions to 40 mg or 20 mg for toxicity allowable). Treatment continued until either confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Serious adverse events	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)	Cohort 2 (MEDI4736 + AZD5069)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	17 / 20 (85.00%)	
number of deaths (all causes)	1	16	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Neutrophil count decreased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Obstruction gastric			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hepatitis			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Biliary sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Viral infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypovolaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1 (MEDI4736 + nab-paclitaxel + gemcitabine)	Cohort 2 (MEDI4736 + AZD5069)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	20 / 20 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Tumour associated fever			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vena cava thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Administration site mass			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Fatigue			

subjects affected / exposed	2 / 3 (66.67%)	10 / 20 (50.00%)	
occurrences (all)	2	11	
Chills			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	1 / 3 (33.33%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Peripheral swelling			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Dysphonia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pulmonary embolism			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 20 (15.00%) 3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Depression			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Blood bicarbonate decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	4	
Blood creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Body temperature increased			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Citrobacter test positive			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	3	
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Prothrombin time prolonged			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	4	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	3	
Fall			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Skin wound			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Soft tissue injury			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Hypoaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Somnolence			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 20 (5.00%) 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Leukopenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	2 / 3 (66.67%)	2 / 20 (10.00%)	
occurrences (all)	6	2	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 3 (33.33%)	2 / 20 (10.00%)	
occurrences (all)	1	3	
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	6 / 20 (30.00%)	
occurrences (all)	0	7	
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Aptyalism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 3 (66.67%)	4 / 20 (20.00%)	
occurrences (all)	2	7	
Constipation			

subjects affected / exposed	0 / 3 (0.00%)	5 / 20 (25.00%)
occurrences (all)	0	6
Colitis		
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)
occurrences (all)	1	0
Dry mouth		
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	2
Dyspepsia		
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)
occurrences (all)	0	3
Glossodynia		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Melaena		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Nausea		
subjects affected / exposed	1 / 3 (33.33%)	9 / 20 (45.00%)
occurrences (all)	1	11
Parotid gland enlargement		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Steatorrhoea		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Rectal discharge		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Peptic ulcer		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Stomatitis		
subjects affected / exposed	0 / 3 (0.00%)	5 / 20 (25.00%)
occurrences (all)	0	5
Tongue coated		

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	9 / 20 (45.00%)	
occurrences (all)	1	12	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Alopecia			
subjects affected / exposed	2 / 3 (66.67%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin mass			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Vasculitic rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Haematuria			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 3 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Temporomandibular joint syndrome			

subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	5 / 20 (25.00%)	
occurrences (all)	0	5	
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Skin infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)
occurrences (all)	1	0
Decreased appetite		
subjects affected / exposed	1 / 3 (33.33%)	7 / 20 (35.00%)
occurrences (all)	2	8
Hyperglycaemia		
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	2
Hypercalcaemia		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Hypoalbuminaemia		
subjects affected / exposed	0 / 3 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	5
Hypokalaemia		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1
Hypocalcaemia		
subjects affected / exposed	1 / 3 (33.33%)	0 / 20 (0.00%)
occurrences (all)	1	0
Hyponatraemia		
subjects affected / exposed	1 / 3 (33.33%)	1 / 20 (5.00%)
occurrences (all)	1	2
Iron deficiency		
subjects affected / exposed	0 / 3 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 March 2016	Updated dose rationale and treatment regimens regarding dose of AZD5069 used, inclusion criteria #3 and #9, and exclusion criteria #14, #15, and #20. Replacement criteria for withdrawn participants in Cohort 1/2 and definition of "evaluable patient" for Cohort 2 clarified. Use, type, and period of contraception before, during, and after trial clarified. Footnotes b, d, and j of Tables 2 and 3 were updated. Removal of section regarding tumor assessment in participants who omit Day 15 dose administration. Removal of requirement for central reading of scans. Management of participants was based solely upon results of assessment conducted by Investigator. Electrocardiogram (ECG) frequency for Cohort 2 updated to screening and Day 1 of each cycle. Vital signs collection time points predose, during and post-dose in Section 5.2.4 clarified. Sections 5.4.5, 5.4.7, and 5.5.5 regarding Biobank used in study amended. Updated to state that recording of AEs in also refers to AESIs. Addition of AESIs associated with MEDI4736. Removal of dose reduction or modification guidance of AZD5069 in as this document does not exist. MEDI4736 dosage and strength clarified. Table 9 removed from Section 7.1.1. Removal of omission of Day 15 treatment in case of participant toxicity Figure 3 updated to correct week schedule of MEDI4736 dose 7. Added clarification that use of cannabinoids must be avoided in participants administered with AZD5069 alone and in combination with MEDI4736. Removal of overall survival text from, as it is duplicate of paragraph. Corrected errors in disease control rate and progression free survival calculation. Start date of study clarified. Removal of soluble programmed cell death ligand 1 tests throughout Protocol. Removal of "lesions <2 centimeters biopsied within screening period (fresh tumor biopsy)" as a non-measurable lesion in as it does not pertain to imaging/RECIST 1.1. Updated toxicity management guidelines to current version.
14 December 2016	Language was updated to reflect fact that recruitment to Cohort 1 was stopped after only 3 participants had been enrolled. Efficacy, immunogenicity and exploratory objectives were removed. New exploratory objectives added. Sections of AZD5069 dose rationale were updated to include language on how dosing was to be managed in Cohort 2, including details regarding a dosing regimen being established at time in Study D4660C00004. Updated introduction, inclusion criterion #3, and exclusion criterion #11, #14, #16, and #19. Discontinuation criterion #9 updated to remove "and Investigator determination that participants is no longer benefiting from treatment with IP". Updated to remove PK, immunogenicity, and biomarker collections from Cohort 1; included collection of circulating soluble factors, pharmacogenetic sample, circulating tumor DNA and updated times for myeloid-derived suppressor cells and peripheral blood mononuclear cells. Updated to specify that 12-lead ECGs were to be recorded in triplicate for Cohort 2. Updated to reflect which samples were to be analyzed for each cohort. Pharmacogenetics section added for Cohort 2. Added toxicity management for AZD5069 40 mg starting dose. Removed all DLT evaluation text for Cohort 1 and included DLT information for Cohort 2. Updated probability table data for Tables 10 and 11. Added table of posterior probabilities of true DLT incidence >33% with various priors as well as explanatory text for Table 12. Disease control rate was to be evaluated at 6 and 12 months, instead of 3 months. Updated to include most current version of "MEDI4736 Dosing Modification and Toxicity Management Guidelines". Added information regarding dose toxicity management and alternative dosing regimen for AZD5069 80 mg twice daily currently under exploration.

17 July 2017	Language was updated to reflect the initial dosing of AZD5069 at 80 mg orally twice daily, with provision for dose reductions described in Section 6.7.3. Text throughout Protocol has been updated for consistency. Primary objective was clarified to be inclusive of safety and tolerability of MEDI4736 + AZD5069 in combination, thus separate safety objective was removed. Section has been updated to include the most current clinical data available for MEDI4736. Inclusion criterion #3 text was simplified and Cohort 2 progression timeline for prior therapy was removed. Added inclusion criterion #9 (Cohort 2) for taking mandatory tumor biopsy in screening period (or <45 days prior to first dosing if adequate tissue samples are available). Text throughout the Protocol has been updated for consistency.
08 February 2018	Blood sample changed to 'serum or plasma' and non-compartmental analysis removed. Potential risks of MEDI4736 updated to reflect MEDI4736 Investigator's Brochure Edition 12. Neutropenia/neutrophil count decreased was considered expected for regulatory purposes in the respiratory indication only, but not yet in the oncology population (change arising from alignment with the clinical trials facilitation group Guidelines). Additional sensitivity analysis for overall response rate was removed.

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.

Due to a programmatic decision, enrollment of additional participants to cohort 1 was not pursued.
Study terminated by sponsor.

Notes: