Clinical trial results:
A Phase II, Open-Label, Multi-Arm Study to Determine the Preliminary Efficacy of Novel Combinations of Treatment in Patients with Platinum Refractory Extensive-Stage Small-Cell Lung Cancer (BALTIC)

Summary

EudraCT number	2016-001202-42
Trial protocol	HU DE ES PL
Global end of trial date	27 November 2023

Results information

Result version number	v1 (current)
This version publication date	08 June 2024
First version publication date	08 June 2024

Trial information

Trial identification

Sponsor protocol code	D419QC00002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02937818
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, 1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, 1 8772409479, information.center@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	18 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2020
Global end of trial reached?	Yes
Global end of trial date	27 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the preliminary efficacy of each treatment arm in terms of objective response rate.

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 Harmonization/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics. The Principal Investigator ensured that each patient was given full and adequate oral and written information about the study. Patients provided signed and dated informed consent before any procedure specific to the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Ukraine: 20
Worldwide total number of subjects	72
EEA total number of subjects	52

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	47
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 11 study centers in 5 countries (Germany, Hungary, Poland, Spain, and Ukraine).

Pre-assignment

Screening details:

Subjects who met the inclusion exclusion criteria were enrolled to the study. All study assessments were performed as per the schedule of assessment.

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	Arm A: Durvalumab + Tremelimumab (Original Cohort)

Arm description:

Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed progressive disease (PD), or other discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 75 mg tremelimumab every 4 weeks.

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 1500 mg durvalumab every 4 weeks.

Arm title	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)

Arm description:

Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed PD, or other discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:	
Subjects received 75 mg tremelimumab every 4 weeks.	
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	MEDI4736
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received 1500 mg durvalumab every 4 weeks.	
Arm title	Arm B: Adavosertib + Carboplatin
Arm description:	
Subjects orally received adavosertib 225 mg twice daily (BID) for 2.5 days from Day 1 + carboplatin area under the curve (AUC) 5 Day 1 IV, every 3 weeks (q3w).	
Arm type	Experimental
Investigational medicinal product name	Adavosertib
Investigational medicinal product code	AZD1775
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received 225 mg adavosertib twice daily.	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Subjects received carboplatin, at a dose calculated to produce an area under the curve (AUC) of 5 every 3 weeks.	
Arm title	Arm C: Ceralasertib (AZD6738) + Olaparib
Arm description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received 300 mg olaparib twice daily.	
Investigational medicinal product name	Ceralasertib
Investigational medicinal product code	AZD6738
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Subjects received 160 mg ceralasertib once daily.	

Number of subjects in period 1	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin
Started	21	20	10
Completed	0	0	0
Not completed	21	20	10
Subjects decision	1	-	1
Disease progression	17	14	7
Subjects ongoing durvalumab at Data cut off (DCO)	1	2	-
Adverse event, non-fatal	2	4	1
Subjects ongoing ceralasertib and olaparib at DCO	-	-	-
Condition under investigation worsened	-	-	1

Number of subjects in period 1	Arm C: Ceralasertib (AZD6738) + Olaparib
Started	21
Completed	0
Not completed	21
Subjects decision	1
Disease progression	18
Subjects ongoing durvalumab at Data cut off (DCO)	-
Adverse event, non-fatal	1
Subjects ongoing ceralasertib and olaparib at DCO	1
Condition under investigation worsened	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Durvalumab + Tremelimumab (Original Cohort)
Reporting group description:	
Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed progressive disease (PD), or other discontinuation criteria.	
Reporting group title	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)
Reporting group description:	
Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed PD, or other discontinuation criteria.	
Reporting group title	Arm B: Adavosertib + Carboplatin
Reporting group description:	
Subjects orally received adavosertib 225 mg twice daily (BID) for 2.5 days from Day 1 + carboplatin area under the curve (AUC) 5 Day 1 IV, every 3 weeks (q3w).	
Reporting group title	Arm C: Ceralasertib (AZD6738) + Olaparib
Reporting group description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	

Reporting group values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin
Number of subjects	21	20	10
Age Categorical Units: Subjects			
< 50	2	0	1
≥ 50 to < 65	13	12	5
≥ 65 to < 75	6	6	3
≥ 75 to < 80	0	2	1
≥ 80	0	0	0
Sex: Female, Male Units: Subjects			
Female	6	4	2
Male	15	16	8
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	21	20	10
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	0

Not Hispanic or Latino	21	19	10
Unknown or Not Reported	0	0	0

Reporting group values	Arm C: Ceralasertib (AZD6738) + Olaparib	Total	
Number of subjects	21	72	
Age Categorical Units: Subjects			
< 50	2	5	
≥ 50 to < 65	12	42	
≥ 65 to < 75	5	20	
≥ 75 to < 80	2	5	
≥ 80	0	0	
Sex: Female, Male Units: Subjects			
Female	7	19	
Male	14	53	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	21	72	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	21	71	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Arm A: Durvalumab + Tremelimumab (Original Cohort)
Reporting group description:	
Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed progressive disease (PD), or other discontinuation criteria.	
Reporting group title	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)
Reporting group description:	
Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed PD, or other discontinuation criteria.	
Reporting group title	Arm B: Adavosertib + Carboplatin
Reporting group description:	
Subjects orally received adavosertib 225 mg twice daily (BID) for 2.5 days from Day 1 + carboplatin area under the curve (AUC) 5 Day 1 IV, every 3 weeks (q3w).	
Reporting group title	Arm C: Ceralasertib (AZD6738) + Olaparib
Reporting group description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Subject analysis set title	Ceralasertib (AZD6738)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Subject analysis set title	Olaparib
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Subject analysis set title	Ceralasertib (AZD6738)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Subject analysis set title	Ceralasertib (AZD6738)
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Subject analysis set title	Olaparib
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Subject analysis set title	Olaparib
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	

Primary: Number of Subjects With Overall Response

End point title	Number of Subjects With Overall Response[1]

End point description:

Overall Response Rate (ORR) using Investigator assessments according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. ORR was defined as the number (percentage) of subjects with a confirmed Complete Response (CR) or confirmed Partial Response (PR) and was estimated for each treatment arm with corresponding 2-sided 95% exact confidence intervals (CIs). A confirmed response of CR/PR meant that a response of CR/PR was recorded at one 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.

End point type	Primary

End point timeframe:

Until disease progression [PD] (Up to 3.5 Years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Pharmacokinetics parameters were not calculated for Arm A: Durvalumab + Tremelimumab.

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin	Arm C: Ceralasertib (AZD6738) + Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	20	10	21
Units: Subjects	2	1	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

The DoR was defined as the time from the date of first documented response (which was subsequently confirmed) CR/PR until the date of documented progression, or death in the absence of disease progression. The DoR in subjects with confirmed objective response are reported. Here, arbitrary number 999.999 denotes data not available as objective response not reached.

End point type	Secondary

End point timeframe:

Until disease progression or data cut-off (DCO) or Death (Up to 3.5 Years)

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin	Arm C: Ceralasertib (AZD6738) + Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	0[2]	1
Units: Months				

median (full range (min-max))	999.999 (1.5 to 999.999)	3 (3 to 3)	(to)	8.5 (8.5 to 8.5)

Notes:

[2] - All subjects were classified as non-responders

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Control at 12 Weeks

End point title	Percentage of Subjects With Disease Control at 12 Weeks

End point description:

The disease control rate (DCR) at 12 weeks was defined as the percentage of subjects who had a best objective response of CR or PR in the first 13 weeks or who had demonstrated stable disease (SD) for a minimum interval of 11 weeks following the start of study treatment. The DCR was determined programmatically based on RECIST 1.1 using site Investigator data and all data up until the first progression event.

End point type	Secondary

End point timeframe:

At 12 Weeks

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin	Arm C: Ceralasertib (AZD6738) + Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	20	10	21
Units: Percentage of subjects				
number (not applicable)	38.1	15.0	30.0	38.1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

The TTR (per RECIST 1.1 as assessed by the Investigator) was defined as the time from the date of first dose until the first date of documented response.

End point type	Secondary

End point timeframe:

Until disease progression or DCO or Death (Up to 3.5 Years)

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin	Arm C: Ceralasertib (AZD6738) + Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	0[3]	1
Units: Months				
median (full range (min-max))	1.8 (1.7 to 1.8)	1.8 (1.8 to 1.8)	(to)	1.7 (1.7 to 1.7)

Notes:

[3] - There were no responses.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

The PFS (per RECIST 1.1 according to the Investigator's assessment) was defined as the time from the date of the first dose of study treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the subject withdrew from allocated therapy or received another anti-cancer therapy prior to progression.

End point type	Secondary

End point timeframe:

Until disease progression or DCO or Death (Up to 3.5 Years)

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin	Arm C: Ceralasertib (AZD6738) + Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	20	10	21
Units: Months				
median (confidence interval 95%)	1.91 (1.77 to 4.34)	1.77 (1.02 to 2.20)	2.60 (0.56 to 4.83)	2.92 (1.81 to 4.53)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The OS was defined as the time from the date of the first dose of study treatment until death due to any cause.

End point type	Secondary

End point timeframe:

Until disease progression or DCO or Death (Up to 3.5 Years)

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin	Arm C: Ceralasertib (AZD6738) + Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	20	10	21
Units: Months				
median (confidence interval 95%)	5.95 (1.91 to 10.61)	3.37 (1.91 to 7.66)	4.67 (0.56 to 5.98)	7.56 (4.21 to 12.58)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum concentration (tmax)

End point title	Time to maximum concentration (tmax)

End point description:

Time to maximum concentration for ceralasertib and olaparib are reported.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 1 (post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Hour				
median (full range (min-max))	1.250 (1.00 to 6.08)	1.800 (1.00 to 6.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration (Cmax)

End point title	Maximum concentration (Cmax)

End point description:

Maximum concentration for ceralasertib and olaparib are reported.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 1 (post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	4.215 (± 27.7129)	6.558 (± 39.9411)		

Statistical analyses

No statistical analyses for this end point

Secondary: Partial area under the concentration-time curve (AUC0-6)

End point title	Partial area under the concentration-time curve (AUC0-6)

End point description:

Partial area under the concentration-time curve for ceralasertib and olaparib are reported.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 1 (post-dose) and Cycle 1 Day 7 (pre-dose and post-dose)

End point values	Olaparib	Ceralasertib (AZD6738)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	20		
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1	26.356 (± 42.2963)	18.346 (± 34.6952)		
Cycle 1, Day 7	42.016 (± 33.7599)	23.666 (± 23.9202)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve from time zero to the last measurable concentration (AUC0-t)

End point title	Area under the concentration-time curve from time zero to the last measurable concentration (AUC0-t)

End point description:

Area under the concentration-time curve from time zero to the last measurable concentration for Ceralasertib and Olaparib are reported.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 1 (post-dose) and Cycle 1 Day 7 (pre-dose and post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1	18.575 (± 34.5074)	26.973 (± 41.4461)		
Cycle 1, Day 7	24.061 (± 23.0923)	62.535 (± 42.4552)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum concentration at steady state (tmax,ss)

End point title	Time to maximum concentration at steady state (tmax,ss)

End point description:

Time to maximum concentration at steady state for Ceralasertib and Olaparib are reported.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 7 (pre-dose and post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: Hour				
median (full range (min-max))	1.875 (0.63 to 6.08)	2.708 (0.63 to 4.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum concentration at steady state (Cmax,ss)

End point title	Maximum concentration at steady state (Cmax,ss)

End point description:

Maximum concentration at steady state for Ceralasertib and Olaparib are reported.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 7 (pre-dose and post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	5.176 (± 23.4058)	9.189 (± 30.4888)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum concentration at steady state (Cmin,ss)

End point title	Minimum concentration at steady state (Cmin,ss)

End point description:

Minimum concentration at steady state for Ceralasertib and Olaparib are reported.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 7 (pre-dose and post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	1.119 (± 55.9070)	2.376 (± 61.8191)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve at steady state (AUCss)

End point title	Area under the concentration-time curve at steady state

	(AUCss)

End point description:

Area under the concentration-time curve at steady state at steady state for Ceralasertib and Olaparib are reported. Here, arbitary number 999.999 denotes data not available as there were not enough pharmacokinetic data points collected to calculate AUCss.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 7 (pre-dose and post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: h*µg/mL				
geometric mean (geometric coefficient of variation)	999.999 (± 999.999)	67.929 (± 37.4297)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance of drug at steady state at steady state (CLss/F)

End point title	Apparent clearance of drug at steady state at steady state (CLss/F)

End point description:

Area under the concentration-time curve at steady state at steady state for Ceralasertib and Olaparib are reported. Here, arbitary number 999.999 denotes data not available as there were not enough pharmacokinetic data points collected to calculate CLss/F.

End point type	Secondary

End point timeframe:

Cycle 1 (each cycle was 28 days in length) Day 7 (pre-dose and post-dose)

End point values	Ceralasertib (AZD6738)	Olaparib		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	9		
Units: Litre/hour				
geometric mean (geometric coefficient of variation)	999.999 (± 999.999)	4.416 (± 42.3171)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of Durvalumab and Tremelimumab

End point title	Serum concentrations of Durvalumab and Tremelimumab[4]

End point description:

Serum concentrations of Durvalumab and Tremelimumab are reported.

End point type	Secondary

End point timeframe:

Durvalumab: Cycle 1 (each cycle was 4 weeks) Day 1(post-dose); Cycle 2 Day 1(pre-dose); Cycle 5 Day 1 (pre-dose); Tremelimumab: Cycle 1 (each cycle was 4 weeks) Day 1 (post-dose); Cycle 2 Day 1 (predose); Cycle 5 Day 1 (No dose); Cycle 7 Day 1 (No dose)

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: Pharmacokinetics parameters were not calculated for Arm A: Durvalumab + Tremelimumab.

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Durvalumab: Cycle 1 Day 1 (Post-dose)	391.192 (± 23.5990)			
Durvalumab: Cycle 2 Day 1 (Pre-dose)	55.590 (± 53.0745)			
Durvalumab: Cycle 5 Day 1 (Pre-dose)	116.846 (± 51.0036)			
Tremelimumab: Cycle 1 Day 1 (Post-dose)	18.299 (± 20.8181)			
Tremelimumab: Cycle 2 Day 1 (Pre-dose)	2.650 (± 53.1007)			
Tremelimumab: Cycle 5 Day 1 (No dose)	5.005 (± 38.3784)			
Tremelimumab: Cycle 7 Day 1 (No dose)	0.784 (± 66.3469)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of Adavosertib and Carboplatin

End point title	Plasma concentrations of Adavosertib and Carboplatin[5]

End point description:

Plasma concentrations of Adavosertib and Carboplatin are reported.

End point type	Secondary

End point timeframe:

Adavosertib: Cycle 1 (each cycle was 21 days) Day 3 (pre-dose and post-dose); Cycle 3 Day 3 (pre-dose and post-dose); Carboplatin: Cycle 1 (each cycle was 21 days) Day 1 (post-dose)

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: Pharmacokinetics parameters were not calculated for Arm A: Durvalumab + Tremelimumab.

End point values	Arm B: Adavosertib + Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: nM				
geometric mean (geometric coefficient of variation)				
Adavosertib: Cycle 1 Day 3 (Pre-dose)	551.489 (± 41.5823)			
Adavosertib: Cycle 1 Day 3 (Post-dose)	728.342 (± 62.3968)			
Adavosertib: Cycle 3 Day 3 (Pre-dose)	606.571 (± 46.7716)			
Adavosertib: Cycle 3 Day 3 (Post-dose)	805.270 (± 68.0275)			
Carboplatin: Cycle 1 Day 1 (Post-dose)	12834.615 (± 27.5493)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. SAE is an AE that results in any untoward medical occurrence that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability, or is a significant medical event.

End point type	Secondary

End point timeframe:

Day 1 until disease progression, and follow-up visit (Up to 3.5 Years)

End point values	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)	Arm B: Adavosertib + Carboplatin	Arm C: Ceralasertib (AZD6738) + Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	20	10	21
Units: Subjects				
Any AE	16	17	8	18

Any AE causally related to any study treatment	10	9	8	16
Any AE with outcome = death	1	0	1	1
Any SAE	6	8	4	7
Any AE to discontinuation of any study treatment	2	4	1	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 until disease progression, and follow-up visit (Up to 3.5 Years)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Arm A: Durvalumab + Tremelimumab (Original Cohort)
Reporting group description: Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed progressive disease (PD), or other discontinuation criteria.	
Reporting group title	Arm C: Ceralasertib (AZD6738) + Olaparib
Reporting group description: Subjects orally received ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.	
Reporting group title	Arm B: Adavosertib + Carboplatin
Reporting group description: Subjects orally received adavosertib 225 mg twice daily (BID) for 2.5 days from Day 1 + carboplatin area under the curve (AUC) 5 Day 1 IV, every 3 weeks (q3w).	
Reporting group title	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)
Reporting group description: Subjects received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 months (4 cycles) followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed PD, or other discontinuation criteria.	

Serious adverse events	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm C: Ceralasertib (AZD6738) + Olaparib	Arm B: Adavosertib + Carboplatin
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	7 / 21 (33.33%)	4 / 10 (40.00%)
number of deaths (all causes)	19	15	10
number of deaths resulting from adverse events	1	1	1
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Burns third degree			

subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Myasthenic syndrome			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 21 (0.00%)	4 / 21 (19.05%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematotoxicity			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	0		
Investigations			
Hepatic enzyme increased			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Burns third degree			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Myasthenic syndrome			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Febrile neutropenia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematotoxicity				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Diarrhoea				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis haemorrhagic				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Gastroenteritis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 20 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypokalaemia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Arm A: Durvalumab + Tremelimumab (Original Cohort)	Arm C: Ceralasertib (AZD6738) + Olaparib	Arm B: Adavosertib + Carboplatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 21 (76.19%)	18 / 21 (85.71%)	8 / 10 (80.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 21 (23.81%)	1 / 21 (4.76%)	3 / 10 (30.00%)
occurrences (all)	6	1	6
Asthenia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	3 / 10 (30.00%)
occurrences (all)	1	1	6
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	3 / 21 (14.29%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 21 (14.29%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Dyspnoea			
subjects affected / exposed	6 / 21 (28.57%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	6	2	0
Productive cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Dysphonia			

subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Bronchial hyperreactivity			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dry throat			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Platelet count decreased			

subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Lipase increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rib fracture			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Somnolence			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Peripheral motor neuropathy			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Peripheral sensorimotor neuropathy			

subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 21 (4.76%)	11 / 21 (52.38%)	3 / 10 (30.00%)
occurrences (all)	1	11	5
Thrombocytopenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	7 / 10 (70.00%)
occurrences (all)	0	2	13
Neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	13
Leukopenia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Febrile neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 21 (0.00%)	3 / 21 (14.29%)	6 / 10 (60.00%)
occurrences (all)	0	4	13
Vomiting			
subjects affected / exposed	0 / 21 (0.00%)	3 / 21 (14.29%)	3 / 10 (30.00%)
occurrences (all)	0	4	6
Diarrhoea			
subjects affected / exposed	2 / 21 (9.52%)	1 / 21 (4.76%)	7 / 10 (70.00%)
occurrences (all)	2	1	14
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 21 (14.29%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Pruritus			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Skin induration			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Urinary hesitation			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hypothyroidism			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Groin pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 21 (0.00%)	2 / 21 (9.52%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Arthralgia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psoriatic arthropathy			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Respiratory tract infection viral			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	3
Bronchitis			

subjects affected / exposed	2 / 21 (9.52%)	1 / 21 (4.76%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Conjunctivitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 21 (4.76%)	1 / 21 (4.76%)	2 / 10 (20.00%)
occurrences (all)	1	1	3
Hyperchloraemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 21 (9.52%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hyponatraemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Arm A: Durvalumab + Tremelimumab (Expansion Cohort)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Dysphonia			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Bronchial hyperreactivity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dry throat			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Confusional state			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Platelet count decreased			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Rib fracture			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Peripheral sensorimotor neuropathy			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Leukopenia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Febrile neutropenia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			

subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 0 / 20 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Skin induration subjects affected / exposed occurrences (all)	 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1		
Renal and urinary disorders Nephritis subjects affected / exposed occurrences (all) Urinary hesitation subjects affected / exposed occurrences (all)	 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1		
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Hypothyroidism			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Groin pain			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psoriatic arthropathy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Respiratory tract infection viral			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Bronchitis			

subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oral candidiasis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Hyperchloraemia			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 20 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2017	Amendment 1 (Version 2): Addition of the timelines between progression and enrolment to target population in Synopsis. -Changes related to weigh based dosing for patients whose weight falls to 30kg or in Changes related to weigh based dosing for patients whose weight falls to 30kg. -Clarification added to inclusion criteria 3, and 4 regarding stage at initial diagnosis and timelines between progression and enrollment respectively, and exclusion criteria 10, and Section 8.7.1 regarding use of sensitive substrates of CYP3A4. -Information added to Study plan and timing of procedures regarding relevant assessments.-Change related to the time of validity of laboratory samples between screening and baseline was from 7 days to 3 days. -clarification added to Section 7.6 Overdose. -Additional information added on Rationale for four cycles of combination therapy followed by durvalumab monotherapy. -Removal of Section 12.7.1.2 Tremelimumab as there will be no tremelimumab monotherapy in the trial. -Information added to Sections 2.7.2, 2.7.2.1, 2.7.2.2 and 2.7.2.3 regarding identified and potential risks for durvalumab, tremelimumab and durvalumab + tremelimumab. -Information added to Section 5 regarding reasons for potential dosing delay. -Additional information added to Section 4.5 regarding AZD1775 dosing. -Addition of a section regarding Patients with a history of Torsades de pointes to the Restrictions Section 4.5.2. -Clarification added to section 7.3.3.3 Nausea and vomiting regarding aprepitant [Emend] and fosaprepitant. -Clarification added to Appendix B Figure 2 AZD1775 + carboplatin therapy dosing schedule. -Addition of Section 8.7.3 Substances known to prolong the ECG QTc interval.
15 December 2017	Amendment 2 (Version 3): Treatment Arm C added to protocol – subprotocol for this Arm is included in APPENDIX C. -Clarification to interim analysis description was added in Synopsis section to clarify the action taken in event of a decision to close Arm after stage 1. -Exploratory objective and specification for Arms was added to Section 3.4, Study Objectives. -Clarification added to Section 4.9 on discontinuation of investigational product. - Information added in Section 4.10.2 regarding possible replacement of withdrawn subjects. -Clarification was added in Section 4.10.3 on consent withdrawal. -Time period for collection of adverse events, revised to address events post the defined safety follow-up period. -Information added to Appendix A, Section 2.8 to provide clarity on study design for Arm A. -Clarification added to inclusion criterion 5 in Appendix A, section 4.1 on prohibition of use of granulocyte-colony stimulating factor for neutrophils raising during screening. -Updated Appendix A Table 7 Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) to version from 1 Nov 2017. -Information was added to Appendix B Section 7.2.2 regarding paternal exposure.

25 June 2018	Amendment 3 (Version 4): Protocol synopsis and Section 2.2.1 Rationale for study design were updated to allow expansion of any arm, to a total of 40 eligible subjects, based on Review Committee assessment of data from the first 20 subjects. -Exploratory objectives were updated for clarification and to allow analysis of further biomarkers including circulating tumour DNA (ctDNA) and tumour mutation burden (TMB). -Synopsis Statistical Methods section and Section 9.2 Sample Size Estimate of Master protocol updated to correct typos, include a row in the table for 40 subjects and remove the column for 25%. -Benefit-risk updated with 6 and 12 months OS data. -Methods for assigning treatment groups updated to clarify that parallel recruitment is allowed. -Information added to Section 6.1 to clarify how to follow up if subjects discontinue study treatment prior to PD. -Analysis following expansion added to explain there is no need for further interim analysis in that group of patients and describe planned sensitivity analysis. -Rationale for study design, doses, and control groups updated to include scientific rationale for expanding Arm A. -Durvalumab and tremelimumab dose and treatment regimen justification updated with latest data and durvalumab IB. -Schedule of assessments updated to remove biomarker samples that are not collected (e.g. CTCs), added (e.g. ctDNA) and tighten requirements for tumour biopsy material. Footnotes updated to clarify that some samples are not required in the expansion group (including PK, anti-drug antibodies (ADA) and mRNA). -Schedule of assessments (post-discontinuation) updated regarding PK samples to clarify not required for expansion group. -Updated to reflect the wording on optional exploratory genetic sample informed consent form, consistent with current durvalumab template. -Updated to reflect information included in latest olaparib IB (edition 15). -
16 January 2020	Amendment 4 (Version 5): Sections on durvalumab and tremelimumab monotherapies and combined therapy updated as per current IBs in Appendix A. -Dosing Modification and Toxicity Management Guidelines for durvalumab and tremelimumab separated from Appendix A (i.e. Arm A study protocol). -Removal of the requirement to collect PK samples after Cycle 6 in Arm C. -Haematological parameters for ongoing treatment, and guidance for dose modifications revised as per updated Cerelasertib guidance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported