Clinical trial results:
An Open-Label, Multi-Centre, Global Study to Evaluate Long Term Safety and Efficacy in Patients Who are Receiving or Who Previously Received Durvalumab in Other Protocols (WAVE)

Summary

EudraCT number	2019-001402-20
Trial protocol	NL FR DE HU PL ES GR BE BG IT RO
Global end of trial date	30 September 2024

Results information

Result version number	v1 (current)
This version publication date	10 April 2025
First version publication date	10 April 2025

Trial information

Trial identification

Sponsor protocol code	D910FC00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04078152
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Karlebyhusentren, B674 Astraallen, Södertälje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca AB, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca AB, +1 877-240-9479, 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	31 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To monitor long-term safety of durvalumab (all cohorts)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	37 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Korea, Republic of: 16

Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Türkiye: 2
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Viet Nam: 1
Worldwide total number of subjects	163
EEA total number of subjects	43

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)	74
From 65 to 84 years	86
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This Phase IV, open-label study was conducted at 112 investigational sites across 31 countries in participants who were receiving durvalumab monotherapy and/or those who previously received durvalumab as a monotherapy or in combination with any other approved or investigational anticancer agent in previously enrolled parent study.

Pre-assignment

Screening details:

A total of 163 participants were enrolled in this study.

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: Durvalumab Continuation

Arm description:

Cohort 1 included participants who had received durvalumab monotherapy or durvalumab combination therapy under the parent clinical study (including those who underwent retreatment per the parent study) who had not clinically progressed and who were eligible to continue durvalumab treatment after completing dosing of all other anticancer agents, including other investigational agents. Participants received durvalumab monotherapy 1500 milligrams (mg) via intravenous (IV) infusion every 4 weeks on Day 1 of each cycle until confirmed progressive disease (PD), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

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

Dosage and administration details:

Durvalumab was supplied as a 500 mg vial solution for infusion after dilution, and it was administered as 1500 mg IV every 4 weeks until protocol-specified discontinuation criteria was met.

Arm title	Cohort 2: Durvalumab Restart

Arm description:

Cohort 2 included participants who had completed durvalumab monotherapy or combination therapy with any other approved or investigational anticancer agents in a parent study, without confirmed PD during the period of treatment, and who were potentially eligible for retreatment with durvalumab. Participants received durvalumab monotherapy 1500 mg via IV infusion every 4 weeks on Day 1 of each cycle until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

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

Dosage and administration details:

Durvalumab was supplied as a 500 mg vial solution for infusion after dilution, and it was administered as 1500 mg IV every 4 weeks until protocol-specified discontinuation criteria was met.

Arm title	Cohort 3: No Restart of Durvalumab

Arm description:

Cohort 3 included participants previously treated with durvalumab monotherapy or in combination with any other approved or investigational anticancer agents who were no longer receiving durvalumab and were not eligible to receive retreatment. Participants did not receive any study drug.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Cohort 1: Durvalumab Continuation	Cohort 2: Durvalumab Restart	Cohort 3: No Restart of Durvalumab
Started	100	25	38
Treated in WAVE/90 days within enrolment	100	7	2
Completed	0	0	0
Not completed	100	25	38
Consent withdrawn by subject	5	-	1
Adverse event, non-fatal	1	-	-
Death	10	2	12
Development of study specific withdrawal criteria	1	1	-
Unspecified	83	22	25

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Durvalumab Continuation
Reporting group description:	
Cohort 1 included participants who had received durvalumab monotherapy or durvalumab combination therapy under the parent clinical study (including those who underwent retreatment per the parent study) who had not clinically progressed and who were eligible to continue durvalumab treatment after completing dosing of all other anticancer agents, including other investigational agents. Participants received durvalumab monotherapy 1500 milligrams (mg) via intravenous (IV) infusion every 4 weeks on Day 1 of each cycle until confirmed progressive disease (PD), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.	
Reporting group title	Cohort 2: Durvalumab Restart
Reporting group description:	
Cohort 2 included participants who had completed durvalumab monotherapy or combination therapy with any other approved or investigational anticancer agents in a parent study, without confirmed PD during the period of treatment, and who were potentially eligible for retreatment with durvalumab. Participants received durvalumab monotherapy 1500 mg via IV infusion every 4 weeks on Day 1 of each cycle until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.	
Reporting group title	Cohort 3: No Restart of Durvalumab
Reporting group description:	
Cohort 3 included participants previously treated with durvalumab monotherapy or in combination with any other approved or investigational anticancer agents who were no longer receiving durvalumab and were not eligible to receive retreatment. Participants did not receive any study drug.	

Reporting group values	Cohort 1: Durvalumab Continuation	Cohort 2: Durvalumab Restart	Cohort 3: No Restart of Durvalumab
Number of subjects	100	25	38
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	65.5	66.4	66.1
standard deviation	± 10.31	± 9.30	± 9.95
Sex: Female, Male Units: participants			
Female	18	7	16
Male	82	18	22
Race/Ethnicity, Customized Units: Subjects			
White	75	16	21
Black or African American	0	1	1
Asian	25	8	16
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	9	0	0
Not Hispanic or Latino	91	23	37
Missing	0	2	1

Reporting group values	Total		

Number of subjects	163		
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	41		
Male	122		
Race/Ethnicity, Customized Units: Subjects			
White	112		
Black or African American	2		
Asian	49		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	9		
Not Hispanic or Latino	151		
Missing	3		

End points

End points reporting groups

Reporting group title	Cohort 1: Durvalumab Continuation

Reporting group description:

Cohort 1 included participants who had received durvalumab monotherapy or durvalumab combination therapy under the parent clinical study (including those who underwent retreatment per the parent study) who had not clinically progressed and who were eligible to continue durvalumab treatment after completing dosing of all other anticancer agents, including other investigational agents. Participants received durvalumab monotherapy 1500 milligrams (mg) via intravenous (IV) infusion every 4 weeks on Day 1 of each cycle until confirmed progressive disease (PD), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Reporting group title	Cohort 2: Durvalumab Restart

Reporting group description:

Cohort 2 included participants who had completed durvalumab monotherapy or combination therapy with any other approved or investigational anticancer agents in a parent study, without confirmed PD during the period of treatment, and who were potentially eligible for retreatment with durvalumab. Participants received durvalumab monotherapy 1500 mg via IV infusion every 4 weeks on Day 1 of each cycle until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Reporting group title	Cohort 3: No Restart of Durvalumab

Reporting group description:

Cohort 3 included participants previously treated with durvalumab monotherapy or in combination with any other approved or investigational anticancer agents who were no longer receiving durvalumab and were not eligible to receive retreatment. Participants did not receive any study drug.

Primary: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]

End point description:

An AE: Development of any untoward medical occurrence (other than progression of malignancy under evaluation) in participant or clinical study participant administered a medicinal product which did not necessarily have a causal relationship with this treatment. SAE:AE occurring during any study phase fulfilling 1 or more of following: resulted in death; was immediately life-threatening; required in-patient hospitalization/prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; was a congenital abnormality or birth defect; was an important medical event that jeopardized participant/required medical treatment to prevent 1 of the outcomes listed above. The Safety analysis set included those participants who received at least 1 dose of durvalumab in this study or enrolled in this study within 90 days of last dose of durvalumab or durvalumab combination in the respective parent clinical study. Data from this study only, not parent study.

End point type	Primary

End point timeframe:

From the time of signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab); approximately 37 months

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: As the endpoint is descriptive in nature, no statistical analysis is presented,

End point values	Cohort 1: Durvalumab Continuation	Cohort 2: Durvalumab Restart	Cohort 3: No Restart of Durvalumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	7	2	
Units: participants				
Any AEs	85	1	0	
Any SAEs	23	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2: Duration of Response (DOR)

End point title	Cohort 2: Duration of Response (DOR)[2]

End point description:

The DOR was defined as the time from first documented CR or PR to time of first documented disease progression or death in the absence of disease progression. Tumor assessments were performed according to RECIST v1.1. The Response evaluable analysis set included those participants who underwent retreatment with durvalumab in Cohort 2. 99999 signifies 'Not Applicable'. As no participant in the response evaluable analysis set was assessed to have had either CR or PR, the DOR analysis was not applicable.

End point type	Secondary

End point timeframe:

Tumor assessments as determined by the Investigator (at least every 12 weeks) until withdrawal of consent, progression or death; approximately 30 months

Notes:

[2] - 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: As the endpoint is descriptive in nature, no statistical analysis is presented,

End point values	Cohort 2: Durvalumab Restart			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Were Alive

End point title	Number of Participants who Were Alive

End point description:

Number of participants who were alive are reported in this outcome measure. 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. The Full analysis set included all participants enrolled in the study, regardless of the treatment received.

End point type	Secondary

End point timeframe:

Up to approximately 37 months

End point values	Cohort 1: Durvalumab Continuation	Cohort 2: Durvalumab Restart	Cohort 3: No Restart of Durvalumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	25	38	
Units: participants	90	23	26	

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2: Overall Response Rate (ORR)

End point title	Cohort 2: Overall Response Rate (ORR)[3]

End point description:

The ORR was defined as the percentage of participants with a confirmed investigator-assessed response of either complete response (CR) or partial response (PR) from the date of re-initiation of treatment with durvalumab monotherapy. Tumor assessments were performed according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1). CR was defined as the disappearance of all target lesions (TLs) since baseline and reduction in short axis diameter to <10 millimeters (mm) for any pathological lymph nodes selected as TLs. PR was defined as at least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameter. The Response evaluable analysis set included those participants who underwent retreatment with durvalumab in Cohort 2.

End point type	Secondary

End point timeframe:

Tumor assessments as determined by the Investigator (at least every 12 weeks) until withdrawal of consent, progression or death; approximately 30 months

Notes:

[3] - 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: As the endpoint is descriAs the endpoint is descriptive in nature, no statistical analysis is presented,ptive in nature, no statistical analysis is presented,

End point values	Cohort 2: Durvalumab Restart			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 84)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab); approximately 37 months

Adverse event reporting additional description:

The Safety analysis set included those participants who received at least 1 dose of durvalumab on this study or enrolled on this study within 90 days of the last dose of durvalumab or durvalumab combination on the respective parent clinical study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Cohort 1 included participants who had received durvalumab monotherapy or durvalumab combination therapy under the parent clinical study (including those who underwent retreatment per the parent study) who had not clinically progressed and who were eligible to continue durvalumab treatment after completing dosing of all other anticancer agents, including other investigational agents. Participants received durvalumab monotherapy 1500 mg via IV infusion every 4 weeks on Day 1 of each cycle until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Reporting group title	Cohort 3

Reporting group description:

Cohort 3 included participants previously treated with durvalumab monotherapy or in combination with any other approved or investigational anticancer agents who were no longer receiving durvalumab and were not eligible to receive retreatment. Participants did not receive any study drug.

Reporting group title	Cohort 2

Reporting group description:

Cohort 2 included participants who had completed durvalumab monotherapy or combination therapy with any other approved or investigational anticancer agents in a parent study, without confirmed PD during the period of treatment, and who were potentially eligible for retreatment with durvalumab. Participants received durvalumab monotherapy 1500 mg via IV infusion every 4 weeks on Day 1 of each cycle until confirmed PD, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Serious adverse events	Cohort 1	Cohort 3	Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 100 (23.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	10	1	0
number of deaths resulting from adverse events	4	0	0
Investigations			
Lipase increased			

subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Malignant melanoma in situ			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Basal cell carcinoma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	2 / 100 (2.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dementia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Blood and lymphatic system disorders			
Anaemia of chronic disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Interstitial lung disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Pneumonitis			

subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Pneumothorax			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Pulmonary oedema			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pemphigoid			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Brain abscess			

subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
COVID-19			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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
Pneumonia			
subjects affected / exposed	3 / 100 (3.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 2 (0.00%)	0 / 7 (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

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

Non-serious adverse events	Cohort 1	Cohort 3	Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 100 (72.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 100 (7.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 100 (11.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	17	0	0
Blood creatinine increased			
subjects affected / exposed	8 / 100 (8.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	12	0	0
Lipase increased			
subjects affected / exposed	7 / 100 (7.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	14	0	0

Amylase increased			
subjects affected / exposed	5 / 100 (5.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 100 (8.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	11	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 100 (6.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	7	0	0
Intracranial aneurysm			
subjects affected / exposed	0 / 100 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 100 (11.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	11	0	0
Asthenia			
subjects affected / exposed	9 / 100 (9.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Pyrexia			
subjects affected / exposed	5 / 100 (5.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 100 (8.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	12	0	0
Neutropenia			
subjects affected / exposed	5 / 100 (5.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	15	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 100 (5.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	8	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	8 / 100 (8.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	10	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 100 (8.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	10	0	0
Rash			
subjects affected / exposed	5 / 100 (5.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	7	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	17 / 100 (17.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	17	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 100 (9.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	11	0	0
Back pain			
subjects affected / exposed	9 / 100 (9.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	11	0	0
Myalgia			
subjects affected / exposed	6 / 100 (6.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	6	0	0
Pain in extremity			
subjects affected / exposed	8 / 100 (8.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	10	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	17 / 100 (17.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	19	0	0
Pneumonia			
subjects affected / exposed	6 / 100 (6.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	6	0	0
Escherichia infection			

subjects affected / exposed	0 / 100 (0.00%)	0 / 2 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	5 / 100 (5.00%)	0 / 2 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2019	An inclusion criterion was added and editorial changes were made in the exclusion criteria. Redundant reference was removed. Appendices were updated.
25 September 2019	Clarification was provided for study assessments and subsequent anticancer therapy after treatment discontinuation. Details for study assessments and exclusion criteria were updated. Time period for prohibition of live (attenuated) vaccines and information for rescue medications was updated. Updates were made in applicable regulations.
12 April 2022	Revised that the last patient visit will be completed in quarter 4 of 2022. Updated the sample size limit. Clarification provided for efficacy and safety analysis and concomitant medications. Updates were made in study completion activities. Participant management details after study completion were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported