Clinical trial results:
ALICE: A randomized placebo-controlled phase II study evaluating atezolizumab combined with immunogenic chemotherapy in patients with metastatic triple-negative breast cancer.

Summary

EudraCT number	2016-003570-40
Trial protocol	DK
Global end of trial date	25 April 2023

Results information

Result version number	v1 (current)
This version publication date	18 October 2024
First version publication date	18 October 2024
Summary attachment (see zip file)	Published article (Røssevold et al. Nature Medicine 2022.pdf)

Trial information

Trial identification

Sponsor protocol code	ML39079_ALICE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03164993
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Oslo University Hospital, Department of Oncology
Sponsor organisation address	Ullernchausseen 70, Oslo, Norway, 0379
Public contact	Dr. Jon Amund Kyte (Principal Investigator), Oslo University Hospital, +47 97569619, jonky@ous-hf.no
Scientific contact	Dr. Jon Amund Kyte (Principal Investigator), Oslo University Hospital, +47 97569619, jonky@ous-hf.no

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	05 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Co-primary objectives:
Assessment of toxicity of combined treatment with atezolizumab, pegylated liposomal doxorubicin and cyclophosphamide.
Assessment of clinical response: Progression-free survival; descriptive comparison of the PFS rates in the total per protocol population, and the PD-L1+ PP population

Protection of trial subjects:

The trial was conducted according to the guidelines of Good Clinical Practice and the principles of the World Medical Association’s Declaration of Helsinki. All patients provided written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 47
Country: Number of subjects enrolled	Denmark: 21
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	53
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial enrolled 68 patients at 5 academic hospitals in Norway (n = 47) and Denmark (n = 21): Oslo University Hospital (Oslo, NO), Stavanger University Hospital (Stavanger, NO), St.Olavs Hospital (Trondheim, NO), Vejle Hospital (Vejle, DK) and Rigshospitalet (Copenhagen, DK).

Pre-assignment

Screening details:

Eligible patients were adult women and men with metastatic or incurable locally advanced, histologically confirmed triple-negative breast cancer who had received a maximum of one previous line of chemotherapy in the metastatic setting.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Blinding implementation details:

Placebo treatment consisted of an identical-looking intravenous infusion of NaCl 0.9% administered in the same manner. The preparation of active drug dilution/placebo, according to the respective randomization code, was facilitated by the hospital pharmacy, in order to maintain the double blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo-chemotherapy

Arm description:

Placebo plus pegylated liposomal doxorubicin plus cyclophosphamide

Arm type	Active comparator
Investigational medicinal product name	Pegylated liposomal doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated liposomal doxorubicin 20 mg/m2 i.v. every 2nd week. An upper limit of 44 mg per dose will be applied to patients with a body surface area >2.2 m2

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide tablets 50 mg per day, daily as continuous treatment for the first 2 weeks in each 4 week period (i.e. every second 2-week cycle)

Arm title	Atezolizumab-chemotherapy

Arm description:

Atezolizumab plus pegylated liposomal doxorubicin plus cyclophosphamide

Arm type	Experimental

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab will be administered intravenously 840 mg every 2nd week

Investigational medicinal product name	Pegylated liposomal doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated liposomal doxorubicin 20 mg/m2 i.v. every 2nd week. An upper limit of 44 mg per dose will be applied to patients with a body surface area >2.2 m2

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cyclophosphamide tablets 50 mg per day, daily as continuous treatment for the first 2 weeks in each 4 week period (i.e. every second 2-week cycle)

Number of subjects in period 1	Placebo-chemotherapy	Atezolizumab-chemotherapy
Started	28	40
Completed	0	2
Not completed	28	38
Physician decision	1	1
Adverse event, non-fatal	1	2
Still on treatment at data lock	-	2
Lack of efficacy	26	33

Baseline characteristics

Reporting groups	
Reporting group title	Placebo-chemotherapy
Reporting group description:	
Placebo plus pegylated liposomal doxorubicin plus cyclophosphamide	
Reporting group title	Atezolizumab-chemotherapy
Reporting group description:	
Atezolizumab plus pegylated liposomal doxorubicin plus cyclophosphamide	

Reporting group values	Placebo-chemotherapy	Atezolizumab-chemotherapy	Total
Number of subjects	28	40	68
Age categorical Units: Subjects			
Adults (18-64 years)	24	29	53
From 65-84 years	4	11	15
Age continuous Units: years			
median	52.5	58.5	
full range (min-max)	28 to 74	31 to 77	-
Gender categorical Units: Subjects			
Female	28	39	67
Male	0	1	1
PD-L1 status			
Programmed death ligand 1 expression by the SP-142 assay			
Units: Subjects			
Positive	10	21	31
Negative	17	19	36
Missing	1	0	1
ECOG performance status			
Eastern Oncology Group Performance status			
Units: Subjects			
ECOG 0	21	27	48
ECOG 1	7	13	20
De novo metastatic disease Units: Subjects			
Yes	8	10	18
No	20	30	50
Bone metastases Units: Subjects			
Yes	16	17	33
No	12	23	35
Liver metastases Units: Subjects			
Yes	13	12	25
No	15	28	43
Lung metastases			

Units: Subjects			
Yes	10	18	28
No	18	22	40
Lymph node metastases Units: Subjects			
Yes	13	22	35
No	15	18	33
CNS metastases Units: Subjects			
Yes	1	1	2
No	27	39	66
Number of metastatic sites Units: Subjects			
≤2	15	27	42
>2	13	13	26
Line of chemotherapy Units: Subjects			
1st	16	24	40
2nd	12	16	28
Previous anthracycline treatment Units: Subjects			
Yes	20	28	48
No	8	12	20
Intrinsic breast cancer subtype Units: Subjects			
Lum A	2	0	2
Lum B	1	1	2
HER2E	2	4	6
Basal	12	22	34
Missing	11	13	24
BRCA mutation status Units: Subjects			
BRCA1 mutation	1	2	3
Normal variant	12	22	34
Missing	15	16	31

Subject analysis sets

Subject analysis set title	Placebo-chemo per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients in placebo-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin

Subject analysis set title	Atezolizumab-chemo per-protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients in atezolizumab-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin

Reporting group values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population	
Number of subjects	23	36	
Age categorical Units: Subjects			
Adults (18-64 years)	19	25	
From 65-84 years	4	11	
Age continuous Units: years			
median	52	59	
full range (min-max)	28 to 74	31 to 77	
Gender categorical Units: Subjects			
Female	23	35	
Male	0	1	
PD-L1 status			
Programmed death ligand 1 expression by the SP-142 assay			
Units: Subjects			
Positive	8	19	
Negative	14	17	
Missing	1	0	
ECOG performance status			
Eastern Oncology Group Performance status			
Units: Subjects			
ECOG 0	16	25	
ECOG 1	7	11	
De novo metastatic disease Units: Subjects			
Yes	6	9	
No	17	27	
Bone metastases Units: Subjects			
Yes	13	14	
No	10	22	
Liver metastases Units: Subjects			
Yes	9	10	
No	14	26	
Lung metastases Units: Subjects			
Yes	9	16	
No	14	20	
Lymph node metastases Units: Subjects			
Yes	13	20	
No	10	16	
CNS metastases Units: Subjects			
Yes	1	1	
No	22	35	
Number of metastatic sites			

Units: Subjects			
≤2	12	26	
>2	11	10	
Line of chemotherapy Units: Subjects			
1st	12	23	
2nd	11	13	
Previous anthracycline treatment Units: Subjects			
Yes	17	25	
No	6	11	
Intrinsic breast cancer subtype Units: Subjects			
Lum A	2	0	
Lum B	1	1	
HER2E	2	4	
Basal	11	20	
Missing	7	11	
BRCA mutation status Units: Subjects			
BRCA1 mutation	1	2	
Normal variant	11	22	
Missing	11	12	

End points

End points reporting groups

Reporting group title	Placebo-chemotherapy
Reporting group description:	
Placebo plus pegylated liposomal doxorubicin plus cyclophosphamide	
Reporting group title	Atezolizumab-chemotherapy
Reporting group description:	
Atezolizumab plus pegylated liposomal doxorubicin plus cyclophosphamide	
Subject analysis set title	Placebo-chemo per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients in placebo-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin	
Subject analysis set title	Atezolizumab-chemo per-protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients in atezolizumab-chemotherapy arm evaluated for tumor response and received a minimum of 4 doses of atezolizumab/placebo and a minimum of 3 doses with pegylated liposomal doxorubicin	

Primary: PFS, per-protocol population

End point title	PFS, per-protocol population
End point description:	
PFS in the per-protocol population. PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per immune-modified RECIST (iRECIST), or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The HR for disease progression or death (atezo-chemo versus placebo-chemo) will be estimated using a Cox proportional hazards model.	
End point type	Primary
End point timeframe:	
Until data cutoff 5 th of July 2022	

End point values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[1]	36[2]		
Units: Months				
median (confidence interval 95%)	3.5 (2.6 to 5.5)	4.3 (3.5 to 7.3)		

Notes:

[1] - Per-protocol population Placebo-chemo

[2] - Per-protocol population Atezo-chemo

Statistical analyses

Statistical analysis title	Cox proportional hazards model
Comparison groups	Placebo-chemo per-protocol population v Atezolizumab-chemo per-protocol population
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.99

Primary: PFS, PD-L1 positive per-protocol population

End point title	PFS, PD-L1 positive per-protocol population

End point description:

PFS in the PD-L1 positive patients (SP142 assay) of the PP population.
PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per immune-modified RECIST (iRECIST), or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The HR for disease progression or death will be estimated using a Cox proportional hazards model.

End point type	Primary

End point timeframe:

Until data cutoff 5th July 2022

End point values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[3]	19[4]		
Units: Months				
median (confidence interval 95%)	3.9 (3.6 to 99)	5.5 (2.9 to 9.6)		

Notes:

[3] - PD-L1 pos PP-population

[4] - PD-L1 pos PP population

Statistical analyses

Statistical analysis title	Cox proportional hazards model
Comparison groups	Placebo-chemo per-protocol population v Atezolizumab-chemo per-protocol population

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.54

Secondary: PFS, full analysis set population

End point title	PFS, full analysis set population

End point description:

Progression-free survival in the full analysis set population (n = 68).
PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per immune-modified RECIST (iRECIST), or death from any cause, whichever occurs first. Data for patients without disease progression or death will be censored at the last tumor assessment date. Data for patients with a PFS event who missed two or more assessments scheduled immediately prior to the date of the PFS event will be censored at the last tumor assessment prior to the missed visits. If no tumor assessment was performed after randomization, data will be censored at the date of randomization +1 day. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. The HR for disease progression or death (atezo-chemo versus placebo-chemo) will be estimated using a Cox proportional hazards model.

End point type	Secondary

End point timeframe:

Until data cutoff 5th of July

End point values	Placebo-chemotherapy	Atezolizumab-chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Months				
median (confidence interval 95%)	3.1 (1.8 to 5.4)	3.9 (3.5 to 5.9)		

Statistical analyses

Statistical analysis title	Cox proportional hazards model
Comparison groups	Placebo-chemotherapy v Atezolizumab-chemotherapy

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.95

Secondary: OS, full analysis set population

End point title	OS, full analysis set population

End point description:

Overall survival in the full analysis set population (n = 68).
Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model. The CI for the HR will be provided. Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm.

End point type	Secondary

End point timeframe:

Until data cutoff 5th of July 2022

End point values	Placebo-chemotherapy	Atezolizumab-chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[5]	40[6]		
Units: Months				
median (confidence interval 95%)	14.6 (8.1 to 21.3)	15.3 (10.9 to 25.5)		

Notes:

[5] - Full analysis set

[6] - Full analysis set

Statistical analyses

Statistical analysis title	Cox proportional hazards model

Statistical analysis description:

Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model.

Comparison groups	Placebo-chemotherapy v Atezolizumab-chemotherapy

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.3

Secondary: OS, per-protocol population

End point title	OS, per-protocol population

End point description:

Overall survival in the per-protocol population (n = 59).
Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model. The CI for the HR will be provided. Kaplan-Meier methodology will be used to estimate the median OS for each treatment arm.

End point type	Secondary

End point timeframe:

Until data cutoff 5th of July 2022

End point values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23[7]	36[8]		
Units: Months				
median (confidence interval 95%)	15.6 (8.1 to 21.3)	15.3 (11.2 to 27.0)		

Notes:

[7] - Per-protocol population

[8] - Per protocol population

Statistical analyses

Statistical analysis title	Cox proportional hazards model

Statistical analysis description:

Overall survival (OS) will be calculated from the time of randomization until death. Patients alive at the time of data analysis will be treated as censored. The HR for OS will be estimated using a Cox proportional hazards model.

Comparison groups	Placebo-chemo per-protocol population v Atezolizumab-chemo per-protocol population

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.3

Secondary: ORR, full analysis set population

End point title	ORR, full analysis set population

End point description:

The proportion of patients in each arm with best overall response either "iPR" or "iCR" by iRECIST in the full analysis set population.

End point type	Secondary

End point timeframe:

Until data cutoff 5th of July 2022

End point values	Placebo-chemotherapy	Atezolizumab-chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[9]	40[10]		
Units: Objective responders				
iPR/iCR	5	11		
Non-iPR/iCR	23	29		

Notes:

[9] - Full analysis set

[10] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: ORR, per-protocol population

End point title	ORR, per-protocol population

End point description:

The proportion of patients in each arm with best overall response either "iPR" or "iCR" by iRECIST in the per-protocol population

End point type	Secondary

End point timeframe:

Until 5th of July 2022

End point values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	36		
Units: Objective responders				
iCR/iPR	5	11		
Non-iCR/iPR	18	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate, full analysis set population

End point title	Clinical benefit rate, full analysis set population

End point description:

The proportion in each arm of the full analysis set population with clinical benefit (CBR). CBR was defined as the proportion of patients who had either an objective response (iPR/iCR) by iRECIST or stable disease lasting at least until the radiological evaluation at 24weeks±7days.

End point type	Secondary

End point timeframe:

Until data cutoff 5th of July 2022

End point values	Placebo-chemotherapy	Atezolizumab-chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Subjects				
CB	10	20		
Non-CB	18	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate, per-protocol population

End point title	Clinical benefit rate, per-protocol population

End point description:

The proportion in each arm of the per-protocol population with clinical benefit (CBR). CBR was defined as the proportion of patients who had either an objective response (iPR/iCR) by iRECIST or stable disease lasting at least until the radiological evaluation at 24weeks±7days.

End point type	Secondary

End point timeframe:

Until data cutoff 5th July 2022

End point values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	36		
Units: Subjects				
CB	10	19		
Non-CB	13	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Durable response rate, full analysis set population

End point title	Durable response rate, full analysis set population

End point description:

The number of subjects in each arm of the full analysis set population with durable response. Durable response rate (DRR) was defined as the proportion of patients with a duration of response of ≥6months.

End point type	Secondary

End point timeframe:

Until data cutoff 5th of July 2022

End point values	Placebo-chemotherapy	Atezolizumab-chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Subjects				
Durable response	1	6		
Non-durable response	27	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Durable response rate, per-protocol population

End point title	Durable response rate, per-protocol population

End point description:

The number of subjects in each arm of the per-protocol population with durable response. Durable response rate (DRR) was defined as the proportion of patients with a duration of response of ≥6months.

End point type	Secondary

End point timeframe:

Until data cut-off 5th of July 2022

End point values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	36		
Units: Subjects				
Durable response	1	6		
Non-durable response	22	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Median duration of response, full analysis set population

End point title	Median duration of response, full analysis set population

End point description:

The median duration of response (iPR/iCR by iRECIST) in each arm of the full analysis set population. The duration of response was defined as the time from the first documentation of an objective response to the time of progression or death.

End point type	Secondary

End point timeframe:

Until 5th of July 2022

End point values	Placebo-chemotherapy	Atezolizumab-chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	40		
Units: Months				
median (inter-quartile range (Q1-Q3))	3.7 (1.6 to 4.8)	7.3 (2.1 to 19.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median duration of response, per-protocol population

End point title	Median duration of response, per-protocol population

End point description:

The median duration of response (iPR/iCR by iRECIST) in each arm of the per-protocol population. The duration of response was defined as the time from the first documentation of an objective response to the time of progression or death.

End point type	Secondary

End point timeframe:

Until data cutoff 5th of July 2022

End point values	Placebo-chemo per-protocol population	Atezolizumab-chemo per-protocol population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	36		
Units: Months				
median (inter-quartile range (Q1-Q3))	3.7 (1.6 to 4.8)	7.3 (2.1 to 19.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From 24th AUG 2017 until data lock 5th of JUL 2022.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Placebo-chemotherapy
Reporting group description: -	
Reporting group title	Atezolizumab-chemotherapy
Reporting group description: -	

Serious adverse events	Placebo-chemotherapy	Atezolizumab-chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 28 (28.57%)	19 / 40 (47.50%)	
number of deaths (all causes)	23	28	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 28 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 28 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	1 / 28 (3.57%)	5 / 40 (12.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 28 (3.57%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 28 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract obstruction			
subjects affected / exposed	0 / 28 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 28 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 28 (0.00%)	3 / 40 (7.50%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infection			
subjects affected / exposed	1 / 28 (3.57%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo-chemotherapy	Atezolizumab-chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 28 (96.43%)	40 / 40 (100.00%)	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 28 (3.57%)	2 / 40 (5.00%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	12 / 28 (42.86%)	20 / 40 (50.00%)	
occurrences (all)	15	23	
Pyrexia			
subjects affected / exposed	1 / 28 (3.57%)	3 / 40 (7.50%)	
occurrences (all)	3	5	
Malaise			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Oedema			
subjects affected / exposed	2 / 28 (7.14%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Pain			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Thirst			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 28 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			
Vulvovaginal dryness			
subjects affected / exposed	0 / 28 (0.00%)	4 / 40 (10.00%)	
occurrences (all)	0	4	
Vaginal haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal pain			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	4 / 28 (14.29%)	5 / 40 (12.50%)	
occurrences (all)	4	5	
Dyspnoea			
subjects affected / exposed	3 / 28 (10.71%)	4 / 40 (10.00%)	
occurrences (all)	3	8	
Painful respiration			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	10 / 28 (35.71%)	18 / 40 (45.00%)	
occurrences (all)	16	19	
Neutrophil count decreased			
subjects affected / exposed	4 / 28 (14.29%)	4 / 40 (10.00%)	
occurrences (all)	5	9	
Weight decreased			
subjects affected / exposed	0 / 28 (0.00%)	3 / 40 (7.50%)	
occurrences (all)	0	3	
Hepatic enzyme increased			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Pancreatic enzymes increased			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences (all)	2	2	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 28 (3.57%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Fracture			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 28 (3.57%)	4 / 40 (10.00%)	
occurrences (all)	1	4	
Headache			
subjects affected / exposed	4 / 28 (14.29%)	4 / 40 (10.00%)	
occurrences (all)	4	4	
Neuropathy peripheral			
subjects affected / exposed	3 / 28 (10.71%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Dysgeusia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Parosmia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Amnesia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Dysarthria			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Leukopenia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	15 / 28 (53.57%)	21 / 40 (52.50%)	
occurrences (all)	16	25	
Mucosal inflammation			
subjects affected / exposed	6 / 28 (21.43%)	19 / 40 (47.50%)	
occurrences (all)	6	25	
Constipation			
subjects affected / exposed	12 / 28 (42.86%)	18 / 40 (45.00%)	
occurrences (all)	12	19	
Dyspepsia			
subjects affected / exposed	3 / 28 (10.71%)	8 / 40 (20.00%)	
occurrences (all)	3	9	
Diarrhoea			
subjects affected / exposed	6 / 28 (21.43%)	4 / 40 (10.00%)	
occurrences (all)	6	4	
Dry mouth			
subjects affected / exposed	2 / 28 (7.14%)	6 / 40 (15.00%)	
occurrences (all)	2	6	
Abdominal pain			
subjects affected / exposed	2 / 28 (7.14%)	5 / 40 (12.50%)	
occurrences (all)	2	6	
Dysphagia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	11 / 28 (39.29%)	26 / 40 (65.00%)	
occurrences (all)	14	36	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 28 (10.71%)	21 / 40 (52.50%)	
occurrences (all)	3	22	
Pruritus			

subjects affected / exposed	2 / 28 (7.14%)	7 / 40 (17.50%)	
occurrences (all)	2	7	
Hair growth abnormal			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Nail ridging			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Pigmentation disorder			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Skin hyperpigmentation			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 28 (7.14%)	5 / 40 (12.50%)	
occurrences (all)	2	5	
Hyperthyroidism			
subjects affected / exposed	2 / 28 (7.14%)	1 / 40 (2.50%)	
occurrences (all)	2	1	
Cushingoid			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	6 / 28 (21.43%)	11 / 40 (27.50%)	
occurrences (all)	9	17	
Infections and infestations			

Skin infection			
subjects affected / exposed	2 / 28 (7.14%)	7 / 40 (17.50%)	
occurrences (all)	2	8	
Upper respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	6 / 40 (15.00%)	
occurrences (all)	0	9	
Urinary tract infection			
subjects affected / exposed	1 / 28 (3.57%)	5 / 40 (12.50%)	
occurrences (all)	3	16	
Oral fungal infection			
subjects affected / exposed	1 / 28 (3.57%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Gastroenteritis			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Conjunctivitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Mastitis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 28 (10.71%)	7 / 40 (17.50%)	
occurrences (all)	3	7	
Hyperglycaemia			
subjects affected / exposed	0 / 28 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	1 / 28 (3.57%)	1 / 40 (2.50%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2020	Updated inclusion/exclusion criteria. Specification of endpoints and hypotheses.
12 February 2021	Update in primary objectives and efficacy measures, and inclusion/exclusion criteria. Interim analysis of PD-L1 negative patients.
22 February 2022	Premature end of patient recruitment. Update in planned statistical analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36482103