Clinical trial results:
Phase II trial of atezolizumab (anti-PD-L1) in the treatment of stage IIb-IV mycosis fungoides/sezary syndrome patients relapsed/refractory after a previous systemic treatment (PARCT)

Summary

EudraCT number	2017-003680-35
Trial protocol	GB DE ES AT GR IT
Global end of trial date	18 August 2022

Results information

Result version number	v1 (current)
This version publication date	30 July 2023
First version publication date	30 July 2023

Trial information

Trial identification

Sponsor protocol code	1652-CLTF

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03357224
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer (EORTC)
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Regulatory Affairs Department, European Organisation for Research and Treatment of Cancer (EORTC), 0032 27741044, regulatory@eortc.org
Scientific contact	Regulatory Affairs Department, European Organisation for Research and Treatment of Cancer (EORTC), 0032 27741044, regulatory@eortc.org

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	07 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2022
Global end of trial reached?	Yes
Global end of trial date	18 August 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the antitumor activity of atezolizumab for patients with refractory or relapsed advanced stages of mycosis fungoides and Sézary syndrome, assessed in terms of the overall response rate, according to EORTC-ISCL-USCLC criteria

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Trial assessing atezolizumab (anti-PD-L1) as treatment option for patients with mycosis fungoides (MF) /sezary syndrome (SS) having progressed under or after previous therapy. For this study, we invite patients suffering from MF and SS who have progressed after initial therapy or have failed to respond to previous therapy.
MF and SS are cancers in which lymphocytes become malignant (cancerous) and affect the skin. In MF, the disease is generally limited to the skin, and people develop flat or raised areas on their skin where the lymphocytes have accumulated. Sometimes even larger aggregations of lymphocytes occur in the skin or lymph nodes, resulting in tumors. In SS, the skin is often reddened or itchy, and some abnormal lymphocytes circulate in the blood. Atezolizumab is already used to treat adults with a cancer that affects the bladder and the urinary system, called urothelial carcinoma, and a cancer that affects the lungs, called non-small cell lung cancer.

In standard practice, the disease will be treated with conventional chemotherapy that unfortunately has a limited lasting benefit. In this study, we want to see if a new treatment option can optimize and improve response and make benefit last as long as possible. This new treatment option is immunotherapy, using atezolizumab (Tecentriq). Immunotherapy is a cancer treatment that uses antibodies made in the laboratory from a single type of immune system cell. These antibodies can identify substances on cancer cells or normal cells that may help cancer cell grow. The antibodies attach to the substances and kill the cancer cells, block their growth, or keep them from spreading. Atezolizumab blocks a protein called PD-L1 (programmed death-ligand 1) from binding to its receptor found on the surface of lymphocytes. It helps to restore the immune activity of the body against the cancer. Atezolizumab is already used to treat adults with a cancer that affects the bladder and the urinary system, and the lungs.

Evidence for comparator:

This is a single arm study. Two arms were provided in various parts of this report due to EUDRACT reporting system limitation.

Actual start date of recruitment	22 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	26
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Following the occurrence of three toxic deaths, an urgent safety measure was put in place and the study was prematurely closed for accrual. At the time of closure, a total of 26 patients had been registered by 7 institutions in 7 countries between 23/10/2018 and 16/09/2019. Nine of the 26 patients did not meet the eligibility criteria.

Pre-assignment

Screening details:

•Male or female patients with diagnosis of CTCL (MF or SS) tumor stage IIB to IVB
•Inadequate response or secondary treatment failure to at least 1 prior systemic therapy for CTCL according to treatment guidelines
•Age ≥ 18 years old
•WHO performance status 0-1
•Adequate bone marrow and organ function prior to receiving the study treatment

Pre-assignment period milestones

Number of subjects started	26
Number of subjects completed	26

Period 1

Period 1 title	Overall period - Full patient population (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

NA

Arms

Arm title	Atezolizumab

Arm description:

Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day. cycle. Patients will receive atezoluzimab 1200 mg IV Q3w for 1 year since start of first protocol treatment administration unless clinically relevant disease progression or other withdrawal criteria.

Arm type	Experimental
Investigational medicinal product name	Atezoluzimab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day. Patients will receive atezoluzimab 1200 mg IV Q3w for 1 year since start of first protocol treatment administration unless clinically relevant disease progression or other withdrawal criteria. Those patients for whom a clinical benefit is documentable at 1 year will be given the possibility to prolong the treatment for a maximum of two additional years unless a withdrawal criterion occurs earlier. In case of any additional adverse event grade 4 or higher is observed, the treatment will be permanently discontinued for all patients.

Number of subjects in period 1	Atezolizumab
Started	26
Completed	4
Not completed	22
Patient decision	4
Disease progression	13
Toxicity	4
Death not due to malignant disease/toxicity	1

Baseline characteristics

Reporting groups	
Reporting group title	Atezolizumab
Reporting group description:	
Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day. cycle. Patients will receive atezoluzimab 1200 mg IV Q3w for 1 year since start of first protocol treatment administration unless clinically relevant disease progression or other withdrawal criteria.	

Reporting group values	Atezolizumab	Total	
Number of subjects	26	26	
Age categorical			
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	16	16	
85 years and over	0	0	
Age continuous			
Age continuous			
Units: years			
arithmetic mean	66.77		
standard deviation	± 11.14	-	
Gender categorical			
Gender			
Units: Subjects			
Female	14	14	
Male	12	12	
Stage			
Disease stage			
Units: Subjects			
IB	1	1	
IIB	9	9	
IIIA	3	3	
IIIB	4	4	
IVA	5	5	
IVB	4	4	
WHO performance status			
Current WHO performance status			
Units: Subjects			
PS 0	15	15	
PS 1	11	11	
Diagnosis of CTCL			

Diagnosis of CTCL			
Units: Subjects			
Mycosis fungoides (MF)	20	20	
Sézary Syndrome (SS)	6	6	
Skin			
Skin stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
T1	1	1	
T2	6	6	
T3	9	9	
T4	10	10	
Node			
Node stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
N0	14	14	
N1	2	2	
N2	1	1	
N3	7	7	
Nx	2	2	
Visceral			
Visceral stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
M0	22	22	
M1	4	4	
Blood			
Blood stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
B0	13	13	
B1	7	7	
B2	6	6	
Node involvement at baseline (N3 vs. others)			
Node involvement at baseline (N3 vs. others)			
Units: Subjects			
No	19	19	
Yes	7	7	
mSWAT score			
Skin assessment is based on the mSWAT (Ref. 22, Ref. 23). This technique involves the direct assessment of the body-surface area (BSA) of each type of MF/SS lesion (palm plus fingers of the patient = approximately 1% BSA) in each of 12 areas of the body, multiplying the sum of the BSA of each lesion type by a weighting factor (patch, plaque and tumor) and generating a sum of the subtotals of each lesion subtype as shown below			
Units: Continuous score			
arithmetic mean	79.98		
standard deviation	± 48.53	-	

Subject analysis sets

Subject analysis set title	Intention-to-treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All registered patients.

All 26 enrolled patients started atezolizumab in this study and were reviewed for eligibility by the project physician and approved by the study coordinator. Nine patients were considered to be ineligible.
Major deviations included;
-Retinoid treatment ongoing at start of study
-Prostate adenocarcinoma diagnosed in 2018
-Targetrin treatment stopped at start of study treatment instead of 4 weeks before
-Latent tuberculosis treated with rifampicin
Uncontrolled diabetes
-Uncontrolled diabetes with glycated hemoglobin above normal ranges
-Tuberculosis infection
-Tagretin and octagam (igg) washout not respected
-No data on glucose level at baseline but patient is diabetic
-Deep venous thrombosis and pulmonary embolism resolved 1 week prior to enrollment

Subject analysis set title	Per protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

All registered patients who are eligible and have started atezolizumab treatment

Reporting group values	Intention-to-treat Population	Per protocol Population	
Number of subjects	26	17	
Age categorical			
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	10	7	
From 65-84 years	16	10	
85 years and over			
Age continuous			
Age continuous			
Units: years			
arithmetic mean	66.77	67.88	
standard deviation	± 11.14	± 8.12	
Gender categorical			
Gender			
Units: Subjects			
Female	14	10	
Male	12	7	
Stage			
Disease stage			
Units: Subjects			
IB	1	1	
IIB	9	7	
IIIA	3	1	
IIIB	4	3	
IVA	5	4	
IVB	4	1	
WHO performance status			
Current WHO performance status			

Units: Subjects			
PS 0	15	9	
PS 1	11	8	
Diagnosis of CTCL			
Diagnosis of CTCL			
Units: Subjects			
Mycosis fungoides (MF)	20	12	
Sézary Syndrome (SS)	6	5	
Skin			
Skin stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
T1	1	1	
T2	6	3	
T3	9	7	
T4	10	6	
Node			
Node stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
N0	14	10	
N1	2	0	
N2	1	0	
N3	7	5	
Nx	2	2	
Visceral			
Visceral stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
M0	22	16	
M1	4	1	
Blood			
Blood stage according to EORTC-ISCL-USCLC criteria			
Units: Subjects			
B0	13	8	
B1	7	5	
B2	6	4	
Node involvement at baseline (N3 vs. others)			
Node involvement at baseline (N3 vs. others)			
Units: Subjects			
No	19	12	
Yes	7	5	
mSWAT score			
Skin assessment is based on the mSWAT (Ref. 22, Ref. 23). This technique involves the direct assessment of the body-surface area (BSA) of each type of MF/SS lesion (palm plus fingers of the patient = approximately 1% BSA) in each of 12 areas of the body, multiplying the sum of the BSA of each lesion type by a weighting factor (patch, plaque and tumor) and generating a sum of the subtotals of each lesion subtype as shown below			
Units: Continuous score			
arithmetic mean	79.98	87.95	
standard deviation	±	± 55.49	

End points

End points reporting groups

Reporting group title	Atezolizumab

Reporting group description:

Atezolizumab at a fixed dose of 1200 mg will be administered intravenously on Day 1 of each 21-day. cycle. Patients will receive atezoluzimab 1200 mg IV Q3w for 1 year since start of first protocol treatment administration unless clinically relevant disease progression or other withdrawal criteria.

Subject analysis set title	Intention-to-treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All registered patients.
All 26 enrolled patients started atezolizumab in this study and were reviewed for eligibility by the project physician and approved by the study coordinator. Nine patients were considered to be ineligible.
Major deviations included;
-Retinoid treatment ongoing at start of study
-Prostate adenocarcinoma diagnosed in 2018
-Targetrin treatment stopped at start of study treatment instead of 4 weeks before
-Latent tuberculosis treated with rifampicin
Uncontrolled diabetes
-Uncontrolled diabetes with glycated hemoglobin above normal ranges
-Tuberculosis infection
-Tagretin and octagam (igg) washout not respected
-No data on glucose level at baseline but patient is diabetic
-Deep venous thrombosis and pulmonary embolism resolved 1 week prior to enrollment

Subject analysis set title	Per protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

All registered patients who are eligible and have started atezolizumab treatment

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

Overall response rate (ORR) is defined as the proportion of patients who achieved complete response (CR) or partial response (PR) as best result up to maximum of 1 year from patient registration.

The study was designed to reject the null hypothesis (H0: ORR=40%) with 90% power under the alternative hypothesis (H1: ORR=65%) using an exact binary test at 10% significance level 1-sided. A total of 29 eligible patients were needed. The drug would be considered to warrant further investigation if 16 or more out of 29 eligible patients who start treatment were responders (CR or PR).

At the time of premature closure, there were only 17 eligible patients. Given the observed sample size , we assumed the same design; H0: ORR=40%, H1: ORR=65% and alpha=0.1. Based on this, with 78% power, at least 10 out of 17 eligible patients should be responders (CR or PR) for the drug to be considered worthwhile for further investigation (exact Type I error = 9.2% and power=78.7%).

End point type	Primary

End point timeframe:

ORR is defined as the proportion of patients who achieved CR or PR as best result up to maximum of 1 year from patient registration.

This is a single arm assessment. This endpoint was analysed in the per-protocol.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[1]	17[2]		
Units: Patients				
Success	4	3		
Failure	22	14		

Notes:

[1] - All registered patients who started atezolizumab.

[2] - All eligible patients who started atezolizumab.

Statistical analyses

Statistical analysis title	Best overall response rate (CR/PR)

Statistical analysis description:

All patients achieving CR or PR are counted as success. All other cases will be considered as failures. ORR will be calculated by summing the number of participants assessed as having a CR or PR and dividing this by the total number of patients who are eligible and started treatment.

This is a single arm assessment. Two arms were provided due to EUDRACT reporting system limitation. This endpoint was analysed in the per-protocol population.

Comparison groups	Per protocol Population v Intention-to-treat Population
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[3]
Method	exact binary test
Parameter estimate	Proportion-Exact binomial 1-sided 90% CI
Point estimate	17.6
Confidence interval	
level	90 %
sides	1-sided
lower limit	6.6

Notes:

[3] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation This analysis was performed in the per protocol population only

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Progression-free survival (PFS) is defined as the time from treatment start to the first date of progressive disease or death from any cause. For patients who did not progress or die, this endpoint will be censored on the date of last disease assessment

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) is defined as the time from treatment start to the first date of progressive disease or death from any cause.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[4]	17[5]		
Units: Months				
median (confidence interval 95%)	3.0 (1.4 to 4.9)	3.0 (1.4 to 4.9)		

Notes:

[4] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation

[5] - This analysis was only performed in the per protocol population

Statistical analyses

Statistical analysis title	Secondary: PFS (per protocol population)

Statistical analysis description:

Progression free survival (PFS) will be analyzed as time to event endpoints. Median PFS will be estimated by the Kaplan Meier technique. The 95% confidence interval (CI) for the median will be calculated using the reflected CI method.

Comparison groups	Per protocol Population v Intention-to-treat Population
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[6]
Method	Kaplan-Meier
Parameter estimate	Median PFS estimate
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	4.9

Notes:

[6] - This is a single arm assessment and PFS was performed only in the per protocol population. Two arms were provided due to EUDRACT reporting system limitation.

Statistical analysis title	Other specified: PFS (ITT population)

Statistical analysis description:

This is a single arm assessment and this analysis was performed only in the intent-to-treat population. Two arms were provided due to EUDRACT reporting system limitation.

Comparison groups	Intention-to-treat Population v Per protocol Population
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[7]
Method	Kaplan-Meier
Parameter estimate	Median PFS estimate
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.4
upper limit	4

Notes:

[7] - Progression free survival (PFS) will be analyzed as time to event endpoints. Median PFS will be estimated by the Kaplan Meier technique. The 95% confidence interval (CI) for the median will be calculated using the reflected CI method.

This is a single arm assessment. Two arms were provided due to EUDRACT reporting system limitation.

Secondary: Overall survival (OS)	
End point title	Overall survival (OS)
End point description:	
Overall survival (OS) is defined as the time from treatment start to the date of death from any cause. Patients who are still alive will be censored at the last date documented to be alive.	
End point type	Secondary
End point timeframe:	
Overall survival (OS) is defined as the time from treatment start to the date of death from any cause.	

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[8]	17[9]		
Units: Months				
median (confidence interval 95%)	33.6 (16.5 to 999)	33.6 (16.5 to 999)		

Notes:

[8] - This is a single arm test. Two arms are provided due to EUDRACT limitation. 999=estimate not reached

[9] - This analysis was only performed in the per protocol population.
999=estimate not reached

Statistical analyses

Statistical analysis title	Secondary: OS(per protocol population)
Statistical analysis description:	
Median OS will be estimated by the Kaplan Meier technique. The 95% confidence interval (CI) for the median will be calculated using the reflected CI method.	
Comparison groups	Intention-to-treat Population v Per protocol Population
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[10]
Method	Kaplan-Meier
Parameter estimate	Median OS estimate
Point estimate	33.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.5
upper limit	999

Notes:

[10] - This is a single arm assessment and OS was performed only in the per protocol population. Two arms were provided due to EUDRACT reporting system limitation.
Note 999= No estimate

Statistical analysis title	Other specified: OS(ITT population)
Comparison groups	Intention-to-treat Population v Per protocol Population

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[11]
Method	Kaplan-Meier
Parameter estimate	Median OS estimate
Point estimate	999
Confidence interval	
level	95 %
sides	2-sided
lower limit	999
upper limit	999

Notes:

[11] - Median OS was not reached.
999=estimate not reached

Secondary: Time to response

End point title	Time to response

End point description:

Time to response is defined as the time from treatment start until the time measurement criteria for CR/PR (whichever is first recorded) are first met. For patients who did not reach CR/PR, this endpoint will be censored on the date of last disease assessment during treatment. Going off protocol treatment without achieving CR/PR is considered a competing risk.
This is a single arm assessment, presented separately in the per-protocol and Intention-to-treat populations.

End point type	Secondary

End point timeframe:

Time to response is defined as the time from treatment start until the time measurement criteria for CR/PR (whichever is first recorded) are first met.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[12]	17[13]		
Units: Patient				
Complete or Partial response	5	4		
Competing event	21	13		

Notes:

[12] - This is a single arm assessment. Results were presented in the intention-to-treat population

[13] - This is a single arm assessment. Results were presented in the per-protocol population

Statistical analyses

No statistical analyses for this end point

Secondary: Response duration

End point title	Response duration

End point description:

Response duration is defined as the interval from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that progressive disease is objectively documented. This endpoint is defined only in the subset of patients who achieve CR/PR. For patients who did not progress, this endpoint will be censored on the date of last disease assessment.

End point type	Secondary

End point timeframe:

Response duration is defined as the interval from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that progressive disease is objectively documented.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[14]	17[15]		
Units: Months				
arithmetic mean (full range (min-max))	12.63 (4.27 to 20.99)	12.63 (4.27 to 20.99)		

Notes:

[14] - This is a single arm assessment. This endpoint was analysed only in the per-protocol population

[15] - Amongst the 4 patients who achieved CR/PR in the per- protocol population, two patients progressed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next systemic treatment

End point title	Time to next systemic treatment

End point description:

Time to next systemic treatment is defined as the time from initiation of the current atezolizumab treatment until the time the next systemic treatment is recorded. For patients who did not have the record of next systemic treatment, this endpoint will be censored on the date of last adequate follow-up assessment.

End point type	Secondary

End point timeframe:

Time to next systemic treatment is defined as the time from initiation of the current atezolizumab treatment until the time the next systemic treatment is recorded.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[16]	17[17]		
Units: Months				
median (confidence interval 95%)	6.2 (3.1 to 14.8)	5.9 (2.8 to 33.4)		

Notes:

[16] - Note: This is a single are study . Here, the analysis is performed in the ITT-population

[17] - Note: This is a single are study . Here, the analysis is performed in the per- protocol population

Statistical analyses

Statistical analysis title	Secondary: Time to next systemic treatment-per pro

Statistical analysis description:

Analysis will be performed in per-protocol population. Median Time to next systemic treatment will be estimated by the Kaplan Meier technique. The 95% confidence interval (CI) for the median will be calculated using the reflected CI method.

Note: This is a single arm test - two arms were provided due to EUDRACT reporting system limitations

Comparison groups	Intention-to-treat Population v Per protocol Population
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[18]
Parameter estimate	Median time to next systemic treatment
Point estimate	5.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	33.4

Notes:

[18] - Note: This is a single arm test - two arms were provided due to EUDRACT reporting system limitations

Statistical analysis title	Other specified: Time to next systemic treatment

Statistical analysis description:

Analysis will be performed in ITT population. Median Time to next systemic treatment will be estimated by the Kaplan Meier technique. The 95% confidence interval (CI) for the median will be calculated using the reflected CI method.

Note: This is a single arm test - two arms were provided due to EUDRACT reporting system limitations

Comparison groups	Intention-to-treat Population v Per protocol Population
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[19]
Parameter estimate	Median time to next systemic treatment
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	14.8

Notes:

[19] - Note: This is a single arm test - two arms were provided due to EUDRACT reporting system limitations.
Analysis will be performed in ITT population.

Other pre-specified: Best overall response(1 year)

End point title	Best overall response(1 year)

End point description:

All patients included in the study will be assessed for global response every 12 weeks (4 cycles), even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), relapse, early death or not evaluable.
PD may be declared based on intermediate 6 weekly (every 2 cycles) blood and skin assessment.
To be assigned a status of CR or PR the response must be confirmed by an assessment performed 4-8 weeks after the criteria for response are first met.

End point type	Other pre-specified

End point timeframe:

Best overall response achieved (according to EORTC-ISCL-USCLC criteria) within 1 year from

registration.
This is a single arm assessment, presented separately in the per-protocol and Intention-to-treat populations.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[20]	17[21]		
Units: Patient				
Complete Response	0	0		
Partial response	4	3		
Stable disease	10	7		
Progression	6	5		
Not evaluable	3	1		
Early death	3	1		

Notes:

[20] - This is a single arm assessment. These results are based on the Intention-to-treat population.

[21] - This is a single arm assessment. These results are based on the per-protocol population.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Best overall response(Follow-up)

End point title	Best overall response(Follow-up)

End point description:

All patients included in the study will be assessed for global response every 12 weeks (4 cycles), even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), relapse, early death or not evaluable.
PD may be declared based on intermediate 6 weekly (every 2 cycles) blood and skin assessment.
To be assigned a status of CR or PR the response must be confirmed by an assessment performed 4-8 weeks after the criteria for response are first met.

End point type	Other pre-specified

End point timeframe:

Best overall response achieved (according to EORTC-ISCL-USCLC criteria) from registration throughout follow-up evaluations.
This is a single arm assessment, presented separately in the per-protocol and Intention-to-treat populations.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[22]	17[23]		
Units: Patients				
Complete response	1	1		
Partial response	4	3		

Stable disease	9	6		
Progression	6	5		
Not evaluable	3	1		
Early death	3	1		

Notes:

[22] - This is a single arm assessment. Results were presented Intention-to-treat population

[23] - This is a single arm assessment. Results were presented in the per-protocol population

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall response rate (ORR)-ITT Population

End point title	Overall response rate (ORR)-ITT Population

End point description:

Standard disease assessment of tumour response status was performed every 2 cycles for skin and blood, and every 4 cycles for lymph nodes and visceral organs by local investigator according to EORTC/ISCL criteria allowing a global response call every 4 cycles. All patients achieving CR or PR are counted as success. All other cases will be considered as failures.
ORR will be calculated by summing the number of participants assessed as having a CR or PR and dividing this by the total number of patients who are eligible and started treatment.

This is a single arm assessment. This endpoint was analysed in the ITT-population.

End point type	Other pre-specified

End point timeframe:

Overall response rate (ORR) is defined as the proportion of patients who achieved complete response (CR) or partial response (PR) as best result up to maximum of 1 year from patient registration.

End point values	Intention-to-treat Population	Per protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26[24]	17[25]		
Units: Subjects				
Success	4	3		
Failure	22	14		

Notes:

[24] - This is a single arm study. Here, ORR was assessed in the ITT population

[25] - This is a single arm study. Here, ORR was assessed in the per-protocol population

Statistical analyses

Statistical analysis title	Other specified: ORR (ITT population)

Statistical analysis description:

The study was designed to reject the null hypothesis (H0: ORR=40%) with 90% power under the alternative hypothesis (H1: ORR=65%) using an exact binary test at 10% significance level 1-sided. A total of 29 eligible patients who start treatment were required, among whom 16 or more needed to responders (CR or PR) to declare the study a success.

Note: This is a single are study . The primary test will only be done in the per-protocol population.

Comparison groups	Intention-to-treat Population v Per protocol Population

Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other[26]
Method	Proportion-Exact binomial 1-sided 90% CI
Parameter estimate	Binomial proportion
Point estimate	15.4
Confidence interval	
level	90 %
sides	1-sided
lower limit	6.8

Notes:

[26] - This is a single arm assessment. This endpoint was analysed here in the ITT population

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events, laboratory and physical abnormalities were collected till three months after the end of treatment. Afterwards, only treatment related AE are collected. For SAEs: all SAEs till 30 days after end of treatment; afterwards, only related SAEs

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. (xx% AEs are reported as "other" and are not reported as not available from the list of SOC).
AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	ARM A - Atezolizumab

Reporting group description: -

Serious adverse events	ARM A - Atezolizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 26 (34.62%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
PYREXIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
PANCREATITIS			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
MYALGIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ABSCESS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SEPSIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ARM A - Atezolizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 26 (84.62%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
PROGRESS DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
NEOPLASM BENIGN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Vascular disorders			
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
General disorders and administration site conditions			
EDEMA FACE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
EDEMA LIMBS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
FATIGUE			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	6 / 26 (23.08%)		
occurrences (all)	6		
FEVER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	4		
MULTI-ORGAN FAILURE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Reproductive system and breast disorders			
IRREGULAR MENSTRUATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
COUGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
DYSPNEA			
alternative dictionary used: CTCAE			

4			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Psychiatric disorders			
DEPRESSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
INSOMNIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
LABILITY OF AFFECT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Investigations			
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	5		
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	5		
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
LIPASE INCREASED			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
CPK INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
THYROID STIMULATING HORMONE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Nervous system disorders			
PARESTHESIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
HEADACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
EOSINOPHILIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Eye disorders			
EYELID FUNCTION DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
CATARACT			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
SENILE ECTROPIUM BOTH EYES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Gastrointestinal disorders			
DENTAL CARIES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
CONSTIPATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
DIARRHEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
PANCREAS, EXOCRINE ENZYME DEFICIENCY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
NAUSEA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
PANCREATITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
RECTAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
ERYTHRODERMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
EZCEMA / CAPILARITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
PAIN OF SKIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
PRURITUS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	5		
SKIN HYPOPIGMENTATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
RASH ANTERIOR TRUNK			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Endocrine disorders			
HYPERTHYROIDISM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
MYALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
LOMBALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
KNEE PAIN RIGHT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
ARTHRALGIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
MYOSITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Infections and infestations			
OTITIS MEDIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
PAPULOPUSTULAR RASH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
SEPSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	6		
SOFT TISSUE INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	2		
TUBERCULOSIS INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
HYPOKALEMIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2020	A scientific amendment (1652 protocol v7.0 20200701) took place on the 01/07/2020, due to a safety concern. The specific rationale for the amendment and its classification were: 1. The amendment followed an Urgent Safety Measures (USM) procedure. This Urgent Safety Measure procedure entailed the immediate closure of the trial recruitment on the 04/10/2019, following the occurrence of three sepsis-related deaths. Although the death event was deemed related to atezolizumab by the investigator only in one of these three cases, the sponsor in agreement with the study coordinators and the Chair of the EORTC CTCL Task Force decided to stop the recruitment. However, patients for whom a therapy effect was documentable were given the possibility to continue the treatment provided that they were properly informed about the USM by the investigator and they signed a PISIC addendum. An Urgent Safety Measures Letter has been sent to sites. 2. Treatment prolongation beyond 1 year for those patients who still benefit from atezolizumab at the treatment completion was extensively discussed with Study Coordinators and Roche. Given the strong ethical implications of stopping the treatment when clinical benefit is still documentable, especially in patients for whom not many therapeutic options are available, the company agreed on the extended drug supply. 3. Mandatory updates and changes concerning atezolizumab-related adverse events have been implemented in order to align with the newest IB (v 15) and addendum 2. 4. With the current sample size, this study is underpowered for the primary endpoint. Therefore a revised statistical analysis plan (SAP) provided details on the modification of the initial analysis plan of the EORTC protocol 1652 version 6 in light of the limited sample size. The revised SAP also includes some additional descriptive analysis of the efficacy and safety endpoints. 5. Addendum 2 v1.0 to PISIC v 3.0 for patient consent to stay on treatment beyond 1 year

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 October 2019	Following the occurrence of three toxic deaths, an urgent safety measure was put in place and further recruitment was closed. For patients already recruited, the treatment regimen was continued if considered beneficial to the patient as per investigator's decision. This continuation remained subject to protocol treatment schedule and dosing and clinical evaluation procedures. If continuation was no longer deemed beneficial or the patient decided to discontinue the treatment, treatment was stopped. However, this patient remained part of the regular protocol follow-up regardless of further anti-cancer therapies.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

We did not meet the minimum number of responders needed to declare the trial as successful. A reason for this could be that the study was underpowered (78.7%) following premature closure. Only 17 eligible patients were enrolled instead of 29.

Notes: