Clinical trial results:
A randomised non-comparative open label phase II trial of atezolizumab plus bevacizumab, with carboplatin-paclitaxel or pemetrexed, in EGFR mutant non-small cell lung carcinoma with acquired resistance

Summary

EudraCT number	2019-001687-30
Trial protocol	ES DE
Global end of trial date	22 July 2024

Results information

Result version number	v1 (current)
This version publication date	06 March 2026
First version publication date	06 March 2026

Trial information

Trial identification

Sponsor protocol code	ETOP 15-19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04245085
WHO universal trial number (UTN)	-
Other trial identifiers	Roche Number: MO40586

Notes:

Sponsors

Sponsor organisation name	ETOP IBCSG Partners Foundation
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	ETOP IBCSG Partners Coordinating Center, ETOP IBCSG Partners Foundation, +41 315119400, etop-regulatory@etop.ibcsg.org
Scientific contact	ETOP IBCSG Partners Coordinating Center, ETOP IBCSG Partners Foundation, +41 315119400, etop-regulatory@etop.ibcsg.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	01 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2023
Global end of trial reached?	Yes
Global end of trial date	22 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to explore the clinical efficacy of atezolizumab and bevacizumab combined with chemotherapy in EGFR mutated patients after failure of standard EGFR targeted therapies.

Protection of trial subjects:

Participating institutions’ ethics committees or Institutional Review Boards approved the trial according to local laws and regulations. All patients gave written informed consent, and the trial was performed in compliance with the Helsinki Declaration. The Data Safety and Monitoring Board reviewed the data from this research throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 41
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Singapore: 10
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 32
Worldwide total number of subjects	95
EEA total number of subjects	33

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)	58
From 65 to 84 years	36
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Overall, 95 patients were registered and randomized in iBiobank from September 29, 2020 until September 12, 2022 (randomization date of the last patient). Randomized patients come from ten centers in Spain, three in Switzerland, two in South Korea, one in Singapore and one in Germany.

Pre-assignment

Screening details:

There were 25 screening failures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles.

Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m2 (at the investigators' discretion), every 3 weeks for 4-6 cycles.

Arm type	Active comparator
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg i.v. on day one of every 3-week (+/-3 days) cycle, until PD1, refusal or unacceptable toxicity

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

Dosage and administration details:

15mg/kg i.v. on day one of every 3-week (+/-3 days) cycle, until PD, refusal or unacceptable toxicity

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

Dosage and administration details:

Patients in treatment Arm A will receive carboplatin, AUC5 plus paclitaxel, 175-200 mg/m2, at the investigator’s discretion, every 3 weeks for 4-6 cycles.

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

Dosage and administration details:

Patients in treatment Arm A will receive carboplatin, AUC5 plus paclitaxel, 175-200 mg/m2, at the investigator’s discretion, every 3 weeks for 4-6 cycles.

Arm title	Arm B

Arm description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m2 every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment

Arm type	Active comparator
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg i.v. on day one of every 3-week (+/-3 days) cycle, until PD1, refusal or unacceptable toxicity

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

Dosage and administration details:

15mg/kg i.v. on day one of every 3-week (+/-3 days) cycle, until PD, refusal or unacceptable toxicity

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m2, Q3W, until PD

Number of subjects in period 1	Arm A	Arm B
Started	45	50
Completed	16	20
Not completed	29	30
Death	26	27
Withdrawal/Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm A

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles.

Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m2 (at the investigators' discretion), every 3 weeks for 4-6 cycles.

Reporting group title	Arm B

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m2 every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment

Reporting group values	Arm A	Arm B	Total
Number of subjects	45	50	95
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	61	63	
full range (min-max)	32 to 93	45 to 75	-

Gender categorical Units: Subjects			
Female	27	17	44
Male	18	33	51
Race/Ethnicity Units: Subjects			
Asian	25	27	52
White	20	21	41
Black	0	1	1
Other	0	1	1
ECOG Performance Status			
0: Fully active, able to carry on all pre-disease performance without restriction; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work;			
Units: Subjects			
Status 0	16	8	24
Status 1	29	42	71
Smoking Status			
Current smoker: Still smokes cigarettes, Former smoker: Smoked at least 100 cigarettes in the past during the whole life, Never smoker: Smoked 0-99 cigarettes during the whole life.			
Units: Subjects			
Current smoker	3	4	7
Former smoker	17	14	31
Never smoked	25	32	57
Stage			
Stage is based on the 8th TNM classification for NSCLC (American Joint Committee on Cancer). Stage IIIB/C: the tumor is 5 cm or smaller (IIIB) or any size (IIIC) and cancer has spread to lymph nodes above the collarbone on the same side of the chest as the primary tumor or to any lymph nodes on the opposite side of the chest as the primary tumor. Stage IVA: cancer has spread within the chest and/or has spread to 1 area outside of the chest. Stage IVB: cancer has spread outside of the chest to more than 1 place in 1 organ or to more than 1 organ.			
Units: Subjects			
IIIB	1	0	1
IVA	10	21	31
IVB	34	29	63
EGFR mutation type			
Histologically or cytologically confirmed exon 19 deletion or exon 21 L858R mutation by a certified local laboratory			
Units: Subjects			
Exon 19 deletion	28	29	57
Exon 21 L858R	16	19	35
Other	1	2	3
Prior TKI treatment			
TKI: tyrosine kinase inhibitors			
Units: Subjects			
Afatinib	9	8	17
Erlotinib	2	3	5
Gefitinib	4	5	9
Lazertinib	1	5	6
Nazartinib	1	0	1
Osimertinib	28	27	55
Osimertinib or Lazertinib	0	1	1
Osimertinib or Savolitinib	0	1	1

Brain metastasis Units: Subjects			
Yes	15	16	31
No	30	34	64

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles.

Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m2 (at the investigators' discretion), every 3 weeks for 4-6 cycles.

Reporting group title	Arm B

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit.

Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m2 every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment

Primary: Progression-free rate at 12 months

End point title	Progression-free rate at 12 months

End point description:

Progression-Free Survival (PFS) rate at 12-months is defined as the rate of patients without a PFS event at 12 months from randomisation. PFS is defined as the time from the date of randomisation until documented progression (according to RECIST v1.1) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the last tumour assessment if the patient is lost to follow-up or refuses further documentation of follow-up.

End point type	Primary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[1]	45[2]		
Units: Patients	9	21		

Notes:

[1] - Primary efficacy cohort, rando pts who are not lost from FU before a PFS event or earlier than 1y FU

[2] - Primary efficacy cohort, rando pts who are not lost from FU before a PFS event or earlier than 1y FU

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Arm B v Arm A
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.367 [3]
Method	Exact binomial one-sample
Parameter estimate	proportion
Point estimate	20.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	36

Notes:

[3] - 1-sided significance level of 2.5%

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The study was design to test the primary efficacy hypothesis that 14 or more patients among the 45 evaluable in each treatment arm should be progression-free in the 12-month timepoint in order to reject the null hypothesis H0: 12-month PFS rate (π0) ≤0.18, versus the alternative hypothesis H1: 12-month PFS rate (π1) >0.18, evaluated at π1=0.37. The rate of progression-free patients at 12 months will be accompanied by 2-sided 95% exact binomial CI.

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.174 [4]
Method	Exact binomial one-sample
Parameter estimate	proportion
Point estimate	24.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.9
upper limit	39.5

Notes:

[4] - 1-sided significance level of 2.5%

Secondary: Objective response (OR)

End point title	Objective response (OR)

End point description:

Objective response is defined as best overall response (CR or PR) across all assessment time-points according to RECIST v1.1, from randomisation until either the end of protocol treatment or the end of follow-up.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[5]	50[6]		
Units: Participant	21	16		

Notes:

[5] - Intention-To-Treat cohort of all randomised patients

[6] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

No statistical analyses for this end point

Secondary: Extra-cranial Progression-free survival (ecPFS)

End point title	Extra-cranial Progression-free survival (ecPFS)

End point description:

Extra-cranial progression-free-survival is the time from randomisation to documentation of disease progression outside the central nervous system (CNS) as per RECIST v1.1 or death, whichever occurred first.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	50		
Units: Molarnth				
median (confidence interval 95%)	7.8 (5.5 to 9.7)	9.2 (4.9 to 9.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intra-cranial Progression-free survival (icPFS)

End point title	Intra-cranial Progression-free survival (icPFS)

End point description:

Intracranial progression-free-survival is defined as the time from randomisation to first documented

radiographic evidence of CNS progression. CNS progression is defined as progression due to newly developed CNS lesions and/or progression of pre-existing baseline CNS lesions.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[7]	50[8]		
Units: Month				
median (confidence interval 95%)	8.3 (5.7 to 15.4)	12.3 (9.8 to 15.8)		

Notes:

[7] - Intention-To-Treat cohort of all randomised patients

[8] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time from the date of randomisation until death from any cause. Censoring will occur at the last follow-up date.

BECAUSE THE SYSTEM DOES NOT ALLOW EMPTY VALUES IN THE RESULTS SECTION, THEY ARE ADDED BELOW INSTEAD:

Arm B
Median: 15.6, 95%CI: 11.8 to NA, the upper 95% confidence limit is not estimable.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[9]	50[10]		
Units: Month				
median (confidence interval 95%)	15.4 (9.4 to 23.9)	0 (0 to 0)		

Notes:

[9] - Intention-To-Treat cohort of all randomised patients

[10] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30)

End point title	Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30)

End point description:

Deterioration is defined as the first time that patient's score for Global health status/QoL shows a ≥10-point decrease from baseline. Deterioration must be held for at least two consecutive assessments or be followed by PD and/or death within the next 3 weeks.

BECAUSE THE SYSTEM DOES NOT ALLOW EMPTY VALUES IN THE RESULTS SECTION, THEY ARE ADDED BELOW INSTEAD:

Results Arm A

Median: 7.2, 95%CI 2.7 to NA, the upper 95% confidence limit is not estimable.

Results Arm B

Median: NA, 95%CI 3.5 to NA, median deterioration time and upper 95% confidence limit are not estimable.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[11]	48[12]		
Units: months				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Notes:

[11] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)
[12] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire lung cancer-specific module (QLQ-LC13)

End point title	Time to deterioration (TTD) assessed by the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire lung cancer-specific module (QLQ-LC13)

End point description:

Deterioration is defined as the first time that patient's score for Cough QLQ-LC13 symptom shows a ≥10-point decrease from baseline. Deterioration must be held for at least two consecutive assessments or be followed by PD and/or death within the next 3 weeks.

BECAUSE THE SYSTEM DOES NOT ALLOW EMPTY VALUES IN THE RESULTS SECTION, THEY ARE ADDED BELOW INSTEAD:

Arm A
Median: NA, 95%CI: 8.6 to NA, median deterioration time and upper 95% confidence limit are not estimable.

Arm B
Median: NA, 95%CI: NA to NA, median deterioration time and lower and upper 95% confidence limit are not estimable.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[13]	48[14]		
Units: Month				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

Notes:

[13] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)
[14] - QoL cohort (at least 1 dose of treatment, with baseline QoL assessment and post-baseline QoL forms)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival

End point description:

PFS is defined as the time from the date of randomisation until documented progression (according to RECIST v1.1) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the last tumour assessment if the patient is lost to follow-up or refuses further documentation of follow-up.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45[15]	50[16]		
Units: Month				
median (confidence interval 95%)	6.4 (5.3 to 8.3)	7.6 (4.1 to 9.7)		

Notes:

[15] - Intention-To-Treat cohort of all randomised patients

[16] - Intention-To-Treat cohort of all randomised patients

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse Events

End point title	Adverse Events

End point description:

Adverse events, graded by CTCAE version 5.0, will be recorded from date of signature of informed consent until 90 days after all trial treatment discontinuation.

End point type	Secondary

End point timeframe:

Evaluated up to approximately 36 months from the randomisation of the first patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44[17]	50[18]		
Units: Participant				
Experienced AE/SAE	43	49		
No AE/SAE	1	1		
Experienced SAE	19	23		

Notes:

[17] - Safety population (all patients who received at least 1 dose of trial treatment).

[18] - Safety population (all patients who received at least 1 dose of trial treatment).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were reported from the date randomisation until 90 days after the last dose of protocol treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit. Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Carboplatin: Patients in treatment Arm A will receive carboplatin, AUC5 every 3 weeks for 4-6 cycles. Paclitaxel: Patients in treatment Arm A will receive paclitaxel, 175-200 mg/m2 (at the investigators' discretion), every 3 weeks for 4-6 cycles.

Reporting group title	Arm B

Reporting group description:

Atezolizumab: Patients in both treatment arms will receive atezolizumab at a fixed dose of 1200 mg i.v. on day one of every 3-week (3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Treatment beyond RECIST-defined progression will be allowed if patient is continuing to derive clinical benefit. Bevacizumab: Patients in both treatment arms will receive bevacizumab at a dose of 15 mg/kg i.v. on day one of every 3-week (+/- 3 days) cycle, until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment. Pemetrexed: Patients in treatment Arm B will receive Pemetrexed, 500 mg/m2 every 3 weeks until progression of disease determined according to RECIST v1.1 or lack of tolerability, or patient declines further treatment.

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 44 (43.18%)	23 / 50 (46.00%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Synchronous urothelial carcinoma			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 44 (0.00%)	4 / 50 (8.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medically assisted suicide			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease (COPD)			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnea			

subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxemic respiratory failure			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 44 (4.55%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 44 (2.27%)	2 / 50 (4.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalitis			

subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresthesia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischemic attacks			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholangitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pressure ulcers			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			

subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 infection			
subjects affected / exposed	0 / 44 (0.00%)	4 / 50 (8.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	3 / 44 (6.82%)	3 / 50 (6.00%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Meningitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shingles			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 44 (4.55%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperuricemia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			

subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (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: 5 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 44 (97.73%)	49 / 50 (98.00%)	
Vascular disorders			
Arterial thromboembolism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Hot flashes			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	10 / 44 (22.73%)	17 / 50 (34.00%)	
occurrences (all)	10	17	
Hypotension			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Thromboembolic event			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Surgical and medical procedures			
Prophylactic femoral intramedullary nailing			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Chills			

subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Edema face			
subjects affected / exposed	0 / 44 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Edema limbs			
subjects affected / exposed	2 / 44 (4.55%)	6 / 50 (12.00%)	
occurrences (all)	2	6	
Fatigue			
subjects affected / exposed	13 / 44 (29.55%)	16 / 50 (32.00%)	
occurrences (all)	13	16	
Fever			
subjects affected / exposed	6 / 44 (13.64%)	3 / 50 (6.00%)	
occurrences (all)	6	3	
Flu like symptoms			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
General deterioration			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
General discomfort			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
General weakness			
subjects affected / exposed	2 / 44 (4.55%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Generalited edema			
subjects affected / exposed	0 / 44 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Infusion site extravasation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Localized edema			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Malaise			

subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Night sweat			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Non cardiac chest pain			
subjects affected / exposed	3 / 44 (6.82%)	5 / 50 (10.00%)	
occurrences (all)	3	5	
Pain			
subjects affected / exposed	4 / 44 (9.09%)	9 / 50 (18.00%)	
occurrences (all)	4	9	
Poor general condition			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Poor oral intake			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Acute bronchitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Aspiration			
subjects affected / exposed	2 / 44 (4.55%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Blood tinged sputum			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Chronic obstructive pulmonary disease (COPD)			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Cough			

subjects affected / exposed	6 / 44 (13.64%)	6 / 50 (12.00%)		
occurrences (all)	6	6		
Dysphonia				
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)		
occurrences (all)	1	0		
Dyspnea				
subjects affected / exposed	5 / 44 (11.36%)	11 / 50 (22.00%)		
occurrences (all)	5	11		
Epistaxis				
subjects affected / exposed	3 / 44 (6.82%)	4 / 50 (8.00%)		
occurrences (all)	3	4		
Hiccups				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Hoarseness				
subjects affected / exposed	2 / 44 (4.55%)	2 / 50 (4.00%)		
occurrences (all)	2	2		
Laryngeal hemorrhage				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Pleural effusion				
subjects affected / exposed	2 / 44 (4.55%)	4 / 50 (8.00%)		
occurrences (all)	2	4		
Pneumonitis				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Productive cough				
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)		
occurrences (all)	1	0		
Pulmonary edema				
subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)		
occurrences (all)	0	2		
Retrosternal pain				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Rhinorrhea				

subjects affected / exposed	1 / 44 (2.27%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Sputum			
subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	2 / 44 (4.55%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Confusion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	3 / 44 (6.82%)	5 / 50 (10.00%)	
occurrences (all)	3	5	
Low mood			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 44 (13.64%)	13 / 50 (26.00%)	
occurrences (all)	6	13	
Alkaline phosphatase increased			
subjects affected / exposed	1 / 44 (2.27%)	5 / 50 (10.00%)	
occurrences (all)	1	5	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 44 (15.91%)	19 / 50 (38.00%)	
occurrences (all)	7	19	
BUN increased			

subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 44 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Cholesterol high			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Creatinine increased			
subjects affected / exposed	1 / 44 (2.27%)	5 / 50 (10.00%)	
occurrences (all)	1	5	
GGT increased			
subjects affected / exposed	1 / 44 (2.27%)	9 / 50 (18.00%)	
occurrences (all)	1	9	
Leukocytes count decreased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Lipase increased			
subjects affected / exposed	5 / 44 (11.36%)	3 / 50 (6.00%)	
occurrences (all)	5	3	
Neutrophil count decreased			
subjects affected / exposed	12 / 44 (27.27%)	4 / 50 (8.00%)	
occurrences (all)	12	4	
Platelet count decreased			
subjects affected / exposed	3 / 44 (6.82%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Serum amylase increased			
subjects affected / exposed	8 / 44 (18.18%)	8 / 50 (16.00%)	
occurrences (all)	8	8	
Transaminitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Weight loss			
subjects affected / exposed	1 / 44 (2.27%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
White blood cell decreased			
subjects affected / exposed	4 / 44 (9.09%)	0 / 50 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Infusion related reaction			
subjects affected / exposed	2 / 44 (4.55%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Seroma			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vaccination complication			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Wound dehiscence			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Chest pain cardiac			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			

subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 44 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Dysgeusia			
subjects affected / exposed	1 / 44 (2.27%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Dysphasia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	6 / 44 (13.64%)	10 / 50 (20.00%)	
occurrences (all)	6	10	
Hydrocephalus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Neurotoxicity			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Neurotoxicity in hands			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Paresthesia			
subjects affected / exposed	4 / 44 (9.09%)	1 / 50 (2.00%)	
occurrences (all)	4	1	
Peripheral sensory neuropathy			
subjects affected / exposed	15 / 44 (34.09%)	3 / 50 (6.00%)	
occurrences (all)	15	3	

Recurrent laryngeal nerve palsy			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Seizure			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	11 / 44 (25.00%)	7 / 50 (14.00%)	
occurrences (all)	11	7	
Febrile neutropenia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Nose bleeding			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Blurred vision			
subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Cataract			

subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	2 / 44 (4.55%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Periorbital oedema			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vision decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Watering eyes			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 44 (9.09%)	5 / 50 (10.00%)	
occurrences (all)	4	5	
Anal fissure			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Anal hemorrhage			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Bloating			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Bowel rhythm change			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Colonic hemorrhage			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	12 / 44 (27.27%)	15 / 50 (30.00%)	
occurrences (all)	12	15	
Dental caries			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Diarrhea			
subjects affected / exposed	3 / 44 (6.82%)	8 / 50 (16.00%)	
occurrences (all)	3	8	
Diverticulitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	3 / 44 (6.82%)	4 / 50 (8.00%)	
occurrences (all)	3	4	
Epigastric pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Esophagal spasm			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Esophagitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastroesophagal reflux disease			
subjects affected / exposed	0 / 44 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Gastrointestinal pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Gum inflammation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hemorrhoids			
subjects affected / exposed	2 / 44 (4.55%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Ileus			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Mucositis oral			
subjects affected / exposed	4 / 44 (9.09%)	3 / 50 (6.00%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed	13 / 44 (29.55%)	18 / 50 (36.00%)	
occurrences (all)	13	18	
Periodontal disease			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Pyrosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	3 / 44 (6.82%)	6 / 50 (12.00%)	
occurrences (all)	3	6	
Hepatobiliary disorders			
Cholangiohepatitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hepatic cytolysis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Alopecia				
subjects affected / exposed	9 / 44 (20.45%)	1 / 50 (2.00%)		
occurrences (all)	9	1		
Dry skin				
subjects affected / exposed	5 / 44 (11.36%)	2 / 50 (4.00%)		
occurrences (all)	5	2		
Eczema				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Mucositis in hands				
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)		
occurrences (all)	1	0		
Palmar plantar erythrodysesthesia syndrome				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Pruritus				
subjects affected / exposed	7 / 44 (15.91%)	5 / 50 (10.00%)		
occurrences (all)	7	5		
Pustules				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Rash acneiform				
subjects affected / exposed	1 / 44 (2.27%)	3 / 50 (6.00%)		
occurrences (all)	1	3		
Rash eczematiform				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Rash maculo papular				
subjects affected / exposed	4 / 44 (9.09%)	5 / 50 (10.00%)		
occurrences (all)	4	5		
Skin induration				
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)		
occurrences (all)	0	1		
Skin rash				

subjects affected / exposed	2 / 44 (4.55%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Toxicoderma			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Umbilical hernia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 44 (4.55%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Proteinuria			
subjects affected / exposed	12 / 44 (27.27%)	9 / 50 (18.00%)	
occurrences (all)	12	9	
Urinary frequency			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	2 / 44 (4.55%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 44 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Hypothyroidism			
subjects affected / exposed	4 / 44 (9.09%)	4 / 50 (8.00%)	
occurrences (all)	4	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 44 (15.91%)	4 / 50 (8.00%)	
occurrences (all)	7	4	
Back pain			

subjects affected / exposed	0 / 44 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Bone pain			
subjects affected / exposed	2 / 44 (4.55%)	4 / 50 (8.00%)	
occurrences (all)	2	4	
Flank pain			
subjects affected / exposed	1 / 44 (2.27%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Generalized muscle weakness			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Hip pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Joint range of motion decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Lumbar pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	3 / 44 (6.82%)	2 / 50 (4.00%)	
occurrences (all)	3	2	
Neck pain			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Other			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	2 / 44 (4.55%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Shoulder and pelvic girdle pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Tingling (fingers, toes)			

subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Belly button infection			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
C reactive protein increased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
COVID 19 infection			
subjects affected / exposed	9 / 44 (20.45%)	7 / 50 (14.00%)	
occurrences (all)	9	7	
Conjunctivitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Gum infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Hepatitis viral			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Herpes simplex reactivation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	1 / 44 (2.27%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Mucosal infection			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Sepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Shingles			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	1 / 44 (2.27%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Upper respiratory infection			
subjects affected / exposed	1 / 44 (2.27%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)	4 / 50 (8.00%)	
occurrences (all)	1	4	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 44 (11.36%)	11 / 50 (22.00%)	
occurrences (all)	5	11	
Dehydration			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hypercalcemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Hyperkalemia			
subjects affected / exposed	0 / 44 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Hypoglycemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Hypokalemia			
subjects affected / exposed	2 / 44 (4.55%)	3 / 50 (6.00%)	
occurrences (all)	2	3	
Hypomagnesemia			

subjects affected / exposed	3 / 44 (6.82%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Hyponatremia			
subjects affected / exposed	3 / 44 (6.82%)	2 / 50 (4.00%)	
occurrences (all)	3	2	
Hyporeflexia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hypovitaminose D			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 44 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2021	During the submission process of the first protocol version ETOP received several requests for protocol changes from authorities in various countries. Main change requests concerned recommendations for the paclitaxel dosing, in particular for the Asian population, and some clarification regarding the eligibility criteria for the liver and renal function, as well as for EGFR status. Furthermore, the amendment accounts for the new safety information for atezolizumab, including the addition of the newly identified risks of Severe Cutaneous Adverse Reactions (SCARs). The management of atezolizumab-related toxicities has been updated based on the latest version of the atezolizumab IB Version 15, July 2019, the Addendum 2, December 2019 to the IB V15. The diagnostic criteria and management guidelines for haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), replacing systemic immune activation (SIS), were updated according to a separate Safety Memorandum from Roche. In addition, the list of AESIs has been updated to reflect the new safety information and history of active diverticulitis has been added to the exclusion criteria. Furthermore, some minor protocol clarifications have been added and ambiguities and typos eliminated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported