Clinical trial results:
A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer

Summary

EudraCT number	2014-005490-37
Trial protocol	DE BE GB GR ES SE DK LV AT FI CZ HU PL EE SI FR RO IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	09 April 2021
First version publication date	09 April 2021

Trial information

Trial identification

Sponsor protocol code	WO29522

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02425891
WHO universal trial number (UTN)	-
Other trial identifiers	IMpassion130: Acronym

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	14 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy, safety, and pharmacokinetics of atezolizumab with nab-paclitaxel compared with placebo with nab-paclitaxelin patients with metastatic or locally advanced triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for metastatic breast cancer (mBC).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	19 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Australia: 42
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Bosnia and Herzegovina: 1
Country: Number of subjects enrolled	Brazil: 59
Country: Number of subjects enrolled	Canada: 43
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Chile: 16
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Costa Rica: 15
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Germany: 88
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 28
Country: Number of subjects enrolled	United Kingdom: 44
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Guatemala: 3

Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	Korea, Republic of: 56
Country: Number of subjects enrolled	Latvia: 5
Country: Number of subjects enrolled	Mexico: 25
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Panama: 6
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Russian Federation: 34
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	United States: 187
Worldwide total number of subjects	902
EEA total number of subjects	233

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)	683
From 65 to 84 years	216
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

This study included in total 246 centers in 41 countries.

Pre-assignment

Screening details:

This study included participants with metastatic or locally advanced, histologically documented triple-negative breast cancer (TNBC) (absence of human epidermal growth factor 2 [HER2], estrogen receptor [ER], and progesterone receptor [PR] expression) by local laboratory assessment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Plus Nab-Paclitaxel

Arm description:

Participants assigned to placebo plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered via IV infusion on Days 1 and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-Paclitaxel was administered at a starting dose of 100 milligrams per square meter via IV infusion on Days 1, 8, and 15 of each 28-day cycle. Nab-Paclitaxel was administered for a target of at least 6 cycles, with no maximum in the absence of disease progression or unacceptable toxicity.

Arm title	Atezolizumab Plus Nab-Paclitaxel

Arm description:

Participants assigned to atezolizumab plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq, MPDL3280A
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab was administered at a fixed dose of 840 milligrams via intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

Investigational medicinal product name	Nab-Paclitaxel
Investigational medicinal product code	
Other name	Abraxane®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-Paclitaxel was administered at a starting dose of 100 milligrams per square meter via IV infusion on Days 1, 8, and 15 of each 28-day cycle. Nab-Paclitaxel was administered for a target of at least 6 cycles, with no maximum in the absence of disease progression or unacceptable toxicity.

Number of subjects in period 1	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel
Started	451	451
Completed	0	0
Not completed	451	451
Adverse event, serious fatal	332	314
Consent withdrawn by subject	27	32
Non-Compliance	1	-
Physician decision	-	1
Accidentally randomized screen failure participant	-	1
Study Terminated By Sponsor	1	-
On-going in Study	79	90
Lost to follow-up	4	6
Protocol deviation	1	1
Not treated	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Plus Nab-Paclitaxel
Reporting group description:	
Participants assigned to placebo plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.	
Reporting group title	Atezolizumab Plus Nab-Paclitaxel
Reporting group description:	
Participants assigned to atezolizumab plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.	

Reporting group values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel	Total
Number of subjects	451	451	902
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	336	347	683
From 65-84 years	112	104	216
85 years and over	3	0	3
Age Continuous Units: Years			
arithmetic mean	55.4	54.3	
standard deviation	± 12.1	± 12.3	-
Sex: Female, Male Units: Participants			
Female	450	449	899
Male	1	2	3
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	23	17	40
Asian	76	85	161
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	32	26	58
White	301	308	609
More than one race	3	2	5
Unknown or Not Reported	16	12	28
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	83	60	143
Not Hispanic or Latino	340	368	708
Unknown or Not Reported	28	23	51

End points

End points reporting groups

Reporting group title	Placebo Plus Nab-Paclitaxel
Reporting group description:	
Participants assigned to placebo plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.	
Reporting group title	Atezolizumab Plus Nab-Paclitaxel
Reporting group description:	
Participants assigned to atezolizumab plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.	

Primary: Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) in all Randomized Participants

End point title	Progression Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1) in all Randomized Participants
End point description:	
PFS was defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per RECIST v1.1, or death from any cause, whichever occurred first. The ITT population is defined as all randomized patients, whether or not the assigned study treatment was received.	
End point type	Primary
End point timeframe:	
Baseline up to approximately 34 months	

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	451	451		
Units: Months				
median (confidence interval 95%)	5.49 (5.32 to 5.59)	7.16 (5.59 to 7.46)		

Statistical analyses

Statistical analysis title	PFS All Randomized Participants
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel
Number of subjects included in analysis	902
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0025
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.92

Primary: PFS According to RECIST v1.1 in Participants with Detectable Programmed Death-Ligand 1 (PD-L1)

End point title	PFS According to RECIST v1.1 in Participants with Detectable Programmed Death-Ligand 1 (PD-L1)

End point description:

PFS was defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments per RECIST v1.1, or death from any cause, whichever occurred first. The PD-L1-selected subpopulation is defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization.

End point type	Primary

End point timeframe:

Baseline up to approximately 34 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	185		
Units: Months				
median (confidence interval 95%)	4.96 (3.81 to 5.55)	7.46 (6.70 to 9.23)		

Statistical analyses

Statistical analysis title	PFS PD-L1-Selected Subpopulation
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.78

Primary: Overall Survival (OS) in all Randomized Participants

End point title	Overall Survival (OS) in all Randomized Participants

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. The ITT population is defined as all randomized patients, whether or not the assigned study treatment was received.

End point type	Primary

End point timeframe:

Baseline until death due to any cause (up to approximately 58 months)

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	451	451		
Units: Months				
median (confidence interval 95%)	18.73 (16.85 to 20.76)	21.03 (19.02 to 23.36)		

Statistical analyses

Statistical analysis title	OS All Randomized Participants
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel
Number of subjects included in analysis	902
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.077
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.02

Primary: OS in Participants with Detectable PD-L1

End point title	OS in Participants with Detectable PD-L1

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. The PD-L1-selected subpopulation is defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization.

End point type	Primary

End point timeframe:

Baseline until death due to any cause (up to approximately 58 months)

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	185		
Units: Months				
median (confidence interval 95%)	17.91 (13.63 to 20.30)	25.43 (19.55 to 30.69)		

Statistical analyses

Statistical analysis title	OS PD-L1-Selected Subpopulation
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0016
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.86

Secondary: Percentage of Participants With an Objective Response of Complete Response (CR) or Partial Response (PR) According to RECIST v1.1 in all Randomized Participants

End point title	Percentage of Participants With an Objective Response of Complete Response (CR) or Partial Response (PR) According to RECIST v1.1 in all Randomized Participants

End point description:

An objective response was defined for participants with measurable disease at baseline as either a partial response (PR) or a complete response (CR) using RECIST v1.1. The ORR-evaluable population is defined as patients in the ITT population with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Baseline up to approximately 34 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	449	450		
Units: Percentage of Participants				
number (not applicable)	45.9	56.0		

Statistical analyses

Statistical analysis title	Objective Response of CR or PR All Randomized
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel
Number of subjects included in analysis	899
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0021
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rates
Point estimate	10.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	16.84

Secondary: Percentage of Participants With an Objective Response of CR or PR According to RECIST v1.1 in Participants with Detectable PD-L1

End point title	Percentage of Participants With an Objective Response of CR or PR According to RECIST v1.1 in Participants with Detectable PD-L1

End point description:

An objective response was defined for participants with measurable disease at baseline as either a partial response (PR) or a complete response (CR) using RECIST v1.1. The PD-L1-ORR-evaluable population is defined as patients in the PD-L1-selected subpopulation with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Baseline up to approximately 34 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	185		
Units: Percentage of participants				
number (not applicable)	42.6	58.9		

Statistical analyses

Statistical analysis title	Objective Response of CR or PR in PD-L1-Selected
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel
Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0016
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rates
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.67
upper limit	26.92

Secondary: Duration of Response (DOR) According to RECIST v1.1 in all Randomized Participants

End point title	Duration of Response (DOR) According to RECIST v1.1 in all Randomized Participants

End point description:

DOR was defined for participants who had an objective response as the time from the first occurrence of a documented unconfirmed response (CR or PR) to the date of disease progression per RECIST v1.1 or death from any cause, whichever occurred first. The duration of response (DOR)-evaluable population is defined as patients with an objective response.

End point type	Secondary

End point timeframe:

Baseline up to approximately 34 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	252		
Units: Months				
number (confidence interval 95%)	5.62 (5.52 to 6.93)	7.39 (6.90 to 9.00)		

Statistical analyses

Statistical analysis title	DOR All Randomized
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0285
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.98

Secondary: DOR Acccording to RECIST v1.1 in Participants with Detectable PD-L1

End point title	DOR Acccording to RECIST v1.1 in Participants with Detectable PD-L1

End point description:

DOR was defined for participants who had an objective response as the time from the first occurrence of a documented unconfirmed response (CR or PR) to the date of disease progression per RECIST v1.1 or death from any cause, whichever occurred first. The duration of response (DOR)-evaluable population is defined as patients with an objective response.

End point type	Secondary

End point timeframe:

Baseline up to approximately 34 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	109		
Units: Months				
number (confidence interval 95%)	5.49 (3.71 to 7.13)	8.48 (7.33 to 9.66)		

Statistical analyses

Statistical analysis title	DOR PD-L1-Selected
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0047
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.86

Secondary: Time to Deterioration (TTD) in Global Health Status/Health Related Quality of Life According to European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) v3.0 in all Randomized Participants

End point title	Time to Deterioration (TTD) in Global Health Status/Health Related Quality of Life According to European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) v3.0 in all Randomized Participants

End point description:

Deterioration in GHS/HRQoL (Items 29, 30 of the EORTC QLQ C30) was defined by the following two criteria: 1. The time from randomization to the first time the participant's GHS/HRQoL scale score showed a >=10-point decrease from the baseline scale score. A 10-point change was defined as the minimally important difference (MID). 2. The score decrease of >= 10-points from baseline was held for at least two consecutive cycles, or an initial score decrease of >= 10-points was followed by death or treatment discontinuation within 3 weeks from the last assessment. The patient-reported outcome (PRO)-evaluable population is defined as patients in the ITT population with a baseline and ≥1 post-baseline PRO assessment.

End point type	Secondary

End point timeframe:

Baseline up to approximately 58 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	406		
Units: Months				
median (confidence interval 95%)	7.98 (5.65 to 11.10)	8.18 (6.01 to 10.94)		

Statistical analyses

Statistical analysis title	TTD All Randomized
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel

Number of subjects included in analysis	806
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8078
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.18

Secondary: TTD in Global Health Status/Health Related Quality of Life According to EORTC QLQ-C30 v3.0 in Participants with Detectable PD-L1

End point title	TTD in Global Health Status/Health Related Quality of Life According to EORTC QLQ-C30 v3.0 in Participants with Detectable PD-L1

End point description:

Deterioration in GHS/HRQoL (Items 29, 30 of the EORTC QLQ C30) was defined by the following two criteria: 1. The time from randomization to the first time the participants's GHS/HRQoL scale score showed a >=10-point decrease from the baseline scale score. A 10-point change was defined as the minimally important difference (MID). 2. The score decrease of >= 10-points from baseline was held for at least two consecutive cycles, or an initial score decrease of >= 10-points was followed by death or treatment discontinuation within 3 weeks from the last assessment. The patient-reported outcome (PRO)-evaluable population is defined as patients in the ITT population with a baseline and ≥1 post-baseline PRO assessment.

End point type	Secondary

End point timeframe:

Baseline up to approximately 58 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	167		
Units: Months				
median (confidence interval 95%)	6.41 (4.57 to 11.24)	7.56 (4.99 to 12.12)		

Statistical analyses

Statistical analysis title	TTD PD-L1 Selected
Comparison groups	Placebo Plus Nab-Paclitaxel v Atezolizumab Plus Nab-Paclitaxel

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8879
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.31

Secondary: Percentage of Participants with Adverse Events (AEs) or Serious AEs (SAEs)

End point title	Percentage of Participants with Adverse Events (AEs) or Serious AEs (SAEs)

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 53 months

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Percentage				
number (not applicable)				

Notes:

[1] - Results will be reported at the time of final results posting.

[2] - Results will be reported at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) Against Atezolizumab

End point title	Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) Against Atezolizumab[3]

End point description:

Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) Against Atezolizumab. The anti-drug antibodies (ADA)-evaluable population is defined as all patients treated with atezolizumab who have at least one post-baseline ADA result.

End point type	Secondary

End point timeframe:

Baseline up to approximately 53 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There is no statistical analysis for this end point.

End point values	Atezolizumab Plus Nab-Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	434			
Units: Percentage of participants				
number (not applicable)				
Baseline Prevalence of ADAs	1.6			
Incidence of Treatment Emergent ADAs	13.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) for Atezolizumab

End point title	Maximum Serum Concentration (Cmax) for Atezolizumab[4]

End point description:

Maximum serum concentration for atezolizumab. The pharmacokinetic (PK)-evaluable population is defined as all patients who received any dose of study medication and who have at least one post-baseline PK sample available.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (Cycle = 28 days)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There is no statistical analysis for this end point.

End point values	Atezolizumab Plus Nab-Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	407			
Units: µg/mL				
arithmetic mean (standard deviation)	329 (± 98.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Serum Concentration (Cmin) for Atezolizumab

End point title	Minimum Serum Concentration (Cmin) for Atezolizumab[5]

End point description:

Minimum serum concentration for atezolizumab. The pharmacokinetic (PK)-evaluable population is

defined as all patients who received any dose of study medication and who have at least one post-baseline PK sample available.

End point type	Secondary

End point timeframe:

Day 27 of Cycle 1, 2, 3, and 7 (Cycle = 28 days)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There is no statistical analysis for this end point.

End point values	Atezolizumab Plus Nab-Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	420			
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 27 (n=420)	145 (± 52.6)			
Cycle 2 Day 27 (n=373)	215 (± 78.3)			
Cycle 3 Day 27 (n=343)	245 (± 90.3)			
Cycle 7 Day 27 (n=188)	274 (± 111)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Total Paclitaxel

End point title	Plasma Concentrations of Total Paclitaxel

End point description:

Plasma concentrations of total paclitaxel. Note: 999999=non-reportable. The pharmacokinetic (PK)-evaluable population is defined as all patients who received any dose of study medication and who have at least one post-baseline PK sample available.

End point type	Secondary

End point timeframe:

Pre-dose (Hour 0) on Cycle 1 Day 1, pre-dose (Hour 0), 5-10 minutes before end of nab-paclitaxel infusion, 1 hour after end of nab-paclitaxel infusion (infusion duration = 30 minutes) on Cycle 3 Day 1 (Cycle = 28 days)

End point values	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	321	436		
Units: ng/mL				
arithmetic mean (standard deviation)				
C1D1/Predose (n=321;n=436)	999999 (± 999999)	999999 (± 999999)		
C3D1/Predose (n=310; n=351)	999999 (± 999999)	999999 (± 999999)		

C3D1/ Before End of Infusion (n=255;n=298)	2970 (± 2300)	3080 (± 2050)		
C3D1/Postdose Paclit (n=221;n=280)	370 (± 244)	400 (± 275)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first study drug to the data cutoff date: 14 April 2020 (up to 53 months)	
Adverse event reporting additional description:	
The safety-evaluable population is defined as participants who received any amount of any study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Atezolizumab (q2w) + nab-Paclitaxel
Reporting group description:	
Participants assigned to atezolizumab plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.	
Reporting group title	Placebo (q2w) + nab-Paclitaxel
Reporting group description:	
Participants assigned to placebo plus nab-paclitaxel received both agents until disease progression or unacceptable toxicity.	

Serious adverse events	Atezolizumab (q2w) + nab-Paclitaxel	Placebo (q2w) + nab-Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	110 / 460 (23.91%)	80 / 430 (18.60%)	
number of deaths (all causes)	322	337	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INFECTED NEOPLASM			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT ASCITES			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

TUMOUR PAIN			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
subjects affected / exposed	2 / 460 (0.43%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 460 (0.22%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL EMBOLISM			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE PAIN			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

FATIGUE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 460 (0.43%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILL-DEFINED DISORDER			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 460 (0.00%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			

subjects affected / exposed	5 / 460 (1.09%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	1 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
CONTRAST MEDIA ALLERGY			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC IMMUNE ACTIVATION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (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			
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPIRATION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	5 / 460 (1.09%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	4 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	2 / 460 (0.43%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	5 / 460 (1.09%)	4 / 430 (0.93%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
STRIDOR			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
AGITATION			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANXIETY			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
DEVICE BREAKAGE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS IN DEVICE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROCEDURAL PAIN			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

WRIST FRACTURE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ANGINA UNSTABLE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARRHYTHMIA			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 460 (0.22%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	0 / 460 (0.00%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			

subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL THROMBOSIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLIC STROKE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL PARALYSIS			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC ENCEPHALOPATHY			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOAESTHESIA			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIRD NERVE PARALYSIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL MOTOR NEUROPATHY			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			

subjects affected / exposed	5 / 460 (1.09%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOLYSIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOCYTOSIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
DIPLOPIA			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KERATITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPTIC NEUROPATHY			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (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 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS ULCERATIVE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 460 (0.22%)	4 / 430 (0.93%)	
occurrences causally related to treatment / all	1 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC HAEMORRHAGE			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL TOXICITY			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MECHANICAL ILEUS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	2 / 460 (0.43%)	3 / 430 (0.70%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			

subjects affected / exposed	2 / 460 (0.43%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
AUTOIMMUNE CHOLANGITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
AUTOIMMUNE HEPATITIS			
subjects affected / exposed	2 / 460 (0.43%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
BILE DUCT STONE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTOCHOLANGITIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEPATITIS			
subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

DERMATOMYOSITIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG ERUPTION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LICHEN PLANUS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOXIC EPIDERMAL NECROLYSIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDRONEPHROSIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
ADDISON'S DISEASE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADRENOCORTICAL INSUFFICIENCY ACUTE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTHYROIDISM			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPHYSITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (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			
BACK PAIN			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			

subjects affected / exposed	3 / 460 (0.65%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIMB DEFORMITY			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	2 / 460 (0.43%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOPATHY			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECK PAIN			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			

subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYARTHRITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TEMPOROMANDIBULAR JOINT SYNDROME			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	5 / 460 (1.09%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	4 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			

subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	2 / 460 (0.43%)	2 / 430 (0.47%)	
occurrences causally related to treatment / all	2 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PLEURAL EFFUSION			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
KLEBSIELLA BACTERAEMIA			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMYELITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	12 / 460 (2.61%)	5 / 430 (1.16%)	
occurrences causally related to treatment / all	8 / 14	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
PNEUMONIA BACTERIAL			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	0 / 460 (0.00%)	3 / 430 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
SINUSITIS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOFT TISSUE INFECTION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL SEPSIS			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOOTH INFECTION			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	5 / 460 (1.09%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DEVICE INFECTION			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			

subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	2 / 460 (0.43%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC KETOACIDOSIS			
subjects affected / exposed	1 / 460 (0.22%)	0 / 430 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 460 (0.22%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 460 (0.00%)	1 / 430 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Atezolizumab (q2w) + nab-Paclitaxel	Placebo (q2w) + nab-Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	450 / 460 (97.83%)	414 / 430 (96.28%)	
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	30 / 460 (6.52%)	32 / 430 (7.44%)	
occurrences (all)	34	35	
HYPERTENSION			
subjects affected / exposed	24 / 460 (5.22%)	21 / 430 (4.88%)	
occurrences (all)	36	32	
LYMPHOEDEMA			
subjects affected / exposed	30 / 460 (6.52%)	30 / 430 (6.98%)	
occurrences (all)	33	31	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	60 / 460 (13.04%)	51 / 430 (11.86%)	
occurrences (all)	80	75	
CHEST PAIN			
subjects affected / exposed	32 / 460 (6.96%)	20 / 430 (4.65%)	
occurrences (all)	34	22	
CHILLS			
subjects affected / exposed	42 / 460 (9.13%)	23 / 430 (5.35%)	
occurrences (all)	58	26	
FATIGUE			
subjects affected / exposed	216 / 460 (46.96%)	194 / 430 (45.12%)	
occurrences (all)	264	238	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	29 / 460 (6.30%)	11 / 430 (2.56%)	
occurrences (all)	35	12	
MUCOSAL INFLAMMATION			
subjects affected / exposed	29 / 460 (6.30%)	16 / 430 (3.72%)	
occurrences (all)	38	18	
OEDEMA PERIPHERAL			
subjects affected / exposed	73 / 460 (15.87%)	66 / 430 (15.35%)	
occurrences (all)	94	86	
PYREXIA			

subjects affected / exposed	89 / 460 (19.35%)	45 / 430 (10.47%)	
occurrences (all)	144	72	
Reproductive system and breast disorders			
BREAST PAIN			
subjects affected / exposed	30 / 460 (6.52%)	21 / 430 (4.88%)	
occurrences (all)	41	22	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	126 / 460 (27.39%)	80 / 430 (18.60%)	
occurrences (all)	167	116	
DYSPNOEA			
subjects affected / exposed	70 / 460 (15.22%)	60 / 430 (13.95%)	
occurrences (all)	90	68	
EPISTAXIS			
subjects affected / exposed	36 / 460 (7.83%)	39 / 430 (9.07%)	
occurrences (all)	49	43	
OROPHARYNGEAL PAIN			
subjects affected / exposed	30 / 460 (6.52%)	13 / 430 (3.02%)	
occurrences (all)	37	16	
Psychiatric disorders			
DEPRESSION			
subjects affected / exposed	18 / 460 (3.91%)	22 / 430 (5.12%)	
occurrences (all)	19	22	
INSOMNIA			
subjects affected / exposed	54 / 460 (11.74%)	52 / 430 (12.09%)	
occurrences (all)	59	54	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	53 / 460 (11.52%)	37 / 430 (8.60%)	
occurrences (all)	91	38	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	49 / 460 (10.65%)	41 / 430 (9.53%)	
occurrences (all)	78	47	
NEUTROPHIL COUNT DECREASED			

subjects affected / exposed	57 / 460 (12.39%)	49 / 430 (11.40%)	
occurrences (all)	163	101	
WEIGHT DECREASED			
subjects affected / exposed	22 / 460 (4.78%)	26 / 430 (6.05%)	
occurrences (all)	26	28	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	39 / 460 (8.48%)	20 / 430 (4.65%)	
occurrences (all)	89	35	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	69 / 460 (15.00%)	43 / 430 (10.00%)	
occurrences (all)	87	49	
DYSGEUSIA			
subjects affected / exposed	52 / 460 (11.30%)	44 / 430 (10.23%)	
occurrences (all)	59	50	
HEADACHE			
subjects affected / exposed	116 / 460 (25.22%)	92 / 430 (21.40%)	
occurrences (all)	170	125	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	100 / 460 (21.74%)	97 / 430 (22.56%)	
occurrences (all)	138	120	
PARAESTHESIA			
subjects affected / exposed	33 / 460 (7.17%)	29 / 430 (6.74%)	
occurrences (all)	43	32	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	74 / 460 (16.09%)	52 / 430 (12.09%)	
occurrences (all)	90	62	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	129 / 460 (28.04%)	115 / 430 (26.74%)	
occurrences (all)	221	182	
LEUKOPENIA			
subjects affected / exposed	30 / 460 (6.52%)	23 / 430 (5.35%)	
occurrences (all)	68	47	
NEUTROPENIA			

subjects affected / exposed	101 / 460 (21.96%)	65 / 430 (15.12%)	
occurrences (all)	236	174	
Eye disorders			
DRY EYE			
subjects affected / exposed	31 / 460 (6.74%)	15 / 430 (3.49%)	
occurrences (all)	33	15	
LACRIMATION INCREASED			
subjects affected / exposed	28 / 460 (6.09%)	33 / 430 (7.67%)	
occurrences (all)	28	33	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	53 / 460 (11.52%)	53 / 430 (12.33%)	
occurrences (all)	59	63	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	28 / 460 (6.09%)	24 / 430 (5.58%)	
occurrences (all)	34	25	
CONSTIPATION			
subjects affected / exposed	115 / 460 (25.00%)	108 / 430 (25.12%)	
occurrences (all)	140	132	
DIARRHOEA			
subjects affected / exposed	151 / 460 (32.83%)	146 / 430 (33.95%)	
occurrences (all)	306	212	
DRY MOUTH			
subjects affected / exposed	39 / 460 (8.48%)	16 / 430 (3.72%)	
occurrences (all)	39	17	
DYSPEPSIA			
subjects affected / exposed	30 / 460 (6.52%)	31 / 430 (7.21%)	
occurrences (all)	34	38	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	24 / 460 (5.22%)	12 / 430 (2.79%)	
occurrences (all)	26	13	
NAUSEA			
subjects affected / exposed	213 / 460 (46.30%)	164 / 430 (38.14%)	
occurrences (all)	338	244	
STOMATITIS			

subjects affected / exposed	49 / 460 (10.65%)	20 / 430 (4.65%)	
occurrences (all)	65	24	
VOMITING			
subjects affected / exposed	92 / 460 (20.00%)	73 / 430 (16.98%)	
occurrences (all)	141	98	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	263 / 460 (57.17%)	247 / 430 (57.44%)	
occurrences (all)	272	249	
DRY SKIN			
subjects affected / exposed	42 / 460 (9.13%)	25 / 430 (5.81%)	
occurrences (all)	45	27	
NAIL DISCOLOURATION			
subjects affected / exposed	38 / 460 (8.26%)	30 / 430 (6.98%)	
occurrences (all)	39	31	
PRURITUS			
subjects affected / exposed	73 / 460 (15.87%)	45 / 430 (10.47%)	
occurrences (all)	93	53	
RASH			
subjects affected / exposed	84 / 460 (18.26%)	71 / 430 (16.51%)	
occurrences (all)	115	96	
Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed	66 / 460 (14.35%)	15 / 430 (3.49%)	
occurrences (all)	77	15	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	89 / 460 (19.35%)	70 / 430 (16.28%)	
occurrences (all)	139	91	
BACK PAIN			
subjects affected / exposed	74 / 460 (16.09%)	58 / 430 (13.49%)	
occurrences (all)	106	68	
BONE PAIN			
subjects affected / exposed	24 / 460 (5.22%)	11 / 430 (2.56%)	
occurrences (all)	28	13	
MUSCLE SPASMS			

subjects affected / exposed	25 / 460 (5.43%)	5 / 430 (1.16%)	
occurrences (all)	30	5	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	26 / 460 (5.65%)	18 / 430 (4.19%)	
occurrences (all)	29	20	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	32 / 460 (6.96%)	27 / 430 (6.28%)	
occurrences (all)	37	33	
MYALGIA			
subjects affected / exposed	71 / 460 (15.43%)	67 / 430 (15.58%)	
occurrences (all)	83	86	
PAIN IN EXTREMITY			
subjects affected / exposed	55 / 460 (11.96%)	41 / 430 (9.53%)	
occurrences (all)	78	53	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	52 / 460 (11.30%)	36 / 430 (8.37%)	
occurrences (all)	79	42	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	55 / 460 (11.96%)	38 / 430 (8.84%)	
occurrences (all)	84	49	
URINARY TRACT INFECTION			
subjects affected / exposed	57 / 460 (12.39%)	42 / 430 (9.77%)	
occurrences (all)	84	60	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	92 / 460 (20.00%)	80 / 430 (18.60%)	
occurrences (all)	117	86	
HYPOCALCAEMIA			
subjects affected / exposed	25 / 460 (5.43%)	10 / 430 (2.33%)	
occurrences (all)	33	11	
HYPOKALAEMIA			
subjects affected / exposed	29 / 460 (6.30%)	9 / 430 (2.09%)	
occurrences (all)	45	10	
HYPOMAGNESAEMIA			

subjects affected / exposed occurrences (all)	26 / 460 (5.65%) 62	11 / 430 (2.56%) 16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2015	Protocol was amended to include modification to the following eligibility criteria: Expansion of the target population to include male participants with TNBC. Contraceptive requirements were updated accordingly. Exclusion of participants with CNS metastasis was clarified. Participants with known PD-L1 expression status from other clinical trials were excluded. In addition, guidelines for the management of nab-paclitaxel-related toxicities were updated and clarified. Also, aspects of standard safety reporting requirements have been updated and clarified, including those related to pregnancies in female partners of male participants.
20 November 2015	Protocol was amendment to include the increase in the number of participants in the study from 350 to up to 900 to support the promotion of overall survival from secondary to co-primary outcome measure. The statistical methods were modified accordingly. Management guidelines for atezolizumab-specific AEs were deleted from the protocol and instead, reference was made to the current IB. Systemic immune activation (SIA) was identified as a potential risk of atezolizumab when given in combination with other immunomodulating agents. The inclusion criterion regarding representative tumor specimens was modified. If no paraffin block was available, at least 20 unstained slides (previously 15 slides) had to be submitted. Additionally, further details were included regarding participant eligibility per archival and fresh tumor tissue quantity and histology. The study inclusion criterion regarding treated, asymptomatic CNS metastases was modified to clarify that cerebellar metastases were permitted. The exclusion criterion regarding history of autoimmune disease was broadened, on the basis of an expanding safety database, to allow for participants with eczema, psoriasis, or lichen simplex chronicus or vitiligo with dermatologic manifestations only to be permitted provided that they met specific conditions. The contraception requirements in the inclusion and exclusion criteria and the pregnancy reporting information were updated to be consistent with the current safety information for nab-paclitaxel. The cap on the percentage of participants with liver metastases was removed in light of results from recently completed randomized studies with atezolizumab.
07 September 2016	Protocol was amended to include removal of the option to treat participants beyond initial radiographic progression and related rationale and procedures were removed. Evaluation criteria of tumor response per immune modified RECIST were removed to reflect the change that participants directly entered survival follow-up after disease progression. For women of childbearing potential, the duration to remain abstinent or use contraceptive methods that result in a failure rate of <1% per year during the treatment period was increased from at least 90 days to at least 5 months after the last dose of atezolizumab. Whole brain radiation within 14 days prior to randomization was added to cancer-specific exclusion criteria. Exclusion of participants with negative PD-L1 status based on screening for entry into another trial was removed from the eligibility criteria. The period that participants must agree not to receive live, attenuated vaccine following the last dose of atezolizumab/placebo was extended from 90 days to 5 months based on a revision of the known half-life of atezolizumab. Traditional herbal medicines were removed from prohibited therapies. Methods of evaluation of PFS were revised.
02 March 2018	Protocol was amended to include the length of time atezolizumab or placebo could be withheld before discontinuing treatment was lengthened from 42 days to 12 weeks.

28 September 2018	Protocol was amended to include allowing for crossover of participants who were originally randomized to receive placebo and who have not experienced disease progression and who have not started any other systemic non-protocol-specified anticancer agents to the atezolizumab arm provided that they still meet the safety-related eligibility criteria for the study. Guidelines for managing participants who experience atezolizumab-associated adverse events have been revised to include nephritis.
31 January 2020	Protocol was amended to include update to the list of atezolizumab risks to include myositis. Systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported