

**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	31 August 2021

**Results information**

Result version number	v2 (current)
This version publication date	16 July 2022
First version publication date	09 April 2021
Version creation reason	

**Trial information****Trial identification**

Sponsor protocol code	WO29522
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**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	Final
Date of interim/final analysis	31 August 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 August 2021
Was the trial ended prematurely?	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:

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### 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.

The observation of Overall Survival events was complete. Participants still on treatment were handed over to follow-up programs or studies. The study status is "Completed" but some participants discontinued the study because the Sponsor terminated it after it reached the "Completed" state.

### 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
<b>Arm title</b>	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.

<b>Arm title</b>	Atezolizumab Plus Nab-Paclitaxel
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Arm description:

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

Arm type	Experimental
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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.

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.

<b>Number of subjects in period 1</b>	Placebo Plus Nab-Paclitaxel	Atezolizumab Plus Nab-Paclitaxel
Started	451	451
Completed	0	0
Not completed	451	451
Consent withdrawn by subject	27	32
Non-Compliance	1	1
Physician decision	-	1
Accidentally randomized screen failure participant	-	1
Study Terminated By Sponsor	85	95
Death	333	314
Lost to follow-up	4	6
Protocol deviation	1	1

## 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.	
Subject analysis set title	Placebo Plus Nab-Paclitaxel Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Placebo Plus Nab-Paclitaxel Safety Population included participants who received any amount of any study drug.	
Subject analysis set title	Atezolizumab Plus Nab-Paclitaxel Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Atezolizumab Plus Nab-Paclitaxel Safety Population included participants who received any amount of any study drug.	

### 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)
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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
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End point timeframe:

Baseline up to approximately 34 months

<b>End point values</b>	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**

<b>Statistical analysis title</b>	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)	

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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
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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
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End point timeframe:

Baseline up to approximately 34 months

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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 According to RECIST v1.1 in Participants with Detectable PD-L1

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

Baseline up to approximately 34 months

<b>End point values</b>	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

<b>Statistical analysis title</b>	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
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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  $\geq 10$ -point decrease from the baseline scale score. A 10-point change was defined as the minimally important difference (MID). 2. The score decrease of  $\geq 10$ -points from baseline was held for at least two consecutive cycles, or an initial score decrease of  $\geq 10$ -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  $\geq 1$  post-baseline PRO assessment.

End point type	Secondary
End point timeframe:	
Baseline up to approximately 58 months	

<b>End point values</b>	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**

<b>Statistical analysis title</b>	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
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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  $\geq 10$ -point decrease from the baseline scale score. A 10-point change was defined as the minimally important difference (MID). 2. The score decrease of  $\geq 10$ -points from baseline was held for at least two consecutive cycles, or an initial score decrease of  $\geq 10$ -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  $\geq 1$  post-baseline PRO assessment.

End point type	Secondary
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End point timeframe:

Baseline up to approximately 58 months

<b>End point values</b>	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**

<b>Statistical analysis title</b>	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 at Least One Adverse Event

End point title Percentage of Participants with at Least One Adverse Event

End point description:

End point type Secondary

End point timeframe:

Baseline up to the data cutoff date: 31 August 2021 (up to approximately 74 months)

End point values	Placebo Plus Nab-Paclitaxel Safety Population	Atezolizumab Plus Nab-Paclitaxel Safety Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	430	460		
Units: Percentage of participants				
number (not applicable)	97.9	99.3		

### 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<sup>[1]</sup>

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:

[1] - 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.

<b>End point values</b>	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<sup>[2]</sup>

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:

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

<b>End point values</b>	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<sup>[3]</sup>

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
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End point timeframe:

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

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	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
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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
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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 ( $\pm$ 2300)	3080 ( $\pm$ 2050)		
C3D1/Postdose Paclit (n=221;n=280)	370 ( $\pm$ 244)	400 ( $\pm$ 275)		

### Statistical analyses

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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: 31 August 2021 (up to approximately 74 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	Atezolizumab (q2w) + nab-Paclitaxel
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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
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Reporting group description:

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

<b>Serious adverse events</b>	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	339	
number of deaths resulting from adverse events	2	1	
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			
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	
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	
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	
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	
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	

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
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
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
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	
<b>Immune system disorders</b>			
<b>CONTRAST MEDIA ALLERGY</b>			
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	
<b>HYPERSENSITIVITY</b>			
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	
<b>SYSTEMIC IMMUNE ACTIVATION</b>			
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	
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>ACUTE RESPIRATORY FAILURE</b>			
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	
<b>ASPIRATION</b>			
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	
<b>CHRONIC OBSTRUCTIVE PULMONARY DISEASE</b>			
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	
<b>DYSPNOEA</b>			
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	

DYSпноEA 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	
<b>CONFUSIONAL STATE</b>			
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	
<b>Product issues</b>			
<b>DEVICE BREAKAGE</b>			
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	
<b>THROMBOSIS IN DEVICE</b>			
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	
<b>Investigations</b>			
<b>ALANINE AMINOTRANSFERASE INCREASED</b>			
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	
<b>ASPARTATE AMINOTRANSFERASE INCREASED</b>			
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	
<b>BLOOD CREATININE INCREASED</b>			
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	
<b>PLATELET COUNT DECREASED</b>			
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			
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	
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	
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	
<b>TACHYCARDIA</b>			
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	
<b>Nervous system disorders</b>			
<b>CEREBRAL HAEMORRHAGE</b>			
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	
<b>CEREBRAL THROMBOSIS</b>			
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	
<b>CEREBROVASCULAR ACCIDENT</b>			
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	
<b>FACIAL PARALYSIS</b>			
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	
<b>EMBOLIC STROKE</b>			
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	
<b>HEADACHE</b>			
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	
<b>HEPATIC ENCEPHALOPATHY</b>			

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	
<b>HYPOAESTHESIA</b>			
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	
<b>IIIRD NERVE PARALYSIS</b>			
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	
<b>LOSS OF CONSCIOUSNESS</b>			
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	
<b>PERIPHERAL MOTOR NEUROPATHY</b>			
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	
<b>PERIPHERAL SENSORY NEUROPATHY</b>			
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	
<b>SEIZURE</b>			
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	
<b>BELL'S PALSY</b>			
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	
<b>Blood and lymphatic system disorders</b>			
<b>FEBRILE NEUTROPENIA</b>			

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	
<b>ANAEMIA</b>			
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	
<b>HAEMOLYSIS</b>			
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	
<b>LEUKOCYTOSIS</b>			
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	
<b>PANCYTOPENIA</b>			
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	
<b>NEUTROPENIA</b>			
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	
<b>Ear and labyrinth disorders</b>			
<b>VERTIGO</b>			
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	
<b>Eye disorders</b>			
<b>DIPLOPIA</b>			
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	
<b>KERATITIS</b>			

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	
<b>OPTIC NEUROPATHY</b>			
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	
<b>Gastrointestinal disorders</b>			
<b>ABDOMINAL PAIN</b>			
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	
<b>ABDOMINAL PAIN UPPER</b>			
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	
<b>COLITIS</b>			
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	
<b>COLITIS ULCERATIVE</b>			
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	
<b>CONSTIPATION</b>			
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	
<b>DIARRHOEA</b>			
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	
<b>GASTRIC HAEMORRHAGE</b>			

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
<b>DYSPHAGIA</b>		
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
<b>GASTROINTESTINAL TOXICITY</b>		
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
<b>GASTROINTESTINAL HAEMORRHAGE</b>		
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
<b>MECHANICAL ILEUS</b>		
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
<b>NAUSEA</b>		
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
<b>SMALL INTESTINAL OBSTRUCTION</b>		
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
<b>STOMATITIS</b>		
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
<b>UPPER GASTROINTESTINAL HAEMORRHAGE</b>		

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	
<b>VOMITING</b>			
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	
<b>Hepatobiliary disorders</b>			
<b>AUTOIMMUNE HEPATITIS</b>			
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	1 / 1	0 / 0	
<b>AUTOIMMUNE CHOLANGITIS</b>			
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	
<b>CHOLECYSTITIS ACUTE</b>			
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	
<b>BILE DUCT STONE</b>			
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	
<b>CHOLECYSTOCHOLANGITIS</b>			
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	
<b>HEPATIC FAILURE</b>			
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	1 / 1	
<b>HEPATITIS</b>			

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	
<b>Skin and subcutaneous tissue disorders</b>			
<b>DERMATOMYOSITIS</b>			
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	
<b>LICHEN PLANUS</b>			
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	
<b>DRUG ERUPTION</b>			
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	
<b>TOXIC EPIDERMAL NECROLYSIS</b>			
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	
<b>RASH</b>			
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	
<b>Renal and urinary disorders</b>			
<b>ACUTE KIDNEY INJURY</b>			
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	
<b>HYDRONEPHROSIS</b>			
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	
<b>RENAL FAILURE</b>			

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	
<b>NEPHROLITHIASIS</b>			
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	
<b>Endocrine disorders</b>			
<b>ADDISON'S DISEASE</b>			
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	
<b>ADRENOCORTICAL INSUFFICIENCY ACUTE</b>			
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	
<b>HYPERTHYROIDISM</b>			
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	
<b>HYPOPHYSITIS</b>			
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	
<b>INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION</b>			
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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>BACK PAIN</b>			

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	
<b>BONE PAIN</b>			
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	
<b>INTERVERTEBRAL DISC PROTRUSION</b>			
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	
<b>LIMB DEFORMITY</b>			
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	
<b>MUSCULAR WEAKNESS</b>			
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	
<b>MYOPATHY</b>			
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	
<b>NECK PAIN</b>			
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	
<b>PAIN IN EXTREMITY</b>			
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	
<b>PATHOLOGICAL FRACTURE</b>			

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	
<b>POLYARTHRITIS</b>			
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	
<b>TEMPOROMANDIBULAR JOINT SYNDROME</b>			
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	
<b>ARTHRALGIA</b>			
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	
<b>MYALGIA</b>			
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	
<b>Infections and infestations</b>			
<b>APPENDICITIS</b>			
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	
<b>CELLULITIS</b>			
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	
<b>CLOSTRIDIUM DIFFICILE COLITIS</b>			
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	
<b>CLOSTRIDIUM DIFFICILE INFECTION</b>			

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
<b>CYTOMEGALOVIRUS INFECTION</b>		
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
<b>DEVICE RELATED INFECTION</b>		
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
<b>ERYSIPELAS</b>		
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
<b>HERPES ZOSTER</b>		
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
<b>INFECTION</b>		
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
<b>INFECTIOUS PLEURAL EFFUSION</b>		
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
<b>INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE</b>		
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
<b>INFLUENZA</b>		

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
<b>KLEBSIELLA BACTERAEMIA</b>		
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
<b>LOWER RESPIRATORY TRACT INFECTION</b>		
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
<b>MASTITIS</b>		
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
<b>NEUTROPENIC SEPSIS</b>		
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
<b>OSTEOMYELITIS</b>		
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
<b>PERITONITIS</b>		
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
<b>PNEUMONIA</b>		
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
<b>PNEUMONIA BACTERIAL</b>		

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
<b>PNEUMONIA PNEUMOCOCCAL</b>		
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
<b>PYELONEPHRITIS</b>		
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
<b>PYELONEPHRITIS ACUTE</b>		
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
<b>RESPIRATORY TRACT INFECTION</b>		
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
<b>RESPIRATORY TRACT INFECTION VIRAL</b>		
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
<b>SEPSIS</b>		
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
<b>SEPTIC SHOCK</b>		
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	1 / 1	0 / 0
<b>SINUSITIS</b>		

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	
<b>STREPTOCOCCAL SEPSIS</b>			
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	
<b>SOFT TISSUE INFECTION</b>			
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	
<b>TONSILLITIS</b>			
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	
<b>TOOTH INFECTION</b>			
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	
<b>UPPER RESPIRATORY TRACT INFECTION</b>			
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	
<b>URINARY TRACT INFECTION</b>			
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	
<b>VASCULAR DEVICE INFECTION</b>			
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	
<b>VIRAL INFECTION</b>			

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	
<b>VIRAL UPPER RESPIRATORY TRACT INFECTION</b>			
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	
<b>WOUND INFECTION</b>			
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	
<b>Metabolism and nutrition disorders</b>			
<b>DEHYDRATION</b>			
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	
<b>DIABETES MELLITUS</b>			
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	
<b>DIABETIC KETOACIDOSIS</b>			
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	
<b>HYPOKALAEMIA</b>			
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	
<b>HYPONATRAEMIA</b>			
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	
<b>HYPOPHOSPHATAEMIA</b>			

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 %

<b>Non-serious adverse events</b>	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%)	
<b>Vascular disorders</b>			
<b>HYPERTENSION</b>			
subjects affected / exposed	25 / 460 (5.43%)	21 / 430 (4.88%)	
occurrences (all)	37	32	
<b>HOT FLUSH</b>			
subjects affected / exposed	30 / 460 (6.52%)	32 / 430 (7.44%)	
occurrences (all)	34	35	
<b>LYMPHOEDEMA</b>			
subjects affected / exposed	30 / 460 (6.52%)	30 / 430 (6.98%)	
occurrences (all)	34	31	
<b>General disorders and administration site conditions</b>			
<b>ASTHENIA</b>			
subjects affected / exposed	60 / 460 (13.04%)	51 / 430 (11.86%)	
occurrences (all)	80	75	
<b>CHEST PAIN</b>			
subjects affected / exposed	33 / 460 (7.17%)	20 / 430 (4.65%)	
occurrences (all)	36	22	
<b>CHILLS</b>			
subjects affected / exposed	42 / 460 (9.13%)	23 / 430 (5.35%)	
occurrences (all)	58	26	
<b>FATIGUE</b>			
subjects affected / exposed	216 / 460 (46.96%)	194 / 430 (45.12%)	
occurrences (all)	264	238	
<b>INFLUENZA LIKE ILLNESS</b>			
subjects affected / exposed	29 / 460 (6.30%)	11 / 430 (2.56%)	
occurrences (all)	35	12	

MUCOSAL INFLAMMATION subjects affected / exposed occurrences (all)	29 / 460 (6.30%) 38	16 / 430 (3.72%) 18	
OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	73 / 460 (15.87%) 94	66 / 430 (15.35%) 86	
PYREXIA subjects affected / exposed occurrences (all)	89 / 460 (19.35%) 145	45 / 430 (10.47%) 72	
Reproductive system and breast disorders BREAST PAIN subjects affected / exposed occurrences (all)	31 / 460 (6.74%) 43	21 / 430 (4.88%) 22	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	127 / 460 (27.61%) 171	80 / 430 (18.60%) 116	
DYSPNOEA subjects affected / exposed occurrences (all)	70 / 460 (15.22%) 90	60 / 430 (13.95%) 68	
EPISTAXIS subjects affected / exposed occurrences (all)	36 / 460 (7.83%) 49	39 / 430 (9.07%) 43	
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	30 / 460 (6.52%) 37	13 / 430 (3.02%) 16	
Psychiatric disorders DEPRESSION subjects affected / exposed occurrences (all)	18 / 460 (3.91%) 19	22 / 430 (5.12%) 22	
INSOMNIA subjects affected / exposed occurrences (all)	54 / 460 (11.74%) 59	52 / 430 (12.09%) 54	
Investigations ALANINE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	53 / 460 (11.52%)	37 / 430 (8.60%)	
occurrences (all)	100	38	
<b>ASPARTATE AMINOTRANSFERASE INCREASED</b>			
subjects affected / exposed	49 / 460 (10.65%)	42 / 430 (9.77%)	
occurrences (all)	80	48	
<b>WEIGHT DECREASED</b>			
subjects affected / exposed	22 / 460 (4.78%)	26 / 430 (6.05%)	
occurrences (all)	26	28	
<b>NEUTROPHIL COUNT DECREASED</b>			
subjects affected / exposed	57 / 460 (12.39%)	49 / 430 (11.40%)	
occurrences (all)	163	101	
<b>WHITE BLOOD CELL COUNT DECREASED</b>			
subjects affected / exposed	39 / 460 (8.48%)	21 / 430 (4.88%)	
occurrences (all)	89	37	
<b>Nervous system disorders</b>			
<b>DIZZINESS</b>			
subjects affected / exposed	69 / 460 (15.00%)	43 / 430 (10.00%)	
occurrences (all)	87	49	
<b>NEUROPATHY PERIPHERAL</b>			
subjects affected / exposed	100 / 460 (21.74%)	97 / 430 (22.56%)	
occurrences (all)	138	120	
<b>HEADACHE</b>			
subjects affected / exposed	116 / 460 (25.22%)	92 / 430 (21.40%)	
occurrences (all)	172	125	
<b>DYSGEUSIA</b>			
subjects affected / exposed	52 / 460 (11.30%)	44 / 430 (10.23%)	
occurrences (all)	59	50	
<b>PARAESTHESIA</b>			
subjects affected / exposed	34 / 460 (7.39%)	29 / 430 (6.74%)	
occurrences (all)	44	32	
<b>PERIPHERAL SENSORY NEUROPATHY</b>			
subjects affected / exposed	74 / 460 (16.09%)	52 / 430 (12.09%)	
occurrences (all)	90	62	
<b>Blood and lymphatic system disorders</b>			

ANAEMIA			
subjects affected / exposed	129 / 460 (28.04%)	115 / 430 (26.74%)	
occurrences (all)	221	186	
LEUKOPENIA			
subjects affected / exposed	30 / 460 (6.52%)	23 / 430 (5.35%)	
occurrences (all)	68	50	
NEUTROPENIA			
subjects affected / exposed	101 / 460 (21.96%)	66 / 430 (15.35%)	
occurrences (all)	238	176	
Eye disorders			
LACRIMATION INCREASED			
subjects affected / exposed	28 / 460 (6.09%)	33 / 430 (7.67%)	
occurrences (all)	28	33	
DRY EYE			
subjects affected / exposed	31 / 460 (6.74%)	15 / 430 (3.49%)	
occurrences (all)	33	15	
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	29 / 460 (6.30%)	25 / 430 (5.81%)	
occurrences (all)	35	26	
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)	307	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	
GASTROESOPHAGEAL REFLUX DISEASE			

subjects affected / exposed occurrences (all)	24 / 460 (5.22%) 26	12 / 430 (2.79%) 13	
NAUSEA subjects affected / exposed occurrences (all)	213 / 460 (46.30%) 338	164 / 430 (38.14%) 244	
STOMATITIS subjects affected / exposed occurrences (all)	49 / 460 (10.65%) 66	20 / 430 (4.65%) 24	
VOMITING subjects affected / exposed occurrences (all)	92 / 460 (20.00%) 141	73 / 430 (16.98%) 98	
Skin and subcutaneous tissue disorders			
NAIL DISCOLOURATION subjects affected / exposed occurrences (all)	38 / 460 (8.26%) 39	30 / 430 (6.98%) 31	
DRY SKIN subjects affected / exposed occurrences (all)	42 / 460 (9.13%) 45	25 / 430 (5.81%) 27	
ALOPECIA subjects affected / exposed occurrences (all)	263 / 460 (57.17%) 272	247 / 430 (57.44%) 249	
PRURITUS subjects affected / exposed occurrences (all)	73 / 460 (15.87%) 93	45 / 430 (10.47%) 53	
RASH subjects affected / exposed occurrences (all)	84 / 460 (18.26%) 115	71 / 430 (16.51%) 96	
Endocrine disorders			
HYPOTHYROIDISM subjects affected / exposed occurrences (all)	67 / 460 (14.57%) 80	15 / 430 (3.49%) 15	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA subjects affected / exposed occurrences (all)	104 / 460 (22.61%) 174	88 / 430 (20.47%) 120	
BACK PAIN			

subjects affected / exposed occurrences (all)	74 / 460 (16.09%) 106	59 / 430 (13.72%) 69	
<b>MUSCLE SPASMS</b>			
subjects affected / exposed occurrences (all)	25 / 460 (5.43%) 31	5 / 430 (1.16%) 5	
<b>BONE PAIN</b>			
subjects affected / exposed occurrences (all)	24 / 460 (5.22%) 28	11 / 430 (2.56%) 13	
<b>MUSCULOSKELETAL CHEST PAIN</b>			
subjects affected / exposed occurrences (all)	25 / 460 (5.43%) 28	18 / 430 (4.19%) 20	
<b>PAIN IN EXTREMITY</b>			
subjects affected / exposed occurrences (all)	56 / 460 (12.17%) 79	41 / 430 (9.53%) 53	
<b>MYALGIA</b>			
subjects affected / exposed occurrences (all)	72 / 460 (15.65%) 84	67 / 430 (15.58%) 86	
<b>Infections and infestations</b>			
<b>NASOPHARYNGITIS</b>			
subjects affected / exposed occurrences (all)	52 / 460 (11.30%) 80	36 / 430 (8.37%) 42	
<b>UPPER RESPIRATORY TRACT INFECTION</b>			
subjects affected / exposed occurrences (all)	55 / 460 (11.96%) 84	38 / 430 (8.84%) 49	
<b>URINARY TRACT INFECTION</b>			
subjects affected / exposed occurrences (all)	57 / 460 (12.39%) 86	42 / 430 (9.77%) 60	
<b>Metabolism and nutrition disorders</b>			
<b>HYPOKALAEMIA</b>			
subjects affected / exposed occurrences (all)	29 / 460 (6.30%) 45	9 / 430 (2.09%) 10	
<b>HYPOCALCAEMIA</b>			
subjects affected / exposed occurrences (all)	25 / 460 (5.43%) 33	10 / 430 (2.33%) 11	
<b>DECREASED APPETITE</b>			

subjects affected / exposed	92 / 460 (20.00%)	80 / 430 (18.60%)
occurrences (all)	117	86
HYPOMAGNESAEMIA		
subjects affected / exposed	26 / 460 (5.65%)	11 / 430 (2.56%)
occurrences (all)	62	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 amended 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:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported