Clinical trial results:
A Phase III Randomized Study to Investigate the Efficacy and Safety of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Neoadjuvant Anthracycline/Nab-Paclitaxel-Based Chemotherapy Compared With Placebo and Chemotherapy in Patients With Primary Invasive Triple-Negative Breast Cancer

Summary

EudraCT number	2016-004734-22
Trial protocol	DE GB BE PL ES IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	14 April 2021
First version publication date	14 April 2021

Trial information

Trial identification

Sponsor protocol code	WO39392

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03197935
WHO universal trial number (UTN)	-
Other trial identifiers	Other Sponsor ID: IMpassion031

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	03 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study were to evaluate the efficacy, safety, and pharmacokinetics of neoadjuvant nab-paclitaxel and atezolizumab followed by doxorubicin and cyclophosphamide with atezolizumab or neoadjuvant nab-paclitaxel and placebo followed by doxorubicin and cyclophosphamide with placebo in participants with T2-4d triple-negative breast cancer (TNBC).

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	24 July 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	50 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 113
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Japan: 36
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	333
EEA total number of subjects	74

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)	287
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with clinically assessed T2-4d early or primary invasive triple-negative breast cancer (TNBC) who were eligible for surgery were included in the study.

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 and Chemotherapy

Arm description:

Participants received placebo matched to atezolizumab via IV infusion every 2 weeks in combination with nab-paclitaxel (125 mg/m^2) via IV infusion every week for 12 weeks, followed by placebo matched to atezolizumab every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants will continue to be followed.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	MPDL3280A, Tecentriq
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo matched to atezolizumab was administered intravenously every 2 weeks for 12 weeks, followed by placebo matched to atezolizumab administered intravenously every 2 weeks for 4 doses.

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

Dosage and administration details:

Nab-paclitaxel was administered at a dose of 125 milligrams per square meter [mg/m^2] intravenously every week for 12 weeks.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin was administered at a dose of 60 mg/m^2 every 2 weeks intravenously for 4 doses.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide was administered at a dose of 600 mg/m^2 every 2 weeks intravenously for 4 doses.

Arm title	Atezolizumab and Chemotherapy

Arm description:

Participants received atezolizumab (840 milligrams [mg]) via intravenous (IV) infusion every 2 weeks in combination with nab-paclitaxel (125 milligrams per square meter [mg/m^2]) via IV infusion every week for 12 weeks, followed by atezolizumab (840 mg) every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants continued to receive unblinded atezolizumab post-surgery at a fixed dose of 1200 mg by IV infusion every 3 weeks for 11 doses, for a total of approximately 12 months of atezolizumab therapy.

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

Dosage and administration details:

Atezolizumab was administered intravenously at a dose of 840 milligrams every 2 weeks for 12 weeks, followed by a dose of 840 mg of atezolizumab administered intravenously every 2 weeks for 4 doses. Participants continued to receive unblinded atezolizumab post-surgery at a fixed dose of 1200 mg intravenously every 3 weeks for 11 doses, for a total of approximately 12 months of atezolizumab therapy.

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

Dosage and administration details:

Nab-paclitaxel was administered at a dose of 125 milligrams per square meter [mg/m^2] intravenously every week for 12 weeks.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin was administered at a dose of 60 mg/m^2 every 2 weeks intravenously for 4 doses.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide was administered at a dose of 600 mg/m^2 every 2 weeks intravenously for 4 doses.

Number of subjects in period 1	Placebo and Chemotherapy	Atezolizumab and Chemotherapy
Started	168	165
Completed	0	0
Not completed	168	165
On-Going in Study	147	146
Consent withdrawn by subject	11	7
Physician decision	-	1
Death due to any cause	9	7
Lost to follow-up	-	3
Did not receive any study treatment	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo and Chemotherapy
Reporting group description:	
Participants received placebo matched to atezolizumab via IV infusion every 2 weeks in combination with nab-paclitaxel (125 mg/m^2) via IV infusion every week for 12 weeks, followed by placebo matched to atezolizumab every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants will continue to be followed.	
Reporting group title	Atezolizumab and Chemotherapy
Reporting group description:	
Participants received atezolizumab (840 milligrams [mg]) via intravenous (IV) infusion every 2 weeks in combination with nab-paclitaxel (125 milligrams per square meter [mg/m^2]) via IV infusion every week for 12 weeks, followed by atezolizumab (840 mg) every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants continued to receive unblinded atezolizumab post-surgery at a fixed dose of 1200 mg by IV infusion every 3 weeks for 11 doses, for a total of approximately 12 months of atezolizumab therapy.	

Reporting group values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy	Total
Number of subjects	168	165	333
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)	139	148	287
From 65-84 years	29	17	46
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	50.3	50.1	
standard deviation	± 13.2	± 11.6	-
Sex: Female, Male Units: Participants			
Female	168	165	333
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	41	47	88
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	15	9	24
White	108	102	210
More than one race	0	4	4

Unknown or Not Reported	4	3	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	47	45	92
Not Hispanic or Latino	114	114	228
Unknown or Not Reported	7	6	13

End points

End points reporting groups

Reporting group title	Placebo and Chemotherapy

Reporting group description:

Participants received placebo matched to atezolizumab via IV infusion every 2 weeks in combination with nab-paclitaxel (125 mg/m^2) via IV infusion every week for 12 weeks, followed by placebo matched to atezolizumab every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants will continue to be followed.

Reporting group title	Atezolizumab and Chemotherapy

Reporting group description:

Participants received atezolizumab (840 milligrams [mg]) via intravenous (IV) infusion every 2 weeks in combination with nab-paclitaxel (125 milligrams per square meter [mg/m^2]) via IV infusion every week for 12 weeks, followed by atezolizumab (840 mg) every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants continued to receive unblinded atezolizumab post-surgery at a fixed dose of 1200 mg by IV infusion every 3 weeks for 11 doses, for a total of approximately 12 months of atezolizumab therapy.

Primary: Number of Participants with Pathologic Complete Response (pCR) Using American Joint Committee on Cancer (AJCC) Staging System in ITT Population

End point title	Number of Participants with Pathologic Complete Response (pCR) Using American Joint Committee on Cancer (AJCC) Staging System in ITT Population

End point description:

Number of participants with Pathologic Complete Response (pCR) Using American Joint Committee on Cancer (AJCC) Staging System in ITT Population. pCR is defined as eradication of invasive tumor from both breast and lymph nodes (ypT0/is ypN0). Participants whose pCR assessment was missing will be counted as not achieving a pCR.

End point type	Primary

End point timeframe:

Up to data cut-off on 3 April 2020

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	168	165		
Units: Number of participants				
number (not applicable)	69	95		

Statistical analyses

Statistical analysis title	pCR in ITT Population
Comparison groups	Placebo and Chemotherapy v Atezolizumab and Chemotherapy

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0044 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in pCR
Point estimate	16.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.91
upper limit	27.1

Notes:

[1] - (one-sided)

Primary: Number of Participants with pCR in Subpopulation with PD-L1-Positive Tumor Status (tumor-infiltrating immune cell [IC] 1/2/3) Using AJCC Staging System

End point title	Number of Participants with pCR in Subpopulation with PD-L1-Positive Tumor Status (tumor-infiltrating immune cell [IC] 1/2/3) Using AJCC Staging System

End point description:

Number of participants with Pathologic Complete Response (pCR) Using American Joint Committee on Cancer (AJCC) Staging System in the subpopulation with programmed death-ligand1 (PD-L1)-positive tumor status(tumor-infiltrating immune cell [IC] IC1/2/3) . pCR is defined as eradication of invasive tumor from both breast and lymph nodes (ypT0/is ypN0). Participants whose pCR assessment was missing will be counted as not achieving a pCR.

End point type	Primary

End point timeframe:

Up to data cut-off on 3 April 2020

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	77		
Units: Number of participants				
number (not applicable)	37	53		

Statistical analyses

Statistical analysis title	pCR in PD-L1-Positive Tumor Status
Comparison groups	Placebo and Chemotherapy v Atezolizumab and Chemotherapy

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0206
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in pCR
Point estimate	19.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.17
upper limit	34.83

Secondary: Event-Free Survival (EFS) in All Participants

End point title	Event-Free Survival (EFS) in All Participants

End point description:

Event-free survival (EFS) defined as the time from randomization until documented disease recurrence, progression, or death from any cause in all participants. EFS events covered under "disease recurrence" will include local, regional, or distant recurrence and contralateral breast cancer. Ipsilateral or contralateral in situ disease and second primary non-breast cancers will not be counted as EFS events.

End point type	Secondary

End point timeframe:

Baseline up to approximately 63 months

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[2] - Data will be submitted at the time of final results posting.

[3] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS) in Subpopulation with PD-L1-Postive Tumor Status

End point title	Event-Free Survival (EFS) in Subpopulation with PD-L1-Postive Tumor Status

End point description:

Event-free survival (EFS) defined as the time from randomization until documented disease recurrence, progression, or death from any cause in the subpopulation with PD-L1-positive tumor status. EFS events covered under "disease recurrence" will include local, regional, or distant recurrence and contralateral breast cancer. Ipsilateral or contralateral in situ disease and second primary non-breast cancers will not be counted as EFS events.

End point type	Secondary

End point timeframe:

Baseline up to approximately 63 months

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Months				
number (confidence interval 95%)	(to)	(to)		

Notes:

[4] - Data will be submitted at the time of final results posting.

[5] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS) in All Participants Who Undergo Surgery

End point title	Disease-Free Survival (DFS) in All Participants Who Undergo Surgery

End point description:

Disease-free survival (DFS) defined as the time from surgery until documented disease recurrence or death from any cause in all patients (ITT population) who undergo surgery.

End point type	Secondary

End point timeframe:

Baseline up to approximately 63 months

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[6] - Data will be submitted at the time of final results posting.

[7] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS) in Subpopulation of Participants with PD-L1-Positive Tumor Status Who Undergo Surgery

End point title	Disease-Free Survival (DFS) in Subpopulation of Participants with PD-L1-Positive Tumor Status Who Undergo Surgery

End point description:

Disease-free survival (DFS) defined as the time from surgery until documented disease recurrence or death from any cause in the subpopulation of participants with PD-L1-positive tumor status who undergo surgery.

End point type	Secondary

End point timeframe:

Baseline up to approximately 63 months

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[8] - Data will be submitted at the time of final results posting.

[9] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) in All Participants

End point title	Overall survival (OS) in All Participants

End point description:

Overall survival (OS) defined as the time from randomization to the date of death from any cause in all participants.

End point type	Secondary

End point timeframe:

Baseline up to approximately 63 months

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[10] - Data will be submitted at the time of final results posting.

[11] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) in Subpopulation with PD-L1-Positive Tumor Status

End point title	Overall survival (OS) in Subpopulation with PD-L1-Positive Tumor Status

End point description:

Overall survival (OS) defined as the time from randomization to the date of death from any cause in the subpopulation with PD-L1-positive tumor status.

End point type	Secondary

End point timeframe:

Baseline up to approximately 63 months

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[12] - Data will be submitted at the time of final results posting.

[13] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Scores for Function (Role/Physical) and GHS/HRQoL by Cycle and Between Treatment Arms as Assessed by the EORTC QLQ-C30

End point title	Mean Scores for Function (Role/Physical) and GHS/HRQoL by Cycle and Between Treatment Arms as Assessed by the EORTC QLQ-C30

End point description:

Mean score in function (role, physical) and global health status(GHS)/ health-related quality of life (HRQoL) by cycle and between treatment arms as assessed by the functional and HRQoL scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core30(QLQ C30). The EORTC QLQ-C30 includes five functional scales; a global health status (GHS)/quality of life (QoL) scale; and items measuring fatigue, pain, nausea and vomiting, dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties. The score range for each scale and single-item measure is 0 to 100, where higher scores indicate a higher response level (i.e., better functioning, better QoL, worse symptoms).

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), on Day 1 of every cycle (C) thereafter (C=28 days from C1 to 5, and 21 days from C6 to 16), at Study Drug Completion/Early Discontinuation, Survival Follow-Up Months 3, 6, 9, 12, 18 and 24 (up to approximately 63 months)

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Score on a 0-100 scale				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[14] - Data will be submitted at the time of final results posting.

[15] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline Scores for Function (Role, Physical) and GHS/HRQoL by Cycle and Between Treatment Arms as Assessed by the EORTC QLQ-C30

End point title	Mean Change From Baseline Scores for Function (Role, Physical) and GHS/HRQoL by Cycle and Between Treatment Arms as Assessed by the EORTC QLQ-C30

End point description:

Mean change from baseline score in function (role, physical) andglobal health status(GHS)/ health-related quality of life (HRQoL) by cycle and between treatment arms as assessed by the functional and HRQoL scales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core30(QLQ C30).

End point type	Secondary

End point timeframe:

Baseline (Cycle 1 Day 1), and on Day 1 of every cycle (C) thereafter (C length=28 days from C1 to 5, and 21 days from C6 to 16), at Study Drug Completion/Early Termination, Survival Follow-Up Months 12, 18, and 24 (up to approximately 63 months)

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: Score on a 0-100 scale				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[16] - Data will be submitted at the time of final results posting.

[17] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Events (AEs)

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

End point description:

End point type	Secondary

End point timeframe:

Baseline up to approximately 63 months

End point values	Placebo and Chemotherapy	Atezolizumab and Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[18] - Data will be submitted at the time of final results posting.

[19] - Data will be submitted at the time of final results posting.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Serum Atezolizumab Concentration (Cmin)

End point title	Minimum Observed Serum Atezolizumab Concentration

End point description:

End point type	Secondary

End point timeframe:

Pre-dose on Day 1 of Cycles 2, 3, 4, 6, 8, 12, and 16 (cycle length = 28 days from Cycles 1 to 5, and 21 days from Cycles 6 to 16)

Notes:

[20] - 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: No statistical analysis for this end point.

End point values	Atezolizumab and Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	164			
Units: µg/mL				
arithmetic mean (standard deviation)				
Cycle 2 Day 1	142 (± 54.3)			
Cycle 3 Day 1	189 (± 64.2)			
Cycle 4 Day 1	207 (± 77.3)			
Cycle 6 Day 1	78.7 (± 50.3)			
Cycle 8 Day 1	204 (± 62.7)			
Cycle 12 Day 1	267 (± 81.1)			
Cycle 16 Day 1	303 (± 89.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Atezolizumab Concentration (Cmax)

End point title	Maximum Observed Serum Atezolizumab Concentration

End point description:

Maximum observed atezolizumab concentration (Cmax).

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 post dose (cycle length = 28 days)

Notes:

[21] - 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: No statistical analysis for this end point.

End point values	Atezolizumab and Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	164			
Units: µg/mL				
arithmetic mean (standard deviation)	334 (± 63.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Drug Antibodies (ADAs) to Atezolizumab

End point title	Percentage of Participants with Anti-Drug Antibodies (ADAs) to Atezolizumab[22]

End point description:

Percentage of participants with ADAs to atezolizumab.

End point type	Secondary

End point timeframe:

Baseline up to approximately 20 months

Notes:

[22] - 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: No statistical analysis for this end point.

End point values	Atezolizumab and Chemotherapy			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: Percentage of participants				
number (not applicable)				
Baseline evaluable participants	2.5			
Post-baseline evaluable participants	13.4			

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 3 April 2020 (up to approximately 32 months)

Adverse event reporting additional description:

Safety evaluable population is defined as all participants who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo + Nab-paclitaxel + AC

Reporting group description:

Participants received placebo matched to atezolizumab via IV infusion every 2 weeks in combination with nab-paclitaxel (125 mg/m^2) via IV infusion every week for 12 weeks, followed by placebo matched to atezolizumab every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants will be unblinded post-surgery and will continue to be followed.

Reporting group title	Atezolizumab + Nab-paclitaxel + AC

Reporting group description:

Participants received atezolizumab (840 milligrams [mg]) via intravenous (IV) infusion every 2 weeks in combination with nab-paclitaxel (125 milligrams per square meter [mg/m^2]) via IV infusion every week for 12 weeks, followed by atezolizumab (840 mg) every 2 weeks in combination with doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks via IV infusions with filgrastim/pegfilgrastim support for 4 doses. Participants continued to receive unblinded atezolizumab post-surgery at a fixed dose of 1200 mg by IV infusion every 3 weeks for 11 doses, for a total of approximately 12 months of atezolizumab therapy.

Serious adverse events	Placebo + Nab-paclitaxel + AC	Atezolizumab + Nab-paclitaxel + AC	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 167 (21.56%)	57 / 164 (34.76%)	
number of deaths (all causes)	9	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
EMBOLISM			

subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 167 (0.00%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			

subjects affected / exposed	2 / 167 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 167 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	2 / 167 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			

subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	2 / 167 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
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			
FRACTURE			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION RELATED REACTION			
subjects affected / exposed	1 / 167 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS CHEMICAL			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ROAD TRAFFIC ACCIDENT			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
WOUND DEHISCENCE			

subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIAC FAILURE			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
GUILLAIN-BARRE SYNDROME			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (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 / 167 (0.60%)	0 / 164 (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	2 / 167 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYNEUROPATHY			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	0 / 167 (0.00%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	3 / 167 (1.80%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

FEBRILE NEUTROPENIA			
subjects affected / exposed	13 / 167 (7.78%)	16 / 164 (9.76%)	
occurrences causally related to treatment / all	14 / 14	16 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	2 / 167 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (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	0 / 167 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 167 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
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 / 167 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OBSTRUCTIVE PANCREATITIS			

subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	0 / 167 (0.00%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATITIS			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DERMATOMYOSITIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL INFARCT			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
HYPOPITUITARISM			
subjects affected / exposed	1 / 167 (0.60%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
BACILLUS BACTERAEMIA			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANDIDA INFECTION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENCEPHALITIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

INFECTION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MASTITIS			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIORBITAL CELLULITIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECII PNEUMONIA			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	1 / 167 (0.60%)	6 / 164 (3.66%)	
occurrences causally related to treatment / all	0 / 1	4 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (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 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	2 / 167 (1.20%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			

subjects affected / exposed	0 / 167 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VITAMIN D DEFICIENCY			
subjects affected / exposed	1 / 167 (0.60%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Nab-paclitaxel + AC	Atezolizumab + Nab-paclitaxel + AC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	167 / 167 (100.00%)	161 / 164 (98.17%)	
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	17 / 167 (10.18%)	28 / 164 (17.07%)	
occurrences (all)	20	31	
HYPERTENSION			
subjects affected / exposed	17 / 167 (10.18%)	14 / 164 (8.54%)	
occurrences (all)	29	26	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	36 / 167 (21.56%)	42 / 164 (25.61%)	
occurrences (all)	40	66	
FATIGUE			
subjects affected / exposed	64 / 167 (38.32%)	62 / 164 (37.80%)	
occurrences (all)	84	91	
MALAISE			
subjects affected / exposed	17 / 167 (10.18%)	15 / 164 (9.15%)	
occurrences (all)	18	34	
MUCOSAL INFLAMMATION			
subjects affected / exposed	15 / 167 (8.98%)	18 / 164 (10.98%)	
occurrences (all)	19	24	
OEDEMA PERIPHERAL			

subjects affected / exposed	23 / 167 (13.77%)	24 / 164 (14.63%)	
occurrences (all)	26	30	
PAIN			
subjects affected / exposed	11 / 167 (6.59%)	19 / 164 (11.59%)	
occurrences (all)	11	21	
PYREXIA			
subjects affected / exposed	21 / 167 (12.57%)	36 / 164 (21.95%)	
occurrences (all)	25	55	
Reproductive system and breast disorders			
BREAST PAIN			
subjects affected / exposed	14 / 167 (8.38%)	14 / 164 (8.54%)	
occurrences (all)	14	16	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	32 / 167 (19.16%)	40 / 164 (24.39%)	
occurrences (all)	39	51	
DYSPNOEA			
subjects affected / exposed	20 / 167 (11.98%)	22 / 164 (13.41%)	
occurrences (all)	22	25	
EPISTAXIS			
subjects affected / exposed	24 / 167 (14.37%)	25 / 164 (15.24%)	
occurrences (all)	26	26	
OROPHARYNGEAL PAIN			
subjects affected / exposed	18 / 167 (10.78%)	19 / 164 (11.59%)	
occurrences (all)	19	20	
RHINORRHOEA			
subjects affected / exposed	0 / 167 (0.00%)	12 / 164 (7.32%)	
occurrences (all)	0	14	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	11 / 167 (6.59%)	11 / 164 (6.71%)	
occurrences (all)	11	11	
DEPRESSION			
subjects affected / exposed	6 / 167 (3.59%)	10 / 164 (6.10%)	
occurrences (all)	6	10	
INSOMNIA			

subjects affected / exposed	30 / 167 (17.96%)	46 / 164 (28.05%)	
occurrences (all)	32	58	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	35 / 167 (20.96%)	38 / 164 (23.17%)	
occurrences (all)	54	61	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	27 / 167 (16.17%)	36 / 164 (21.95%)	
occurrences (all)	43	59	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	4 / 167 (2.40%)	14 / 164 (8.54%)	
occurrences (all)	4	19	
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	7 / 167 (4.19%)	10 / 164 (6.10%)	
occurrences (all)	7	11	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	30 / 167 (17.96%)	29 / 164 (17.68%)	
occurrences (all)	67	61	
WEIGHT DECREASED			
subjects affected / exposed	8 / 167 (4.79%)	15 / 164 (9.15%)	
occurrences (all)	8	17	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	15 / 167 (8.98%)	14 / 164 (8.54%)	
occurrences (all)	35	33	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
subjects affected / exposed	10 / 167 (5.99%)	16 / 164 (9.76%)	
occurrences (all)	16	28	
PROCEDURAL PAIN			
subjects affected / exposed	2 / 167 (1.20%)	13 / 164 (7.93%)	
occurrences (all)	2	16	
RADIATION SKIN INJURY			

subjects affected / exposed	0 / 167 (0.00%)	28 / 164 (17.07%)	
occurrences (all)	0	28	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	15 / 167 (8.98%)	18 / 164 (10.98%)	
occurrences (all)	16	31	
DYSGEUSIA			
subjects affected / exposed	25 / 167 (14.97%)	16 / 164 (9.76%)	
occurrences (all)	27	20	
HEADACHE			
subjects affected / exposed	35 / 167 (20.96%)	50 / 164 (30.49%)	
occurrences (all)	45	76	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	34 / 167 (20.36%)	39 / 164 (23.78%)	
occurrences (all)	42	47	
PARAESTHESIA			
subjects affected / exposed	19 / 167 (11.38%)	12 / 164 (7.32%)	
occurrences (all)	22	13	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	43 / 167 (25.75%)	57 / 164 (34.76%)	
occurrences (all)	46	64	
POLYNEUROPATHY			
subjects affected / exposed	14 / 167 (8.38%)	9 / 164 (5.49%)	
occurrences (all)	15	9	
TASTE DISORDER			
subjects affected / exposed	13 / 167 (7.78%)	10 / 164 (6.10%)	
occurrences (all)	13	11	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	63 / 167 (37.72%)	64 / 164 (39.02%)	
occurrences (all)	78	87	
LEUKOPENIA			
subjects affected / exposed	17 / 167 (10.18%)	22 / 164 (13.41%)	
occurrences (all)	28	42	
NEUTROPENIA			

subjects affected / exposed	59 / 167 (35.33%)	64 / 164 (39.02%)	
occurrences (all)	122	137	
THROMBOCYTOPENIA			
subjects affected / exposed	5 / 167 (2.99%)	12 / 164 (7.32%)	
occurrences (all)	6	14	
Eye disorders			
DRY EYE			
subjects affected / exposed	5 / 167 (2.99%)	13 / 164 (7.93%)	
occurrences (all)	5	13	
LACRIMATION INCREASED			
subjects affected / exposed	18 / 167 (10.78%)	18 / 164 (10.98%)	
occurrences (all)	18	21	
VISION BLURRED			
subjects affected / exposed	11 / 167 (6.59%)	16 / 164 (9.76%)	
occurrences (all)	12	16	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	16 / 167 (9.58%)	22 / 164 (13.41%)	
occurrences (all)	21	28	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	13 / 167 (7.78%)	20 / 164 (12.20%)	
occurrences (all)	16	22	
CONSTIPATION			
subjects affected / exposed	54 / 167 (32.34%)	51 / 164 (31.10%)	
occurrences (all)	63	73	
DIARRHOEA			
subjects affected / exposed	74 / 167 (44.31%)	73 / 164 (44.51%)	
occurrences (all)	117	106	
DRY MOUTH			
subjects affected / exposed	5 / 167 (2.99%)	10 / 164 (6.10%)	
occurrences (all)	6	10	
DYSPEPSIA			
subjects affected / exposed	21 / 167 (12.57%)	17 / 164 (10.37%)	
occurrences (all)	23	20	
NAUSEA			

subjects affected / exposed	110 / 167 (65.87%)	107 / 164 (65.24%)	
occurrences (all)	189	214	
STOMATITIS			
subjects affected / exposed	29 / 167 (17.37%)	40 / 164 (24.39%)	
occurrences (all)	32	48	
VOMITING			
subjects affected / exposed	51 / 167 (30.54%)	62 / 164 (37.80%)	
occurrences (all)	70	100	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	129 / 167 (77.25%)	124 / 164 (75.61%)	
occurrences (all)	132	126	
DERMATITIS ACNEIFORM			
subjects affected / exposed	10 / 167 (5.99%)	6 / 164 (3.66%)	
occurrences (all)	10	8	
DRY SKIN			
subjects affected / exposed	13 / 167 (7.78%)	18 / 164 (10.98%)	
occurrences (all)	13	20	
ERYTHEMA			
subjects affected / exposed	5 / 167 (2.99%)	14 / 164 (8.54%)	
occurrences (all)	5	16	
NAIL DISCOLOURATION			
subjects affected / exposed	29 / 167 (17.37%)	24 / 164 (14.63%)	
occurrences (all)	29	24	
NAIL DISORDER			
subjects affected / exposed	10 / 167 (5.99%)	21 / 164 (12.80%)	
occurrences (all)	10	22	
PRURITUS			
subjects affected / exposed	24 / 167 (14.37%)	33 / 164 (20.12%)	
occurrences (all)	30	45	
RASH			
subjects affected / exposed	42 / 167 (25.15%)	51 / 164 (31.10%)	
occurrences (all)	53	65	
RASH MACULO-PAPULAR			
subjects affected / exposed	12 / 167 (7.19%)	12 / 164 (7.32%)	
occurrences (all)	14	12	

Endocrine disorders			
HYPOTHYROIDISM			
subjects affected / exposed	0 / 167 (0.00%)	16 / 164 (9.76%)	
occurrences (all)	0	16	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	39 / 167 (23.35%)	38 / 164 (23.17%)	
occurrences (all)	59	61	
BACK PAIN			
subjects affected / exposed	20 / 167 (11.98%)	22 / 164 (13.41%)	
occurrences (all)	24	24	
BONE PAIN			
subjects affected / exposed	12 / 167 (7.19%)	11 / 164 (6.71%)	
occurrences (all)	13	12	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	3 / 167 (1.80%)	15 / 164 (9.15%)	
occurrences (all)	4	16	
MYALGIA			
subjects affected / exposed	40 / 167 (23.95%)	51 / 164 (31.10%)	
occurrences (all)	49	84	
PAIN IN EXTREMITY			
subjects affected / exposed	19 / 167 (11.38%)	27 / 164 (16.46%)	
occurrences (all)	25	33	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	13 / 167 (7.78%)	23 / 164 (14.02%)	
occurrences (all)	16	28	
PARONYCHIA			
subjects affected / exposed	21 / 167 (12.57%)	18 / 164 (10.98%)	
occurrences (all)	21	19	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	16 / 167 (9.58%)	23 / 164 (14.02%)	
occurrences (all)	16	30	
URINARY TRACT INFECTION			
subjects affected / exposed	11 / 167 (6.59%)	18 / 164 (10.98%)	
occurrences (all)	11	25	

Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	33 / 167 (19.76%)	28 / 164 (17.07%)	
occurrences (all)	36	37	
HYPOKALAEMIA			
subjects affected / exposed	7 / 167 (4.19%)	12 / 164 (7.32%)	
occurrences (all)	8	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2017	Protocol was amended to add a cardiac safety cohort. A mandatory baseline pulmonary function evaluation conducted via spirometry has been added to the Schedule of Activities. It has been clarified that patients who do not initially meet all eligibility criteria, other than TNBC status, may be rescreened only once. Pregnancy reporting timeline requirement for nab-paclitaxel has been amended to be 1 month after last dose. Event-free survival (EFS) has been clarified, EFS is defined as "the time from randomization to the first documented occurrence of disease recurrence, disease progression, or death from any cause." Language has been updated to indicate that if nab-paclitaxel is discontinued due to any reason, patients can proceed to AC chemotherapy plus atezolizumab/placebo at the discretion of the investigator. If AC chemotherapy is discontinued, the date of surgery can be brought forward and patients can proceed to surgery at the discretion of the investigator.
11 May 2018	Protocol was amended to include addition of history of cerebrovascular accident within 12 months prior to randomization as an exclusion criteria. Ductal carcinoma in situ (DCIS) is no longer an exception to the exclusion criterion of history of other malignancy within 5 years prior to screening as there was already a dedicated section to DCIS. History of a cerebrovascular accident within 12 months prior to randomization has been added as an exclusion criterion. It has been clarified that anticipation of need for a major surgical procedure as an exclusion criterion does not pertain to anticipated breast surgery. The risks associated with atezolizumab have been updated to include hypophysitis and myocarditis as adverse events. The safety profile of and risk management guidelines for nab-paclitaxel has been updated or clarified to include febrile neutropenia, infections, and depression.
10 October 2018	Protocol was amended to add an adaptive two stage design using accumulating data to inform the study. Study duration and recruitment period were updated to reflect potential change in study duration. The primary efficacy objective was modified to include the endpoint of pCR in the subpopulation with the PD-L1-positive tumor status (moved from the secondary efficacy objective). The secondary efficacy endpoints were modified to include disease-free survival. Lists of risks for atezolizumab and guidelines for managing participants who experience atezolizumab-associated adverse events have been revised to include nephritis.
07 June 2019	Protocol was amended to clarify the baseline staging and surgical management of clinically enlarged and/or suspicious internal mammary and infraclavicular and/or supraclavicular lymph nodes. Language has been modified to reflect the fact that systemic immune activation is a potential risk with atezolizumab, regardless of whether atezolizumab is given alone or in combination with other immunomodulating agents. The lists of risks associated with doxorubicin and cyclophosphamide have been updated to align with the latest safety information available on their corresponding SmPCs.

11 February 2020	Protocol was amended to include changing "immune-related" to "immune-mediated" when describing events associated with atezolizumab. Systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome. In addition, systemic immune activation has been removed from the list of adverse events of special interest. To align with the nab-paclitaxel (Abraxane®) prescribing information, the risk of tumor lysis syndrome has been included. The atezolizumab adverse event management guidelines have been revised to add laboratory and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis. The management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for cytokine-release syndrome (CRS).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported