



Clinical trial results:

A randomized phase II study to investigate the addition of PD-L1 antibody durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer. (GeparNuevo)

Summary

EudraCT number	2015-002714-72
Trial protocol	DE
Global end of trial date	19 July 2018

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	GeparNuevo CSR Synopsis (CSR_G9_V1.0_20181210 Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	GBG89
-----------------------	-------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02685059
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GBG Forschungs GmbH
Sponsor organisation address	Martin Behaim Str. 12, Neu-Isenburg, Germany, 63263
Public contact	Medicine and Research, GBG Forschungs GmbH, GBG Forschungs GmbH, Publications@gbg.de
Scientific contact	Medicine and Research, GBG Forschungs GmbH, GBG Forschungs GmbH, Publications@gbg.de

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	16 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pathological complete response (pCR= ypT0 ypN0) rates of neoadjuvant treatment of sequential nab-paclitaxel followed by epirubicin and cyclophosphamide (EC) +/- PD-L1 antibody MEDI4736 in patients with early triple negative breast cancer (TNBC).

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving. IDMC was to ensure the ethical conduct of the trial and to protect patients' safety interests in this study.

Background therapy:

For all patients nab-paclitaxel 125 mg/m² every week for 12 weeks; epirubicin 90 mg/m² i.v. in combination with cyclophosphamide 600 mg/m² every 2 weeks for 4 cycles. These agents are used according to marketed formulation via normal procedures at each site and applied according to recommendations of the manufacturers.

Evidence for comparator:

Standard of Care

Actual start date of recruitment	15 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 174
Worldwide total number of subjects	174
EEA total number of subjects	174

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	159
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between June 2016 and October 2017, 235 patients were screened, 174 patients were randomised (88 in durvalumab arm and 86 in placebo arm) and started therapy, of whom 173 (99.4%, one patient in the placebo arm did not have available data on surgery due to withdrawal of informed consent) underwent surgery.

Pre-assignment

Screening details:

Patients of at least 18 years of age with untreated primary uni- or bilateral primary, nonmetastatic invasive TNBC with a tumour of at least 2 cm (cT2-cT4a-d) were included in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	durvalumab

Arm description:

A total of 88 patients were randomized to receive durvalumab plus nab-paclitaxel followed by EC (experimental arm) and started treatment, 56 patients completed all treatment regularly, and 88 received surgery.

Arm type	Experimental
Investigational medicinal product name	durvalumab
Investigational medicinal product code	
Other name	Imfinzi, MEDI4736
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

1.5 g total i.v. every 4 weeks

Arm title	placebo
------------------	---------

Arm description:

A total of 86 patients were randomized to receive placebo in combination with nab-paclitaxel followed by EC (placebo arm) and started treatment, 51 patients completed all treatment regularly, and 86 received surgery (one patient did not receive surgery due to withdrawal of consent).

Arm type	Placebo
Investigational medicinal product name	n.a.
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

placebo i.v. every 4 weeks

Number of subjects in period 1	durvalumab	placebo
Started	88	86
Completed	56	51
Not completed	32	35
discontinued any treatment	32	35

Baseline characteristics

Reporting groups

Reporting group title	durvalumab
Reporting group description: A total of 88 patients were randomized to receive durvalumab plus nab-paclitaxel followed by EC (experimental arm) and started treatment, 56 patients completed all treatment regularly, and 88 received surgery.	
Reporting group title	placebo
Reporting group description: A total of 86 patients were randomized to receive placebo in combination with nab-paclitaxel followed by EC (placebo arm) and started treatment, 51 patients completed all treatment regularly, and 86 received surgery (one patient did not receive surgery due to withdrawal of consent).	

Reporting group values	durvalumab	placebo	Total
Number of subjects	88	86	174
Age categorical			
age at baseline			
Units: Subjects			
Adults (18-64 years)	83	76	159
From 65-84 years	5	10	15
Age continuous			
age at baseline			
Units: years			
median	49.5	49.5	
full range (min-max)	25.0 to 74.0	23.0 to 76.0	-
Gender categorical			
Units: Subjects			
Female	88	86	174
Male	0	0	0

End points

End points reporting groups

Reporting group title	durvalumab
Reporting group description: A total of 88 patients were randomized to receive durvalumab plus nab-paclitaxel followed by EC (experimental arm) and started treatment, 56 patients completed all treatment regularly, and 88 received surgery.	
Reporting group title	placebo
Reporting group description: A total of 86 patients were randomized to receive placebo in combination with nab-paclitaxel followed by EC (placebo arm) and started treatment, 51 patients completed all treatment regularly, and 86 received surgery (one patient did not receive surgery due to withdrawal of consent).	

Primary: pathological complete response (pCR=ypT0 ypN0)

End point title	pathological complete response (pCR=ypT0 ypN0)
End point description: The primary efficacy endpoint was pCR of breast and lymph nodes (ypT0 ypN0), defined as no microscopic evidence of residual invasive and no non-invasive viable tumor cells in all resected specimens of the breast and axilla.	
End point type	Primary
End point timeframe: from start of treatment until surgery; the entire treatment period was 22 weeks prior to amendment 2 (including 2 weeks in the window of opportunity) and 20 weeks after amendment 2	

End point values	durvalumab	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	86		
Units: percent				
number (confidence interval 95%)				
pCR	53.4 (42.5 to 64.1)	44.2 (33.5 to 55.3)		

Attachments (see zip file)	GeparNuevo_Primary endpoint.pdf
----------------------------	---------------------------------

Statistical analyses

Statistical analysis title	pCR rates between the treatment arms - difference
Statistical analysis description: The analysis of the primary endpoint pCR (ypT0 ypN0) was performed in the mITT analysis set. The difference in the rates of pathological complete remissions between groups was evaluated as absolute difference, and its 80% and 95% confidence intervals.	
Comparison groups	durvalumab v placebo

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.287
Method	Chi-squared corrected
Parameter estimate	absolute difference
Point estimate	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	24

Notes:

[1] - two-sided continuity corrected χ^2 -test

Statistical analysis title	pCR rates between the treatment arms - odds ratio
-----------------------------------	---

Statistical analysis description:

The analysis of the primary endpoint pCR was performed in the mITT analysis set. The difference in the pCR rates between treatment arms evaluated as an odds ratio and its 95% CI are presented.

Comparison groups	durvalumab v placebo
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.182
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.84

Notes:

[2] - multivariate logistic regression analysis adjusted for stratification factor (sTILs)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported.

Adverse event reporting additional description:

AEs are reported per patient during the complete treatment duration for the overall safety population. Non-serious AEs any grade per patient occurring more frequently (> 20%) are presented. Of note, overall number of single AE occurrences per term was not assessed, only per patient; SAEs are reported regardless of causality.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.1
--------------------	------

Reporting groups

Reporting group title	durvalumab
-----------------------	------------

Reporting group description:

durvalumab plus nab-paclitaxel followed by epirubicin and cyclophosphamide (experimental arm)

Reporting group title	placebo
-----------------------	---------

Reporting group description:

placebo in combination with nab-paclitaxel followed by epirubicin plus cyclophosphamide (placebo arm)

Serious adverse events	durvalumab	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 92 (32.61%)	29 / 82 (35.37%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			
subjects affected / exposed	2 / 92 (2.17%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Axillary vein thrombosis			

subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 92 (2.17%)	4 / 82 (4.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 92 (4.35%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
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 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	2 / 92 (2.17%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
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	2 / 92 (2.17%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			

subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	0 / 92 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 92 (1.09%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 92 (2.17%)	4 / 82 (4.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 92 (2.17%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 92 (1.09%)	6 / 82 (7.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 92 (2.17%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toothache			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 92 (2.17%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Herpes zoster			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (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 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 92 (2.17%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 92 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	durvalumab	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 92 (100.00%)	82 / 82 (100.00%)	
Vascular disorders			
Hot flashes	Additional description: Hot flushes		
subjects affected / exposed	25 / 92 (27.17%)	24 / 82 (29.27%)	
occurrences (all)	25	24	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	70 / 92 (76.09%)	68 / 82 (82.93%)	
occurrences (all)	70	68	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	22 / 92 (23.91%)	28 / 82 (34.15%)	
occurrences (all)	22	28	
Dyspnea			
subjects affected / exposed	30 / 92 (32.61%)	20 / 82 (24.39%)	
occurrences (all)	30	20	
Cough			
subjects affected / exposed	25 / 92 (27.17%)	15 / 82 (18.29%)	
occurrences (all)	25	15	
Psychiatric disorders			
Sleep disturbance			

subjects affected / exposed occurrences (all)	22 / 92 (23.91%) 22	17 / 82 (20.73%) 17	
Investigations			
Alkaline phosphatase increased subjects affected / exposed occurrences (all)	43 / 92 (46.74%) 43	40 / 82 (48.78%) 40	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	45 / 92 (48.91%) 45	28 / 82 (34.15%) 28	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	53 / 92 (57.61%) 53	45 / 82 (54.88%) 45	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	38 / 92 (41.30%) 38	28 / 82 (34.15%) 28	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	76 / 92 (82.61%) 76	69 / 82 (84.15%) 69	
Blood and lymphatic system disorders			
Anemia subjects affected / exposed occurrences (all)	87 / 92 (94.57%) 87	79 / 82 (96.34%) 79	
Leukopenia subjects affected / exposed occurrences (all)	81 / 92 (88.04%) 81	79 / 82 (96.34%) 79	
Neutropenia subjects affected / exposed occurrences (all)	71 / 92 (77.17%) 71	67 / 82 (81.71%) 67	
Thrombopenia subjects affected / exposed occurrences (all)	35 / 92 (38.04%) 35	28 / 82 (34.15%) 28	
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	24 / 92 (26.09%) 24	22 / 82 (26.83%) 22	

Gastrointestinal disorders	Nausea			
	subjects affected / exposed	54 / 92 (58.70%)	53 / 82 (64.63%)	
	occurrences (all)	54	53	
	Diarrhoea			
	subjects affected / exposed	26 / 92 (28.26%)	34 / 82 (41.46%)	
	occurrences (all)	26	34	
	Constipation			
	subjects affected / exposed	29 / 92 (31.52%)	34 / 82 (41.46%)	
	occurrences (all)	29	34	
	Mucositis			
	subjects affected / exposed	32 / 92 (34.78%)	33 / 82 (40.24%)	
	occurrences (all)	32	33	
Skin and subcutaneous tissue disorders				
	Alopecia			
	subjects affected / exposed	85 / 92 (92.39%)	78 / 82 (95.12%)	
	occurrences (all)	85	78	
	Skin reactions			
	subjects affected / exposed	45 / 92 (48.91%)	39 / 82 (47.56%)	
	occurrences (all)	45	39	
	Nail changes			
	subjects affected / exposed	46 / 92 (50.00%)	43 / 82 (52.44%)	
	occurrences (all)	46	43	
	Rash	Additional description: Rash NOS		
	subjects affected / exposed	21 / 92 (22.83%)	22 / 82 (26.83%)	
	occurrences (all)	21	22	
Musculoskeletal and connective tissue disorders				
	Arthralgia			
	subjects affected / exposed	39 / 92 (42.39%)	38 / 82 (46.34%)	
	occurrences (all)	39	38	
	Myalgia			
	subjects affected / exposed	34 / 92 (36.96%)	25 / 82 (30.49%)	
	occurrences (all)	34	25	
Infections and infestations				
	Infection			

subjects affected / exposed occurrences (all)	50 / 92 (54.35%) 50	39 / 82 (47.56%) 39	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	32 / 92 (34.78%)	37 / 82 (45.12%)	
occurrences (all)	32	37	
Free Triiodothyronine high			
subjects affected / exposed	18 / 92 (19.57%)	21 / 82 (25.61%)	
occurrences (all)	18	21	
Anorexia			
subjects affected / exposed	20 / 92 (21.74%)	19 / 82 (23.17%)	
occurrences (all)	20	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2016	Amendment 1: The study protocol and informed consent form (ICF) were amended to implement substantial changes in the durvalumab investigator's brochure (IB durvalumab Edition 9.0 [2016-01-22] which overruled Edition 8.0 [2015-09-01]). Mainly these changes related to the frequency of AEs in the so far 910 patients investigated within clinical studies. Moreover, the definition of progressive disease was corrected to 25% increase to reflect WHO criteria. Within the laboratory requirements for inclusion, the endocrinologic parameter T3 was removed since laboratories hardly used this parameter routinely due to a change the guidelines. Amendment 1 also contained changes in the translational research program: the investigation of xenograft tumor models was removed from the correlative science objectives. The biomaterial collection was amended to comprise mandatory additional blood samples for research projects on immunomonitoring and germline RNA analysis. The informed consent form was amended to depict the analysis of whole genome (exome) in tumor and normal cells. Patients who consented before amendment 1 was in force had to re-consent to this change.
25 April 2017	Amendment 2: Following recommendation of the IDMC, the window of opportunity phase in which durvalumab/placebo was given as monotherapy for the first two weeks (part 1) was removed and the protocol and ICF amended accordingly in all parts. The IDMC considered the time interval from diagnostic biopsy to start of chemotherapy inadequate and strongly recommended to terminate the window part of the study. Three inclusion criteria were changed. The mandatory sizes of tumor lesions were removed and instead tumor lesions in the breast or the nodes had to be measurable in two dimensions, preferably by sonography. The definition of PgR negative was changed from <1% stained cells to <10% stained cells. Breast imaging could be performed by ultrasound and either bilateral mammography or breast MRI, instead of a mandatory imaging with all methods. In the exclusion criteria, patients with uncontrolled or poorly controlled arterial hypertension were re-defined as having blood pressure >140 / 90 mm Hg under treatment with at maximum two antihypertensive drugs. Amendment 2 also clarified that, while sex hormones were not allowed and prior treatment had to be stopped before study entry, the use of GnRH- analogues for ovarian protection was permitted. Due to recruitment being faster than expected, the number of safety interim analyses was reduced to 4: after the first 10 patients and the first 20 patients having completed part 2 of the study and after the first 10 patients and the first 30 patients having completed part 3 of the study. After amendment 2, administration of durvalumab via port was permitted. Furthermore, the ICF was amended to implement substantial changes in the durvalumab IB (Durvalumab Edition 10.0 [2016-12-12] which overruled Edition 9.0 [2016-01-22]).
05 July 2017	Amendment 3: substantial amendment of the ICF only, due to changes in the safety profile of durvalumab (IB Durvalumab Edition 11.0 [2017-04-28] which overruled Edition 10.0 [2016-12-12]).

09 July 2018	Amendment 4: The study protocol and ICF were amended to implement substantial changes in the durvalumab IB (Durvalumab Edition 12.0 [2017-11-03] which overruled Edition 11.0 (2017-04-28)). Changes mainly related to the update on side effects and had an impact on the toxicity management guidelines for immune-related AEs associated with durvalumab. In the protocol section "Evaluation during chemotherapy before and after surgery", the analysis of 'planned therapy after surgery' was inserted. Moreover, the sequence of analyses in this section was improved. The description of the analysis of 'progression during neoadjuvant treatment' was clarified in such that it was not considered as an event for the analyses of IDFS, LRFS, LRRFS, and EFS. However, progression of disease that precluded surgery was considered an event in the analysis of EFS. The ICF was additionally amended to contain a paragraph on the planned follow-up data collection and procedures.
--------------	---

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31095287>

<http://www.ncbi.nlm.nih.gov/pubmed/33593886>

<http://www.ncbi.nlm.nih.gov/pubmed/32461104>

<http://www.ncbi.nlm.nih.gov/pubmed/33199511>