



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

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

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

Reporting groups

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|-----------------------|------------|
| 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 | <p>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.</p> <p>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.</p> |
| 25 April 2017 | <p>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]).</p> |
| 05 July 2017 | <p>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]).</p> |

| | |
|--------------|---|
| 09 July 2018 | <p>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.</p> <p>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.</p> |
|--------------|---|

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>