1. SYNOPSIS

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Title of Study:

A randomized phase II study to investigate the addition of PD-L1 antibody MEDI4736 to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (GeparNuevo)

Investigators:

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Study Center(s): See Annex

Publication (reference):

Loibl S, Untch M, Burchardi N et al. Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). J Clin Oncol 36, 2018 (suppl; abstr 104)

Loibl S, Untch M, Burchardi N et al. A randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab, a PD-L1 antibody to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). J Clin Oncol 35, 2017 (suppl; abstr 3062)

Loibl S, Sinn BV, Karn T et al. mRNA signatures predict response to durvalumab therapy in triple negative breast cancer (TNBC)- Results of the translational biomarker programme of the neoadjuvant double-blind placebo controlled GeparNuevo trial. Poster discussion #PD2-07, SABCS 2018 (4-8 Dec 2018).

Sinn BV, Loibl S, Karn T et al. Pre-therapeutic PD-L1 expression and dynamics of Ki-67 and gene expression during neoadjuvant immune-checkpoint blockade and chemotherapy to predict response within the GeparNuevo trial. Poster discussion #PD5-05, SABCS 2018 (4-8 Dec 2018).

Massa C, Schneeweiss A, Karn T et al. Immunomonitoring of triple negative breast cancer patients undergoing neoadjuvant therapy with durvalumab - Results from the prospectively randomized GeparNuevo trial. Poster presentation #P4-06-01, SABCS 2018 (4-8 Dec 2018).

Studied Period (years):

Date of the first patient enrolled: 24 June 2016
Date of the last patient completed: 28 March 2018

Phase of Development:

Phase II

Objectives:

Primary Objectives:

To compare the pathological complete response (ypT0 ypN0) rates of neoadjuvant treatment of sequential, nab-paclitaxel followed by epirubicin-cyclophosphamide +/- the PD-L1 antibody durvalumab in patients with early triple negative breast cancer

Secondary Objectives:

- To assess the pathological complete response rates per arm separately for the stratified subpopulations

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- To determine the rates of ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0
- To determine the response rates of the breast tumor and axillary nodes based on physical examination and imaging tests (sonography, mammography, or magnetic resonance imaging) after treatment in both arms
- To assess clinical response rate after taxane in both groups
- To determine the breast conservation rate after each treatment
- To assess the toxicity and compliance
- To examine and compare pre-specified molecular markers and gene expression signatures such as tumor infiltrating lymphocytes, PD-1, PD-L1, Ki-67, etc. on core biopsies before chemotherapy, after the window phase and surgical tissue after end of chemotherapy
- To determine loco-regional invasive recurrence free survival, distant-disease-free survival, invasive disease-free survival, event free survival (per United States Food and Drug Administration definition) and overall survival in both arms and according to stratified subpopulations
- To examine quality of life using functional assessment of cancer therapy-Taxane questionnaire

Methodology:

This was a multicenter, prospective, randomized, double-blinded, placebo-controlled phase II study to test the addition of immunotherapy with the PD-L1 antibody durvalumab to standard taxane/anthracycline-based neoadjuvant chemotherapy in patients with untreated early triple negative breast cancer.

Patients were randomized in a 1:1 ratio to either durvalumab or placebo as monotherapy (part 1) followed by:

durvalumab or placebo in combination with nab-paclitaxel (part 2) followed by durvalumab or placebo in combination with epirubicin plus cyclophosphamide (part 3).

Stratification factor for randomization was tumor infiltrating lymphocytes (low (0-10%) vs. intermediate (11-59%) vs. high (60-100%).

In both study arms, treatment was to be given until surgery, disease progression, unacceptable toxicity, withdrawal of consent of the patient or termination by the sponsor.

The study was blinded, to assess efficacy and safety in an optimal way. The pathologist was not informed about the study treatment and histology reports were also centrally reviewed in a blinded fashion.

The Protocol Board and the Independent Data Monitoring Committee reviewed and monitored the conduct of the study.

Since amendment 2, the window phase of the study (part 1) was terminated due to Independent Data Monitoring Committee recommendation.

Number of patients (planned and analyzed):

planned: 174, screened: 235, randomized: 174, analyzed (safety): 174, analyzed (efficacy): 174

Diagnosis and Main Criteria for Inclusion:

The study included patients of at least 18 years of age with unilateral or bilateral primary carcinoma of the breast, histologically confirmed by core biopsy and measurable disease (i.e. tumor lesion in the breast or the nodes measurable in two dimensions, preferably by sonography). Patients had to have stages cT1b - cT4a-d

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irrespective of nodal involvement. Patients with triple negative disease with centrally confirmed estrogen receptor negative (defined as <1% stained cells), progesterone negative (defined as <10% stained cells) and human epidermal growth factor receptor 2 negative (defined as either immunohistochemistry 0/1+ or immunohistochemistry 2+ and in-situ hybridisation of either ratio <2.0 or less than 6 copies of human epidermal growth factor receptor 2 per tumor cell), and centrally confirmed Ki-67 value were eligible.

Test Products, Dose and Mode of Administration, Batch Number:

Investigational products in this study were durvalumab/placebo and nab-paclitaxel (Abraxane®).

Patients were treated with either

- durvalumab 1.5 g total i.v. every 4 weeks

or

- placebo i.v. every 4 weeks

Prior to amendment 2, durvalumab/placebo was given as monotherapy for the first two weeks (a total of 0.75 g) (part 1) followed by

- durvalumab/placebo in combination with nab-paclitaxel 125 mg/m² every week for 12 weeks (part 2) followed by
- durvalumab/placebo in combination with epirubicin 90 mg/m² plus cyclophosphamide 600 mg/m² every 2 weeks for 4 cycles (part 3).

Duration of Treatment:

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. Durvalumab/placebo was given every 4 weeks throughout; nab-paclitaxel was given every week for 12 weeks, afterwards epirubicin and cyclophosphamide were given every 2 weeks for 4 cycles.

Reference Therapy, Dose and Mode of Administration, Batch Number:

See above for details on therapy and dose

Criteria for Evaluation:

Efficacy:

Primary endpoint

The primary efficacy endpoint of this study was pathological complete response 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.

Secondary endpoints:

Short term secondary efficacy endpoints were:

- ypT0/is ypN0, ypT0 ypN0/+, ypT0/is ypN0/+, ypT(any) ypN0. Clinical and imaging response was assessed after taxane and before surgery by physical examination and imaging tests. Clinical (imaging) response of the breast was specified as complete response, partial response, stable disease, and progressive disease. Clinical response was reported before surgery (end of treatment) and early response

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after the taxane (at approximately 12 weeks of treatment)

- Breast conservation was defined as tumor resection, segmental resection or quadrant resection as last surgical procedure

Long-term secondary efficacy is not part of this report and will be analyzed with sufficient follow up data at a later time point.

Safety and Compliance:

Safety objectives of the study were to assess and compare toxicity between treatment arms, which included but was not limited to (immune-related) adverse events, and serious adverse events. Supportive therapy was assessed and compared between treatment arms. Time to onset and resolution of peripheral sensory neuropathy was analyzed with the objectives to assess and compare between treatment arms the time to onset of peripheral sensory neuropathy of grade 2 or higher and to grade 3-4, the time to resolution of peripheral sensory neuropathy grade 2 or higher to grade ≤1, and the time to resolution of peripheral sensory neuropathy grade 3-4 to grade ≤1.

Corresponding endpoints were:

- Toxicity (adverse events, including pre-defined adverse events of special interest) assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
- Patients' rates with the following supportive treatment: Dexamethasone, Pegfilgrastim, Lipegfilgrastim, Non-pegylated granulocyte-colony stimulating factor, Antibiotics, Neurokinin 1-antagonist, 5-hydroxytryptamine inhibitor, Other.
- Endpoints regarding onset or resolution of peripheral sensory neuropathy were:
    - time to onset of peripheral sensory neuropathy grade ≥ 2 was defined as time in weeks from start of nab-paclitaxel to the first documentation of peripheral sensory neuropathy grade 2
    - time to onset of peripheral sensory neuropathy grade 3-4 was defined as time in weeks from start of nab-paclitaxel to the first documentation of peripheral sensory neuropathy grade 3-4
    - time to resolution of peripheral sensory neuropathy grade ≥ 2 to grade ≤1 was defined as time in weeks from onset of peripheral sensory neuropathy grade 2 to documentation of peripheral sensory neuropathy grade ≤1;
    - time to resolution of peripheral sensory neuropathy grade 3-4 to grade ≤1 was defined as time in weeks from onset of peripheral sensory neuropathy grade 3-4 to documentation of peripheral sensory neuropathy grade ≤1;

Compliance objectives were to assess and compare dose reductions, treatment delays, treatment interruptions and premature treatment discontinuations as well as relative total dose and relative total dose intensity.

Statistical Methods:

A modified 'intent-to-treat' analysis was conducted for all patients who were randomized and actually started therapy. In addition, a 'per-protocol' analysis was conducted.

The primary endpoint was summarized as pathological complete response rate for each treatment group. Two-

sided 95% confidence intervals were calculated according to Pearson and Clopper (1934). The difference in the rates of pathological complete response was evaluated as odds ratio and the significance was tested with the continuity corrected χ^2 test. The significance level was set to 2-sided $\alpha = 0.2$. There was no adjustment for multiple comparisons in the analyses for the stratified subpopulations. The null hypothesis was that there was no difference in pathological complete response rates between treatment arms, the alternative hypothesis was that there was a difference. A secondary logistic regression analysis correcting for the stratification factor was conducted for the primary endpoint. Uni- and multivariate logistic regression analyses were performed for pathological complete response to adjust for the known factors (treatment group, age, tumor size, nodal status, grade, histological type, and PDL-1), based on the modified 'intent-to-treat' population.

The sample size calculation was based on the following assumptions:

- pathological complete response rate in the placebo arm was expected to be 48%, which was the pathological complete response rate of the triple-negative breast cancer patients treated with nab-paclitaxel in the GeparSepto study
- pathological complete response rate in the durvalumab arm was expected to be 66% because this was considered a clinically meaningful benefit which would eventually translate into a better disease-free survival and overall survival

158 patients (79 in each arm) in the modified 'intent-to-treat'-set would achieve 80% power on the 2-sided significance level α=0.2 to show the superiority of the durvalumab arm using a χ^2-test. It was planned to recruit 174 subjects into this study assuming a 10% drop-out rate.

Secondary short-time efficacy endpoints (ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0, response by physical examination, imaging response, breast conservation) were also summarized as rates in each treatment group, two-sided 95% confidence intervals were calculated according to Pearson and Clopper, and the continuity corrected Pearson χ^2 test were performed to evaluate the difference of rates in treatment arms; these tests were considered explorative.

SUMMARY

Efficacy Results:

In the GeparNuevo study, all of the 174 randomized patients started therapy, of those 173 (99.4%) underwent surgery. Overall, 47 out of 88 patients who started durvalumab treatment (53.4% [95% confidence interval 42.5%, 64.1%]) achieved a pathological complete response (ypT0 ypN0) compared to 38 out of 86 who started placebo treatment (44.2% [33.5%, 55.3%]; continuity corrected χ2-test (p=0.287) corresponding to an odds ratio of durvalumab vs. placebo 1.45 (95% confidence interval 0.797-2.63). There were no differences between treatment groups in pathological complete response rates according to other definitions or for other short-term secondary efficacy endpoints.

pCR (ypT0 ypN0), primary endpoint

pCR (ypT0 ypN0, primary)	*Durvalumab N=88 N(%)*	*Placebo N=86 N(%)*	*Overall N=174 N(%)*	*p-value*
yes	47 (53.4)	38 (44.2)	85 (48.9)	0.287
95% CI	(42.5%, 64.1%)	(33.5%, 55.3%)		
Difference, 95% CI			9.2% (-5.6%, 24.0%)	

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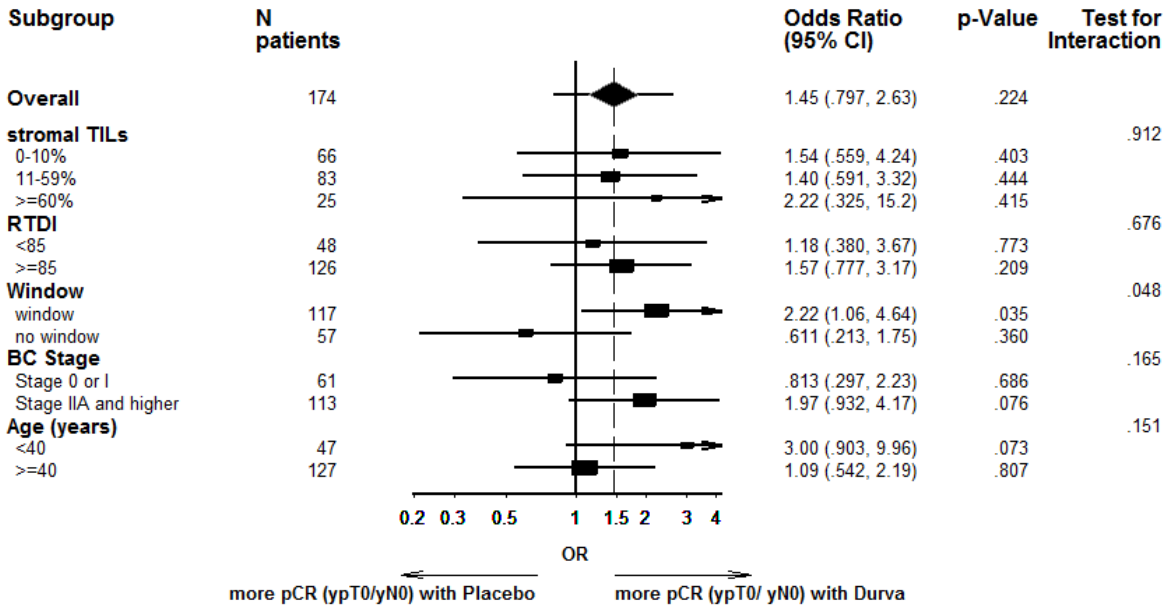
Pathological complete response (ypT0 ypN0) rate was not significantly different in the two treatment arms in any of the stratified and prospectively defined subgroups. There was a trend for higher rates of pathological complete response following treatment with durvalumab compared to placebo (61.0% vs 41.4%) in patients participating in the window part of the study (p=0.052).

Logistic regression analysis, showed that the proportion of patients achieving a pathological complete response was significantly higher in the window subgroup when patients were treated with durvalumab as compared to placebo (odds ratio durvalumab vs placebo: 2.22; 95% confidence interval 1.06-4.64, p=0.035). The test for interaction for the treatment effect in patients participating in the window part of the study versus not on the pathological complete response rate was significant (p=0.048). In all other predefined subgroups no effect of treatment on the pathological complete response rate could be seen.

Forest plot for primary pCR in subgroups



Multivariable logistic regression analysis confirmed that treatment with durvalumab did not predict for achievement of pathological complete response after adjustment for baseline and stratification factors (odds ratio: 1.53; 95% confidence interval, 0.81-2.88; p=0.191). Among the stratification factors, stromal tumor-infiltrating lymphocytes (≥60% vs 0-10% odds ratio: 4.01, 1.34–11.9, p=0.013) were independent predictors for achievement of pathological complete response.

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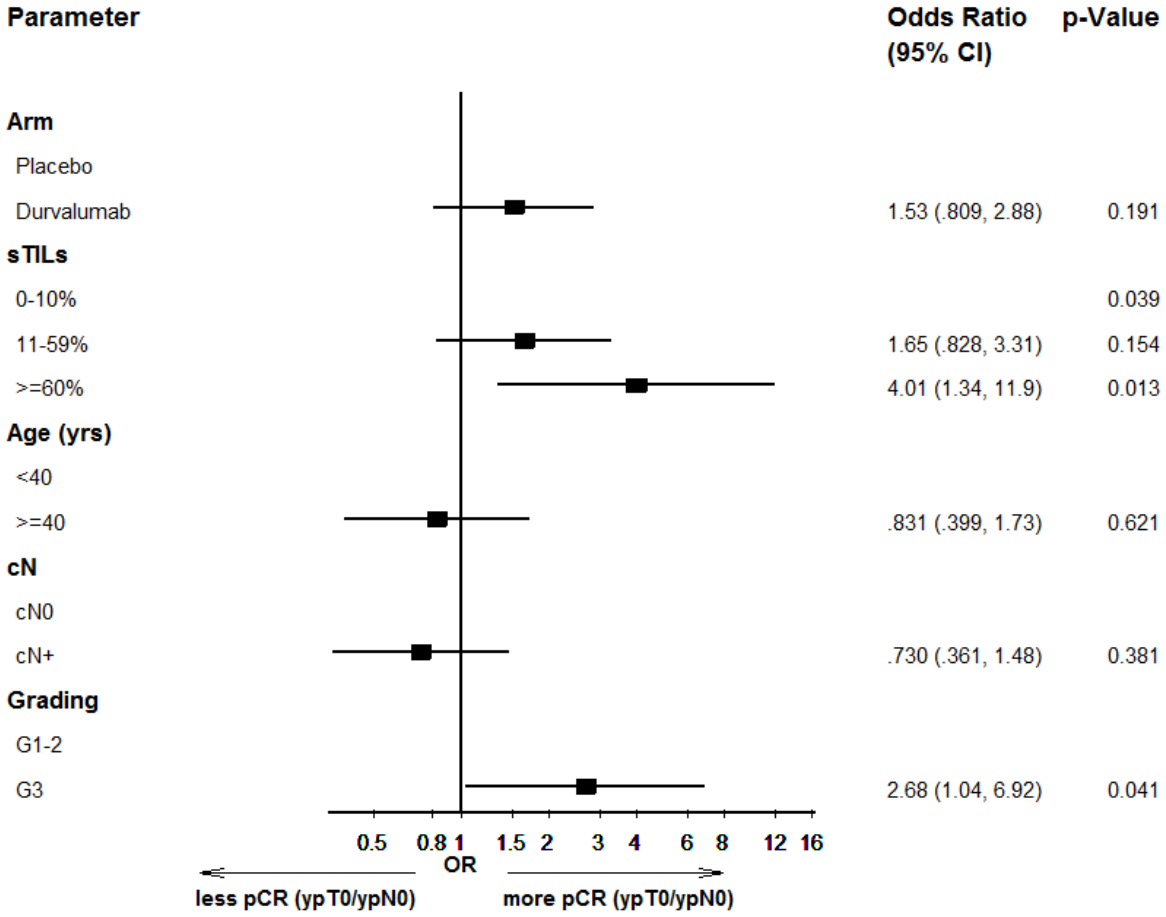
Treatment effect on primary endpoint adjusted for predefined covariates, multivariate logistic regression



Safety Results:

Adverse events were analyzed in the safety population, overall and separately for all parts of the study (window, nabPaclitaxel, epirubicin/cyclophosphamide). In four patients randomized in the placebo arm, durvalumab was given at least once. Safety data of these patients were analyzed in the durvalumab arm.

In the overall safety population, taking all patients that started treatment into account, all patients experienced at least one adverse event of any grade during the 22-week neoadjuvant treatment. No significant differences were seen between arms in terms of any high grade adverse events, and any grade and high grade hematological and non-hematological adverse events.

When looking at the different predefined adverse events, nausea (grade 3-4, durvalumab: 0.0%; placebo:

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8.5%, p=0.004) and thyroid dysfunction (thyroid-stimulating hormone low any grade, durvalumab: 16.3%; placebo: 4.9%, p=0.026; thyroid-stimulating hormone high any grade: durvalumab: 13.0%; placebo: 1.2%, p=0.003) were significantly different between the two study arms.

Adverse events N (%)	**Durvalumab N=92+**		**Placebo N=82**		**p-value any grade**	**p-value grade 3-4**
	any grade	**Grade 3-4**	**any grade**	**Grade 3-4**		
Nausea	54 (58.7)	0 (0.0)	53 (64.6)	7 (8.5)	0.439	0.004
Thyroid dysfunction*	46 (50.0)	0 (0.0	36 (43.9)	0 (0.0	0.514	n.a.
TSH low*	15 (16.3)	0 (0.0)	4 (4.9)	0 (0.0)	0.026	n.a.
TSH high	12 (13.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.003	n.a.

* immune related adverse events of special interest

There were no significant differences in adverse events in patients participating in the window part of the study, where 41.3% of patients in the durvalumab arm compared to 48.1% in the placebo arm experienced at least one adverse event of any grade. In Part II of the study, frequencies of any grade hematological adverse events were significantly higher in the placebo arm (durvalumab: 89.1%; placebo: 97.6%, p=0.036), while there were no relevant differences for any high grade hematological adverse events, or any and high grade non-hematological adverse events. For patients that started with epirubicin/cyclophosphamide in part III of the study, no relevant differences in terms of adverse events were observed.

Predefined AEs	**Durvalumab N(%)**	**Placebo N(%)**	**Overall N(%)**	**p-value**
All patients	**N=92**	**N=82**	**N=174**	
Any AE, any grade	92 (100)	82 (100)	174 (100)	n.a.
Any AE, high grade	58 (63.0)	55 (67.1)	113 (64.9)	0.634
Hematological AE, any grade	90 (97.8)	82 (100)	172 (98.9)	0.499
Hematological AE, high grade	40 (43.5)	41 (50.0)	81 (46.6)	0.447
Non-hematological AE, any grade	92 (100)	82 (100)	174 (100)	n.a.
Non-hematological AE, high grade	32 (34.8)	26 (31.7)	58 (33.3)	0.748
Part I (window)	**N=63**	**N=54**	**N=117**	
Any AE, any grade	26 (41.3)	26 (48.1)	52 (44.4)	0.463
Any AE, high grade	0 (0.0)	1 (1.9)	1 (0.9)	0.462
Hematological AE, any grade	1 (1.6)	0 (0.0)	1 (0.9)	1.00
Hematological AE, high grade	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
Non-hematological AE, any grade	22 (34.9)	18 (33.3)	40 (34.2)	1.00
Non-hematological AE, high grade	0 (0.0)	1 (1.9)	1 (0.9)	0.462
Part II (nabPaclitaxel)	**N=92**	**N=82**	**N=174**	

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Any AE, any grade	92 (100)	82 (100)	174 (100)	n.a.
Any AE, high grade	26 (28.3)	25 (30.5)	51 (29.3)	0.868
Hematological AE, any grade	82 (89.1)	80 (97.6)	162 (93.1)	0.036
Hematological AE, high grade	10 (10.9)	10 (12.2)	20 (11.5)	0.816
Non-hematological AE, any grade	91 (98.9)	82 (100)	173 (99.4)	1.00
Non-hematological AE, high grade	14 (15.2)	15 (18.3)	29 (16.7)	0.685
Part III (EC)	**N=86**	**N=75**	**N=161**	
Any AE, any grade	86 (100)	75 (100)	161 (100)	n.a.
Any AE, high grade	47 (54.7)	46 (61.3)	93 (57.8)	0.427
Hematological AE, any grade	84 (97.7)	73 (97.3)	157 (97.5)	1.00
Hematological AE, high grade	35 (40.7)	37 (49.3)	72 (44.7)	0.341
Non-hematological AE, any grade	86 (100)	75 (100)	161 (100)	n.a.
Non-hematological AE, high grade	21 (24.4)	18 (24.0)	39 (24.2)	1.00

AE = Adverse event; EC = Epirubicin, Cyclophosphamide; n.a. = not applicable;

The occurrence of serious adverse events and adverse events of special interest did not significantly differ between the two treatment arms neither in the overall population nor in the different parts of the study. In the overall population, when looking at the different predefined adverse events of special interest, the incidence of hyperthyroidism any grade was significant higher in the durvalumab arm compared to placebo (durvalumab: 7.6%; placebo: 0.0%, p=0.015).

There was no difference between treatment arms in terms of overall treatment discontinuation. All treatment (nabPaclitaxel, epirubicin/cyclophosphamide and durvalumab/placebo) was completed by 63.6% of patients in the durvalumab arm compared to 59.3% in the placebo arm. Durvalumab/placebo treatment was completed by 77.3% of patients in the durvalumab arm compared to 80.2% in the placebo arm. nabPaclitaxel and epirubicin/cyclophosphamide was completed by 68.2% in the durvalumab arm compared to 64.0% in the placebo arm. A total of 85.4% of patients in the durvalumab arm and 82.3% of patients in the placebo arm completed treatment with EC.

Status	Durvalumab N=88 N(%)	Placebo N=86 N(%)	Overall N=174 N(%)	p-value
Completed all treatment	56 (63.6)	51 (59.3)	107 (61.5)	0.666
Completed Durva/Placebo	68 (77.3)	69 (80.2)	137 (78.7)	
Completed nabP and EC	60 (68.2)	55 (64.0)	115 (66.1)	
Completed EC	70 (85.4)	65 (82.3)	135 (83.9)	

There were no significant differences in dose delays for any medication and any reason between the

durvalumab and placebo arm, except for delays for any reason of EC treatment (durvalumab: 61%; placebo:44.3%, p=0.041). Also, the duration of delay was not different between arms for any medication. The most prominent reason for dose delays was the category "organizational reason for up to 3 days" in both treatment groups and for all treatments. Dose reductions were not allowed for durvalumab/placebo treatment. The addition of durvalumab did not lead to more frequent dose reductions and discontinuations of the underlying chemotherapy nab-paclitaxel and epirubicin/cyclophosphamide compared to placebo. There were no differences in the frequency of skipped infusions for any reason in patients receiving durvalumab/placebo treatment (durvalumab: 5.7%, placebo: 3.5%), or in patients receiving nabPaclitaxel treatment (2.3%, in each arm). No epirubicin/cyclophosphamide infusions were omitted.

There were no deaths during the conduct of the GeparNuevo study.

CONCLUSIONS:

The addition of durvalumab to chemotherapy did numerically but not statistically significantly increase the pathological complete response rate by absolute 9%. Nevertheless, the results support further investigation of durvalumab as treatment for early triple-negative breast cancer patients, especially if at high risk. Small tumors achieve a pathological complete response with chemotherapy alone. Based on our results priming with durvalumab seems warranted. Whether an adjuvant portion as currently inbuilt into other studies investigating checkpoint inhibitors will improve the disease-free and overall survival beyond the pathological complete response effect is a matter of debate. The safety profile of durvalumab is in line with those seen for other checkpoint inhibitors. Immune-related effects were rare in both arms, with the exception of thyroid dysfunctions, which were more frequently observed with durvalumab. No patient died during the study. No new safety concerns have emerged from the trial. Taken together, the results of the GeparNuevo trial showed a favorable safety/benefit ratio for high-risk triple-negative breast cancer patients treated with the checkpoint inhibitor durvalumab in addition to standard taxane/anthracycline-based neoadjuvant chemotherapy.

Date of the Report:

December 10th, 2018

Annex

Klinik	Abteilung	Strasse	PLZ	Ort	Anrede	Titel	Vorname	Nachname PI
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Frauenärztl. Gemeinschafts- u. Schwerpunktpraxis Onkologie	Dr. Ralf Lorenz & Nadeshda Hecker & Helge Wesche	Caspari Str. 5-6	38100	**Braunschweig**	Herr	Dr.	Ralf	**Lorenz**
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Europäisches Brustzentrum Dr. Rezai am Luisenkrankenhaus	(Praxis) Senologische Onkologie Dr. Rezai	Luise-Rainer-Straße 6-10	40235	**Düsseldorf**	Herr	Dr.	Mahdi	**Rezai**
St. Antonius Hospital	Klinik für Hämatologie u. Onkologie	Dechant-Deckers-Str. 8	52249	**Eschweiler**	Herr	PD Dr.	Peter	**Staib**
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