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)

#157

Loibl S[1,2], Untch M[3], Burchardi N[1], Huober J[4], Blohmer JU[5], Grischke E-M[6], Furlanetto J[1], Tesch H[2], Hanusch C[7], Rezai M[8], Jackisch C[9], Schmitt WD[15], von Minckwitz G[1], Thomalla J[10], Kümmel S[11], Rautenberg B[12], Fasching PA[13], Rhiem K[14], Denkert C[15], Schneeweiss A[16]

[1]German Breast Group, Neu-Isenburg, Germany; [2]Centrum für Hämatologie und Onkologie Bethanien Frankfurt, Germany; [3]HELIOS Klinikum Berlin Buch, Germany; [4]Universitätsfrauenklinik Ulm, Germany; [5]Brustzentrum Charité, Berlin, Germany; [6]Universitätsfrauenklinik Tübingen, Germany; [7]Klinikum zum Roten Kreuz München, Germany; [8]Medical Center, Luisenkrankenhaus, Düsseldorf, Germany; [9]Sana-Clinic, Offenbach, Germany; [10]Praxisklinik für Hämatologie und Onkologie, Koblenz, Germany; [11]Brustzentrum, Kliniken Essen-Mitte, Essen, Germany; [12]Klinik für Frauenheilkunde, Universitätsklinikum Freiburg, Germany; [13]Brustzentrum Universitätsklinikum Erlangen, Germany; [14]Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln, Germany; [15]Institute of Pathology, Charité University Hospital Berlin, Germany; [16]National Center for Tumor Diseases (NCT), Heidelberg, Germany

Background

Chemotherapy (CT) is the only treatment option in triple negative breast cancer (TNBC) since so far targeted agents are under clinical investigation[1]. High levels of tumor infiltrating lymphocytes (TILs) in TNBC are associated with higher pathological complete response (pCR) and better outcome[2]. Programmed cell death ligand-1 (PD-L1) provides an important target to help reactivate the immune system. Durvalumab (D) (MEDI4736) is a human IgG1 monoclonal antibody that binds to PD-L1 expressed on tumor cells, thereby blocking its binding to and activation of its receptor PD-1 expressed on activated T-cells. This may overcome/prevent PD-L1-mediated inhibition/suppression of T-cell activation[3]. Therefore the addition of an anti-PD-L1 checkpoint inhibitor to standard CT may increase the pCR rate in patients with early TNBC. Here we reported the results of the safety interim analysis (SIA).

Patients and Methods

Trial design:

GeparNuevo (GBG89; NCT02685059) is a multicenter, prospective, randomized, double-blinded, placebo controlled phase II study. The study design is presented in Figure 1.

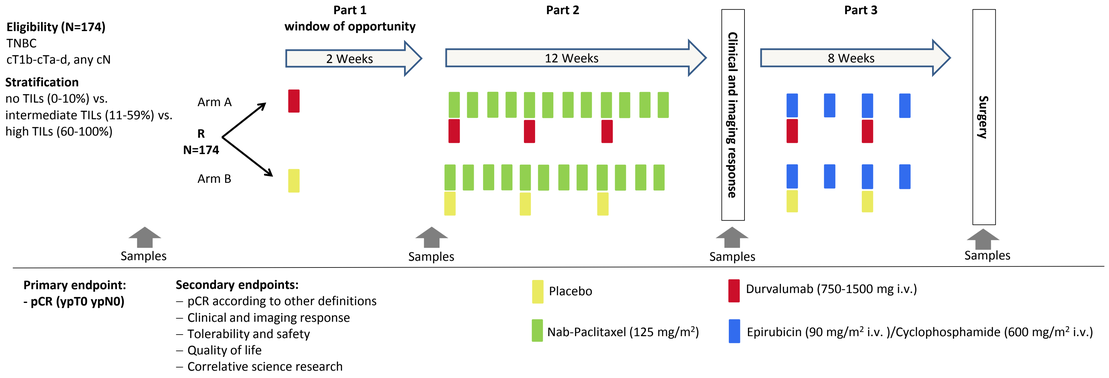
Statistical considerations:

The sample size calculation is based on the following assumptions:

- pCR rate in the Placebo (pl) arm is expected to be 48%, which was the pCR rate of the TNBC patients treated with nab-paclitaxel (nP) in the GeparSepto study[4]
- pCR rate in the D arm is expected to be 66% because this would be a clinically meaningful benefit which might eventually translate into a better DFS and OS
- In the mITT-set 158 patients (79 in each arm) will achieve 80% power on the 2-sided significance level α=0.2 to show the superiority of the D arm using a $\chi 2$-test. It is planned to recruit 174 subjects into this study assuming a 10% drop-out rate

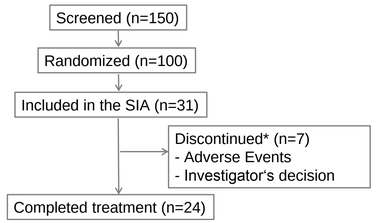
To monitor overall patient's safety the blinded safety data are presented as of May 2017 (Figure 2).

Figure 1. GeparNuevo study design



Results

Figure 2. Consort statement



*Patients discontinued at least one study medication

Table 1. Baseline characteristics

Parameter	Category	N (%)
Age, years	Median (range)	49.0 (25.0-74.0)
cT (sonography)	cT1	14 (45.2)
	cT2	13 (41.9)
	cT3	4 (12.9)
	cT4	0 (0.0)
cN (sonography)	cN0	15 (50.0)
	cN1	13 (43.3)
	cN2	1 (3.3)
	cN3	1 (3.3)
Tumor grading	G1	0 (0.0)
	G2	5 (16.1)
	G3	26 (83.9)
Histological tumor type	ductal/ductal-lobular invasive	27 (87.1)
	other	4 (12.9)
Stromal TILs	0-10%	11 (35.5)
	11-59%	17 (54.8)
	≥60%	3 (9.7)

Table 2. Most common Adverse Events

Adverse events (AEs)	Any grade N (%)		Grade 3-4 N (%)	
Any AEs	31	(100)	17	(54.8)
Hematological AEs	31	(100)	11	(35.5)
Anemia	29	(93.5)	0	(0.0)
Leukopenia	30	(96.8)	8	(25.8)
Neutropenia	26	(83.9)	9	(29.0)
Thrombopenia	6	(19.4)	2	(6.5)
Non-hematological AEs	31	(100)	7	(22.6)
Fatigue	24	(77.4)	2	(6.5)
Nausea	17	(54.8)	2	(6.5)
PSN	29	(93.5)	4	(12.9)
Alopecia	29	(93.5)		n.a.
SAEs	16			
Immune related AESI				
Hypothyroidism	4	(12.9)	0	(0.0)
Hyperthyroidism	2	(6.5)	0	(0.0)
Neuropathy	1	(3.2)	0	(0.0)
Infusion related reaction	1	(3.2)	0	(0.0)

Abbreviations: AESI, adverse event of special interest; SAE, serious adverse event

Since May 2016, 100 patients were randomized in the study. The Baseline characteristics of the patients are presented in Table 1. Of 7 patients who discontinued at least one study medication, one patient discontinued all study medications, one discontinued D/pl and epirubicin/cyclophosphamide (EC), one discontinued nP and EC and 4 discontinued only EC mainly due to hematological toxicity. Treatment delay was observed in 17 patients (54.8%) treated with D/pl, in 21 (67.7%) with nP and in 12 (40.0%) with EC. Dose reduction was reported in 10 patients (32.2%) with nP and in 5 (16.7%) with EC mainly due to non-hematological toxicity. Overall 11 high grade hematological and 7 non-hematological AEs were reported. There were 8 any grade immune related AEs of special interest (AESI) and 16 SAEs (Table 2).

Conclusions

The addition of Durvalumab to the standard nP-EC treatment is feasible and does not result in an increased toxicity.

References

1. von Minckwitz G, Martin M. Neoadjuvant treatments for triple-negative breast cancer (TNBC). Ann Oncol. 2012;23 Suppl 6:vi35-9.
2. Adams S, Gray RJ, Demaria S et al. Prognostic value of tumor infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol. 2014;32:2959-66.
3.Homet Moreno B, Ribas A. Anti-programmed cell death protein-1/ligand-1 therapy in different cancers. Br J Cancer. 2015;112(9):1421-7.
4. Untch M, Jackisch C, Schneeweiß A et al. A randomized phase III trial comparing neoadjuvant chemotherapy with weekly nanoparticle-based paclitaxel with solvent based paclitaxel followed by anthracyline/ cyclophosphamide for patients with early breast cancer (GeparSepto); GBG 69. SABCS 2014 Oral presentation S2-07.

Presented at ASCO Annual Meeting 2017, Chicago, IL, USA, June 2-6, 2017

Financial and Drug Supply was provided by Astra Zeneca & Celgene

For further information and for permission to reprint and/or distribute please contact German Breast Group, Neu-Isenburg, Germany, email: publications@gbg.de