Impact of Immune Checkpoint Inhibition (CPI) on Fertility in Young Women with Early Triple-Negative Breast Cancer (TNBC) receiving neoadjuvant Chemotherapy (NACT): A Prospective Substudy of the NSABP B-59/GBG-96-GeparDouze Trial

Mattea Reinisch[1], Andreas Schneeweiss[2], Vanessa Schaser[3], Christine Solbach[4], Carsten Denkert[5], Priya Rastogi[6,7], Fernando Moreno[8,9], Tanner Freeman[6,7], Theresa Link[10], João Mouta[11], Sabine Seiler[12], Ralf Meyer[13], Álvaro Rodríguez Lescure[9,14], Vesna Bjelic-Radisic[15,16], Peter Fasching[17], Marija Balic[6,7], Michael Untch[18], Kerstin Rhiem[19], Kerstin Lüdtke-Heckenkamp[20], Jens Huober[21], Serafin Morales[9,22], Isabel Blancas[9,23], Johannes Holtschmidt[3], Valentina Nekljudova[3], Norman Wolmark[6,7], Charles E. Geyer, Jr.[6,7], Sibylle Loibl[3,24]

[1]Interdisciplinary Breast Unit, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany, [2]National Center for Tumor Diseases, University Hospital and German Cancer Research Center, Heidelberg, Germany, [3]GBG Forschungs GmbH, Neu-Isenburg, Germany, [4]Breast Unit, University Medical Center, Goethe-University Frankfurt, [5]Institute of Pathology, Philipps-Universität Marburg and University Hospital Marburg, Marburg, Germany, [6] NSABP Foundation, Inc., Pittsburgh, PA, USA, [7]University of Pittsburgh School of Medicine, and UPMC Hillman Cancer Center, Pittsburgh, PA, USA, [8]Department of Medical Oncology, Hospital Universitario Clínico San Carlos, Madrid, Spain, [9]GEICAM Spanish Breast Cancer Group, Spain, [10]Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, [11]Roche Farmacêutica Química Lda, Amadora, Portugal, [12]Sana Klinikum Offenbach, Offenbach, Germany, [13]Hämato-Onkologie im Medicum Bremen, Germany, [14]Hospital General Universitario de Elche, Elche, Spain, [15]Helios University Clinic Wuppertal, Germany, [16]University Witten/Herdecke, Germany, [17]Department of Gynecology and Obstetrics, University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany, [18]Interdisciplinary Breast Cancer Center, HELIOS Hospital Berlin Buch, Berlin, Germany, [19]Center for Hereditary Breast and Ovarian Cancer, University Hospital Cologne, Germany, [20] Niels-Stensen-clinics, Harderberg, German, [21]Breast Center, HOCH Health Ostschweiz, Cantonal hospital, St. Gallen, Switzerland, [22]Hospital Arnau de Vilanova, Lleida, Spain, [23]Medicine Department, Granada University, Hospital Universitario Clinico San Cecilio, Instituto de Investigación Biosanitaria de Granada (ibs.Granada), Spain, [24]Goethe University Frankfurt, Germany

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Background

Neo-/adjuvant chemotherapy (NACT) carries a substantial risk of ovarian failure in premenopausal women with breast cancer, leading to reduced fertility and negatively affecting quality of life, bone health, and cardiovascular health (1–3). The impact of adding checkpoint inhibitors to NACT on chemotherapy-induced ovarian failure (CIOF) is not well defined, and while immunotherapies have become established components of standard treatment for patients with triple-negative breast cancer (TNBC), their influence on ovarian function and fertility is still largely unexplored (4).

To address this, we prospectively assessed hormonal parameters in patients with early-stage TNBC treated within the multicenter, randomized Phase III NSABP B-59/GBG-96-GeparDouze trial. Participants received NACT with anthracycline, cyclophosphamide, taxane, and carboplatin, and were randomized to atezolizumab (CTA) or placebo (CT) between December 2017 and May 2021 (Fig. 1). Post-neoadjuvant capecitabine treatment was permitted at the investigator's discretion in cases of non-pCR.

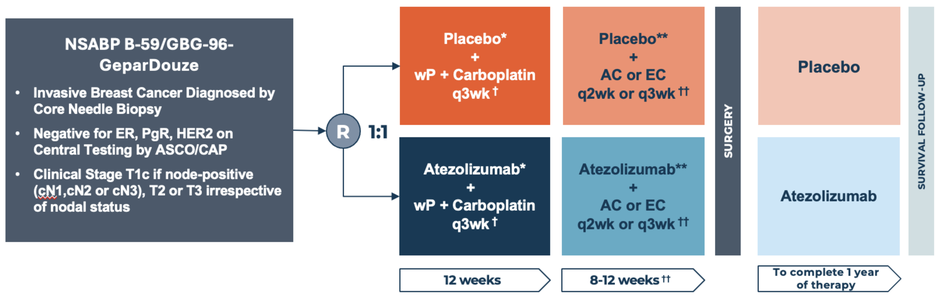
Patients and Methods

This prospective substudy enrolled women ≤45 years with an early TNBC without prior hysterectomy/oophorectomy. Blood samples were collected at baseline, end of therapy (EOT), and 6, 12, 18, 24 months after EOT (**Figure 2**). Patients required ≥1 baseline (BL) sample and ≥1 follow-up sample for evaluation.

Study design

Atezolizumab (atezo) 1200 mg or placebo IV Day 1 every 3 wks for 4 doses. Paclitaxel 80 mg/m2 IV weekly x 12 doses (WP) + Carboplatin AUC of 5 IV Day 1 every 3 wks for 4 cycles; **Atezo 1200 mg or placebo IV Day 1 every 3 wks for 3 to 4 doses depending on AC/EC schedule used; †† Doxorubicin (A) 60 mg/m2 IV + cyclophosphamide (C) 600 mg/m2 IV Day 1 every 2 or 3 wks for 4 cycles OR Epirubicin (E) 90 mg/m2; IV + cyclophosphamide (C) 600 mg/m2 IV Day 1 every 2 or 3 wks for 4 cycles (**Figure 1**).

Figure 1: Study design



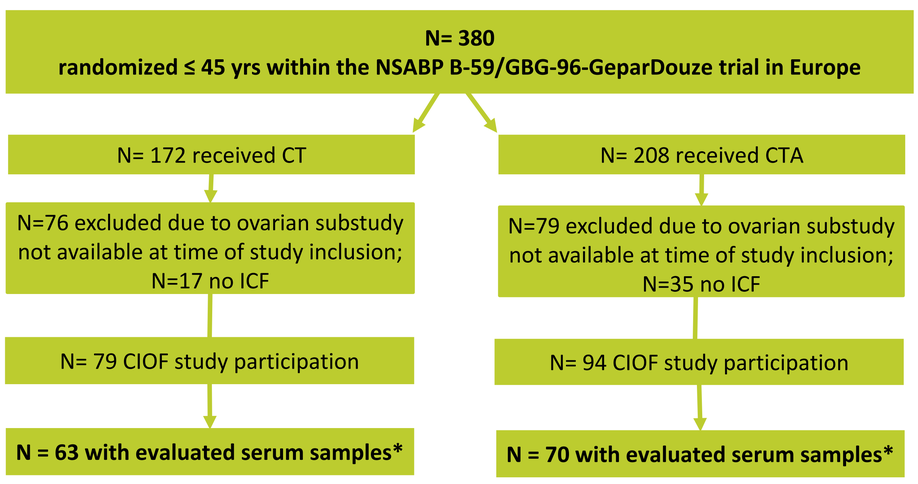
Primary objectives of the substudy

The assessment of the CIOF rate, defined as postmenopausal levels Estradiol (E2 <5 pg/ml) and of follicle-stimulating hormone (FSH >25.8 IU/l) for patients not fulfilling the CIOF criteria at BL until 24 months after therapy.

Secondary objectives of the substudy

The assessment of ovarian reserve by measuring Anti-Mullerian Hormone (AMH) levels and the rate of amenorrhea at different time points. AMH levels below 0.22 ng/ml indicate a severely reduced ovarian reserve, whereas levels below 0.1 ng/ml are considered undetectable.

Figure 2: Patient Disposition



* Samples were analyzed only if baseline and ≥1 additional sample were available.
Please note that patients with a reported ovariectomy/adnexectomy or pregnancy during the considered study visits were excluded. From the time of documentation, patients with ovariectomy/adnexectomy or pregnancy were no longer included in the analyses

Results

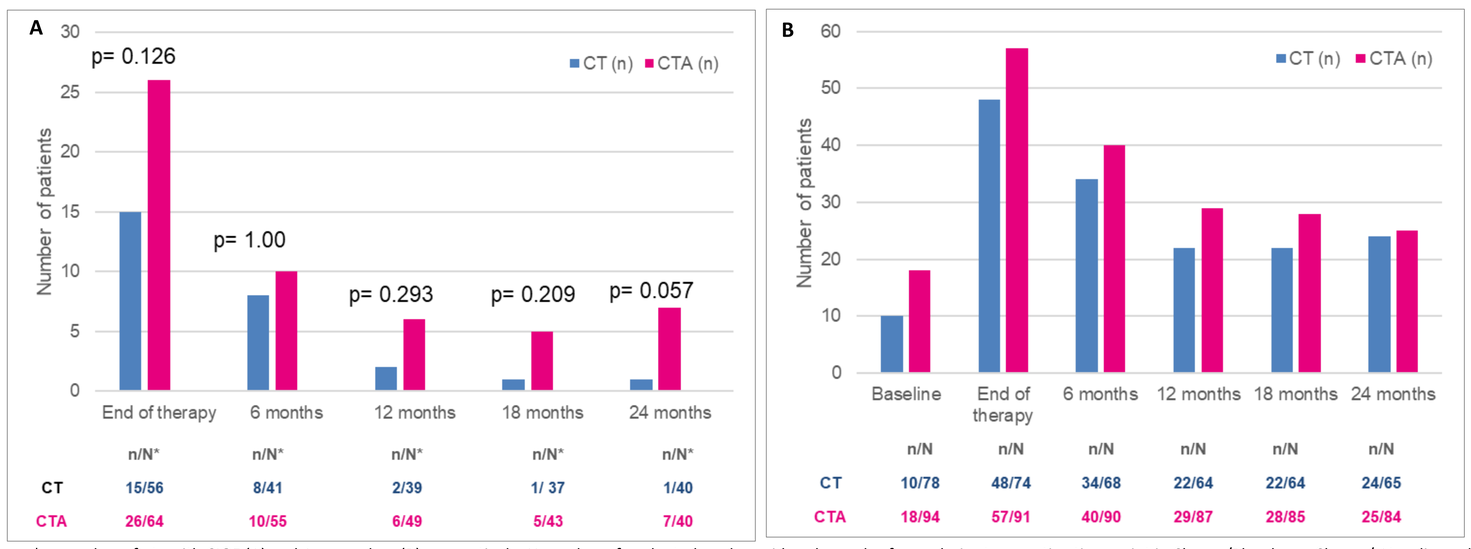
- Of 173 enrolled patients, 133 (CTA n=70; CT n=63) had ≥2 evaluable time points. Median baseline age was 37 years (**Table 1**).
- At EOT, 34.2% experienced CIOF, with higher but non-significant rates in the CTA versus CT group (40.6% vs. 26.8%; **Figure 3A**).
- 24 months after EOT, 10% of participants had persistent CIOF, with a trend toward a higher rate in those receiving atezolizumab (CTA: 17.5%; CT: 2.5%; p=0.06).
- Baseline amenorrhea was reported in 12.8% of CT and 19.1% of CTA patients (**Figure 3B**).
- The number of patients with reported amenorrhea was highest at EOT (CT 64.9%; CTA 62.9%), subsequently decreased to approximately 33% after 12 months and remained stable thereafter.

Table 1. Baseline Characteristics

	Chemo / Placebo N=79 N (%)	Chemo / Atezolizumab N=94 N (%)	Overall N=173 N (%)
Age, median (range)	38.0 (23 - 45)	36.5 (22 - 45)	37 (22 - 45)
% of patients < 35 years at diagnosis	29 (36.7)	35 (37.2)	64 (37.0)
Clinical Tumorsize 1.1 – 3.0 cm	41 (51.9)	59 (62.8)	100 (57.8)
Clinical Tumorsize > 3.0 cm	38 (48.1)	35 (37.2)	73 (42.2)
Clinically node pos. (cN+)	27 (34.2)	35 (37.2)	62 (35.8)
Received GnRHa at any time point under therapy*	7 (7.4)	6 (7.6)	13 (7.5)
Received salpingoovarectomy during NACT/ FU	6 (6.4)	7 (8.9)	13 (7.5)
Germline BRCA 1/2 positive (known)	18 (24.3)	19 (24.7)	37 (24.5)
AC/EC Schedule: Every 2 weeks (q2w)	50 (63.3)	64 (68.1)	114 (65.9)
AC/EC Schedule: Every 3 weeks (q3w)	29 (36.7)	30 (31.9)	59 (34.1)
Relative total dose intensity (%) of cyclophosphamide median (Q1 – Q3)	88.7 (80.2 - 95.2)	87.9 (80.0 - 91.9)	88.3 (80.1 - 92.7)
Body Mass Index (BMI) median (range)	24.2 (17.9 - 40.7)	24.1 (16.4 - 43.9)	24.2 (16.4 - 43.9)
- BMI normal (18.5-24.9 kg/m²)	42 (53.2)	54 (57.4)	96 (55.5)
- BMI overweight (≥ 25 kg/m²)	36 (45.6)	39 (41.5)	75 (43.3)
Received capecitabine postneoadjuvant	18 (22.8)	14 (14.9)	32 (18.5)
Received atezolizumab postneoadjuvant	n.a.	73 (77.7)	-

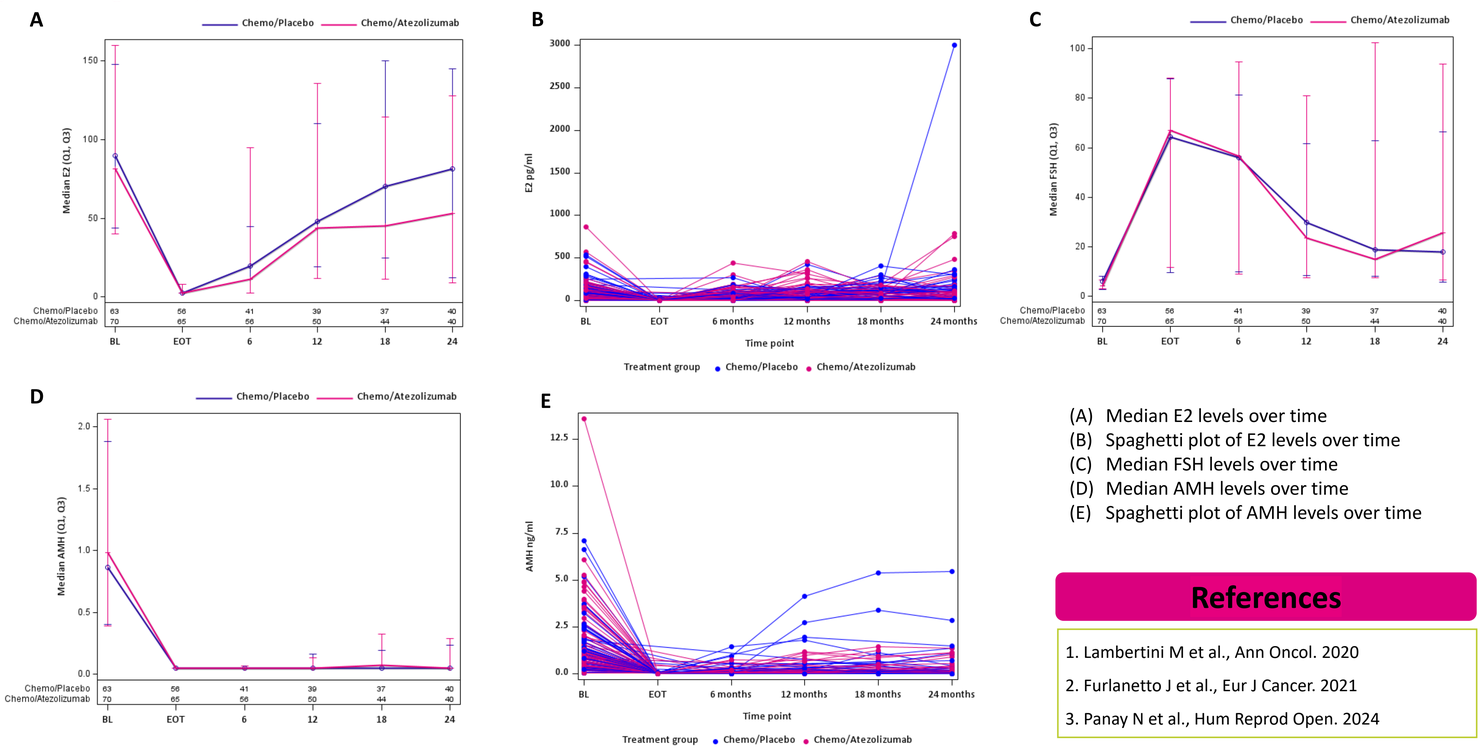
*Collected as concomitted medication

Figure 3: Rate of CIOF (A) and Amenorrhea (B) at different time points



*n: number of pts with CIOF (A) and Amenorrhea (B), respectively; N number of evaluated and considered samples for analysis at respective time point in Chemo/Placebo or Chemo/ Atezolizumab arm respectively

Figure 4: Changes of E2, FSH and AMH levels from baseline to 24 months



(A) Median E2 levels over time
(B) Spaghetti plot of E2 levels over time
(C) Median FSH levels over time
(D) Median AMH levels over time
(E) Spaghetti plot of AMH levels over time

References

1. Lambertini M et al., Ann Oncol. 2020
2. Furlanetto J et al., Eur J Cancer. 2021
3. Panay N et al., Hum Reprod Open. 2024

- A numerical recovery of hormonal levels was observed in both arms during FU, indicating a regain of ovarian function. This change was more pronounced in the CT arm (Fig.4).
- At EOT, Estradiol and FSH levels were within postmenopausal ranges but subsequently recovered (**Figures 4A+C**).
- 24 months after EOT 10% (8/80) showed persistent postmenopausal Estradiol levels and 46.2% (37/80) postmenopausal FSH levels (based on all evaluated and considered samples).
- At BL, 10.5% of the cohort had values below the threshold for severely reduced ovarian reserve (< 0.22 ng/ml) with no difference between the arms. All patients had severely reduced ovarian reserve at EOT with no recovery until 2 years and without statistically significant differences between treatment groups (**Figures 4D+E**).

Conclusions

- This is the first prospective study evaluating the effect of a checkpoint inhibitor on ovarian function through assessment of hormonal parameters in premenopausal patients with early TNBC.
- Patients treated with a checkpoint inhibitor exhibited numerically higher but not statistically significant differences in the CIOF rates at all time points until 24 months after EOT (10% overall; 2.5% in CT and 17.5% in CTA arm).
- These findings support the hypothesis that checkpoint inhibitor may adversely affect fertility and warrant further studies (with higher sample size) to elucidate the underlying mechanism.

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