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DECEMBER 9–12, 2025
HENRY B. GONZALEZ CONVENTION CENTER • SAN ANTONIO, TX

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

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NSABP Foundation, Inc. IDDI PASSION. SCIENCE. EXPERIENCE. GEICAM investigación en cáncer de mama TRIO TRANSLATIONAL RESEARCH IN ONCOLOGY US Oncology Research GBG GERMAN BREAST GROUP

Disclosure Information

Mattea Reinisch

I have the following relevant financial relationships to disclose:

Employee of: Medical University of Mannheim

Consultant for: Daiichi Sankyo, Exact Science, Roche, Somatex,

Speaker's Bureau for: none

Grant/Research support from: none

Stockholder in: none

Honoraria from: AstraZeneca, Daiichi Sankyo, Exact Science, Gilead, JenaPharmaceutics, Lilly, MSD, Novartis, Pfizer, Roche, OnkowissenTV, Seagen, Somatex, Stemline Menarini and Streamed Up.

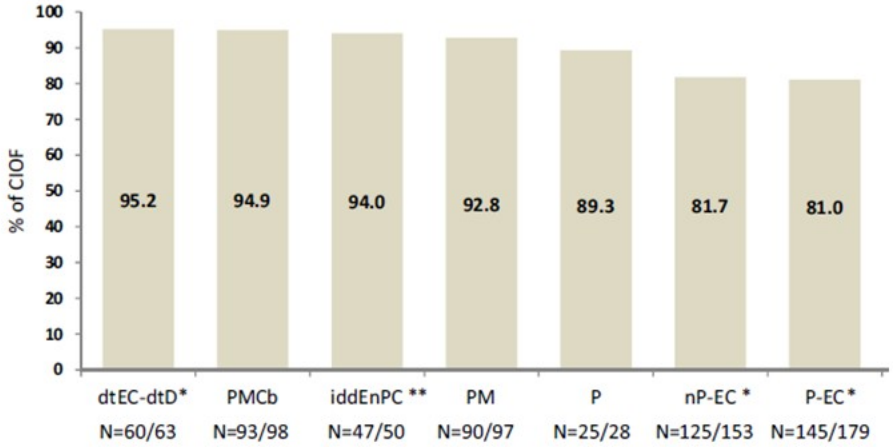
- and -

My additional financial relationship disclosures are:

Travel support from: AstraZeneca, Daiichi Sankyo, Gilead, Lilly, Novartis, Pfizer, Roche, Stemline Menarini.

Background

- Neo-/adjuvant Chemotherapy (NACT) is associated with a high risk of ovarian failure in premenopausal women with breast cancer, leading to a reduced fertility in young women[1,2].
- Furthermore, preterm ovarian failure can lead to a decreased overall well-being, quality of life and bone- and cardiovascular health[3].
- While immunotherapies have become part of the standard of care for patients with TNBC, their effects on ovarian function and fertility remain largely unknown [4].



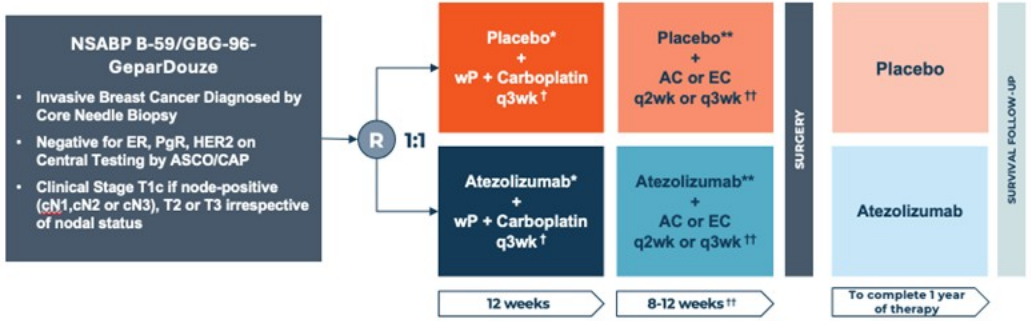
1. Furlanetto J et al., Eur J Cancer. 2021; 2. Lambertini M et al., Ann Oncol. 2020,
3. Panay N et al., Hum Reprod Open. 2024., 4. Winship, A.L., et al. Nat Cancer 2022

Background

- We prospectively assessed different hormonal parameters in patients with early TNBC receiving NACT within the prospective multicentre randomized Phase III NSABP B-59/GeparDouze Trial.
- Patients received anthracycline, cyclophosphamide, taxane and carboplatin containing NACT and were randomized to receive either atezolizumab (CTA) or placebo (CT).
- Post-neoadjuvant treatment with capecitabine in case of non-pCR was allowed at the discretion of the investigator.

Geyer C et al., SABCS 2024; Clin Cancer Res. 2025.

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.

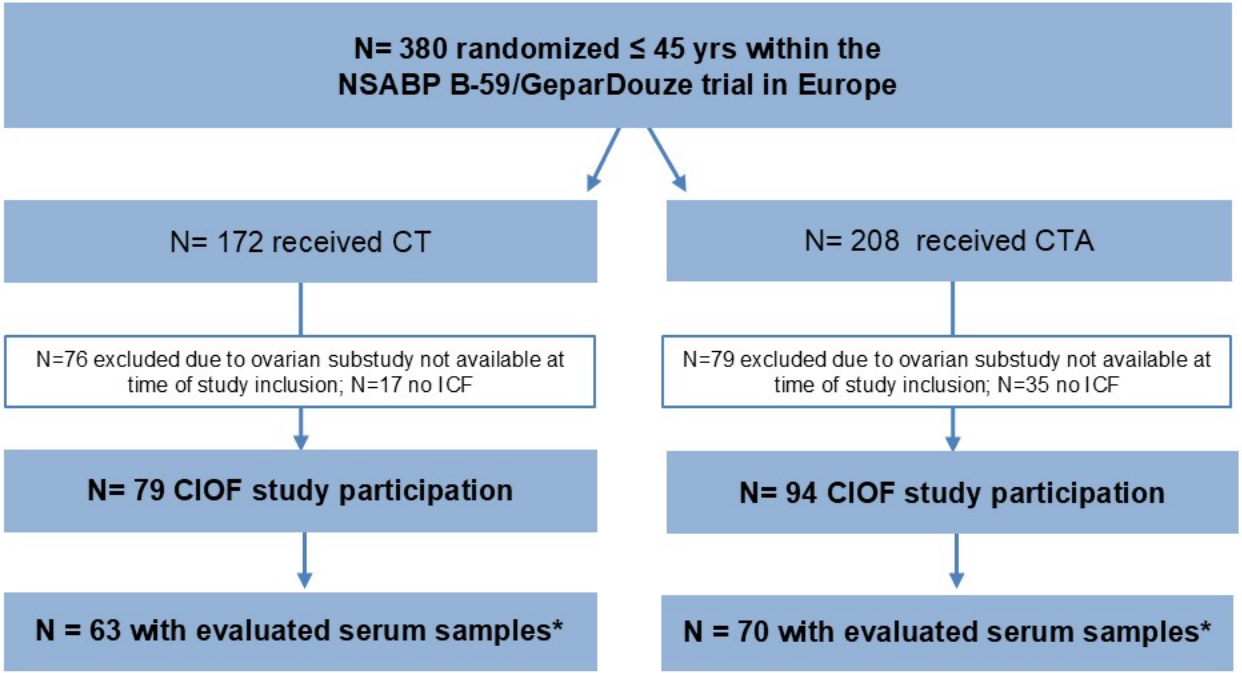


Main Inclusion Criteria and Main Objectives

- This prospective, substudy included women aged ≤45 years (yrs) at diagnosis with an early TNBC without history of hysterectomy and/or salpingo-ovarectomy enrolled within the NSABP B-59/GeparDouze trial.
- The main objective was to assess the rate of CIOF, 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 baseline (BL) until 24 months after therapy.
- Further objectives included 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.

Patient Disposition

All serum samples were prospectively collected at predefined time points and centrally evaluated



*Samples were analyzed only if baseline and ≥1 additional sample were available.
Data were documented only for patients with amenorrhea at the respective visit. Patients with adnexectomy or pregnancy during follow-up were excluded. From the time of documentation, patients with ovariectomy/adnexectomy or pregnancy were no longer included.

Patients Characteristics

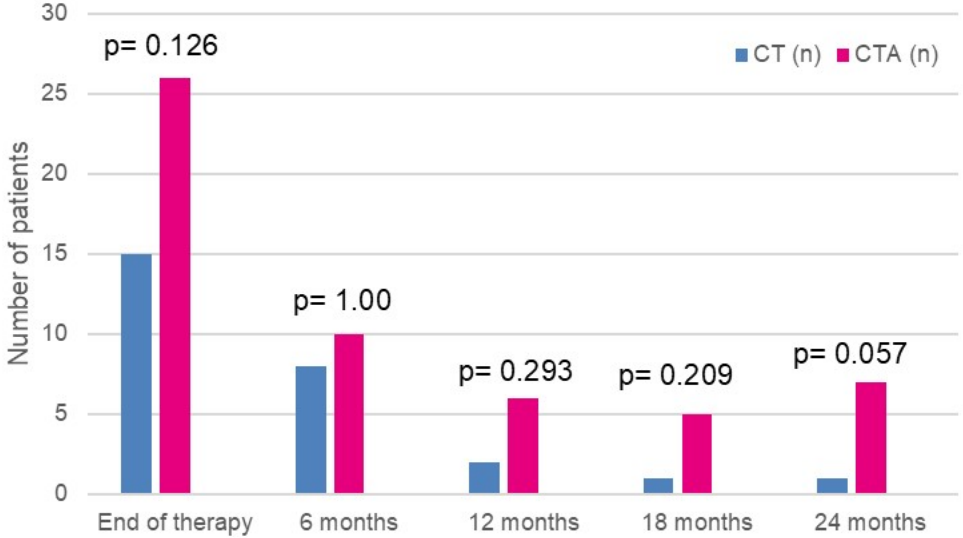
are comparable to that of the main NSABP B-59 GeparDouze trial

	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)
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)
AC/EC Schedule: Every 2 weeks (q2w)	50 (63.3)	64 (68.1)	114 (65.9)
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 if non-pCR	18 (22.8)	14 (14.9)	32 (18.5)
Received atezolizumab postneoadjuvant	n.a.	73 (77.7)	-

*Collected as concomitted medication

CIOF at Different Time Points

Only patients with premenopausal hormone levels (E2 and FSH) at baseline were included*

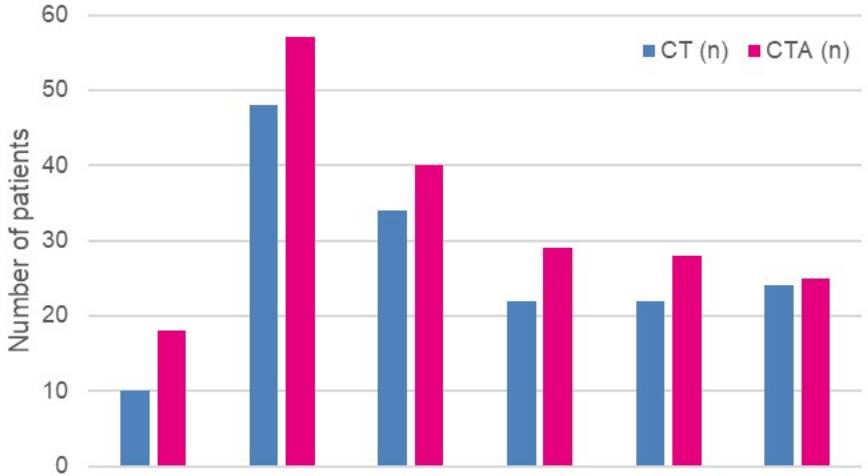


	n/N*	n/N*	n/N*	n/N*	n/N*
CT	15/56	8/41	2/39	1/ 37	1/40
CTA	26/64	10/55	6/49	5/43	7/40

- Patients who received checkpoint inhibitor in addition to CT had higher rates of CIOF at EOT and remained higher during FU.
- 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.
- No statistical significant differences in CIOF rates between the treatment groups were observed.

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

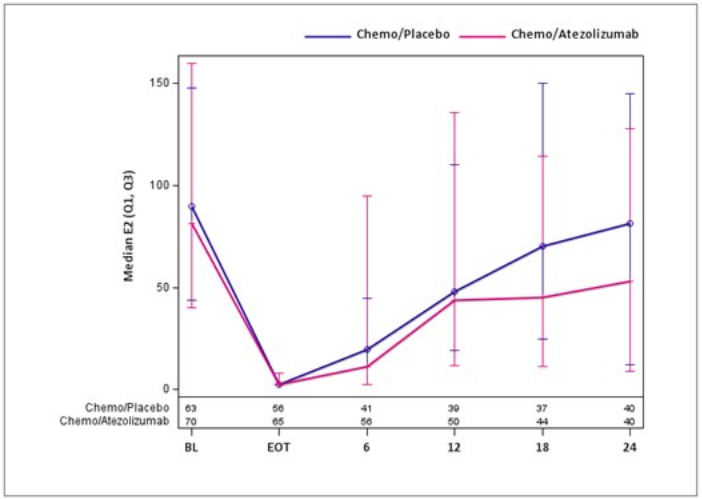
Rate of Amenorrhea

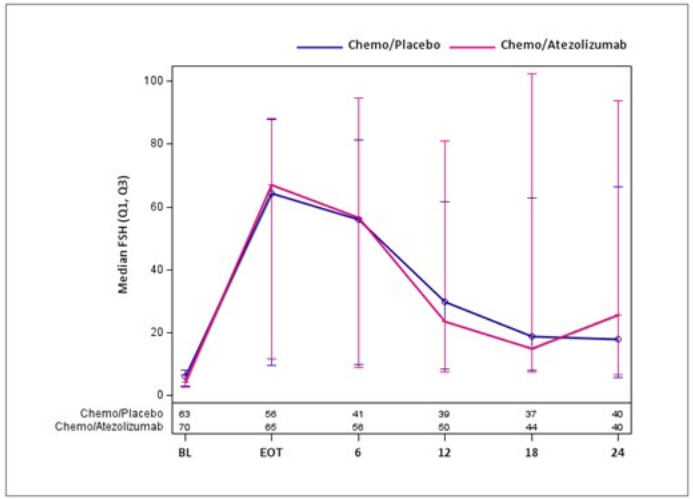


	n/N	n/N	n/N	n/N	n/N	n/N
CT	10/78	48/74	34/68	22/64	22/64	24/65
CTA	18/94	57/91	40/90	29/87	28/85	25/84

- At baseline, amenorrhea (as reported by investigator) was present in 12.8% in the CT and 19.1% in the CTA group.
- The number of patients with reported amenorrhea was highest at EOT (CT 64.9%; CTA 62.9%) and declined to approximately 33% after 12 months of FU and remained stable thereafter.

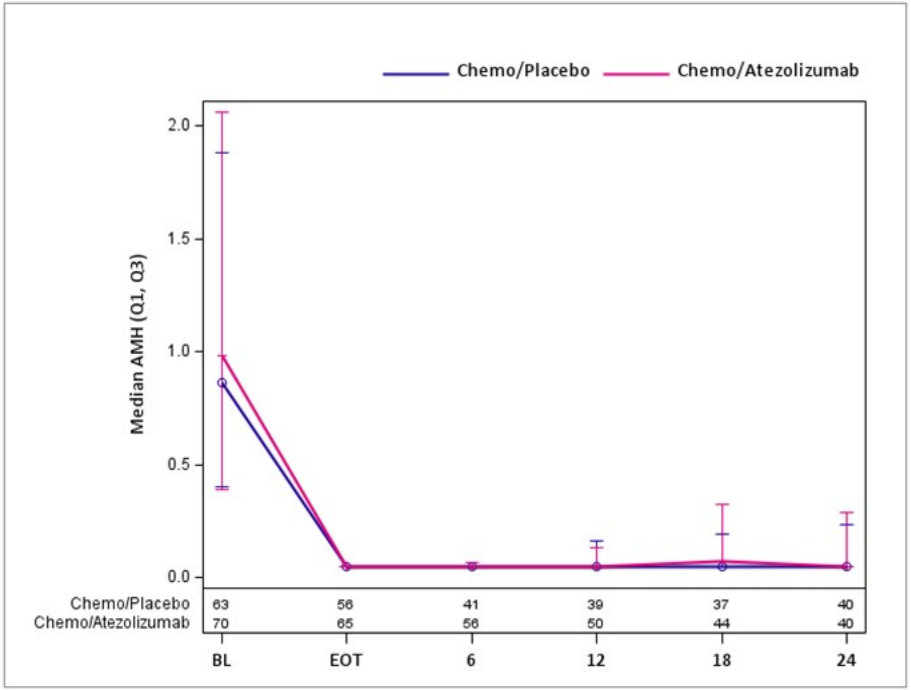
Changes of E2 and FSH Levels





- At EOT, Estradiol and FSH levels were within postmenopausal ranges but recovered during FU.
- 24 months after EOT 10% (8/80) showed persistent postmenopausal Estradiol levels and 46.2% (37/80) postmenopausal FSH levels (overall).

Changes of AMH Levels



- At BL, median AMH levels were lower in comparison to the age-based median reference levels.
- At BL, 10.5% in our 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 statistical significant differences between the treatment groups.

Conclusion

- This is the first prospective study evaluating the effect of a checkpoint inhibitor on ovarian function through assessment of different hormonal parameters in premenopausal patients with early TNBC treated within a prospective randomized trial.
- Patients treated with a checkpoint inhibitor exhibited numerically higher but not statistically significant differences in the rate of CIOF at all time points until 24 months after EOT (10% overall; 2.5% in CT; 17.5% in CTA, n.s.).
- These findings support the hypothesis that checkpoint inhibitors may adversely affect fertility and underscore the need for further studies to elucidate the underlying biological mechanisms and to improve counselling strategies for this patient population.

Acknowledgements

THANK YOU

To all the patients who participated in this trial and their families.

To the investigators and their research staff of NSABP, GBG, GEICAM, USOR, and TRIO, and the headquarter teams at NSABP, GBG, and IDDI.

To the members of the DSMB for the trial.

To Genentech/Roche for the funding to support the development, conduct, and analysis of the trial.