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Impact of neoadjuvant pembrolizumab on ovarian function in young patients with triple-negative breast cancer (TNBC): Longitudinal analysis from NeoSTOP and NeoPACT trials

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Background

- Neoadjuvant chemotherapy plus pembrolizumab (NACT+P) is standard-of-care for most patients with stage II-III TNBC.[1-2]
- There is lack of clinical data on the ovarian toxicity of immune checkpoint inhibitors in patients with breast cancer.

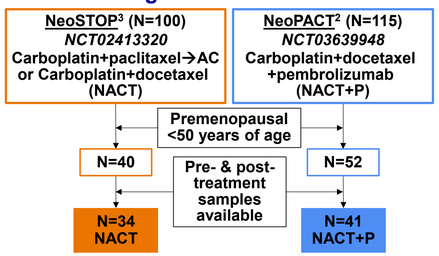
Aim

Compare ovarian toxicity of chemotherapy and chemoimmunotherapy in the NeoSTOP and NeoPACT neoadjuvant trials.

Methods

- Patients <50 years of age enrolled in NeoSTOP and NeoPACT trials and self-reported premenopausal with available pre-treatment (pre-tx) and at least one serial post-treatment serum samples were included in this analysis (Figure 1).[2-3]
- Anti-Müllerian hormone (AMH), estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were assessed at serial time points (Table 2). Assay-specific cut points (per package inserts) were used to categorize biochemical menopausal status (Table 3). AMH measures functional ovarian reserve; level of <10 pg/ml was considered postmenopausal.

Figure 1. REMARK



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Table 1. Patient characteristics (N=75)

Characteristic – N (%)		NACT (N=34)	NACT+P (N=41)	p
Age, y - median (range)		40 (29–49)	41 (27–49)	0.865
Race	White	26 (77%)	34 (83%)	0.881
	Black	6 (18%)	5 (12%)	
	Asian	1 (3%)	1 (2%)	
	Other	1 (3%)	1 (2%)	
Pre-menopausal		34 (100%)	41 (100%)	1.000
Ovaries intact		34 (100%)	41 (100%)	1.000
Hysterectomy		1 (3%)	3 (7%)	0.622
g*BRCA1/2* mutation[a]		6 (18%)	4 (10%)	0.496
BMI – median (IQR)		28 (24–35)	29 (24–33)	0.952
Nodal positivity		14 (41%)	14 (34%)	0.633
GnRHa during neoadjuvant therapy[b]		4 (12%)	7 (18%)	0.522
Pre-tx levels – median (IQR)	AMH, pg/mL	200 (35–659)	109 (20–464)	0.299
	E2, pg/mL	136 (33–186)	91 (49–139)	0.184
	FSH, mIU/mL	3.1 (1.4–6.7)	2.6 (1.3–5.2)	0.745
	LH, mIU/mL	3.4 (1.8–9.4)	2.7 (1.4–5.6)	0.409
Adjuvant chemotherapy		5 (15%)	12 (29%)	0.171

[a] *gBRCA1/2* status unknown for N=1 patient in NACT group and N=2 in NACT+P group.
[b] GnRHa use unknown for N=3 patients in NACT+P group.

Table 2. Serial time points

Available samples	All (N=75)	NACT (N=34)	NACT+P (N=41)
Pre-treatment	75 (100%)	34 (100%)	41 (100%)
Pre-surgery (end of neoadjuvant therapy)	74 (99%)	34 (100%)	40 (98%)
3-12 months after all chemotherapy*	41 (55%)	16 (47%)	25 (61%)
12-24 months after all chemotherapy*	18 (24%)	3 (9%)	15 (37%)

*After completing all chemotherapy in neoadjuvant +/- adjuvant setting.

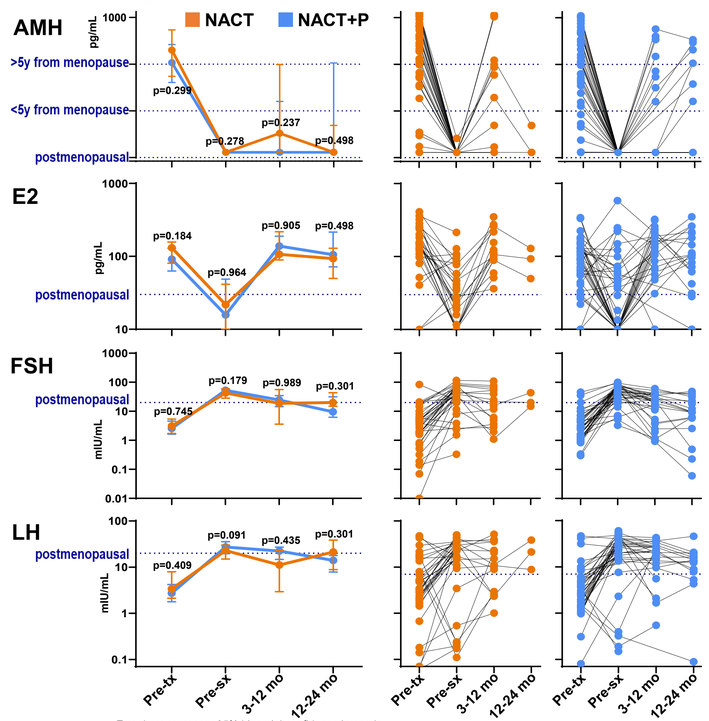
Table 3. Assay cut points

Analyte	Assay	Lower limit of detection	Cut point for postmenopausal
AMH	Quantitative ELISA (MenoCheck picoAMH)	1.3 pg/mL	<10 pg/mL*
E2	Magnetic bead-based fluorometric immunoassays (MILLIPLEX)	10 pg/mL	≤30 pg/mL
FSH		0.01 mIU/mL	>20 mIU/mL
LH		0.01 mIU/mL	>7 mIU/mL

*Per the AMH assay package insert, levels <10 pg/mL associate with being at final menstrual period (FMP) or later (i.e., biochemically postmenopausal); levels 10 pg/mL to 99 pg/mL are indicative of ovarian reserve of <5 years from FMP; levels >100 pg/mL are indicative of ovarian reserve of >5 years from FMP.

References: 1. Schmid et al, *NEJM* 2022. 2. Sharma et al, *JAMA Oncol* 2024. 3. Sharma et al, *Clin Cancer Res* 2021.

Figure 2. Changes in hormone levels by treatment



Error bars represent 95% binomial confidence intervals

Figure 3. Biochemical premenopausal status

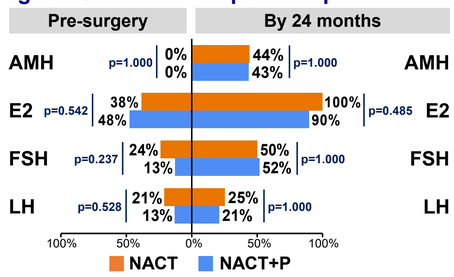
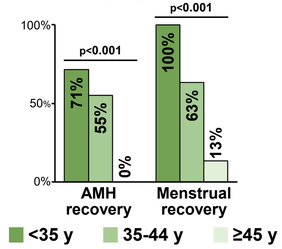


Figure 4. AMH and menstrual recovery by age



Results

- Baseline characteristics including age, BMI, race, and pre-treatment (pre-tx) hormone levels were similar in NACT and NACT+P groups (Table 1). There was moderate correlation between pre-tx AMH and age (ρ -0.522, p<0.001).
- Pre-surgery, there was significant decline in AMH and E2 and increase in FSH and LH compared to pre-tx levels in both NACT and NACT+P groups (Figure 2). 100% of patients in both treatment groups had postmenopausal AMH levels at pre-surgery (Figure 3).
- By 24 months after all chemotherapy, hormone recovery was noted in a modest proportion of patients in both groups (Figures 2 & 3). AMH recovered to non-postmenopausal range in 43% and 44% of patients in NACT and NACT+P groups, p=1.000 (Figure 3).
- Median AMH levels did not recover to pre-tx levels in either group. There was no difference in AMH levels between NACT and NACT+P groups at 3-12 months (p=0.227) and 12-24 months (p=0.498), indicating similar impact of NACT and NACT+P on ovarian reserve (Figure 2).
- AMH recovery to non-postmenopausal range was age-dependent (p<0.001) (Figure 4). On univariate analysis, age, GnRHa use, and pre-treatment AMH predicted AMH recovery. On multivariate analysis, age (p=0.026) and pre-tx AMH (p=0.021) predicted AMH recovery.
- 50% patients in the NACT group and 68% in the NACT+P group reported return of menstrual cycles (p=0.193). Return of menstrual cycles was associated with AMH recovery (p<0.001) and age (p<0.001) (Figure 4).

Conclusions

- Our study provides important information regarding impact of pembrolizumab on ovarian function and recovery in young premenopausal patients with breast cancer.
- Immediate post-treatment hormone levels are in postmenopausal range in majority of patients and not good indicators of long-term ovarian toxicity.
- By 24 months, over 40% of patients had AMH recovery to premenopausal levels. However, AMH levels did not recover to pre-tx levels in either the chemotherapy or chemoimmunotherapy group, indicating impact of treatment on ovarian reserve.
- Younger age at diagnosis and higher pre-treatment AMH levels were associated with higher rates of AMH and menstrual recovery.
- Similar rates of biochemical hormone recovery and menstrual recovery were noted with chemotherapy and chemoimmunotherapy, suggesting that pembrolizumab may not have an additive effect on ovarian toxicity in the context of the regimen used in NeoPACT trial. Notably, NeoPACT regimen did not include neoadjuvant anthracycline/cyclophosphamide or adjuvant pembrolizumab.
- Ovarian function and recovery/reserve should be prospectively evaluated in other chemoimmunotherapy trials.

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