Peripheral immune subsets and circulating tumor DNA (ctDNA) in patients (pts) with residual triple negative breast cancer (TNBC) treated with adjuvant immunotherapy and/or chemotherapy (chemo): the OXEL study

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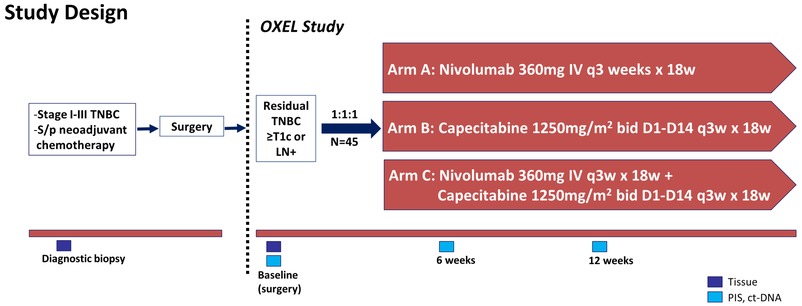
BACKGROUND

- Long-term follow-up of neoadjuvant studies demonstrates poor clinical outcomes in pts with TNBC who do not achieve pathologic complete response (pCR).[1]
- The addition of adjuvant cape prolonged DFS and OS in pts with HER2 neg breast cancer with residual invasive disease, with more striking benefit in TNBC.[2] Checkpoint inhibitors added to standard chemotherapy in the neoadjuvant and metastatic setting improve outcomes in TNBC.[3,4]
- We characterized peripheral immune subsets and the role of minimal residual disease (MRD) detection via ctDNA in pts who participated in the OXEL study. Here we report the translational endpoints of the OXEL study.

Study Design



METHODS

- OXEL (Opdivo® -XELoda®) is a recently completed phase II open-label 3-arm randomized study of nivo, cape or the combination as adjuvant treatment (tx) for pts with residual TNBC after appropriate neoadjuvant chemo (NCT03487666). Eligible pts had completed definitive local tx.
- Peripheral blood mononuclear cells (PBMCs) and ctDNA were assessed at baseline, 6, and 12 wks and at time of recurrence, if applicable. PBMCs were stained with 30 markers and analyzed by flow cytometry to identify changes in 158 immune cell subsets at 6 wks, as a percent of total PBMCs.[5]
- RaDaR^{TM}, a deep sequencing based, tumor-informed personalized assay was utilized to detect the presence of ctDNA in plasma.[6]
- Distant disease-free survival (DDFS) and OS were analyzed by the Kaplan-Meier method and Log-Rank test was used to compare DDFS and OS according to baseline MRD results.
- All pts will be followed for distant recurrence and survival for 3 yrs.

RESULTS

Patients' characteristics

Variable		N=45 (%)
Age (mean (SD))		51 (11.54)
Race	Black	14 (31)
	White	29 (65)
	Other	2 (4)
Ethnicity	Latino	3 (7)
	Non-Latino	42 (93)
Prior chemotherapy regimen	Taxane + anthracyclines	42 (93)
	Taxanes only	3 (7)
Prior Carboplatin	Yes	14 (31)
	No	31 (69)
Germline mutation	BRCA1/2	3 (7)
	PALB2	2 (4)
	Not identified	40 (89)

Baseline ctDNA by tx arm and stage

	Baseline ctDNA (n=33)	
	Detected	Undetected
	12 (36%)	21 (64%)
Treatment Arm		
A (Nivo)	6	7
B (Cape)	4	6
C (Combo)	2	8
Clinical stage		
IA	1	1
IB	0	1
IIA	1	10
IIB	4	2
IIIA	6	4
IIIB	0	3

- 45 pts enrolled between 8/2018 and 6/2021 with 15 pts randomized to each arm.
- DDFS probability at 1-yr and 2-yrs was 0.73 (+/- 0.07) and 0.66 (+/-0.08) respectively.
- At 17 mos of median follow up, 14/45 pts (31%) had distant recurrence, no local recurrences.

PBMC subsets:

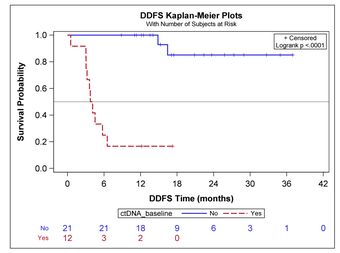
- 43 pts were evaluated for PBMC subsets. Changes in PBMC subsets at 6 wks were different amongst the arms:
  - Arm A: reductions in NK subsets, including a 33% reduction in CD56dimCD16- cells
  - Arm B: increases in naïve CD4+ (+45%) and CD73+CD8+ T cells (+12%) and reductions in ki67+CD8+ T cells (-48%)
  - Arm C: increases in conventional dendritic cells (+36%), effector memory ki67+CD4+ T cells (+46%), and CD56dimCD16- NK cells (+29%).

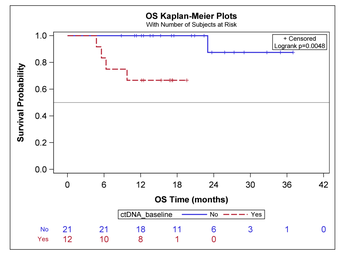
MRD analysis:

- To date 33 pts have completed successful MRD analysis. 12 of the 14 pts who experienced distant recurrence had completed baseline ctDNA.
- 12/33 (36%) pts were MRD+ at baseline. 3/12 pts MRD+ at baseline subsequently cleared MRD, with undetectable ctDNA on future time points; only one of these patient has experience recurrence to date. The remaining 9/12 MRD+ pts (75%) that didn't clear MRD have experienced distant recurrence.
- 21/33 (64%) pts were ctDNA negative at baseline; 20/33 remained negative for all follow up timepoints. 10/12 pts who completed baseline ctDNA and experienced distant recurrence were MRD+ at baseline and 1/12 became MRD+ at wk 6 post tx initiation.
- At 17 mos of median follow-up, baseline MRD+ testing (range 0.0012% - 3.6% variant allele frequency (VAF)) was significantly associated with an inferior DDFS (p<0.0001 Log-rank test, median DDFS 4.0 mos vs. not reached) and OS (p=0.0048 Log-rank test, median OS not reached for both groups).

RESULTS

Kaplan-Meier DDFS and OS curves comparing patients with detected vs undetected baseline ctDNA





CONCLUSIONS

- Changes in PBMC subsets were associated with receipt of chemo and/or immunotherapy.
- Our results suggest that baseline MRD+ in pts without pCR is a poor prognostic factor. 25% of ctDNA levels detected at baseline were below 0.01% VAF indicating the need to use sensitive MRD testing platforms.
- Future trials aiming to optimize adjuvant tx with chemo and/or immunotherapy in residual TNBC should consider incorporating ctDNA as a selection marker of pts at higher risk of recurrence or assure that tx arms are balanced for ctDNA neg/pos pts.

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