129P - INTEGRATION OF GENE EXPRESSION AND TUMOR INFILTRATING LYMPHOCYTES (TILS) TO PREDICT PCR AFTER NEOADJUVANT CHEMOTHERAPY AND NIVOLUMAB FOR PATIENTS WITH LUMINAL B-LIKE BREAST CANCER IN THE PHASE II GIADA TRIAL.

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Background and aim

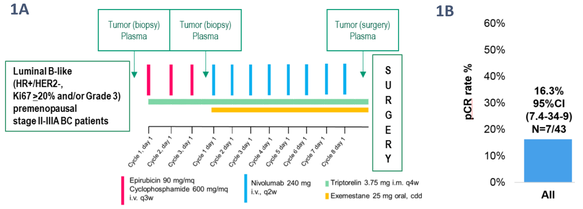
- HR+/HER2- BC is not considered highly immunogenic, thus the role of immunotherapy for this BC subtype is underexplored[1].
- However, this is a heterogeneous disease that may present with immunogenic features[1-4].

Here, we investigated the impact of PAM50 molecular subtypes, immune gene expression signatures and TILs on the pathological response to neoadjuvant chemotherapy followed by nivolumab for HR+/HER2- BC patients.

Methods

In the phase II GIADA trial, 43 premenopausal patients with stage II-IIIA Luminal B-like breast cancer received neoadjuvant anthracycline chemotherapy followed by nivolumab and endocrine therapy. The rate of pCR was 16.3%, not meeting the primary endpoint[5]. **Figure 1** shows study design (1A) and pCR results (1B).

Figure 1



For this analysis, PAM50 subtypes and gene expression signatures (by nCounter®, Breast Cancer 360® panel), as well as TILs were evaluated on the tumor sample collected by core-biopsy at baseline.

PAM50 subtypes and TILs were available for all 43 patients, gene expression signatures were evaluable for 40 patients.

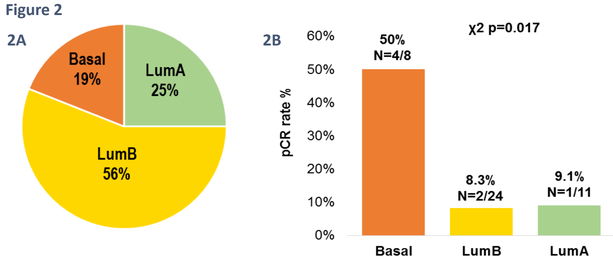
1. Dieci MV, et al. *Cancer Treat Rev* 2016;46:9–19; 2. Criscitiello C et al., *Breast Cancer Res Treat* 2020;183:347–354; 3. Luen S, et al. *Breast* 2016;29:241–250; 4. Anurag M, et al. *J Natl Cancer Inst* 2020;112:737–746; 5. Dieci MV, et al. ESMO 2020.

Results

1. PAM50 intrinsic subtypes

The distribution of PASM50 subtypes is shown in **Figure 2A**. pCR rate was significantly higher for Basal-like tumors as compared to other subtypes (**Figure 2B**).

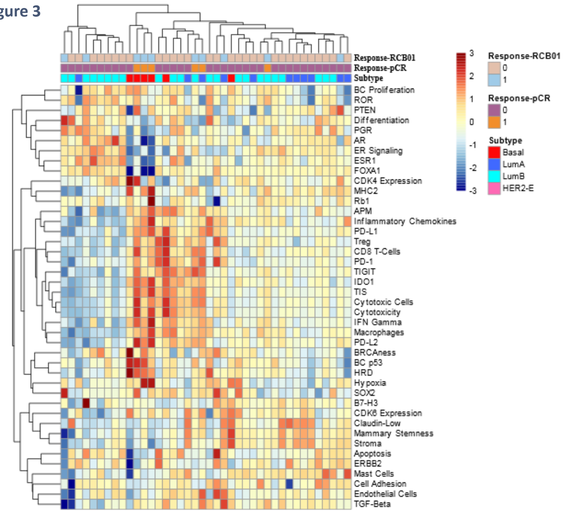
Figure 2



2. Gene expression signatures

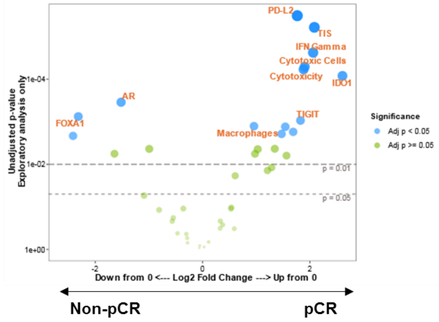
Figure 3 shows a heatmap of gene expression data by unsupervised hierarchical clustering. Signatures are displayed in rows; each column is a unique sample.

Figure 3



As shown in the Volcano plot of **Figure 4**, several inflammatory response and immune gene signatures were significantly overexpressed in pCR as compared to non-pCR patients: CD8 T-cells, cytotoxic cells, cytotoxicity, IFN gamma, inflammatory chemokines, macrophages, PD-L1, PD-L2, IDO-1, TIGIT and tumor inflammation signature.

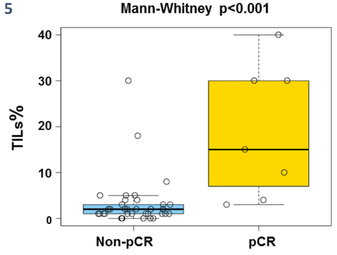
Figure 4



3. TILs

The median level of TILs in samples from patients achieving a pCR (15%; Q1:Q3, 4%:30%) was significantly higher as compared to non-pCR patients (2%; Q1:Q3, 1%:3%, p<0.001, **Figure 5**).

Figure 5



4. Correlation between PAM50 subtypes and immune markers

There was a weak to moderate positive correlation of Basal subtype signature with TILs and immune signatures associated with pCR (Pearson's coefficients ranging from 0.319 to 0.606), suggesting a partial biological overlap only. Therefore, we investigated how to integrate PAM50 subtypes with immune markers (TILs) in a combined score.

5. Integration of PAM50 and TILs

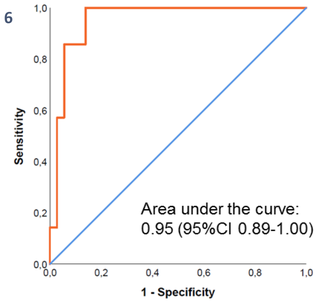
In bivariate logistic regression analysis TILs and Basal subtype were associated with pCR (**Table 1**).

Table 1	OR (95%CI)	P
TILs (1% increment)	1.16 (1.04-1.31)	0.001
Basal vs non-Basal	10.71(1.01-113.07)	0.049

A combined score was calculated from the estimated coefficient of each variable in the bivariate model: *TILs(%) x 0.15 + Basal (0=no, 1=yes) x 2.37.*

Figure 6 shows the ROC curve describing the performance of the combined Basal subtype and TILs score to predict pCR.

Figure 6



Conclusions

- Molecular subtype and immunity contribute to determining the sensitivity of Luminal B-like tumors to neoadjuvant sequential chemotherapy and anti-PD-1.
- Integrated assessment of these biomarkers should be incorporated in clinical trials of combined immuno-chemotherapy for Luminal-like BC patients.

Conflicts of interest (MVD): personal fees from EliLilly, Exact Sciences, Novartis, Pfizer, Seagen for advisory/consultancy role.
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