Immune response following neoadjuvant ribociclib plus letrozole vs. chemotherapy in Luminal B early breast cancer: a correlative analysis of the SOLTI-1402/CORALLEEN phase 2 randomized trial

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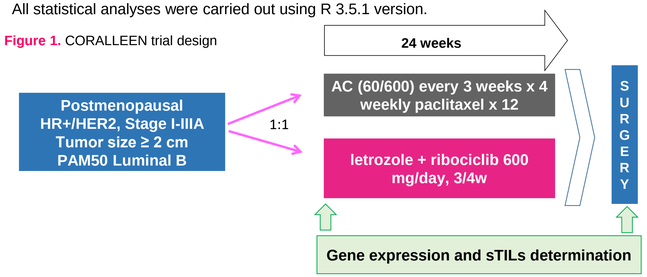
BACKGROUND AND OBJECTIVES

- The PAM50 Luminal B subtype represents ~30-40% of all Hormone Receptor positive (HR+)/HER2-negative (HER2-) early breast cancer (eBC)[1].
- In HR+/HER2- eBC, high tumor infiltrating lymphocytes (TILs) levels predict higher pathological complete response (pCR) rates to neoadjuvant chemotherapy (CHT), but are associated with shorter overall survival[2].
- CDK4/6 inhibitors increase tumor immunogenicity in preclinical models of BC[3]. Despite this, little is known regarding distribution of TILs levels and immune gene expression and response data in tumor samples from patients (pts) treated with CDK4/6 inhibitors.
- In this study, we explored the immune response in patients treated with ribociclib plus letrozole (R+L) versus CHT in PAM50 Luminal B eBC (Gavilá et al. SABCS 2019; Abstract #1037)

PATIENTS AND METHODS

- Formalin-fixed Paraffin-embedded (FFPE) tumor samples from the CORALLEEN trial (**Figure 1**) were obtained at screening (SCR) and surgery (SUR).
- Stromal tumor infiltrating lymphocyte (sTILs) levels were assessed in the hematoxylin/eosin (H/E) samples[4].
- Expression of 770 genes and 31 biological signatures were determined using the Breast360™ nCounter-based assay (Nanostring Techonologies, Seattle, USA).
- Differences in sTILs were determined by ANOVA tests. Interaction tests between each variable and tumor ROR response (i.e. relative decrease in ROR score) according to type of therapy were explored using logistic regression models.
- Low and high responders were defined as <50% and ≥50% relative decrease in ROR score.
- All statistical analyses were carried out using R 3.5.1 version.

Figure 1. CORALLEEN trial design



RESULTS

Table 1. Patients baseline characteristics

Characteristic, n (%)	CHT (n=54)	R+L (n=52)
Median age (range)	64 (49-79)	63 (50-78)
Tumor size (%)		
cT1	3 (5.5%)	3 (5.8%)
cT2	43 (79.6%)	40 (76.9%)
cT3	8 (14.8%)	9 (17.3%)
Axillary Nodes (%)		
cN0	31 (57.4%)	31 (59.6%)
cN1	22 (40.8%)	19 (36.6%)
cN2	1 (1.8%)	2 (3.8%)
Ki67 median (range)	35 (12-70)	30 (5-75)
Median ROR score (range)	77 (51-97)	70 (52-93)
ROR risk class (%)		
Intermediate	6 (11.1%)	8 (15.4%)
High	48 (88.9%)	44 (84.6%)

sTILs and immune genes at surgery based on treatment

Figure 2. sTILs at surgery in each arm based on ROR response (HighR and LowR). *p<0.05

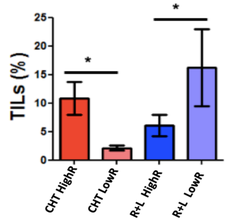


Figure 3. H/E images showing sTILs from SUR samples in CHT HighR (A); CHT LowR (B); R+L LowR (C) and R+L HighR (D).

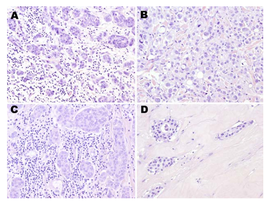
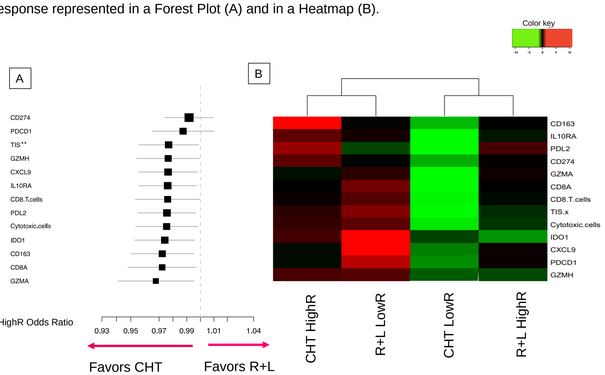


Table.3 Mean of sTILs between High and Low responders between two arms of treatment

	CHT arm (SUR n=46)	R+L arm (SUR n= 49)
Mean sTILs in HIGH response (n)	10.7% (29)	7.1% (41)
Mean sTILs in LOW response (n)	2.3% (17)	13.4% (8)

Figure 6. Interaction between arm of treatment (CHT vs R+L) and immune genes related with response represented in a Forest Plot (A) and in a Heatmap (B).



**TIS signature consists in genes related to Interferon gamma signaling, antigen presentation, natural killer and T cell inhibitory pathway.

sTILs and immune genes before and after therapy

- sTILs were not found to consistently increase at surgery in both arms of treatment (**Figure 4**)
- 27.1% (13/48) of pts in R+L arm had ≥10% of sTILs at SUR compared to 15.2% (7/46) in CHT arm.
- From the 27.1% of pts in R+L arm with ≥ 10% of sTILs at SUR, a 38.5% (5/13) had sTILs <10% at SCR.

Table 2. Median, Mean and interquartil range of sTILs in the 2 arms.

Characteristic	sTILs CHT (SCR n= 51) (SUR n= 46)	sTILs R+L (SCR n= 49) (SUR n= 48)
Median (range)		
SCR	5% (0-90)	5% (0-70)
SUR	5% (1-50)	5% (0-60)
Mean (range)		
SCR	6.6% (0-90)	12.6% (0-70)
SUR	7.4% (1-50)	8.2% (1-60)
Interquartil range		
SCR (Q1-Q3)	9 (1-10)	10.3 (1-11.3)
SUR (Q1-Q3)	4 (1-5)	9 (1-10)

Figure 4. sTILs changes in R+L arm and in CHT arm.

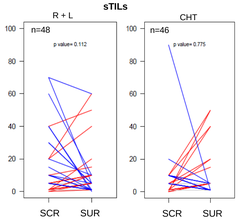
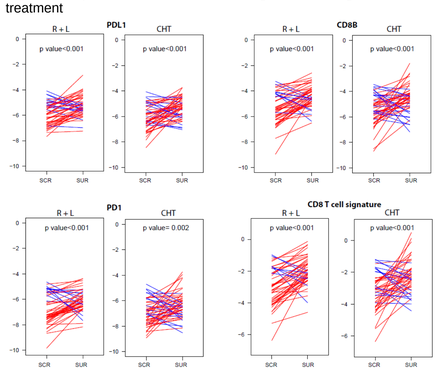


Figure 5. Expression of selected immune genes following R+L and CHT treatment



CONCLUSION

- An increase in sTILs following 24-weeks of R+L occurs in ~30% of pts with high-risk Luminal B tumors, regardless of tumor ROR response.
- The increase of immune gene expression after 24-weeks of CDK4/6 inhibition is related with poor ROR response.
- These findings suggest that immune checkpoint blockade might be an interesting strategy to explore following low ROR response after R+L.

Acknowledgements

We thank the patients and their families for participating in the study. We also thank Novartis for their provision of Ribociclib and their financial contribution to cover part of this clinical study. This study was founded, in part, by the Breast Cancer Research Foundation-AACR Career Development Award and Breast Cancer Now and the PhD4MD grant to N.C.

References

1. Cejalvo JM, et al; *CTR*, 2018
2. Denkert C, et al; *Lancet Oncol*, 2018
3. Schaer et al; *Cell Reports*, 2018
4. Salgado R, et al. Ann Oncol 2015