Introduction

- Invasive lobular carcinoma (ILC) is the second most common type of invasive breast cancer and accounts for 10-15% of all cases.
- Though ILC has distinct clinical, prognostic, and molecular features, studies specific to this subtype are limited and include smaller numbers of patients.
- ILCs show a decreased response to neoadjuvant chemotherapy and an increased resistance to endocrine therapy. Thus, there is a great need for alternative therapies, such as immunotherapy, that could improve overall survival.
- Success of immunotherapy largely depends on tumor immunogenicity which varies with histologic type. Determination of predictive and prognostic biomarkers for ILC will help determine who can benefit the most.

Tumor sites

- Our study investigates canonical markers of immunogenicity – PD-L1 expression and Tumor Mutational Burden (TMB) – in patients with ILC compared to invasive ductal carcinoma (IDC).
- We also analyze differences in immune cell profiles constituting the tumor microenvironment (TME) in ILC and IDC.
- Lastly, we investigated the genomic alterations associated with immunogenicity in ILC.

Methods

- A retrospective data analysis was performed on 868 tumor samples to identify breast cancer tumors with ILC or IDC histology profiled at Cancer Life Sciences.
- Upon review of the data and discussions with numerous breast clinicians, we decided to exclude triple negative breast cancers (TNBC) given the rarity of the association between TNBC and ILC.
- The VENTANA PD-L1 (SP142) assay was used to score PD-L1 expression on immune cells, and PD-L1 expression in tumor cells was assessed by laboratory-developed test using SP142 clone with staining higher than 2+ considered positive.
- TMB was measured by counting somatic non-synonymous missense mutations on the 502 gene panel (NextSeq) next generation sequencing (NGS) assay, and > 10 mutations/megabase (mut/Mb) was considered high.
- Using the whole transcribed RNA sequencing (NextSeq) data we analyzed the differences in immune cell profiles constituting the TME using a computational RNA deconvolution approach.
- Next generation sequencing (NGS) was used to identify significant differences in genomic alterations in the tumors.

Tumor receptor status

- PD-L1 expression is seen in both tumor and immune cells and is thought to contribute towards immune evasion. It is currently one of the only approved biomarkers used to predict response to immune checkpoint inhibition.
- PD-L1 expression in immune cells was lower in ILC when compared to IDC and this implies lower immunogenic nature of ILCs.
- PD-L1 score 1 was significantly higher in IDC, however there was no significant difference between the study groups where PD-L1 score > 10 was assessed. We assessed PD-L1 expression in tumor cells in a similar sample and this analysis showed lower PD-L1 expression in ILC tumor cells.

Figure 2. Immune cell profiling of ILC vs. IDC reveals ILC has significantly more M2 macrophages and fewer M1 macrophages suggestive of a more immunosuppressed TME.

Figure 3. PD-L1 expression is seen in both tumor and immune cells and is thought to contribute towards immune evasion. It is currently one of the only approved biomarkers used to predict response to immune checkpoint inhibition.

Summary

- PD-L1 expression in immune cells was lower in ILC, however ILC was associated with significantly higher TMB.
- Immune cell profiling supports a cold or less immunogenic TME for ILC.
- ILC with high TMB was associated with significantly higher genomic alterations, some of these could be potential biomarker to predict response to immune therapy. This needs further investigation in large studies.
- A composite immune biomarker may be able to better characterize immunogenicity of ILC.

References


Acknowledgements

Grant funding: USC department of Medicine, USC IURAP grant, Caris Life Sciences