1499 MOLECULAR AND IMMUNE PROFILING OF LOBULAR-ENRICHED VERSUS NON-LOBULAR INVASIVE BREAST CANCERS

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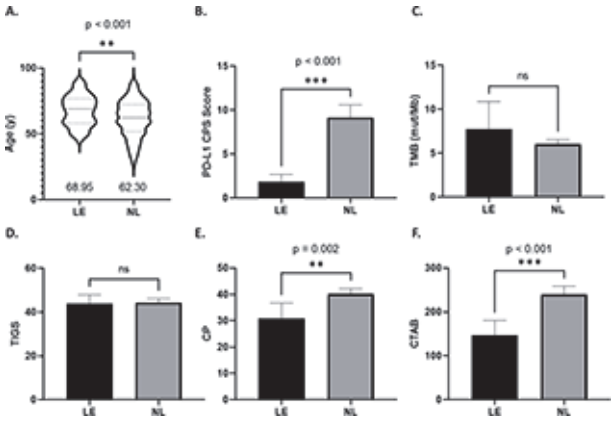
Background Invasive lobular carcinoma (ILC) is a morphologically distinct endocrine-sensitive sub-type of invasive breast cancer. Invasive ductal carcinoma has been extensively characterized, however, the genomic and immune characteristics of ILC are relatively understudied. It is known that the vast majority of ILCs harbor alterations in *CDH1*, the gene encoding E-cadherin, but a more thorough understanding of the genomic and immune profiles of lobular-type carcinomas may provide insight into the underlying molecular mechanisms of tumorigenesis, metastasis, and potential therapeutic strategies to counter resistance mechanisms.

Methods We performed comprehensive genomic and immune profiling on 528 invasive breast cancers using panel-based next-generation DNA (523 genes) and RNA sequencing (55 genes for fusions/splice site variants, 395 for immune gene expression). PD-L1 expression was assessed by combined positive score (CPS) following 22C3 immunohistochemistry. Diagnostic and molecular pathology reports were reviewed by a board-certified anatomic pathologist for all tumors that harbored mutations in *CDH1* or had a diagnosis of ILC from the test order to create a 'lobular-enriched' (LE) cohort, which was compared to other non-lobular (NL) breast carcinomas, which included *CDH1*-mutated tumors diagnosed as ductal-type carcinomas. For each tumor, we determined immune-related expression signatures, including a tumor immunogenicity score (TIGS, 161 genes), a cellular proliferation signature (CP, 10 genes including Ki-67), and a cancer testis antigen burden score (CTAB, 21 genes). Differences between cohorts were assessed using the Mann-Whitney test.

Results The LE cohort contained 52 tumors (including 30 ILCs, 20 mammary carcinomas not otherwise specified, and 2 mammary carcinomas with lobular features), and the non-lobular (NL) cohort contained 476 cases (including 14 cases of *CHD1*-mutated ductal carcinomas). Compared to NL tumors, LE tumors were sequenced at advanced age (68.95 vs. 62.30 y, $p<0.001$), less likely to harbor a *TP53* mutation (15.4% vs 54.2%, $p<0.001$) and had lower PD-L1 CPS ($p<0.001$). By RNAseq, LE tumors demonstrated significantly lower cellular proliferation ($p=0.002$), and lower CTAB ($p<0.001$) than NL tumors (figure 1). No differences were identified in TMB, TIGS, or proportion of *ESR1* alterations.

Conclusions Our study demonstrates that the LE cohort exhibited distinct molecular and immunologic features from other breast cancers, including a lower frequency of *TP53* alterations, lower PD-L1 expression, lower cellular proliferation, and lower expression of cancer testis antigens. Overall, these findings suggest striking differences in the cellular biology of ILCs but perhaps similar overall immune infiltration to other breast cancer subtypes, which may be important context to consider in future clinical studies.

Ethics Approval Ethics approval for this study was obtained from WCG IRB (Study #1340120), an independent institutional review board, including waiver of informed consent.



Abstract 1499 Figure 1 Demographics, genomic, and immune profiling results for lobular-enriched (LE) and and non-lobular (NL) breast cancer cohorts. The figures above illustrate comparisons fo (A) age (y). (B) PD-L1 CPS (score), (C) TMB (mut/Mb), and gene expression signatures for (D) tumor immunogeniciry (TIGS), (E) cellullar proliferation (CP), and (F) cancer testis antigen burden (CTAB)

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