TP53 status and licensing complex/IFNγ transcriptional profiles to stratify endocrine-related outcomes with CDK4/6i exposure in 10,833 real-world ER+/HER2- breast cancers and a treatment-naïve subset

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Background

Endocrine therapy (ET) durability for ER+/HER2- breast cancer (BC) with CDK4/6 inhibitor (CDK4/6i) exposure is vastly heterogeneous. We have shown that aberrant activation of CDK4/6-Rb axis is mechanistically linked to DNA replication origin licensing programs[1], and that IFNγ-mediated signaling is observed at onset of CDK4/6i resistance[2]. We also previously reported licensing complex (LC) mRNA to be predictive of survival in primary ER+/HER2- BCs[3]. Here, we assessed and extended these findings in a large, real-world cohort of primary and metastatic ET±CDK4/6i-treated tumors.

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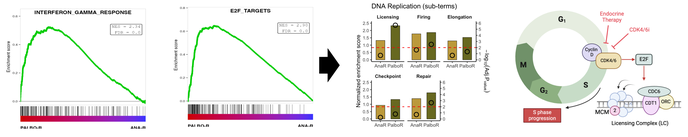
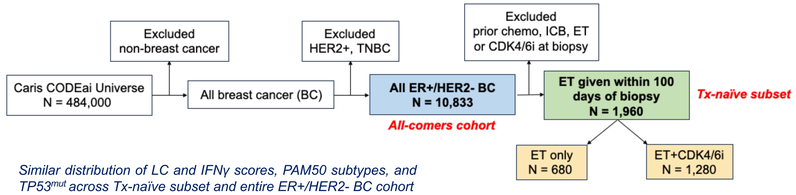


Methods

- Retrospective review of Caris Life Sciences NGS profiling of ER+/HER2- BCs
- Tumor stratification by LC- and IFNγ-score[4]: Q1 (low) mRNA≤25th percentile, Q4 (high) mRNA>75th percentile
- HRs and p-values for outcomes derived from log-rank test or uni-/multi-variate Cox-proportional hazard models, adjusting for clinicopathological variables
- Mutational analysis performed using Chi-squared test and FDR corrected q-values
- TME proportions estimated via quanTIseq deconvolution, PD-L1 measured by IHC (IHC-positive: ≥ 10+ CPS)



Similar distribution of LC and IFNγ scores, PAM50 subtypes, and TP53^{mut} across Tx-naïve subset and entire ER+/HER2- BC cohort

Acknowledgements

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Real-world validation confirms the LC and IFNγ-stimulated transcriptional state jointly stratify outcomes in the ET+CDK4/6i-treated setting, where low co-expression of these profiles is associated with longer therapeutic benefit

Though associated with TP53^{mut}, convergence of LC/IFNγ may hold potential predictive value in TP53^{WT} disease

Results

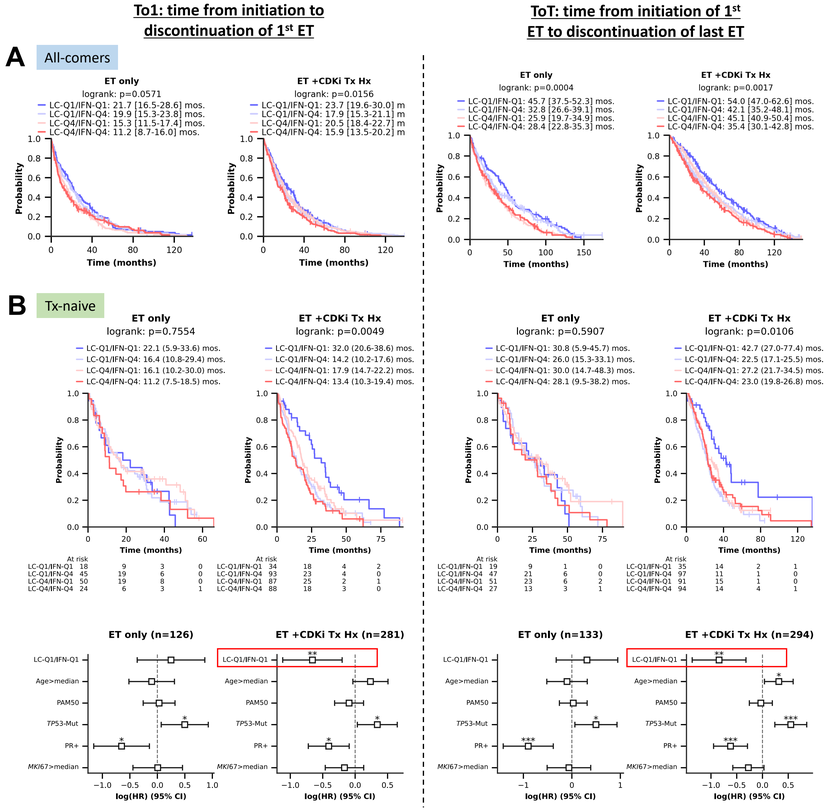

Fig 1. Low co-expression of LC and IFNγ profiles is independently associated with better therapeutic response in the CDK4/6i-treated setting. To1 (left) and ToT (right) analyses for tumors treated with ET or ET+CDK4/6i stratified by various LC/IFNγ quartiles. **(A)** Kaplan Meier (KM) curves for the all-comers cohort and **(B)** KM curves and multivariate regression analysis for the treatment-naïve subset. ** = *p<0.01*

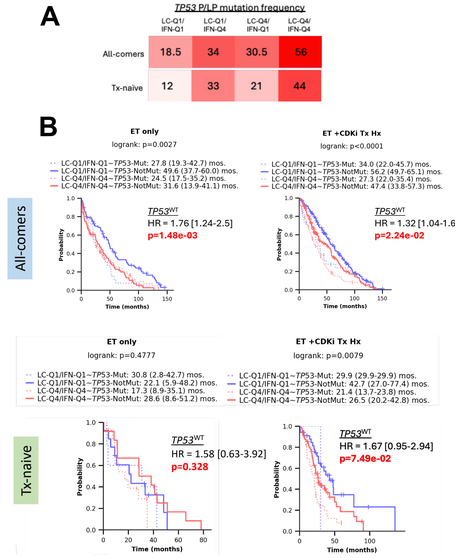

Fig 2. LC/IFNγ-high tumors are enriched for *TP53*^{mut}, though low co-expression stratifies ToT in the *TP53*^{WT} setting. (A) *TP53* variant frequency in various LC/IFN quartile strata ($p<0.05$). **(B)** ToT KM curves under different *TP53* genomic backgrounds with HR reported for *TP53*^{WT} LC-Q1/IFN-Q1 vs LC-Q4/IFN-Q4 tumors. In Tx-naïve, Q1/Q1 trends towards longer ToT in *TP53*^{WT} setting, without reaching significance at $p<0.05$.

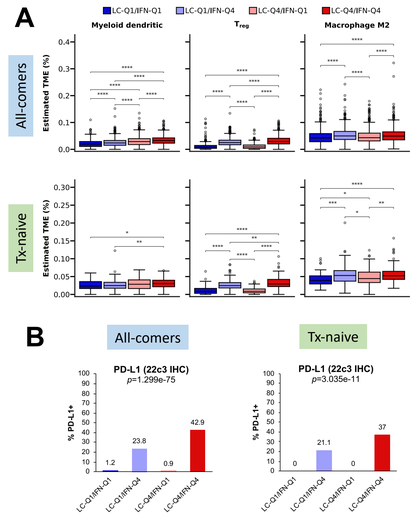

Fig 3. Tumors co-expressing high levels of IFNγ-stimulated and LC genes are associated with a more inflamed tumor immune microenvironment (TME) and tumor cell immune evasion. (A) TME myeloid dendritic, T_{reg}, and M2 macrophage cell proportions estimated via quanTIseq deconvolution and **(B)** PD-L1 22c3 IHC staining in different LC/IFNγ quantile strata. *p*-values calculated by Chi-square. **p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.*

Conclusions

Across both treatment-naïve and all-comer ER+/HER2- BC, only the LC-low/IFNγ-low subgroup, reflecting preserved CDK4/6-pathway dependence and a non-immunosuppressive TME, achieved durable benefit on ET+CDK4/6i, an advantage lost in *TP53*^{mut} disease. The composite *TP53*^{WT}/LC-low/IFNγ-low biomarker represents a candidate predictor of durable CDK4/6i response, pending prospective validation.