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Identification of blood immune biomarkers as surrogate measures of CDK4/6i treatment efficacy in ER+HER2- advanced breast cancer

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Introduction:

CDK4/6 inhibitors (CDK4/6i) have revolutionized the treatment and survival outcomes for estrogen receptor-positive (ER+) HER2-negative advanced breast cancer (ABC). However, resistance to CDK4/6i remains a challenge, and reliable biomarkers of response are needed. Mounting evidence suggests that antitumor immunity plays a critical role in determining CDK4/6i efficacy. In this study, we explore immune gene expression signatures and the expression of immune checkpoint molecules (CTLA-4 and PD-1) on circulating T cells as potential predictors of CDK4/6i clinical efficacy.

Methods:

We enrolled a cohort of 100 (ER+) HER2-negative ABC patients initiating CDK4/6i treatment since 2018. Clinical and biological data were collected, and treatment response was monitored longitudinally. Blood samples were obtained before treatment initiation and every 3 months for up to 2 years or until disease progression. Tumor gene expression was assessed using the BC360™ panel (NanoString) in formalin-fixed paraffin-embedded biopsies. Immune function was evaluated by flow cytometry-based immunophenotypic characterization of circulating immune cells. Survival analysis was performed using Kaplan-Meier and Cox regression models.

Results:

The study cohort included a heterogeneous population of ABC patients, including 60% first line treatment with CDK4/6i + hormonal therapy, >40% with visceral disease and achieving a median progression-free survival (PFS) of 14 months (m).

To identify factors determining CDK4/6i efficacy, gene expression profiles were evaluated in tumor biopsies. Multivariate Cox regression analysis revealed five RNA expression signatures, that independently correlated with significant longer PFS. Notably, four of the signatures were immune-related, including high expression of IFN-gamma (12.7m vs. NR, p=0.001), tumor infiltration signature (TIS) (14m vs. NR, p=0.03), and Treg signature (11.3m vs. 35.9m, p=0.03) in first-line treatment showed worse PFS. On the contrary, high expression of PD-1 was associated with prolonged PFS (NR vs. 15.9m; p=0.006), overall highlighting the influence of host immunity on CDK4/6i efficacy.

Then, the amount and function of circulating immune cells was characterized in basal blood samples, prior to treatment initiation. Although no significant differences in major immune cell subset were identified, patients with high expression of CTLA-4 and/or PD-1 on circulating CD4+ T cells exhibited significantly shorter PFS (8.1 m vs. 17.3 m, p=0.001 and 8.6 m vs. 14 m, p=0.02, respectively). These findings open the door to the use of blood immune biomarkers as surrogate measures of treatment efficacy and emphasize the pivotal role of immune dysfunction in determining CDK4/6i efficacy.

Conclusion:

Our study demonstrates that dysregulated immune function within the tumor and peripheral immune system is

associated with limited CDK4/6i clinical efficacy. Albeit our results suggest that peripheral blood may be used to monitor treatment efficacy, its robustness and feasibility to clinical application must be further investigated. The use of immunotherapeutic or immunomodulatory agents in this setting are warranted to enhance the efficacy of CDK4/6i in ABC patients.