Molecular plasticity of luminal breast cancer and response to CDK 4/6 inhibition – the biomarker program of the PENELOPE-B trial investigating post-neoadjuvant Palbociclib

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Molecular plasticity of breast cancer can contribute to the development of therapy-resistant disease. In this investigation, we aimed to identify genes in molecular signatures between pretherapy (pre-Tx) and post-therapy (post-NACT) tumor samples from patients included in the PENELOPE-B (NCT01864746) trial (Figure 1). The comparison of PENELOPE-B patients was randomized to palbociclib versus placebo in addition to standard endocrine therapy. The PENELOPE-B study did not show a significant benefit from treatment with palbociclib in women with HR+/HER2- primary breast cancer without a pathological complete response after taxane-containing neoadjuvant chemotherapy (NACT) and at high-risk of relapse (CSG-ESG score 3 or ≥2 pT2N1). However, the first translational investigations showed that some patients with a luminal-B tumor at pretherapy showed on absolute intrinsic molecular subtype switching after NACT, had a numeric benefit from post-NACT palbociclib. We have therefore extended the analysis and included a cohort of pre-Tx and post-NACT samples.

Methods

We investigated gene expression in pre-Tx (n=540) tumor tissue samples using the 97-gene Oncology Biomarker Panel including 2549 genes (HTG Molecular Diagnostics Inc.), for the same patients the same panel on post-NACT residual tumor samples were available. Based on 91 genes of this panel, the AIMS subtype was calculated. In addition, we performed exploratory biomarker analyses to identify genes with prognostic and predictive relevance.

Results

AIMS subtypes were prognostic in pre-therapy biopsies (Figure 2A) and post-therapy tumors (Figure 2B). The prevalence of LumA in particular Lum-B vs LumC changes from pre-Tx 1.30 to post-NACT tumors (Figure 3). In the pre-Tx samples, 278 (51%) and 232 (43%) of tumors had LumA and LumC subtypes, respectively, as expected from this panel, the AIMS subtype was calculated. In addition, we performed exploratory biomarker analyses to identify genes with prognostic and predictive relevance.

Conclusions

Our findings show that the switch from high-risk molecular subtypes (in particular LumB) to low-risk subtypes (in particular LumA) is common in neoadjuvant therapy of luminal tumors. The adaptation of luminal high-risk tumors to chemotherapy-induced stress is crucial for the clinical outcome and the response to therapy. Molecular defined tumor subtypes might not be as stable as originally thought.

References


Table 1: Pre-therapeutic and post-therapeutic AIMS subtypes (LumBasal/HER2 vs LumA/Norm) are independent prognostic parameters for DFS

<table>
<thead>
<tr>
<th>Model</th>
<th>Pre-therapeutic</th>
<th>Post-therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>0.58 (0.25–1.33)</td>
<td>0.73 (0.36–1.46)</td>
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<tr>
<td>p-value</td>
<td>0.24</td>
<td>0.31</td>
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