Introduction

Trilaciclib (COSELÀ™, G1 Therapeutics, Inc.) is an intravenous cyclin-dependent kinase (CDK)4/6 inhibitor that transiently arrests CDK4/6-dependent human breast cancer cell cycle progression in vitro and in vivo, and prolongs overall survival (OS) when administered in combination with chemotherapy (Ref. 1, 2). The current research aimed to further investigate potential immune mechanisms of antitumor efficacy among patients receiving trilaciclib prior to GCb.

Study Design and Participants

Full details of the clinical trial design have been published previously (3, 4). Briefly, patients with mTNBC enrolled in the COSELÀ™ phase 2 trial (NCT03772254) were randomized 1:1 to receive trilaciclib 8 mg/kg or placebo orally for 1 cycle (C1D1) followed by 2 cycles (C3D1) of trilaciclib plus GCb (trilaciclib plus GCb; GCb-alone). Patients were stratified by cross-sectional PD-L1 expression of 60% or higher, T-cell/NK-cell abundance, and cross-sectional inflammation signature score compared with responders (Figure 5).

Methods

Tissue samples were collected according to the study protocol, with written informed consent. The primary end points were OS (primary endpoint) compared with GCb-alone (median 19.8 vs 12.6 months; P < 0.0001) (3, 4).

Results

CD8+ T-cell infiltration and related pathways were identified by Gene Set Enrichment Analysis (GSEA) software (5, 6) using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

Conclusions

The data suggest that administering trilaciclib prior to GCb may enhance antitumor efficacy by modulating the composition and response of immune cell subsets. Certain immune cell subsets, including the PD-L1+ T- and NK-cell population, may be selectively enriched by trilaciclib treatment and may be involved in the antitumor effects observed in this study.

References


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Table S1: Subgroup Analysis of OS According to PD-L1 Status

<table>
<thead>
<tr>
<th>PD-L1 Positive</th>
<th>PD-L1 Negative</th>
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<tbody>
<tr>
<td>GA (months)</td>
<td>26 (23–29)</td>
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<tr>
<td>OS (months)</td>
<td>23 (19–25)</td>
</tr>
<tr>
<td>Median OS</td>
<td>17 (15–19)</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.34 (0.2–0.6)</td>
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<tr>
<td>P Value</td>
<td>0.025</td>
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Figure 1. Changes to (A) CD4+ and (B) CD8+ T-cell function in peripheral blood over 2 cycles (C1D1 vs C3D1) for Trilaciclib Plus GCb Versus GCb Alone


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Figure 2. (A) Differential Gene Expression Analysis and (B) T-cell exhaustion in tumor samples from trilaciclib responders versus nonresponders


Figure 3. Changes to Immune Cell Populations in Peripheral Blood Over 2 Cycles (C1D1 vs C3D1) for Trilaciclib Plus GCb Versus GCb Alone


Figure 4. Changes to (A) CD4+ and (B) CD8+ T-cell function in peripheral blood over 2 cycles (C1D1 vs C3D1) for trilaciclib responders versus nonresponders


Figure 5. TIS in tumor samples from trilaciclib responders versus nonresponders according to PD-L1 status


Figure 6. Changes to (A) CD4+ and (B) CD8+ T-cell function in peripheral blood over 2 cycles (C1D1 vs C3D1) for trilaciclib responders versus nonresponders