Background Trilaciclib is an intravenous cyclin-dependent kinase 4/6 inhibitor approved to reduce the incidence of chemotherapy-induced myelosuppression in patients with extensive-stage small cell lung cancer (myeloprotection). In a randomized, open-label phase 2 trial in patients with metastatic triple-negative breast cancer (mTNBC), adding trilaciclib prior to gemcitabine/carboplatin (GCb) increased overall survival in both PD-L1–positive and –negative populations versus GCb alone.1 2 We investigated potential immune mechanisms of anti-tumor efficacy among patients who received trilaciclib plus GCb.

Methods Peripheral blood was collected prior to and on treatment for flow cytometric analysis, and total RNA isolated from diagnostic tumor biopsies for sequencing. Differential gene expression analysis between responders and non-responders was based on negative binomial distribution and related pathways identified by Kyoto Encyclopedia of Genes and Genomes pathway analysis. Tumor inflammation signatures and deconvolution-based approaches were used to assess the tumor immune microenvironment. PD-L1 expression was considered positive if ≥1% of the total tumor area contained PD-L1–labelled immune cells (Ventana SP142 assay). Patients were defined as responders (confirmed complete or partial response) or non-responders (stable or progressive disease) according to RECIST criteria.

Results Of 68 patients who received trilaciclib prior to GCb, tumor response status and RNA sequencing data were available for 51 patients, comprising 24 responders and 27 non-responders. Tumors from responders had 253 differentially expressed genes compared with non-responders. Analysis of immune gene signatures revealed a higher T-cell exhaustion score at baseline among responders versus non-responders (P=0.044). Among patients with PD-L1–positive tumors, responders had a greater peripheral immune response at baseline compared with non-responders, including more T cells (P=0.037; particularly memory CD8 T cells [P=0.042]), and a trend toward fewer myeloid-derived suppressor cells (MDSCs). Additionally, tumors from responders had more dendritic cells (P=0.044) and a trend toward enriched tumor inflammation signatures compared with non-responders. By contrast, among patients with PD-L1–negative tumors, responders had similar peripheral immune populations at baseline compared with PD-L1–negative non-responders, but fewer MDSCs (P=0.016), and a trend toward increased T-cell numbers after two cycles of trilaciclib plus GCb. Responders with both PD-L1–positive and –negative tumors had increased numbers of naïve CD8 T cells after two treatment cycles compared with non-responders.

Conclusions The data suggest that adding trilaciclib prior to GCb enhances antitumor efficacy by modulating the composition of immune cell subsets. The impact of trilaciclib on changes to the tumor-infiltrating immune response is being further investigated in a phase 3 trial in patients with mTNBC (NCT04799249).

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Trial Registration www.clinicaltrial.govNCT02978716

REFERENCES

Ethics Approval The study protocol and all associated amendments and study-related materials were approved by the institutional review board or independent ethics committee of each investigational site.

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