First-in-human neoadjuvant study of the immunogenomic impact of the oral IDO inhibitor epacadostat on the tumor microenvironment of ovarian cancer

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1. Abstract

Background: The tryptophan catabolizing enzyme indole-amine 2,3 dioxygenase 1 (IDO1) has been identified as a pivotal immunosuppressive mechanism that fundamentally alters the immune tumor microenvironment (TME) and effect T cell function in ovarian cancer. Epacadostat is a novel oral IDO1 inhibitor that suppresses the immunosuppressive system by blocking IDO1 and is currently being evaluated in ongoing clinical trials. Although the pharmacodynamics (PD) effects of epacadostat in reducing tryptophan concentration in plasma has been demonstrated, it is currently unknown whether the PD effects will occur at the TME and alter it to become more immunogenic.

Methods: Seventeen patients with newly diagnosed stage III or IV ovarian cancer underwent pre-treatment tumor biopsy and post-treatment tumor specimens, indicative of reactivation of IFN signaling in the TME. Likewise, a tryptophan catabolism pathway map generated using patient samples identified as a potent immunosuppressive mechanism that fundamentally alters the ovarian tumor microenvironment (TME) and effect T cell function in ovarian cancer. Epacadostat is a novel oral IDO1 inhibitor that suppresses the immunosuppressive system by blocking IDO1 and is currently being evaluated in ongoing clinical trials. Although the pharmacodynamics (PD) effects of epacadostat in reducing tryptophan concentration in plasma has been demonstrated, it is currently unknown whether the PD effects will occur at the TME and alter it to become more immunogenic.

Results: Expression profiling identified an upregulated IFN signaling in a subset of metastatic tumor specimens, indicative of reactivation of IFN signaling in the TME. Likewise, in increase in CD8 T cells was detected in some, but not all subjects. Of note, IFN signaling and catabolism in CD8 T cell frequency was not consistently observed in all subjects. Evidence of reduced IDO1 enzyme activity (Kyn:Trp ratio) was observed not only in plasma but also in ascites fluid for a subset of patients (5 of 7 evaluable patients). Although IDO1 activity was blocked, IDO1 expression within the TME was not altered. Mitochondrial spare respiratory capacity of T cells in peripheral blood increased in 8 of 12 patients after treatment. Additional immunogenomic analyses identified molecular and metabolic pathways impacted by epacadostat.

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2. Study design and biospecimen collection schedule

3. Patient characteristics and reported adverse events

4. CD8+ TIL and tumoral IDO1 expression track with Kyn:Trp ratio

5. Humoral response to cancer-testis and overexpressed antigens

6. Metabolic attributes of T cells following IDO1 inhibition

7. Unique differential gene signature based on Kyn : Trp ratio

8. Translational significance and steps to the clinic

• First demonstration of the effect on tumor tissue inhibition of IDO1 enzyme activity
• Alteration of the Kyn : Trp ratio in the TME by epacadostat induces a unique gene signature
• This study identifies novel prognostic features of IDO1 in ovarian cancer highlighting the importance of evaluating this pathway in regulating anti-tumor immune responses

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