INTEGRIN αvβ8 INHIBITOR IMPROVES IMMUNE CHECKPOINT THERAPY IN ADVANCED OVARIAN CANCER MODEL AND ITS ACTIVITY CAN BE MONITORED IN BLOOD

Background Ovarian cancer (OC) is the most lethal gynecologic malignancy. Despite the initial high response rate to chemotherapy, most patients relapse. Immunotherapy offers potential for long-term remission but single checkpoint inhibition benefits less than 15% of patients. Growing evidence suggests that immune-checkpoint blockade (ICB) is enhanced when combined with therapies that target tumor tolerance. Transforming growth factor beta (TGF-β) is associated with resistance to immunotherapy and tumor tolerance. Integrin αvβ8 controls cell-type-specific activation of TGF-β and αvβ8 antagonism promotes anti-tumor immunity leading to tumor regression in ICB refractory tumors.1,2 We explored the impact of αvβ8 inhibition to restore ICB response in a murine ovarian carcinoma model and performed blood cytokine profiling to search for pharmacodynamic markers of response to treatment.

Methods Bioinformatic analysis on bulk and single-cell levels of public OC datasets was performed to evaluate ITGB8 and TGF-β-related gene signatures. qPCR was used for the detection of TGF-β and ITGB8 expression in ID8, a murine ovarian carcinoma model (ID8-Luc-mCh-Puro.TD1). ID8 tumors unresponsive to PD-1/L1 inhibition were established to mimic advanced-stage disease. The efficacy of αvβ8 mAbs in combination with PD-L1 blockade was evaluated. Mice were evaluated for survival for 65 days. Blood samples were harvested before treatment and on days 1, 8, and 14. Plasma was analyzed via Luminex for a total of 30 cytokines. Transcriptomic analyses of MC38 and EMT6 mouse tumors were performed by bulk RNA seq.

Results In high-grade serous OC, ITGB8 expression is associated with shorter overall survival and increased gene signatures of TGF-β1/3 pathways. The ID8 murine ovarian carcinoma model is unresponsive to PD-1/L1 inhibition and expresses Iggb8 together with TGF-β 1/3. The combination of αvβ8 and PD-L1 mAbs led to complete tumor regression in 9/10 mice relative to 0/10 in the PD-L1 group, resulting in superior survival (P=0.0001) (Fig 1 A, B). The combination therapy led to upregulation of blood granzyme B (P=0.05), IL-27 (P=0.03), and IL-1α (P=0.008) at 14-day post-treatment and transient upregulation of CCL3 (P<0.0001) and CCL7 (P=0.0005) at 8-day post-treatment. Cross-analysis of tumor tissues from the colon and breast syngeneic models after treatment showed similar transcript upregulation for cytokines.

Conclusions Inhibition of αvβ8 renders advanced ID8 tumors sensitive to immune checkpoint therapy, leading to tumor eradication and superior survival. These data provide evidence that a treatment modality targeting αvβ8-mediated TGF-β 1/3 pathways may enhance patients’ sensitivity to checkpoint therapies. Plasma blood-based biomarkers serve as a non-invasive method for response assessment to αvβ8-based therapy.

REFERENCES

Abstract 834 Figure 1 Efficacy of αvβ8 inhibitor (mAb clone C6D4) combined with PD-L1 (clone 10F.9G2) against an advanced syngeneic model of ovarian carcinoma, ID8. (A) The combination of αvβ8 mAb (7 mg/kg three times weekly for 3 weeks) and PD-L1 mAb (10 mg/kg twice weekly for 2 weeks) was efficacious in the checkpoint-resistant ID8 model and resulted in superior tumor regression. Shown are spaghetti plots for each individual mouse in each treatment group. Tumor burden measurements performed weekly by bioluminescence imaging (BLI). (B) Kaplan-Meier curves presenting time to progression. αvβ8 and PD-L1 mAb markedly improved survival over monotherapy with either αvβ8 or PD1 mAb. Statistics by log-rank test. CR-complete responders