595 INHIBITION OF INTEGRIN αVβ8 IN COMBINATION WITH LOW DOSE RADIATION INDUCES ANTITUMOR EFFECT IN ADVANCED IMMUNE CHECKPOINT BLOCKADE REFRACTORY TUMOR MODEL

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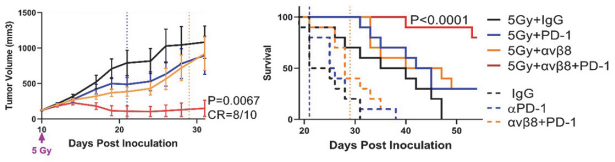
Background Integrin αvβ8 activates TGFβ in immune cells. αvβ8 inhibitors have been shown to potentiate immune checkpoint blockade (ICB) in preclinical models [1]. Radioimmunotherapy (RIT) induces immunogenic cell death and antigen presentation, however it concurrently activates immunosuppressive pathways. Interestingly, αvβ8 immunosuppressive activity was implicated in radiotherapy resistance [2]. We have explored whether antagonizing αvβ8 overcomes the suppressive effect of TGFβ and restores anti-tumor immunity in advanced ICB and RIT resistant tumors.

Methods Efficacy was evaluated after combination treatment with low dose radiation, αvβ8 (clone C6D4) and PD-1 (clone J43) mAb in an advanced CT26 colon cancer syngeneic mouse model. Mice were treated at tumor volume of >120 mm3 and euthanized at 2,000 mm3. Flow cytometry and transcriptomic analysis were used to assess the mechanism of action. Tumor volumes are presented as mean±SEM. Statistics were performed by one-way ANOVA, or log-rank test. Bone marrow derived dendritic cell (BMdDC) cultures were isolated from C57BL/6 mice.

Results Cell death, including radiation-induced apoptosis, induced immunoregulatory and maturation program in a population of ex vivo cultured BMdDC, recently described as mregDC/DC3 [3,4]. mregDC/DC3 signature was associated with increased αvβ8 expression, suggesting a role of this integrin in inducing an immunosuppressive phenotype.A CT26 model was established to mimic the progression of late-stage tumors and was unresponsive to radiation, ICB and RIT. In CT26 implanted mice, αvβ8 is expressed on tumor stoma, and is not detectable on cancer cells. Addition of αvβ8 mAb to RIT markedly increased tumor regression (P=0.0067) and survival (P<0.0001). There were 8/10 complete responders with addition of αvβ8 mAb relative to 3/10 in RIT alone. Improved efficacy correlated with enhanced T cell activation and improved DC functionality. Consistent with a recent report in a less advanced CT26 model [5], αvβ8 mAb + radiation resulted in similar efficacy as conventional RIT although the effect was modest in more advanced tumors (Figure 1, A, B).

Conclusions Inhibition of αvβ8 in combination with RIT eradicated an advanced tumor, unresponsive to the respective monotherapies or conventional RIT. The anti-tumor effect was driven by enhancement of adaptive immunity, improvement of DC function and reduced tumor tolerance. These data provide evidence that αvβ8 inhibition enhances RIT and may be effective against ICB refractory tumors.



Abstract 595 Figure 1 Complete response (CR) with improved survival when αvβ8 inhibition is added to RIT in CT26 syngeneic model of colorectal cancer in an advanced, ICB and RIT unresponsive stage. (A) Effect of combination therapy with low dose radiation (small animal radiation research platform (SARRP) at 5 Gray (Gy) on the day of staging (day 10)), PD-1 mAb (10 mg/kg twice weekly for 2 weeks) and αvβ8 mAb (7 mg/kg three times weekly for 3 weeks) measured by tumor burden. 5Gy+PD-1 and 5Gy+αvβ8 has a minimal effect on tumor growth inhibition showing slight improvement relative to radiation alone (5Gy+IgG). Addition of αvβ8 antagonism (5Gy+αvβ8 +PD-1) improves anti-tumor responses leading to CR in 8 of 10 mice. (B) Kaplan-Meier Curve presenting time to progression. 5Gy+IgG improved survival over monotherapy with either αvβ8 or PD1 mAb. 5Gy+αvβ8+PD-1 resulted in a profound improvement of the survival over all other treatment conditions

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Ethics Approval All animal work was approved by the site Institutional Animal Care and Use Committee and was performed in conformance with the Guide for the Care and Use of Laboratory Animals within an AAALAC-accredited program. Humane euthanasia criteria were predetermined on the basis of body weight and defined clinical observations.

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