SITC Annual Meeting 2020

Validation of the Combinatorial Effect of Blinatumomab and Nivolumab in Cancer Therapy

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Abstract ID: 781

Background

Cancer immunotherapies, including immune checkpoint inhibitors, CAR-T, cancer vaccines and bispecific antibodies, have been brought to spot light in recent years as several therapeutic strategies targeting the immune system have produced exciting clinical results. Bispecific antibody typically play dual roles in blocking the immune checkpoint and redirecting/re-boosting the function of the immune effector cells. Blinatumomab belongs to CD3 bispecific T cell engager (CD3 BiTE), which was engineered to harbor two arms binding with CD3 and CD19 simultaneously and direct CD8+ T cells to specifically recognize CD19 positive lymphoma cells to execute cytotoxicity. Approval of Blinatumomab for patients with relapse/refractory B cell acute lymphoblastic leukemia (ALL) has driven remarkable increase in combination studies of Blinatumomab with other immunotherapies such as checkpoint inhibitors.

In this study, we developed CD8+ T cytotoxic system targeting different B lymphoma cell line and fully validated the function of Blinatumomab in promoting target tumor cell lysis by primary CD8+ T cells. In addition, we established a mixed lymphocyte and tumor system to mimic physiological TME to dissect the combinational role of Nivolumab and Blinatumomab

Methods

CD8+ T Cytotoxicity Assay

CD8+ T cell isolated from PBMC using negative selection kit. Target cancer cell (Raji, Daudi) was labeled with CellTrace™ Violet and then co-culture with CD8+ T for 3 days

CD8+ T cell was analyzed of proliferation, CD25 and PD1 expression by FACS.

Cancer cell was analyzed of lysis ratio

Supernatant was analyzed for IFNr

PBMC Cancer MLR:

PBMC was labeled with CellTrace™ Violet

PBMC and Raji was co-cultured in the Ratio of 10:1 (PBMC: Raji) for 48 hours

T cell was analyzed by flow and supernatant was analyzed for IFNr by ELISA

Results

CD8+ T cell co-culture with Raji cell in the presence of Blincyto. Blincyto can promote T cell activation by increase CD25 expression and promote T cell proliferation. In addition, Blincyto promote Raji cell lysis in a dose dependent manner.

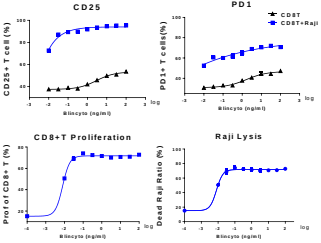
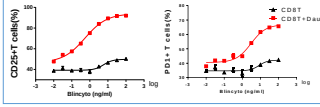


Figure 1 Blincyto mediate T cell activation and target cell lysis in CD8+ T and Raji co-culture system

CD8+ T cell co-culture with Daudi cell in the presence of Blincyto. Blincyto can promote T cell activation by increase CD25 expression and promote T cell proliferation. In addition, Blincyto promote Daudi cell lysis in a dose dependent manner.



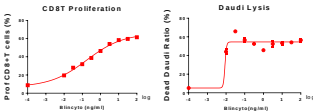


Figure 2 Blincyto mediate T cell activation and target cell lysis in CD8+ T and Daudi co-culture system

Co-culture of PBMC and Raji cell line in the presence of Blincyto and Opdivo at the Ratio of 10:1 (PBMC: Raji) for 48 hours. Opdivo can further promote T cell proliferation and function under the treatment of Blincyto and the assay window is highly depend on dosage of Blincyto.

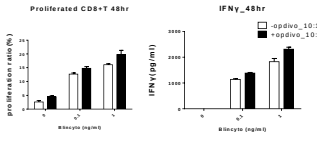


Figure 3 Opdivo further promote CD8+ T cell proliferation and activation in the context of Blincyto treatment.

2M Raji mixed with 3M hPBMC, co-inoculated into right flank of 6-8wks female NOG mice. Dosing was started when average tumor size reached to approx. 50mm3.

Blincyto significantly inhibit tumor growth compare to Opdivo only group. Tumor from Blincyto and Opdivo combo group share the similar growth curve with Blincyto only group. But at early time window, tumor from combo group display slower growth dynamic.

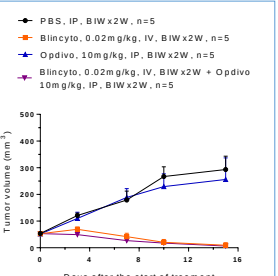


Figure 4 Effect of Blincyto and combination with opdivo in Raji humanized mouse model.

Summary

- Blincyto significantly promote T cell activation and increase cancer cell lysis in the in-vitro human PBMC model
- The effect of Opdivo under treatment of Blincyto is highly depend on the concentration of Blincyto and also related to PBMC/Raji ratio, suggesting combinatory treatment of opdivo with Blincyto should take the consideration of Blincyto dosage and also the tumor micro-environment of patients. With more Macrophage/DC infiltration, more chance of get synergistic effect.

Reference

Judith Feucht, et al. T-cell responses against CD19+ pediatric acute lymphoblastic leukemia mediated by bispecific T-cell engager (BiTE) are regulated contrarily by PD-L1 and CD80/CD86 on leukemic blasts. Oncotarget. 2016 Nov 22; 7(47): 76902–76919.