Translational assessment of triple combination with Tislelizumab (anti-PD-1), LBL-007 (anti-LAG-3) and Surzebicilimab (anti-TIM-3) highlights its strong anti-tumor activity and clinical potential in solid tumors such as HNSCC

Hengrui Zhu, Jinhui Zhang, Han Yan, Xiaodong, Juan Yang, Yu Jiang, Minjuan Deng, Haoxuan Song, Fangfang Ping, Fuyun Sun, Xiaoyu Li, Lijie Zhang, Bin Jiang, Weiwei Song, Zhirong Shen, Wei Jin, Jiayuan Zhang, Yun Zhang

Authors’ Affiliations: Translational Discovery, Research and Medicine, BeiGene (Beijing) Co., Ltd, Beijing, China.

Background: Therapeutics targeting PD-(L)1 have demonstrated impressive clinical activity in several type of cancers. However, only a small proportion of patients develop long-term response and resistance frequently occurs. LAG-3 and TIM-3 are inhibitory immune checkpoints frequently upregulated and co-expressed with PD-1 on tumor-infiltrating T cells, contributing to T cell dysfunction. Thus, we hypothesized that simultaneously targeting PD-1/LAG-3/TIM-3 would further restore T cell response and the triple combination of Tislelizumab (Tisle, anti-PD-1), LBL-007 (anti-LAG-3) and Surzebiclimab (Surze, anti-TIM-3) would provide greater clinical benefit.

Methods: To evaluate the rationale and the anti-tumor activity of triple combination, LAG-3 and TIM-3 expression were analyzed in in vitro T cells, syngeneic mouse models and cancer patients with anti-PD-(L)1 therapy. The effects of dual blockade of PD-1/LAG-3, PD-1/TIM-3 and the triple blockade of PD-1/LAG-3/TIM-3 on T cell function were evaluated in in vitro activated PBMCs and the anti-tumor efficacy were evaluated in syngeneic mouse models. Relevant gene expression and immune signatures were ranked across 31 solid tumor types in TCGA.

Results: Both LAG-3 and TIM-3 expression on T cells were upregulated by anti-PD-1 treatment in syngeneic mouse tumors, similar trend was observed in cancer patients with anti-PD-(L)1 therapy. Dual combination of Tisle/LBL-007 or Tisle/Surze enhanced IFNγ production in in vitro activated human T cells. The dual blockade of PD-1/LAG-3 or PD-1/TIM-3 significantly enhanced tumor growth inhibition compared with anti-PD-1 monotherapy in syngeneic mouse models. The triple combination of Tisle/LBL-007/Surze further enhanced IFNγ production in in vitro activated T cells. In a mouse MC38 colon carcinoma model, the triple blockade of PD-1/LAG-3/TIM-3 demonstrated enhanced anti-tumor activity compared with either dual combination, evidenced by trend of increased tumor growth inhibition and higher tumor-free incidence rate. Finally, the responsiveness of PD-1/LAG-3/TIM-3 triple combination was predicted using 5 signatures, including early effector T cell signature, inflamed signature, LAG-3, TIM-3 and PD-L1 expression. The in silico analyses indicated strong potential in clinical utility such as squamous cell carcinoma of the head and neck (HNSCC).

Conclusions: The concurrent blockade of PD-1/LAG-3/TIM-3 represents a promising strategy to enhance T cell function and anti-tumor activity. The results demonstrated the therapeutic potential of the triple combination. A Ph2 study evaluating Tisle in combination with LBL-007 and/or Surze in first-line treatment of recurrent or metastatic HNSCC (NCT05909904) is recruiting.