Abstract

The success of cancer immunotherapy is often limited by multiple mechanisms of tumor-induced immune suppression often as a result of suppressive myeloid cells. M2-like tumor associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), and tolerogenic dendritic cells (DC) constitute this immunosuppressive tumor microenvironment (TME) and have repeatedly been associated with poorer prognosis. Therapies designed to overcome this suppressive immune microenvironment could substantially enhance the efficacy of multiple immunotherapeutic approaches.

Imprime PGG (Imprime; BTH1677) is a yeast β1,3/1,6 glucan that has shown compelling efficacy in multiple phase II trials with tumor-targeting and antiangiogenic antibodies. As a Pathogen Associated Molecular Pattern (PAMP), Imprime activates myeloid cells (monocytes/macrophages, neutrophils, dendritic cells). Our previous in vivo human and in vivo mouse studies have shown that Imprime promotes repolarization of M2 macrophages to an anti-tumor, M1-like orientation and enhances DC maturation, driving T cell expansion and the production of interferon gamma (IFN-γ) that promotes activation of human MDSCs and repolarizes human monocyte-derived M2 macrophages to an M1-like phenotype.

Results

1. **Figure 1**: The general structure of Imprime PGG.

2. **Figure 2**: Imprime regoloralizes human monocyte-derived M2 macrophages to an M1-like phenotype.

3. **Figure 3**: Imprime promotes activation of human MDSCs.

4. **Figure 4**: Imprime + DC101 (anti-mouse VEGFR2 antibody) modulates the MDSC phenotype and function coinciding with enhanced anti-tumor efficacy in a H441 human NSCLC xenograft model.

5. **Figure 5**: H1299 Xenograft model of NSCLC utilizing combination Imprime + Bevacizumab (Bev) show M1 polarization of splenic MDSCs.

6. **Figure 6**: Imprime treatment results in a decrease in splenic M-MDSCs in the CT26 syngeneic mouse model of colon carcinoma.

Background

- Imprime is a soluble yeast-derived (β1,3/1,6) glucan immunomodulator (Figure 1) being developed in combination with anti-tumor antibodies.
- In a randomized phase II clinical study, stage IV NSCLC patients treated with Imprime plus the anti-VEGF antibody bevacizumab (bev), carboplatin and paclitaxel showed a median overall survival of 16.1 months versus 11.6 months in patients not receiving Imprime.
- Imprime, a pathogen associated molecular pattern (PAMP), forms an immune complex with endogenous α-glucan antibodies, then binds and primes innate immune cells including macrophages, monocytes, neutrophils and DCs. Activation of these innate cells is central to influencing adaptive immune responses (i.e., T cell responses). Generating functional and long-lived anti-tumor innate and adaptive immune responses is key to providing durable tumor control.

**OBJECTIVE**: To evaluate the ability of Imprime to modulate the immunosuppressive properties of immature myeloid cells-the myeloid derived suppressor cells (MDSCs).

Summary

- Imprime interacts with multiple human myeloid subsets in vitro including macrophages and MDSCs resulting in a more immunostimulatory phenotype and function.
- Imprime treatment in vivo can activate splenic MDSCs to orchestrate a profound shift in the immune microenvironment, which may be connected to tumor recognition and therapeutic efficacy.