Imprime PGG triggers PD-L1 expression on tumor and myeloid cells and prevents tumor establishment in combination with αPD-L1 treatment in vivo.

Kathryn Fraser, Anissa SH. Chan, Ross Fulton, Steven Leonardo, Adria Bykowski Jonas, Xiaohong Qiu, Nadine R. Ottoson, Takashi Kangas, Keith Gordon, Jeremy R. Graff, NANDita Bose, Biothera Pharmaceuticals, Inc., Eagan, MN, USA 55121; kfraser@biothera.com

Abstract

Immunologic checkpoint inhibitors, including α-PD-1/PD-L1 antibodies, have revolutionized cancer therapy, yielding compelling long-term clinical responses in cancers resistant to traditional treatment. Translational studies have reported that expression of PD-L1 on the surface of tumor or infiltrating immune cells correlates to greater objective responses. However, a large number of cancer patients are still refractory to treatment with checkpoint inhibitors, suggesting that the efficacy of anti-PD-1/PD-L1 immunotherapies may be improved by combination with agents that can boost other immune responses within the tumor microenvironment and induce PD-L1 expression. Imprime PGG (Imprime), a β-glucan PAMP (Pathogen Associated Molecular Pattern) is currently in clinical development in combination with tumor-targeting antibodies, anti-angiogenic antibodies and immune checkpoint inhibitors. As a PAMP, Imprime is readily recognized by, and binds to, innate immune cells, triggering a coordinated immune response that includes neutrophil activation, polarization of M2 macrophages and dendritic cell (DC) maturation. Co-culture of Imprime-treated M2s or DCs with T cells elicits increased PD-L1 expression on the surface of these myeloid cells, drives T cell expansion and induces interferon gamma (IFNγ) production. When exposed to the IFNγ-rich media from these co-cultures, tumor cell lines from numerous cancers (lung, breast, and pancreas) routinely upregulate surface expression of PD-L1. In vivo treatment of Imprime in tumor free mice also reprogrammed splenic macrophages to M1 functionality, and furthermore, could enhance the ability of antigen presenting cells to prime antigen-specific CD8+ T cells. These results suggest that Imprime has the potential to enhance the efficacy of checkpoint inhibitors. We therefore evaluated anti-tumor efficacy in the MC-38 syngeneic murine tumor model. Tumors were injected subcutaneously and three days later, mice were randomized to treatment groups. Tumors were evident at day 29 in 17/18 vehicle-treated mice, 16/18 Imprime-treated mice and 12/18 α-PD-L1 (10F.9D)-treated mice. Remarkably, though tumors grew initially, only 3/17 mice treated with α-PD-L1 + Imprime showed palpable tumors at day 29. To assess the durability of this response, these mice were re-challenged by injection of MC-38 tumor cells on the opposite flank. These mice remained tumor-free even after tumor rechallenge, whereas 16/18 vehicle-treated mice, 16/18 α-PD-L1 (10F.9D)-treated mice and 3/17 mice treated with α-PD-L1 + Imprime remained tumor-free even after tumor rechallenge. These results indicate that Imprime enhances anti-tumor efficacy in a syngeneic colon carcinoma model.

Background

• Imprime is a soluble yeast-derived (ß-1,3/1,6 glucan immunomodulator (Figure 1) being evaluated for cancer treatment in combination with anti-tumor antibodies.

• In a randomized phase ll 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 anti-ß-glucan antibodies, then binds primes innate and adaptive immune cells including macrophages, monocytes, neutrophils and DCs. Activation of the above innate cells is central to influencing adaptive immune 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 complement the effect of checkpoint inhibitors in in vivo syngeneic models of colon carcinoma.

Results

Figure 1: The general structure of yeast-derived Imprime PGG

Figure 2: Imprime triggers a coordinated immune response in human ex vivo studies.

Figure 3: Imprime enhances expression of PD-L1 on human M2 macrophages and MoDCs resulting in enhanced T cell proliferation

A. M2 Macrophages

B. Mo-DCs

Figure 4: Supernatant from Imprime-treated M2 macrophages or MoDCs and CD4 T cell co-cultures induce PD-L1 expression on human tumor cells

Figure 5: In vivo Imprime treatment activates splenic macrophages

Figure 6: Combination anti-PD-L1 plus Imprime dramatically enhances the efficacy of anti-PD-L1 treatment in mice

Summary

1. Imprime interacts with multiple human myeloid subsets in vitro including neutrophils, macrophages and MoDCs resulting in a more immunostimulatory phenotype and function.

2. Imprime treatment in vivo can activate myeloid cells within both the tumor and spleen to orchestrate a shift in the immune microenvironment which could promote tumor recognition and suppression.

3. Combination Imprime + anti-PD-L1 treatment in vivo dramatically increases the frequency of tumor-free mice (83% Imprime+anti-PD-L1 group versus 33% anti-PD-L1 group alone) in the MC38 tumor model.