Imprime PGG triggers a coordinated anti-cancer immune response in concert with anti-angiogenic antibodies, re-polarizing the immune microenvironment to suppress tumor growth

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Abstract

Imprime PGG (Imprime) is a soluble, yeast-derived β-1,3/1,6 glucan in clinical development for the treatment of cancer in combination with other anti-cancer therapies. Imprime acts as a Pathogenic Associated Molecular Pattern (PAMP) and can be recognized by cells of the innate immune system. Preclinical data using human whole blood from healthy volunteers show that Imprime binding to innate immune cells triggers a coordinated immune response that includes repolarization of M2 macrophages, activation of neutrophils and maturation of dendritic cells. This response ultimately leads to cross-talk with the adaptive immune system driving T cell expansion and the production of interferon gamma (IFNγ). In a randomized, phase 2 clinical study in stage IV non-small cell lung carcinoma (NSCLC), patients treated with Imprime plus bevacizumab (bev; anti-VEGF antibody), carboplatin and paclitaxel showed a median overall survival of 16.1 months versus 11.6 months in patients not receiving Imprime. We sought to explore a mechanistic understanding for this promising clinical activity.

Angiogenic factors, such as VEGF, not only drive the formation of new leaky vessels but also facilitate the establishment of a suppressive immune microenvironment enabling tumor survival and growth. Recent work has shown that anti-angiogenics not only block neovascularization but may also promote a shift in the immune microenvironment, enabling immune recognition and destruction of the tumor. We therefore sought to evaluate whether Imprime may complement the effect of anti-angiogenics on the immune microenvironment.

We tested Imprime in combination with either bev or DC101 (anti-VEGFR2) in distinct NSCLC xenograft models in athymic nude mice. Once tumors reached a mean size of 100mm³, mice were treated with bev, dc or DC101. H1299 and H441 tumor-bearing mice were used in the bev and DC101 studies, respectively. In the bev study, Imprime plus bev induced >75% tumor growth inhibition in ~50% of mice vs 20% in the bev alone groups. Both macrophages and neutrophils from spleen and tumor tissue of combination-treated mice showed significant upregulation of the activation marker CD86 compared to tissue from bev alone treated mice. Moreover, splenic MDSCs in combination-treated mice showed significantly increased iNOS expression with reduced Arg-1 expression compared to bev alone treated mice. Tumors from the Imprime plus bev groups showed significantly increased iNOS expression compared to tumors from mice treated only with bev with the greatest reduction evident in the tumors with the greatest growth inhibition. In the H441 tumor-bearing mice treated with Imprime and DC101, a significant suppression of tumor growth compared to DC101 alone was also observed and additional mechanistic studies in this model are ongoing. These data show that Imprime binding to innate immune cells triggers a coordinated immune response in concert with anti-angiogenic therapy.

Results

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

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

**Figure 3: Anti-tumor efficacy of Imprime PGG with anti-angiogenics in vivo.**

**Figure 4: Splenic macrophages isolated from Imprime+Bev treated mice display a M1-like phenotype.**

**Figure 5: Imprime+Bev splenic MDSC display an increase in inOS and decrease in Arg1.**

**Figure 6: Imprime+Bev tumors have cells that show a more activated phenotype and a decrease in TGFβ.**

**Figure 7: Imprime+DC101 treated animals have reduced splenic MDSCs, an increase in activated splenic macrophages and an increase in Th1-like phenotype on cells within the tumor microenvironment.**

Background

- Imprime is a soluble yeast-derived β-1,3/1,6 glucan immunomodulator (Figure 1) being developed for cancer treatment in combination with anti-tumor antibodies.
- In a randomized phase 2 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-glucan antibodies, then binds and primes innate immune cells including macrophages, neutrophils, and DCs (Figure 2). 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.
- In addition to blocking neovascularization, anti-angiogenics can promote a shift in the immune microenvironment enabling immune activation.

Objective: To evaluate the ability of Imprime to complement the effect of anti-angiogenics on the immune microenvironment in vivo in xenograft models of NSCLC.

Summary

**Ex-Vivo studies:**
- Imprime enhances human macrophage and MDSC activation and function which leads to macrophage activation of the adaptive immune system.
- Imprime blocks the generation of Reactive Oxygen Species (ROS) from neutrophils specifically in response to antibody-coated tumor cells.

**In-Vivo studies:**
- Imprime plus treatment in vivo can activate myeloid cells within both the tumor and spleen to orchestrate a profound shift in the immune microenvironment which promotes tumor recognition and suppression.