ELSEVIER

Blood 142 (2023) 2791–2792

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

604.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: MYELOID NEOPLASMS

Spatial Response to Pivekimab Sunirine (IMGN632) *In Vivo* in a BPDCN Model

Margaux Poussard[1], *Morgane Boichut*[1], *Imane Belakri*[1], *Sabeha Biichle*[1], *Maxime Fredon*[1], *Florian Renosi*[2], *Francine Garnache Ottou, PhD*[3], *Krystal Watkins*[4], *Callum Mortimer Sloss, PhD*[4], *Patrick A. Zweidler-McKay, MDPhD*[4], *Fanny Delettre, PhD*[1]

[1] INSERM, UMR1098-RIGHT, EFS Bourgogne Franche-Comté, Université Bourgogne Franche-Comté, BESANCON, France
[2] Université de Franche-Comté, CHU Besançon, EFS, INSERM, UMR RIGHT, BESANCON, France
[3] CHU Besancon, Cellular immunology and hematology laboratory, Université de Franche-Comté, CHU Besançon, EFS, INSERM, UMR RIGHT, Besançon, France
[4] ImmunoGen, Inc., Waltham, MA

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy, which often manifests with skin lesions in addition to lymph node, blood, and bone marrow involvement. Standard of care treatments for BPDCN patients are intense chemotherapy or tagraxofusp (Elzonris®). Although many patients initially respond to standard-of-care therapies, most will eventually relapse. Overexpression of CD123 (IL-3Rα receptor) is a hallmark of BPDCN thus making this antigen an attractive target.

Pivekimab sunirine is an antibody-drug-conjugate (ADC) comprised of a humanized anti-CD123 monoclonal antibody conjugated to a potent DNA-damaging agent, FGN849 via a cleavable linker. Pivekimab sunirine was granted orphan drug and Breakthrough Therapy designation and is currently being tested for the treatment of BPDCN patients as monotherapy and, as a triplet therapy in combination with azacitidine and venetoclax for the treatment of AML patients. Preclinically, pivekimab sunirine has demonstrated potent activity against BPDCN cells (Blood 2018 132:3956) and importantly, showed a favorable safety profile and promising efficacy in BPDCN patients (Hemasphere. 2022 Jun; 6 (Suppl): 1708-1709; ASH 2021, Abstract #1284). The goal of this study was to investigate the response to pivekimab sunirine in a pre-clinical model of BPDCN and to monitor spatial response in vivo.

Pivekimab sunirine efficacy was evaluated in vitro on GEN2.2, a patient-derived BPDCN cell line, for 24h, 48h, or 72h at different concentrations. We observed a concentration and time-dependent efficacy at 48h or 72h of treatment with EC50s between 4pM and 12pM and between 1.3pM and 3pM respectively. Limited cytotoxicity was observed at the 24h time point.

The efficacy of pivekimab sunirine was further confirmed in vivo in the GEN2.2 BPDCN model. Pivekimab sunirine treatment with either 0.024mg/kg or 0.08mg/kg doses at QWx3 (once weekly for 3 weeks) dosing regimen was able to restrain the tumor burden and significantly enhance survival compared to the vehicle group

To assess spatial response to pivekimab sunirine, we utilized a bioluminescent (BLI) GEN2.2-luc model. Briefly, NSG mice were injected with 1x10 ^{6} GEN2.2-luc cells followed by Fc receptor blockade on Day 2 for 24h. On Day 3, mice were treated with pivekimab sunirine (0.024mg/kg; QWx3) or vehicle intravenously. Organs were harvested on day 16 for the vehicle-treated group and day 30 for the pivekimab sunirine-treated group and tumor burden was assessed using luciferin. The vehicle group showed the presence of tumor cells in the bone marrow, spleen, and lungs. These results were confirmed by HES staining. Pivekimab sunirine treated mice showed no sign of tumor cells in any of the organs in BLI evaluation. HES staining confirmed the elimination of tumor cells in the lungs and the liver while few remaining tumor cells were observed in the spleen and the bone marrow.

Overall, this work enabled us to validate the efficacy of pivekimab sunirine in a BPDCN model and to monitor its spatial effect. Data showed that pivekimab sunirine treatment significantly reduced tumor burden and increased survival compared to the vehicle group. Pivekimab sunirine treatment eradicated tumor cells in the lungs and the liver, while reducing the number of tumor cells in the spleen and bone marrow.

Pivekimab sunirine is a potent ADC targeting CD123 and is highly efficacious against an aggressive BPDCN cell line model. This finding reinforces the importance of its use for the treatment of BPDCN patients.

Disclosures Poussard: *Immunogen Inc.:* Research Funding; *Stemline Menarini:* Research Funding. **Boichut:** *Immunogen Inc.:* Research Funding; *Stemline Menarini:* Research Funding. **Belakri:** *Stemline Menarini:* Research Funding; *Immunogen Inc.:* Research Funding. **Garnache Ottou:** *Stemline Menarini:* Research Funding; *Immunogen Inc.:* Research Funding. **Watkins:** *Immunogen Inc.:* Ended employment in the past 24 months. **Sloss:** *Immunogen Inc.:* Current Employment. **Zweidler-McKay:** *Immunogen Inc.:* Current Employment. **Delettre:** *Stemline Menarini:* Research Funding; *Immunogen Inc.:* Research Funding.

https://doi.org/10.1182/blood-2023-185602