**Background**

- Immune checkpoint inhibitors (ICI) directed against PD-L1/L2 are associated with improved response rates in melanoma, and squamous/non-squamous non-small cell lung cancer (NSCLC) (1-4).
- Conversely, anti-PD-L1 blockade is minimally efficacious in microsatellite stable (MSS) colorectal carcinoma (CRC).
- Pixatimod is a heparan sulfate (HS) mimetic with unique NK- and T cell-dependent immunomodulatory properties that is currently being evaluated in a variety of different tumors.

**Stimulation of Human DCs in Vitro**

Pixatimod and CpG activate plasmacytoid dendritic cells (pDC) in vitro (Fig. 3). pDCs were treated with Pixatimod (5 μg/mL) and CpG (ODN-2006, 3 μg/mL) for 24 h and then pDC (CD123+) were assessed by flow cytometry. pDC expressing high levels of the surface markers CD40 and CD80 and the intracellular cytokine IFN-γ were quantified and expressed as a percentage of the total pDC population. Data are averages of experiments with PBMC from two donors.

**Hypothesis**

- The management of PD-L1-relapsed/refractory (R/R) tumors is challenging. Anti-PD-L1 therapy is minimally efficacious in MSS CRC.
- Low dose Cy has immunostimulatory and antiangiogenic properties and has synergy with CpG, and PD-1 IC (11-13).
- The combination of pixatimod and anti-PD-1 may reverse PD-1 resistance in PD-L1/R metastasis and NSCLC.
- The addition of low-dose Cy may augment the efficacy of pixatimod and anti-PD-1 in MSS CRC.

**Pixatimod Structure and Immunomodulatory Function**

- The chemical structure of pixatimod (PSG45) is shown in Fig. 1. Atoms of the sugar backbone are colored blue, sulfate groups in orange, and the cholesterol moiety in green.

**Inclusion Criteria (Select)**

- Male/female participants who are at least 18 years of age on the day of signing informed consent with advanced/metastatic cutaneous melanoma, NSCLC or MSS mCRC.
- Presence of measurable disease based on RECIST v1.1.
- Adequate organ function.
- PIV cutoff of 1200 obtained on labs done during Screening based on previous data (10).
- PO-1 refractory disease as defined as progression on treatment with anti-PD-(L1) inhibitor administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies (14) (cohorts 2 and 3 only).
- Cohort 1 (MSS CRC) specific criteria: Progression on prior therapy with a fluoropyrimidine, oxaliplatin, and/or cetuximab.
- Progression on prior therapy with BRAF/MEK inhibitor therapy (if BRAF mutated) and/or EGFR targeted antibody (if KRAS WT).
- Cohort 2 (PD-1/R/R metastasis) specific criteria: Prior treatment with an anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody is allowed but not required. Prior treatment with BRAF/MEK inhibitor therapy (if BRAF mutated) is allowed but not required. No more than 5 prior lines of therapy.
- Cohort 3 (PD-1/R/R NSCLC) specific criteria: Patients with NSCLC with known oncopgenic driver (including but not limited to BRAF, EGFR, ALK, ROS, MET alterations) must have received and progressed past driver-specific therapy.
- History of allergy and/or hypersensitivity to heparin and/or heparin-type anticoagulants.
- Use of hepatic (including low molecular weight hepatic and/or fondaparinux) within 2 weeks prior to enrollment.
- Patients who are receiving low molecular weight heparin (or fondaparinux or other hepatic product) for therapeutic anticoagulation may be enrolled if they have tested negative for anti-heparin antibodies at Screening.
- Active CNS metastases.
- Known secondary malignancies.
- Systemic disease requiring systemic pharmacologic doses of corticosteroids greater than 10 mg daily prednisone (or equivalent).
- Rejection doses in patients with autoimmune disease(s) allowed.

**Statistical Plan**

- Simon 2-stage design with parallel enrollment into disease-specific cohorts.
- In the 1st stage of Cohort 1 (MSS mCRC), we will enroll 13 patients. If 21 response(s) are seen, 14 additional patients will be enrolled in the 2nd stage.
- In the 2nd stage of Cohorts 2 (PD-1/R/R melanoma) and 3 (NSCLC), we will enroll 5 patients. If 31 response(s) are seen, 8 additional patients will be enrolled in the 2nd stage.
- Target ORR: 15% (Cohort 1), 18% (Cohorts 2 and 3).
- Accrual is ongoing.

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**References**

5. Small RK, et al. "Screening. May be enrolled if they have tested negative for anti-heparin antibodies at Screening."
6. Zarrour H, et al. "How can we combine anti-PD-1 antibody alone (9)."
8. "All patients will be monitored for both clinical and laboratory adverse events."
9. "Any malignancies in the last 5 years, including melanoma of any stage, must have been resected and not recurrence/progression after resection, and must be curative intent therapy and have no evidence of recurrence or progression, with no evidence of active disease requiring systemic therapy, or the patient is not a candidate for systemic therapy, or has a stable disease that does not require systemic therapy."
10. "Cohorts 1 and 2 may be enrolled if they have tested negative for anti-heparin antibodies at Screening.
11. "Any malignancies in the last 5 years, including melanoma of any stage, must have been resected and not recurrence/progression after resection, and must be curative intent therapy and have no evidence of recurrence or progression, with no evidence of active disease requiring systemic therapy, or the patient is not a candidate for systemic therapy, or has a stable disease that does not require systemic therapy."
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