Duvelisib is a dual inhibitor of PI3K-δ and PI3K-γ. PI3K-δ inhibition decreases immunosuppressive Tregs (PI3K-δ) & myeloid cells (PI3K-γ). Duvelisib is a dual PI3K-δ/γ inhibitor. These data support further exploration of duvelisib in combination with anti-PI-1 mAb to co-inhibitory antibodies in patients with B cell malignancies.

**Results**

Combination of Duvelisib + anti-PI-1 is Synergistic in Induction of Tumor Growth Inhibition and Survival in A20 B Cell Lymphoma Model

**Figure 2:** Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm³ and treated with either vehicle + rat IgG2a control, duvelisib (50 mg/kg, PO, BID), or vehicle + anti-PI-1. Tumor volume was measured by caliper. For Kaplan-Meier, an event was defined by death or tumor growth beyond 1000 mm³.

Combination of Duvelisib + anti-OX40 Induces Tumor Regressions and Long-Term Survival in A20 B Cell Lymphoma Model

**Figure 3:** Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm³ and treated with either vehicle + rat IgG2a control, duvelisib (50 mg/kg, BID, po through end of experiment) + rat IgG2a control, anti-OX40 (clone RMPI-114, 100 mg/mouse, i.p. twice weekly x 2), or duvelisib + anti-PI-1. Tumor volume was measured by caliper. For Kaplan-Meier, an event was defined by death or tumor growth beyond 1000 mm³.

Combination of Duvelisib + anti-OX40 Induces Memory Immunity

**Figure 4:** Mice bearing A20 B cell lymphoma tumors were treated with vehicle + rat IgG2a control, duvelisib (50 mg/kg, BID, po through end of experiment) + rat IgG2a control, anti-OX40 (100 mg/mouse, i.p. biweekly x 2), or duvelisib + anti-OX40. Curves show tumor growth for individual mice in each group. Only mice treated with the combination of duvelisib + anti-OX40 show tumor regression.

**Figure 5:** Mice bearing A20 tumors were treated with anti-OX40 alone or duvelisib + anti-OX40. On day 44, all mice with no detectable tumor from the anti-OX40 (n = 2) and duvelisib + anti-OX40 (n = 5) groups were re-injected with A20 B cell lymphoma cells in the contralateral flank with no further treatment to assess immune memory. Both mice previously treated with anti-OX40 alone grew new tumors, whereas all mice previously treated with duvelisib + anti-OX40 remained tumor-free.

**Figure 6:** Mice previously treated with the duvelisib + anti-OX40 combination show increased memory T cells in the blood and spleen compared to untreated control mice bearing A20 tumors.

**Summary**

- Duvelisib is a dual PI3K-δ/γ inhibitor
- Duvelisib has proven activity as monotherapy in patients with B cell malignancies
- Dual inhibition of PI3K-δ & PI3K-γ confers reduction of both immunosuppressive Tregs (PI3K-δ) & myeloid cells (PI3K-γ)
- Duvelisib greatly enhanced efficacy of anti-PI-1 mAb and induced tumor regression and immune memory in combination with anti-OX40 mAb in an A20 B cell lymphoma model
- These data support further exploration of duvelisib in combination with anti-PI-1/PI-1L-1 or co-stimulatory antibodies against B cell malignancies