Duvelisib is a Dual Inhibitor of PI3K-δ and PI3K-γ. Inhibition of LPS-stimulated monocytes and fMLP-stimulated monocytes were used to measure blood polyclonal of PI3K inhibitors against PI3K-δ and PI3K-γ, respectively. The graph shows dose responses with monocytes from human donors. In the table, whole blood samples from 5 donors, which encompass enzyme inhibition, cell proliferation and protein binding of inhibitors, are presented in a format of clinical plasma exposures of each agent at RP2D. Only duvelisib covers IC50 values for both PI3K-δ and PI3K-γ at clinically achievable exposures. Treatment with duvelisib combined with anti-OX40 alone or anti-OX40 + duvelisib was well-tolerated. In the Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60–90 mm3 in size and were treated with either vehicle or rat IgG2a control, anti-OX40 (250 mg/kg, BID, i.p. through end of experiment), anti-OX40 + duvelisib (150 mg/kg, i.p., biweekly x 2), or duvelisib alone. Myeloid MDSCs were quantified by flow cytometry from mice bearing A20 tumors after 8 days of treatment.

CONCLUSIONS: The dual inhibition of PI3K-δ and PI3K-γ appears to make Duvelisib especially attractive for treatment of B cell malignancies that are PI3K-δ and PI3K-γ dependent and B cell malignancies that contain PI3K-δ and PI3K-γ expressing immunosuppressive populations, enhancing the anti-tumor efficacy of immune checkpoint and co-stimulatory antibodies. These data support potential clinical applications of Duvelisib in combination with checkpoint or co-stimulatory antibodies.

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

Figure 2: Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60–90 mm in size and were treated with either vehicle or rat IgG2a control, duvelisib (50 mg/kg, BID, i.p. through end of experiment), anti-OX40 (150 mg/kg, i.p., biweekly x 2), or duvelisib + anti-OX40. Treatment with duvelisib alone resulted in tumor regression and immune memory in combination with anti-OX40. Both mice previously treated with anti-OX40 alone grew new tumors, whereas mice previously treated with duvelisib + anti-OX40 grew tumors.

Figure 5: Mice bearing A20 B cell lymphoma tumors were treated with anti-OX40 alone or duvelisib + anti-OX40. On day 44, 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. Whereas mice that had received anti-OX40 alone or anti-OX40 + duvelisib were injected with A20 cells in the contralateral flank with no further treatment. Whereas mice that had received anti-OX40 alone or anti-OX40 + duvelisib did not grow tumors, mice that had received anti-OX40 + duvelisib regrew tumors.

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

Summary

• Duvelisib is a dual PI3K-δ/π 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) and myeloid cells (PI3K-γ)
• Duvelisib greatly enhances anti-tumor activity in the re-challenge setting 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-OX40 mAb or anti-CD137+IgG2a antibodies in patients with B cell malignancies