Synergistic Efficacy of Duvelisib with Checkpoint or Co-Stimulatory Antibodies in a B Cell Lymphoma Model: Advantages of Dual Inhibition of PI3K-δ and PI3K-γ

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Figure 1: Duvelisib is a dual inhibitor of PI3K-δ & PI3K-γ. Inhibition of LPS-stimulated monocytes and ILML-stimulated monocytes were used to measure whole blood potencies of PI3K inhibitors against PI3K-δ and PI3K-γ, respectively. The graphs show dose responses of monocytes from human donors. In the table, whole blood assay IC50 values, which encompass enzyme inhibition, cell penetration and protein binding of inhibitors, are related to reported clinical plasma exposures of each agent at RP2D. Only duvelisib covers IC50 values for both PI3K-δ and PI3K-γ at clinically achievable exposures.

Figure 2: Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm3. A) Mice were treated with either vehicle + rat IgG2a control, duvelisib + anti-OX40 control, duvelisib + anti-PD-1, or duvelisib + anti-PD-1 + anti-OX40. B) Mice were treated with either vehicle + rat IgG2a control, duvelisib + anti-OX40, or duvelisib + anti-OX40 + control. Tumor volumes were measured by caliper. Tregs, macrophages and MDCs were quantified by flow cytometry from mice bearing A20 tumors after 8 days of treatment.

RESULTS: In the A20 model, duvelisib, anti-PD-1, and anti-OX40 treatments each induced tumor growth delay. When duvelisib and anti-PD-1 were combined in mice with pre-existing A20 tumors, strong anti-tumor synergy was observed. When anti-OX40 and duvelisib were combined, tumor regression was observed which correlated with strong reduction of tumor Tregs, M2 macrophages and MDCS. To assess immune memory, tumor-free mice following 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 grew new tumors upon A20 re-challenge, all tumor-free mice that had received anti-OX40 + duvelisib did not grow tumors upon re-challenge and showed elevated memory T cells in blood and spleen. These findings indicate that anti-OX40 + duvelisib treatment established immune memory, potentially contributing to the observed tumor regressions. Mechanically, duvelisib was found to reduce Tregs, M2 macrophages and MDCS in the context of combinations with PD-1 or OX40 antibodies, and duvelisib (dual PI3Kδ/γ inhibition) was found to inhibit all 3 immunosuppressive cell populations more effectively than idelalisib (PI3K-δ only) or IPI-549 (PI3K-γ only).

CONCLUSIONS: These data demonstrate that duvelisib treatment stimulates anti-tumor immunity. Furthermore, the unique dual inhibition of PI3K-δ and PI3K-γ appears to make duvelisib especially effective in enhancing the anti-tumor efficacy of immune checkpoint and co-stimulatory antibodies. These data support further exploration of duvelisib in combination with anti-PD-1/PDL-1 or co-stimulatory antibodies in patients with various cancers.

Acknowledgements:

References: 1) Synergistic Efficacy of Duvelisib with Checkpoint or Co-Stimulatory Antibodies in a B Cell Lymphoma Model: Advantages of Dual Inhibition of PI3K-δ and PI3K-γ

Figure 5: 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 inhibitor of PI3K-δ and PI3K-γ
- Duvelisib is an FDA approved agent with activity as monotherapy in CLL/SLL and FL
- Dual inhibition of PI3K-δ/γ by duvelisib confers greater reduction of immunosuppressive Tregs and myeloid cells than inhibitors of only PI3K-δ or PI3K-γ
- Duvelisib greatly enhances efficacy of anti-PD-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 clinical testing of duvelisib in combination with anti-PD-1/PDL-1 or co-stimulatory antibodies in patients with hematologic malignancies or solid tumors