The Dual PI3K-δ,γ Inhibitor Duvelisib Stimulates Anti-Tumor Immunity and Enhances Efficacy of Immune Checkpoint and Co-Stimulatory Antibodies in a B Cell Lymphoma Model

1541

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Abstract

Duvelisib is an orally active, dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ, which has shown clinical activity as a monotherapy in chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma (FL), and T cell lymphoma[1] and is being developed broadly for the treatment of B cell malignancies. Recent publications have demonstrated that PI3K-δ inhibition decreases immunosuppressive regulatory T cells (Tregs) in the tumor microenvironment[2] whereas PI3K-γ inhibition decreases immunosuppressive myeloid cells (MDSCs and M2 tumor-associated macrophages).[3] Accordingly, duvelisib has recently been shown to reduce tumor and spleen MDSCs in a preclinical tumor model.[4] These data collectively suggest that reduction of Tregs and immunosuppressive myeloid cells in the tumor microenvironment may contribute to the activity of duvelisib as a monotherapy, and may also augment the efficacy of immune checkpoint or co-stimulatory antibodies.

These findings led us to investigate the efficacy of duvelisib (50 mg/kg po, BID) in combination with immune checkpoint (anti-PD-1, RMP1-14) or co-stimulatory (anti-OX40, clone OX86) antibodies. In the murine syngeneic A20 B cell lymphoma model, duvelisib and anti-PD-1 treatments each induced tumor growth delay. When duvelisib and anti-PD-1 were combined in mice bearing pre-existing A20 tumors, strong synergy was observed in the anti-tumor response (see figure). Similarly, duvelisib and anti-OX40 each induced tumor growth delay as single agents in the A20 model. When anti-OX40 and duvelisib were combined, striking tumor regression was observed. To assess immune memory, tumor-free mice following anti-OX40 alone or anti-OX40 + duvelisib combination were injected with A20 lymphoma cells in the contralateral flank with no further treatment. Whereas the mice that had received anti-OX40 alone grew new tumors upon A20 re-challenge, all tumor-free mice that had received the anti-OX40 + duvelisib combination did not grow A20 tumors upon re-challenge and showed elevated memory T cells in the blood and spleen. These findings indicate that the anti-OX40 + duvelisib treatment established immune memory, potentially contributing to the observed tumor regression.

These data demonstrate that duvelisib treatment stimulates anti-tumor immunity. Furthermore, the unique dual inhibition of PI3K-δ and PI3K-γ may 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/PD-L1 or co-stimulatory antibodies in patients with B cell malignancies.

Background

Duvelisib is a Dual Inhibitor of PI3K-δ and PI3K-γ

Potencies of Duvelisib vs. PI3K-δ and PI3K-γ

Assay	PI3K-δ	PI3K-γ
Biochemical K_d	0.023 nM	0.24 nM
Enzymatic IC_{50}	2.5 nM	27 nM
Cellular IC_{50}	0.36 nM	19.6 nM

Figure 1: Duvelisib is a dual inhibitor of PI3K-δ & PI3K-γ. Biochemical binding affinities were determined with recombinant human PI3K-δ and PI3K-δ. Enzymatic potencies were measured in presence of 3 mM ATP. Cellular potencies were assessed by pAKT inhibition in RAJI cells stimulated with anti-IgM (PI3K-δ) and in RAW264.7 cells stimulated with C5a (PI3K-γ).[5]

Concept

- Duvelisib is clinically active as a monotherapy in B cell malignancies
- PI3K-δ inhibition is known to reduce immunosuppressive Tregs
- PI3K-γ inhibition is known to reduce immunosuppressive myeloid cells
- Duvelisib may potentiate efficacy of checkpoint & co-stimulatory antibodies against B cell malignancies

Results

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

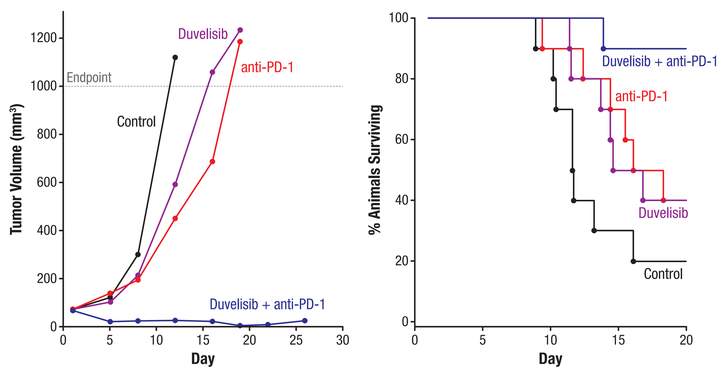

Figure 2: Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm³ and treated with either vehicle + rat IgG2a control, duvelisib (50 mg/kg, BID, po through end of experiment) + rat IgG2a control, anti-PD-1 (clone RMP1-14, 100 mg/mouse, i.p. biweekly x 2), or duvelisib + anti-PD-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

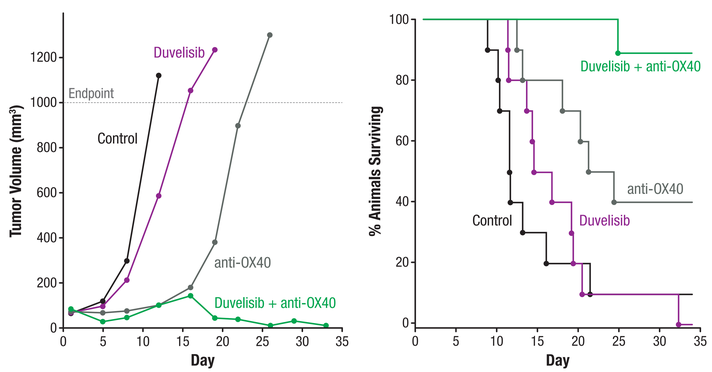

Figure 3: Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm³ and treated with either vehicle + rat IgG2a control, duvelisib (50 mg/kg, BID, po through end of experiment) + rat IgG2a control, anti-OX40 (clone OX86, 100 mg/mouse, i.p. biweekly x 2), or duvelisib + anti-OX40.

Combination of Duvelisib + anti-OX40 Induces Tumor Regressions

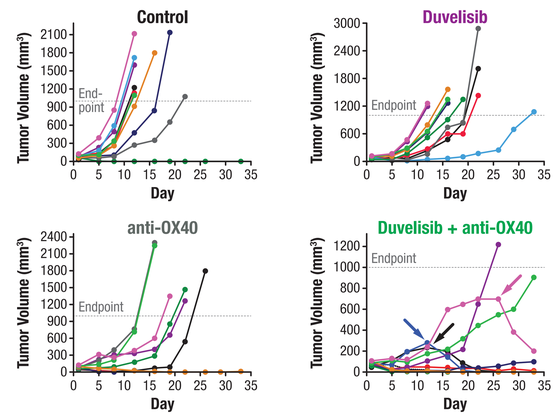

Figure 4: Mice bearing A20 B cell lymphoma tumors were treated with vehicle + rat IgG2a control, duvelisib (50 mg/kg, BID, po through end of experiment) + rat IgG2a control, anti-OX40 (100 mg/mouse, i.p. biweekly x 2), or duvelisib + anti-OX40. Curves show tumor growth for individual mice in each group.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

Combination of Duvelisib + anti-OX40 Induces Immune Memory

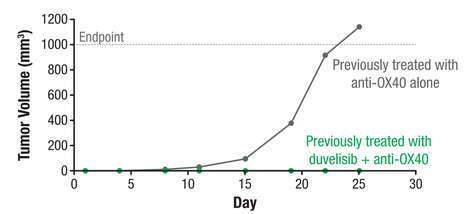

Figure 5: Mice bearing A20 tumors were treated with anti-OX40 alone or duvelisib + anti-OX40. On day 44, all mice with no detectable tumor from the anti-OX40 (n=2) and duvelisib + anti-OX40 (n=5) groups were re-injected with A20 B cell lymphoma cells in the contralateral flank with no further treatment 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.

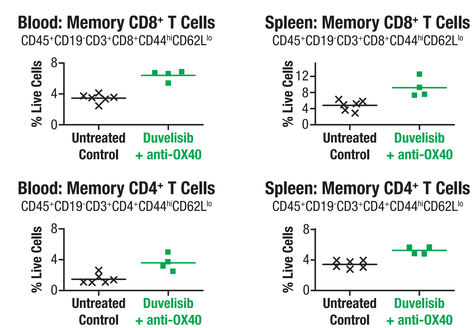

Figure 6: Mice previously treated with the duvelisib + anti-OX40 combination show increased memory T cells in the blood and spleen compared to untreated control mice bearing A20 tumors.

The Dual PI3K-δ/PI3K-γ Inhibitor Duvelisib Suppresses Both Immunosuppressive Tregs and Immunosuppressive Myeloid Cells

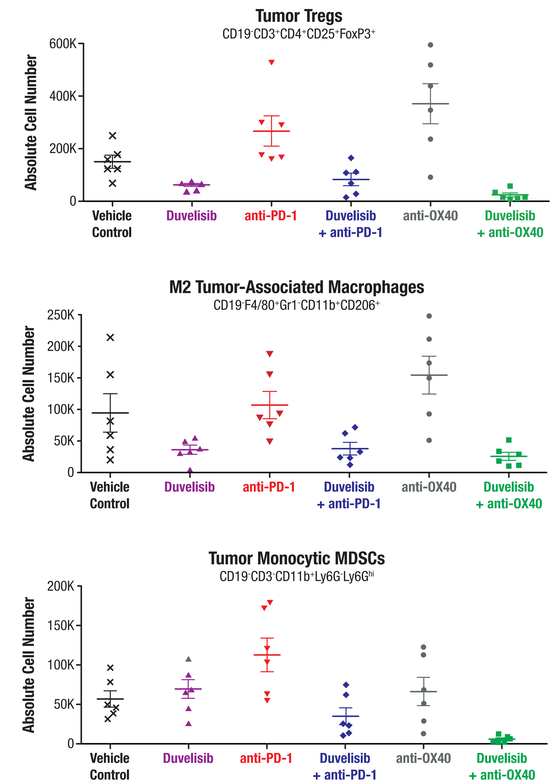

Figure 7: Effects of duvelisib ± anti-PD-1 or anti-OX40 on Tregs and myeloid immunosuppressive cells in A20 B cell lymphoma tumors. Female BALB/c mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm³ and treated as indicated. On day 9 of treatment, mice were euthanized, tumors removed, and immune cell populations in the tumors were analyzed by flow cytometry using the indicated marker sets.

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-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 further exploration of duvelisib in combination with anti-PD-1/PD-L1 or co-stimulatory antibodies in patients with B cell malignancies

References: **1)** O'Brien ASH 2014; Flinn ASH 2014; Horwitz ASH 2014 **2)** Ali, *Nature*, 2014; Ahmad, *Cancer Res*, 2017 **3)** Kaneda, *Nature*, 2016; De Henau, *Nature*, 2016 **4)** Davis, *Cancer Res*, 2017 **5)** Winkler et al., *Chem Biol*, 2013

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