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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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 anti-tumor efficacy of checkpoint & co-stimulatory antibodies

Abstract

BACKGROUND: Duvelisib is an oral dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ which has shown clinical activity as monotherapy in chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma (FL), and T cell lymphoma.[1,2] Duvelisib was approved as a monotherapy for CLL, SLL, and FL by the FDA in September 2018. Recent publications have demonstrated that PI3K-δ inhibition reduces immunosuppressive Tregs and enriches memory T cells,[3,4] whereas PI3K-γ inhibition reduces immunosuppressive myeloid cells.[5,6] Hence, we postulated that duvelisib may augment the efficacy of immune checkpoint or co-stimulatory antibodies.

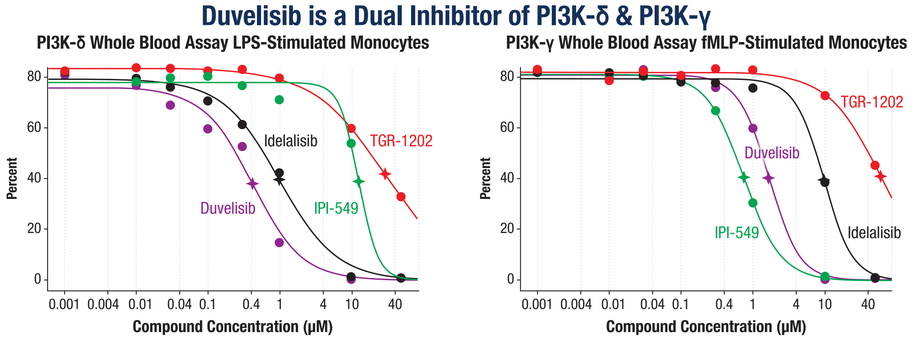
METHODS: Syngeneic mice bearing human A20 B cell lymphoma tumors (60-90 mm^3) were treated with vehicle, duvelisib, anti-PD-1, anti-PD-1 + duvelisib, anti-OX40, or anti-OX40 + duvelisib. Tumor volumes were measured by caliper. Tregs, macrophages and MDSCs were quantified by flow cytometry from mice bearing 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 MDSCs. 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 regression. Mechanistically, duvelisib was found to reduce Tregs, M2 macrophages and MDSCs in the context of combinations with PD-1 or OX40 antibodies, and duvelisib (dual PI3K-δ/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/PD-L1 or co-stimulatory antibodies in patients with various cancers.

References: 1) Flinn IW, O'Brien S, Kahl B, Patel M, Oki Y, Foss FF, Porcu P, Jones J, Burger JA, Jain N, Kelly VM, Allen K, Douglas M, Sweeney J, Kelly P, Horwitz S., Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. *Blood* 2018; 131:877-887. **2)** Horwitz SM, Koch R, Porcu P, Oki Y, Moskowitz A, Perez M, Myskowski P, Officer A, Jaffe JD, Morrow SN, Allen K, Douglas M, Stern H, Sweeney J, Kelly P, Kelly V, Aster JC, Weaver D, Foss FM, Weinstock DM, Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. *Blood* 2018; 131: 888-898. **3)** Ali K, Soond DR, Pineiro R, Hagemann T, Pearce W, Lim EL, Bouabe H, Scudamore CL, Hancox T, Maecker H, Friedman L, Turner M, Okkenhaug K, Vanhaesebroeck B., Inactivation of PI(3)K p110δ breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature* 2014; 510:407-411. **4)** Abu Eid R, Ahmad S, Lin Y, Webb M, Berrong Z, Shrimali R, Kumai T, Ananth S, Rodriguez PC, Celis E, Janik J, Mkrtichyan M, Khleif SN, Enhanced Therapeutic Efficacy and Memory of Tumor-Specific CD8 T Cells by Ex Vivo PI3K-δ Inhibition. *Cancer Res* 2017; 77:4135-4145. **5)** Kaneda MM, Messer KS, Ralainirina N, Li H, Leem CJ, Gorjestani S, Woo G, Nguyen AV, Figueiredo CC, Foubert P, Schmid MC, Pink M, Winkler DG, Rausch M, Palombella VJ, Kutok J, McGovern K, Frazer KA, Wu X, Karin M, Sasik R, Cohen EE, Varner JA, PI3Kγ is a molecular switch that controls immune suppression. *Nature* 2016; 539:437-442. **6)** De Henau O, Rausch M, Winkler D, Campesato LF, Liu C, Cymerman DH, Budhu S, Ghosh A, Pink M, Tchaicha J, Douglas M, Tibbitts T, Sharma S, Proctor J, Kosmider N, White K, Stern H, Soglia J, Adams J, Palombella VJ, McGovern K, Kutok JL, Wolchok JD, Merghoub T, Overcoming resistance to checkpoint blockade therapy by targeting PI3Kγ in myeloid cells. *Nature* 2016; 539: 443-447.

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



Drug	Mechanism of Action	PI3K-δ IC_{50} (μM)	PI3K-γ IC_{50} (μM)	C_{max} (ss) (μM)
Duvelisib	Dual PI3K-δ/PI3K-γ Inhibitor	0.4 ± 0.1	1.6 ± 0.2	2.5
Idelalisib	PI3K-δ Inhibitor	1.0 ± 0.2	9.4 ± 2.3	4.8
IPI-549	PI3K-γ Inhibitor	12 ± 0.5	0.5 ± 0.2	9.1
TGR-1202		25 ± 8	55 ± 16	3.1

Green = IC_{50} < Clinical $C_{max\text{-}ss}$ at RP2D. Red = IC_{50} > Clinical $C_{max\text{-}ss}$ at RP2D

Figure 1: Duvelisib is a dual inhibitor of PI3K-δ & PI3K-γ. Inhibition of LPS-stimulated monocytes and fMLP-stimulated monocytes were used to measure whole blood potencies of PI3K inhibitors against PI3K-δ and PI3K-γ, respectively. The graphs show dose responses with monocytes from human donors. In the table, whole blood assay IC_{50} 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 IC_{50} values for both PI3K-δ and PI3K-γ at clinically achievable exposures.

Combinations of Duvelisib + anti-PD-1 and Duvelisib + anti-OX40 are Synergistic in Inhibition of Tumor Growth and Long-Term Survival in A20 B Cell Lymphoma Model

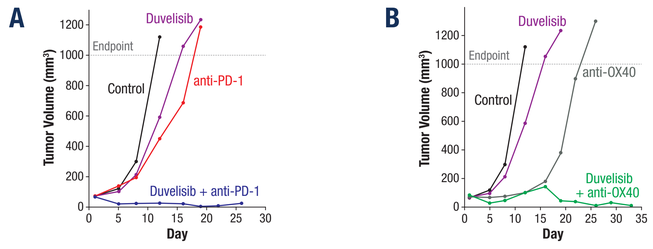


Figure 2: Mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm^3. **A)** Mice were treated with either vehicle + rat IgG2a control, duvelisib + rat IgG2a control, anti-PD-1, or duvelisib + anti-PD-1. **B)** Mice were treated with either vehicle + rat IgG2a control, duvelisib + rat IgG2a control, anti-OX40, or duvelisib + anti-OX40. Tumor volume was measured by caliper. [Dosage: duvelisib 50 mg/kg, BID, po through end of experiment; anti-PD-1 clone RMP1-14, 100 μg/mouse, i.p. biweekly x 2; anti-OX40 clone OX86, 100 μg/mouse, i.p. biweekly x 2]

Combination of Duvelisib + anti-OX40 Induces Tumor Regressions

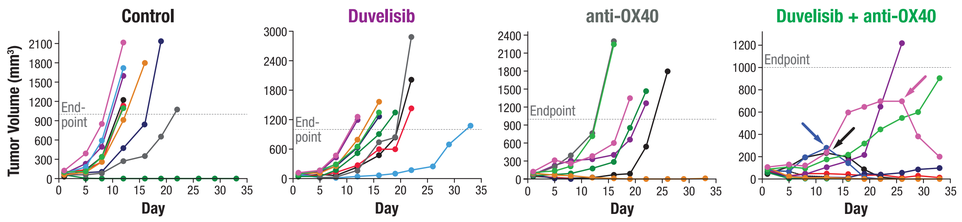


Figure 3: Mice bearing A20 B cell lymphoma tumors were treated with vehicle + rat IgG2a control, duvelisib (50 mg/kg, BID, po through end of experiment) + rat IgG2a control, anti-OX40 (100 Mg/mouse, i.p. biweekly x 2), or duvelisib + anti-OX40. Curves show tumor growth for individual mice in each group. Only mice treated with the combination of duvelisib + anti-OX40 show tumor regression (arrows).

Combination of Duvelisib + anti-OX40 Induces Immune Memory

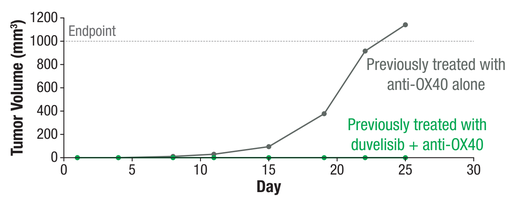


Figure 4: Mice bearing A20 tumors were treated with anti-OX40 alone or duvelisib + anti-OX40. On day 44, all mice with no detectable tumor from the anti-OX40 (n=2) and duvelisib + anti-OX40 (n=5) groups were re-injected with A20 B cell lymphoma cells in the contralateral flank with no further treatment 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.

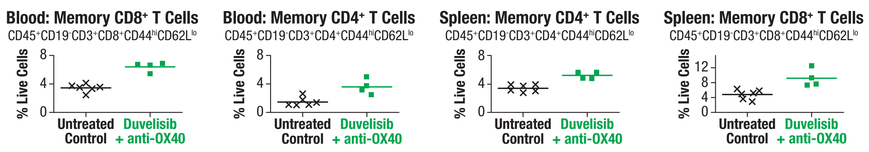


Figure 5: Mice previously treated with the duvelisib + anti-OX40 combination show increased memory T cells in the blood and spleen compared to untreated control mice bearing A20 tumors.

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

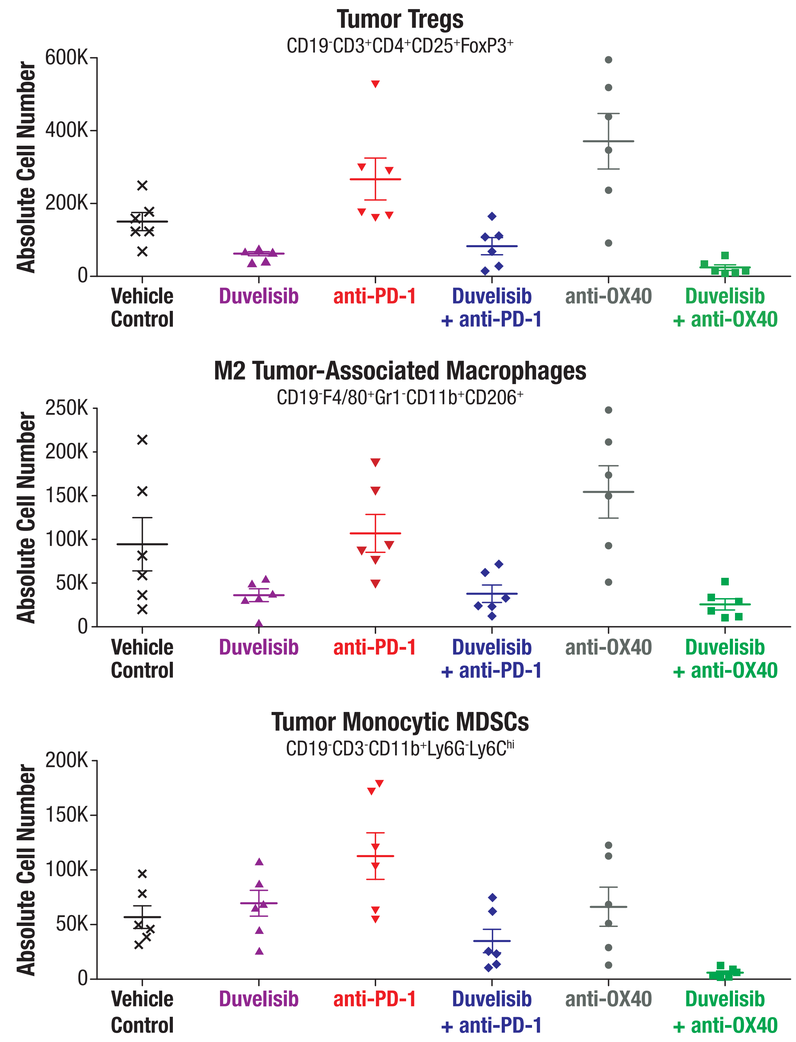


Figure 6: Effects of duvelisib ± anti-PD-1 or anti-OX40 on Tregs and myeloid immunosuppressive cells in A20 B cell lymphoma tumors. Female BALB/c mice bearing syngeneic A20 B cell lymphoma tumors were randomized once tumors reached 60-90 mm^3 and treated as indicated. On day 9 of treatment, mice were euthanized, tumors removed, and immune cell populations in the tumors were analyzed by flow cytometry using the indicated marker sets.

Dual PI3K-δ/PI3K-γ Inhibition by Duvelisib is Most Effective in Reducing Tregs & Myeloid Immunosuppressive Cells

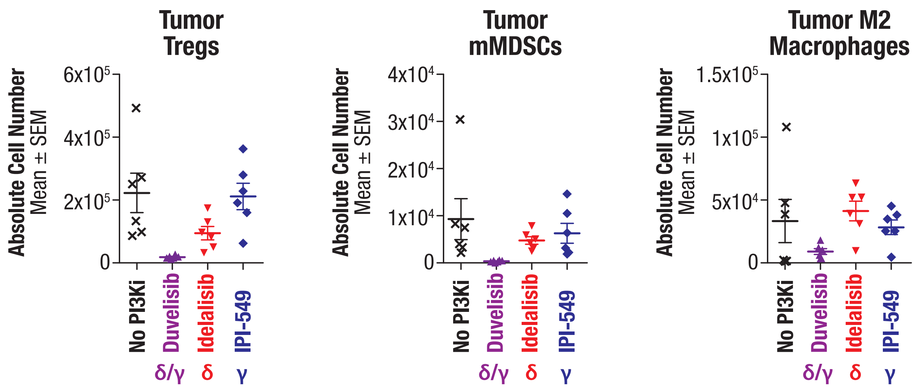


Figure 7: All measurements by flow cytometry following 8 days treatment of A20 B-cell lymphoma model in presence of OX40 antibody. Doses of PI3K inhibitors based on prior publications: 50 mg/kg duvelisib po BID; 50 mg/kg idelalisib po BID; 15 mg/kg IPI-549 po BID[6]

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 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 clinical testing of duvelisib in combination with anti-PD-1/PD-L1 or co-stimulatory antibodies in patients with hematologic malignancies or solid tumors

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