Abstract #3534
Poster #663

The dual PI3K-δ/PI3K-γ inhibitor duvelisib inhibits signaling and proliferation of solid tumor cells expressing PI3K-δ and/or PI3K-γ

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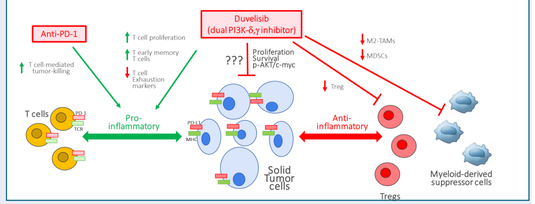
BACKGROUND

- Duvelisib (DUV), a dual PI3K-δ,γ inhibitor, is US FDA approved at 25 mg twice daily (BID) for the treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia or small lymphocytic lymphoma after ≥ 2 lines of prior therapy and R/R follicular lymphoma after ≥ 2 prior systemic therapies. Accelerated approval for R/R follicular lymphoma was based on overall response rate and continued approval may be contingent upon confirmatory trials (1).
- In addition to targeting malignant B cells, duvelisib regulates key immune cells in the tumor microenvironment (TME), including Tregs and immunosuppressive myeloid cells, making it a promising candidate for combination with immunotherapy in both hematological malignancies and solid tumors (2-6).
- Accordingly, clinical studies are underway investigating the combination of duvelisib plus nivolumab in aggressive lymphomas (Richter's transformation or transformed FL; NCT03892044) and duvelisib plus pembrolizumab in head and neck squamous cell carcinoma (NCT04193293).

Effects of dual PI3K-δ,γ inhibitor duvelisib on cells of the TME in solid tumors based on preclinical data. This poster examines direct effects of duvelisib on signaling and proliferation of solid tumors cells.



- Although PI3K-δ and PI3K-γ play roles in immune cells of the TME, it had not been determined whether PI3K-δ and PI3K-γ are functionally relevant in solid tumor cells directly.
- See also poster #3993 describing single cell expression of PIK3CD (PI3K-δ) & PIK3CG (PI3K-γ) in HNSCC patient samples.

REFERENCES

(1) COPIKTRA® (duvelisib) [package insert]. Needham, MA: Verastem, Inc;. 2018.
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(5) Davis et al., Anti-PD-L1 efficacy can be enhanced by inhibition of myeloid derived suppressor cells with a selective inhibitor of PI3Kδ/γ. Cancer Research 2017
(6) Pachter & Weaver, 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. SITC 2018

DISCLOSURES

SC, DTW & JAP are Verastem Oncology employees.

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RESULTS

1) PIK3CD [PI3K-δ] is highly expressed in hematological malignancies as well as in a number of solid tumors, including melanoma and head and neck squamous cell carcinoma (HNSCC)

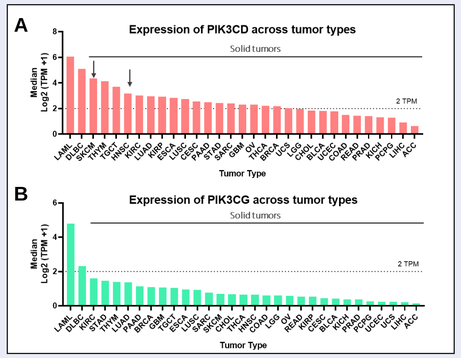


Figure 1. The GEPIA webserver was used to analyze the expression of PIK3CD [PI3K-δ] (A) and PIK3CG [PI3K-γ] (B) from the TCGA database. Whereas PIK3CG was highly expressed in hematological malignancies (log2 TPM+1 > 2) but not in solid tumors, PIK3CD was highly expressed in hematological malignancies (log2 TPM+1 = 5.1 in DLBCL) as well as in a number of solid tumors, including melanoma (log2 TPM+1 = 4.4) and HNSCC (log2 TPM+1 = 3.2). TPM: Transcripts per million.

ACC: Adrenocortical carcinoma; BLCA: Bladder Urothelial Carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma;CHOL: Cholangio carcinoma; COAD: Colon adenocarcinoma; DLBCL: Diffuse Large B-cell Lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and Neck squamous cell carcinoma; KICH: Kidney Chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute Myeloid Leukemia; LGG: Brain Lower Grade Glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; OV: Ovarian serous cystadenocarcinoma; PAAD: Pancreatic adenocarcinoma; PCPG: Pheochromocytoma and Paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin Cutaneous Melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular Germ Cell Tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine Corpus Endometrial Carcinoma; UCS: Uterine Carcinosarcoma

2) PIK3CD [PI3K-δ] is more highly expressed in melanoma and HNSCC human tumor samples compared to adjacent normal tissue

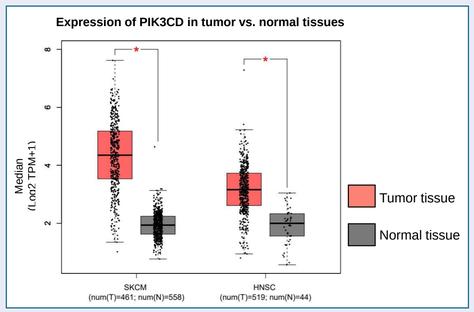


Figure 2. The GEPIA webserver was used to analyze the expression of PIK3CD [PI3K-δ] in tumor samples and adjacent normal tissue from the TCGA database. PIK3CD was more highly expressed in melanoma and HNSCC human tumor samples compared to adjacent normal tissue, suggesting a potential tumorigenic role of PI3K-δ. TPM: Transcripts per million.

3) 57% of the melanoma and 22% of the HNSCC cell lines express high levels of PIK3CD [PI3K-δ], while 7% of melanoma cell lines expressed high levels of PIK3CG [PI3K-γ]

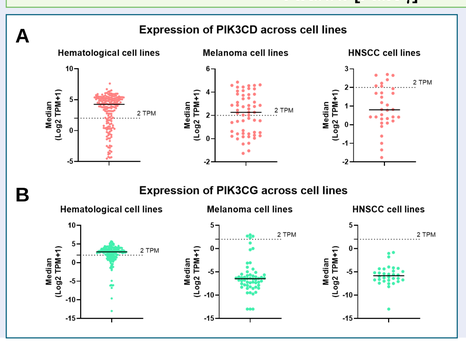
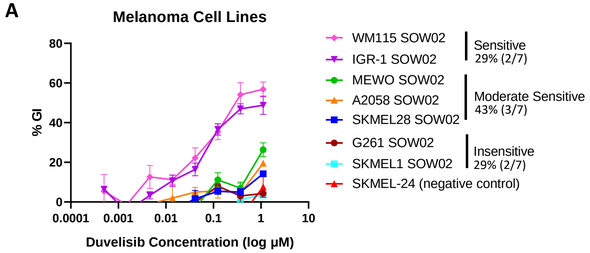


Figure 3. The expression of PIK3CD [PI3K-δ] (A) and PIK3CG [PI3K-γ] (B) in human tumor cell lines was analyzed using the Cancer Cell Line Encyclopedia database. It was found that 57% of the melanoma and 22% of the HNSCC cell lines expressed high levels (log2 TPM+1 > 2) of PIK3CD, while 7% of melanoma cell lines expressed high levels of PIK3CG.

4) Duvelisib inhibits proliferation of melanoma cell lines expressing PIK3CD [PI3K-δ] and/or PIK3CG [PI3K-γ]

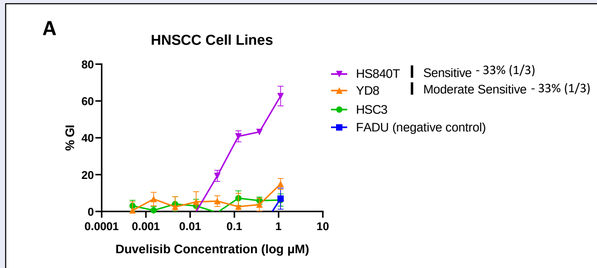


B

Cell Line	PIK3CD (log2TMP +1)	PIK3CG (log2TMP +1)	% GI at 1 μM
WM115	-0.02 (-)	2.95 (+)	57
IGR1	4.43 (+)	-8.21 (-)	49
MEWO	4.63 (+)	-8.27 (-)	26
A2058	2.88 (+)	2.32 (+)	20
SKMEL28	4.86 (+)	-5.87 (-)	14
G361	4.58 (+)	-8.54 (-)	4
SKMEL1	4.44 (+)	-7.21 (-)	4
SKMEL24 (negative control)	-1.26 (-)	-7.35 (-)	8

Figure 4. To assess possible direct effects of duvelisib on solid tumor cells, the growth inhibitory activity of duvelisib was evaluated across 7 melanoma cell lines expressing high levels of PI3K-δ and/or PI3K-γ. One melanoma cell line negative for both PI3K-δ and PI3K-γ was also evaluated. Cell viability was measured after 72-hour treatment with duvelisib (0.5 nM-1 μM) and reported as growth inhibition (GI) at 1μM. Maximal GI values between 0% and 100% are indicative of a cytostatic effect on growth for duvelisib, whereas, values greater than 100% are indicative of a cytotoxic effect of the drug. (A) Proliferation curves. (B) Expression levels of PIK3CD and PIK3CG (Cancer Cell Line Encyclopedia database) and %GI at 1 μM.

5) Duvelisib inhibits proliferation of HNSCC cell lines expressing PIK3CD [PI3K-δ]



B

Cell Line	PIK3CD (log2TMP +1)	PIK3CG (log2TMP +1)	% GI at 1 μM
HS840T	2.65 (+)	-4.25 (-)	63
YD8	2.66 (+)	-5.98 (-)	15
HSC3	2.70 (+)	-6.73 (-)	6
FADU (negative control)	-1.00 (-)	-6.79 (-)	7

Figure 5. To assess possible direct effects of duvelisib on solid tumor cells, the growth inhibitory activity of duvelisib was evaluated across 3 HNSCC cell lines expressing high levels of PI3K-δ. One HNSCC cell line negative for both PI3K-δ and PI3K-γ was also evaluated. Cell viability was measured after 72-hour treatment with duvelisib (0.5 nM-1 μM) and reported as growth inhibition (GI) at 1μM. Maximal GI values between 0% and 100% are indicative of a cytostatic effect on growth for duvelisib, whereas, values greater than 100% are indicative of a cytotoxic effect of the drug. (A) Proliferation curves. (B) Expression levels of PIK3CD and PIK3CG (Cancer Cell Line Encyclopedia database) and %GI at 1 μM.

6) Duvelisib inhibits cell proliferation and PI3K pathway, as measured by p-AKT and c-myc, in hematological, melanoma, and HNSCC cell lines expressing PIK3CD [PI3K-δ] and/or PIK3CG [PI3K-γ]

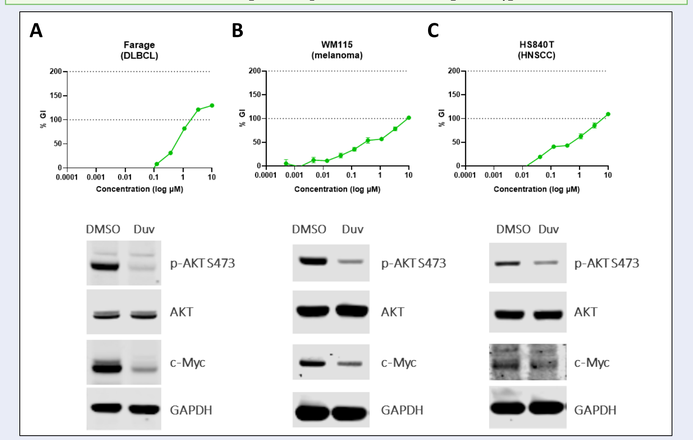


Figure 6. Duvelisib treatment inhibits cell proliferation (top panels) and leads to inhibition of p-AKT and c-myc (bottom panels) in (A) hematological malignancies (Farage cells) as well as in (B) melanoma (WM115) and (C) HNSCC (C, HS840T) cell lines. Proliferation assays: Cell viability was measured after 72-hour treatment with duvelisib (0.5 nM-1 μM) and reported as growth inhibition (GI) at 1μM. Maximal GI values between 0% and 100% are indicative of a cytostatic effect on growth for duvelisib, whereas, values greater than 100% are indicative of a cytotoxic effect of the drug. Western blots: Western blot analysis of cells treated with duvelisib (1 μM) for 4 hours and stained with pAKT (S473).

CONCLUSIONS

- In addition to expression in immune cells of the TME, PIK3CD is expressed in solid tumors, including melanoma and HNSCC, with higher expression in tumor vs adjacent normal
- PIK3CD shows high expression in some melanoma (57%) and HNSCC (22%) human cell lines. PIK3CG was also highly expressed in some melanoma (7%) human cell lines
- The dual PI3K-δ,γ inhibitor duvelisib shows moderate to strong anti-proliferative activity in 5/7 (71%) of melanoma and 2/3 (66%) of HNSCC cell lines that express high levels of PIK3CD and/or PIK3G
- The anti-proliferative activity of duvelisib correlated with inhibition of p-AKT and c-myc
- These findings suggest that duvelisib can directly inhibit signaling and proliferation of solid tumor cells expressing PI3K-δ and/or PI3K-γ, in addition to the established effects of duvelisib on malignant B cells and non-malignant immune cells of the TME
- The combination of duvelisib with pembrolizumab is currently being evaluated in patients with head and neck squamous cell carcinoma (NCT04193293)