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 leukemia 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 on confirmatory trials (1).

• In addition to targeting malignant B cells, duvelisib regulates key immune cells in the tumor microenvironment (TME), including Treg and immunosuppressive myeloid cells, making it a promising candidate for combination with immunotherapy in both hematologic malignancies and solid tumors (2, 3).

• Accordingly, clinical studies are underway investigating the combination of duvelisib plus rivalumab in aggressive lymphomas (Richner’s transcription or transformed FL) TCT03890044 and duvelisib plus pembrolizumab in head and neck squamous cell carcinoma (NCT01392393).

REFERENCES

(4) Duvelisib (DUV) is a biaryl urea inhibitor of PI3K-δ and PI3K-γ and is currently under investigation in solid tumors and hematologic malignancies.

DISCLOSURES

SC, DTW & JAP are Verastem Oncology employees.

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RESULTS

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

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)

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

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

HNSCC cell lines (E) HNSCC cell lines (D)

HCC1937 84% (4/5) 69% (7/10)
HNSCC 2 92% (8/9) 82% (10/12)
HNSCC 4 69% (2/3) 54% (1/2)
HNSCC 5 89% (2/2) 57% (2/4)
HNSCC 7 81% (2/3) 69% (2/3)
HNSCC 9 58% (2/3) 40% (1/3)
HNSCC 18 82% (2/3) 64% (2/3)
HNSCC 28 80% (1/3) 50% (1/2)
HNSCC 34 72% (2/3) 54% (2/4)
HNSCC 35 77% (2/3) 67% (2/3)
HNSCC 47 71% (2/3) 60% (1/3)
HNSCC 71 72% (3/4) 54% (1/2)
HNSCC 82 75% (2/3) 54% (2/4)
HNSCC 1104 82% (8/10) 68% (8/12)
HNSCC 1153 82% (8/10) 68% (8/12)
HNSCC 1156 82% (8/10) 68% (8/12)
HNSCC 1157 82% (8/10) 68% (8/12)
HNSCC 1167 82% (8/10) 68% (8/12)
HNSCC 1169 82% (8/10) 68% (8/12)
HNSCC 1169 82% (8/10) 68% (8/12)

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

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 PIK3CG.

• The anti-proliferative activity of duvelisib correlated with inhibition of p-AKT and p-c-myc.

• These findings suggest that duvelisib can directly inhibit signaling and proliferation of solid tumor cells expressing PIK3-δ and/or PIK3-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)