Dual Inhibition of PI3K-δ and PI3K-γ by Duvelisib Eliminates CLL B Cells, Impairs CLL-Supporting Cells, and Overcomes Ibrutinib Resistance in a Patient-Derived Xenograft Model

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INTRODUCTION

• There are several effective agents in clinical trials for the treatment of chronic lymphocytic leukemia (CLL), including ibrutinib and duvelisib.

• The Bruton tyrosine kinase (BTK) inhibitor ibrutinib is widely used to treat CLL; we also evaluate the in vivo inhibitory activity of duvelisib against CLL B cells from patients whose disease progressed with ibrutinib.

• In this study, we investigated the inhibition of CLL B cells, CLL-Supporting Cells, and M2 tumor-associated macrophages (TAM) by PI3K-δ and PI3K-γ inhibitors, as well as the interaction of PI3K-δ and PI3K-γ inhibitors with BTK inhibitor ibrutinib.

• We used a patient-derived xenograft model of CLL (PDX) to evaluate the in vivo inhibitory activity of PI3K-δ and PI3K-γ inhibitors alone or in combination with ibrutinib.

• Our results suggest that dual inhibition of PI3K-δ and PI3K-γ may be effective for treating CLL and M2 TAMs, and may be synergistic with BTK inhibition via ibrutinib.

RESULTS

• A CLL-PDX model was used to assess the impact of duvelisib on the number of patient-derived CLL B cells and tumor microenvironment (TME) cells and murine macrophages (mGr1 γ–, IL-4 + M-CSF) in vivo.

• Duvelisib 180 nM significantly reduced the number of CLL B cells (Figure 1A) and the percentage of Ki-67+ cells (Figure 1B).

• Duvelisib 180 nM also significantly reduced the number of patient-derived T cells (Figure 1C) and tumor microenvironment (TME) cells (Figure 1D) in vivo.

• In contrast to the potent activity of PI3K-δ and PI3K-γ inhibitors, the number of M2 TAMs was not significantly reduced by ibrutinib alone.

• Both duvelisib and ibrutinib significantly reduced the number of murine NK cells from BMDMs and in vivo, whereas PI3K-δ inhibitor alone did not significantly reduce murine NK cell number.

• This model suggests that inhibiting both PI3K-δ and PI3K-γ may be effective for treating CLL and M2 TAMs, and may be synergistic with BTK inhibition via ibrutinib.

• In addition, the combination of PI3K-δ and PI3K-γ inhibitors with ibrutinib may be more effective than either agent alone.

• These results support the development of dual inhibition of PI3K-δ and PI3K-γ as a potential therapeutic strategy for treating CLL and M2 TAMs.

CONCLUSIONS

• PI3K-δ and PI3K-γ isoforms play distinct roles in CLL B cells and cells of the TME that support CLL survival and growth.

• PI3K-δ signaling primarily mediates CLL B-cell survival, proliferation, and homing to the spleen in vivo.

• PI3K-γ signaling regulated T cells to the spleen and potentiated the suppressive function of M2 TAMs.

• Ibrutinib was biochemically active against CLL B cells, T cells, and macrophages in vitro.

• Dual PI3K-δ/γ inhibition was more effective at inhibiting CLL B cells in vivo than PI3K-δ inhibition alone.

• Duvelisib demonstrated in vivo inhibitory activity against CLL cells from patients whose disease had progressed during ibrutinib therapy, regardless of BTK mutation status.

REFERENCES

4. Kanches Center for Oncology Research, The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY; Infinity Pharmaceuticals, Cambridge, MA; Department of Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; Ferster Oncology, Needham, MA.

DISCLOSURES

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