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PI3K inhibitor-resistant B-cell lymphomas show distinct functional phenotypes characterized by sensitivity to Bcl-2- or proteasome-inhibition

Johanne U. Hermansen[1,2], Paschalis Athanasiadis[3,4], Yanping Yin[1,2,5], Alberto J. Arribas[6], Lene Skou Nilsen[7], Anthony R. Mato[8], Francesco Bertoni[6], Geir E. Tjønnfjord[2,5], Tero Aittokallio[3,4,9], Sigrid S. Skånland[1,2]

[1]Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway, [2]K. G. Jebsen Centre for B Cell Malignancies, Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [3]Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway, [4]Oslo Centre for Biostatistics and Epidemiology (OCBE), Faculty of Medicine, University of Oslo, Oslo, Norway, [5]Department of Haematology, Oslo University Hospital, Oslo, Norway, [6]Institute of Oncology Research, Faculty of Biomedical Sciences, USI, Bellinzona, Switzerland, [7]University Hospital of North Norway, Tromsø, Norway, [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [9]Institute for Molecular Medicine Finland (FIMM), HiLIFE, University of Helsinki, Helsinki, Finland

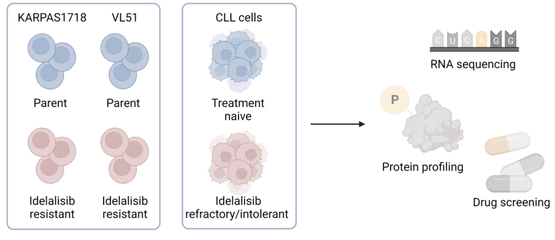
INTRODUCTION

The phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib is approved for treatment of relapsed chronic lymphocytic leukemia (CLL), but its use is limited by severe toxicity and development of resistance. However, other therapeutic options are not necessarily available or safe to all patients. Neither are they curative. Therefore, idelalisib remains in clinical use, and patients who relapse on this therapy most often have no remaining standard of care. Novel treatment strategies are therefore needed for idelalisib-relapsed patients.

OBJECTIVES

- To elucidate idelalisib resistance mechanisms
- Identify subsequent treatment options for relapsed/refractory patients

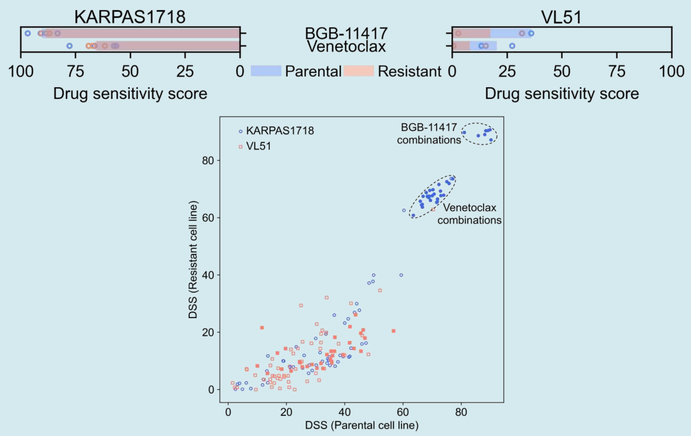
METHODS



We studied parental and idelalisib-resistant versions of the B-cell lymphoma cell lines KARPAS1718 and VL51, CD19+ B cells from healthy blood donors (n=9), and peripheral blood mononuclear cells from treatment naïve (n=8) and idelalisib-exposed (n=13) CLL patients. Drug sensitivity was assessed with the CellTiter-Glo assay. (Phospho)protein profiling was performed by flow cytometry.

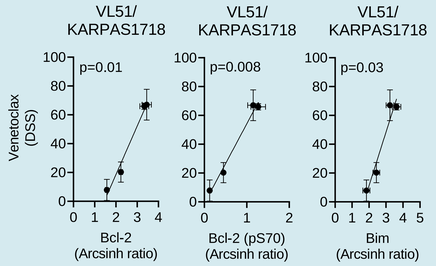
RESULTS

Idelalisib-resistant lymphoma models show distinct sensitivity to Bcl-2 inhibitors

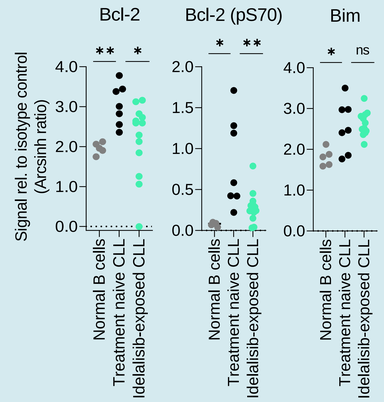


The idelalisib resistant KARPAS1718 strain remained sensitive to Bcl-2 antagonists, while the drug sensitivity was reduced in the resistant VL51 strain.

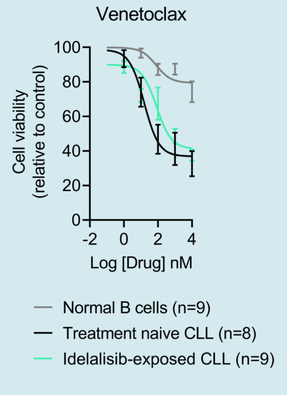
High Bcl-2 or Bim (phospho)protein levels correlate with high sensitivity to venetoclax



Bcl-2 and Bim phosphorylation/expression correlated with venetoclax sensitivity in both parental and resistant cell lines.

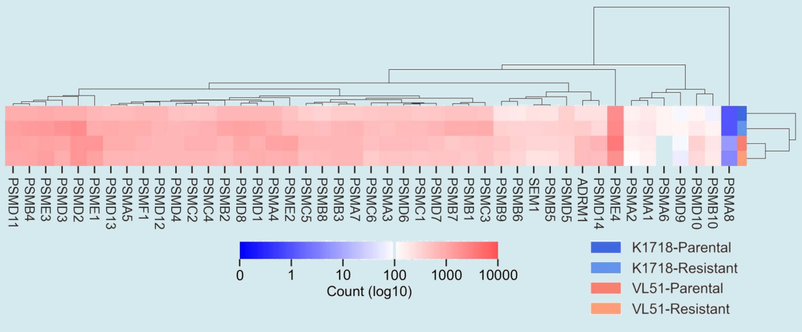


Bcl-2/Bim phosphorylation/expression were reduced in CLL cells from idelalisib intolerant/refractory patients compared to CLL cells from treatment naive patients.

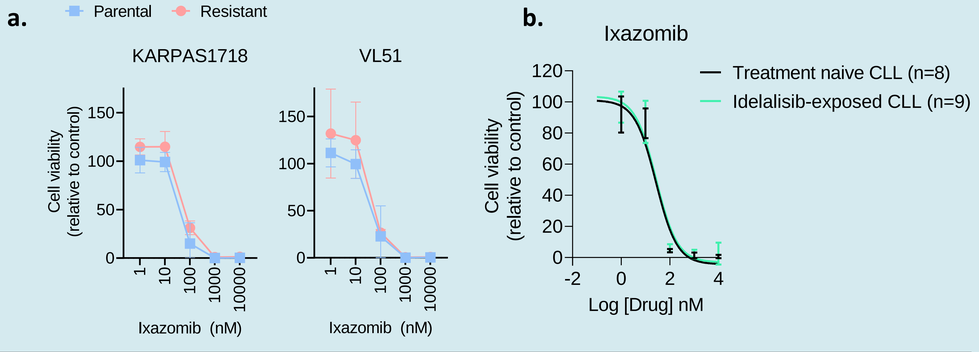


CLL cells from idelalsib intolerant patients were less sensitive to venetoclax than CLL cells from treatment naive patients.

Proteasome inhibitors are effective in idelalisib-resistant lymphoma cells independently of their Bcl-2 inhibitor sensitivity profile



RNA transcripts for the proteasome remained unaffected by induced resistance to idelalisib in all lymphoma *in vitro* models.



a) The proteasome inhibitor ixazomib equally reduced the cell viability in all cell lines independently of their Bcl-2 inhibitor sensitivity profile. **b)** Proteasome inhibition was equally effective in CLL cells from treatment naive and idelalisib exposed patients.

CONCLUSION

We have identified distinct phenotypic responses to idelalisib resistance in B-cell lymphomas and actionable treatment sensitivities. Proteasome inhibition was shown to have broad efficacy. Clinical investigations of proteasome inhibition as a salvage strategy in relapsed/refractory CLL is ongoing (NCT04817956).

CONTACT INFORMATION

E-mail: j.u.hermansen@medisin.uio.no
LinkedIn: juhermansen

Oslo University Hospital

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