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# PARP INHIBITION INDUCES PHILADEPHIA P190 POSITIVE ACUTE LYMPHOID LEUKEMIA CELL DEATH IN LEVELS SIMILAR TO IMATINIB TREATMENT

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## Introduction

While pediatric acute lymphoid leukemia (ALL) patients tend to have a milder prognosis, both younger and elderly adults afflicted with ALL have worst outcomes, with a median overall survival of only 5 years. Philadelphia positive (Ph+) ALL is more severe than Ph- cases and the standard treatment choice relies on chemotherapy plus tyrosine-kinase inhibitors. However, the development of new therapeutic approaches is of utmost importance in the oncological practice when facing the inevitable cases of resistance originated from conventional and targeted therapies.

## Aim and Methods

In this study, we aim to determine the in vitro efficacy of AZD2461, a poly-ADP-ribose polymerase (PARP) inhibitor, against an ALL Ph p190+ cell line and other Ph- lymphoid cell lines, as well as compare its activity to that of Imatinib, the standard of care in Ph+ cases.

Cytotoxicity analyses of the compounds AZD2461, imatinib mesylate and vincristine were performed by Alamar blue assay in three different cell lines: SUP-B15 – B-lymphoblast Ph p190+ ALL –, Raji – B-lymphocyte Burkitt's lymphoma –, and Namalwa – B-lymphocyte Burkitt's lymphoma – at 72 hours of treatment. Viability results were analyzed by non-linear regression using GraphPad Prism (v. 5.01).

## Results

AZD2461 showed cytotoxic activity comparable to that of imatinib in Ph+ SUP-B15, represented by an IC50 of 352 nM and 343.3 nM, respectively. However, the use of PARP inhibitors showed little to no efficacy when treating either of the remaining cell lines, with an IC50 that was not reached in our treatment of Raji and a high IC50 of 20.9 µM in the treatment of Namalwa cell line. Vincristine, a potent inhibitor of mitotic spindle formation, showed high cytotoxic activity against all cell lines, with IC50 values of low nanomolar levels; 0.14 nM, 1.5 nM and 0.22 nM for SUP-B15, Raji and Namalwa, respectively

## Results

**Figure 1.** Non-linear regression of AZD2461, Imatinib (IMA) and Vincristine (VCT) treatment on different cell lines

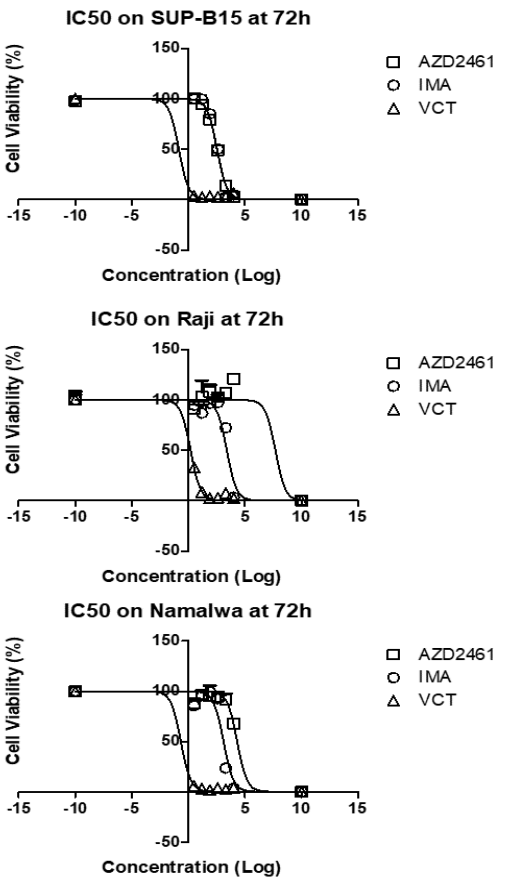


**Table I. Minimum inhibitory concentration for 50% of cell viability (IC50) on different cell lines at nanomolar (nM) measurements.**

| Drug\Cell line | SUP-B15 | Raji | Namalwa |
|---|---|---|---|
| AZD2461 | 352 nM (323.5 to 383.1) | NR | 20938 nM (16152 to 27143) |
| Imatinib | 343.3 nM (272.7 to 432.4) | 2509 nM (1622 to 3882) | 1296 nM (803.8 to 2089) |
| Vincristine | 0.1467 nM (0.05651 to 0.3806) | 1.569 nM (1.242 to 1.982) | 0.2215 nM (0.1062 to 0.4620) |

## Conclusions

In conclusion, PARP inhibition has potential as a new viable strategy to inhibit Ph p190+ ALL growth *in vitro* and further investigations into this topic are warranted in order to elucidate PARP's actual role in leukemogenesis.

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