



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

605. MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

TP53 Aberrant B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) Are Uniquely Sensitive to a Combination of Pyrimidine De Novo Synthesis Blockade and Replication Checkpoint Inhibition

Gawin R. Stoll, MSc¹, Dorette Van Ingen Schenau¹, Willem P. J. Cox, MSc¹, Ziqin Tang¹, Emmely M. Wagener¹, Laurens T. van der Meer, PhD¹, Frank N. van Leeuwen, PhD¹

¹Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands

Background

Unlike most solid tumors, the incidence of TP53 aberrations in ALL is only 3% at diagnosis. However, in relapsed ALL this number increases to 12%. More importantly, at relapse, loss of p53 function is associated with therapy failure, with an overall survival of only 20%. Hence, there is a clear clinical need for more effective strategies to treat TP53 aberrant relapsed ALL. Owing to their high proliferative state, leukemic blasts show a high dependency on pyrimidines for DNA synthesis. A lack of pyrimidines leads to replication stress, causing activation of p53 and the DNA damage response pathway.

Results

We used CRISPR/Cas9 to generate TP53 deficient variants of the TP53 proficient BCP-ALL cell lines Nalm6 and RCH-ACV. We used these cell lines in a CRISPR screens and high throughput drug screen, and identified a strong synergy between the targeting of pyrimidine synthesis and DNA checkpoint kinase ATR and its downstream effectors Chk1 and Wee1 in TP53 deficient ALL. To validate these results, we tested the efficacy of a checkpoint inhibition together with Orlistat (BAY-2402234), an inhibitor of Dihydroorotate Dehydrogenase (DHODH), a key enzyme in de novo pyrimidine biosynthesis. This clinical grade inhibitor was evaluated in either wild type or TP53 deficient BCP-ALL and T-ALL cell line models and patient derived xenografts (PDX).

A strong apoptotic response was observed when Orlistat was combined with the ATR inhibitor Berzosertib, most notably in TP53 deficient ALL. This p53 dependency was confirmed using ex vivo cultures of patient derived xenografts (PDX) of diagnosis and relapse pairs, where each diagnostic sample was wild type for TP53, and the relapse carried a TP53 aberration. While little or no synergy was observed in the diagnostic samples, a strong efficacy of the combination was observed in the matched TP53 deficient relapsed samples (Figure 1 A).

Preliminary results from *in vivo* experiments using p53 deficient patient derived xenografts indicate that the combination of Orlistat and Berzosertib is well tolerated, while significantly delaying leukemic growth (Figure 1 B).

Conclusion

Together, our findings suggest that the combined targeting of de novo pyrimidine synthesis and ATR signaling may present a specific and non-genotoxic vulnerability for TP53 aberrant ALL.

Disclosures No relevant conflicts of interest to declare.

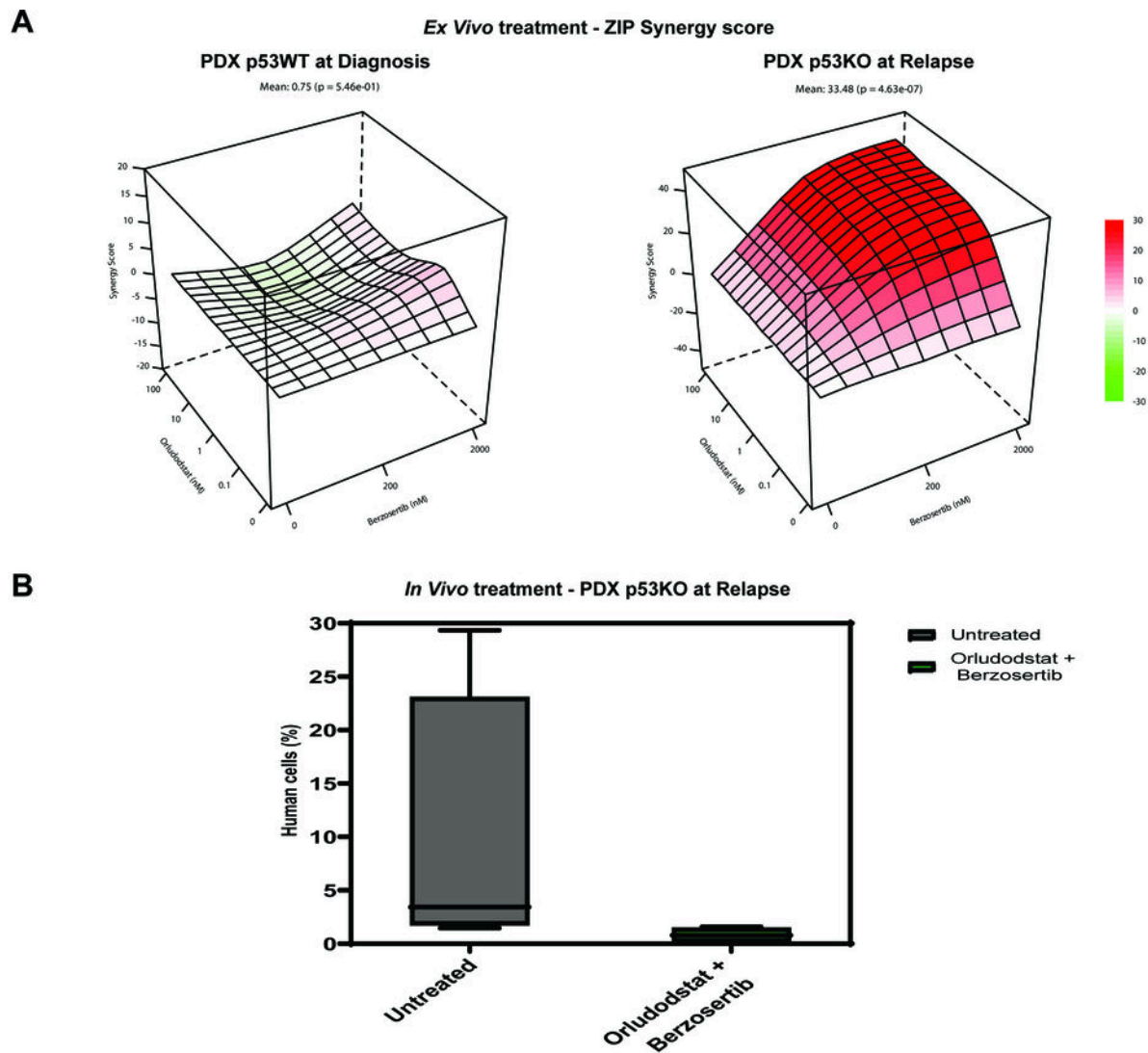


Figure A: p53 dependence was highlighted using ex vivo cultures of patient derived xenografts (PDX), representing diagnosis-relapse pairs where the diagnostic sample was wild type for p53, and the relapse carried a TP53 aberration. While little or no synergy was observed in the diagnostic sample, strong synergy was observed in the matched TP53 aberrant relapsed sample. Responses to Orludostat were determined by quantification of cells positive for amine-reactive dyes using flow cytometry. ZIP Synergy scores were calculated; p53WT patient; ZIP = 0.75, p=5.46e-1 and p53KO patient; ZIP = 33.48, p=4.63e-7.

Figure B: Percentage of human cells in NRG-SM3 mice transplanted with PDX harboring a p53 deletion. Mice were included in untreated (double vehicle), Orludostat (4 mg/kg bodyweight, Monday-Friday), Berzosertib (60 mg/kg bodyweight, Monday-Friday) or the combination of both drug treatments.

Figure 1

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