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A rationale for dual PIM and PI3K inhibition in peripheral T-cell lymphoma

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*P*rovirus *I*ntegration site for *M*oloney leukemia virus (PIM) family members are involved in cellular development, immunoregulation and oncogenesis. In adult organisms, PIM expression is mostly restricted to hematopoietic cells, gastrointestinal tract and urinary tract. Downstream effects of PIMs are several pathways including cell cycle regulation, transcriptional regulation, regulation of mRNA translation and apoptosis, making it a promising target for lymphoma treatment. Previous studies in PTCL cells revealed frequent expression of PIM kinases in patient samples of PTCL and cytotoxic in vitro effects of knockdowns of PIM kinases (Martin-Sanchez et al. 2014). Moreover, the pan-PIM inhibitor AZD1208 showed promising results on ATL-patient material, in vitro as well as in xenograft mice (Bellon et al. 2016; Smedt et al. 2019). The aim of this study was to characterize the response of PTCL lines with different genetic characteristics to pan-PIM kinase inhibition. We point out functional relevance of PIM kinases in cell line models of PTCL but also discovered a PI3K/AKT-driven escape mechanisms to PIM inhibition. This finding provides a rational for dual PIM/PI3K inhibition to increase the efficacy of the treatment. Therefore, 8 PTCL lines of different subtypes were treated either with AZD1208 and/or the PI3K-inhibitor copanlisib.The study at hand demonstrated a rather cytostatic effect of AZD1208 mono-treatment on PTCL cells, depicted by GRmax values >0. Although copanlisib alone showed mild cytotoxic effects in most of the tested lines, combination of AZD1208 and copanlisib increased cytotoxicity significantly in 5 out of 8 tested PTCL lines. As expected, remaining cells showed an abnormal proportion of cells in the G0/G1 state, indicating cell cycle arrest. Furthermore, combination of both inhibitors, but not either of the inhibitors alone, induced a strong decrease in S6 phosphorylation.
Supply with survival factors is one of the requirements for a cancer cell and amongst others regulated by the PI3K/AKT pathway. PIM kinases are able to phosphorylate the BH3-only protein BAD, thereby mimicking high levels of survival factors, preventing apoptosis. Consequential, dual PIM/PI3K inhibition leads to apoptotic priming, indicated by cytochrome C release.
In summary, we here identified a PI3K/AKT-driven escape mechanism upon inhibition of PIM kinases in PTCL and propose dual inhibition of the PI3K and PIM pathways as a promising strategy to treat PTCL.