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Blood 142 (2023) 7133–7134

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

AZD4573 in Combination with CHOP Increases Combination Benefit in Preclinical Peripheral T-Cell Lymphomas Models

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Peripheral T-cell Lymphoma (pTCL) make up about 10% of non-Hodgkin's lymphoma in the United States. Patients with relapsed/refractory pTCL have limited treatment options and poor outcomes to standard of care therapy. Current standard of care for pTCL revolves around the chemotherapy regimens CHOP/E and for CD30-postive pTCLs, brentuximab vedotin is approved.

CDK9 regulates transcription elongation through phosphorylation of RNA polymerase II. AZD4573 is a highly potent and selective CDK9 inhibitor, acute inhibition with AZD4573 downregulates short-lived proteins such as MCL-1, BFL-1, and c-MYC, which are frequently overexpressed in haematologic tumours. It has been previously shown that the expression pattern of the anti-apoptotic BCL-2 family members in pTCL cell line models closely resembled the expression patterns in pTCL patient samples (Koch *et al.* 2019). Expression and dependencies of the anti-apoptotic BCL-2 family members is highly heterogeneous in pTCL; however MCL-1 is the most universally expressed BCL-2 family member. Using the MCL-1 inhibitor AZD5991, we have shown statistically significant benefit in survival when combined with CHOP in 2 MCL-1 dependent preclinical pTCL PDX models (Koch *et al.* 2019). In addition to MCL-1, we have previously reported the importance of the anti-apoptotic protein BFL-1 in mediating cell survival in NHL, including a subset of pTCL (Boiko *et al* 2021).

Consistent with these findings, AZD4573 treatment exhibited a range of activity across the panel of 18 human TCL cell lines, in a 6-hour caspase-3/7 activation assay. 14 of the cell lines were sensitive, having EC_{50} values < 100 nM, and 13 reached a max caspase-3/7 activation of greater than 40%. pTCL cell lines that responded to AZD4573 treatment including ALCL, NK-TCL, and PTCL-NOS and CTCL subtypes. Acute AZD4573 treatment of pTCL cell lines resulted in decreased p-SerRNApoll II and reduced levels of c-MYC and MCL-1 protein levels. To determine if MCL-1 or c-MYC was driving the apoptotic phenotype, we used ribonucleoprotein (RNP) mediated CRISPR knock out (KO) of *MYC* and *MCL1* genes. While pTCL cell lines were dependent on c-MYC and MCL-1 after long term KO, only MCL-1 KO impaired AZD4573 treatment, suggesting that AZD4573 efficacy is mediated through MCL-1, in ALCL pTCL cell lines tested. To determine if combining AZD4573 with CHOP improved efficacy, we tested 5 pTCL cell lines in a 6x6 combination dosing matrix and assessed for viability after 24-72 hours using RealTime-Glo after 18hr exposure to CHOP and AZD4573 added for the last 6hrs. Adding AZD4573 treatment to CHOP schedule *in vitro* increased the combination benefit in pTCL ALCL cell lines that show MCL-1 dependency, but not in CTCL cell line which show a BCL-xL dependency and resistance to AZD4573. CHOP treatment *in vitro* resulted in a decrease in c-MYC levels at 24-48 hours, but not MCL-1 suggesting that combination benefit may be driven through decreased c-MYC levels, as KO of c-MYC resulted is loss of cell viability in these models. These data suggested that treatment with AD4573 either as a monotherapy or in combination with CHOP, would be an effective therapeutic strategy in pTCL. AZD4573 monotherapy is currently being evaluated in a phase 2 study (NCT05140382) to assess the efficacy, safety, and PK in patients with relapsed/refractory pTCL.

Disclosures Potter: *Astra Zeneca:* Current Employment, Current equity holder in publicly-traded company. **Ott:** *Astra Zeneca:* Current Employment, Current equity holder in publicly-traded company. **Saeh:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company. **Olsson:** *AstraZeneca:* Current Employment, Current equity holder in publicly-traded company. **Fawell:** *Astra Zeneca:* Current Employment, Current equity holder in publicly-traded company. **Drew:** *As-*

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https://doi.org/10.1182/blood-2023-179419