Abstract: P1413

Title: PRE-CLINICAL DEVELOPMENT OF AZD5492, A CD8-GUIDED T CELL ENGAGER, FOR B-NON HODGKIN LYMPHOMA INDICATIONS

Abstract Type: Poster Presentation

Topic: Gene therapy, cellular immunotherapy and vaccination - Biology & translational research

Background:

Non-Hodgkin lymphomas (NHL) include diverse neoplasms of the lymphoid compartment, with the majority originating from the B-cell lineage. Bispecific CD20xCD3 T cell engagers (TCEs), both monovalent and bivalent, have shown promising rates of ORRs and CRs in the clinic leading to several FDA approvals for the treatment of R/R DLBCL and FL. However, these treatments are still associated with significant toxicities, including CRS and ICANS, limiting their therapeutic window and potential for clinical combinations.

Aims:

We engineered a first-in-class CD8-guided TCE, AZD5492, for B-NHL malignancies. AZD5492 is an asymmetric, trispecific monoclonal IgG1 antibody which harbors two Fab binding domains to CD20, one VHH binding domain to TCR, one VHH binding domain to CD8 co-receptor.

Methods:

AZD5492 binding and mechanism of action were extensively interrogated, in vitro and in vivo. Control TCEs with abrogated binding domains were generated to evaluate the relative contribution of each antibody component. In addition, the biological activity of AZD5492 was compared to conventional CD3xCD20 TCEs.

Results:

The VHH domains of AZD5492 allow preferential engagement of CD8+ T cells through CD8/TCR binding, leading to the formation of an artificial immunological synapse with CD20+ target cells, T-cell activation and target B cell killing. Compared to conventional CD20xCD3 TCEs, which equally engage and activate CD4+ and CD8+ T cells, AZD5492 drives potent B cell killing through preferential engagement of CD8+ T cells, with reduced CD4+ T cell activation and associated cytokine production.

Potent cytolytic activity of AZD5492 was confirmed across a large array of CD20+ B cell lines of DLBCL, MCL, and CLL origin. Importantly, cytolytic activity was consistently associated with significantly lower cytokine release profiles compared to conventional bivalent CD20xCD3 TCEs.

Additionally, in both subcutaneous and disseminated xenograft B cell tumor models in NSG humanized mice, AZD5492 conferred potent and dose-dependent anti-tumor efficacy. When compared to conventional bivalent CD20xCD3 TCEs, comparable anti-tumor efficacy was achieved with significantly less systemic cytokine production.

Summary/Conclusion:

AZD5492 represents a first-in-class T cell engager for the treatment of B cell lymphomas and has the potential to significantly improve therapeutic index. These findings provide a strong biological rational to evaluate AZD5492 in the clinic.

Keywords: NHL, CD20, Bispecific, CD8 T cells