TPS7091 Poster Session

TITANium: An open-label, global multicenter phase 1/2 study of AZD5492, a first-in-class subcutaneous CD8-guided tri-specific T-cell engager (TCE), in patients (pts) with relapsed or refractory (r/r) B-cell malignancies.

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Background: Bispecific CD20 x CD3 TCEs are changing the treatment landscape for pts with r/r non-Hodgkin lymphomas (NHL); however, they are associated with immune-related toxicities, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which limit their use. AZD5492 is a first-in-class, humanized, asymmetric, subcutaneously-administered, trispecific monoclonal IgG1 antibody that harbors two Fab binding domains to CD20, one VHH binding domain to T-cell receptor and one VHH binding domain to a CD8 co-receptor. Preclinical data have shown that AZD5492 drives B-cell killing through preferential engagement of CD8+ T cells, with reduced CD4+ T-cell activation and associated cytokine production. Thus, AZD5492 may have a wider therapeutic index and safety advantage compared with first generation CD20 x CD3 TCEs which equally engage and activate CD4+ and CD8+ T cells. In an in vivo NHL model, AZD5492 showed potent antitumor activity with reduced cytokine release compared with a CD20 x CD3 comparator. TITANium is a global Phase 1/2 multicenter dose escalation (Part A) and expansion (Part B) study (NCT06542250) of AZD5492 in pts with r/r B-cell malignancies. **Methods:** We present the study design of Part A. Eligible pts are aged ≥18 years with histologically documented CD20+ mature B-cell neoplasm, specifically large B-cell lymphoma (LBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL), with ≥1 measurable lesion (except for CLL) and r/r disease after ≥2 prior lines of therapy. Pts with history of Grade ≥3 CRS or ICANS, post-transplant lymphoproliferative disease, Ritcher's transformation, Burkitt's lymphoma or Burkitt-like lymphoma are excluded. Part A will consist of two independent dose escalation groups: Part A1 will enroll pts with MCL or CLL/SLL; Part A2 will enroll pts with LBCL or FL. Dose escalation will start with pts receiving AZD5492 subcutaneously at a fixed dose per dose-level. An immune-related toxicity during Part A will trigger a double step-up strategy. Thereafter, treatment will continue for a limited duration. Each part will continue dose escalation independently, using fixed or step-up dosing. Part A will initially follow an accelerated titration design and will switch to a modified toxicity probability interval-2 design when triggered by emerging data. The primary objective is to assess safety and tolerability of AZD5492. Key secondary objectives are to evaluate preliminary efficacy, pharmacokinetics and immunogenicity of AZD5492. Enrollment began in September 2024 and is currently ongoing. Clinical trial information: NCT06542250. Research Sponsor: AstraZeneca.