TPS3160 Poster Session

Design of a first-in-human multicenter open-label study of ZW171, a mesothelin x CD3 targeting bispecific T-cell engager, in participants with advanced solid tumors: ZWI-ZW171-101.

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Background: Mesothelin (MSLN) is a membrane glycoprotein overexpressed in several solid tumors, making it a promising target for cancer treatments, including T cell engagers (TCEs). ZW171 is a humanized trivalent bispecific TCE antibody that targets a threshold level of MSLN expression with 2 binding sites and CD3e receptor on T cells with 1 binding site. Preclinical studies of ZW171 demonstrated favorable pharmacology, pharmacokinetics (PK), and toxicology, showing it preferentially kills MSLN-overexpressing cells, activates T cells without significant toxicity, inhibits tumor growth, and is well tolerated in cynomolgus monkeys, suggesting its potential for treating MSLN-expressing tumors[1] while sparing healthy tissues with low levels of expression. This first-in-human, phase 1, ongoing study (ZWI-ZW171-101) evaluates safety, tolerability, PK, and anti-tumor activity of ZW171 in participants with advanced solid tumors. **Methods:** This 2-part study enrolls eligible adult participants with unresectable MSLN-expressing ovarian cancer (OC), non-small cell lung cancer (NSCLC), or other MSLN-expressing cancers, with measurable disease per RECIST v1.1, ECOG PS score of 0 to 1, adequate organ function, and a minimum life expectancy of 12 weeks. Participants with additional progressing malignancies, recent transplants, clinically significant ongoing toxicity, uncontrolled renal, pancreatic or liver disease, or active autoimmune diseases requiring high-dose corticosteroids or immunosuppressive drugs are excluded. Part 1 evaluates the safety and tolerability of ZW171 and Part 2 evaluates the anti-tumor activity while continuing to evaluate safety and tolerability. Part 1 is dose escalation to identify maximum tolerated dose (using modified toxicity probability interval [mTPI-2] design, n=40) among participants with OC or NSCLC receiving subcutaneous ZW171 monotherapy on days 1, 8, and 15 of 3-week (21-day) cycles. Approximately 6 dose levels will be explored based on safety and tolerability. Step-up dosing will be used for cycle 1. Dose level 1, determined by QSP-based MABEL approach[2], is administered at 4.2 μg (day 1), 12.6 μg (day 8), and 38.0 μg (day 15). Part 2 is dose expansion in participants with OC, NSCLC, and other MSLN-expressing cancers (MSLN expression evaluated retrospectively). Primary objectives are to evaluate safety and tolerability of ZW171 and determine the maximum tolerated dose. Key secondary objectives are to assess PK, anti-drug antibodies, and anti-tumor activity. This is a global study with sites in North America, Europe, and Asia; and actively enrolling participants into Part 1. References: 1. Afacan N, et al. Presented at AACR Annual Meeting 2023; abstract 2942. 2. Afacan N, et al. Presented at SITC Annual Meeting 2024; abstract 1062. Clinical trial information: NCT06523803. Research Sponsor: Zymeworks BC Inc.