ZW220, a novel NaPi2b-targeting antibody drug conjugate bearing a topoisomerase I inhibitor payload


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Introduction

ZW220 is a novel NaPi2b-targeting antibody drug conjugate (ADC) targeting human NaPi2b. The ADC is comprised of a novel fully humanized IgG1 antibody covalently conjugated to a novel topoisomerase I inhibitor payload, a maleimidocaproyl derivative, via endogenous interchain cysteines. The drug-linker consists of a maleimidocaproyl (MC) anchor and a GSGF-aminomethyl (AM) protease cleavable sequence. Drug to antibody ratios (DAR) of 8 and 4 have been evaluated with ZW220 ADC.

Mechanism of action

Following NaPi2b binding and receptor-mediated internalization of ZW220, intracellular payload release induces targeted cell death in NaPi2b-positive cells, and subsequent death of NaPi2b-negative cells through bystander-mediated killing.

ZW220 ADC

- **NaPi2b is overexpressed in ovarian and lung cancers**

Expression

NaPi2b is highly expressed in ovarian and lung carcinomas; some NaPi2b expression is also found in endometrioid, thyroid, colorectal, and breast cancers. Normal tissue expression of NaPi2b is observed in lung, liver, and small intestine.

Function

NaPi2b is a multi-pass transmembrane sodium-dependent phosphate transport protein, encoded by SLC34A2 gene, involved in phosphate homeostasis.

ZW220 demonstrates robust anti-tumor activity in ovarian cancer models and NSCLC xenograft models with a range of NaPi2b-expression

- **ZW220 exhibits rapid internalization, potent target-mediated cytotoxicity and bystander killing in tumor cell lines**

ZW220 efficiently internalizes and colocalizes with lysosomes

- **ZW220 mAb binds to NaPi2b with high affinity and specificity**

- **ZW220 is well tolerated in non-human primates**

- **ZW220 has a favorable pharmacokinetic profile**

Conclusions

- ZW220 demonstrates robust preclinical anti-tumor activity in ovarian and lung cancer xenograft models with low NaPi2b expression levels (H-score ≥ 115).
- ZW220 is tolerated at high doses in non-human primates, with an MTD of 45 mg/kg for DAR 8 ADC, and 90 mg/kg for DAR 4 ADC.
- Potential for improvement over NaPi2b-targeting microtubule inhibitor-based ADCs on basis of efficacy, tolerability, and payload mechanism.
- Robust preclinical data package supports the continued development of ZW220 as a best-in-class NaPi2b ADC.

References