ZW439, a novel CLDN18.2-targeting pan-RAS inhibitor antibody-drug conjugate for the treatment of RAS mutated pancreatic cancer

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Introduction

Targeting RAS in pancreatic cancer

Pancreatic cancer remains one of the most difficult to treat cancers, with 5-year survival rates of just 13%[1], and there is an urgent unmet need for novel, differentiated, and effective therapeutics. Recently, encouraging progress has been made through inhibition of RAS, a key oncogenic driver mutated in over 90% of pancreatic ductal adenocarcinoma (PDAC)[2].

RAS inhibitor ADC strategy

Antibody-drug conjugates (ADCs) have demonstrated clinical success at improving the effectiveness of multiple respective classes of small molecules. The full therapeutic potential of pan-RAS inhibitors (pan-RASi) has been limited by toxicities likely arising from on-target inhibition of wild-type RAS in normal tissues, as well as by the emergence of resistance. These challenges may be improved upon by enhancing delivery of a RASi via an ADC mechanism.

A novel and compelling RASi-ADC

Targeted delivery of a novel pan-RASi payload to the tumor

- **Improved response** from payload delivery and exposure
- **Differentiated safety profile** to mitigate toxicity limitations of current small molecule pan-RASi
- **Drug combination** potential improved

ZW439's novel pan-RASi ADC payload: tricomplex RAS inhibitor that forms a ternary complex with cyclophilin A (CypA) and the active, GTP-bound conformation of RAS [RAS(ON)], thereby blocking downstream signaling[3].

CLDN18.2 is a validated oncology target and is commonly expressed in PDAC

- **Clinically validated target**: zolbetuximab approved for CLDN18.2 positive gastric cancer[4]
- **Pancreatic cancer expression**: CLDN18.2 is expressed in 30-70% pancreatic cancer cases[5], ~third of patient tumors considered high[6]
- **Metastatic** lesions from PDAC retain CLDN18.2 expression[7]
- **Intersection of RAS & CLDN18.2** expression and biology presents an opportunity to be exploited for therapeutic gain in PDAC. Experimental evidence suggests a modulation of CLDN18.2 expression and localization upon targeting of RAS[8,9].

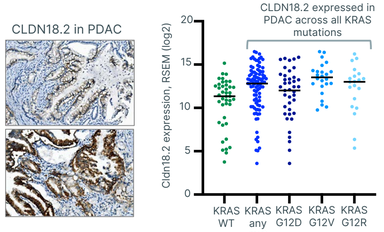

Figure 1. Representative images of PDAC stained with a CLDN18.2 IHC antibody (clone 43-14A). Gene expression of Cldn18.2 in PDAC with WT or mutant KRAS (data sourced from TCGA hosted by Firebrowse, batch normalized from Illumina HiSeq_RNASeqV2). RSEM: RNA-Seq by Expectation-Maximization.

ZW439's novel CLDN18.2 mAb shows favorable binding, internalization and tumor cell spheroid penetration

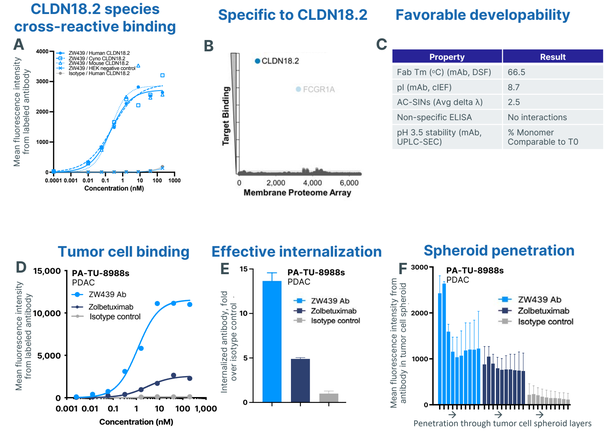

Figure 2. *In vitro* assessment of the ZW439 antibody. **(A)** Species cross-reactive binding to HEK cells expressing human, monkey, or mouse CLDN18.2 by flow cytometry. **(B)** Specificity binding screen of the ZW439 antibody to >6000 membrane proteins (FCGR1A is a common non-specific interaction). **(C)** Developability profile of the ZW439 antibody. **(D)** Binding of the ZW439 antibody compared to zolbetuximab to tumor cells by flow cytometry. **(E)** Internalization of AF488 labelled antibodies to CLDN18.2 expressing SNU-601 cells after 24 h at 50 nM. **(F)** Penetration of AF488 labelled antibodies as quantified by high content imaging of spheroid layers at 24 h post-treatment at 50 nM.

ZW439's novel pan-RASi payload enables potent bystander active cytotoxicity

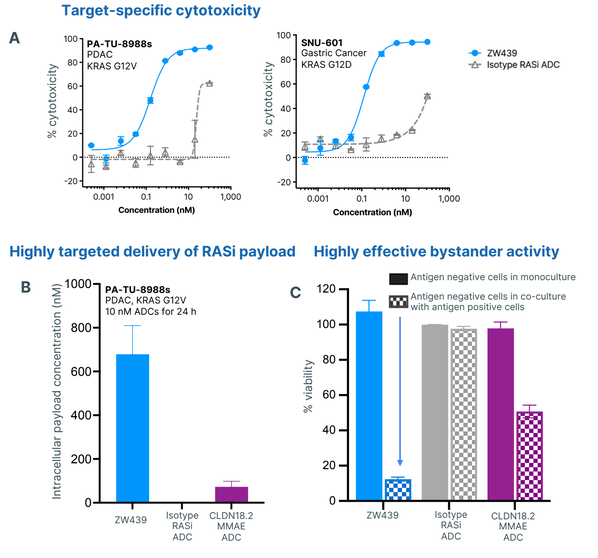

Figure 3. *In vitro* functional assessment of the ZW439 ADC with early candidate pan-RASi payload. **(A)** Cytotoxicity of ZW439 and an isotype control ADC bearing a highly related pan-RASi payload by CellTiter-Glo reagent after treatment of 3D spheroid cultures for 6 days. **(B)** Mass spectrometry quantification of intracellular delivered ADC payloads following treatment of cells with 10 nM of ZW439 (DAR 8), CLDN18.2-MMAE ADC (DAR 4) or isotype control (DAR 8) for 24 h. **(C)** Bystander activity of ZW439 and control ADCs assessed by measuring the viable cell population of fluorescently labelled antigen negative cells (SK-CO-1) in monoculture and in co-culture with antigen positive cells (PA-TU-8988s) by flow cytometry following treatment at 10 nM for 4 days.

ZW439 is highly active in CLDN18.2 expressing xenograft tumor models with favorable PK

- **Target-dependent activity in models with heterogeneous CLDN18.2 expression**
- **ZW439 active at doses as low as 1 mg/kg**
- **ZW439 well tolerated, while body weight loss observed from RMC-6236 dosing**
- **Favorable PK profile**

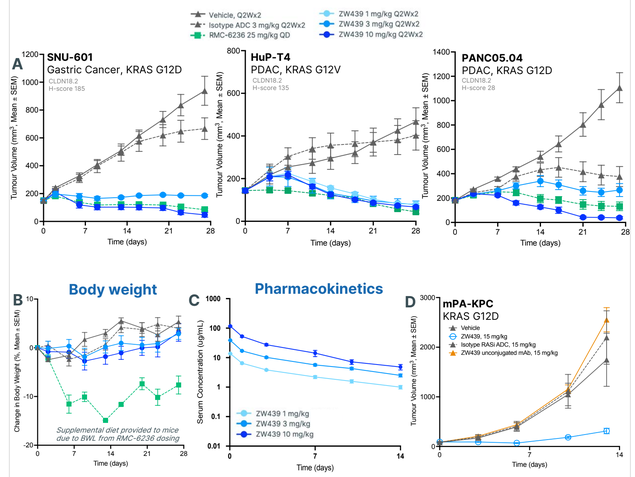

Figure 4. (A) *In vivo* efficacy of the ZW439 ADC with early candidate pan-RASi payload. Antitumor efficacy was assessed in CLDN18.2 expressing cell line derived xenograft (CDX) models of PDAC and gastric cancer in nude mice, n=4 per treatment group. ZW439 was compared to an isotype ADC bearing a highly related pan-RASi payload, and to oral dosing of RMC-6236. H-scores of CDX tumors based on tumor cell membrane CLDN18.2 positivity were determined from a research level IHC assay on archive xenograft FFPE tissues. **(B)** Body weight of mice from the SNU-601 xenograft study following ADC or RMC-6236 dosing. **(C)** Total antibody pharmacokinetics of the ZW439 ADC in mouse serum from the HuP-T4 xenograft study was determined by ELISA. **(D)** *In vivo* efficacy of the ZW439 ADC with early candidate pan-RASi payload in the murine KPC cell line derived allograft model of PDAC driven by KRAS G12D in C57Bl/6 mice (n=6 per group). ZW439 activity was compared to an isotype ADC bearing a highly related pan-RASi payload and to unconjugated antibody.

ZW439 demonstrates targeted RAS pathway inhibition

- **Effective and selective ADC RAS inhibition**
- **RAS inhibition by ZW439 is more targeted than RAS inhibition by a small molecule RAS inhibitor**

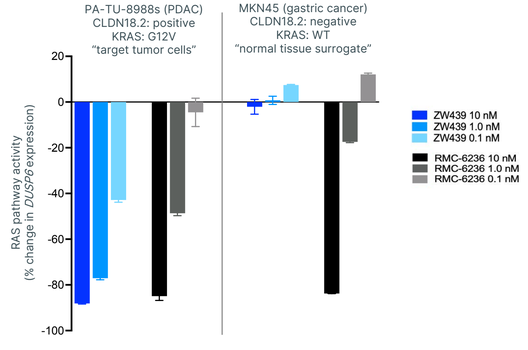

Figure 5. RAS pathway inhibition was assessed by treatment of PA-TU-8988s pancreatic cancer cells (KRAS mutated, CLDN18.2 expressing) and MKN45 gastric cancer cells (KRAS WT, negligible CLDN18.2 expression) for 24 h with the indicated concentrations of ZW439 or free RMC-6236. Expression of *DUSP6* was measured by qPCR and the % change in expression compared to vehicle control was calculated.

RASi-ADC platform demonstrates favorable tolerability in rodents and NHP

RASi ADC platform tolerated in rodents with MTD ≥ 200 mg/kg

- Pan-RASi ADCs of varying potency assessed; highest dose tested was 200 mg/kg [3]
- No mortality, body weight effects, clinical pathology effects
- No observations of GI or skin toxicity

RASi ADC platform tolerated in NHP with MTD ≥ 120 mg/kg

- Pan-RASi ADCs of different potencies assessed [3]
- TAA-RASi ADCs cross-reactive to NHP target
- Highest dose tested 120 mg/kg
- No mortality or body weight effects
- No in-life observations of GI toxicity or skin toxicity

NHP study design and observations

ADC (DAR8)	Dose (mg/kg); schedule	Clinical Signs & Body Weights	Clinical Pathology	MTD
TAA-RASi ADC 1	90; single dose	No treatment related signs or effects	Effects consistent with a transient inflammatory response	≥ 120 mg/kg
	120; single dose			
TAA-RASi ADC 2	90; q3wx2			
	120; q3wx2			

NHP study design: ADCs dosed at single administration or every 3 weeks for 2 doses (2M and 1F cynomolgus monkey per group), with termination 7 days post-final dose; histopathology pending.
Rodent study design: Single dose of ADCs to female BALB/c mice. In-life observations included serum chemistry and hematology, with gross necropsy and histopathology assessment at 1 and 3 weeks post dose.
NHP: non-human primate; TAA: tumor associated antigen.

Conclusions

- ZW439 is designed to target the intersection of RAS biology and CLDN18.2 expression in PDAC.
- ZW439's novel antibody demonstrates favorable properties for application to the ADC modality.
- ZW439 demonstrates target-dependent delivery of novel pan-RASi payload to tumor cells, with associated potent inhibition of RAS activity, cytotoxicity, and strong bystander activity.
- ZW439 demonstrates strong antitumor activity in all CLDN18.2 expressing RAS mutant xenograft models tested, at doses as low as 1 mg/kg, with favorable PK.
- RASi-ADC platform shows a highly encouraging nonclinical safety profile, supporting doses and drug exposures that are expected to be highly efficacious.
- **ZW439 presents a first-in-class opportunity for PDAC patients with severe unmet clinical need.**

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