Development of CLIO-8221: A clinical stage HER2-targeted dual-payload ADC to address ADC resistance

Poster No. 4427

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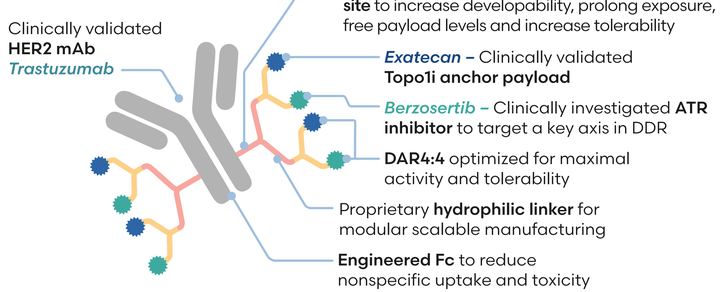
Background

- Antibody-drug conjugates (ADCs) are transforming cancer treatment but remain limited by narrow therapeutic index and rapid resistance
- Studies have reported that tumors retain target expression post treatment with ADCs[1] and sequencing ADCs with the same payload MOA but different targets results in poor outcomes[2], suggesting resistance to the payload rather than the target
- DNA damage response (DDR) drives resistance to Topo1i payloads. Combining Topo1i with DDR inhibition may improve response durability[3], especially in resistant disease
- Dual-payload ADCs are a novel modality with the potential for efficient delivery of combination therapies to the same tumor cell to address resistance

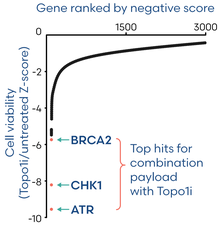
CLIO-8221 targets HER2 to co-deliver Topo1i and ATRi payloads to overcome Topo1i resistance

1.

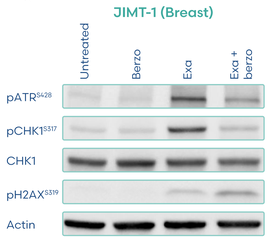


Addition of ATRi to Topo1i augments DNA damage and tumor cell killing

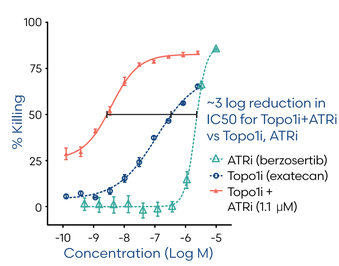
2A.



2B.



2C.



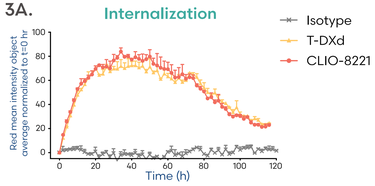
2A. *ATR, a critical component on the DNA damage response, was a top hit in a genome wide screen to identify targets to overcome chemoresistance[4]*

2B. *Western blot analysis of DDR pathway (pATR, pCHK1) and DNA damage induction (pH2AX) with Topo1i, ATRi or the combination*

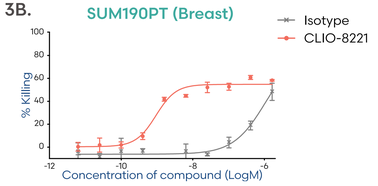
2C. *In vitro cell killing in response to dose ranges of ATRi, Topo1i or the combination*

CLIO-8221 is rapidly internalized and drives cell killing

3A.



3B.

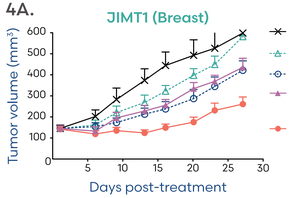


3A. *Internalization of CLIO-8221 into JIMT1 (breast cancer) cells*

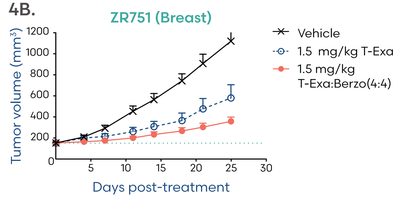
3B. *Tumor cell killing by CLIO-8221*

Topo1i and ATRi dual-payload ADC demonstrates superior activity to single-payload comparators

4A.



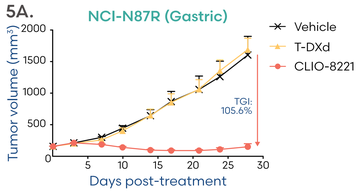
4B.



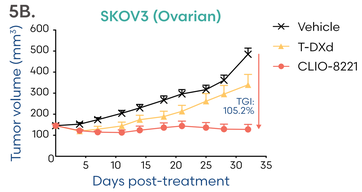
4A, 4B. *CLIO-8221 demonstrates superior activity to single-payload ADCs or a combination of each single-payload control*

CLIO-8221 demonstrates activity in models that are resistant or refractory to T-DXd

5A.



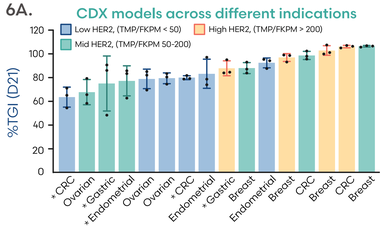
5B.



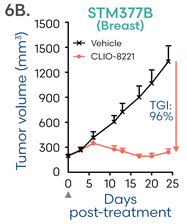
5A, 5B. *CLIO-8221 shows superior activity vs. T-DXd in models that are insensitive to T-DXd*

CLIO-8221 shows strong anti-tumor activity across different indications, HER2 levels, and in PDX models

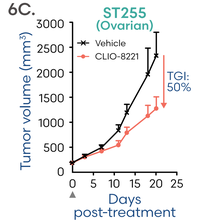
6A.



6B.



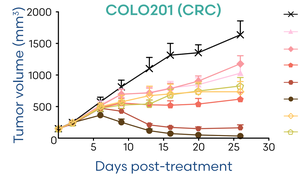
6C.



6A. *Anti-tumor activity of CLIO-8221 denoted by %TGI at 3 weeks post-dose across CDX models denoted by tumor indication; models span a range of HER2 expression and include T-DXd–insensitive tumors (*)*

6B, 6C. *CLIO-8221 shows strong anti-tumor efficacy across PDX models*

CLIO-8221 drives anti-tumor activity at doses ≥3 mg/kg



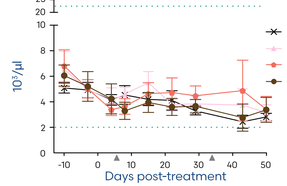
7. *CLIO-8221 demonstrates strong anti-tumor activity in CDX tumor model at doses ≥ 3 mg/kg, this is a lower minimum effective dose (MED) than T-DXd*

MED: Average minimum dose from 3 disparate models that leads to ≥ 75% TGI at D21

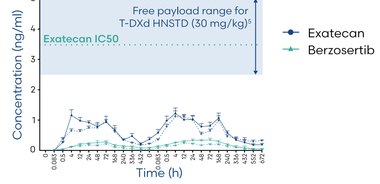
CLIO-8221 is well tolerated in NHP with an NOAEL of 70 mg/kg

- CLIO-8221 was administered IV every Q3W ×2 at 30, 50 and 70 mg/kg. Necropsy was performed on Day 29 and Day 50 for recovery animals
- No test article-related clinical signs were observed; no changes in injection site, body weight, food intake, or serum chemistry were seen; hematology remained within reference ranges
- Overall TK data supports that the PK profiles of total mAb and conjugated ADC are all comparable and exhibit exposure similar to naked antibody with a half life of ~8-13 days demonstrating favorable stability with sustained tumor exposure and with minimal systemic free payload exposure

8A.



8B.



8A. *No changes outside of normal ranges were seen for neutrophils and all other hematology measures (not shown)*

8B. *Levels of free payloads in the 70 mg/kg group were several fold decreased vs those reported with a 30 mg/kg HNSTD T-DXd dose. Solid lines denote male animals while dashed represent females*

Conclusion

- CLIO-8221 is a novel, first-in-class dual-payload ADC. The anti-HER2 antibody is conjugated to exatecan, a Topo1i, and berzosertib, an ATRi, at a DAR (4:4) ratio, selected to maximize anti-tumor efficacy, overcome Topo1i resistance, and reduce systemic toxicity
- CLIO-8221 rapidly internalizes into cancer cells to co-deliver the payloads and drive strong tumor cell killing
- CLIO-8221 induces robust anti-tumor activity across CDX tumor models with varying levels of HER2 and in both T-DXd-sensitive and -insensitive models
- CLIO-8221 drives potent activity at doses of ≥ 3 mg/kg with high tolerability in NHPs of > 70 mg/kg providing a wide therapeutic window
- A phase I trial of CLIO-8221 in patients with advanced solid tumors has been initiated (NCT07300943) and is actively enrolling patients

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References

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