Phase 1/2 study of CLIO-8221, a first-in-class, HER2-targeted, dual-payload exatecan and ATR inhibitor antibody-drug conjugate (ADC) in patients with advanced HER2-expressing solid tumors

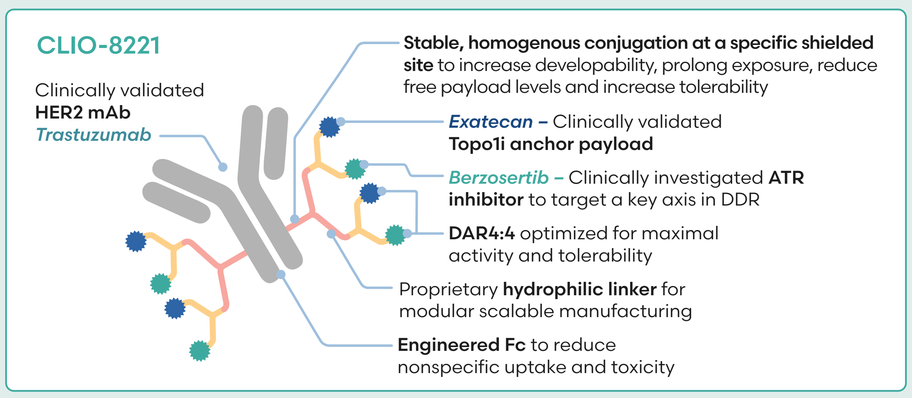
Timothy A. Yap[1], Charlotte Lemech[2], Peter Lau[3], Jermaine Coward[4], Malaka Ameratunga[5], Stephen J. Luen[6], Amita Patnaik[7], Justin Call[8], Erika Hamilton[9], Hongxia Wang[10], Naomi Hunder[11], Sharon Ma[11], Alyson J. Smith[11], Akshaya Bansal[12], Ben Ayers[12], Jerome Boyd-Kirkup[12], Piers J. Ingram[12], Filipa Lynce[13]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Scientia Clinical Research, Sydney; Prince of Wales Hospital School of Clinical Medicine, UNSW Sydney, NSW, Australia; [3]Linear Clinical Research, Perth, WA, Australia; [4]Icon Cancer Care, South Brisbane, QLD, Australia; [5]Alfred Health, Melbourne, VIC, Australia; [6]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [7]The START Center for Cancer Research, San Antonio, TX, USA; [8]The START Center for Cancer Research, Salt Lake City, UT, USA; [9]Sarah Cannon Research Institute, Nashville, TN, USA; [10]Fudan University Affiliated Cancer Hospital, Shanghai, China; [11]Callio Therapeutics Inc., Seattle, WA, USA; [12]Callio Therapeutics Inc., Singapore; [13]Dana-Farber Cancer Institute, Boston, MA, USA

contact@calliotx.com

Background

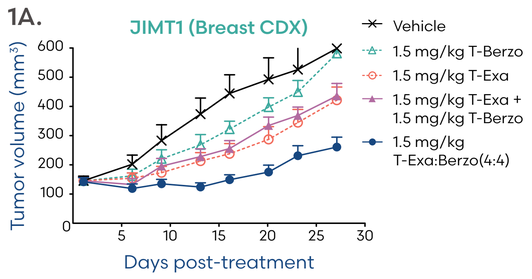
- CLIO-8221 is a novel anti-HER2 dual-payload ADC designed to overcome Topoisomerase 1 inhibitor (Topo1i) resistance by incorporating both the Topo1i exatecan and an inhibitor of ataxia telangiectasia and rad3-related protein (ATRi), a key component of the DNA Damage Response (DDR) pathway, as the payloads
- Trastuzumab deruxtecan (T-DXd) is a standard-of-care treatment for HER2-expressing breast and gastric cancers and has clinical activity in other HER2 IHC 3+ solid tumors. However, most patients develop resistance and disease progression
- Activation of the DDR pathway is a key driver of resistance to Topo1i payloads. Combining Topo1i with DDR inhibition may improve depth and durability of response[1], especially in resistant disease
- In preclinical studies, CLIO-8221 has demonstrated superior activity to T-DXd in HER2-expressing *in vivo* models and was well tolerated with no toxicity findings observed at 70 mg/kg

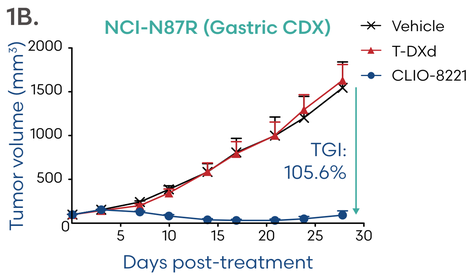


Preclinical anti-tumor activity of CLIO-8221

CLIO-8221 demonstrates superior activity to single-payload comparators and T-DXd

- In preclinical studies, CLIO-8221 binds HER2-expressing tumor cells and is rapidly internalized releasing the dual payloads, driving direct tumor cell killing with a strong bystander effect
- CLIO-8221 shows superior *in vivo* efficacy to single-payload ADCs and shows strong activity in T-DXd-resistant and -refractory xenograft models
- CLIO-8221 drives anti-tumor activity at doses as low as 1.5 mg/kg

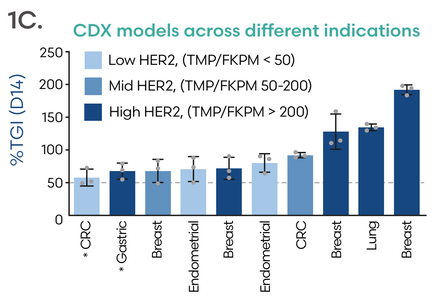


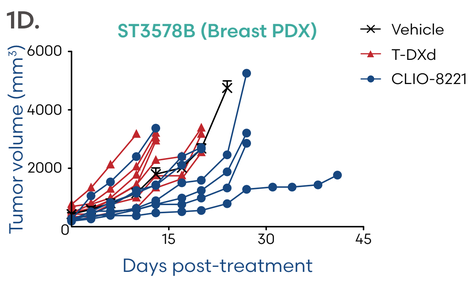


1A. *CLIO-8221 demonstrates superior activity to single-payload ADCs or a combination of each single-payload control[2]*

1B. *CLIO-8221 shows superior activity vs. T-DXd in models that are insensitive to T-DXd[2]*

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





1C. *Anti-tumor activity of CLIO-8221 denoted by %TGI at 2 weeks post-dose across CDX models denoted by tumor indication[2]; models span a range of HER2 expression and include T-DXd–insensitive tumors (*)*

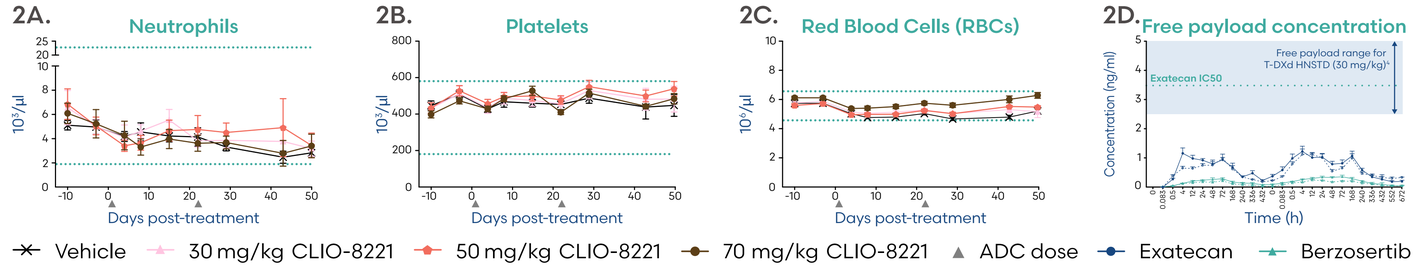
1D. *CLIO-8221 shows anti-tumor efficacy in a T-DXd-refractory breast PDX model*

References

1. *Cancer Res (2014) 74 (23):6968-6979*
2. *AACR 2026. Poster 4427. Callio Therapeutics*
3. *ema.europa.eu/en/documents/assessment-report/enhertu-epar-public-assessment-report_en.pdf*
4. *accessdata.fda.gov/drugsatfda_docs/nda/2019/761139Orig1s000MultidisciplineR.pdf*

CLIO-8221 is well tolerated in NHP and causes no significant adverse effects at doses of 70 mg/kg (highest dose tested)

- CLIO-8221 was administered IV every three weeks at 30, 50 and 70 mg/kg on Days 1 and 22. Necropsy was performed on Day 29 and Day 50 for recovery animals
- CLIO-8221 Q3wx2 was found to be well tolerated up to 70 mg/kg. No test article related clinical signs were observed. No changes in body weight, serum chemistry, histology (including liver, lung, eyes or bone marrow) were seen; hematology remained within reference ranges
- The No-Observed-Adverse-Effect Level (NOAEL) of CLIO-8221 at 70 mg/kg is significantly higher than the NOAEL of ~3-10 mg/kg and the highest non-severely toxic dose (HNSTD) of 30 mg/kg seen for T-DXd[3]

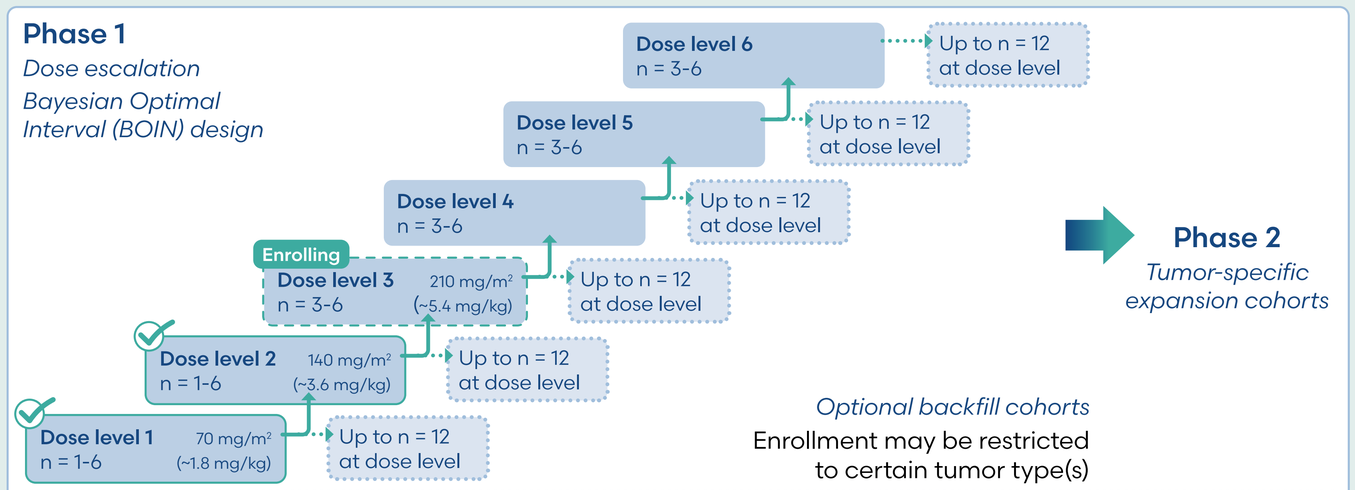


2A, 2B, 2C. *Hematology in NHPs in response to CLIO-8221. Levels of neutrophils[2], platelets and RBCs were measured in animals over time post first and second dose (grey triangles) and showed no changes outside normal ranges (dotted lines)*

2D. *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[2]*

Methods

- CLIO-8221-001 is a Phase 1/2, first in human dose-escalation and -expansion study
- Phase 1 of the study utilizes a BOIN dose-escalation design with optional dose level expansions, while Phase 2 comprises tumor-specific expansion cohorts treated at the doses recommended from Phase 1



Dose escalation may enroll across 7 tumor types:

- HER2+ (HER2 IHC 3+ or 2+/ISH+) breast#
- HER2 low (HER2 IHC 2+/ISH- or IHC 1+) breast*
- HER2+ (HER2 IHC 3+ or 2+/ISH+) gastroesophageal adenocarcinoma (GEA)#
- Other selected HER2-expressing solid tumors

#Prior T-DXd required

**One prior line of Topo1i required*

Key eligibility criteria

- Adults with metastatic or unresectable HER2-expressing solid tumors, including those who previously received T-DXd
- Measurable disease per RECISTv1.1
- Previous receipt of therapies known to confer clinical benefit unless ineligible, refused by the patient, or not available in the region

Treatment regimen

- CLIO-8221 will initially be given by IV infusion on Day 1 of a 21-day cycle
- Treatment may continue until disease progression, unacceptable toxicity, or other reason for discontinuation

Objectives

Primary objectives	*Secondary and exploratory objectives*
Assess the safety and tolerability of CLIO-8221 and to identify the maximum tolerated dose, if reached, and recommended Phase 2 dose	Evaluate antitumor activity, PK, immunogenicity, and biomarkers including HER2 status and ctDNA biomarkers

Key Takeaways

- CLIO-8221 is a first-in-class dual-payload ADC designed to resensitize tumors to Topo1 inhibition, with the potential to provide a new treatment option for T-DXd-resistant cancers and additional HER2-expressing solid tumors
- Study recruitment is ongoing in Australia and the United States, with plans to activate sites in China
- ClinicalTrials.gov identifier: NCT07300943