Abstract 3121

Therapeutic potential of a HER3 antibody-drug conjugate for the treatment of HER3-expressing cancers

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INTRODUCTION

- HER3 (ERBB3) is expressed on the cell surface of breast cancer, EGFR-mutated non-small cell lung cancer and other solid tumors
- HER3 is a promising antibody-drug conjugate (ADC) target
- Patritumab deruxtecan[1] is currently in clinical evaluation for breast cancer and EGFR-mutated NSCLC with encouraging clinical data in phase I/II clinical trials[2]
- We sought to identify a differentiated HER3 ADC with the potential for improved anti-tumor activity in HER3-expressing solid tumors
- As a proof-of-concept, seribantumab[3], a fully human IgG2 anti-HER3 mAb, was conjugated with a cleavable valine-citrulline linker and MMAE payload via the stochastic cysteine conjugation method to yield an average DAR of 4

METHODS

HER3-ADC1 was evaluated in vitro and in vivo, with patritumab-DXd as a comparator. Binding to BT474 breast carcinoma cells (HER3 high; immunohistochemical (IHC) staining intensity 3+) was measured by flow cytometry. In vitro cytotoxicity was evaluated for HER3-ADC1, isotype-MMAE and free MMAE payload as well as patritumab deruxtecan, isotype-DXd and free deruxtecan payload in BT474, SK-BR-3 breast adenocarcinoma (HER3 high; IHC 3+), and NCI-H446 lung carcinoma (HER3 low; IHC 0 – 1+) cells. In vivo anti-tumor activity was assessed for HER3-ADC1, isotype-MMAE, patritumab-DXd and isotype-DXd in patient-derived xenograft (PDX) models of pancreatic (CTG-0307, HER3 high; IHC 3+) and breast cancer (ST941, HER3 low; IHC 0 – 1+).

CONCLUSIONS

- HER3-ADC1 demonstrated target-dependent in vitro cytotoxicity
- HER3-ADC1 exhibited superior anti-tumor activity compared to patritumab-DXd and induced tumor regressions in a HER3-expressing pancreatic cancer PDX model
- Results from in vitro and in vivo studies highlight the promising therapeutic potential of a seribantumab-based ADC for patients with HER3-expressing cancers
- Studies on the optimization and characterization of a HER3 ADC drug candidate are ongoing

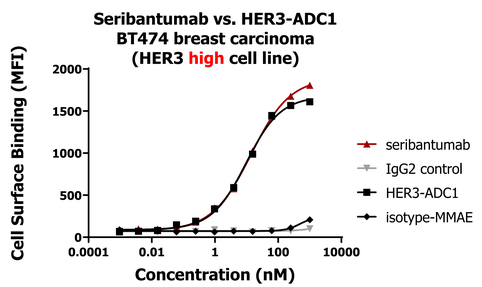
REFERENCES

1. Hashimoto Y, et al. Clin Cancer Res (2019) 25 (23): 7151–7161.
2. Daiichi-Sankyo. 22 Dec 2023. [Press Release] https://www.daiichisankyo.com/files/news/pressrelease/pdf/202312/20231222_E.pdf
3. Curley MD, et al. Mol Cancer Ther (2015) 14 (11): 2642–2652.

Abbreviations: ADC, antibody-drug conjugate; DAR, drug-antibody ratio; DXd, deruxtecan; EC_{50}, half-maximal effective concentration; IC_{50}, half-maximal inhibitory concentration; IgG1, immunoglobulin G1; IgG2, immunoglobulin G2; IHC, immunohistochemistry; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; nd, not determined; qw, once-weekly

Figure 1. Cell surface binding of A. seribantumab vs. HER3-ADC1 and B. patritumab vs. patritumab-DXd in BT474 cells. C. EC_{50} values and ratios for in vitro cell surface binding study

A



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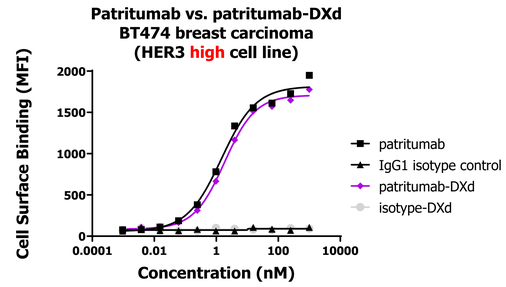


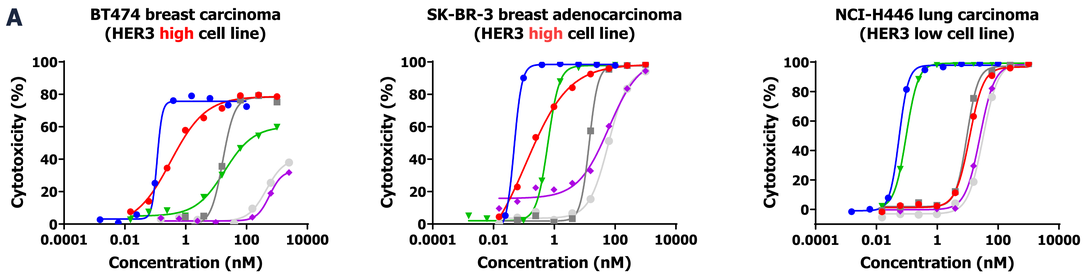
C

EC_{50} (nM), BT474 cell line	
Seribantumab	13.9
HER3-ADC1	9.7
Patritumab	1.5
Patritumab-DXd	1.9
HER3-ADC1 EC_{50}/Seribantumab EC_{50}:	0.70
Patritumab-DXd EC_{50}/Patritumab EC_{50}:	1.27

- Seribantumab and HER3-ADC1 bind to cell surface HER3 with comparable affinity

Figure 2. A. In vitro cytotoxicity of HER3-ADC1 in cell lines expressing varying levels of HER3. B. IC_{50} values for in vitro cytotoxicity study

A



B

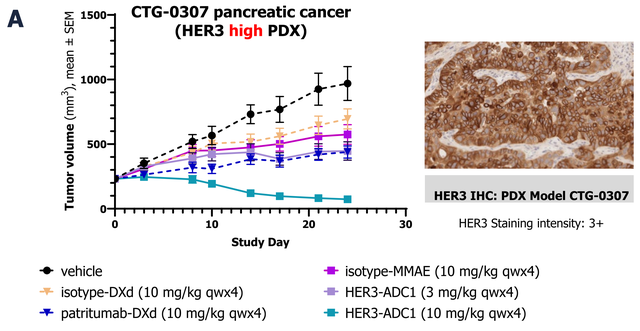
IC_{50} (nM)	SK-BR-3	BT474	NCI-H446
HER3-ADC1	0.09	0.28	9.48
isotype-MMAE	12.78	16.20	8.08
patritumab-DXd	62.55	>1000	34.61
isotype-DXd	60.62	>1000	30.61
MMAE	0.05	0.11	0.05
DXd	0.60	18.60	0.09

isotype-MMAE IC_{50}/HER3-ADC1 IC_{50}		
SK-BR-3	**BT474**	**NCI-H446**
142.00	57.86	0.85

- HER3-ADC1 displays potent in vitro cytotoxicity that is dependent upon HER3 expression levels
- HER3-ADC1 outperforms patritumab-DXd across cell lines in vitro based on cytotoxicity

Figure 3. Anti-tumor activity for model A. CTG-0307 (pancreatic cancer; HER3 high) and B. ST941 (breast cancer; HER3 low/absent). C. % TGI values for PDX models

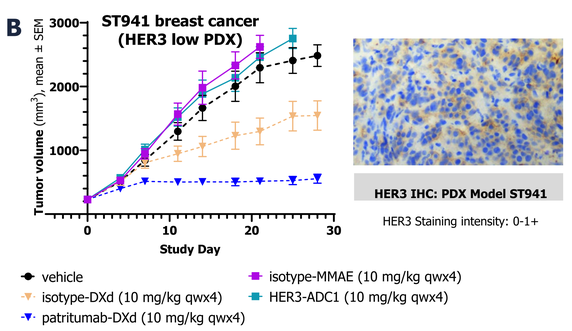
A



HER3 IHC: PDX Model CTG-0307

HER3 Staining intensity: 3+

B



HER3 IHC: PDX Model ST941

HER3 Staining intensity: 0-1+

C

% Tumor Growth Inhibition (TGI) vs. Vehicle	CTG-0307[a]	ST941[b]
HER3-ADC1 (10 mg/kg)	121.68%	-8.14%
HER3-ADC1 (3 mg/kg)	70.73%	nd
isotype-MMAE (10 mg/kg)	53.38%	-15.93%
patritumab-DXd (10 mg/kg)	71.82%	86.14%
isotype-DXd (10 mg/kg)	37.12%	48.25%

[a]Day 24; [b]Day 21; nd, not determined

- HER3-ADC1 (10 mg/kg) induces tumor regression in the HER3 high-expressing CTG-0307 model (A) but does not induce an anti-tumor effect in the HER3 low/null ST941 model (B)
- HER3-ADC1 (10 mg/kg) exhibited superiority over patritumab-DXd (10 mg/kg) in the HER3 high-expressing CTG-0307 model

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