HMBD-501 – a novel Fc engineered, exatecan-based next-generation HER3-targeting Antibody-Drug Conjugate (ADC) shows robust tolerability and efficacy in pre-clinical solid tumor models

#2660

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HMBD-501 – a differentiated, potentially best-in-class HER3 ADC enabled by state-of-the-art technologies

- HER3, a member of the epidermal growth factor receptor (ERBB) family of tyrosine kinase receptors, is overexpressed in a broad range of solid tumors and is associated with disease progression and poor survival[1]. This widespread expression in tumors makes it an ideal target for antibody-drug conjugates (ADCs)
- Fcγ receptor[2] (FcγR)- and macropinocytosis[3]-mediated off-target uptake of ADCs by normal cells have been linked to clinically-observed ADC treatment-related toxicities
- HMBD-501 is a next-generation ADC composed of a best-in-class anti-HER3 Fab with picomolar affinity and an engineered IgG1 Fc domain to abrogate FcγR binding. An exatecan payload is site-specifically conjugated to the antibody with a hydrophilic linker that enhances ADC stability and reduces macropinocytosis

HMBD-501

Best-in-class Fab
- Binding **unaffected by NRG1 levels** — improves activity in high ligand contexts
- **High affinity binding** — ensures relevance across heterogeneous HER3 contexts
- **Best-in-class Fab** — enables optimal ADC profile and DAR

Site-specific stable conjugation
- Enhanced ADC **homogeneity and stability** — improves exposure and reduces toxicity
- **Non-cysteine/maleimide-based conjugation** — avoids *in vivo* retro-Michael instability and reduces systemic toxicity

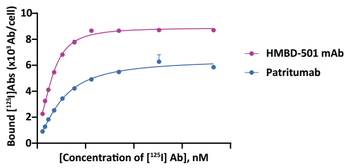
Hydrophilic linker
- **Increased hydrophilicity of linker** — reduces impact of lipophilic payload, reduces macropinocytosis, improves ADC stability and off-target toxicity profile

Clinically-validated payload
- **Topoisomerase I inhibitor** — provides an efficacious, derisked payload in HER3 and other solid tumor targets, with reduced resistance risk

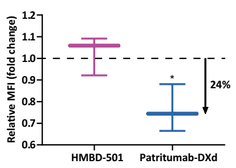
Engineered Fc domain
- **Fc engineering** — abrogates off-target FcγR-mediated uptake and enhances ADC exposure profile and potentially reduces dose frequency

HMBD-501 binds to HER3 with high affinity and is unaffected by the presence of NRG1 ligand

(1a) Specific binding of ^{125}I-anti-HER3 antibodies on T47D cells at 4°C for 4 h



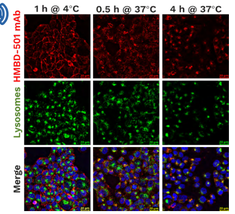
(1b) Relative change in binding of anti-HER3 ADCs in presence of 20 nM NRG1



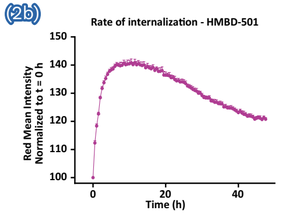
(1a) Comparison of native binding of ^{125}I-labelled anti-HER3 antibodies on HER3+ T47D cells. (1b) FACS binding of HMBD-501 and patritumab-DXd (clinical-stage HER3-ADC) was measured, in the presence or absence of NRG1 ligand, for 3 different cell lines. Mean of relative MFI fold change across cell lines was calculated (p value< 0.01).*

HMBD-501 is rapidly internalized by HER3 expressing cells

(2a)



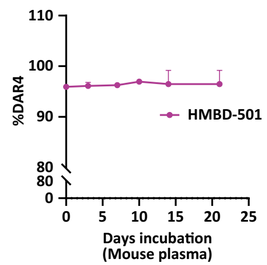
(2b) Rate of internalization - HMBD-501



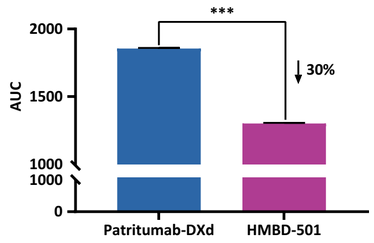
(2a) HMBD-501 mAb internalization into lysosomes in T47D cells (red: HMBD-501, green: LAMP1) imaged using high-resolution fluorescence microscope. (2b) Rate of internalization measured by live cell imaging of pH-sensitive dye-labelled HMBD-501 in T47D cells for 48 h.

HMBD-501 is stable in plasma, shows reduced macropinocytosis, does not bind FcγRs and has significantly decreased binding to FcγR-expressing cells

(3a) Plasma stability assay



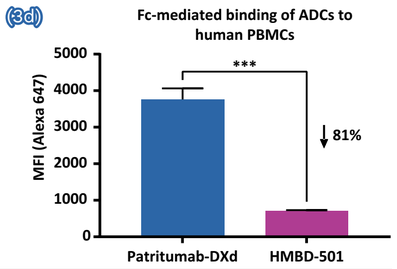
(3b) Megakaryocyte uptake of ADCs via macropinocytosis



(3c) FcγR binding kinetics

Biacore binding kinetics assay		K_D (nM)
CD64 (FcγR I)	Patritumab-DXd	1.8
	HMBD-501	**n.d.**
CD32a (FcγR IIA)	Patritumab-DXd	34.3
	HMBD-501	**n.d.**
CD16a (FcγR IIIA)	Patritumab-DXd	183
	HMBD-501	**n.d.**

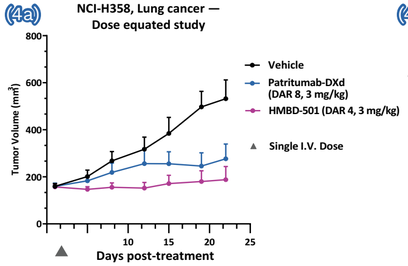
(3d) Fc-mediated binding of ADCs to human PBMCs



*(3a) HMBD-501 was incubated in mouse plasma at 37°C and the DAR assessed by hybrid LC-MS using anti-IgG1 capture. (3b) Live cell imaging of pH-sensitive dye-labelled ADC internalization by human megakaryocytes over 24 h (*** p value<0.001). (3c) Biacore binding kinetics of ADCs to three key FcγRs (n.d. — not detected). (3d) Flow cytometry measurement of Fc-mediated binding of ADCs to human PBMCs from three different donors (*** p value<0.001).*

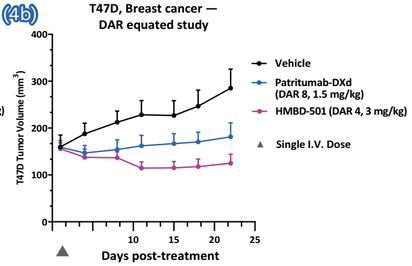
HMBD-501 shows superior tumor growth inhibition in lung and breast cancer CDX models

(4a) NCI-H358, Lung cancer — Dose equated study



NCI-H358 (Lung)	TGI(%)
Patritumab-DXd (DAR 8, 3 mg/kg)	68.5
HMBD-501 (DAR 4, 3 mg/kg)	91.6

(4b) T47D, Breast cancer — DAR equated study



T47D (Breast)	TGI(%)
Patritumab-DXd (DAR 8, 1.5 mg/kg)	82.3
HMBD-501 (DAR 4, 3 mg/kg)	124.6

(4a) NCI-H358 cells, subcutaneous CDX in male NcR Nude mice. Single 3 mg/kg dose of ADC or vehicle I.V. (4b) T47D cells, subcutaneous CDX in female NOD/SCID mice. Single 3 mg/kg dose of HMBD-501 (DAR 4) or DAR-balanced 1.5 mg/kg dose of patritumab-DXd (DAR ~8) or vehicle I.V.

References

[1]Gandullo-Sánchez et al, J Exp Clin Cancer Res (2022) 41:310
[2]P. Thompson et al, Journal of Controlled Release (2016) 236:100-116
[3]Uppal et al, Clin Cancer Res (2015) 21(1):123-33
[4]Hashimoto et al, Clin Cancer Res (2019) 25 (23): 7151–7161.

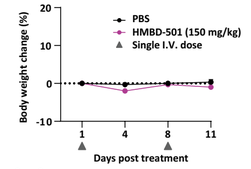
For more information on the HMBD-501 program

hummingbirdbioscience.com/hmbd-501/

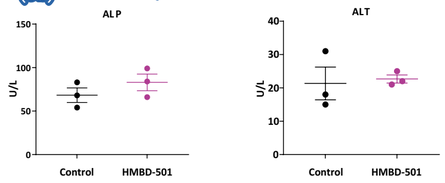
HMBD-501 is well tolerated in mice and rats, with no statistically significant change from baseline observed for body weight, biochemistry or hematology

Mice

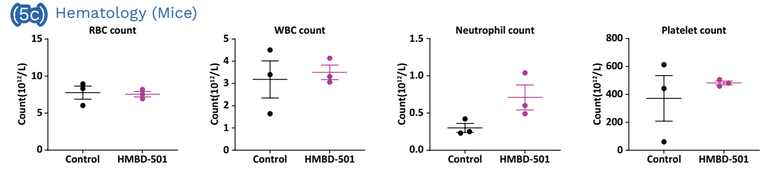
(5a) Body Weight Change (%) (Mice)



(5b) Biochemistry (Mice)

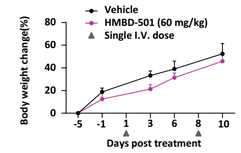


(5c) Hematology (Mice)

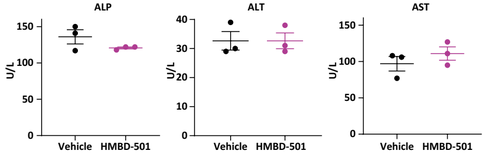


Rats

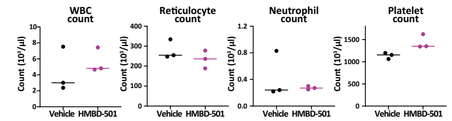
(5d) Body Weight Change (%) (Rats)



(5e) Biochemistry (Rats)



(5f) Hematology (Rats)



(5g)

	Patritumab-DXd (Q3Wx5)*	HMBD-501 (QWx2)
Dose level	60 mg/kg	60 mg/kg
Anemia	Yes	No
WBC decrease	Yes	No
ALT increase	Yes	No
AST increase	Yes	No
Treatment related deaths	Yes @ 194 mg/kg (1/10)	No

Two doses of HMBD-501 on day 1 and 8 were given I.V., at (5a-5c) 150 mg/kg to female SWISS (IcrTac:ICR) mice, and at (5d-5f) 60 mg/kg to female S.D. rats, and necropsy and blood collection was performed on day 11. Percentage change in body weight (5a) in mice and (5d) in rats. Select liver damage markers, (5b) alkaline phosphatase (ALP), and alanine aminotransferase (ALT) in mice and (5e) ALP, ALT and aspartate aminotransferase (AST) in rats. Select blood cell counts shown for red blood cells (RBCs), reticulocytes, white blood cells (WBCs), neutrophils and platelets in (5c) mice and (5f) rats. (5g) Comparison of rat tox data from published patritumab-DXd study to HMBD-501 study at 60 mg/kg

Conclusion

- HMBD-501 is a next generation ADC that combines a best-in-class Fc engineered antibody and an exatecan payload conjugated site-specifically
- HMBD-501 shows high binding affinity to HER3 in the presence or absence of NRG1, and is rapidly internalized into lysosomes
- HMBD-501 demonstrates superior *in vivo* inhibition of tumor growth compared to patritumab-DXd, a clinical-stage HER3-ADC
- HMBD-501 shows reduced macropinocytosis mediated uptake in human megakaryocytes, no FcγR binding, and therefore is well-tolerated in rodents, showing a superior safety profile vs patritumab-DXd
- Our findings strongly support the development of HMBD-501 as a promising ADC therapeutic in the treatment of HER3-expressing solid tumors