Trastuzumab-Dolaflexin, a Highly Potent Fleximer-Based Antibody-Drug Conjugate, Demonstrates a Favorable Therapeutic Index in Exploratory Toxicology Studies in Multiple Species

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Summary

Fleximer® ADCs utilize a polymer-based conjugation platform to enable high drug-antibody ratios (DAR) and significantly greater anti-tumor potency compared to ADCs with DAR 3-4. T-dolaflexin is efficacious at a single dose of 0.67 mg/kg in mouse xenograft models, and achieves prolonged tumor-free survival after a single 2 mg/kg dose in HER2 2+ expressing model that is insensitive to ado-trastuzumab emtansine (T-DM1).

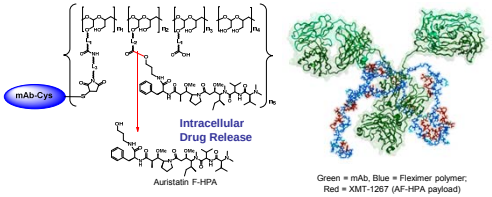
In mouse the 20 and 30 mg/kg doses were well-tolerated based on body weight loss and mortality and achieved a therapeutic index (TI) >40.

In cynomolgus monkeys treated with a single dose of vehicle or T-dolaflexin at 0.67, 1.34 or 2.68 mg/kg all animals survived until scheduled necropsy with limited body weight loss. There were no test-article related findings on gross pathology. Most notable clinical pathology findings were transaminase elevations (primarily AST), and decreased platelet counts at Day 8.

There was no evidence of myelosuppression. Microscopic pathology findings were limited, with no test-article related findings in HER2-expressing organs including heart, lungs and GI tract. All doses were considered well-tolerated.

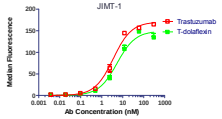
Pharmacokinetics of T-dolaflexin in the range of dose level tested was linear, with excellent conjugated drug stability and minimal exposure to free payload. Exposure based TI observed in cynomolgus monkey was calculated as 3.

Dolaflexin ADC Structure and Drug Release



Green = mAb, Blue = Fleximer polymer;
Red = XMT-1267 (AF-HPA payload)

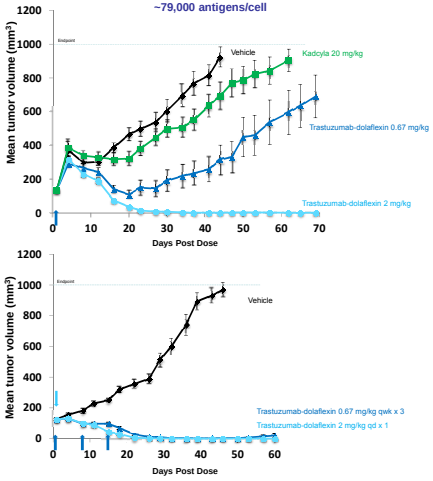
Dolaflexin conjugation does not adversely affect ADC target binding



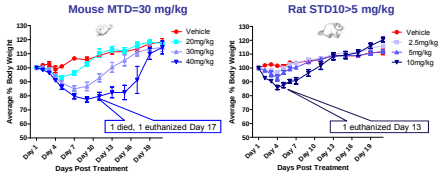
	Trastuzumab	T-dolaflexin
Kd	3.53	5.37

Trastuzumab-dolaflexin ADC MED <0.67 mg/kg

HER2 2+ JIMT-1 breast cancer xenograft model
~79,000 antigens/cell

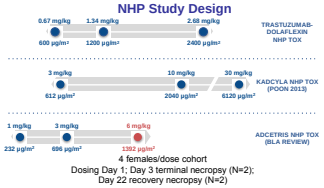


Trastuzumab-dolaflexin ADC well tolerated

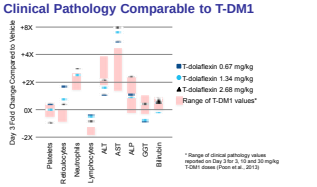


Trastuzumab-dolaflexin ADC achieved a therapeutic index (TI) >40

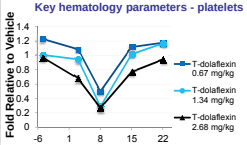
NHP Study Design



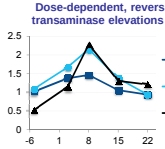
Day 3 Clinical Pathology Comparable to T-DM1



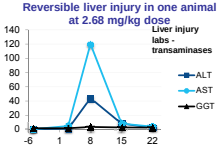
Key hematology parameters - platelets



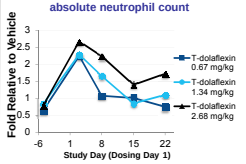
Dose-dependent, reversible transaminase elevations ALT



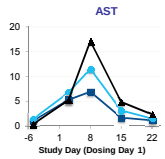
Reversible liver injury in one animal at 2.68 mg/kg dose

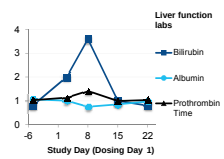


absolute neutrophil count

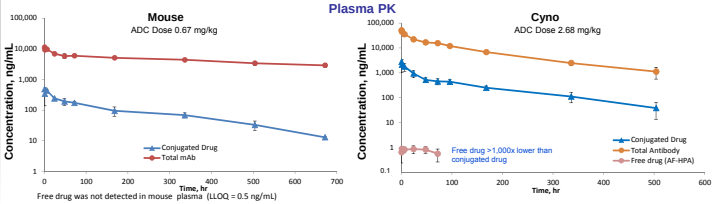


AST





Plasma PK



Species	Dose Level (mg/kg)	Plasma Exposure $AUC_{0\text{-}504}$ (µg*hr/mL)	Calculated TI	Plasma half-life $T_{1/2}$ (dose range average, days)		
				Conjugated Drug*	Total Antibody**	Drug Release
Cyno	2.68	158	3	4.1+/-0.8	4.2+/-0.5	>30
Mouse	0.67	53		6.4 +/-1.0	19.9 +/-4.8	9.4+/-1.1

*) Conjugated Toxin BioA by LC/MS/MS; **) Total mAb analysis by ELISA

Discussion and Conclusions

- T-dolaflexin is efficacious at a single dose of 0.67 mg/kg in JIMT-1 (HER2 2+) model that is insensitive to ado-trastuzumab emtansine while three weekly doses lead to 100% complete responses including tumor free survivors
- T-dolaflexin has excellent PK and is well tolerated (MTD > 30 mg/kg) in mouse
- T-dolaflexin achieved a therapeutic index > 40 in mouse
- T-dolaflexin is well tolerated in cynomolgus monkeys at all tested doses including the highest 2.68 mg/kg. No test-article related findings in HER2-expressing organs - heart, lungs and GI tract
- Adverse effects in cyno are very comparable to adverse findings described for T-DM1
- The lack of neutropenia differentiates T-dolaflexin from ADCs with similar payload class (vc-MMAE)
- T-dolaflexin demonstrates good stability of drug conjugate in plasma and very low exposure to free drug
- T-dolaflexin achieved TI > 3 in cyno compared to exposure of a complete regression dose in mouse

Acknowledgements

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References

1. Poon KA, Flagella K, Beyer J, Tibbitts J, Kaur S, Saad O, Yi JH, Girish S, Dybdal N, Reynolds T. Preclinical safety profile of trastuzumab emtansine (T-DM1): mechanism of action of its cytotoxic component retained with improved tolerability. Toxicol Appl Pharmacol. 2013. 273(2):298-313.
2. Yurkovetskiy A, Bodyak N, Mao Yin, Thomas JD, Conlon P, Stevenson C, Uttard A, Liu Qin, Gumerov D, Ter-Ovanesyan E, Gurijula VR, McGillicudy D, Glynn RE, DeVit M, Poling LP, Park PU, Lowinger TB. Advantages of Polyacetal Polymer-Based Antibody Drug Conjugates: application to low expression targets. 2014 Annual AACR Meeting (San Diego, CA), Abstract #2645