Abstract #2661

Novel albumin-binding maytansinoids inducing long-term partial and complete tumor regressions in several human cancer xenograft models in nude mice

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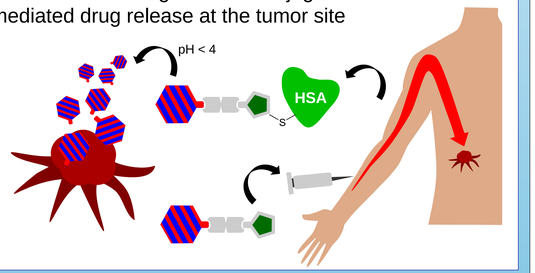
INTRODUCTION & RATIONALE

Maytansine and its analogs (e.g. DM1 and DM4) are potent microtubule-targeting compounds with a narrow therapeutic window. So far, only T-DM1, an antibody-maytansinoid conjugate targeting the HER2 receptor, has been approved for the treatment of Herceptin®-resistant breast cancer.

Our design of two novel albumin-binding maytansinoids (LADR-9 and LADR-10) is based on:

- Identification of two novel maytansine-based highly potent payloads (**ANSA-05**, **ANSA-13**), selected from screening a library of maytansinoids *in vitro* (**Poster #1657**)
- Derivatization with a new water-solubilizing linker (SULF-07) resulting in **LADR-9** and **LADR-10** which bind *in situ* to the Cys-34 position of endogenous albumin
- Accumulation of the drug-albumin conjugate in tumor tissue
- Acid-mediated drug release at the tumor site



IN VITRO EVALUATION

pH-Dependent stability of both drug-albumin conjugates

Compound	pH-Dependent Release of Active Component after 4 h (24 h) [%]	
	pH 4.0	pH 7.4
SA-LADR-9	19 (44)	0.9 (3.3)
SA-LADR-10	22 (54)	1.1 (3.8)

The serum albumin (SA) conjugates of **LADR-9** and **LADR-10** are cleaved under acidic conditions and release the active component.

Plasma stability of both free drugs and drug-albumin conjugates

Compound	Remaining in Plasma after 4 h (24 h) [%]			
	Mouse	Rat	Beagle	Human
Ansa-05	88 (68)	96 (78)	98 (80)	92 (75)
SA-LADR-9	98 (96)	99 (98)	98 (96)	95 (92)
Ansa-13	87 (50)	88 (43)	93 (75)	94 (42)
SA-LADR-10	94 (94)	98 (97)	97 (95)	94 (92)

The *in situ* binding to endogenous albumin significantly stabilizes the drug against degradation in plasma (also see **Poster #1657**).

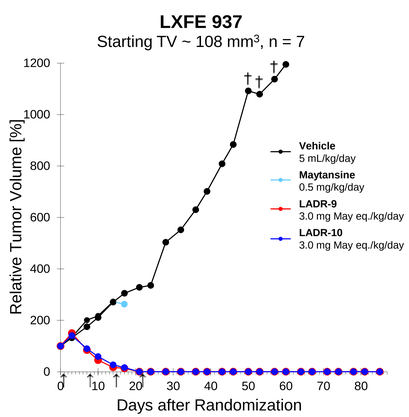
ANTITUMOR ACTIVITY *IN VIVO*

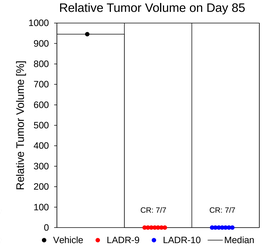
Overview of the antitumor activity of maytansine and both albumin-binding drugs in various human PDX and CDX xenograft tumor models in nude mice

maintained complete remission · complete remission · partial remission · stable disease · partial progressive disease · progressive disease · toxic dose · not available

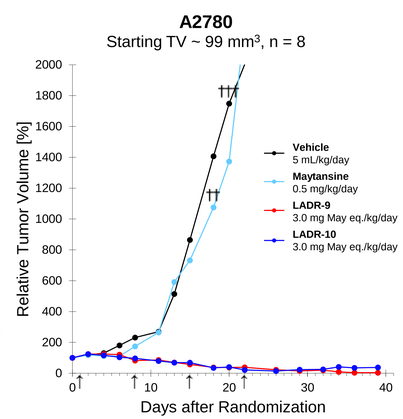
		Median start tumor volume [mm³]	Number of animals per group	Days of observation after last treatment	Maytansine 0.4 mg/kg (1xqWx4)	Maytansine 0.5 mg/kg (1xqWx4)	LADR-9 2.0 mg May eq./kg (1xqWx4)	LADR-9 3.0 mg May eq./kg (1xqWx4)	LADR-10 2.0 mg May eq./kg (1xqWx4)	LADR-10 3.0 mg May eq./kg (1xqWx4)	
Lung	LXFE 937	108	7	63		(7/-)		(-/-)	(1/2)	(-/-)	*
		270	8	63	(-/7)			(2/-)		(-/-)	*
	LXFA 737	331	8	37	(1/-)			(4/-)		(1/-)	
Breast	MDA-MB 231	76	7	41		(-/1)	(1/-)		(-/-)		
	MDA-MB 468	73	7	35		(7/-)		(3/-)		(7/-)	
		87	7	39	(3/-)			(-/-)		(1/-)	
Ovarian	A2780	99	8	17		(-/8)		(2/-)		(2/-)	*
		350	8	51	(-/7)			(-/2)		(-/1)	*
Renal	RXF 631	109	7	42		(-/4)			(-/-)		
		98	7	34	(-/1)			(-/-)		(-/-)	
Head & Neck	HN 10114	103	1	36							
	HN 10913	117	1	32							
	HN 11142	110	1	39							
	HN 11269B	115	1	36							
	HN 11204B	99	1	31							

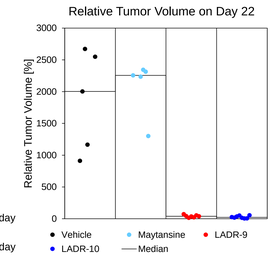
The experiments were evaluated based on the T/C values (by LOCF; MCR <5 %, CR 5-10 %, PR >10-50 %, SD >50-75 %,>75-125 % PP, >125 % PD). The compounds were administered i.v. in a solution of 20 % propylene glycol in 10 mM sodium phosphate buffer (pH 7.0). The pattern fill (dots) indicates a regrowth of tumors towards the end of the experiment. In parentheses, the number of deaths related to toxicity and tumor growth, respectively, are shown. *denotes the experiments shown in detail.



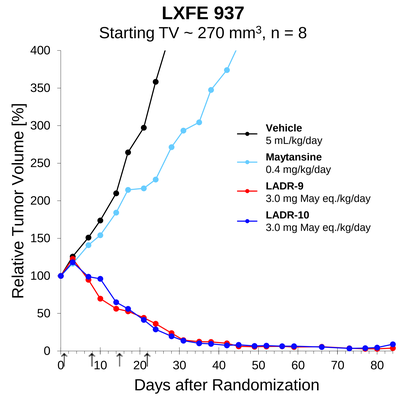


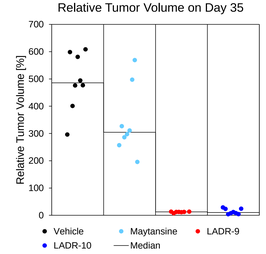
Performed at Charles River Freiburg, Germany using adult female NMRI nu/nu mice (CRL). Fragments of the tumor were transplanted subcutaneously.
The antitumor efficacy of LADR-9 and LADR-10 was statistically significant compared to the control ($p < 0.01$). p-Values were calculated with the Kruskal-Wallis test followed by Dunn's method on day 50.



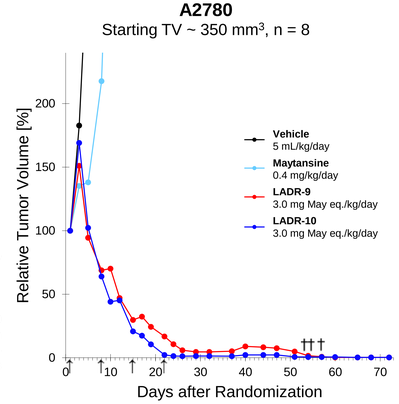


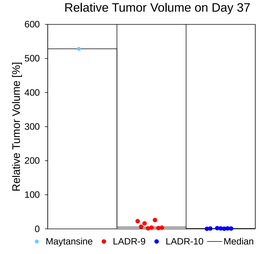
Performed at Epo GmbH, Germany using adult female NMRI nu/nu mice (Janvier, France). $1x10^7$ cells were transplanted subcutaneously.
The antitumor efficacy of LADR-9 and LADR-10 was statistically significant compared to both control and maytansine ($p < 0.01$). p-Values were calculated with the Mann-Whitney U-test on day 22.





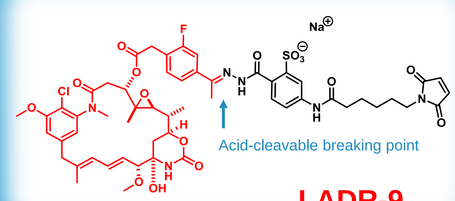
Performed at Charles River Freiburg, Germany using adult female NMRI nu/nu mice (CRL). Fragments of the tumor were transplanted subcutaneously.
The antitumor efficacy of LADR-9 and LADR-10 was statistically significant compared to both control and maytansine at its MTD ($p < 0.01$). p-Values were calculated with the Kruskal-Wallis test followed by Dunn's method on day 49.





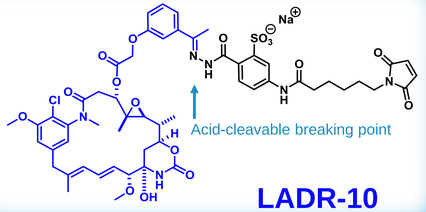
Performed at Epo GmbH, Germany using adult female NMRI nu/nu mice (Janvier, France). $1x10^7$ cells were transplanted subcutaneously.
The antitumor efficacy of LADR-9 and LADR-10 was statistically significant compared to maytansine ($p < 0.01$). p-Values were calculated with the Mann-Whitney U-test on day 37.

ANSA-05 | SULF-07



LADR-9

ANSA-13 | SULF-07



LADR-10

CONCLUSION

Both albumin-binding maytansinoids **LADR-9** and **LADR-10** were evaluated in six human tumor xenograft models and showed excellent antitumor activity inducing long-term partial and complete remission in all rodent models. In addition, both albumin-binding drugs were consistently superior over maytansine which was essentially inactive (statistically significant results). Importantly, even the treatment of large tumors with starting volumes up to 350 mm³ was highly effective.

In a few cases (namely, LXFE 937, MDA-MB 468 and HN 10913), which depended on the tumor type, significant body weight loss (>20 %) with maytansine as well as with the albumin-binding drugs was observed in the animals.