Abstract # 3703

Superior Efficacy of Novel Albumin-binding Auristatin E-based Drugs Compared to Auristatin E in a Panel of Human Xenograft Models in Mice

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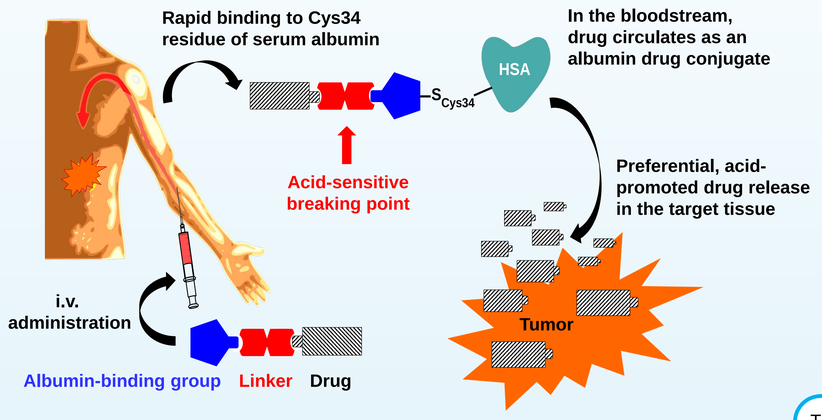
INTRODUCTION & RATIONALE:

Albumin-based Drug Delivery Concept



AE-Keto-Sulf07 (LADR-7) and **AE-Ester-Sulf07 (LADR-8)** albumin-binding are rationally designed to release highly-potent auristatin E derivatives at the tumor site in a pH-dependent manner.

Our design of albumin-binding drugs is based on:

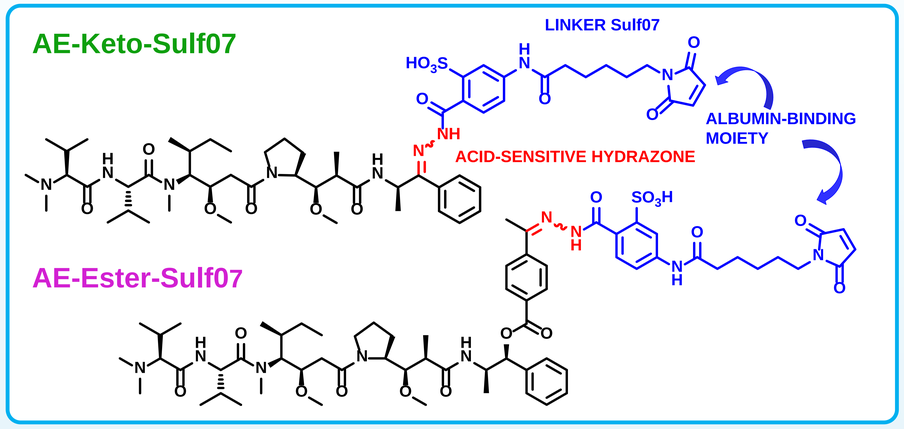
- Auristatin E (AE) cannot be used as a free drug due to toxicity.
- AE derivatives bind to endogenous albumin after i.v. administration with subsequent accumulation in tumor tissue.
- The novel LADR® (linker activated drug release) cleavable linker Sulf07 confers aqueous solubility to the hydrophobic drug.
- The acid-sensitive hydrazone moiety promotes the release of the active drug at the tumor site.

RESULTS:

pH- and plasma-stability of the two albumin drug conjugates

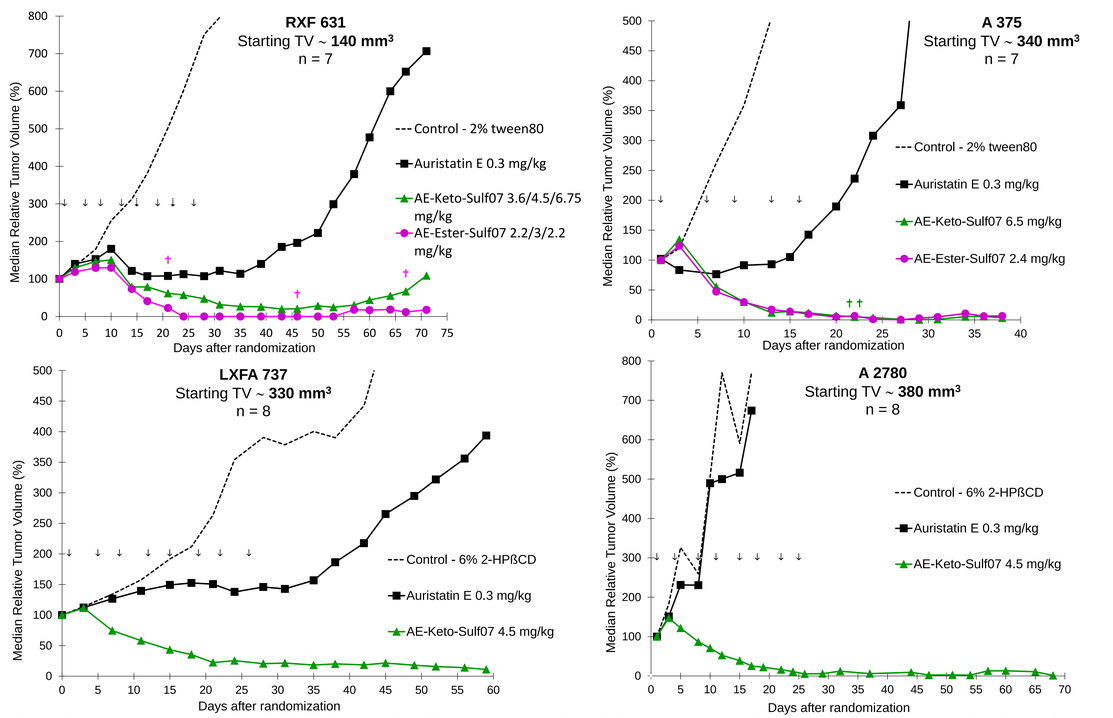
	AE-Keto-Sulf07 % free drug released		AE-Ester-Sulf07 % free drug released	
	4 h	20 h	4 h	20 h
pH 7.4	< 1	< 1	1.0	3.4
pH 4.1	5	19	36	86
Murine Plasma (CD1)	**< 0.1**	**< 0.1**	**2.3**	**7**
Human Plasma (pooled)	**< 0.1**	**< 0.1**	**< 0.1**	**10.8**

pH-stability: AE-Keto-Sulf07 releases AE-Keto. AE-Ester-Sulf07 releases AE-Ester. At acidic pH, the release of AE-Keto is significantly lower than that of AE-Ester.
Plasma-stability: AE-Keto-Sulf07 as well as its release product, AE-Keto, are stable in both murine and human plasma. For AE-Ester-Sulf07, a higher release is observed. In murine plasma, the released AE-Ester is rapidly converted to Auristatin E, while in human plasma the conversion to AE is significantly slower.



Evaluation of the albumin-binding drugs vs. auristatin E in four human tumor xenograft models in nude mice

The antitumor efficacy of AE-Keto-Sulf07 and AE-Ester-Sulf07 was statistically significant compared to the control group and to auristatin E at its MTD (**p < 0.05**) in all four xenograft models. All doses are stated as **AE equivalents**.



Charles River Discovery Research Services Germany GmbH used adult female NMRI nu/nu mice (Charles River Laboratories) for RXF 631 and LXFA 737 xenograft studies. p-values were calculated with Kruskal-Wallis test followed by Dunn's method. Epo GmbH, Germany, used adult female NMRI nu/nu mice (Janvier, France) for A 375 and A 2780 xenograft studies. p-values were calculated with Mann-Whitney U-test. † = mouse died/sacrificed; ↓ = injection day; ↓ = dose change. 2-Hydroxypropyl-β-cyclodextrin = 2-HPβCD.

Antitumor activity of both albumin-binding drugs in further human xenograft models in nude mice

Tumor type	Starting tumor volume (mm^3)	Dose in AE equiv. (mg/kg), 2xqWx4, i.v.	Efficacy (end of study)	No. Death (end of study)	No. mice per group
AE-Keto-Sulf07					
A 375 melanoma	130	3.0[a]	5 CR 2 PR	0	7
MDA-MB 435 melanoma	90	4.0	6 CR 1 PD	0	7
A 2780 ovarian	140	3.0 5.0	2 CR 4 PR 3 CR 3 PR	1 1	7 7
LXFA 737 NSCLC	130	4.5	7 CR	0	7
LXFE 937 NSCLC	270	4.5	8 CR	0	8
AE-Ester-Sulf07					
A 2780 ovarian	170	2.2 3.8[b]	2 CR 6 CR 2 PR	5[c] 0	7 8
LXFA 737 NSCLC	130	2.4	2 CR	5[d]	7
LXFE 937 NSCLC	270	3.8[b]	2 CR	6[d]	8

Complete remission (CR) <10%; partial remission (PR) >10-50%; minor remission (MR) >50-75%; stable disease (SD) >75-125%; progressive disease (PD) >125%.
a) Drug injected 2xqWx3. b) Drug injected 1xqWx4. c) Toxicity due to skin lesions induced by scratching and biting. Mice had to be euthanized. d) Toxicity caused by both skin lesions and body weight loss > 15%.

In addition, a preliminary study in a series of ten head&neck tumor xenografts (n = 1) showed PR and CR in 80-90% of the models.

CONCLUSIONS:

Efficacy:

- Both **AE-Keto-Sulf07** and **AE-Ester-Sulf07** demonstrated excellent antitumor activity in all selected human tumor xenograft models.
- The albumin-binding drugs induced long-term partial and complete tumor regressions, even in models with large starting tumor volumes (270-380 mm^3).
- The albumin-binding drugs showed statistically significant superior activity compared to the parent drug auristatin E in 8 of the 9 models tested.

Toxicity:

- **AE-Keto-Sulf07** induced average body weight change of +6% at the end of the studies.
- **AE-Ester-Sulf07** induced body weight loss only in the NSCLC models (> 15%). However, nude mice related skin lesions due to scratching and biting were consistently observed.