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First in human PK analysis of antibody conjugated liposome encapsulating doxorubicin (HF-K1) in advanced cancer patients: Comparison with ADCs.

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Background: Antibody drug conjugates (ADCs) have been shown to have a better therapeutic index however there have been reports of serious toxicity limiting their use. We propose that it may be due to the relatively low drug to antibody ratio (DAR) which limits the efficacy and toxicity window. HF-K1 is a liposome containing trastuzumab FAB conjugated lipid (TL01) in lipid bilayer encapsulating doxorubicin. Each HF-K1 liposome has in average 12 TL01 and 2.9K molecules of doxorubicin with a calculated drug to antibody ratio of 245. The liposomes bind to HER2 on cancer cells with similar affinity as ADCs, are taken up via endocytosis and release the drug intracellularly. **Methods:** For examining the liposome particle pharmacokinetics, intact liposomes were captured using an anti-trastuzumab Mab and quantified based on an ELISA assay. The liposome particle number vs. time curve was fitted with a one-compartment model. In addition, the liposome penetration into tumor tissues and the binding and uptake processes were modeled using a physiology-based model. For comparison, PK parameters from reported DS8201a and T-DM1 clinical data were converted into the unit of molecular numbers and estimated. **Results:** Table 1 listed the liposome particle PK parameters at the liposome dose of $1.3*10^{13}$ /kg. Compared to ADCs, the liposome particles are bigger, fewer particles are injected, and the circulation half-life is slightly shorter. However, since efficacy mainly results from the drugs taken up by cancer cells rather than the systemic exposure, we calculated the numbers of liposome particles and ADC molecules that could be internalized from 0 to 72 hours after injection. We modeled different scenarios when the cancer cells have either high or low HER2 expression and fast or slow endocytosis. **Conclusions:** Based on the analysis, we identified that with similar endocytosis rates, the greater DAR could lead to higher intracellular drug uptake with HF-K1 as compared to DS8201a and T-DM1. We therefore anticipate better clinical efficacy with HF-K1. HF-K1 is currently being evaluated in an ongoing study (NCT05861895) in patients with advanced solid tumors with HER2 expression (IHC 1+, 2+, 3+). Clinical trial information: NCT05861895. Research Sponsor: Hangzhou Highfield Biopharmaceuticals.

	HF-K1 (45mg/m^2 doxorubicine)					DS8201a (5.4mg/kg)	T-DM1 (3.6mg/kg)
Dose (number/kg)	$1.3*10^{13}$					$2.16*10^{16}$	$1.46*10^{16}$
Cmax (number/ml)	$8*10^{12}$					$5.0*10^{14}$	$3.22*10^{14}$
T1/2 (hours)	~70					~139	~96
Systemic AUC (number*h/mL)	$8*10^{14}$					$5.7*10^{16}$	$4.5*10^{16}$
Clearance (mL/h/kg)	0.8					0.42	0.33
Vss (mL/Kg)	58					75.2	~40
***Tumor cell HER2 expression**	High			Low		Low	High
***Tumor cell endocytosis rate (number/h)**	50	300	1000	50	300	3000	3000
Internalized number per tumor cell (number/72hr)	5243	5903	4870	929	2962	152204	556304
Estimated drug/payloads per tumor cell (millions/72hr)	16	18	15	3.0	9.0	1.2	2.0

*: These parameters were hypothesized based on studies of HER2 expression and cell endocytosis in the literature.