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Translational PK/PD/efficacy modelling and efficacious human dose prediction for a first in class MUC1xEGFR (M1231) bispecific antibody drug conjugate

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CONCLUSIONS

- **A multi-scaled QSP model for M1231, a first-in-class bispecific MUC1xEGFR ADC, was developed incorporating and scaling interactions from the cellular level to enable clinical translation of antitumor activity**
- **M1231 demonstrated a rapid internalization half life of 1 hour with a transit time of approximately 5 hours and a release of payload within 14 hours *in vitro***
- **M1231 was active in the LUX003 PDX model, which was used to predict the efficacy of the ADC**
- **M1231 exhibited a TMDD effect in the monkey due to the binding on EGFR and this was scaled to predict the PK in humans**
- **The TSD was estimated as 2.40 mg/kg and the TRD was estimated as 4.28 mg/kg**
- **A Phase I, first–in-human clinical trial (NCT04695847) is ongoing**

BACKGROUND & OBJECTIVES

- M1231 is a first-in-class, bispecific MUC1xEGFR ADC that delivers a cytotoxic hemiasterlin-related payload to tumor cells expressing MUC1 and EGFR causing cell death through disruption of microtubule dynamics
- M1231 is a homogenous ADC with a consistent DAR of 4

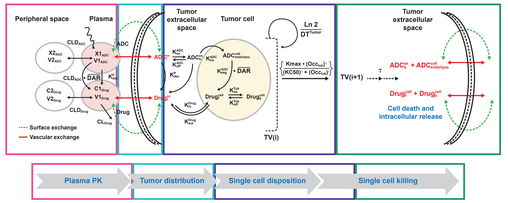
Objectives

- To predict the efficacious dose range for M1231 in NSCLC solid tumors using a multi-scaled QSP modeling approach

METHODS

- A multi-scaled QSP model was developed to quantitatively analyze and expand the interactions of M1231 from the cellular level, to PDX tumor models, and to enable clinical translation of antitumor activity

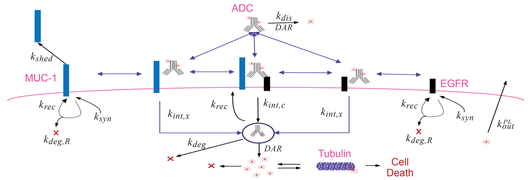
Figure 1: Multi-scaled QSP model



METHODS

- At the cellular level, the interactions of M1231 were characterized from the binding, internalization, intracellular transport and release of the payload kinetics

Figure 2: Cellular interactions of M1231 (with rate constants)

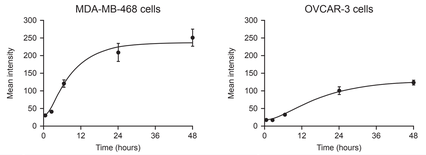


k_{dis} = stability; k_{syn} = synthesis; k_{int} = internalization; k_{rec} = recycling; k_{deg} = degradation; k_{out} = efflux

RESULTS

Figure 3: Model based analysis of the internalization and intracellular transit rate of M1231

- M1231 demonstrated rapid internalization and payload release within 14 hours



Parameter	MDA-MB-468		OVCAR-3	
	Reaction rate, k	Mean time, 1/k	Reaction rate, k	Mean time, 1/k
Internalization	2.0 (1/hour)	0.5 hours	0.7 (1/hour)	1.5 hours
Transit	0.527 (1/hour)	2 hours	0.180 (1/hour)	5.5 hours
Degradation	0.126 (1/hour)	8 hours	0.070 (1/hour)	14 hours

ABBREVIATIONS

ADC: antibody drug conjugate; **DAR**: drug-to-antibody ratio; **EGFR**: epidermal growth factor receptor; **MUC1**: mucin-1; **NSCLC**: non-small cell lung cancer; **PDX**: patient-derived xenograft; **PK-PD**: pharmacokinetics and pharmacodynamics; **QSP**: quantitative systems pharmacology; **TGI**: tumor growth inhibition; **TMDD**: target-mediated drug disposition; **TRD**: tumor regression dose; **TSD**: tumor stasis dose

RESULTS

- Estimating the potency of M1231 in the LUX003 PDX model (PK-PD data fits and relevant parameters)
- M1231 was active in the LUX003 PDX model

Figure 4: Two compartment PK model (left) and TGI fits to the Simeoni model (right)

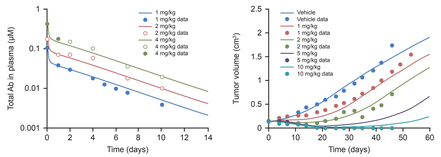


Figure 5: Model estimated curves overlayed on data for total antibody and unconjugated payload in tumor

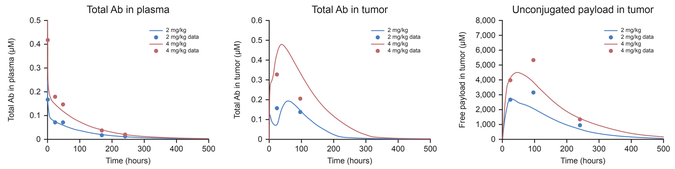


Table 1: Two compartment PK parameters for LUX003

TGI model	Mouse strain	V1 (mL/kg)	V2 (mL/kg)	CL (mL/day/kg)	CLD (mL/day/kg)
PDX LUX003	Ctl:Nu-Foxn1nu	61.59	93.31	35.76	374.35

V1 = volume of distribution central; **V2** = volume of distribution peripheral; **CL**: clearance; **CLD** = clearance distributional

Table 2: TGI parameters for LUX003

	Parameter	Unit	LUX003	Definition
TUMOR GROWTH	k_{g0}	1/day	0.07528	Tumor growth rate, exponential phase
	k_g	cm^3/day	0.0459	Tumor growth rate, linear phase
	PSI	–	20	Transition factor from exponential to linear phase
	V_{max}	cm^3	5	Maximum tumor volume
TUMOR KILLING	k_{max}	1/day	0.39	Maximum rate of tumor killing
	Tau	day	1.738	Time between cell death phases
	Gamma	–	1	Hill coefficient of IC_{50} curve
	IC_{50} (mean)	nM	3,038	ADC concentration at IC_{50}
	IC_{50} (5 and 95 percentiles)	nM	2,127, 7,596	
	Binding sites	#/cell	5E5 MUC1/ 1.3E5 EGFR	
	Internalization rate	1/hour	0.7	

RESULTS

- Translating the PK of M1231 from monkey to human and using the model to project the efficacious dose range to achieve tumor stasis and tumor regression
- M1231 exhibited a TMDD effect in the monkey and scaled allometrically to human

Figure 6: Two compartment PK model with TMDD (left) with fitting of observed data from the monkey (right)

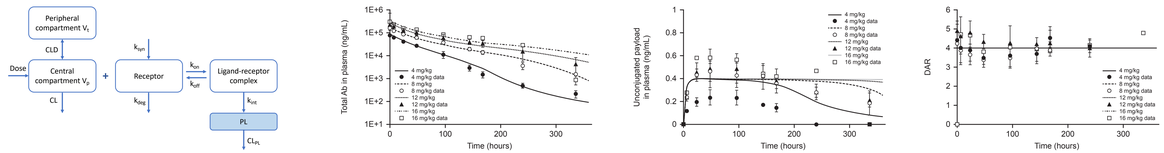


Table 3: TMDD PK parameters for M1231 in the monkey allometrically scaled to human

Parameter	Unit	Cyno			Human		
		Estimate	S.D.	Note	Estimate	S.D.	Note
Vp	L/kg	0.051	0.0006	Estimated	0.051	0.001	Allometric scaling
Vt	L/kg	0.064	0.003	Estimated	0.064	0.003	Allometric scaling
CL	L/day/kg	0.012	0.0003	Estimated	0.008	0.0002	Allometric scaling
CLD	L/day/kg	0.014	0.0007	Estimated	0.009	0.0004	Allometric scaling
k_{PL}	1/hour	0.23	Fixed	Estimated	0.1	Fixed	Allometric scaling
K_{D_TMDD}	nM	3.78	Fixed	Cyno KD	1.47	Fixed	Human KD
K_{ON_TMDD}	1/nM/ hour	2.23	Fixed	Cyno kon	2.25	Fixed	Human kon
k_{SYN_TMDD}	nmol/ day/kg	1.57	Fixed	Estimated	1.57	Fixed	Assumed Cyno value
k_{DEG_TMDD}	1/hour	0.139	Fixed	Estimated	0.139	Fixed	Assumed Cyno value

Vp = volume of distribution in plasma; **Vt** = volume of distribution in tissue/periphery; **CL** = total clearance; **CLD** = distributional clearance; k_{SYN} = synthesis; K_D = affinity; k_{DEG} = degradation; k_{PL} = efflux

Figure 7: Simulated human PK of total M1231 (total antibody) (left) and unconjugated payload (right)

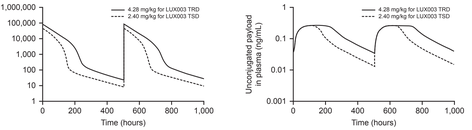


Table 4: Projected efficacious dose and PK parameters of M1231 in humans

Parameter	Unit	PROJECTED					
		TSD			TRD		
		Mean	5 percentile	95 percentile	Mean	5 percentile	95 percentile
Dose	mg/kg	2.40	1.98	4.53	4.28	3.54	8.50
C_{avg}	ng/mL	4,471	3,352	11,262	10,397	7,910	27,489
C_{max}	ng/mL	46,844	38,681	88,358	83,564	69,117	165,811
C_{min}	ng/mL	8.00	6.00	26.00	23.00	16.00	110.00
AUC	ng/mL*hr	2,253,345	1,689,399	5,675,883	5,240,023	3,986,781	13,854,643

TSD = +73% to −66% of tumor volume change from baseline at end of 2 dosing cycles; **TRD** = ≤−66% of tumor volume change from baseline at end of 2 dosing cycles. *TSD and TRD were defined based on back translating clinical RECIST criteria to preclinical TGI

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Anup Zutshi, **Berend Neuteboom**, **Seema Kumar**, **Jianguo Ma** and **Karthik Venkatakrishnan** are employees of EMD Serono Inc, Billerica, MA, USA. **Christine Knuehl**, **Willem Sloot**, **Julia Dotterweich** and **Christiane Amendt** are employees of the healthcare business of Merck KGaA, Darmstadt, Germany. **Taeshin Park**, **John Pappas** and **Kyoung-Ae Kim** are employees of RES Inc, Needham, MA, USA.
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