P814

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MCLA-145 (CD137xPD-L1): a potent CD137 agonist and immune checkpoint inhibitor that does not show signs of peripheral toxicity in preclinical models

Kees Bol[1], Wilfred Marissen[1], Jeroen Elassiass-Schaap[3], Paul Tacken[1], Steef Engels[1], Liang-Chuan Wang[2], Arpita Mondal[2], Mark Throsby[1], Alan Roberts[2], Patrick Mayes[2], Cecile Geuijen[1]

[1]Merus NV, Utrecht, Netherlands; [2]Incyte Corporation, Wilmington, DE; [3]PD-value BV, Utrecht, Netherlands

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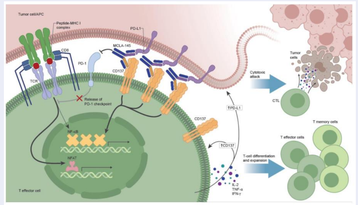
Introduction

- Attempts to improve efficacy of immune checkpoint inhibitors (ICI) by combining with costimulatory receptor agonists such as CD137 (4-1BB) show anti-tumor activity preclinically but systemic toxicity in the clinic.
- MCLA-145 is a human CD137xPD-L1 bispecific common light chain antibody (bAb), identified through functional screening of agonist and ICI bAb combinations (see also P820 on MoA at this SITC conference).
- MCLA-145 can overcome Treg and macrophage suppression to potently activate T cells in these immune suppressive conditions (Fig. 1). In two ICI insensitive xenograft models, MCLA-145 demonstrated anti-tumor activity and CD8+ T cells were enriched in tumors post treatment.

Fig. 1. Schematic of the MCLA-145 mechanism of action



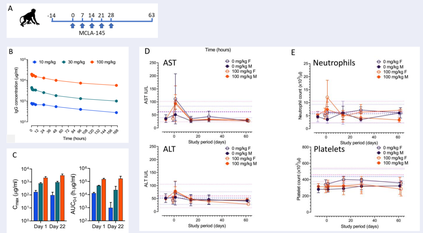
In the MCLA-145 driven synapse, T cells would benefit from effective TCR signaling relieved of PD-1 inhibition and potent CD137 activation. In this way MCLA-145 may effectively and specifically promote antigen presentation and target cell lysis

- In contrast to other ICI mAbs no signs of GvHD were observed in mice following treatment with MCLA-145.
- MCLA-145 possesses some of the 'factors of risk' discussed in regulatory guidelines [FDA guideline on Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (FDA, 2005) and the EMEA guidelines on risk mitigation for first-in-human (FIH) studies (EMEA, 2007, 2018)].
- Therefore, the starting dose of MCLA-145 for the FIH study was selected based on estimates of the MABEL (Minimal Anticipated Biological Effect Level) and not on the no-observable-adverse-effect level (NOAEL).

In vivo cynomolgus toxicity studies

- MCLA-145 is fully cross-reactive with the cynomolgus orthologues of PD-L1 and CD137
- In a GLP repeat dose study, male and female cynomolgus monkeys received 5 weekly doses of MCLA-145 with a subset of animals being observed for a further 4.5 weeks (Fig. 2A)
- Repeated doses of MCLA-145 up to 100 mg/kg/wk were well tolerated without major adverse effects, and dose-dependent increases in serum MCLA-145 concentrations were observed (Fig. 2B and C)
- No change in organ weight or any gross or microscopic pathological findings were noted. Blood chemistry was within normal ranges at all doses and time points including the liver enzymes AST and ALT (Fig. 2D). There was no effect on hematological parameters including neutrophil and platelets numbers (Fig. 2E). Pathological examination of liver and other tissues did not show evidence of increased immune infiltration.
- Based on the results, 100 mg/kg/week was considered to be the NOAEL for this study.

Fig. 2. Safety of MCLA-145 in repeat dose non-human primate study

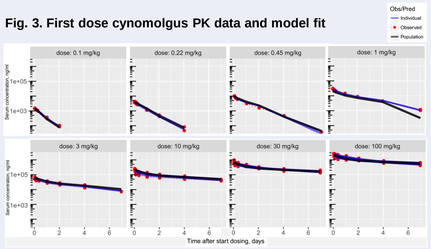


(A) Design of the repeat dose safety study; (B) Serum concentrations of MCLA-145 measured over one cycle (n=10 vehicle and 100mg/kg, n=6 other groups); (C) Cmax and AUC at 10mg/kg (blue), 30 mg/kg (green) and 100 mg/kg (orange) of MCLA-145 measured 24 h after the first and fifth dose combined for males and females; error bars are SD; (D) Serum concentrations of AST and ALT and (E) mean number of circulating neutrophils and platelets measured over the study period at the indicated doses. Reference means with + 1 or -1 SD indicated by blue and pink lines (male and female respectively)

PK in cynomolgus monkeys

- Pharmacokinetic (PK) parameters were assessed during the repeat dose toxicity study (3, 10, 30, 100 mg/kg).
- A single-dose PK study was performed to investigate non-linear PK profiles at lower dose levels (0.1-1 mg/kg).
- Half-life increased markedly with increasing dose (Fig.3), suggesting target-mediated drug disposition (TMDD) at lower doses, with a greater contribution from endogenous IgG clearance mechanisms as doses increased.

Fig. 3. First dose cynomolgus PK data and model fit

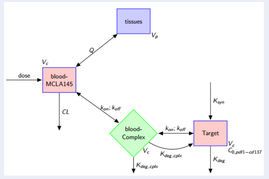


MCLA-145 serum concentrations (ng/mL) were plotted against time. Observed values were compared to predicted values from the PK model.

Development of PK model: TMDD

- A 2-compartment PK model coupled to a TMDD component for which target binding was modeled as dynamic binding with association (kon) and dissociation (koff) constants fixed to values obtained in vitro for binding to PD-L1 (Fig. 4). Target turnover was incorporated and estimated as a degradation rate.
- The PK model was generated based on all available MCLA-145 cynomolgus monkey serum concentration data from the toxicology and PK studies.
- For animals with clear effects of ADA on the PK curves, day 22 samples were removed from the data set
- The model could fit the concentration-time curve well (Fig. 3) with reliable parameters estimates (Tab.1)

Fig. 4. 2-compartment model scheme



Tab. 1. Estimated model parameters

	Parameter	SE
CL, l/day	0.0247	10.8
VC, l	0.141	3.28
Q, l/day	0.104	23.9
VP, l	0.136	5.69
Kdeg, 1/day	0.673	5.75
Baseline, uM	0.00476	12.0
IIV(CL), (log-sd)	0.160	105.
IIV(VC), (log-sd)	0.148	49.7
IIV(Q), (log-sd)	0.786	18.8
IIV(VP), (log-sd)	0.0707	
IIV(Kdeg), (log-sd)	0.0707	
IIV(Baseline), (log-sd)	0.0707	
Residual error, l/day	0.157	29.8

- Allometric scaling was used to scale parameters from monkey to man: Volume of distribution (VC, VP) as proportional to body weight ratio, and clearances as proportional to this ratio raised to the power of 0.75 (Tab.2) This approach generally predicts human antibody kinetics well.
- C0, Koff and Kon were assumed to be equal between man and monkey

Tab. 2. Parameters and factors used for allometeric scaling to man

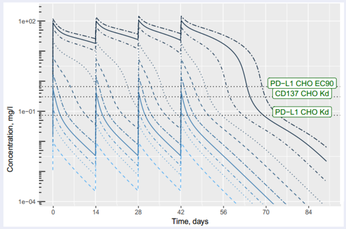
	Parameter	Translation	Factor	Human	Comment
CL, l/day	0.0247	allometric	0.75	0.266	Estimated
VC, l	0.141	allometric	1	3.35	Estimated
Q, l/day	0.104	allometric	0.75	1.12	Estimated
VP, l	0.136	allometric	1	3.24	Estimated
Kdeg, 1/day	0.673	allometric	-0.25	0.305	Estimated
C0, nM	4.76	equal		4.76	Assumed the same between man and monkey
koff, 1/s	0.00110	equal		0.00110	PD-L1 koff; same between man and monkey
kon, 1/s/M	2.24e+06	equal		2.24e+06	PD-L1 kon; same between man and monkey

- This model was used to predict MCLA-145 exposure in humans following a 2-hour IV infusion of MCLA-145 administered Q2W (Fig. 5).

Determination FIH dose levels

- A starting dose for MCLA-145 was selected based on a MABEL strategy.
- It is predicted that MCLA-145 exposure at the proposed starting dose for the FIH study will be >10E4 times lower than the observed exposures at the NOAEL in the monkey (safety margins based on Cmax and AUC) .
- Up to the highest dose in the planned dose escalation part of the FIH study (1200 mg) positive safety margins would still exist.

Fig. 5. Predicted human concentration-time profiles of MCLA-145



Simulated human serum concentration-time profiles of MCLA-145 for various dose levels using allometric PK model. Horizontal lines indicate concentrations corresponding to 50% binding (Kd) to CD137 and PD-L1, and 90% binding to PD-L1 (EC90)

Conclusion

- A safe MCLA-145 starting dose was determined following a MABEL approach.
- MCLA-145 does not exhibit the safety liabilities that have been observed with other potent CD137 agonists in preclinical models.
- A PK model was used to predict exposure in humans following MCLA-145 given IV every 2 weeks.
- Conditional activation of CD137 signaling by MCLA-145, triggered by neighboring target cell expressing of PD-L1, may provide both improved efficacy and safety.
- MCLA-145 is currently undergoing clinical investigation (NCT03922204).

Acknowledgments

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Disclosures

Kees Bol, Wilfred Marissen, Paul Tacken, Steef Engels, Mark Throsby, Cecile Geuijen: Employment and stock ownership – *Merus NV*
Liang-Chuan Wang, Arpita Mondal, Alan Roberts, Patrick Mayes: Employment and stock ownership – *Incyte Corporation;*
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