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

Kees Bol, Wilfred Marseisen, Jeroen Elssassi-Schaap, Paul Tacken, Steef Engels, Liang-Chuan Wang, Apita Mondal, Mark Throsby, Alan Roberson, Patrick Meyers, Cecile Geuijen

In vivo coximogenicity studies

- MCLA-145 is fully cross-reactive with the coximogenic epitopes 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).
- 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. 2C).
- Pharmacokinetic model was used to predict exposure in humans

PK in cynomolgus monkeys

- 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 and CD137.
- Target turnover was incorporated and estimated as a degradation rate.
- The model was used to predict MCLA-145 exposure in humans following a 2-hour iv infusion of MCLA-145 administered Q2W (Fig. 5).

Development of PK model: TMDD

- A safe MCLA-145 starting dose was selected based on a MABEL approach.
- It is predicted that MCLA-145 exposure at the proposed starting dose for the FIH study will be 50-100 mg/kg 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/kg) positive safety margins would still exist.

Conclusion

- MCLA-145 is currently undergoing clinical investigation (NCT03922204).

Disclosures


References


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

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

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

Fig. 4. 2 compartment model scheme

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

Fig. 6. A2-compartment model scheme

Tab. 1. Estimated model parameters

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