ESTABLISHING THE PRECLINICAL/TRANSLATIONAL PK/PD RELATIONSHIP FOR BT7480, A NECTIN-4/CD137 BICYCLE TUMOR-TARGETED IMMUNE CELL AGONIST™ (BICYCLE TICA™)

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Background A new class of modular synthetic drugs, termed *Bicycle* tumor-targeted immune cell agonists (*Bicycle* TICAs), based on constrained bicyclic peptides has been developed as agonists of immune costimulatory receptors in cancer therapeutics.¹ One example is BT7480 which binds simultaneously to Nectin-4 on tumor cells and CD137 on primed immune cells with activation (agonism) of CD137 being dependent on co-ligation of Nectin-4.

Methods *In vitro* CD137 reporter activity and cytokine secretion data were generated using *Bicycle* TICAs including BT7480. These *Bicycle* TICAs could display a concentration-dependent activation (e.g. CD137 activation increases IFN- γ production) reaching a maximal activity, which then decreases as the drug concentration increases.² We developed a mathematical model to analyse this behaviour. We also modelled plasma and tumor pharmacokinetics of BT7480 in CT26-Nectin-4 tumor-bearing mice. A two-compartment model described the drug plasma profile after intravenous dosing and the tumor profile was described by a one effect compartment model. A tumor growth inhibition model for BT7480 was used to describe the preclinical data by placing the model within a mixed effect framework to estimate the population model parameters, i.e., tumor size at time 0 and tumor size growth rate, and to predict the parameter values for each mouse. We assessed how the tumor growth rate values correlate with the immune system markers collected.

Results We assessed the predictions of the *in vitro* model against the experimental observations and found that the position of the turning point could be predicted from the dissociation constants (K_d 's). The combined BT7480 pharmacokinetic model shows that the elimination rate from plasma is faster than that from the tumor. We hypothesized that this results from BT7480 binding to Nectin-4 in the tumor. Also, we found that the level of tumor infiltrating CD8+ T-cells fully captures the treatment effect of BT7480 on tumor growth. Therefore, we established a likely causal link: from pharmacokinetic/dose to CD8+ T-cell infiltration changes and ultimately to tumor growth inhibition.

Conclusions A PK/PD modelling framework was developed that predicts preclinical biomarker level and tumor growth inhibition in response to changes in the BT7480 dose and dosing schedule. In addition, plasma and tumor drug concentration levels can be associated with the target concentration estimated using *in vitro* data.² Namely, the product of the square-root of the two target K_d s is likely to be the free drug concentration at which maximal activity of the trimer [T-Cell—BT7480—Tumor-Cell] is achieved.

REFERENCES

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