1293 ESTABLISHING THE PRECLINICAL PKPD RELATIONSHIP FOR NM32–2668 A ROR1 TARGETING T CELL ENGAGER

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Background NM32-2668 is a fragment-based multispecific antibody therapeutic[1] that has been designed to activate T-cells (via CD3) in the presence of tumour antigen receptor tyrosine kinase-like orphan receptor 1 (ROR1). The objective of this work was to build a mathematical model to establish a PKPD relationship using both *in vitro* and *in vivo* data for NM32-2668.

Methods Data were collected from *in vitro* studies measuring CD4/8 activation and cytotoxicity from a panel of cell lines and patient samples to increasing concentrations of NM32-2668, and from *in vivo* tumour growth inhibition (TGI) data from a humanised mouse model in one cell line with two different donors with increasing doses of NM32-2668. Nonlinear mixed-effects models were used to assess the variability in cytotoxicity as a function of drug concentration and immune system activation. The translatability of *in vitro* potency values for immune system activation was assessed by linking PK to *in vitro* data and to TGI *in vivo* data.

Results The combination of ROR1 expression and CD8 activation fully explained the variance in cytotoxicity across all *in vitro* data. The estimated *in vitro* potency for CD8 activation could successfully be used to provide a link between PK and TGI in vivo.

Conclusions A PK-PD-Efficacy model based on the *in vitro* data was established showing that the cytotoxicity response was strongly correlated to ROR1 expression and CD8 activation. Building on this *in vitro* model, we developed an *in vivo* PK-TGI model that can link immune system activation to TGI.

REFERENCE

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