TRANSLATIONAL PK/RO MODEL OF TETRAVALENT BISPECIFIC ANTIBODY CTX8371: RECEPTOR OCCUPANCY ESTIMATION, PD1 LOSS AND BISPECIFIC BINDING-RELATED AVIDITY INCREASE IN LOW DOSES

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Background Bispecific antibodies (bsAb) might have superior additional mechanisms of action compared to monovalent ones. Not only bsAbs with two binding sites are available, but also tetravalent (novel antibody CTX8371). Additional binding sites might impact antibody pharmacodynamics. We developed a translational PK/RO model of tetravalent bispecific antibody CTX8371 to predict PK, receptor occupancy (RO) and investigate potential effects of bispecific binding on the RO.

Methods PK was described by conventional 2-compartment model. Binding of bsAb to PD1 and PDL1 on T cells in plasma and tumor and on malignant cells in tumor, including cis-binding with tri-, tetra- and pentameric complexes formation was described. Parameters were identified with published data for cynomolgus monkeys,1 translation to the human was made using a common allometric scaling approach.

Results Predicted median [CI] of CTX8371 trough concentrations in plasma were 24.69 ug/ml [2.26; 92.31] (3 mg/kg Q3W), 45.29 ug/ml [7.07; 148.31] (3 mg/kg Q2W), 151.06 ug/ml [23.62; 494.66] (10 mg/kg Q2W) and 100.54 [5.09; 439.64] (20 mg/kg Q4W). Predicted PD1 trough RO on T cells in plasma and tumor, and PDL1 trough RO on T cells in plasma was high (>90%) for all simulated multiple doses. Predicted PDL1 trough RO in tumor was lower (figure 1), median [CI] 63.4% [23.38; 82.94] (3 mg/kg Q3W) - 88.77% [63.06;95.72] (10 mg/kg Q2W). Doses of 80% RO on T cells in blood are 0.01 and 0.2 mg/kg for PD1 and PDL1, correspondingly.

Predicted PD1 RO for simulated single and multiple doses are consistent with RO during canonical Nivolumab treatment.2 For the low doses (<1 mg/kg) increased avidity of CTX8371 is observed: for 0.1 mg/kg Q2W predicted trough PD1 RO on T cells in blood is 87% with cis binding to PDL1 (as for CTX8371), and 77% - without (as for Nivolumab). Predicted through PDL1 RO on T cells in blood is 56% with cis binding to PD1 and 49% - without. The effect increases with lower doses.

Internalization of PD1-antibody complexes in model might explain the observed PD1 loss without any additional effects introduction.

Conclusions First-in-human dose estimated by RO simulations in blood (0.01 - 0.2 mg/kg) corresponds to those selected for clinical trial (0.1 mg/kg).3 Increased avidity is observed for low doses of CTX8371 due to the multimeric bsAb complexes formation. PD1 loss demonstrated in vivo for cynomolgus monkeys4 might be described by the internalization of bsAb-Target complexes only.

REFERENCES

