A population modelling framework to support early clinical development of BI-1910, an agonist monoclonal antibody for tumor necrosis factor 2

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Objective

To develop a population model to characterize pharmacokinetics (PK), receptor occupancy (RO), and the response of the target engagement biomarker soluble TNFR2 (sTNFR2) at different BI-1910 doses, to support early clinical development and guide dose recommendations.

Background

Tumor necrosis factor receptor 2 (TNFR2) is a type I transmembrane protein highly expressed by myeloid cells and specific T cells subsets [1]. TNFR2 is involved in both anti- and pro-inflammatory. Accordingly, **TNFR2 has been suggested as a promising novel target for anticancer treatment**, with both agonists and antagonists demonstrating potent anti-tumor activity in preclinical settings [2].

We are developing **BI-1910**, an **agonistic** human IgG2 monoclonal antibody **targeting TNFR2** that does not block the engagement of TNFR2 with its natural ligand, TNF-α. BI-1910 is currently being evaluated in an ongoing Phase 1/2a, as a single agent and in combination with pembrolizumab, in subjects with advanced/metastatic solid tumors whose disease has progressed after standard therapy (NCT06205706).

Data and methods

PK, RO and sTNFR2 data from **30 patients** receiving BI-1910 **as a single agent** every 3 weeks in doses ranging from 4 to 900 mg were available for the analysis.

Model building was performed in a sequential and integrative manner:

- A PK model was developed and link to RO
- The PK/RO model was extended to include sTNFR2 information

Analyses were performed in NONMEM 7.5, using FOCEI algorithm

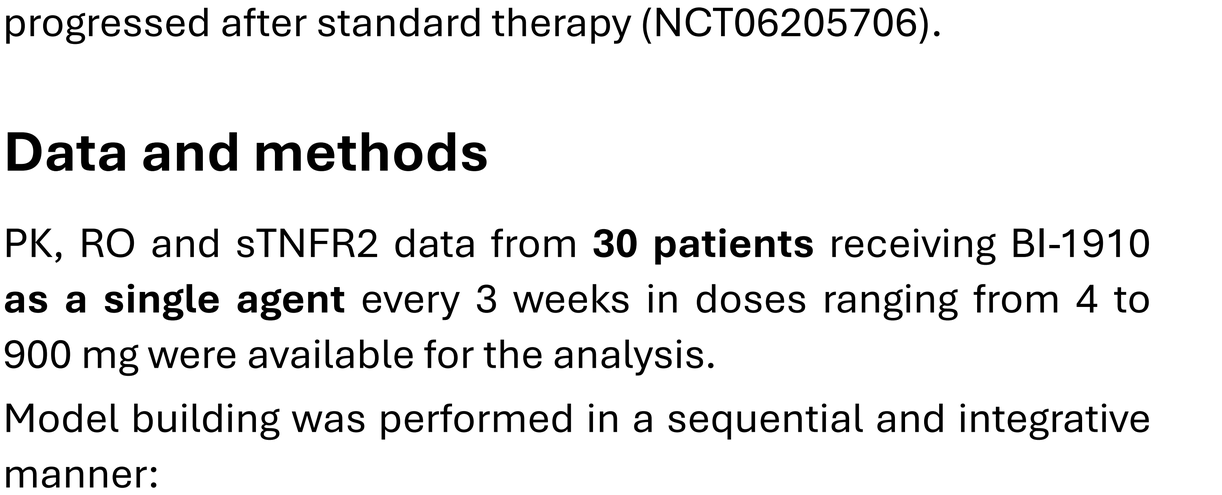

Figure 1: Schematic representation of the final structural model. BI-1910 concentrations were described with a 2-compartment model with first order linear clearance (CL), intercompartmental clearance (Q) and volume of distribution in the central (V_1) and peripheral compartments (V_2). Receptor occupancy (RO) was described with a direct and saturable ($E_{MAX,RO}$ and $EC_{50,RO}$) model driven by BI-1910 drug levels at the central compartment (C_P); while for soluble tumor necrosis factor receptor 2 (sTNFR2) an indirect response model with zero order input rate constant (K_{IN}) and first-order degradation rate constant (K_{OUT}) was selected with drug effect inhibiting biomarker via a saturable model (I_{MAX}, IC_{50}).

Conclusions

A PK/RO/sTNFR2 joint model has been successfully developed to characterize BI-1910 pharmacokinetics and pharmacodynamics across a broad range of doses using early clinical stage information. The model can be used to support dose selection for upcoming studies.

Results

The final joint model (Figure 1) provided a **satisfactory description of all sources of data** (Figure 2), with adequate parameter precision (relative standard errors < 35 %).

The estimated BI-1910 concentration triggering 50 % of maximum effect was one order of magnitude higher for sTNFR2 (35900 ng/ml) compared to RO (1630 ng/ml), suggesting a **potential disconnection between RO and pharmacodynamic effects.**

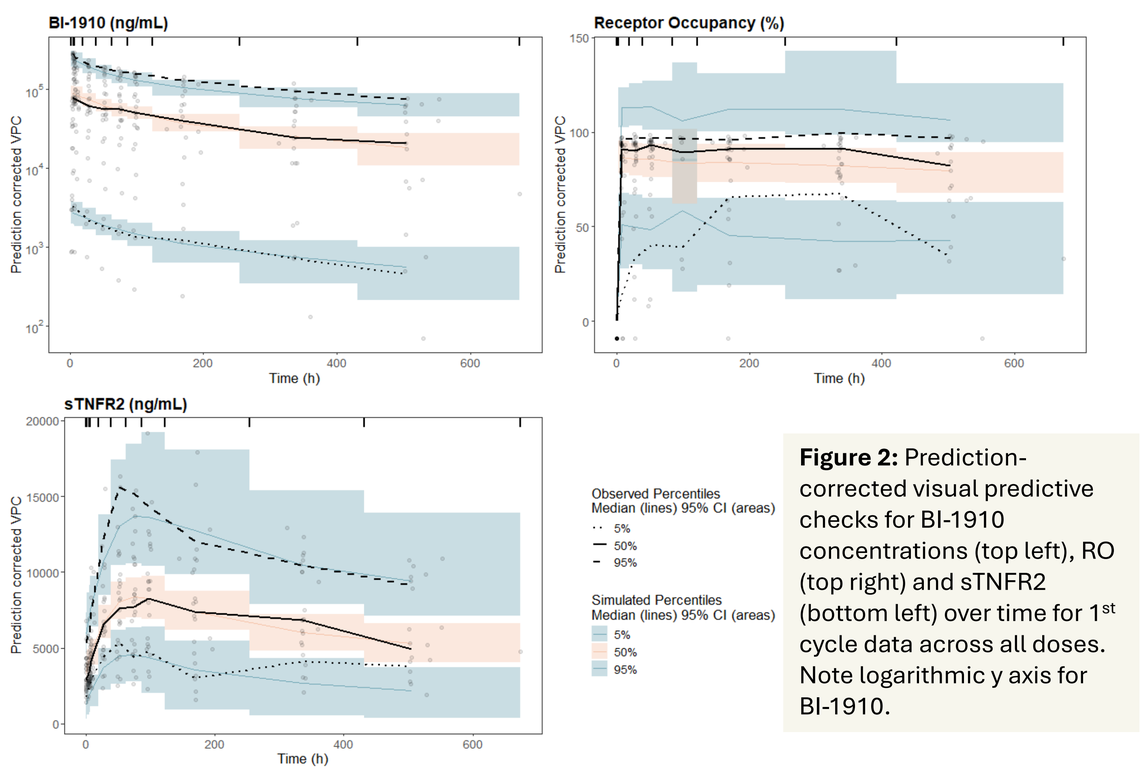

Figure 2: Prediction-corrected visual predictive checks for BI-1910 concentrations (top left), RO (top right) and sTNFR2 (bottom left) over time for 1st cycle data across all doses. Note logarithmic y axis for BI-1910.

Simulations (Figure 3) showed RO saturation close to maximum for dose levels above 300 mg, and increasing sTNFR2 levels with increasing doses, although eith overlapping intervals.

Figure 3: Stochastic simulations for BI-1910 concentrations (top), receptor occupancy (mid) and sTNFR2 (lower) across different dose levels. Areas represent 90 % prediction intervals.

References

[1] Ye et al. Frontiers in Immunology, 9:583 (2018)

[2] Medler et al. Cancers, 14: 2603 (2022)

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