Model-informed early clinical development of BI-1808, a novel monoclonal antibody to tumor necrosis factor receptor 2

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Objective

To characterize the population pharmacokinetics (PK), receptor occupancy (RO), and concentrations of the target engagement biomarker soluble tumor necrosis factor receptor 2 (sTNFR2) at different BI-1808 doses, to support the dose selection for a dose expansion trial.

Conclusions

A simultaneous model of the BI-1808 PK, RO, and sTNFR2 successfully explained the observed profiles across a wide dose range. Simulations provided insights into the expected PK, RO, and sTNFR2 levels across potential dose levels and dosing frequencies and will support the selection of doses for further exploration.

Background

BI-1808, a monoclonal antibody, is a novel immunotherapy targeting tumor necrosis factor receptor 2 (TNFR2), which is abundantly expressed on tumor-resident regulatory T cells (Tregs) [1]. Binding of BI-1808 to TNFR2 results in a reduction of intratumoral Tregs and the simultaneous expansion of intratumoral effector T cells.

BI-1808 is currently in early clinical development for the treatment of advanced malignancies or T cell lymphoma. A favorable safety profile has so far been observed across a wide dose range (25 mg – 1000 mg), making the dose selection for a dose expansion trial non-trivial.

Data and methods

PK data were available for 32 subjects included in the ongoing Phase 1/2a dose-escalation trial KEYNOTE-D20. RO and sTNFR2 data were available for 17 and 20 of the 32 subjects. Subjects received BI-1808 with or without pembrolizumab (Table 1) every three weeks (q3w) via i.v. infusion.

Model building and application proceeded in a sequential manner:

- Development of a joint PK-RO model to simultaneously characterize BI-1808 concentrations and TNFR2 receptor occupancy.
- Extension of the PK-RO model with a sTNFR2 PD model.
- Typical value simulations for RO as well as PK and sTNFR2 (not shown) considering different doses and dosing frequencies.

Table 1. Number of included subjects per dose group and pembrolizumab co-treatment in the PK analysis data set.

Dose group	n (%)
25 mg*	3
75 mg*	5
225 mg*	3
225 mg**	9
675 mg*	3
1000 mg*	9

*BI-1808 dose groups without pembrolizumab, **BI-1808 dose groups with pembrolizumab

Modeling results

The structure of the final model is shown in Figure 1. The BI-1808 PK was described by a two-compartment model with parallel linear and non-linear clearance and the RO by a direct effect model. Both models were linked through a joint K_M parameter. The sTNFR2 submodel was an indirect response model, with BI-1808 inhibiting the sTNFR2 k_{out} via an E_{max} model. Using RO instead of BI-1808 as driver for the sTNFR2 response resulted in worse model fit.

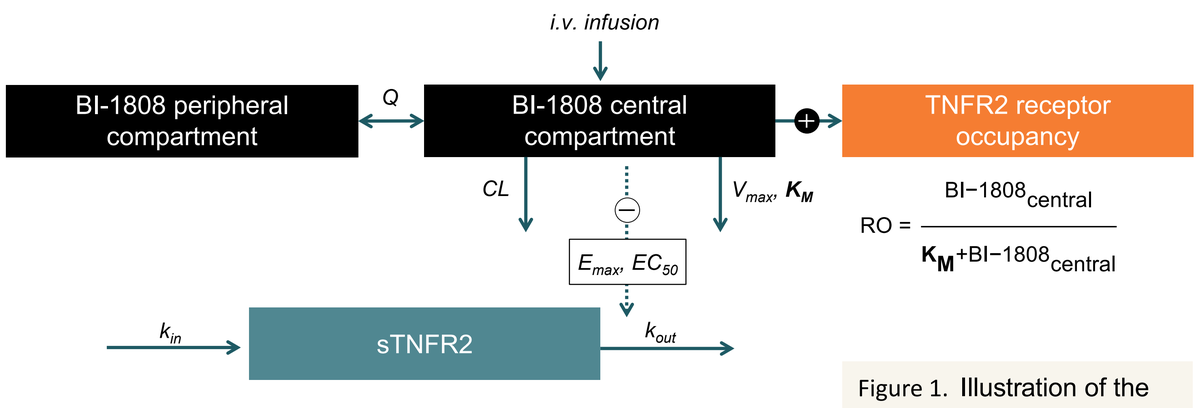

Figure 1. Illustration of the final structural model.

Parameters were estimated with acceptable precision (relative standard errors ≤51.9%) and visual predictive checks indicated adequate predictive performance across dose groups (Figure 2).

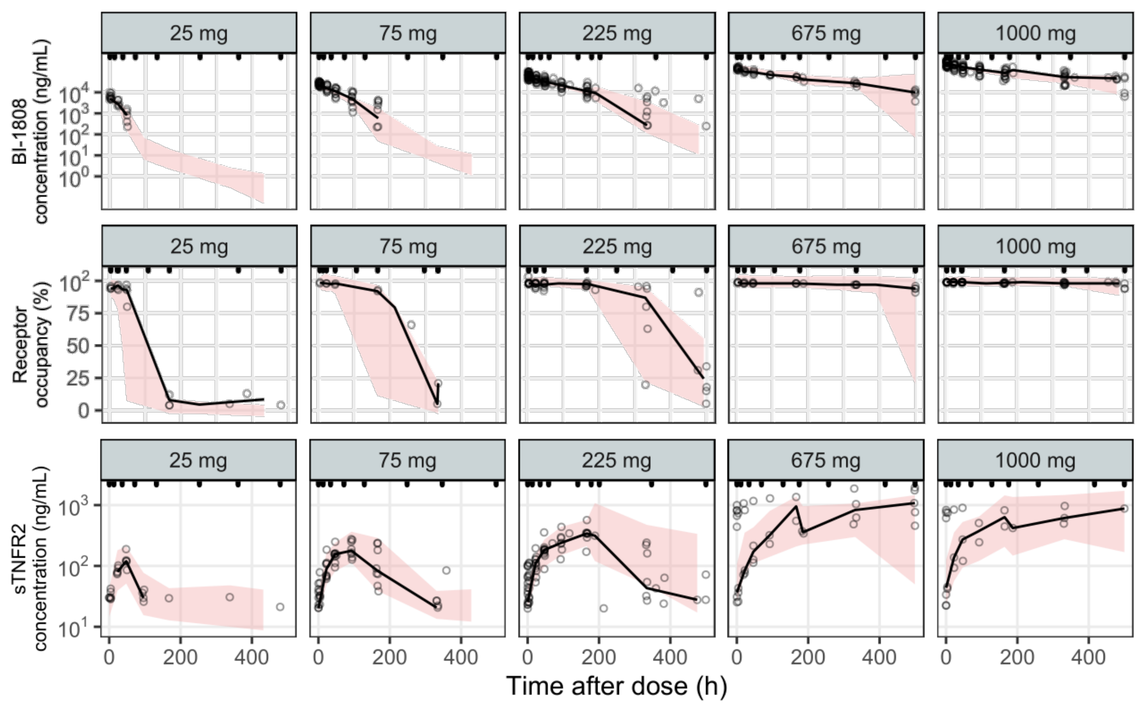

Figure 2. Visual predictive checks of BI-1808 concentrations (top), RO (middle), and sTNFR2 (bottom), versus time after dose, for the BI-1808 PKPD analysis data set, using the final model. Data are presented on the semi-logarithmic scale (PK, sTNFR2), or the linear scale (RO). BLOQ values were censored for the observed data and plotted for the simulated data. The open circles represent the observations, the black solid line is the median for the observations and the red shaded area displays the 90% confidence interval of the predicted median. The black ticks at the top, along with the x-axis, indicate the bins across time.

Simulation results

Steady-state simulations indicated RO close to 100% throughout a dosing interval for doses ≥450 mg q3w (Figure 3). The mean simulated RO within a dosing interval was ≥80% for doses ≥250 mg, and RO exceeded 50% for a full dosing interval for doses ≥350 mg.

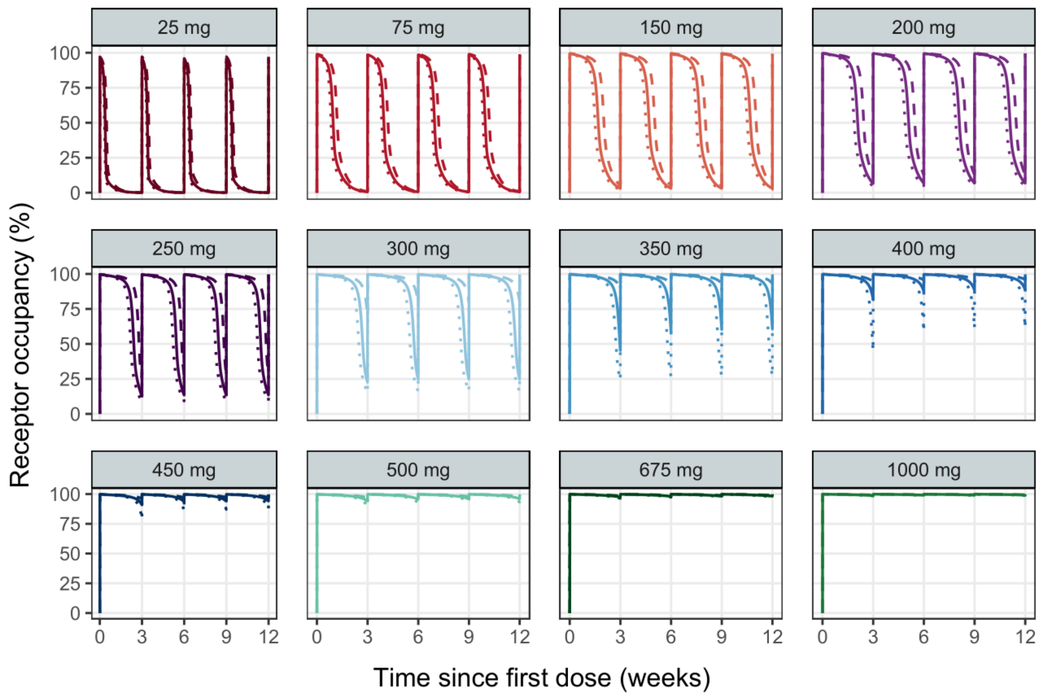

Figure 3. Typical value simulations of receptor occupancy at different doses administered every 3 weeks. The dashed, solid, and dotted lines show the RO for a typical subject with a body weight of 40 kg, 80 kg, or 120 kg, respectively.

References

1. Vanamee, ÉS, Faustman, DL (2017) Trends Mol. Med., 23(11), 1037-1046

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