Prediction of target receptor occupancy for ALX148, a CD47 blocker, using mechanistic PK/RO modeling

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INTRODUCTION AND AIMS

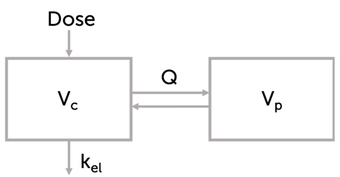
Assessment of target receptor occupancy (RO) in the site of action is increasingly important for selection of optimal doses for biologically-based therapeutic agents. While direct measurement of actual RO in tissues is difficult, mechanistic PK/RO modeling can provide valuable information that can be extrapolated to the clinic. Here we implemented such approach for Fc-fusion protein ALX148 — checkpoint inhibitor, which blocks CD47.

The aim of this work is to develop mechanistic PK/RO model that will be capable to describe pharmacokinetics of ALX148 and predict CD47 RO by ALX148 in the site of action.

MODEL DESCRIPTION

Structure was developed on the basis of two-compartmental PK model with additional mechanistic description of ALX148-CD47 interaction in central compartment. Two-step binding on the surface of RBCs and T cells (tumor) was implemented into the model with several assumptions on CD47 turnover:

1) Rate of CD47 receptor synthesis is constant for a given cell type
2) Degradation of free receptor and its monovalent and bivalent complexes is characterized by the same k_{deg}



Key features of the model:

- based on two-compartmental PK model
- two-step binding of ALX148 with CD47 on the surface of RBCs and tumor cells
- nonlinear clearance described by ALX148 consumption during CD47 binding on RBCs

Binding of ALX148 to CD47 (on the surface of RBCs and tumor cells):

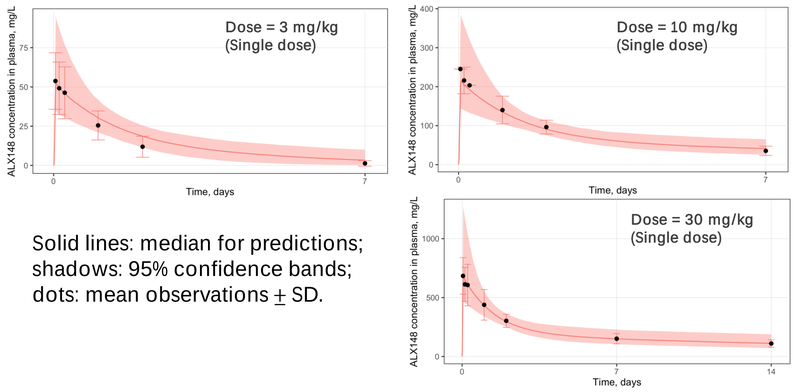
Clearance is described as a combination of linear and nonlinear components, with the latter being reflected by ALX148 consumption during binding to CD47 on RBCs. Several other modifications of the model on nonlinear clearance were analyzed (consumption by platelets and tumor cells, Michaelis-Menten clearance), but were rejected on the basis of Akaike criterion (comparison of models' fitting).

Parameters for the model were either taken/calculated from *in vitro* and *in vivo* data or identified via fitting. Thus, PK/RO model was developed to predict RO in the site of action and was verified and validated against ALX148 clinical data on PK in plasma and RO on RBCs for 3 dosages.

MODEL FITTING: PK IN PLASMA

Unknown parameters of the model were fitted against PK data in plasma for 3 dosages obtained during ALX148 phase 1 clinical trials.

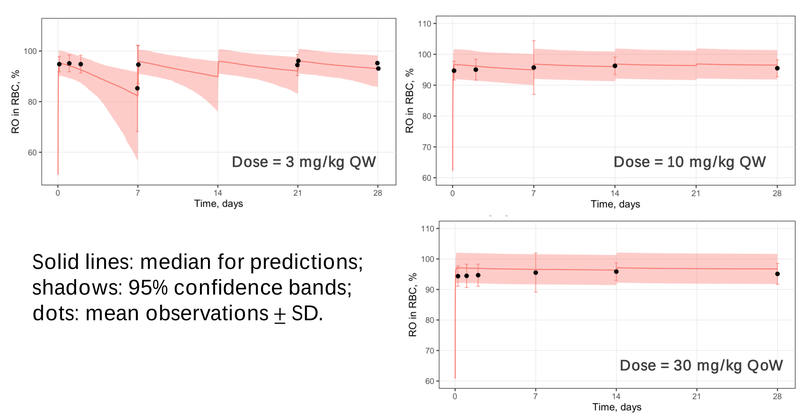
The model adequately describes PK data in plasma and was chosen as optimal among additional modifications tested (with consumption by tumor cells and platelets, or with no consumption by any cell type) based on Akaike criterion.



Solid lines: median for predictions; shadows: 95% confidence bands; dots: mean observations ± SD.

MODEL VALIDATION: RO ON RBC

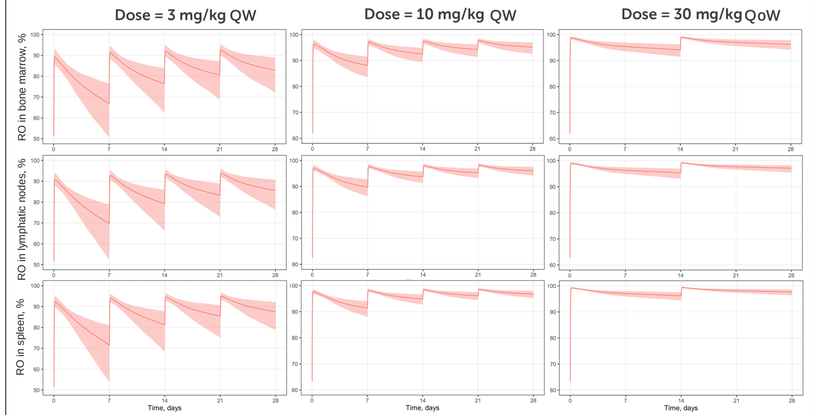
RO data on RBCs for 3 dosages was used for model validation. Model predictions of RO on RBCs were in agreement with observed clinical data. Variability of experimental data was also captured by 95% confidence bands.



Solid lines: median for predictions; shadows: 95% confidence bands; dots: mean observations ± SD.

PREDICTIONS: RO IN TUMOR

PK/RO model was used to predict CD47 RO in T cell NHL. Assessment of tumor RO was performed in such organs as bone marrow, lymphatic nodes and spleen. ALX148 concentration in these organs was evaluated based on plasma pharmacokinetics using biodistribution coefficients [PMID: 26496429]. Calculated coefficients for ALX148 were 0.232, 0.2523, and 0.3817 in bone marrow, lymphatic nodes and spleen, respectively.



Solid lines: median for predictions; shadows: 95% confidence bands.

According to the model predictions, dose increase leads to higher RO values with difference between organs becoming less apparent at higher doses. After first dose mean trough RO values reach 88, 90 and 92% for dosage 10 mg/kg QW, while 30 mg/kg QoW yields ~95% RO in all three organs.

95% confidence bands become narrower with dose increase, which can be explained by saturation of the target receptors. After first dose trough CD47 RO at 3 mg/kg ranges from 50 to 80%, at 10 mg/kg – from 84 to 94% and for 30 mg/kg - from 92 to 96%. At the end of 4th week average RO at doses 10 and 30 mg/kg reaches ~95%, while 3 mg/kg yields RO values ranging from 80 to 90%.

Overall, tumor RO >50%, >80% and >90% were predicted to be maintained over dosages 3 mg/kg QW, 10 mg/kg QW and 30 mg/kg QoW, respectively.

Thus, among doses tested in phase I, model recommends 30 mg/kg QoW or at least 10 mg/kg QW.

CONCLUSIONS

- Developed model successfully described clinical PK & CD47 RO ALX148 data.
- Model predicted 30 mg/kg QoW is best regimen among tested in phase I trial.
- This model can be applied to the other anti-CD47 biotherapeutic agents.

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