Selection of the optimal dose for ALX148, a CD47 blocker, using pharmacokinetic/pharmacodynamic modeling

InSysBio
QSP Company

Elena Vasileva[1,d], Oleg **Demin** Jr[1,d]

[1]InSysBio, Moscow, Russia

d: no conflicts of interest to declare

Poster number:
1019P

INTRODUCTION AND AIMS

ALX148 is a promising anti-CD47 blocker currently undergoing clinical trials, which is designed to enhance the activity of anti-cancer target antibodies. Optimal doses selection is increasingly important in clinical setup and can be guided by assessment of target receptor occupancy (RO) and pharmacodynamics (PD) effect in the site of action. While direct measurement of actual RO in tumor tissues is challenging, mechanistic PK/RO/PD modelling can provide valuable information that can be extrapolated to the clinic.

The aim of this work is to develop mechanistic PK/RO/PD model that will be capable to describe ALX148 PK, predict CD47 RO in tissues and estimate ALX148 effect on antibody-dependent cellular phagocytosis (ADCP).

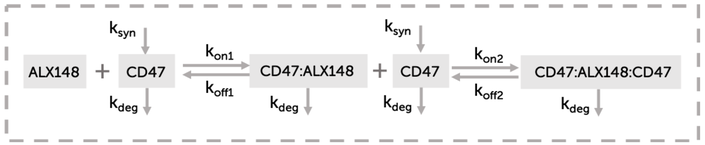
MODEL DESCRIPTION

Structure was developed on the basis of two-compartmental PK model with mechanistic description of ALX148-CD47 interaction in central compartment.

Key features of the model:

- two-step binding of ALX148 with CD47 on the surface of RBCs and T cells (tumor)
- clearance is described as a combination of linear and nonlinear components, with the latter being reflected by ALX148 internalization during CD47 binding on RBCs

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



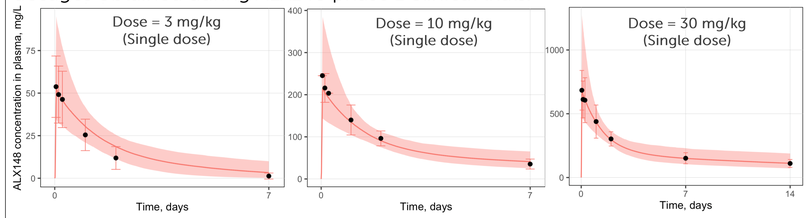
Parameters for the model were either taken/calculated from *in vitro* and *in vivo* data or identified via fitting. Thus, PK/RO model was developed to predict RO in the site of action and was verified and validated against ALX148 clinical data on PK in plasma and RO on RBCs for 3 dosages.

RO predictions were made for RBCs and tumor cells taking into account their amount in the body and CD47 expression (molecules per cell).

ADCP enhancement by ALX148 was described on the basis of RO using the direct PD effect model. Parameters for the PD effect model were fitted against *in vitro* data on phagocytosis using a separate model, which was developed to reproduce experimental phagocytosis data for cancer cell lines (Daudi, DLD-1, MM1.R, OE19).

MODEL FITTING: PK IN PLASMA

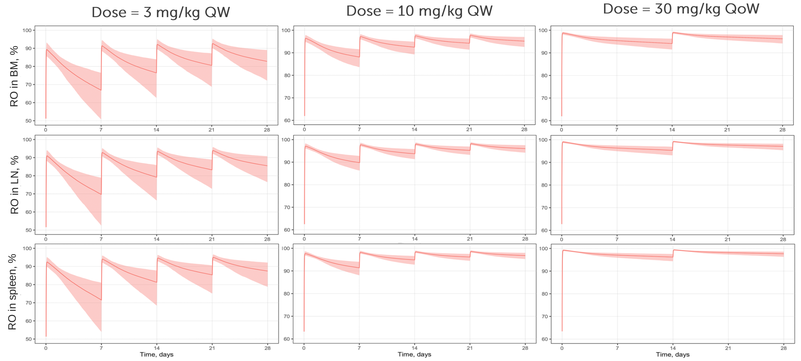
Unknown parameters of the model were fitted against PK data in plasma for 3 dosages obtained during ALX148 phase 1 clinical trials.



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 (BM), lymphatic nodes (LN) 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.

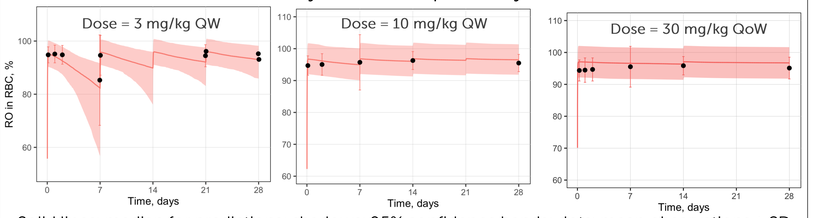


Solid lines: median for predictions; shadows: 95% confidence bands.

Predicted concentrations in tissues were similar and approximately 3 times lower than in blood plasma, which is caused by the relatively small size of ALX148 (78 kDa). High doses (10 mg/kg QW and 30 mg/kg Q2W) of ALX148 resulted in more than 98% of mean trough steady state CD47 RO in the tumor tissues, whereas a lower 95% confidence band was above 90%. Corresponding values after administration of 3 mg/kg QW were lower and ranged between 85-90%.

MODEL VALIDATION: RO ON RBC

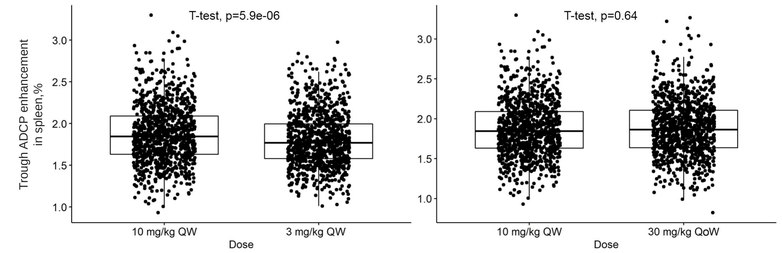
Model predictions of RO on RBCs were in agreement with clinical data used for model validation. Data variability was also captured by 95% confidence bands.



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

PREDICTIONS: EFFECT ON ADCP

ALX148-induced phagocytosis was successfully described for 4 cancer cell lines using *in vitro* model. Average 80% RO was needed to produce 1.5 fold ADCP enhancement by ALX148 in combination treatments based *on in vitro* data.
ADCP of cancer cells in tumor tissues was predicted to be increased by ~1.8 times during administration of high doses (10 mg/kg QW and 30 mg/kg Q2W). Slightly lower phagocytosis enhancement was observed in case of 3 mg/kg.



The difference in ADCP induction after administration of 3 mg/kg QW and 10 mg/kg QW of ALX148 was statistically significant: p-value < 0.001.

CONCLUSIONS

- Developed model successfully described clinical PK & RO ALX148 data.
- Model predicted that at least 10 mg/kg of ALX148 should be administered weekly to achieve more than 90% of CD47 occupancy in tumor tissues with an average 1.8-fold increase in ADCP.

Oleg Demin Jr by e-mail:
demin_jr@insysbio.com

www.insysbio.com