Model informed dosage regimen optimization of anti-CD47 antibody using target-mediated drug disposition model.

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INTRODUCTION & PURPOSE

- Target-mediated drug disposition (TMDD) model is used to describe a nonlinear pharmacokinetics (PK) phenomenon that is caused by high-affinity binding of a compound to its pharmacologic targets. [1] TMDD has received most interest as a saturable clearance mechanism for biologics, specifically monoclonal antibodies. [2]
- IMC-002 is a fully human Immunoglobulin (Ig) G4 monoclonal antibody that targets cluster of differentiation 47 (CD47). It blocks the CD47-signal regulatory protein alpha interaction, thereby increasing phagocytosis of cancer cell by macrophages.
- During the phase 1 clinical trial, IMC-002 exhibited non-linear pharmacokinetics due to the in vivo mechanisms of IgG. The neonatal Fc receptor for IgG (FcRn) binds to IgG to prevent its degradation in lysosomes and recycles it through the lymphatic system.
- The objectives of the study are to develop a pharmacokinetic (PK) model for IMC-002 that explains its non-linear pharmacokinetics and to refine the dosage regimen for the phase 2 trial using this PK model.

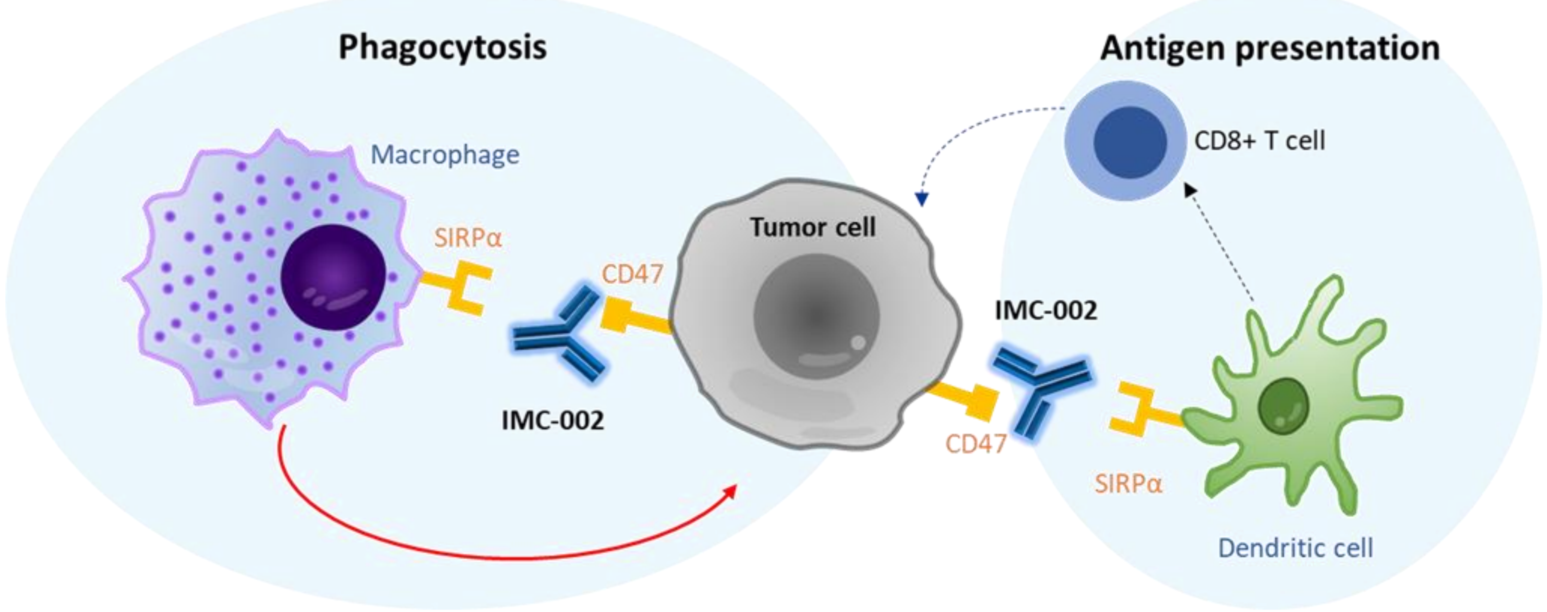
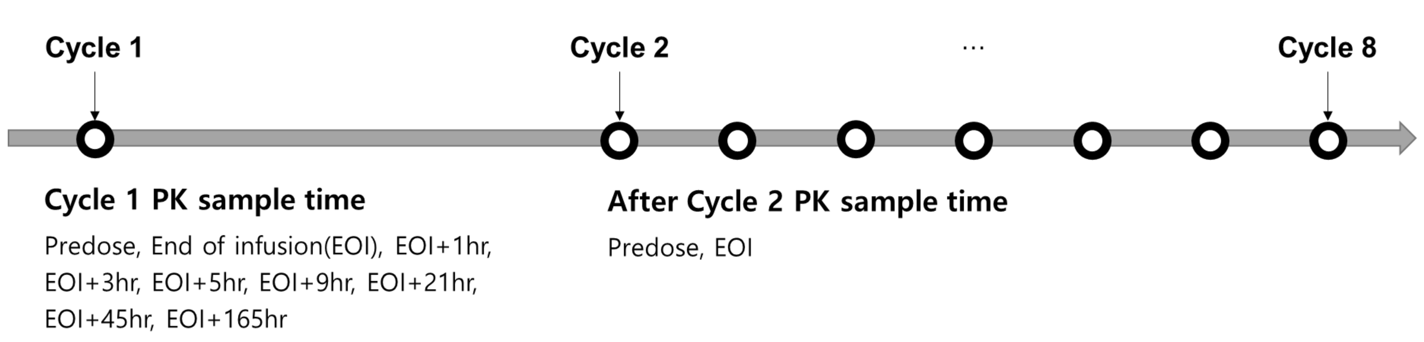


Figure 1. Mechanism of action for IMC-002

METHOD

- **Dataset: Phase I dose escalation clinical study**
  - Patient: advanced solid tumor patients (n=12)
  - Dose level: 5, 10, 20, and 30 mg/kg
  - Dosing route and interval: Intravenous infusion over 3 hours every 2 weeks
  - Pharmacokinetic study design and sample point



- **Pharmacokinetic model development**
  - Population PK of IMC-002 was analyzed using NONMEM software (version 7.5) with the first order conditional estimation method with interaction (FOCE INTER). Assessment of model was applied through general modeling building criteria. (i.e. Objective function value, Goodness of fit plot, Visual predictive checks, etc.)
- **Simulation of the optimal dose for the recommended Phase 2 dose**
  - Scenario: Q3W IV infusion, 5 cycles
  - Dose level: 5 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg
  - Population: 64.45 ± 12.12 kg (n=1000, each dose levels)
  - Optimal dose regimen for patients: Maintain concentration of IMC-002 above minimum effect concentration (MEC) for solid cancer patients.

RESULT

- **Model development**

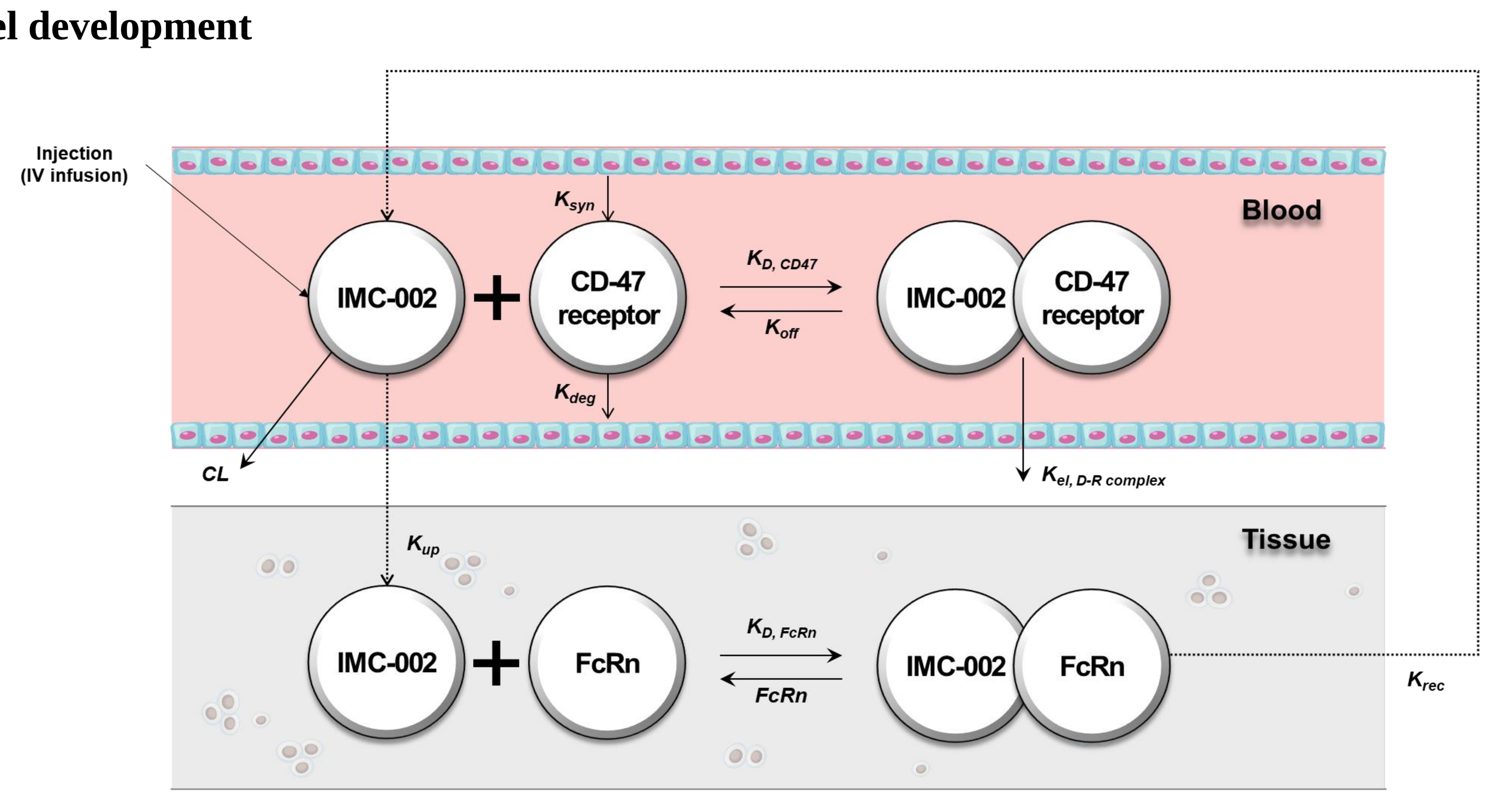


Figure 2. Scheme of the pharmacokinetic model for IMC-002

K_{syn} : synthesis rate constant of CD-47 receptor, **K_{deg}** : Degradation rate constant of CD-47 receptor, **$K_{D,CD47}$** : Binding rate constant of IMC-002, **K_{off}** : Dissociation rate constant of IMC-002, **$K_{el,D\text{-}R\ complex}$**: Elimination rate constant of Drug-Receptor complex, **CL** : Clearance of IMC-002, **K_{up}** : Uptake rate constant from Blood to tissue, **$K_{D,FcRn}$**: Binding rate constant of FcRn receptor, **FcRn** : Dissociated concentration of FcRn receptor, **K_{rec}** : Recycling rate constant of drug-FcRn complex

RESULT

- **Model development**
  - The final pharmacokinetic (PK) model for IMC-002 was defined by a target-mediated drug disposition (TMDD) model that includes the lymphatic circulation of IgG.
  - The degradation constant of CD47 (0.0213 h^{-1}), dissociation constant of CD47 (0.046 uM), dissociation constant of FcRn (0.117 uM), total receptor of FcRn (0.291 uM), and dissociation rate of drug-CD47 complex (90.4 h^{-1}) were fixed using literature and in-house experimental data. Performance of final population PK model was acceptable.
  - Parameter estimates were: synthesis rate of CD47 (0.0027 h^{-1}), reuptake rate of IMC-002 (0.0097 h^{-1}), recycling rate of drug-FcRn complex (0.0142 h^{-1}), free drug clearance (0.0114 L/h), and elimination rate of drug-CD47 complex (0.0188 h^{-1}).
- **Simulation of the optimal dose for the recommended Phase 2 dose**
  - AUC_{tau} above MEC was utilized to comparatively assess the exposure of IMC-002 that showed the efficacy of IMC-002 for patients.
  - Adequate dosing regimen was confirmed to be 20 mg/kg, simulated data`s trough concentration above MEC (24 ug/mL) at steady-state.

Table 1. Pharmacokinetic parameter of Q3W Simulation for each dose level.

Timepoint	Parameters	5 mg/kg	10 mg/kg	20 mg/kg	30 mg/kg
Cycle 1 at First dose	AUC_{tau} (μg*h/ml)	6518 ± 2239	16603 ± 6431	41225 ± 16368	68568 ± 26636
	AUC_{tau} above MEC (μg*h/ml)	1374 ± 1259	7540 ± 4815	29188 ± 15192	56187 ± 26622
	C_{trough} (μg/mL)	3.68 ± 1.22	9.29 ± 4.24	27.6 ± 17.1	53.7 ± 33.9
Cycle 5 First dose after steady state	AUC_{tau} (μg*h/ml)	8433 ± 2961	24231 ± 13421	66661 ± 37544	119097 ± 66493
	AUC_{tau} above MEC (μg*h/ml)	2028 ± 1615	12592 ± 9797	54421 ± 37459	106778 ± 66581
	C_{trough} (μg/mL)	5.19 ± 2.10	15.6 ± 11.09	61.6 ± 55.7	128.4 ± 109.0

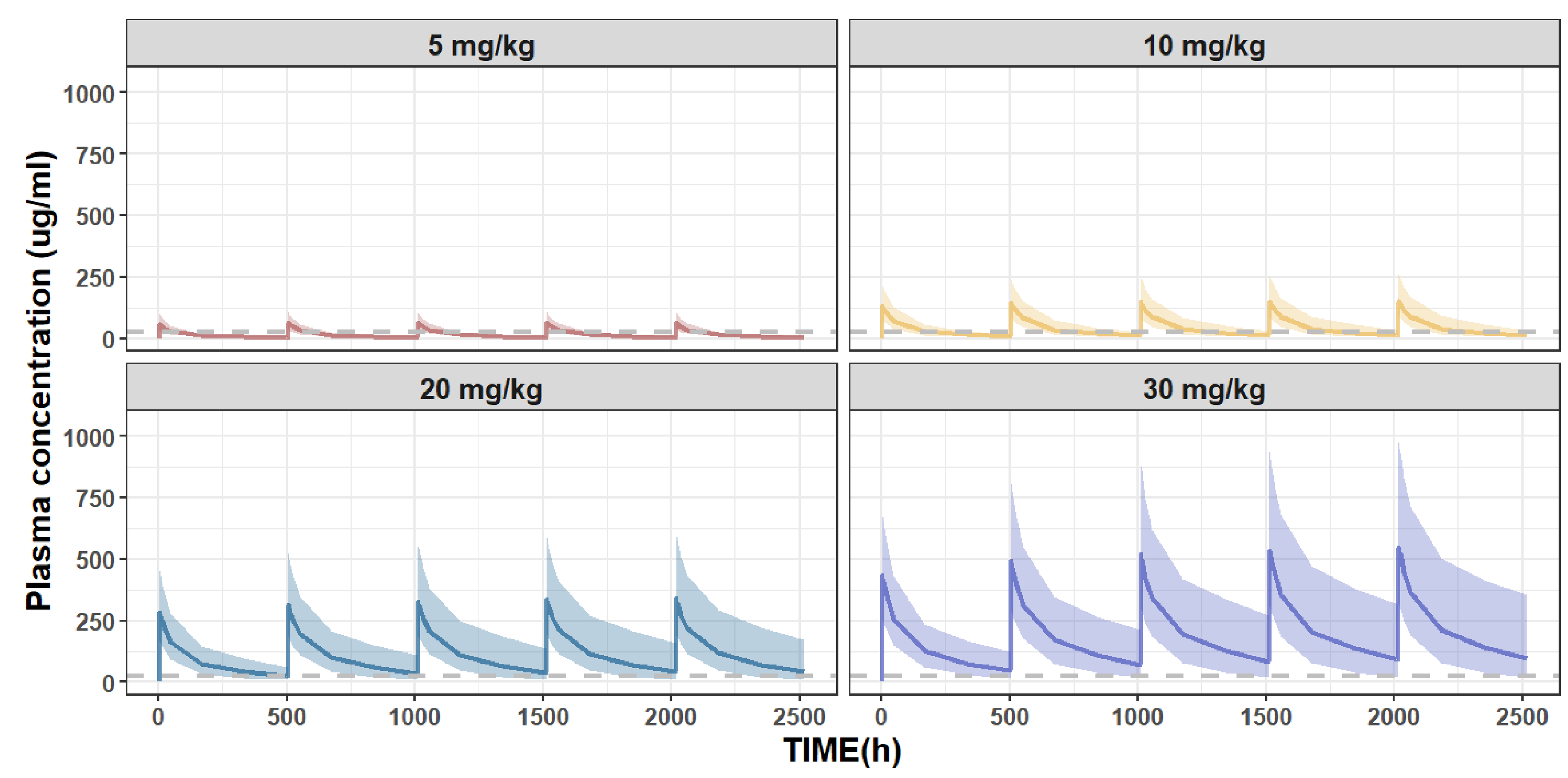


Figure 3. Simulation result of administration IMC-002 via IV-infusion every three weeks(Q3W)

CONCLUSION&DISCUSSION

- In the study, a robust population pharmacokinetic model for IMC-002 was developed. The detailed TMDD model successfully explained the non-linear pharmacokinetics of IMC-002, including FcRn-mediated circulation.
- Also, this model supports a dosing regimen of 20 mg/kg every 3 weeks based on the proportion exceeding the minimum effective concentration for future clinical trials.

Reference

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[2] Aston, Philip J et al. "Mathematical analysis of the pharmacokinetic-pharmacodynamic (PKPD) behaviour of monoclonal antibodies: predicting in vivo potency." Journal of theoretical biology vol. 281,1 (2011): 113-21. doi:10.1016/j.jtbi.2011.04.030

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