Population Pharmacokinetic Analysis of PD-L1 Checkpoint Inhibitor Cosibelimab in Subjects with Advanced Cancers

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PD-L1 inhibitor **Cosibelimab**: PopPK **supports comparability of 800 mg Q2W and 1200 mg Q3W dosing regimens** based on recent FDA criteria[2]

Background & Objective

PD-L1 is an immune-inhibitory checkpoint molecule that may be expressed by cancer cells, thereby evading the body's immune response. Cosibelimab is a high-affinity, fully human monoclonal antibody (mAb) of immunoglobulin G1 subtype that directly binds to PD-L1, which can reactivate anti-tumor immune response. Additionally, cosibelimab has a functional fragment crystallizable domain capable of inducing antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity against tumor cells. Cosibelimab is in clinical development for the treatment of subjects with advanced cutaneous squamous cell carcinoma (CSCC) and other cancers. Aims of the analysis were:

- To determine the impact of relevant intrinsic and extrinsic factors on cosibelimab exposure via population pharmacokinetic (PopPK) analysis
- To assess comparability between cosibelimab dosing regimens

Data and Methods

- Phase 1, open-label, multicenter, multiregional, dose-escalation and cohort-expansion study of cosibelimab administered intravenously (IV) to subjects with advanced cancer[1]
- Fixed 60 minute i.v. infusions of 200, 400, or 800 mg once every two weeks (Q2W), or 1200 mg once every three weeks (Q3W)
- Dense PK sampling on day one of cycle one, followed by sparse sampling at later time points and cycles → 2527 evaluable samples from 206 subjects
- PopPK and covariate analysis (NONMEM version 7.3) and simulations (R version 4.1.2)
- Comparison of exposures between dosing regimens (both visually and via ANOVA-based geometric mean ratios and 95% confidence intervals for exposure parameters)

Results

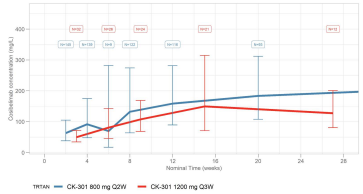
Exploratory analysis of geometric mean trough concentrations versus nominal time (Figure 1) confirmed sustained cosibelimab exposure across treatment cycles. Also, trough values increased to similar concentrations between 800 mg Q2W and 1200 mg Q3W dosing regimens.

Conclusions

- Cosibelimab PK well characterized with linear 2-compartment model
- **Identified covariates** are **well established** to impact the PK of other mAbs in oncology[4]
- PK parameters were similar among metastatic CSCC, locally advanced CSCC, and all CSCC subjects and other tumor types, as well as the overall patient population.
- **Population PK** modeling and simulation **supports** the **comparability of** the **800mg Q2W and 1200mg Q3W** dosing regimens

Results – Continued

Figure 1. Cosibelimab Trough Concentrations



Abbreviations: N = number of data points; TRTAN = actual treatment code; Q2W = every 2 weeks; Q3W = every 3 weeks. Note: The plot shows geometric mean concentrations and associated geometric standard deviation. Statistics were not calculated for times with < 5 data points.

A **two-compartment model with linear elimination** (Table 1) provided the best fit to log-transformed cosibelimab data (Figure 2 & 3). The model did not indicate any trends across dosing regimens. Predicted half-life was 17.4 days. **Baseline body weight** was incorporated as a **covariate** on all **clearance** (CL) and **volume** parameters during base model development, with estimated allometric exponents. **Final covariate effects**: albumin, target lesion diameter, and race on CL as well as an effect of sex on central volume.

Table 1. Cosibelimab Final Model Parameters

Parameter	Estimate	%RSE
Clearance CL (L/day)	0.238	2.70%
Central Volume V1 (L)	3.58	2.40%
Intercomp. Clearance (L/day)	0.456	7.90%
Peripheral Volume (L)	2.31	6.10%
WT on Clearance	0.722	19.70%
WT on Volume	0.395	11.60%
Albumin effect Clearance	-1.04	18.20%
DIAM effect Clearance	0.172	15.30%
Clearance difference Asians	0.384	11%
V1 difference females	-0.178	17.90%
Random effects	**Estimate (CV%)**	**%RSE**
IIV on CL	0.0905 (30.8%)	14.90%
Covariance CL-V1	0.0135	46.50%
IIV on V1	0.0277 (16.8%)	23.80%
IIV on V2	0.248 (53.0%)	32.70%
Additive res. error	0.104	9.70%

Abbreviations: ALB = albumin (time-varying); CV = Coefficient of variation; DIAM = target lesion diameter (time-varying); IIV = inter-individual variability; RSE = relative standard error; WT = baseline body weight. CV% calculated as $\sqrt{e^{\omega^2}-1}\cdot 100$. RSE values are provided on the variance scale.

In line with FDA criteria[2] (also considering exposure-response analysis results, not shown) and expectations from other anti-PD-1/PD-L1 mAbs, average steady-state concentrations of 800 mg Q2W and 1200 mg Q3W **cosibelimab dosing regimens** were **comparable** (Table 2, Figure 4).

Table 2. Geometric Mean Parameter Ratios for 800 mg Q2W and 1200 mg Q3W at Steady State

Treatment	GMR - C_{avg}	GMR - C_{max}	GMR - C_{min}	GMR – $t_{1/2}$
800 mg Q2W	1 (0.93 - 1.08)	1 (0.95 - 1.05)	1 (0.9 - 1.11)	1 (0.93 - 1.07)
1200 mg Q3W	1.02 (0.94 - 1.09)	1.27 (1.21 - 1.33)	0.85 (0.76 - 0.95)	1 (0.93 - 1.07)

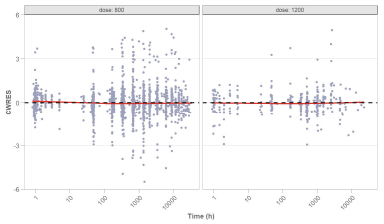
Abbreviations: Cavg = average concentration at steady state; Cmax = maximum concentration at steady state, Cmin = minimum concentration at steady state; GMR = geometric mean ratio (95% confidence interval); Q2W = every 2 weeks; Q3W = every 3 weeks; t1/2 = terminal half-life
Note: Simulations for both regimens were based on the full Phase 1 study population (i.e. the same subject was assumed to receive both dosing regimens).

FDA PD-L1 alternative dosing regimen criteria[2]

- C_{ave} and C_{trough} at steady state no more than 20% lower as compared to reference
- No more than 25% increase in C_{max} or adequate clinical evidence for acceptable safety profile (e.g. flat/shallow ER relationship)

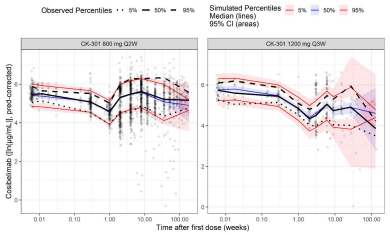
Additional Figures and Tables

Figure 2. Goodness-of-fit by Dose



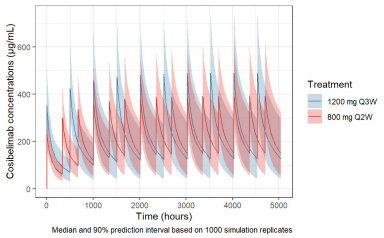
Abbreviations: CWRES = Conditional Weighted Residuals; GOF = goodness-of-fit; LOESS=locally weighted scatterplot smoothing Q2W = every 2 weeks. Note: Data points from 200 mg Q2W and 400 mg Q2W were excluded for plotting purposes, since each of these doses was only administered to a single patient. Dots are individual data points (log-transformed), and solid red lines are smoothed LOESS lines. Dashed black lines are included for reference to indicate zero or line of unity.

Figure 3. Visual Predictive Check by Dose



Time axis is presented on log-scale to enable improved assessment of dense PK profiles obtained after the first dose. Log-transformed prediction-corrected[3] concentrations are presented on the ordinate. Black circles correspond to individual observations.

Figure 4. Visual Comparison Between 800 mg Q2W and 1200 mg Q3W Dosing Regimen



Abbreviations: Q2W = every 2 weeks; Q3W = every 3 weeks
Note: For each replicate, the predicted median, as well as 5th and 95th percentiles, were calculated. The visual representation was then based on the median values of each of these percentiles across the 1000 simulation replicates, providing a plot of the expected median profile along with the 90% prediction interval.

References

[1] ClinicalTrials.gov Identifier: NCT03212404
[2] FDA guideline: FDA-2021-D-0691
[3] AAPS J. 2011;13(2):143–151
[4] Br J Clin Pharmacol. 2019 Sep;85(9):2045-2058

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