Pharmacokinetic Analyses and Population Pharmacokinetic Modeling of Maplirpacept in Patients With Newly Diagnosed Acute Myeloid Leukemia

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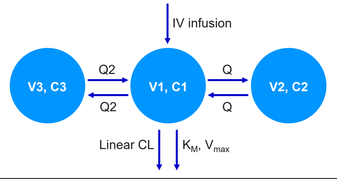
Introduction

- Maplirpacept is a fusion protein directed against CD47 and is in development for hematologic malignancies, including acute myeloid leukemia (AML).

Objectives

- Here, we conducted non-compartmental analysis (NCA) to estimate pharmacokinetic (PK) parameters, and population PK (PPK) analyses to describe the PK of maplirpacept in untreated patients with AML in combination with either azacitidine (AZA) or AZA and venetoclax (VEN), and to identify potential covariates that impact maplirpacept PK.

Figure 1: Structure of population PK base model of maplirpacept



CL=clearance; CX=maplirpacept concentration in compartment X; IV=intravenous; K_M=concentration at which elimination is half maximum; Q, Q2=intercompartmental clearance; V_{max}=maximum elimination rate; V_x=volume of distribution where X=1 (central compartment), 2 (peripheral compartment 1); 3 (peripheral compartment 2).

Methods

- The dataset for the analyses was based on the phase 1a/1b (NCT03530683) dose-escalation and expansion trial of maplirpacept-treated patients with advanced hematologic malignancies.
- Patients with newly-diagnosed TP-53-mutated AML received either 8, 16, or 24 mg/kg once weekly (QW) maplirpacept in combination with approved doses of AZA, whereas elderly/unfit patients with newly diagnosed TP-53 wild-type AML received either 8, 16, or 24 mg/kg QW maplirpacept in combination with approved doses of AZA and VEN.
- Serial serum samples for PK assessments were collected at pre-specified time points and concentrations measured using a validated assay. PK parameters were estimated using oNCA v2.7.8, Pfizer's proprietary tool for NCA. NONMEM v7.4.3 was used for PPK modeling and stepwise covariate model selection was performed using Perl-speaks-NONMEM v4.9.0.
- Post-processing of outputs was completed with R v4.1.3.
- Model selection was based on the assessment of objective function values, visual inspection of diagnostic plots, precision of the parameter estimates, prediction-corrected visual predictive checks, and decrease in residual variability.
- Based on clinical relevance and/or visual inspection of data, potential covariates were selected and tested for statistical significance.

Results and Discussion

- As of 20 March 2023, data from 53 patients with ≥1 measurable PK sample were available in the AML cohorts.
  - 508 measurable serum maplirpacept concentrations from these patients were included in the analyses.
- Of the 53 patients, 23 received maplirpacept in combination with AZA at 3 dose levels and 30 received maplirpacept in combination with AZA and VEN at 2 dose levels.
  - Data from maplirpaceptat 24 mg/kg in combination with AZA and VEN was not available at the time of the analyses.
- The single and multiple dose PK parameters of maplirpacept are summarized in **Table 1**.
- Generally, maplirpacept exhibited a greater than dose-proportional increase in systemic exposures, likely due to target-mediated drug disposition.
- A 3-compartment PK model with simultaneous linear and non-linear clearance components described the PK of maplirpacept.
- The final parameter estimates for V_{max} (maximum elimination rate) 2.01 mg/hr; K_m (concentration at which elimination is half maximum) 14.7 mg/L; CLL (linear clearance) 0.023 L/h; V1, V2, V3 (volume terms for central (1) and peripheral compartments (2,3) 5.54 L, 6.12 L, 9.35 L, respectively; and inter-compartment clearance Q1 and Q2 (intercompartment clearance) 0.094 L/hr and 0.0068 L/h, respectively.
- Baseline body weight and sex were determined to be significant covariates on V1. Women had a 20% lower V1 compared with men.
- Baseline body weight was not a significant covariate of clearance.

Table 1: Single and multiple dose PK parameters of maplirpacept

Maplirpacept Dose (mg/kg QW)	Combination Agent	C_{max} (µg/mL)		AUC_{168} (µg·hr/mL)		CL (mL/hr)
		Week 1	Week 6	Week 1	Week 6	Week 6
8	Aza	116 (15.2) [12]	162 (24.7) [8]	5450 (26.5) [9]	9670 (36.3) [8]	61.5 (45.0) [8]
16		287 (35.1) [6]	447 (ND) [1]	11900 (8.62)[3]	32700 (ND) [1]	42.5 (ND) [1]
24		376 (26.6) [4]	NA	29500 (19.1) [4]	NA	NA
8	Aza/Ven	126 (28.1) [13]	153 (33.0) [8]	5130 (49.4) [11]	8750 (38.6) [8]	70.3 (47.9) [8]
16		288 (30.3) [17]	309 (47.7) [5]	14500 (41.7) [8]	25700 (ND) [1]	53.5 (ND) [1]

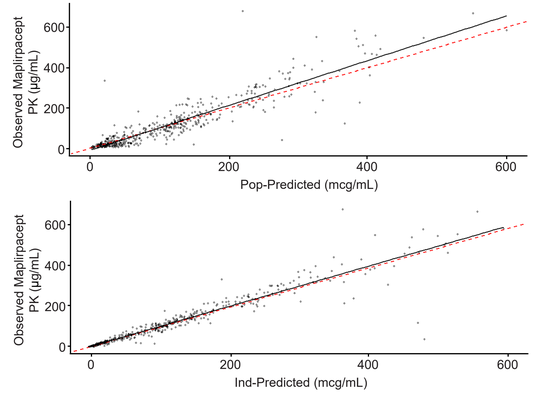
Data reported as geometric mean (geometric % coefficient of variation) [n]. CL calculated as total dose (mg)/ AUC_{tau}.
Two subjects did not meet criteria for PK parameter reporting and were excluded from NCA but included in the population PK analyses.
AUC=area under the concentration–time curve; AZA=azacitidine; CL=clearance; C_{max}=maximum serum concentration; NA=not available; ND=Not determined; PK=pharmacokinetic; QW=once weekly; VEN= venetoclax

Table 2: Summary of population PK parameters from the final model

Parameter	Unit	Estimate	RSE%	Shrinkage %
V_{max}	mg/hr	2.01	30.05	28.8
K_m	mg/L	14.7	34.56	-
CLL	L/hr	0.023	25.085	17.799
V1	L	5.54	4.22	20.24
V2	L	6.12	6.52	-
V3	L	9.35	20	-
Q	L/hr	0.094	10	-
Q2	L/hr	0.0068	13.93	-
Body weight on V1		0.0073	23.36	-
Sex on V1		−0.22	−24.23	

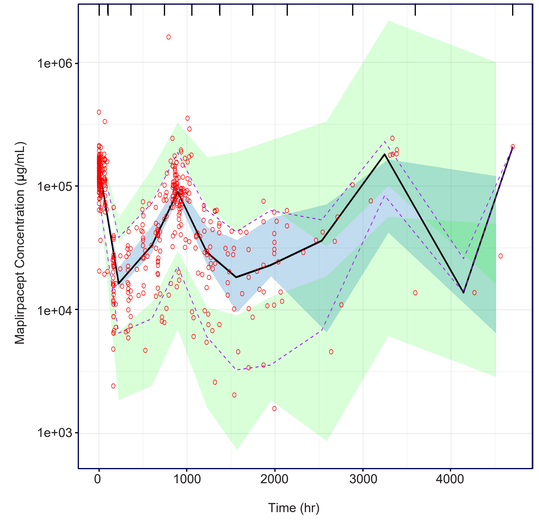
CLL=linear clearance; K_M=concentration at which elimination is half maximum; Q and Q2=intercompartmental clearance; RSE=relative standard error; V_{max}=maximum elimination rate; VX=volume of distribution where X=1 (central compartment), 2 (peripheral compartment 1); 3 (peripheral compartment 2).

Figure 2: Population and individual predictions vs observed plots



Ind=individual predictions; PK=pharmacokinetics; Pop=predicted observed plots

Figure 3: Prediction-corrected visual predicted check



The solid black line represents the median of the observed maplirpacept concentrations over time.
Blue field represents a simulation-based 95% CI for the median.
The observed 5% and 95% percentiles are presented with dashed blue lines, and the 95% CI for the corresponding model predicted percentiles are shown as green fields.
The observed maplirpacept concentrations (prediction corrected in the pcVPC) are represented by red circles.

Disclosures: Victor Lincha, Yibo Wang, and Luke Kuttschreuter were Pfizer employees at the time of abstract development.

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