T-093

Adjusted Ideal Body Weight Dosing Reduces Pharmacokinetic Variability of the PD-L1–Targeted Antibody-Drug Conjugate PDL1V (PF-08046054)

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Conclusions

- Preliminary PDL1V antibody-conjugated MMAE (acMMAE) population pharmacokinetic (PK) modeling and simulations support adjusted ideal body weight (AiBW)-based dosing to reduce the PK variability of PF-08046054, thereby mitigating the risk of overdosing high-body-weight patients and underdosing low-body-weight patients, and potentially widening the therapeutic window of PDL1V

Introduction

- PDL1V (PF-08046054) is a novel programmed cell death ligand 1 (PD-L1)–directed vedotin antibody-drug conjugate designed to deliver the cytotoxic agent monomethyl auristatin E (MMAE) to tumor cells expressing the PD-L1 cell surface protein[1]
- The safety and antitumor activity of PDL1V in solid tumors is being investigated in the phase 1 study C5851001 (NCT05208762), at doses ranging from 0.5 to 1.75 mg/kg AiBW on days 1 and 8 every 3 weeks (2Q3W) and from 1.75 to 2.0 mg/kg AiBW on days 1 and 15 every 4 weeks (2Q4W)[2-4]
- AiBW dosing is used for all patients over a wide range of body weights (37.40-117.85 kg) and is calculated from ideal body weight (iBW) and total body weight (TBW), as follows[5]:
  - AiBW = iBW + 0.4 × (TBW − iBW) where iBW is a function of the patient's sex and height, as follows:
  - iBW (men) = 50 kg + 0.91 × (height, cm − 152.4)
  - iBW (women) = 45.5 kg + 0.91 × (height, cm − 152.4)
- Here, we developed a preliminary population PK model to characterize the PK of PDL1V acMMAE and evaluate the impact of baseline demographics, laboratory results, and patient disease characteristics on PDL1V acMMAE (the antibody-conjugated payload) PK
- Using population PK model, impact of TBW vs AiBW on PK variability was evaluated through simulations

Methods

- A population PK model was developed via nonlinear mixed effects modeling using NONMEM version 7.4.3
- The population PK model included preliminary acMMAE plasma concentration data (n=3751) from a total of 162 patients treated with PDL1V as a monotherapy in the C5851001 study
- The primary tumor types were head and neck squamous cell cancer (53.1%) and non-small cell lung cancer (42.6%); other tumor types were triple-negative breast cancer (3.1%) and esophageal squamous cell carcinoma (1.2%)
- The impact of demographics, laboratory values, and patient disease characteristics on acMMAE PK were evaluated by visual examination followed, as applicable, by forward selection and backward elimination
- The average plasma concentration of acMMAE in the first 2 cycles (6 weeks) was simulated for both AiBW dosing and TBW dosing using individual post hoc estimates

Results

- A 2-compartment model with linear elimination described PDL1V acMMAE plasma concentrations well (**Figure 1**)
- Among the covariates that were evaluated, increased AiBW was associated with higher acMMAE clearance (CL) and higher central volume of distribution (**Table 1**)
- The AiBW exponent on acMMAE CL was 0.91 (ie, CL increased almost proportionally with AiBW) (**Table 1**)
- Higher baseline tumor size and higher Eastern Cooperative Oncology Group performance status were associated with increase in acMMAE clearance with statistical significance; however, the magnitude of the effect was minimal (**Table 1**)
- PK simulations showed that, in comparison with TBW dosing, AiBW dosing reduced overall variability in acMMAE exposure, lowered acMMAE exposure in high-body-weight patients, and slightly increased exposure for low-body-weight patients (**Figure 2**)

Figure 1. Diagnostic plots for the linear 2 compartment model of PDL1V acMMAE plasma concentrations

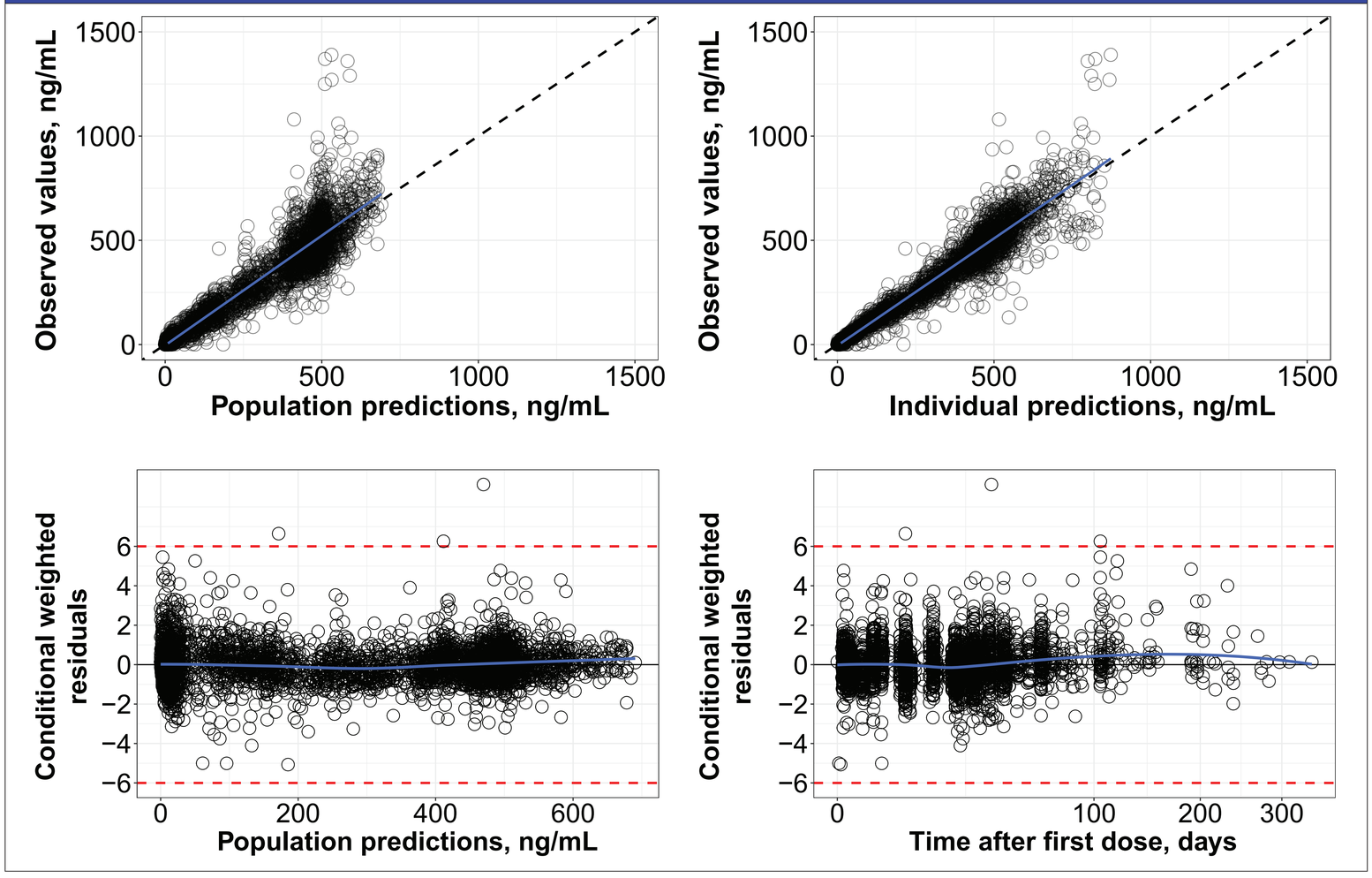

Figure 2. Model-predicted average PDL1V acMMAE concentration in the first 6 weeks for 1.5 mg/kg AiBW 2Q3W and 1.5 mg/kg TBW 2Q3W

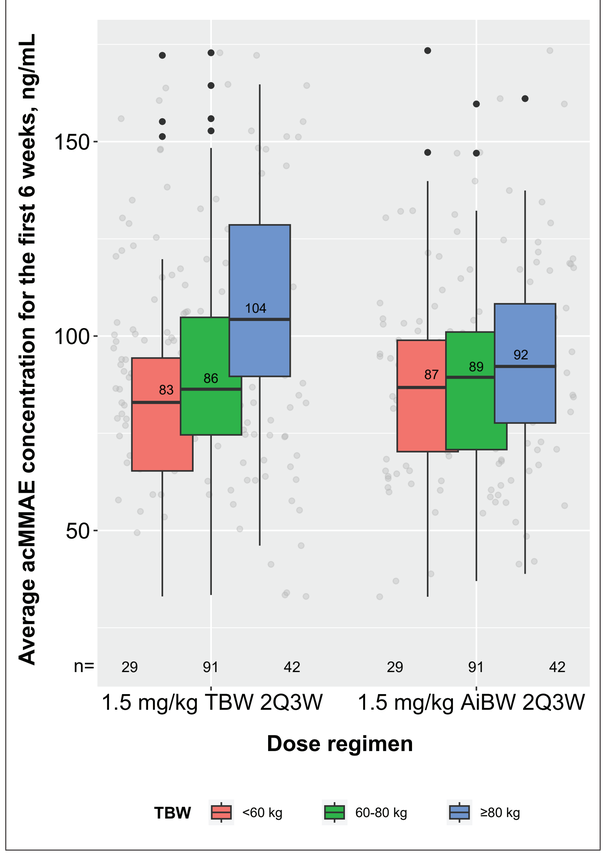

Table 1. Summary of preliminary PDL1V acMMAE population PK model estimates

Parameter	Point estimate	RSE, %
Systemic clearance (CL), L/day	2.23	2.58
Central volume of distibution (V_c), L	3.81	1.29
Peripheral volume of distibution (V_p), L	1.42	7.96
Intercompartmental clearance (Q), L/day	0.365	6.25
Covariate effect of AiBW on CL	0.905	16.2
Covariate effect of AiBW on V_c	1.04	7.62
Covariate effect of baseline tumor burden on CL	0.157	19.2
Covariate effect of ECOG = 0 on CL	−0.184	19.4
Interpatient variance		
ω^2_{CL}	0.0703	13.5
$\omega^2_{V_c}$	0.0233	13.4
Standard deviation of proportional error, σ_{prop}	0.0360	13.3
Standard deviation of additive error σ_{add}, ng/mL	11.3	27.8

Continuous covariates (AiBW, baseline tumor burden) were standardized to their median and assessed using a power model.
Categorical covariates (ECOG) were assessed using a proportional shift model.
ECOG, Eastern Cooperative Oncology Group

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