Population Pharmacokinetic and Exposure-Response Safety Analyses of Mecbotamab Vedotin (BA3011) in Patients with Advanced Solid Tumors

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Background

Mecbotamab vedotin (BA3011) is antibody-drug conjugate (ADC) consisting of a conditionally active biologic (CAB) anti-AXL humanized (IgG1) monoclonal antibody conjugated to monomethyl auristatin E (MMAE) using a cleavable linker. BA3011 is being developed for the treatment patients with advanced solid tumors including sarcoma with AXL expression.

Methods

As of data cutoff date 19 April 2022, BA3011 was administered by intravenous infusion to 67 patients, with doses ranged from 0.3 to 3 mg/kg once every three weeks (Q3W), 1.2 to 1.8 mg/kg once every two weeks (Q2W) and 1.8 mg/kg twice every three weeks (2Q3W). Population pharmacokinetics (popPK) analysis was performed using sequential modeling approach, where a PK model was first developed for BA3011 ADC alone, and then an integrated model was developed for BA3011 ADC and MMAE.

The popPK base model for BA3011 ADC and MMAE was used to generate empirical Bayes estimates of PK parameters for patients in Study BA3011-001 and used for the exposure-response (E-R) safety analysis. E-R time-to-event models were developed to characterize the relationship between BA3011 ADC or MMAE exposure and the time to first incidence of adverse events (AEs).

Results

A popPK model with two-compartment disposition and parallel linear and nonlinear elimination of BA3011 ADC, formation of MMAE from ADC, and two-compartment disposition and linear elimination of MMAE, adequately described the PK profiles of BA3011 ADC and MMAE in patients based on model evaluation using prediction-corrected visual predictive checks. Key PK parameter estimates are summarized in the table below.

Parameters	ADC	MMAE
Linear Clearance (L/day)	1.47	3.85
Volume of the Central Compartment (L)	3.58	3.58*
Vmax (mg/day)	5.77	--
Km (mg/L)	1.85	--

*Fixed to ADC value to ensure model identifiability

In the E-R safety analysis, statistically significant correlations were demonstrated between BA3011 ADC exposure and all safety endpoints explored (TEAE Grade ≥3, neutropenia Grade ≥3, increase in AST or ALT Grade ≥1, anemia Grade ≥2, and peripheral neuropathy Grade ≥1). Correlations were statistically significant between MMAE exposure and TEAE Grade ≥3, neutropenia Grade ≥3, increase in AST or ALT Grade ≥1, but not anemia Grade ≥2 or peripheral neuropathy Grade ≥1. Time-varying Cmax was selected as the most appropriate exposure metric for each model developed, calculated over the past 24 hours, 1 week, or 3 weeks, depending on the model.

Conclusions

The popPK relationship between ADC and MMAE were adequately characterized using a sequential modeling approach. BA3011 ADC exposure was correlated with all safety endpoints evaluated whereas MMAE exposure did not demonstrate correlations with anemia Grade ≥2 or peripheral neuropathy Grade ≥1. These models are essential to generate predictions of exposure and safety for dosing regimens to be evaluated in a planned Phase 2 clinical trial.