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Population Pharmacokinetic (PK) Analysis of Mirvetuximab Soravtansine (MIRV) in Patients With Folate Receptor α (FRα)-Positive Cancer

Kathleen N. Moore,[1] Domenica Lorusso,[2] Ana Oaknin,[3] Sandro Pignata,[4] Hannelore Denys,[5] Nicoletta Colombo,[6] Toon Van Gorp,[7] Jason A. Konner,[8] Margarita Romeo,[9] Philipp Harter,[10] Conleth G. Murphy,[11] Yaping Tu,[12] Fengying Zhu,[12] Brooke Esteves,[12] Michael Method,[12] Michael J. Birrer,[13] Robert L. Coleman,[14] Ursula A. Matulonis,[15] David M. O'Malley[16]

[1]Stephenson Cancer Center/Oklahoma University College of Medicine, Oklahoma City, Oklahoma, USA; [2]Fondazione Policlinico Gemelli IRCCS, Rome, Italy; [3]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [4]IRCCS National Cancer Institute, Naples, Italy; [5]Universitair Ziekenhuis Gent, Ghent, Belgium; [6]Istituto Europeo di Oncologia, Milan, Italy; [7]Universitair Ziekenhuis Leuven, Leuven, Belgium; [8]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [9]ICO – Institut Català d'Oncologia Badalona, Barcelona, Spain; [10]Kliniken Essen-Mitte Evang, Essen, Germany; [11]Bon Secours Cork and Cancer Trials Ireland; [12]ImmunoGen, Inc., Waltham, Massachusetts, USA; [13]The Winthrop P. Rockefeller Cancer Institute at UAMS, Little Rock, Arkansas, USA; [14]US Oncology Research, The Woodlands, Texas, USA; [15]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [16]James CCC/The Ohio State University, Columbus, Ohio, USA

BACKGROUND

- Mirvetuximab soravtansine (MIRV) is a first-in-class antibody-drug conjugate (ADC) comprising a folate receptor alpha (FRα)-binding antibody, cleavable linker, and maytansinoid DM4 payload, a potent tubulin-targeting agent[1]
- MIRV has demonstrated clinically meaningful antitumor activity with a favorable safety profile in patients with FRα-positive[a] ovarian cancer[2,3]
- A population PK (PopPK) model was derived to evaluate the effects of patient demographics and clinical characteristics on MIRV PK parameters
- Here we report the results of the PopPK analyses of MIRV from 3 clinical studies (IMGN853-0401 [phase 1]; FORWARD I [phase 3]; SORAYA [phase 3])[4-6]

[a]Antitumor activity with MIRV has been demonstrated with single-agent MIRV in FRα-high PROC (≥75% tumor cells FRα-positive by PS2+)[3] and in combination with other agents in FRα low-to-high PROC (≥25% tumor cells FRα-positive by PS2+).[3]

Objectives

- Characterize the PK of MIRV following single and multiple doses of MIRV in patients with FRα-positive EOC[a]
- Explore the impact of patient demographics and clinical characteristics on relevant PK parameters

[a]In addition to EOC, patients with primary peritoneal cancer and/or fallopian tube cancer were also considered for enrollment.

Methods

Table 1. Trial Descriptions and PopPK Model Source Data

	Data source for base MIRV PopPK model development			Data source for final model validation
	IMGN853-0401 phase 1 trial[4]	FORWARD I phase 3 trial[5]	SORAYA phase 3 trial[6]	
ClinicalTrials.gov ID	NCT01609556	NCT02631876	NCT04296890	
Design/description	First-in-human study with single-agent MIRV[a] *Open-label, nonrandomized, dose-escalation and dose-expansion trial*	Compared single-agent MIRV with investigator's choice of chemotherapy[b] *Open-label, randomized trial*	Single-arm trial with single-agent MIRV[c] *Open-label, nonrandomized trial*	
Patients in analysis	n=203	n=242	n=98	
Total patients	n=543			
Total PK observations	12,634 PK observations (6704 observations for MIRV PK)			
Patients treated with final recommended dose (6 mg/kg AIBW[d] every 3 weeks), n (%)	477 (87.8)			

[a]In patients with relapsed or refractory ovarian or other FRα-positive solid tumors. [b]In patients with FRα-positive platinum-resistant EOC with ≤3 prior systemic anticancer therapies. [c]In patients with bevacizumab-pretreated FRα-high platinum-resistant, advanced, high-grade EOC with 1 to 3 prior systemic anticancer therapies. [d]AIBW, also known as AdjBW, is calculated as IBW (kg) + 0.4 (actual weight - IBW). IBW for females is calculated as 0.9*height (cm) - 92.

Modeling Strategies

- Data collected from the IMGN853-0401 and FORWARD I trials were used to develop a base MIRV PopPK model, followed by a stepwise covariate search that identified statistically significant relationships
- MIRV PK parameters were optimized for a semi-mechanistic model
- The final MIRV PopPK model was determined to be a 2-compartment model with both linear (non-specific) and nonlinear (target-mediated) elimination pathways for MIRV
- This model was then validated using data collected from the SORAYA study

Methods (cont)

Data Used in Modeling

- Baseline demographics and clinical characteristics were used as covariates in a stepwise covariate search that identified statistically significant relationships between:
  - AIBW: CL, Vd (V1 and V2)
  - Albumin: CL
  - Age: Vd (V1 and V2)
- The doses of MIRV that were evaluated ranged from 0.15 mg/kg to 7 mg/kg based on TBW or 0.161 mg/kg to 8.71 mg/kg AIBW
  - AIBW, also known as AdjBW, is calculated as IBW (kg) + 0.4 (actual weight - IBW). IBW for females is calculated as 0.9*height (cm) - 92

Baseline Demographics and Clinical Characteristics

Table 2. Summary of Baseline Patient Characteristics

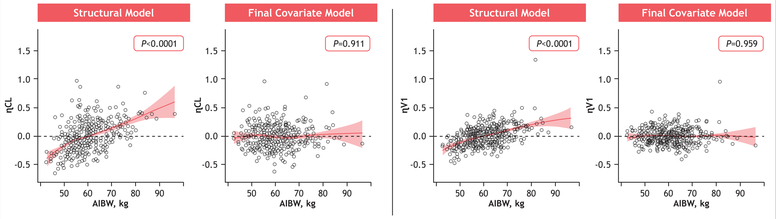
	IMGN853-0401	FORWARD I	SORAYA	Total
Age				
Median (range), y	62 (37-86)	64 (34-89)	62 (35-85)	63 (34-89)
≥65 y, n (%)	83 (40.9)	112 (46.3)	43 (43.9)	238 (43.8)
<65 y, n (%)	120 (59.1)	130 (53.7)	55 (56.1)	305 (56.2)
Race, n (%)				
White	185 (91.1)	219 (90.5)	94 (95.9)	498 (91.7)
Black	5 (2.5)	7 (2.9)	0 (0)	12 (2.2)
Asian	7 (3.4)	6 (2.5)	2 (2.0)	15 (2.8)
American Indian	2 (1.0)	0 (0)	0 (0)	2 (0.4)
Other or not reported	4 (2.0)	10 (4.1)	2 (2.0)	16 (2.9)
Weight, median (range), kg	69.3 (46.4-136)	67.0 (36.1-125)	66.5 (41.8-124)	68.3 (36.1-136)
AIBW, mean (range), kg	60.5 (45.2-96.7)	59.1 (42.8-87.1)	58.4 (44.8-83.4)	59.5 (42.8-96.7)
Albumin, median (range), g/dL[a]	3.8 (2.0-5.0)	4.1 (2.6-5.3)	3.9 (2.6-4.6)	4.0 (2.0-5.3)
FRα expression, n (%)[b,c]				
High	81 (39.9)	142 (58.7)	98 (100)	NA
Medium	40 (19.7)	100 (41.3)	0 (0)	NA
Low	44 (21.7)	0 (0)	0 (0)	NA
Very Low	29 (14.3)	0 (0)	0 (0)	NA
Unknown	9 (4.4)	0 (0)	0 (0)	NA
Renal function, n (%)[d]				
Normal	64 (31.5)	92 (38.0)	41 (41.8)	197 (36.3)
Mild	84 (41.4)	101 (41.7)	32 (32.7)	217 (40.0)
Moderate	53 (26.1)	49 (20.2)	25 (25.5)	127 (23.4)
Severe	2 (1.0)	0 (0)	0 (0)	2 (0.4)
Hepatic function, n (%)[e]				
Normal	163 (80.3)	197 (81.4)	80 (81.6)	440 (81.0)
Mild	30 (14.8)	33 (13.6)	14 (14.3)	77 (14.2)
Moderate	1 (0.5)	0 (0)	0 (0)	1 (0.2)
Missing	9 (4.4)	12 (5)	4 (4.1)	25 (4.6)
Concomitant CYP3A4 inhibitor, n (%)				
Strong	6 (3.0)	5 (2.1)	4 (4.1)	15 (2.8)
Moderate	27 (13.3)	33 (13.6)	4 (4.1)	64 (11.8)
Weak	4 (2.0)	18 (7.4)	0 (0)	22 (4.1)

[a]Missing covariates were imputed to the median value of the analysis population. [b]FRα scoring: very low, <25%; low, 25% to 49%; medium, 50% to 74%; high ≥75% of tumor cells with ≥2+ staining intensity. [c]In FORWARD I, FRα expression was defined as medium, 50% to 74%, and high, ≥75% of tumor cells with any FRα membrane staining visible at ≤10× microscope objective therefore, total FRα levels of expression could not be summarized across the 3 studies. [d]Renal function was defined as normal CrCl ≥90 mL/min; mild CrCl 60 to 89.9 mL/min; moderate CrCl 30 to 59.9 mL/min; severe CrCl <30 mL/min. [e]Hepatic function was defined based on the National Cancer Institute classifications scoring system for hepatic dysfunction.

Results: Statistically Significant Covariates

- The final MIRV PopPK model included AIBW as a statistically significant covariate on CL, V1, (Figure 1) and V2

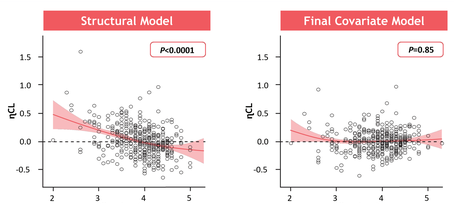
Figure 1. Random Effects of CL and V1 vs AIBW Before and After Inclusion of AIBW in the Model



Circles: observed values; dashed black line: IIV zero line; solid red line and shaded area: smoother with the 95% CI.

- The final MIRV PopPK model included albumin on CL (Figure 2) and age on Vd (V1 and V2) as statistically significant covariates

Figure 2. Random Effects of CL vs Albumin Before and After Inclusion of Albumin in the Model



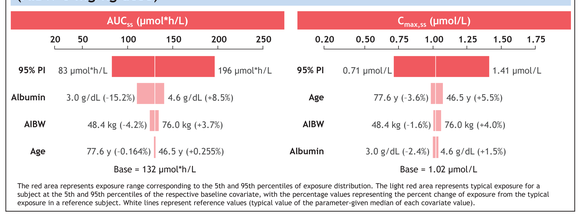
Circles: observed values; dashed black line: IIV zero line; solid red line and shaded area: smoother with the 95% CI.

Results: Covariate Effects on MIRV Exposure

- Although AIBW demonstrated the largest effect on PK parameters, the impact of AIBW on MIRV exposure was negligible with 6 mg/kg AIBW dosing; AUC_{ss} and $C_{max,ss}$ were predicted to vary by less than ±5% (Figure 3)
- Albumin levels had significant impact on CL but not Vd; thus, variations in albumin were found to have a greater impact on AUC_{ss} than on $C_{max,ss}$ (Figure 3)
  - Patients with albumin in the 5th percentile (3.0 g/dL) or 95th percentile (4.6 g/dL) were predicted to have an AUC_{ss} that was 15.2% lower or 8.5% higher, respectively, than the AUC_{ss} predicted for a patient with median albumin (4.0 g/dL)
- Age had an effect on Vd and $C_{max,ss}$ but did not demonstrate an impact on CL or AUC_{ss} (Figure 3)
  - Patients aged in the 5th percentile (46.5 years) or 95th percentile (77.6 years) were determined to have had a $C_{max,ss}$ that was 5.5% higher or 3.6% lower, respectively, than the $C_{max,ss}$ for patients of the median age (63 years)

Results: Covariate Effects on MIRV Exposure (cont)

Figure 3. Covariate Effects on MIRV Exposure at Steady State (AIBW 6 mg/kg dose)



The red area represents exposure range corresponding to the 5th and 95th percentiles of exposure distribution. The light red area represents typical exposure for a subject at the 5th and 95th percentiles of the respective baseline covariate, with the percentage values representing the percent change of exposure from the typical exposure in a reference subject. White lines represent reference values (typical value of the parameter-given median of each covariate value).

Results: Other Covariates and MIRV Terminal Elimination

Other Covariates

- Tumor FRα expression (categorized as low, medium, or high) was not found to be a statistically significant covariate on MIRV PK
- Mild or moderate renal impairment and mild hepatic impairment did not significantly alter MIRV PK
- Coadministration with weak and moderate CYP3A4 inhibitors did not have clinically meaningful effects on PK parameters for MIRV
  - Inducers were not evaluated

Terminal Elimination

- The terminal elimination half-life was found to be 4.8 days (115 hours) after first dose and approximately 24 days at steady state

CONCLUSIONS

- A PopPK model was developed to determine the impact of patient demographics and clinical characteristics on MIRV exposure
- Covariates of statistical significance include AIBW, age, and albumin; however, the impact of these factors on evaluated PK parameters is negligible following a 6 mg/kg AIBW MIRV dose
- Dosing adjustments do not appear to be necessary for patients with mild or moderate renal impairment or mild hepatic impairment

This PopPK analysis supports the recommended dose of MIRV 6 mg/kg AIBW, with MIRV exposure maintained within the target range for patients with FRα-positive ovarian cancer

Abbreviations: ADC, antibody-drug conjugate; AdjBW, adjusted body weight; AIBW, adjusted ideal body weight; AUC, area under the concentration-time curve at steady state; CL, clearance; $C_{max,ss}$, maximum concentration at steady state; CrCl, creatinine clearance; CYP3A4, cytochrome P450 3A4 isozyme; DM4, N2'-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2'-deacetylmaytansine; EOC, epithelial ovarian cancer; FRα, folate receptor alpha; IBW, ideal body weight; IIV, inter-individual variability; MIRV, mirvetuximab soravtansine; NA, not applicable; PI, prediction interval; PK, pharmacokinetic; PopPK, population pharmacokinetics; PROC, platinum-resistant ovarian cancer; PS2+, positive staining intensity ≥2; TBW, total body weight; V1, central volume of distribution; V2, peripheral volume of distribution; Vd, volume of distribution.

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