592P

Exposure Response (ER) Analysis for Efficacy and Safety of Mirvetuximab Soravtansine (MIRV) in Patients With Folate Receptor α (FRα)-Positive Cancer

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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]
- An exposure-response (ER) analysis was conducted to establish the relationship between exposure to single-agent MIRV therapy and the efficacy and safety responses from the IMGN853-0401 (phase 1), FORWARD I (phase 3), and SORAYA (phase 3) clinical trials[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+)[2] and in combination with other agents in FRα low-to-high PROC (≥25% tumor cells FRα-positive by PS2+).[3]

Methods

- Clinical PK, efficacy, and safety data were collected from 542 patients in 3 clinical MIRV monotherapy studies (IMGN853-0401, FORWARD I, and SORAYA)
- Efficacy endpoints evaluated in the ER analysis included ORR and PFS
- Due to differences in study design, specifically the inclusion criteria for FRα expression, efficacy endpoints were evaluated in 2 data pools: one SORAYA data pool and one IMGN853-0401 + FORWARD I data pool
- Safety outcomes evaluated in this ER analysis were pooled from the 3 studies (n=542), and included ocular AEs and peripheral neuropathy

Table 1. Overview of Clinical Studies Included in the ER Analysis

	SORAYA data pool	IMGN853-0401 + FORWARD I data pool	
	SORAYA phase 3 trial[4]	**IMGN853-0401 phase 1 trial[5]**	**FORWARD I phase 3 trial[6]**
ClinicalTrials.gov ID	NCT04296890	NCT01609556	NCT02631876
Design/description	Single-arm trial with single-agent MIRV[b] *Open-label, nonrandomized trial*	First-in-human study with single-agent MIRV[b] *Open-label, nonrandomized, dose-escalation and dose-expansion trial*	Compared single-agent MIRV with investigator's choice of chemotherapy[c] *Open-label, randomized trial*
Patients in ER analysis	n=97	n=203	n=242
No. of MIRV PK records	417	4159	2128

[b]In patients with bevacizumab-pretreated FRα-high platinum-resistant, advanced, high-grade EOC with 1 to 3 prior systemic anticancer therapies. [c]In patients with relapsed or refractory ovarian cancer or other FRα positive solid tumors. [c]In patients with FRα positive platinum-resistant EOC with ≥3 prior systemic anticancer therapies.

- MIRV exposure metrics used for this ER analysis (eg, $AUC_{0\text{-}d21}$, C_{max}, and C_{trough}) were derived from a population PK model developed using data from patients in the IMGN853-0401, FORWARD I, and SORAYA studies
- Covariates evaluated for ER analysis included patient demographics and clinical laboratory values
  - Continuous covariates: age, AIBW[a], albumin, ALP, CrCl, and baseline tumor burden
  - Categorical covariate: race
- A stepwise automated covariate model selection procedure was implemented, and a forward and backward, Akaike information criterion (AIC)-based, automatic selection process was used to identify important exposure relationships and covariates
- Dichotomous endpoints (ORR, AEs) were modeled using logistic regression. Time-to-event endpoints (PFS) were explored using Kaplan-Meier plots. The ER relationship was characterized using Cox proportional hazards model

[a]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.

Patient Demographics and Baseline Characteristics

Table 2. Summary of Baseline Patient Characteristics

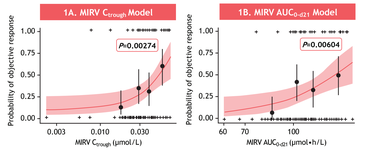
Study	SORAYA (N=97)	IMGN853-0401 (N=203)	FORWARD I (N=242)	All (N=542)
Age				
Median (range), y	62 (35-85)	62 (37-86)	64 (34-89)	63 (34-89)
Race, n (%)				
White	93 (95.9)	185 (91.1)	219 (90.5)	497 (91.7)
Black	0 (0)	5 (2.5)	7 (2.9)	12 (2.2)
American Indian	0 (0)	2 (1.0)	0 (0)	2 (0.4)
Asian	2 (2.1)	7 (3.4)	6 (2.5)	15 (2.8)
Others or not reported	2 (2.1)	4 (2.0)	10 (4.1)	16 (3.0)
AIBW				
Median (range), kg	58.5 (44.8-83.4)	60.5 (45.2-96.7)	59.1 (42.8-87.1)	59.5 (42.8-96.7)
Albumin				
Median (range), g/dL	3.9 (2.6-4.6)	3.8 (2.0-5.0)	4.1 (2.6-5.3)	4.0 (2.0-5.3)
FRα expression category, n (%)[a,b]				
High	97 (100)	81 (39.9)	142 (58.7)	NA
Medium	0 (0)	40 (19.7)	100 (41.3)	NA
Low	0 (0)	44 (21.7)	0 (0)	NA
Very low	0 (0)	29 (14.3)	0 (0)	NA
Unknown	0 (0)	9 (4.4)	0 (0)	NA
Alkaline phosphatase				
Median (range), IU/L	96.0 (48.0-799.0)	90.0 (11.0-1.24e+03)	84.8 (30.0-573.0)	89.0 (11.0-1.24e+03)
Investigator-assessed tumor sum of diameters at baseline				
Median (range), mm	44.0 (10.0-351.0)	55.0 (10.0-294.0)	56.0 (10.0-271.0)	55.0 (10.0-351.0)
Creatinine clearance				
Median (range), mL/min	78.2 (32.0-232.0)	75.9 (27.5-211.0)	81.5 (31.3-217.0)	78.6 (27.5-232.0)

[a]FRα scoring: very low, <25%; low, 25% to 49%; medium, 50% to 74%; high, ≥75% of tumor cells with ≥2+ staining intensity. [b]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.

Results: Objective Response Rate

- In both data pools, logistic regression modeling found ORR correlates with MIRV C_{trough} and $AUC_{0\text{-}d21}$
- The MIRV C_{trough} model was selected as the final model (based on the lowest AIC) for the SORAYA and IMGN853-0401 + FORWARD I data pools
  - In both data pools, the ORR increased with increasing C_{trough} (Figures 1A and 2A)
- An ORR model based on MIRV $AUC_{0\text{-}d21}$ in the SORAYA data pool found that ORR increased with increasing exposure of MIRV (Figure 1B)
- In the IMGN853-0401 + FORWARD I data pool, the C_{trough} was also found to correlate with ORR. In addition, albumin was identified as a significant covariate (Figures 2A and 2B)

Figure 1. SORAYA Data Pool: Observed ORR Model vs MIRV Exposure With Model-Predicted Probability Overlay



Figures 1A and 1B. Red: the predicted probability (mean + 95% CI) for the variable (C_{trough}, $AUC_{0\text{-}d21}$) at the median/mode value of any other variables. Black points and range: the exact binomial estimate of the response for quantiles (4) of the exposure variable.

Figure 2. IMGN853-0401 + FORWARD I Data Pool: Observed ORR Model vs MIRV Exposure With Model-Predicted Probability Overlay

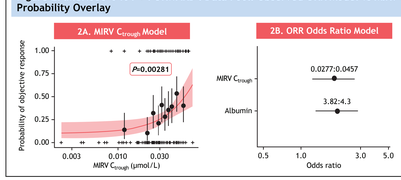


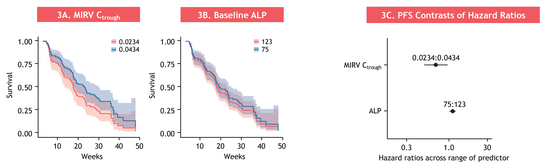
Figure 2A. Red: the predicted probability (mean + 95% CI) for the variable (C_{trough}) at the median/mode value of any other variables. Black points and range: the exact binomial estimate of the response for quantiles (4) of the exposure variable.

Figure 2B. The point and bar denote the hazard ratio contrast mean and 90% CI across the IQR (25th to 75th percentiles) for continuous variables.

Results: Progression-Free Survival

- In both data pools, Cox proportional hazards analyses found that PFS correlates with MIRV C_{trough}
- In the SORAYA data pool, Cox proportional hazards analyses found a significant relationship for PFS with $AUC_{0\text{-}d21}$
- The MIRV C_{trough} model was selected as the final model for PFS (based on the lowest AIC), and significant relationships were found in both data pools
- The Cox proportional hazards models showed that patients with C_{trough} at the 75th percentile demonstrated longer survival than those with C_{trough} at the 25th percentile (Figures 3A and 4A)

Figure 3. SORAYA Data Pool: Effects of Exposure Metrics and Covariates on PFS

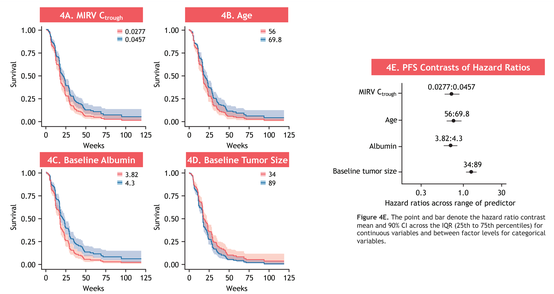


Figures 3A and 3B. The model-based curves visualize the survival probability curves across the IQR (25th [red] to 75th [blue] percentiles) for continuous variables.

Figure 3C. The point and bar denote the hazard ratio contrast mean and CI across the IQR (25th to 75th percentiles) for continuous variables and between factor levels for categorical variables.

- In the SORAYA data pool, ALP was found as a covariate in the PFS model; however, the effect of ALP on survival time was marginal (Figure 3B)

Figure 4. IMGN853-0401 + FORWARD I Data Pool: Effects of Exposure Metrics and Covariates on PFS



Figures 4A–4D. The model-based curves visualize the survival probability curves across the IQR (25th [red] to 75th [blue] percentiles) for continuous variables.

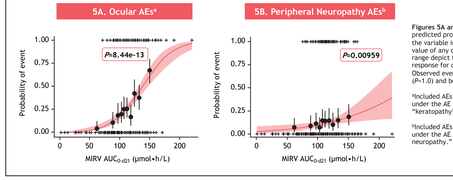
Figure 4E. The point and bar denote the hazard ratio contrast mean and 90% CI across the IQR (25th to 75th percentiles) for continuous variables and between factor levels for categorical variables.

- In the IMGN853-0401 + FORWARD I data pool, age, albumin, and tumor size (Figures 4B, 4C, and 4D) were also found as covariates in the PFS model

Results: Safety Analysis

- In the pooled safety analysis, logistic regression was performed to analyze the relationships between ocular AEs and MIRV $AUC_{0\text{-}d21}$, C_{max}, and C_{trough}
  - The $AUC_{0\text{-}d21}$ was found to correlate with the ocular AEs (lowest AIC)
  - Few patients in the lowest $AUC_{0\text{-}d21}$ decile developed a grade ≥2 ocular AE, but a trend suggested incidence rate increased with increasing $AUC_{0\text{-}d21}$ (Figure 5A)
- Logistic regression was performed to analyze the relationships between the incidence of peripheral neuropathy and MIRV $AUC_{0\text{-}d21}$, C_{max}, and C_{trough}
  - The $AUC_{0\text{-}d21}$ was found to correlate with the incidence of peripheral neuropathy (lowest AIC)
  - This relatively flat ER relationship suggests a limited impact of MIRV exposure on peripheral neuropathy AEs
  - During these clinical studies, few patients developed grade ≥2 peripheral neuropathy, but there was a trend for slightly increased incidence rates with increasing exposure (Figure 5B)

Figure 5. Observed AE (Grade ≥2) Occurrence vs MIRV $AUC_{0\text{-}d21}$ With Model-Based Predicted Probability Overlay



Figures 5A and 5B. These plots show the predicted probability (mean + 95% CI) in red for the variable in the x-axis at the median/mode value of any other variables. The black points and range depict the exact binomial estimate of the response for deciles (10) of the exposure variable. Observed events are indicated by a "+" at the top (P=1.0) and bottom (P=0.0) of the plot.

[a]Included AEs of grade 2 and higher recorded under the AE preferred term variables of "keratopathy" and "vision blurred."

[b]Included AEs of grade 2 and higher recorded under the AE preferred term variable "peripheral neuropathy."

CONCLUSIONS

- Overall, both efficacy and ocular AEs were found to increase with increased exposure to MIRV
  - ORR and PFS increased with increasing MIRV $AUC_{0\text{-}d21}$ and C_{trough}
  - Ocular AEs were shown to increase with increasing MIRV $AUC_{0\text{-}d21}$
- The covariates (AIBW, age, and albumin) identified by the population PK models had limited impact on efficacy and safety, and are likely not of clinical significance

These data demonstrate the impact of MIRV exposure on both efficacy outcomes and the risk for ocular AEs; thus, highlighting the importance of adherence to recommended MIRV dosing guidelines in clinical practice

Abbreviations: ADC, antibody-drug conjugate; AdjBW, adjusted body weight; AEs, adverse events; AIBW, adjusted ideal body weight; AIC, Akaike information criterion; ALP, alkaline phosphatase; $AUC_{0\text{-}d21}$, area under the concentration time curve over the first 21-day treatment cycle; C_{max}, maximum concentration; CrCl, creatinine clearance; C_{trough}, trough concentration; DM4, N2′-[4-[(3-carboxypropyl)dithio]-4-methyl-1-oxo-2-sulfopentyl]-N2′-deacetylmaytansine; EOC, epithelial ovarian cancer; ER, exposure response; FRα, folate receptor alpha; IBW, ideal body weight; IQR, interquartile range; MIRV, mirvetuximab soravtansine; NA, not applicable; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetic; PROC, platinum-resistant ovarian cancer; PS2+, positive staining intensity ≥2.

References: 1. Moore KN, et al. *Cancer*. 2017;123(16):3080-3087. 2. Matulonis UA, et al. Poster presented at: 2022 American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, IL. Poster 391. 3. Matulonis UA, et al. Presented at: 2018 European Society for Medical Oncology Congress; October 19-23, 2018; Munich, Germany. Abstract 949P. 4. ClinicalTrials.gov Identifier: NCT04296890. Updated April 21, 2022. Accessed August 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04296890 5. ClinicalTrials.gov Identifier: NCT01609556. Updated February 17, 2021. Accessed August 5, 2022. https://clinicaltrials.gov/ct2/show/NCT01609556 6. ClinicalTrials.gov Identifier: NCT02631876. Updated October 14, 2020. Accessed August 5, 2022. https://clinicaltrials.gov/ct2/show/NCT02631876

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