Integrated Safety Summary of Single-Agent Mirvetuximab Soravtansine in Patients With Folate Receptor Alpha (FRα)-Positive Recurrent Ovarian Cancer: Phase 1 and 3 Clinical Trials

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BACKGROUND

- Treatment options for platinum-resistant ovarian cancer (PROC) are limited, consisting primarily of single-agent chemotherapy as many patients will have received prior bevacizumab[1,2]
  - Single-agent chemotherapy has limited activity (objective response rate [ORR], 4%-13%) and considerable toxicity[3-6]
- Folate receptor alpha (FRα), also known as folate receptor 1 (FOLR1), has limited expression on normal tissues but is elevated in most ovarian cancers, which makes FRα an attractive target for the development of novel therapies[7,8]
- Mirvetuximab soravtansine (MIRV) is a first-in-class antibody-drug conjugate (ADC) comprising an FRα-binding antibody, cleavable linker, and maytansinoid DM4 payload, a potent tubulin-targeting agent.[9] MIRV has demonstrated significant antitumor activity in patients with PROC as a single agent and in combination therapy[10,11]
- Toxicity profiles differ widely among ADC therapies,[12-14] and MIRV has a safety profile distinct from other tumor-targeting ADCs.[11] Here we provide an integrated safety summary, demonstrating the consistency of the safety profile of MIRV[11]

METHODS

Objective

- To characterize the safety profile of single-agent MIRV in patients with FRα-positive recurrent ovarian cancer, based on a retrospective, pooled analysis of data from three clinical trials

Methods

- Safety data from three single-agent trials in 15 countries were pooled (N=464) (*Table 1*)
  - Patients included had FRα-positive recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (collectively referred to as epithelial ovarian cancer [EOC])
  - Highest enrollments (≥10%) came from the United States (45%), Italy (15%), and Spain (14%)
- FRα positivity was defined as follows:
  - Phase 1 trial: ≥25% cells stained (PS2+ scoring method)
  - FORWARD I trial: ≥50% of cells (10x scoring method)
  - SORAYA trial: ≥75% cells stained (PS2+ scoring method)
- This Integrated Safety Population included patients with FRα-positive ovarian cancer who had received MIRV at 6 mg/kg adjusted ideal body weight (AIBW) on day one of a 21-day cycle; this comprised all patients in the SORAYA trial and patients from the phase 1 and FORWARD I trials

Safety Monitoring

- For this integrated analysis, all adverse events (AEs) were coded using MedDRA™ (version 24.0), associating lower-level terms with preferred term (PT) and system organ class (SOC) by the primary hierarchy. The severity of AEs was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0
- Relationship of an AE or serious AE (SAE) to study drug was determined by the investigator
- Predefined AEs of interest included ocular events, peripheral neuropathy, pneumonitis, and infusion-related reactions

Table 1. Integrated Safety Population: EOC Patients Who Received ≥1 Dose of MIRV at 6 mg/kg AIBW Q3W (N=464)

	Phase 1 Trial	FORWARD I Phase 3 Trial	SORAYA Phase 3 Trial
ClinicalTrials.gov ID	NCT01609556	NCT02631876	NCT04296890
Design/description	First-in-human, open-label, nonrandomized, dose-escalation and dose-expansion trial	Open-label, randomized trial	Open-label, nonrandomized, single-arm trial
Patients included in Integrated Safety Population	Patients with FRα-positive relapsed/refractory EOC amenable to biopsy or FRα-positive platinum-resistant/ refractory EOC	Patients with FRα-positive platinum-resistant EOC with ≤3 prior systemic anticancer therapies	Patients with bevacizumab-pretreated FRα-positive platinum-resistant, advanced, high-grade EOC with 1-3 prior systemic anticancer therapies
Countries	US, Canada	US, Canada, Europe	Global
Data cutoff date	February 2018 (database lock)	March 18, 2020	November 16, 2021
No. MIRV-treated patients included in Integrated Safety Population	**113**	**245**	**106**

Q3W, every 3 weeks.

RESULTS

Table 2. Baseline Demographics and Disease Characteristics

	Integrated Safety Population (N=464)
Demographics	
Median age (range), y	63 (34-89)
Age category, n (%)	
≥18 to <65 y	264 (57)
≥65 y	200 (43)
Race, n (%)	
White	424 (91)
Black or African American	10 (2)
Asian	13 (3)
American Indian or Alaska Native	2 (<1)
Other	2 (<1)
Not reported	13 (3)
Medical history	
Neuropathy peripheral, n (%)	101 (22)
Peripheral sensory neuropathy, n (%)	56 (12)
Eye disorders, n (%)	201 (43)
Cataract	101 (22)
Dry eye	61 (13)
Vision blurred	34 (7)
Vitreous floaters	26 (6)
Keratopathy	11 (2)
Baseline disease characteristics	
ECOG PS scale score, n (%)	
0	252 (54)
1	212 (46)
Primary diagnosis, n (%)	
Epithelial ovarian cancer	391 (84)
Fallopian tube cancer	30 (6)
Other; tubal/ovarian cancer	1 (<1)
Primary peritoneal cancer	41 (9)
Other[a]	1 (<1)
FRα expression level per protocol, n (%)[b]	
Low (≥25%-49% of tumor cells)	23 (5)
Medium (≥50%-74% of tumor cells)	130 (28)
High (≥75% of tumor cells)	311 (67)
Prior cancer therapies	
No. of prior systemic therapies, n (%)	
1-2 prior	225 (48)
3 prior	179 (39)
4+ prior	60 (13)
Median no. prior systemic therapies, (range) no.	3 (1-11)
Prior systemic therapy, n (%)	
Bevacizumab	301 (65)
PARP inhibitor	116 (25)
Platinum therapy as the last line of treatment, n (%)	248 (53)
Platinum-free interval, n (%)[c]	
0-3 mo	182 (39)
3-6 mo	243 (52)
≥6 mo	38 (8)
Missing	1 (<1)

ECOG, Eastern Cooperative Oncology Group; PARP, poly (ADP-ribose) polymerase; PS, performance status.
[a]One patient with primary diagnosis categorized as "other" had histopathology consistent with the inclusion/exclusion criteria.
[b]Percentages refer to the proportion of cells with PS2+ staining (phase 1 or SORAYA trials) or proportion of cells with any membrane staining visible at 10x magnification (FORWARD I).
[c]Time from last dose of the latest-line platinum therapy to the date of disease progression and/or relapse following that line of therapy.

Figure 1. Patient Disposition

- Disease progression was the primary reason for discontinuation in this safety population

[a]The primary reason for discontinuation of MIRV in these 3 patients was clinical deterioration/disease worsening.

CONCLUSIONS

- Pooled data from three clinical trials (N=464) demonstrated that MIRV has a differentiated safety profile consisting primarily of low-grade gastrointestinal and ocular events
- Adverse events generally resolved and were managed with supportive care and, if needed, dose modifications
  - 7% treatment-related discontinuations
- MIRV administration did not result in any corneal ulcers or perforations, and no patients had permanent ocular sequelae
  - The majority of patients with ocular events did not require dose delay or dose reduction
  - <1% of patients discontinued MIRV treatment due to an ocular event
- The safety profile of MIRV in recurrent ovarian cancer along with significant antitumor activity in PROC (ORR, 32.4%)[10] support a favorable benefit-risk ratio

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Table 3. Dose Exposure and Modifications

	Integrated Safety Population (N=464)
MIRV exposure	
Total exposure, person-week	11,253
Median duration of dosing (range), wk	19 (3-132)
Median relative dose intensity (ratio of actual dose to planned daily dose) (range), %	99.8 (29-110)
No. of cycles, median (range)	6.0 (1-44)
Patients with dose modifications, n (%)	216 (47)
TRAEs leading to dose modification	
TRAEs leading to dose delay, n (%)	
All grades	151 (33)
Grade ≥3	38 (8)
TRAEs leading to dose reduction, n (%)	
All grades	97 (21)
Grade ≥3	33 (7)
TRAEs leading to discontinuation, n (%)	
All grades	31 (7)
Grade ≥3	15 (3)

TRAE, treatment-related adverse event.

Dose Exposure and Modifications

- Median duration of dosing was 19 weeks
- TRAEs leading to discontinuation: 7% (all-grade TRAEs), 3% (grade ≥3)

Table 4. Most Common (≥10%) TRAEs

	Integrated Safety Population (N=464)		SORAYA Safety Population* (N=106)	
Adverse event	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
Patients with any TRAE	**431 (93)**	**121 (26)**	**91 (86)**	**32 (30)**
Most common TRAEs (all-grade, ≥10% of patients)				
Vision blurred	195 (42)	12 (3)	43 (41)	6 (6)
Nausea	187 (40)	7 (2)	31 (29)	0
Diarrhea	151 (33)	10 (2)	23 (22)	2 (2)
Fatigue	143 (31)	9 (2)	25 (24)	1 (<1)
Keratopathy	121 (26)	12 (3)	31 (29)	9 (9)
Dry eye	104 (22)	5 (1)	26 (25)	2 (2)
AST increased	73 (16)	6 (1)	7 (7)	2 (2)
Decreased appetite	72 (16)	4 (<1)	14 (13)	1 (<1)
Vomiting	71 (15)	7 (2)	12 (11)	0
Headache	64 (14)	1 (<1)	8 (8)	0
Neuropathy peripheral	64 (14)	4 (<1)	14 (13)	0
Asthenia	63 (14)	3 (<1)	16 (15)	1 (<1)
ALT increased	57 (12)	5 (1)	6 (6)	1 (<1)
Visual acuity reduced	56 (12)	4 (<1)	3 (3)	0
Photophobia	49 (11)	2 (<1)	14 (13)	0
Eye pain	48 (10)	3 (<1)	8 (8)	0
Abdominal pain	45 (10)	4 (<1)	7 (7)	2 (2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
*Data shown from SORAYA safety population are derived from a separate data cutoff of April 29, 2022

Treatment-Related Adverse Events

- TRAEs (all grades) occurred in 93% of patients; the most common TRAEs included blurred vision, nausea, diarrhea, fatigue, keratopathy, and dry eye (*Table 4*)
- Most TRAEs were grade 1 or 2; 26% of patients had at least one reported grade ≥3 TRAE
  - The most common grade ≥3 TRAEs were keratopathy and blurred vision (3% each); cataract, diarrhea, nausea, vomiting, increased γ-glutamyltransferase, and fatigue (2% each)
- Most TRAEs were managed with standard supportive care, with only 7% of patients experiencing a TRAE leading to discontinuation (*Table 3*)
  - Standard premedication/management included corticosteroids, antihistamines, antipyretics, antiemetics, antidiarrheals, lubricating eye drops, and ophthalmic topical steroid eye drops
- One death was recorded as possibly related to study drug
  - An 86-year-old patient in the SORAYA trial died from respiratory failure thought possibly related to study drug. Autopsy confirmed advanced metastatic ovarian cancer with lung involvement and diffuse alveolar damage in the background of idiopathic pulmonary fibrosis with recent bronchopneumonia. There was no evidence of drug reaction
  - Another patient had a fatal treatment-emergent AE (small intestinal obstruction), but this was not considered to be a TRAE

Patients in the SORAYA trial experienced less nausea (29% vs 40%) and diarrhea (22% vs 33%) than patients in the Integrated Safety Population experienced as a whole; this likely reflects the recommended early implementation of symptom-directed treatment and prophylactic antiemetics in the SORAYA trial

Ocular AEs in the Integrated Safety Population

- An ophthalmic exam was performed at baseline for all patients. All patients with any ocular symptoms were referred to an eye care specialist for evaluation and were monitored with ocular exams every other cycle (every 6 weeks) thereafter
- 231 of 464 patients (50%) had any reported ocular event (all grades; blurred vision or keratopathy[a])
  - 208 patients (45%) experienced ocular events that were grade ≤2 in severity; 22 patients (5%) experienced a grade 3 event
  - One patient had a grade 4 event, which was recorded as keratopathy, based upon the visual acuity evaluation of one eye (20/200). This patient had nonconfluent corneal deposits treated as dry eye syndrome. Visual acuity and corneal changes both resolved completely (grade 0) in 15 days
- Onset of ocular events typically occurred during cycle two of treatment (median time to onset approximately 1.5 months)
  - Median time to onset of vision blurred was 41.5 days (range, 1-394), and median time to onset of keratopathy was 50.0 days (range, 23-394)

[a]Keratopathies included corneal cyst, corneal deposits, corneal disorder, corneal epithelial microcysts, corneal epithelium defect, corneal erosion, corneal opacity, corneal pigmentation, keratitis, keratitis interstitial, keratopathy, limbal stem cell deficiency, and punctate keratitis.

Table 5. MIRV Dose Modifications Due To Ocular Events

MIRV Dosing Modification	Total Integrated Safety Population (N=464)	Integrated Safety Population With Ocular Events (N=231)
No dosing-related action taken, n/N (%)	132/464 (28%)	132/231 (57%)
Dose delayed or interrupted, n/N (%)	91/464 (20%)	91/231 (39%)
Dose reduced, n/N (%)	54/464 (12%)	54/231 (23%)
Permanent discontinuation, n/N (%)	3/464 (<1%)	3/231 (1%)

Individual patients may have experienced more than one dosing modification.

- For all patients with complete follow-up data, ocular AEs resolved to grade 1 or 0
  - 90% of patients reporting blurred vision and 93% of patients with keratopathy had resolution to grade 1 or 0, confirmed by an eye care specialist; follow-up data are incomplete and ongoing for the remaining 10% and 7%, respectively
- Single-agent MIRV administration did not result in any corneal ulcers or corneal perforations, and no patients had permanent ocular sequelae

Other AEs of Interest: Alopecia, Neuropathy, and Myelosuppression

- In FORWARD I (the only trial in the Integrated Safety Population with a chemotherapy comparator arm), MIRV was associated with less peripheral neuropathy than paclitaxel (15% vs 28%, grade ≥2), less alopecia (3% vs 22%, all grades), and less myelosuppression (neutropenia: 7% vs 39%, all grades; thrombocytopenia: 11% vs 16%, all grades; anemia: 14% vs 29%, all grades)
- In the Integrated Safety Population, there were no peripheral neuropathy TRAEs grade ≥4

Peripheral neuropathy includes the following related terms: neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, and hypoesthesia.

Table 6. Other TRAEs of Interest

	Integrated Safety Population (N=464)		SORAYA* (N=106)	
Adverse event	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
Alopecia	3 (<1)	0	1 (<1)	0
Neuropathy peripheral	64 (14)	4 (<1)	14 (13)	0
Peripheral sensory neuropathy	36 (8)	4 (<1)	4 (4)	2 (2)
Peripheral motor neuropathy	4 (<1)	1 (<1)	2 (2)	1 (<1)
Paresthesia	21 (5)	0	5 (5)	0
Anemia	43 (9)	4 (<1)	8 (8)	1 (<1)
Thrombocytopenia	43 (9)	1 (<1)	10 (9)	2 (2)
Neutropenia	35 (8)	2 (<1)	14 (13)	2 (2)

*Data shown from SORAYA safety population are derived from a separate data cutoff of April 29, 2022

For additional information, including ongoing clinical trials, please contact medicalaffairs@immunogen.com

REFERENCES

1. Indini A, et al. *Cancers (Basel)*. 2021;13(7):1663. doi:10.3390/cancers13071663. **2.** McClung EC, Wenham RM. *Int J Womens Health*. 2016;8:59-75. **3.** Pujade-Lauraine E, et al. *J Clin Oncol*. 2014;32(13):1302-1308. **4.** Gaillard S, et al. *Gynecol Oncol*. 2021;163(2):237-245. **5.** Hamanishi J, et al. *J Clin Oncol*. 2021;39(33):3671-3681. **6.** Pujade-Lauraine E, et al. *Lancet Oncol*. 2021;22(7):1034-1046. **7.** Birrer MJ, et al. *Oncologist*. 2019;24(4):425-429. **8.** Zamarin D, et al. *J Immunother Cancer*. 2020;8(1):e000829. **9.** Moore KN, et al. *Cancer*. 2017;123(16):3080-3087. **10.** Matulonis UA, et al. Presented at: Society of Gynecologic Oncology 2022 Annual Meeting on Women's Cancer; March 18-21, 2022; Phoenix, AZ. **11.** ImmunoGen Inc. Data on file. **12.** Eaton JS, et al. *J Ocul Pharmacol Ther*. 2015;31(10):589-604. **13.** Lievano FA, et al. *Drug Saf*. 2021;44(7):733-742. **14.** Masters JC, et al. *Invest New Drugs*. 2018;36(1):121-135.

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