Mirvetuximab Soravtansine in Patients with Platinum-Resistant Ovarian Cancer with High Folate Receptor Alpha (FRα) Expression: Characterization of Anti-Tumor Activity in the SORAYA Study

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BACKGROUND AND OBJECTIVE:

- 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 a FRα-binding antibody, cleavable linker, and maytansinoid DM4 payload, a potent tubulin-targeting agent[9]
- SORAYA (ClinicalTrials.gov ID NCT04296890) is a global, single-arm pivotal study evaluating MIRV in patients with FRα-high PROC who had received 1 to 3 prior therapies, including required prior bevacizumab[10]
- In previously presented SORAYA data, MIRV demonstrated clinically meaningful antitumor activity in patients with FRα-high PROC, regardless of number of prior lines of therapy or prior PARP inhibitor use.[10] Here we present results from a longer-term follow-up, including details of antitumor activity that are important for clinical decision-making[11]

METHODS:

Table 1. SORAYA Study Design

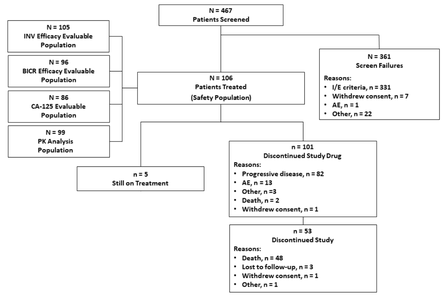
Enrollment and Key Eligibility Criteria	
• Enrolled 106 patients • At least one lesion that meets RECIST v 1.1 criteria for measurable disease • Platinum-resistant disease (PFI ≤6 mo) • Primary platinum-refractory disease excluded (primary PFI <3 mo)	• Prior bevacizumab required; prior PARP inhibitor allowed • 1-3 prior lines of therapy • Patients with *BRCA* mutations allowed • FRα-high (≥75% of cells staining positive with ≥2+ staining intensity)[a]
MIRV Dosing	
• Patients received MIRV 6 mg/kg, adjusted ideal body weight, IV once every 3 weeks	
Primary End Point	
• Confirmed ORR by investigator assessment	
Secondary End Points[b]	
• DOR • Safety and Tolerability • PFS	• OS • ORR, DOR, and PFS by BICR as sensitivity analyses • CA-125 response by GCIG criteria
Statistical Assumptions	
• The study was designed to test the null hypothesis that the ORR was 12%, based on ORR for single-agent chemotherapy in prior trials of PROC (range, 4%-13%) • 91% power to detect a difference in ORR of 12% (24% vs 12%) in sample size of 105 efficacy evaluable patients using 1-sided binomial test and 1-sided α level of 0.025 • ~110 patients were planned to be enrolled, to result in ~105 efficacy-evaluable patients	

AE, adverse event; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; DOR, duration of response; GCIG, Gynecologic Cancer Intergroup; IV, intravenous; OS, overall survival; PFI, platinum-free interval; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

[a]PS2+ scoring method, sum of staining of 2+ and 3+ intensity. [b]Secondary end points were evaluated to further characterize the efficacy of MIRV. No formal hypothesis testing was performed on secondary end points.

RESULTS:

Figure 1. Patient Disposition



I/E, inclusion/exclusion; INV, investigator; PK, pharmacokinetic(s); ULN, upper limit of normal.

Analysis Populations

- Safety population: 106 patients who received at least 1 dose of MIRV
- Efficacy-evaluable population: 105 patients who had measurable disease at baseline by investigator assessment per RECIST v1.1

Table 2. Baseline Demographics and Clinical Characteristics

Characteristic		All Patients (N=106)
Age, median (range), y		62 (35-85)
Primary cancer diagnosis,[a] n (%)	Epithelial ovarian cancer Fallopian tube cancer Primary peritoneal	85 (80) 8 (8) 12 (11)
Stage at initial diagnosis,[b] n (%)	I - II III IV	2 (2) 63 (59) 40 (38)
ECOG PS, n (%)	0 1	60 (57) 46 (43)
BRCA mutation, n (%)	Yes No/unknown	21 (20) 85 (80)
No. of prior systemic therapies, n (%)	1 2 3 >3	10 (9) 41 (39) 54 (51) 1 (<1)
Prior exposure, n (%)	Bevacizumab PARPi	106 (100) 51 (48)
Primary platinum-free interval, n (%)	3-12 mo[c] >12 mo	63 (59) 43 (41)
Platinum-free interval, n (%)	0-3 mo 3-6 mo ≥6 mo	39 (37) 64 (60) 3 (3)

ECOG PS, Eastern Cooperative Oncology Group performance status; PARPi, PARP inhibitor.
Data cutoff for protocol-specified primary analysis: November 16, 2021. Longer cutoff presented here of April 29, 2022.
[a]Primary cancer diagnosis includes 1 patient with "other" diagnosis. [b]One patient missing information for stage at initial diagnosis; none of the patients were at stage II when initially diagnosed. [c]Includes 1 patient with primary platinum-free interval of 2.8 months.

Table 3. Response-Related Efficacy End Points

End Point	Investigator-Assessed (N=105)	BICR-Assessed (N=96)
Response rates[a]		
ORR, n (%)[b] 95% CI[c]	**34 (32.4)** [23.6-42.2]	**29 (30.2)** [21.3-40.4]
Best overall response, n (%)		
Complete response	**5 (4.8)**	**6 (6.3)**
Partial response	29 (27.6)	23 (24.0)
Stable disease[d]	48 (45.7)	54 (56.3)
Progressive disease	20 (19.0)	9 (9.4)
Not evaluable	3 (2.9)	4 (4.2)
Duration of response / time to response[a]		
mDOR[e], months 95% CI	**6.9** [5.6, 9.7]	**NR** [5.0, NR]
Median time to response, months (range)	**1.5** (1.0-5.6)	**1.4** (1.0-5.4)

CR, complete response; NR, not reached; PD, progressive disease; PR, partial response.
Data cutoff: April 29, 2022.
[a]Based on RECIST v1.1. [b]ORR is defined as the proportion of patients with a confirmed CR or PR. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable. [c]Clopper-Pearson exact CI. [d]Minimum duration of 35 days from date of first dose of MIRV. [e]Kaplan-Meier estimate. DOR was defined as time from the date of first response (CR or PR) to the date of PD or death from any cause, whichever occurred first. DOR was only defined for patients with a confirmed best overall response (BOR) of CR or PR only.

Table 4. Other Outcomes

Investigator-Assessed Outcomes	N=105
Disease control rate (DCR)[a], n (%) 95% CI[b]	54 (51.4) [41.5-61.3]
Tumor reduction[c], n (%)	75 (71.4)
CA-125 Response	**N=86**
CA-125 response, % 95% CI	46.5% [35.7-57.6]

[a]Proportion of patients who achieved a CR, PR, or stable disease maintained for ≥12 weeks. [b]Clopper-Pearson exact CI. [c]Occurred if the sum of the diameters of target lesions was reduced from the baseline value during the study.

Subgroup Analysis

- A subgroup analysis was performed to estimate response rate in the 20 patients[a] with *BRCA1* or *BRCA2* mutations (*BRCAmt*, germline or somatic mutations) *(Table 5)*

Table 5. BRCAmt Subgroup Analysis

BRCAmt with prior PARPi (n=16)	*BRCAmt* without prior PARPi (n=4)
Responders, n	6	3
ORR	38%	75%

[a]Data from one patient was not included in the subgroup analysis as it was unknown if patient had received PARPi or placebo. Best overall response for this patient was stable disease.

CONCLUSIONS

- MIRV is the first biomarker-directed agent demonstrating antitumor activity in patients with FRα-high PROC
  - Tumor reduction occurred in 71% of patients, and DCR (CR, PR, SD ≥ 12 weeks) was 51%
  - Patients with *BRCA* mutations, both with and without prior PARPi, demonstrated robust antitumor activity
  - In responders, depth and duration of response did not appear to be affected by dose reductions
  - Preliminary mOS was 13.8 months
- Safety and tolerability of MIRV in SORAYA are consistent with that observed in previous studies
  - Adverse events were primarily low-grade gastrointestinal and ocular events that generally resolved with supportive care or, if needed, dose modifications
  - The discontinuation rate due to TRAEs was 9%
- In SORAYA, MIRV demonstrated a favorable benefit-risk profile in patients with FRα-high PROC

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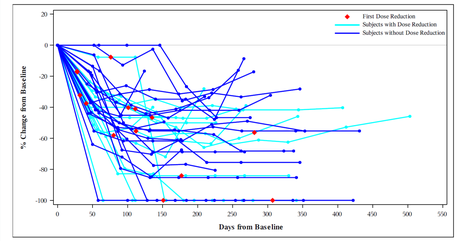
Impact of MIRV Dose Modification on Tumor Size

- Dose reduction did not appear to impact the extent of tumor reduction (*Figure 2*)

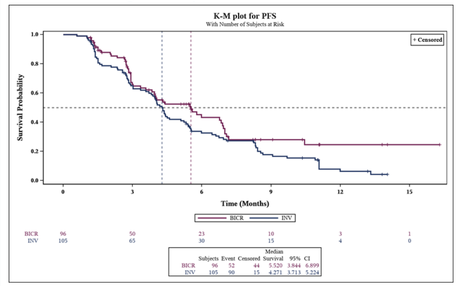
Figure 2. Spider Plot of Change From Baseline in Tumor Size[a] (Responders Only) for Patients With or Without Dose Reduction



- 5 of 14 responders had dose reduction prior to first response
- 9 of 14 responders had dose reduction after first response
- At data cutoff, 5 responders were still receiving MIRV

[a]Based on the investigator's assessment of the sum of the longest diameter of target lesions.

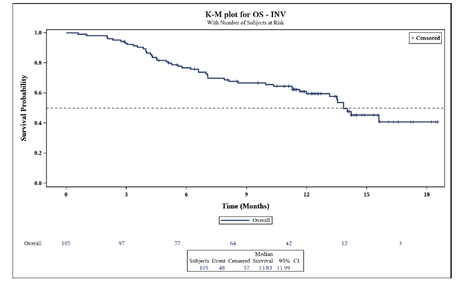
Figure 3. Kaplan-Meier Plot for PFS



- PFS (a secondary end point) was defined as the time from the date of first dose of MIRV until the date of PD or death from any cause, whichever occurred first
- Median PFS (mPFS)
  - mPFS assessed by Investigator: 4.3 months (95% CI, 3.7-5.2)[a]
  - mPFS assessed by BICR: 5.5 months (95% CI, 3.8-6.9)[b]

[a]Investigator efficacy evaluable population. [b]BICR efficacy evaluable population.

Figure 4. Kaplan-Meier Plot for OS



- OS (a secondary end point) was defined as the time from the date of first dose until the date of death from any cause
- Median OS (mOS): 13.8 months (95% CI, 12.0-NE)[a]
  - OS data is still immature at this point and is descriptive in nature

[a]Investigator efficacy evaluable population.

Treatment-Related Adverse Events

Table 6. Treatment-Related Adverse Events (≥10%) (N=106)

TRAEs, n (%)	All Grades	Grade 3	Grade 4
Patients with any event	**91 (86)**	**30 (29)**	**1 (1)**
Blurred vision	43 (41)	6 (6)	0 (0)
Keratopathy	31 (29)	8 (8)	1 (1)
Nausea	31 (29)	0 (0)	0 (0)
Dry eye	26 (25)	2 (2)	0 (0)
Fatigue	25 (24)	1 (1)	0 (0)
Diarrhea	23 (22)	2 (2)	0 (0)
Asthenia	16 (15)	1 (1)	0 (0)
Photophobia	14 (13)	0 (0)	0 (0)
Peripheral neuropathy	14 (13)	0 (0)	0 (0)
Decreased appetite	14 (13)	1 (1)	0 (0)
Vomiting	12 (11)	0 (0)	0 (0)
Neutropenia	14 (13)	2 (2)	0 (0)

AEs, adverse advents; TRAEs, treatment-related adverse events.

- Serious grade ≥3 TRAEs were reported in 9% of patients
- Ten patients (9%) discontinued treatment due to TRAEs
  - One patient discontinued due to an ocular TRAE
- TRAEs led to dose delay in 33% of patients and dose reduction in 20% of patients
- One death was recorded as possibly related to study drug
  - Respiratory failure
  - Autopsy: no evidence of drug reaction; lung metastases

Ocular Events With MIRV

- An ophthalmic exam was performed at baseline for all patients enrolled. Before the start of each cycle, patients with any symptoms were referred to an eye care specialist for evaluation
- In this dataset (data cutoff: April 29, 2022), 58 of 106 patients (55%) had any reported ocular event (blurred vision or keratopathy; all grades)
  - 46 patients (43%) experienced ocular events that were grade 2 or lower in severity; 12 patients (11%) experienced a grade ≥3 ocular event
- Onset of ocular events typically occurred during cycle 2 of treatment (median time to onset 1.3 months)
  - Median time to onset of vision blurred was 1.3 months (range, 0.0-9.9), and median time to onset of keratopathy was 1.5 months (range, 1.1-8.6)

For all patients with complete follow-up, ocular AEs resolved to grade 1 or 0
At data cutoff: >96% of patients with grade 2–3 events had resolved to grade 1 or 0

- Discontinuations due to ocular AEs were rare; one patient of 106 (<1%) discontinued MIRV due to an ocular event
  - This patient discontinued due to grade 4 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
- MIRV administration did not result in any corneal ulcers or corneal perforations, and no patients had permanent ocular sequelae

Future Directions for Research

MIRV monotherapy trials

- MIRASOL (ClinicalTrials.gov ID NCT04209855): phase 3 confirmatory trial of MIRV monotherapy in patients with FRα-high PROC
- PICCOLO (ClinicalTrials.gov ID NCT05041257): single-arm phase 2 trial of MIRV in patients with FRα-high platinum-sensitive ovarian cancer

MIRV combination trials (planned initiation mid-2022)

- GLORIOSA: randomized phase 3 trial of MIRV + bevacizumab maintenance in patients with FRα-high platinum-sensitive ovarian cancer
- Trial 420: single-arm phase 2 trial of MIRV + carboplatin followed by MIRV continuation in patients with FRα-low, medium, or high platinum-sensitive ovarian cancer

For additional information, please contact medicalaffairs@immunogen.com

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Mirvetuximab soravtansine is an investigational agent.

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