Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), with pembrolizumab in platinum-resistant ovarian cancer (PROC): Initial results of an expansion cohort from FORWARD II, a Phase Ib study

Abstract 949P

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INTRODUCTION

Mirvetuximab soravtansine (IMGN853) is an antibody-drug conjugate (ADC) comprising a folate receptor alpha (FRα)-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent, that is currently in clinical development both as monotherapy and in combination regimens to treat ovarian cancer. In less heavily pretreated patients (1-3 priors) with platinum-resistant ovarian cancer (PROC) with medium/high FRα expression, mirvetuximab soravtansine monotherapy generated a confirmed objective response rate (ORR) of 47% with a median progression-free survival (mPFS) of 6.7 months, forming the basis for the patient population enrolled in the phase 3 trial FORWARD I.[1]

In phase I expansion in a broader, more heavily pretreated ovarian cancer population (n=113; 85% platinum-resistant; 50% with 4+ prior lines of therapy; 20% FRα low), mirvetuximab soravtansine monotherapy generated a confirmed ORR of 30%, mPFS of 4.3 months, and median duration of response (DOR) of 4.4 months.[2] To improve outcomes, particularly duration of clinical benefit, combination regimens have subsequently been assessed, including the addition of an anti-PD1 antibody.

Immune checkpoint blockade is a validated approach for cancer therapy, as evidenced by the approval of the anti-PD1 antibody pembrolizumab in a variety of tumor indications, which has catalyzed interest in exploring this approach in epithelial ovarian cancer (EOC). Pembrolizumab monotherapy has shown low ORRs and short PFS outcomes in PROC.[3-4] Further, recent combination studies, with pegylated liposomal doxorubicin (PLD) or niraparib, have also reported modest clinical activity in PROC (confirmed ORRs of 19% [5/26 patients] and 18% [11/60 patients], respectively, each in populations with a median of 2 prior lines of therapy),[5,6] in line with expectations for single-agent cytotoxics in this setting.

Preclinical studies have provided a mechanistic rationale for combining immune checkpoint blockade alongside mirvetuximab soravtansine as a novel avenue for therapeutic intervention in EOC[7], with the goal of prolonging clinical benefit of this ADC in later-line patients through concomitant activation of the immune system. The dose-escalation safety findings from the FORWARD II phase 1b study (NCT02606305) evaluating the combination of mirvetuximab soravtansine and pembrolizumab in patients with PROC were previously reported.[8] Here we present initial safety and preliminary efficacy data from the expansion stage of the trial, including escalation patients who received the combination at full dosing (10 patients from escalation and 46 patients from expansion).

Patient Population, Methods, and Objectives

Primary Objective: Evaluate the safety and tolerability of mirvetuximab soravtansine when administered in combination with pembrolizumab* in patients with PROC

Treatment schedule†: Pembrolizumab (200 mg) + mirvetuximab soravtansine (6 mg/kg, adjusted ideal body weight) administered on Day 1 of a 3-week cycle (Q3W)

Eligibility:

- Platinum-resistant EOC, primary peritoneal cancer, or fallopian tube cancer; platinum-resistant defined as progression within 6 months from completion of platinum-containing therapy
- At least one lesion that meets the definition of measurable disease according to RECIST 1.1
- FRα positivity by IHC (≥ 25% of tumor cells with ≥ 2+ staining intensity)

*Pembrolizumab is being provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA
†Last patient enrolled 3 months prior to data cut; imaging performed every six weeks

Baseline Demographics

Characteristic	n = 56
Age	
Median (range)	62 (40-78)
Primary cancer diagnosis, *n (%)*	
Epithelial ovarian cancer	42 (75)
Fallopian tube cancer	12 (21)
Primary peritoneal cancer	2 (4)
ECOG PS, *n (%)*	
0	27 (48)
1	29 (52)
No. of prior systemic therapies, *n (%)*	
2	22 (39)
3	13 (23)
4	17 (30)
5+	4 (7)
Median (range)	3 (2-7)
FRα expression* *n (%)*	
Low	16 (29)
Medium	14 (25)
High	26 (46)
Prior exposure, *n (%)*	
Platinum compounds	56 (100)
Taxanes	56 (100)
Bevacizumab	24 (43)
PARP inhibitor	26 (46)

*Low, 25-49%; Medium, 50-74%; High, ≥ 75% of tumor cells with ≥ 2+ staining intensity

Treatment Emergent Adverse Events ≥ 20% (n = 56)

	Grade 1		Grade 2		Grade 3		All Grades	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Diarrhea	22	39	6	11	2	4	30	54
Nausea	16	29	10	18	2	4	28	50
Fatigue	17	30	9	16	1	2	27	48
Peripheral neuropathy*	16	29	7	13	0	0	23	41
Blurred vision	12	21	9	16	1	2	22	39
Abdominal pain	9	16	10	13	0	0	20†	36
Vomiting	12	21	6	11	2	4	20	36
AST increased	15	27	3	5	1	2	19	34
Dry eye	12	21	5	9	0	0	17	30
ALT increased	10	18	3	5	2	4	15	27
Constipation	12	21	2	4	1	2	15	27
Decreased appetite	11	20	2	4	1	2	14	25
Myalgia	11	20	1	2	0	0	12	21
Cough	10	18	1	2	0	0	11	20
Keratopathy**	4	7	7	13	0	0	11	20

AST: aspartate aminotransferase; ALT: alanine aminotransferase
*Includes neuropathy peripheral, peripheral sensory neuropathy, and peripheral motor neuropathy
**Includes keratopathy, keratitis, punctate keratitis, corneal epithelial microcysts, and corneal deposits; †Includes one case of Grade 5 abdominal pain secondary to progressive disease

- The majority of AEs reported were Grade 1 or 2 and manageable. Overall, Grade 3 and 4 events were seen in 21 (38%) and 4 (7%) patients, respectively
- Two patients (4%) discontinued pembrolizumab and/or mirvetuximab soravtansine due to treatment-related AEs: Grade 3 pleurisy/Grade 1 pneumonitis; Grade 3 pneumonitis/Grade 4 acute kidney injury
- Pneumonitis, considered an AE of special interest, was reported in 10 patients (18%), 8 of these cases were Grade 1/2
- One treatment-related death, due to encephalitis, was seen on study

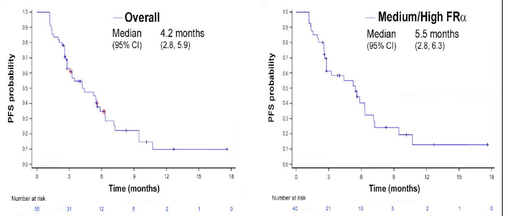
Confirmed ORR and Duration of Response

Endpoint	Total (n = 54)	Medium/High FRα (n = 39)
ORR (confirmed)*	30%	31%
95% CI	(18, 44)	(17, 48)
DOR (months)		
Median	6.9	8.1
95% CI	(4.2, 8.3)	(4.2, -)

*Confirmed radiographic response rate in patients with at least 1 post-baseline scan

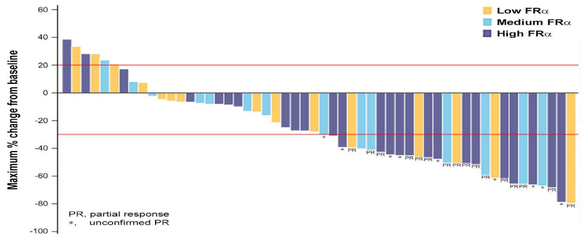
Median follow up: 8.3 months (range 1.2-17.6)

Progression-Free Survival



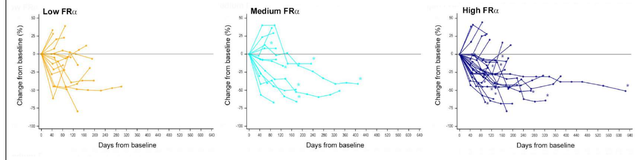
- Highlighted circles denote three censored patients (all low FRα) no longer on study; all other censored patients in the efficacy-evaluable population are ongoing

Maximum Tumor Change (%) in Target Lesions from Baseline



- Overall, 83% of patients (45/54) experienced tumor shrinkage of their target lesions in response to combination treatment
- Confirmed partial responses (PRs) were observed in 16 patients, and another 9 individuals had unconfirmed PRs at the time of analysis

Tumor Changes (%) in Target Lesions by FRα Expression Level



Asterisks denote patients ongoing (0/15 low, 6/14 medium, and 10/25 high FRα patients, respectively)

CONCLUSIONS

- The combination of mirvetuximab soravtansine and pembrolizumab continues to demonstrate favorable tolerability in patients with PROC, with predominantly mild-to-moderate (≤ Grade 2) events
- The safety profile is consistent with the known adverse drug reactions of each agent, with pneumonitis representing a potential overlapping toxicity
- The initial antitumor activity of mirvetuximab soravtansine combined with pembrolizumab is consistent with mirvetuximab soravtansine monotherapy in heavily pretreated patients and encouraging when considering outcomes reported for pembrolizumab-based combinations evaluated to date in PROC
  - 83% of patients had tumor shrinkage with combination treatment, with more robust reductions seen in medium/high FRα tumors
  - 30% confirmed ORR in heavily pretreated PROC (37% with 4+ prior lines) compares favorably to that observed for other pembrolizumab combinations in less heavily pretreated populations[5,6]
  - Early DOR data (median 6.9 months) suggest a trend towards improvement over mirvetuximab soravtansine monotherapy
- With 16 patients still on study (all with medium/high FRα expression) and a median follow up time of 8.3 months, the efficacy data are immature. Final data will be presented with longer-term follow up

References: 1. Moore et al, *Future Oncol* 2018 14(17):1669-78; 2. Moore et al, *J Clin Oncol* 2017 35(15):abstract 5547; 3.Varga et al, *J Clin Oncol* 2017 35(15):abstract 5513; 4. Matulonis et al, *J Clin Oncol* 2018 36(15):abstract 5511; 5. Matulonis et al, *Gynecol Oncol* 2018 14 (1):24: 6. Konstantinopoulos et al, *J Clin Oncol* 2018 36(15): abstract 106; 7. Skaletskaya et al, *J Immuno Ther Cancer* 2016 4(1):73;8. Matulonis et al, *Gynecol Oncol* 2018 149(1):38

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