Abstract 74

Initial safety and activity findings from a phase 1b escalation study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with pembrolizumab in platinum-resistant epithelial ovarian cancer patients

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INTRODUCTION

- A majority of patients diagnosed with epithelial ovarian cancer (EOC) relapse following first-line therapy and ultimately develop platinum-resistant disease. Current treatment options for these individuals are hampered by limited efficacy and drug-specific toxicities; hence an urgent need remains for effective therapeutic approaches to improve outcomes in this population
- 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 has shown promising clinical activity and a favorable safety profile in heavily pretreated FRα-positive EOC patients - both as a single agent and in combination regimens with bevacizumab in platinum-resistant disease and with carboplatin in the platinum-sensitive setting[1-3]
- In preclinical studies, mirvetuximab soravtansine activates monocytes and upregulates immunogenic cell death markers on ovarian tumor cells[4], providing a mechanistic rationale for combining this agent alongside the modality of immune checkpoint blockade
- Updated analyses from the KEYNOTE-028 Phase 1b study evaluating pembrolizumab as monotherapy in patients with PD-L1-positive ovarian cancer report an overall response rate (ORR) of 11.5% and median progression-free survival of 1.9 months[5]
- Currently, mirvetuximab soravtansine is being evaluated in combination with pembrolizumab as part of the phase 1b FORWARD II trial (NCT02606305) in patients with platinum-resistant EOC as part of an ongoing Phase I trial (NCT01609556)

Patient Population, Methods, and Objectives

Primary Objective of Dose Escalation Phase: Evaluate the safety and tolerability of mirvetuximab soravtansine when administered in combination with pembrolizumab* in patients with EOC, primary peritoneal cancer, or fallopian tube cancer

Treatment schedule:

- Pembrolizumab + mirvetuximab soravtansine administered on Day 1 of a 3-week cycle (Q3W)
- The first 4 patients were dosed with mirvetuximab soravtansine at 5 mg/kg (adjusted ideal body weight) and then the remaining 10 were treated at the phase 3 monotherapy dose of 6 mg/kg; pembrolizumab dosing remained constant at 200 mg

Eligibility:

- Platinum-resistant EOC, primary peritoneal, or fallopian tube cancer; 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 & Co., Inc., Kenilworth, NJ

Baseline Demographics

Characteristic	n = 14
Age	
Median	63.5
Range	47-78
Race, *n (%)*	
White	14 (100)
Primary cancer diagnosis, *n (%)*	
Epithelial ovarian cancer	9 (64)
Fallopian tube cancer	3 (21)
Primary peritoneal cancer	1 (7)
Papillary ovarian cancer	1 (7)
ECOG PS, *n (%)*	
0	8 (57)
1	6 (43)
No. of prior systemic therapies, *n (%)*	
1-2	1 (7)
3	4 (29)
4-6	7 (50)
7	2 (14)
Median (range)	4.5 (2-7)
FRα expression* *n (%)*	
High	5 (36)
Medium	3 (21)
Low	6 (43)
Prior exposure, *n (%)*	
Platinum compounds	14 (100)
Taxanes	14 (100)
Bevacizumab	6 (43)
PARP inhibitor	7 (50)

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

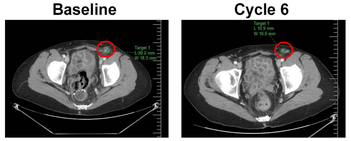
Treatment Emergent Adverse Events (AEs) >20% (n = 14)

	Grade 1		Grade 2		Grade 3		All Grades	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Fatigue	8	57	4	29	1	7	13	93
Nausea	6	43	3	21	2	14	11	79
Diarrhea	5	36	2	14	1	7	8	57
Dry eye	5	36	2	14	0	0	7	50
Peripheral neuropathy*	3	21	3	21	0	0	6	43
Constipation	4	29	1	7	0	0	5	36
Keratopathy**	2	1	3	21	0	0	5	36
Blurred vision	1	7	4	29	0	0	5	36
Decreased appetite	3	21	0	0	1	7	4	29
Vomiting	1	7	1	7	2	14	4	29
Anemia	1	7	2	14	0	0	3	21
Arthralgia	2	14	1	7	0	0	3	21
Dyspnea	2	14	1	7	0	0	3	21
Hypokalemia	3	21	0	0	0	0	3	21
Insomnia	3	21	0	0	0	0	3	21
Pneumonitis	3	21	0	0	0	0	3	21
Small intestinal obstruction	0	0	0	0	3	21	3	21

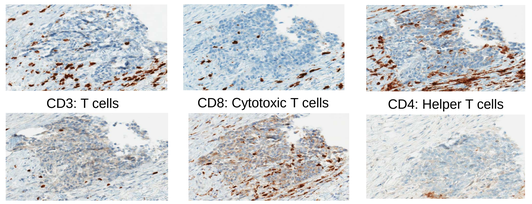
*Includes neuropathy peripheral and peripheral sensory neuropathy
**Includes corneal epithelial microcysts, keratitis, keratopathy, and punctate keratitis

- The majority of AEs reported were Grade 1 or 2 and manageable
- Only one Grade 3 AE (small intestinal obstruction) was observed in more than 2 patients; no Grade 4 events were seen
- 1 patient discontinued for a related AE (Grade 1 pneumonitis, possibly progressive)
- 1 drug-related death (colonic perforation) occurred on study

Case Study



- 49-year-old patient, with platinum-resistant fallopian tube cancer (high FRα tumor expression)
- 2 prior lines of therapy (both platinum-based doubles)
- Partial response (PR) seen after two cycles of combination treatment
- CA-125 levels decreased from 128 at screening to 65 at Cycle 2, and a nadir of 5 at Cycle 6
- Discontinued due to progressive disease (new lesion) observed at Cycle 14



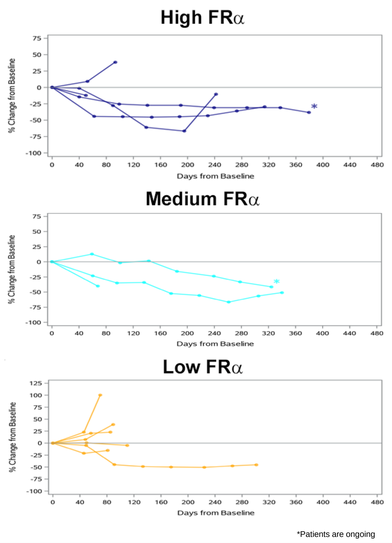
- Biomarker staining from this patient showed intratumoral and tumor-associated stromal infiltration of both lymphocytes and macrophages
- Assessment of immune markers is ongoing and will be correlated with response as part of the expansion cohort evaluation

Confirmed ORR and Time-to-Event Endpoints

Endpoint	Total (n = 14)	Medium/High FRα (n = 8)
ORR (confirmed)	43%	63%
95% CI	(18, 71)	(25, 92)
PFS (months)		
Median	5.2	8.6
95% CI	(1.6, 9.5)	(1.6, -)
DOR (weeks)		
Median	30.1	36.1
95% CI	(14.9, -)	(14.9, -)

- Confirmed partial responses (PRs) were observed in 6/14 patients treated with the mirvetuximab soravtansine-pembrolizumab combination as part of dose-escalation
- Five of these PRs occurred in individuals with medium or high FRα expression levels (i.e. ≥ 50% of tumor cells with 2+ staining intensity), with two patients continuing on therapy with ongoing responses
- An expansion cohort is now enrolling with enrichment for FRα medium and high expressing patients

Percent Tumor Change in Target Lesions by FRα Expression Level



*Patients are ongoing

CONCLUSIONS

- The phase 3 monotherapy dose of mirvetuximab soravtansine was readily combined with full dose pembrolizumab, with the combination demonstrating favorable tolerability and encouraging signals of efficacy in patients with platinum-resistant ovarian cancer
- The AE profile of the combination was manageable and as expected based on the known profiles of each agent, with predominantly mild-to-moderate (≤ Grade 2) events seen
- Promising early evidence of response and durable antitumor activity was observed in this heavily pretreated population (median 4.5 prior lines of systemic therapies)
  - In the subset of patients with medium or high FRα expression, the confirmed ORR was 63% and median PFS was 8.6 months
- These data support ongoing enrollment of an additional 35 patients in an expansion cohort, with medium/high tumor FRα expression levels, to further evaluate this combination in the setting of platinum-resistant disease

References: 1. Moore et al, *Cancer* 2017 123:3080-3087 2. Moore et al, *J Clin Oncol* 2017 35:1112-1118 3. O'Malley et al, *J Clin Oncol* 2017 35 (Suppl 15):abstract 5553 4. Skaletskaya et al, *J Immuno Ther Cancer* 2016 4(Suppl 1):73 5. Varga et al, *J Clin Oncol* 2017 35 (Suppl 15):abstract 5513

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