Abstract 1028P

Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with carboplatin and bevacizumab: Initial results from a Phase 1b study in patients (pts) with ovarian cancer

David M. O'Malley[1], Debra L. Richardson[2], Ignace Vergote[3], Lucy Gilbert[4], Lainie P. Martin[5], Gina M. Mantia-Smaldone[6], Cesar M. Castro[7], Diane Provencher[8], Ursula A. Matulonis[9], Karim Malek[10], Kathleen N. Moore[2]

[1]James CCC – The Ohio State University, Columbus, OH; [2]Stephenson Oklahoma Cancer Institute, Oklahoma City, OK/Sarah Cannon Research Institute, Nashville, TN; [3]University Hospital Leuven, Leuven Cancer Institute, Leuven, European Union; [4]McGill University Health Center, Montreal, Canada; [5]University of Pennsylvania, Philadelphia, PA; [6]Fox Chase Cancer Center, Philadelphia, PA; [7]Massachusetts General Hospital, Boston, MA; [8]Centre Hospitalier de l'Université de Montréal, Montreal, Canada; [9]Dana Farber Cancer Institute, Boston, MA; [10]ImmunoGen, Inc., Waltham, MA

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. As monotherapy, mirvetuximab soravtansine has demonstrated impressive anti-tumor activity, along with a differentiated safety profile and favorable tolerability in FRα-positive platinum-resistant ovarian cancer.[1]

In separate combinations with carboplatin[2] and with bevacizumab,[3] mirvetuximab soravtansine is well-tolerated, with promising anti-tumor activity, as anticipated based on preclinical studies in ovarian cancer models showing improved in vivo efficacy with these combinations compared with carboplatin or bevacizumab alone.[4]

Bevacizumab is approved in combination with platinum-based doublets after initial surgical resection of advanced ovarian cancer and for platinum-sensitive disease that recurred after 1 prior line of therapy. For the carboplatin/gemcitabine/bevacizumab combination, the overall response rate (ORR) is 78%, with a complete response (CR) rate of 17%; for the carboplatin/paclitaxel/bevacizumab combination, the ORR is also 78%, with a CR rate of 32% in patients with measurable disease assessable for response.[5,6]

Advances in the treatment of platinum-sensitive disease with the introduction of targeted therapies including PARP maintenance and bevacizumab-based combinations followed by bevacizumab maintenance have contributed to an increase in the prevalence of ovarian cancer.[7] As the patient population expands, there is a need for additional active, well-tolerated combinations in the platinum-sensitive setting.

Here we report the initial safety and efficacy findings from the phase 1b FORWARD II study (NCT02606305) evaluating the combination of mirvetuximab soravtansine with carboplatin and bevacizumab in patients with platinum-sensitive ovarian cancer.

Patient Population, Methods, and Objectives

Primary objective: Evaluate the safety, tolerability, and preliminary activity of mirvetuximab soravtansine when administered in combination with carboplatin and bevacizumab to patients with recurrent platinum-sensitive ovarian cancer

Treatment schedule: Mirvetuximab soravtansine (6 mg/kg, adjusted ideal body weight) + carboplatin (AUC 5) + bevacizumab (15 mg/kg) administered on Day 1 of a 3-week cycle (Q3W); continuation of mirvetuximab soravtansine and bevacizumab as maintenance therapy

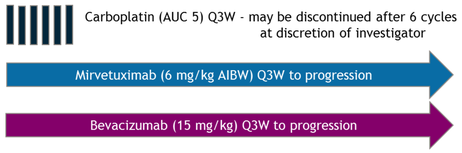
Eligibility:

- Platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer; defined as having not progressed within 6 months of last dose of platinum-containing therapy
- At least one lesion that met the definition of measurable disease (per RECIST 1.1)
- FRα positivity by IHC (≥ 50% of tumor cells with ≥ 2+ staining intensity)
- At least one, but not more than two, prior systemic treatment regimens
- Patients with a history (or evidence) of bowel obstruction, abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess were excluded

Date of data cut: August 15, 2019

Dosing Schema and Summary of Drug Exposure

A



B

No of Cycles Received	Carboplatin	Mirvetuximab soravtansine	Bevacizumab
Median (range)	6 (3-11)	11 (3-21)	11 (1-23)

Baseline Demographics

Characteristic	All Patients (n = 41)
Age	
Median (range)	63 (39-85)
Primary cancer diagnosis, *n (%)*	
Epithelial ovarian cancer	31 (76)
Fallopian tube cancer	9 (22)
Primary peritoneal cancer	1 (2)
ECOG PS, *n (%)*	
0	23 (56)
1	18 (44)
No. of prior systemic therapies, *n (%)*	
1	31 (76)
2	10 (24)
Platinum-free treatment interval, *n (%)*	
≤ 12 months	24 (59)
> 12 months	17 (41)
FRα expression* *n (%)*	
High	20 (49)
Medium	21 (51)
Prior exposure, *n (%)*	
Platinum compounds	41 (100)
Taxanes	40 (98)
Bevacizumab	10 (24)
PARP inhibitor	17 (41)

*High, ≥ 75% and Medium, 50-74% of tumor cells with ≥ 2+ staining intensity

Treatment-Emergent Adverse Events > 25% (n = 41)

Adverse Event	Grades 1-2		Grade 3		Grade 4		All Grades	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Diarrhea	29	71	3	7	0	0	**32**	**78**
Nausea	30	73	1	2	0	0	**31**	**76**
Fatigue	26	63	2	5	0	0	**28**	**68**
Thrombocytopenia	7	17	17	41	4	10	**28**	**68**
Vision blurred	26	63	0	0	0	0	**26**	**63**
Abdominal pain	23	56	0	0	0	0	**23**	**56**
Headache	21	51	1	2	0	0	**22**	**54**
Keratopathy*	19	46	0	0	0	0	**19**	**46**
Peripheral neuropathy†	19	46	0	0	0	0	**19**	**46**
Vomiting	17	41	0	0	0	0	**17**	**41**
Decreased appetite	16	39	0	0	0	0	**16**	**39**
Neutropenia	3	7	9	22	3	7	**15**	**37**
Dry eye	15	37	0	0	0	0	**15**	**37**
Hypertension	8	20	4	10	0	0	**12**	**29**
Arthralgia	12	29	0	0	0	0	**12**	**29**
Anemia	7	17	4	10	0	0	**11**	**27**
AST increased	9	22	2	5	0	0	**11**	**27**

AST, aspartate aminotransferase
*Includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, and hypoesthesia
†Includes keratopathy, keratitis, corneal deposits, and corneal epithelial microcysts

- 18 pts (44%) discontinued at least one drug due to treatment-related AEs
  - Primary carboplatin discontinuations occurred in 12 pts (29%) due to grade 2/3 thrombocytopenia
  - 7 pts (17%) discontinued mirvetuximab soravtansine due to a related AE (primarily grade 2 peripheral neuropathy [3 pts] or grade 2 thrombocytopenia [2 pts])
  - 1 pt discontinued bevacizumab due to a related AE (grade 3 hypoalbuminemia)
- Infusion-related reactions due to carboplatin seen in 4 pts (10%; three grade 2 and one grade 4 event)
- One death due to sepsis, considered not treatment-related

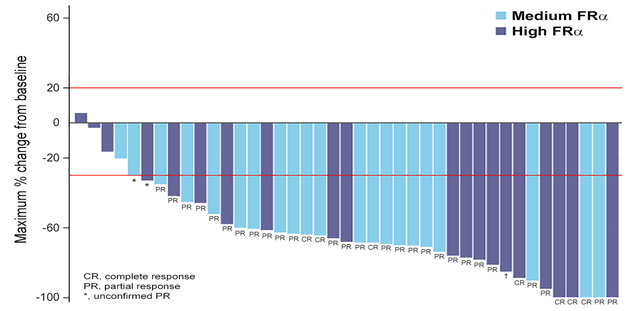
Confirmed ORR and Time-to-Event Endpoints

Endpoint	Total (n=41)	FRα Expression Medium (n=21)	FRα Expression High (n=20)
ORR (confirmed; 95% CI)	83% (68, 93)	90% (70, 99)	75% (51, 91)
CR rate	17%	19%	15%
DOR (median; 95% CI)	8.7 mo. (7.6, -)	ND (6.5, -)	8.7 mo. (6.4, -)

DOR, duration of response; ND, not determined

- ORR in subset of patients with 1 prior line of therapy 90% (28/31), with CR rate of 19% (6/31)

Maximum Tumor Change (%) in Target Lesions from Baseline



CRs with <100% decrease: Lymph node target lesions that met CR definition per RECIST 1.1 (i.e. all pathological lymph nodes have reduction in short axis to <10 mm)
†Despite target lesion PR, overall response of patient at cycle 4 was PD due to appearance of new lesions

- Confirmed tumor responses were observed in 34 patients, consisting of 7 complete responses (CR) and 27 partial responses (PR); two additional patients had unconfirmed PRs as best response

CONCLUSIONS

- The combination of full dose mirvetuximab soravtansine, carboplatin, and bevacizumab is well tolerated
  - No new safety signals were seen; adverse events observed with the triplet were as expected based on the side effect profiles of each agent, with thrombocytopenia as the most common cause of drug-related discontinuations
- Post-carboplatin (median 6 cycles), mirvetuximab soravtansine and bevacizumab continuation/maintenance is well tolerated
- In patients with recurrent platinum-sensitive disease, the triplet shows encouraging activity in both the overall population (ORR 83% and CR rate 17%) and the subset of individuals with only 1 prior line (ORR 90% and CR rate 19%)
- The efficacy outcomes observed with the triplet are encouraging relative to those reported in similar patient populations for other triplet therapy (OCEANs and GOG213) studies[5,6]
- With a median follow up 9.3 months, PFS data are maturing

References:

1. Moore et al, ESMO Congress 2019 Abstract 9920; 2. Moore et al, *Gynecol Oncol* 2018 151:46-52; 3.O'Malley et al, *J Clin Oncol* 2019 37 (suppl) abstract 5520; 4. Ponte et al, *Neoplasia* 2016 18:775-784; 5 Aghajanian et al, *J Clin Oncol* 2012 30:2039-2045; 6. Coleman et al, *Lancet Oncol* 2017 18:779-791; 7. https://seer.cancer.gov/statfacts/html/ovary.html

Study sponsored by ImmunoGen, Inc. The authors would like to especially thank the patients who consented to be included in this study, as well as their families