Abstract 5520

Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-resistant ovarian cancer: final analyses from the FORWARD II study

David M. O'Malley[1], Ursula A. Matulonis[2], Michael J. Birrer[3], Cesar Castro[4], Ignace Vergote[5], Lainie P. Martin[6], Gina M. Mantia-Smaldone[7], Lucy Gilbert[8], Antonio González Martin[9], Raquel Bratos[10], Brooke Esteves[11], Karim Malek[11], Kathleen N. Moore[12]

[1]Ohio State University, Columbus, OH; [2]Dana Farber Cancer Institute, Boston, MA; [3]University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL; [4]Massachusetts General Hospital, Boston, MA; [5]University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; [6]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [7]Fox Chase Cancer Center, Philadelphia, PA; [8]McGill University Health Center, Montreal, Canada; [9]Clinica Universidad de Navarra, Madrid, Spain; [10]MD Anderson Cancer Center Madrid, Madrid, Spain; [11]ImmunoGen, Inc., Waltham, MA; [12]University of Oklahoma Health Sciences Center, Oklahoma City, OK/Sarah Cannon Research Institute, Nashville, TN

INTRODUCTION

Current treatment options for patients with platinum-resistant epithelial ovarian cancer (EOC) are hampered by limited efficacy and drug-specific toxicities. Bevacizumab was the first biologic agent approved for platinum-resistant EOC based on the findings of the AURELIA trial[1] which showed that the addition of bevacizumab to chemotherapy significantly improved progression-free survival (median PFS, 6.7 months) and objective response rate (ORR, 27%) over chemotherapy alone (3.4 months and 13%, respectively) in platinum-resistant EOC.[1,2] Given the side effect profiles and modest efficacy of approved bevacizumab-chemotherapy combinations, more active and better tolerated regimens are needed in this disease.

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. Mirvetuximab soravtansine is currently in clinical development as monotherapy and as part of combination regimens in EOC, where it has exhibited favorable tolerability and promising activity in FRα-positive EOC patients, in both platinum-sensitive and -resistant settings.[3]

Preclinical studies revealed that mirvetuximab soravtansine could potentiate the antitumor activity of bevacizumab in models of EOC,[4] thus providing a mechanistic rationale for the combination as a novel treatment approach in this disease. Here we report mature safety and efficacy findings from the phase 1b FORWARD II study (NCT02606305) evaluating the combination of mirvetuximab soravtansine and bevacizumab in patients with platinum-resistant EOC. The analyses include all patients who received full dosing as part of both the escalation and expansion stages of the study (11 and 55 patients, respectively).

Patient Population, Methods, and Objectives

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

Treatment schedule: Bevacizumab (15 mg/kg) + mirvetuximab soravtansine (6 mg/kg, adjusted ideal body weight) administered on Day 1 of a 3-week cycle (Q3W)

Eligibility for expansion cohort:

- Platinum-resistant EOC, primary peritoneal cancer, or fallopian tube cancer; defined as progression within 6 months from completion of platinum-containing therapy
- At least one lesion that met the definition of measurable disease (per RECIST 1.1)
- FRα positivity by IHC (≥ 25% of tumor cells with ≥ 2+ staining intensity)
- Patients with a history (or evidence) of bowel obstruction, abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess were excluded

Subset Analyses

- Total population: all pooled patients from the escalation and expansion cohorts (n = 11 and 55, respectively) who received the combination at full dosing; includes bevacizumab-naïve and -pretreated individuals, irrespective of FRα expression levels and number of prior lines of systemic therapy
- FRα expression level: low, medium, or high (25-49%, 50-74%, and ≥ 75% of tumor cells with ≥ 2+ staining intensity, respectively)
- AURELIA-type subset: bevacizumab-naïve and 1-2 prior lines of therapy, with medium/high FRα expression
- Date of data cut: April 22, 2019

Baseline Demographics

Characteristic	All Patients (n = 66)
Age	
Median (range)	63 (39-81)
Primary cancer diagnosis, *n (%)*	
Epithelial ovarian cancer	52 (79)
Fallopian tube cancer	12 (18)
Primary peritoneal cancer	2 (3)
ECOG PS, *n (%)*	
0	38 (58)
1	28 (42)
No. of prior systemic therapies, *n (%)*	
1-2	27 (41)
3	11 (17)
4-8	28 (42)
Median (range)	3 (1-8)
FRα expression* *n (%)*	
High	28 (42)
Medium	24 (36)
Low	13 (20)
Prior exposure, *n (%)*	
Platinum compounds	66 (100)
Taxanes	65 (98)
Bevacizumab	41 (62)
PARP inhibitor	20 (30)

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

Treatment-Related TEAEs > 20% (n = 66)

	Grades 1-2		Grade 3		All Grades	
Adverse Event	No.	%	No.	%	N	%
Diarrhea	33	50.0	1	1.5	34	51.5
Blurred vision	32	48.5	1	1.5	33	50.0
Nausea	29	43.9	1	1.5	30	45.5
Fatigue	26	39.4	1	1.5	27	40.9
Peripheral neuropathy*	23	34.8	0	0	23	34.8
Thrombocytopenia	17	25.8	3	4.5	20	30.3
Dry eye	17	25.8	1	1.5	18	27.3
Hypertension	8	12.1	9	13.6	17	25.8
AST increased	13	19.7	4	6.1	17	25.8
Decreased appetite	17	25.8	0	0	17	25.8
ALT increased	13	19.7	3	4.5	16	24.2
Vomiting	15	22.7	1	1.5	16	24.2
Headache	16	24.2	0	0	16	24.2
Keratopathy†	16	24.2	0	0	16	24.2

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

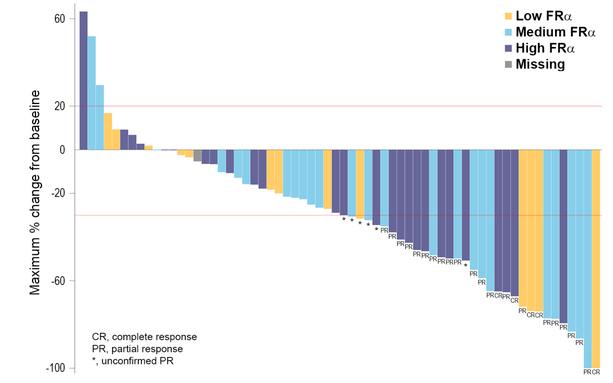
- Pneumonitis, an AE of special interest, was reported in 6 patients (9%); all cases were either grade 1 or 2
- Nineteen patients (29%) discontinued bevacizumab and/or mirvetuximab soravtansine due to treatment-related AEs
- One death related to bevacizumab (intestinal perforation) occurred on study

Confirmed ORR and Time-to-Event Endpoints

Endpoint	Total (n = 66)	FRα Expression* Low (n = 13)	Medium (n = 24)	High (n = 28)	AURELIA-type** (n = 16)
ORR (confirmed)	39%	31%	46%	39%	56%
95% CI	(28, 52)	(9, 61)	(26, 67)	(22, 59)	(30, 80)
PFS (months)					
Median	6.9	6.0	6.9	7.1	9.9
95% CI	(4.9, 8.6)	(2.1, 8.8)	(4.4, 9.9)	(4.4, 14.5)	(4.1, 15.9)
DOR (months)					
Median	8.6	ND	7.4	12.0	12
95% CI	(4.9, 14.9)	(3.7, -)	(2.6, -)	(4.9, -)	(6.0, 14.9)

DOR, duration of response; ND, not determined
*Data missing for one individual
**AURELIA-type subset: bevacizumab-naïve and 1-2 prior lines of therapy; with medium/high FRα expression

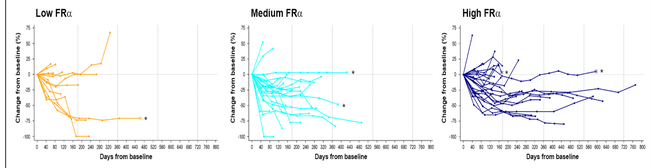
Maximum Tumor Change (%) in Target Lesions from Baseline



Missing patient was efficacy-eligible but FRα status not in the database at the time of analysis
CRs with ~60-70% decreases: Target lesions were lymph nodes and met CR definition per RECIST 1.1 (i.e. all pathological lymph nodes have reduction in short axis to <10 mm)

- Confirmed tumor responses were observed in 26 patients, consisting of 5 complete responses (CR) and 21 partial responses (PR); an additional 6 patients had unconfirmed PRs as best response

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



No. patients on study:

≥ 6 mo.	6/13 (46%)	12/24 (50%)	14/26‡ (54%)
≥12 mo.	1/13 (8%)	4/24 (17%)	7/26‡ (27%)

Asterisks denote patient still ongoing
Dashed vertical lines represent 6, 12, 18 and 24 months from baseline
‡Data are presented from 26/28 high FRα evaluable patients as target lesion measurements not available for 2 individuals

- Marked disease control at 6 months for all FRα expression levels seen with the combination
- Trend toward more durable responses and time on treatment with increasing tumor FRα expression

CONCLUSIONS

- Mirvetuximab soravtansine combines well with bevacizumab
  - The adverse events observed with the combination were as expected based on the side effect profiles of each agent
  - No new safety signals or clinically significant potentiation of known toxicities were seen
- In this heavily pre-treated platinum-resistant EOC population (59% with ≥3 previous lines; 62% with prior bevacizumab), mirvetuximab soravtansine is an active partnering agent with bevacizumab, with a confirmed ORR of 39% and median PFS of 6.9 months
- Combination treatment shows a trend toward improved duration of response seen with increasing tumor FRα expression, with marked disease control at 6 months across all groups and 27% of high FRα-expressing patients having not progressed within 12 months
- The antitumor activity observed in the subset of medium/high FRα-expressing, AURELIA-matched patients (56% ORR, mPFS 9.9 months) is encouraging with respect to outcomes reported in similar patient populations for bevacizumab plus chemotherapy[1]
- Further exploration of this combination is warranted in EOC; expansion studies are ongoing in 'platinum-agnostic' patients (those for whom a non-platinum based doublet would be appropriate) as well as evaluation of a triplet combination with carboplatin in the platinum-sensitive setting

References:

1. Pujade-Lauraine et al, *J Clin Oncol* 2014 32:1302-1308; 2. Poveda et al, *J Clin Oncol* 2015 33: 3836-3838; 3. Moore et al, *J Clin Oncol* 2017 35:1112-1118; 4. Ponte et al, *Neoplasia* 18:775-784.

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