Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-resistant ovarian cancer: maturing safety and activity profile from the FORWARD II Phase 1b study

Abstract 5549

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INTRODUCTION

Current treatment options for patients with platinum-resistant epithelial ovarian cancer (EOC) are hampered by limited efficacy and drug-specific toxicities. More effective and safe therapeutic alternatives represent an urgent unmet medical need for 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. A maturing clinical profile has revealed favorable safety and promising activity in FRα-positive EOC patients - either as a single agent or in combination regimens with carboplatin in platinum-sensitive disease and pembrolizumab in the platinum-resistant setting[1-3]

Bevacizumab was the first biologic agent approved for relapsed EOC, and is used in both the treatment and maintenance settings. Approval of this angiogenesis inhibitor was based, in part, on the findings of the pivotal AURELIA trial,[4] which showed that the addition of bevacizumab to chemotherapy significantly improved progression-free survival (PFS; 6.7 months) and objective response rate (ORR; 27%) over chemotherapy alone (3.4 months and 13%, respectively) in platinum-resistant EOC[4,5]

Preclinically, mirvetuximab soravtansine potentiates the antitumor activity of bevacizumab in models of EOC,[6] thereby providing a rationale for this combination as a novel approach to therapeutic intervention in this disease

The dose-escalation safety findings of the phase 1b FORWARD II study (NCT02606305), evaluating the combination of mirvetuximab soravtansine and bevacizumab in patients with platinum-resistant EOC, were previously reported (ASCO 2017, abstract 5553). Here we present updated safety and efficacy data from the same trial, including all patients across both the escalation and ongoing expansion stages that have received the combination at full dosing (11 patients from escalation and 48/55 planned patients from expansion)

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 meets the definition of measurable disease according to RECIST 1.1
- FRα positivity by IHC (≥ 25% of tumor cells with ≥ 2+ staining intensity)
- Patients with clear cell or low grade ovarian cancer were excluded

Subset Analyses

- Total population: all pooled patients from the escalation and expansion cohorts (n = 11 and 48, respectively) who received the combination at full dosing; includes bevacizumab-naïve and -pretreated individuals, irrespective of FRα expression levels and prior lines of system therapy
- FRα expression levels: low (25-49% of tumor cells with ≥ 2+ staining intensity by IHC) versus medium and high (50-74% and ≥ 75%, respectively)
- Prior lines of therapy: 1-3 versus ≥ 4
- FORWARD I-matched subset (medium/high FRα expression; 1-3 prior lines of therapy): corresponds to the target population enrolled in the pivotal Phase III monotherapy study [NCT02631876]
- AURELIA-matched subset (bevacizumab-naïve, 1-2 prior lines of therapy) with medium/high FRα expression
- Date of data cut: April 27, 2018

Baseline Demographics

Characteristic	All Patients (n = 59)	FORWARD I-matched† (n = 25)
Age		
Median (range)	63 (39-81)	64 (46-75)
Primary cancer diagnosis, *n (%)*		
Epithelial ovarian cancer	48 (81)	19 (76)
Fallopian tube cancer	10 (17)	6 (24)
Primary peritoneal cancer	1 (2)	0 (0)
ECOG PS, *n (%)*		
0	35 (59)	18 (72)
1	24 (41)	7 (28)
No. of prior systemic therapies, *n (%)*		
1-2	24 (41)	19 (76)
3	11 (19)	6 (24)
4-8	24 (41)	0 (0)
Median (range)	3 (1-8)	2 (1-3)
FRα expression* *n (%)*		
High	26 (44)	16 (64)
Medium	18 (31)	9 (36)
Low	12 (20)	0 (0)
Missing	3 (5)	0 (0)
Prior exposure, *n (%)*		
Platinum compounds	59 (100)	25 (100)
Taxanes	58 (98)	24 (96)
Bevacizumab	34 (58)	9 (36)
PARP inhibitor	17 (29)	6 (24)

†FORWARD I-matched population: medium/high FRα expression, 1-3 prior lines of therapy
*Low, 25-49%; Medium, 50-74%; High, ≥ 75% of tumor cells with ≥ 2+ staining intensity

Treatment Emergent Adverse Events ≥ 20% (n = 59)

	Grade 1		Grade 2		Grade 3		All Grades	
Adverse Event	No.	%	No.	%	No.	%	No.	%
Nausea	23	39	5	9	1	2	29	49
Diarrhea	17	29	9	15	2	3	28	48
Blurred vision	19	32	8	14	0	0	27	46
Fatigue	9	15	15	25	0	0	24	41
Peripheral neuropathy*	13	22	7	12	0	0	20	34
Abdominal pain	11	19	7	12	0	0	18	31
Hypertension	2	3	8	14	8	14	18	31
Vomiting	11	19	4	7	1	2	16	27
Headache	12	20	2	3	1	2	15	25
AST increased	12	20	0	0	3	5	15	25
ALT increased	10	17	1	2	3	5	14	24
Constipation	14	24	0	0	0	0	14	24
Decreased appetite	11	19	3	5	0	0	14	24
Dry eye	11	19	2	3	1	2	14	24
Thrombocytopenia	6	10	6	10	2	3	14	24
Cough	11	19	1	2	0	0	12	20
Dyspepsia	8	14	4	7	0	0	12	20
Myalgia	11	19	1	2	0	0	12	20

AST, aspartate aminotransferase; ALT, alanine aminotransferase;
*Includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, and hypoesthesia

- Fifteen patients (25%) discontinued bevacizumab and/or mirvetuximab soravtansine due to treatment-related AEs, the most frequent of which was thrombocytopenia
- One bevacizumab-related death (intestinal perforation) occurred on study

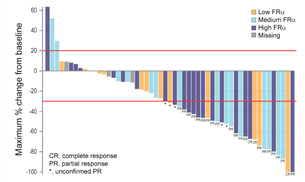
Confirmed ORR and Time-to-Event Endpoints

Endpoint	Total (n = 54)	FRα expression: Low (n = 12)	FRα expression: Medium/High (n = 39)	Prior Lines of Therapy: 1-3 (n = 33)	Prior Lines of Therapy: ≥ 4 (n = 21)	FORWARD I-matched (n = 23)
ORR (confirmed)	43%	33%	49%	42%	43%	48%
95% CI	(29, 57)	(10, 65)	(32, 65)	(26, 61)	(22, 66)	(27, 69)
PFS (months)						
Median	7.8	6.0	9.5	9.9	7.2	9.9
95% CI	(5.6, 10.2)	(2.1, 10.2)	(5.6,12)	(4.6, 14.5)	(3.9,10.2)	(4.6, 14.5)
DOR (months)						
Median	10.6	ND	10.6	10.6	ND	10.6
95% CI	(4.9, -)	(-, -)	(3.3, -)	(3.3, 12)	(2.6, -)	(3.3, 12.0)

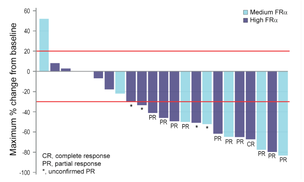
DOR, duration of response; ND, not determined

Maximum Tumor Change (%) in Target Lesions from Baseline

A. Overall population



B. FORWARD I-matched subset



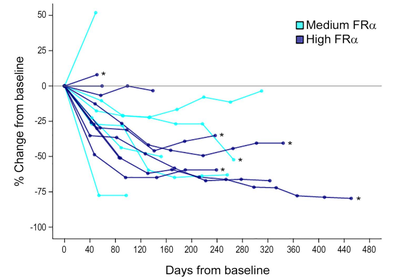
- "Missing" patients were efficacy-eligible but FRα results were not in the database at the time of analysis
- CRs with ~60-70% decreases: Target lesions were lymph nodes and met CR definition per RECIST 1.1 (i.e. all pathological lymph nodes have reduction in short axis to <10 mm)

AURELIA-Matched* Subset Analysis

A. Time-to-event endpoints

Endpoint	AURELIA-matched (n = 16)
ORR (confirmed)	50%
95% CI	(25, 75)
PFS (months)	
Median	9.9
95% CI	(2.8, 14.5)
DOR (months)	
Median	12
95% CI	(6, 12)

B. Percent tumor changes in target lesions



*AURELIA-matched subset: bevacizumab-naïve and 1-2 prior lines of therapy; with medium/high FRα expression

In plot B, asterisks denote patients still on study at time of analysis

CONCLUSIONS

- The phase 3 monotherapy dose of mirvetuximab soravtansine was readily combined with full dose bevacizumab, with the AE profile of the combination being manageable and consistent with the known profiles of each agent, with predominantly mild-to-moderate (≤ Grade 2) events
- The early activity findings are consistent with other mirvetuximab soravtansine studies with respect to trends toward higher response rates and improved PFS seen with medium/high versus low tumor FRα-expression
- The median PFS and median DOR seen for the combination in the FORWARD I-matched subset (9.9 and 10.6 months, respectively) are promising in relation to that observed with mirvetuximab soravtansine monotherapy in a similar population (6.7 and 5.8 months, respectively)[2]
- The efficacy measures observed for the subset of medium/high FRα-expressing, AURELIA-matched patients (50% ORR, mPFS 9.9 months) are encouraging when considering outcomes reported for bevacizumab plus chemotherapy[4]
- Overall, the data support continued exploration of this combination in the setting of platinum-resistant disease, as well as an additional expansion study in platinum-sensitive patients evaluating a triplet combination of mirvetuximab soravtansine with bevacizumab and carboplatin

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. Pujade-Lauraine et al, *J Clin Oncol* 2014 32:1302-1308; 5. Poveda et al, *J Clin Oncol* 2015 33: 3836-3838; 6. Ponte et al, *Neoplasia* 18:775-784