Abstract 5553

Safety findings from FORWARD II: a Phase 1b study evaluating the folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC) mirvetuximab soravtansine (IMGN853) in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin (PLD), or pembrolizumab in patients with ovarian cancer

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INTRODUCTION

Combination chemotherapy with a platinum-based regimen is the foundation of current first-line treatment for epithelial ovarian cancer (EOC). However a majority of patients relapse and ultimately develop platinum-resistant disease

Elevated folate receptor alpha (FRα) expression is observed in approximately 80% of recurrent ovarian cancers, thus providing an attractive candidate for targeted therapeutic strategies in this indication

Mirvetuximab soravtansine (IMGN853) is an antibody-drug conjugate (ADC) comprised of a FRα-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent

Mirvetuximab soravtansine has shown promising single-agent clinical activity and a favorable safety profile as part of a first-in-human Phase 1 study in heavily pretreated FRα-positive EOC patients (NCT01609556)[1,2]

The use of targeted agents as part of combination regimens has improved patient outcomes for a number of human malignancies. In preclinical models, mirvetuximab soravtansine potentiates the antitumor activity of a number of established therapeutics used for the treatment of EOC including bevacizumab, carboplatin, and pegylated liposomal doxorubicin (PLD).[3] These findings prompted the clinical exploration of these combinations in patients with FRα-positive EOC

Patient Population, Methods, and Objectives

Primary Objective of Dose Escalation Phase: Evaluate the safety and tolerability of mirvetuximab soravtansine when administered in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin (PLD), or pembrolizumab* in patients with EOC, primary peritoneal cancer, or fallopian tube cancer

Treatment schedule:

Bevacizumab + mirvetuximab soravtansine† administered on Day 1 of a 3 week cycle (Q3W)

Carboplatin + mirvetuximab soravtansine administered on Day 1 of a 3 week cycle (Q3W)

PLD + mirvetuximab soravtansine administered on Day 1 of a 4 week cycle (Q4W)

Pembrolizumab + mirvetuximab soravtansine administered on Day 1 of a 3 week cycle (Q3W)

Eligibility:

For the bevacizumab, PLD, and pembrolizumab arms: platinum-resistant EOC, primary peritoneal, or fallopian tube cancer

For the carboplatin arm: disease that is platinum-sensitive (did not progress within 6 months of completing platinum therapy)

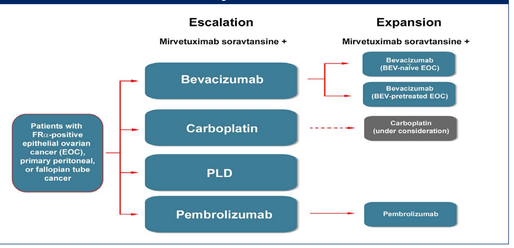
At least one lesion that meets the definition of measurable disease according to RECIST 1.1

FRα positivity by IHC (≥ 25% of tumor cells with 2+ staining intensity)

*Pembrolizumab is being provided by Merck & Co., Inc., Kenilworth, NJ

†Mirvetuximab soravtansine dosed according to adjusted ideal body weight

Study Schema



Dose Level, Patient Allocation, and DLTs

Mirvetuximab soravtansine (Q3W)	Bevacizumab (Q3W)	No.	Mirvetuximab soravtansine (Q3W)	Carboplatin (Q3W)	No.	Mirvetuximab soravtansine (Q4W)	PLD (Q4W)	No.	Mirvetuximab soravtansine (Q3W)	Pembrolizumab (Q3W)	No.
5 mg/kg	15 mg/kg	3	5 mg/kg	AUC4	4	5 mg/kg	30 mg/m^2	4	5 mg/kg	200 mg	4
6 mg/kg	15 mg/kg	11	5 mg/kg	AUC5	4	5 mg/kg	40 mg/m^2	5	6 mg/kg	200 mg	9
			6 mg/kg	AUC5	10	6 mg/kg	40 mg/m^2	7			

DLTs:

Bevacizumab combination: Grade 2 neutropenia and thrombocytopenia (one patient; 6 mg/kg/15 mg/kg dose)

Carboplatin combination: Grade 3 vasculitis (6 mg/kg/AUC5 dose)

Baseline Demographics

Characteristic		Mirvetuximab soravtansine + Bevacizumab (n=14)	Carboplatin (n=18)	PLD (n=16)	Pembrolizumab (n=13)
Age					
Median		64	66	64	62
Range		50-81	47-82	47-73	47-78
Race, *n (%)*					
White		13 (93)	18 (100)	16 (100)	13 (100)
Not reported		1 (7)	-	-	-
Primary cancer diagnosis, *n (%)*					
Ovarian cancer		13 (93)	16 (89)	14 (88)	8 (62)
Fallopian tube cancer		1 (7)	2 (11)	1 (6)	3 (23)
Peritoneal cancer		-	-	1 (6)	1 (8)
Other		-	-	-	1 (8)
ECOG PS, *n (%)*					
0		3 (21)	7 (39)	9 (56)	8 (62)
1		11 (79)	11 (61)	7 (44)	5 (38)
No. of prior systemic therapies, *n (%)*					
1-2		1 (7)	9 (50)	9 (56)	1 (8)
3		0 (0)	5 (28)	4 (25)	4 (31)
4-6		10 (71)	4 (22)	3 (19)	7 (54)
7+		3 (21)	0 (0)	0 (0)	1 (8)
Median (range)		6 (2-8)	3 (1-5)	2 (1-6)	5 (2-7)
FRα expression* *n (%)*	(n=61)				
High	29 (48)	9 (64)	7 (39)	8 (50)	5 (38)
Medium	14 (23)	3 (21)	4 (22)	5 (31)	2 (15)
Low	18 (30)	2 (14)	7 (39)	3 (19)	6 (46)
Prior exposure, *n (%)*					
Platinum compounds		14 (100)	18 (100)	16 (100)	13 (100)
Taxanes		14 (100)	18 (100)	16 (100)	13 (100)
Bevacizumab		9 (64)	5 (28)	9 (56)	6 (46)
PARP inhibitor		6 (43)	9 (50)	4 (25)	4 (31)

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

Treatment Emergent Adverse Events >20%

Preferred Term	BEV (n = 14)	Carboplatin (n = 18)	PLD (n = 16)	Pembrolizumab (n = 13)
Abdominal distension (%)	3 (21)	1 (6)	2 (13)	0
Abdominal pain (%)	3 (21)	1 (6)	4 (25)	1 (8)
ALT increased (%)	3 (21)	3 (17)	2 (13)	0
Anemia (%)	3 (21)	5 (28)	2 (13)	0
AST increased (%)	3 (21)	3 (17)	4 (25)	0
Constipation (%)	3 (21)	3 (17)	8 (50)	2 (15)
Decreased appetite (%)	2 (14)	5 (28)	1 (7)	2 (15)
Dehydration (%)	3 (21)	0	0	0
Diarrhea (%)	7 (50)	10 (56)	9 (56)	2 (15)
Dry eye (%)	3 (21)	1 (6)	1 (6)	1 (8)
Fatigue (%)	5 (36)	7 (39)	7 (44)	4 (31)
Headache (%)	3 (21)	4 (22)	4 (25)	1 (8)
Hypertension (%)	3 (21)	1 (6)	0	1 (8)
Hypokalemia (%)	1 (7)	7 (39)	2 (13)	0
Hypomagnesemia (%)	3 (21)	5 (28)	0	0
Keratopathy* (%)	3 (21)	2 (11)	1 (7)	0
Myalgia (%)	3 (21)	3 (17)	1 (7)	0
Nausea (%)	6 (43)	9 (50)	7 (44)	3 (23)
Neutropenia (%)	2 (14)	8 (44)	4 (25)	0
Peripheral neuropathy** (%)	4 (29)	6 (33)	5 (31)	4 (31)
Proteinuria (%)	5 (36)	0	0	0
Small intestinal obstruction (%)	3 (21)	0	1 (6)	1 (8)
Stomatitis (%)	3 (21)	0	2 (13)	0
Thrombocytopenia (%)	4 (29)	10 (56)	2 (13)	0
Urinary tract infection (%)	3 (21)	1 (6)	5 (31)	0
Vision blurred (%)	6 (43)	10 (56)	4 (25)	2 (15)
Vomiting (%)	4 (29)	5 (28)	5 (31)	1 (8)

*Includes corneal cyst, corneal disorder, corneal deposits, corneal epithelial microcysts, keratitis, keratopathy, limbal stem cell deficiency, and punctate keratitis
**Includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paraesthesia, and hypoesthesia

Blue text indicates incidence >40%

Treatment Emergent Adverse Events Grade 3+

Preferred Term	Bevacizumab n (%)
Hypertension	3 (21)
Small intestinal obstruction	2 (14)
Ascites	1 (7)
Blood creatinine increased	1 (7)
Cataract	1 (7)
Cognitive disorder	1 (7)
Dehydration	1 (7)
Diarrhea	1 (7)
Fatigue	1 (7)
Gastrointestinal hemorrhage	1 (7)
Headache	1 (7)
Hyperglycemia	1 (7)
Hypokalemia	1 (7)
Hyponatremia	1 (7)
Neutropenia	1 (7)
Rectal hemorrhage	1 (7)
Thrombocytopenia	1 (7)
Vomiting	1 (7)

Preferred Term	Carboplatin n (%)
Neutropenia	3 (17)
Anemia	2 (11)
Thrombocytopenia	2 (11)
Hypokalemia	2 (11)
Cataract	1 (6)
Diarrhea	1 (6)
Fatigue	1 (6)
Hyponatremia	1 (6)
Pulmonary embolism	1 (6)
Vasculitis	1 (6)

Preferred Term	Pembrolizumab n (%)
Febrile neutropenia	1 (8)
Small intestinal obstruction	1 (8)

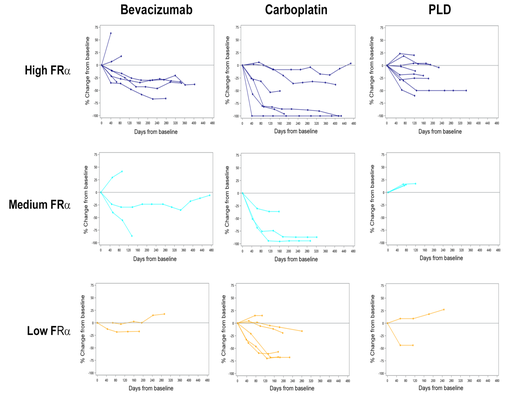
Preferred Term	PLD n (%)
Anemia	2 (13)
Vomiting	2 (13)
Cataract	1 (6)
Constipation	1 (6)
Diarrhea	1 (6)
Metastases to meninges	1 (6)
Nausea	1 (6)
Neutropenia	1 (6)
Neutrophil count decreased	1 (6)
Hand foot syndrome	1 (6)
Pulmonary embolism	1 (6)
Pyrexia	1 (6)
Small intestinal obstruction	1 (6)

Blue text indicates occurrence in >1 patient

Confirmed ORR and Progression-Free Survival

Endpoint	Bevacizumab (n = 14)	Carboplatin (n = 17)	PLD (n = 16)
ORR (confirmed)	29%	65%	13%
95% CI	(8, 58)	(38, 86)	(2, 38)
PFS (months)			
Median	9.5	12.1	7.0
95% CI	(3.5, 15.2)	(9.0, 15.0)	(1.7, -)

Percent Change in Tumor Target Lesions by FRα Level



Data are presented from 12, 15, and 13 evaluable patients in the bevacizumab, carboplatin, and PLD arms respectively as target lesion measurements were not available for some individuals

CONCLUSIONS

- The Phase 3 monotherapy dose of mirvetuximab soravtansine was readily combined with the highest doses (per protocol) of bevacizumab, carboplatin, PLD, and pembrolizumab
- The adverse event profiles for all combinations were manageable and as expected based on the known profiles of each agent
  - No new safety signals were identified
- Bevacizumab combination: the encouraging signs of activity observed in heavily pretreated patients (median of 6 prior lines of therapy) support the planned expansion cohorts evaluating this combination
- Carboplatin combination: clinical benefit was also observed with the carboplatin combination in patients with recurrent, platinum-sensitive disease, suggesting a path forward for future exploration in the platinum-sensitive setting
- Pembrolizumab combination: preliminary safety data from dose escalation warrant continued exploration of this combination

References: 1. KN Moore et al. (2017) *Cancer* doi:10.1002/cncr.3073; 2. KN Moore et al. (2017) *J Clin Oncol* 35:1112-1118; 3. JF Ponte et al (2016) Neoplasia 18:775-784

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