Abstract 61

Characterization of folate receptor alpha (FRα) expression in archival tumor and biopsy samples in a Phase I study of mirvetuximab soravtansine, a FRα-targeting antibody drug conjugate (ADC), in relapsed epithelial ovarian cancer patients

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INTRODUCTION

- Mirvetuximab soravtansine (IMGN853) is an antibody-drug conjugate (ADC) comprising a folate receptor alpha (FRα)-binding antibody and the maytansinoid DM4, a potent tubulin-targeting agent
- FRα is highly expressed in epithelial ovarian cancer (EOC), thus providing a rational therapeutic target for this malignancy. Moreover, receptor expression is not altered by chemotherapy, further supporting a FRα-targeting strategy in the treatment of recurrent EOC[1]
- We have recently reported encouraging clinical activity and manageable safety for mirvetuximab soravtansine in EOC patients within the setting of platinum-resistant disease[2]
- Patient selection for clinical studies of mirvetuximab soravtansine is based on FRα positivity of archival tumor tissue
- As part of an ongoing Phase I trial (NCT01609556), an expansion cohort was opened in order to characterize FRα expression in archival and fresh biopsy samples (pre-and post-treatment) in patients with relapsed EOC
- A total of 27 heavily pre-treated individuals (up to 11 prior lines of therapy) were enrolled into this heterogeneous cohort of ovarian cancer patients, beginning in July 2015

Study Objectives

- Characterize FRα expression in archival and in pre- and post-treatment biopsy samples obtained from a heterogeneous cohort of relapsed EOC patients
- Determine concordance rate between archival and pre-treatment FRα expression levels
- Compare FRα expression in pre-treatment versus post-treatment biopsy samples

Patient Population, Methods, and Biopsy Collection

Treatment schedule:

- Mirvetuximab soravtansine was administered intravenously at 6.0 mg/kg (adjusted ideal body weight) once every 3 weeks

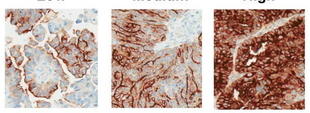
Eligibility:

- Relapsed EOC, primary peritoneal, or fallopian tube cancer that is amenable to biopsy
- Patients may have measurable or non-measurable disease as per RECIST 1.1
- FRα positivity by immunohistochemistry (IHC; ≥ 25% of cells with ≥ 2+ staining intensity) based on archival tissue
- No limit on the number of prior treatment regimens

Biomarker analyses:

- Biopsy collection: core needle biopsies were collected before (baseline) and after (Cycle 2 Day 8) mirvetuximab soravtansine treatment
- FRα assay: anti-FOLR1 2.1 IMGN-generated antibody was used in an assay developed in collaboration with and validated at Ventana Medical Systems (Tucson, AZ), and run on a Benchmark XT IHC staining platform

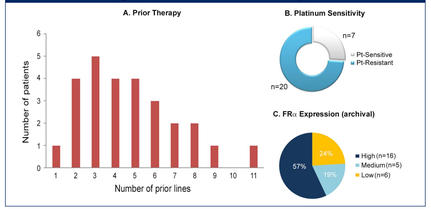
FRα Expression Scoring



Baseline Demographics

	Patients (N = 27)	
Characteristic	**No.**	**%**
Age, years		
Median (range)	62 (38-76)	
Race		
White	25	93
Asian	2	7
Primary diagnosis		
Epithelial ovarian cancer (serous)	22	81
Epithelial ovarian cancer (endometrioid)	1	4
Carcinosarcoma	1	4
Fallopian tube cancer	3	11
ECOG PS		
0	10	37
1	17	63
No. of prior systemic therapies		
Median (range)	4 (1-11)	
1 - 3	10	37
4 - 6	11	41
7+	6	22
Prior exposure		
Platinum compounds	27	100
Taxanes	27	100
Bevacizumab	23	85
PARP inhibitor	9	33

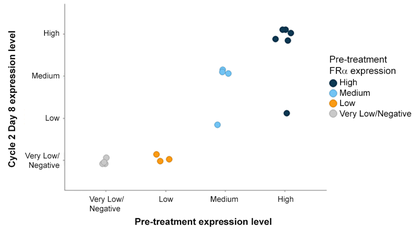
Heterogeneous Patient Population



Concordance of FRα Expression in Archival and Pre-Treatment Biopsy Samples

- 71% concordance: of 21 evaluable pre-treatment samples,15 met the eligibility criterion (≥ 25% cells with ≥ 2+ intensity)
- Of 5 patients with low archival receptor levels, two were subsequently shown to exceed 50% FRα positivity in their pre-treatment biopsy samples
- 22% of patients (6/27) did not have pre-treatment biopsies evaluable for FRα IHC due to insufficient tumor cells present in the specimen
- 100% of archival samples provided sufficient tumor tissue for FRα testing

FRα Expression is Similar in Pre- and Post-Treatment Biopsy Samples



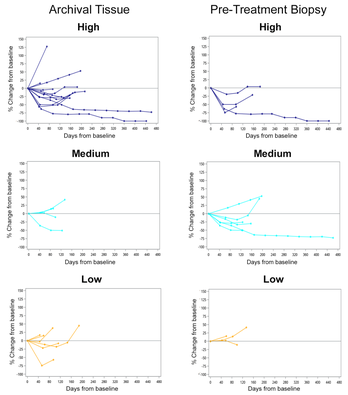
Treatment Emergent AEs >20% (n = 27)

	Grade 1		Grade 2		Grade 3		Grade 4		All Grades	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%
Keratopathy*	7	25.9	6	22.2	0	0	0	0	13	48.1
Fatigue	6	22.2	6	22.2	0	0	0	0	12	44.4
Diarrhea	9	33.3	1	3.7	0	0	0	0	10	37.0
Vision blurred	4	14.8	6	22.2	0	0	0	0	10	37.0
Nausea	7	25.9	2	7.4	0	0	0	0	9	33.3
Abdominal pain	5	18.5	2	7.4	1	3.7	0	0	8	29.6
AST increased	8	29.6	0	0	0	0	0	0	8	29.6
ALT increased	7	25.9	0	0	0	0	0	0	7	25.9
Peripheral neuropathy**	5	18.5	2	7.4	0	0	0	0	7	25.9
Dyspnea	3	11.1	2	7.4	1	3.7	0	0	6	22.2
Headache	5	18.5	1	3.7	0	0	0	0	6	22.2
Vomiting	4	14.8	2	7.4	0	0	0	0	6	22.2

*Includes corneal cyst, corneal deposits, corneal epithelial microcysts, keratitis, keratitis interstitial, keratopathy, and punctate keratitis
**Includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paraesthesia, and hypoesthesia

- The majority of AEs reported were grade 1 or 2
- 26% of patients (7/27) underwent one dose reduction due to an AE
- One patient discontinued for a related AE (organizing pneumonia)

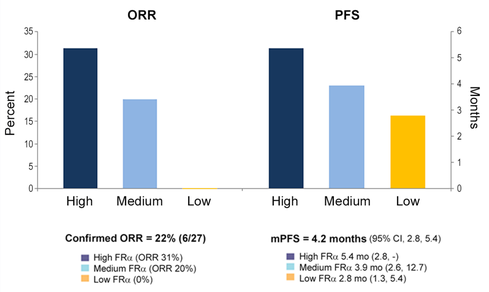
Percent Tumor Change in Target Lesions by Archival and Pre-Treatment Biopsy FRα Expression



Note: Data is presented from 22 and 13 evaluable patients (archival and biopsy, respectively) as target lesion measurements and/or IHC were not available for some individuals

- Regardless of the tissue source analyzed (archival or pre-treatment biopsy), higher FRα expression is associated with greater antitumor activity

Measures of Clinical Activity Based on FRα Expression



- In this heavily pre-treated population, the confirmed objective response rate (ORR) was 22%, and the median progression-free survival (mPFS) was 4.2 months
- Two complete responses (CRs) were observed in individuals with high FRα expression
- Three patients remain on mirvetuximab soravtansine >12 months

CONCLUSIONS

- Concordance of FRα expression in pre-treatment biopsies versus archival tumor samples suggests that archival tissue may be reliably used to identify patients with receptor-positive tumors
  - Archival tissue is appropriate for patient selection in mirvetuximab soravtansine clinical trials
  - Fresh biopsy may be considered if archival tissue is not available or if FRα levels are below eligibility criterion
- Matched pre- and post-treatment biopsies showed similar FRα expression levels following two doses of mirvetuximab soravtansine
- In this heterogeneous cohort of heavily pre-treated ovarian cancer patients, mirvetuximab soravtansine continues to demonstrate encouraging clinical activity and manageable safety
- Regardless of the tissue source analyzed (archival or biopsy), higher FRα expression is associated with greater antitumor activity
- These data support the use of archival tissue for patient selection in the recently initiated Phase 3 trial of mirvetuximab soravtansine (FORWARD I; NCT02631876) in patients with platinum-resistant EOC, medium/high FRα expression, and 1-3 prior lines of therapy

References: 1. Despierre et al, Gynecol Oncol 2013 130:192-199

2. Moore et al, J Clin Oncol 2016 Dec 28:JCO2016699538