Genomic and Transcriptomic Analysis To Uncover Potential Biomarkers of Response and Primary Resistance to Mirvetuximab Soravtansine in Patients with Ovarian Cancer

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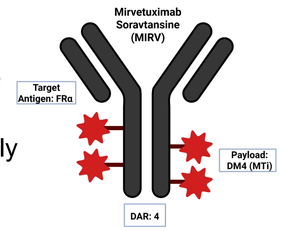
Background

- **Mirvetuximab soravtansine (MIRV**) is a folate receptor alpha (FRα) ADC with a microtubule inhibitor payload (DM4).
- In the phase III MIRASOL trial, MIRV demonstrated an overall survival benefit (mOS 16.5 vs 12.7 months; HR 0.67)[1]
- High FRα IHC expression is currently the primary predictor of response; however, additional predictive biomarkers are poorly defined.
- Mechanisms underlying primary and acquired resistance to MIRV are largely unknown.
- **Here we investigated genomic and transcriptomic alterations associated with response and primary resistance to MIRV.**



Methods

Figure 1. Retrospective Study Design

Patients with primary diagnosis of epithelial ovarian, fallopian or primary peritoneal cancer in Tempus Lens database who received xT(DNA panel)/xR (RNA expression)-testing (N=7,466)

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Patients with biospecimen received any time before MIRV and with known treatment start date (N= 154)

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Patients treated with MIRV and had known or inferred length of time on therapy (N= 106)

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MIRV Non- Responders (on treatment ≤ 9 wks (3 cycles) **N= 30**

MIRV Responders (on treatment > 9 wks (3 cycles) **N= 76**

- **Primary Objective**: Differential gene expression of prespecified MIRV relevant genes (see Table 1) in responders vs non-responders
- **Secondary Objective**: Real-world OS in responders vs non-responders

References

1. Moore et al, N Engl J Med 2023;389:2162-2174

Acknowledgements

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High *FOLR1* mRNA may contribute to MIRV response and upregulation of *MAPK, VEGF and JAK* pathways may contribute to primary resistance.

Table 1. Prespecified MIRV-relevant Genes of Interest

ADC mechanisms	Genes of interest
FOLR1 expression regulation	Downregulate: Estrogen Receptor (ER) Upregulate: HES1, FGFR4, OCT4, SOX2, and KLF4
Folate receptors	FOLR1, FOLR2, FOLR3, FOLR4, MTHFR
ADC processing	SLC46A3 (Lysosomal degradation), GCL (Rate-limiting step), GSS (Glutathione production)
Downstream FOLR1 pathways	JAK, STAT3, ERK1, ERK2 (MAP Kinase), MEK, Progesterone receptor, Tyrosine kinase SRC, TSLC1
Drug Efflux Pumps	MDR1, ABCC1 (MRP1), ABCC2 (MRP2), ABCC4 (MRP4), ABCB1 (multidrug-resistance protein 1 [MDR1, P-glycoprotein]), and ABCG2 (breast cancer resistance protein [BCRP])
Payload Resistance	Escape from DM4-mediated Cytotoxicity: Cyclin B1 (CCNB1), CDK1, CDC20, PLK1
Clinically Relevant Biomarkers	BRCA1/2, MMR, HER2 (amplification and IHC)

Results

Table 2. Cohort Clinical Characteristics

Characteristic	Non-Responders (N = 30)	Responders (N = 76)	p-value
Age at diagnosis, median (IQR)	65 (56, 73)	63 (57, 71)	0.5
Biospecimen collection from MIRV start, days, median(IQR)	−633 (−944, −380)	−559 (−1,079, −277)	0.7
Tissue site of sample for analysis			0.3
Retroperitoneum and Peritoneum	13 (43%)	29 (38%)	
Female Genital Organs	7 (23%)	30 (39%)	
Serous histology	20 (67%)	69 (91%)	**0.007**
MIRV line of therapy			0.6
2	7 (23%)	15 (20%)	
3	9 (30%)	31 (41%)	
4	4 (13%)	12 (16%)	
>5	10 (33%)	17 (23%)	
BRCA1/BRCA2 mutation status			0.5
Wild-type	27 (90%)	64 (84%)	
Mutated	3 (10%)	12 (16%)	
Received bevacizumab with MIRV	5 (17%)	7 (9.2%)	0.3
Received PARP inhibitor at any point	19 (63%)	50 (66%)	0.8

Results

Figure 2. Pre-Treatment Gene Expression Differences in Responders vs Non-responders

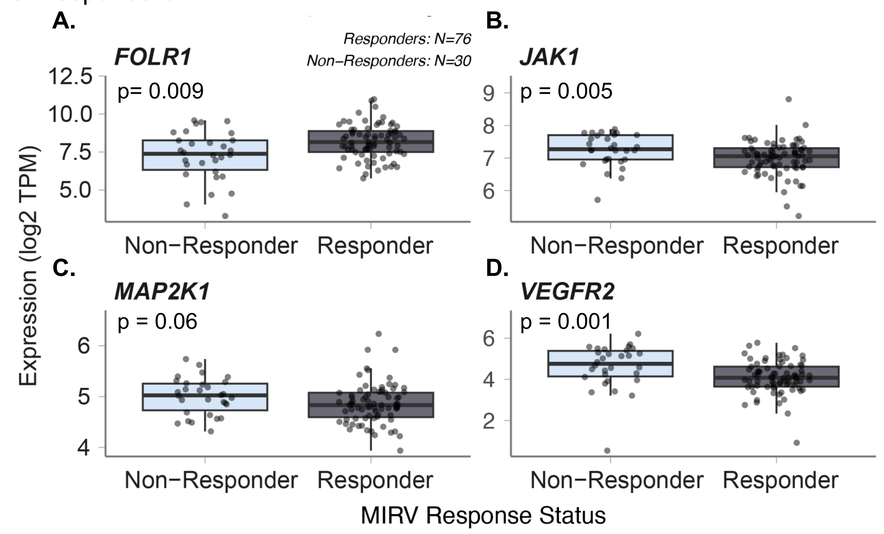
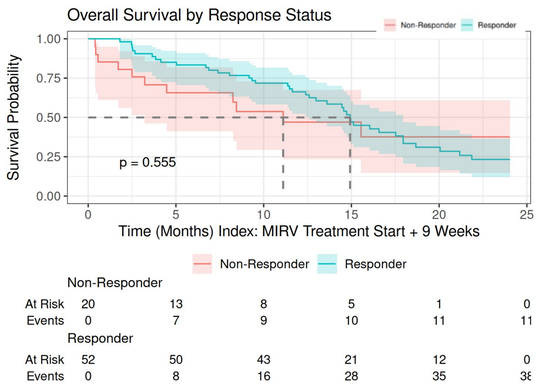


Figure 3. Real-World Survival Responders vs Non-responders



MIRV non-responders had a significantly higher risk of death within the first 6 months of treatment compared to responders (HR: 2.86, p=0.047), though this survival disadvantage did not persist beyond that period (p=0.3)

Conclusions

- MIRV responders had higher pre-treatment FOLR1 mRNA expression vs. non-responders, consistent with target-dependent ADC activity.
- Non-responders showed increased expression of JAK1 and VEGFR2, with a trend toward MAPK pathway upregulation, suggesting primary MIRV resistance may be driven by pro-survival and proliferative signaling.
- Larger studies integrating genomic and transcriptomic profiling with clinical outcomes are needed to validate these findings and inform rational combination strategies to further improve efficacy with MIRV.