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FORWARD I (GOG 3011): A Phase III study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate, versus chemotherapy in patients with platinum-resistant ovarian cancer

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ClinicalTrials.gov identifier: NCT02631876; This study was sponsored by ImmunoGen, Inc. and conducted in partnership with the Gynecologic Oncology Group (GOG 3011)

DISCLOSURES

K. Moore reports advisory board participation for Astra Zeneca, Aravive, Clovis, Cue, Genentech/Roche, ImmunoGen, Merck, OncoMed, Samumed, Tesaro;

Steering Committee participation for Astra Zeneca, Genentech/Roche, ImmunoGen, Tesaro;

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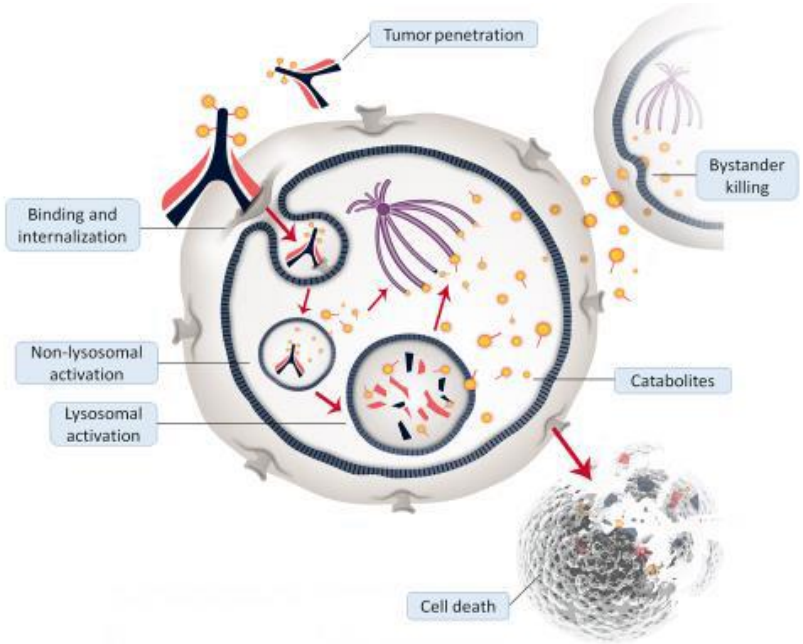
Disclosures for all authors available on ESMO website

BACKGROUND

- Incorporation of PARPi and anti-angiogenic agents throughout the treatment course of ovarian cancer has contributed to the increasing prevalence of women living with their disease
- Despite these advances, most patients will eventually develop platinum resistant disease, with limited options characterized by poor efficacy and tolerability
- Mirvetuximab soravtansine is an antibody–drug conjugate that targets folate receptor-α (FRα) to deliver the microtubule-disrupting agent DM4 directly to the tumor
- **FORWARD I** is a randomized Phase III study to compare the safety and efficacy of mirvetuximab soravtansine versus investigator's choice chemotherapy in FRα-positive, platinum-resistant ovarian cancer



STUDY DESIGN

FORWARD I

- Platinum-resistant ovarian cancer
- FRα-positive tumor expression
  - Medium (50-74% cells positive)
  - High (≥75% cells positive)
- ECOG performance status 0 or 1
- 1-3 prior therapies

Statistical Assumptions

- Hochberg procedure
- α=0.05 (two-sided), power = 90%
  HR=0.58; control arm mPFS 3.5 mos

Mirvetuximab Soravtansine
(n=248)

6 mg/kg (adjusted ideal body weight) once every 3 weeks

2:1 Randomization

Stratification Factors:
FRα expression (medium or high)
Prior therapies (1 and 2, or 3)
Choice of chemotherapy

Investigator's Choice Chemotherapy
Paclitaxel, PLD†, or Topotecan
(n=118)

***Paclitaxel**: 80 mg/m² weekly*
***PLD**: 40 mg/m² once every 4 weeks*
***Topotecan**: 4 mg/m² on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m² on Days 1-5 every 3 weeks*

Primary Endpoint

Progression-free survival (PFS; by BIRC*) for ITT and high FRα populations

*BIRC = Blinded Independent Review Committee; analyzed by Hochberg procedure

Secondary Endpoints

Overall response rate (ORR)
Overall survival (OS)
Patient reported outcomes (PRO)

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†Pegylated liposomal doxorubicin
ClinicalTrials.gov Identifier: NCT02631876

BASELINE CHARACTERISTICS

Disease Characteristics

	Mirvetuximab soravtansine (n=248)	IC Chemo (n=118)
Primary Diagnosis		
Ovarian	83%	89%
Fallopian Tube	6%	4%
Primary Peritoneal	11%	7%
Histology		
High Grade Serous	99%	97%
Other	1%	3%
ECOG		
0	57%	51%
1	43%	48%
Prior Therapy		
Bevacizumab	49%	47%
PARPi	11%	10%
Any BRCA Mutation		
Yes	9%	7%
Platinum-Free Interval		
0-3 months	39%	38%
3-6 months	57%	58%
≥ 6 months	4%	4%

Stratification Factors

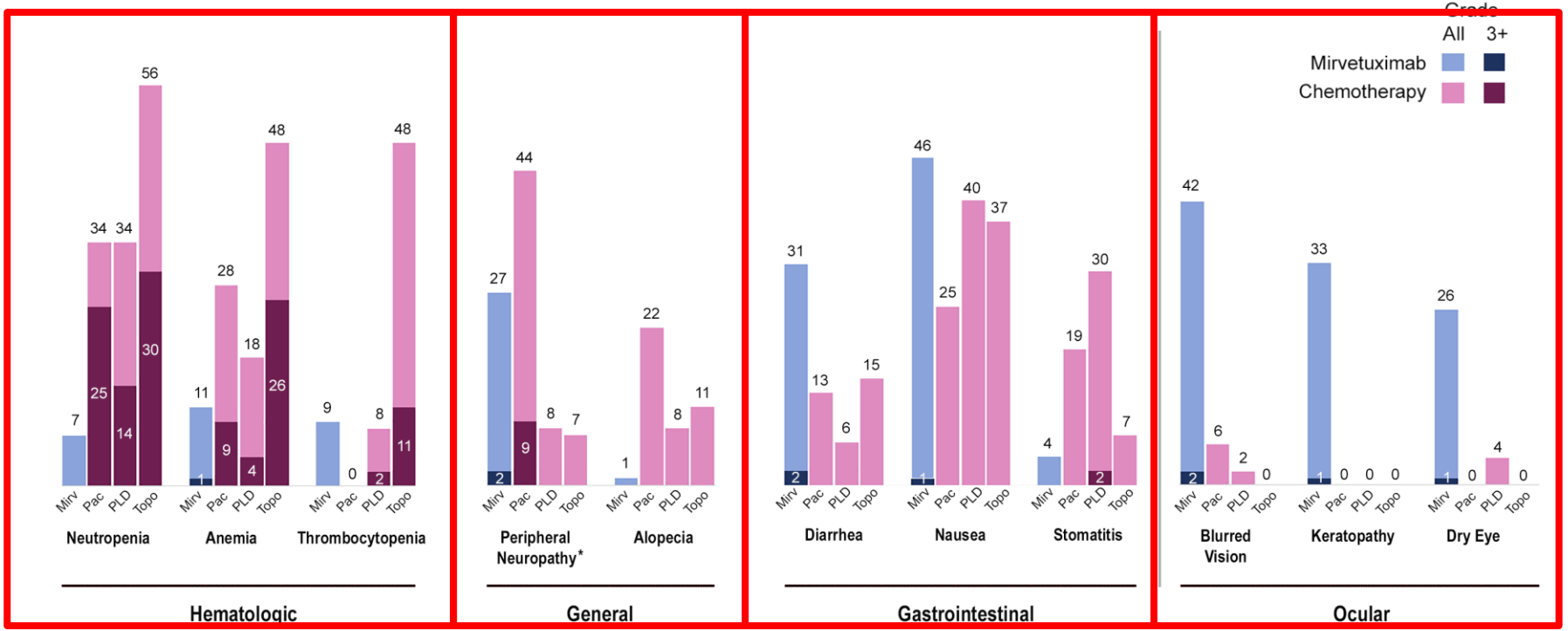
	Mirvetuximab soravtansine (n=248)	IC Chemo (n=118)
FRα Status		
Medium	42%	42%
High	58%	58%
No. Prior Lines		
1 or 2	65%	65%
3	35%	35%
IC Chemotherapy		
Paclitaxel	32%	31%
PLD	44%	46%
Topotecan	23%	23%

SAFETY SUMMARY

	Mirvetuximab soravtansine (n=243*)	IC Chemotherapy (n=109*)
Any TEAE	>99%	98%
Grade 3+ TEAEs	46%	61%
SAEs	28%	28%
Deaths on study drug or within 30 days of last dose	4%	6%
Dose reductions due to related TEAEs	20%	30%
Dose delays due to related TEAEs	29%	28%
Discontinuations due to related TEAEs	5%	8%

*Five and nine patients randomized into the mirvetuximab soravtansine and chemotherapy arms, respectively, did not receive any allocated intervention and were not included in the safety analyses

MOST COMMON TREATMENT-RELATED ADVERSE EVENTS (> 20%): DIFFERENTIATED SAFETY PROFILE



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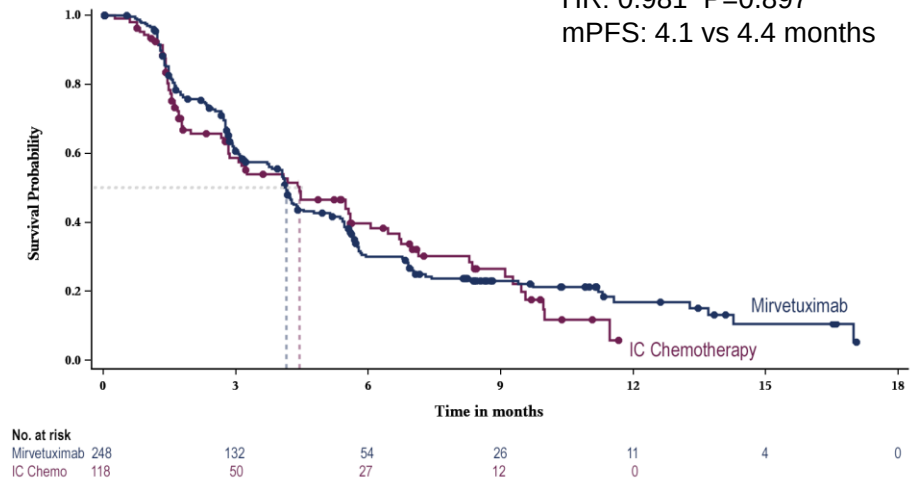
*Grade 2+ peripheral neuropathy events were observed in 12% and 28% of patients that received mirvetuximab soravtansine or paclitaxel, respectively.

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (BY BIRC)

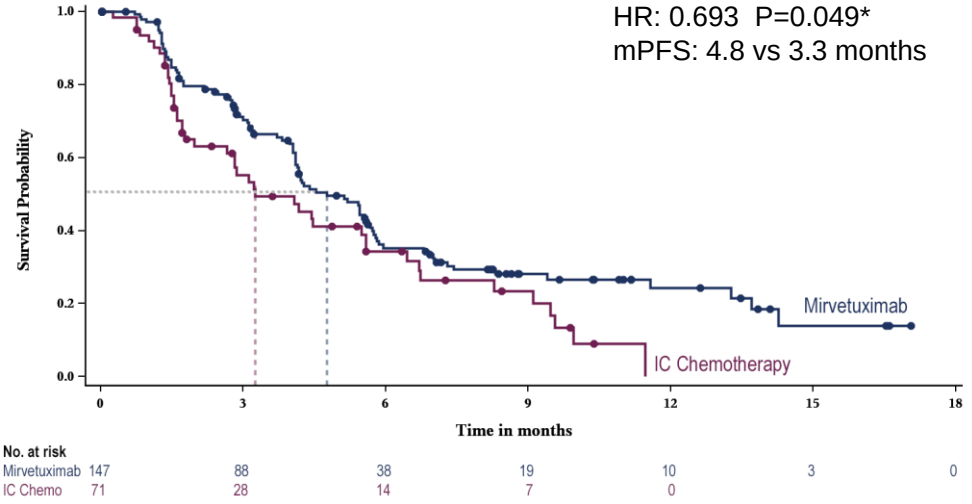
ITT

HR: 0.981 P=0.897
mPFS: 4.1 vs 4.4 months



FRα High

HR: 0.693 P=0.049*
mPFS: 4.8 vs 3.3 months



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*not significant per Hochberg procedure

EFFICACY RESULTS

ITT Population

Endpoint	Treatment effect size [Mirv (n=248) vs IC Chemo (n=118)]	P value*
PFS by BIRC (mo.)	HR: 0.981 (0.734, 1.310) mPFS: 4.1 vs 4.4	0.897^
ORR by BIRC 95% CIs	22% vs 12% (17%, 28%) vs (7%, 19%)	0.015
OS (August 2019)	HR: 0.846 (0.625, 1.145) mOS: 15.6 vs 13.9	0.278
PRO†	32% vs 14%	0.011

FRα High Population

Endpoint	Treatment effect size [Mirv (n=147) vs IC Chemo (n=71)]	P value*
PFS by BIRC (mo.)	HR: 0.693 (0.480, 1.000) mPFS: 4.8 vs 3.3	0.049^
ORR by BIRC 95% CIs	24% vs 10% (17%, 32%) vs (4%, 19%)	0.014
OS (August 2019)	HR: 0.678 (0.460, 0.999) mOS: 16.4 vs 12.0	0.048
PRO†	28% vs 13%	0.096

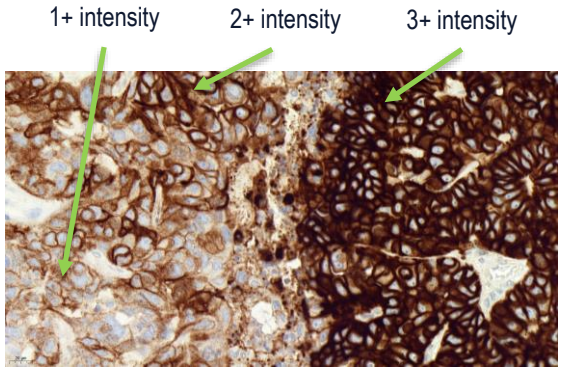
*Nominal p-value
^Not significant based on Hochberg Procedure
†≥15-point improvement in the EORTC QLQ-OV28 Abdominal/GI Symptom Subscale

FRα SCORING IN THE MIRVETUXIMAB SORAVTANSINE PROGRAM

PS2+ Scoring

- In all prior studies, PS2+ scoring was used to assess FRα expression
- Eligibility determined by staining intensity and percentage of tumor cells staining at 0, 1+, 2+, or 3+

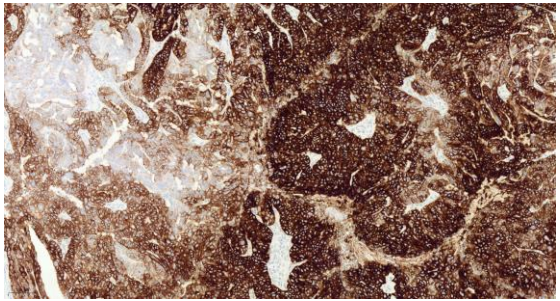
PS2+ Scoring
Positive: ≥ 50% of tumor cells with FRα membrane staining with ≥ 2+ intensity



10X Scoring

- In FORWARD I, a simplified scoring method to assess FRα expression was implemented
- Eligibility was determined by scoring just the percentage of cells with membrane staining by ≤10X magnification, without regard to intensity

10X Scoring
Positive: ≥ 50% of tumor cells with FRα membrane staining visible at 10X microscope objective



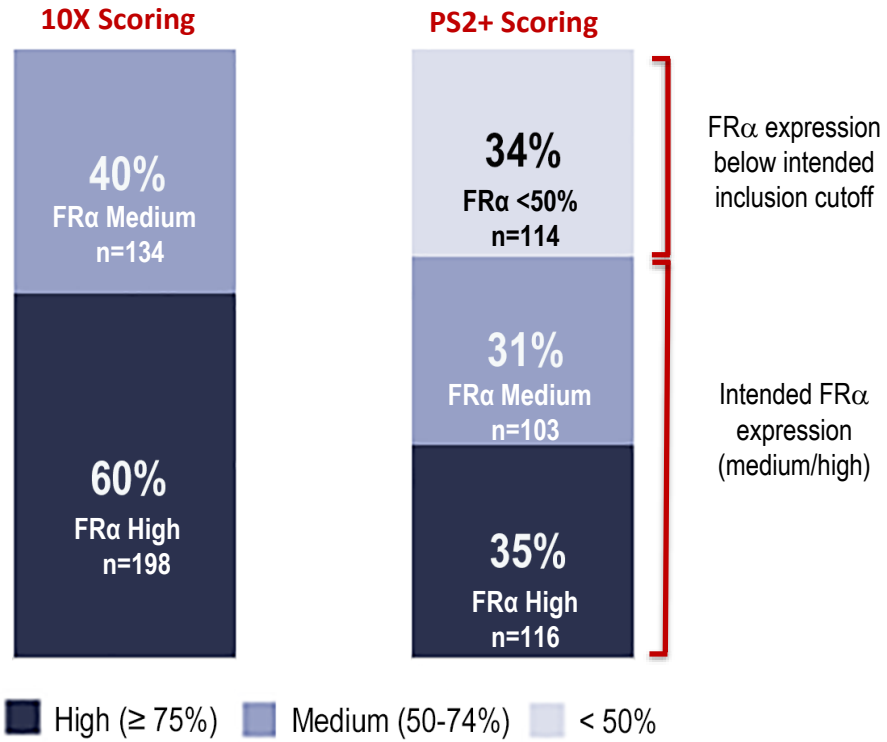
Bridging study indicated that 10X scoring was sufficient for patient selection

Exploratory analyses suggest that the change in scoring method from PS2+ to 10X introduced a population of patients into FORWARD I with lower levels of FRα expression than intended

FORWARD I 10X SCORING COMPARED WITH EXPLORATORY PS2+ SCORING

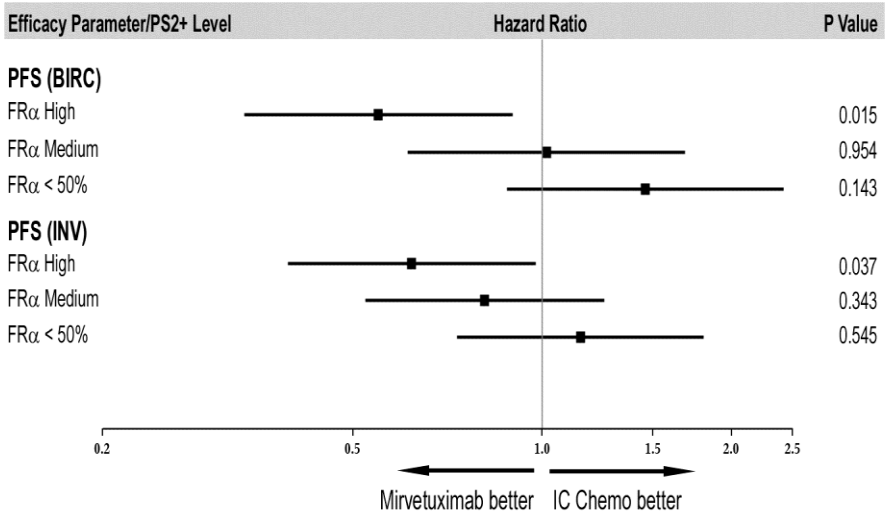
Rescoring of the FORWARD I samples using PS2+ indicates:

- 34% of patients enrolled in FORWARD I had low FRα levels that should have precluded enrollment; and
- the protocol-defined FRα high subset contained patients with a mixture of FRα expression levels



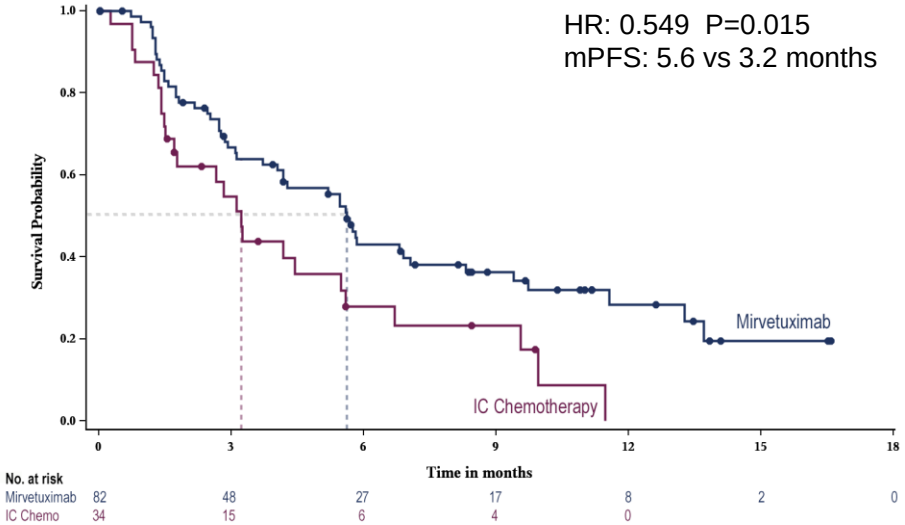
PS2+ RE-SCORING: PFS TRENDS ACROSS SUBGROUPS

PFS Hazard Ratio Plot



P values from unstratified log-rank test

PFS (by BIRC) - FRα High (n=116)



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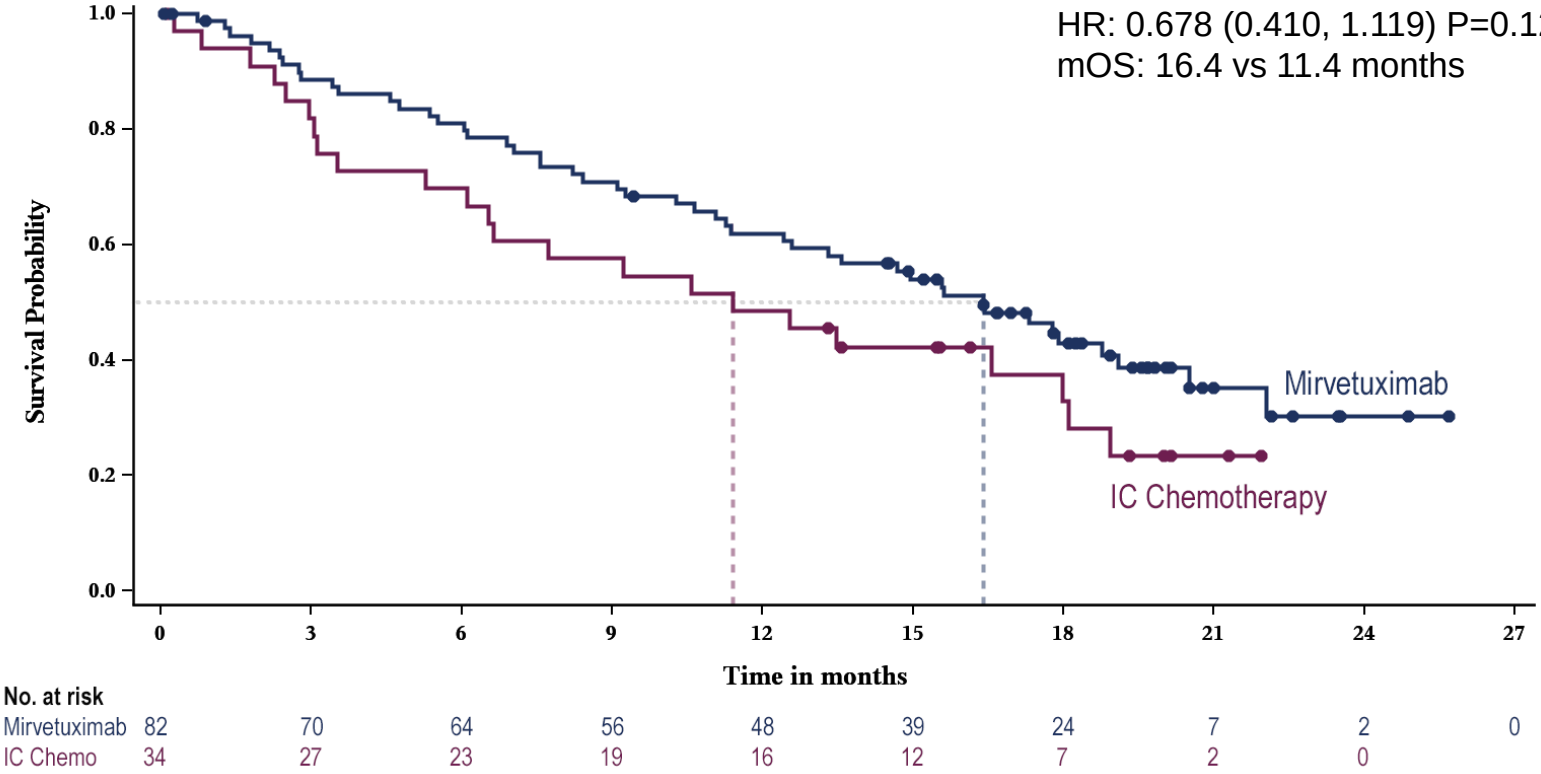
PS2+ RE-SCORING: OVERALL SURVIVAL IN FRα HIGH (n=116)



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PS2+ RE-SCORING: TRENDS ACROSS SUBGROUPS

Endpoint	FRα < 50% (n=114) (Mirv vs IC Chemo)	FRα Medium (n=103) (Mirv vs IC Chemo)	FRα High (n=116) (Mirv vs IC Chemo)
PFS by BIRC (mo.)	HR: 1.458 (0.878, 2.420) mPFS: 3.8 vs 5.5	HR: 1.015 (0.611, 1.687) mPFS: 4.3 vs 5.6	HR: 0.549 (0.336, 0.897) mPFS: 5.6 vs 3.2
ORR by BIRC 95% CIs	16% vs 16% (8%, 26%) vs (6%, 31%)	28% vs 18% (18%, 40%) vs (7%, 35%)	29% vs 6% (20%, 40%) vs (1%, 20%)
OS (*August 2019*) (mo.)	HR: 0.923 (0.548, 1.554) mOS: 14.0 vs 13.4	HR: 0.936 (0.542, 1.616) mOS: 15.9 vs 20.7	HR: 0.678 (0.410, 1.119) mOS: 16.4 vs 11.4
PFS by INV (mo.)	HR: 1.149 (0.732, 1.803) mPFS: 4.0 vs 4.5	HR: 0.810 (0.523, 1.254) mPFS: 5.1 vs 2.8	HR: 0.619 (0.394, 0.975) mPFS: 5.6 vs 3.7
ORR by INV 95% CIs	18% vs 21% (11%, 29%) vs (10%, 37%)	36% vs 24% (25%, 49%) vs (11%, 41%)	38% vs 9% (27%, 49%) vs (2%, 24%)

CONCLUSIONS

- FORWARD I did not meet the PFS primary endpoint in the ITT or FRα high populations
- In the FRα high population (by 10X scoring), consistent efficacy signals were observed with mirvetuximab soravtansine
- Mirvetuximab soravtansine was well tolerated with a differentiated safety profile, fewer grade 3+ adverse events, fewer drug-related dose reductions/discontinuations and more patients with improved abdominal/GI symptoms compared to chemotherapy
- Exploratory analyses suggest that the change in scoring method from PS2+ to 10X introduced a population of patients into FORWARD I with lower levels of FRα expression than intended
- Re-analysis of the FRα high population (by PS2+ scoring) demonstrates improved outcomes correlated with FRα expression, with the strongest treatment effects for all efficacy endpoints in this population
- Data support the design of MIRASOL, the next phase III trial in PS2+ high FRα patients, which is expected to begin by the end of 2019

MIRASOL STUDY DESIGN: PHASE 3 REGISTRATION TRIAL FOR MIRVETUXIMAB SORAVTANSINE USING PS2+ SCORING IN FRα HIGH PATIENTS

MIRASOL

Enrollment and Key Eligibility

- 430 patients/330 events for PFS by INV
- Platinum resistant disease (<6 months PFI)
- Prior Bev and PARP allowed
- BRCAmut patients allowed

Statistical Assumptions

- α=0.05 (two-sided), Power = 90%, HR=0.7; control arm mPFS 3.5 mo

Mirvetuximab Soravtansine

6 mg/kg (adjusted ideal body weight) once every 3 weeks

1:1 Randomization

STRATIFICATION FACTORS

IC Chemotherapy Choice (Paclitaxel, PLD, Topotecan)

Prior therapies (1 vs 2 vs 3)

Investigator's Choice Chemotherapy

Paclitaxel, PLD†, or Topotecan

Paclitaxel: *80 mg/m² weekly*
PLD: *40 mg/m² once every 4 weeks*
Topotecan: *4 mg/m² on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m² on Days 1-5 every 3 weeks*

Primary Endpoint

Progression-free survival by INV

BICR for sensitivity analysis*

Secondary Endpoints

Overall response rate by INV
Overall survival
Patient reported outcomes

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*BICR: Blinded Independent Central Review
†PLD: pegylated liposomal doxorubicin

We are indebted to the women and their families who chose to participate on FORWARD-1
Thank you to all the FORWARD-1 investigators