

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

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# DISCLOSURES

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

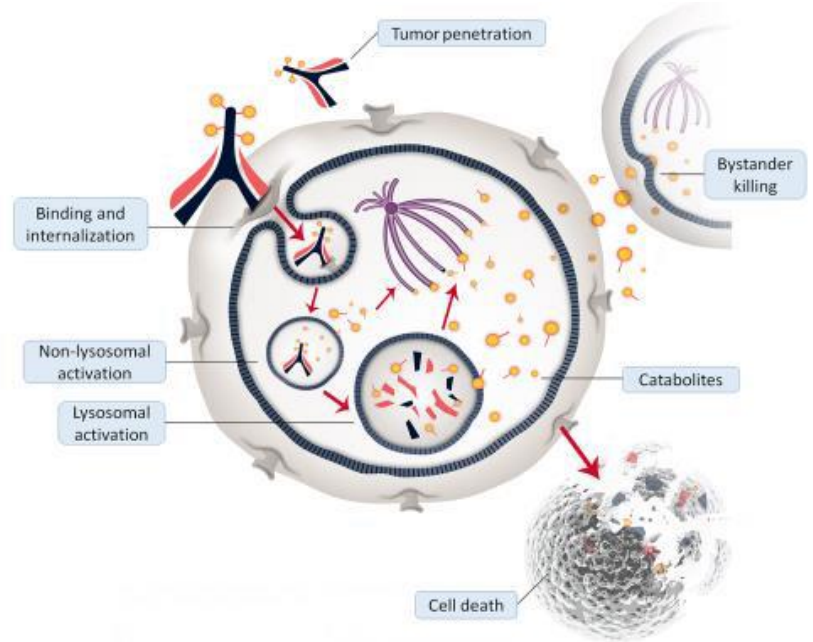
Steering Committee participation for Astra Zeneca, Genentech/Roche, ImmunoGen, Tesaro;

Research funding from PTC Therapeutics, Merck, Lilly, Tesaro

**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- $\alpha$  (FR $\alpha$ ) 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 FR $\alpha$ -positive, platinum-resistant ovarian cancer



# STUDY DESIGN



- Platinum-resistant ovarian cancer
- FR $\alpha$ -positive tumor expression
  - Medium (50-74% cells positive)
  - High ( $\geq$ 75% cells positive)
- ECOG performance status 0 or 1
- 1-3 prior therapies

## Statistical Assumptions

- Hochberg procedure
- $\alpha=0.05$  (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:

*FR $\alpha$  expression (medium or high)  
Prior therapies (1 and 2, or 3)  
Choice of chemotherapy*

## Investigator's Choice Chemotherapy Paclitaxel, PLD<sup>†</sup>, or Topotecan (n=118)

*Paclitaxel: 80 mg/m<sup>2</sup> weekly*

*PLD: 40 mg/m<sup>2</sup> once every 4 weeks*

*Topotecan: 4 mg/m<sup>2</sup> on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m<sup>2</sup> on Days 1-5 every 3 weeks*

## Primary Endpoint

Progression-free survival (PFS; by BIRC\*) for ITT and high FR $\alpha$  populations

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

## Secondary Endpoints

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

# BASELINE CHARACTERISTICS

## Disease Characteristics

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

## Stratification Factors

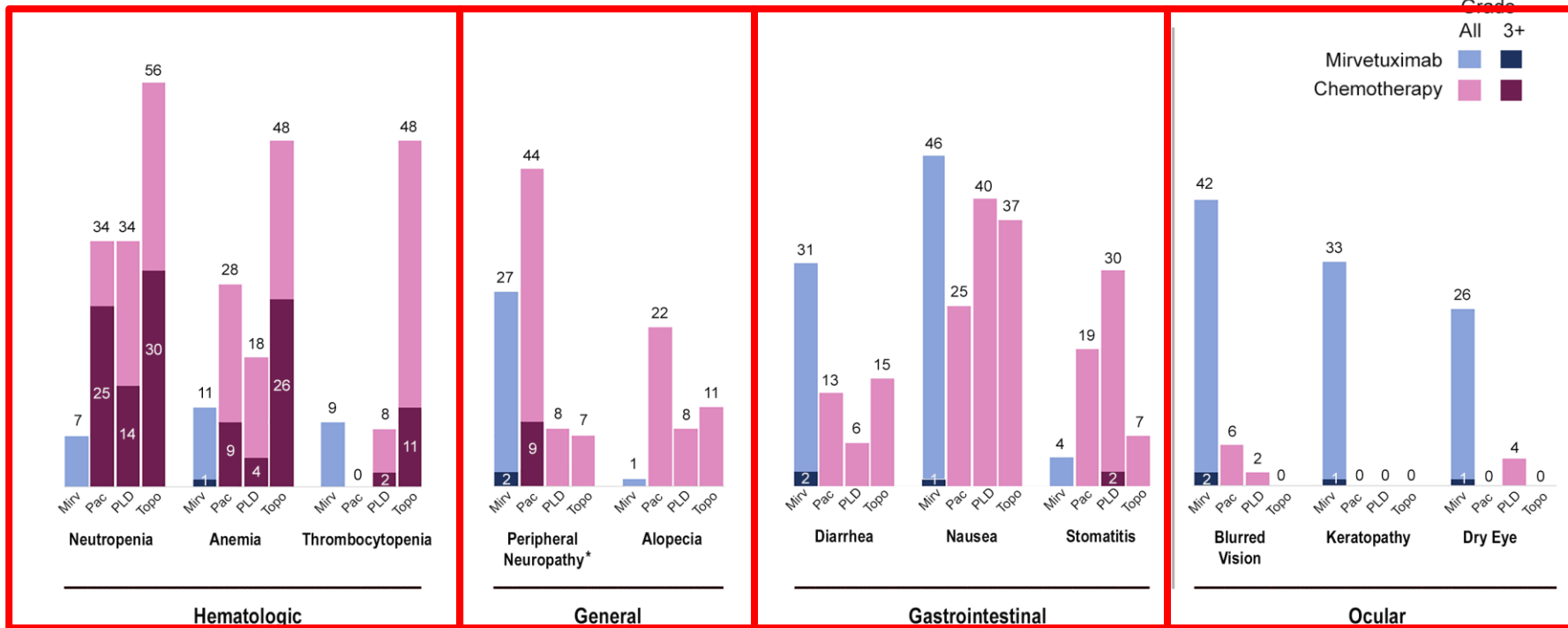
	Mirvetuximab soravtansine (n=248)	IC Chemo (n=118)
<b>FR<math>\alpha</math> Status</b>		
Medium	42%	42%
High	58%	58%
<b>No. Prior Lines</b>		
1 or 2	65%	65%
3	35%	35%
<b>IC Chemotherapy</b>		
Paclitaxel	32%	31%
PLD	44%	46%
Topotecan	23%	23%

# 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

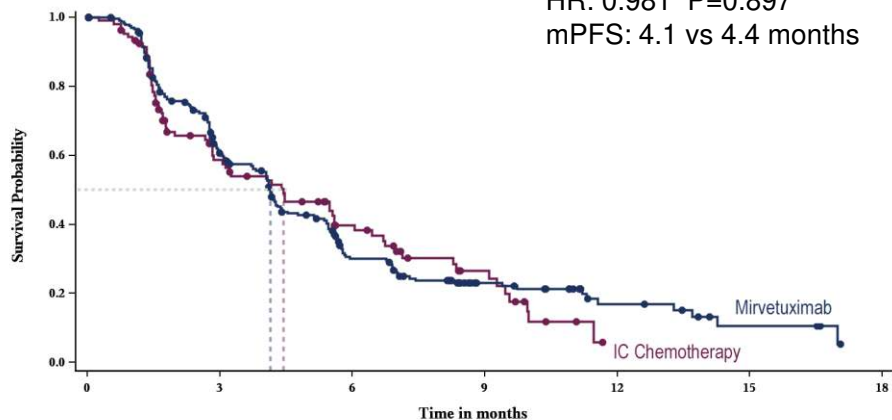


\*Grade 2+ peripheral neuropathy events were observed in 12% and 28% of patients that received mirvetuximab soravtansine or paclitaxel, respectively.

# PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL (BY BIRC)

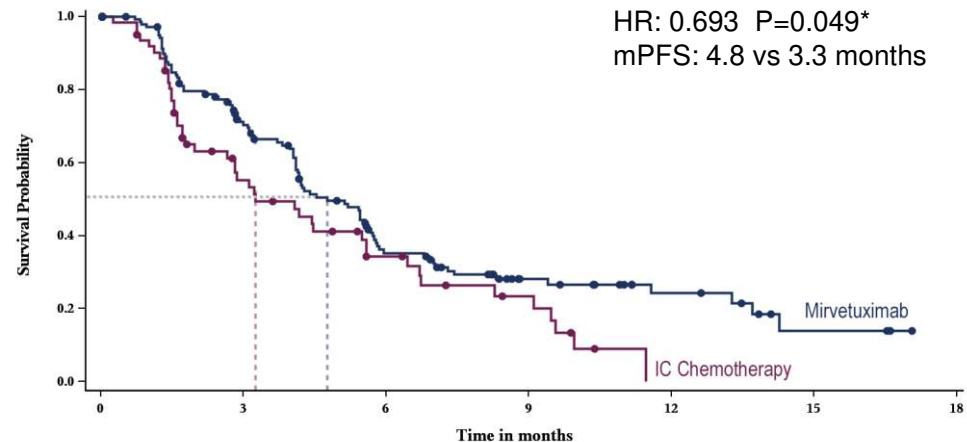
## ITT

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



## FR $\alpha$ High

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





# 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 <sup>^</sup>
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 <sup>†</sup>	32% vs 14%	0.011

\*Nominal p-value

<sup>^</sup>Not significant based on Hochberg Procedure

<sup>†</sup>≥15-point improvement in the EORTC QLQ-OV28 Abdominal/GI Symptom Subscale

## FR<sub>α</sub> 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 <sup>^</sup>
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 <sup>†</sup>	28% vs 13%	0.096

# FR $\alpha$ SCORING IN THE MIRVETUXIMAB SORAVTANSINE PROGRAM

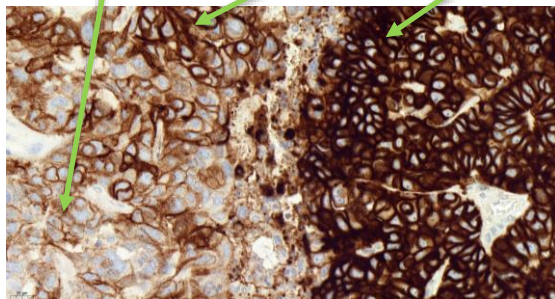
## PS2+ Scoring

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

1+ intensity      2+ intensity      3+ intensity

### PS2+ Scoring

Positive:  $\geq 50\%$  of tumor cells with FR $\alpha$  membrane staining with  $\geq 2+$  intensity

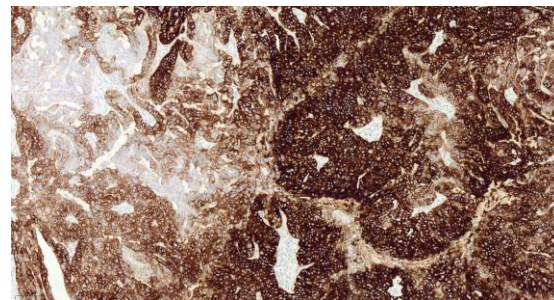


## 10X Scoring

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

### 10X Scoring

Positive:  $\geq 50\%$  of tumor cells with FR $\alpha$  membrane staining visible at 10X microscope objective



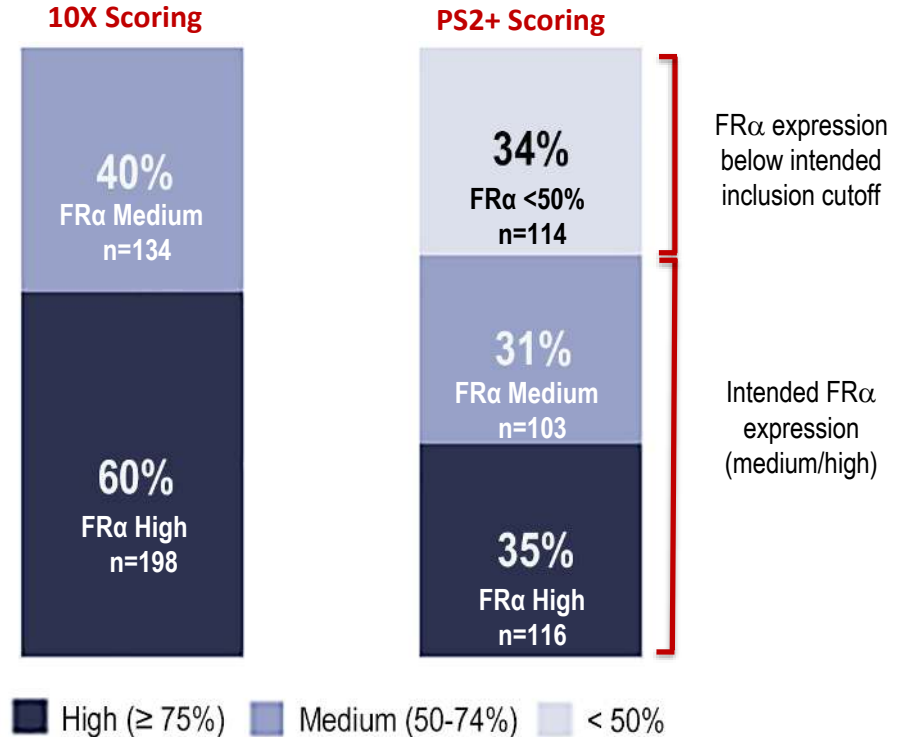
Bridging study indicated that 10X scoring was sufficient for patient selection

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 FR $\alpha$  expression than intended

# FORWARD I 10X SCORING COMPARED WITH EXPLORATORY PS2+ SCORING

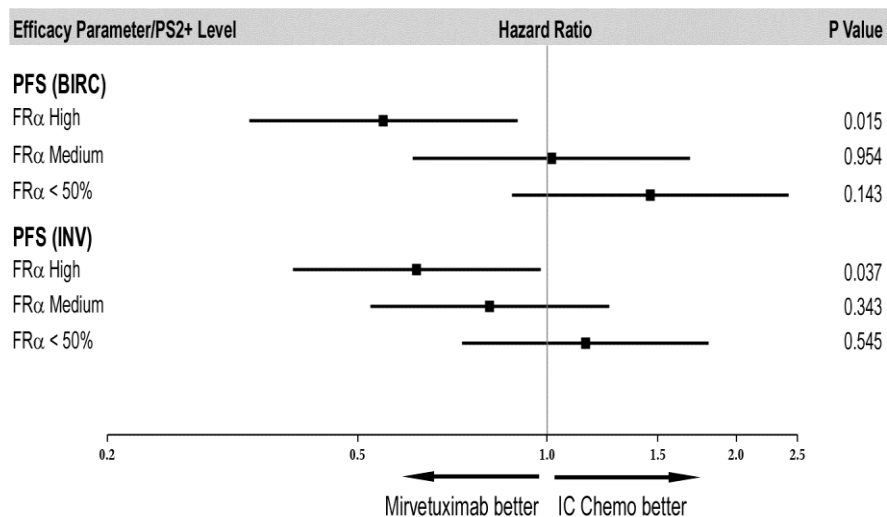
Rescoring of the FORWARD I samples using PS2+ indicates:

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



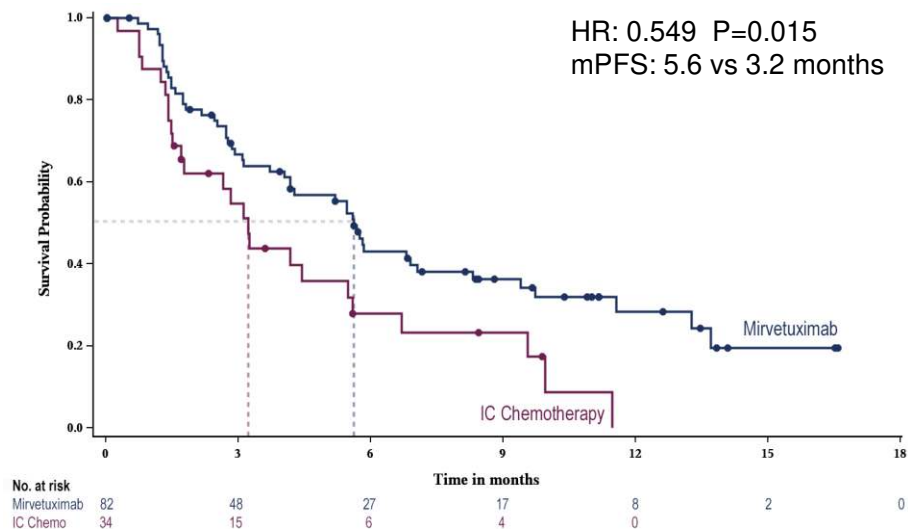
# PS2+ RE-SCORING: PFS TRENDS ACROSS SUBGROUPS

## PFS Hazard Ratio Plot

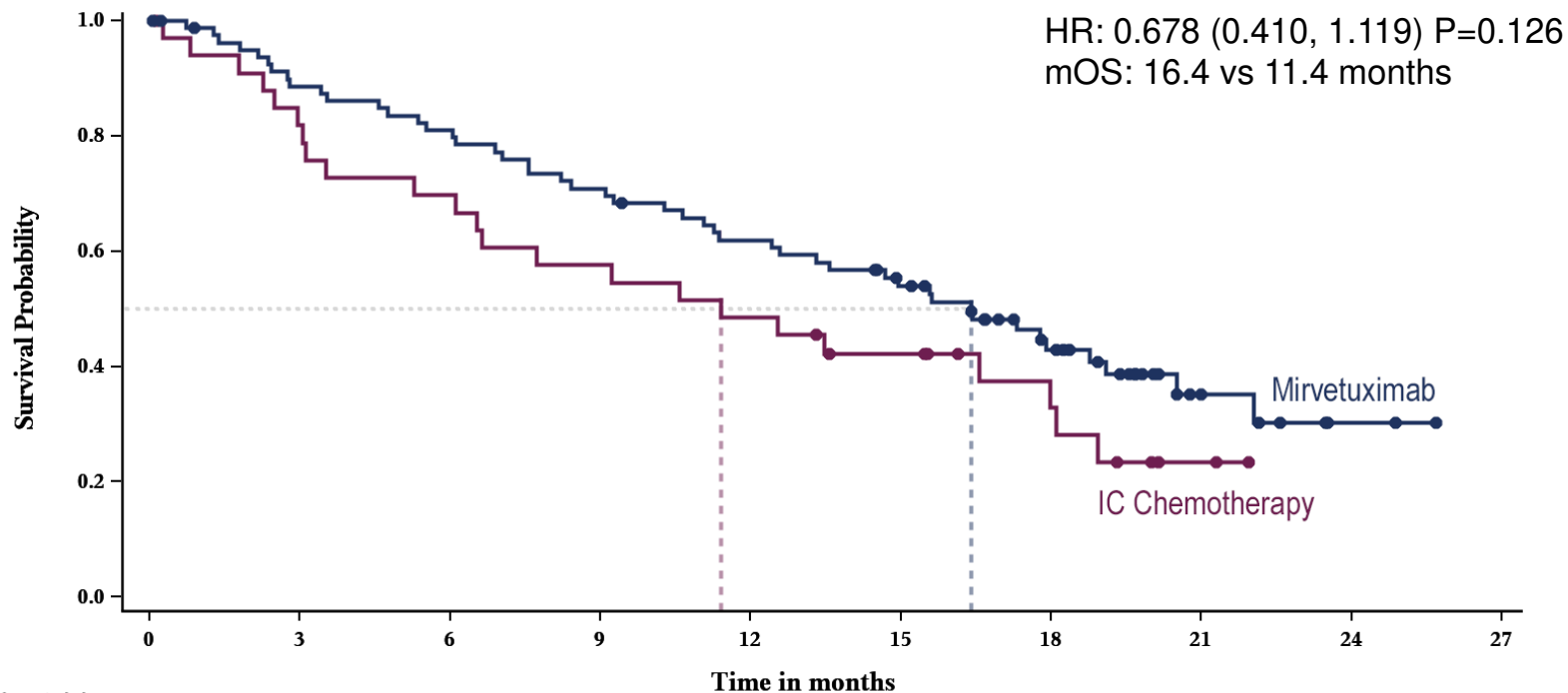


P values from unstratified log-rank test

## PFS (by BIRC) - FR $\alpha$ High (n=116)



# PS2+ RE-SCORING: OVERALL SURVIVAL IN FR $\alpha$ HIGH (n=116)



## No. at risk

	0	3	6	9	12	15	18	21	24	27
Mirvetuximab	82	70	64	56	48	39	24	7	2	0
IC Chemo	34	27	23	19	16	12	7	2	0	

# PS2+ RE-SCORING: TRENDS ACROSS SUBGROUPS

Endpoint	FR $\alpha$ < 50% (n=114) (Mirv vs IC Chemo)	FR $\alpha$ Medium (n=103) (Mirv vs IC Chemo)	FR $\alpha$ 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 ( <i>August 2019</i> ) (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 FR $\alpha$  high populations
- In the FR $\alpha$  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 FR $\alpha$  expression than intended
- Re-analysis of the FR $\alpha$  high population (by PS2+ scoring) demonstrates improved outcomes correlated with FR $\alpha$  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 FR $\alpha$  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 FR $\alpha$ 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

- $\alpha=0.05$  (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<sup>†</sup>, or  
Topotecan

*Paclitaxel: 80 mg/m<sup>2</sup> weekly*  
*PLD: 40 mg/m<sup>2</sup> once every 4 weeks*  
*Topotecan: 4 mg/m<sup>2</sup> on Days 1, 8, and 15 every 4 weeks; or 1.25 mg/m<sup>2</sup> 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



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

Thank you to all the FORWARD-1 investigators