Targeting FRα: Clinical Data

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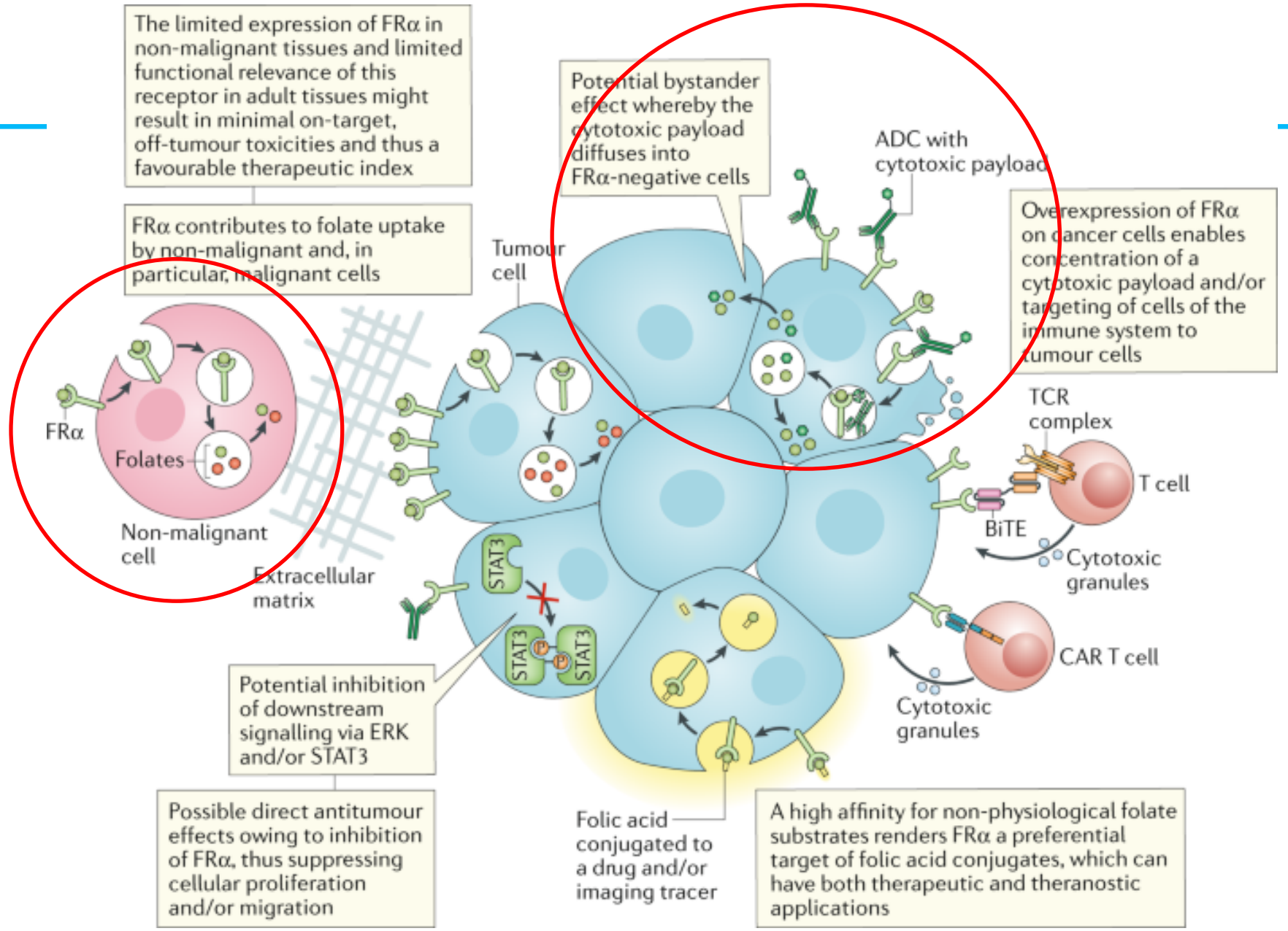
LGOG UZ LEUVEN KU LEUVEN BGOG ENGOT European Network of Gynaecological Oncological Trial groups

Disclosures

All payments institutional

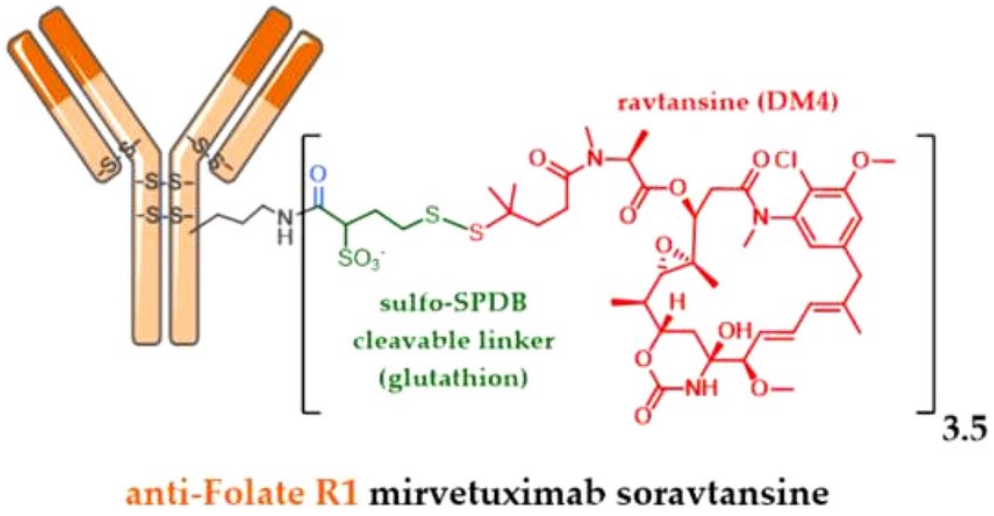
- **Consulting/Advising**
  - AbbVie, AstraZeneca, BioNTech, Cancer Communications and Consultancy Ltd, Daiichi Sankyo, Eisai, GSK, ImmunoGen, Incyte, Karyopharm, MSD/Merck, OncXerna Therapeutics, Seagen, Tubulis, Zentalis
- **Honoraria for lectures**
  - AbbVie, AstraZeneca, Eisai, GSK, ImmunoGen, MSD
- **Travel, accommodations, and/or expenses**
  - AstraZeneca, GSK, ImmunoGen, MSD, and PharmaMar
- **Research funding**
  - Amgen, AstraZeneca, and Roche
- **Leadership in a society, committee or advocacy group, paid or unpaid**
  - Chair of the Belgian and Luxembourg Gynaecological Oncology Group (BGOG) (unremunerated)

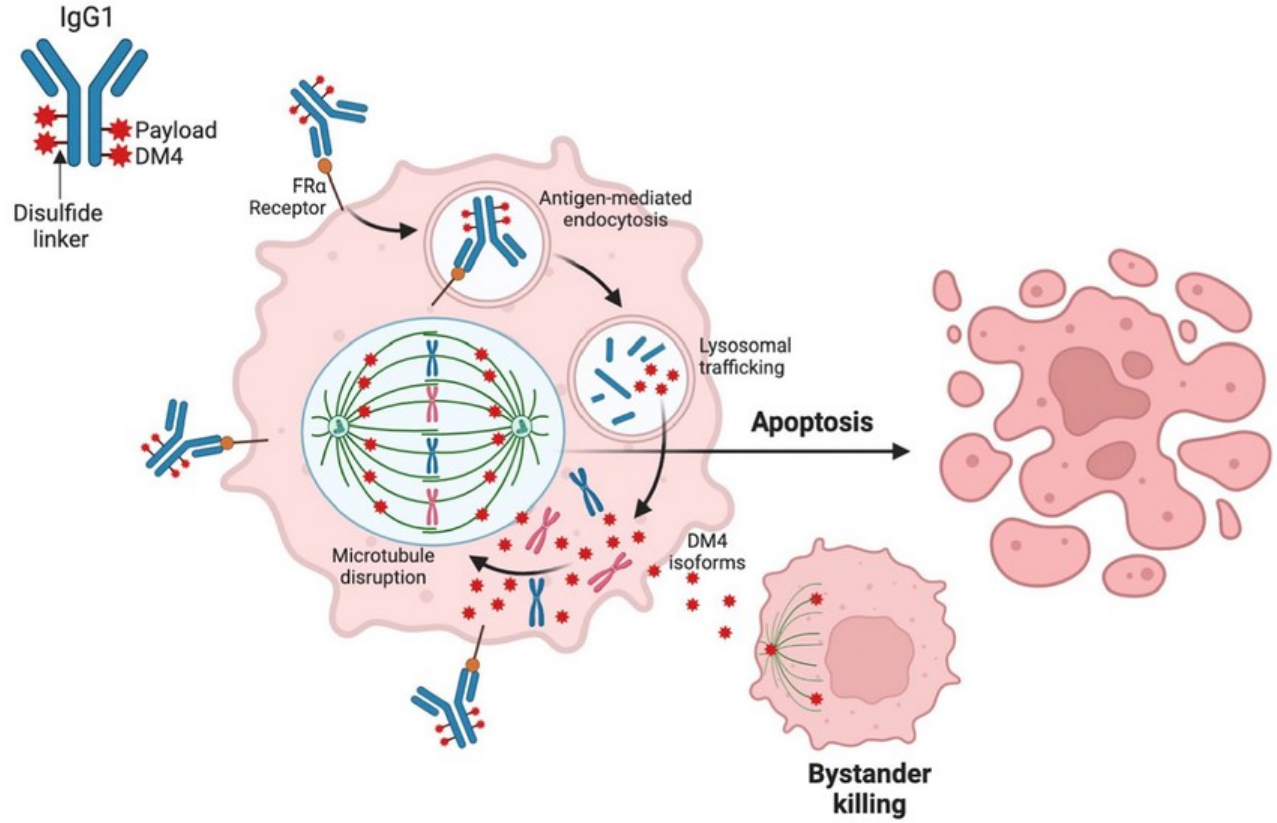

The limited expression of FRα in non-malignant tissues and limited functional relevance of this receptor in adult tissues might result in minimal on-target, off-tumour toxicities and thus a favourable therapeutic index
FRα contributes to folate uptake by non-malignant and, in particular, malignant cells
FRα
Folates
Non-malignant cell
Extracellular matrix
Tumour cell
Potential bystander effect whereby the cytotoxic payload diffuses into FRα-negative cells
ADC with cytotoxic payload
Overexpression of FRα on cancer cells enables concentration of a cytotoxic payload and/or targeting of cells of the immune system to tumour cells
TCR complex
T cell
BiTE
Cytotoxic granules
CAR T cell
Cytotoxic granules
STAT3
STAT3
STAT3
Potential inhibition of downstream signalling via ERK and/or STAT3
Possible direct antitumour effects owing to inhibition of FRα, thus suppressing cellular proliferation and/or migration
Folic acid conjugated to a drug and/or imaging tracer
A high affinity for non-physiological folate substrates renders FRα a preferential target of folic acid conjugates, which can have both therapeutic and theranostic applications

Multiple ADCs targeting FRα are under development

Example ADCs under development		Linker	Payload	MOA	Stage of development	Clinicaltrials.gov
	AZD5335	Undisclosed	AZ14170132	TOP1i	Phase 1/2	NCT05797168
Farletuzumab ecteribulin	MORAb-202	Cleavable	Eribulin	MTi	Phase 1/2	NCT04300556
	IMGN151	Cleavable	DM21	MTi	Phase 1	NCT05527184
Luveltamab tazevibulin	STRO-002	Cleavable	Hemiasterlin	MTi	Phase 2/3 ongoing	NCT05870748
Mirvetuximab soravtansine	Mirv; IMGN853	Cleavable	DM4	MTi	Phase 3 complete	NCT04209855
Rinatabart sesutecan	Rina-S; PRO1184	Cleavable	Exatecan	TOP1i	Phase 1/2 ongoing	NCT05579366

Mirvetuximab-soravtansine (Mirv)





SORAYA study: design

A phase II single arm trial with Mirvetuximab soravtansine

Prior 1L: 3-6m
Prior 2-3L: <6m

- High grade serous platinum-resistant ovarian cancer
- Platinum resistant disease (PFI <6m)
- **FRα-high** tumor expression -> **PS2+ scoring**
- ECOG performance status 0 or 1
- 1-3 prior therapies
- **Prior Bev**

Mirvetuximab Soravtansine (n=106)

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

Primary Endpoint

Confirmed ORR by investigator (ORR by BICR for sensitivity analysis)

Key Secondary Endpoints

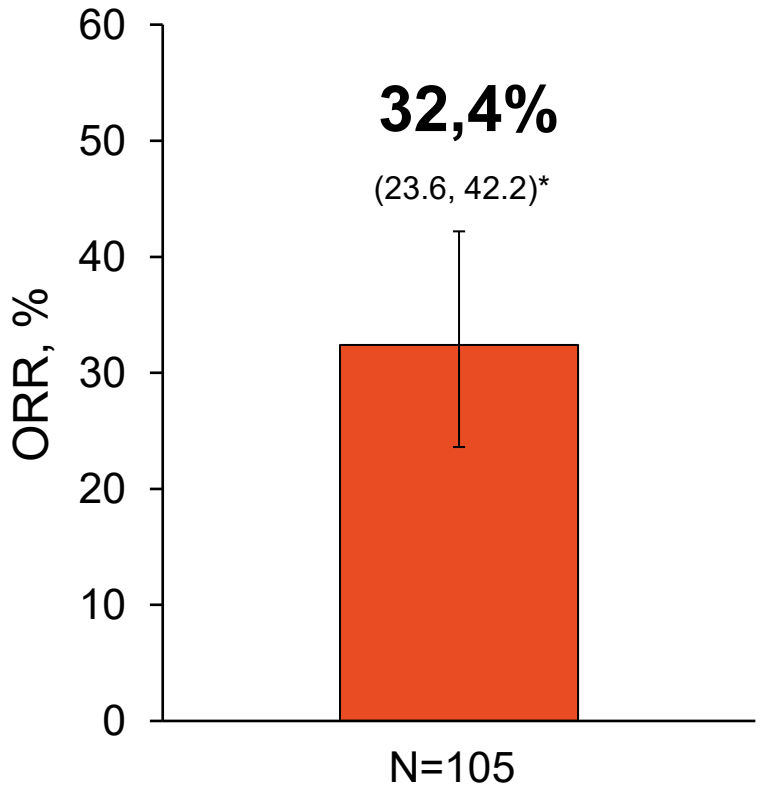
Duration of response (DOR)

Statistical Assumptions

- α=0.025 (one-sided)
- power = 90%
- ORR 24% (vs 12% based on single agent chemo)

Matulonis et al. SGO 2022
Matulonis et al. J Clin Oncol 41:2436-2445

Objective Response Rate (Inv)

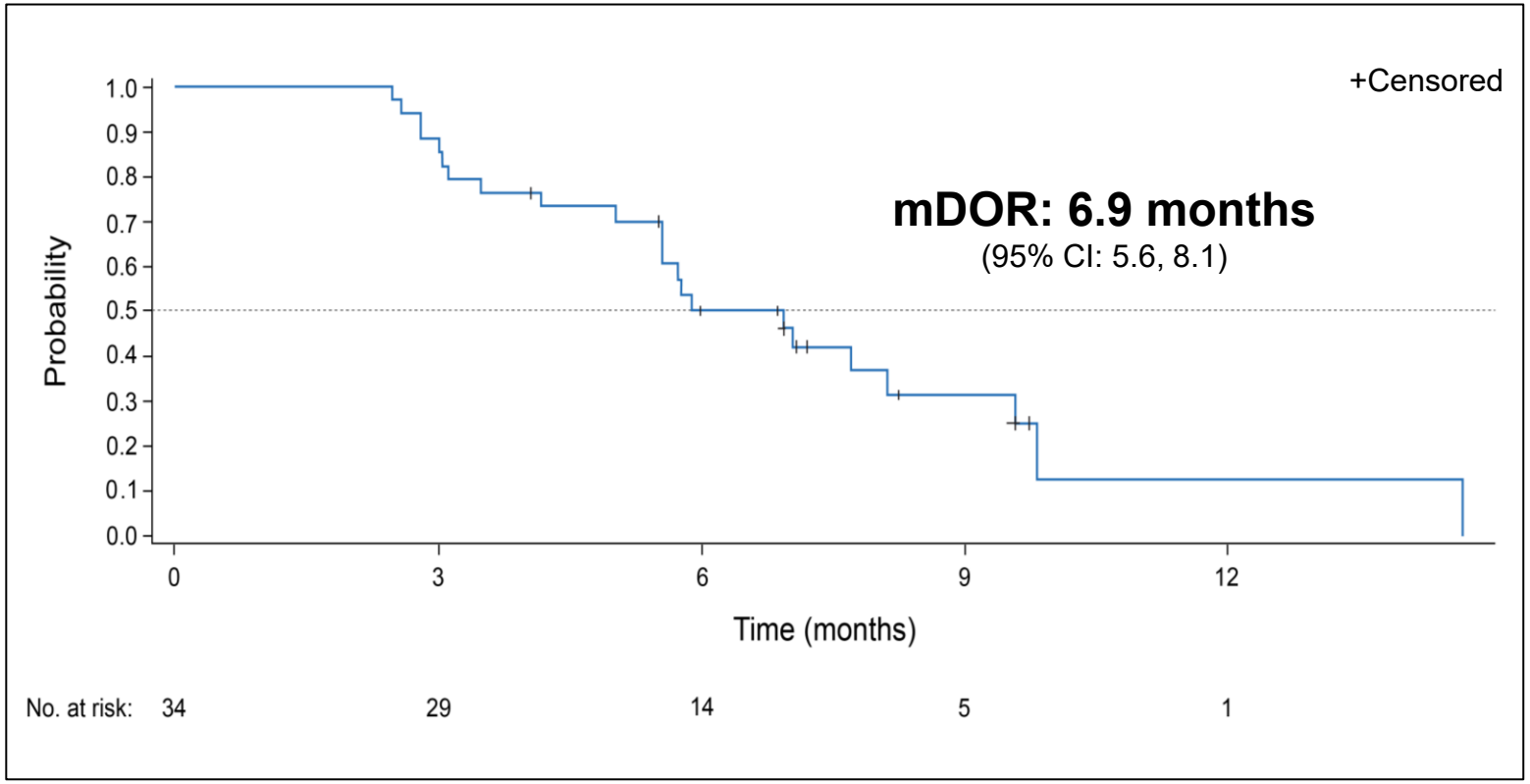


34 responders

- 5 complete responses
- 29 partial responses

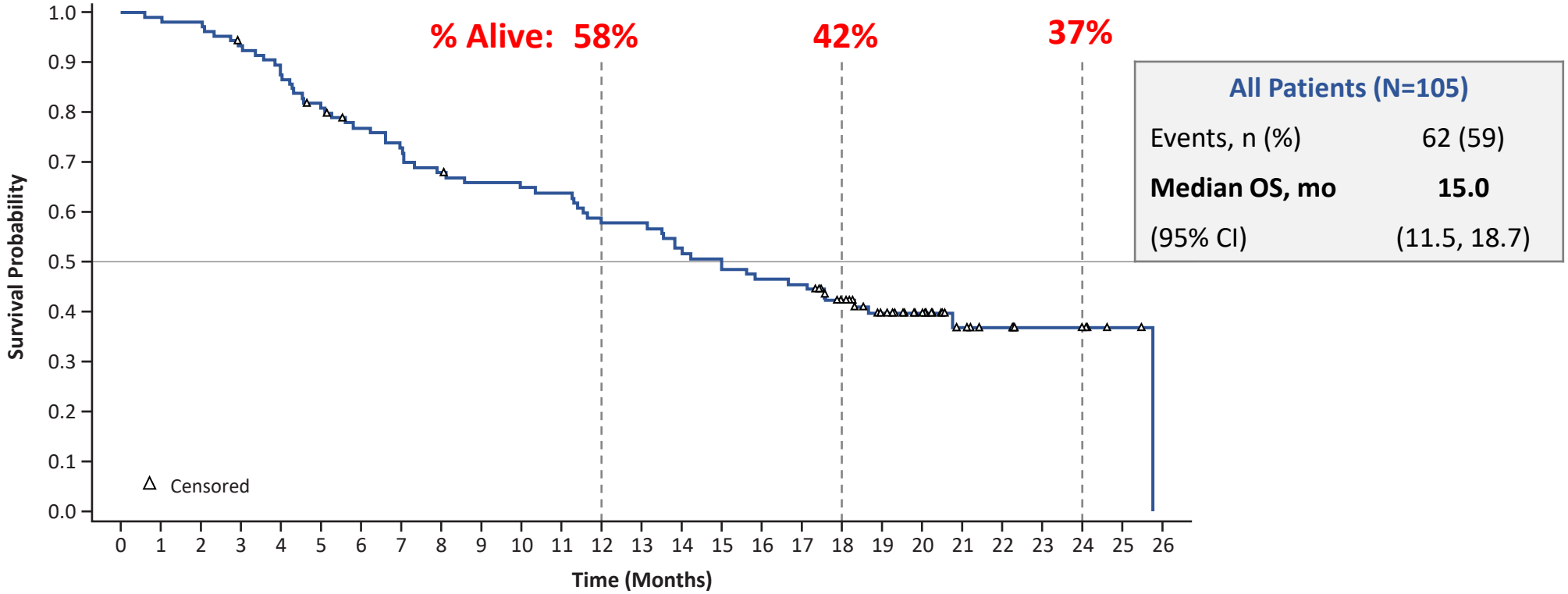
Matulonis et al. SGO 2022
Matulonis et al. J Clin Oncol 41:2436-2445

Duration of Response (Inv)



Overall Survival

Final Overall Survival* in INV Efficacy Evaluable Population



All Patients (N=105)	
Events, n (%)	62 (59)
Median OS, mo	**15.0**
(95% CI)	(11.5, 18.7)

Number of Patients at Risk

MIRV	105	104	103	97	91	83	77	73	68	65	64	63	57	57	52	48	46	45	36	27	21	12	9	6	5	2	0

Coleman et al. SGO 2023
Matulonis et al. J Clin Oncol 41:2436-2445

FDA

14 Nov 2022

FDA grants accelerated approval to mirvetuximab soravtansine-gynx for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer

ENGOT-ov55/MIRASOL

Phase 3 registration trial for Mirvetuximab Soravtansine 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

Prior 1L: 3-6m
Prior 2-3L: <6m

Statistical Assumptions

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

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

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

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

Baseline characteristics

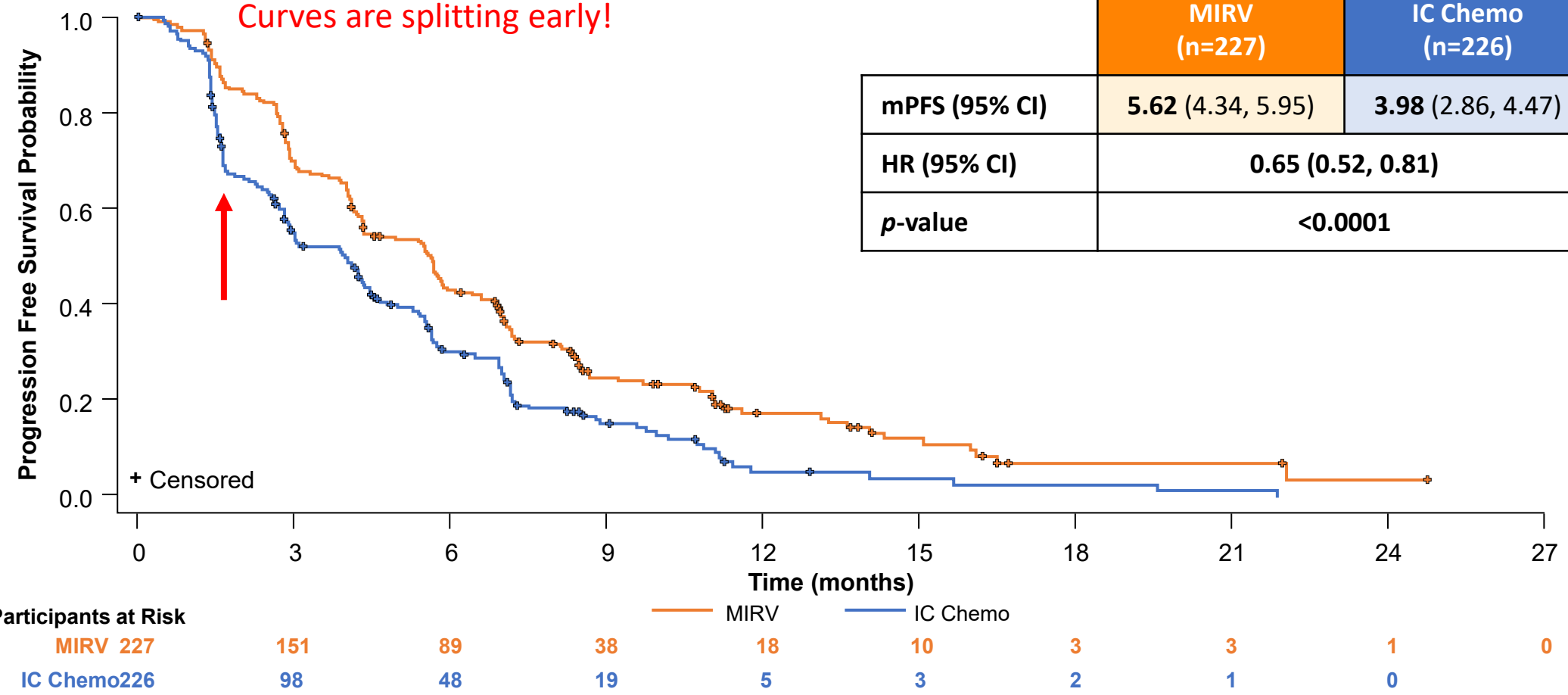
Characteristics	MIRV (n = 227)	IC Chemotherapy (n = 226)
Age		
Median (range), yr	64 (32-88)	62 (29-87)
Primary cancer diagnosis, no. (%)		
Epithelial ovarian cancer	182 (80.2)	182 (80.5)
Fallopian tube cancer	27 (11.9)	23 (10.2)
Primary peritoneal cancer	16 (7.0)	20 (8.8)
Other	2 (0.9)	1 (0.4)
Stage at initial diagnosis, n (%)[a]		
IA or IIA	7 (3.1)	1 (0.4)
IIB or IIC	2 (0.9)	8 (3.5)
IIIA	14 (6.2)	16 (7.1)
IIIB	16 (7.0)	11 (4.9)
IIIC	107 (47.1)	120 (53.1)
IV	76 (33.5)	65 (28.8)
BRCA mutation, n (%)		
BRCA1 positive	24 (10.6)	29 (12.8)
BRCA2 positive	9 (4.0)	7 (3.1)
Negative or unknown	198 (87.2)	190 (84.1)

Characteristics, continued.	MIRV (n = 227)	IC Chemotherapy (n = 226)
Previous lines of systemic therapy, n (%)		
1	29 (12.8)	34 (15.0)
2	90 (39.6)	88 (38.9)
3	108 (47.6)	104 (46.0)
Previous exposure, n (%)		
Bevacizumab	138 (60.8)	143 (63.3)
PARP inhibitor	124 (54.6)	127 (56.2)
Taxane	227 (100)	224 (99.1)
Doxorubicin or PLD	130 (57.3)	133 (58.8)
Topotecan	1 (0.4)	2 (0.9)
Primary platinum-free interval, n (%)[b]		
≤12 months	146 (64.3)	142 (62.8)
>12 months	80 (35.2)	84 (37.2)
Platinum-free interval, n (%)[c]		
≤3 months	88 (38.8)	99 (43.8)
>3 to ≤6 months	138 (60.8)	124 (54.9)
>6 months	1 (0.4)	3 (1.3)

Tables adapted from Moore KN, et al.[1] Data cutoff: March 6, 2023. 14% of patients remain on MIRV; 3% remain on IC Chemotherapy at data-cut off.
[a]Five patients (2%) in the MIRV arm and five patients in the IC chemotherapy arm (2%) were missing information for stage at initial diagnosis. [b]One patient (<1%) in the MIRV arm was missing information on primary platinum-free interval. [c]One patient (<1%) in the MIRV arm and 3 patients (1%) in the IC chemotherapy arm enrolled with platinum-free interval of >6 months.
BRCA, BReast CAncer gene; IC, investigator's choice; MIRV, mirvetuximab soravtansine; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; PLD, pegylated liposomal doxorubicin.

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

Primary Endpoint: PFS (Inv)



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	**5.62** (4.34, 5.95)	**3.98** (2.86, 4.47)
HR (95% CI)	**0.65 (0.52, 0.81)**	
***p*-value**	**<0.0001**	

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

ORR (INV)

	MIRV (n=227)	IC Chemo (n=226)
ORR **n, 95% CI**	**42%** 96, (5.8, 49.0)	**16%** 36, (11.4, 21.4)
Best overall response, n (%)		
CR	12 (5%)	0
PR	84 (37%)	36 (16%)
SD	86 (38%)	91 (40%)
PD	31 (14%)	62 (27%)
Not evaluable	14 (6%)	37 (16%)

ORR Difference 26.4% (18.4, 34.4)
OR 3.81 (2.44, 5.94)
***p*<0.0001**

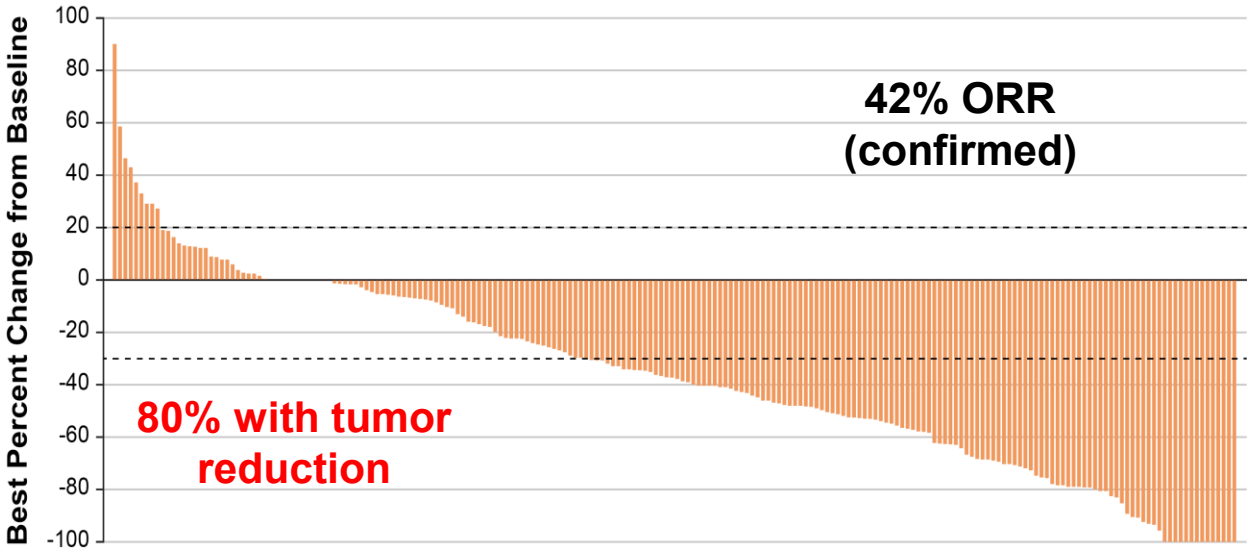
Data cutoff: March 6, 2023. MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, odds ratio.

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

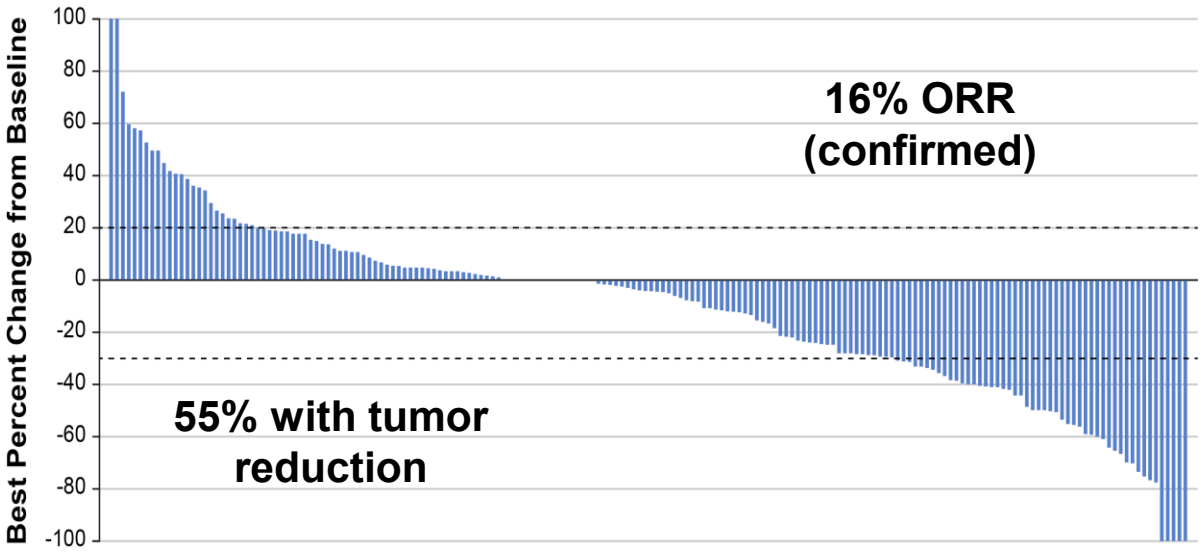
Change in target lesion size from baseline

MIRASOL

MIRV



IC Chemo



Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate.

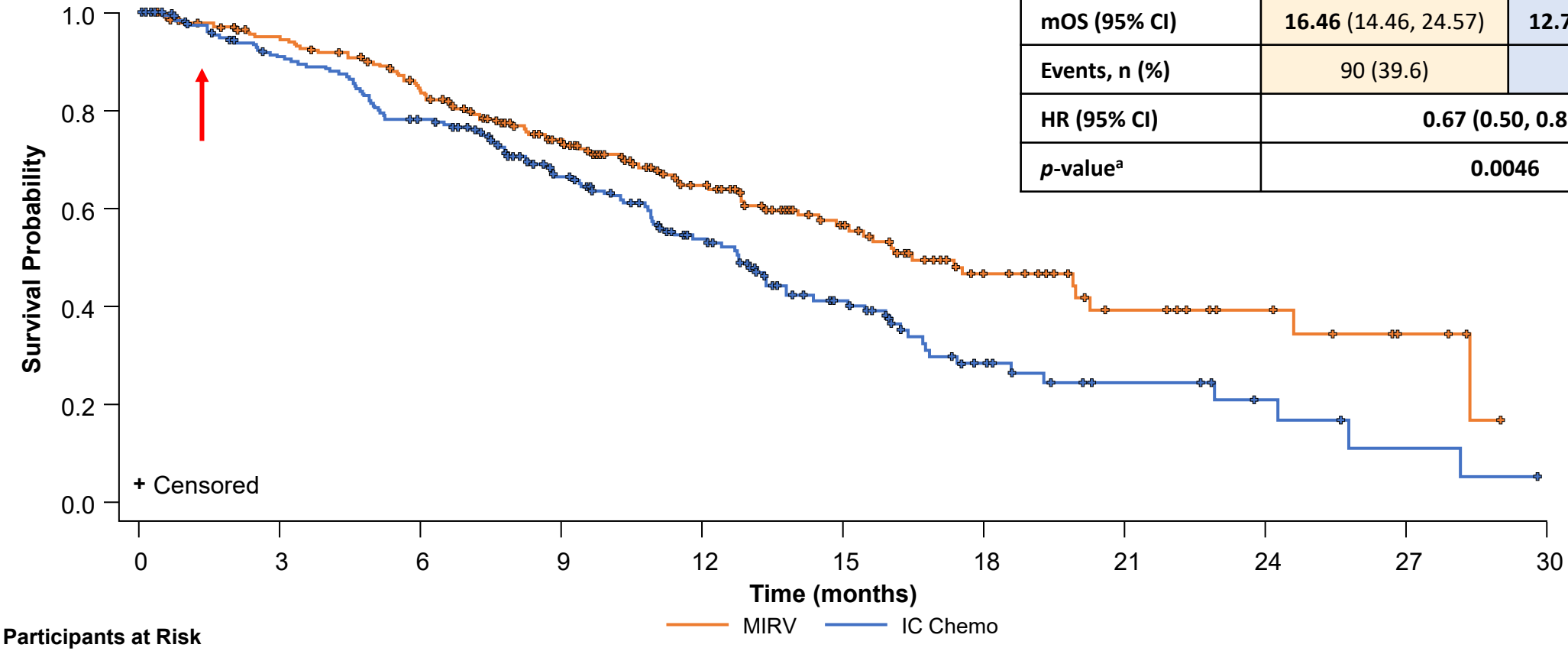
LGOG UZ LEUVEN KU LEUVEN BGOG ENGOT European Network of Gynaecological Oncological Trial groups

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

Overall Survival

	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	**16.46** (14.46, 24.57)	**12.75** (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	**0.67 (0.50, 0.89)**	
p-value[a]	**0.0046**	

Again the curves are splitting early!



No. Participants at Risk

MIRV 227	204	175	128	82	53	28	15	9	4	0
IC Chemo226	185	157	107	68	39	18	9	5	2	0

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

PFS/OS according to prior Bevacizumab use (Inv)

	Bev-Naïve		Prior Bev	
	MIRV	IC Chemo	MIRV	IC Chemo
mPFS (95% CI)	7.0 (5.6, 8.4)	5.6 (3.0, 6.5)	4.4 (4.0, 5.8)	3.0 (2.5, 4.3)
Events n (%)[a]	65 (73.0)	57 (69.0)	111 (80.4)	109 (76.2)
HR (95% CI)	**0.66 (0.46, 0.94)**		**0.64 (0.49, 0.84)**	
Nominal *p*-value	0.0210		0.0011	
mOS (95% CI)	20.2 (14.8, NE)	14.4 (11.8, 16.7)	15.4 (11.3, 17.5)	10.9 (9.4, 13.3)
Events n (%)[a]	23 (25.8)	39 (47.0)	67 (48.6)	75 (52.4)
HR (95% CI)	**0.51 (0.31, 0.86)**		**0.74 (0.54, 1.04)**	
Nominal *p*-value	0.0099		0.0789	

Data cutoff: March 6, 2023

[a]Percentage of events was calculated out of the total number of patients in each treatment arm: n=227 for MIRV and n=226 for IC Chemo.

mPFS, median progression-free survival; HR, hazard ratio; CI, confidence interval; mOS, median overall survival; MIRV, mirvetuximab soravtansine; Bev, bevacizumab; IC Chemo, investigator's choice chemotherapy.

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

Safety

- See next presentation

Summary

- Compared to IC chemo, MIRV demonstrated:
  - **35% improvement in PFS:** HR of 0.65, $p<0.0001$
  - **26% increase of the ORR**: 42% vs 16%, $p<0.0001$
  - **33% improvement in OS:** HR of 0.67, $p=0.0046$

- **Both BEV-naïve and BEV-pretreated** subgroups demonstrated a consistent benefit with MIRV

- These data are practice-changing and position MIRV as a **new standard of care** for patients with FRα-positive PROC

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

FDA and now also EMA approval!

FDA U.S. FOOD & DRUG ADMINISTRATION

14 Nov 2022

FDA grants accelerated approval to mirvetuximab soravtansine-gynx for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or peritoneal cancer

22 Mar 2024

FDA approves mirvetuximab soravtansine-gynx for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

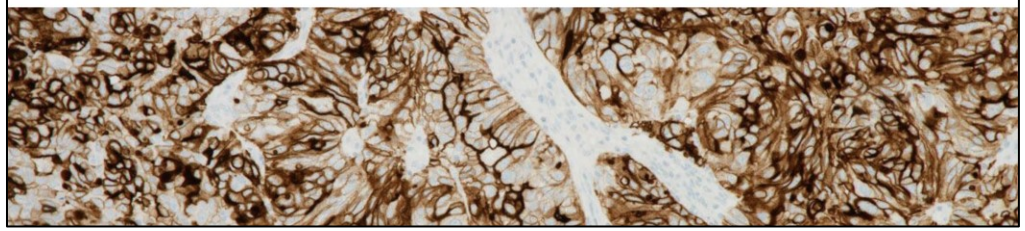
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 Nov 2024

November 18, 2024

AbbVie Receives European Commission Approval of ELAHERE® (mirvetuximab soravtansine) for the Treatment of Platinum-Resistant Ovarian Cancer

Roche receives CE Mark for VENTANA FOLR1 (FOLR1-2.1) RxDx Assay as the first IHC-based companion diagnostic to identify ovarian cancer patients eligible for ELAHERE

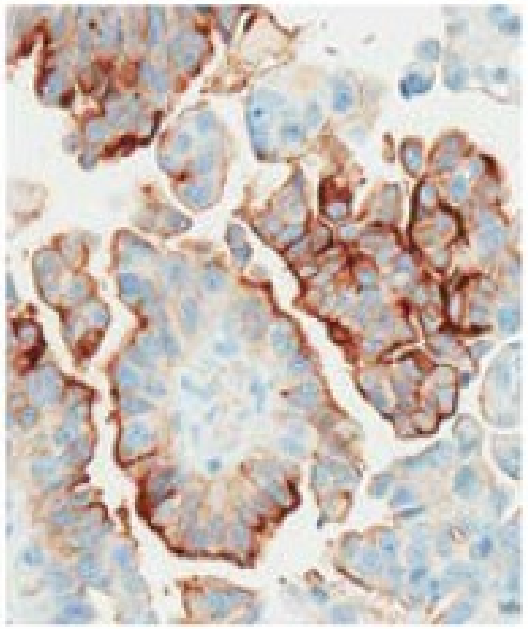


Using the correct test & interpretation is essential

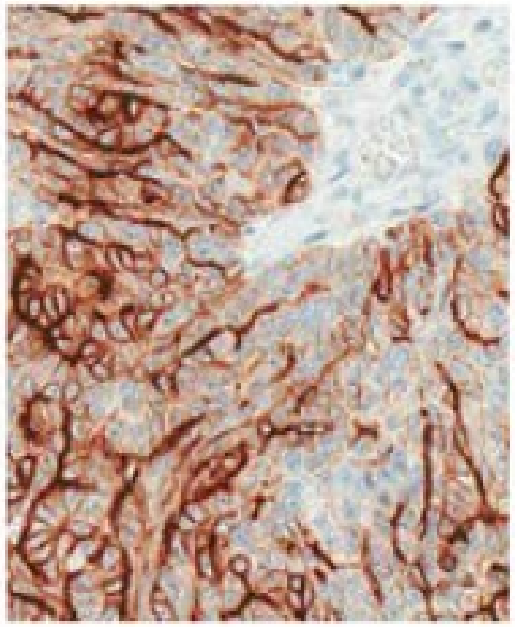
1. Views and experience of Prof. Dr. Philipp Harter, Evangelische Kliniken Essen-Mitte, Essen, Germany.

Characterization of FRα expression

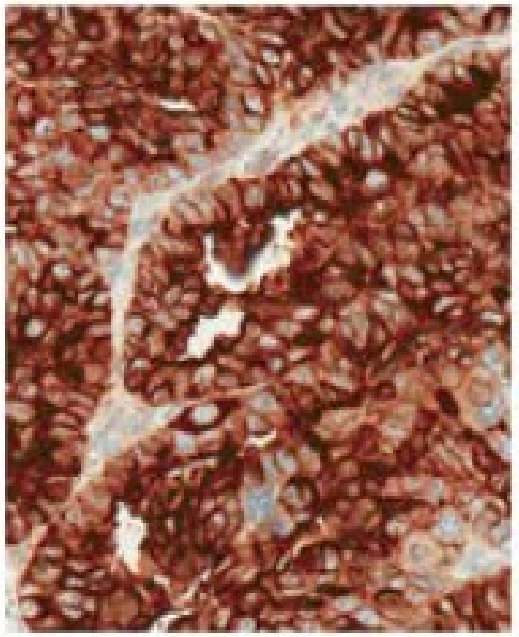
Representative low, medium, and high staining patterns for FRα from archival tumour specimens



Low
25–49% of cells with ≥2+ intensity



Medium
50–74% of cells with ≥2+ intensity

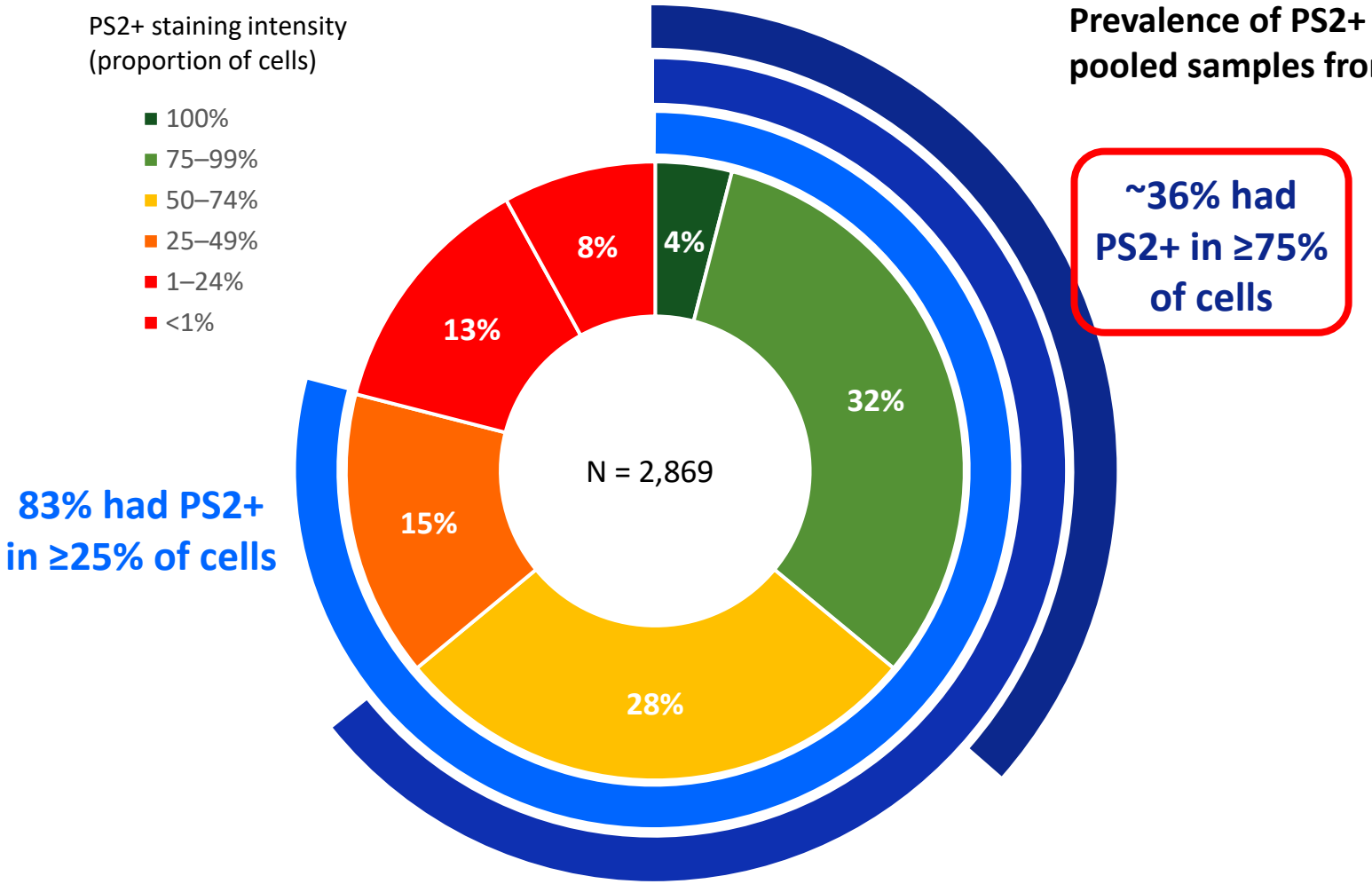


High
≥75% of cells with ≥2+ intensity

FRα, folate receptor alpha; HGSOC, high-grade serous ovarian cancer; MIRV, mirvetuximab soravtansine; PS2+, positive staining intensity ≥2.

Martin LP, et al. Gynecol Oncol. 2017;147(2):402-407

Characterization of FRα expression



Prevalence of PS2+ FRα expression in 2,869 pooled samples from patients with HGSOC[2]

~36% had PS2+ in ≥75% of cells

83% had PS2+ in ≥25% of cells

64% had PS2+ in ≥50% of cells

FRα, folate receptor alpha; HGSOC, high-grade serous ovarian cancer; MIRV, mirvetuximab soravtansine; PS2+, positive staining intensity ≥2.

Figure adapted with a modified layout
Deutschman E, et al. 36th European Congress of Pathology (ECP). 2024; Abs 2093 and poster.

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) Q3W

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 Q4W; or 1.25 mg/m² on Days 1-5 Q3W*

Primary Endpoint

PFS by BIRC*
for ITT and high FRα populations

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

Secondary Endpoints

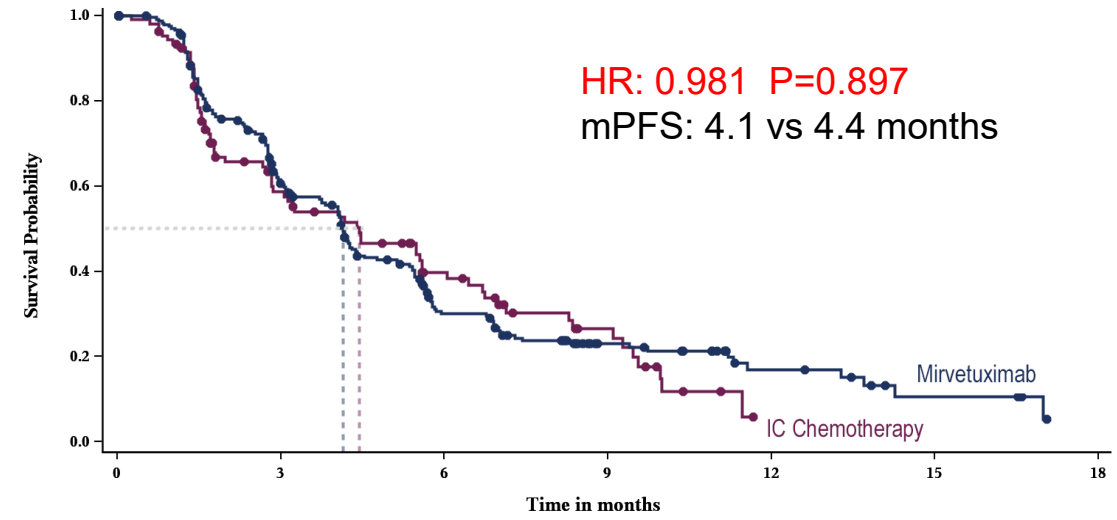
Overall response rate (ORR)
Overall survival (OS)
Patient reported outcomes (PRO)

†Pegylated liposomal doxorubicin

Moore et al. ESMO 2019
ClinicalTrials.gov Identifier: NCT02631876

Primary endpoint: PFS (BICR)

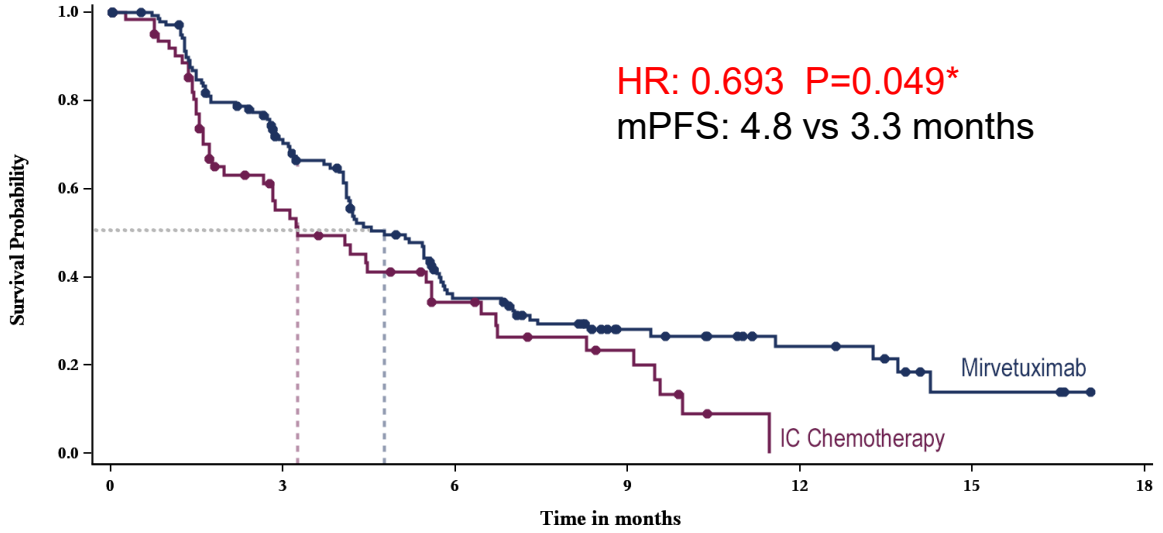
ITT



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

No. at risk							
Mirvetuximab	248	132	54	26	11	4	0
IC Chemo	118	50	27	12	0		

FRα High



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

No. at risk							
Mirvetuximab	147	88	38	19	10	3	0
IC Chemo	71	28	14	7	0		

*not significant per Hochberg procedure

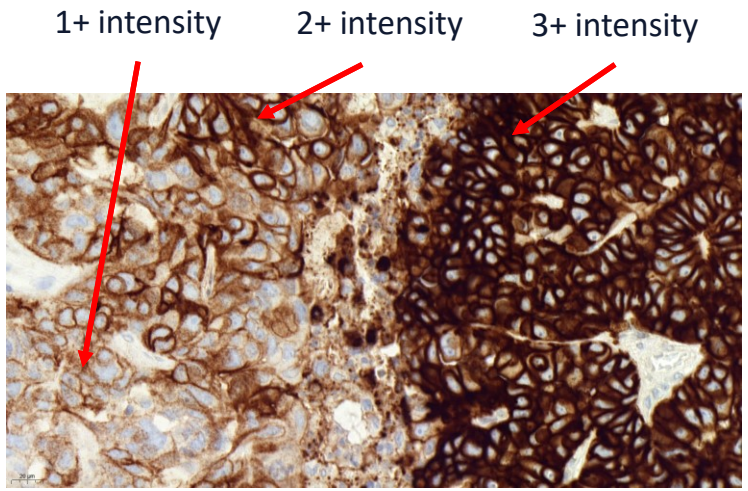
Moore et al. ESMO 2019
ClinicalTrials.gov Identifier: NCT02631876

FRα scoring in the mirvetuximab soravtansine program

PS2+ Scoring

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

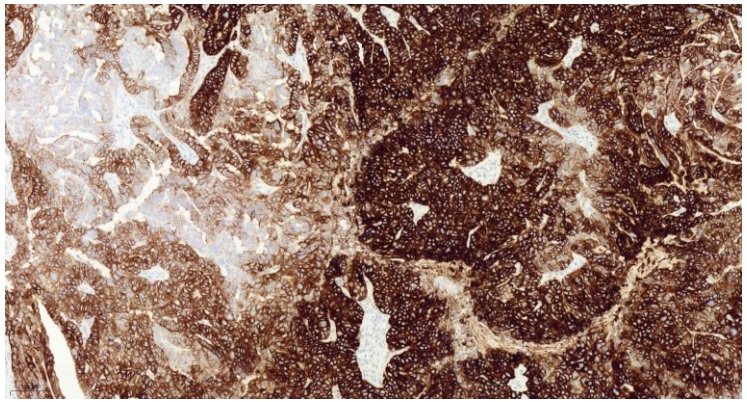
PS2+ Scoring
Positive: ≥ 50% of tumor cells with FRa membrane staining with ≥ 2+ intensity



10X Scoring

- In FORWARD I, a simplified scoring method to assess FRa 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

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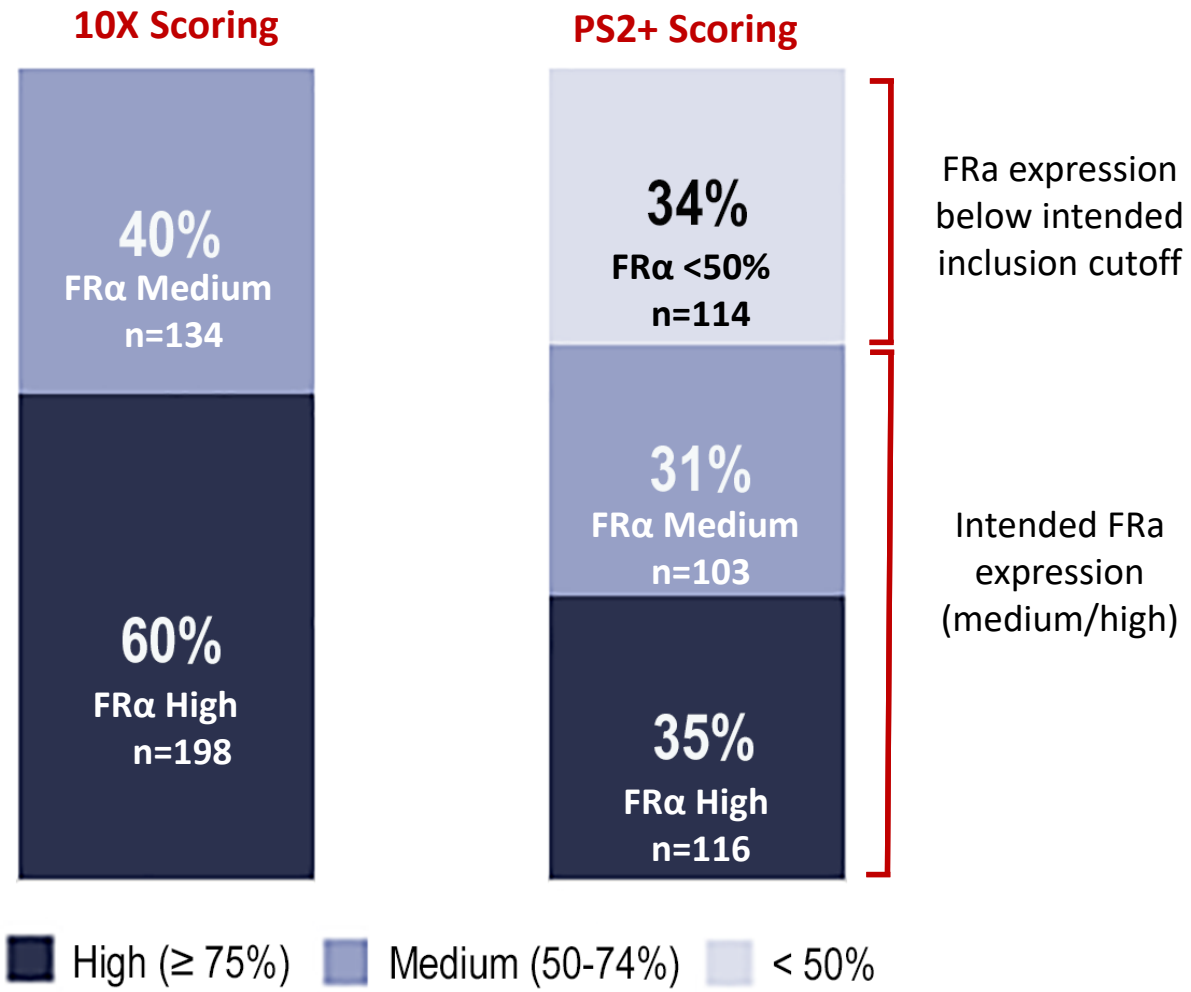
Moore et al. ESMO 2019
ClinicalTrials.gov Identifier: NCT02631876

10X scoring vs exploratory PS2+ scoring

Rescoring of the FORWARD I samples using PS2+ indicates:

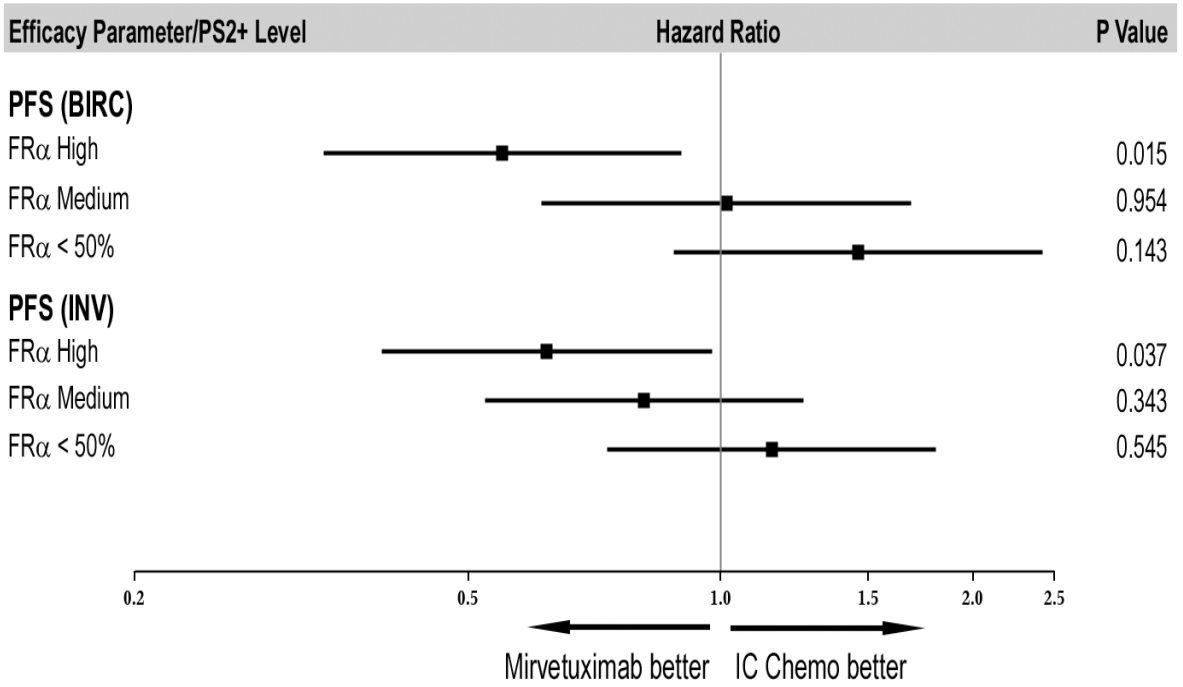
- **34% of patients enrolled in FORWARD I had low FRα levels** that should have precluded enrollment; and
- the protocol-defined **FRα high subset contained patients with a mixture of FRα expression levels**



Moore et al. ESMO 2019
ClinicalTrials.gov Identifier: NCT02631876

PS2+ re-scoring: PFS trends

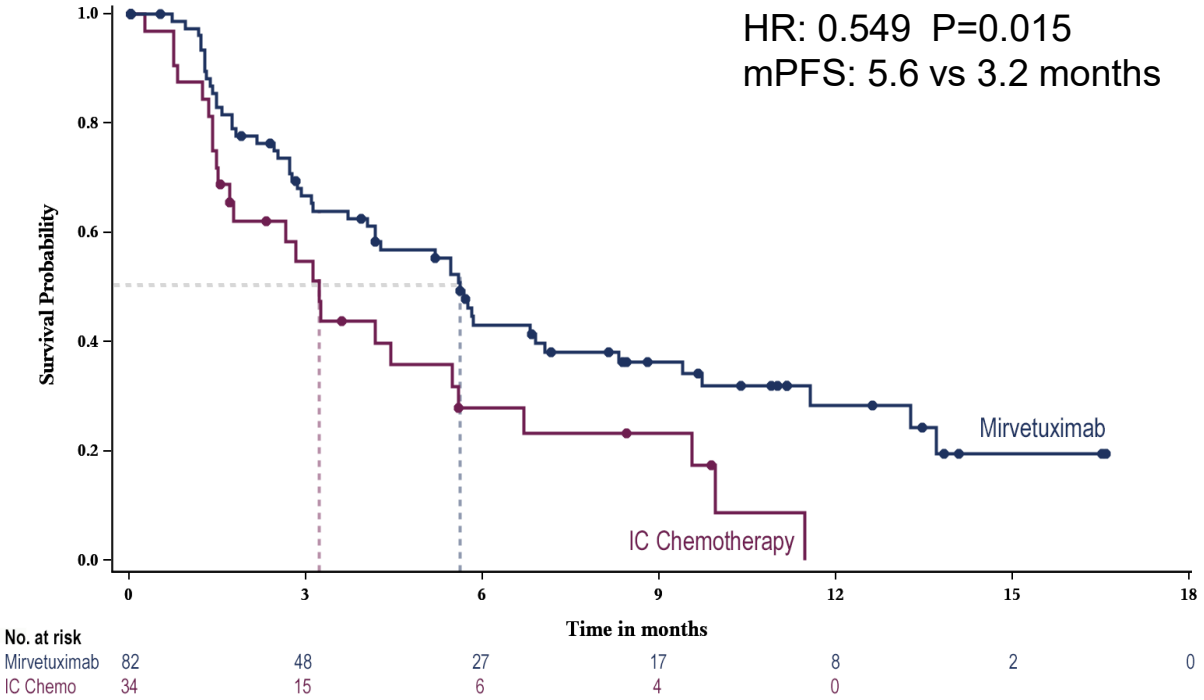
PFS Hazard Ratio Plot



P values from unstratified log-rank test

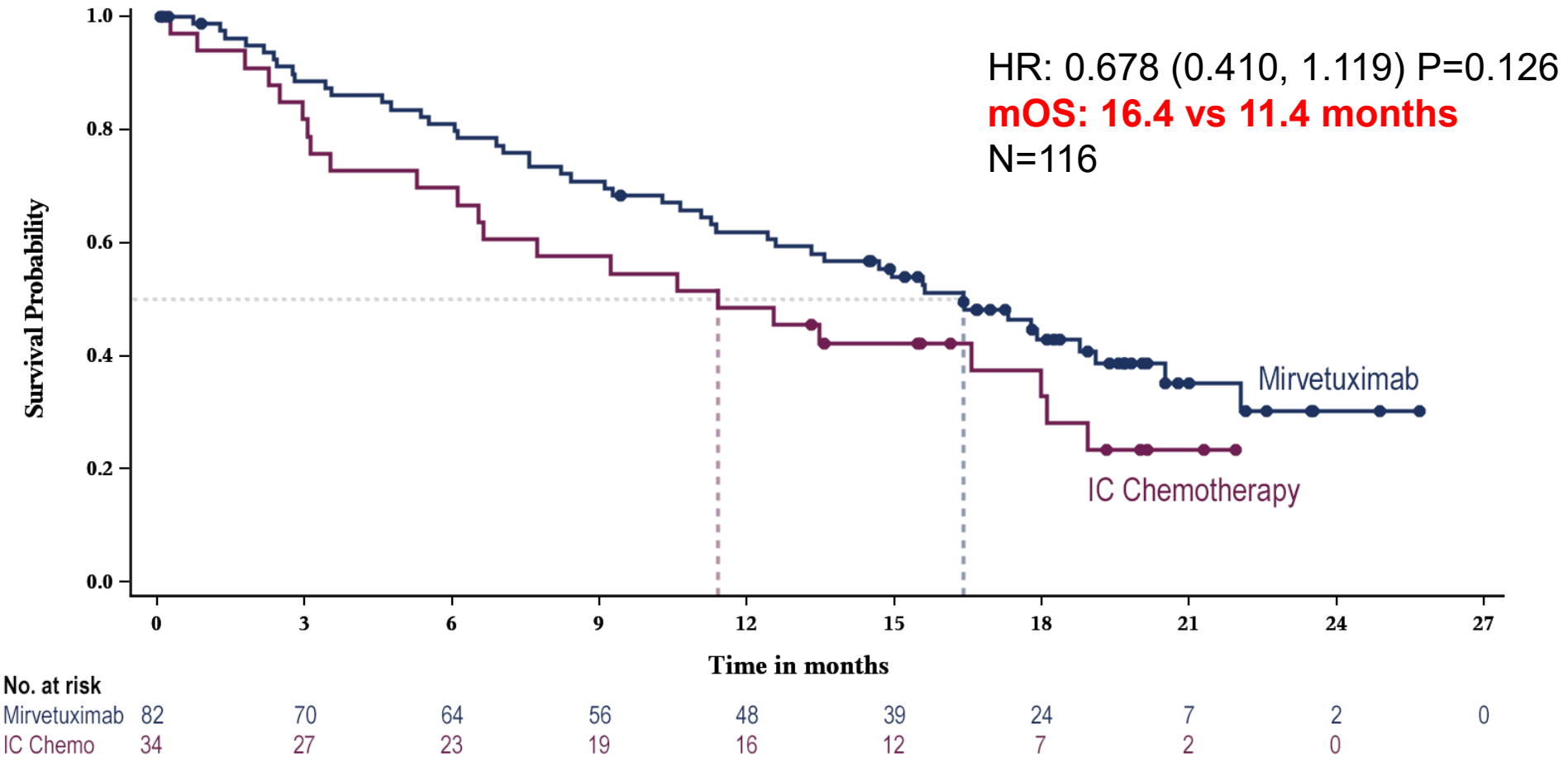
PFS (by BIRC) - FRα High (n=116)

HR: 0.549 P=0.015
mPFS: 5.6 vs 3.2 months



Moore et al. ESMO 2019
ClinicalTrials.gov Identifier: NCT02631876

PS2+ re-scoring: OS in FRα HIGH



Moore et al. ESMO 2019
ClinicalTrials.gov Identifier: NCT02631876

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Roche receives CE Mark for VENTANA FOLR1 (FOLR1-2.1) RxDx Assay as the first IHC-based companion diagnostic to identify ovarian cancer patients eligible for ELAHERE

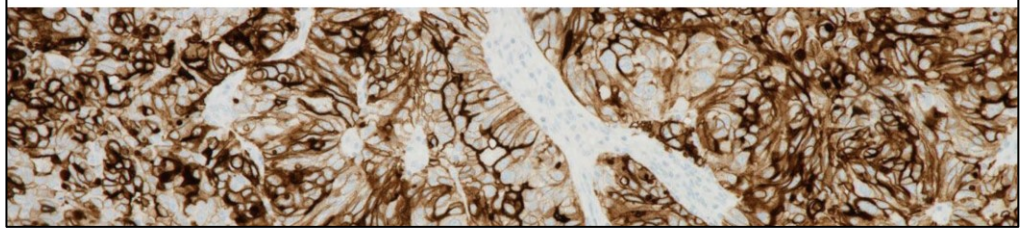


Table 11. Within-Reader and Between- Reader and Precision of VENTANA FOLR1 (FOLR1-2.1) RxDx Assay of EOC specimens.

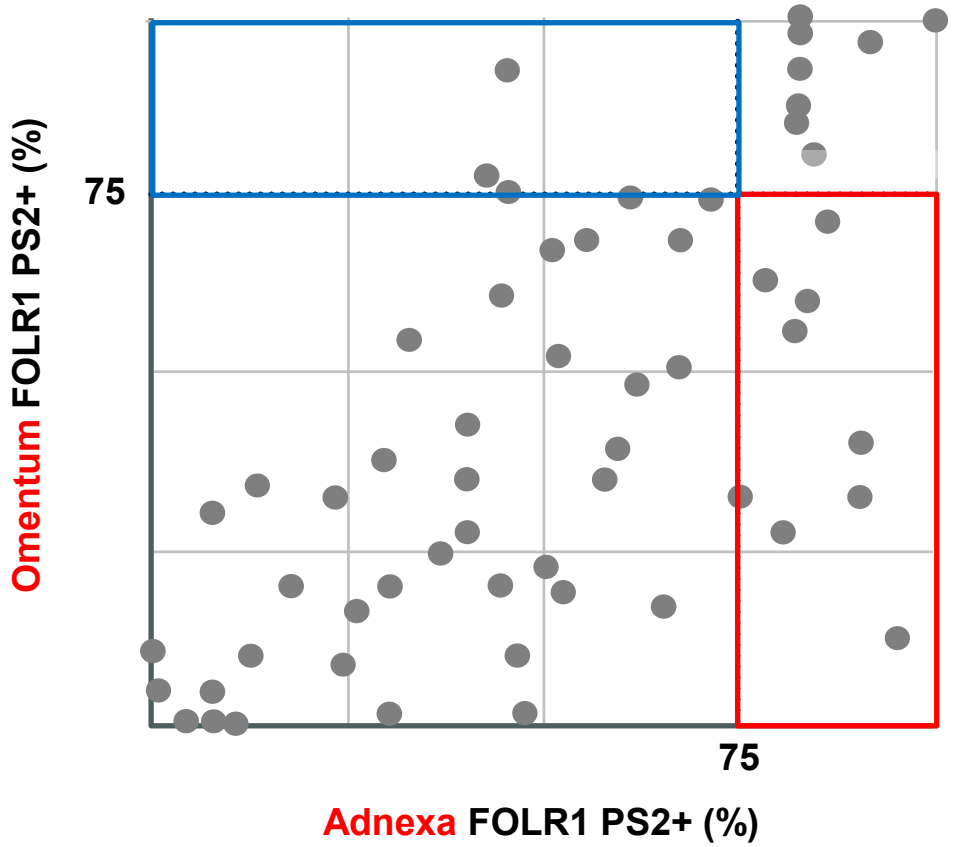
Precision	Agreement			
	Type	n/N	%	95% CI
Within-Reader	APA	286/295	96.9	(95.1, 98.6)
	ANA	296/305	97.0	(95.1, 98.7)
	OPA	291/300	97.0	(95.0, 98.7)
Between-Reader	APA	276/296	93.2	(89.4, 96.8)
	ANA	284/304	93.4	(89.9, 96.8)
	OPA	280/300	93.3	(90.0, 96.7)

Note: Average Positive Agreement (APA), Average Negative Agreement (ANA), Overall Percent Agreement (OPA).

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay insert
https://www.accessdata.fda.gov/cdrh_docs/pdf22/P220006C.pdf

But!

- FRα in Patient-Matched Primary vs Metastatic Lesions

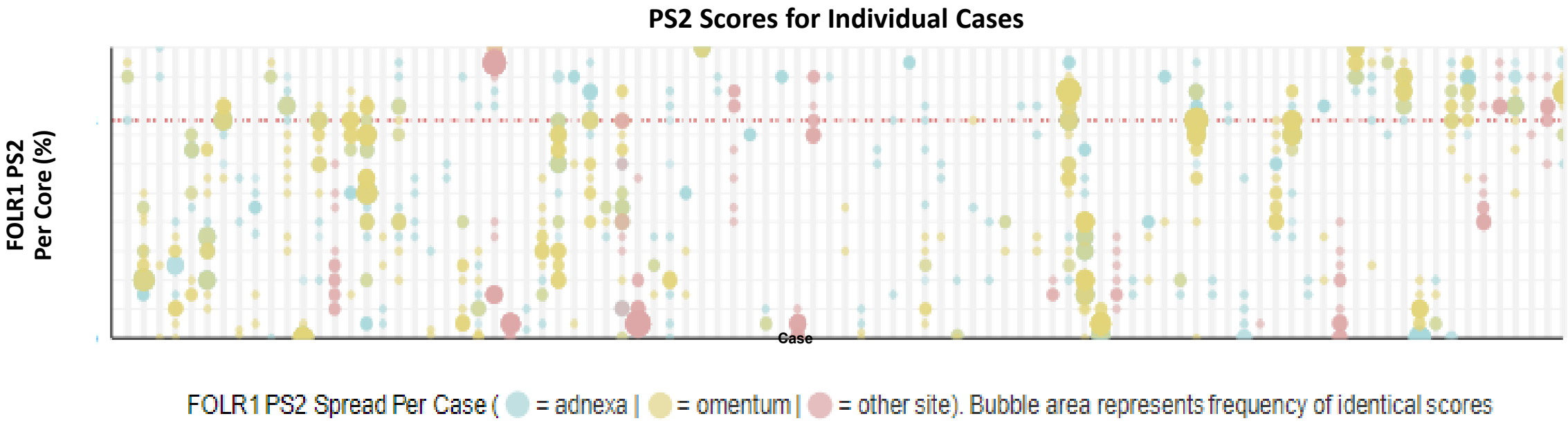


Matched Sample Summary		Correlation Coefficient
Cases with Matched Omental and Adnexal Tumor	59	
Average Omental FOLR1 PS2+ Score	50.6	0.65
Average Adnexal FOLR1 PS2+ Score	48.3	
	n/N (%)	
Cases with Concordant Results	46/59 (78)	
Cases with Discordant Results	13/59 (22)	
Positive to Negative	10/59 (17)	
Negative to Positive	3/59 (5)	

Deutschman E, et al. 36th European Congress of Pathology (ECP). 2024; Abs 2093 and poster.

But!

- FRα variation among specimens within the same biopsy



Core FOLR1 Result	Primary Tumor n (%)	Metastatic Tumor n (%)
Mixed	20 (27)	20 (34)
All Positive	16 (22)	7 (12)
All Negative	38 (51)	31 (53)

73%

66%

Deutschman E, et al. 36th European Congress of Pathology (ECP). 2024; Abs 2093 and poster.

What is next?

1. Views and experience of Prof. Dr. Philipp Harter, Evangelische Kliniken Essen-Mitte, Essen, Germany.

What is next?

- Platinum resistant disease
  - Combination with bevacizumab?

- Platinum sensitive disease
  - Monotherapy (platinum free regimen)?
  - Combination with carboplatinum?
  - Maintenance?

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FORWARD II

Phase 2: MIRV in combination with bevacizumab in platinum agnostic OC

- Histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube cancer
- Recurrent disease with up to 3 prior regimens
- FRα-positive tumor expression
  - Medium (≥ 50%, <75% TC at ≥2+ intensity)
  - High (≥75% TC at ≥2+ intensity)

→ MIRV + Bev (N=94)

- Primary Endpoint
  - Objective Response Rate
- Secondary Endpoints included
  - DOR
  - PFS
  - Safety

NCT02606305

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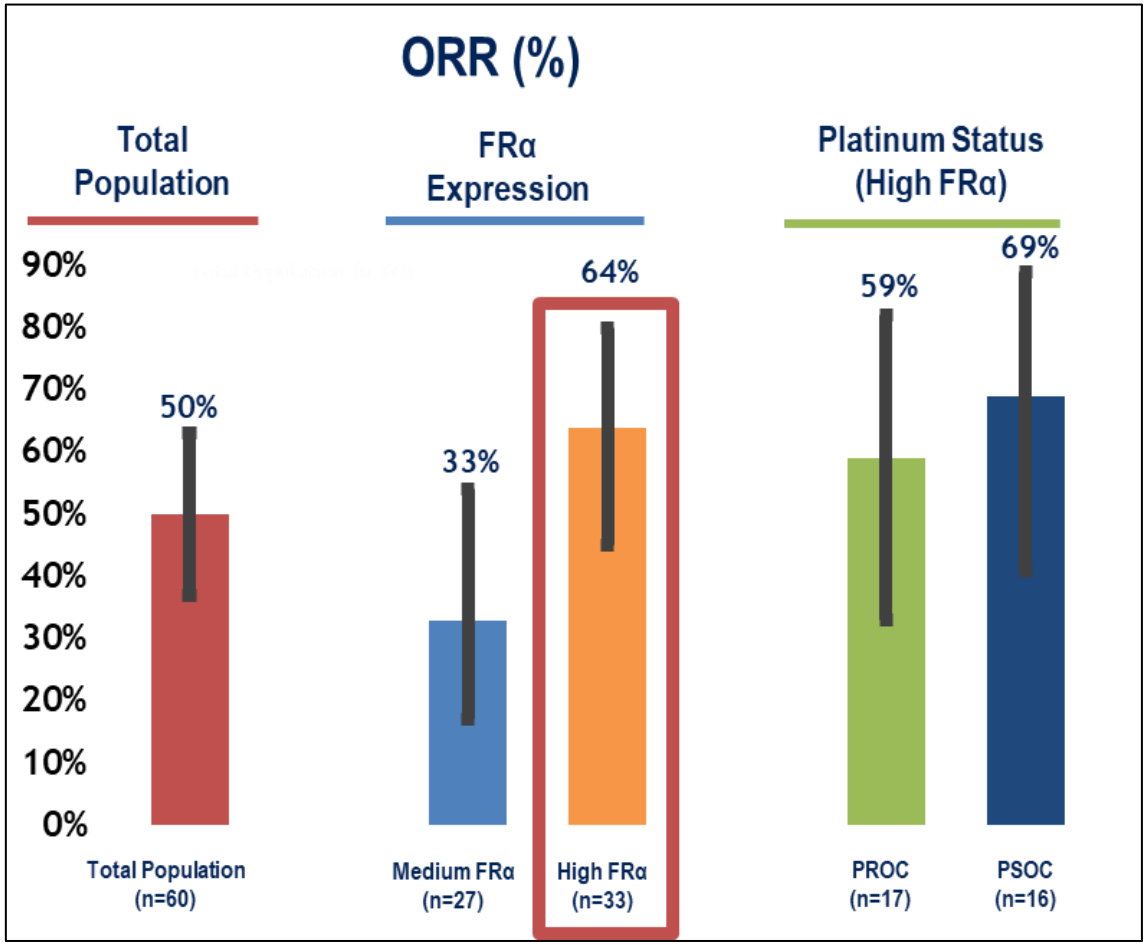
Gilbert L et al. *Gynecologic Oncology* 2023

FORWARD II

- Confirmed ORR by FRα Expression and Platinum Status

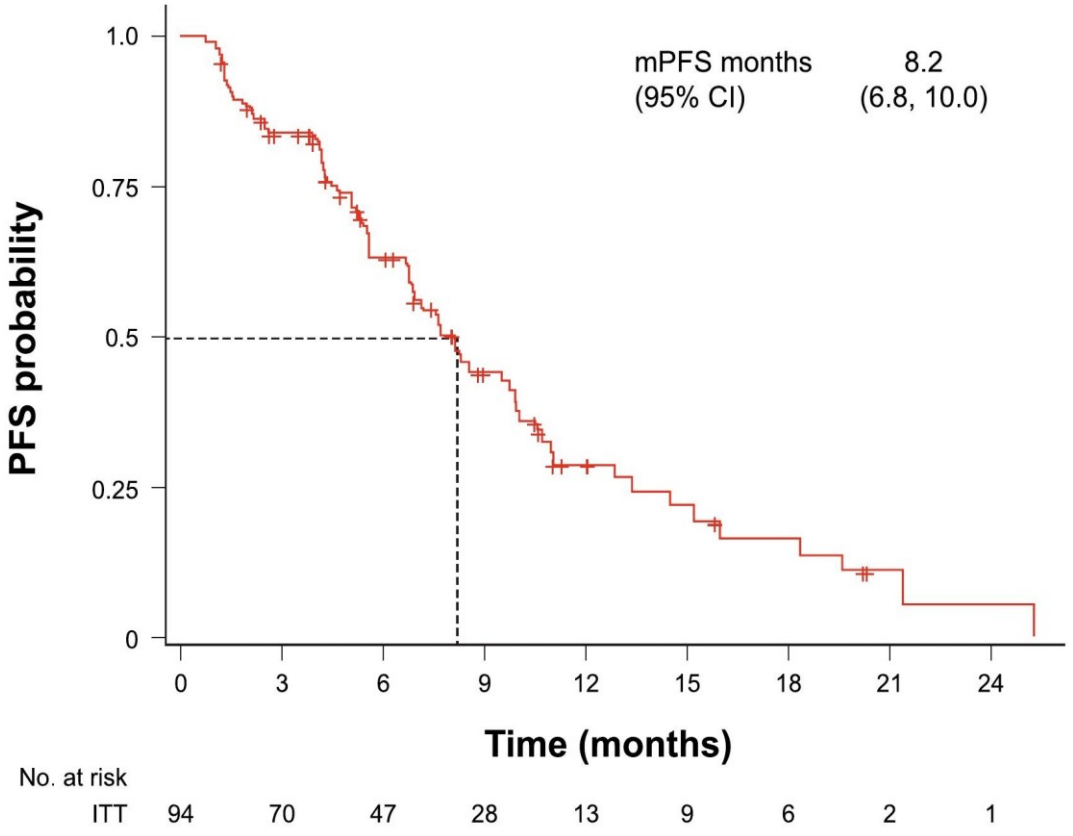


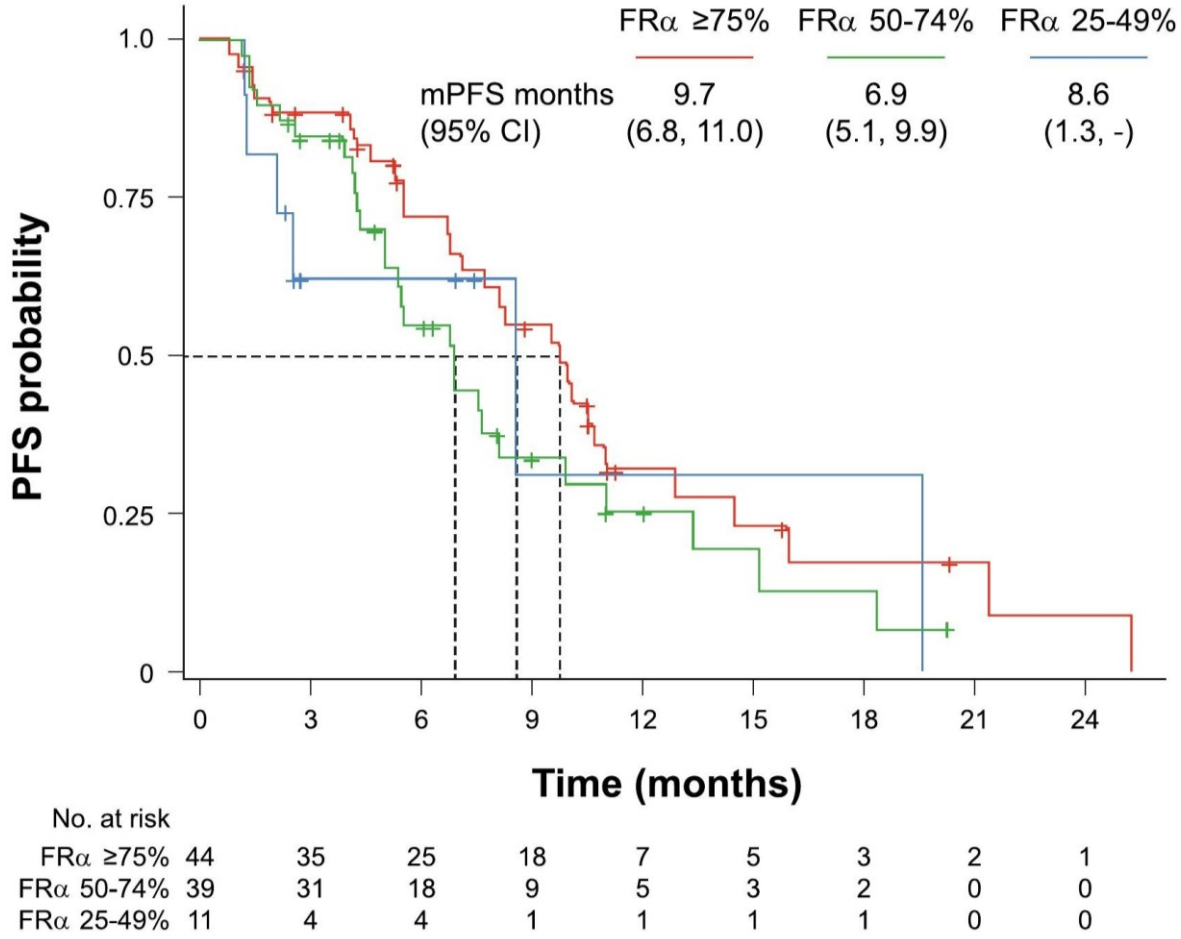
- **50% ORR** (30/60) for overall cohort
- **64% ORR** (21/33) in high FRα tumors
  - **59% ORR** (10/17) in PROC subset
  - **69% ORR** (11/16) in PSOC subset

O'Malley DM et al Gynecol Oncol 2020

FORWARD II

- Results: longer PFS in High FRα tumors





Gilbert L et al. *Gynecologic Oncology* 2023

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PICCOLO

A single-arm, open-label, phase 2 trial of MIRV in patients with ≥3L platinum-sensitive ovarian cancer with FRα-high expression

PICCOLO Patient Population

Enrollment and Key Eligibility

- **Platinum-sensitive disease** (defined as radiographic progression >6 months from last dose of most recent platinum therapy)
- **FRα high**, detected by IHC with PS2+ intensity among ≥75% of viable tumor cells[a]
- At least 2 prior platinum-containing regimens[b]
- Prior PARPi required if *BRCA*+
- Prior BEV not required
- Appropriate for single-agent therapy

Treatment Regimen

MIRV
(6 mg/kg AIBW Q3W)

N=79

Primary Endpoint

ORR by INV

Key Secondary Endpoint

DOR by INV

Other Secondary Endpoints

- Safety and tolerability
- CA-125 response (GCIG criteria)
- PFS
- OS
- Sensitivity analyses[c]

Alvarez Secord et al. ESMO 2024
ClinicalTrials.gov identifier: NCT05041257

Baseline Demographics and Characteristics

Characteristics	N=79
Age, median (range), years	66 (41-84)
Race, n (%)	
White	65 (82.3)
Black or African American	4 (5.1)
Asian	1 (1.3)
Not reported	8 (10.1)
Other	1 (1.3)
Number of prior lines of systemic therapy, n (%)	
1-2	49 (62.0)
≥3	30 (37.9)
Prior exposure to taxanes, n (%)	
Yes	77 (97.5)
Exposed in multiple lines	20 (25.3)
No	2 (2.5)

Characteristics	N=79
Prior exposure to PARPi,n (%)	
Yes	64 (81.0)
Progression	59 (74.7)
No progression	5 (6.3)
No	12 (15.2)
Prior exposure to bevacizumab, n (%)	
Yes	51 (64.6)
No	28 (35.4)
Platinum-free interval (months), n (%)	
≤12	43 (54.4)
>12	34 (43.0)

Of the 302 patients screened, 124 (44%) had ≥75% ≥2+ FRα tumor expression

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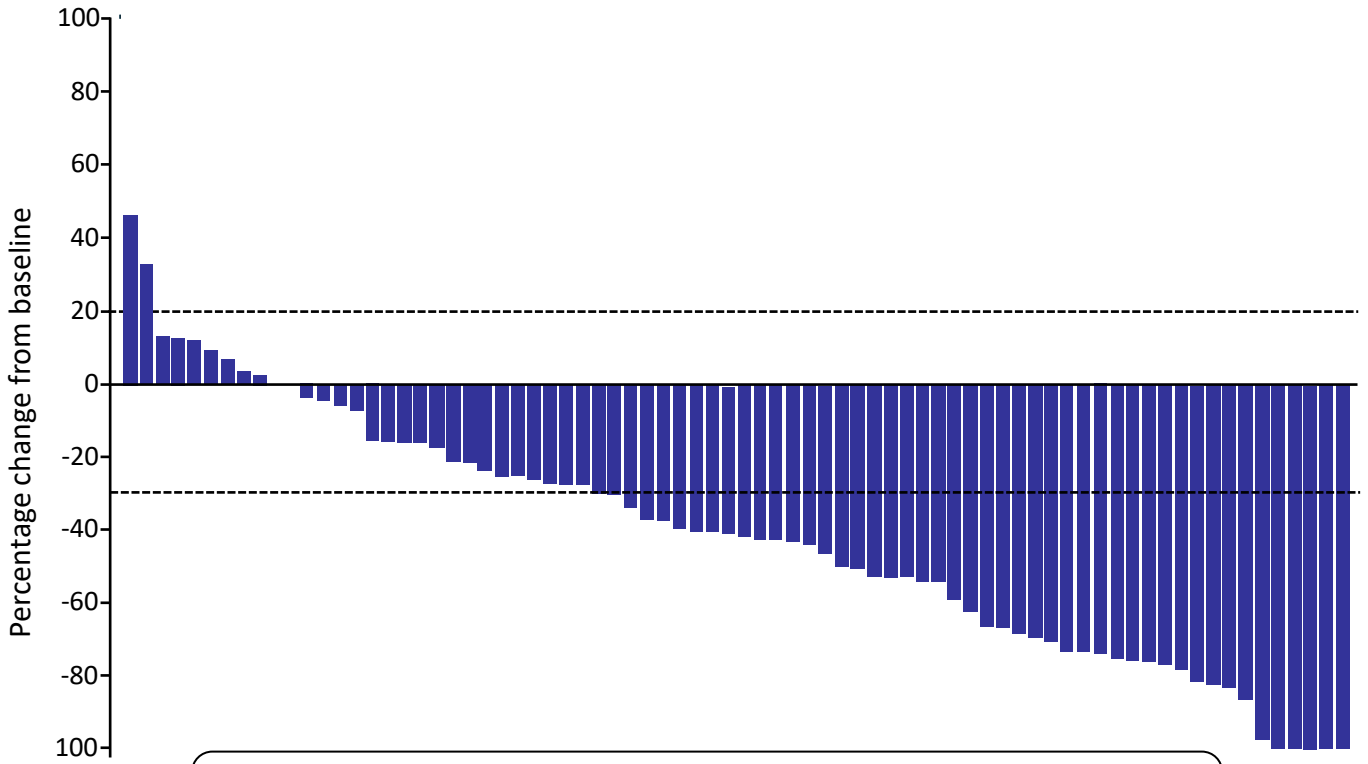
Alvarez Secord et al. ESMO 2024
ClinicalTrials.gov identifier: NCT05041257

Investigator-Assessed Efficacy Measures

Maximum Tumor Percentage Change From Baseline With MIRV



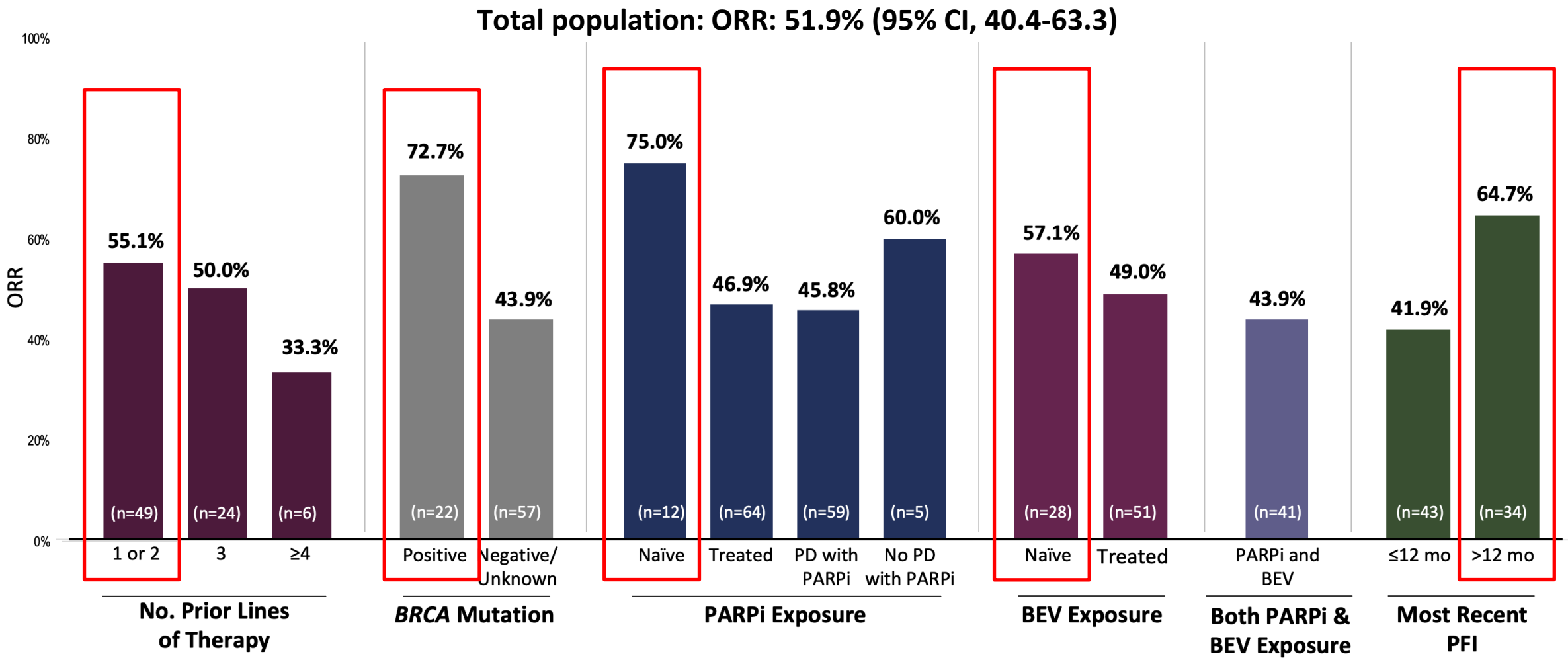
Median time to response was 1.58 months
Median number of treatment cycles was 9 (range, 1 to 27)

Primary Endpoint	N=79
ORR, n (%) (95% CI)	41 (**51.9**) 40.4-63.3
Best overall response, n (%)	
CR	6 (7.6)
PR	35 (44.3)
SD	29 (36.7)
PD	7 (8.9)
Not evaluable	2 (2.5)

Secondary Endpoints	
Median DOR: months (95% CI)	**8.25** (5.55-10.78)
Median PFS: months (95% CI)	**6.93** (5.85-9.59)

Alvarez Secord et al. ESMO 2024
ClinicalTrials.gov identifier: NCT05041257

ORR by Subgroups



Alvarez Secord et al. ESMO 2024
ClinicalTrials.gov identifier: NCT05041257

What is next?

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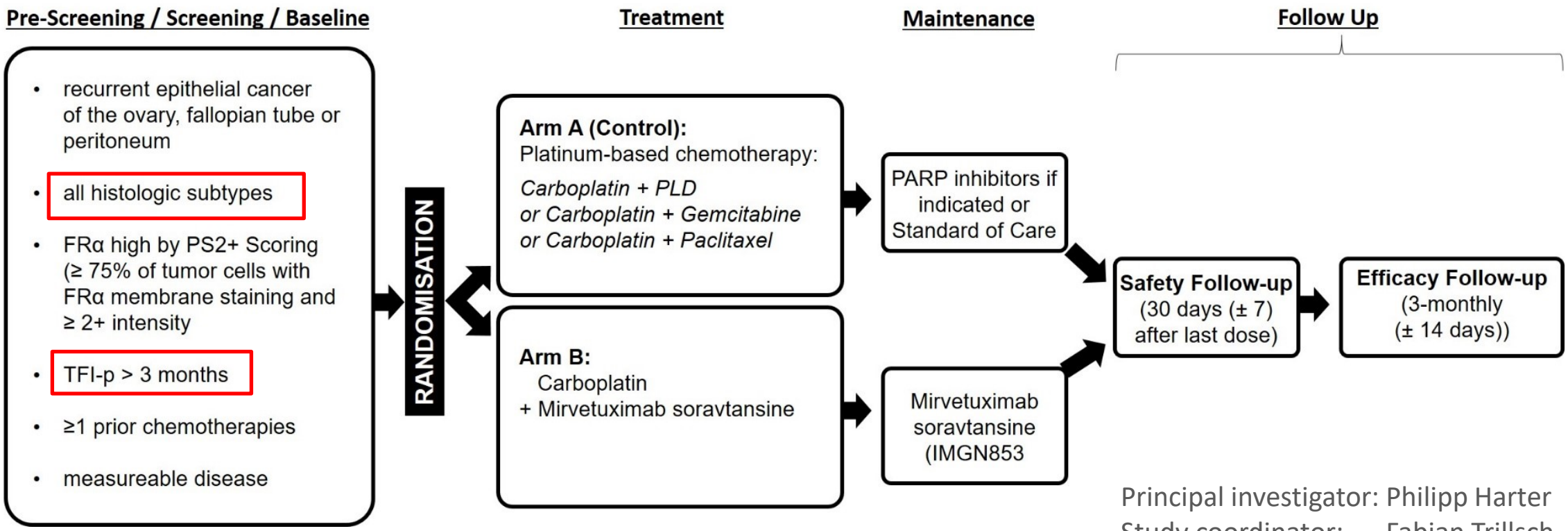
  - Combination with carboplatinum?
  - Maintenance?

AGO-OVAR 2.34 (MIROVA): Study design



Principal investigator: Philipp Harter
Study coordinator: Fabian Trillsch
Status: Follow up

FRα, folate receptor alpha; PLD, pegylated liposomal doxorubicin; PS2+, positive staining intensity ≥2; TFI-p, platinum therapy-free interval.

1. NCT04274426. Accessed on 6.4.2024 from https://www.clinicaltrials.gov/study/NCT04274426. 2. Trillsch F, et al. European Society of Gynaecological Oncology (ESGO) Congress. 2022; Abs 2022-RA-835-ESGO and poster presentation.

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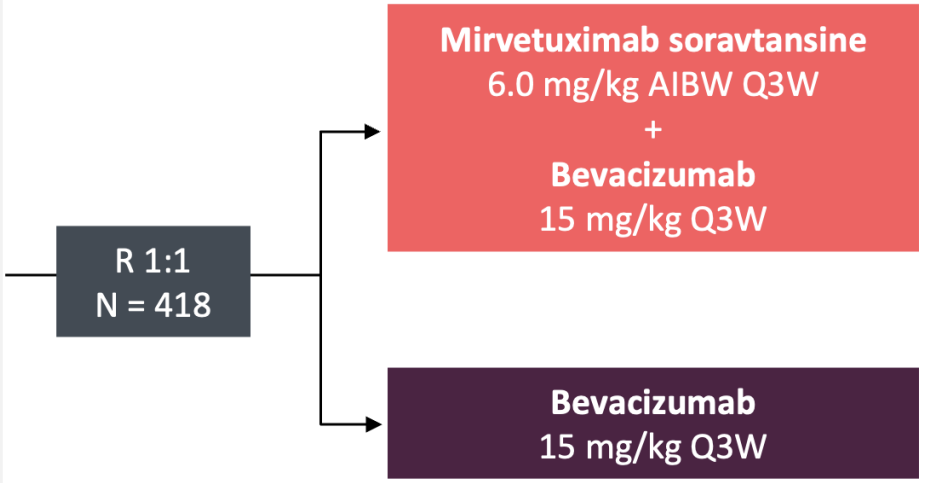
  - Maintenance?

GLORIOSA

MIRV + Beva maintenance in FRα-high, platinum-sensitive disease

Eligible patients

- High-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer
- **Relapsed after 1L platinum-based chemo**
  - **Platinum-sensitive disease** (PFI >6 months)
  - 1L PARPi maintenance required if *BRCA*m
- Appropriate for, **currently receiving, or completed 2L platinum-based triplet therapy**
  - **CR, PR, or SD** after 2L platinum-based triplet, which included ≥3 cycles of bevacizumab
  - Randomized ≤8 weeks from the last dose of 2L platinum-based triplet therapy
- **FRα-high** by IHC with PS2+ intensity in ≥75% of viable tumour cells



Stratification

- Prior PARPi
- Prior bevacizumab
- CR, PR or SD

Primary endpoint

- PFS

Key Secondary endpoint

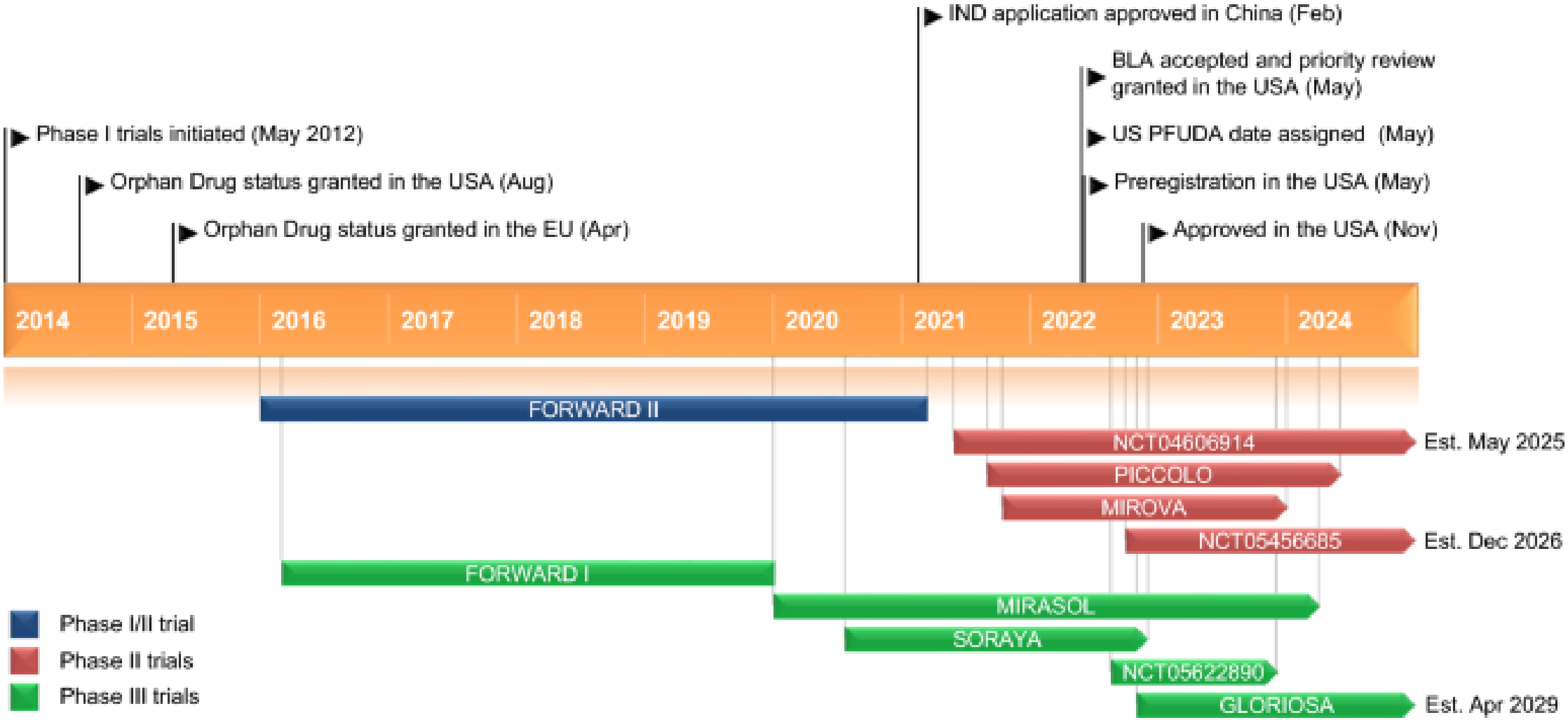
- OS

Other Secondary endpoints

- Safety and tolerability
- PFS2
- ORR
- DOR
- DFS
- CA-125 response by GCIG criteria
- PROs

NCT05445778

O'Malley DM, et al. ASCO 2023; Abs TPS5622 and poster



Heo YA. Drugs 2023;83:265–273.

Conclusions

- Mirvetuximab soravtansine has shown an PFS and OS benefit in platinum-resistant ovarian cancer

- Multiple further trials with drugs targeting FRα are ongoing or under development

- Areas of interest:
  - Efficacy in a broader patient population regarding FRα status
  - Efficacy in earlier lines of therapy

Questions?

Targeting FRα: Management of Adverse Events

Prof. Dr. T. Van Gorp

Div. Gynaecological Oncology

Leuven Cancer Institute

University Hospital Leuven, Belgium

LGOG UZ LEUVEN KU LEUVEN BGOG ENGOT European Network of Gynaecological Oncological Trial groups

Disclosures

All payments institutional

- **Consulting/Advising**
  - AbbVie, AstraZeneca, BioNTech, Cancer Communications and Consultancy Ltd, Daiichi Sankyo, Eisai, GSK, ImmunoGen, Incyte, Karyopharm, MSD/Merck, OncXerna Therapeutics, Seagen, Tubulis, Zentalis
- **Honoraria for lectures**
  - AbbVie, AstraZeneca, Eisai, GSK, ImmunoGen, MSD
- **Travel, accommodations, and/or expenses**
  - AstraZeneca, GSK, ImmunoGen, MSD, and PharmaMar
- **Research funding**
  - Amgen, AstraZeneca, and Roche
- **Leadership in a society, committee or advocacy group, paid or unpaid**
  - Chair of the Belgian and Luxembourg Gynaecological Oncology Group (BGOG) (unremunerated)

ENGOT-ov55/MIRASOL

Phase 3 registration trial for Mirvetuximab Soravtansine 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

Prior 1L: 3-6m
Prior 2-3L: <6m

Statistical Assumptions

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

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

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

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

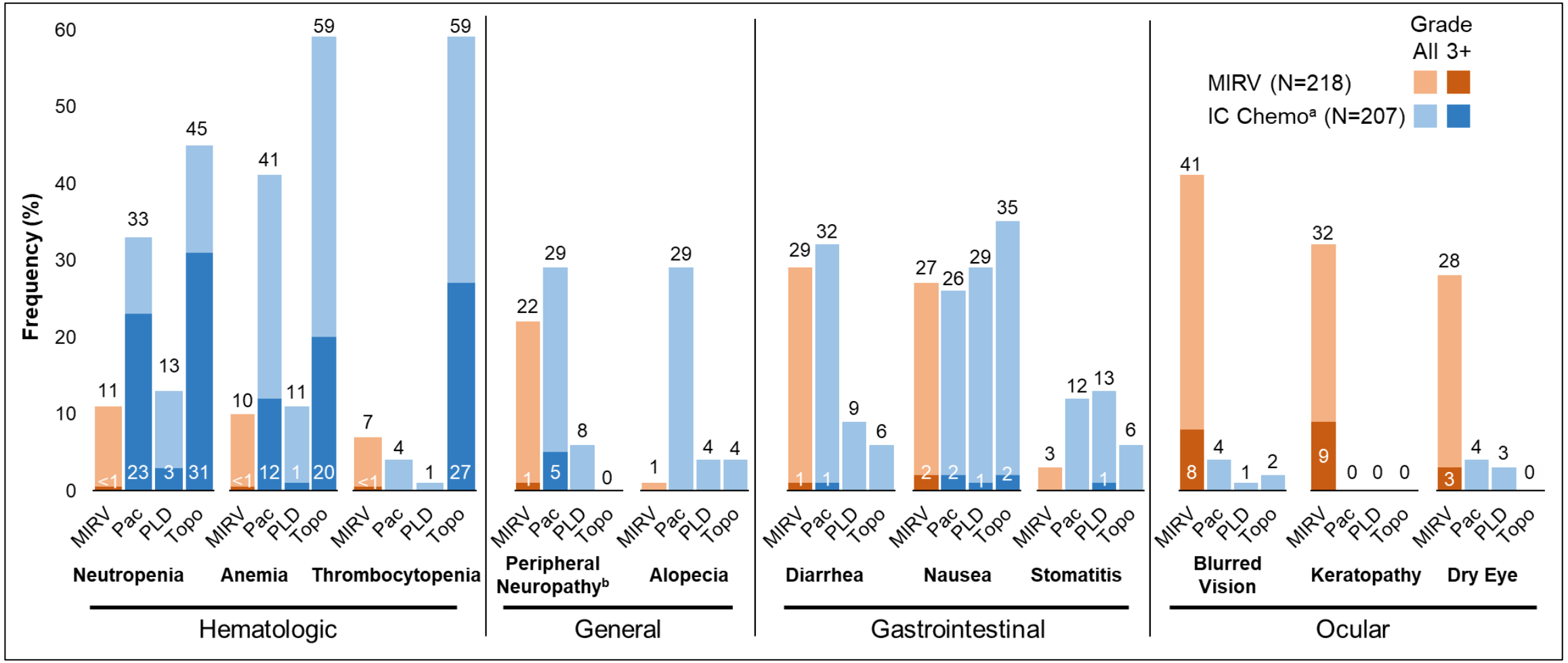
Safety summary

	MIRV (n=218)	IC Chemo (n=207)
Any TEAE, n (%)	210 (96)	194 (94)
Grade 3+ TEAEs, n (%)	91 (**42**)	112 (**54**)
SAEs, n (%)	52 (**24**)	68 (**33**)
Deaths on study drug or <30 days of last dose, n (%)	5 (2)	5 (2)
Dose reductions due to TEAEs, n (%)	74 (34)	50 (24)
Dose delays due to TEAEs, n (%)	117 (54)	111 (54)
Discontinuations due to TEAEs, n (%)	20 (**9**)	33 (**16**)

Data cutoff: March 6, 2023. The safety population comprises all patients who received at least one dose of MIRV or IC Chemo. TEAEs, treatment-emergent adverse events; SAEs, serious adverse events; MIRV, mirvetuximab soravtansine; IC, investigator's choice chemotherapy.

Treatment-Emergent Adverse Events

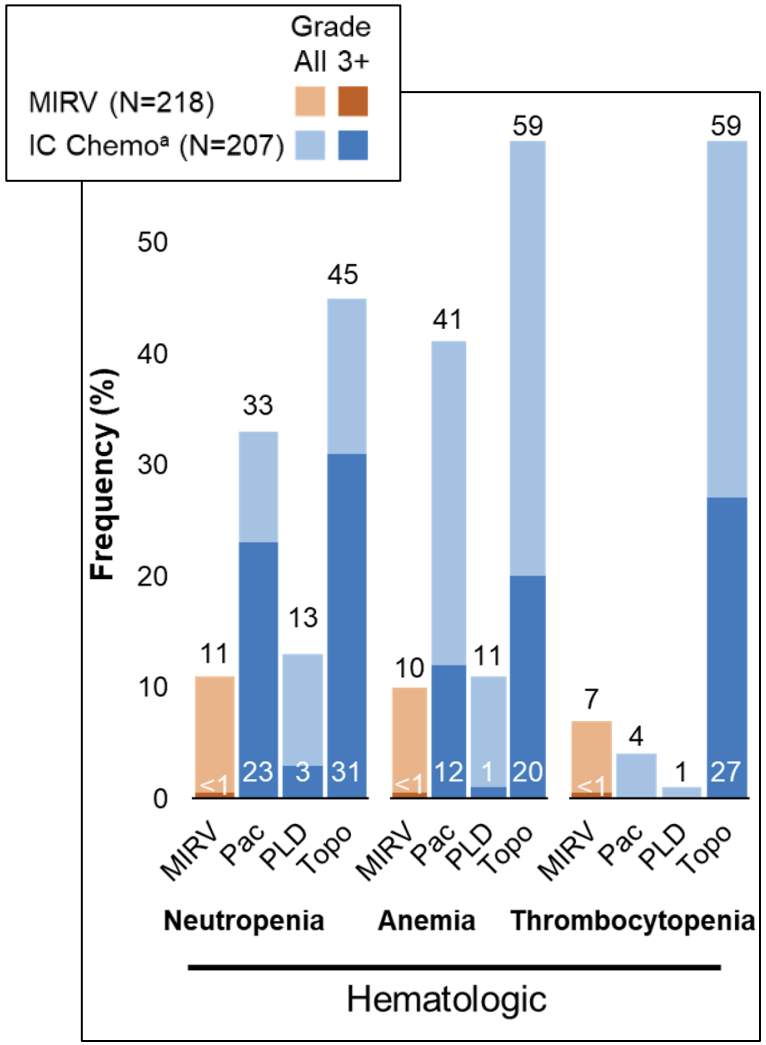
Differentiated Safety Profile



ClinicalTrials.gov identifier: NCT04209855

Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

Hematologic



- Off-target cytotoxic damage into hematopoietic stem cells of the bone marrow

- Incidence < 12%
- Mostly Grade 1-2

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

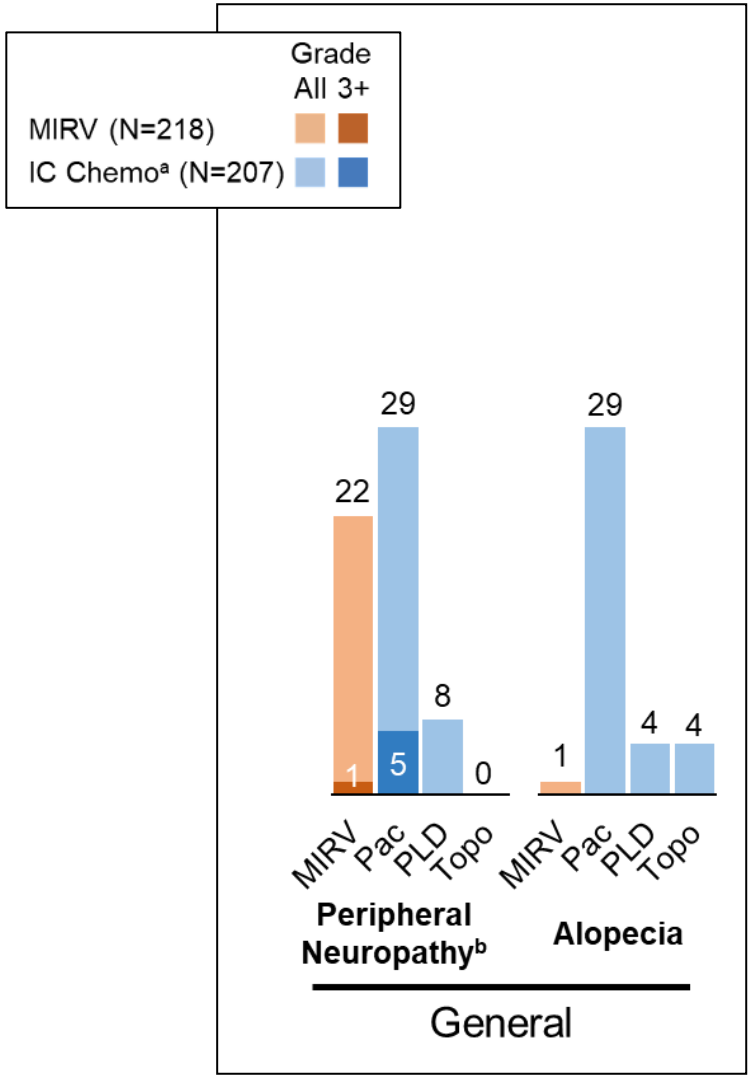
Hematologic

Dose modifications

- Criteria to receive Mirv:
  - ANC ≥ 1.5x10^9/L
  - Plat. count ≥ 80 x 10^9/L

Severity Grade (CTCAE v4.03)	**Dose Modifications for IMGN853**
Hematological	
Neutropenia	
Grade 2 and Grade 3	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /µL) and resume at the same dose level
Grade 4	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /µL) and then resume at a lower dose level
Febrile neutropenia Grade 3 or 4 (with a single temperature reading ≥ 38.3°C or a sustained temperature of > 38°C for > one hour)	Hold drug until ANC is ≥ 1.5 x10^9/L (1500 /µL) and then resume at a lower dose level
Thrombocytopenia	
Grade 2 and Grade 3	Hold drug until Platelet count is ≥ 80 x 10^9/L (80,000/µL) and resume at same dose level
Grade 3 associated with clinically significant bleeding that requires transfusion therapy and Grade 4	Hold drug until Platelet count is ≥ 80 x 10^9/L (80,000/µL) and then resume at a lower level

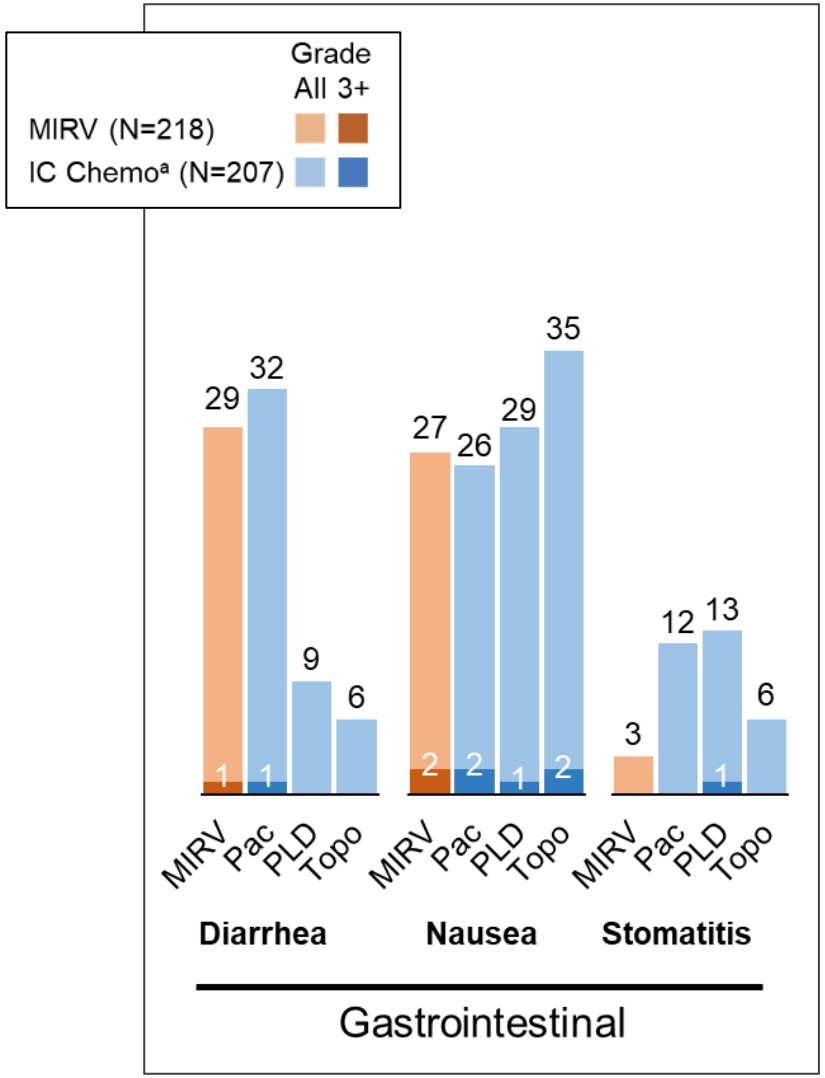
Peripheral neuropathy and alopecia



- Peripheral neuropathy
  - Off-target: Non-specific uptake of ADC in peripheral nerves and release of payload.
  - AE of all microtubule inhibitors such DM1, DM4, MMAE, and MMAF
  - Mirv 22 % ↔ Pac 29%
    - Mostly Grade 1-2
    - G3+: Mirv only 1% ↔ Pac 5%
  - Dose reduction was considered in the case of G2 interfering patient's normal life
- Almost no alopecia!

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

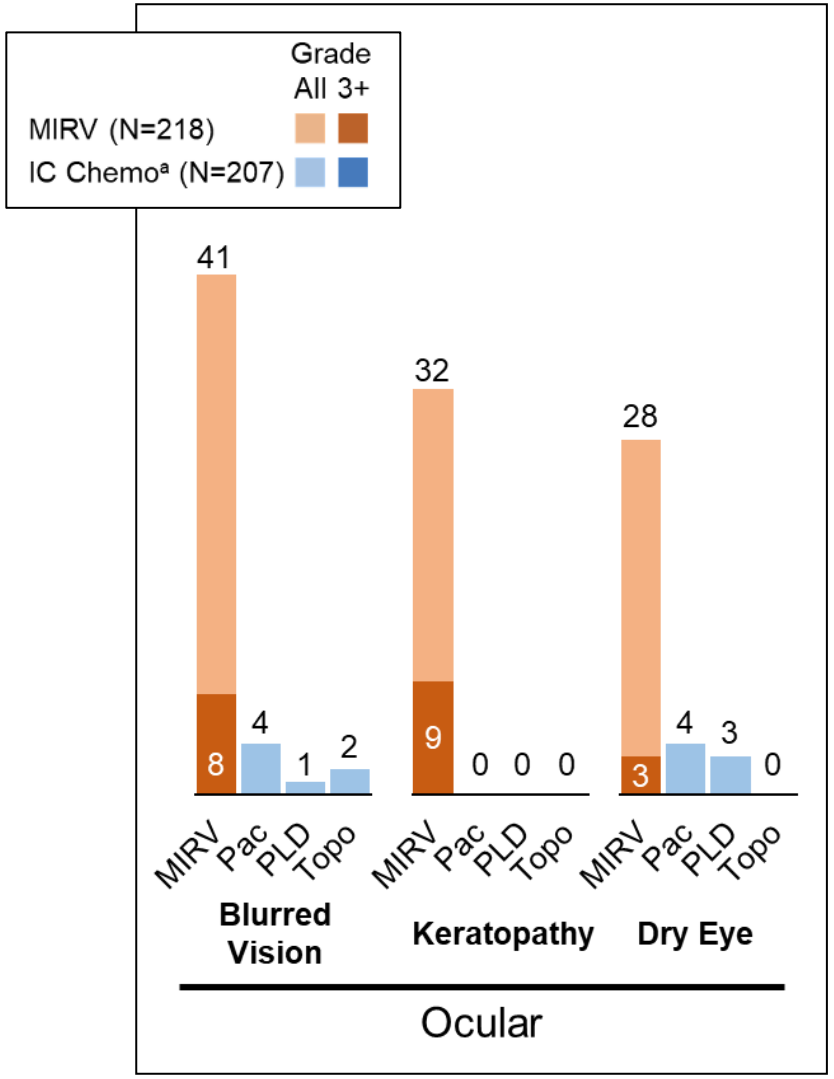
Gastro-intestinal



- Off-target effect
  - ∽ standard chemo
- Incidence 27-29 %
- Mostly Grade 1-2 (only 1-2% G3+)
- In the case of G3 despite optimal use of anti-emetic or anti-diarrheal treatment: Drug was held until resolution to < G1, then resumed at a lower level

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

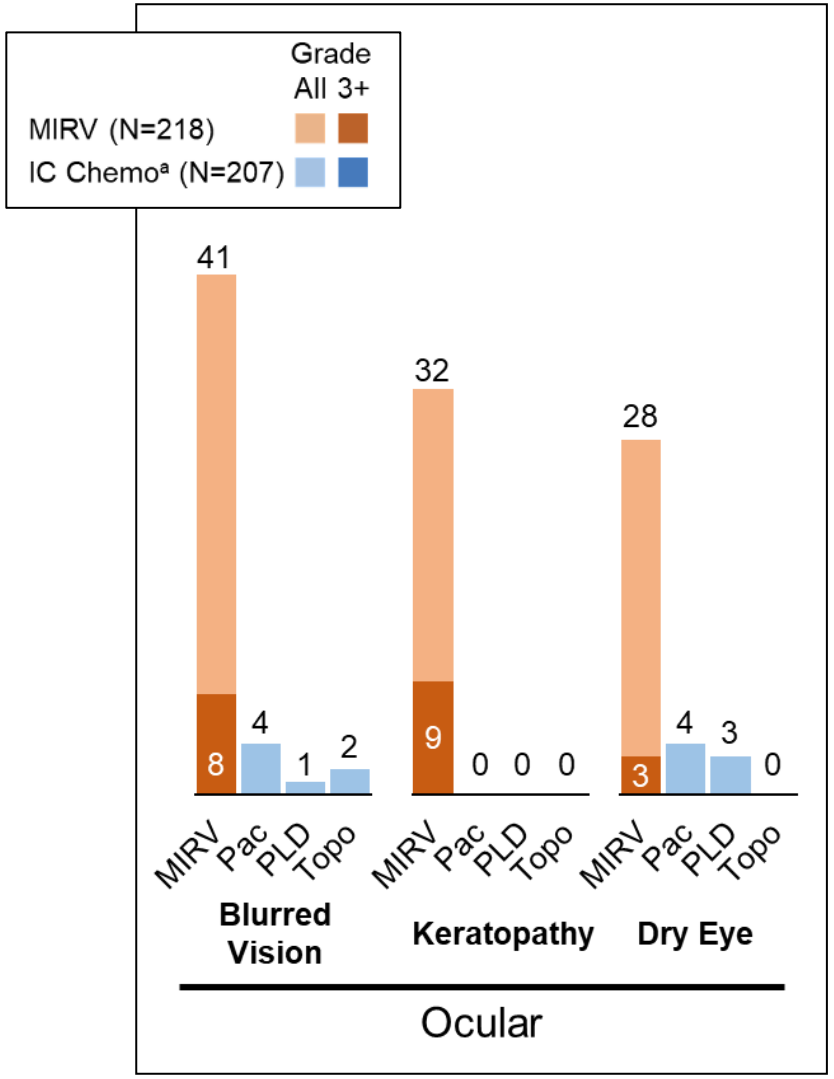
Ocular

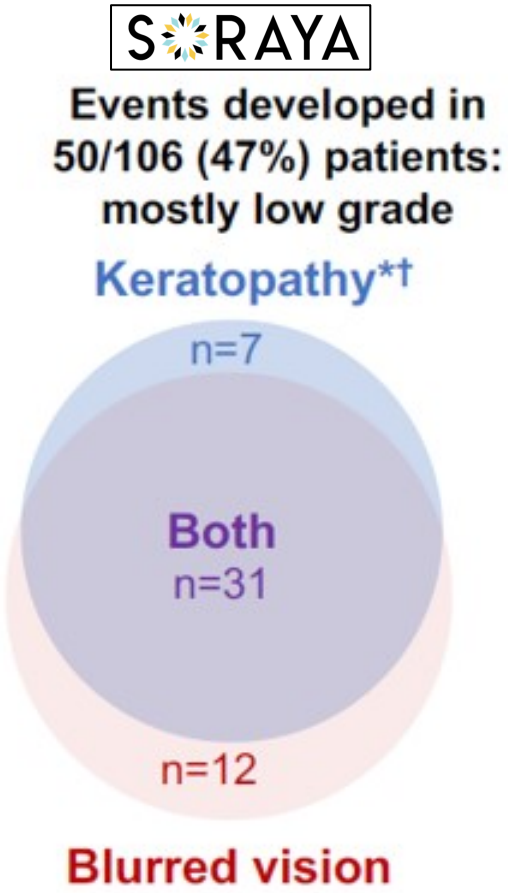


- Off-target toxicity
  - There is no FRα expression in corneal epithelial tissues
- Significant more frequent with MIRV compared to IC Chemo
- Among the most common AEs in pts treated w/ MIRV (59%)
- Predominantly G1-2

ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174

Ocular

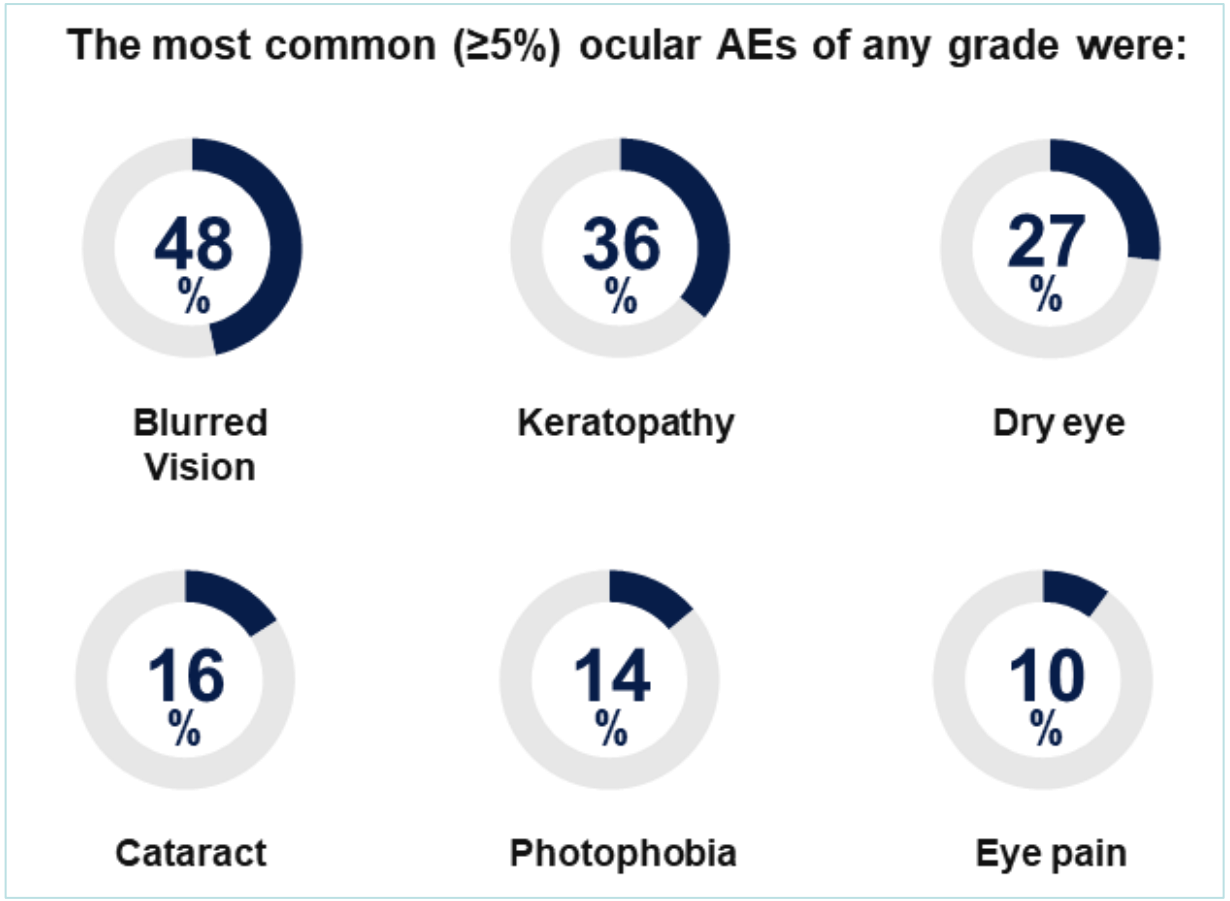




ClinicalTrials.gov identifier: NCT04209855
Moore KN et al. ASCO 2023
Moore KN et al. N Engl J Med. 2023;389(23):2162-2174
Matulonis et al. SGO 2022
Matulonis et al. J Clin Oncol 2023;41(13):2436-45

Ocular

Pooled safety analysis of **4 clinical trials** which involved **682** patients with FRα positive rOC



Rehim S et al. 2023

Ocular

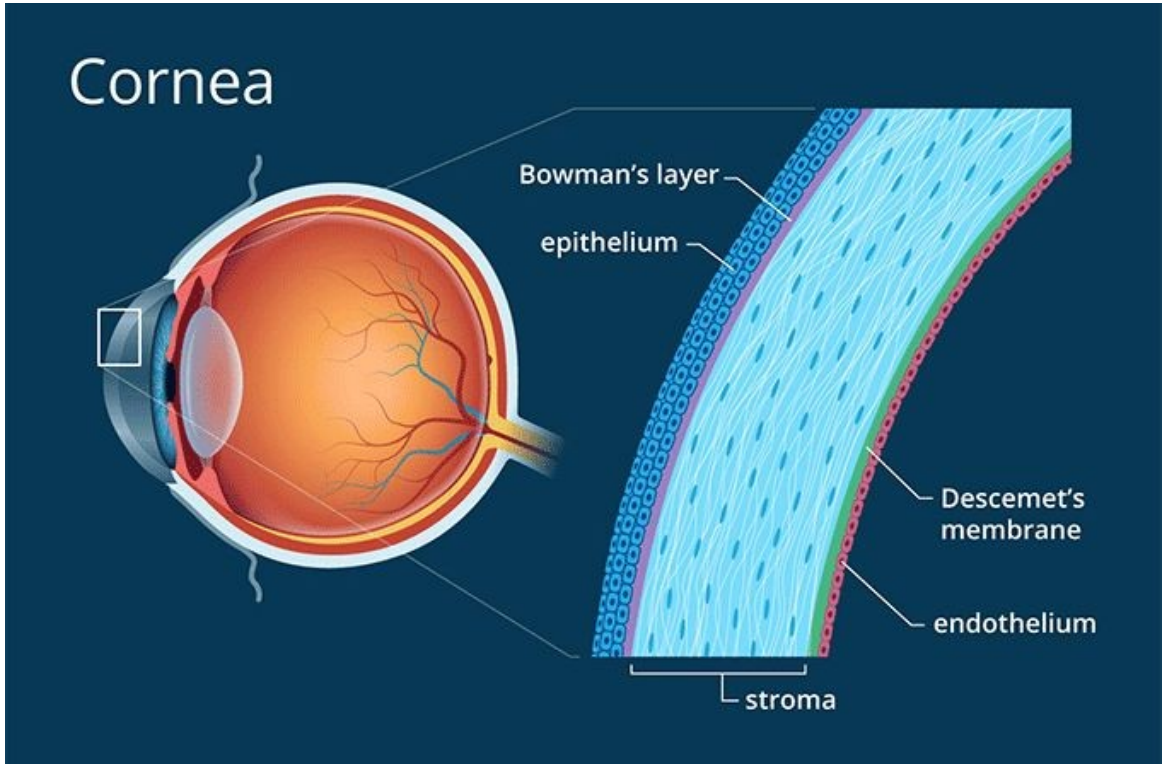
Pooled safety analysis of **4 clinical trials** which involved **682** patients with FRα positive rOC

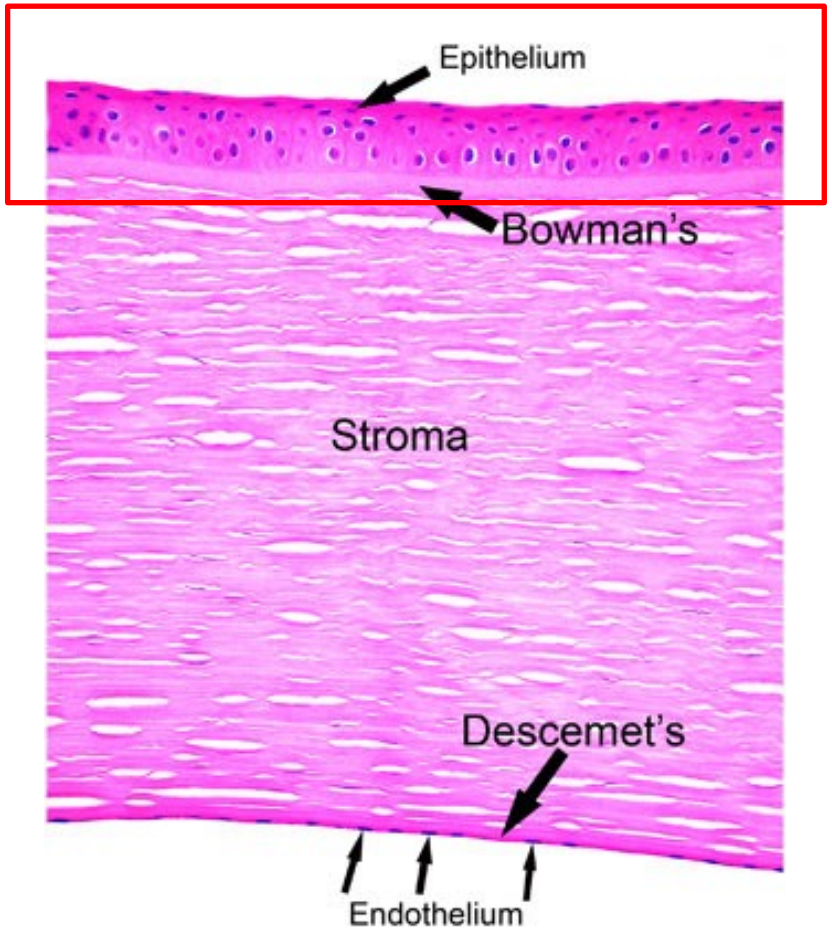
	Integrated Safety Summary (N=682)
Participants with ocular AEs	**N= 405**
Action taken due to ocular AEs	
No dosing-related action taken	221 (55%)
Dose delayed/not given or interrupted	174 (**43%**)
Dose reduced	105 (**26%**)
Permanent discontinuation	8 (**2%**)

Rehim S et al. 2023

Ocular

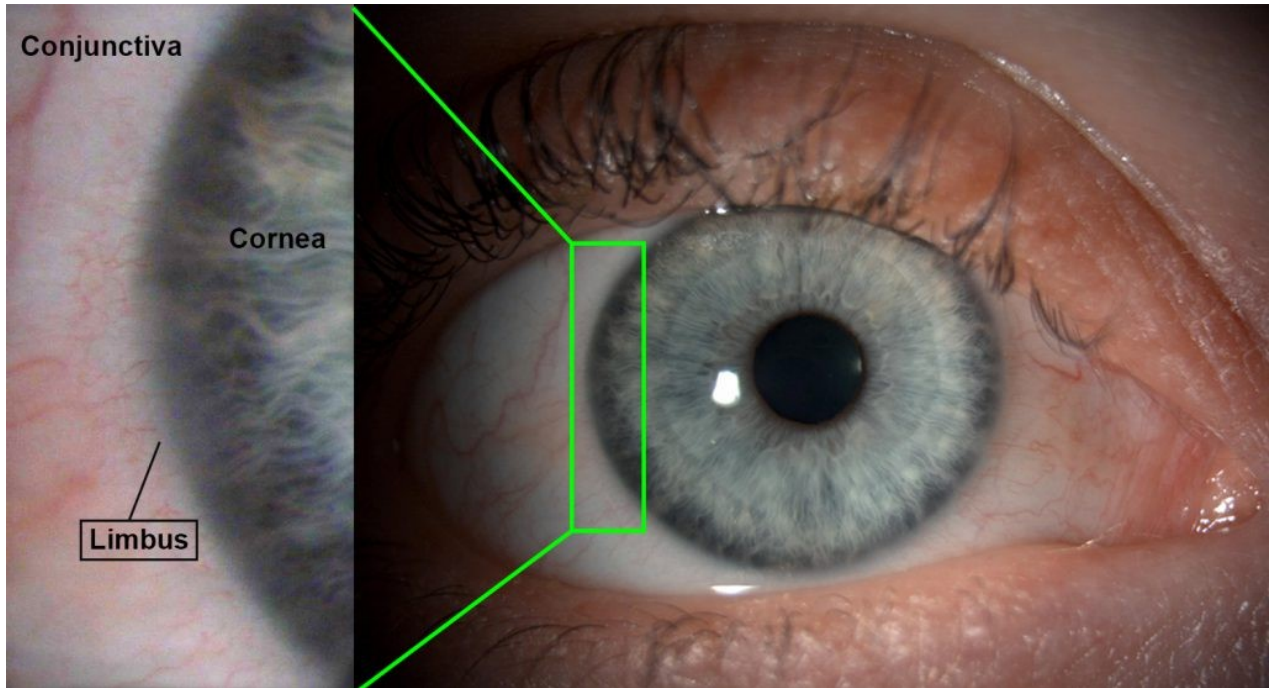
- Mechanism

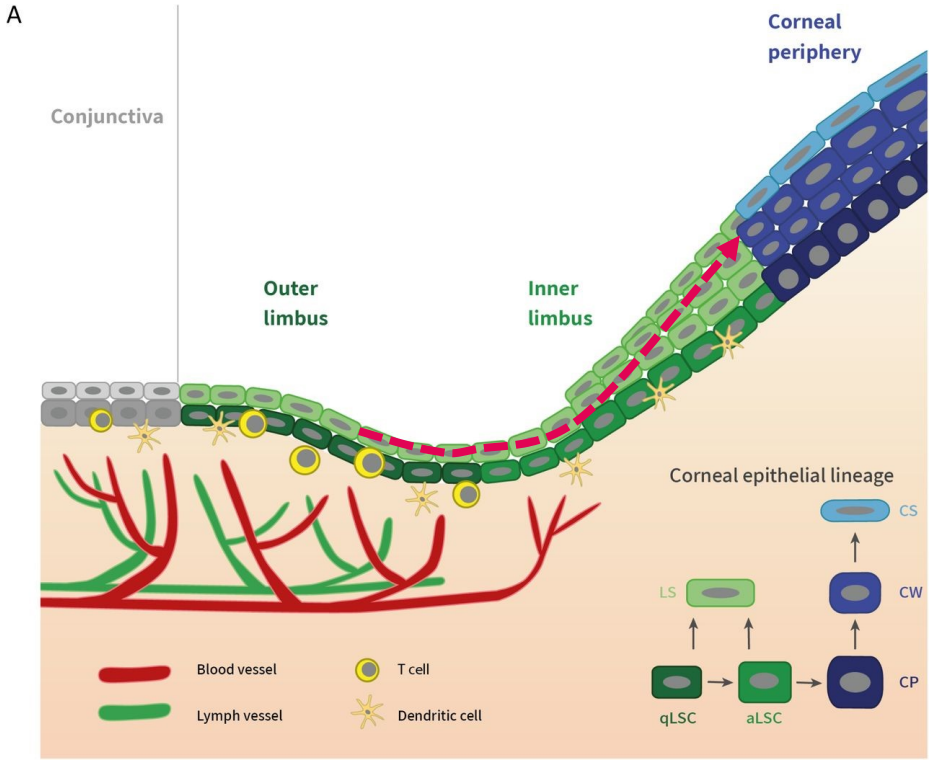




Ocular

- Mechanism





The limbus provides a reservoir of stem cells for the regeneration corneal epithelium.

Ocular

- Mechanism

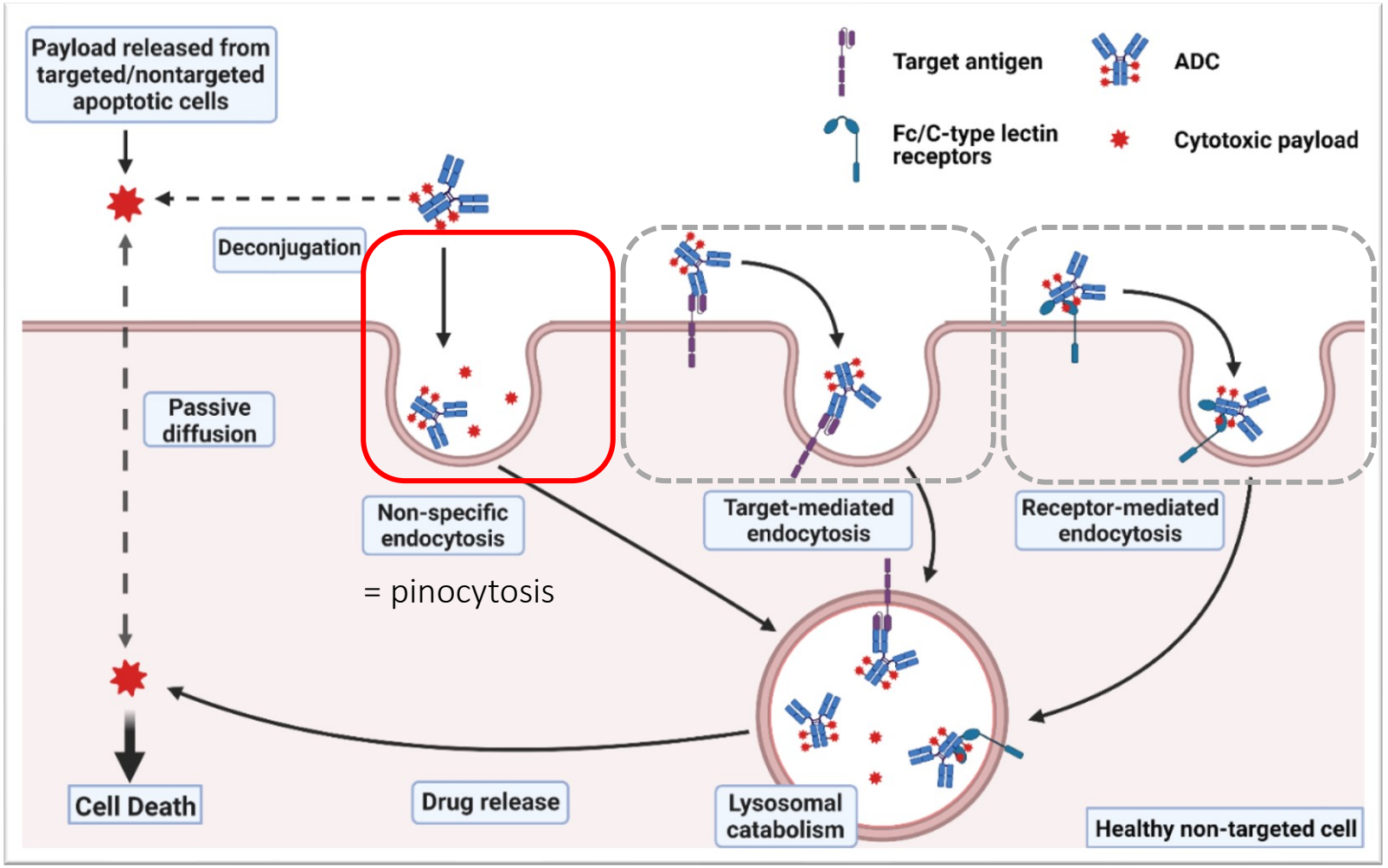
Pinocytosis in limbal cells
= the non-specific uptake into large cytoplasmatic vesicles

↓

Payload toxicity

↓

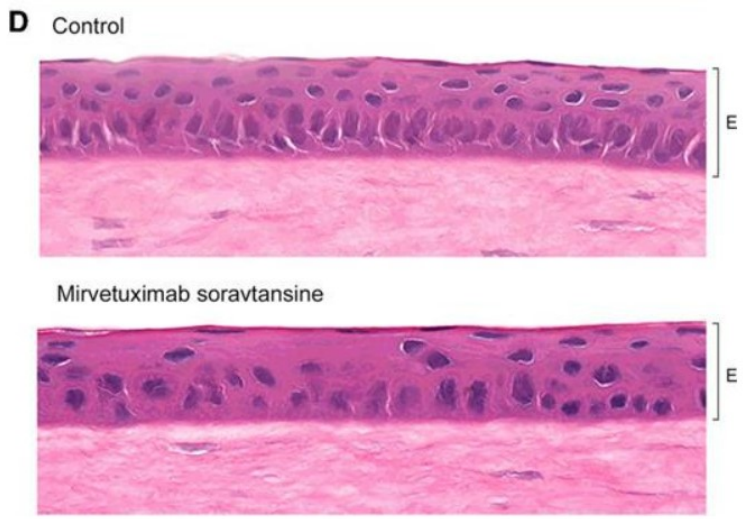
Microcysts



Nguyen et al. Cancers. 2023; 15(3):713.

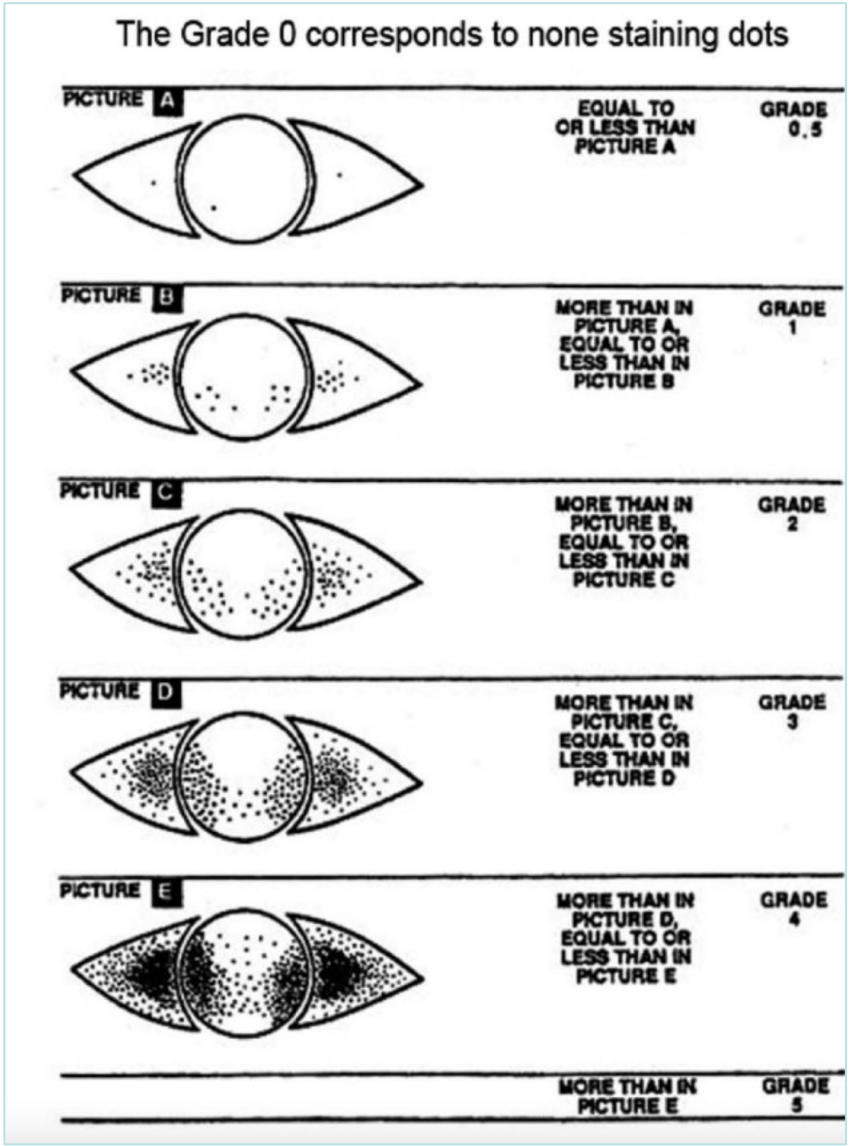
Ocular

- Mechanism



Deeper corneal layers are not affected
(stroma, endothelial layer)

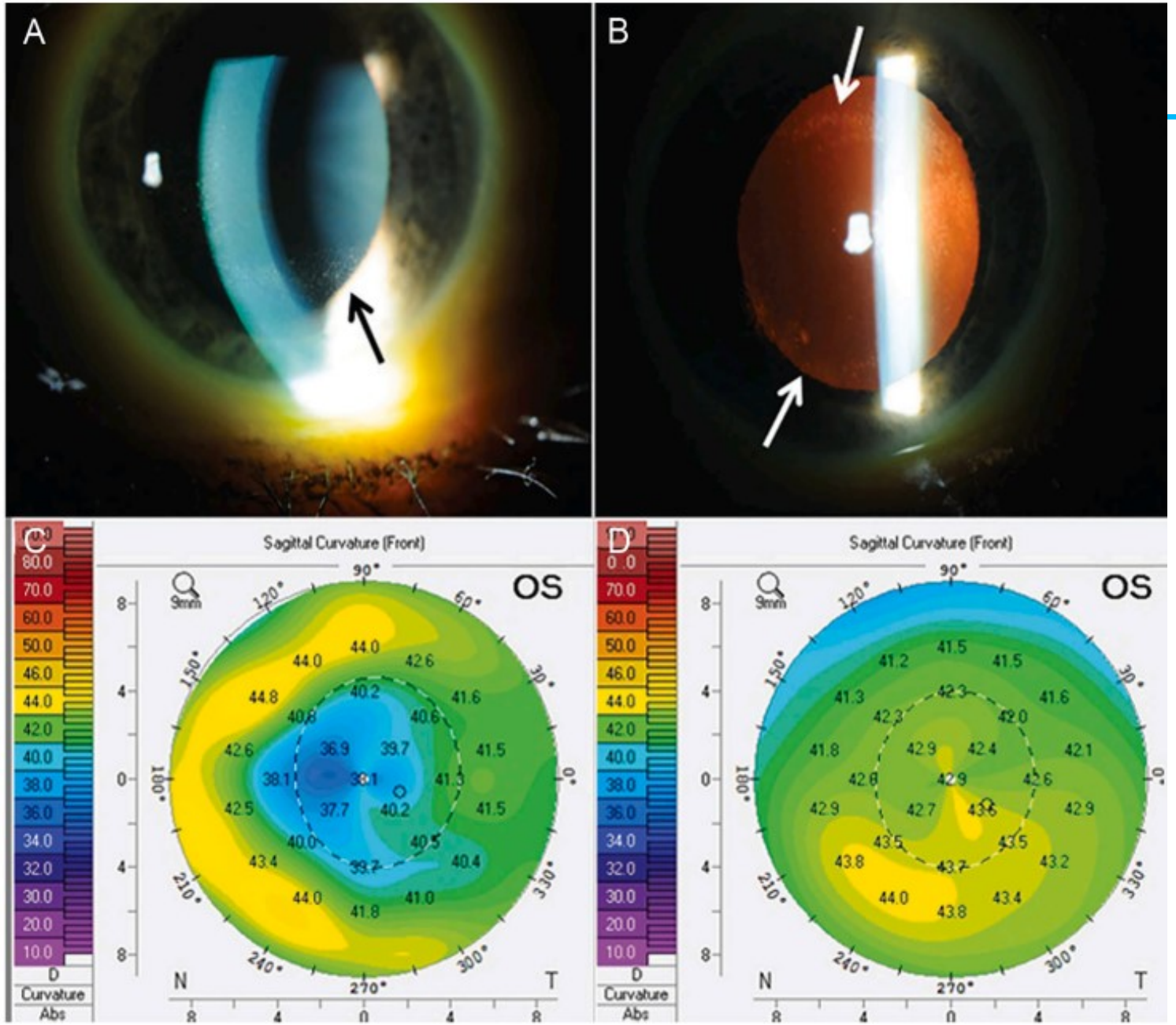
Matulonis et al. Clin Can Res 2019

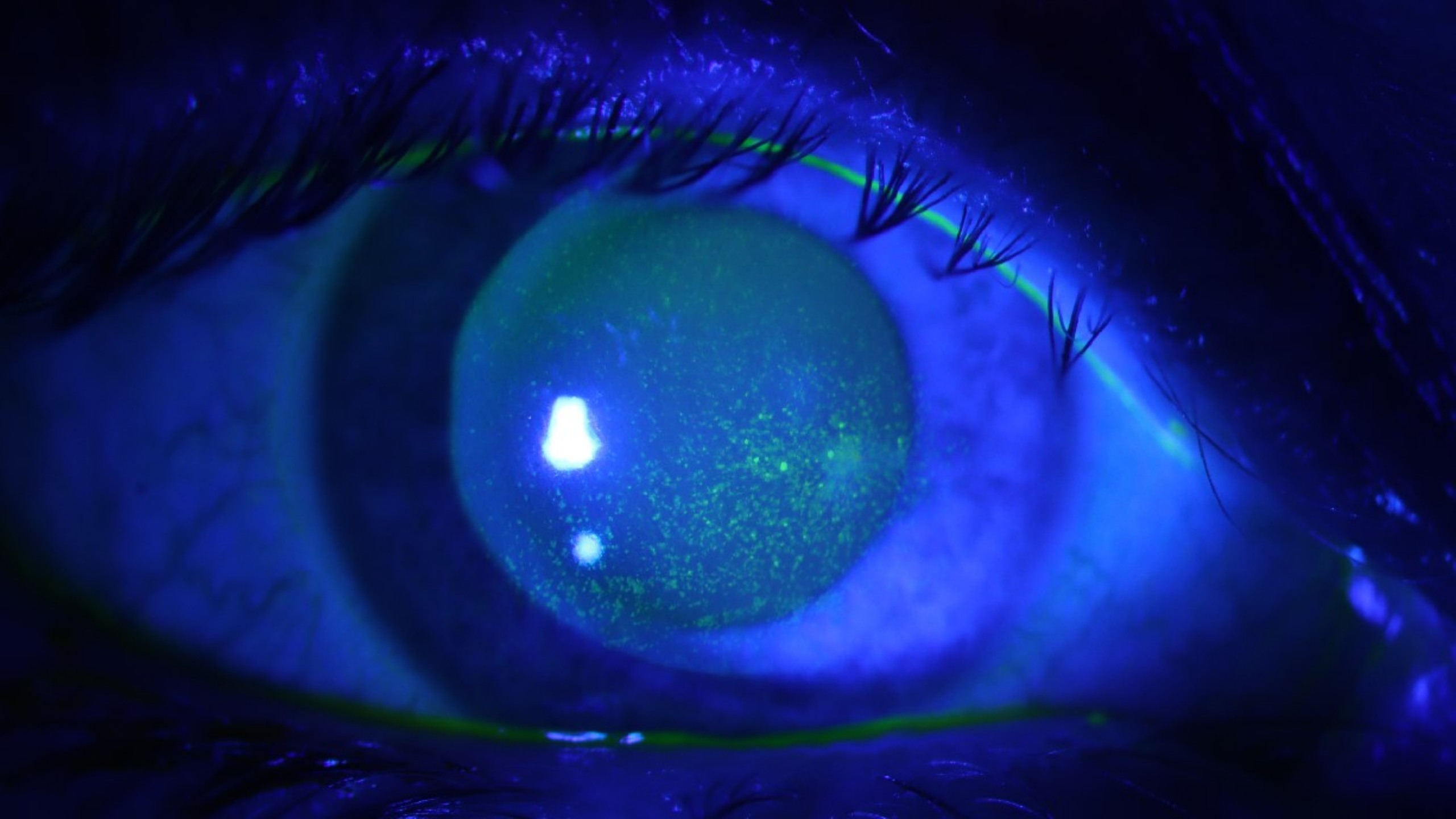


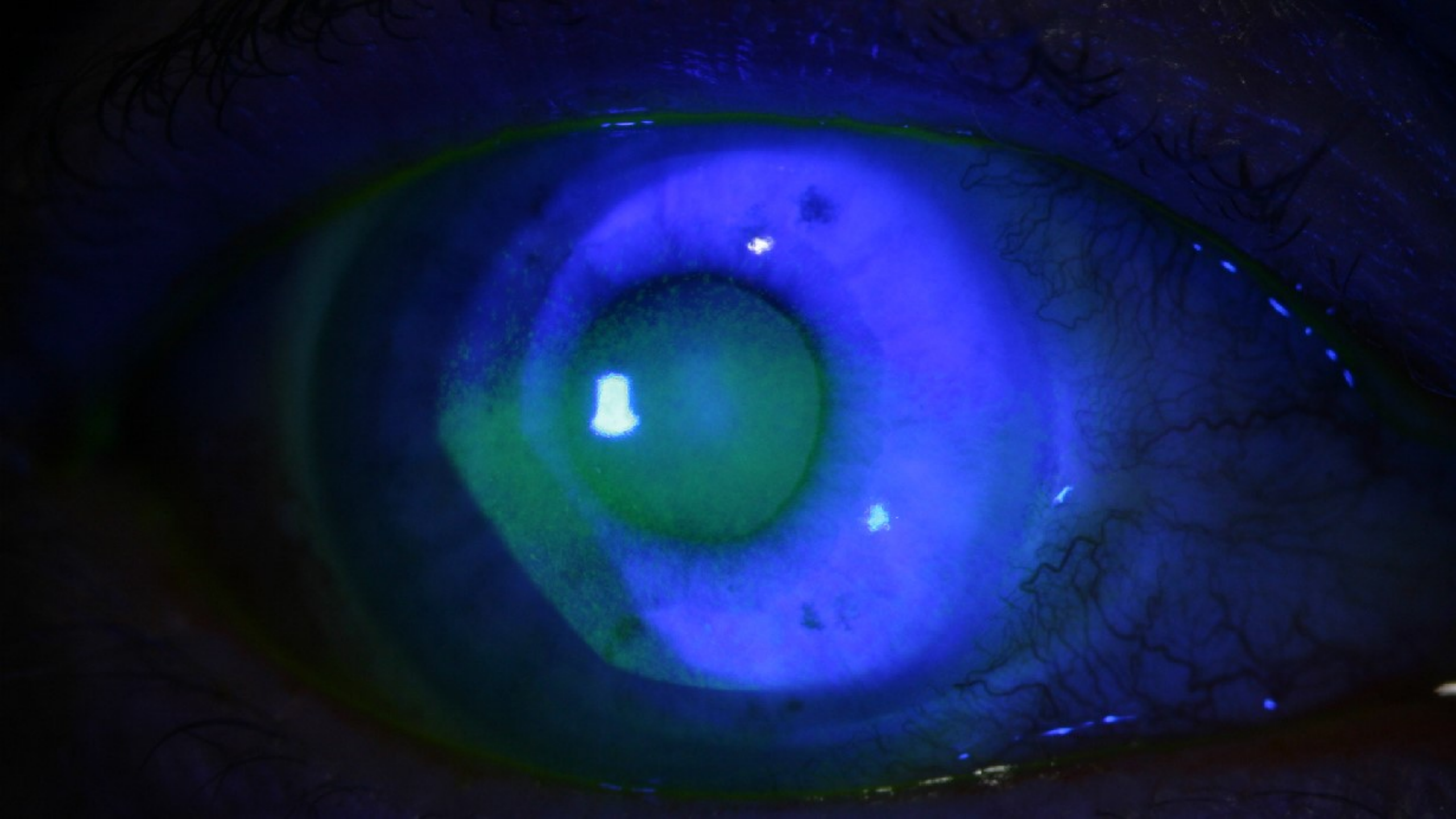
Ocular

Corneal microcysts

Flattening of the corneal surface curvature







Ocular AE's when using ADCs in general

Dry eyes

Dry eyes

Schirmer test

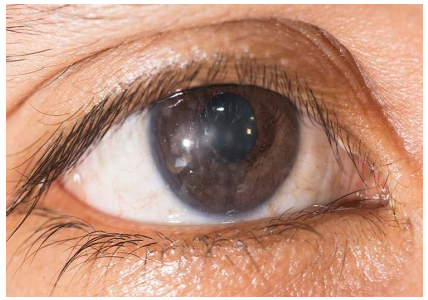
Conjunctivitis

Inflammation of the conjunctiva

Patient may experience pink eye

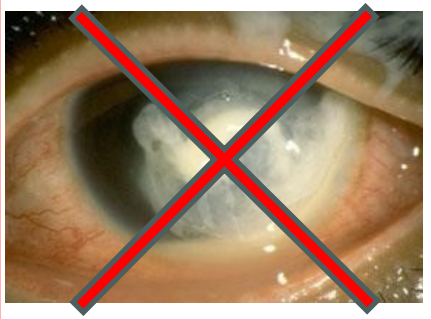
Keratitis

Keratopathie



Blurred vision

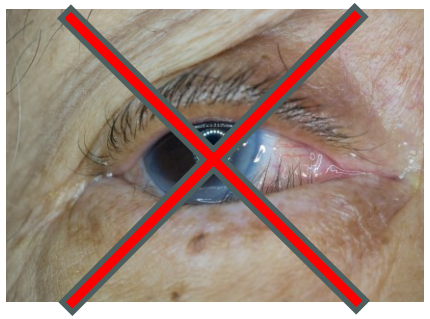
May manifest as a corneal ulcer



Vision impairment
Photophopia
Eye pain

Entropion

Lower eyelid turns inward towards eyeball



Irritation
Photophopia
Eye pain

Mirvetuximab
Soravtansine

Ocular

- Evolution after Mirv treatment:
  - **Regeneration** of corneal epithelium, with eventual shedding of areas demonstrating epithelial damage
  - For all patients with complete follow-up data, **ocular AEs resolved to grade 0/1**
  - Single-agent MIRV administration did **not result in any corneal ulcers or corneal perforations, and no patients had permanent ocular sequelae**

Ocular

Protocol management of ocular toxicity?

- Prophylactic and mitigative measures
- Treatment and dose modification

Recommendations for Patients and Caregivers

Use recommended and prescribed eye drops

Use ophthalmic topical steroids by administering 1 drop in each eye 6x daily (starting the day prior to each infusion) until Day 4; then 1 drop in each eye 4x daily for Days 5-8 of each cycle of MIRV

Use preservative-free lubricating eye drops at least 4x daily, and as needed

– Wait at least 10 min after ophthalmic topical steroid administration before instilling lubricating eye drops

Implement best practices for eye health

Practice good eyelid margin hygiene (eg, clean around eyes, apply warm compresses)

Use sunglasses during full daylight

Avoid use of contact lenses during treatment (unless directed by an HCP)

Know the risks for dry eye disease (eg, extended screen use, certain medications, environmental factors)

Patient/Healthcare Team Collaboration

Proactively monitor ocular health and ensure prompt ophthalmic examination upon occurrence of ocular signs or symptoms

Oncologist and ECP Responsibilities

Ensure patients undergo baseline and routine ophthalmic examinations

Conduct an ophthalmic examination (including BCVA, slit lamp examination, and evaluation of intraocular pressure) prior to initiation of MIRV, every other cycle for the first 8 cycles, and as clinically indicated

– Corneal topography may be useful to further evaluate transient changes in refractive status associated with the presence of MECs

Implement prophylactic and mitigative steps for ocular events

Instruct patients on best eye health practices and the importance of monitoring for ocular symptoms

Ensure patients have access to the correct types of eye drops: preservative-free lubricating eye drops and ophthalmic topical steroids

– The initial prescription and renewals of any corticosteroid medication should be made only after examination with a slit lamp

Upon occurrence of any new or worsening ocular signs or symptoms, promptly refer patients to an ECP for ophthalmic examination

Withhold, reduce, or permanently discontinue MIRV based on severity and persistence of ocular events, using the recommendations in the MIRV PI

Corticosteroid eye drops (1% prednisolone)

- Day -1 to 4: 6x/day
- Days 5 to 8: 1x/day

Lubricating eye drops

- 4x/day throughout the cycle

Elahere, 2022. Prescribinginformation. ImmunoGen Inc.

Summary of the Grading of Key Ocular Adverse Events in MIRV Clinical Trials (NCI CTCAE v5.0, 2017).

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4
Blurred vision[a]	Intervention not indicated	Symptomatic; moderate decrease in visual acuity; limiting instrumental ADL[b]	Symptomatic, with marked decrease in visual acuity; limiting self-care ADL[c]	Best corrected visual acuity of **20/200 or worse** in the affected eye
Keratitis[d] *(Included in keratopathy group term)*	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity	Symptomatic, with marked decrease in visual acuity; corneal ulcer; limiting self-care ADL[c]	Perforation; best corrected visual acuity of **20/200 or worse** in the affected eye
Dry eye[e]	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity	Symptomatic, with marked decrease in visual acuity; limiting self-care ADL[c]	
Photophobia[f]	Symptomatic but not limiting ADL	Limiting instrumental ADL[b] **Definition: "Moderate decrease in visual acuity"** Best corrected visual acuity 20/40 and better or ≤3 lines of decreased vision from known baseline	Limiting self-care ADL[c] **Definition: "Marked decrease in visual acuity"** Best corrected visual acuity worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200	

Protocol Recommended[2]
Permanently discontinue

Protocol Recommended: Withhold dose until improved or resolved, then reduce by one dose level[2]

Protocol Guidance For Management

Severity (CTCAE Grade)	
Grade 1	• Complete eye exam • Monitor for worsening symptoms • No change in mirvetuximab soravtansine dose or schedule of administration
Grade 2	• Complete eye exam • Weekly symptomatic ocular assessments until symptoms resolve or return to baseline • Hold mirvetuximab soravtansine until improvement to Grade 1 or better

Dose modifications

Trial Protocol Recommended Starting Dose and Dose Modifications

Recommended dose reduction schedule for adverse events[1]	
	Dose Level
Starting dose	6 mg/kg AIBW
First dose reduction	5 mg/kg AIBW
Second dose reduction	4 mg/kg AIBW[a]

[a]Permanently discontinue in patients who cannot tolerate 4 mg/kg AIBW.

AIBW = IBW + 0.4(Actual weight in kg – IBW)
IBW (female) = 0.9(Height in centimeters) – 92

Interstitial Lung Disease (ILD) or Pneumonitis

- Condidered as a ‘Class effect’ of ADCs
- Cause not clearly elucidated
  - We presume mainly off-target
- Evaluate immediately in case of shortness of breath, cough or respiratory distress

Interstitial Lung Disease (ILD) or Pneumonitis

	All grades (%)	Grade 1-2 (%)	Grade ≥3 (%)	Reference
FORWARD I	**2.9**	2.9	0	Matulonis et al. J Clin Oncol 2023;41:2436
FORWARD II	**6.7**	6.7	0	Gilbert L et al. ASCO 2020
SORAYA	**10.4**	8.5	1.9	Matulonis et al. SGO 2022 Matulonis et al. J Clin Oncol 41:2436-2445
MIRASOL	**?**	?	?	Moore KN et al. NEJM 2023;389(23):2162 Moore KN e al. ASCO 2023
PICCOLO	**10.1**	6.3	3.7*	Secord et al. ESMO 2024
All	2.9 – 10.4	2.9 – 8.5	0 – 3.7	

* 1 death reported

ILD/Pneumonitis

- Management

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.

Depending on ADC  Discontinue

Grade 1: Continue

Grade 2: Interrupt
Low dose steroids

Multidisciplinary approach !

ILD/Pneumonitis

CTCAE v4.03 Grade	Medical Management of Pneumonitis	Guidelines for Dose Modifications
Grade 1	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Monitor for pulmonary symptoms.	• **Continue dosing** after discussion with the Sponsor.
Grade 2	• Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. • Patient must be evaluated by a **pulmonary specialist.** • Treatment with **corticosteroids** may be indicated	• **Hold dosing** until symptoms resolve to ≤ Grade 1. • MIRV **may be resumed at same dose level** after discussion with the Sponsc
Grade 3	• Same radiologic assessments and evaluation by a pulmonary specialist as in case of Grade 2. • Treatment with high dose corticosteroids until resolution of symptoms may be indicated • **Bronchoscopy** with lavage and/or biopsy when clinically feasible should be performed. • The pneumonitis event must be **followed until resolution.**	• **Hold** resolve to ≤ Grade 1. • MIRV **may be resumed at a lower dose level** after discussion with the Sponsor.
Grade 4	• Same as grade 3	• **Permanently discontinue MIRV**

Be careful, consider to reduce!

Be careful, consider to discontinue!

STRO-002-GM1 safety

Most common TEAEs (>25%), n (%)	4.3 mg/kg (n=23)		5.2 mg/kg (n=21)		Total (N=44)	
	Any Grade	G3+	Any Grade	G3+	Any Grade	G3+
Patients reporting ≥1 event	**23 (100)**	**18 (78.3)**	**21 (100)**	**20 (95.2)**	**44 (100)**	**38 (86.4)**
Haematological						
Neutropenia*	**17 (73.9)**	**15 (65.2)**	**18 (85.7)**	**16 (76.2)**	**35 (79.5)**	**31 (70.5)**
Febrile neutropenia	**1 (4.3)**	**1 (4.3)**	**1 (4.8)**	**1 (4.8)**	**2 (4.5)**	**2 (4.5)**
Platelet count decreased	11 (47.8)	1 (4.3)	10 (47.6)	2 (9.5)	21 (47.7)	3 (6.8)
Anaemia	8 (34.8)	1 (4.3)	12 (57.1)	5 (23.8)	20 (45.5)	6 (13.6)
whate blood cell count decreased	11 (47.8)	6 (26.1)	4 (19)	4 (19)	15 (34.1)	10 (22.7)
Non-haematological						
Nausea	17 (73.9)	0	16 (76.2)	0	33 (75)	0
Fatigue	16 (69.6)	3 (13)	11 (52.4)	1 (4.8)	27 (61.4)	4 (9.1)
Arthralgia	**14 (60.9)**	**6 (26.1)**	**12 (57.1)**	**2 (9.5)**	**26 (59.1)**	**8 (18.2)**
Constipation	9 (39.1)	0	13 (61.9)	1 (4.8)	22 (50)	1 (2.3)
Neuropathy†	**11 (47.8)**	**1 (4.3)**	**8 (38.1)**	**0**	**19 (43.2)**	**1 (2.3)**
Abdominal pain	8 (34.8)	0	10 (47.6)	0	18 (40.9)	0
Decreased appetite	8 (34.8)	0	10 (47.6)	0	18 (40.9)	0
Diarrhoea	8 (34.8)	2 (8.7)	7 (33.3)	1 (4.8)	15 (34.1)	3 (6.8)
Vomiting	7 (30.4)	0	8 (38.1)	2 (9.5)	15 (34.1)	2 (4.5)
Pyrexia	8 (34.8)	0	7 (33.3)	1 (4.8)	15 (34.1)	1 (2.3)
AST increased	8 (34.8)	0	7 (33.3)	0	15 (34.1)	0
ALT increased	8 (34.8)	0	6 (28.6)	0	14 (31.8)	0
Myalgia	6 (26.1)	0	7 (33.3)	0	13 (29.5)	0
Headache	9 (39.1)	0	3 (14.3)	0	12 (27.3)	0

Table adapted from Oaknin A, et al.[1] *Neutropenia included the following preferred terms: neutropenia, febrile neutropenia, and neutrophil count decreased. †Neuropathy included the following preferred terms: neuropathy peripheral and peripheral sensory neuropathy. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

1. Oaknin A, et al. American Society of Clinical Oncology (ASCO) Annual Meeting. 2023; Abs 5508 and presentation.

Farletuzumab ecteribulin (FZEC; MORAb-202)

- Study 101: dose expansion phase safety data

Most common TEAEs (≥10% in either cohort)

Parameter, n (%)	Cohort 1: FZEC 0.9 mg/kg (n = 24)		Cohort 2: FZEC 1.2 mg/kg (n = 21)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAEs	**24 (100)**	**8 (33.3)**	**20 (95.2)**	**6 (28.6)**
Any treatment-related TEAEs	**22 (91.7)**	**2 (8.3)**	**18 (85.7)**	**4 (19.0)**
ILD / pneumonitis	**9 (37.5)**	**0**	**14 (66.7)**	**1 (4.8)**
Pyrexia	8 (33.3)	0	9 (42.9)	0
Nausea	6 (25.0)	0	7 (33.3)	0
Nasopharyngitis	5 (20.8)	0	1 (4.8)	0
Increased ALT level	5 (20.8)	0	4 (19.0)	0
Increased γ-glutamyl transferase	5 (20.8)	1 (4.2)	1 (4.2)	0
Malaise	4 (16.7)	0	6 (28.6)	0
Vomiting	4 (16.7)	0	1 (4.8)	0
Increased AST level	4 (16.7)	0	4 (19.0)	0
Headache	3 (12.5)	0	10 (47.6)	0
Diarrhoea	3 (12.5)	0	5 (23.8)	0
Constipation	3 (12.5)	0	3 (14.3)	0
Anaemia	3 (12.5)	1 (4.2)	4 (19.0)	1 (4.8)
Decreased appetite	3 (12.5)	1 (4.2)	2 (9.5)	0
Cataract	2 (8.3)	1 (4.2)	3 (14.3)	1 (4.8)
Arthralgia	2 (8.3)	0	3 (14.3)	0
Dysgeusia	2 (8.3)	0	3 (14.3)	0
Stomatitis	1 (4.2)	0	3 (14.3)	0
Decreased white blood cell count	0	0	4 (19.0)	0
Peripheral sensory neuropathy	0	0	3 (14.3)	0

Respiratory AEs

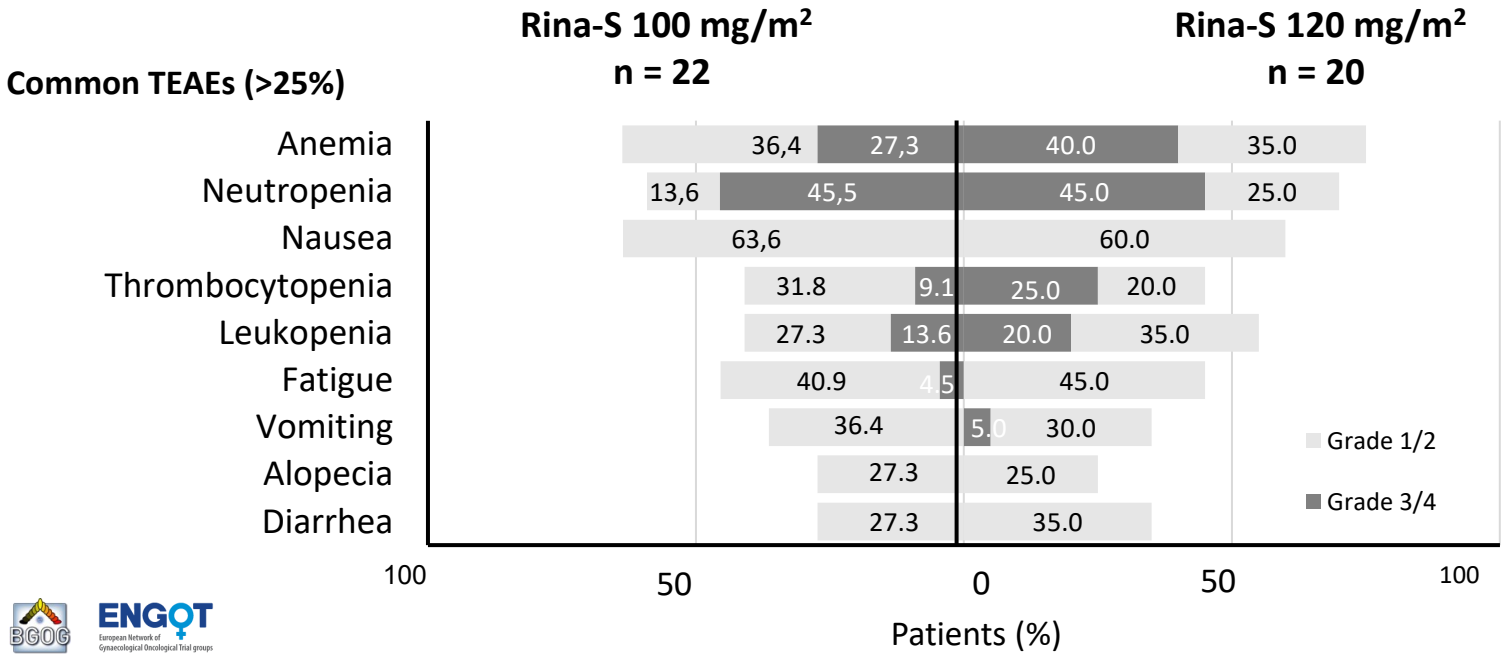
Parameter, n (%)	Cohort 1: FZEC 0.9 mg/kg (n = 24)	Cohort 2: FZEC 1.2 mg/kg (n = 21)
Any ILD / pneumonitis event	**9 (37.5)**	**14 (66.7)**
Severity:		
Grade 1	8 (33.3)	6 (28.6)
Grade 2	1 (4.2)	7 (33.3)
Grade 3	0	1 (4.8)
Grade 4	0	0
Grade 5	0	0
Serious event of ILD / pneumonitis / dyspnea	2 (8.3)	3 (14.3)
ILD / pneumonitis event leading to FZEC:		
Discontinuation	1 (4.2)	5 (23.8)
Dose reduction	5 (20.8)	9 (42.9)
Dose interruption	1 (4.2)	4 (19.0)

Tables adapted from Nishio S, et al.[1]

Data cutoff date: October 31, 2021. AE, adverse event; FZEC, farletuzumab ecteribulin; ILD, interstitial lung disease; TEAE, treatment emergent adverse event. 1. Nishio S, et al. American Society of Clinical Oncology (ASCO) Annual Meeting. 2022; Abs 5513 and poster.

Rinatabart sesutecan: Phase 1/2 study safety data

- In dose escalation at 100 - 120 mg/m^2 (n = 35):
  - Most common any grade TEAEs were cytopenias[a] (34.3% - 60.0%)
  - No signals of ocular toxicities, neuropathy, or ILD were observed
- OC dose expansion at 100 - 120 mg/m^2:



Lee et al. ESMO 2024

Summary

- Compared to chemotherapy, MIRV is associated with lower rates of:
  - Grade 3 or greater TEAEs (42% vs 54%)
  - Serious adverse events (24% vs 33%)
  - TEAEs leading to discontinuation of study drug (9% vs 16%)

- Most frequent adverse events were **ocular**
  - Predominantly Grade 1-2
  - Mitigation strategy and ophthalmologic follow-up were mandatory
  - Mostly reversible in nature

Summary

- Non-ocular adverse events are
  - **GI**: nausea, diarrhoea and fatigue grade 1-2
  - **Peripheral neuropathy**:
    - incidence was lower than paclitaxel (22% vs 29%)
    - mostly grade 1-2
  - **Haematological toxicity**
    - less than 12% (mostly grade 1-2)
  - Be aware of **ILD/pneumonitis** although not the most frequent AE

Summary

- ADCs have their own unique toxicities/adverse events (mainly off-target)
- Get to know your ADC!

- The following measures are key!
  - Supportive measures
  - Interruptions
  - Reductions
  - Discontinuations

Questions?