The Trojan Horse Effect: Targeting Folate Receptor-Alpha with ADCs

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DISCLOSURES

- I serve on advisory boards for Astra Zeneca, Abbvie, Aravive,Blueprint pharmaceuticals, Eisai/Serono, Elevar, Genentech/Roche, Hengrui, Immunogen, INXmed, Imab, Lilly, VBL Therapeutics , Mersana, Myriad, Mereo, Merck, Novartis, Vavotar, Tarveda, GSK/Tesaro

- I serve on steering committees for Genentech/Roche, Immunogen, and VBL Therapeutics

- I receive research funding from PTC Therapeutics, Lilly, GSK/Tesaro, Merck

- I serve as Associate Director for GOG Partners and am on the GOG Foundation BOD

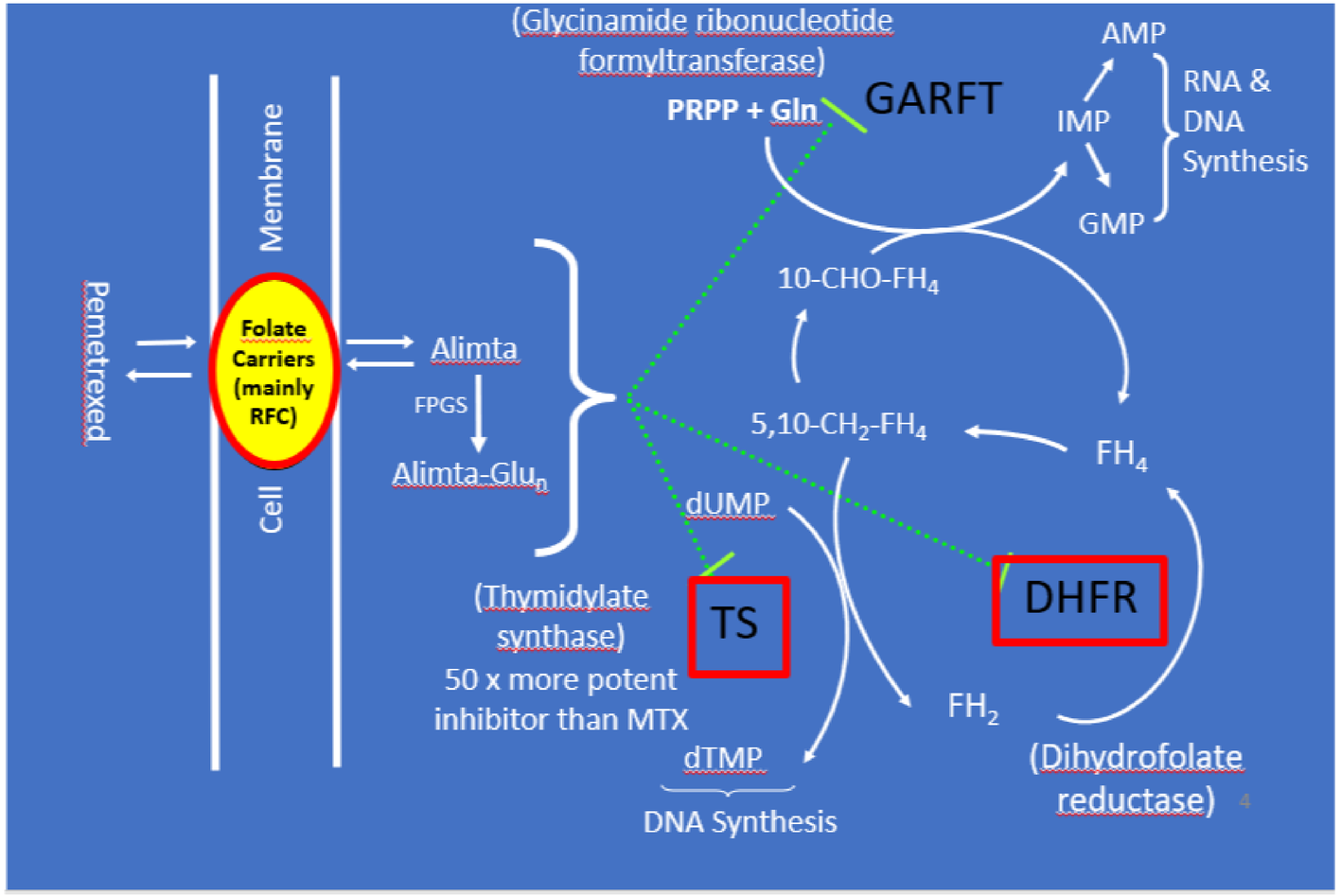
Folate as a target in oncology is not new….

Efforts to exploit folates in the pursuit of anti-cancer therapies started with the anti-metabolites including methotrexate and pemetrexed

These efforts focused on mechanisms of folate uptake including the reduced folate carriers (RFC) shown here.

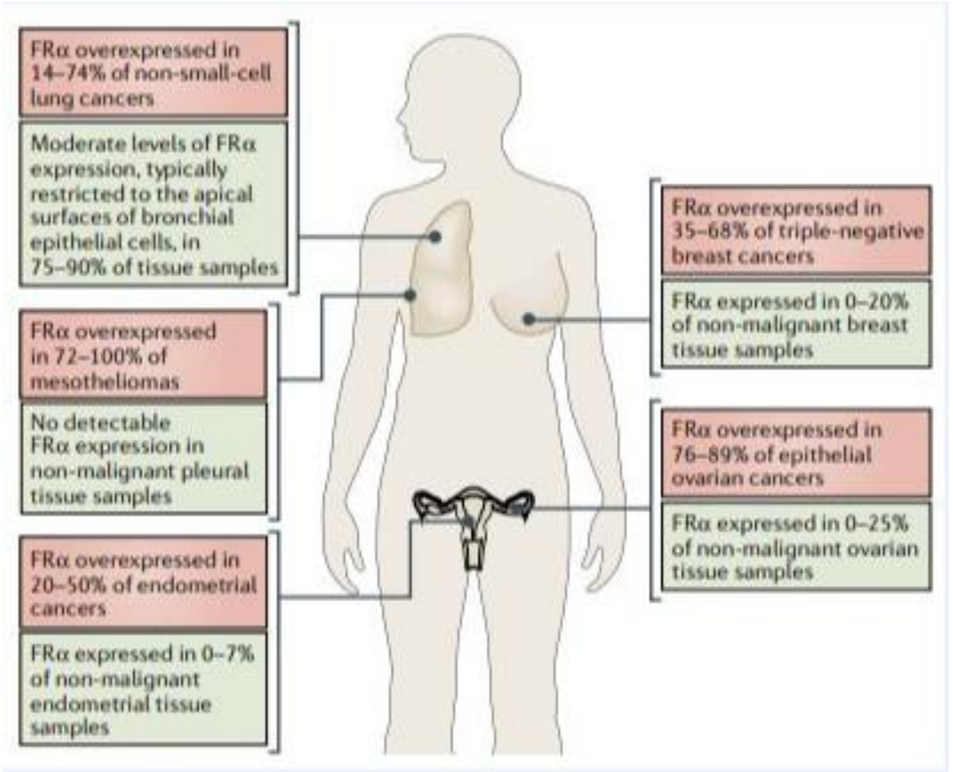
More recent efforts have focused on the folate receptor itself (FR) and specifically – FRα

Current research is seeking to utilize FRα as a therapeutic target, possible CAR-T target, as a diagnostic target and potentially as an imaging modality to improve cytoreduction



Targeting Folate Receptor Alpha (FRα) – an ideal target for ovarian cancer

- FRα is a cell surface folate receptor which mediates folate transport into epithelial cells.
- FRα expression is limited on normal cells, but is upregulated on cancers, primarily ovarian, but also endometrial, and triple negative breast
- FRα may be expressed on the alveoli of the lungs and on renal proximal tubules however these receptors are located on the surface of the cell facing the alveolar and tubular lumen which reduces the exposure of the targets to circulating anti-folate agents



Scaranti et al. Nature Reviews (17) 2020

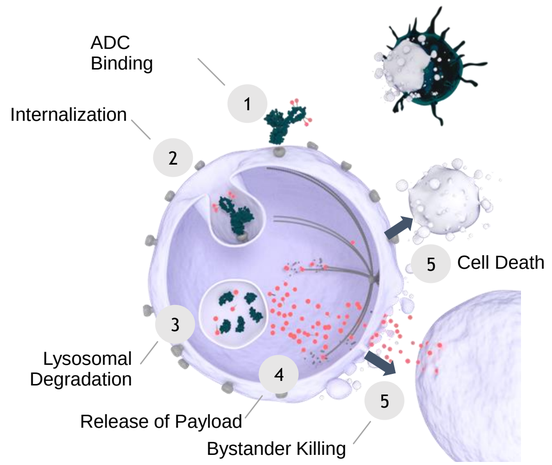
ADCs Under Evaluation in Gynecologic Cancers

Targeting FRα

Generic Name	Conjugate	Indication	Target	Phase	NCT
Mirvetuximab soravtansine	Maytansinoid (DM4)	Ovary	Folate Receptor α	3: Gloriosa 3: MIRASOL 2: SORAYA 2: PICCOLO 2: FL NACT 2: Study 420 (+Carbo)	NCT05445778 NCT04209855 NCT04296890 NCT05041257 NCT04606914 NCT05456685
STRO-002 Luveltamab Tazevibulin	SC209 (tubulin targeting)	Ovary	Folate Receptor α	1 2: REFRaME-01	NCT03748186 NCT05870748
MORAb-202	Eribulin	Ovary	Folate Receptor α	2	NCT05613088
IMGN-151	DM21-L-G	Ovary and Endo	Folate Receptor α	1	NCT05527184
PRO1184	Exotecan	Ovary	Folate Receptor α	1	NCT05579366
Upifitamab Rilsodotin	AF-HPA (DolaLOck-controlled bystander effect)	Ovary	NaPi2b	1 UP-Grade 2 UPLIFT 3: UP-NEXT	NCT04907968 NCT03319628 NCT05329545
Sacituzumab Govitecan (IMMU-132)	SN-38 (metabolite of topo 1 inhibitor)	Solid tumor (endo)	TROP2	2	NCT04251416
KL 264 01/SKB264	Belotecan (novel camptothecin derivative)	Solid tumors	TROP2	1	NCT04152499
BDC-1001	TLR 7/8 dual agonist	Solid tumor	HER2	1	NCT04278144
DB1303	Topoisomerase 1 inhibitor (P1003)	Solid tumor (endo)	HER2	1	NCT05150691
Ado-trastuzumab emtansine	DM1	Solid tumor (endo & ovary)	HER2	2	NCT04439110
Trastuzumab Deruxtecan	Deruxtecan	Solid tumor (endo, ovary, cervix)	HER2	2	NCT04482309
Trastuzumab duocarmycin	Duocarmycin	Solid tumor (endo)	HER2	2	NCT04205630
DS6000a	deruxtecan	Solid tumor	CDH6	1	NCT04707248
XB002	auristatin	Solid tumor	TF	1	NCT04925284
Tisotumab vedotin	MMAE	Cervix	TF	3	NCT04697628

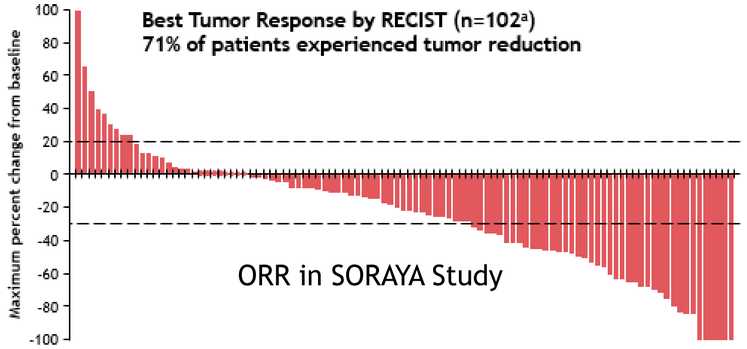
Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers: Mirvetuximab Soravtansine

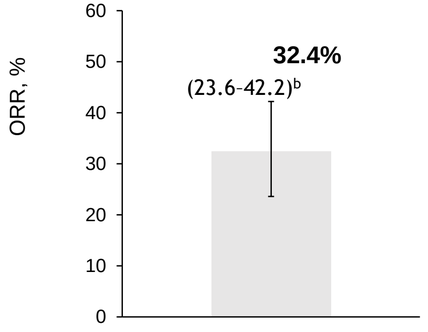
Mirvetuximab Soravtansine: MOA



ADC targeting folate receptor alpha conjugated to DM4 – a microtubule toxin

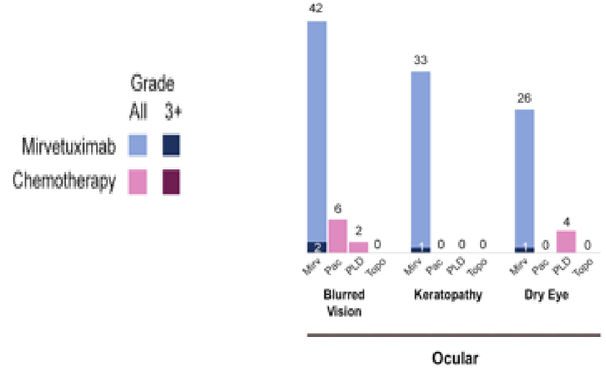
Efficacy (SORAYA: Single Arm Ph3)





Matulonis et al. J Clin Oncol. 2023 Onlinie ahead of print.

Key TRAEs



	Integrated Safety Population (N=464)		SORAYA* (N=106)	
Adverse event	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
Alopecia	3 (<1)	0	1 (<1)	0
Neuropathy peripheral	64 (14)	4 (<1)	14 (13)	0
Peripheral sensory neuropathy	36 (8)	4 (<1)	4 (4)	2 (2)
Peripheral motor neuropathy	4 (<1)	1 (<1)	2 (2)	1 (<1)
Paresthesia	21 (5)	0	5 (5)	0
Anemia	43 (9)	4 (<1)	8 (8)	1 (<1)
Thrombocytopenia	43 (9)	1 (<1)	10 (9)	2 (2)
Neutropenia	35 (8)	2 (<1)	14 (13)	2 (2)

Moore et al. J. Clin Oncol 40, 2022 (suppl 16; abstr 5574)

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

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MIRASOL: Phase III Study of Mirvetuximab Soravtansine vs. Investigator Choice Chemotherapy in Platinum Resistant, Advanced High Grade Epithelial Ovarian Cancer with High Folate Receptor Alpha Expression (GOG 3045/ENGOT-ov55) is the Confirmatory Trial for **Global Regulatory Approval**

Content current as of:
11/14/2022

Regulated Product(s)
Drugs

MIRASOL (NCT04209855) – Study Design[1,2]

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population
(N=453)

Enrollment and Key Eligibility
Platinum-resistant disease
(PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

High-grade serous histology

1º platinum-refractory disease excluded (primary PFI <3 mo)

1-3 prior lines of therapy

Prior BEV and PARPi allowed

Patients with BRCA mutations allowed

1:1 Randomization

Treatment Regimen-Experimental

MIRV
(6 mg/kg AIBW Q3W)

Treatment Regimen-Control

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors
IC chemo: paclitaxel, PLD, or topotecan
Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint

PFS by INV
(BICR sensitivity analysis)

Key Secondary Endpoints

1) ORR by INV
2) OS
3) PROs[a]

Secondary Endpoints
Safety and tolerability
DOR
CA-125 response[b]
PFS2

AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.
[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

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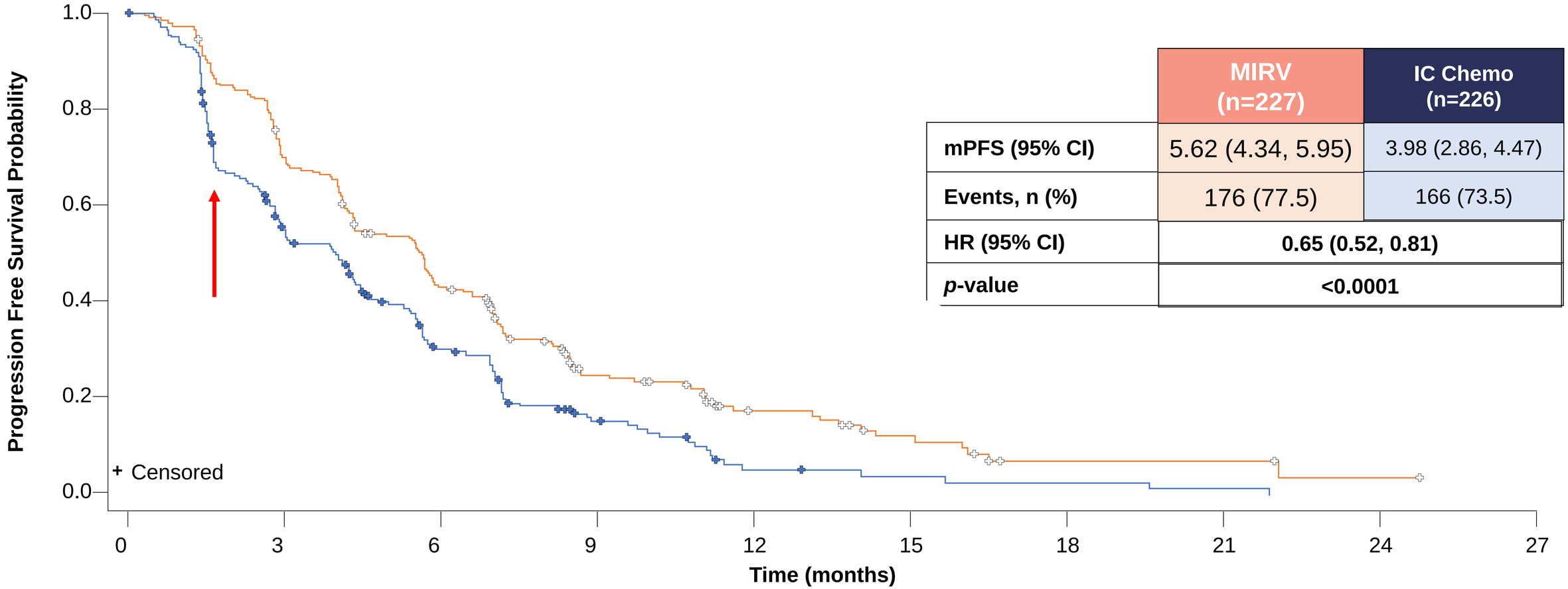
Baseline Demographics and Stratification Factors (N=453)

Characteristics		MIRV (n=227)	IC Chemo (n=226)
Age, median (range)	Age in years	63 (32-88)	62 (29-87)
Stage at initial diagnosis, n (%)[a]	I-II III IV	9 (4) 137 (60) 76 (33)	9 (4) 147 (65) 65 (29)
BRCA mutation, n (%)	Yes No/Unknown	29 (13) 198 (87)	36 (16) 190 (84)
Prior exposure, n (%)	Bevacizumab PARPi Taxanes	138 (61) 124 (55) 227 (100)	143 (63) 127 (56) 224 (99)
Primary platinum-free interval, n (%)[b]	≤ 12 months > 12 months	146 (64) 80 (35)	142 (63) 84 (37)
Platinum-free interval, n (%)[c]	≤ 3 months > 3 - ≤6 months	88 (39) 138 (61)	99 (44) 124 (55)
Stratification Factor **No. of prior systemic therapies, n (%)**	1 2 3	31 (14) 91 (40) 105 (46)	32 (14) 91 (40) 103 (46)
Stratification Factor **Investigator Choice of Chemotherapy**	Paclitaxel PLD Topotecan	93 (41) 82 (36) 52 (23)	92 (41) 81 (36) 53 (23)

Data cutoff: March 6, 2023. **14% of patients remain on MIRV; 3% remain on IC Chemo**
BRCA, BReast CAncer gene; PARPi, poly (ADP-ribose) polymerase inhibitors; MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; PLD, pegylated liposomal doxorubicin,.
[a]Five patients (2%) in the MIRV arm and five patients in the IC chemo 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 chemo arm enrolled with platinum-free interval of >6 months

Primary Endpoint: Progression-Free Survival by Investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	**0.65 (0.52, 0.81)**	
***p*-value**	**<0.0001**	

No. Participants at Risk

MIRV — IC Chemo

MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

Data cutoff: March 6, 2023

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

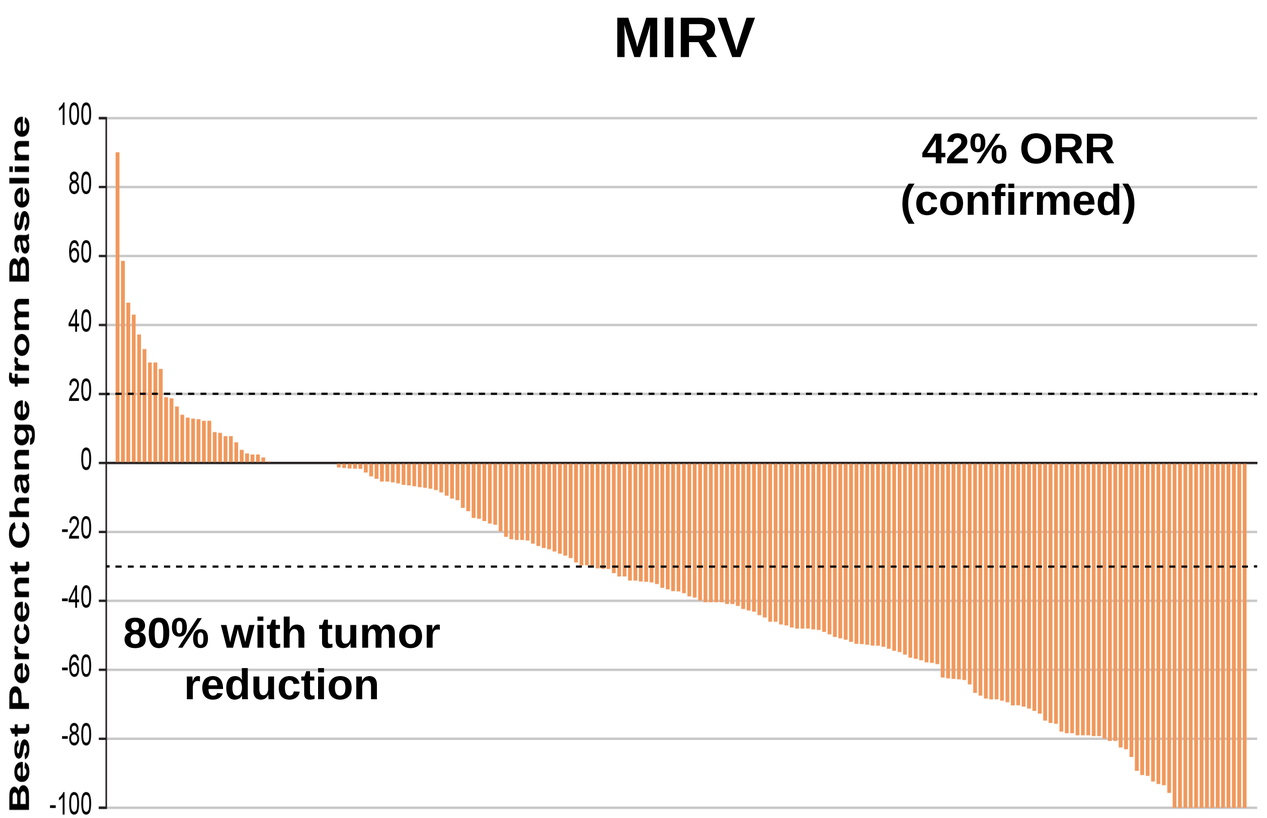
Overall Response Rate by Investigator (N=453)

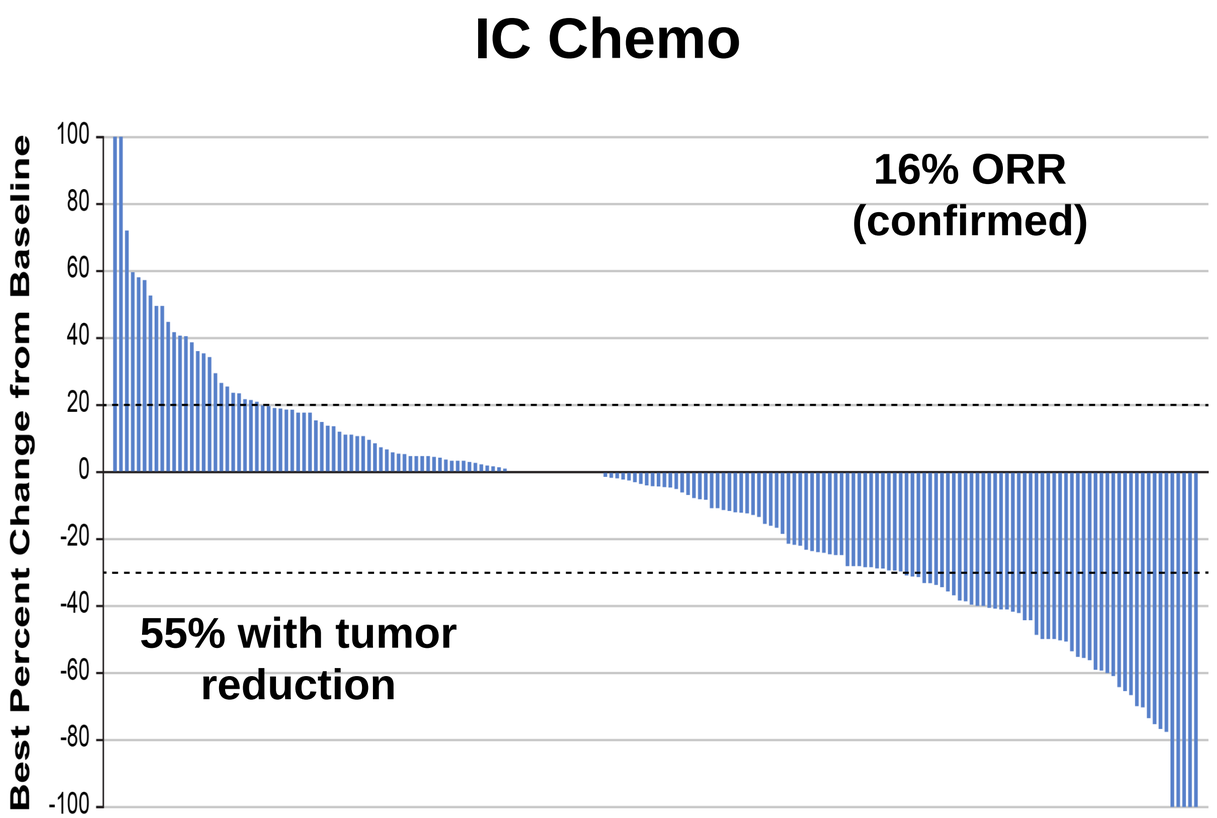
	MIRV (n=227)	IC Chemo (n=226)
ORR **n, 95% CI**	**42%** 96, (35.8, 49.0)	**16%** 36, (11.4, 21.4)
Best overall response, n (%)		
CR	12 (5%)	0
PR	84 (37%)	36 (16%)
SD	86 (38%)	91 (40%)
PD	31 (14%)	62 (27%)
Not evaluable	14 (6%)	37 (16%)

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.

Maximum Percentage Change in Target Lesion Size from Baseline by Investigator (N=453)





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

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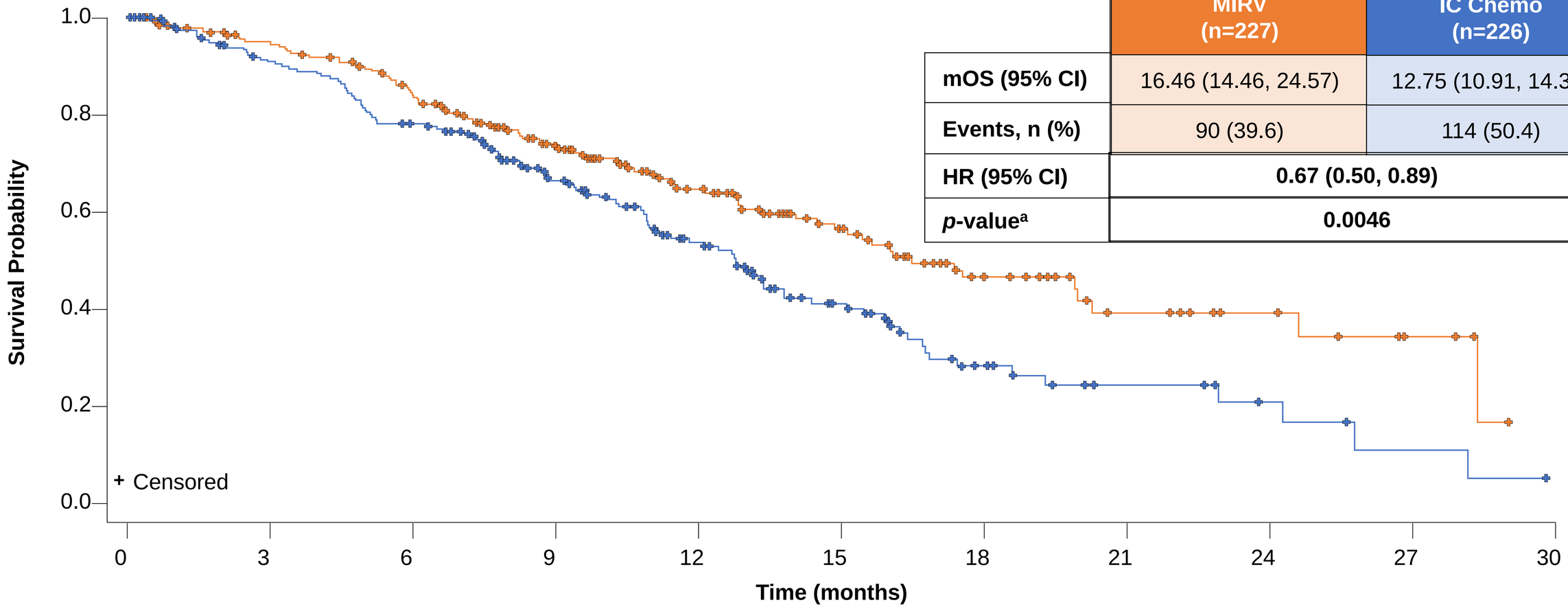
Overall Survival



	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**	

No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

Data cutoff: March 6, 2023; median follow-up time: 13.11 months

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.

[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

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Progression-Free and Overall Survival in Bevacizumab-Naïve and Prior Bevacizumab-Treated Subsets by Investigator

	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.

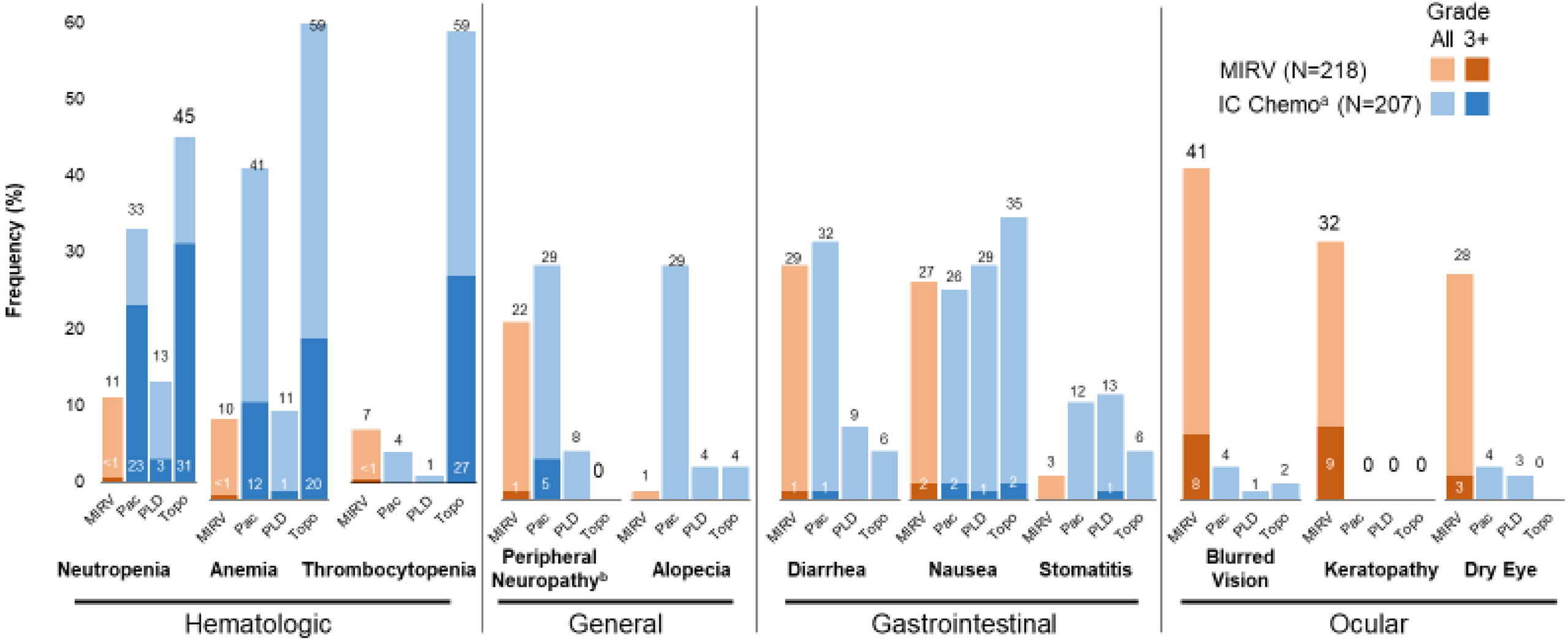
Safety Summary (N=425)

MIRV has a tolerable safety profile compared with IC Chemo

	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 within 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.

Differentiated Safety Profile: Treatment-Emergent Adverse Events



Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

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Mirvetuximab Soravtansine: The Basics

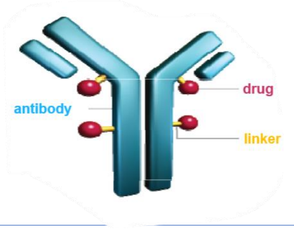
Who is Eligible and How Dosed?

Eligibility?

- Platinum resistant ovarian cancer (including fallopian tube and peritoneal)
- 1-3 prior lines of therapy (per label)
- Folate receptor alpha (FRα) high by the FDA approved CDx

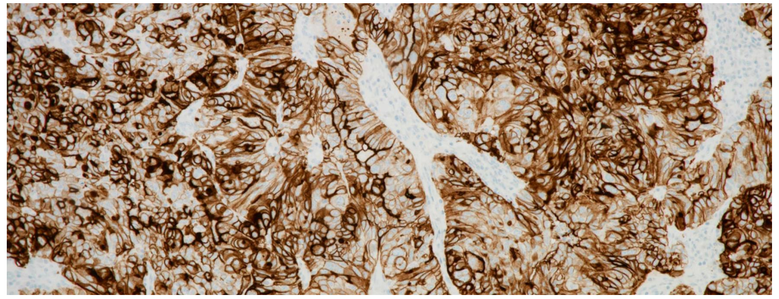
Dosing?

- Starting dose is 6mg/kg IV dosed by adjusted ideal body weight (AIBW)
- AIBW = IBW +0.25 x(actual weight – IBW)



FRα Testing

- FRα status is determined by an IHC test
- ~35% of (mainly serous) tumors are FRα high and eligible for Mirvetuximab
- FRα high is defined as > 75% of tumor cells staining with 2+ or 3+ intensity by VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

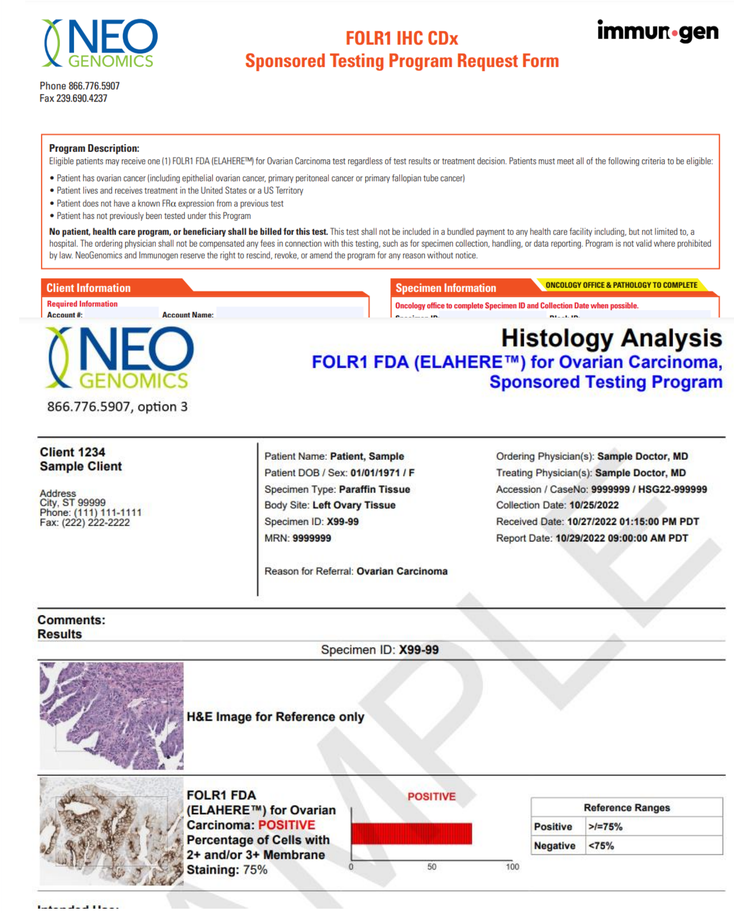


- CARIS
- LabCorb
- Neogenomics

https://diagnostics.roche.com/global/en/products/tests/ventana-folr1-folr-2-1-rxdx-assay-us-fda-approved.html

How is testing ordered?

https://neogenomics.com/sites/default/files/requisitions/FOLR1_IHC_CDx_Sponsored_Testing_Program_Request_Form_111622_Final_FF.pdf



NEO GENOMICS

Phone 866.776.5907
Fax 239.690.4237

FOLR1 IHC CDx
Sponsored Testing Program Request Form

immun•gen

Program Description:
Eligible patients may receive one (1) FOLR1 FDA (ELAHERE™) for Ovarian Carcinoma test regardless of test results or treatment decision. Patients must meet all of the following criteria to be eligible:

- Patient has ovarian cancer (including epithelial ovarian cancer, primary peritoneal cancer or primary fallopian tube cancer)
- Patient lives and receives treatment in the United States or a US Territory
- Patient does not have a known FRα expression from a previous test
- Patient has not previously been tested under this Program

No patient, health care program, or beneficiary shall be billed for this test. This test shall not be included in a bundled payment to any health care facility including, but not limited to, a hospital. The ordering physician shall not be compensated any fees in connection with this testing, such as for specimen collection, handling, or data reporting. Program is not valid where prohibited by law. NeoGenomics and Immunogen reserve the right to rescind, revoke, or amend the program for any reason without notice.

Client Information
Required Information
Account #: Account Name:

Specimen Information ONCOLOGY OFFICE & PATHOLOGY TO COMPLETE
Oncology office to complete Specimen ID and Collection Date when possible.

NEO GENOMICS
866.776.5907, option 3

Histology Analysis
FOLR1 FDA (ELAHERE™) for Ovarian Carcinoma, Sponsored Testing Program

Client 1234
Sample Client

Address
City, ST 99999
Phone: (111) 111-1111
Fax: (222) 222-2222

Patient Name: **Patient, Sample**
Patient DOB / Sex: **01/01/1971 / F**
Specimen Type: **Paraffin Tissue**
Body Site: **Left Ovary Tissue**
Specimen ID: **X99-99**
MRN: **9999999**

Reason for Referral: **Ovarian Carcinoma**

Ordering Physician(s): **Sample Doctor, MD**
Treating Physician(s): **Sample Doctor, MD**
Accession / CaseNo: **9999999 / HSG22-999999**
Collection Date: **10/25/2022**
Received Date: **10/27/2022 01:15:00 PM PDT**
Report Date: **10/29/2022 09:00:00 AM PDT**

Comments:
Results

Specimen ID: **X99-99**

H&E Image for Reference only

FOLR1 FDA (ELAHERE™) for Ovarian Carcinoma: POSITIVE Percentage of Cells with 2+ and/or 3+ Membrane Staining: 75%

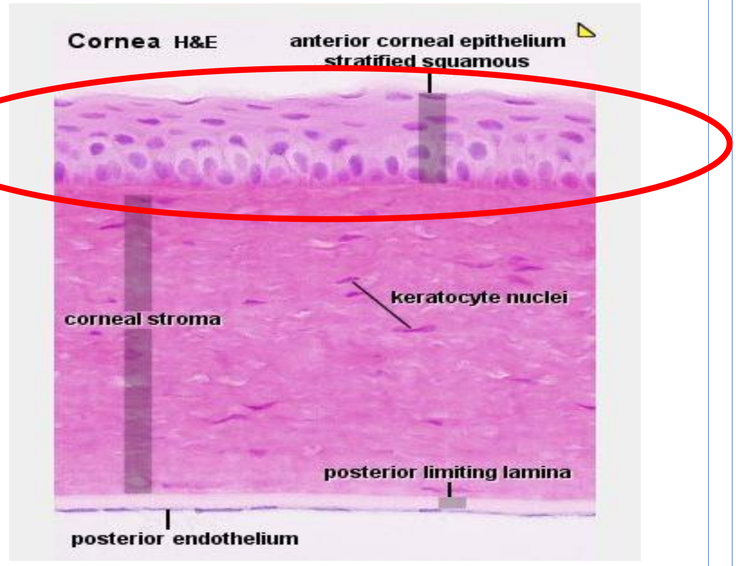
POSITIVE
0 50 100

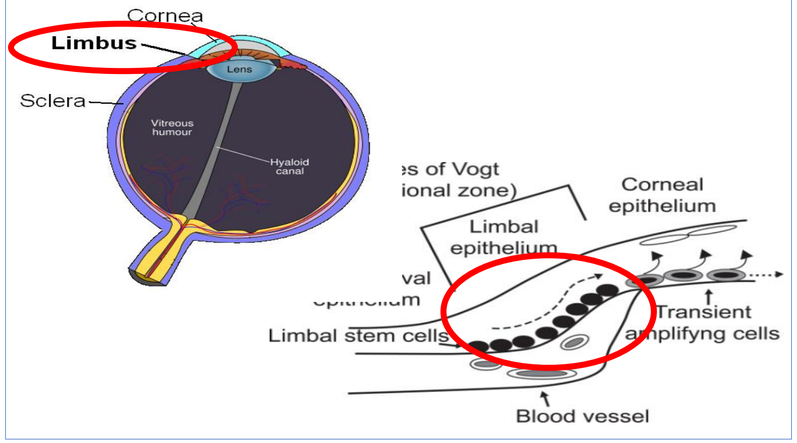
Reference Ranges	
Positive	>/=75%
Negative	<75%

SAMPLE

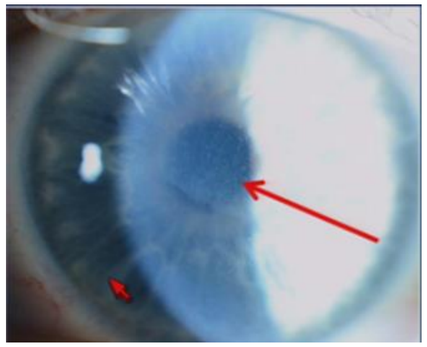
Antibody Drug Conjugates (ADCs)
Mitigation of Treatment Related Adverse Events: Ocular

Keratopathy

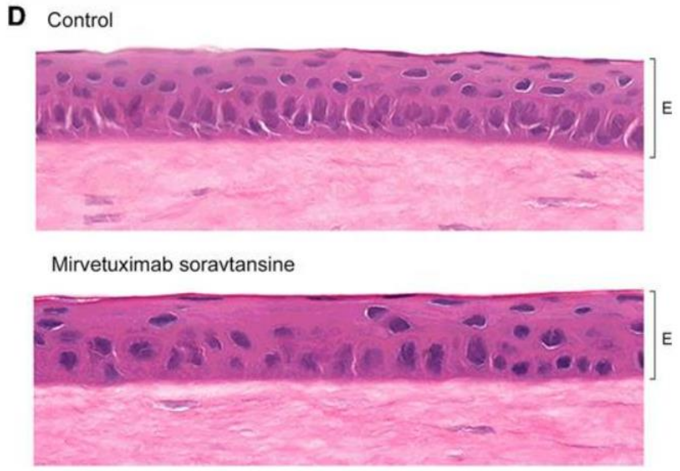




Mechanism



(L) Microcysts (R) coalescing centrally. Photo co S. Kim, MD



Matulonis et al. Clin Can Res 2019

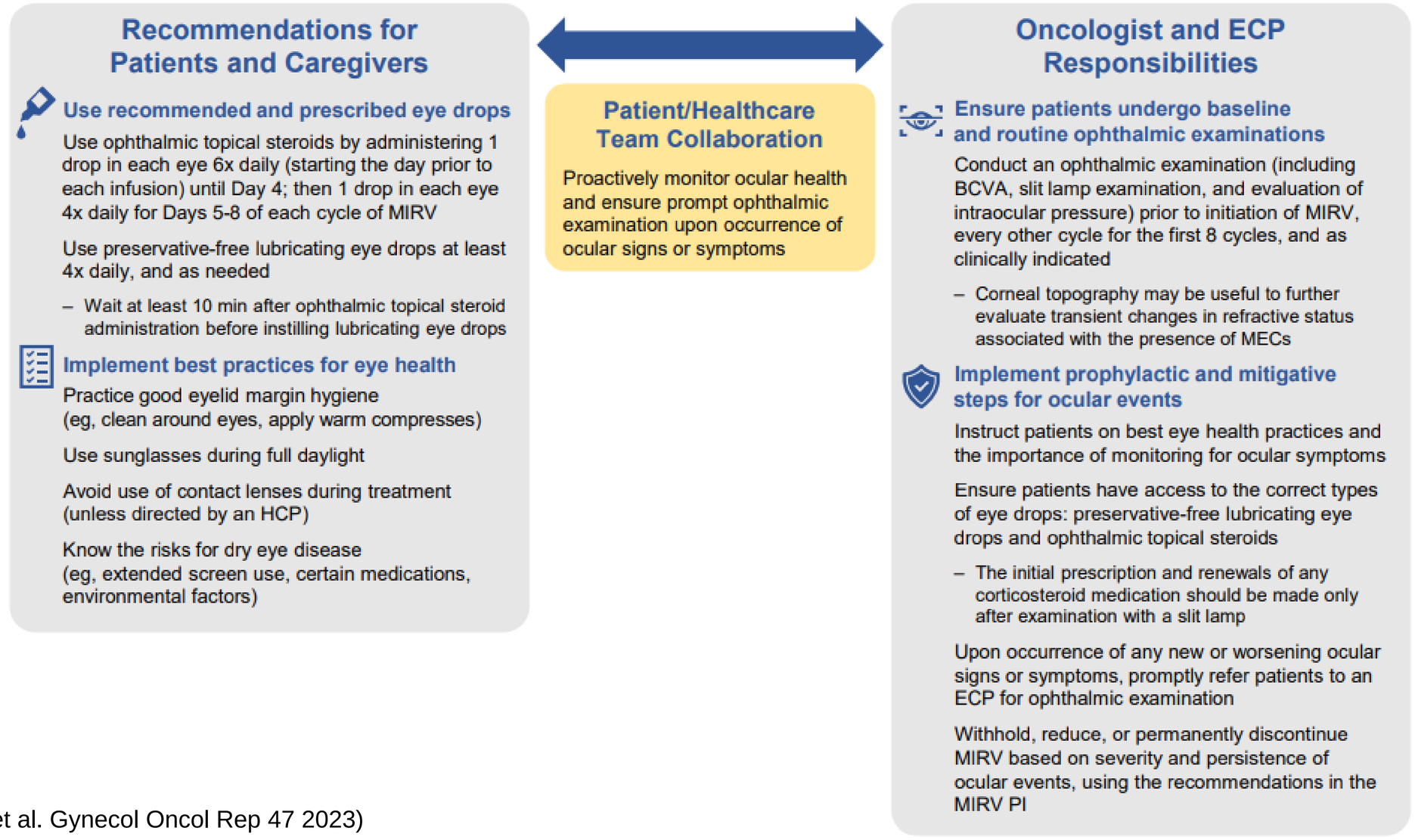
Mitigation

Table 5. MIRV Dose Modifications Due To Ocular Events

MIRV Dosing Modification	Total Integrated Safety Population (N=464)	Integrated Safety Population With Ocular Events (N=231)
No dosing-related action taken, n/N (%)	132/464 (28%)	132/231 (57%)
Dose delayed or interrupted, n/N (%)	91/464 (20%)	91/231 (39%)
Dose reduced, n/N (%)	54/464 (12%)	54/231 (23%)
Permanent discontinuation, n/N (%)	3/464 (<1%)	3/231 (1%)

- For all patients with complete follow-up data, ocular AEs resolved to grade 0/1
  - 90% of patients reporting blurred vision and 93% of patients with keratopathy had resolution to grade 1 or 0, confirmed by an eye care specialist; follow-up data are incomplete and ongoing for the remaining 10% and 7%, respectively
- Single-agent MIRV administration did not result in any corneal ulcers or corneal perforations, and no patients had permanent ocular sequelae
- On MIRASOL specifically – only 4 patients discontinued due to ocular events

Mirvetuximab Soravtansine: Prevention of Eye Tox



Hendershot et al. Gynecol Oncol Rep 47 2023)

Antibody Drug Conjugates (ADCs)
Mitigation of Treatment Related Adverse Events: Ocular

How to grade eye tox

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	

Hendershot et al. Gynecologic Oncology Reports 2023; Moore et al. Fut Oncol 2018

Mitigation Results

	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
Recommended guidelines	
	• Avoid use of contact lenses • Regular cleaning (baby shampoo, soft cloth) • Warm compress before sleep • Sunglasses in direct sunlight
Prophylactic Measures	
Lubricating eye drops (required)	• Daily administration of preservative-free eye drops (Days 1-21)
Corticosteroid eye drops (expansion cohort)	• 1% prednisolone acetate during active study treatment • Administered six times daily (Days 1-5) • Administered four times daily (Days 6-10)

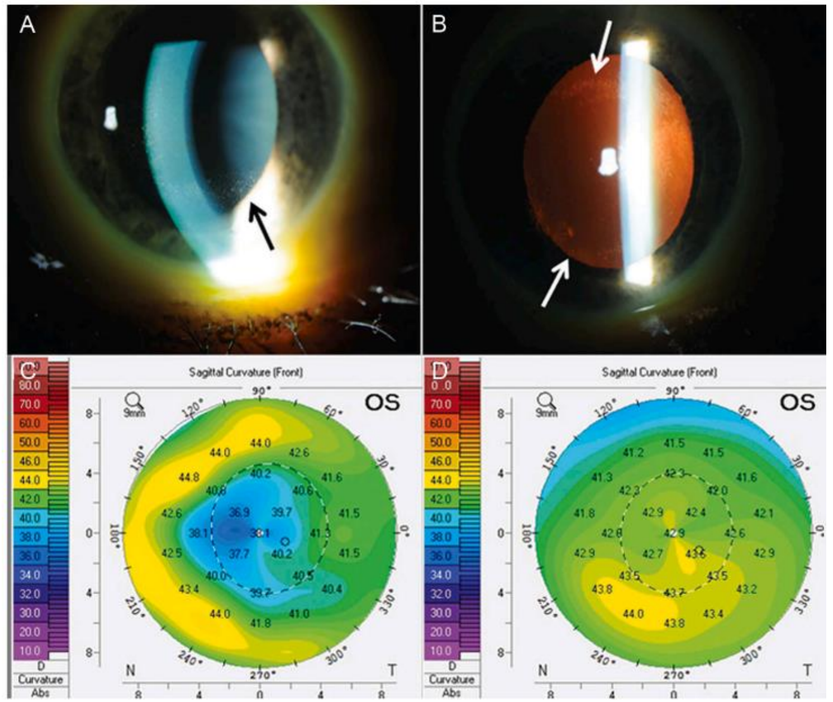
Moore et al. ASCO 2022, Moore et al. Ann Oncol 2021

Mirvetuximab Soravtansine: Case

Case 1

- 56 year old woman with normal baseline eye exam on treatment with MIRV
- After 5 weeks, she presents with complaints of blurry vision and dry eye
- She is sent to the opthomologist who performs a slit lamp
- The upper panels show the corneal microcysts while the lower panel to the left shows flattening of the corneal surface curvature

Optho Exam



Resolution

- Treatment with tobramycin/dexamethasone eye drops were started
- Symptoms resolved in 1 week
- Pt maintained on MIRV
- Figure on the lower left shows resolution of corneal topography

Hendershot et al. Gynecol Oncol Rep 47 2023); Graefe's Arch Clin Exp Opthalmol. 2019; 257(8): 1771-1781

PICCOLO

SINGLE-ARM TRIAL FOR MIRVETUXIMAB IN HIGH FRα PATIENTS WITH PLATINUM-SENSITIVE OVARIAN CANCER

Enrollment completed

Global Trial Top Line Results 2024

PRIMARY ENDPOINT
ORR by Investigator

SECONDARY ENDPOINT
DOR by Investigator

ENROLLMENT AND KEY ELIGIBILITY
75 patients
Platinum-sensitive ovarian cancer
2+ prior systemic treatments
At least 2 prior platinum-containing regimens
Prior PARPi required if BRCA+
Appropriate for single-agent therapy

ORR: overall response rate; DOR: duration of response; BRCA: BReast CAncer gene

GLORIOSA

RANDOMIZED PHASE 3 TRIAL FOR MIRVETUXIMAB + BEVACIZUMAB MAINTENANCE IN FRα-HIGH PSOC PATIENTS

TARGET TIMELINES

- Open for Accrual
- Global trial
- POTENTIAL APPROVAL 2026

PRIMARY ENDPOINT

PFS

SECONDARY ENDPOINT

OS by BICR

ENROLLMENT AND KEY ELIGIBILITY

438 patients
Platinum-sensitive ovarian cancer
1 prior systemic treatment
Prior PARPi required if BRCA+
CR, PR, or SD after treatment with platinum-based doublet + bevacizumab required

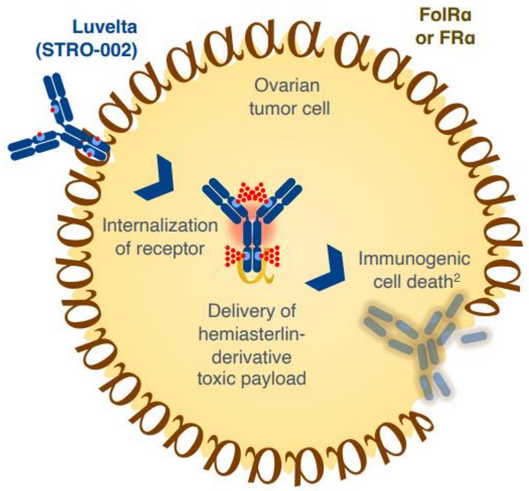
PRIOR MIRV EXPERIENCE

Strong MIRV/BEV treatment efficacy and tolerability in > 120 patients
FRα high rPSOC, MIRV/BEV has an ORR of 69% and mPFS of 13.3 months

PFS (progression-free survival); BICR (blinded independent central review); OS (overall survival); CR (complete response); PR (partial response); SD (stable disease); BRCA (BReast CAncer gene); MIRV (mirvetuximab soravtansine); DOR: duration of response; ORR: overall response rate

Other Antibody Drug Conjugates (ADCs) Targeting FRα
Luveltamab Tazevibulin (STRO-002) Phase 1

Luveltamab Tazevibulin



ADC targeting the FRα transmembrane protein, Cathepsin B linker and Hemiasterlin derivative cytotoxic payload which is less susceptible to tumor efflux pumps, causes immunogenic cell death and bystander effect
DAR=4

Efficacy

- Recurrent disease
  - Platinum resistant 1–3 prior regimens or platinum-sensitive 2–3 prior regimens
- Fresh or archival tissue required
- No mandate for FolRα expression
- At least 1 target lesion

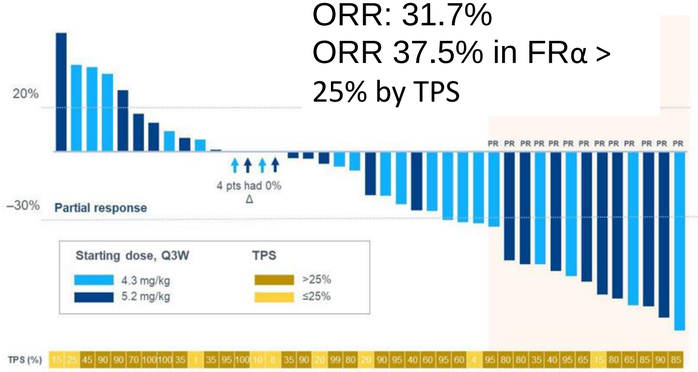
N=44

R 1:1

Luveltamab 4.3 mg/kg Q3W n=23

Luveltamab 5.2 mg/kg Q3W n=21

ORR: 31.7%
ORR 37.5% in FRα > 25% by TPS



Key TRAEs

TEAEs leading to dose reduction in 61.4%

- Neutropenia* in 17 patients (39%)
  - Primarily G3/4 uncomplicated (abnormal lab value only)
  - Febrile neutropenia in 2 patients (4.5%)
  - Resolved without growth factor support in most patients
  - Median duration of G3+ AEs, 8 days
- Arthralgia in 8 patients (18%)
- Peripheral neuropathy in 3 patients (6.8%)
  - Mostly G1/2

TEAEs leading to dose discontinuation in 3 patients (6.8%)

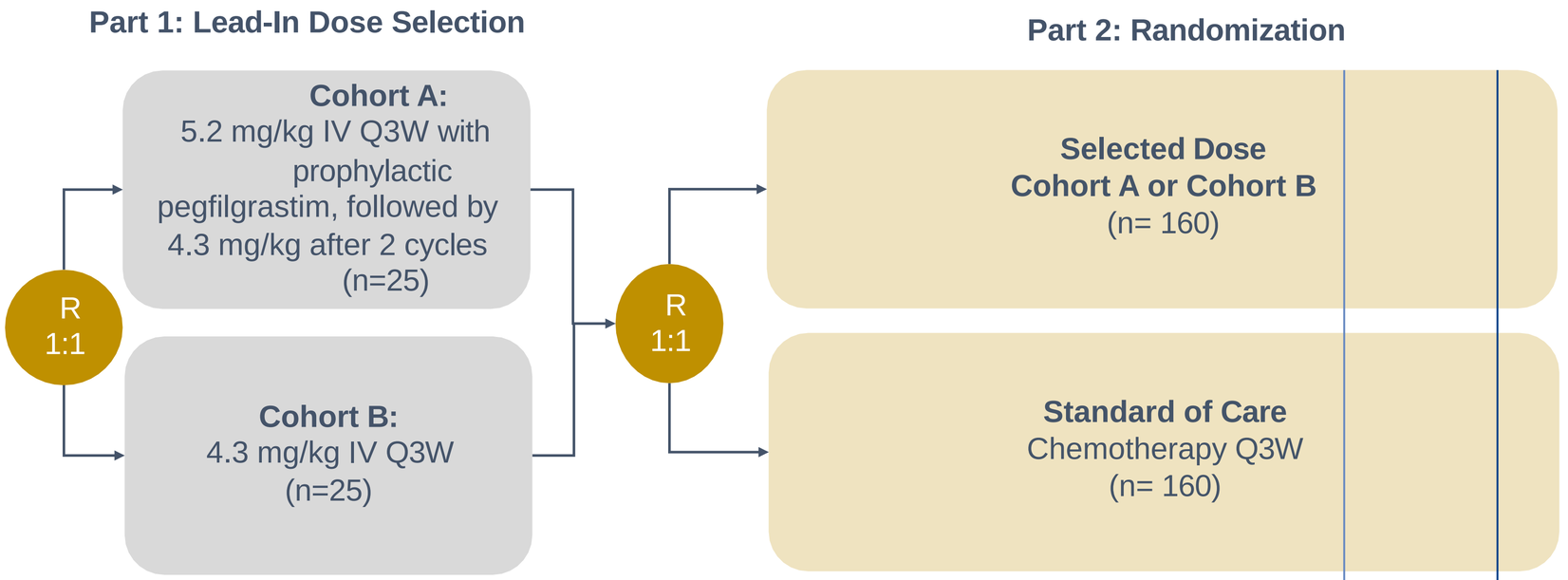
- G3 fatigue
- G2 neuropathy†
- G5 sepsis

Oaknin et al. ASCO 2023

Clinical Integrated Strategy for Phase 2/3 Study, REFRaME

LUVELTA
REFRαME|O1

Integrated design to potentially support accelerated and full approvals in platinum-resistant ovarian cancer



Key eligibility criteria

- Platinum resistant ovarian cancer, prior bevacizumab required
- 1–3 prior lines, exclude primary platinum refractory
- FolRα-selected (TPS > 25%)

Interim analysis for Accelerated Approval

- Endpoints: ORR with DOR, safety
- Interim analysis on n=110 in luvelta arm
- Minimal hit to alpha
- Estimated time to accelerated approval unchanged vs. estimated time for a single arm pivotal Ph 2 design

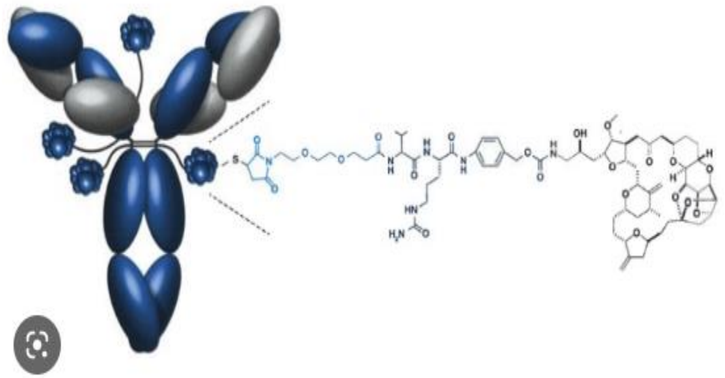
Final analysis for full approval

- Endpoint: PFS
- Full approval on PFS analysis at 160 patients, each in luvelta and standard of care
- Power 80%, HR, 0.72
- Provides most rapid time course for full approval

HR, hazard ratio; IV, intravenous; Q3W, every 3 weeks.
TPS, tumor proportion score; ORR, overall response rate; DOR, duration of response; PFS, progression free survival; HR, hazard ratio.

Other Antibody Drug Conjugates (ADCs) Targeting FRα
MORAb202

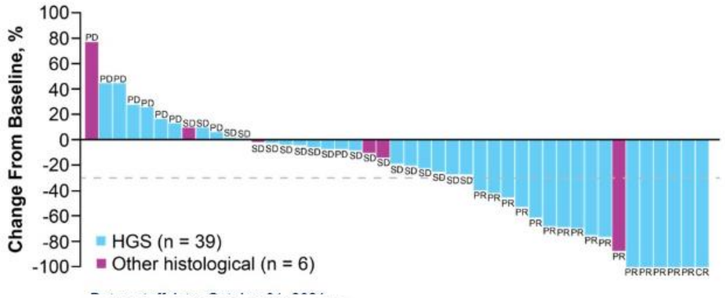
MORAb-202

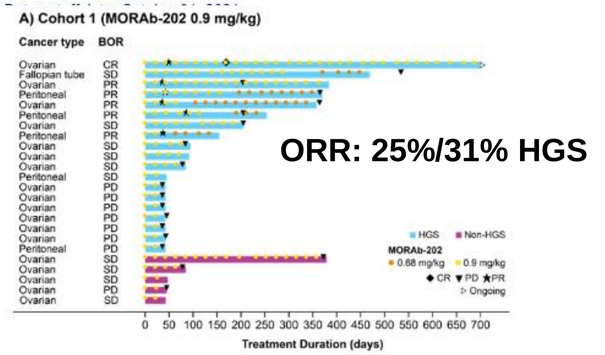


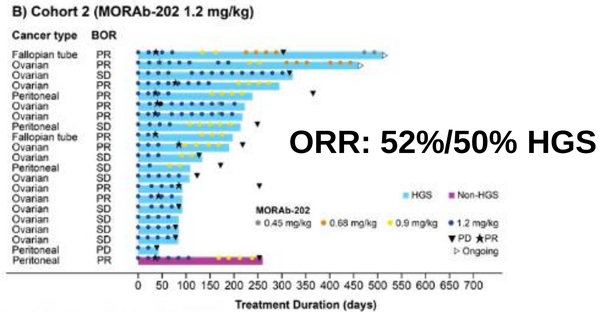
ADC targeting the FRα transmembrane protein using the monoclonal Ab Farletuzumab conjugated to the microtubule toxin eribulin

Two doses are being explored: 0.9 mg/kg and 1.2 mg/kg every 3 weeks

Efficacy







Nishio et al. ASCO 2022

Key TRAEs

- The most common TEAE at both dose levels was ILD/pneumonitis.
- Bone marrow suppression, as indicated by neutropenia, anemia, and leukopenia, was mostly low-grade (2 events of grade 3 anemia) in Study 101.
  - Neutropenia, anemia, and leukopenia were reported as non-serious TEAEs occurring in 4.4%, 8.9% and 2.2% of patients in the overall PROC cohort, respectively.

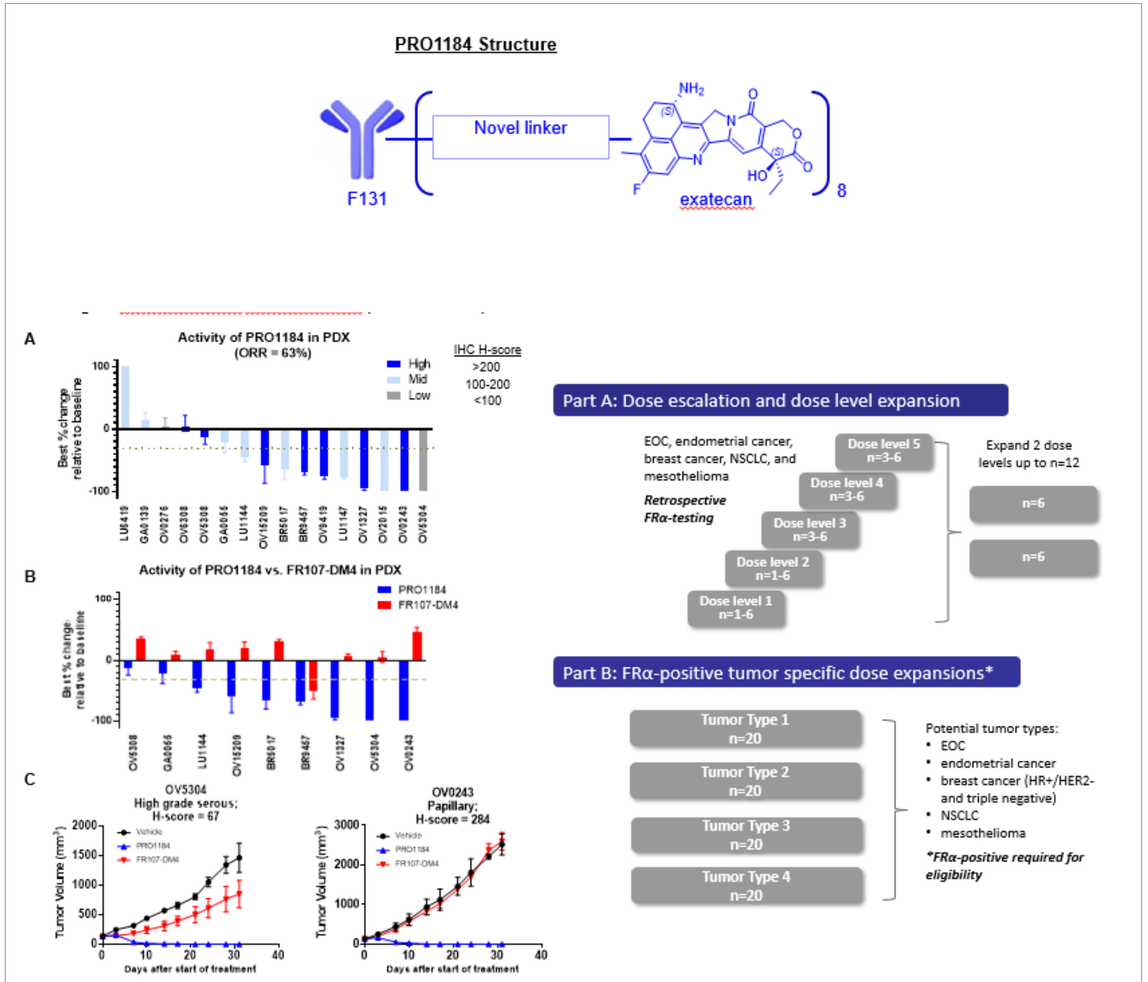
Parameter, n (%)		Cohort 1 (n = 24) MORAb-202 0.9 mg/kg	Cohort 2 (n = 21) MORAb-202 1.2 mg/kg
Any ILD/Pneumonitis event		9 (37.5)	14 (66.7)
Severity:	Grade 1	8 (33.3)	6 (28.6)
	Grade 2	1 (4.2)	7 (33.3)
	Grade 3	0	1 (4.8)
	Grade 4	0	0
	Grade 5	0	0
Serious respiratory event[a]		2 (8.3)	3 (14.3)
ILD/Pneumonitis event leading to MORAb-202:			
	Discontinuation	1 (4.2)	5 (23.8)
	Dose reduction	5 (20.8)	9 (42.9)
	Dose interruption	1 (4.2)	4 (19.0)

Data cutoff date: October 31, 2021.
[a]Includes pneumonitis, ILD, dyspnea.

Dose optimization is ongoing in the RPh2 NCT05613088 in PROC 0.9 mg/kg vs 1.2 mg/kg vs IC chemo

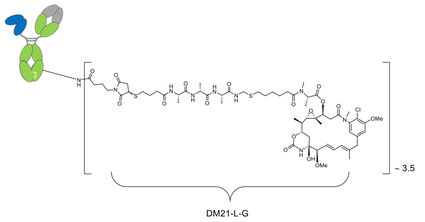
Other Antibody Drug Conjugates (ADCs) Targeting FRα
PRO1184 & IMGN151 Phase I Studies

PRO1184

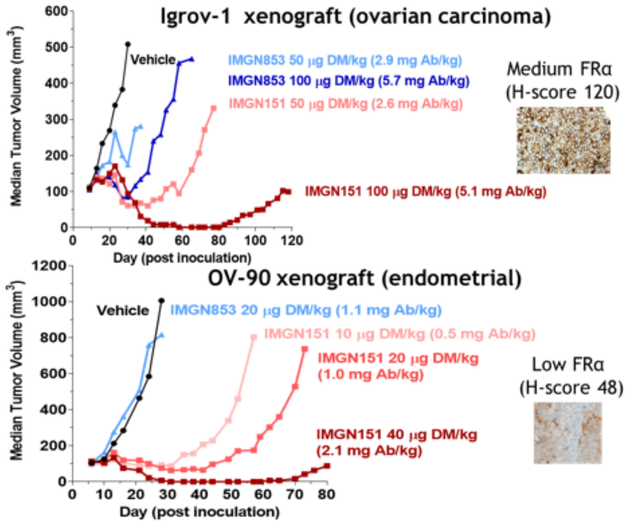


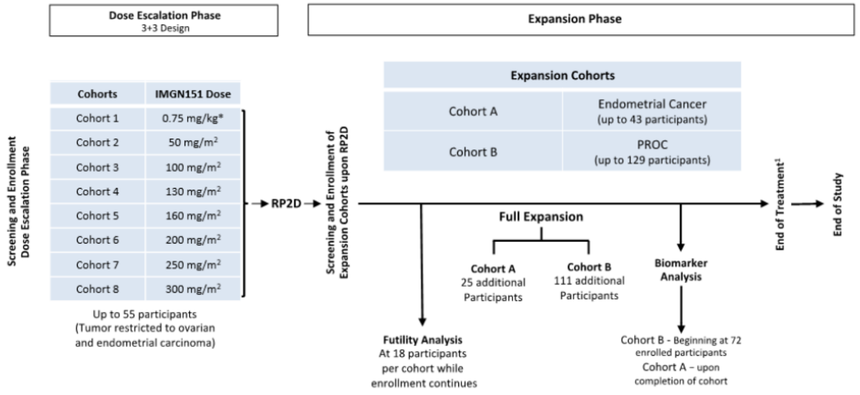
Call et al. AACR 2023 Abstract #9329

IMGN 151



- B5327A: asymmetric biparatopic anti-FRα antibody comprised of IMGN853 arm and a scFv-arm targeting an independent epitope of FRα
- DM21-L-G: new more potent maytansine-derived payload/linker





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Conclusions

- Mirvetuximab Soravtansine (Elahere) is now FDA approved based on Accelerated Approval in the US as of Nov 2022.
- Results of MIRASOL to be released ASCO 2023 with anticipated full FDA approval as well as global authorization
- Current indication is for platinum resistant ovarian cancer with folate receptor alpha high expressing tumors
- Dosing is IV, every 3 weeks with a differentiated safety profile and enhanced efficacy as compared to standard medicines
- Mitigation strategies and attention to ocular disorders allows patients to maintain dosing and benefit from MIRV without permanent ocular impairment
- Several other agents with novel targets and payloads are UD