



VÅRMÖTE I PATOLOGI

NPM2025
19–21 MAY

NORDIC PATHOLOGY MEETING



The FOLR1 Biomarker: Advancing Tubo-Ovarian Cancer Management Beyond Chemotherapy

Gold sponsor symposium – Roche Diagnostics

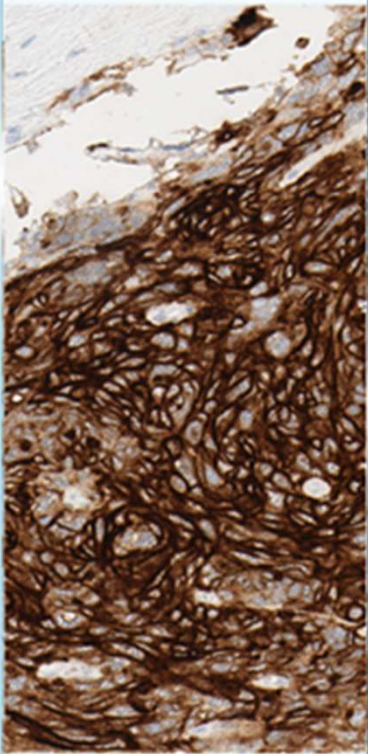
Emilia Andersson
MD, PhD, Pathologist
Oncology lead Roche Diagnostics Medical and Government Affairs EMEA-LATAM

20.05.2025 Elite Hotel Marina Tower in Stockholm

Disclaimer

- Emilia Andersson is a full time employee of Roche Diagnostics
- The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is approved in the EU and Roche Diagnostics is providing this medical and scientific education to prepare pathologists to be confident in the interpretation of the VENTANA FOLR1 Assay to ensure there is no delay in identifying patients eligible for mirvetuximab soravtansine
- **This presentation is for educational purposes only**

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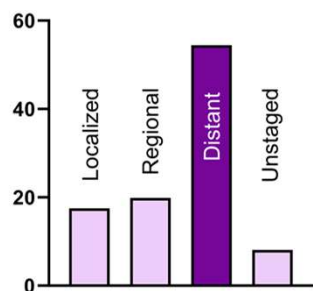
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VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Disease context

Tubo-Ovarian cancer (OC) background

Disease Burden²



- Asymptomatic in early stages
- Majority of diagnosis occurs at advanced stages

Epidemiology¹

- 300 000 new cases per year
- 8th most common cancer in women worldwide
- Over 200,000 deaths per year
- Number of annual deaths is projected to increase 50% by 2040

Histology

- OC can be of epithelial, mesenchymal, sex cord stromal and germ cell origin
- Majority of cases are epithelial ovarian cancers (EOC)
- EOC is comprised of 5 distinct subtypes³
 - High-grade serous (HGSOC), low-grade serous, endometrioid, clear cell & mucinous

HGSOC & Treatment^{4,5}

- **Accounts for 75% of all OC & 90% of all mortalities⁶**
- **Molecular testing for BRCA ½ and HRD recommended for all OC patients to guide 1L treatment**
- **Surgery** → platinum/taxane chemotherapy +/- bevacizumab (anti-VEGF)
- **Maintenance:** bevacizumab +/- PARPi

¹ Globocan database, <https://gco.iarc.fr/>, accessed June 2023, SEER database, <https://seer.cancer.gov/>, accessed June 2023

² SEER database: <https://seer.cancer.gov/>, accessed in Jan. 2022

³ De Leo, A, et al. What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors. *Diagnostics*. 2021; 11(4):697. <https://doi.org/10.3390/diagnostics11040697>

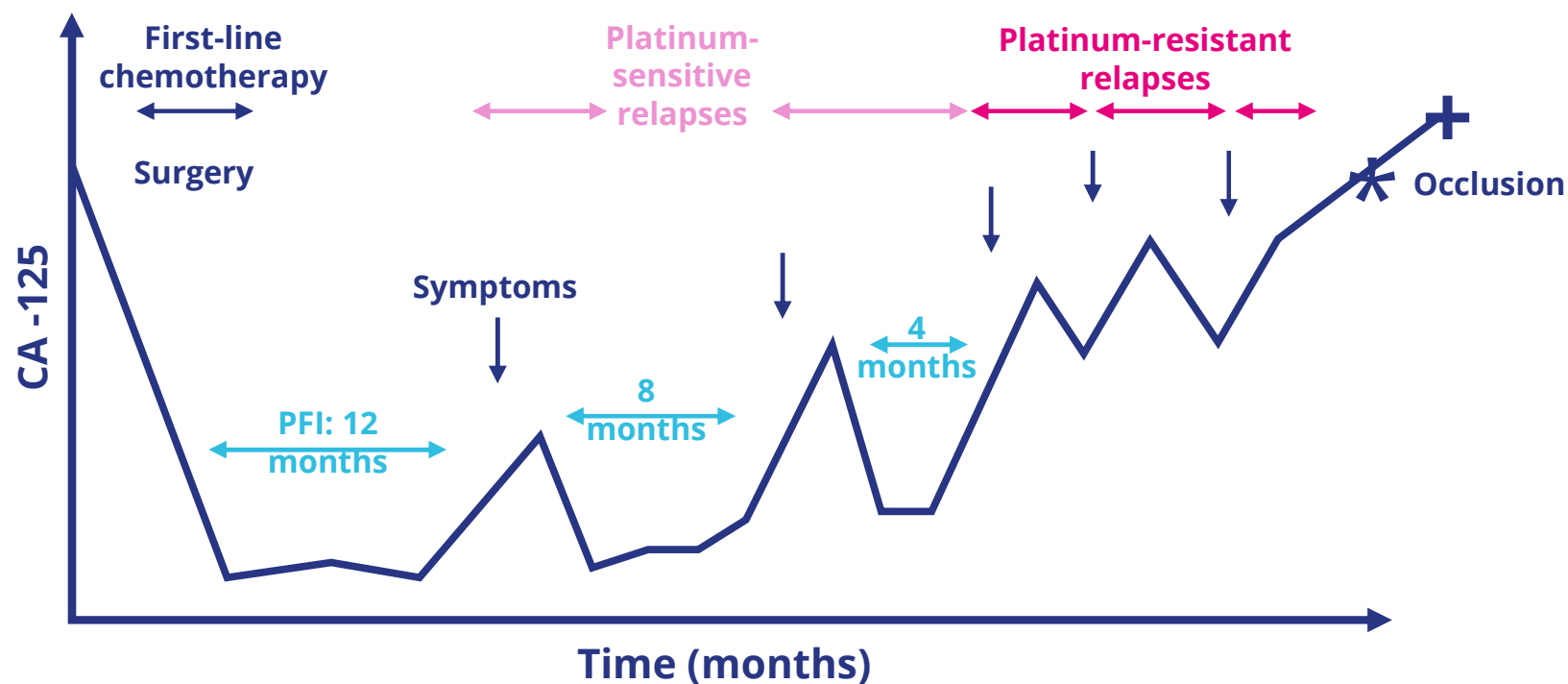
⁴ NCCN Guidelines for Epithelial Ovarian Cancer Version 1.2022 (www.nccn.org)

⁵ Ledermann, J. A., et al. (2013). "Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Ann Oncol* 24 Suppl 6: vi24-32.DOI: 10.1093/annonc/mdt333

⁶ Lheureux, S., et al. (2019). "Epithelial ovarian cancer." *Lancet* 393(10177): 1240-1253.DOI: 10.1016/S0140-6736(18)32552-2

Advanced ovarian cancer: a “chronic” disease with multiple relapses

Despite aggressive therapy (surgery/chemotherapy) 70% of patients with advanced EOC will have their disease recur¹



PFI: platinum-free interval or duration of disease control without chemotherapy.

¹ Richardson, Debra L et al. "Advances in Ovarian Cancer Care and Unmet Treatment Needs for Patients With Platinum Resistance: A Narrative Review." JAMA oncology vol. 9,6 (2023): 851-859. doi:10.1001/jamaoncol.2023.0197
Du Bois a, Pfisterer J. Zentralbl Gynakol. 2004;126:312-4.

Folate receptor-alpha (FR α)

Background and therapeutic targeting in cancer

Folate is a water soluble vitamin essential for

- **DNA and RNA synthesis** in normal cell **growth and development**

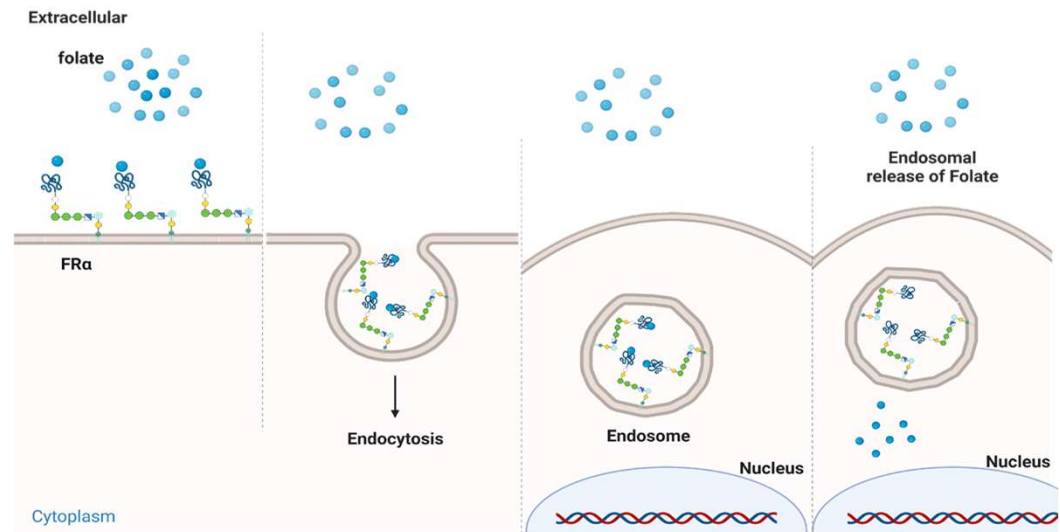
Expression of membrane bound cell surface **FR α** is high during periods of rapid cell growth and division,

- such as **pregnancy and embryogenesis**, but is **limited** in most (not all) **adult tissues**, as they utilize an alternative transporter for folate uptake

Due to FR α 's role in cell growth, FR α is **overexpressed in certain**

- **cancers**

The combination of restricted expression in normal tissue and overexpression in tumor tissue makes FR α an ideal clinical **target**



Tumors shown to overexpress* FR α :

Breast, Lung, Endometrial, Ovarian



35-70%



15-75%



20-50%



75-90%

*derived from the literature using different detection techniques, numbers of specimens and thresholds for determining expression

Review of Folate receptor-alpha (FR α) targeting clinical trials

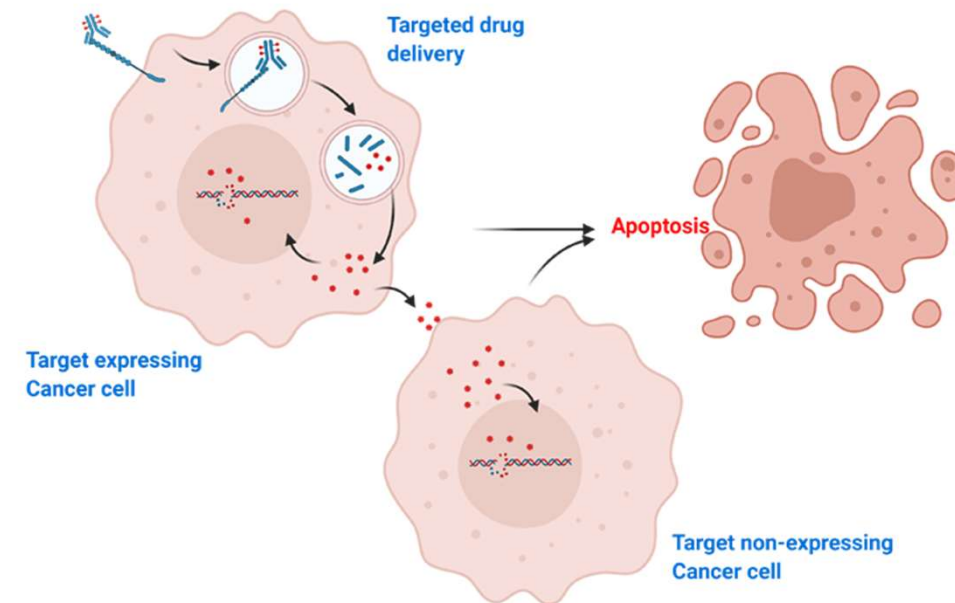
Mirvetuximab soravtansine

Mirvetuximab soravtansine-gynx (ELAHERE®)

Drug mechanism

- ELAHERE is an antibody-drug conjugate (ADC) targeting the FR α protein¹ on the cell surface and is internalized by the cell
- As the ADC is broken down, the cytotoxic drug is released, resulting in cell death including bystander effects due to diffusion of toxic metabolites
- By selectively targeting tumors express FR α , physicians can target the patient's cancer and reduce unwanted drug side effects
- Efficacy correlates directly with FR α protein expression levels

Identifying the level of FR α present in a patient's tumor is critical to ensure efficacy of ELAHERE



Developed by ImmunoGen, Inc. (now AbbVie)

Phase 2 & 3 MIRV Clinical Development Timeline

Overview of key clinical trials

FORWARD 1 Double arm

Did not meet primary endpoint but promising activity in a predefined subset of patients with high FOLR1 expression

SORAYA Single arm

Robust evidence for the efficacy of mirvetuximab soravtansine vs historical data

Led to accelerated conditional FDA approval
Nov 2022

MIRASOL Double arm

Confirmatory study.

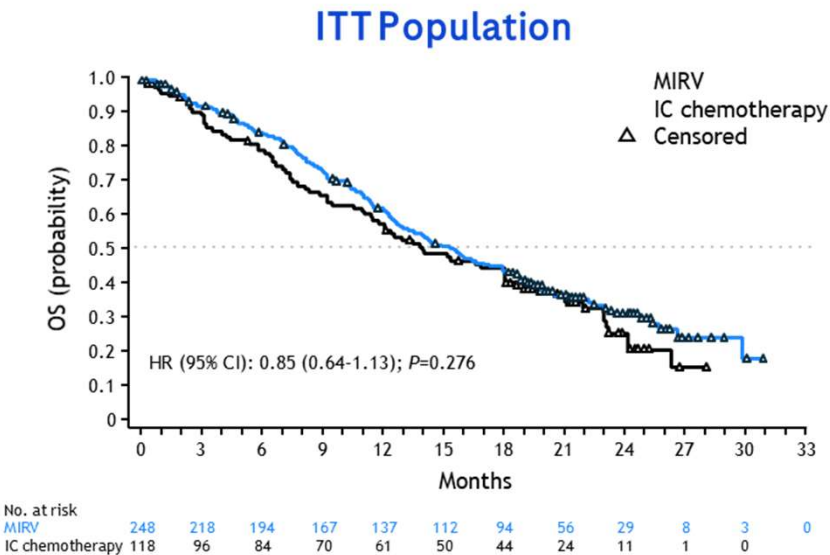
Led to full FDA approval
Mar 2024 and EMA approval Nov 2024

All trials used the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay to determine patient FRa expression

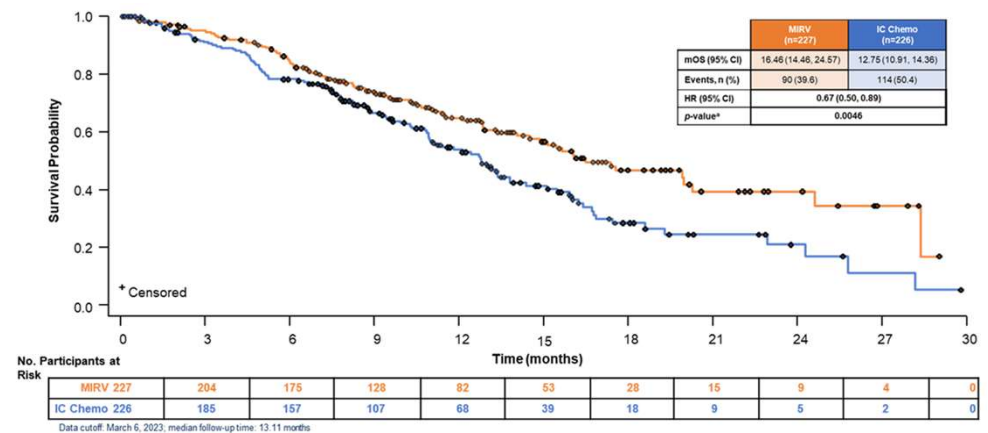
VENTANA® FOLR1 (FOLR1-2.1) RxDx Assay

The cutoff for eligibility

- FORWARD 1 trial: Negative results
 - Patient selection: (**≥50%** with membrane staining visible at 10x)



- MIRASOL trial: Positive results
 - Patient selection: (**≥75%** of cells with ≥2+ membrane staining intensity)



FDA and EMA granted full approval in 2024

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

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On March 22, 2024, the Food and Drug Administration approved mirvetuximab soravtansine-gynx (Elahere, ImmunoGen, Inc. [now a part of AbbVie]) for adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Patients are selected based on an FDA-approved test. Mirvetuximab soravtansine-gynx previously received accelerated approval for this indication.

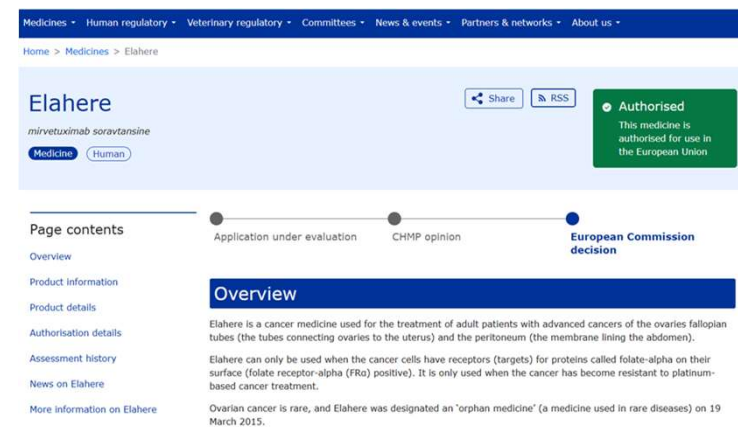
Full prescribing information for Elahere will be posted [here](#).

Efficacy was evaluated in Study 0416 (MIRASOL, NCT04209855), a multicenter, open-label, active-controlled, randomized, two-arm trial in 453 patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients were permitted to receive up to three prior lines of systemic therapy. The trial enrolled patients whose tumors were positive for FRα expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Patients were randomized (1:1) to receive mirvetuximab soravtansine-gynx 6 mg/kg (based on adjusted ideal body weight) as an intravenous infusion every 3 weeks or investigator's choice of chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or

Content current as of:
03/22/2024

INDICATIONS AND USAGE

ELAHERE is a folate receptor alpha (FRα)-directed antibody and microtubule inhibitor conjugate indicated for the treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Select patients for therapy based on an FDA-approved test. (1, 2.1)



4.1 Therapeutic indications

ELAHERE as monotherapy is indicated for the treatment of adult patients with folate receptor-alpha (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens (see section 4.2).

Archives of Pathology & Laboratory Medicine Manuscript

Available [online](#)



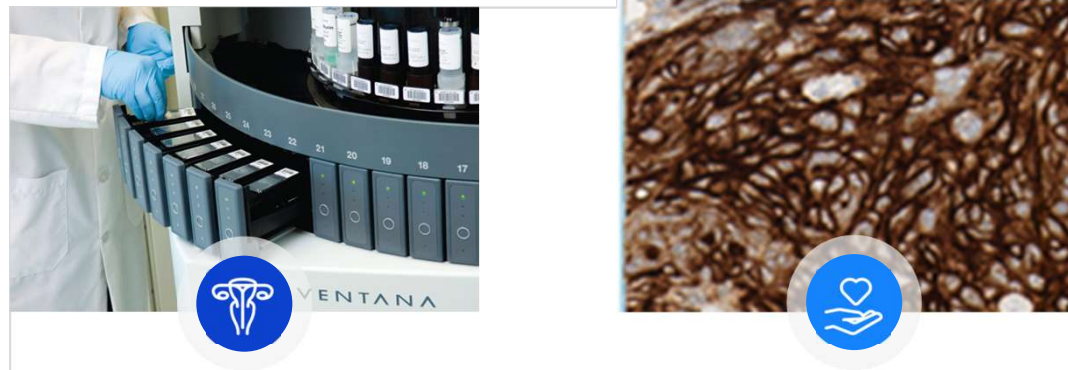
Development of an FR α Companion Diagnostic Immunohistochemical Assay for Mirvetuximab Soravtansine

Racheal L. James, BS; Taryn Sisserson, MS; Zhuangyu Cai, PhD; Megan E. Dumas, PhD; Landon J. Inge, PhD; James Ranger-Moore, PhD; Albert Mason, MD; Callum M. Sloss, PhD; Katherine McArthur, MS



- Describes the analytical verification performed to ensure the VENTANA FOLR1 Assay was reproducible for the clinical setting
 - Inter/Intra reader precision
 - Inter antibody, detection, instrument and day precision
 - Interlaboratory Reproducibility
- Reports the assay performance in the registrational SORAYA trial

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay



Analytically and clinically validated IHC assay to detect FR α in epithelial ovarian, primary peritoneal, and primary fallopian tube cancer.

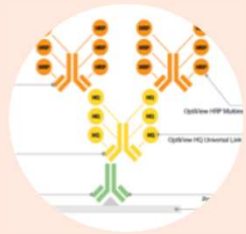
VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is the first and only FDA-and CE-IVD approved IHC companion diagnostic for determining FR α protein expression in high grade EOC patients who may benefit from ELAHERE therapy.

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Assay configuration



VENTANA FOLR1
(FOLR1-2.1) RxDx
Assay



OptiView DAB IHC
Detection Kit



Negative Control
(monoclonal)



BenchMark IHC/ISH
instruments



Interpretation Guide /
Scoring Algorithm



Mirvetuximab soravtansine

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Specimen Types

Validated specimens

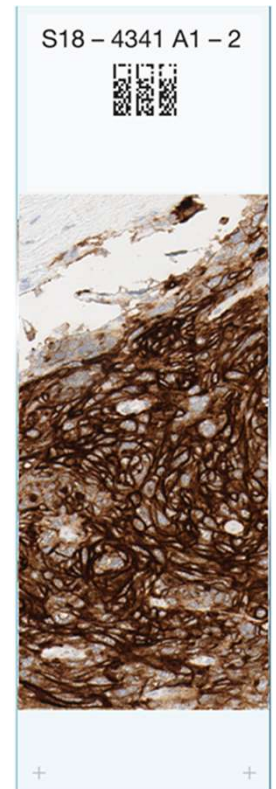
- Primary ovarian cancer, fallopian tube cancer and primary peritoneal cancer
- Formalin-fixed and paraffin embedded
- Archival or fresh tissues from resections, excisions, and biopsies
- Primary and metastatic sites

Non-validated specimens

- Cytology samples
- Decalcified metastatic bone lesions

System level control

- Fallopian tube with 2+ staining intensity in the epithelial cells



VENTANA FOLR1 (FOLR1-2.1) Rx Dx Assay

Specimen Pre-analytical Factors



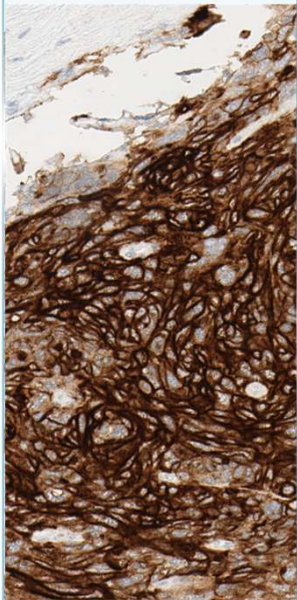
Specimens should be:

- Fixation (12-72 hours) with 10% neutral buffered formalin
- 6 hour minimum fixation for small biopsies
- Sectioned at a thickness of 4µm and placed onto positively charged slides
- Cut slide stability: no more than 45 days

***Fixation with alcohol based fixatives is not recommended**

Fixation Time (hrs)	10% NBF
1*	
6*	
12	
24	
48	
72	

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VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Staining Interpretation

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

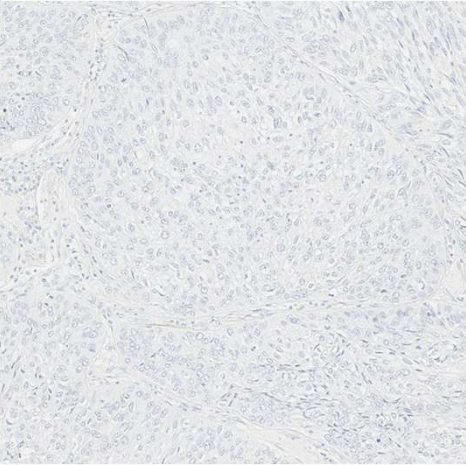
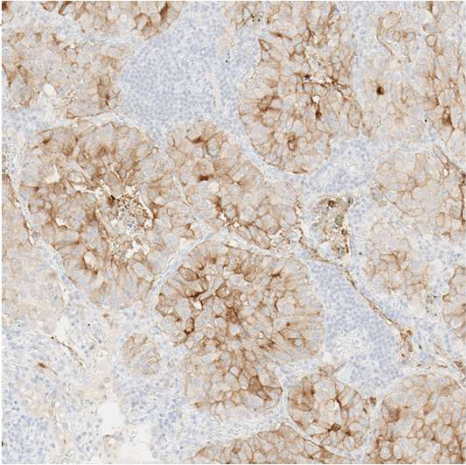
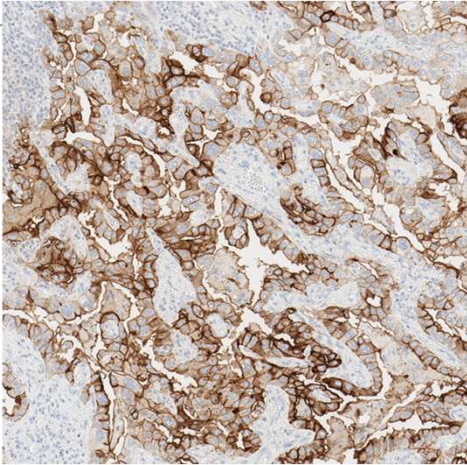
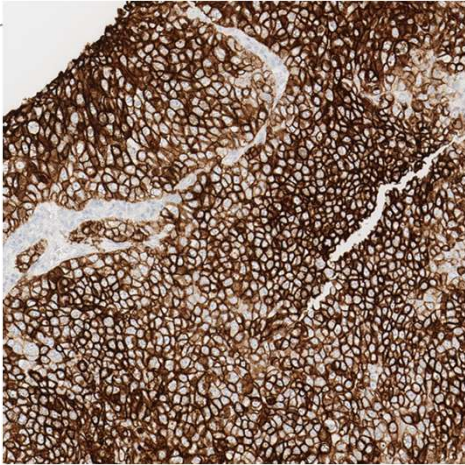
Scoring Criteria

- **membrane** staining is included in scoring
 - **Partial** and/or **complete**
 - **Apical, circumferential** distribution
 - When variable intensities are seen in a single cell, the **highest intensity** is scored
- Excluded from scoring:
 - Necrotic, crushed or cauterized cells
 - Cytoplasmic staining

VENTANA® FOLR1 (FOLR1-2.1) RxDx Assay



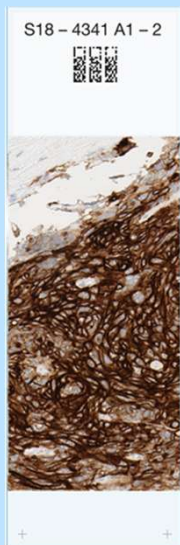
Tumor cell intensity characteristics

0	1+	2+	3+
			
Absence of any detectable signal. Negative cases may still exhibit pale grey cytoplasmic and/or membranous discoloration.	Signal intensity is characterized by a faint gold/light brown hue	Signal intensity is characterized by a chocolate brown to thickened dark brown, black hue	

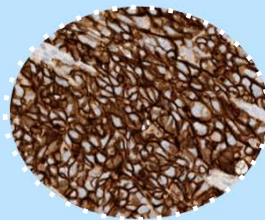
Note: Relative ease of visualization of membrane staining can be impacted by presence/absence of concurrent cytoplasmic staining and its intensity

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

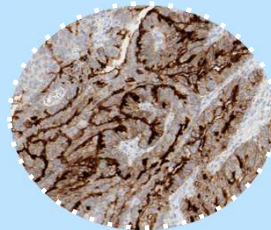
Staining Characteristics



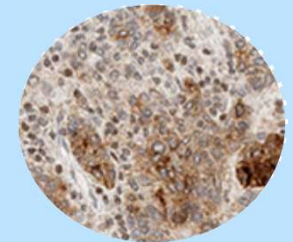
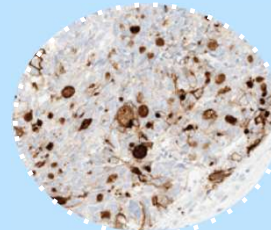
Membrane Staining



Apical Staining



Dot Like Staining



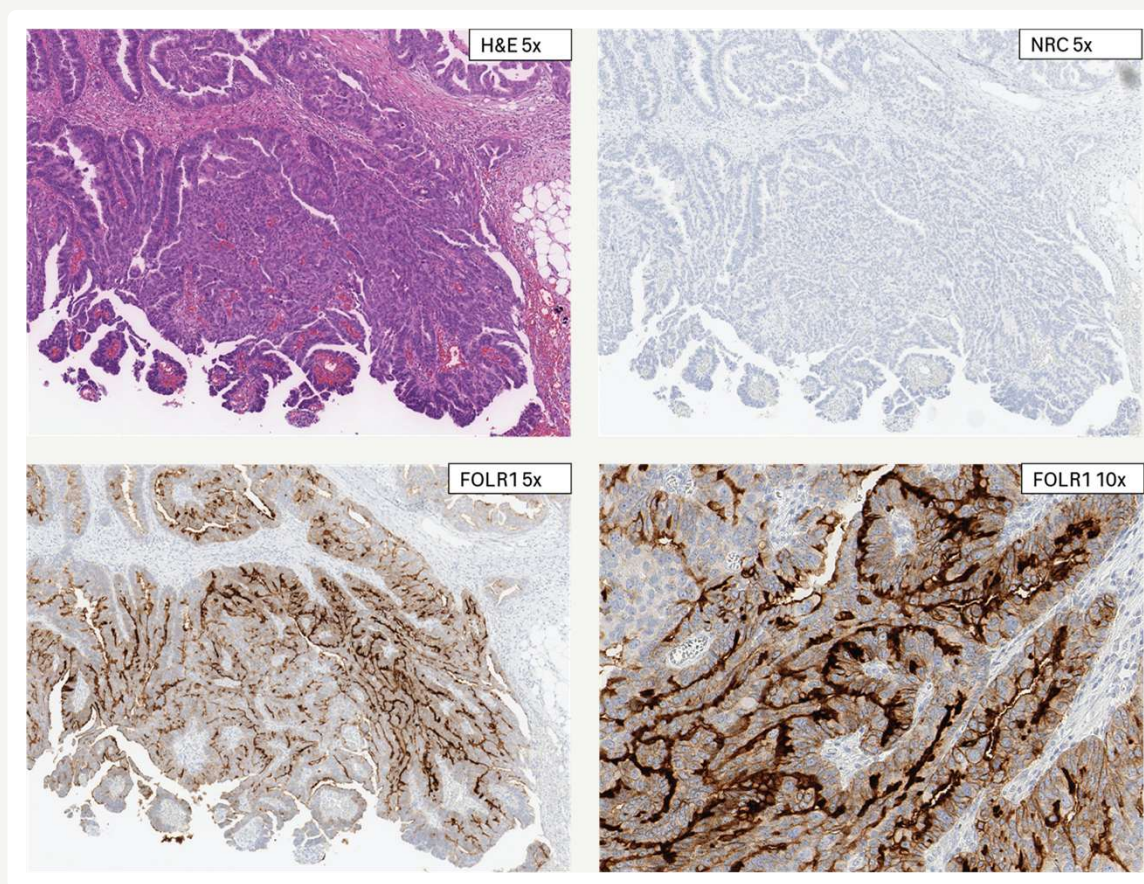
Cytoplasmic

Though rare, EOC cases can exhibit dot-like or apical staining that can make interpretation challenging. Both are considered as membranous staining.

FRa cytoplasmic staining should not be scored

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Apical staining



VENTANA FOLR1 (FOLR1-2.1) Rx Dx Assay

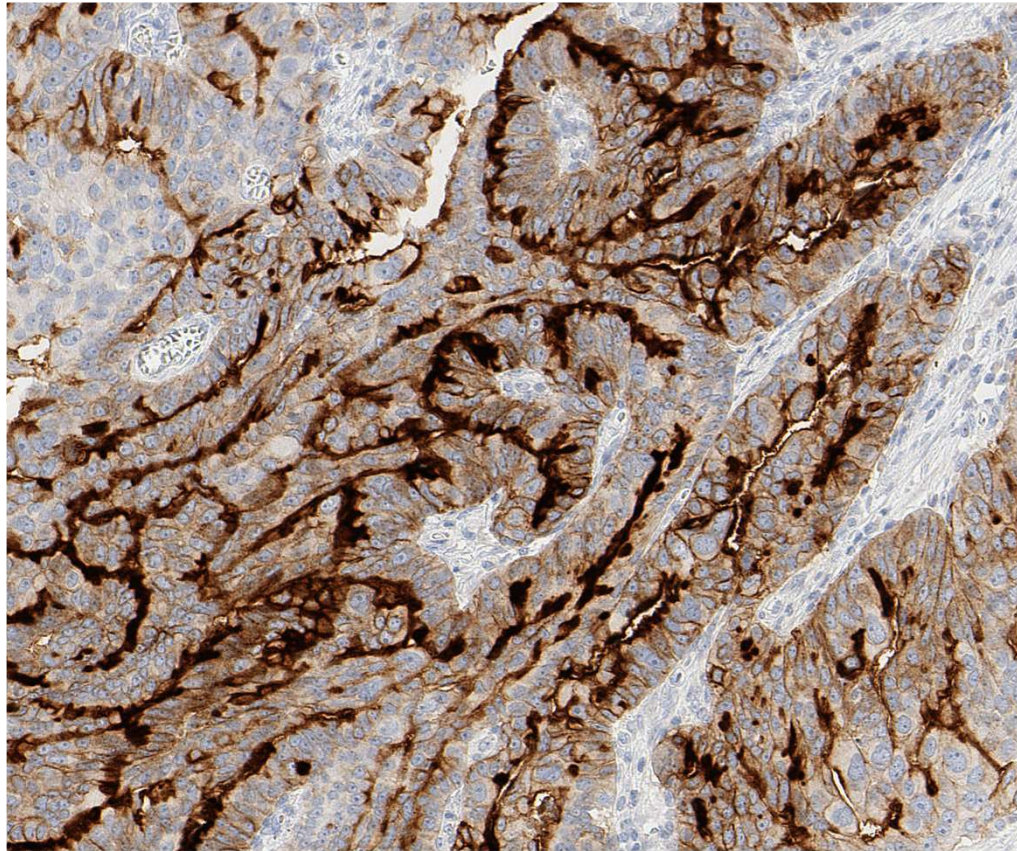
Apical staining

Apical Staining:

When there is apical staining in a cell, the entire cell should be **considered positive**.

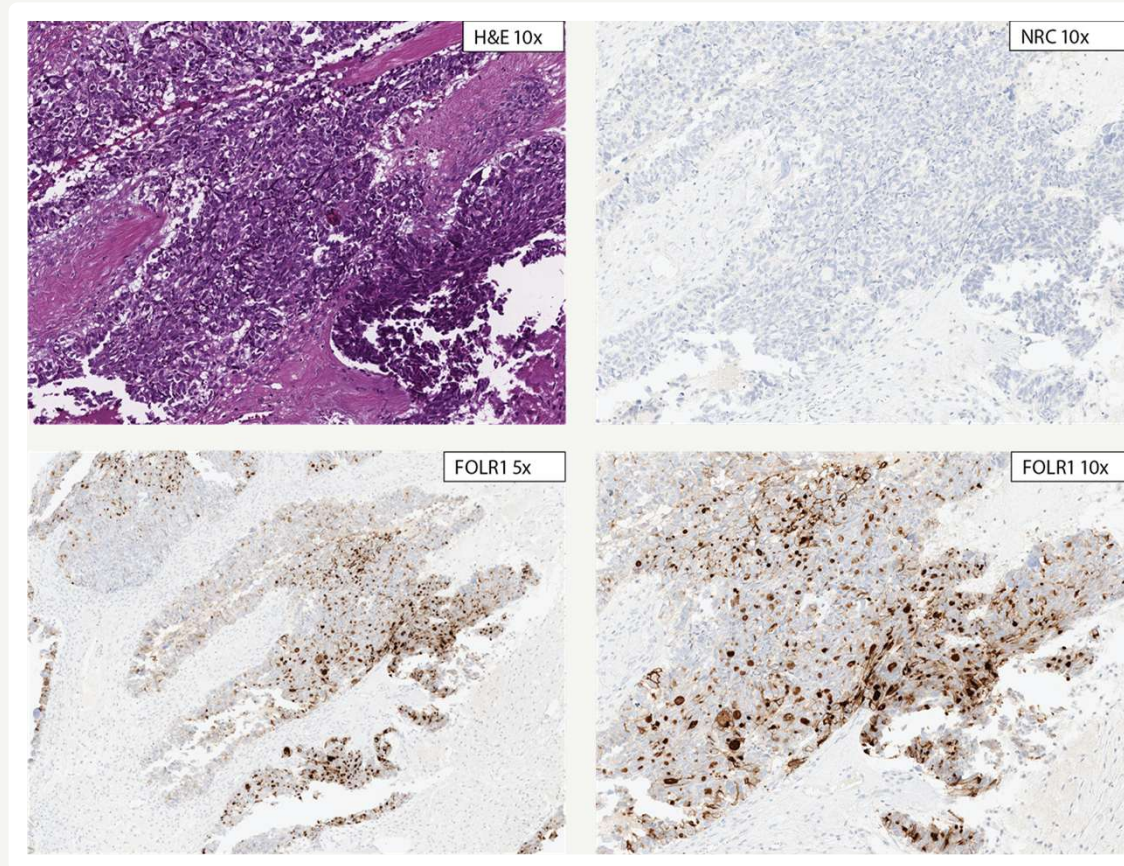
When variable intensities are seen in a single cell, **the highest intensity is scored**

Risk of underscoring



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Dot-like staining pattern



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Dot-like staining pattern

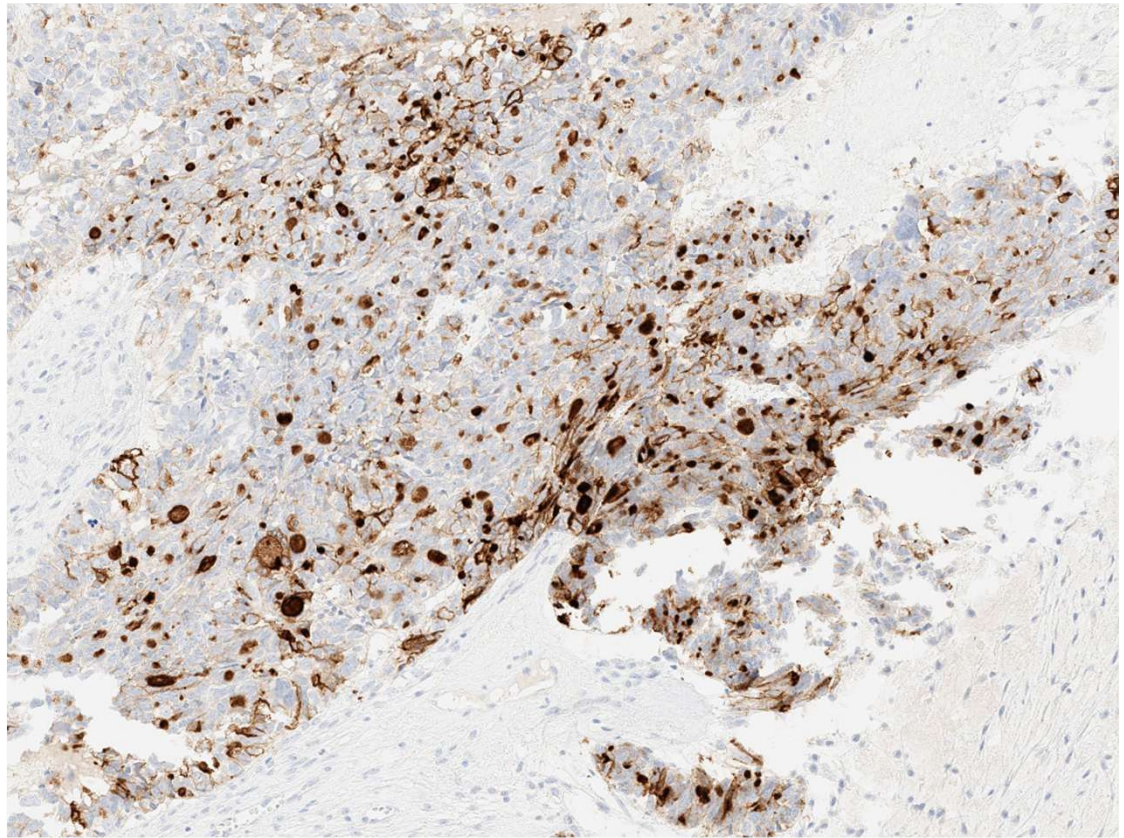
Dot-like Pattern Staining:

Apical staining in gland forming morphology.

The entire cell should be **considered positive.**

When variable intensities are seen in a single cell, **the highest intensity is scored**

Risk of underscoring



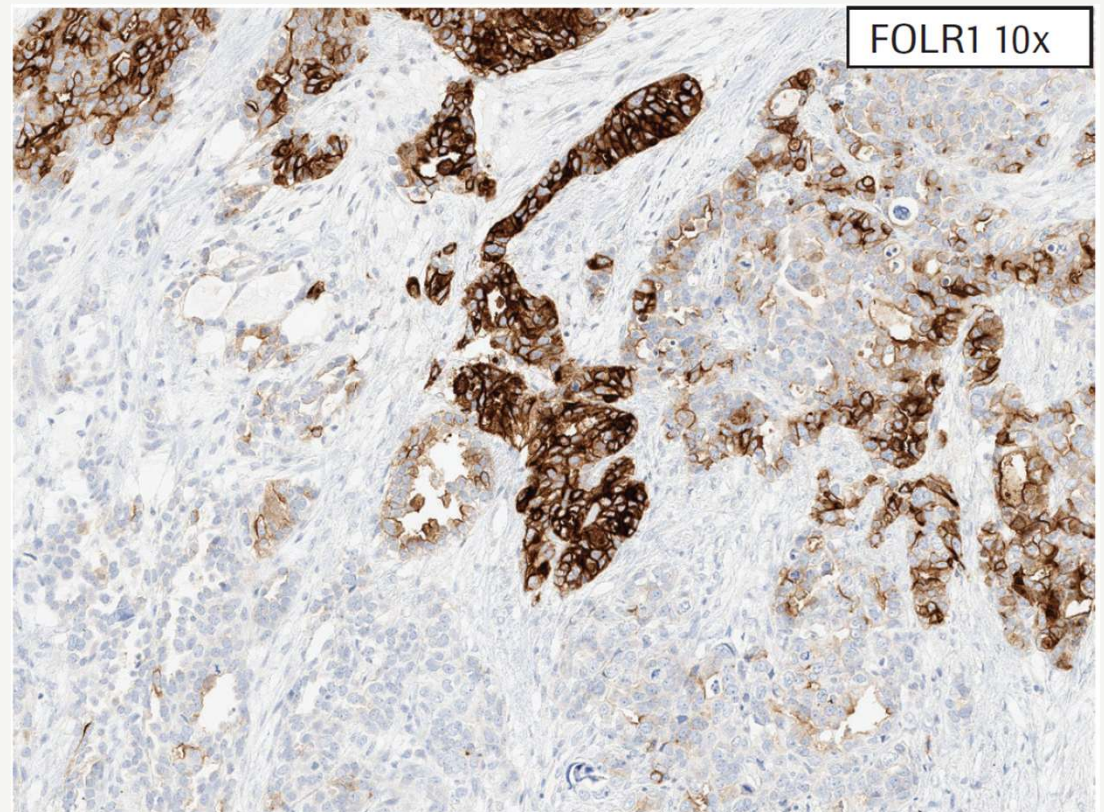
VENTANA FOLR1 (FOLR1-2.1) Rx Dx Assay

Heterogeneity

Heterogeneous Staining:

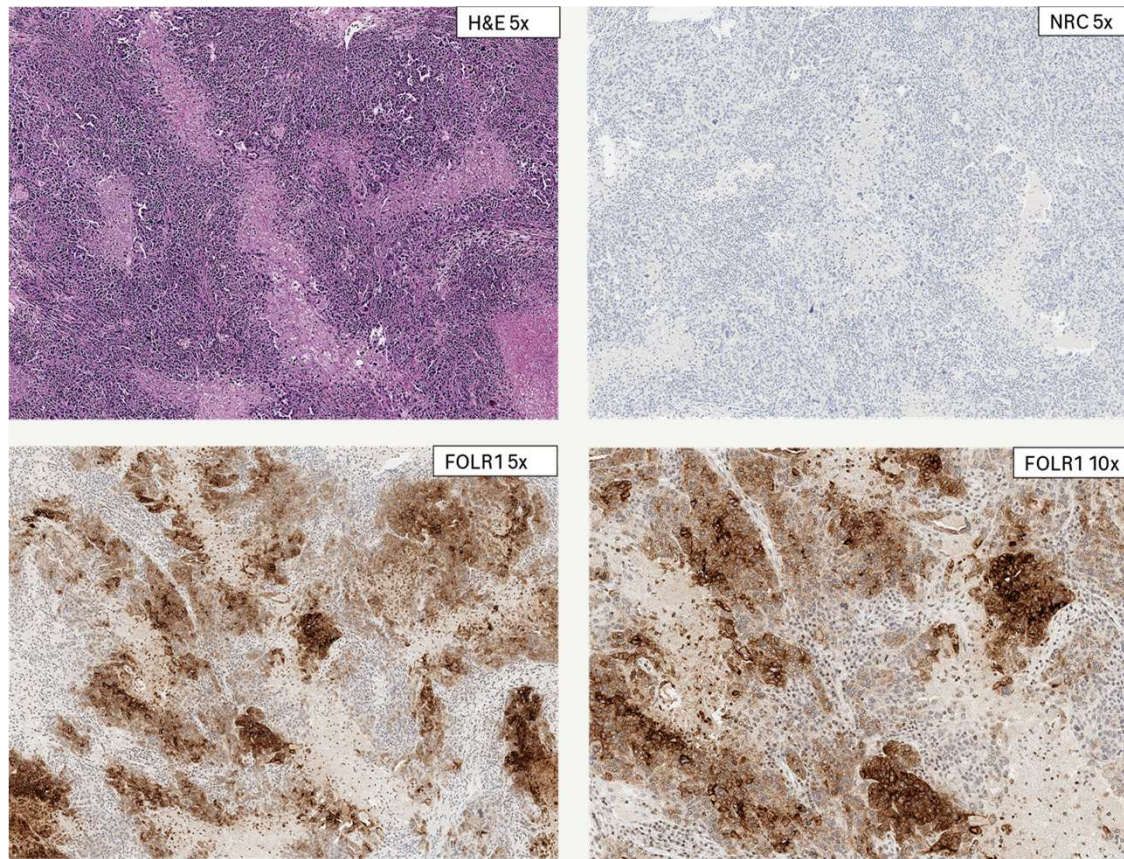
Pay attention to non staining areas.

Risk of overscoring



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

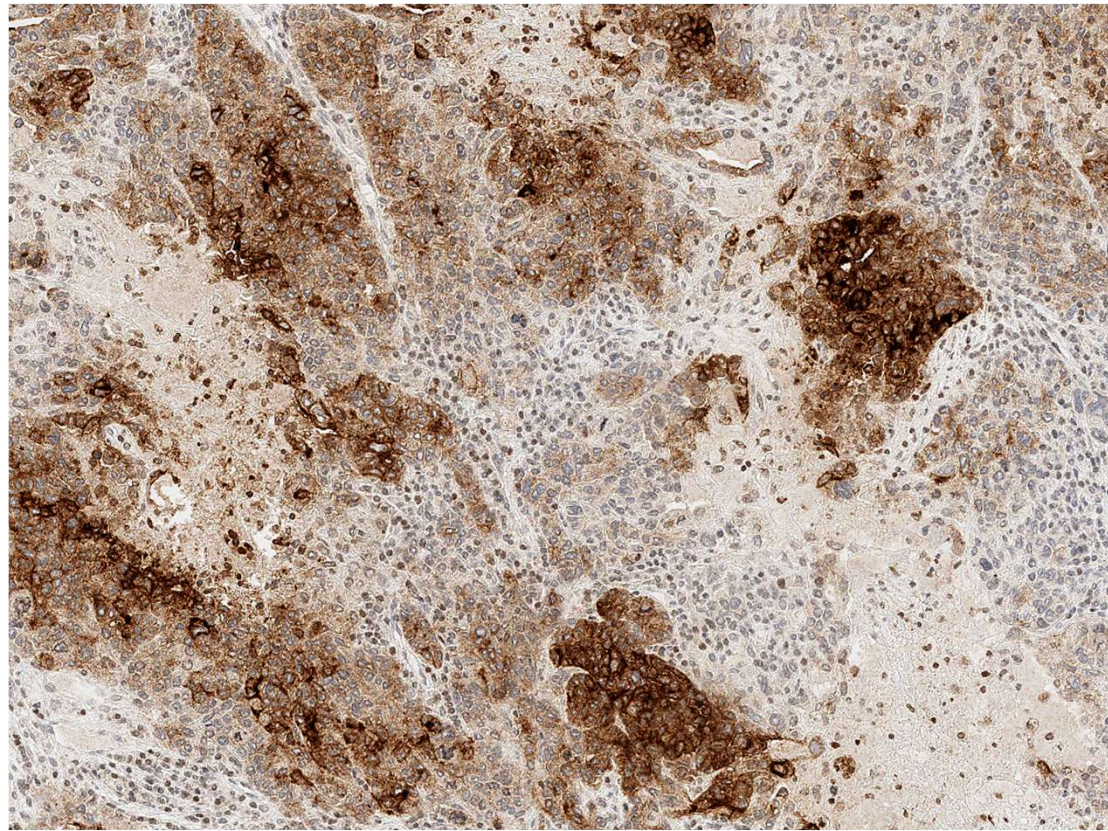
Mix of cytoplasmic and membrane staining



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Cytoplasmic and membrane staining

Cytoplasmic Staining:
Only include cells with membrane
staining.
Risk of overscoring

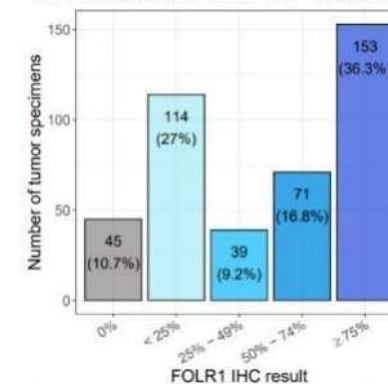


Real world FOLR1 data

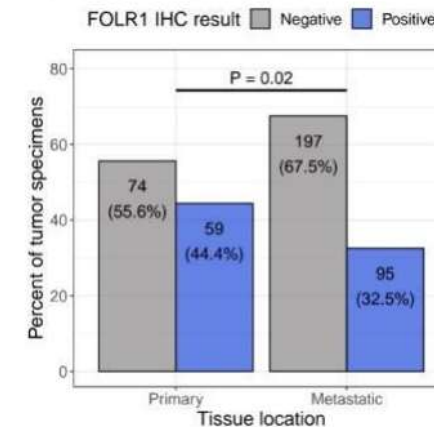
Analysis of real world FOLR1 testing in ovarian, fallopian tube, and primary peritoneal cancer

- Retrospective study 432 patients tested with FOLR1 RxDx assay in standard of care setting
- 90% of tested specimens had some level of FOLR1 expression
- 36.3% of patients tested positive defined as >75% tumor cells staining at 2+/3+ intensity
- Primary tumors had higher positivity rates (44.4%) compared to metastatic tumors (32.5)
- 8 patients had more than 1 specimen tested; 3 (37.5%) of them had discordant results

Distribution of IHC results



Results of IHC from primary versus metastatic sites



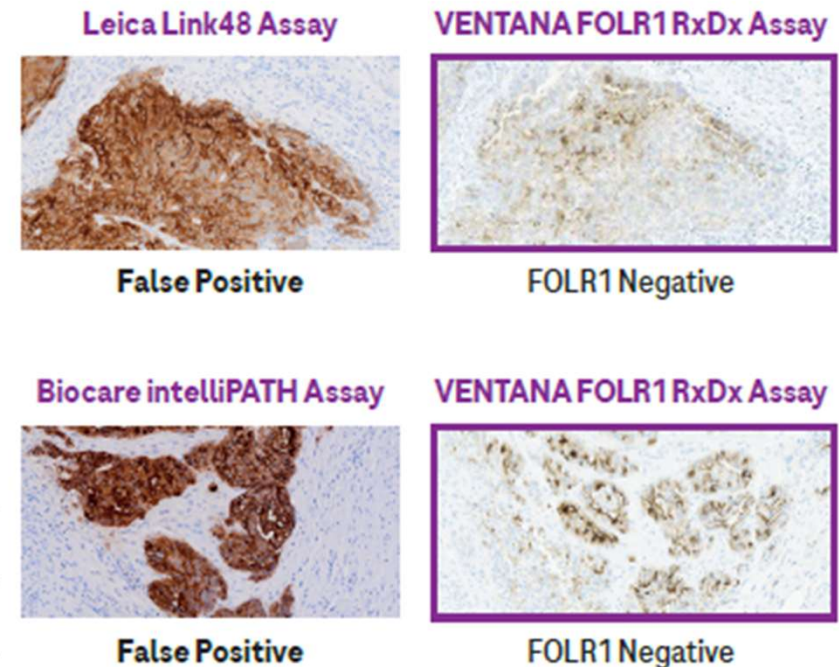
Analytical and clinical validity

Of other commercially available antibodies

Six commercially available assays were investigated.

Four failed analytical validation due to high background, incorrect staining patterns on a subcellular level, or both, and did not proceed to comparison with the VENTANA FOLR1 RxDx Assay.

	Agreement with VENTANA FOLR1 RxDx Assay	
	False positive	False negative
Leica link48 assay	40%	0%
Biocare intelliPATH assay	26%	14%



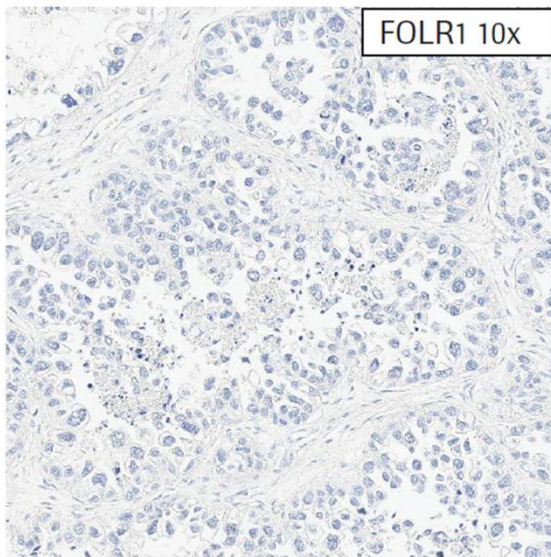
Two assays which succeeded analytical validity were compared to the VENTANA FOLR1 RxDx Assay. Both show low agreement with the clinically validated VENTANA FOLR1 RxDx Assay. As shown in the previous FORWARD I study, including patients with low FOLR1 expression does not translate in benefit from treatment.

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

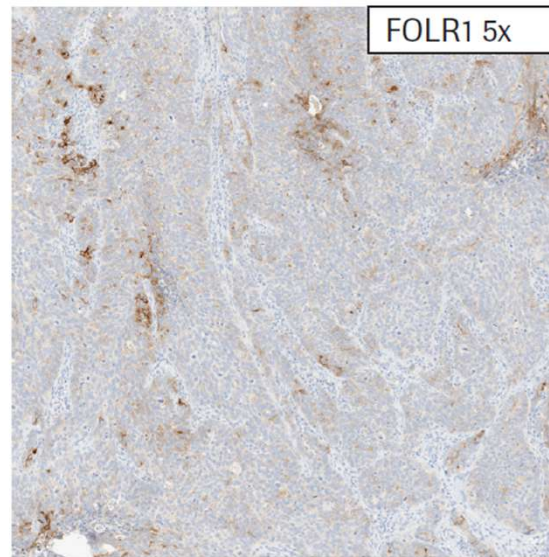
Negative Case Examples



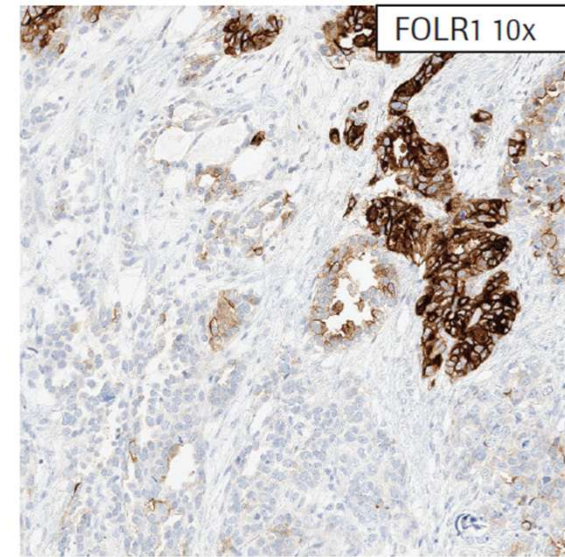
Clinical Diagnosis Negative



Exhibits no moderate or strong tumor cell membrane staining or < 75% moderate and/or strong tumor cell membrane staining



Exhibits 7% moderate and strong membrane staining or < 75% moderate and/or strong tumor cell membrane staining



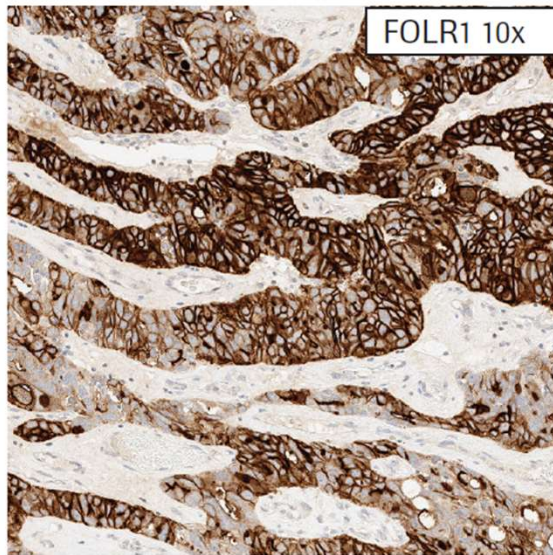
Exhibits 20% moderate and strong membrane staining or < 75% moderate and/or strong tumor cell membrane staining

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

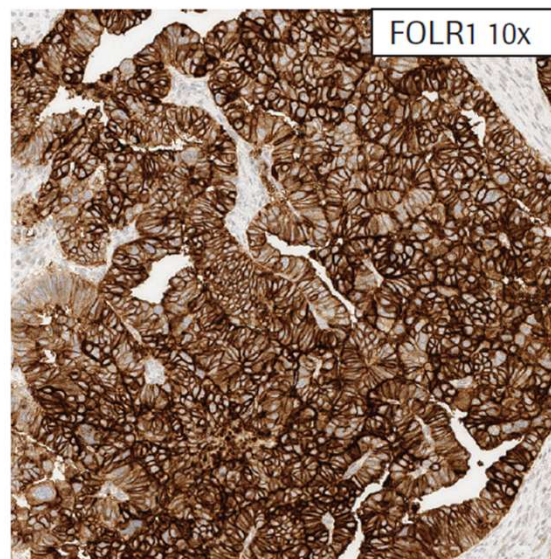
Positive Case Examples



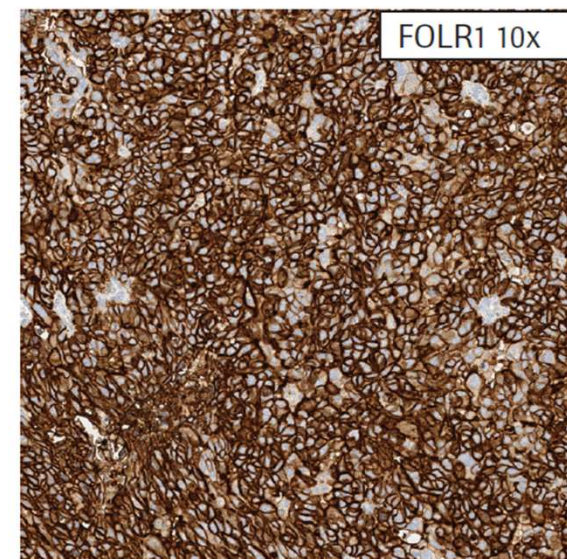
Clinical Diagnosis Positive



Exhibits 95% moderate and strong membrane staining or $\geq 75\%$ moderate or strong membrane staining with complete circumferential pattern*



Exhibits 98% moderate and strong membrane staining or $\geq 75\%$ tumor cells membrane staining with complete circumferential pattern*



Exhibits 98% moderate and strong membrane staining or $\geq 75\%$ tumor cells membrane staining with complete circumferential pattern*

For more cases and background

[Education.ventana.com](https://education.ventana.com)

or reach out to your Roche contact.



Thank you
for your attention

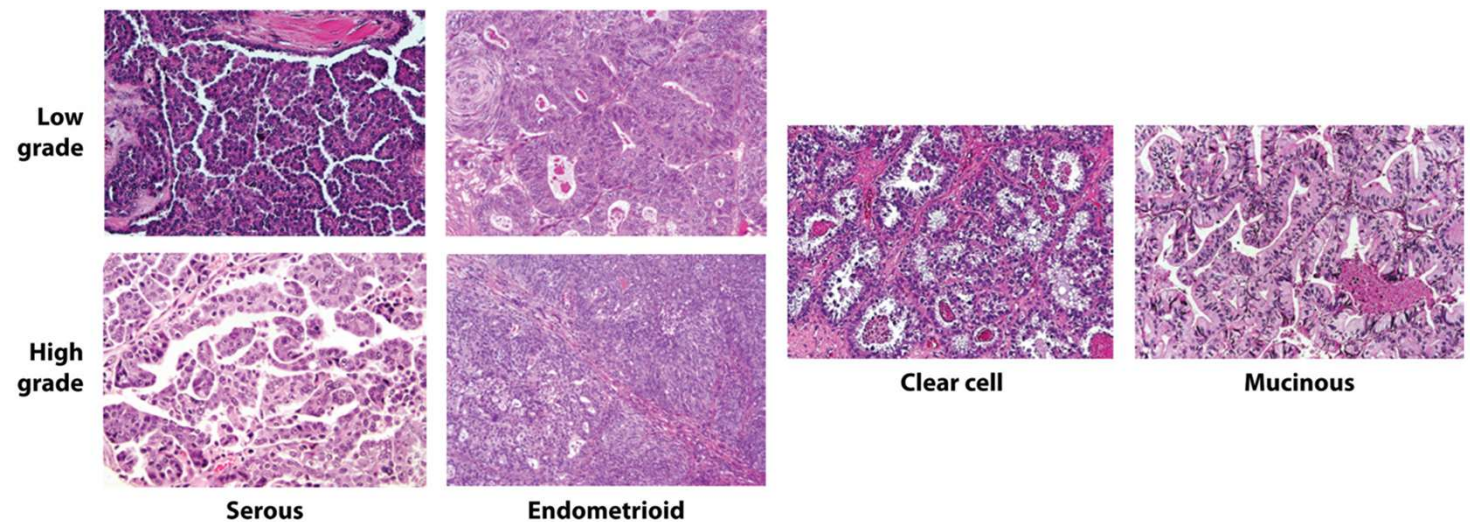
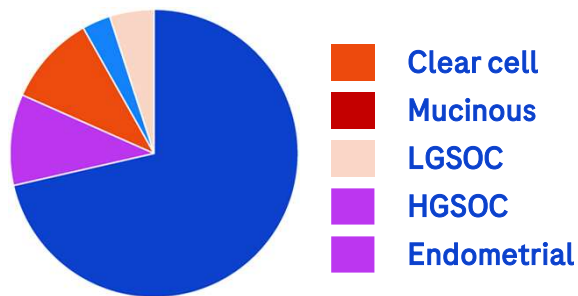
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Doing now what patients need next

Ovarian Cancer Histologies



- High-grade serous (HGSOC) (70%), endometrial (10%), Clear Cell (10%), Mucinous (3%), Low-grade serous (LGSOC) (<5%)
 - Each one has a borderline classification wherein frank invasion is not identified but features are otherwise consistent with malignancy, the malignant potential is unclear on for these tumors
- HGSOC, LGSOC thought to originate in the fallopian tube

Options in patients with recurrent ovarian cancer

Platinum is an option for 'platinum-sensitive'

- Surgery
- Platinum-doublet eg carboplatin with paclitaxel, carboplatin with gemcitabine, carboplatin with PLD
- BRCA mutated/HRD+: PARP inhibitor treatment (Olaparib, rucaparib, niraparib)

Platinum not an option 'platinum-resistant/refractory'

- Weekly Paclitaxel (+/-Bevacizumab)
- PLD (Caelyx) (+/-Bevacizumab)
- Carboplatin with Gemcitabine*, Gemcitabine alone
- Weekly carboplatin/paclitaxel
- Topotecan (+/-Bevacizumab)

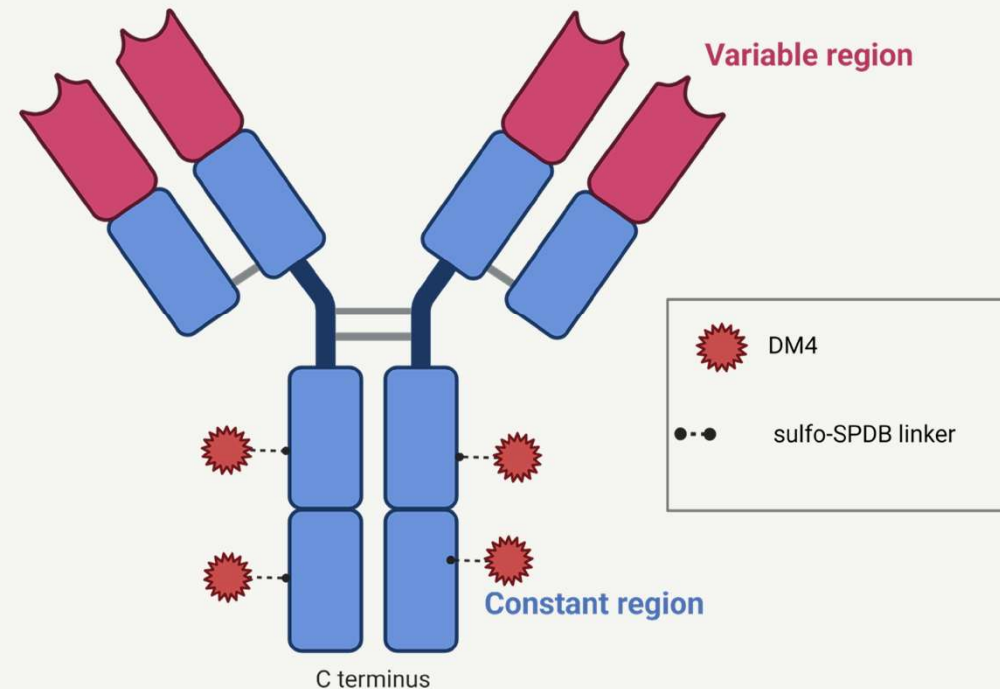
Mirvetuximab soravtansine-gynx (ELAHERE®)

ADC Characteristics

- FR α specific monoclonal antibody
- Cleavable antibody-drug linker
- 3-4 molecules of cytoplasmic payload (the maytansinoid DM4) per antibody

Preclinical Data

- Efficacy in HGSOC correlates directly with FR α protein expression levels
- Bystander effects due to diffusion of toxic metabolites



FORWARD I clinical study

NCT02631876

A phase 3, open label, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer



Enrolled 366 patients

Inclusion criteria:

- Ovarian cancer including epithelial ovarian cancer, peritoneal cancer, fallopian tube cancer
- Majority (99%) where high grade serous
- 1-3 prior therapies
- **FR α expression ($\geq 50\%$ of tumor cells with any FR α membrane staining visible at $\leq \times 10$ microscope objective determined by VENTANA FOLR1 (FOLR1-2.1) RxDx Assay**



Arm 1, n=248

Patients were administered mirvetuximab soravtansine-gynx once every 3 weeks



Arm 2, n=118

Patients were administered paclitaxel, pegylated liposomal doxorubicin, or topotecan

2:1 randomization

Primary outcome:

- Progression-free survival

Secondary outcomes:

- Objective response rate
- Overall survival
- Patient reported outcome
- Duration of response
- CA-125 response
- Time to progression or death

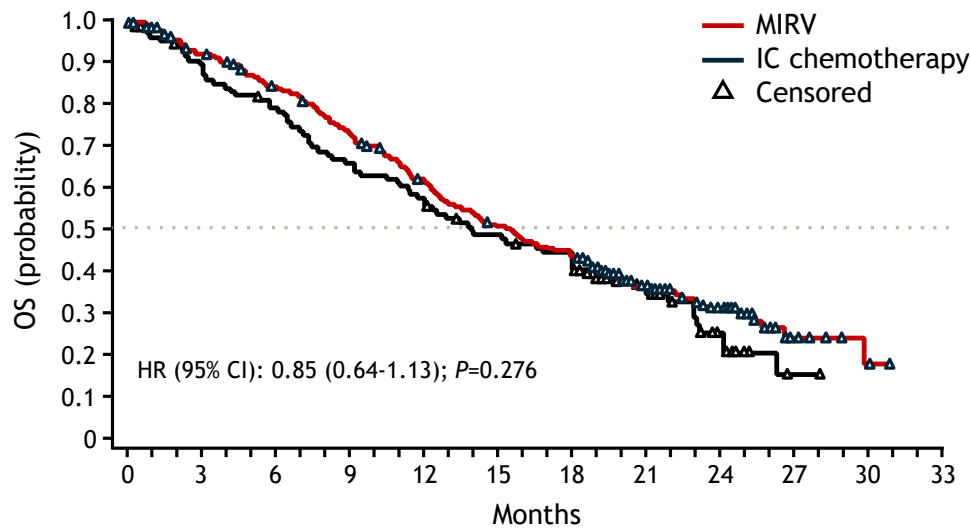
FORWARD clinical study



No significant difference in OS in the ITT population.

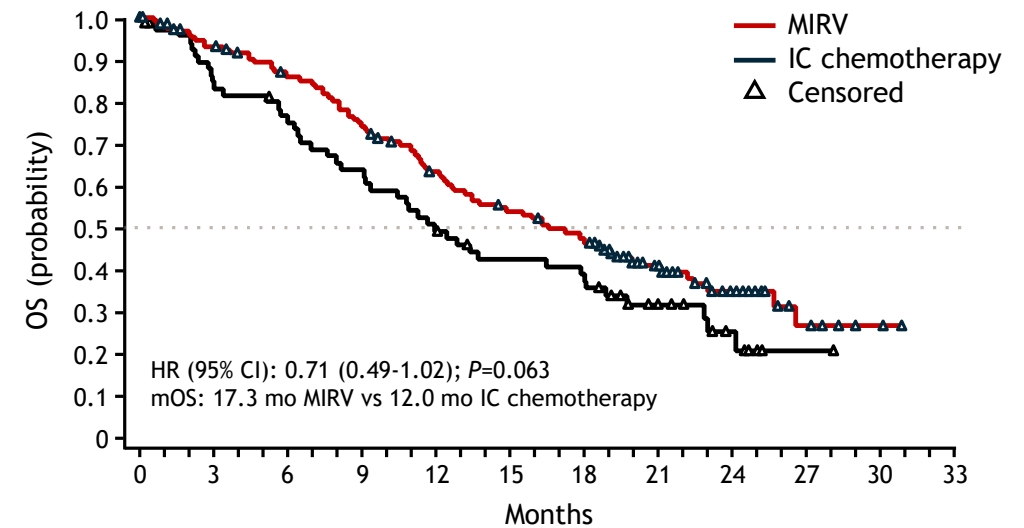
Longer OS in the FOLR1 high group but not statistically significantly

ITT Population



No. at risk		248	218	194	167	137	112	94	56	29	8	3	0
MIRV		248	218	194	167	137	112	94	56	29	8	3	0
IC chemotherapy		118	96	84	70	61	50	44	24	11	1	0	

FR α -High Population



No. at risk		147	128	116	100	81	68	58	33	17	6	2	0
MIRV		147	128	116	100	81	68	58	33	17	6	2	0
IC chemotherapy		71	36	48	40	32	25	23	12	6	1	0	

The study did not meet its primary endpoint of superior OS in the MIRV arm in the ITT population.
"The method of determining FOLR1 positivity for patient enrollment may not have been reliable".

SORAYA clinical study

NCT04296890

A phase 2, single arm study of mirvetuximab soravtansine-gynx in platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor alpha expression



106 patients enrolled

Inclusion criteria:

- High grade serous ovarian cancer including epithelial ovarian cancer, peritoneal cancer, fallopian tube cancer
- 1-3 prior therapies
- FR α expression ($\geq 75\%$ TCs with **moderate & strong intensity**) as determined by **VENTANA FOLR1 (FOLR1-2.1) RxDx Assay**



Patients were administered mirvetuximab soravtansine-gynx once every 3 weeks

Primary outcome:

- Objective response rate (compared to historic ORR for SOC)

Secondary outcomes:

- Duration of response
- Adverse events
- Progression-free survival
- Overall survival
- CA-125 response

SORAYA clinical study

Outcome data is favorable for patients with FR α protein expression $\geq$ 75% TC staining moderate and strong intensity

Endpoint	SORAYA ¹	AURELIA ²
Confirmed objective response rate (ORR) (95% confidence interval (CI))	32.4% (23.6, 42.2); P<.0001	12.6% P<.001
Complete response rate	4.8%	NE
Partial response rate	27.6%	NE
Duration of response (DOR)		NE
Number of responders	34	
Median DOR, months (95% CI)	6.9 (5.6, 9.7)	
Median PFS, months (95% CI)	4.3 [3.7-5.2]	3.4 [2.2, 3.7]

DOR is defined as the time from the date of first response (CR or PR) to the date of progressive disease or death from any cause, whichever occurred first; NE (not evaluated)

32.4% of EOC patients whose tumors were positive for FR α protein ($\geq$ 75% TC staining with moderate and strong intensity) demonstrated a partial or complete response (ORR) to ELAHERE therapy.

¹ Matulonis UA, et al., Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study. J Clin Oncol. 2023 Jan 30;JCO2201900. doi: 10.1200/JCO.22.01900. PMID: 36716407
² Pujade-Lauraine E, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. Journal of Clinical Oncology 2014 32:13, 1302-1308. PMID: 24637997



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