XXII ASSEMBLEA MaNGO MILANO

STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-29th, 2025

Responsabili Scientifici:
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Mario Negri Gynecologic Oncology

Biomarker testing in advanced OC: the pathologist's role

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DISCLOSURES

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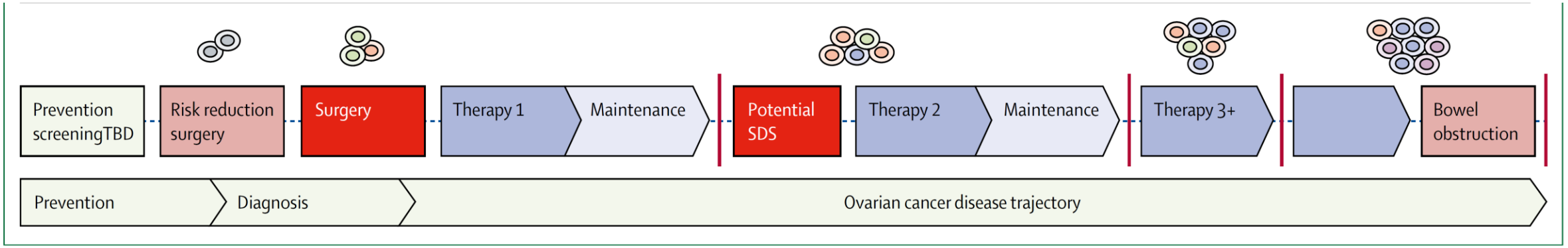
AbbVie, AstraZeneca, Exact Sciences, GSK, Illumina, Lilly, Novartis, MSD, Pfizer, Roche, Sophia Genetics, Stemline (Menarini), Thermo Fisher Scientific

The Pathologist's Role in Advanced Ovarian Cancer (OC)



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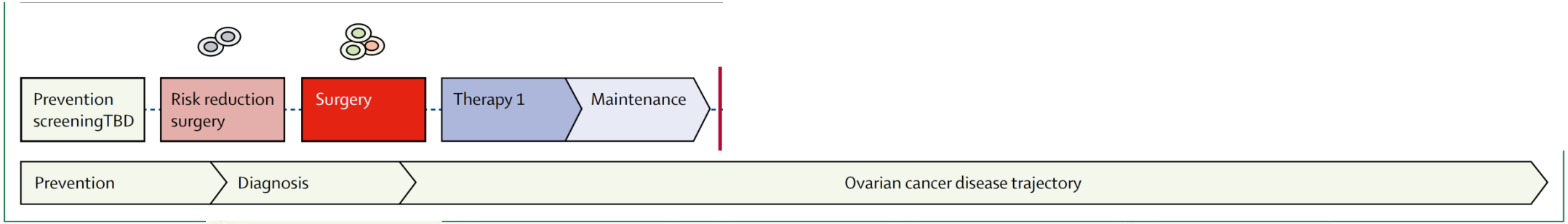
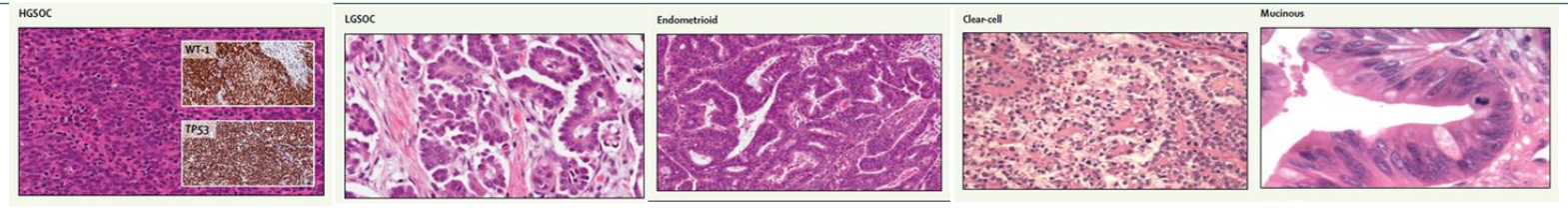
The Pathologist's Role in advanced OC





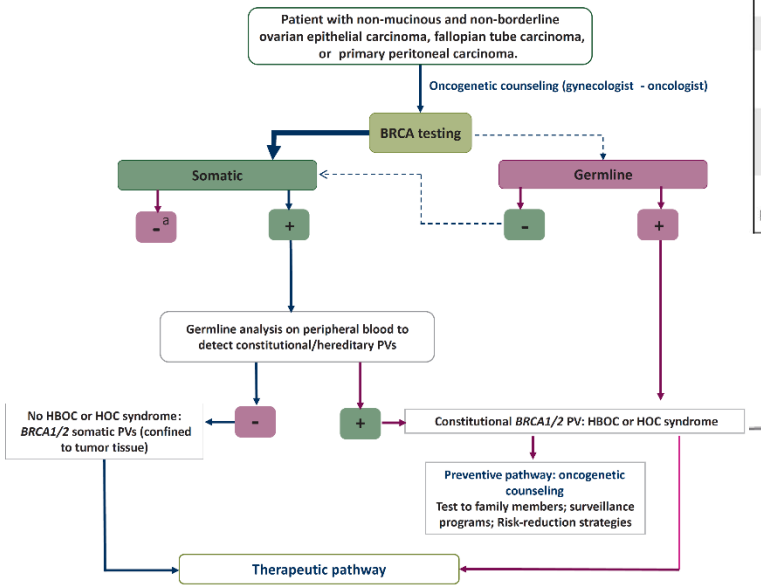
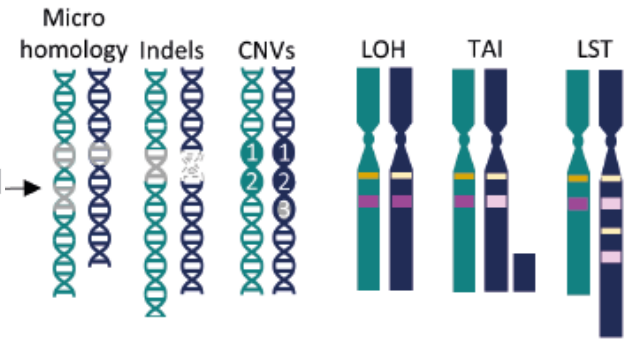
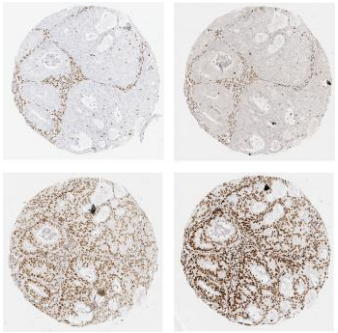


Table 3. Criteria for the Chemotherapy Response Score

CRS 1	No or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration.
CRS 2	Appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes with multifocal residual tumor, which is easily identifiable.
CRS 3	Complete or near-complete response with no residual tumor OR minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases no or very little residual tumor in the complete absence of any inflammatory response. It is advisable to record whether there is no residual tumor or whether there is microscopic residual tumor present.

NOTE. Regression-associated fibroinflammatory changes consist of fibrosis associated with macrophages, including foam cells, mixed inflammatory cells, and psammoma bodies, as distinguished from tumor-related inflammation or desmoplasia.





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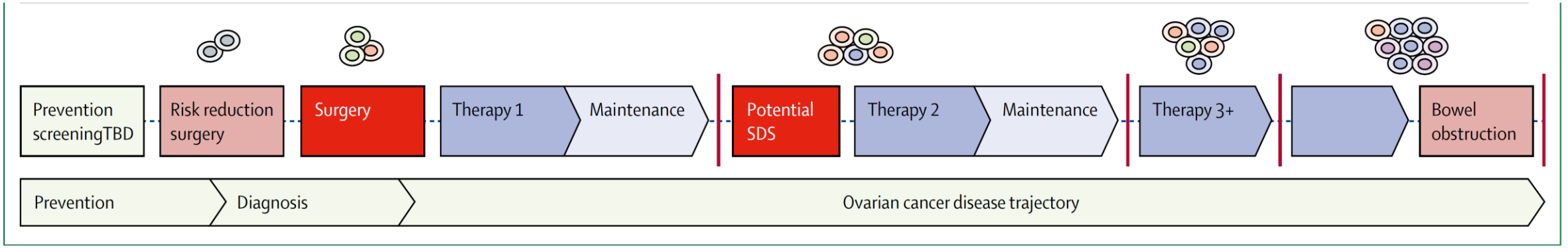
The Pathologist's Role in advanced OC



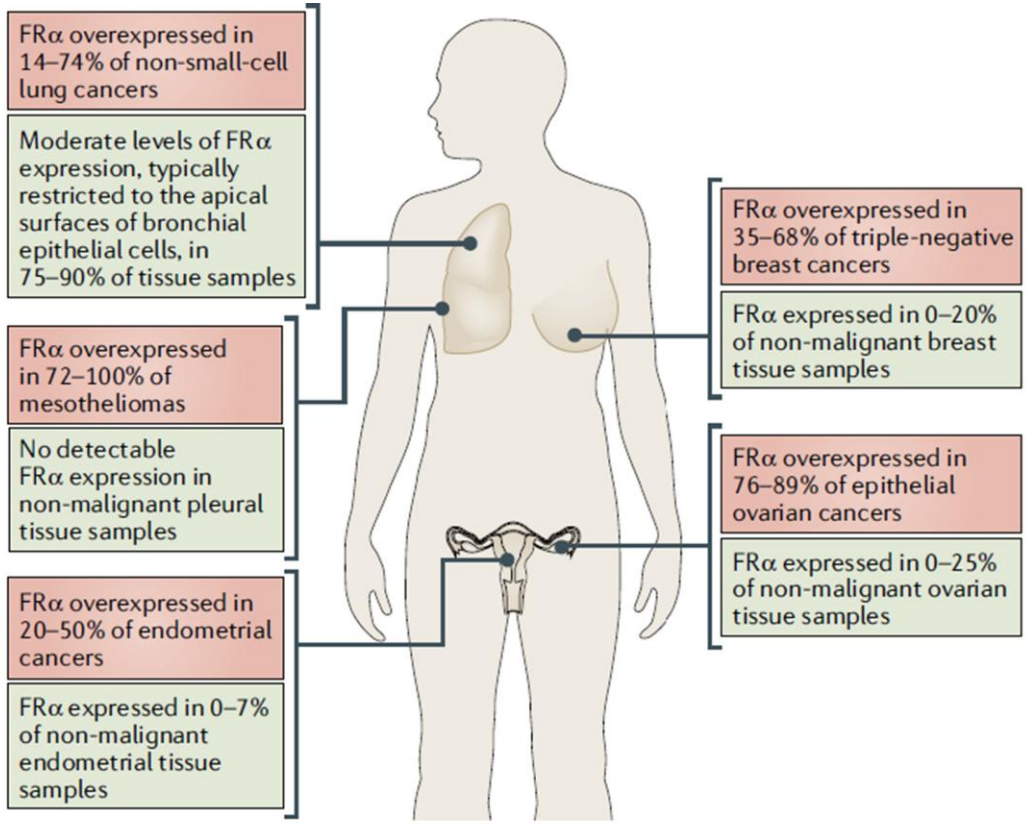
- FRalfa testing

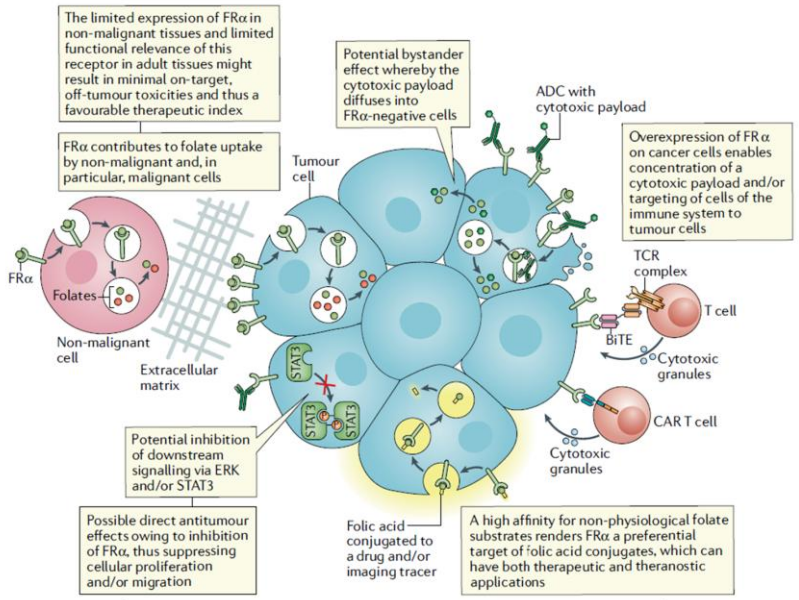
- What (if) else?

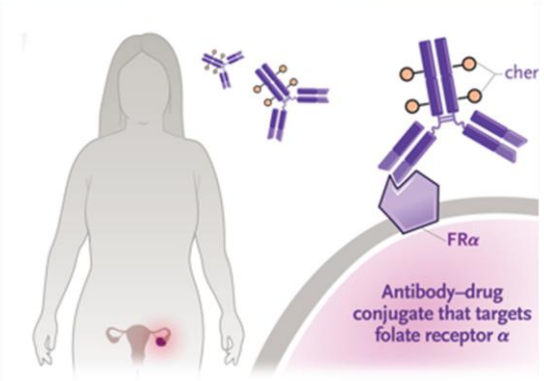
Lheureux S, Gourley C, Vergote I, Oza AM.. Lancet. 2019 Mar 23;393(10177):1240-1253. .

FRalfa

- Folate Receptor 1 protein (FOLR1) / Folate Receptor alpha (FRα)
  - cell surface protein encoded by the FOLR1 gene







Scaranti M, Cojocaru E, Banerjee S, Banerji U. Nat Rev Clin Oncol. 2020 Jun;17(6):349-359.
Moore KN, Angelergues A, Konecny GE, et al. N Engl J Med. 2023 Dec 7;389(23):2162-2174.

FRalfa in Ovarian Cancers

- Folate Receptor 1 protein (FOLR1) / Folate Receptor alpha (FRα)

Table 1
Cohort characteristics for the population of patients undergoing standard of care testing for FRα immunohistochemistry.

	All patients (n = 425)	FRα negative (*n* = 271)	FRα positive (*n* = 154)	OR/Beta	p
Age, years (Median)	67	66.8	68.2	1.39 [−0.79; 3.57]	0.21
Histology of tumor (N, %)					
High grade serous	199 (46.8 %)	97 (35.8 %)	102 (66.2 %)	3.54 [2.34; 5.39]	**0.000000001**
Serous NOS	73 (17.2 %)	48 (17.7 %)	25 (16.2 %)	0.9 [0.52; 1.51]	0.69
Endometrioid	11 (2.6 %)	11 (4.1 %)	0 (0 %)	0.07 [0; 0.56]	**0.006**
Carcinosarcoma	8 (1.9 %)	7 (2.6 %)	1 (0.6 %)	0.36 [0.04; 1.66]	0.21
Clear cell	7 (1.6 %)	7 (2.6 %)	0 (0 %)	0.11 [0; 0.94]	**0.042**
Low grade serous	5 (1.2 %)	5 (1.8 %)	0 (0 %)	0.15 [0; 1.33]	0.098
Mixed	4 (0.9 %)	2 (0.7 %)	2 (1.3 %)	1.61 [0.25; 10.58]	0.6
Uterine serous	2 (0.5 %)	1 (0.4 %)	1 (0.6 %)	1.67 [0.13; 20.73]	0.66
Cervix NOS	1 (0.2 %)	1 (0.4 %)	0 (0 %)	0.57 [0; 11.04]	0.72
Mucinous	1 (0.2 %)	0 (0 %)	1 (0.6 %)	5.02 [0.26; 739.81]	0.28
Mucinous borderline	1 (0.2 %)	1 (0.4 %)	0 (0 %)	0.56 [0; 10.77]	0.71
NOS	113 (26.6 %)	91 (33.6 %)	22 (14.3 %)	0.33 [0.2; 0.55]	**0.000009**

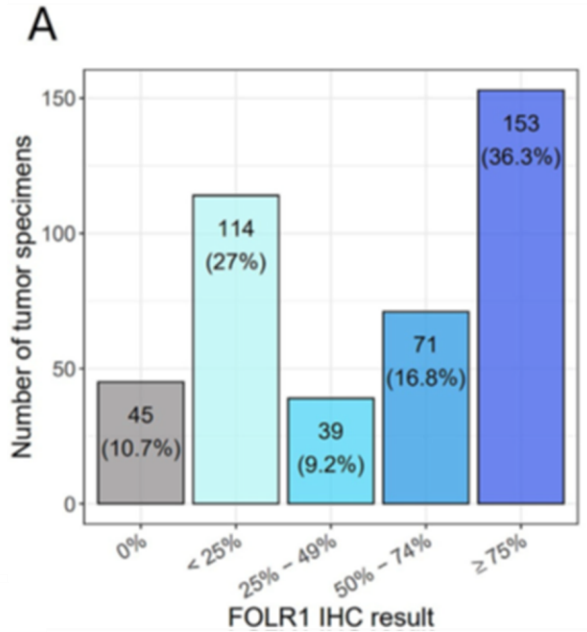


Table 1
Patient characteristics and associations with folate receptor alpha (FRα) status.

Characteristic	LGSC (total *n* = 89)	FRα-negative (*n* = 53)	FRα-high (*n* = 36)	*P* value[1]	SBT (total *n* = 42)	FRα-negative (*n* = 33)	FRα- high (*n* = 9)	*P* value[1]
%FRα-positive cells (median, range)	60.1% (0.0–100.0%)	24.1% (0.0–72.9%)	85.5% (77.5%–100.0%)		21.0% (0.0–93.2%)	12.2% (0.0–73.4%)	83.0% (75.0%–93.2%)	

Previs RA, et al. Gynecol Oncol. 2025 Jan;192:102-110.
Manning-Geist BL, et al. Gynecol Oncol. 2024 Sep;188:52-57.

FRalfa in Ovarian Cancers

Table 1. Efficacy of MIRV in FRα-positive platinum-resistant ovarian cancer.

	FRα SCORE	ORR, %		MPFS, MO		MOS, MO	
		ALL PATIENTS	FRα HIGH	ALL PATIENTS	FRα HIGH	ALL PATIENTS	FRα HIGH
IMGN853-0401 *Phase I (n=46)*[51]	PS2+	26	26	4.8	NA	NA	NA
FORWARD I MIRV vs ICC *Phase III (n=243)*[55,56]	10X	22 vs 12	24 vs 10	4.1 vs 4.4 *HR 0.98* *(0.73-1.31)* *P=.89*	4.8 vs 3.3 *HR 0.69* *(0.48-1.0)* *P=.049*	16.4 vs 14.0 *HR 0.82* *(0.58-0.15)* *P=.24*	17.3 vs 12.0[a] *HR 0.71* *(0.49-1.02)* *P=.06*
	PS2+ (Exploratory)	NA	29 vs 6	NA	5.6 vs 3.2 *HR 0.54* *(0.33-0.89)* *P=.01*	NA	16.4 vs 11.4 *HR 0.67* *(0.41-1.19)* *P=.12*
SORAYA *Single arm (n=106)*[57]	PS2+	†	32	†	4.3	†	13.8
MIRASOL MIRV vs ICC *Phase III* (n=453)[58]	PS2+	†	42 vs 16 *OR 3.81* *P=<.0001*	†	5.6 vs 3.9 *HR 0.65* *(0.52-0.81)* *P=<.0001*	†	16.4 vs 12.7 *HR 0.67* *(0.50-0.89)* *P=.0046*
FORWARD II *MIRV + BEV* *Phase Ib/II (n=94)*[59]	PS2 +	44	48	8.2	9.7	NA	NA

PS2+ score: ⩾25% of tumor cells with ⩾2 + staining intensity (low = 25%-50%, medium = 50%-74%, high ⩾ 75%).
10X score: ⩾50% of tumor cells with any FRα staining visible at ⩽10 microscope objective (medium = 50%-74%, high ⩾ 75%).
†All patients were FRα high.
[a]Final analysis.
Abbreviations: BEV, bevacizumab; ICC, investigator's choice of chemotherapy; FRα, Folate receptor alpha; MIRV, Mirvetuximab soravtansine; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; OR, odds ratio; ORR, overall response rate.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

K.N. Moore, A. Angelergues, G.E. Konecny, Y. García, S. Banerjee, D. Lorusso, J.-Y. Lee, J.W. Moroney, N. Colombo, A. Roszak, J. Tromp, T. Myers, J.-W. Lee, M. Beiner, C.M. Cosgrove, D. Cibula, L.P. Martin, R. Sabatier, J. Buscema, P. Estévez-García, L. Coffman, S. Nicum, L.R. Duska, S. Pignata, F. Gálvez, Y. Wang, M. Method, A. Berkenblit, D. Bello Roufai, and T. Van Gorp, for Gynecologic Oncology Group Partners and the European Network of Gynaecological Oncological Trial Groups*

*"Among participants with platinum-resistant, **FRα-positive ovarian cancer,** treatment with MIRV showed a significant benefit over chemotherapy with respect to progression-free and overall survival and objective response"*

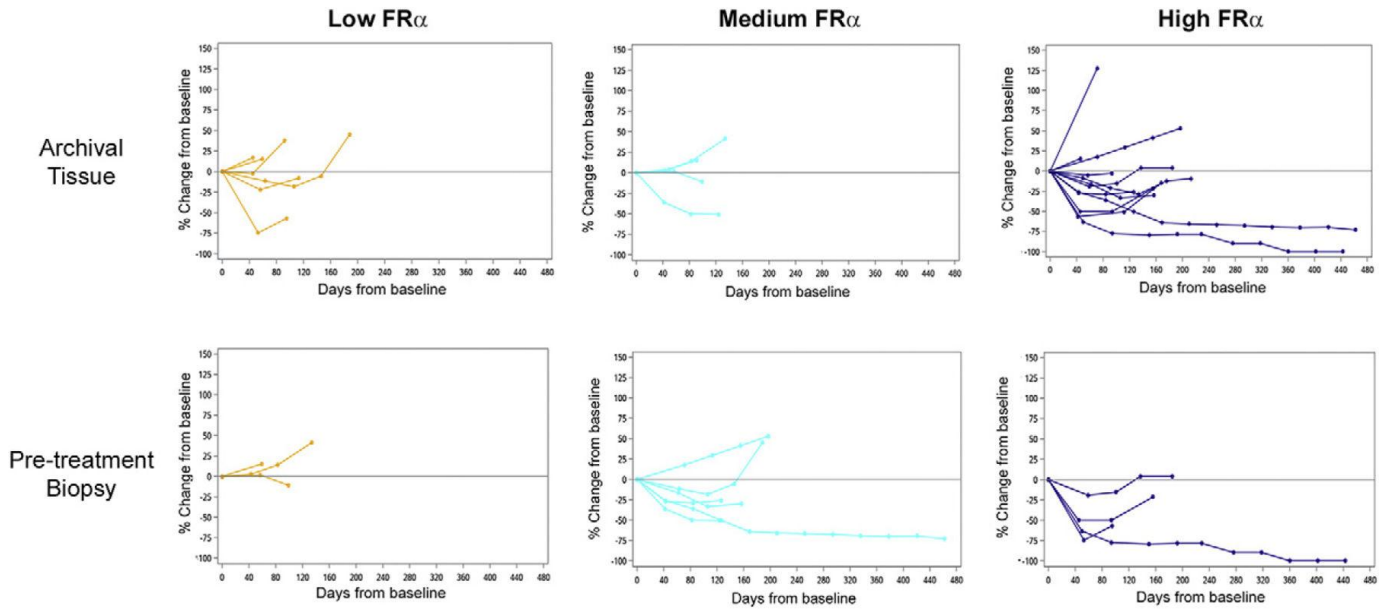
*"[…]high FRα tumor expression (**≥75% of cells with ≥2+ staining intensity**)"*

Gonzalez-Ochoa E, Veneziani AC, Oza AM.. Clin Med Insights Oncol. 2023 Jul 25;17:11795549231187264.
Moore KN, Angelergues A, Konecny GE, et al. N Engl J Med. 2023 Dec 7;389(23):2162-2174.

FRalfa Testing

- **WHERE / WHEN (i.e. timing / sample)**
  - *Platinum-resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens*

- Clinical trials enrolled patients whose tumors were tested from both archived and new biopsies
- Archival tumor samples vs. pre-treatment new biopsy → 71% concordance



Lheureux S, et al. Lancet. 2019 Mar 23;393(10177):1240-1253.
Martin LP, Konner JA, Moore KN, et al. Gynecol Oncol. 2017 Nov;147(2):402-407.

FRalfa Testing

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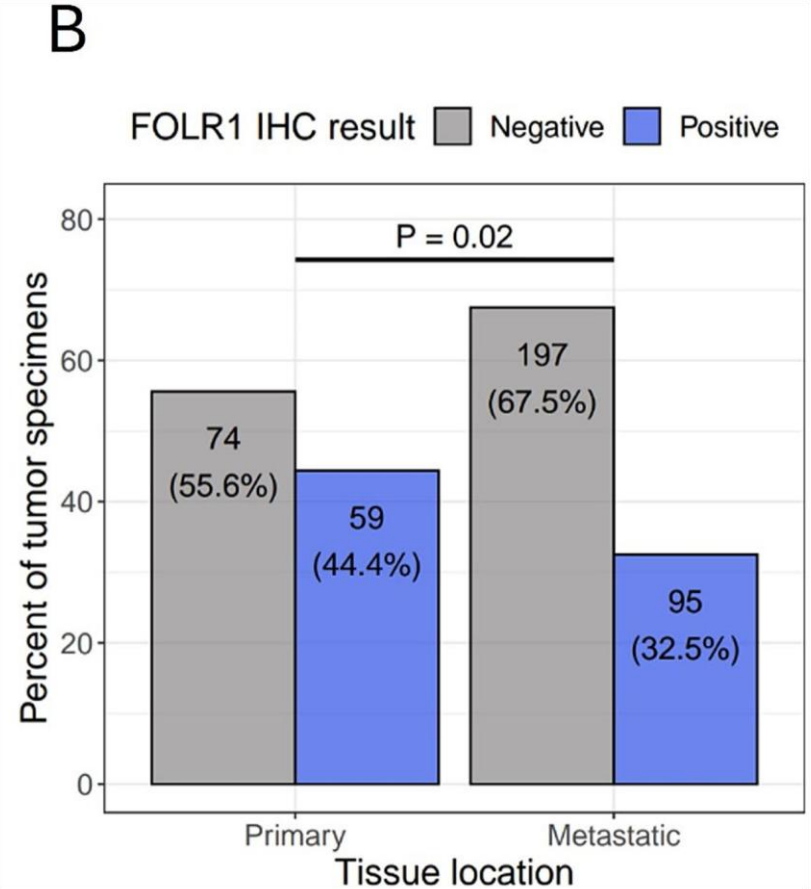

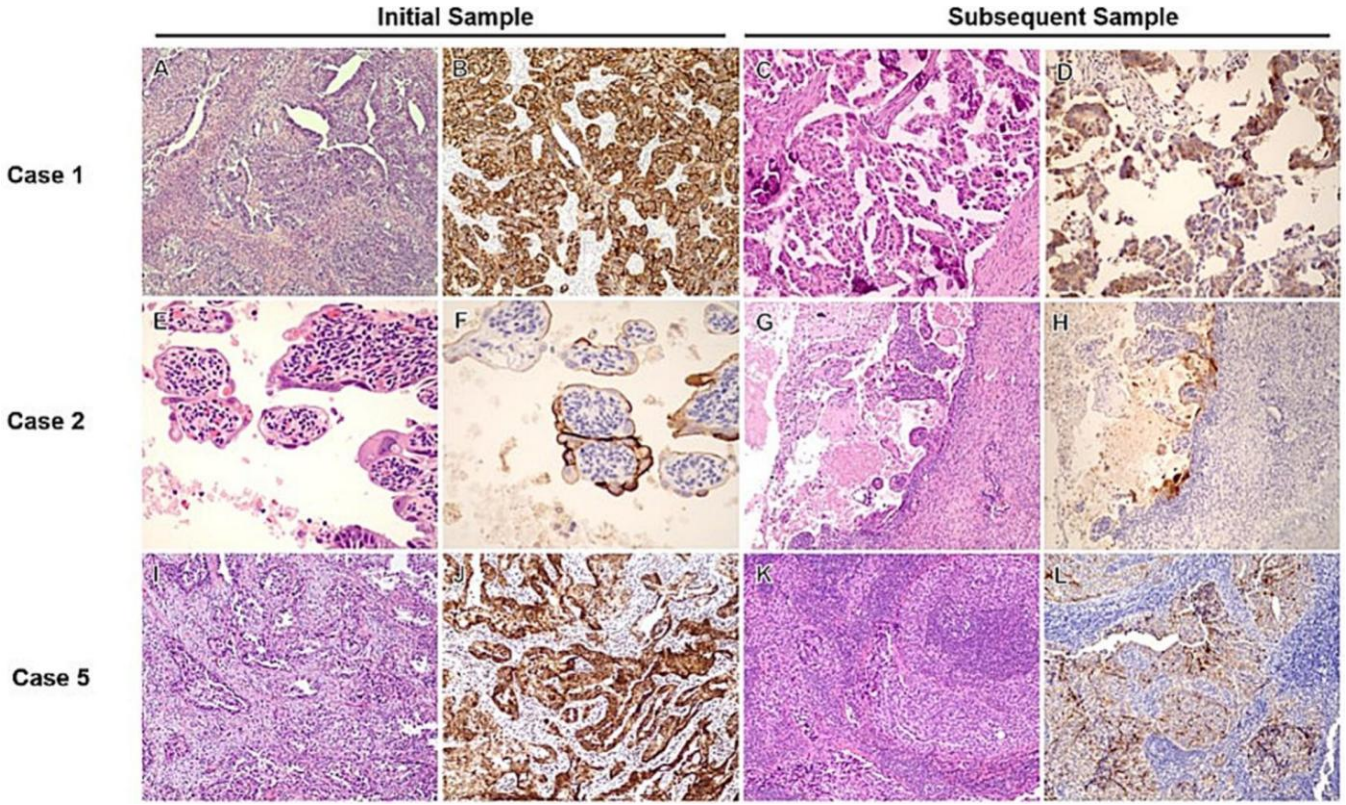

Primary sites include the ovary, fallopian tube, adnexa, or pelvic mass.

Previs RA, et al. Gynecol Oncol. 2025 Jan;192:102-110.

FRalfa Testing

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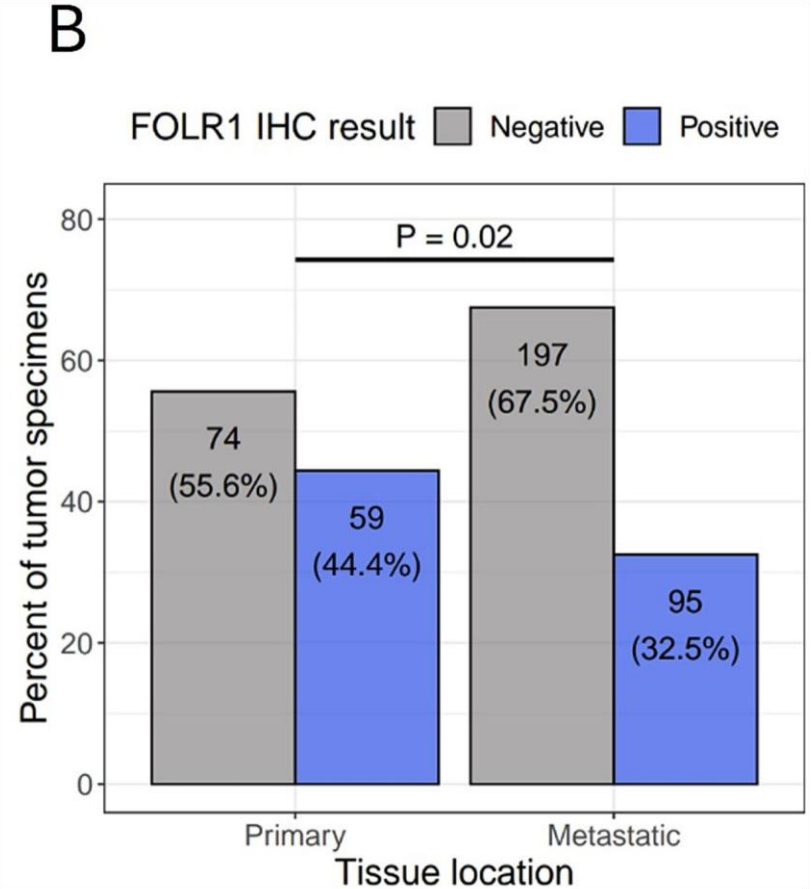
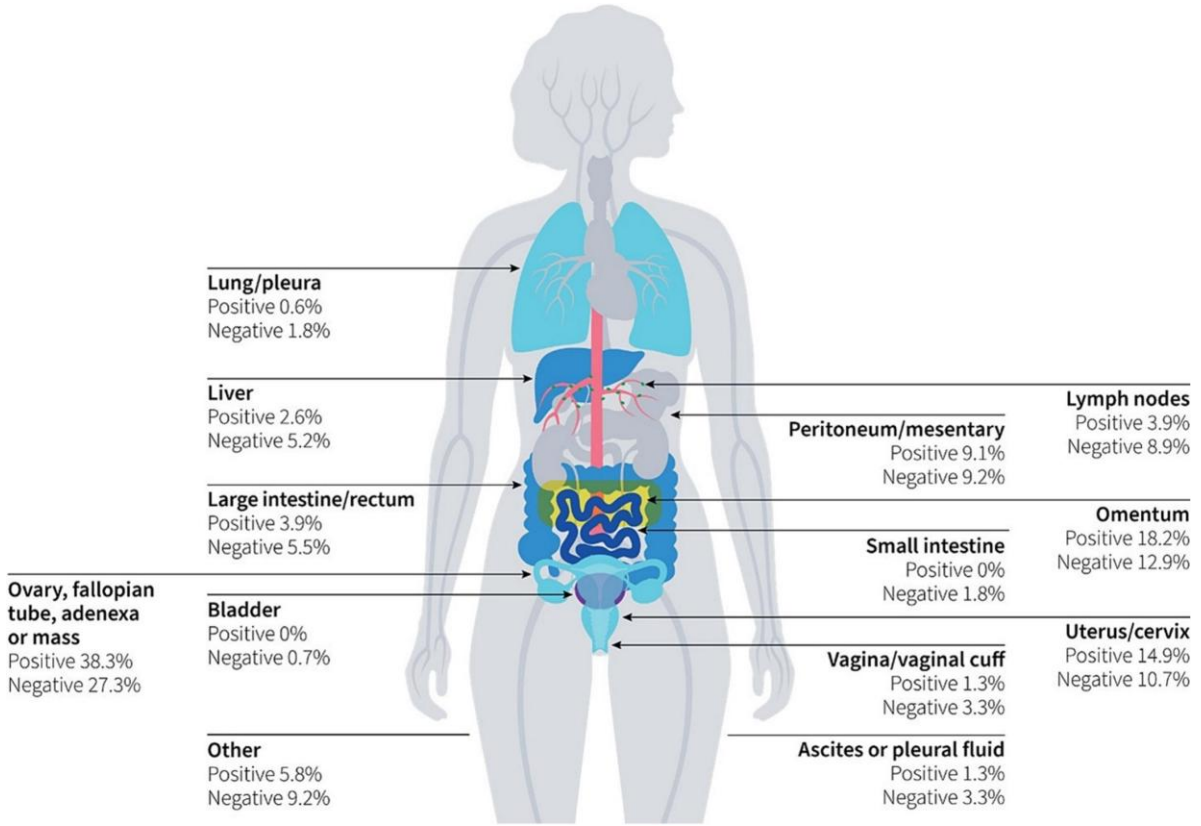


Primary sites include the ovary, fallopian tube, adnexa, or pelvic mass.



Previs RA, et al. Gynecol Oncol. 2025 Jan;192:102-110.

Abstract 5568

Real-World Analysis of Folate Receptor Alpha (FRα; FOLR1) Expression in Pan-Tumor Samples From Over 6000 Patients in the US

Thomas Krivak[1], Roisin Puentes[2], Tori Gannon[2], Vladislav Chizhevsky[3], Robert Schwartz[2], Thomas Lee[3], Callum Mortimer Sloss[4], Emily Deutschman[5], Yajun Emily Zhu[6], Zahra Majd[6], and Emilee Gagliardi[5]

[1]Division of Gynecologic Oncology, Allegheny Health Network Cancer Institute, Pittsburgh, PA, USA; [2]NeoGenomics Laboratories, Inc., Fort Myers, FL, USA; [3]NeoGenomics Laboratories, Inc., Aliso Viejo, CA, USA; [4]ImmunoGen, Waltham, MA, USA; [5]AbbVie Inc, Waltham, MA, USA; [6]AbbVie Inc, North Chicago, IL, USA

OBJECTIVE

To evaluate the expression and prevalence of the clinically actionable biomarker FRα in one of the largest real-world datasets of FRα testing

CONCLUSIONS

Real-world analysis of 6699 patient tumor samples demonstrated an FRα-positive prevalence of 43.5% among the 5867 FRα-evaluable samples. Among the 1574 ovarian cancer samples, FRα-positive prevalence was 39.6%, consistent with the FRα-positive prevalence observed in MIRV clinical trials (32–44%)[6,8-9]

The multivariable logistic regression demonstrated that the choice of sample acquisition procedure impacted FRα expression results. FRα expression results from resection samples had 74% higher odds of having a positive FRα status compared with biopsy samples

The multivariable logistic regression indicated that histological subtype impacted FRα expression results. FRα expression results from samples classified as serous had 121% higher odds of having a positive FRα status compared with samples that were classified as non-serous

Collectively, this large real-world dataset helps to characterize the real-world prevalence of the clinically actionable biomarker FRα and supports using FRα testing for personalized ovarian cancer treatment plans

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Presenting author: Thomas Krivak (tomkrivak@gmail.com)

To submit a medical question, please visit www.abbviemedinfo.com

AbbVie and the authors thank the participants, study sites, and investigators who participated in this study. Erik Hunziker, PhD, and Amita Mistry, MD, from AbbVie provided expertise with selecting representative images for FRα expression.

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Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, May 30-June 3, 2025, Chicago, IL, USA [DV-015422]

BACKGROUND

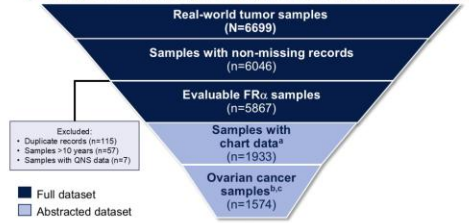
- FRα is overexpressed in several cancers, including ovarian and endometrial[1]
- Mirvetuximab soravtansine-gynx (MIRV) is a first-in-class FRα-targeting antibody-drug conjugate that delivers a potent cytotoxic microtubule inhibitor, DM4, to selectively kill tumor cells, approved to treat FRα-positive platinum-resistant ovarian cancer (PROC)[2-5]
- In the phase III, confirmatory MIRASOL trial of MIRV vs investigator's choice chemotherapy in FRα-positive PROC, MIRV demonstrated clinically meaningful and statistically significant survival benefit and a differentiated safety profile consisting predominantly of low-grade peripheral neuropathy, gastrointestinal, and resolvable ocular adverse events[6]
- Understanding how FRα expression and prevalence vary by tumor origin, histological subtype, tumor grade, cancer stage, body site, and sample acquisition procedure in real-world settings may improve the adoption of effective methods and procedures for FRα testing in biomarker-guided treatment strategies

METHODS

- FRα testing of 6699 real-world patient tumor samples from various healthcare settings in the US was completed over a 12-month period (November 18, 2022, to November 30, 2023)
- FRα expression was assessed by immunohistochemistry (IHC) using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay[a] (Roche Diagnostics)
- FRα-positive expression was defined as ≥75% tumor cells with ≥2+ membrane staining as determined by a trained pathologist
- The *P* values from the univariate analysis were calculated utilizing Chi-squared test
- A multivariable logistic regression model (stepwise selection method) was employed to identify statistically significant factors associated with FRα status, adjusting for available variables, including tumor histology, grade, sample age, body site, cancer stage, metastatic status, and procedure

[a]The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is a qualitative immunohistochemical assay using mouse monoclonal anti-FOLR1, clone FOLR1-2.1, intended for use in the assessment of folate receptor alpha (FOLR1) protein in formalin-fixed, paraffin-embedded epithelial ovarian, fallopian tube, or primary peritoneal cancer tissue specimens by light microscopy. This assay is for use with Ophthew DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument (Roche Diagnostics).[7]

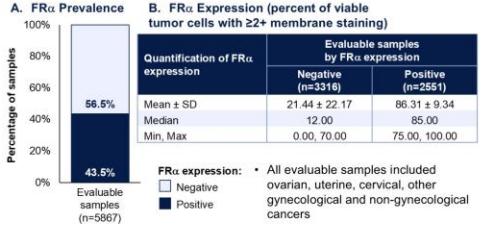
Flow of Data Abstraction: Inclusion and Exclusion Criteria



[a]Patients without chart data (n=3934) were excluded. [b]Patients with non-ovarian cancer malignancies with chart data (n=359) were excluded. [c]Ovarian tumors did not include peritoneal, omental, Müllerian, or uterine tumors.

RESULTS

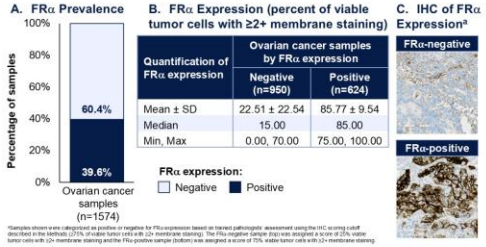
Figure 1. FRα Prevalence and Expression Among Evaluable FRα Samples (n=5867)



Quantification of FRα expression	Evaluable samples by FRα expression	
	Negative (n=3316)	Positive (n=2551)
Mean ± SD	21.44 ± 22.17	86.31 ± 9.34
Median	12.00	85.00
Min, Max	0.00, 70.00	75.00, 100.00

- All evaluable samples included ovarian, uterine, cervical, other gynecological and non-gynecological cancers

Figure 2. FRα Prevalence and Expression Among Ovarian Cancer Samples (n=1574)

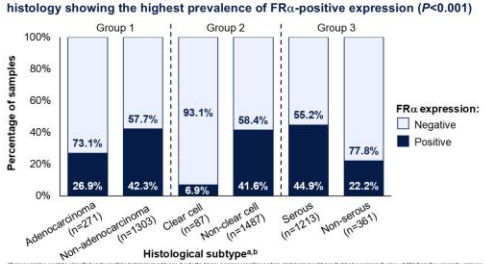


Quantification of FRα expression	Ovarian cancer samples by FRα expression	
	Negative (n=950)	Positive (n=624)
Mean ± SD	22.51 ± 22.54	85.77 ± 9.54
Median	15.00	85.00
Min, Max	0.00, 70.00	75.00, 100.00

[a]Samples shown were categorized as positive or negative for FRα expression based on trained pathologists' assessment using the IHC scoring cutoff described in the Methods (≥75% of viable tumor cells with ≥2+ membrane staining). The FRα-negative tumor sample (top) was assigned a score of 25% viable tumor cells with ≥2+ membrane staining and the FRα-positive sample (bottom) was assigned a score of 75% viable tumor cells with ≥2+ membrane staining.

Figure 3. FRα Prevalence Among Ovarian Cancer Samples by Histological Subtype (n=1574)

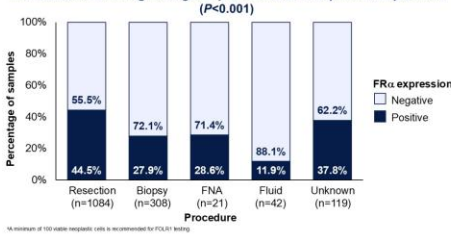
Histological subtype significantly impacted FRα prevalence, with serous histology showing the highest prevalence of FRα-positive expression (*P*<0.001)



[a]Tumor samples could be classified under multiple histological subtypes due to the binary (yes/no) reporting system. Histological subtypes that had a nominal *P* value <0.001 from the univariate analysis are reported here, resulting in the exclusion of the statistically significant endometrioid (*P*=0.005) and mucinous (*P*=0.006) subtypes, and nonepithelial adenosquamous (*P*=0.416), carcinoma (*P*=0.668), carcinosarcoma (*P*=0.624), granulosa (*P*=0.418), mixed epithelial (*P*=0.732), papillary (*P*=0.971), squamous (*P*=0.416), transitional cell (*P*=0.277), and undifferentiated (*P*=0.140) subtypes. [b]Groups 1, 2, and 3 were analyzed separately by univariate analysis and each had a nominal *P* value <0.001.

Figure 4. FRα Prevalence Among Ovarian Cancer Samples by Acquisition Procedure[a] (n=1574)

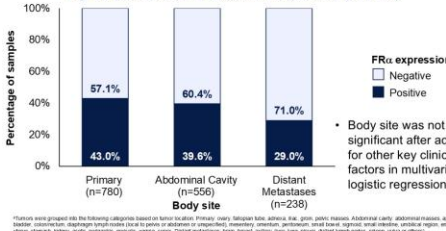
Sample acquisition procedure significantly impacted FRα prevalence, with resection showing the highest prevalence of FRα-positive expression (*P*<0.001)



[a]A minimum of 100 viable neoplastic cells is recommended for FOLR1 testing.

Figure 5. FRα Prevalence Among Ovarian Cancer Samples by Body Site[a] (n=1574)

Body site significantly impacted FRα prevalence, with primary showing the highest prevalence of FRα-positive expression (*P*<0.001)

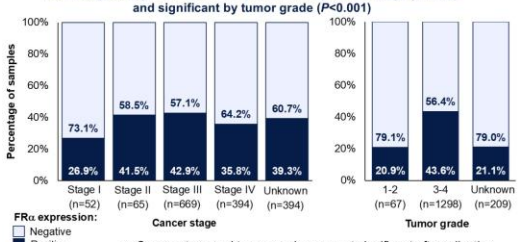


- Body site was not significant after adjusting for other key clinical factors in multivariable logistic regression model

[a]Tumors were grouped into the following categories based on tumor location: Primary: ovary, fallopian tube, adnexa, true, groin, pelvic masses. Abdominal cavity: abdominal masses, appendix, bladder, colon/rectum, diaphragm lymph nodes (local to pelvis or abdomen or unspecified), mesentery, omentum, peritoneum, small bowel, sigmoid, small intestine, umbilical region, endometrium, uterus, stomach, kidney, ascitic, peritgastric, pericolic, vagina, cervix. Distant metastases: brain, breast, axillary, liver, lung, pleura, distant lymph nodes, spleen, vulva or others).

Figure 6. FRα Prevalence Among Ovarian Cancer Samples[a] by Cancer Stage and Tumor Grade (n=1574)

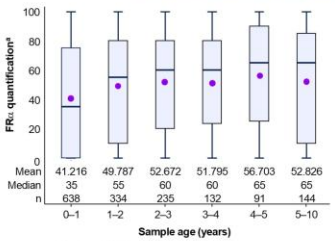
FRα expression was measurable across all cancer stages and tumor grades, with marginal significance in FRα prevalence by cancer stage (*P*=0.06) and significant by tumor grade (*P*<0.001)



- Cancer stage and tumor grade were not significant after adjusting for other key clinical factors in multivariable logistic regression model

Figure 7. FRα Expression Among Ovarian Cancer Samples by Sample Age (n=1574)

FRα expression was measurable among ovarian cancer samples regardless of sample age (*P*=0.001)



- FRα expression was measurable in samples ranging from <1 to >5 years old
- Sample age was not significant after adjusting for other key clinical factors in multivariable logistic regression model

[a]Quantification of the percent of viable tumor cells with ≥2+ membrane staining.

Figure 8. Odds Ratio Among Ovarian Cancer Samples from Multivariable Logistic Regression Model[a] (n=1574)

Adenocarcinoma, clear cell, and serous histological subtypes and sample acquisition procedure were significant predictors of FRα expression

Variable	Odds ratio (95% CI) (Less ← FRα expression[b] → More)	Odds ratio (95% CI)
Histological subtype		
Adenocarcinoma (yes vs no)		0.70 (0.51, 0.95)
Clear cell (yes vs no)		0.18 (0.08, 0.43)
Serous (yes vs no)		2.21 (1.56, 3.13)
Procedure		
Resection vs biopsy		1.74 (1.31, 2.33)
FNA vs biopsy		0.99 (0.37, 2.67)
Fluid vs biopsy		0.35 (0.13, 0.94)
Unknown vs biopsy		2.18 (1.31, 3.63)

[a]A logistic regression employed stepwise selection to identify significant factors adjusting all baseline variables, including all histological subtypes, cancer stage, tumor body site, tumor grade, metastatic status, procedure, and sample age. [b]Arrows indicate higher or lower odds of detecting FRα expression positivity; lower/higher bar of odds ratio excluding 1 indicates a statistically significant difference.

- Body site, tumor grade, and sample age were significant factors from the univariate analysis; however, these factors were not significant after adjusting for key clinical factors in multivariable logistic regression model

Study Strengths and Limitations

Strengths

- This study leveraged one of the largest real-world datasets of FRα testing and utilized both univariate and multivariable analyses to identify key factors influencing FRα expression.
- Histological subtype and sample acquisition procedure can significantly influence FRα status. These data may improve the adoption of important considerations and effective procedures for FRα testing.

Limitations

- Real-world data are susceptible to unmeasured confounding; missing and incomplete records reduced the sample size for this analysis.
- Tumor samples could be classified under multiple histological subtypes and as "Unknown" for sample acquisition procedure, cancer stage, and tumor grade.

ABBREVIATIONS. FOLR1, folate receptor 1 protein; FNA, fine-needle aspiration; FRα, folate receptor alpha; IHC, immunohistochemistry; max, maximum; min, minimum; MIRV, mirvetuximab soravtansine-gynx; PROC, platinum-resistant ovarian cancer; QNS, quantity not sufficient; SD, standard deviation.

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Abstract 5591

Folate Receptor Alpha (FRα, FOLR1) Expression and Persistence in Ovarian Cancer in Clinical Trial Samples and Real-World Patient Cohorts

Elizabeth M. Swisher[1], Qu Zhang[2], Emilee Gagliardi[2], Manal Mehibel[2], David Masica[2], Sribalaji Lakshmikanthan[2], Emily Deutschman[2], Peter Ansell[2], and Robert L. Coleman[3]

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OBJECTIVE

To investigate real-world and clinical FRα expression prevalence, consistency over time, concordance with mRNA expression, and prognostic value in patients with ovarian cancer

CONCLUSIONS

In one of the largest known real-world datasets (N=1337) of patients with ovarian cancer, 32.8% of tumor samples were FRα-high (≥75% of viable tumor cells with ≥2+ membrane staining), including in those with and without *BRCA* mutations, consistent with rates seen in MIRV clinical trials to date[1,2]

FRα status was consistent in 78.5% of longitudinally collected paired-matched samples, demonstrating biological stability in the largest known dataset that was evaluated using the VENTANA FOLR1 CDx[a]

In both real-world and clinical trial datasets, FRα protein and mRNA expression derived from the same tumor biopsy demonstrated high correlation; in the absence of MIRV, patients with high *FOLR1* expression had poor prognosis in the 1L setting in the VELIA trial

These data support that FRα protein expression using IHC is feasible, stable, and concordant with mRNA; tissue-derived FRα mRNA levels may be a negative prognostic factor in ovarian cancer, independent of MIRV treatment, and further studies are required to confirm this observation and evaluate the prognostic role of FRα protein expression

For additional information or to obtain a PDF of this poster

Presenting author: Peter Ansell (peter.ansell@abbvie.com)

To submit a medical question, please visit www.abbviemedinfo.com

AbbVie and the authors thank the participants, study sites, and investigators who participated in the VELIA clinical trial. AbbVie and the authors would also like to acknowledge the partnership with Caris Life Sciences for providing the data of paired-matched patient tumor samples tested at Caris Life Sciences, and Ming Poi, MSHI, PharmD, PhD, of Caris Life Sciences for planning the study and performing analyses on the dataset.

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Elizabeth M. Swisher received compensation from IDEAYA Biosciences. Robert L. Coleman is employed by Veriam Group and US Oncology; serves as a consultant or advisory board member or has received honoraria, travel, or research support from Veriam Group, Clovis Oncology, Genentech/Roche, AstraZeneca, Genmab, ImmunoGen, AbbVie, Merck, Alkermes, GSK, Gradalis, Eisai, GOG Foundation, Karyopharm Therapeutics, Array BioPharma, Research To Practice, and SOTIO Biotech; and has stock or other ownership interests in McKesson/US Oncology Network. Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors. Qu Zhang, Emilee Gagliardi, Manal Mehibel, David Masica, Sribalaji Lakshmikanthan, Emily Deutschman, and Peter Ansell are full-time employees of AbbVie.

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, May 30-June 3, 2025, Chicago, IL, USA [DV-015423]

INTRODUCTION

- The FRα-directed antibody-drug conjugate mirvetuximab soravtansine-gynx (MIRV) showed a survival benefit vs investigator's choice chemotherapy for FRα-high, platinum-resistant ovarian cancer in the MIRASOL trial[3]
- In MIRASOL, >90% of patients were enrolled using an archived, diagnostic sample, suggesting biologic stability of FRα
- Data showing tumor FRα stability and correlation with mRNA in the real-world setting are limited
- Understanding the dynamics of targetable FRα expression in the real-world setting is important to inform patient care and guide clinical trial development

METHODS

Data sources

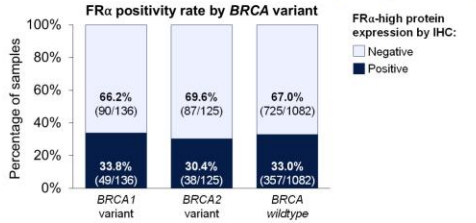
- VELIA (NCT02470585, GOG-3005) was a phase 3 trial of veliparib with first-line chemotherapy in high-grade serous ovarian cancer (N=1140)[4]
- Tumor samples from patients with ovarian cancer in the real-world setting were tested at Caris Life Sciences
  - Cohort 1 (N=1337): ConcertAI RWD360®-Caris linked dataset was used to assess FRα prevalence and confirm IHC:mRNA concordance observed with VELIA trial samples
  - Cohort 2 (N=233): Caris Life Sciences dataset used to assess biological stability

FRα expression

- FRα protein expression was retrospectively established by IHC using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (FOLR1 CDx; Roche Diagnostics)[a]
  - FRα-high positivity was defined as ≥75% of viable tumor cells with ≥2+ membrane staining (used for MIRV treatment eligibility with approved FOLR1 CDx)[3,5]
- *FOLR1* RNA expression from tumor samples was measured using whole transcriptome RNAseq
- Paired-matched tissue samples collected >3 months apart from real-world patients with ovarian cancer were used to examine FRα biological stability
- IHC and mRNA concordance was determined using receiver operating curve (ROC) analysis

RESULTS

FRα Prevalence Is Similar Regardless of *BRCA* Mutation Status in Real-World Patient Samples (N=1337)



- 32.8% (439/1337) of real-world samples from the ConcertAI RWD360®-Caris linked dataset were FRα-high by IHC, which was consistent with that observed in patients in MIRASOL (31.9% [737/2307])[1]
- *BRCA1* and *BRCA2* variants were present in 10.2% (136/1337) and 9.3% (125/1337), respectively, consistent with rates observed in ovarian cancers[6]

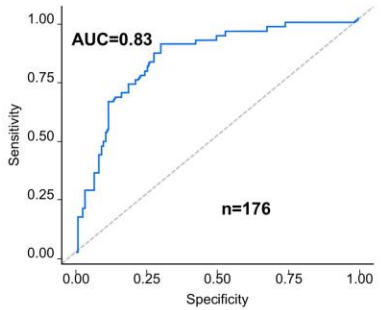
FRα Status Is Consistent Over Time in Real-World Samples From MIRV-Naïve Patients (N=233)

Tissue Sample 1

Tissue Sample 2	Positive	Negative	*Total*
Positive	**39** (16.7%)	**29** (12.4%)	*68*
Negative	**21** (9.0%)	**144** (61.8%)	*165*
Total	*60*	*173*	*233*

- FRα status was consistent in 78.5% (183/233) of longitudinal, paired-matched tissue samples from MIRV-naïve patients (Cohort 2, N=233)
  - 21.5% (50/233) of samples showed discordant FRα status, with 35.0% (21/60) shifting to negative and 16.8% (29/173) shifting to positive in the second sample
- Paired-matched tissue samples were collected at a median interval of 10.0 mo (range, 3.0-144.4)

FRα mRNA and Protein Expression Are Concordant in Tumor Tissue-Derived HGSOC Samples From the VELIA Trial (n=176)

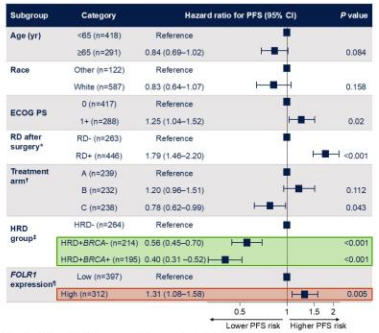


Specificity	Sensitivity	Accuracy (95% CI)	Kappa (*P* value)
69.9%	88.7%	75.6% (68.5%, 81.7%)	0.50 (<0.001)

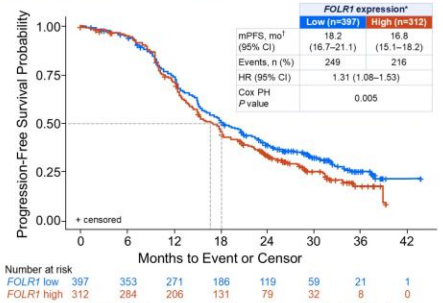
Observed Prevalence	Predicted Prevalence	F1	auROC (95% CI)
30.1%	47.7%	0.69	83.1% (76.4%, 89.7%)

- Concordance of FRα tissue mRNA expression and IHC was confirmed in tumor samples from the ConcertAI RWD360®-Caris linked dataset (n=1228); auROC was 87.6% (95% CI 85.7%-89.4%) using a cutoff maximizing Youden's Index
- mRNA can be an exploratory tool to evaluate FRα protein biology

High *FOLR1* mRNA Is a Negative Prognostic Indicator for Progression-Free Survival in 1L Maintenance Therapy in VELIA (n=709)



*Residual disease (RD) after surgery by those without RD (RD-) and those with RD (RD+).
†VELIA treatment arms: Arm A received carboplatin + paclitaxel followed by placebo maintenance; Arm B received veliparib + carboplatin + paclitaxel followed by placebo maintenance; Arm C received veliparib + carboplatin + paclitaxel followed by veliparib maintenance.
‡HRD groups were those without HRD deficiency (HRD-), those with HRD deficiency and without *BRCA* mutation (HRD+*BRCA*-), and those with HRD deficiency and *BRCA* mutation (HRD+*BRCA*+).
¶*FOLR1* expression (high and low) was defined using the cutoff identified in the ROC analysis.



- HRD and *BRCA* were positive prognostic indicators
- High *FOLR1* was a negative prognostic indicator for PFS in the multivariable analysis, consistent with previous reports[7]

*FOLR1 expression (high and low) was defined using the cutoff identified in the ROC analysis.
†In treated patients across the trial cohorts who had FRα expression and PFS data available.

[a]VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is a qualitative IHC assay using mouse monoclonal anti-FOLR1, clone FOLR1-2.1, intended for use in the assessment of folate receptor alpha (FOLR1) protein in formalin-fixed, paraffin-embedded epithelial ovarian, fallopian tube, or primary peritoneal cancer tissue specimens by light microscopy. This assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument.

1L, first-line; AUC, area under the curve; auROC, area under the receiver operating curve; *BRCA*, BReast CAncer gene; CDx, companion diagnostic; ECOG PS, Eastern Cooperative Oncology Group performance status; HGSOC, high-grade serous ovarian cancer; HR, hazard ratio; HRD, homologous recombination deficiency; IHC, immunohistochemistry; MIRV, mirvetuximab soravtansine-gynx; mPFS, median progression-free survival; mRNA, messenger RNA; PFS, progression-free survival; PH, proportional hazards; RD, residual disease.

REFERENCES: 1. Moore KN, et al. Supplementary appendix. *N Engl J Med.* 2023;389(23):2162-2174. **2.** Matulonis UA, et al. *J Clin Oncol.* 2023;41(13):2436-2445. **3.** Moore KN, et al. *N Engl J Med.* 2023;389(23):2162-2174. **4.** Coleman RL, et al. *N Engl J Med.* 2019;381(25):2403-2415. **5.** Ventana FOLR1 (FOLR1-2.1) RxDx Assay. Package insert. VENTANA Medical Systems Inc.; 2022. **6.** Alsop K, et al. *J Clin Oncol.* 2021;30(21):2654-2663. **7.** Kulbe H, et al. *J Clin Oncol.* 2020;38(suppl 15):6078.

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FRalfa Testing

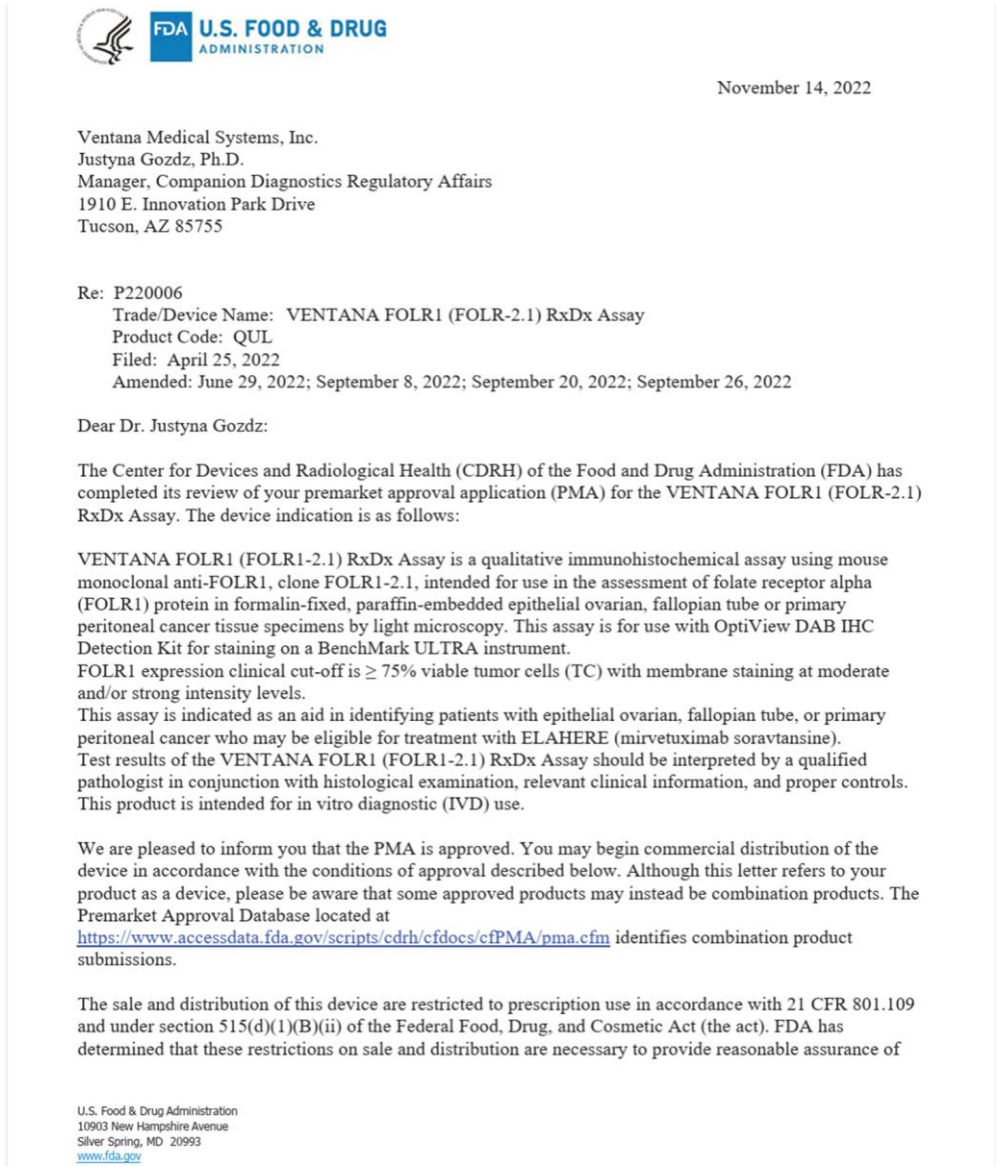
- **HOW**

- **FDA**

The trial enrolled patients whose tumors were positive for FRα expression as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay”

- **EMA**

Eligible patients should have **FRα tumour status defined as >75% viable tumour cells demonstrating moderate (2+) and/or strong (3+) membrane staining by immunohistochemistry (IHC)**, assessed by a CE-marked in vitro diagnostic (IVD) with the corresponding intended purpose. If a CE-marked IVD is not available, an alternative validated test should be used.



U.S. FOOD & DRUG ADMINISTRATION

November 14, 2022

Ventana Medical Systems, Inc.
Justyna Gozdz, Ph.D.
Manager, Companion Diagnostics Regulatory Affairs
1910 E. Innovation Park Drive
Tucson, AZ 85755

Re: P220006
Trade/Device Name: VENTANA FOLR1 (FOLR-2.1) RxDx Assay
Product Code: QUL
Filed: April 25, 2022
Amended: June 29, 2022; September 8, 2022; September 20, 2022; September 26, 2022

Dear Dr. Justyna Gozdz:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the VENTANA FOLR1 (FOLR-2.1) RxDx Assay. The device indication is as follows:

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is a qualitative immunohistochemical assay using mouse monoclonal anti-FOLR1, clone FOLR1-2.1, intended for use in the assessment of folate receptor alpha (FOLR1) protein in formalin-fixed, paraffin-embedded epithelial ovarian, fallopian tube or primary peritoneal cancer tissue specimens by light microscopy. This assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument.
FOLR1 expression clinical cut-off is ≥ 75% viable tumor cells (TC) with membrane staining at moderate and/or strong intensity levels.
This assay is indicated as an aid in identifying patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who may be eligible for treatment with ELAHERE (mirvetuximab soravtansine).
Test results of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.
This product is intended for in vitro diagnostic (IVD) use.

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. Although this letter refers to your product as a device, please be aware that some approved products may instead be combination products. The Premarket Approval Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm identifies combination product submissions.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of

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Silver Spring, MD 20993
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https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-mirvetuximab-soravtansine-gynx-fra-positive-platinum-resistant-epithelial-ovarian.

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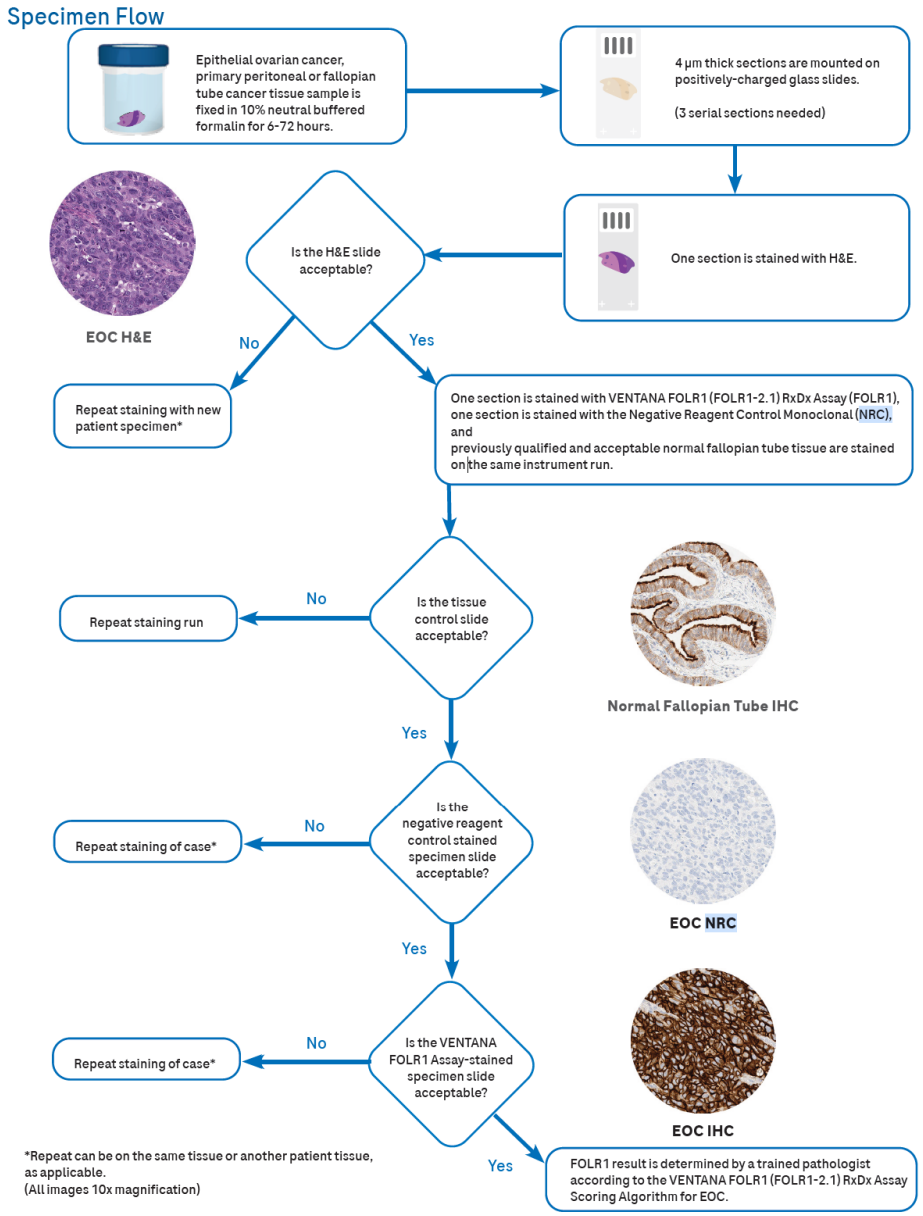
FRalfa Testing

- **HOW**

Clinical Interpretation	Staining Criteria / Characteristics
Positive for FOLR1*	≥ 75% of viable tumor cells with moderate (2+) and/or strong (3+) membrane staining
Negative for FOLR1*	< 75% of viable tumor cells with moderate (2+) and/or strong (3+) membrane staining
Not Evaluable	Artifacts making interpretation not possible



FRalfa Testing

- **HOW**

Regime: Interno
Codice contatto:

Pervenuta al servizio il XX/XX/XXXX
Eseguito il: XX/XX/XXXX
Esame associato a:

MATERIALE IN ESAME:
BIOPSIA PERITONEO nodulo parete sigma

UNITÀ DI CURA RICHIEDENTE:

MEDICO RICHIEDENTE:

Esame richiesto e Valutazione adeguatezza del campione
Determinazione immunoistochimica dello stato del recettore FOLR1
[XX FOLR1 RxDx Assay (anticorpo FOLR1-2.1 su piattaforma xx)]

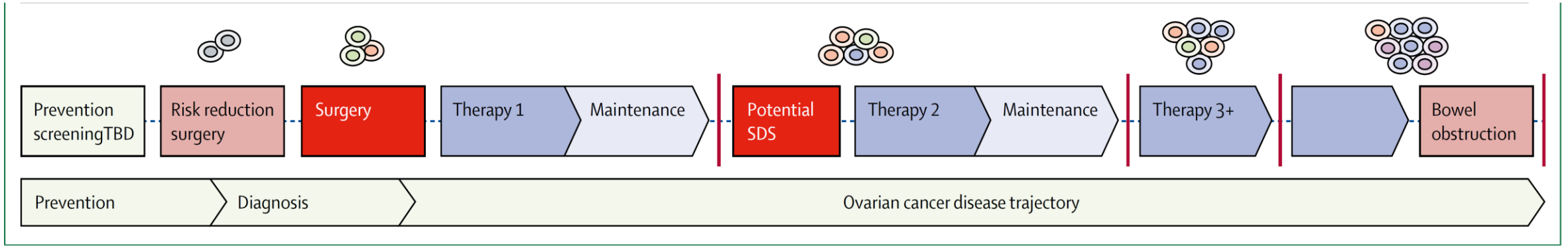
Adeguatezza tessuto tubarico di controllo: sì
Adeguatezza del numero di cellule neoplastiche vitali presenti (>100 cellule): sì
Valutazione immunoistochimica: positività di membrana (score 2+/3+) nel 75% delle cellule neoplastiche
Scoring condiviso: sì

DIAGNOSI
POSITIVO per l'espressione di FOLR1

NOTE:
Interpretazione del test:
Una neoplasia epiteliale di ovaio/salpinge/peritoneo è considerata positiva se almeno il 75% delle cellule neoplastiche mostra una colorazione di membrana (apicale o circonferenziale; con o senza colorazione endoluminale "*dot-like*", di moderata (2+) o forte (3+) intensità (Matulonis UA, et al. 2023).
Casi "*borderline*" (65-85% di cellule con positività score 2+ o 3+) necessitano di rivalutazione da parte di un secondo Patologo e, se possibile, di rideterminazione su una differente inclusione in paraffina.

Referto firmato digitalmente
da XX in data XX/XX/XXXX

Biomarker testing in advanced OC

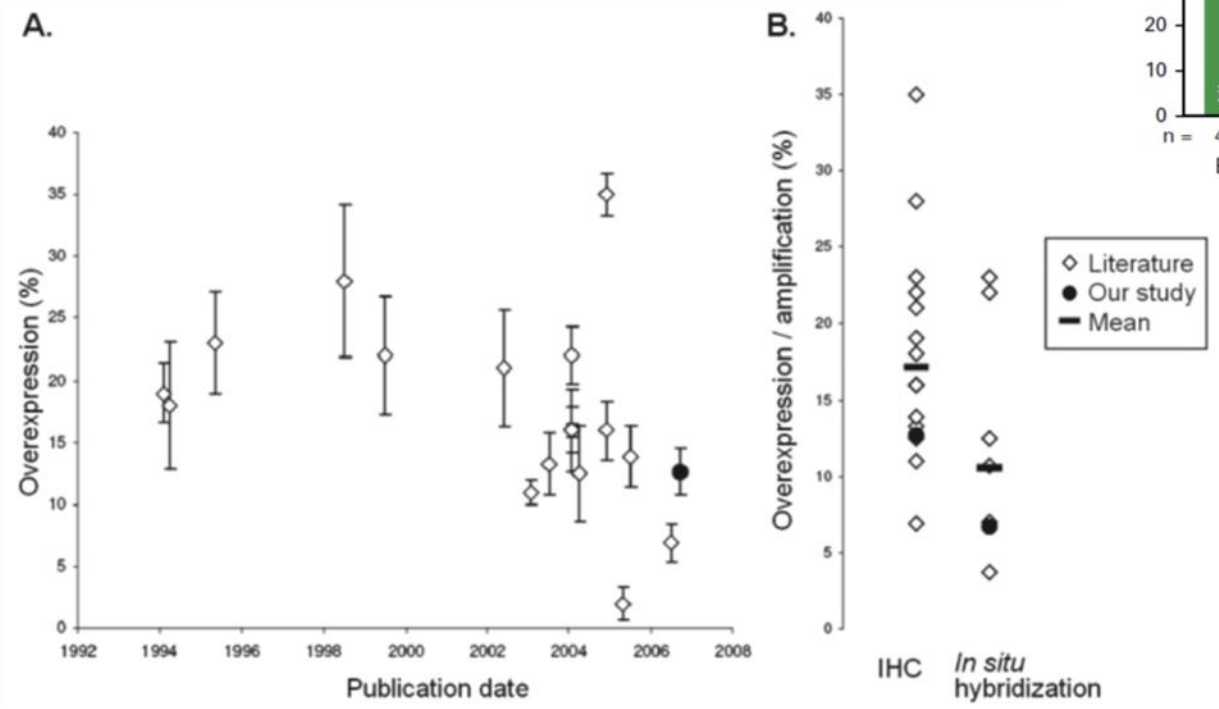


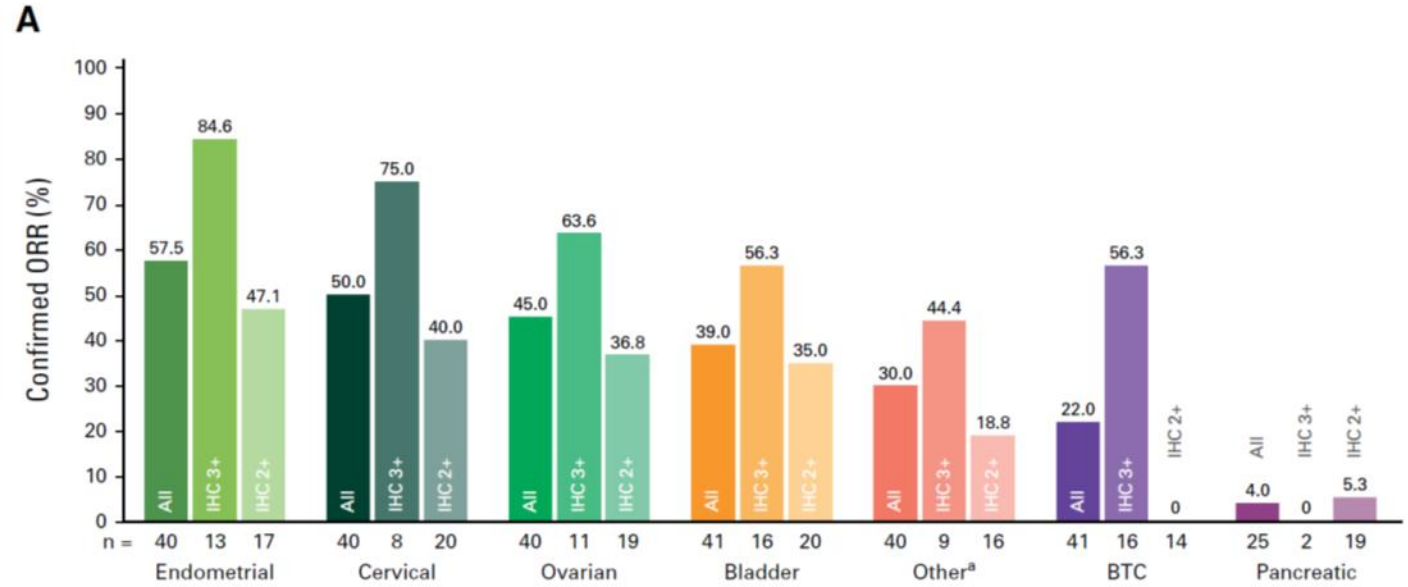
- What (if) else?

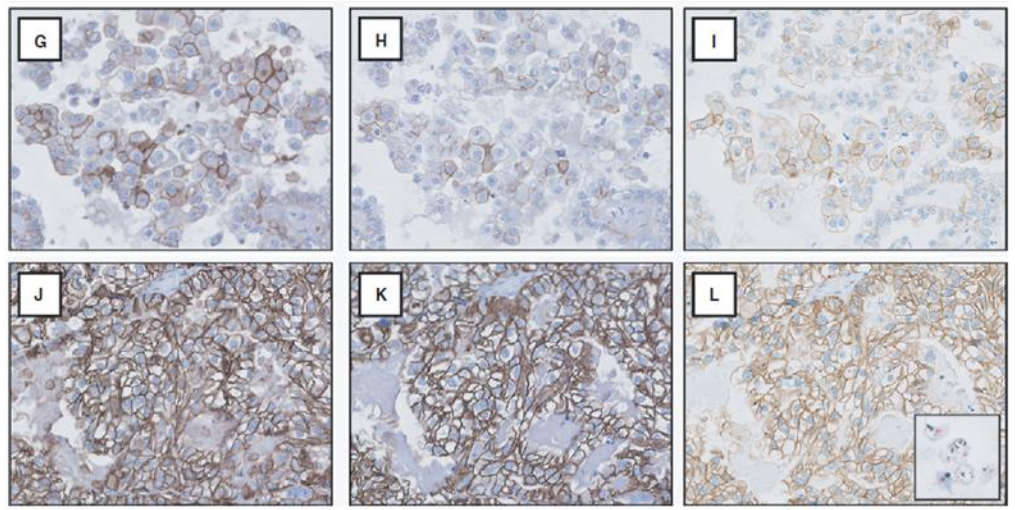
Lheureux S, Gourley C, Vergote I, Oza AM.. Lancet. 2019 Mar 23;393(10177):1240-1253. .

Biomarker testing in advanced OC

- ***HER2***







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Biomarker testing in advanced OC

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MINISTERO DELLA SALUTE

DECRETO 30 maggio 2023.

Istituzione dei *Molecular tumor board* e individuazione dei centri specialistici per l'esecuzione dei test per la profilazione genomica estesa *Next generation sequencing* (NGS).

1) Caratteristiche del paziente con malattia oncologica in fase avanzata:

- ✓ assenza di valide alternative terapeutiche autorizzate ed erogate dal SSN;
- ✓ aspettativa di vita non inferiore a 3 mesi;
- ✓ PS 0-2 che renda il paziente candidabile ad un trattamento;
- ✓ volontà del paziente.

2) Disponibilità dei farmaci:

- ✓ farmaci oggetto di sperimentazione clinica per il quale il paziente potrebbe essere potenzialmente eleggibile (in questo caso l'Articolazione del MTB-R propone uno o più protocolli di ricerca attivi a cui il paziente può essere eleggibile);
- ✓ farmaci disponibili attraverso il "c.d. uso compassionevole" ai sensi del DM Salute del 07/09/2017;
- ✓ farmaci per i quali siano disponibili evidenze cliniche che un trattamento mirato abbia efficacia terapeutica e che sono quelle previste per lo specifico tumore dai livelli I e II secondo ESCAT-ESMO.

THANKS

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