To Target We Need to Test: Why and How to Identify Folate Receptor Alpha–Positive Ovarian Cancer

Key Clinical Summaries From the PeerVoice Live Event on Ovarian Cancer

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In this video CME activity, Diana N. Ionescu, MD, Kathleen Moore, MD, MS, and Barrett C. Lawson, MD, explore the need for folate receptor alpha testing and the optimal integration of folate receptor alpha testing and reporting in ovarian cancer. Watch at the URL below, or you may review the key clinical summaries of the most salient science presented as part of the activity.

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CME Information

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Funding Disclosure
This activity is supported by an independent medical educational grant from AbbVie.

Activity Description and Educational Objectives
In this activity, an expert panel discusses the need for folate receptor alpha (FRα) testing and explores the optimal integration of FRα testing and reporting in ovarian cancer.

Upon completion of this activity, participants should be better able to:
- Use the clinical data for folate receptor alpha (FRα)-targeted therapies for ovarian cancer to evaluate the need for establishing FRα status
- Describe the immunohistochemical characteristics of FRα-positive ovarian cancer
- Apply guideline recommendations for FRα testing and targeted treatment in patients with ovarian cancer

Target Audience
This activity has been designed to meet the educational needs of oncologists, pathologists, and other clinicians involved in the management of individuals with ovarian cancer.

Accreditation
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Media: Enduring Material
Release and Expiration Dates: April 16, 2025 – April 15, 2027
Time to Complete: 60 minutes

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Advances in FRα Targeting: Revolutionizing Ovarian Cancer Treatment

- The importance of multidisciplinary, patient-centered care is growing, enabling individualized, transformative therapies through collaboration between oncologists and pathologists.
- Targeted therapies (eg, olaparib for BRCA+ ovarian cancer, vemurafenib for BRAF V600E melanoma, KRAS inhibitors for lung cancer) have dramatically improved survival, but many cancers still lack identifiable drivers.
- Protein-targeted therapies (eg, HER2 in breast cancer, folate receptor alpha in ovarian cancer) are expanding treatment options, with HER2 as a proven model, now being tested across cancers.
- Precision medicine is complex, requiring integration of multiple biomarkers (mutations, protein expression, HRD status) to guide therapy, especially in overlapping or conflicting cases (eg, BRCA+/HER2+ patients).
- Pathologists now play a critical role beyond traditional diagnostics, using tools like IHC, NGS, and liquid biopsies to identify biomarkers, monitor treatment response, and detect resistance.
- The future hinges on collaborative interpretation of tumor biology, combining histology, genomics, and clinical context to optimize personalized therapy for each patient.
- Platinum-based chemotherapy + surgery induces remission in ~80% of patients with ovarian cancer, but 80% recur within 2-3 years, entering a cycle of therapies until platinum resistance develops.
- Frontline treatment is the only curative opportunity; extending remission requires individualized approaches.
- Ovarian cancer subtypes (HGSOC, low-grade serous, clear cell) have distinct molecular drivers (eg, TP53, MAPK, ARID1A), necessitating histology-specific therapies.
- Folate receptor alpha (FRα) is expressed in ~80% of HGSOC (35-40% at high levels) and is a promising therapeutic target due to low normal-tissue expression.
- Mirvetuximab soravtansine (MIRV), an FRα-targeting antibody-drug conjugate, showed 33% objective response rate (ORR) in platinum-resistant HGSOC in the SORAYA trial.
- MIRASOL was the global confirmatory phase 3 trial for mirvetuximab soravtansine, comparing it to investigator's choice chemotherapy in platinum-resistant, FRα-high epithelial ovarian tumors (1-3 prior lines, bevacizumab not mandated).
- The trial met its primary endpoint with a 35% reduction in progression-free survival hazard and demonstrated a 33% reduction in risk of death (overall survival) at interim analysis, leading to full FDA approval.
- Unlike SORAYA, MIRASOL included broader eligibility (no prior bevacizumab required) and showed a 42% ORR vs 16% with chemotherapy, with tumor shrinkage observed in most patients, correlating with clinical benefit.
- Testing FRα status is now essential (like HRD or HER2). While currently approved for platinum-resistant disease, many clinicians test earlier due to tumor heterogeneity.

Abbreviation(s):
HGSOC; high grade serous ovarian cancer; HER2: human epidermal growth factor receptor 2; HRD: homologous recombination deficiency; IHC: immunohistochemistry; NGS: next-generation sequencing.

Reference(s):
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FRα-Testing and Scoring in Ovarian Cancer

- FRα is highly expressed in ovarian tumors but shows limited expression in normal tissue, with some staining observed in the fallopian tube, which is used as tissue external control.
- FRα functions as a membrane receptor for folate transport and is overexpressed in ovarian, endometrial, triple-negative breast, and some lung cancers.
- Testing uses FFPE tissue, with strict pre-analytical requirements, and is performed on both primary and metastatic tumor sites.
- A small study showed 70% concordance between archival and pre-treatment biopsy FRα expression, supporting use of archival tissue in trials.
- Categorization by positivity expression score showed 64% of high-grade serous tumors had medium expression and 31% had high expression.
- Clinical trial data suggest FRα expression rates are consistent across site types, and platinum-sensitive populations may show higher FRα positivity.
- Intra-tumoral heterogeneity in FRα expression complicates prediction of drug response and test interpretation.
- Real-world data showed 45% overall FRα positivity, with higher rates in high-grade serous tumors and in resections versus biopsies.
- Pathologists are recommended to use the FDA-approved Ventana FOLR1 assay, scoring ≥75% of tumor cells with 2+ or 3+ membranous staining as positive. Fallopian tube epithelium serves as essential external control for assay.

Abbreviation(s):
FFPE: formalin-fixed paraffin-embedded.

Reference(s):
Bax HJ et al. *Br J Cancer*. 2023;128:342-353.
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Lawson BC et al. *Int J Gynecol Pathol*. 2025;44:167-173.
Ventana FOLR1 (FOLR1-2.1) RxDx Assay. Ventana Medical Systems Inc/Roche Diagnostics International Inc; 2022. https://www.accessdata.fda.gov/cdrh_docs/pdf22/P220006C.pdf. Accessed March 13, 2025.

Implementation of FRα-Testing and Reporting in Ovarian Cancer Management

- Folate receptor alpha (FRα) testing is sometimes performed at diagnosis, with results used to guide treatment at recurrence, though there's no current consensus on retesting.
- Some cases show differing FRα expression over time, suggesting spatial or temporal tumor heterogeneity may affect results.
- In some centers, pathologists often wait for oncologists to order FRα testing,
- FRα testing is not validated for cytology specimens like cell blocks; only biopsies or resections are used.
- All clinical trials used the same Ventana FOLR1 assay with central interpretation.
- Some clinicians prefer detailed staining reports (percentages at 2+/3+) instead of binary results to accommodate future changes in treatment eligibility.
- Pathologists assess tumor blocks with a minimum of 100 viable tumor cells; cases with borderline expression may require second opinions.
- Resection samples tend to show higher FRα positivity than smaller biopsies, potentially due to heterogeneity.

Reference(s):

Washington K and Salaria SN. https://www.personalizedmedonc.com/articles/3564:expanding-roles-for-pathologists-as-members-of-the-multidisciplinary-cancer-care-team. Accessed March 13, 2025.

National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2024 Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer.

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