Folate Receptor Alpha Testing: The Shifting Target in Platinum-Resistant Ovarian Cancer

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Folate receptor alpha (FRα) expression is a clinically actionable biomarker in high-grade serous ovarian carcinoma (HGSOC), guiding treatment decisions for platinum-resistant disease with therapies like mirvetuximab soravtansine. However, the dynamic nature of ovarian cancer raises a critical question for clinicians: does a patient's FRα status remain stable over time, particularly after prior chemotherapy? A recent retrospective study by Neisani, Marrero, and Angeli-Morales revealed that FRα expression is not entirely stable, with approximately 30% of patients experiencing a change in status between initial diagnosis and recurrence.

KEY TAKEAWAYS

- The Pivot: FRα expression in ovarian cancer is not static; it can change between primary diagnosis and recurrence, impacting eligibility for targeted therapies.
- The Data: Concordance rates for FRα expression between primary and recurrent tumors ranged from 60% to 75% in retrospective analyses, with discordance more common after chemotherapy.
- The Action: Re-testing for FRα expression at recurrence, particularly in platinum-resistant settings, is essential to ensure patients are appropriately selected for MIRV.

High-grade serous ovarian carcinoma (HGSOC) frequently expresses folate receptor alpha (FRα), making it a clinically actionable biomarker. The FDA approved mirvetuximab soravtansine (MIRV) for platinum-resistant disease in patients whose tumors exhibit high FRα expression, defined as ≥75% of tumor cells with 2+ staining. This approval followed compelling data from trials like MIRASOL, which established MIRV's efficacy in this specific patient population.2,3 But the clinical utility of FRα testing hinges on the stability of its expression over time. Ovarian cancer is a heterogeneous disease, and its molecular profile can evolve under selective pressures from prior treatments. This raises a critical question for clinicians: does a patient's FRα status at initial diagnosis reliably predict their status at recurrence, especially after multiple lines of chemotherapy? The answer directly impacts treatment decisions, particularly for therapies like MIRV, which require a current, accurate biomarker assessment.1

The Shifting Biomarker Landscape

A retrospective study by Neisani, Marrero, and Angeli-Morales, published in Gynecologic Oncology Reports, directly addressed the temporal concordance of FRα expression.1 The investigators evaluated paired tumor specimens from a single institution, comparing FRα status at primary diagnosis with that at recurrence in patients with ovarian cancer. This cohort included patients with various histological subtypes, though HGSOC predominated, reflecting its prevalence in ovarian cancer. The study aimed to quantify the degree of change in FRα expression, providing insights for clinical

practice.1

The study enrolled 120 patients who had undergone at least two surgical resections for ovarian cancer, allowing for paired tissue analysis. The median time between primary diagnosis and recurrence biopsy was 24 months, with a range spanning several years, capturing a clinically relevant interval for disease progression and treatment exposure. All samples were centrally reviewed by expert pathologists using the same immunohistochemistry (IHC) assay for FR± ensuring consistency in scoring. High expression was defined as ≥75% of tumor cells staining at 2+ intensity, aligning with the criteria used in MIRV clinical trials.1

The primary endpoint was the concordance rate of FR± expression between the paired samples. Secondary endpoints included identifying factors associated with discordance, such as prior chemotherapy regimens, time to recurrence, and histological subtype. The investigators meticulously documented prior treatment histories, including platinum-based chemotherapy, taxanes, and other targeted agents, to assess their potential influence on FR± status. This detailed approach allowed for a more granular understanding of biomarker dynamics.1

Concordance and Clinical Implications

The Neisani et al. study revealed that FR± expression is not entirely stable over time. The overall concordance rate for high FR± expression between primary and recurrent tumors was approximately 70% (95% CI, 62%-78%). This means that in about three out of ten patients, the FR± status changed between initial diagnosis and recurrence. Specifically, 20% of patients who initially had high FR± expression lost it at recurrence, while 10% of patients who initially had low expression converted to high expression.1

The investigators identified prior platinum-based chemotherapy as a significant factor influencing discordance. Patients who received multiple lines of chemotherapy, particularly those with platinum-resistant disease, showed a higher likelihood of FR± status change. This observation suggests that treatment-induced selective pressures might drive the evolution of FR± expression, making re-testing even more critical in this heavily pre-treated population. The median progression-free survival (PFS) for patients with concordant high FR± expression was 10.5 months, compared to 6.2 months for those who lost expression, though this was a retrospective analysis and not powered for survival outcomes.1 These findings highlight the importance of re-evaluating FR± status at the time of recurrence, especially when considering MIRV. Relying solely on the initial diagnostic biopsy could lead to inappropriate treatment selection, either denying an eligible patient a potentially effective therapy or administering MIRV to a patient whose tumor no longer expresses the target. This is particularly relevant given the ASCO Living Guideline, Version 2026.1.0, which emphasizes biomarker-driven treatment decisions in recurrent ovarian cancer.3

Treatment Sequencing and Evolving Guidelines

The market of platinum-resistant epithelial ovarian cancer treatment has evolved rapidly with the introduction of MIRV and other targeted agents. Liu, Xu, and Ma, in their review in the International Journal of Women's Health, discuss the implications of trials like MIRASOL, KEYNOTE-B96, and ROSELLA on treatment sequencing.2 MIRASOL, a Phase III trial, demonstrated a significant overall survival benefit for MIRV compared to investigator's choice chemotherapy in patients with high FR± expression, establishing it as a standard of care in this setting.2

The ASCO Living Guideline, Version 2026.1.0, provides updated recommendations for systemic treatment of ovarian cancer recurrence.3 This guideline explicitly incorporates FR± testing as a critical step in the management algorithm for

platinum-resistant disease. It recommends testing for FR± expression at recurrence to guide the use of MIRV, aligning with the evidence that expression can change. For patients with high FR± expression, MIRV is a preferred option, offering a median overall survival of 16.4 months compared to 10.9 months with chemotherapy (HR 0.65; 95% CI, 0.52-0.81; P2,3

The guideline also addresses the sequencing of other agents, such as PARP inhibitors and bevacizumab, in relation to MIRV. It emphasizes that FR± testing should be performed on the most recent tumor tissue available, preferably from a biopsy taken at the time of platinum-resistant recurrence. This recommendation directly addresses the concerns raised by studies on FR± concordance. The guideline also acknowledges the practical challenges of obtaining fresh biopsies, but prioritizes accurate biomarker assessment over convenience.3

Still, the logistical challenges of re-biopsy are not trivial. Patients with advanced ovarian cancer often have extensive disease, making biopsy technically difficult or risky. Turnaround times for FR± IHC testing can delay treatment initiation, which is a concern in rapidly progressing disease. These practical considerations necessitate a careful discussion between the clinician and the patient, balancing the need for accurate biomarker information with the urgency of treatment. The role of molecular testing in oncology continues to expand, but its practical implementation requires careful thought.

The Neisani et al. study, while retrospective and from a single institution, provides compelling evidence that FR± expression is a dynamic biomarker. The relatively small sample size of 120 paired samples is an obvious caveat, and larger prospective studies would strengthen these observations. But the consistent trend of discordance, particularly after chemotherapy, cannot be ignored. The study did not explore the specific mechanisms driving FR± changes, which could involve epigenetic modifications or clonal selection under therapeutic pressure. Future research should investigate these underlying biological processes to better predict and manage biomarker evolution.1

Another limitation is the reliance on IHC for FR± assessment. While IHC is the current standard for clinical decision-making with MIRV, it is a semi-quantitative method that can be subject to inter-observer variability, even with central review. The definition of 'high expression' at ≥75% staining is a pragmatic threshold derived from clinical trials, but the biological continuum of FR± expression might be more complex. More precise quantitative methods could offer a clearer picture of FR± status and its changes.1

The implications extend beyond MIRV. As more antibody-drug conjugates and other targeted therapies emerge for ovarian cancer, accurate and timely biomarker testing will become increasingly critical. The experience with FR± highlights a broader principle in precision oncology: biomarkers are not static, and their re-evaluation at disease progression is often necessary. Clinicians managing ovarian cancer patients should consider these dynamics when planning subsequent lines of therapy, consulting resources like the Oxford Handbook of Oncology for up-to-date guidance. The evolving understanding of tumor biology demands a flexible approach to biomarker-driven treatment.2,3

The question of how best to integrate serial biomarker testing into routine clinical practice remains. Should all patients with platinum-resistant disease undergo re-biopsy for FR±? What if a biopsy is not feasible? Liquid biopsies, which detect circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs), offer a less invasive alternative for biomarker assessment. While not yet validated for FR± in this specific context, the development of such assays could revolutionize how clinicians monitor biomarker status and guide treatment decisions, potentially overcoming some of the practical hurdles associated with tissue biopsies. The field is actively exploring new molecular testing methods for various cancers.

The data from Neisani et al. directly informs the ASCO guideline's recommendation for re-testing FR±This convergence of real-world evidence and expert consensus strengthens the argument for dynamic biomarker assessment. The clinical benefit of MIRV is clear in the highly selected population, but that selection depends on an accurate, current FR±status. Without re-testing, clinicians risk misidentifying eligible patients, potentially compromising outcomes in a disease where every effective treatment option matters.1,3

CLINICAL IMPLICATIONS

The notion that a biomarker status, once determined, remains immutable throughout a patient's cancer journey is a comfortable but often incorrect assumption. The Neisani et al. study on FR±concordance in ovarian cancer provides a stark reminder that tumor biology evolves, particularly under the selective pressure of chemotherapy. Clinicians must internalize this dynamism; a primary biopsy from years ago may not reflect the current therapeutic target. Re-testing for FR±at recurrence is not merely good practice; it is essential for appropriate patient selection for mirvetuximab soravtansine.

The ASCO guideline's explicit recommendation for re-testing FR±on the most recent tissue available is a direct response to this evolving understanding. This means that for patients with platinum-resistant ovarian cancer, the default should be to obtain a new biopsy or, at minimum, review the most recent available tissue. Relying on initial diagnostic samples risks missing patients who have gained FR±expression or, more commonly, treating those who have lost it, thereby exposing them to an ineffective therapy and its associated toxicities.

But the practicalities are not always straightforward. Biopsies can be invasive, and delays in obtaining results can impact treatment timelines. This tension between ideal biomarker assessment and clinical urgency will persist. The industry, particularly companies like ImmunoGen, which developed MIRV, must continue to support research into less invasive and faster methods for FR±assessment, such as liquid biopsies, to streamline this critical step in patient management.

The message for European GPs and specialists is clear: FR±status is a moving target. Do not assume. Test. The efficacy of mirvetuximab soravtansine is contingent on high FR±expression, and that expression can change. Integrating this dynamic approach into routine practice will ensure that patients receive the most appropriate, targeted therapy for their current disease state, optimizing outcomes in a challenging clinical setting.

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