Folate Receptor Alpha Testing: Why Timing Matters in Platinum-Resistant Ovarian Cancer

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Platinum-resistant ovarian cancer remains a clinical challenge, with limited effective treatment options. Mirvetuximab soravtansine (MIRV), an antibody-drug conjugate targeting folate receptor alpha (FRα), offers a new avenue for patients with high FRα expression. But the dynamic nature of biomarker expression raises critical questions about optimal testing strategies and treatment sequencing, especially when considering the ASCO Living Guideline, Version 2026.1.0.3

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 like mirvetuximab soravtansine.
- The Data: Concordance rates for FRα expression between primary and recurrent tumors ranged from 58% to 75%, with a significant proportion of initially positive tumors becoming negative.
- The Action: Re-biopsy and re-testing for FRα at the time of platinum-resistant recurrence are essential to accurately identify patients who will benefit from mirvetuximab soravtansine.

High-grade serous ovarian carcinoma (HGSOC) frequently expresses folate receptor alpha (FRα), making it a compelling target for antibody-drug conjugates. Mirvetuximab soravtansine (MIRV) received accelerated FDA approval for platinum-resistant HGSOC patients whose tumors exhibit high FRα expression, defined as ≥75% of tumor cells with 2+ staining intensity. This approval was based on compelling efficacy data, but the clinical utility hinges entirely on accurate and timely biomarker assessment.1,2,3

The drug's mechanism involves a humanized anti-FRα antibody conjugated to a potent microtubule-disrupting agent, DM4. After binding to FRα on the cancer cell surface, the complex internalizes, releasing DM4 to induce mitotic arrest and apoptosis. This targeted delivery aims to reduce systemic toxicity while maximizing anti-tumor activity. The challenge, however, lies in the stability of the target itself.1,2

The Shifting Target: FRα Expression Over Time

A retrospective study by Neisani, Marrero, and Angeli-Morales, published in Gynecologic Oncology Reports, directly addressed the longitudinal variability of FRα expression.1 The investigators evaluated paired tumor specimens from a single institution, comparing FRα status at primary diagnosis with that at recurrence, specifically in platinum-resistant disease. This cohort included patients with HGSOC, the primary indication for MIRV.1

The study enrolled 112 patients with paired samples. The median time between primary diagnosis and recurrence biopsy was 21 months (range, 6-68 months). This interval is clinically relevant, reflecting the typical course of platinum-sensitive

disease progressing to platinum resistance. Investigators used a validated immunohistochemistry (IHC) assay, the Ventana FOLR1 (FOLR1-2.1) CDx assay, which is the companion diagnostic for MIRV.1

The concordance rate for FR± expression between primary and recurrent tumors was 68% (95% CI, 60-76%). This figure, while seemingly moderate, masks critical shifts. Among patients initially classified as FR± high at primary diagnosis (n=45), 31% (n=14) had lost high FR± expression by the time of recurrence. Conversely, among those initially FR± low (n=67), 18% (n=12) converted to FR± high status at recurrence.1

These numbers are not trivial. Nearly one-third of patients who would have been eligible for MIRV based on their initial biopsy became ineligible, while a substantial minority who were initially ineligible gained eligibility. This dynamic suggests that relying solely on primary tumor biopsy for FR± status in the platinum-resistant setting risks both overtreatment and undertreatment.1

Implications for Treatment Sequencing and Testing

The MIRASOL trial, a study that was central to the approval of mirvetuximab soravtansine, demonstrated a significant overall survival benefit for patients with FR± high platinum-resistant ovarian cancer. Patients treated with MIRV had a median overall survival of 16.4 months compared to 12.7 months for those receiving investigator's choice chemotherapy (HR 0.67; 95% CI, 0.50-0.89; P=.0046).2 This outcome highlights the importance of accurately identifying the FR± high population. If FR± status changes, then the benefit observed in MIRASOL would not extend to patients whose tumors have lost expression.2

Liu, Xu, and Ma, in their review of treatment sequencing in platinum-resistant epithelial ovarian cancer, highlighted the critical role of biomarker testing in guiding therapy after trials like MIRASOL.2 They emphasize that the market of available therapies, including PARP inhibitors, bevacizumab, and now MIRV, necessitates a precise understanding of tumor biology at each stage of disease progression. The variability in FR± expression directly impacts this precision.2

The ASCO Living Guideline, Version 2026.1.0, for systemic treatment of ovarian cancer recurrence, acknowledges the evolving role of biomarkers.3 While specific recommendations for re-biopsy frequency are still being refined, the guideline emphasizes that treatment decisions for targeted therapies should be based on the most current tumor biology. This implicitly supports re-testing for actionable biomarkers like FR±, especially in a disease where tumor heterogeneity and clonal evolution are well-documented.3

But the practicalities of re-biopsy are not insignificant. Patients with platinum-resistant disease often have a poorer performance status, and repeat invasive procedures carry risks and patient burden. The choice between a new biopsy and relying on archival tissue must weigh these factors against the potential for therapeutic benefit. Still, the data on FR± discordance makes a strong case for re-biopsy.1

Challenges and Considerations for Clinical Practice

The Neisani study, while informative, has limitations. It was a single-institution retrospective analysis, which inherently carries selection bias. The sample size of 112 paired specimens, while adequate for detecting significant shifts, may not capture the full spectrum of FR± variability across diverse patient populations. The median follow-up time of 21 months between biopsies is also a factor; longer intervals might reveal even greater discordance.1

Another consideration is the method of FR± assessment. While the Ventana FOLR1 (FOLR1-2.1) CDx assay is standardized, inter-observer variability in IHC interpretation, particularly for a threshold-based biomarker like FR± (≥ 75%

of cells with 2+ staining), can exist. This highlights the need for experienced pathologists and robust quality control in clinical laboratories. For clinicians seeking to stay current on these complex diagnostic considerations, the Oxford Handbook of Oncology (4th ed) offers a concise reference.

The mechanism behind FR± expression changes is not fully understood. It could involve clonal selection under chemotherapy pressure, epigenetic modifications, or changes in the tumor microenvironment. Understanding these mechanisms might eventually lead to strategies to stabilize FR± expression or predict its changes. This is similar to the challenges faced in understanding HER2 heterogeneity in gastric cancer, where single-block testing can miss treatment targets. The dynamic nature of biomarkers is a recurring theme in oncology.1,2

The clinical implications extend beyond just MIRV. As more targeted therapies emerge for ovarian cancer, each with its own biomarker, the need for repeat testing will likely increase. This creates a logistical and financial burden on healthcare systems. Developing less invasive methods for biomarker assessment, such as liquid biopsies, could offer a solution, but these technologies still require extensive validation for FR±.2

The current standard of care for platinum-resistant ovarian cancer often involves single-agent chemotherapy, with modest response rates and progression-free survival. The addition of MIRV for FR± high patients represents a meaningful improvement. But this benefit is only realized if the patient truly has FR± high disease at the time of treatment initiation. The data from Neisani and colleagues make a compelling case that this status cannot be assumed from an initial biopsy.1,2

The ASCO guideline's emphasis on current tumor biology is a pragmatic approach.3 It acknowledges that cancer is not a static disease and that treatment strategies must adapt to its evolution. For FR±, this means accepting the necessity of re-biopsy, despite its challenges, to ensure patients receive the most appropriate and effective targeted therapy. The alternative is to risk administering an expensive, targeted agent to a patient whose tumor no longer expresses the target, or conversely, withholding a beneficial therapy from a patient who has developed the target expression. This is a critical distinction in personalized oncology.1,3

The ongoing research into treatment sequencing, as discussed by Liu, Xu, and Ma, will continue to refine these strategies.2 The integration of new agents like MIRV into existing treatment algorithms requires not only efficacy data but also a deep understanding of biomarker dynamics. The question remains: how frequently should these biomarkers be re-evaluated, and what is the optimal timing for re-biopsy in the context of disease progression and prior therapies?

CLINICAL IMPLICATIONS

Clinicians managing platinum-resistant ovarian cancer must internalize a simple truth: FR± expression is not a fixed characteristic. Relying on a primary tumor biopsy for MIRV eligibility in recurrent disease is a gamble, and the odds are not in the patient's favor, given that nearly a third of initially positive tumors lose high expression. Re-biopsy at recurrence is not merely good practice; it is essential to ensure appropriate patient selection for a therapy that offers a clear survival benefit.

The logistical hurdles of repeat biopsies are real, but they pale in comparison to the cost and futility of administering an expensive targeted therapy to a patient whose tumor no longer expresses the target. Conversely, missing an opportunity to treat a patient who has developed FR± positivity at recurrence is equally detrimental. This calls for a shift in mindset, treating FR± status as a dynamic, rather than static, biomarker.

> Payers and guideline bodies should reinforce the necessity of re-testing. The data clearly show that a significant proportion of patients will either gain or lose eligibility for MIRV over time. Without current FR± status, treatment decisions are based on outdated information, leading to suboptimal outcomes and inefficient resource allocation. This is a clear case where precision medicine demands precision diagnostics at the point of decision.

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