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EDITORIAL

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Mirvetuximab soravtansine: current and future applications

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Abstract

Ovarian epithelial cancer (OEC), particularly high-grade serous carcinoma (HGSC), remains a clinical challenge due to its late-stage diagnosis, high recurrence rates, and poor survival outcomes. Mirvetuximab soravtansine (MIRV), an antibody-drug conjugate targeting folate receptor alpha (FRα), has demonstrated promising efficacy in platinum-resistant OEC, particularly in high FRα-expressing populations, as evidenced by key clinical trials such as FORWARD I, FORWARD II, SORAYA, and MIRASOL. These trials highlight MIRV's ability to improve progression-free survival, response rates, and quality of life in advanced disease settings. Emerging data suggest that FRα is also highly expressed in serous tubal intraepithelial carcinoma (STIC), a non-invasive precursor lesion to HGSC. Although MIRV has not yet been studied for STIC management, we propose its potential application in this context to prevent progression to invasive carcinoma, particularly in high-risk populations undergoing risk-reducing bilateral salpingo-oophorectomy. This novel use could bridge the gap between prevention and treatment, offering a proactive strategy for hereditary cancer management. Furthermore, MIRV's therapeutic versatility extends to other FRα-positive tumors, such as endometrial and breast cancers, broadening its clinical relevance. Despite challenges such as accessibility and cost, MIRV represents a significant advancement in precision medicine, with potential to redefine prevention and treatment strategies for hereditary and sporadic cancers.

Keywords MIRV, Ovarian cancer, High-grade serous carcinoma, BRCA carriers, Serous tubal intraepithelial carcinoma, Risk-reducing bilateral salpingo-oophorectomy, Cancer prevention strategies

Ovarian epithelial cancer (OEC) management has relied on platinum-based chemotherapy for over four decades. While this approach has brought significant advancements, a considerable proportion of cancers develop resistance to platinum-based treatments. High-grade serous carcinoma (HGSC), the most lethal subtype of OEC, accounts for the majority of ovarian cancer deaths, with a five-year survival rate below 50% for advanced-stage diagnoses. The introduction of biological agents, such as bevacizumab and PARP inhibitors, has further enhanced therapeutic efficacy, particularly in tumors with BRCA mutations or homologous recombination deficiencies [1]. However, recurrence remains common and is often associated with poor outcomes. This underscores the press-

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ing need for novel biomarkers and targeted therapeutic strategies.

Mirvetuximab soravtansine-gynx (MIRV), an antibody-drug conjugate targeting folate receptor alpha (FRα), has emerged as a promising treatment for platinum-resistant ovarian cancer [2]. Recent clinical trials have highlighted MIRV's potential to improve outcomes, particularly in high-grade serous carcinoma (HGSC), a prevalent and aggressive form of OEC. In this editorial, we summarize the latest clinical evidence supporting MIRV's efficacy and propose its potential application in serous tubal intraepithelial carcinoma (STIC), a non-invasive precursor lesion identified in patients undergoing risk-reducing bilateral salpingo-oophorectomy (rrBSO).

Folate and FRα play crucial roles in cancer development, particularly in DNA replication, methylation, and nucleotide precursor synthesis. FRα, predominantly expressed on the surface of cancer cells, facilitates the targeted delivery of therapies like MIRV [3, 4]. This specificity stems from the differential expression of FRα in cancerous versus normal tissues. Emerging evidence suggests that FRα overexpression in OEC is significantly higher than in fallopian tubal mucosa, making it a valuable target for therapy. Moreover, high FRα expression has been linked to chemotherapy resistance, further supporting its role in managing HGSC.

The therapeutic role of MIRV in ovarian cancer: clinical applications from key trials

MIRV has shown significant promise in the treatment of ovarian epithelial cancers (OECs), particularly in folate receptor alpha (FRα)-positive tumors. In platinum-resistant ovarian cancer, the Phase I study (NCT01609556) demonstrated a 26.1% objective response rate and a median progression-free survival (PFS) of 4.8 months in heavily pre-treated patients [5]. Building on these results, the FORWARD I trial (NCT02631876) provided further evidence of MIRV's efficacy, with high FRα-expressing patients achieving a PFS of 4.8 months and an improved response rate of 22%, despite challenges posed by differences in FRα scoring methods [6].

The FORWARD II trial (NCT02606305) expanded MIRV's application by exploring its combination with bevacizumab. This combination yielded a 44% response rate and a median PFS of 8.2 months, demonstrating enhanced efficacy in heavily pre-treated populations [7]. Further trials, such as SORAYA (NCT04296890) and MIRASOL (NCT04209855), narrowed their focus to high FRα-expressing populations, producing remarkable results [8, 9]. SORAYA reported a 32.4% response rate, while MIRASOL demonstrated a 33% reduction in the risk of death, with MIRV consistently outperforming chemotherapy in secondary outcomes like quality of life and CA125 response [8].

In platinum-sensitive ovarian cancer, the FORWARD II trial highlighted a 71% response rate and a median PFS of 15 months when MIRV was combined with carboplatin [7]. Additionally, the PICCOLO trial (NCT05041257) evaluated MIRV as monotherapy, showcasing its meaningful antitumor activity and favorable tolerability in high FRα-expressing patients with ≥ 2 prior platinum regimens or platinum allergy [10].

While MIRV has demonstrated significant efficacy in advanced disease settings, its potential to address precursor lesions like STIC could redefine early prevention strategies. Ongoing studies are also investigating FRα expression in STIC and exploring MIRV's potential use in neoadjuvant or maintenance therapies, which could further expand its application in managing ovarian cancers. Such developments highlight the importance of continued research to fully leverage MIRV's therapeutic potential across diverse clinical contexts.

The key clinical trials relevant to MIRV's development are summarized in Table 1. Altogether, these findings underscore MIRV's therapeutic efficacy for OECs, particularly HGSC, across platinum-resistant and platinum-sensitive settings. With its global adoption steadily expanding, MIRV is increasingly becoming a routine application for patients with OECs in numerous academic centers. These promising results support the proposal to extend MIRV's application to patients with isolated STIC, a precursor lesion of HGSC, to prevent progression to invasive disease (see below).

Expanding the scope: preventing HGSC through targeted strategies

The lifetime risk of OEC is less than 2% in the general population. However, this risk escalates dramatically in patients with BRCA1/2 germline mutations, who are significantly predisposed to ovarian, tubal, and peritoneal HGSC [11]. HGSC predominantly presents at an advanced stage, emphasizing the critical need for prevention and early detection.

The majority of HGSCs originate from the fallopian tube epithelium, specifically from STIC, a non-invasive precursor lesion found in the distal fallopian tube epithelium. STIC and HGSC share striking morphological and immunohistochemical similarities, supporting the hypothesis that STIC cells may dislodge, implant on ovarian or peritoneal surfaces, and evolve into invasive HGSC [3]. This progression is particularly concerning for BRCA mutation carriers, where STIC often serves as a precursor for HGSC.

Risk-reducing bilateral salpingo-oophorectomy (rrBSO) remains the gold standard for HGSC prevention in high-risk individuals. While rrBSO is highly effective in reducing cancer incidence, the procedure carries significant long-term consequences, including infertility,

Table 1 Representative clinical trials of Mirvetuximab Soravtansine-Gynx in ovarian epithelial cancers

Study name	Clinical trial information	Study detail	Patients	> 3 previous lines of therapy	Previous bevacizumab exposure	Previous PARPi exposure	ORR	Complete response	Partial response	Stable disease	Progressive disease	Unknown	mDOR	PFS (months)
N/A [5]	NCT01609556	Phase I	46 pts receiving mirvetuximab	> 50%*	NR	NR	26.1%	1%	11%	28%	4%	2%	19.1 weeks	4.8
FORWARD I [6]	NCT02631876	Phase III	366 pts (243 receiving mirvetuximab)	86 (34%)	121 (48.8%)	44 (17.7%)	22%	NR	NR	NR	NR	NR	5.7 months	4.1
SORAYA [8]	NCT04296890	Phase II	106 pts receiving mirvetuximab	54 (51%)	106 (100%)	51 (48%)	30.2%	5 (4.8%)	29 (27.6%)	48 (45.7%)	20 (19.0%)	3 (2.9%)	NR	5.5
FORWARD II [7]	NCT02606305	Phase Ib/II	94 pts receiving mirvetuximab plus bevacizumab	49 (52%)	55 (59%)	25 (27%)	44%	5 (6%)	36 (38%)	44 (47%)	8 (9%)	1 (1%)	9.7 months	8.2
MIRASOL‡ [9]	NCT04209855	Phase III	227 pts receiving mirvetuximab	105 (46%)	138 (61%)	124 (55%)	42%	12 (5%)	84 (37%)	86 (38%)	31 (14%)	14 (6%)	NR	5.9

*23 (50%) received ≥ 4 lines

‡Preliminary data reported at ASCO 2023;

FRα, folate receptor alpha; mDOR, median duration of response; NR, not reported; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFS, progression-free survival; pts, patients

induced menopause, and increased risks of cardiovascular and bone diseases, alongside diminished sexual function [12, 13]. These adverse effects necessitate a nuanced approach to balancing cancer prevention with quality-of-life considerations, underscoring the importance of informed, patient-centered decision-making.

Addressing the challenges of isolated STIC

Women with isolated STIC lesions following rrBSO are at a measurable risk for developing HGSC, with studies showing 5- and 10-year risks of peritoneal carcinomatosis at 10.5% and 27.5%, respectively, particularly in BRCA1 mutation carriers [14]. These findings suggest that STIC may not only be a precursor lesion but could also represent an early manifestation of HGSC. In some cases, incidental STIC detection has even led to the upstaging of presumed low-risk populations to HGSC [15].

The management of isolated STIC remains an area of ongoing uncertainty. There is no consensus on whether adjuvant chemotherapy is necessary for isolated STIC in the absence of concurrent invasive carcinoma, creating ambiguity for patients and clinicians alike [16]. Limited data hinder the evaluation of chemotherapy's efficacy in these cases, although tailored risk assessments may help guide treatment decisions. For instance, a study of 54 patients with STIC reported only two recurrences among those receiving chemotherapy for positive peritoneal washings, highlighting the need for individualized approaches [17].

MIRV's emerging role in STIC management

Recent advances in targeted therapies have brought MIRV to the forefront of HGSC treatment [18–20]. MIRV's mechanism of action relies on the expression of FRα as discussed above. However, there is currently no study directly addressing whether FRα is expressed in STIC. Notably, there is emerging evidence to suggest FRα expression in STIC lesions. An analysis of 52 STIC cases with PS2 + scoring revealed more than 75% FRα expression in over half of the lesions, closely mirroring expression levels in HGSC (Zheng et al., unpublished, abstract presented in the International Academy of Pathology in Cancun, Mexico, Nov. 2024). These findings indicate that MIRV may hold therapeutic potential for managing STIC, particularly in post-rrBSO patients at high risk for HGSC.

Toward precision medicine in HGSC prevention

Collectively, these findings underscore MIRV's potential to bridge the gap between HGSC prevention and treatment. Beyond HGSC, MIRV's applications could extend to other FRα-positive cancers, such as endometrial and breast cancers, which also express FRα. This highlights MIRV's versatility as a targeted therapy in

managing a broader spectrum of solid tumors. By integrating targeted therapy into the management of isolated STIC lesions, MIRV offers a novel approach to reducing HGSC progression in high-risk populations. This proactive strategy aligns with the broader goals of precision medicine and calls for continued collaboration and innovation to improve outcomes in hereditary cancer prevention and management. This represents a significant step toward precision medicine, where innovative strategies like MIRV can be tailored to address the unique challenges of hereditary cancer risk management. Expanding MIRV's clinical application to include STIC-associated lesions underscores the need for ongoing research and collaboration to optimize outcomes for patients with hereditary and sporadic ovarian cancers. However, it is important to acknowledge current limitations of MIRV, including limited accessibility in some countries and high costs for patients without insurance coverage, which may hinder its broader adoption.

Abbreviations

ADC	Antibody/antigen-drug conjugates
BRCA	Breast cancer gene
FRα	Folate receptor alpha
HGSC	High-grade serous carcinoma
MIRV	Mirvetuximab Soravtansine
OEC	Ovarian epithelial cancer
PARP	Poly (ADP-ribose) polymerase
PFS	Progression-free survival
rrBSO	Risk-reducing bilateral salpingo-oophorectomy
STIC	Serous tubal intraepithelial carcinoma

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Publisher's note

Beihua Kong is the president of the Chinese Society of Gynecologic Oncology and a distinguished gynecologic oncologist with extensive experience in treating various gynecologic cancers including ovarian cancers. Dr. Kong frequently manages patients with serous tubal intraepithelial carcinoma (STIC) identified during prophylactic surgeries and is acutely aware of the challenges in optimizing care for these patients.

Wenxin Zheng is a tenured professor of pathology and obstetrics and gynecology, as well as an internationally recognized gynecologic pathologist. His research focuses on ovarian cancer prevention and early detection. Dr. Zheng was among the first to describe folate receptor alpha (FRα) expression in ovarian endometriosis, some of which are believed to originate from the fallopian tube. Given the high expression of FRα in ovarian HGSC, including STIC and the fallopian tube, Dr. Zheng is deeply invested in exploring the application of MIRV for managing STIC and other FRα-expressing diseases.