



Review Article

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Claudin-6 (CLDN6) and Folate Receptor Alpha (FR α) Targeted Antibody-Drug Conjugates: Bypassing Platinum Resistance and Tumor Heterogeneity in High-Grade Serous Ovarian Carcinoma

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Abstract

High-grade serous ovarian carcinoma (HGSOC) is the most lethal gynecologic malignancy. Predicting its outcomes is complicated by two interlinked adversaries: the near-inevitable development of platinum resistance, which depletes the most successful drug class against the disease, and a profound molecular and antigenic heterogeneity that defies targeted therapy. Antibody-drug conjugates (ADCs) directed against tumor-associated antigens offer a strategically attractive answer to both challenges. They kill through a cytotoxic mechanism of microtubule disruption by a delivered payload that is largely independent of the DNA-repair and drug-handling pathways that confer platinum resistance, and the bystander effect of their membrane-permeable payloads can reach antigen-negative cells within a heterogeneous tumor. This review examines two complementary antigens that researchers are pursuing in HGSOC. Folate receptor alpha (FR α), overexpressed in the great majority of these tumors, is the target of mirvetuximab soravtansine, the first agent of any class to demonstrate an overall-survival benefit in platinum-resistant ovarian cancer and the first ADC approved for this disease. Claudin-6 (CLDN6), an oncofetal tight-junction protein essentially absent from normal adult tissue and expressed in roughly half of HGSOC, is the target of the first-in-class ADC TORL-1-23, which has shown encouraging response rates in platinum-resistant disease in early-phase testing. This review examines the biology and resistance mechanisms of HGSOC, the rationale by which antigen-directed payload delivery bypasses platinum resistance, and the design, clinical validation, and pipeline of FR α - and CLDN6-targeted ADCs. It further considers how bystander killing, complementary antigen coverage, and biomarker-guided selection address tumor heterogeneity, along with safety and resistance.

Keywords: Folate receptor alpha; High-grade serous ovarian carcinoma; Mirvetuximab soravtansine; Platinum resistance; TORL-1-23.

استهداف كلودين-6 (CLDN6) ومستقبل الفولات ألفا (FR α) التركيبات بين الأجسام المضادة والدواء: تجاوز مقاومة البلاتين وتباين الورم في سرطان المبيض المصلي عالي الدرجة

الخلاصة

سرطان المبيض المصلي عالي الدرجة (HGSOC) هو أكثر الأورام الخبيثة فتكا في أمراض النساء. يتعقد التنبؤ بنتائجه بسبب خصمين مترابطين: التطور شبه الحتمي لمقاومة البلاتين، الذي يستنزف أنجح فئة الأدوية ضد المرض، وتباين جزيئي ومستضدي عميق يتحدى العلاج المستهدف. يقدم العلاج بالأجسام المضادة مع الأدوية (ADCs) الموجهة ضد المستضدات المرتبطة بالورم إجابة استراتيجية جذابة لكلا التحديين. تعمل هذه الأدوية من خلال آلية سمية لاضطراب الأنابيب الدقيقة بواسطة حمولة ترسل مستقلة إلى حد كبير عن مسارات إصلاح الحمض النووي والتعامل مع الأدوية التي تمنح مقاومة البلاتين، ويمكن لتأثير المشاهد لحمولاتها القابلة للنفوذ إلى الغشائية أن يصل إلى الخلايا السلية للمستضد داخل ورم غير متجانس. تفحص هذه المراجعة مستضدين مكملين يسعى الباحثون لتطويرهما في HGSOC. مستقبل الفولات ألفا (FR α)، الذي يعبر عنه بشكل زائد في الغالبية العظمى من هذه الأورام، هو هدف ميرفيتوكسينماب سورافانتسين، وهو أول عامل من أي فئة يظهر فائدة عامة للبقاء في سرطان المبيض المقاوم للبلاتين، وأول ADC معتمد لهذا المرض. كلودين-6، وهو بروتين محكم في الأورام الجينية يغيب أساسا عن الأنسجة البالغة الطبيعية ويعبر عنه تقريبا نصف HGSOC، وهو هدف أول من فئة TORL-1-23 ADC، الذي أظهر معدلات استجابة مشجعة في الأمراض المقاومة للبلاتين في الاختبارات المبكرة. تفحص هذه المراجعة بيولوجيا وآليات المقاومة لـ HGSOC، والمنطق الذي يجعل توصيل الحمولة الموجهة بالمستضد يتجاوز مقاومة البلاتين، وتصميم والتحقق السريري وخط أنابيب ADCs المستهدفة لـ FR α و CLDN6. كما يتناول كيف تعالج القتل، وتغطية المستضدات التكميلية، والانتقاء الموجه بالمؤشرات الحيوية، إلى جانب السلامة والمقاومة.

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Key Messages

Resolving the Dual Burden: Platinum-resistant high-grade serous ovarian carcinoma (HGSOC) remains one of the most intractable cancers, being characterized by almost inevitable and rapid development of platinum resistance along with profound tumor heterogeneity. Molecular Strategy for Bypass: This strategy involves the delivery of a potent antimitotic payload through conjugated antibodies (antibody-drug conjugates, ADCs) to escape the DNA-repair and drug-handling mechanisms that govern platinum resistance. Folate receptor α (FR α) is a validated target that has an early success story, as represented by mirvetuximab soravtansine, the first

ADC that has shown an overall survival advantage in platinum-resistant disease. The preclinical candidate TORL-1-23 is a very specific, first-in-class oncofetal target represented by claudin-6 (CLDN6), which is associated with high early-phase clinical responses. The membrane-permeable bystander effect, complementary antigen coverage, and robust biomarker-driven patient selection together mitigate intratumoral and inter-site heterogeneity. Extending the efficacy of ADCs will demand the implementation of chaining toxicities to the payload, the mitigation of acquired resistance, and the definition of correct sequencing.

INTRODUCTION

The clinical problem of high-grade serous ovarian carcinoma

High-grade serous ovarian carcinoma is the most common and most lethal histologic subtype of epithelial ovarian cancer, and it remains one of the few major solid tumors whose overall survival has improved modestly over several decades [1]. Most patients present with advanced, disseminated intraperitoneal disease, are treated with cytoreductive surgery and platinum-based chemotherapy, and respond well initially only to relapse repeatedly, with progressively less responsive disease [2,3]. The biology underlying this clinical course is now well understood, and two features of it dominate the prognosis and define the therapeutic challenge addressed in this review: the development of platinum resistance and the extensive heterogeneity of the disease.

Platinum resistance as the defining unmet need

Platinum compounds are the backbone of ovarian cancer therapy, and the interval between completing platinum treatment and relapse—the platinum-free interval—is the single most important determinant of prognosis and subsequent treatment choice [4]. Disease that recurs within six months of platinum therapy is termed platinum-resistant and is associated with poor clinical outcomes: response rates to further chemotherapy are low, and median overall survival from the point of platinum resistance has historically been on the order of twelve to fourteen months [3, 5]. Platinum-resistant ovarian cancer (PROC) is therefore the central unmet need in the disease, the setting in which conventional cytotoxic options are most exhausted and in which a mechanistically distinct therapy could have the greatest impact [6].

The promise of antigen-directed therapy

Antibody-drug conjugates are uniquely suited to this setting for two reasons that form the thesis of this review. First, by delivering a cytotoxic payload, typically a microtubule inhibitor, through binding to a tumor-associated surface antigen, an ADC kills cancer cells through a mechanism that is largely independent of the pathways that render a cell resistant to platinum, so that platinum-resistant tumors generally remain susceptible [7,8]. Second, the heterogeneity that defeats many targeted agents can be partially circumvented by the bystander effect of ADC payloads and by the use of complementary antigens. This review develops both arguments around two specific, complementary targets in HGSOC; folate receptor alpha (FR α), the most clinically validated, and claudin-6 (CLDN6), among the most promising emerging targets [9]. Together they illustrate how antigen-directed payload delivery can bypass the two adversaries—platinum resistance and tumor

heterogeneity—that have made this disease so intractable [10].

METHODS

Study design

This narrative review was designed to provide a clinically and biologically integrated synthesis of antibody-drug conjugate (ADC) strategies directed against folate receptor alpha (FR α) and claudin-6 (CLDN6) in high-grade serous ovarian carcinoma (HGSOC), with particular attention to the mechanistic bypass of platinum resistance and to the problem of tumor heterogeneity. A narrative rather than a systematic approach was chosen because the relevant evidence is markedly heterogeneous in study design, developmental stage, biomarker definitions, treatment setting, and reported endpoints—ranging from a randomized phase 3 trial for the most mature agent to single-arm, early-phase, and preclinical data for emerging conjugates, thereby limiting the feasibility of a formal quantitative synthesis focused specifically on this question.

Search strategy

A literature search of MEDLINE/PubMed, Embase, and [ClinicalTrials.gov](https://clinicaltrials.gov) (January 2000–February 2026) was supplemented by recent oncology congress abstracts (ASCO, ESMO, and the Society of Gynecologic Oncology (SGO), AACR), using terms related to HGSOC, FR α /*FOLR1*, CLDN6, and the specific ADCs discussed in this review, including mirvetuximab soravtansine and TORL-1-23.

Eligibility criteria

Prospective and retrospective clinical studies, meta-analyses, and key translational or preclinical reports informing biological rationale were included, with priority given to randomized and pivotal datasets, validated biomarker assessment (for example, FR α and CLDN6 immunohistochemistry), and the most recent, clinically relevant evidence. Case reports, very small case series, and studies without relevance to ovarian cancer or to the ADC mechanism were excluded.

Data synthesis

Evidence was synthesized qualitatively and organized around the two target antigens (FR α and CLDN6) and the two central therapeutic challenges addressed by this review: platinum resistance and tumor heterogeneity, together with cross-cutting considerations of safety, acquired resistance, and translational development. Common to narrative reviews, selection and interpretation of evidence were based on author judgment and are susceptible to selection bias. Because much of the evidence for emerging agents derives from early-phase, single-arm trials and conference abstracts, the corresponding findings should be regarded as

hypothesis-generating, and the review should be interpreted as a qualitative, clinically oriented synthesis rather than as a fully reproducible systematic review.

High-Grade Serous Ovarian Carcinoma: Biology and Two Clinical Adversaries *The molecular landscape*

HGSOC is characterized by a unique and relatively homogeneous molecular signature but an extraordinary downstream complexity. Almost all (approximately 97%) of the cases carry mutations in TP53, rendering p53 dysfunction practically a hallmark of the disease [11]. Homologous-recombination deficiency (HRD) occurs in approximately 50% of tumors, primarily due to germline or somatic mutations in BRCA1/2 but also arising from alterations affecting several non-BRCA homologous-recombination-repair genes, including *RAD51*, *ATM*, *BRIP1*, and *PALB2* [11,12]. HRD is of clinical relevance, as it results in sensitivity to platinum and poly(ADP-ribose) polymerase (PARP) inhibitors, and HRD-positive tumors are generally more sensitive to platinum than HRD-proficient tumors [12]. In contrast, a subset of HGSOC tumors instead show amplification of CCNE1, associated with primary platinum resistance. Beyond these recurrent lesions, the HGSOC genome is marked by pervasive copy-number instability that drives the heterogeneity discussed below [11,13].

Platinum chemotherapy and the definition of resistance

Platinum agents exert their cytotoxic activity in cellular pathways that include formation of DNA intrastrand and interstrand crosslinks that, if unrepaired, lead to apoptosis as they interfere with replication and transcription processes [14]. Ovarian cancer can be classified clinically by platinum sensitivity—platinum-sensitive, partially platinum-sensitive, or platinum-resistant—based on the platinum-free interval. This classification, which reflects the tumor's ability to survive DNA damage, has long guided the relationship between biological evidence and clinical outcome. It remains the main framework guiding therapy at relapses [3]. We need to understand how a tumor acquires platinum resistance to understand why an ADC can work when further doses of platinum fail.

Mechanisms of Platinum Resistance *Altered drug influx and efflux*

One major route to resistance is simply reducing the amount of platinum that reaches the DNA. Tumor cells can downregulate the copper transporter CTR1, which mediates cellular platinum uptake, and can upregulate efflux transporters, including the copper-transporting ATPases ATP7A and ATP7B and members of the multidrug-resistance-associated protein family—that export platinum or sequester it away from the nucleus [12,14,15]. The net effect is a lower intracellular

concentration of active drug and diminished DNA adducts formation.

Enhanced DNA damage repair and homologous-recombination restoration

A second, and in HGSOC particularly important, route is enhanced repair of platinum-induced DNA damage. Increased activity of the nucleotide-excision-repair machinery, marked by high ERCC1 expression, removes platinum adducts more efficiently [14]. Most strikingly, tumors that were initially HRD and therefore platinum-sensitive can acquire secondary reversion mutations that restore the reading frame and function of BRCA1 or BRCA2, regenerating competent homologous recombination and thereby restoring the capacity to repair the double-strand breaks that platinum and PARP inhibitors exploit [13,15]. Restoration of DNA repair is a recurrent and well-documented mechanism of acquired platinum and PARP-inhibitor resistance in HGSOC.

Detoxification and evasion of apoptosis

Additional mechanisms include intracellular detoxification, in which elevated glutathione and metallothionein bind and inactivate platinum before it can reach DNA, and the downstream evasion of apoptosis through alterations in p53-dependent and p53-independent death pathways, allowing cells to tolerate DNA damage that would otherwise be lethal [14,15]. Resistance in any given tumor is typically multifactorial, combining several of these mechanisms, which is one reason it has proven so difficult to overcome pharmacologically by targeting the platinum pathway itself.

Tumor heterogeneity: intratumoral, inter-site, and temporal

Layered onto platinum resistance is heterogeneity, which operates at several levels. Within a single tumor deposit, distinct subclones coexist (intratumoral heterogeneity); across the multiple peritoneal and metastatic sites characteristic of disseminated HGSOC, different lesions can harbor different dominant clones (inter-site heterogeneity); and over the course of treatment, clonal composition shifts under therapeutic pressure (temporal heterogeneity) [16,17]. Phylogenetic analyses of HGSOC have demonstrated marked spatial and temporal divergence among sites within the same patient [17]. This heterogeneity has two therapeutic consequences central to this review: it underlies the clonal evolution that produces resistance, and because antigen expression is itself heterogeneous, it means that no single tumor-associated antigen is expressed by every malignant cell, creating the possibility of antigen-negative escape from any single antigen-directed therapy [18]. Notably, this heterogeneity differs between the two antigens discussed in this review: FR α is highly expressed but heterogeneous both between patients and within

individual tumors, whereas CLDN6 shows a more uniformly tumor-specific expression pattern, underscoring why biomarker-driven patient selection is essential [1].

The Antibody-Drug Conjugate as a Strategic Answer

The ADC concept recapitulated

An antibody-drug conjugate couples a monoclonal antibody, which binds a chosen tumor-associated antigen, to a highly potent cytotoxic payload through a chemical linker, with the number of payload molecules per antibody defined as the drug-to-antibody ratio [19,20]. The canonical mechanism is antigen binding, internalization of the antigen-ADC complex, intracellular processing cleavage of the linker or degradation of the antibody—and release of the payload, which then kills the cell. The payloads used in the FR α - and CLDN6-targeted ADCs discussed here are microtubule inhibitors: the maytansinoid DM4 and the auristatin monomethyl auristatin E (MMAE), both of which disrupt microtubule dynamics to cause mitotic arrest and apoptosis [20]. The ADC thus functions as a targeted delivery vehicle that concentrates a potent antimitotic at the tumor, as presented in Figure 1.

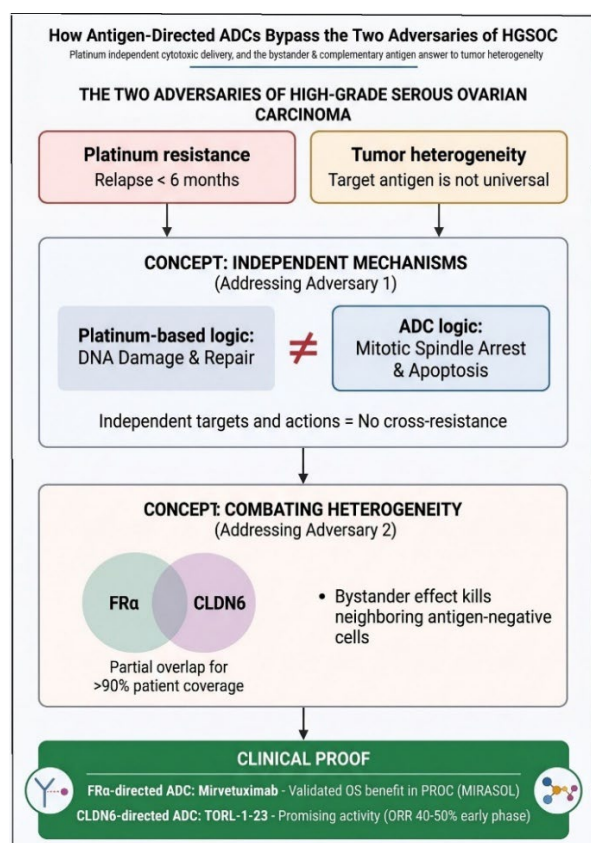


Figure 1: How antigen-directed antibody–drug conjugates bypass the two adversaries of high-grade serous ovarian carcinoma (HGSOC).

Because platinum resistance acts on the DNA-damage axis and the ADC acts on the mitotic-spindle axis, the mechanisms do not intersect, so platinum-resistant tumors generally remain ADC-sensitive (Bypass 1) [3],

unless they acquire specific ADC resistance through antigen downregulation or other mechanisms. Complementary antigen coverage (FR α ~80–90%, CLDN6 ~45–55%, partially overlapping), the bystander effect, and biomarker-guided selection address tumor heterogeneity, though ADC-specific resistance (antigen loss, trafficking defects, and P-glycoprotein payload efflux) remains possible (Bypass 2).

Why an antigen-directed payload bypasses platinum resistance

The mechanistic crux of this review is that the cytotoxic action of these ADC payloads is entirely independent of the pathways that confer platinum resistance. Platinum kills by damaging DNA and depends on its effect on DNA adduct formation and on the failure of DNA repair; resistance arises from reduced platinum uptake, enhanced DNA repair, detoxification, and apoptosis evasion specific to DNA damage. A microtubule inhibitor, by contrast, kills by disrupting the mitotic spindle, a process that has nothing to do with DNA repair, platinum transport, or glutathione conjugation [14,20]. A tumor cell that has become platinum-resistant through restored homologous recombination or reduced CTR1 expression has done nothing to protect itself against a delivered antimitotic. Consequently, platinum-resistant HGSOC remains, in principle, susceptible to an FR α - or CLDN6-directed ADC; the resistance mechanism and the new drug's mechanism simply do not intersect. This mechanistic non-overlap is the conceptual foundation for using these agents specifically in the platinum-resistant setting, and it is borne out by the clinical data reviewed below [21].

The bystander effect as an answer to antigen heterogeneity

The second strategic advantage concerns heterogeneity. Both mirvetuximab soravtansine and TORL-1-23 use cleavable linkers that release a membrane-permeable payload DM4 [5], and its metabolite S-methyl-DM4 in the former and MMAE in the latter, capable of diffusing out of the targeted cell into neighboring cells, including those expressing little or no target antigen [5,22,23]. Membrane-permeable payloads such as DM4 and MMAE cross the cell membrane and diffuse into neighboring cells, unlike membrane-impermeable payloads (for example, DM1), which remain confined to the cell in which they are released. This bystander effect allows an ADC to eliminate antigen-negative malignant cells in the vicinity of antigen-positive ones, because the diffusible payload is delivered directly into the local tumor microenvironment rather than requiring antigen binding by the antigen-negative cell itself, partially compensating for the intratumoral antigen heterogeneity that would otherwise permit antigen-negative subclones to survive [7]. The bystander effect does not fully solve heterogeneity; distant antigen-negative deposits remain out of reach, but it

meaningfully broadens the cytotoxic footprint of an antigen-directed therapy within a heterogeneous tumor, and it is one of several complementary strategies, discussed later [9], by which the heterogeneity problem is addressed [24].

Folate Receptor Alpha (FR α) as a Target *FR α biology and tumor-selective expression*

Folate receptor alpha, encoded by *FOLR1* [11], is a glycosylphosphatidylinositol-anchored cell-surface protein that binds folate with high affinity and mediates its cellular uptake. Its appeal as a therapeutic target rests on a favorable expression pattern [25]; FR α is overexpressed in the large majority of epithelial ovarian cancers—reported in roughly eighty to ninety percent of HGSOc, often at high levels—while its expression in normal tissues is restricted and largely confined to the apical, luminal surface of certain epithelia (such as the kidney and lung) where it is sequestered from the bloodstream and therefore relatively inaccessible to an intravenously administered antibody [26,27]. This combination of frequent, high tumor expression and limited accessible normal-tissue expression, together with the receptor's capacity to internalize bound macromolecules, makes FR α an excellent ADC target in ovarian cancer [26].

Mirvetuximab soravtansine: Molecular design

Mirvetuximab soravtansine is an antibody-drug conjugate (ADC) consisting of a humanized anti-FR α monoclonal antibody coupled to the maytansinoid DM4 via a cleavable, reducible sulfo-SPDB disulfide linker, at a drug-to-antibody ratio (DAR) of ~3.4 [5,28]. After binding to FR α and internalization, intracellular processing releases DM4 and its active metabolite S-methyl-DM4. These compounds inhibit microtubule dynamics, blocking the cell cycle and triggering apoptosis. Because these catabolites are membrane-permeable, they also produce the bystander activity described above [5,13]. This is a prototype design for the second-generation ADC, redeployed against a classic, well-studied ovarian target.

Clinical validation: SORAYA and the practice-changing MIRASOL trial

Mirvetuximab soravtansine was evaluated in two phase III clinical trials for patients with FR α -high, platinum-resistant ovarian cancer [29]. The single-arm phase 2 SORAYA trial included patients with FR α -high platinum-resistant HGSOc who had undergone one to three prior regimens that included bevacizumab and met its primary endpoint with a confirmed objective response rate of around thirty-two percent, including complete and partial responses, with a median duration of response of almost seven months [5,30]. These results provided the basis for accelerated approval by the US Food and Drug Administration in 2022 [28]. Then, this was followed in the confirmatory, randomized phase 3 MIRASOL trial comparing

mirvetuximab soravtansine in FR α -high platinum-resistant disease against investigator's-choice chemotherapy, which showed significant benefits for progression-free survival, objective response, and importantly overall survival [31]. This overall-survival benefit was historically significant, as mirvetuximab soravtansine is the first agent of any class and the first ADC to improve survival in platinum-resistant ovarian cancer, and it was granted full approval in 2024 [28,31]. MIRASOL then affords the ultimate evidence that an antigen-directed ADC can alter the outcome in the same platinum-resistant context in which conventional therapy falters [32].

The companion diagnostic and FR α expression heterogeneity

A key element of the mirvetuximab program is the use of a companion diagnostic to enrich patients with sufficient expression of the target. A validated assay that scored the proportion of tumor cells with at least moderate membranous staining using a high cutoff (a substantial majority of tumor cells positive), termed FR α -high, was required for eligibility by immunohistochemistry [5,31]. These modalities face a core challenge of tumor heterogeneity: FR α expression varies in intensity and distribution both between tumors and within a single tumor, so the success of the therapy depends on there being enough target present to bind. Because borderline and heterogeneous patterns of FR α staining can be difficult to score by visual examination, reproducible, standardized FR α immunohistochemistry scoring remains an area requiring further refinement [26]. The diagnostic-therapeutic pairing, in essence, is a method of identifying the small subset of a heterogeneous disease that will most likely respond.

The wider FR α ADC pipeline

This opens FR α to multiple ADCs with various payloads/engineering (by both expanding the addressable population and altering the cytotoxic mechanism). Luveltamab tazevibulin (STRO-002) is an anti-FR α ADC with a tubulin-inhibiting hemiasterlin payload, chosen in part for its reduced susceptibility to drug-efflux pumps, which is site-specifically conjugated, and the first of its kind to show activity in platinum-resistant ovarian cancer over a greater range of FR α expression than with mirvetuximab [33,34]. Farletuzumab ecteribulin (MORAb-202) is an antibody to FR α conjugated to the microtubule inhibitor eribulin and has shown encouraging response rates in HGSOc, including durable responses in early-phase testing [35]. Novel designs targeting as many as two FR α epitopes (biparatopic IMG151) may further enhance internalization and therapeutic activity, potentially extending benefit even to tumors that express lower levels of FR α [36]. Such heterogeneity-diversity relationships are important because agents with lower expression thresholds will extend benefit to a larger portion of the treatable population.

The toxicity profile and its management

The safety profile of mirvetuximab soravtansine is distinctive and largely on-target or payload-related. Ocular toxicity, keratopathy, blurred vision, and dry eye are characteristic and are mitigated by prophylactic lubricating and corticosteroid eye drops, dose modification, and ophthalmologic monitoring; gastrointestinal effects (nausea, diarrhea) and peripheral neuropathy also occur, and pneumonitis is a less common but important risk [5,28,31]. Ocular toxicity is thought to arise primarily from off-target uptake of the released payload by corneal epithelial cells rather than from FR α expression in ocular tissue, since FR α is not substantially expressed in the eye. These events are predominantly low-grade and manageable, and the overall tolerability favorable relative to cytotoxic chemotherapy in the randomized comparison contributed to the drug's adoption [31]. Understanding the ocular signal is important because it differs from the toxicities of other payloads and bears on the design of combination and sequential regimens. Similarly, the peripheral neuropathy associated with MMAE-containing ADCs such as TORL-1-23 is thought to reflect off-target uptake of the released payload by peripheral neurons and Schwann cells, consistent with the known neurotoxicity of tubulin-targeting auristatins, rather than a CLDN6-specific effect. Antibody-specific determinants of activity deserve equal attention. Internalization rate, receptor recycling versus lysosomal routing, and intracellular payload metabolism all shape the effective payload dose delivered per binding event, and together with linker stability and systemic pharmacokinetics, they determine the therapeutic index and the pace at which resistance can emerge; these parameters remain incompletely characterized for several agents discussed here and warrant more systematic reporting in future trials.

Claudin-6 (CLDN6) as a Target

CLDN6 oncofetal biology and exceptional tumor specificity

Claudin-6 is a member of the claudin family of tight-junction proteins, which comprises more than two dozen members involved in cell-cell adhesion and epithelial barrier function. CLDN6 is an oncofetal antigen: it is expressed during embryonic and fetal development, silenced in essentially all normal adult tissues, and aberrantly re-expressed in a range of cancers, including ovarian, endometrial, testicular germ-cell, and lung tumors [23,37]. Analyses of dozens of normal tissue types have found little or no CLDN6 expression, and this near-absence from normal adult tissue provides CLDN6 exceptional tumor specificity. This translates into a potentially wide therapeutic window—a key advantage for any targeted therapy, and particularly for one delivering a potent cytotoxin [23]. This tumor-restricted profile is the principal reason CLDN6 has attracted intense therapeutic interest across multiple modalities.

Expression in high-grade serous ovarian carcinoma

In ovarian cancer specifically, CLDN6 is expressed in a clinically meaningful fraction of tumors and is enriched in the high-grade serous subtype. Immunohistochemical surveys report CLDN6 positivity in roughly one-third of epithelial ovarian carcinomas overall but in approximately forty-five to fifty-five percent of HGSOc, with around half of HGSOc expressing CLDN6 at moderate-to-high levels [23,38,39]. CLDN6 expression is associated with adverse prognosis—shorter progression-free and overall survival. Importantly for a therapeutic target, expression is maintained from primary to recurrent disease and is detectable in malignant cells within ascites, the medium of peritoneal dissemination [38,39]. The persistence of the target through recurrence and in disseminated disease is precisely what is needed for a therapy intended to treat relapsed, platinum-resistant tumors.

The selectivity challenge: CLDN6 versus its family members

A non-trivial obstacle in targeting CLDN6 is the high sequence and structural homology among claudin family members, particularly between CLDN6 and CLDN9, which share nearly identical extracellular domains. A therapeutic (precision) antibody must therefore discriminate CLDN6 from its closest relatives to avoid off-target binding and toxicity, a demanding antibody engineering requirement [23]. Demonstrating selective binding to CLDN6 over other claudins—and confirming the absence of meaningful normal-tissue cross-reactivity—is consequently an essential element of validating any CLDN6-directed agent, and it is a feature that the leading clinical candidates have specifically established [23].

TORL-1-23 (CLDN6-23-ADC): design and preclinical efficacy

TORL-1-23 is a first-in-class ADC consisting of a humanized anti-CLDN6 IgG1 monoclonal antibody conjugated to MMAE (monomethyl auristatin E) through a cleavable valine-citrulline linker [23,40]. In preclinical characterization, the antibody bound CLDN6 selectively relative to other claudin family members, and the ADC was rapidly internalized. It produced robust, durable tumor regressions in CLDN6-positive cell-line xenografts and patient-derived xenograft models of ovarian and endometrial cancer, with activity tracking target expression and sparing CLDN6-negative models [23,41]. The use of MMAE with a cleavable linker confers bystander activity analogous to that of Mirvetuximab's DM4, relevant again to intratumoral heterogeneity [22,23]. These data established the rationale for clinical testing in CLDN6-expressing cancers, with ovarian carcinoma as a lead indication (Table 1).

Table 1: Molecular design and clinical activity of FR α - and CLDN6-targeted antibody–drug conjugates in high-grade serous ovarian carcinoma

Agent	Target	Payload (class)	Linker / DAR	Key trial(s), phase	Selected efficacy	Development status
Mirvetuximab soravtansine [44,45]	FR α	DM4 (maytansinoid; microtubule inhibitor)	Cleavable disulfide (sulfo-SPDB); DAR $\approx$ 3.4	SORAYA (ph 2); MIRASOL (ph 3)	SORAYA ORR $\approx$ 32%, mDoR $\approx$ 7 mo; MIRASOL improved PFS, ORR and OS (first OS benefit in PROC)	FDA accelerated approval 2022; full approval 2024 (FR α -high PROC)
Luveltamab tazevivulin (STRO-002) [46,47]	FR α	Hemiasterlin (tubulin inhibitor; low efflux susceptibility)	Cleavable; site-specific, homogeneous; DAR NR	Early phase	Activity across a broader range of FR α expression than mirvetuximab	Clinical development
Farletuzumab ecteribulin (MORAb-202) [48]	FR α	Eribulin (microtubule inhibitor)	Cleavable; DAR NR	Early phase	Encouraging ORR, including durable responses	Early phase
IMGN151 [49]	FR α (biparatopic; two epitopes)	Maytansinoid (next-generation)	DAR NR	Preclinical / early	Designed to improve internalization and extend benefit to lower-FR α tumors	Early development
TORL-1-23 [38,40]	CLDN6	MMAE (auristatin; microtubule inhibitor)	Cleavable valine-citrulline; DAR NR	CATALINA-1 (ph 1)	ORR $\approx$ 40–50% and DCR $\approx$ 90% in CLDN6-positive PROC at active doses; durable responses	Early phase (first-in-class anti-CLDN6 ADC)

DAR, drug-to-antibody ratio; DCR, disease-control rate; mDoR, median duration of response; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer.

Early clinical activity in platinum-resistant disease

The first-in-human phase 1 study of TORL-1-23 (the CATALINA-1 program) enrolled patients with advanced solid tumors, including platinum-sensitive and platinum-resistant ovarian cancer, in dose-escalation and dose-expansion cohorts, with administration every three weeks and patient selection by CLDN6 immunohistochemistry [38, 40]. The activity reported in CLDN6-positive platinum-resistant ovarian cancer has been notably encouraging for an early-phase study: at one dose level the objective response rate was approximately 50% with a disease-control rate near 90%, and at another active dose the response rate was around 40%—responses described as durable [38]. These figures, achieved in heavily pretreated, platinum-resistant disease, provide early clinical support for the central thesis that an antigen-directed antimitotic ADC can produce meaningful responses in platinum-resistant HGSO, and they position CLDN6 alongside FR α as a credible ADC target in this setting [38]. As with mirvetuximab, these results derive from biomarker-selected populations, underscoring the role of target-expression testing [42]. Resistance mechanisms specific to CLDN6-targeted ADCs have not yet been well characterized clinically, given the early stage of TORL-1-23 development; by analogy with FR α -targeted agents, antigen downregulation, altered intracellular trafficking, and payload efflux are plausible candidate mechanisms that will require dedicated study as clinical experience matures.

Bypassing Platinum Resistance: Mechanism and Evidence

Why do platinum-resistant tumors stay ADC-sensitive

Drawing together the preceding threads, the case that FR α - and CLDN6-targeted ADCs bypass platinum resistance is both mechanistic and empirical. Mechanistically, platinum resistance involves a set of adaptations, including reduced uptake, enhanced DNA repair, detoxification, and apoptosis evasion, all of

which are directed against DNA-damaging chemotherapy; however, none of these adaptations protect against a microtubule inhibitor delivered to the cytoplasm by an internalizing antibody [14,20]. The ADC's lethal event, spindle disruption and mitotic catastrophe, lies entirely outside the platinum-resistance repertoire. There is thus little reason to expect substantial cross-resistance between platinum and these ADCs and reasonable grounds to expect retained sensitivity [50].

The clinical proof

The empirical confirmation is now substantial. Mirvetuximab soravtansine produced clinically meaningful response rates and, in the randomized MIRASOL trial, improved overall survival specifically in platinum-resistant disease, the most rigorous possible demonstration that the mechanism works where platinum has failed [30,31]. TORL-1-23 produced response rates of roughly forty to fifty percent in CLDN6-positive platinum-resistant ovarian cancer in early-phase testing [38]. That two structurally distinct ADCs, directed against two different antigens and carrying two different microtubule-inhibitor payloads, both yield substantial responses in platinum-resistant HGSO is corroborating evidence that the benefit derives from the shared, platinum-independent mechanism rather than from any peculiarity of one agent [51].

The limits

ADC-specific resistance and the multidrug-resistance caveat

Bypassing platinum resistance does not mean bypassing resistance altogether, and a balanced assessment requires noting the limits. Tumors can become resistant to ADCs through mechanisms specific to ADC function, including the loss or downregulation of the target antigen, defects in internalization or lysosomal trafficking, and the export of the payload by ATP-binding cassette efflux pumps

such as P-glycoprotein, which is relevant to the microtubule payloads used here, as both MMAE and the maytansinoids are substrates for these pumps [52,53]. This last point is important: although ADCs bypass the DNA-repair-based mechanisms of platinum resistance, they remain vulnerable to classical multidrug resistance acting on their payloads, which is one reason that newer payloads less susceptible to efflux, such as the hemiasterlin used in luveltamab tazevibulin, are of interest [33,53]. Platinum resistance and ADC resistance are thus distinct phenomena; a platinum-resistant tumor is not inherently ADC-resistant, but it can acquire ADC resistance through its own separate routes [54].

Bypassing Tumor Heterogeneity: Complementary Antigens and Combinatorial Logic
The non-overlapping coverage of FRα and CLDN6

Table 2: Comparison of folate receptor alpha (FRα) and claudin-6 (CLDN6) as antibody–drug-conjugate targets in high-grade serous ovarian carcinoma

Feature	Folate receptor alpha (FRα)	Claudin-6 (CLDN6)
Molecular nature [56]	GPI-anchored folate-binding protein (<i>FOLR1</i>)	Oncofetal tight-junction protein (claudin family)
Expression in HGSOc [57]	~80–90% of tumors, often at high levels	~45–55% of tumors; about half at moderate–high levels
Normal adult tissue [58]	Restricted to apical/luminal surfaces (e.g., kidney, lung), largely sequestered from the bloodstream	Essentially absent (oncofetal); little or no expression across normal tissues
Basis of therapeutic window [59]	Limited accessible normal-tissue expression	Exceptional tumor specificity
Principal selectivity challenge [60]	Variable expression intensity and distribution; requires a validated high-expression IHC cut-off	High homology with CLDN9 (near-identical extracellular domain); demands a highly selective antibody
Lead ADC [61]	Mirvetuximab soravtansine (approved)	TORL-1-23 (first-in-class; investigational)
Payload of lead ADC [62]	DM4 (maytansinoid)	MMAE (auristatin) both microtubule inhibitors with bystander activity
Patient selection [63]	FRα IHC (validated FRα-high cut-off)	CLDN6 IHC
Persistence in relapsed/disseminated disease [64]	Expressed in the majority of tumors, with variable intensity	Maintained from primary to recurrent disease; detectable in ascites
Other modalities targeting the antigen [65,66]	Multiple ADCs (luveltamab tazevibulin, farletuzumab ecteribulin, IMG151)	CAR-T cells (± amplifying RNA vaccine); bispecific T-cell engagers

ADC, antibody–drug conjugate; GPI, glycosylphosphatidylinositol; HGSOc, high-grade serous ovarian carcinoma; IHC, immunohistochemistry.

Bystander killing and intratumoral antigen-negative cells

Within an individual tumor, the bystander effect addresses the antigen-negative subclones that heterogeneity inevitably produces. Because both mirvetuximab and TORL-1-23 release membrane-permeable payloads from cleavable linkers, the cytotoxic effect extends beyond the antigen-positive cells that internalize the ADC to neighboring antigen-low or antigen-negative cells, mitigating the antigen-negative escape that would otherwise limit a strictly antigen-restricted therapy [22,23]. The bystander effect is most useful where antigen-positive and antigen-negative cells are intermixed, as within a heterogeneous tumor deposit, and less beneficial for spatially separate antigen-negative metastases, so it is a partial, not complete, solution to intratumoral heterogeneity [67].

Biomarker-driven patient selection and the diagnostic challenge

The flip side of antigen heterogeneity is the necessity of measuring it, and biomarker-driven selection is

One important manifestation of HGSOc's broader molecular and clonal heterogeneity is variation in antigen expression, and no single antigen is universal. FRα is expressed in a large majority of HGSOc but at variable intensity, and only a subset reaches the high-expression threshold required for mirvetuximab eligibility; CLDN6 is expressed in roughly half of HGSOc, in a population that overlaps only partially with FRα-high tumors [23,26,38]. The two antigens are therefore complementary rather than redundant: a tumor that is FRα-low may be CLDN6-positive and vice versa, so the availability of ADCs against both antigens expands the fraction of patients for whom an antigen-directed ADC is an option [55]. At the population level, having two complementary targets is itself a partial answer to intertumoral heterogeneity, allowing more patients to be matched to an effective targeted therapy (Table 2).

integral to deploying these ADCs effectively. Both FRα and CLDN6 ADC programs rely on immunohistochemical assessment of target expression to identify likely responders, and the success of mirvetuximab in FRα-high disease versus its more modest activity at lower expression illustrates the stakes [5,31]. This situation makes the development of robust, reproducible, standardized diagnostic assays with clear scoring criteria and, increasingly, digital pathology support as important as the drugs themselves, because misclassification in either direction either denies an effective therapy or exposes a patient to a drug unlikely to help [26]. The diagnostic challenge is compounded by heterogeneity itself, since a single biopsy may not represent the antigen expression of the entire tumor burden. Antigen expressions are also dynamic and can change over time and with treatment exposure, further complicating the interpretation of a single biopsy taken at one point in the course of disease.

Toward dual, sequential, and combination targeting

The logical extension of complementary antigens is to target more than one. Several approaches are

conceivable: sequential use of an FR α ADC and a CLDN6 ADC as a tumor evolves and its antigen profile shifts; rational combination, constrained by overlapping toxicities; or single agents engineered to engage two antigens. The broader ADC field has explored dual-payload conjugates and combinations precisely to combat heterogeneity and resistance, and the same logic applies for targeting HGSOc through two independent antigens reduces the probability that an antigen-negative or antigen-loss subclone can escape [68,69]. Realizing this will require careful attention to cumulative toxicity, particularly the ocular effects of mirvetuximab and the neuropathy and myelosuppression associated with MMAE, and to the sequencing question of which agent to use first. Nonetheless, the existence of two validated, complementary antigens in the same disease is an unusual and promising opportunity to address heterogeneity systematically [70].

Safety, Resistance, and Translational Challenges *Overlapping and distinct toxicities*

The toxicity profiles of these ADCs are shaped largely by their payloads and, where relevant, by on-target effects. Mirvetuximab's maytansinoid payload is associated with the characteristic ocular toxicity and with gastrointestinal effects and neuropathy; MMAE-based ADCs such as TORL-1-23 are associated with peripheral neuropathy, neutropenia, and other auristatin-class effects [5,23,31]. These differences matter for combination and sequencing strategies, since stacking agents with overlapping toxicities, for instance, may be limiting, whereas agents with non-overlapping toxicities may combine more readily. The relatively favorable, manageable toxicity of these ADCs compared with cytotoxic chemotherapy is a genuine advantage, but it is not negligible, and on-target normal-tissue effects must be watched as new antigens are pursued [71].

Acquired resistance to ADCs

As discussed above, ADCs can develop resistance through mechanisms distinct from platinum resistance, including antigen downregulation or loss, impaired internalization and trafficking, and payload efflux. In a disease as genomically unstable and heterogeneous as HGSOc, the selective pressure of an effective ADC can be expected to enrich for resistant subclones over time, and antigen loss is a particular concern for a strategy predicated on antigen expression [72]. This is a genuine limitation rather than a fatal one: it argues for monitoring target expression over the course of treatment and for having non-cross-resistant alternatives—such as the complementary antigen or a different payload class—available for when resistance emerges, rather than for abandoning antigen-directed therapy altogether. Monitoring target expression at relapse and having complementary antigens and non-cross-resistant payloads available are therefore practical responses to the near-certainty that resistance will eventually emerge. The durability of responses

observed to date is encouraging but, especially for the newer CLDN6 agent, still relatively short-term [73,33]. A decrease in antigen levels can also occur following multiple cycles of ADC exposure, which is one mechanism by which repeated dosing itself may erode the target density needed for a continued response.

Sequencing and combination with the broader therapeutic landscape

Finally, these ADCs must be integrated into a treatment landscape that already includes PARP inhibitors, anti-angiogenic therapy with bevacizumab, and, in selected settings, immunotherapy [2,74]. Questions of sequencing—where an ADC fits relative to PARP-inhibitor maintenance and further platinum rechallenge—remain open. So does the question of rational combination, for example, pairing an ADC with bevacizumab or with agents that might enhance antigen expression or counter resistance; both are active areas of investigation. The MIRASOL demonstration that an ADC can extend survival in platinum-resistant disease has shifted these agents from being last-resort options to earlier consideration, and ongoing trials are evaluating their use in earlier treatment lines and in combination, which will define their ultimate role in the management of HGSOc.

Future Prospects

Several priorities will shape the field. The continued diversification of payloads—toward less susceptible classes to efflux and with distinct mechanisms—will help counter the multidrug resistance that constrains current microtubule-inhibitor ADCs. Separately, the development of agents active at lower antigen-expression thresholds will enlarge the treatable population and blunt the impact of heterogeneity [37]. The systematic exploration of complementary and combinatorial targeting of FR α and CLDN6, whether sequential or simultaneous, offers a rational route to addressing antigen heterogeneity at both the intertumoral and intratumoral levels, contingent on managing cumulative toxicity. Robust, standardized, and ideally multiplexed companion diagnostics capable of assessing several antigens from limited tissue and accounting for spatial heterogeneity will be essential to match patients to the optimal agent or combination. The movement of these ADCs into earlier lines of therapy and into rational combinations with PARP inhibitors, anti-angiogenics, and immunotherapy will be tested in ongoing and future trials. And the maturation of long-term follow-up will reveal the true durability of responses and the patterns of acquired resistance, informing the next generation of agents. Underlying all of these is the recognition that HGSOc is unlikely to be conquered by any single antigen or agent and that durable benefit will come from an intelligently sequenced and combined armamentarium built on the antigen-directed principle these two targets exemplify.

Conclusion

High-grade serous ovarian carcinoma has long resisted improvement in survival because of two reinforcing adversaries: platinum resistance, which disarms the disease's most effective chemotherapy, and a deep heterogeneity that lets tumors evade narrowly targeted attack. Antibody-drug conjugates directed against tumor-associated antigens offer a coherent strategy against both. By delivering a microtubule-inhibiting payload through antigen binding, they kill via a mechanism largely independent of the DNA-repair and drug-handling pathways that confer platinum resistance, so platinum-resistant tumors generally remain susceptible—a prediction now confirmed by mirvetuximab soravtansine's historic overall-survival benefit in platinum-resistant disease and by the encouraging early activity of the first-in-class CLDN6 ADC TORL-1-23. And through the bystander effect, the availability of two complementary antigens, and biomarker-guided selection, they begin to address the heterogeneity that has defeated other approaches. Folate receptor alpha and claudin-6 are, in this sense, two expressions of a single strategy: antigen-directed cytotoxic delivery applied to the hardest problem in gynecologic oncology. Important limits remain in that ADCs are themselves subject to antigen loss and payload efflux, no single antigen covers the whole disease, toxicities constrain combinations, and resistance will inevitably emerge. But the demonstration that this strategy can prolong survival where platinum has failed and can do so against a disease defined by its heterogeneity marks a genuine advance and a template for the rational, biomarker-driven, combination-minded development that the disease demands. Realizing this advance in practice will also require confronting practical barriers: the high acquisition cost of these agents, dependence on standardized biomarker testing to select appropriate patients, and the diagnostic and infrastructural resources needed to implement that testing across treatment centers.

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Abbreviations

AACR: American Association for Cancer Research; ADC: Antibody-Drug Conjugate; aOR: Adjusted Odds Ratio; ASCO: American Society of Clinical Oncology; ATM: ATM Serine/Threonine Kinase; ATP: Adenosine Triphosphate;

ATP7A: ATPase Copper Transporting Alpha; ATP7B: ATPase Copper Transporting Beta; BRCA1: Breast Cancer Gene 1; BRCA2: Breast Cancer Gene 2; BRIP1: BRCA1 Interacting Helicase 1; CAR: Chimeric Antigen Receptor; CAR-T: Chimeric Antigen Receptor T-cell; CCNE1: Cyclin E1; CI: Confidence Interval; CLDN6: Claudin-6; CLDN9: Claudin-9; CTR1: Copper Transporter 1; DAR: Drug-to-Antibody Ratio; DCR: Disease-Control Rate; DM4: N2'-deacetyl-N2'-(4-mercapto-4-methyl-1-oxopentyl)maytansine; DNA: Deoxyribonucleic Acid; ERCC1: Excision Repair Cross-Complementation Group 1; ESMO: European Society for Medical Oncology; FDA: Food and Drug Administration; FOLR1: Folate Receptor 1; FRα: Folate Receptor Alpha; GPI: Glycosylphosphatidylinositol; HGSO: High-Grade Serous Ovarian Carcinoma; HRD: Homologous-Recombination Deficiency; IgG1: Immunoglobulin G Subclass 1; IHC: Immunohistochemistry; mAb: Monoclonal Antibody; mDoR: Median Duration of Response; MEDLINE: Medical Literature Analysis and Retrieval System Online; MINSA: Ministerio de Salud; MMAE: Monomethyl Auristatin E; NR: Not Reported; ORR: Objective Response Rate; OS: Overall Survival; p53: Tumor Protein p53; PALB2: Partner and Localizer of BRCA2; PARP: Poly(ADP-ribose) Polymerase; PFS: Progression-Free Survival; P-gp: P-glycoprotein; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROC: Platinum-Resistant Ovarian Cancer; PSS-4: 4-item Perceived Stress Scale; RAD51: RAD51 Recombinase; RNA: Ribonucleic Acid; SE: Standard Error; SGO: Society of Gynecologic Oncology; S-methyl-DM4: S-methylated DM4 metabolite; SPDB: N-succinimidyl 4-(2-pyridyldithio)butanoate; SPSS: Statistical Package for the Social Sciences; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TP53: Tumor Protein p53 Gene; Val-Cit: Valine-Citrulline; WHO: World Health Organization.

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