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Expert recommendation

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Rethinking ovarian cancer III: the past decade and future directions

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Abstract

Approximately 80% of deaths from ovarian cancer are due to high-grade serous carcinoma (HGSC), which has the highest proportion of *BRCA1* or *BRCA2* (*BRCA1*/*BRCA2*) mutations of any cancer type and is a highly chromosomally unstable disease. Despite the introduction of targeted therapies benefitting some patients with HGSC as well as surgical advances, only 50% of patients will survive more than 5 years, and just 30% of patients who present with advanced disease without *BRCA1*/*BRCA2* mutations will survive this long. This Expert Recommendation is based on discussions among emerging and leading ovarian cancer researchers at the 15th Helene Harris Memorial Trust International Forum on ovarian cancer hosted by Ovarian Cancer Action in October 2024. The meeting considered advances in HGSC research and treatment made over the last decade, current challenges, emerging technologies in prevention, early detection, and treatment, and research priorities for the years ahead.

Sections

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Introduction

For almost four decades, the Helene Harris Memorial Trust, in conjunction with Ovarian Cancer Action (UK), has invited leaders in ovarian cancer management and research from around the world to discuss new approaches to understanding and treating the disease. Influential Perspective articles authored by meeting delegates published in *Nature Reviews Cancer* in 2011[1] and 2015[2] outlined roadmaps for understanding ovarian cancer broadly and then more specifically for high-grade serous carcinoma (HGSC), the most common histotype. As discussed below, substantial progress has been made in understanding the cellular origins, genetic risk factors, molecular composition, tumour microenvironment (TME) and immunobiology of ovarian cancer. Although once controversial, there is now consensus among HGSC researchers and clinicians worldwide that the Fallopian tube is the site of origin for the majority of HGSC[3–5].

Over the decades since the introduction of platinum-based chemotherapy, there have been notable improvements in the clinical management of HGSC, including the use of some targeted drugs and improved surgical approaches (Fig. 1). One of the most impactful therapeutic advances during this period has been the introduction of poly(ADP-ribose) polymerase inhibitors (PARPi). These confer a survival benefit, particularly in first-line maintenance treatment, for patients with HGSC with *BRCA1* or *BRCA2* (*BRCA1*/*BRCA2*) mutations or other genes that render tumour cells homologous recombination-deficient (HRD)[6,7]. Despite the benefit of PARPi treatment, disease progression during PARPi therapy remains a challenge, necessitating a deeper exploration of resistance mechanisms[8]. Furthermore, nearly half of patients, particularly those with homologous recombination-proficient (HRP) cancer, do not benefit from maintenance PARPi. Thus, frontline treatment with carboplatin and paclitaxel, with or without the anti-angiogenic agent bevacizumab, remains unchanged. Given that 50–70% of patients experience multiple relapses[9], treating recurrent ovarian cancer remains a challenge. Surgical developments include the expansion of cytoreductive surgery to patients with higher tumour burden without an associated increase in surgical morbidity and mortality, and the broader introduction of secondary cytoreductive surgery in the relapsed setting, with the definition of well-defined selection criteria for surgical candidates[10]. The timing and appropriate patient population for hyperthermic intraperitoneal chemotherapy remain to be firmly established[11–13].

Although the use of immune-checkpoint inhibitors (ICIs) in cancer types such as melanoma and microsatellite instability-high colorectal cancer has been successful[14], large randomized controlled trials of ICIs in ovarian cancer, even in the first-line setting with chemotherapy and bevacizumab, have been disappointing in unstratified patient populations[15–17]. While the lack of efficacy of ICIs in HGSC may be due to a lower mutational burden relative to microsatellite instability-high colorectal cancer and melanoma[18], there is ample evidence that the endogenous immune response in HGSC is strongly associated with survival[19]. Modulation of immunosuppressive cells and factors present in the TME[20–23], patient and/or tumour stratification, and optimal timing of treatment[23,24] may be required to achieve greater efficacy of ICIs and other immunotherapies in HGSC.

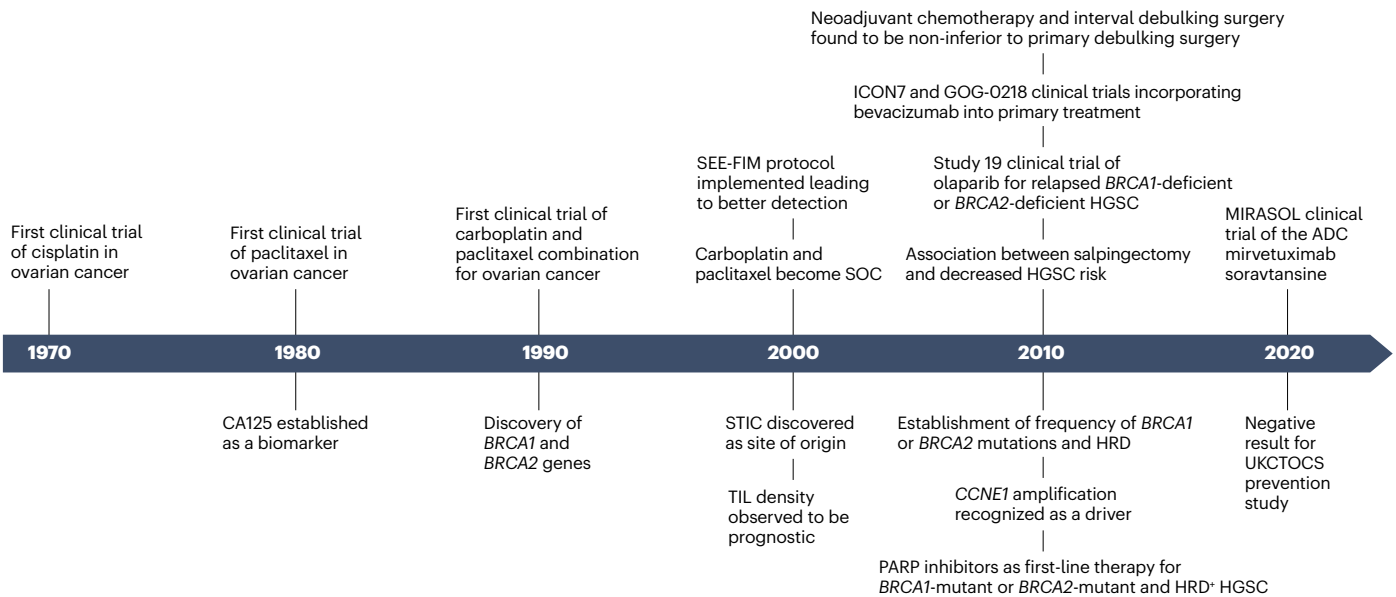

Fig. 1 | Timeline of major practice-changing clinical studies relevant to HGSC over the preceding decades. High-grade serous carcinoma (HGSC) has the highest frequency of pathogenic germline mutations in *BRCA1* or *BRCA2* (*BRCA1*/*BRCA2*) of any cancer type, imparting defective homologous recombination DNA repair. In addition to the importance of these genes in identifying genetically at-risk individuals, germline or somatic mutations in *BRCA1*/*BRCA2* or other genes involved in homologous recombination DNA repair are the main determinant of response to carboplatin and poly(ADP-ribose) polymerase (PARP) inhibitors. The identification of the distal Fallopian tube as the major source of HGSC had important implications for approaches to risk-reducing surgery and the development of accurate animal models of the disease. In addition to the established therapeutic backbone of cisplatin, and later carboplatin and paclitaxel, targeted therapies that have become standard of care (SOC) in recent years include PARP inhibitors, the vascular endothelial growth factor (VEGF)-attenuating monoclonal antibody bevacizumab, and the antibody–drug conjugate (ADC) mirvetuximab soravtansine targeting the folate receptor-α (FRα). CA125, cancer antigen 125; HRD, homologous recombination-deficient; SEE-FIM, Sectioning and Extensively Examining the Fimbriated End; STIC, serous tubal intraepithelial carcinoma; TIL, tumour-infiltrating lymphocyte; UKCTOCS, UK Collaborative Trial of Ovarian Cancer Screening.

Box 1 | Patient advocate perspectives at the 15th Helene Harris Memorial Trust International Forum on Ovarian Cancer

At the 15th Helene Harris Memorial Trust International Forum on Ovarian Cancer, each supporting global charity partner — Ovarian Cancer Action (UK), Ovarian Cancer Research Alliance (USA), Ovarian Cancer Canada and Ovarian Cancer Research Foundation (Australia) — invited patient advocates to share their experiences and hopes for research. Their videos, shown before each session discussion, connected delegates' thinking to real-world impact.

Advocates very strongly emphasized the need for treatments that would be more efficacious and less toxic than conventional therapies, which can have life-changing consequences. They were very concerned that information was lacking about how to manage symptoms in non-white women and the lack of guideline care provided to these women[254]. They highlighted the effects of primary resistance, which typically occurs in the non-BRCA group who have not benefited from the development of poly(ADP-ribose) polymerase (PARP) inhibitors. The added distress of being diagnosed with a rare form of ovarian cancer was highlighted, and they emphasized the need for international collaboration for laboratory studies and clinical trials to overcome the small numbers of patients at single centres. The distressing effects of the evolution of progressive drug resistance were a consistent cause of great concern. They noted that the observation that early detection of recurrence does not alter long-term survival had been made before important newer therapeutic developments, and hence, they valued increased research attention on the early detection of recurrence. Immunotherapy in its several forms — cellular, antibody, vaccines, immune modulators of the tumour microenvironment — were seen as a continuing vital research priority.

These videos are included in the Supplementary Information to highlight how patient voices shaped the recommendations in this paper and their potential to drive global change. Informed consent was obtained from all patients.

In October 2024, 38 established and emerging leaders in ovarian cancer research and treatment were invited by the Helene Harris Memorial Trust and Ovarian Cancer Action to reflect on advances made over the last decade and debate critical directions for research and treatment, focusing on HGSC. For the first time, representatives from other major ovarian cancer philanthropic research foundations and alliances, involving Ovarian Cancer Research Foundation (Australia), Ovarian Cancer Research Alliance (USA) and Ovarian Cancer Canada, joined the meeting to discuss how the challenges identified by the researchers could be collectively addressed.

The meeting programme covered five themes: prevention, initiation and early detection; tumour spatial ecosystem; immunity and immunotherapy; acquired resistance; and new therapeutic approaches. Recorded personal experiences shared by patient advocates (Box 1) were played before the discussion session of each theme, providing a powerful context for the dialogue. In these videos, advocates emphasized the need for treatments that would be more efficacious and less toxic than therapies that have been used for decades, and for increased attention to the early detection of recurrence. Disparities experienced globally by non-white women formed an additional theme that cut across all sessions, and this is summarized in Box 2.

In this Expert Recommendation, we present some of the main advances in our understanding and treatment of HGSC over recent years, outline challenges in the field, and provide research priorities that were identified during the meeting.

Prevention, initiation and early detection

Context and challenges

The identification of secretory epithelial cells of the distal Fallopian tube (FT-SECs) as the progenitors of most HGSC has catalysed a broad effort to understand Fallopian tube biology in the context of cancer risk, microenvironmental influences and age-related changes[25]. This growing knowledge base is reshaping how we conceptualize HGSC initiation and lays the groundwork for new prevention and detection strategies.

Recent single-cell and spatial transcriptomic studies have revealed substantial heterogeneity within the Fallopian tube epithelium, highlighting region-specific transcriptional programmes and immune microenvironments that may influence cancer susceptibility[26–31]. The median age of HGSC diagnosis is 60 years and is only slightly lower in carriers of high-risk mutations (50–53 years old in *BRCA1* mutation carriers and 57–59 years old in *BRCA2* mutation carriers). This suggests that age-related changes may play a role in tumour initiation. With menopause, the Fallopian tube undergoes substantial remodelling, including epithelial thinning, ciliary loss and stromal remodelling. These changes are accompanied by increased inflammatory and interferon signalling, which together may foster a pro-tumorigenic niche in the distal tube[32–35].

Serous tubal intraepithelial carcinomas (STICs) are precursors of invasive HGSC and arise predominantly from transformed FT-SECs. *TP53* mutations are seen in all STICs and HGSC tumours[36,37]. Notably, age-related epigenetic alterations, changes in stem-like cell populations and an accumulation of *TP53*-mutant clones have been described in histologically benign Fallopian tubes from both *BRCA1*/*BRCA2* mutation carriers and the general population[38–41]. These findings suggest that Fallopian tube epithelium may acquire oncogenic alterations long before the development of HGSC, potentially decades earlier[42–44]. Other studies indicate a 5–7 year gap between a STIC diagnosis and HGSC development[43–47].

Recent results indicate that mesenchymal stem cells (MSCs) contribute to HGSC initiation[35]. With age and/or a BRCA mutation, Fallopian tube-derived MSCs can become epigenetically altered in a manner that mirrors cancer-associated MSCs (CA-MSCs). These MSCs, termed high-risk MSCs (hrMSCs), can be found prior to the emergence of STICs. They are also enriched in the stroma underlying STICs and can induce oxidative stress by producing high levels of lipid peroxidase, which catalyses lipid peroxidation as well as driving DNA double-strand breaks in FT-SECs in vitro. Such interactions can induce full malignant transformation of otherwise healthy human Fallopian tube epithelial cells in mice, inducing *BRCA1* and *APC* (encoding adenomatous polyposis coli) mutations and ultimately resulting in metastatic cancers that genomically mirror HGSC. In vitro analyses indicated that hrMSC loss of AMP-activated protein kinase (AMPK) and the subsequent production of reactive oxygen species and lipid peroxides is a key mediator of the effects of hrMSCs on Fallopian tube epithelium, suggesting that AMPK agonists and anti-oxidant therapies may represent approaches for prevention[35].

The recognition that the Fallopian tube is the predominant site of origin for HGSC has also led to a paradigm shift in prevention strategies for HGSC. For women with *BRCA1* or *BRCA2* mutations, risk-reducing salpingo-oophorectomy has been typically offered; however, international clinical trials are now evaluating whether salpingectomy with delayed oophorectomy can offer equivalent protection, while potentially preserving hormonal function, quality of life and even fertility[48–50]. Importantly, early findings indicate high uptake of the procedure and acceptance of these protocols, particularly among younger women who are mutation carriers and are concerned about the long-term effects of premature menopause. Studies show that removal of the Fallopian tubes may interrupt early clonal evolution or dissemination from occult STICs from both *BRCA1*/*BRCA2* mutation carriers and women at average risk, but most of the data so far are from women at high risk[51–53].

In populations at average risk, findings from large epidemiological retrospective studies suggest that opportunistic salpingectomy performed for benign indications is associated with a substantial reduction in the incidence of ovarian cancer. This appears to occur without added perioperative risk or impact on ovarian function[54–58]; however, long-term data are not yet available. Findings from cost-effectiveness analyses and modelling studies increasingly support the integration of opportunistic salpingectomy into routine gynaecological care, particularly during hysterectomy or sterilization procedures, as a feasible and impactful population-level intervention strategy[59–61]. The concept of opportunistic salpingectomy has also expanded into non-gynaecological procedures in recent years as a further preventative strategy. Initial results demonstrate feasibility and cost-effectiveness during general abdominal surgeries such as cholecystectomy and bariatric surgery[62]. Current large-scale clinical trials are in progress to provide further evidence of safety and an estimate of the number of patients required to receive risk-reducing salpingectomy for a cancer to be prevented[57]. Its broader, more routine establishment will require increased education and awareness from both patients and physicians, and coordination between the different surgical disciplines[57,62].

Despite a deeper understanding of Fallopian tube biology and the identification of STICs as key precursors to HGSC, early detection remains a major unmet need. STIC lesions are typically microscopic, asymptomatic and lack an anatomical barrier to prevent dissemination into the peritoneal cavity. Currently available screening methods, including measurements of the cancer antigen 125 (CA125) in the blood and transvaginal ultrasound, lack the sensitivity to detect early lesions, and randomized trials such as the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) have failed to show a survival benefit with these approaches[63]. Furthermore, the Sectioning and Extensively Examining the Fimbriated End protocol, involving systematic sectioning of salpingectomy samples as part of the diagnostic pathological assessment to identify STICs, yields limited tissue for research analysis and thus restricts opportunities for molecular and cellular characterization. Currently, there is little consensus on whether adjuvant chemotherapy should be given to patients with an isolated STIC, even though the risk of subsequent invasive disease is substantial[64,65].

Molecular and cellular characterization of early Fallopian tube lesions. Advances in single-cell RNA sequencing, spatial transcriptomics and proteomics, and artificial intelligence-enhanced histopathology are enabling unprecedented resolution of precancerous lesions, such as STICs, within the Fallopian tube epithelium[66–68]. These technologies are helping to dissect early mutational events, transcriptional plasticity and chromatin alterations that precede malignant transformation, while also illuminating the interactions between epithelial, immune, and stromal cells that may promote or constrain tumour progression[66,69,70]. Precancerous lesions, including STICs, coincide with progressive shifts in the TME, transitioning from active immune surveillance, characterized by the presence of immune cells, including tissue-resident memory $CD8^+$ T cells in early STICs, to an immune-suppressive microenvironment in advanced STICs

Box 2 | Social and ethnic disparities in high-grade serous carcinoma incidence and outcomes

The burden of ovarian cancer globally is expected to increase by 40% in 2045 (ref. 255). However, different regions are projected to have a significant increase in incidence, including Africa (102%) and Latin America and the Caribbean (52%), compared to theprojected increase in Europe (9%) and in North America (28%)[256]. The rise in global incidence of ovarian cancer aligns with the increase in non-communicable disease burdens in developing countries.

Women from the African diaspora face a higher incidence of high-grade aggressive ovarian tumours[257–259]. Subgroup survival differences across different Asian and Hispanic ethnic groups have also been observed[254]. Despite advances, innovative approaches to clinical care, such as personalized genomic medicine, remain infrequently used by populations who may benefit. While overall mortality due to ovarian cancer is decreasing in the USA, Black women or women of African ancestry continue to experience the worst survival rates among all racial groups[260]. Historically, these women and others have faced medical and scientific marginalization, leading to disparities in disease aetiology and outcomes.

Relatively little is known about the prevalence of hereditary ovarian cancer among the African diaspora, with initial findings suggesting substantial differences between populations. For example, among women of Caribbean ancestry in the Bahamas, 20–25% of those with a personal history of breast or ovarian cancer have a pathogenic mutation in *BRCA1* or *BRCA2*, compared with 11% for those from the islands of Trinidad and Tobago[260–264]. Improved understanding of germline mutation frequency offers important opportunities for risk-reducing surgery for a disease for which there is currently no effective early detection test.

Recognizing disparities experienced by many non-white women, increased efforts are required in understanding individual-level factors, including how genetic, biological, environmental and/or socioeconomic factors influence disease risk and survival[258,265,266]. Improvement in outcomes requires access to timely equitable care, awareness of the influence of social determinants of health, access to personalized genomic medicine, and inclusion in clinical trials[267] — all factors that could 'level the playing field'.

Finally, it is vital that research in populations with a disproportionate increase in incidence and demonstrated worse outcomes includes investigators from these populations to ensure contextualization of the data, obtain buy-in, and ensure future dissemination and implementation of findings.

and cancer[66]. Complementary studies of normal and menopausal Fallopian tube tissues, especially in the context of germline risk variants, are further refining our understanding of tissue susceptibility and clonal evolution[26,29,35].

Meeting insights and recommendations

Fallopian tube secretory cell vulnerability. Given that BRCA1 and BRCA2 are critical to homologous recombination-mediated DNA repair, a process that is expected to be required by a wide range of cell types, a critical question is why FT-SECs in particular should be vulnerable to tumorigenesis in carriers with germline mutations in these genes. Recent data indicate that even normal Fallopian tube cells, whether ciliated or secretory, mount a slower replication stress response and activate cell cycle checkpoints less efficiently than ovarian surface epithelial cells, and that BRCA heterozygosity further exacerbates these defects[71]. Haploinsufficiency resulting from germline BRCA mutations impairs the DNA damage response, particularly by compromising the repair of stalled replication forks, leading to increased replication stress and genomic instability, both for mammary[72–74] and Fallopian tube epithelial cells[71]. Surprisingly, mammary epithelial cells and skin fibroblasts from *BRCA1* or *BRCA2* heterozygous cells do not exhibit haploinsufficiency for homologous recombination[72,74]. It is plausible that haploinsufficiency arising from germline BRCA mutations, combined with intrinsically delayed DNA damage responses, and compounded by randomly occurring *TP53* mutations, may trigger the early evolution of STICs in carriers. The underlying causes of the delayed response to DNA damage apparent in FT-SECs are unknown but, if modifiable, they could potentially reduce initial events in STIC formation and therefore cancer risk in *BRCA1*/*BRCA2* mutation carriers.

Novel detection approaches. Insights into early stages of HGSC are also fuelling the development of novel detection approaches, including the possibility that aberrant expression of retrotransposon elements, such as long interspersed element 1 (LINE1) open reading frame 1p (ORF1p), which is detectable in early lesions, may serve as a useful biomarker[75–79]. Additionally, artificial intelligence-assisted profiling of cell-free DNA (cfDNA) fragmentation patterns ('fragmentomic profiling'), epigenetic modifications or mutational signatures has demonstrated potential to outperform CA125 in sensitivity and specificity for detecting early HGSC[80,81]. In particular, cfDNA fragmentomes combined with existing protein biomarkers non-invasively detected early-stage ovarian cancer and distinguished these lesions from benign ovarian masses, providing a new accessible approach for early detection of ovarian cancer[80].

Another promising approach for early detection involves endocervical sampling. A recent systematic review of studies employing DNA methylation or mutation analysis, microbiome profiling, and proteomics on cervicovaginal specimens concluded that DNA methylation techniques show the greatest potential for detecting ovarian and endometrial cancers. This conclusion is supported by the relatively high diagnostic accuracy of these tests and the large sample sizes included in the analysed studies[82].

Together, these approaches reflect a worthwhile effort to translate molecular understanding of Fallopian tube tumorigenesis into clinically actionable strategies for early detection of disease.

Genetic risk variants. All of the multi-case, multi-generational, high-risk germline genetic variants and many of the moderate-risk and low-risk germline genetic variants for HGSC have been identified[83]. Rare, highly penetrant loss-of-function variants in *BRCA1* and *BRCA2* are responsible for almost all multi-case, multi-generation ovarian cancer cases in families and account for ~30% of the inherited component of ovarian cancer risk in most populations. Rare, moderately penetrant variants in *BRIP1* (encoding BRCA1-interacting protein C-terminal helicase 1), *RAD51C*, *RAD51D*, *PALB2* (encoding partner and localizer of BRCA) and the mismatch repair genes, and more than 40 common low penetrance susceptibility alleles identified by large-scale genome-wide association studies, contribute less than 10% of risk[84,85]. Thus, less than half of the inherited component of risk is explained by the known variants. Other common variants are estimated to account for 40%[85], with rare variations in the non-coding genome likely to be responsible for the remainder.

The identification of rare genetic variants in the non-coding genome that are associated with disease susceptibility presents a considerable challenge. In principle, it would be possible to sequence a very large number of cases and controls and evaluate the disease associations on a variant-by-variant basis. This has been the approach to common risk variant discovery in genome-wide association studies. However, the cost of sequencing tens of thousands of cases and controls in a single project remains prohibitively expensive. Even then, the statistical power would be limited to detecting an association for individual rare variants. Additionally, the best approach to estimating the contribution of individual rare non-coding variants to risk and functionally evaluating non-coding variants remains unclear.

Genetic testing for high-risk and moderate-risk genes is well established in family cancer clinics as part of familial risk assessment and risk management; however, uptake is uneven within and between countries[86]. Mainstream testing of patients with HGSC for *BRCA1*/*BRCA2* mutations to guide therapeutic decision-making, most commonly to guide access to PARPi, is standard practice in many countries. By contrast, the role of polygenic risk evaluation for newly diagnosed patients and their families or in the general population is yet to be established, and we recommend its further investigation[87]. Most genetic studies have surveyed the white population, and there is a need to understand the influence of genomic ancestral variations on risk factors (Box 2).

Tumour ecosystem

Context and challenges

As with other solid cancers, the TME in HGSC is highly complex, encompassing not only immune cells like tumour-infiltrating lymphocytes and myeloid cells[20,88,89] but also cancer-associated fibroblasts (CAFs), adipocytes, MSCs, abnormal vasculature and other recently identified cell types such as sensory nociceptive fibres[90,91]. Extracellular matrix (ECM) composition is also a key feature in shaping the TME[92,93]. Despite these insights, therapeutic targeting of the tumour ecosystem in HGSC remains challenging due to the heterogeneous nature of both the TME and malignant cells, both within and between patients.

In HGSC, the foundational context of the tumour ecosystem is built by clinical features and patient characteristics, which influence tumour initiation and progression. Tumour genomic and molecular features reflect the tumour's intrinsic properties, further shaping the tumour–host interaction dynamics and responses to treatments. For example, *BRCA1*/*BRCA2*-mutated HGSCs show higher T cell infiltration compared to BRCA wild-type tumours in different regions of the patient's tumour, including primary tumours, metastases and ascites[20,22,89,94,95]. Antitumour immunity is differentially activated depending on the histological, genomic and anatomical context, and

these factors likely play a role in the patient's response to treatments such as chemotherapies and immunotherapies.

The TME structure is dynamic and evolves over the course of HGSC initiation and progression[66] and with the evolution of therapy resistance; for example, via increased infiltration of inflammatory CAFs associated with chemotherapy resistance[21,96]. Neoadjuvant chemotherapy (NACT) also alters the TME composition and organization[23] and elicits augmented lymphocyte infiltration with concurrent immune modulation[97–100]. NACT responses may reveal patient-specific immune activation and escape mechanisms amenable to therapeutic targeting.

Bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, is the only TME-targeted treatment widely used in HGSC[101]. Post hoc analyses from clinical trials have shown that certain molecular subtypes may derive the greatest benefit from this treatment and suggest that further validation of such biomarkers may help to stratify patient selection from a heterogeneous patient population[102,103]. VEGF receptor 2 (VEGFR2) is also expressed on HGSC cells[104], potentially indicating a role in autocrine or paracrine signalling, and could therefore also be important in determining tumour response to VEGF inhibition.

To enhance TME targeting and patient stratification, it is crucial to understand the spatial and functional dynamics of the TME and how these dynamics relate to treatment responses. Tumour progression, immune evasion and resistance mechanisms are ultimately driven by the functional TME via molecular interactions, including distinct cellular phenotypes and signalling networks. These interconnected factors form a complex ecosystem that governs the biology and clinical outcomes in ovarian cancer. There is a clear need for a coordinated effort to collect tumour samples from clinical trials, including window-of-opportunity studies[105], that allow for pre-treatment and post-treatment biopsies to better investigate the molecular response and differences due to treatment.

Meeting insights and recommendations

Emerging technologies, such as spatial transcriptomics and imaging-based proteomics, provide unique opportunities to detect and map tumour and host cell populations in situ. However, further advancements are needed in spatial DNA-based analytics for accurate tumour clonal mapping and in spatial mass spectrometry to detect cytokines and ECM to link the physical and functional elements of the TME.

Non-immune components of the TME. While there has been a concerted effort to characterize and understand the immune components of HGSC[106], as discussed below, recent work underscores the importance of various non-immune cells in the TME in HGSC biology. Local tissue-derived MSCs in the TME can be epigenetically reprogrammed by tumour cells and hypoxia to assume a pro-tumour phenotype[107]. CA-MSCs are multipotent cells that can differentiate into CAFs or adipocytes[108]. CA-MSCs perform many pro-tumour functions in established tumours: increasing chemotherapy resistance via secreted factors such as bone morphogenetic protein (BMP) and Hedgehog family members, generation of polyunsaturated fatty acids, and induction of a cancer stem-like state[108–111]. CA-MSCs also differentiate into CAFs to increase tumour desmoplasia, recruiting and polarizing macrophages to an immunosuppressive $CCR2^{hi}F4/80^{+}CX3CR1^{+}CD206^{+}$ phenotype to drive tumour immune exclusion[110–112].

Other locally derived mesenchymal cell types, mesothelial cells, adipocytes and CAFs similarly play a critical role in the ovarian TME, influencing both metastasis and treatment response. For example, mesothelial cells are known to promote metastasis through the secretion of ECM-associated factors such as angiopoietin-like 4 (ANGPTL4) and lysyl oxidase-like 2 (LOXL2)[113,114]. LOXL2 is implicated in some fibrotic diseases and cancer[115], and inhibitors are being explored clinically[116]. The identification of stromal factors such as these suggests potential for the additional development of TME-targeted therapeutics given that ECM-associated factors may contribute to therapeutic resistance[117]. Adipocytes are a key component of the TME, as they are a predominant cell type in the omentum, the primary site of HGSC metastasis. Despite this, a complete rather than a partial omentectomy has not been found to improve survival if there is no visible disease. Additionally, several clinical trials have shown that there is no improvement in survival with upfront radical debulking compared to debulking after NACT[118–120]. However, functional crosstalk between nutrient-rich adipocytes and malignant cells within the TME has been demonstrated to reprogramme the cellular metabolism of disseminating cancer cells as well as to contribute to therapy resistance[121,122].

Additionally, interactions between CAFs and malignant cells contribute to cancer progression and treatment sensitivity through the regulation of metabolic[114,123] and stress pathways[96]. Expression of nicotinamide *N*-methyltransferase (NNMT), an enzyme involved in nicotinate and nicotinamide metabolism, in CAFs is necessary and sufficient to promote ovarian cancer migration and proliferation in vitro as well as growth and metastasis in vivo[124]. High levels of NNMT attenuate histone methylation in fibroblasts via depletion of *S*-adenosyl methionine, leading to increased production of tumour-promoting cytokines that affect malignant cell migration and proliferation[124]. Subsequent studies have highlighted the ability of this metabolic pathway to not only influence tumour cell behaviour but also to modulate immune infiltration and activity[125]. NNMT and other metabolic pathways in CAFs may be amenable to therapeutic targeting[114]. Indeed, a recent paper describes a potent NNMT inhibitor that inhibited tumour growth and metastases in a range of preclinical models, restoring the action of immune-checkpoint blockade[126].

A role for sensory nociceptor neurons in modulating tumour immunity has been identified in several tumour types[91], including HGSC[90]. Recent studies demonstrated a significant increase in $TRPV1^{+}$ sensory nerves in ovarian tumours as compared to control tissues[90,127]. Genetic or pharmacological ablation of these nerves in mouse models led to improved disease control, underscoring the importance of tumour–nerve interactions in disease progression[90]. These findings highlight nociceptor neurons as a novel therapeutic target that could complement conventional treatment strategies.

While cellular components of the TME are an important focus, it is critical to also consider the physical microenvironment of the ECM scaffold upon which these components are arranged. Certain features of the ECM, such as the expression and alignment of collagens as well as the expression of proteoglycans, glycoproteins, and their associated molecules, predict disease characteristics, including response to chemotherapeutic agents, in both mouse and human HGSC[92,114,128]. For example, the proteoglycan versican is highly expressed in many cancer types, including HGSC, and can either facilitate or impede T cell trafficking, facilitated through the type of chondroitin sulfate glycans attached to its peptide backbone[129].

Complex models of the TME. Increasing insight into the roles of different cell types within the TME should accelerate the development of models more complex than patient-derived xenografts (PDXs) or malignant cell monocultures. Models of the human TME are essential

to develop therapies that are influenced by its composition, including immunotherapies. HGSC organoids as well as the other 3D models, which re-aggregate combinations of cell types in defined matrices in combination with live cell imaging, may represent important in vitro models to evaluate interactions identified through genomic and proteomic studies[130,131]. Additionally, short-term cultures of precision-cut tumour slices can remain viable for at least 7 days and appear to be valuable in moderate-throughput screens of immunotherapies[132,133]. Furthermore, recent syngeneic mouse models may more completely mirror HGSC genomics, immunobiology, and tumour epithelial and TME interactions than PDX HGSC tumours that usually have human malignant cells with a mouse TME[128,134–136]. A recently developed, humanized stromal PDX model[137] should allow testing of new agents in vivo in the context of a human TME.

Coupling drug response data from models that incorporate the TME to genomic data obtained from the starting tumour material, possibly assisted by artificial intelligence-based computational modelling, may reveal insights into mechanisms of immune suppression and biomarkers of response. Therefore, emphasis should be given to exploring the development and use of these complex models to predict patient response to therapy, including the development of affordable and scalable methods that could ultimately be used for routine clinical pathology assessment.

Immunity and immunotherapy

Context and challenges

HGSC was one of the first human cancers in which the extent and location within the tumour of tumour-infiltrating lymphocytes were shown to correlate with patient survival[19]. The density of tumour-infiltrating T cells (TIL-Ts) in tumours at diagnosis is strongly linked to improved prognosis[138,139], especially of $CD8^+$ T cells expressing PD1, CD103 (also known as integrin αE), CD39 and CXC-chemokine ligand 13 (CXCL13)[140,141]. Intratumoural γδ T cells also predict survival in HGSC, and their modulation in vivo by targeting CD277 leads to increased activity of tumour-specific αβ TIL-Ts[142]. While the identity of ovarian tumour antigens recognized by TIL-Ts remains under investigation, $CD4^+$ and $CD8^+$ T cell populations recognizing neoantigens and shared tumour-associated antigens (TAAs; for example, NY-ESO-1, human epidermal growth factor receptor 2 (HER2), mesothelin, human telomerase reverse transcriptase (hTERT)) can be detected in most patients[143–145].

Highly immune-infiltrated HGSC tumours also contain tumour-infiltrating B cells and antibody-producing plasma cells (collectively termed TIL-Bs), which are among the strongest predictors of long-term survival[146,147]. Such tumours often contain tertiary lymphoid structures (TLS)[95,148], which are induced by CXCL13-producing $CD4^+$ T cells[149] and are associated with increased cytolytic T cells[148,150]. TIL-Bs from HGSC make IgG and IgA antibodies against TAAs, possibly leading to disruption of target protein function and induction of antibody-dependent phagocytic and cytotoxic responses[151–153].

HGSC tumours are myeloid-dominated but distinct anatomical sites and immune phenotypes exhibit different TIL-T and myeloid cell networks[22,89,154,155]. For example, during NACT, tumour-associated myeloid cell programmes can modulate the exhaustion states of TIL-Ts that arise from persistent antigenic stimulation[89]. Recent work[155] showed that myeloid cell networks actively re-establish original immune phenotypes at recurrence, suggesting a form of immune memory within the HGSC microenvironment. This study also found that *BRCA1*-mutant (HRD) tumours retained $CD8^+$ T cell and $CD11c^+$ dendritic cell niches, whereas wild-type *BRCA1* tumours evolved towards $TREM2^+$ macrophage and galectin 3^+ malignant cell dominance, underscoring how genomic background dictates TME remodelling and immunotherapy sensitivity. Myelonets, defined as networks of spatially interacting myeloid cells, also spatially interact with $TIM3^+$ exhausted $CD8^+$ T cells, with evidence of substantial suppressive interactions between macrophages and T cells[89].

In 'inflamed' tumours, that is, tumours with a strong inflammatory infiltrate, antigen-specific T cells secrete interferon-γ (IFNγ), which activates myeloid antigen-presenting cells to recruit additional $CD8^+$ TIL-Ts via CXCL9[155,156] together with tumour-derived CC-chemokine ligand 5 (CCL5). Myeloid antigen-presenting cells sustain antitumour $CD8^+$ TIL-Ts and are crucial for effective PD1 blockade[145,155]. By contrast, 'immune excluded' and 'immune desert' ovarian cancers exhibit low intraepithelial $CD8^+$ T cell infiltration restrained by stromal endothelial and CAF barriers[92,106] and immune-suppressive tumour-associated myeloid cell states[22,154,155]. With respect to HGSC metastasis, in mouse studies, neutrophils facilitate the formation of premetastatic omental niches by expanding immunosuppressive innate-like B cells that, in turn, recruit regulatory T cells[30,155]. Immune-modulating mechanisms that support progression from precursor STIC lesions to invasive cancer have been described, including persistent interferon signalling and changes in the T cell repertoire[66].

Despite extensive evidence that treatment-naive HGSC tumours are immunologically active, ICIs and other immunotherapies applied in the first line and recurrent setting have shown limited efficacy. This may be due to the relatively low tumour mutational burden of HGSC, which, combined with prevalent major histocompatibility complex (MHC) allelic loss, results in a low number of clonal neoantigens[22,155,157]. HGSC also exhibits very high copy number variation and whole-genome duplication[158], the latter of which has been associated with diminished expression of genes encoding proteins involved in immune pathways such as stimulator of interferon genes (STING) and MHC class II[159]. In a study of long-term survivors of HGSC, the prognostic benefit of pre-treatment TIL-T and TIL-B levels was most evident in tumours with a 'differentiated' molecular phenotype[147], which is characterized by a more stable genome and reduced sub-clonality[160]. Specific mutations may establish an immunological set point in HGSC, with HRD tumours generally showing stronger immune and/or inflammatory features and spatial immune surveillance[89]. In contrast, tumours bearing foldback inversions tend to have an immunosuppressed phenotype[22,89,146,155]. Mutational landscape notwithstanding, patients with HGSC often present with a mixture of immunologically 'hot' and 'cold' tumour sites[21,157], which presents a major challenge to personalized immunotherapy approaches. Oncogenic signalling pathways can also influence antitumour immunity; for example, out of 21 solid cancers in The Cancer Genome Atlas, HGSC ranks third for expression of *MYCN*, the protein product of which suppresses tumour-intrinsic immune signalling, including DNA-sensing and RNA-sensing pathways[161,162]. Activated PI3K–AKT signalling via PTEN loss, detectable in up to 59% of HGSCs, is associated with the presence of suppressive $HMOX1^+$ resident macrophages in both mouse models and HGSC biopsy samples[163]. Ovarian cancer cell-encoded immune mediators can further drive immune recognition or exclusion. In a mouse model, IL-4 production by cancer cells promoted differentiation of suppressive myeloid cells in the HGSC TME[164]; however, the prevalence of this mechanism in human HGSC remains to be determined.

Other features that may make HGSC less sensitive to immunotherapy include exceptionally potent regulatory T cells as compared to melanoma[165], fewer and less mature TLS and associated stem-like

$CD8^+$ TIL-Ts as compared to lung cancer[150], and the immunosuppressive nature of malignant ascites, which induces endoplasmic reticulum stress-mediated immune suppression of αβ T cells via lipid signalling[166–168].

While most of our understanding of the TME in HGSC comes from untreated tumours, several studies have shown that standard chemotherapy enhances immune infiltrates. However, TIL-T patterns post-NACT are not associated with improved prognosis[97,98,169], raising questions about their functional properties. Indeed, NACT was recently shown to promote $CD8^+$ T cell exhaustion via T cell–myeloid interactions involving the TIGIT–NECTIN2 pathway[23] and to limit priming of T cell responses via upregulation of stabilin 1 on tumour-associated macrophages[136], both of which represent potential therapeutic targets on myeloid cells in the TME. Furthermore, TREM2 blockade restored leukocyte infiltration and delayed recurrence after chemotherapy in *BRCA1*-wild-type models, highlighting the potential therapeutic advantage of reprogramming rather than deleting suppressive myeloid populations[155]. This study also suggests that cyclooxygenase (COX)–prostaglandin E_2 (PGE_2) signalling drives immune dysfunction in *BRCA1*-mutant tumours following chemotherapy or PARP inhibition, providing a rationale for combining PARPi with prostanoid-pathway modulators[155]. Finally, immune escape appears to be common in end-stage disease, where there is a dramatic increase in immunologically cold tumours associated with CCL5 promoter hypermethylation, MHC loss of heterozygosity, and lower expression of MHC class II transactivator (CIITA)[106,170]. The chemokine CCL5 is a major mediator of lymphocyte infiltration, and its hypermethylation, leading to its downregulation, could explain the immunologically cold nature of these tumours[106,170].

Despite having a relatively low single-nucleotide variant-derived neoantigen load, HGSC may have a wider antigenic landscape than previously thought. For instance, a higher number of neoantigens were predicted to originate from alternative splicing events than single-nucleotide variants in breast and ovarian cancer[171]. Moreover, with the advent of in situ T cell receptor (TCR) and B cell receptor (BCR) sequencing paired to spatial gene expression data[172], researchers can now visualize the locations of individual TIL-T and TIL-B clones in relation to tumour cells and to each other. This may help distinguish tumour-reactive clones from bystanders based on their intratumoural versus stromal location and could enable the identification of T cell–B cell pairs that functionally interact through recognition of shared antigens.

Recent proteogenomic studies on primary and metastatic HGSC samples have identified MHC class I-associated peptides derived from non-coding transcripts, including pseudogenes, long non-coding RNAs and antisense RNAs[173,174]. These cryptic peptides outnumber TAAs and neoantigens and are often overexpressed in tumours and shared across patients, making them attractive targets for personalized cancer vaccines. Chimeric transcripts containing expressed segments of transposable elements may also represent potential TAAs in ovarian cancer[175]. There is encouraging precedent for personalized vaccine approaches in HGSC[176], and clinical-grade proteogenomic workflows have been developed[177]. Such strategies are further enabled by advances in circulating tumour DNA (ctDNA) profiling, which allows continuous tracking of tumour evolution[178,179].

Meeting insights and recommendations

Although HGSC is generally unresponsive to single-agent ICIs[180], neoadjuvant anti-PD1 combined with chemotherapy can enhance $CD8^+$ T cell infiltration and may have therapeutic benefit[181]. In contrast with a number of trials showing limited benefit from immune-checkpoint inhibition in HGSC, the phase III KEYNOTE-B96/ENGOT-ov65 trial (NCT05116189) showed that combining anti-PD1 to weekly paclitaxel (with or without bevacizumab) improved progression-free survival (PFS) for patients with platinum-resistant ovarian cancer[182]. Moreover, dual immune-checkpoint inhibition with CTLA4 and PD1 antibodies showed an improved response rate[183] but this trial was not sufficiently positive to alter clinical care. Such findings suggest that targeting more than just the PD1 pathway, for instance, with the recently developed anti-VEGFA–anti-PD1 bispecific antibody, may be efficacious in HGSC[184]. Likewise, combination therapies targeting two or more of the immune checkpoints with VEGF or PARP pathways are under clinical evaluation[185]. Notably, however, it remains difficult to predict the outcome of combination therapies; for example, results published in abstract form from the phase III ATHENA trial[17] (NCT03522246) suggested that the combination of anti-PD1 and PARPi was associated with shorter PFS than PARPi alone. With hundreds of immunotherapies in clinical development, complex human tumour models that include immune effector cells and immunosuppressive elements of the human TME are needed that allow rapid functional evaluation of individual drugs, gene-engineered cell constructs and combinations[130,131,133].

In other cancer types, TIL-Bs and TLS are predictive of response to ICIs, suggesting that enhancing this immune axis in HGSC through vaccination may prove effective for sensitizing tumours to ICIs. Moreover, the antibodies made by TIL-Bs could themselves have therapeutic potential, as demonstrated in mouse models of HGSC[151]. However, on a cautionary note, studies to date have shown that TIL-Bs primarily recognize self-antigens, which brings with it the risk of autoimmune toxicities that needs to be carefully considered[186]. Moreover, while there has been limited characterization of the antigens recognized by tumour-associated antibodies in HGSC to date, a considerable proportion appear to be intracellularly located (B.H.N. and D.D.B. unpublished observations).

The use of gene-engineered cells, including chimeric antigen receptor (CAR) T cells and TCR T cells, is feasible in HGSC, with some responses reported[180]. HGSC has several attractive cell surface antigens for CAR-T cell therapy, and efforts are under way to identify new targets by studying TIL-B responses. Non-conventional immune cell types, including γδ T cells and natural killer cells, are being evaluated owing to their innate tumour recognition mechanisms, which may help combat intra-tumour heterogeneity[187,188].

Metabolic states associated with HGSC can shape immune responses. Disturbances in glucose and lipid metabolism, NAD^+ availability, amino acid and metal deprivation, and production of immunoregulatory metabolites all result in T cell anergy[125,168,189,190]. Therefore, an increased understanding of the metabolomic profile of HGSC offers opportunities for novel forms of immune modulation[191,192].

The assembly of international cohorts and tissue samples from rare but exceptional immunotherapy responders, followed by advanced multi-dimensional immune profiling, could uncover the key determinants of treatment success versus failure in this malignancy (Box 3). Likewise, systematic longitudinal tissue collection before and after treatment in clinical trials should be prioritized to decipher how tumour and immune clonal dynamics are affected by ICIs and VEGF and PARP inhibitors.

Single-cell RNA and TCR sequencing of matched non-cancerous Fallopian tubes and tumour metastases demonstrated a significant overlap between their clonotypes. These results provide a plausible

Box 3 | Exceptional responders in ovarian cancer

Exceptional responders are patients who exhibit unusual responses to treatment such as particularly prolonged survival that exceeds the expected outcomes for their cancer type and treatment. Understanding the biological mechanisms underlying clinical outliers may point to new therapeutic approaches with broader application. Exceptional patients with ovarian cancer may include long-term survivors (10+ years from diagnosis), multiple responders (≥3 complete responses to the same drug), durable responders (long progression-free interval), or rapid or hyper-progressors[219]. Multiple tumour and patient features have been linked to durable treatment response and/or long-term survival, including:

- The extent of tumour mutational burden, genomic scarring and DNA repair deficiency[146,220,268,269].
- Active immune responses, including the presence of tumour-infiltrating T cells, B cells, macrophages and natural killer cells at diagnosis[147,270–272].
- Loss of the RB1 tumour suppressor and/or increased proliferation of cancer cells[219,273,274].
- Reduced pro-tumorigenic signalling and fibroblasts in the tumour microenvironment[275].
- Healthy lifestyle factors such as not smoking and regular green tea consumption[276,277].

rationale for personalized adjuvant vaccines following surgery for established disease[193].

Therefore, although current immunotherapies appear to have limited efficacy in HGSC, a number of novel approaches are suggested by current experimental data from preclinical models and patient samples. These emerging concepts are summarized in Fig. 2.

Acquired resistance to current treatments

Context and challenges

The length of remission following first-line therapy is primarily determined by the extent of surgical debulking and the sensitivity of the tumour to platinum-based chemotherapy, which in turn is a function of its homologous recombination status. One in five patients experiences disease progression less than 6 months after completing first-line treatment, displaying intrinsic resistance to chemotherapy[194]. A more common pattern is an initial response to chemotherapy followed by the development of treatment resistance over a period of months to several years following successive lines of therapy. Known resistance mechanisms (Fig. 3) to platinum chemotherapy and PARPi overlap.

Tumour cell and TME phenotypes at relapse remain poorly characterized as most samples are obtained at diagnosis or after NACT, thereby hampering the exploration of tumour adaptation and resistance. Impediments to the collection of research samples late in a patient's journey include the fact that surgery and/or biopsy at recurrence is not standard of care, the time required for biopsies may lead to treatment delays, and biopsy samples are typically small, likely with clinical priorities for their use. To understand mechanisms of resistance to new therapies, sequential collection of tissue samples from patients on clinical trials is probably the best opportunity to obtain prospective cohorts that allow summation of resistance mechanisms arising over the course of multiple therapies. However, such an approach is only possible in well-resourced centres with highly motivated patients and clinicians, or where secondary debulking is performed[10].

Multi-site tumour sampling has revealed distinct tumour evolutionary patterns[195] and spatial and temporal tumour heterogeneity within patients, even for HRD testing[157,196,197]. These genomic assays are typically performed on one tumour site and, for example, may fail to reflect a functional homologous recombination status[198]. Genomic changes that mark restoration of homologous recombination status and that could be easily used as biomarkers only occur in a minority of patients, and they are typically subclonal[170,199]. Mutations in genes impairing homologous recombination activity result in genomic damage or scars and thus provide a biomarker of homologous recombination deficiency[196]. However, these are not dynamic biomarkers and therefore cannot be relied on to ascertain homologous recombination status on relapse.

With the advent of HRD testing as part of standard care in many countries, a new challenge is the management of patients with a 'positive' HRD test performed ON primary tissue who nevertheless progress early on maintenance PARPi. While some of these cases will be because current HRD testing methods typically use a binary threshold for what is a continuous numeric variable, sampling confounders and inconsistencies associated with undynamic genomic scaring that do not truly reflect the functional homologous recombination status of the tumour add to the imprecision[200–203].

Meeting insights and recommendations

Understanding how tumours evolve to drug-resistant states remains a critical question. High-resolution proteomic and metabolomic approaches that address cell state and properties of the ECM should provide insight in combination with ex vivo functional experiments[195]. Spatial studies that map individual tumour clones and the associated microenvironment might also identify cooperative interactions fostering acquired resistance[204]. Such spatial analyses are augmented by rapid autopsy studies that enable sampling from distinct metastatic locations[170,205]. However, autopsy programmes, involving consent of terminally ill patients, are ethically and logistically complex and, to our knowledge, few HGSC programmes exist worldwide[206]. Leveraging artificial intelligence for the identification of biomarkers may facilitate early prediction of resistance and optimize patient selection for clinical trials by analysing otherwise inscrutable biological patterns[207,208] but requires large standardized, multimodal datasets. It appears that sufficient genomic characterization has been completed using relapse and autopsy samples to identify the most common DNA-level alterations associated with conventional therapy[170,199,205]. Alterations, for example, *BRCA1*, *BRCA2* and *BRIP1* reversion mutations, *TP53BP1* (encoding p53-binding protein 1) loss and *MRE11* amplification, are largely subclonal and, when present, occur in only some of the metastatic sites. The almost complete absence of recurring, clonal driver-acquired resistance mutations suggests that yet-to-be-defined non-genetic changes in cell state, including stemness, dormancy, quiescence and subsequent reactivation, may be especially important. Quiescent or dormant cells can be inherently resistant to therapy and secrete paracrine factors that increase the therapeutic resistance of surrounding cancer cells[209]. By definition, some cancer cells must withstand therapy to cause relapse. Evidence from other tumour types suggests that these persistent cells provide the necessary pool of cells to develop diverse mechanisms of drug resistance[210]. Of particular interest in the HGSC setting is the phenotype of non-reverted tumour cells in metastatic sites where subclonal *BRCA1* or *BRCA2* reversions have been detected.

Reversion mutations, most likely mediated by the microhomology end-joining pathway, are the most-studied genetic mechanism of resistance in *BRCA1*/*BRCA2*-mutated tumours[211]. However, the sub-clonality of reversion mutations and other genetic resistance mechanisms poses a major challenge for both understanding resistance and effective targeting. Indeed, it is unclear whether and to what extent targeting any individual mechanism of resistance will be clinically beneficial.

Currently, molecular assessment of specific mechanisms of resistance is not part of the routine clinical management of patients with HGSC. Dynamic biomarkers of homologous recombination status obtained from biopsies or liquid biopsies (for example, ctDNA) might be used to guide second-line treatments, moving beyond the simple dichotomy of platinum-sensitive versus platinum-resistant relapse, for example, by making use of functional markers of homologous recombination status such as phospho-replication protein A (RPA2)[212].

Conventionally used DNA-damaging agents, such as carboplatin, may promote resistance by generating enrichment for ovarian cancer stem-like cells[213] in the residual viable tumour; therefore, research should explore non-genotoxic strategies to target and eliminate cancer cells. Targeting vulnerabilities that exploit a common abnormality in cancer cells, such as whole-genome doubling[214,215], while sparing normal cells, is a focus of ongoing research in HGSC. Epigenetic-modifying drugs show potential pre-clinically[216,217] but clinical efficacy and toxicity remain hurdles[218]. Lastly, studying exceptional responders may reveal

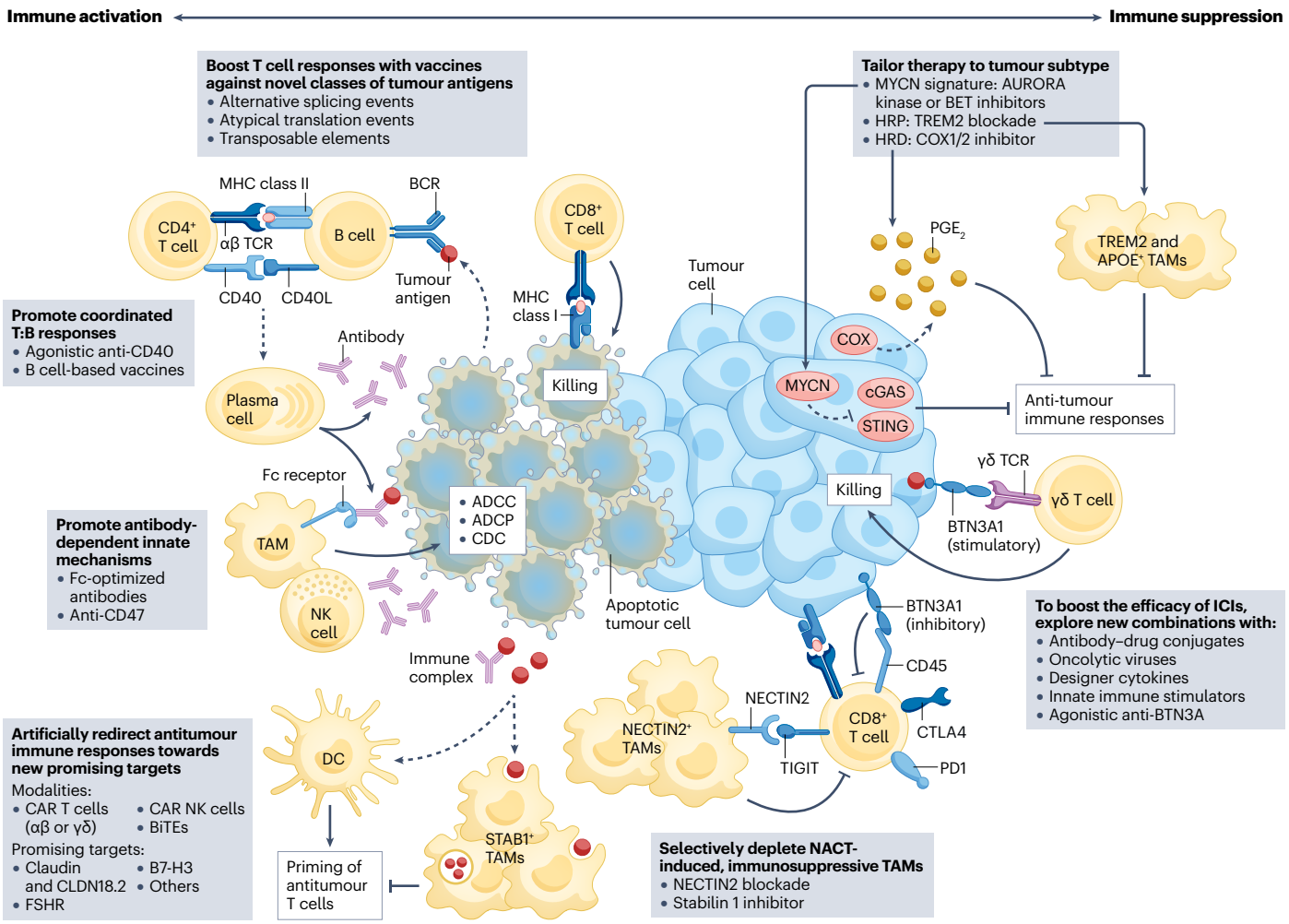

Fig. 2 | Emerging immunotherapy concepts in HGSC. Schematic summary of new therapeutic ideas arising from recent insights into the positive and negative features of the tumour–immune interface in high-grade serous carcinoma (HGSC). To ensure clinical success, all these emerging immunotherapy approaches should be evaluated first with in vitro models and then with more complex in vivo models that recapitulate key features of HGSC. ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; APOE, apolipoprotein E; BCR, B cell receptor; BET, bromodomain and extraterminal; BiTEs, bispecific T cell engagers; CAR, chimeric antigen receptor; CDC, complement-dependent cytotoxicity; CLDN, claudin; COX, cyclooxygenase; DC, dendritic cell; FSHR, follicle-stimulating hormone receptor; HRD, homologous recombination-deficient; HRP, homologous recombination-proficient; ICIs, immune-checkpoint inhibitors; MHC, major histocompatibility complex; NACT, neoadjuvant chemotherapy; NK, natural killer; PGE_2, prostaglandin E_2; STING, stimulator of interferon genes; TAM, tumour-associated macrophage; TCR, T cell receptor; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; TREM2, triggering receptor expressed on myeloid cells 2.

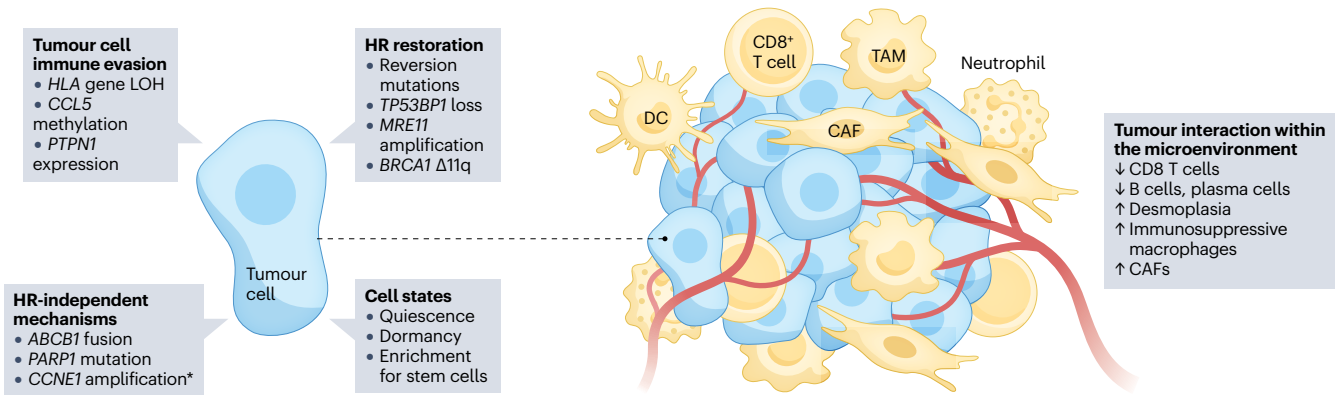

Fig. 3 | Acquired resistance mechanisms in high-grade serous carcinoma. High-grade serous carcinoma can acquire resistance to therapy through a variety of tumour cell-autonomous changes, including restoration of DNA repair, such as intra-genic mutations that restore the reading frame of *BRCA1*-mutated and *BRCA2*-mutated genes, upregulation of hypomorphic *BRCA1* alleles, or increased chemotherapy efflux through over-expression of the ABCB1 (also known as P-glycoprotein 1) transporter. However, DNA mutations seem to explain only a minority of resistance changes, and it appears that non-genetic alterations, such as enhanced stem-like and dormancy properties, may be important. Non-autonomous changes to the tumour microenvironment include enhanced stromal deposition that reduces drug perfusion. Coincident with acquired resistance, increased immune evasion and depletion of immune effectors accompany progressive disease. *Note that, although *CCNE1* amplification may be acquired, it is principally associated with primary resistance. Δ11q, Δ11q alternative splice isoform; CAF, cancer-associated fibroblast; DC, dendritic cell; HR, homologous recombination; LOH, loss of heterozygosity; TAM, tumour-associated macrophage.

important factors that may be therapeutically harnessed to prevent relapse or promote long-term survival[146,219,220] (Box 3).

New therapeutic approaches

Context and challenges

Broadly, therapy for HGSC following initial diagnosis comprises debulking surgery and adjuvant carboplatin and paclitaxel, and this has remained mostly unchanged for over 30 years. An important modification of this regime involves the timing of surgery, which has shifted in many centres to favour NACT before interval debulking surgery over primary debulking surgery (PDS) and subsequent adjuvant chemotherapy. While the use of NACT is associated with lower morbidity, there remains debate about whether overall survival is impacted by surgical timing, and guidelines continue to recommend PDS if complete surgical excision can be achieved[221,222]. The performance status of an individual patient can influence the choice of NACT versus PDS and can therefore act as a confounder in evaluating overall survival in patients receiving these options. Thus, current trials randomize patients for NACT versus PDS with a maximal surgical approach to better understand whether timing of surgery may affect overall survival[223].

Precision medicine approaches. Overall, precision medicine approaches are much less developed in HGSC compared to other cancer types. The relatively high response rates to first-line therapy[224,225], complex structural variants in HGSC and lack of actionable mutations present challenges for improvement on existing therapy[205].

Although there is a high rate of initial response, this poorly predicts long-term disease control, and the factors that trigger recurrence after an initial complete response are not understood. Maintenance therapy with PARPi following first-line treatment has provided improved outcomes but the highest benefit is limited to patients with *BRCA1*/*BRCA2* mutations[7,226]. Maintenance therapy with bevacizumab produces only modest improvements in PFS[101] in the overall population but demonstrates greater benefit in patients at high risk, defined as having stage 4 disease or those with residual disease in the ICON7 trial, including a significant improvement in overall survival[101]. The lack of first-line curative treatments for most patients and effective second-line treatments is reflected in limited improvement in long-term survival. Despite extensive research to understand and overcome acquired resistance to current treatments, the complex adaptive mechanisms in HGSC are yet to be fully deciphered (see previous section).

Currently, the largest area of drug development in HGSC centres around the use of antibody–drug conjugates (ADCs). Targeting folate receptor-α (FRα) with the use of an ADC (mirvetuximab soravtansine) has shown benefit in patients with recurrent disease with high FRα expression in a large phase III trial[227] and novel agents possessing distinct characteristics are currently under development[228]. ADCs may substantially increase the therapeutic index for the linked therapeutic warhead, typically a cytotoxic agent, and hold potential for therapies targeting stromal and immune components[229]. However, the degree to which ADCs increase the therapeutic window in patients should be carefully evaluated given that most ADC molecules are catabolized in healthy cells, contributing to substantial off-tumour toxicity[230]. Further research is needed to understand their biodistribution and pharmacodynamics[231]. Besides ADCs, the development of small-molecule therapy has focused on targeting the DNA damage response pathway and cell cycle-checkpoint pathways[232,233].

Meeting insights and recommendations

Novel targeted agents. DNA damage response inhibitors, including inhibitors targeting ATR, checkpoint kinase 1 (CHK1) or CHK2, ATM and ATR, and WEE1 and PKMYT1, are currently being evaluated in clinical trials, although toxicity seen in the early trials of WEE1 inhibitors has been a major barrier[234]. Epigenetic therapies that evoke viral mimicry also offer potential new therapeutic approaches[235,236]. Currently, there

are many ADCs in development against a range of targets for HGSC, including those targeting claudin 6, TROP2, HER2, cadherin 6, B7H4 or mesothelin[237], and some have reached clinical trials. Most ADCs are not associated with a predictive biomarker, and the molecular and clinical contexts in which these therapies are most effective are undefined. ADCs also carry the potential for side-effects, which present a considerable challenge for trial designs that aim to add ADCs to, or serve as maintenance following, conventional therapy[227].

Other promising therapeutic targets include the cell cycle regulator cyclin E1, encoded by *CCNE1*, which is amplified in approximately 30% of the HRP subgroup[238,239]. Cyclin E1 is also overexpressed in tumours without amplification; however, these tumours appear to be biologically distinct from the amplified group[240]. Clinical trials in the *CCNE1*-amplified HGSC subgroup include the use of recently developed, more selective cyclin-dependent kinase 2 (CDK2) inhibitors as well as the targeting of synthetic lethality associated with inhibition of PKMYT1 or WEE1 (refs. 234,238,239,241).

DNA Polθ[242], CDK12 and CDK13 (ref. 243), and RNA-binding motif protein 39 (RBM39)[244] show promise as therapeutic targets, especially against HRD tumours and those with acquired PARPi resistance. Targeting these proteins will likely benefit only specific subsets of patients with HGSC, and stratifying patients with HGSC based on molecular features can present challenges for trial accrual. However, recent studies in patients with *CCNE1*-amplified tumours showed that such trials can nevertheless meet accrual targets in an acceptable time in tertiary centres[234]. Finally, a recent phase III study showed that modulating the cortisol pathway can benefit some patients, underscoring the necessity of elucidating the mechanisms involved[245].

Glossary

Ascites
An abnormal accumulation of fluid in the peritoneal cavity due to malignancy or portal hypertension.

Bariatric surgery
A surgical operation on the stomach and/or intestines to achieve weight loss.

Cholecystectomy
Surgical removal of the gallbladder.

Cytoreductive surgery
Surgical removal of macroscopic tumour material either following initial diagnosis (primary debulking surgery) or after several cycles of chemotherapy (interval debulking surgery).

Desmoplasia
Formation of dense, fibrous connective tissue around a tumour, produced by cancer-associated fibroblasts that can contribute to cancer stiffness and resistance to therapy.

Endoplasmic reticulum stress
Occurs when the endoplasmic reticulum cannot properly fold proteins, leading to the accumulation of misfolded or unfolded proteins in the endoplasmic reticulum.

Foldback inversions
Large, inverted DNA duplications, common in high-grade serous carcinoma genomes, especially those with amplification of the *CCNE1* gene encoding cyclin E1.

Haploinsufficiency
Where a single allele of a gene is not enough for the normal function of the gene product.

Homologous recombination
A DNA repair process that fixes double-strand breaks by copying information from an intact homologous DNA sequence.

Hyperthermic intraperitoneal chemotherapy
The direct application into the peritoneal space of chemotherapy that has been warmed, typically to 41–43 °C, for 30 to 90 min. This is generally given after interval debulking surgery.

Hysterectomy
Surgical removal of the uterus.

Maintenance treatment
Treatment given after an initial response to prevent or delay tumour recurrence or progression.

Microhomology end-joining pathway
An imprecise mechanism of DNA repair in which short homologous sequences flanking a double-stranded break are used during the repair process, resulting in deletions flanking the break.

Microsatellite instability
A type of genomic instability where insertion or deletion mutations accumulate because DNA mismatch repair is defective.

Omentum
Fat-containing apron-like visceral peritoneal structure overlying abdominal organs that is a frequent site of metastasis in high-grade serous carcinoma.

Oophorectomy
Surgical removal of the ovaries as part of debulking surgery for newly diagnosed patients or for risk reduction in individuals with increased genetic risk of high-grade serous carcinoma.

Oxidative stress
Occurs when production of reactive oxygen species exceeds the capacity of antioxidants, leading to damage in the cell.

Platinum-sensitive versus platinum-resistant relapse
The length of remission following the last use of carboplatin provides a measure of platinum response, with greater than 6 months from the end of chemotherapy being regarded as the most common threshold for a tumour to be regarded as platinum sensitive.

Replication stress
Occurs when DNA replication forks are disrupted, leading to incomplete or faulty DNA replication.

Retrotransposon elements
Mobile genetic elements that can move within the genome through an RNA intermediate.

Salpingo-oophorectomy
Removal of both the Fallopian tubes (salpingectomy) and ovaries.

Synthetic lethality
Occurs when inactivation of two genes together is lethal but inactivation of one gene is not. This principle is exploited in poly(ADP-ribose) polymerase (PARP) inhibitor treatment of patients with *BRCA1* or *BRCA2* mutations.

Tertiary lymphoid structures
(TLS). Ectopic immune cell aggregates within the tumour whose lymphocytic and vascular structure resembles that of germinal centres of lymph nodes and spleen.

Viral mimicry
Cellular responses, typically elicited by exogenous RNA or DNA, that resemble the changes associated with viral infection.

Window-of-opportunity studies
Short clinical trials with pathological and/or molecular read-outs, carried out in a short 'window' before commencing standard treatment. May provide a cost-effective stepping-stone before longer, more expensive therapeutic trials.

Box 4 | Priorities for reducing incidence and improving outcomes in HGSC

Prevention, initiation and early detection

- Monitor data on salpingectomy and high-grade serous carcinoma (HGSC) incidence.
- Identify the earliest driver events in serous tubal intraepithelial carcinoma lesions.
- Develop insights into the ubiquity of *TP53* mutation.
- Understand the impact of menopause, ageing and microenvironment on initiation.
- Unravel secretory cell vulnerability to *BRCA1* or *BRCA2* mutations.
- Develop novel technologies and biomarkers for early detection.
- Ensure equitable access to high-risk and medium-risk mutation screening.

Tumour ecosystem

- Integrate spatial proteomics, including cytokine measurements, and DNA analytics to interpret cell–cell associations and clonal mapping.
- Improve multi-cellular in vitro human cell and mouse models of the tumour microenvironment to allow faster testing of small molecules, antibodies, and cell therapies and combinations.
- Increase research on non-immune components of the tumour microenvironment.
- Explore interactions between cells and the extracellular matrix.
- Increase understanding of the metabolomic profile.

Immunity and immunotherapy

- Investigate combinations of immune-checkpoint therapies with existing treatments.
- Characterize antigens recognized by tumour-associated antibodies.
- Further develop gene-engineered immune cells.
- Establish models that allow rapid functional evaluation of novel immunotherapies.
- Investigate therapies that target myeloid cells.
- Understand the metabolomic profile of HGSC and its influence on immune response.
- Exploit the latest information on exceptional responders.

Acquired resistance to current therapies

- Prioritize sequential sampling of tissue during clinical trials.
- Explore non-genetic mechanisms of quiescence, dormancy or desmoplasia.
- Use high-resolution proteomic and metabolomic approaches to define cell state and extracellular matrix properties.
- In patients with BRCA1 or BRCA2 germline mutations, where the tumour has undergone subclonal BRCA reversion mutations, determine the homologous recombination status and resistance mechanisms of non-reverted tumour cells.
- Target vulnerabilities associated with whole-genome doubling.

New therapeutic approaches and future trial design

- Develop therapies targeting homologous recombination-proficient tumours.
- Conduct window-of-opportunity studies with biomarkers and/or pathological surrogates of long-term outcome in patients with platinum-sensitive relapse.
- Address barriers to access to patient samples from industry-sponsored studies to allow translational research.
- Basket trial designs to allow sub-setting of patients based on molecular features.

The influence of social and ethnic disparities underpins all these themes.

Clinical considerations. There is a need to revisit clinical and molecular concepts of platinum sensitivity and resistance, particularly in recurrent disease settings[246]. The arbitrary cut-off of 6 months for platinum sensitivity needs to be redefined in the precision oncology era[247] as discussed in current international guidelines[248]. As most patients respond well to first-line treatments but still relapse, there may be substantial value in focusing on how best to detect, quantify and molecularly assess minimal residual disease to treat patients earlier in disease progression. Minimal residual disease can be identified as biochemically detected relapse as observed by an increase in CA125 levels or, as newer data suggest, positive ctDNA, but how the latter is defined in HGSC is currently being assessed[249].

Considerable limitations persist in determining the optimal dose and schedule for existing agents as well as the potential for biomarker-directed treatment optimization in HGSC. For example, the efficacy of drug combinations is rarely truly synergistic[250], they require careful balancing of toxicities, and it is unclear which patients actually benefit from the carboplatin–paclitaxel combination. Approximately 50% of HGSCs are HRP, and typically, such tumours are relatively resistant to platinum[196]. Consequently, early identification of patients who are resistant or refractory to platinum could enable the use of non-platinum or targeted combination therapies for these patients. However, many patients present in an acutely unwell state at diagnosis, necessitating immediate treatment and limiting the implementation of biomarker-driven trial designs in the first-line setting.

Maintenance therapy with associated side-effects may be less acceptable to patients who have no visible evidence of disease. Future efforts should be centred on translational research to enable optimal patient selection and interrogate the sequencing of treatment with the potential impact of subsequent therapy. A remaining question is determining the optimal duration of maintenance therapy, particularly for patients who achieve sustained disease control, to minimize unnecessary treatment exposure and associated toxicity. For example, this remains an unresolved issue, years later, for some patients who were enrolled on the early trials of PARPi where the trial protocol specified continuation until progression[251]. New tools for disease monitoring, such as cfDNA, should be evaluated. As ADC use in HGSC gains approval by regulatory agencies and enters wider use, it will become important to understand the mechanisms of ADC resistance, which are highly likely to emerge.

Clinical trial design. Early treatment in patients in whom an increase in CA125 was detected had no impact on overall survival compared with treatment that commenced upon radiological or clinical progression[252]. Therefore, early biochemical relapse may provide

a window to investigate novel treatment options without delaying subsequent treatment with conventional therapy. Patients with HGSC who have responded to a carboplatin-containing regime for 6 months or more without detectable disease recurrence are considered platinum sensitive. After this time, rising CA125 levels, positive ctDNA or measurable disease detected by imaging may occur. Targeted therapies that attenuate a rising biomarker or show pathological changes in pre-treatment and post-treatment biopsies of measurable and biopsy-accessible tumours may provide surrogates of a longer-term clinical response. The initial phase of such trials would typically take a few months, after which patients would transition to carboplatin-based care or continue on the experimental therapy if a substantial pathological response was observed. This approach is attractive as outcome data, albeit using surrogate markers, are obtained relatively rapidly compared to a trial where long-term disease control is studied. An additional logistic advantage of the platinum-sensitive relapse period is that there should have been sufficient time to perform molecular tests with initial diagnostic samples that could pre-stratify patients for trial inclusion. By contrast, patients with platinum-resistant disease are more likely to be entered directly into a therapeutic trial as re-treatment with carboplatin-based therapy is usually not considered, and overall response rates to other chemotherapies are generally less than 27%[253].

Access to patient samples from industry-sponsored trials remains a considerable barrier to biomarker discovery. For example, in the decades since the introduction of anti-VEGF treatment, there remains a poor understanding of the precise mechanisms of action, development of acquired resistance, and which patient populations would benefit most from treatment. Prioritizing access to clinical trial samples for collaborative research and inclusion of translational objectives as fundamental components in trials will facilitate better identification of biomarkers that are crucial for implementing precision oncology in HGSC. The increasing use of NACT for the primary treatment of ovarian cancer should be exploited to perform window-of-opportunity studies and procure biospecimens prior to and after treatment to better understand tumour response to therapy.

Currently, commercial trials aim for therapies applicable to a wide patient population, but this approach may not be compatible with the genomic and clinical heterogeneity observed in HGSC. Biomarker-focused, molecularly stratified trials, while providing insights into tumour biology, adaptive responses and the value of patient stratification, also represent a challenge to recruitment and evaluation of outcomes due to small sample sizes, highlighting the need for international collaboration. In some circumstances, a small sample size may be partially countered by the use of basket trials that span more than one cancer type but share common molecular features. Investigator-led trials that prioritize biological discovery should remain an important focus for consumers, clinicians and researchers rather than relying on large-scale, one-size-fits-all strategies[234]. Future trial designs should answer questions about treatment scheduling, agent synergy, and the interplay between cancer cells and the TME. This will help improve our understanding of HGSC and, ultimately, drive the development of more effective therapies.

The future of HGSC treatment lies in moving away from the universal application of platinum-based chemotherapy towards more personalized therapeutic approaches, underpinned by comprehensive tumour and TME analysis and multi-dimensional trial designs. The integration of advanced technologies and tumour profiling into clinical trial strategies will be essential to overcoming the current challenges in patient stratification and improving outcomes for patients with HGSC.

Conclusion

Several aspects of HGSC biology combine to hinder rapid improvements in outcome. These include the potential for rapid dissemination from tiny STIC lesions to widespread invasion of the peritoneal cavity, where there is ample room for asymptomatic growth, chromosomal instability as a driver of oncogenesis rather than dominant targetable point mutations, extreme tumour heterogeneity, and a highly dynamic TME. Despite these challenges, advances have been made in the area of risk reduction through a detailed understanding of genetic drivers, demonstrated benefit of PARPi when the right patient subgroup is treated soon after diagnosis, and ever-growing evidence that the endogenous immune response can promote long-term survival. A summary of our recommended areas of research focus is provided in Box 4. Critical consideration of what has and has not worked and integrating that knowledge into future research directions and innovative clinical trial design are essential if substantial progress is to be made. Addressing disparities apparent in low-income and regionally remote communities will be important for women to access timely diagnosis, referral to specialist surgical intervention, genetic risk assessment, and current and new advances in HGSC detection and treatment.

Supplementary Information

HHMT24 Patient Video - GEORGIE Session 2 Early Detection
HHMT24 Patient Video - SBBA Session 3 Tumour Microenvironment
HHMT24 Patient Video - ANNE Session 4 Immunity
HHMT24 Patient Video - LILIANA Session 5 Resistance
HHMT24 Patient Video - LISA Session 6 New Therapeutic Approaches

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Author contributions

All authors researched data for the article, wrote the article, contributed to discussion of the content, and reviewed and/or edited the manuscript.

Competing interests

J.D.B. is a shareholder in Tailor Bio. A.A.A. is a founder, director, and consultant for Singular Bio Ltd. S.H.L.G. receives research grants from Pfizer, Advenchen, and GSK. K.O. is a co-founder of Tactiva Therapeutics. D.Z. reports institutional grants from Merck, Genentech, AstraZeneca, Xencor, Zymeworks, and Synthekine; personal fees from AstraZeneca, Xencor, Memgen, Daichi Sankyo, Gilead, Synthekine, Immunos, Hervolution, Accurius, Replimune, and Calidi Biotherapeutics; and holds a patent on the use of oncolytic Newcastle Disease Virus for cancer therapy. K.B.C. reports consulting fees from ROME Therapeutics and Daiichi Sankyo, and has a sponsored research agreement with Enara Bio. J.R.C.-G. receives consulting fees from Alloy Therapeutics and licensing fees from Anixa Biosciences; holds intellectual property with Anixa Biosciences and Compass Therapeutics; and is co-founder of Cellepus Therapeutics, a CAR gamma/delta T cell company. E.L. receives research funding from AbbVie through the University of Chicago to study ovarian cancer. D.D.L. has received research grants from Hoffmann-La Roche AG and 10xGenomics. S.A. receives clinical trial funding from AstraZeneca. F.R.B. receives an honorarium from GSK and research funding from AstraZeneca. D.D.B. has received research grant funding from Hoffmann-La Roche and Astra Zeneca. C.M.L., N.B., O.L.S., D.W.G., W.R.G., A.M.N., M.S.R., Z.K., R.Z., J.S.L., I.M., R.R., P.D.P.P., C.A.I., C.F., R.J.B., I.L.-G., D.P.C., S.L., R.D., K.P.N., S.P., B.H.N., A.F., K.F., and B.G.N. all declare no competing interests.

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