https://doi.org/10.1038/s44294-024-00010-6

Enhancing precision oncology in high-grade serous carcinoma: the emerging role of antibody-based therapies

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High-grade serous ovarian carcinoma is an aggressive and heterogeneous disease with a poor prognosis, and it is often diagnosed at an advanced stage. Genetic information on DNA repair is increasingly used in diagnosis, risk assessment, and treatment selection and will ostensibly translate to an overall survival benefit—at least for certain subgroups of patients. In this commentary, we outline the promise and challenges of precision oncology and discuss how the prospects depend not only on genomic data but also on deep-tissue immune profiling. The technological breakthroughs in antibody-based therapies have paved the way for the introduction of new therapeutics.

High-grade serous ovarian carcinoma (HGSOC) is the most common and most lethal form of ovarian cancer (OC). Molecularly, HGSOC tumors are characterized by chromosomal instability, extensive copy number alterations, and marked inter- and intra-patient genomic heterogeneity. HGSOC cancer cells do not encounter anatomical barriers as they detach from the site of origin (i.e., the fallopian tube) and spread via the peritoneal fluid to sites within the peritoneal cavity, a process called transcoelomic dissemination[1]. This creates a unique intra-abdominal environment comprising the primary tumor, peritoneal implants, omental metastasis, and ascitic fluid. The reciprocal interplay between cancer cells and the tumor microenvironment (TME) is a prerequisite for tumor growth, tumor progression, and response to therapy. The tumor genotypes seem to shape the TME, while spatial cell–cell interactions determine the CD8+ T cell phenotypes[2]. Variations between primary tumors depend on genomic signatures, while the immune resistance patterns that evolve during metastasis are influenced by the location of the secondary sites[2].

Since 1999, when the foundation document for precision medicine was published, the term precision oncology has been used to substantiate the importance of genomic information for risk assessment, diagnosis, and treatment selection in cancer[3]. Increasingly, more genomic tests are being conducted in clinical practice to identify targetable alterations. In 2012, the antitumor activity of poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors in OC patients with *BRCA1/BRCA2* mutations was demonstrated[4], and the introduction of testing for homologous recombination deficiency (HRD) has made HGSOC an example for how genomic data can be used in treatment selection. As more molecular profiling data from trials involving PARP inhibitors become available, better-individualized treatment strategies might be the result[5]. Attempts to inhibit kinases of DNA damage responses, such as ATR, WEE1, and CHK1, have shown to sensitize cancer cells to chemotherapy and PARP inhibitor both in vitro[6,7] and clinically (the CAPRI trial[8]). Small molecules like eprenetapopt (APR-246) have been identified to restore the function of mutant p53, which is present in more than 90% of HGSOC. To our knowledge, the effects have so far only been evaluated in the Phase I/II PiSARRO trial[9]. The proposed categorization of HGSOC into whole-genome duplication and HRD tumors will further increase the complexity and potentially lead to the identification of new therapeutic targets.

The molecular understanding of tumor biology has advanced over decades of scientific research and technical innovation. The prospect of precision oncology depends not only on genomic data in a static map but also on a biological, real-time understanding of spatial resolution and interrogation of cell–cell interactions to deliver the right treatment to the right patient at the right dose and at the right time. Spatial omics and multiplexed imaging are needed to explore cancer subclones and/or molecular biomarkers within their native spatial contexts[2,10,11]. The tumor profiler observational clinical study (TuPro) integrates e.g. a multiomics and functional approach to generate a high-resolution map to provide treatment recommendations based on tumor heterogeneity, tumor microenvironment interaction, and overexpression of tumor-specific biomarkers to support clinical decision-making and improve personalized treatment for metastatic OC[11,12]. To integrate these advanced molecular profiling tools, experts from different disciplines must be involved and technologies that incorporate clinically interpretable unsupervised analysis tools, standardized structured reporting, and validation must be available[13].

An effective anticancer response is often impaired by an immunosuppressive TME. Immune checkpoint inhibitors (ICIs) have been exploited to enhance immune response in heavily pretreated OC patients[14]. Thus far, no αPD-L1 (pembrolizumab, avelumab, and atezolizumab), αPD-1 (nivolumab), or αCTLA-4 (ipilimumab) antibodies evaluated as monotherapy in OC clinical trials have shown persuasive overall response rates[15]. The introduction of new biomarkers such as transcriptomic signatures, including TGF-ß score[16], and drug signature databases[17], the integration of next-generation ICIs (e.g., αCSF1R, αCCR2, αCD73, and αTIM3)[18], as well as the combination of ICI with PARP inhibitor and αVEGF (MEDIOLA trial[19]) could modify the existing treatment strategies.

In-depth characterization of the HGSOC tumor biology, including the identification and categorization of the various cell types within the heterogenous TME, might reveal better suitable biomarker[20]. Based on the tissue profiling, tumors can be categorized into immune inflamed, immune excluded, and immune desert tumor immune phenotypes[21]. These tumor immune phenotypes represent a key challenge in broadening the response to ICI therapy. While immune-inflamed tumors may benefit from targeting

exhausted cytotoxic T cells with ICIs, immune-excluded tumors, which are characterized by an activated TGF-β signaling pathway and resistance to ICIs, may profit from agents that stimulate immune infiltration[22,23]. Immune desert tumors exhibit a lack of antitumor response owing to the absence of neoantigen presentation due to either an absence of dendritic cells or an immunosuppressive environment[23]. The administration of growth factors such as FLT3L and GM-CSF may increase the infiltration of dendritic cells into the tumor and have thus been explored in immunotherapy to increase the neoantigen load and infiltration by dendritic cells[24].

To optimize treatment precision for HGSOC patients, it is essential to secure approval of more tailored drugs. Due to their ability to discriminate cancer cells from normal tissues, monoclonal antibodies can be used as the backbone for the design of diagnostic assays and therapeutics. The recent technological breakthroughs in antibody engineering have enabled the generation of antibody-drug conjugates (ADCs), fluorescence tracers for fluorescence image-guided surgery (FIGS), chimeric antigen receptors (CARs), and bi-specific T cell engagers (BiTEs).

FRα is expressed in 60% of OC and 80% of HGSOC tumor cells. Two antibody-based drugs directed against this antigen have been approved by the FDA. The first FDA approval came in 2021 after the Study 6 trial (NCT03180307) had shown that targeting FRα with a fluorescently labeled antibody, pafolacianine (Cytalux, On Target Laboratories, LCC) resulted in enhanced real-time detection of FRα positive cancerous lesions during cytoreductive surgery[25], while the ADC mirvetuximab soravtansine-gynx (Elahere, ImmunoGen, Inc) was approved based on promising data from the SORAYA study in 2022[26]. The ADC field is expanding and new targets for HGSOC have been identified (like TROP-2, mesothelin, and Her2) and are tested in ongoing trials[27]. Approximately 35 clinical studies on OC have explored chimeric antigen receptor (CAR) T cell therapies directed against mesothelin, Tag72, and Her2/ErbB2. Preclinical and clinical investigations have demonstrated the efficacy of CAR T cells in reducing tumor growth, underscoring their therapeutic potential[28]. Nonetheless, the observed challenge of severe toxicity—attributed partly to missing tumor-specific antigens in OC, which leads to off-target effects—must be improved before clinical implications can be determined. Notably, there is currently no FDA-approved CAR therapy for solid tumors, primarily because of limited CAR T cell persistence, antigen evasion, and low tissue penetration due to physical and chemical barriers; however, this can be remedied through improvements to the CAR design, such as dual targeting together with anti-VEGF scFv and the administration of multiple doses[29].

Last, therapies targeting myeloid cells in the OC microenvironment are attracting interest[30]. Macrophages represent the major immune population in most solid tumors in humans. In OC, tumor-associated macrophages (TAMs) account for over 50% of all cells in peritoneal tumors and ascites[31]. Since the early metastatic microenvironment is rich in myeloid and stromal cells, reprogramming or depleting TAMs into immune-activating and pro-tumorigenic cells offers a unique therapeutic window. FDA-approved targets for re-educating macrophages include CD40, CD47, SIRPα, CSF1R (AZD7507), CCR2-CXCR4 (plerixafor, and MEDI3185)[32], and PI3Kγ[33] (Eganelisib, and AZD3458)[34]. Targeting activated macrophages in the TME may also reverse resistance to PARP inhibitors and chemotherapy[35]. In addition, CD11 agonists have been shown to repolarize macrophages and increase the recruitment of conventional dendritic cells (cDCs) and T cells. If targeting immunosuppressive myeloid cells is successful, this could additionally improve the potential of ICIs and other antibody-based interventions, such as CAR T and BiTEs, and thus broaden the choice of treatment for each patient at diagnosis and recurrence.

Conclusion

Precision oncology in HGSOC holds immense promise, primarily leveraging genomic characteristics to tailor therapeutic approaches. However, a comprehensive understanding of the disease requires acknowledgment of tumor biology, including cell–cell interaction in the TME at the time of treatment. While genomic data provide valuable insights into the molecular alterations driving tumorigenesis, real-time biological assessments of dynamic cellular interactions are equally critical. Approved antibody-based drug designs, such as ADCs and fluorescence tracers targeting FRα, have paved the way, with ongoing investigations exploring promising new targets. The remaining challenge is integrating inter- and intratumor heterogeneity into the treatment regime. To overcome tumor cell heterogeneity, we need to combine the optimal therapies at the most favorable time for each patient, as monotherapy will not result in the desired outcome. The combination of αVEGF and CAR T cell therapy, αCSF1 in combination with anti-IL-1 and CAR T, has shown promise in other solid cancers. Incorporating technologies that capture the dynamic interplay between tumor cells, immune cells, and the surrounding stroma becomes imperative to adapt to patients' needs and ultimately achieve an effective precision oncology strategy with a combinatorial approach. Future studies will reveal how ADCs can be combined with traditional and/or new innovative drugs. The introduction of excessive characterization is both resource-intensive and expensive, and as usage increases, a multidisciplinary decision-making approach is required. Hopefully, the different ongoing drug rediscovery initiatives that redefine approved drug use beyond their labels to patients with potentially actionable variants and profiles will represent a move forward, especially when real-time information about cell–cell interactions are included.

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Received: 10 November 2023; Accepted: 14 February 2024;
Published online: 01 March 2024

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Acknowledgements
The work is supported with grants from Helse Vest RHF (project number F-12183/4800003665) and the Research Council of Norway through its Centers of Excellence funding scheme (project number 223250).

Author contributions
K.K. and L.B. formulated the concept and design of the commentary and wrote the manuscript. Both authors reviewed and approved the revised version of the manuscript.

Funding
Open access funding provided by University of Bergen.

Competing interests
The authors declare no competing interests.

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