Gynecologic Oncology Reports 54 (2024) 101450

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Review article

Targeted therapy in high grade serous ovarian Cancer: A literature review

Kaitlyn Dinkins [a], Wade Barton [a], Lauren Wheeler [b], Haller J. Smith [a], Karthikeyan Mythreye [c], Rebecca C. Arend [a,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL
[b] Lister Hill Library, University of Alabama at Birmingham, Birmingham, AL
[c] Department of Pathology, O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL

A B S T R A C T

Ovarian cancer continues to have a high mortality rate despite therapeutic advances. Traditionally, treatment has focused on surgery followed by systemic platinum-based chemotherapy. Unfortunately, most patients develop resistance to platinum agents, highlighting the need for targeted therapies. PARP inhibitors and anti-angiogenic agents, such as bevacizumab, have more recently changed upfront therapy. Unfortunately, other targeted therapies including immunotherapy have not seen the same success. Emerging therapeutic targets and modalities such as small molecule tyrosine kinase inhibitors, lipid metabolism targeting agents, gene therapy, ribosome targeted drugs as well as several other therapeutic classes have been and are currently under investigation. In this review, we discuss targeted therapies in high grade serous ovarian cancer from preclinical studies to phase III clinical trials.

1. Introduction

In 2024 it is estimated that there will be 19,680 new cases of ovarian cancer diagnosed in the United States with 12,740 estimated deaths (Siegel et al., 2024). While the overall incidence of ovarian cancer has been decreasing by 1–2 % per year, the morbidity and mortality associated with advanced disease remains constant. The standard treatment of ovarian cancer combines surgical resection of disease and platinum-based chemotherapy (Bachmann, 2023; Havasi, 2023). Despite 80 % of patients being initially platinum-sensitive, the duration of response is usually short-lived, with a majority developing platinum resistance and recurrent disease (Bachmann, 2023; Havasi, 2023). Once deemed platinum resistant, further treatment options are plagued by limited efficacy and harsh side-effect profiles (Bachmann, 2023; Havasi, 2023; McMullen et al., 2021). The high relapse rate and inferior treatment options greatly underscore the need to identify safe and effective treatments in patients with advanced ovarian cancer.

Epithelial ovarian cancer is comprised of multiple, histological subtypes. High grade serous ovarian cancer (HGSOC) is the most common, making up 70 % of cases (Bachmann, 2023; Havasi, 2023). In the last decade, great advances have been made in understanding the genetics and molecular biology of high grade serous ovarian cancer, ushering in the introduction of novel targeted therapies. Genetic and epigenetic changes combined with increasing genetic heterogeneity in advanced disease are thought to drive the stymie in development of a universal treatment (Bachmann, 2023; Havasi, 2023; [1]). These new and developing therapies facilitate a shift in ovarian cancer management from empirical cytotoxic therapies to individualized approaches targeted against specific pathological features of each patient's tumor that aid in tumor growth and metastasis. In this review, we summarize the current understanding of targeted therapies, including poly-ADP ribose polymerase inhibitors (PARPi), angiogenesis inhibitors, immunotherapy, tyrosine kinase directed therapy, lipid and ribosomal targeting agents, serine/threonine kinase therapies, folate receptor alpha, and other smaller drug classes, in high grade serous ovarian cancer.

2. Methods

This review's search strategy and data abstraction were performed using the PRISMA flow diagram (Moher, 2009). Eligible articles were identified by searching the PubMed database via PubMed.gov from 1946 to present and Embase via embase.com from 1947 to present. The keywords "high-grade-serous" AND "ovarian neoplasms" or "ovarian cancer" and "molecular targeted therapy" were used in single-line searches. For PubMed, this was done in the "Advanced" search area. In Embase, this performed in the "Results" tab. All studies written in English that included these keywords were eligible. After our search, 82 articles were identified and 78 remained eligible after de-duplication. Eleven articles were removed as they did not reference high grade serous pathology (4 clear cell, 5 low grade serous, 1 mucinous, 1 all non-

* Corresponding author at: 1824 6th Avenue South, WTI 430J, Birmingham, AL 35294.
E-mail address: rarend@uabmc.edu (R.C. Arend).

https://doi.org/10.1016/j.gore.2024.101450
Received 17 May 2024; Received in revised form 27 June 2024; Accepted 27 June 2024
Available online 6 July 2024

serous). Eighteen articles were removed as they did not discuss targeted therapies, and three full text articles could not be retrieved. 46 total articles were eligible for inclusion in this review (Fig. 1). In accordance with the journal's guidelines, our data will be available for independent analysis for reproducibility or additional data analysis.

3. Results

3.1. PARP inhibitors

3.1.1. Background

PARPi are crucial in preventing DNA repair. PARP enzymes typically repair single-strand DNA breaks. PARP-1 repairs DNA via the base excision repair pathway. It also modifies proteins in the homologous recombination (HR) pathway and recognizes replication fork disruptions. PARP-1–3 all provide negative feedback to the non-homologous end joining pathway (Darwish, 2023). Inhibition of single-strand break repair causes the accumulation of double-strand DNA breaks. In tumors that are HR deficient (HRD), double-strand DNA breaks are unable to be repaired, ultimately leading to cell death. In HGSOC, about 50 % of tumors have mutations in the HR pathway largely due to Breast Cancer gene 1/2 (BRCA1/2) mutations. However, alterations in other genes, including ATM, ATR CHEK1/2, PALB2 and RAD51, can also lead to HRD (Bachmann, 2023; Darwish, 2023; Chiappa, 2021; Della Corte, 2021; Govindarajan, 2020; Cancer, 2024).

There have been several clinical trials that have solidified the role of PARPi, including olaparib, niraparib and rucaparib, as maintenance therapy in ovarian cancer depending on HR status. These agents have also been studied as treatment for patients with recurrent ovarian cancer; however, due to concerns regarding potential long-term overall survival (OS) detriment, the treatment approvals were ultimately withdrawn and no PARPi is currently approved as treatment for recurrent ovarian cancer (Moher, 2009; Chiappa, 2021; Della Corte, 2021; Cancer, 2024; Asif, 2024).

3.1.2. Olaparib

Study-19 was the first to evaluate olaparib as maintenance therapy in recurrent, platinum-sensitive HGSOC. In this trial, there was a progression free survival (PFS) and OS benefit in the overall population with the largest benefit seen in the BRCA1/2 mutant group (Darwish, 2023; Della Corte, 2021; Ledermann, 2012). Subsequently, the SOLO trials further investigated the role of olaparib as maintenance therapy in both the primary (SOLO-1) and recurrent (SOLO-2) setting in patients with germline or somatic BRCA1/2 mutations. SOLO-1 established olaparib as maintenance therapy in the upfront setting, demonstrating a superior PFS compared to placebo (Darwish, 2023; Chiappa, 2021; Della Corte, 2021; Govindarajan, 2020; Cancer, 2024; Moore, 2018). While not statistically significant, there was a clinically significant difference in 7-year OS with 67.0 % surviving in the olaparib group vs. 46.5 % in the placebo group ($p = 0.0004$; $p < 0.0001$ required to declare statistical significance). Similarly at 7 years, 45.3 % of patients who received olaparib were alive and had not had additional treatment whereas only 20.6 % of patients who received placebo were alive without subsequent treatment (DiSilvestro, 2023). SOLO-2 showed an improved PFS and OS in the recurrent maintenance setting (Darwish, 2023; Chiappa, 2021; Della Corte, 2021; Cancer, 2024; Pujade-Lauraine, 2017).

3.1.3. Niraparib

While olaparib was evaluated in the germline or somatic BRCA1/2 mutated population, niraparib was evaluated in all patients, regardless of BRCA1/2 or HR status. The ENGOT OV16/NOVA study evaluated niraparib as maintenance therapy in the recurrent setting. The niraparib group had an improved PFS compared to the placebo group, particularly in the germline BRCA1/2 mutant population (Della Corte, 2021; Mirza, 2016).These results were confirmed by the QUADRA study (Della Corte, 2021; Moore, 2019).The PRIMA trial assessed niraparib as maintenance therapy in HGSOC and endometrioid ovarian cancer and noted improved PFS in the overall population, resulting in niraparib being the first PARPi approved for use in the primary setting regardless of HR status (Darwish, 2023; Chiappa, 2021; Govindarajan, 2020; Cancer, 2024; Gonzalez-Martin, 2019).

3.1.4. Rucaparib

Like niraparib, Rucaparib was evaluated in all patients regardless of BRCA1/2 or HR status. In ARIEL-2 and ARIEL-3, rucaparib was analyzed in the recurrent, platinum sensitive setting and demonstrated improved PFS, specifically in the BRCA1/2 mutant population. The second phase of ARIEL-2 evaluated patients with ≥ 3 prior lines of chemotherapy with the greatest benefit seen in patients with BRCA1/2 mutant, platinum-sensitive disease (Darwish, 2023; Chiappa, 2021; Della Corte, 2021;

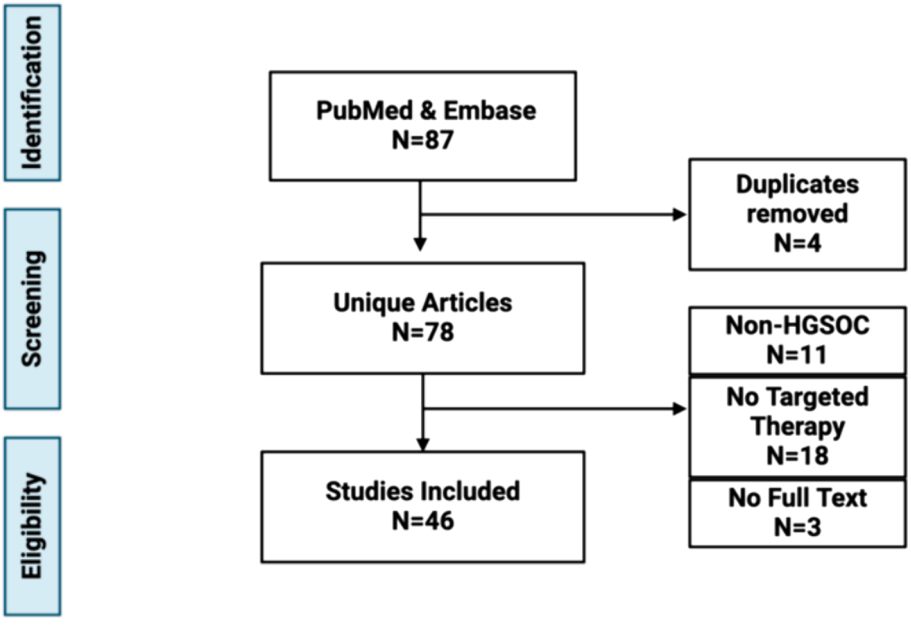

Fig. 1. PRISMA diagram of article selection process.

Coleman, 2017; Swisher, 2017). Currently olaparib and niraparib are approved in the frontline maintenance and recurrent maintenance settings whereas rucaparib is only approved in the recurrent maintenance setting (Cancer, 2024).

3.1.5. Other

Two newer PARPi, veliparib and talazoparib, are also being investigated. The VELIA trial evaluated veliparib in combination with induction chemotherapy followed by maintenance veliparib in the upfront setting in HGSOC for all patients. This trial noted an improved PFS compared to placebo in the BRCA1/2 mutant and HRD populations. Veliparib is not currently approved for use in ovarian cancer (Darwish, 2023; Cancer, 2024; Coleman, 2019). Talazoparib is being evaluated in the recurrent ovarian cancer setting for patients with BRCA1/2 mutations with results pending (Della Corte, 2021).

There have been several trials assessing PARPi in combination with targeted VEGF therapies. In PAOLA-1, olaparib and bevacizumab were investigated as upfront maintenance therapy in patients with advanced HGSOC or endometrioid ovarian cancer regardless of BRCA1/2 status with an improvement in PFS in the overall population with the combination therapy. The largest benefit was seen in the BRCA1/2 mutant population (Darwish, 2023; Chiappa, 2021; Govindarajan, 2020; Cancer, 2024; Ray-Coquard, 2023). CONCERTO and BAROCCO evaluated PARPi with VEGF targeted therapy in patients with recurrent, platinum sensitive disease with CONCERTO demonstrating an ORR (objective response rate) of 15.3 % and BOROCCO with a non-superior PFS compared to standard chemotherapy alone (McMullen et al., 2021; Lee, 2022; Colombo, 2022).

3.1.6. PARPi resistance

Like other therapies, most patients eventually develop resistance to PARPi. These resistance mechanisms, largely evaluated in the preclinical setting, include increased drug efflux, decrease in PARP trapping, reactivation of HR via BRCA1/2 reversion mutations or other mechanisms, stabilization of replication forks, and others. There have been several trials evaluating PARPi in combination with other therapies such as chemotherapy, anti-angiogenic agents, and immune check point inhibitors in both the upfront and recurrent settings in order to improve response to PARPi and prevent resistance, which are reviewed here (Chiappa, 2021).

CCAAT/enhancer-binding protein B (C/EBPB), a transcription factor, has been shown to be associated with PARPi sensitivity in both in vitro and in vivo models. PARPi exposure increased C/EBPB expression causing upregulation of several HR genes such as BRCA1, BRIP1, BRIT1 and RAD51, ultimately leading to PARPi resistance. C/EBPB may serve as a marker for PARPi resistance, but also as a future therapeutic target in HRP HGSOC (Tan, 2021).

3.2. Angiogenesis inhibitors

3.2.1. Background

Tumor growth and metastasis is dependent on angiogenesis (Bachmann, 2023). Common angiogenic proteins include vascular endothelial growth factor (VEGF), Interleukin-8 (IL-8), and basic fibroblast growth factor (bFGF) (Romero and Bast, 2012). In ovarian cancer, increased VEGF expression is associated with poor prognosis and disease progression (Bachmann, 2023). Angiogenic factors that serve the endothelial cells of tumor vessels represent potential therapeutic targets. Several inhibitors of these angiogenic proteins or their receptors such as bevacizumab and aflibercept (VEGF), AMG386 (angiopoetins), imatinib (platelet derived growth factor (PDGF)), pazopanib (PDGF and vascular endothelial growth factor receptor (VEGFR)) and sorafenib, sunitinib and BIBF1120 (VEGFR) have been studied (Romero and Bast, 2012).

3.2.2. Bevacizumab

GOG-0218 and ICON 7 evaluated the role of bevacizumab, a monoclonal antibody that targets VEGF, in the upfront setting. GOG-0218 demonstrated an improved PFS in patients who received carboplatin/paclitaxel/bevacizumab with bevacizumab maintenance compared to patients who only carboplatin/paclitaxel. (Govindarajan, 2020; Cancer, 2024; Banerjee and Kaye, 2013; Burger, 2011). Similarly, in ICON 7, patients who received carboplatin/paclitaxel/bevacizumab with bevacizumab maintenance had a small PFS benefit compared to those who received carboplatin/paclitaxel alone. However, in patients with stage IV disease or a suboptimal debulking, there was an OS benefit (Govindarajan, 2020; Cancer, 2024; Banerjee and Kaye, 2013; Nwani, 2018; Mittempergher, 2016; Perren, 2011).

In the recurrent setting, bevacizumab has been shown to improve progression free survival in combination with cytotoxic chemotherapy. This is thought to be due to its anti-angiogenic effect, change in tumor vasculature, reduction in ascites, synergy with cytotoxic chemotherapy agents and delay in treatment resistance. (Bachmann, 2023; McMullen et al., 2021; Cancer, 2024). In both OCEANS and GOG-213, patients with platinum sensitive recurrence who received bevacizumab with cytotoxic chemotherapy had an improved outcomes compared to cytotoxic chemotherapy alone. OCEANS demonstrated an improved PFS while GOG-213 showed an OS benefit (Banerjee and Kaye, 2013; Nwani, 2018; Mittempergher, 2016; Coleman, 2017). AURELIA studied patients with platinum resistant recurrent disease and showed an improved PFS with investigator's choice single agent chemotherapy with bevacizumab compared to single-agent chemotherapy alone (Banerjee and Kaye, 2013; Nwani, 2018; Mittempergher, 2016; Pujade-Lauraine, 2014).

3.2.3. Other

Similarly, in a phase I trial, apatanib, a VEFGR2 inhibitor, demonstrated a modest short-term benefit in recurrent, platinum resistant ovarian cancer (Bachmann, 2023; McMullen et al., 2021; Banerjee and Kaye, 2013). Pazopanib, a PDGF and VEGFR inhibitor, has demonstrated improved PFS as maintenance therapy in platinum sensitive patients in clinical trials (Govindarajan, 2020; Cancer, 2024; Nwani, 2018). Trebananib (AMG386), a tyrosine kinase inhibitor targeting the angiopoetin-Tie2 complex, has been combined with pembrolizumab, a monoclonal antibody that inhibits programmed death protein 1(PD-1), in a phase I trial of advanced platinum-resistant ovarian cancer with results still pending (Bachmann, 2023; Banerjee and Kaye, 2013). Sorafenib, a VEGFR and PDGFR inhibitor, in combination with topotecan demonstrated an improved OS and PFS compared to topotecan plus placebo in platinum-resistant ovarian cancer patients (McMullen et al., 2021). Cediranib, a receptor tyrosine kinase inhibitor blocking VEGFR1-3, platelet-derived growth factor α and β and c-kit has also been studied. In a phase II trial, single-agent cediranib was used in persistent/recurrent ovarian cancer following at least one line of platinum-based chemotherapy. Platinum sensitive patients had a 26 % ORR and platinum resistant patients had no complete responses (CR) or partial responses (PR) (Nwani, 2018). Cediranib plus olaparib was assessed in a phase II study with an ORR of 20 % in the platinum resistant group (McMullen et al., 2021).

3.3. Immunotherapy

3.3.1. Background

While immunotherapy has changed the landscape for treatment in many different cancers, it has only shown modest benefit in epithelial ovarian cancer. Immunotherapy can be broken down into three categories: active, passive, and immunomodulatory. Active immunotherapy includes vaccines, chimeric antigen receptor-T cell (CAR-T cell) therapy, and various targeted therapies. Passive immunotherapy promotes immune activity, largely through immune checkpoint inhibitors, which then generates a response to tumor cells. Immunomodulators regulate the immune system through cytokines, agonists, adjuvants, and immune check point inhibitors (Bachmann, 2023). Immune checkpoint inhibitors are the most used immunotherapy in clinical practice in ovarian

cancer, particularly (PD-1/programmed death ligand 1 (PD-L1)) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (Bachmann, 2023; Nwani, 2018).

3.3.2. Monoclonal antibodies

To date, single agent immunotherapy has not shown significant benefit in epithelial ovarian cancer. Keynote-100 evaluated pembrolizumab in the recurrent ovarian cancer setting and demonstrated a modest ORR of 7–10 %, which was improved in patients with higher PD-L1 expression (Bachmann, 2023; McMullen et al., 2021; Matulonis, 2019). Given the limited response with single agent immunotherapy, there has been a shift towards evaluating multi-agent immunotherapy as well as immunotherapy plus other targeted therapy and/or cytotoxic chemotherapy. Ipilimumab (anti-PD-1) in combination with nivolumab (anti-CTLA-4) demonstrated a promising ORR of 34 % (Bachmann, 2023; McMullen et al., 2021). PROMPT, MITO27, and OCTOPUS evaluated anti-PD-1 or anti-PD-L1 in combination with systemic chemotherapy. While PROMPT and MITO-27 results are pending, OCTOPUS showed no significant difference in PFS or OS between combination therapy and chemotherapy alone (McMullen et al., 2021; Banerjee, 2023).

In JAVELIN-200 avelumab, a monoclonal antibody that binds PD-L1, +/- chemotherapy vs. chemotherapy was evaluated in platinum resistant/refractory ovarian cancer with no significant difference in OS or PFS, though this was not stratified by PD-1 status (Bachmann, 2023; McMullen et al., 2021; Pujade-Lauraine, 2021). This trial highlighted the importance of biomarkers in evaluating treatment response.

3.3.3. Combination therapy

In AMBITION; KGOG trial, patients were randomized based on HRD status and PD-L1 status if HRD negative. There was a difference in ORR between groups: 50 % (olaparib and cediranib) and 24.9 % (olaparib and durvalumab) in the HRD group vs. 33.3 % (durvalumab and systemic chemotherapy) and 29.4 % (durvalumab and tremelimumab) in the HRP group in PD-L1 positive and PD-L1 negative patients respectively (Lee, 2020).

Keynote-162 evaluated pembrolizumab in combination with niraparib in patients with recurrent ovarian cancer with an ORR 18 % (Bachmann, 2023; McMullen et al., 2021). Similarly, an intended phase I/II trial, though it was stopped before phase II escalation evaluated tremelimumab (CTLA-4 inhibitor) vs. tremelimumab and olaparib. 20 patients, 10 in each arm, were evaluable for response. In the tremelimumab alone arm, there were three patients with stable disease and in the tremelimumab/ olaparib combination arm one patient had partial response and three patients had stable disease (Bachmann, 2023; Konstantinopoulos, 2019). NINJA looked at nivolumab vs. gemcitabine or chemotherapy, with no difference in OS between groups. These studies highlight the need for further investigation of this combination therapy (Bachmann, 2023; Hamanishi, 2021). There are several active phase I-III trials currently ongoing evaluating immunotherapy in combination with other targeted therapy reviewed here (Bachmann, 2023; McMullen et al., 2021).

3.3.4. Vaccines

Vaccination has also been investigated in platinum-resistant ovarian cancer. Intraperitoneal oncolytic viral immunotherapy (Olvi-Vec) showed a small ORR 9 % in a phase I study and is currently being investigated in a phase III trial. There have been limited clinical studies evaluating dendritic vaccines in ovarian cancer. However, peptide vaccination sensitization has been studied in in vivo ovarian cancer models. Oregovomab, a monoclonal antibody, in combination with standard of care therapy demonstrated an increase in CA125-specific CD8 + T lymphocytes, which has been shown to improve response to peptide vaccinations (Bachmann, 2023).

3.3.5. Fibroblasts

Fibroblast activation protein (FAP) is overexpressed in epithelial ovarian cancer and is associated with immunosuppression, cellular invasion and migration, and an overall poor prognosis. Given this, FAP has been a therapeutic target of interest. However, FAP inhibition has not proved to be successful in clinical trials. In preclinical transgenic mouse models, inhibition of FAP-expression cancer associated fibroblasts decreased tumor growth. Vaccines targeting FAP have been promising in colon cancer and lung cancer likely through promotion of CD8+ +/- CD4 + T-cell response (Nwani, 2018).

3.3.6. Transforming growth factor beta (TGF-β)

TGF-β, a cytokine secreted by tumor cells and fibroblasts, has been shown to contribute to the tumor immune microenvironment. TGF-β targeting therapies have been evaluated in in vivo models, demonstrating a reduction in tumor growth (Roane, 2021). In preclinical studies, TGF-β therapy has shown promise in treatment resistance. The addition of a TGF-β receptor inhibitor to cisplatin prevented tumor growth in cisplatin-resistant xenograft models. Unfortunately, TGF-β inhibitors have not yet been successful in clinical trials as a single agent in clinical studies due to broad expression and toxicity concerns (Nwani, 2018).

3.3.7. Tissue inhibitor of metalloproteinases 1 (TIMP1)

TIMP1 has been shown to regulate TGF-βand promote tumor growth (Albini, 2021). A study of circulating tumor cells using EpCAM-based inmunoisolation followed by RT-q-PCR analysis demonstrated the presence of TIMP1 in high grade serous ovarian cancer patients, suggesting that TIMP1 should be evaluated as a potential therapeutic target (Abreu, 2020).

3.3.8. Ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)

ENPP1 is type II transmembrane glycoprotein that is highly expressed in ovarian cancer and is associated with poor cellular differentiation, later stage at diagnosis and worse outcomes (Chu, 2023). In pre-clinical in vivo models, drug-antibody conjugates (ADCs), IgG-based bispecific T-cell engagers and CAR T-cells, have been developed and demonstrated high affinity and specificity towards human ENPP1. Given that ovarian cancer expresses high levels of ENPP1, these ADCs represent a potential future therapeutic option (Chu, 2023).

3.3.9. Future directions

Given the overall modest success of immunotherapy in ovarian cancer, new targets continue to be sought and investigated. Anti-LYPD1, PAX8 HGSOC tumor antigen, CD3-T-cell-binding specific antibodies cause T cell activation and decrease tumor growth in in vivo models. CD47, a myeloid immune checkpoint, is overexpressed in most epithelial ovarian cancers. A phase I trial evaluating Hu5F9-G4, an anti-CD47 antibody, with avelumab is currently being investigated (Bachmann, 2023).

3.4. Targeting receptor tyrosine kinases

3.4.1. Epidermal growth factor receptor (EGFR)

30–70 % of HGSOC have increased EGFR expression, which is associated with chemoresistance and poor outcomes. The EGFR family consists of epidermal growth factor receptor (EGFR/ErbB1), human epidermal growth factor receptor 2 (HER2/ErbB2) and ErbB3-4 (Skorda and Kinase, 2022). While small-molecule kinase inhibitors targeting EGFR have shown some benefit in other solid tumors, they have not shown benefit in HGSOC to date (Sheng and Liu, 2011).

Other tyrosine kinases such as HER2, may also be overexpressed in ovarian cancer. The literature suggests HER2 has a wide range of positivity in ovarian cancer ranging from 8-66 %. As such, trastuzumab, a monoclonal antibody against HER2, has shown some benefit in ovarian cancer with HER2 overexpression (Tuefferd, 2007).

3.4.2. Fibroblast growth factor receptors (FGFRs)

In addition to VEGF targeted therapies discussed above, FGFRs have also been evaluated as targets of interest. Amplifications or activating mutations in FGFR1-4 have been observed in HGSOC. Several clinical trials are currently ongoing evaluating FGFR TKIs in ovarian cancer patients (Skorda and Kinase, 2022).

3.4.3. Insulin-like growth factor (IGF)

Dysregulation in IGF signaling has been witnessed in HGSOC. Specifically, IGF1/2 and IFGR1/2 signaling is crucial in cell growth regulation, which has led to their investigation as potential targeted therapies. Unfortunately, pre-clinical studies with IGF1R monoclonal antibodies alone or in combination with other treatments did not demonstrate a benefit. There are no current anti-IGF TKIs in development (Skorda and Kinase, 2022).

3.4.4. Phosphatidylinositol 3-Kinase and protein kinase B (PI3K-AKT)

The PI3K-AKT pathway is crucial in anti-apoptotic signaling and is commonly mutated in HGSOC (Skorda and Kinase, 2022; Jacome Sanz, 2021). There are multiple inhibitor classes aimed at targeting this pathway including PI3K inhibitors, AKT inhibitors, and mammalian/mechanistic target of rapamycin (mTOR) inhibitors (Lee, 2020; Skorda and Kinase, 2022; Jacome Sanz, 2021). Several drugs in each of these classes have been approved by the FDA for other malignancies; however, to date, there are none approved for ovarian cancer. Dual PI3K-mTOR inhibitors have not progressed beyond phase I trials due to safety concerns and adverse events (Skorda and Kinase, 2022).

3.4.5. Mitogen-Activated protein kinase extracellular signal Regulated-Kinase (MAPK-ERK)

The MAPK-ERK pathway is involved in cell proliferation, and survival and is mutated in roughly 30 % of HGSOC patients (Skorda and Kinase, 2022; Chesnokov, 2021). In vivo, trametinib, a mitogen activated protein kinase kinase (MEK) inhibitor, decreased tumor growth in HGSOC models (Chesnokov, 2021). In phase I-III clinical trials, MEK inhibitors trametinib and selumetinib failed to show a benefit in HGSOC. P38 MAPK-selective inhibitors have been evaluated in patients with recurrent, platinum-sensitive HGSOC, though only a slight improvement in PFS was observed (Skorda and Kinase, 2022; Vergote, 2020). AXL, a receptor tyrosine kinase, promotes tumor growth, epithelial-mesenchymal transition, and immune evasion through the MAPK-ERK. Bemcentinib, an AXL inhibitor, has been studied in combination with carboplatin/paclitaxel showed to improve tumor response in preclinical models. AXL inhibitors have failed to show benefit in clinical trials thus far (Bartoletti, 2021).

3.4.6. High-mobility group box 3 (HMGB3)

HMGB3 also known as HMG2A or HMG 4 is involved in DNA recombination, repair, and replication as well as acts as a cytokine to regulate immune response. HMGB3 typically has been shown to be overexpressed in HGSOC whereas in normal cells it has low expression. In preclinical studies, HMGB3 was shown to activate MAPK/ERK in ovarian cancer, warranting further investigation (Ma, 2023).

3.4.7. Cyclin-dependent kinases (CDKs)

CDKs regulate cell cycle progression along with cell-cycle checkpoint kinases (CHKs) (Skorda and Kinase, 2022; Gorski et al., 2020). CCNE1, a cell-cycle protein that is commonly amplified in platinum resistant ovarian cancer, and CDK 4/6, have been investigative targets of interest (Mittempergher, 2016; Skorda and Kinase, 2022; Gorski et al., 2020). Several pan-CDK inhibitors with CDK2 targeted activity such as AT7519, AG-024322, CYC065, Roniciclib, TG02 and Milciclib have been assessed in clinical trials. Unfortunately, none have progressed to phase II trials (Gorski et al., 2020). Palbociclib, a CDK4/6 inhibitor (CKD4/6i), has been studied in ovarian cancer patients with multiple lines of prior therapy and demonstrated a median PFS of 3.7 months (Skorda and Kinase, 2022). Combination therapy with ribociclib, a CDK4/6i, with letrozole in estrogen receptor positive (<10 %) endometrial and ovarian cancer patients yielded a 50 % PFS rate at 3 months (Skorda and Kinase, 2022). PHI-101, a selective checkpoint kinase 2 inhibitor, has demonstrated anti-tumor activities in in vitro ovarian cancer models and synergistic activity with PARPi in in vivo ovarian cancer models (Bachmann, 2023). Prexasertib, a CHK1/2 inhibitor, was studied in breast and ovarian cancer models with a 10.0 % PR in BRCA1/2 mutated disease and 30.8 % PR in BRCA wildtype disease (McMullen et al., 2021).

3.4.8. Ataxia telangiectasia and Rad3-related protein kinase

ATR causes phosphorylation of CHK1, ultimately leading to cell cycle arrest. Berzosertib, an ATR inhibitor, was evaluated in combination with gemcitabine in HGSOC platinum resistant patients. This combination therapy showed improved PFS compared to gemcitabine alone (Bartoletti, 2021). Unfortunately, CHK inhibitor use is somewhat limited due to an overall poor safety profile (Skorda and Kinase, 2022). However, mitosis inhibitor protein (Wee1) kinase inhibitor, adavosertib, did improve TP53-mutated HGSOC response to chemotherapy compared to chemotherapy alone with an improved PFS of 4.6 months compared to three months in the control arm (Bachmann, 2023; McMullen et al., 2021; Skorda and Kinase, 2022; Gorski et al., 2020).

3.5. Lipid metabolism

Changes in lipid metabolism have been implicated in ovarian cancer metastasis and poor prognosis. Alterations in the lipid uptake, lipid synthesis, desaturation, and fatty acid oxidation pathways are associated with peritoneal metastasis, stem cell survival, change in the tumor microenvironment, and response to therapy (Zhao et al., 2019). Given this, several new targeted therapies, largely small molecule inhibitors, targeting fatty acid synthesis such as fatty acid synthase, Acetyl CoA Carboxylase, stearoyl-CoA 9-desaturase, sterol regularly element-binding protein 1, CTP1, and ATP citrate lyase are being tested (Zhao et al., 2019; Sawyer, 2020; Huang, 2021). Etomoxir, a fatty acid oxidase inhibitor, has been studied in patient-derived xenograft models and has been shown to decrease tumor progression (Sawyer, 2020). Proprotein convertase subtilisin/kexin type-9 (PCKS9) is a cholesterol regulating enzyme and is key component of ovarian cancer cell survival as it increases AKT phosphorylation, ERK1/2, and MEK1/2 expression. Metabolic and mTOR inhibitors have been studied to target this enzyme in preclinical models, demonstrating that inhibition of PCKS9 may prevent HGSOC cell survival (Jacome Sanz, 2021). Development of these targeted drugs as monotherapy or combination therapy is currently ongoing (Jacome Sanz, 2021; Zhao et al., 2019; Huang, 2021).

Similarly, adipocytes play a key role in ovarian cancer metastasis, particularly to the omentum. Fatty acid binding protein 4 (FABP4) has been identified as a key regulator of lipid response in ovarian cancer cells when cultured with adipocytes. Knockdown of FABP4 caused a downregulation in gene signatures associated with ovarian cancer metastasis and cancer cell survival. In vivo HGSOC models demonstrated decreased metastatic disease in CRISPR-mediated knockout FABP4. A small-molecular FABP4 inhibitor reduced tumor burden in in vivo models as well as increased carboplatin sensitivity in both in vitro and in vivo models (Mukherjee, 2020).

4. Ribosomes

Cancer growth is supported by ribosome biogenesis leading to an increase in protein synthesis. This process is largely supported by enhanced polymerase I (Pol I) transcription. CX-5461 inhibits Pol-1 transcription by preventing the interaction between SL-1 and rDNA promoter. This causes both p53 independent and dependent cell cycle arrest or cell death. This drug has mainly been studied in lymphoma (phase I) and breast cancer (phase I/II) but has therapeutic potential in

HGSOC as upregulation of polymerase I transcription is common in HGSOC (Yan, 2017).

Additionally, PI3K, AKT/mTOR, RAS/MAPK and c-MYC pathways are commonly activated in ovarian cancer. In in vivo Myc-driven lymphoma models, CX-5461 was shown to sensitize fibroblasts to DNA-damaging agents. Given that primary adjuvant treatment for HGSOC involves platinum therapy and PARPi, the combination of CX-5461 with these upfront therapies as well as other targeted drugs, i.e. mTOR inhibitors, could be promising in this space (Yan, 2017).

4.1. miRNA

MiR0506, a miRNA, has been shown to inhibit the epithelial-mesenchymal transition (EMT) by targeting SNAI1, which causes EMT by suppressing E-cadherin. When valuated in orthotopic mouse models, MiR-506 reduced tumor growth when delivered to lipid-based nanoparticles, warranting further investigation (Mittempergher, 2016).

4.2. Serine/Threonine kinases

Protein kinase C (PKC) and protein kinase D (PKD) are serine/threonine kinases that are involved in many signaling cascades involving MAPK, NK-KB, WNT5a and HDAC5/7. Therefore, aberrant activity of PKC/D is heavily involved in tumorigenesis by altering cell proliferation, migration, invasion, and angiogenesis. Many clinical trials have evaluated PKC/D targeting drugs with mixed results. To date, there have not been any phase III trials evaluating these drugs (Tyagi and Roy, 2021).

Calcium/calmodulin dependent protein kinase kinase 2 (CaMKK2) is a serine/threonine kinase that is involved with cell proliferation, survival, and metabolism. In ovarian xenograft models, inhibition of CaMKK2 prevented metastatic spread of primary tumors (Mukherjee, 2023).

Liver kinase B1 (LKB1) and substrate NUAK1 have been shown to impact inflammatory mediation via NF-κB and metastasis through spheroid cell survival in in vivo models. LKB1-NUAK1 loss leads to upregulated NF-κB signaling and reactive oxygen species generation. Dual inhibition should be evaluated as a potential therapy (Buensuceso, 2022).

4.3. Chemodynamic therapy

Chemodynamic therapy is an exciting treatment approach as it has minimal side effects due to its Fenton/Fenton-like reactions. Typically, metal cations are used to break down endogenous hydrogen peroxide, creating toxic radicals and reactive oxygen species (ROS), ultimately inducing apoptosis of cancer cells. Cancer cells have higher levels of hydrogen peroxide compared to normal cells, which spares normal cells. In an ex vivo, pre-clinical ovarian cancer organoid model, bimetallic silver nitroprusside was evaluated and demonstrated both a high level of activity of and low toxicity. These promising results warrant more testing in the pre-clinical space and future clinical evaluation (Asif, 2024).

4.4. Gene therapy

The OVAL study evaluated paclitaxel with ofranergene obadenovec (VB-111), an anti-cancer gene therapy, versus paclitaxel plus placebo in patients with platinum resistant HGSOC. In the interim analysis, there was a 53 % CA-125 response with an assumed VB-111 response of 58 % (Arend, 2021). Unfortunately, there was no difference in PFS or OS in the final analysis (Arend, 2024).

4.5. BET bromodomain protein 4

BET bromodomain protein 4 (BRD4), an epigenetic transcription modulator, is the 4th most amplified gene in HGSOC and is associated with cancer cell growth/survival and poor prognosis. This amplification is associated with an increased expression of MYC, NOTCH3 and NRG1, increasing tumor cell growth, genomic instability, epithelial-mesenchymal transcription, chemoresistance and metastasis (Drumond-Bock and Bieniasz, 2021; Baratta, 2015). Bromodomain inhibitors (BETi) and degraders have shown to halt BRD4 activity in preclinical and clinical settings, leading to decreased tumor growth. When used in combination therapy, BETi has been shown to sensitize ovarian cancer cells to platinum agents. Further investigation is needed to understand the mechanisms of BRD4′s role in ovarian cancer proliferation and BETi as potential targeted therapy (Drumond-Bock and Bieniasz, 2021).

4.6. Tumor protein P53 (P53)

P53 is the most frequently mutated gene in many aggressive cancers such as HGSOC. APR-26, a p53 reactivating compound, plus carboplatin/doxorubicin was evaluated in a phase Ib trial in HGSOC in patients with p53 positive disease. Findings suggested this drug had an acceptable safety profile and ORR 74 %. ReACp53, a peptide blocking amyloid-like aggregation of mutant p53 proteins containing R248Q or R175H, restored p53 wild-type properties. In ovarian cancer in vivo models, ReACp53 caused decreased tumor growth.

4.7. Enzyme inhibition

StarD13 is a Rho GTPase activating protein (GAP) that activates both CDC42 and RhoA and inhibits actin fiber assembly. In preclinical studies, StarD13 was found to inhibit CDC42, preventing cellular invasion and metastasis (Abdellatef, 2022). Ribonucelotide reductase inhibitor 3-aminopyridine-2-carboxyaldehyde-thiosemicarbazone (3-AP) was evaluated in patients with platinum resistant ovarian cancer and found that 3-AP restored platinum sensitivity, though the ORR was only 17 % (Ivy, 2019).

4.8. Folate receptor alpha (Frα)

There are several other targeted drugs that have been developed based on novel biomarker discovery. Frα is expressed in over 80 % of ovarian tumors with low levels of expression in normal cells (Matulonis, 2023). Due to this expression discrepancy, mirvetuximab soravtansine, a Frα-binding antibody, has been investigated as a targeted therapy. SORAYA, a single-arm phase II trial evaluation mirvetuximab in platinum resistant disease, demonstrated an ORR of 32 % (Matulonis, 2023). Similarly, MIRASOL, a randomized control trial in platinum resistant disease, demonstrated improved ORR, PFS and OS in patients who received mirvetuximab vs. cytotoxic chemotherapy (Moore, 2023). Evaluation of mirvetuximab in the upfront setting is currently being investigated in NCT04606914 (Study of Carboplatin, 2024).

5. Conclusion

While traditional therapy in HGSOC has focused on surgery and systemic chemotherapy, the heterogeneous nature of this disease demands a more targeted approach. While there have been several classes of targeted therapy studied, only a small subset has shown a benefit in PFS and OS. In the upfront and platinum sensitive recurrence settings, only olaparib has shown both a PFS and OS benefit, which was demonstrated via SOLO-1 and Study-19 respectively. In platinum resistant disease, mirvetuximab remains the only therapy to demonstrate both a PFS and OS benefit. Key phase III trials evaluating targeted therapy in ovarian cancer are shown in Table 1. Even with the advances made with targeted therapies, the overall five-year survival remains approximately 50 %. Given the molecular diversity of HGSOC, continued efforts to discover novel biomarkers and develop new targeted therapies are imperative.

Table 1
Key Phase III Trials in High Grade Serous Ovarian Cancer.

Study	Patients	Arms	PFS (months)	OS (months)	Author	Year
Upfront Therapy						
SOLO-1	n = 260 vs. n = 131 Stage III/IV, CR or PR to platinum-based chemo, germline or somatic BRCA1/2mt	olaparib vs. placebo maintenance	3 yr: 60 % vs. 27 % (p < 0.001)	7 yr: 67.0 % vs. 46.5 % (p = 0.0004)	Moore et al.	2018
PRIMA	n = 487 vs. n = 246 Stage III/ IV, CR or PR to platinum-based chemo	niraparib vs. placebo maintenance	All: 13.8 vs. 8.2 (p < 0.001) HRD: 21.9 vs. 10.4 (p < 0.001)	24 mos: 84 % vs. 77 % (HR 0.7)	Gonzalez-Martin et al.	2019
VELIA	n = 375 vs. n = 383 vs. n = 382 Stage III/IV	C/T + veliparib + veliparib maintenance vs. C/T + veliparib + placebo maintenance vs. C/T + placebo + placebo maintenance	34.7 vs. 22.0 (p < 0.001) HRD: 31.9 vs. 20.5 (p < 0.001) *results compare veliparib throughout vs. placebo	--	Coleman et al.	2019
PAOLA-1	n = 537 vs. n = 269 Stage III/IV, CR/PR after platinum-based chemo and bevacizumab	olaparib + bevacizumab maintenance vs. placebo + bevacizumab maintenance	22.1 vs. 16.6 (p < 0.001) HRD, BRCA1/2mt: 37.2 vs. 17.7 (HR 0.33) HRD, BRCA1/2 wt: 28.1 vs. 16.6 (HR 0.43)	56.5 vs. 51.6 (p = 0.41)	Ray-Coquard et al.	2019
GOG-0218	n = 623 vs. n = 625 vs. n = 625 Stage III/IV within 12 weeks of primary debulking	C/T + bevacizumab + bevacizumab maintenance vs. C/T + bevacizumab + placebo maintenance vs. C/T + placebo + placebo maintenance	14.1(p < 0.001) vs. 11.2 (p = 0.16) vs. 10.3	39.7 (p = 0.45) vs. 38.7 (p = 0.76) vs. 39.3	Burger et al.	2011
ICON-7	n = 764 vs. n = 764 High risk early stage (I or IIA clear cell, grade 3) or advanced (FIGO IIB to IV)	C/T + bevacizumab + bevacizumab maintenance vs. C/T	24.1 vs. 22.4 (p = 0.04)	45.5 vs. 44.6 (p = 0.85)	Perren et al.	2011
Platinum sensitive recurrence						
Study-19	n = 136 vs. n = 129 ≥2 lines of therapy	olaparib vs. placebo	8.4 vs. 4.8 (p < 0.001)	29.8 vs. 27.8 (p = 0.02)	Ledermann	2012
SOLO-2	n = 196 vs. n = 99 ≥2 lines of therapy	olaparib vs. placebo	19.1 vs. 5.5 (p < 0.0001)	51.7 vs. 38.8 (p=0.05)	Pujade-Lauraine et al.	2017
ENGOT OV16/ NOVA	Stratified by gBRCA1/2 status: gBRCA1/2mt: n = 138 vs. n = 65 gBRCA1/2 wt: n = 234 vs. n = 116 ≥2 lines of therapy	niraparib vs. placebo	HRD, BRCA1/2mt: 21.0 vs. 5.5 HRD, BRCA1/2 wt: 12.9 vs. 3.8 HRP: 6.9 vs. 3.8	HRD, gBRCA1/2mt: 40.9 vs. 38.1 (NS), HRD: 35.6 vs. 41.4 (NS), HRP: 27.9 vs. 27.9 (NS)	Del Campo et al.	2019
ARIEL-3	n = 375 vs. n = 189 ≥2 lines of therapy	rucaparib vs. placebo	All: 10.8 vs. 5.4 (p < 0.0001) HRD, BRCA1/2mt: 16.6 vs. 5.4 (p < 0.0001) HRD, BRCA1/2 wt: 13.6 vs. 5.4 (p < 0.0001)	No significant diffence in OS	Coleman et al.	2017
OCEANS	n = 242 vs. n = 242 First recurrence after frontline chemotherapy with measurable disease	gemcitabine + carboplatin + bevacizumab vs. gemcitabine + carboplatin + placebo	12.4 vs. 8.4 (p < 0.001)	33.6 vs. 32.9 (p = 0.65)	Aghajanian et al.	2012
Platinum resistant recurrence						

(*continued on next page*)

Table 1 (*continued*)

Study	Patients	Arms	PFS (months)	OS (months)	Author	Year
Javelin-200	n = 188 vs. n = 190 vs. n = 188 ≤3 lines of therapy for platinum sensitive disease, no therapy for platinum resistant disease	avelumab + PLD vs. avelumab vs. PLD	3.7 (p = 0.03) vs. 1.9 (p > 0.99) vs. 3.5	15.7 (p = 0.89) vs. 11.8 (p = 0.21) vs. 13.1	Pujade-Lauraine et al.	2021
NINJA	n = 157 vs. n = 159 ≤1 line of therapy after platinum resistance diagnosed	nivolumab vs. chemotherapy	2.0 vs. 3.8 (p = 0.002)	10.1 vs. 12.1 (p = 0.81)	Hamanishi et al.	2021
AURELIA	n = 182 vs. n = 179 <3 lines of therapy	bevacizumab + chemotherapy vs. chemotherapy	6.7 vs. 3.4 (p < 0.001)	16.6 vs. 13.3 (p < 0.174)	Pujade-Lauraine et al.	2014
MIRASOL	n = 227 vs. n = 226 1–3 lines of therapy, high FRα	mirvetuximab vs. chemotherapy	5.62 vs. 3.98 (p < 0.001)	16.46 vs. 12.75 (p = 0.005)	Moore et. al	2023

CRediT authorship contribution statement

Kaitlyn Dinkins: Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization. **Wade Barton:** Writing – original draft. **Lauren Wheeler:** Data curation. **Haller J. Smith:** Writing – review & editing. **Karthikeyan Mythreye:** Writing – review & editing. **Rebecca C. Arend:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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