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REVIEW

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Potential targeted therapies for ovarian cancer beyond PARP inhibitors

Yagmur Sisman[1,2,*], Dan Høgdall[3], Tine Henrichsen Schnack[4], Claus Høgdall[2], Estrid Høgdall[1]

[1]Department of Pathology, Copenhagen University Hospital—Herlev Hospital, 2730 Herlev, Denmark
[2]Department of Gynecology, Copenhagen University Hospital—Rigshospitalet, 2100 Copenhagen, Denmark
[3]Department of Oncology, Copenhagen University Hospital—Herlev Hospital, 2730 Herlev, Denmark
[4]Department of Gynecology, Odense University Hospital, 5000 Odense, Denmark

***Correspondence**
yagmur.sisman@regionh.dk
(Yagmur Sisman)

Abstract

This review aimed to investigate the clinical utility of next-generation sequencing (NGS) in treating high-grade serous ovarian cancer (HGSC) with targeted therapies other than Poly (ADP-ribose) polymerase (PARP) inhibitors. The search was performed in PubMed and Embase. The literature search combined screening the reference sections of relevant studies. A total of 1882 studies were screened, and 6 case reports met the inclusion criteria. The patients were treated with trametinib, crizotinib, alectinib, a protein kinase B (AKT) inhibitor, everolimus-letrozole or trastuzumab-pertuzumab. A partial response was observed in patients (n = 3) treated with trametinib, crizotinib or trastuzumab-pertuzumab. One patient treated with alectinib had a complete response, while the patients (n = 2) treated with AKT inhibitor or everolimus-letrozole had stable disease and progressive disease. The results suggest that NGS may have a role in identifying effective targeted therapies for patients diagnosed with HGSC. Further research, including basket trials, is needed to confirm the results.

Keywords

Ovarian neoplasm; Ovarian epithelial cancer; Genetic testing; Precision medicine; Target therapy

1. Introduction

Ovarian cancer is the fifth most common cause of cancer death in women. It is a highly heterogeneous disease predominantly characterized by epithelial tumors, which can be classified into four main histological subtypes: serous-, endometrioid-, mucinous- and clear cell carcinomas. In some cases, mixed histological features are observed within these tumors. High-grade serous ovarian carcinoma (HGSC) is the most frequent and lethal histological subtype of epithelial ovarian cancers [1–3].

The standard treatment of HGSC includes surgical cytoreduction and platinum-based chemotherapy with the addition of bevacizumab for cases diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IV disease or with residual disease. PARP inhibitors are used as maintenance treatment in patients responding to first-line platinum-based chemotherapy. Despite this multimodal approach, approximately 80% will relapse and die from the disease [4–6]. Therefore, the development of new therapies remains an urgent and unmet need.

HGSC is characterized by significant molecular heterogeneity [7, 8]. The most common genetic and molecular alterations in HGSC include mutations in *TP53*, *Breast Cancer gene 1* (*BRCA1*), *BRCA2*, and homologous recombination deficiency (HRD). Consequently, recent guidelines from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology (NCCN Guidelines®) and European Society for Medical Oncology (ESMO) recommend upfront germline and somatic testing for *BRCA1/2* mutations and HRD in HGSC patients [9, 10]. The clinic routinely uses these changes to select platin sensitive patients for PARP inhibitors [4, 9]. However, there is currently no approved therapy specifically targeting *TP53* mutations [11, 12].

Various studies have identified several other pathogenic mutations in HGSC beyond the commonly recognized ones [7, 8]. This molecular heterogeneity presents considerable challenges for treatment, underscoring the necessity for personalized approaches in managing the disease on individual basis. Comprehensive genomic profiling is essential to identify druggable targets and tailor treatment strategies [13–15]. While this heterogeneity complicates treatment, it also offers opportunities for developing personalized and more effective therapeutic strategies. Understanding the diverse nature of HGSC is crucial for improving patient outcomes, as clinical management remains challenging due to high recurrence rates.

Next-generation sequencing (NGS) addresses these challenges by enabling the sequencing of a high number of nucleotides in a short time frame at an affordable cost. This allows identification of druggable targets within a tumor. By integrating NGS data with clinical information, oncologists can offer personalized treatments tailored to the genetic profile of each patient's tumor. This approach not only enhances the efficacy of the treatment but may also minimizes adverse

effects by avoiding ineffective therapies [13, 15]. Moreover, NGS generates an extensive amount of data by sequencing the cancer genome. This comprehensive information is important for the development of new therapies, as it provides insights into mechanisms driving tumorigenesis and potential therapeutic targets. The data obtained through NGS enable a more nuanced understanding of the disease, enabling innovative treatment strategies. Additionally, NGS plays a critical role in patient stratification for clinical trials. By analyzing genetic profiles, NGS helps identify patients who are most likely to benefit from new treatments. This stratification ensures that clinical trials include appropriate patient populations, enhancing successful outcomes and the development of effective therapies [16, 17]

This review aims to overview whether NGS-based results may support information on targeted therapies other than PARP inhibitors in patients diagnosed with HGSC.

2. Method

The search in PubMed and Embase was performed on 22 April 2023 (Fig. 1). The search criteria were “high grade serous ovarian cancer”, “ovarian cancer”, “tubal cancer”, “fallopian tube cancer”, “peritoneal cancer”, “targeted therapy”, “precision medicine”, “personalized medicine” and “druggable targets”. The literature search combined screening the reference sections of relevant studies, adding one study. Furthermore, Clinicaltrials.gov and the basket trials Targeted Agent and Profiling Utilization Registry Study (TAPUR) and Combo-MATCH were screened [18, 19]. The screening was performed independently by two persons. There was no disagreement about which studies should be included. In total, 1882 studies were screened, and the full text of for-ty-one studies was reviewed. Inclusion criteria were clinical trials, including case reports, in HGSC patients who received targeted therapies with targets identified using NGS. Required reported outcomes were objective response rates, progression-free survival (PFS) or overall survival (OS). Patients who received treatment with

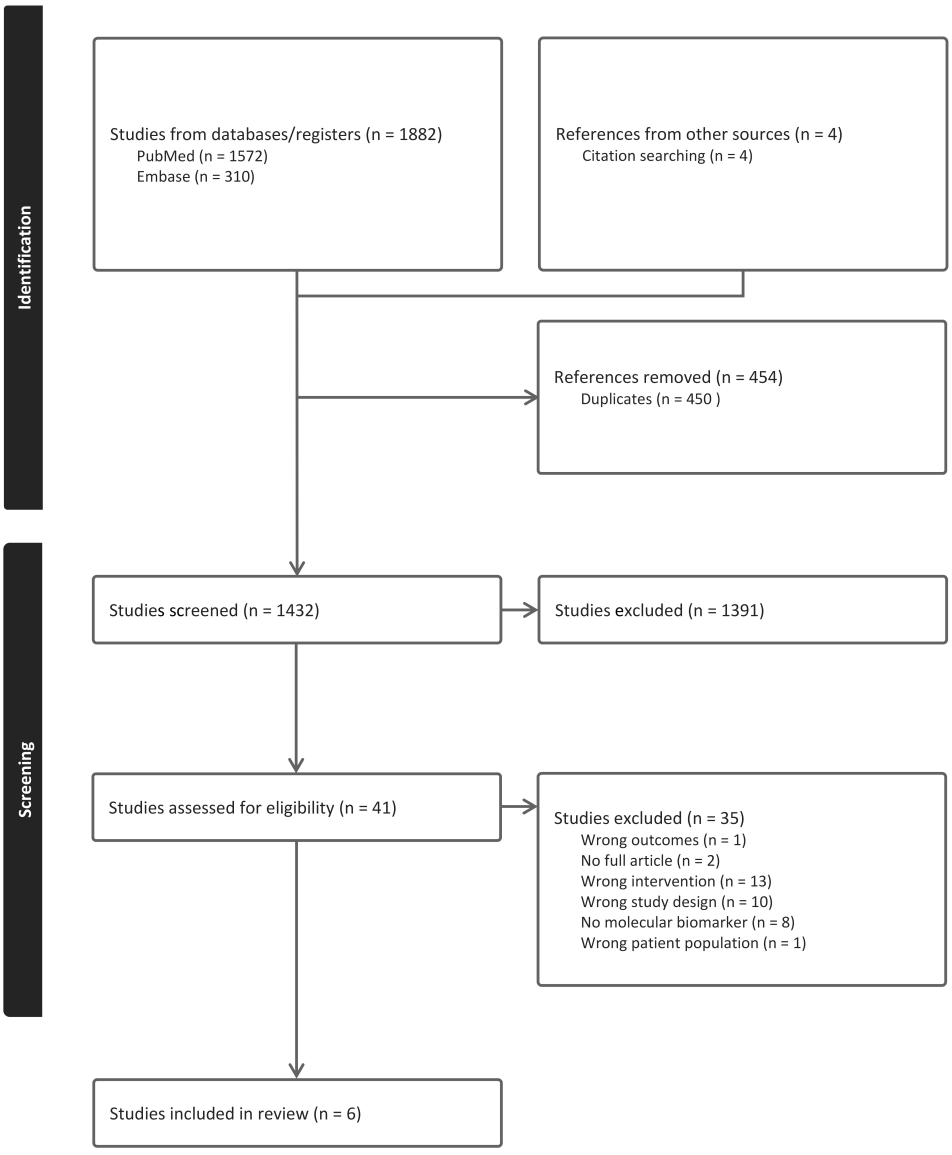

FIGURE 1. Flow diagram of the literature search in PubMed and Embase database performed 22 April 2022.

PARP inhibitors were excluded, except in cases where the patients were heavily pretreated, provided no other targeted therapies were used concurrently with PARP inhibitors. Studies in languages other than English, Danish, Swedish or Norwegian were excluded (Fig. 1). The PRISMA statement for reviews was followed [20].

3. Overview of the publications

A total of six studies were included describing NGS targeted treatment in 6 patients. The cases were treated with trametinib, crizotinib, alectinib, AKT inhibitor, everolimus-letrozole and trastuzumab-pertuzumab. A partial response (PR) was observed in patients treated with trametinib, crizotinib or trastuzumab. The patient treated with alectinib had a complete response (CR). In contrast, the patients treated with AKT inhibitor or everolimus-letrozole had stable (SD) and progressive diseases (PD), respectively.

A case report by Cappuccio *et al*. [21] described a case of a 50-year-old woman who was diagnosed with advanced HGSC (Table 1, Ref. [21–26]). The molecular profiling of the tumor identified a *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) mutation, which indicates a response to mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors such as trametinib [27]. Trametinib acts downstream of *KRAS* to suppress signaling through the mitogen-activated protein kinase (MAPK) cascade and has been approved in combination with dabrafenib for treating *BRAF600E* mutated anaplastic thyroid cancer, non-small cell lung cancer (NSCLC), and melanoma (dailymed.nlm.nih.gov accessed 10 December 2022). The patient was heavily pretreated with chemotherapy, bevacizumab and PARP inhibitors. Oral treatment with trametinib was initiated, and the computerized tomography (CT) scan evaluations after three and six months confirmed PR and SD, according to the Response Evaluation Criteria in Solid Tumors (RECIST), respectively. After eight months of treatment, the patient had disease progression, and trametinib was discontinued.

The case report by Dong *et al*. [22] presented a 69-year-old patient with advanced platin-based treatment refractory HGSC. NGS-based testing of 1021 cancer-related genes was performed, identifying *a golgi-associated PDZ and coiled-coil motif-containing protein gene with the c-ros oncogene 1 gene* (*GOPC-ROS1*) fusion. Crizotinib was administered orally, which functions as a protein kinase inhibitor and is used as a first-line treatment of advanced ROS1-positive NSCLC (dailymed.nlm.nih.gov accessed 10 December). After one month of treatment, the CT scan evaluation confirmed PR, according to RECIST. Only two months of follow-up were reported, awaiting long-term follow-up by authors.

Hui *et al*. [23] presented a case report with a 53-year-old Chinese woman with advanced HGSC pretreated with platinum-based chemotherapy and bevacizumab. The primary tumor was analyzed using NGS with a panel consisting of 425 cancer-associated genes. The results showed an *echinoderm microtubule-associated protein-like 4 gene with the anaplastic lymphoma kinase gene* (*EML4-ALK*) fusion. Rearrangement of the *ALK* gene is a potent carcinogenic driver in some cancers, especially *ALK* fusion-positive NSCLC, showing significant clinical response to ALK inhibitors [28]. The patient was treated with alectinib, an ALK inhibitor. PR was achieved after one month, and CR after four months. The response continued for a year without adverse events; with the last follow-up in January 2020, imaging and Cancer Antigen 125 (CA125) indicated no signs of disease relapse.

Lee *et al*. [24] conducted a retrospective study of 84 ovarian cancer patients where tumor tissue underwent NGS. Seven cases received targeted therapy based on the sequencing results. Five received PARP inhibitors, and one patient with LGSC received a PD-1 inhibitor. One patient fulfilled the inclusion criteria for our review as she had HGSC with a *Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha* (*PIK3CA*) mutation. The Phosphatidylinositol 3-Kinase/Protein Kinase B/Mechanistic Target of Rapamycin (PI3K/AKT/mTOR) signaling pathway plays a role in cell proliferation, cell cycle, apoptosis and cancer cell metabolism [29]. This pathway is one of the most frequently aberrantly regulated pathways in human tumors [30], why inhibiting this pathway may clinically benefit patients harboring mutations in genes associated with this pathway. Therefore, the patient was treated with the AKT inhibitor TAS-117 for two months and achieved SD.

Sawada *et al*. [25] treated a 41-year-old patient with advanced-stage HGSC disease. The sequencing of 160 cancer-related genes revealed that the patient had a *neurofibromin 1* (*NF1*) loss. Loss-of-function mutations in the NF1 tumor suppressor gene lead to constitutive mTOR signaling. As such, she received everolimus, an mTOR inhibitor, in combination with letrozole, an aromatase inhibitor, since the combination has been synergistic in advanced endometrial cancer [31]. The patient progressed during treatment.

Thouvenin *et al*. [26] published a case report about a 46-year-old woman diagnosed with advanced-stage ovarian cancer. She was pretreated with neoadjuvant platinum-based chemotherapy followed by palliative chemotherapy with doxorubicin. NGS using a 409 gene panel, did not find any actionable mutations, but the copy number analysis showed amplification of the 17q12 chromosomal region containing *Erb-B2 Receptor Tyrosine Kinase 2* (*ERBB2*), also known as *Human Epidermal Growth Factor Receptor 2* (*HER2*). *ERBB2* is amplified in 15–20% of patients with breast cancer and was associated with poor prognosis until the advent of HER2-directed therapies [32]. Therefore, treatment with the anti-HER2 agents trastuzumab and pertuzumab was initiated. After three months, the radiologic assessment showed SD. PR lasted until thirty-seven months of treatment, where disease progression prompted a multidisciplinary tumor board, resulting in a decision to continue trastuzumab and pertuzumab supplemented with radiotherapy.

4. Discussion

In this review, we screened 1882 studies resulting in 6 case reports matching our inclusion criteria. We aimed to report the clinical utility of NGS-based potential targeted therapies in HGSC excluding PARP inhibition. A total of six studies were included, each describing NGS used to suggest targeted therapy in six patients with HGSC. The cases involved various

TABLE 1. Summary of included studies.

	Population	Target	Therapy	Outcome
Cappuccio *et al*. [21] Case report	50-year-old, HGSC stage IIIC.	MAPK pathway (*KRAS* mutation)	Trametinib (MEK inhibitor)	Partial response (3 mon) Stable disease (6 mon)
Dong *et al*. [22] Case report	69-year-old, HGSC stage IIIC.	*GOPC-ROS1* fusion	Crizotinib (ROS1 tyrosine kinase inhibitor)	Partial response
Hui *et al*. [23] Case report	53-year-old, Chinese, HGSC stage IIb.	*EML4-ALK* fusion	Alectinib (ALK inhibitor)	Partial response (1 mon) Complete response (4 mon)
Lee *et al*. [24] Phase II trial	HGSC (n = 1)	*PIK3CA* mutation	TAS-117 (AKT inhibitor)	Stable disease
Sawada *et al*. [25] Case report	41-year-old, HGSC stage IVB.	*NF1* loss	Everolimus (mTOR inhibitor) Letrozole	Progressive disease
Thouvenin *et al*. [26] Case report	46-year-old, Caucasian, HGSC stage IV, *BRCA*wt	*ERBB2* amplification	Trastuzumab-pertuzumab (HER2 inhibitor)	Partial response

ALK: Anaplastic Lymphoma Kinase; AKT: Protein Kinase B; BRCAwt: Breast Cancer wild type; EML4-ALK: echinoderm microtubule-associated protein-like 4 gene with the anaplastic lymphoma kinase gene; ERBB2: Erb-B2 Receptor Tyrosine Kinase 2; GOPC-ROS1: golgi-associated PDZ and coiled-coil motif-containing protein gene with the c-ros oncogene 1 gene; HER2: Human Epidermal Growth Factor Receptor 2; KRAS: Kirsten rat sarcoma viral oncogene homolog; MAPK: mitogen-activated protein kinase; MEK: mitogen-activated extracellular signal-regulated kinase; NF1: Neurofibromin 1; mTOR: Mammalian Target of Rapamycin; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; HGSC: high-grade serous ovarian cancer.

targeted therapies: trametinib, crizotinib, alectinib, an AKT inhibitor, everolimus-letrozole and trastuzumab-pertuzumab. Among these, PR were observed in patients treated with trametinib, crizotinib or trastuzumab, while CR was noted in the patient treated with alectinib, according to RECIST [33]. In contrast, the patient treated with an AKT inhibitor had SD, and the patient treated with everolimus-letrozole experienced PD. These cases underscore the heterogeneity of HGSC and the varied responses to targeted therapies. They highlight the importance of understanding the biological significance of these targets and the mechanisms of resistance to optimize treatment strategies and improve patient outcomes.

To our knowledge, no previous reviews have evaluated targeted therapies, beyond PARP inhibitors, with druggable targets identified by NGS in ovarian HGSC patients. In a recent study from our research group, we used NGS to identify known druggable targets and potential targeted therapies in 128 HGSC patients [8]. The mutational profiles were characterized using Oncomine™ Comprehensive Assay (OCAv3). Overall, 27 (21%) had druggable targets. Most of these patients (n = 25) were potentially eligible for PARP inhibitors. Only five patients (4%) had other druggable targets in the *Epidermal Growth Factor Receptor* (*EGFR*), *MutS Homolog 2* (*MSH2*), *MutL Homolog 1* (*MLH1*), *PIK3CA*, and *Fibroblast Growth Factor Receptor 3* (*FGFR3*) genes. Thus, based solely on their NGS findings, they were potential candidates for targeted therapies other than PARP, such as tyrosine kinase inhibitors, immuno-therapy, alpesilib in combination with hormone therapy, and erdafitinib. Our analysis also reported mutations in the *KRAS* (n = 3) and *NF1* (n = 10) genes. However, as we defined druggable targets as genetic alterations class 4 or 5 according to the American College of Medical Genetics and Genomics (ACMG) classification [34], these chans were not considered druggable in our study.

Other studies have investigated the potential of known targeted therapies through large international basket trials. In the WINTHER trial, 107 patients were prospectively treated according to findings from either DNA sequencing (n = 69) or RNA expression (n = 38) [35]. The most common diagnoses were colon, head, neck and lung cancers. No ovarian cancer patients were included. The rate of SD $\geq$6 months and PR or CR was 26.2%. PFS of targeted treatment compared with the individual patient's latest treatment was 22.4% and did not meet the pre-specified primary endpoint. Fewer prior therapies, better performance status, and higher matching scores correlated with longer PFS. All patients were heavily pretreated, which may have affected the response rates.

A key focus in the future is to include ovarian cancer patients in extensive basket trials such as the WINTHER trial and investigate the efficacy of targeted therapies on a broader scale in this patient group rather than solely individual cases [35–38]. Examples of trials that involve ovarian cancer patients are the large national basket trials, such as National Cancer Institute (NCI)-MATCH (US) and ProTarget (DK). In basket trials, patients all receive the same treatment that targets the specific mutation or biomarker found in their cancer. NCI-MATCH was launched in August 2015 by NCI and Eastern Cooperative Oncology Group-American College

of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group (https://ecog-acrin.org/clinical-trials/eay131-nci-match-precision-medicine/nci-match-eay131-findings/ accessed February 2023). Tumor biopsy specimens from 5954 patients with refractory malignancies were analyzed using NGS. Patients with actionable targets were assigned to one of thirty phase II subprotocols. The assignment rate for ovarian cancer was 14% (n = 75), and fifty assigned patients received treatment in a subprotocol. Unfortunately, the druggable targets for ovarian cancer divided by histological subtypes are not specified [38]. However, the results are published continuously, and the details and results from ovarian cancer patients will be specified in these studies. In the present study, we reviewed the available publications from NCI-MATCH. None of them included HGSC patients.

The ProTarget study is an ongoing Danish nationwide clinical phase II trial on targeted cancer treatment based on genomic profiling (NCT04341181). Twelve drugs are being investigated in ten arms, and patients are followed for standard toxicity and outcomes, including tumor response, PFS, and OS. Interestingly two arms investigate the use of alectinib and trastuzumab-pertuzumab, which were also described in two cases that responded in the present review. The trial is estimated to end in April 2025.

Some meta-analyses have demonstrated that biomarker-driven trials have better outcomes than trials lacking bi-omarkers [39–41]. However, not all patients' tumors have actionable DNA/RNA alterations. Thus, extending the application of precision medicine requires a deeper understanding of cancer biology. Exploring oncogenic mechanisms beyond DNA alterations, such as RNA expression, is needed. A phase 2 trial (NCT02203513) published in Nature demonstrated the relevance of RNA sequencing to identify signaling pathways that might correlate with Checkpoint Kinase 1 (CHK1) inhibitor resistance or response [42]. Transcriptomic analysis revealed high levels of *DNA Polymerase Alpha 1* (*POLA1*), *DNA Polymerase Epsilon* (*POLE*) and *GINS Complex Subunit 3* (*GINS3*) genes were associated with lack of clinical benefit.

However, somatic testing with NGS requires implementation as part of the daily routine [43, 44]. Physicians need to familiarize themselves with the various testing modalities for NGS in collaboration with the pathological and mo-lecular departments [13, 45, 46]. Collaborative approaches, such as molecular tumor boards, that use a multi-disciplinary approach to assess patient factors and genomic information to make recommendations for patients not responding to standard-of-care therapy. Recent studies have shown improved response rates based on recommendations by molecular tumor boards [47–49]. Moreover, as the use of NGS-based technologies to find targets for biological treatment in HGSC are increasing, it becomes crucial to understand the biological significance of these targets in ovarian cancer pathogenesis and their resistance mechanisms.

Only a few studies were found to treat HGSC patients with targeted therapies other than PARP inhibitors. This undeniably calls into question whether targeted therapies beyond PARP inhibitors can benefit HGSC patients. HGSC is a genomically heterogeneous disease with few mutations that recur among patients [7]. Yet, most HGSC patients have a TP53 mutation and efficient treatments targeting TP53 may improve the treatment of HGSC remarkably. APR-246 is a drug that reactivates mutant p53 encoded by TP53 in cancer cells [50, 51]. The effect of APR-246 has yet to be examined in large clinical trials. A phase 1/2 multicenter study is ongoing to assess the efficacy of PC14586, an oral, small molecule p53 reactivator that is selective for the TP53 Y220C mutation (PYNNACLE). Although only a few patients have this specific mutation, it points toward new perspectives and directions in the future treatment of HGSC.

Our review has several strengths. Firstly, two independent researchers with knowledge of ovarian cancer conducted a literature review with predefined outcomes. Secondly, to reduce reviewer bias, we used objective and reproducible criteria to select relevant publications. However, despite adhering to the PRISMA guidelines and using consistent outcomes for study inclusion, there were notable differences among the patients included. The age of patients varied significantly, ranging from 41 to 69 years. Additionally, none of the patients received the same targeted therapy, nor did they possess similar druggable targets. This variability highlights the heterogeneity of HGSC and underscores the challenges in standard treatment approaches. Thirdly, case reporting offers the advantage of detecting novelties, presenting unusual uncontrolled observations, and formulating new hypotheses. Lastly, when it is not possible to enroll enough patients in randomized controlled trials for rare actionable targets, research on targeted therapies should be based on less rigorous methodologies, such as case reports and basket trials summarized in systematic reviews [52–54].

We might have missed relevant studies because we only searched for basket trials that mentioned ovarian cancer in their abstract. Moreover, the included studies were all case reports where the population of ovarian cancer patients was not described. Thus, the studies were all without statistical power and possible negative results were not presented. Therefore, generalization is not possible, as it requires a cause-effect relationship and a representative population. Furthermore, publication bias may be another limiting factor, as journals and authors tend to favor positive outcome findings, especially case reports [55]. Lastly, the falsification criterion within science, tested by repeating an experiment, cannot be applied to case reports.

5. Conclusions

The precision medicines focus on ovarian cancer patients with HGSC has been PARP inhibitors due to the promising results obtained. However, there is an unmet need for novel treatment strategies for patients who are not candidates for PARP inhibitor treatment, not least in the recurrent setting. In this review, different targeted therapies have demonstrated a response in patients with HGSC. Based on our study, it appears that HGSC patients could potentially benefit from an expanded molecular characterization including both DNA and RNA sequencing analysis. However, the current state of knowledge in this field is limited, making it challenging to evaluate current and future targeted therapies. Therefore,

further studies and basket trials are needed to validate the efficacy of targeted therapies in ovarian cancer patients with HGSC.

AVAILABILITY OF DATA AND MATERIALS

Data is contained within the article.

AUTHOR CONTRIBUTIONS

YS—contributed to the conceptualization, literature search, literature review, and writing (original draft, figure preparation, and editing). DH—contributed to the conceptualization, literature search, literature review, and writing (review and editing). THS—contributed to conceptualization and writing (review and editing). CH—contributed to the conceptualization and writing (review and editing). EH—contributed to the conceptualization, writing (design of study, review and editing). All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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