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Clinical applications of PARP-1 inhibitors in gynaecological cancers

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ABSTRACT

Poly (ADP-ribose) polymerase (PARP) acts as an essential DNA repair enzyme. PARP inhibitors are novel small molecule targeted drugs based on the principle of "Synthetic Lethality", which affect DNA repair process by competitively inhibiting the activity of PARP enzyme and thereby kill cancer cells. Currently, four PARP inhibitors including olaparib, rucaparib, niraparib, and talazoparib have been approved by FDA for cancer treatment and have achieved great success in the treatment of ovarian cancer, breast cancer, and pancreatic cancer, etc. This paper provides a general overview on role of PARP-1 inhibitors in gynaecological cancers (cervical, ovarian and endometrial cancers)

Keywords: PARP-1; DNA Repair; Breast cancer; ovarian cancer; Endometrial cancer.

INTRODUCTION

Recently it is estimated 110,070 new gynecologic cancers were diagnosed in women in the United States, with 32,120 deaths(1). Ovarian cancer remains the 5th leading cause of cancer deaths in women in the US, and uterine cancer is the 6th

leading cause of cancer deaths in women(2). Cervical cancer is far less common in the US because of effective screening and prevention with the human papillomavirus vaccine. With few exceptions, recurrent gynecologic malignancies are incurable. However, recent advances in treatment options are helping prolong the lives of women with gynecologic cancers(3). There are many ongoing clinical trials in gynecologic malignancies that will hopefully result in new options for the treatment of women with these cancers. The landscape of cancer treatment has shifted dramatically in recent years because of advances in tumor molecular profiling and associated discoveries of predictive molecular targets. As a result, greater understanding of the tumor microenvironment and antitumor immunity has catapulted immuno-oncology to preeminent status as the future of cancer care. Successful translational research has not only identified druggable targets but also produced therapies that now prolong survival of patients with otherwise poor prognoses and limited therapeutic options. In this article, the authors provide an overview of studies of immune checkpoint blockade as a therapeutic strategy in gynaecologic cancers and highlight their current utility, challenges, and opportunities for further research(4).

The discovery of poly-(ADP-ribose) polymerase inhibitors (PARP-1) has changed the landscape of gynaecological cancers significantly(5). PARP-1 exploit defects in DNA repair by leveraging synthetic lethality, resulting in cell sickness or death. Synthetic lethality, the principle that 2 deficiencies in cellular mechanisms lead to cell death but individually do not, is seen when PARP-1 are administered to patients whose tumors have lost the ability to repair double stranded DNA breaks via the process of homologous recombination, a state referred to as homologous recombination deficiency (HRD). PARPs are a class of 18 enzymes that play multiple roles in DNA damage repair, including base excision repair after single-stranded DNA breaks. When this pathway is inhibited by PARP-1 during DNA synthesis, double stranded DNA breaks may occur. Normally, such double-stranded breaks are repaired in cells through homologous recombination repair (HRR), but in cells with deficiencies in HRR (including BRCA mutations or alterations in other HRR genes), effective repair of these breaks does not occur, leading to subsequent cell death. Beyond direct inhibition of the PARP enzyme, additional research also has demonstrated that PARP-1 also may mediate their effects by the process of PARP trapping, in which PARP enzymes are trapped on

damaged DNA sites, inhibiting efficient appropriate DNA repair and replication(5).

In the present review we discuss the pharmacological role, recent advances and challenges in application of PARP-1 in gynaecological cancers (ovarian cancer, cervical cancer and endometrial cancer).

1. PARP-1 IN GYNAECOLOGICAL CANCERS

1.1. Ovarian cancer

Ovarian cancer is one of the most challenging gynaecologic malignancies to treat. Despite initial aggressive treatment, tumour debulking and chemotherapy always result in high recurrence rate. Given the deeply researching of oncogenesis, many therapeutic targets have been identified, which driven the management of cancer into individualized treatments.

1.1.1. Applications of PARP-1 ovarian cancer

Clinical trials designed to evaluate PARP-1 in ovarian cancer are divided into five main indications: (1) first-line treatment (i.e., SOLO1, PRIMA, PAOLA-1, and NEO), (2) platinum-sensitive relapse (i.e., AVANOVA2, SOLO3, and ARIEL4), (3) maintenance after chemotherapy in platinum-based disease (i.e., NOVA, SOLO2, and ARIEL3), (4) platinum-resistant disease (i.e., Study 42 and CLIO), and (5) combination with target drugs, immune checkpoint inhibitors, or other biological drugs**(Table 1).**

Olaparib

Olaparib was the first PARP-1 introduced in clinical practice. Two phase I trials reported that olaparib had a good safety and tolerability at a dose of 400 mg bis in die. The antitumor activity appeared to be related to platinum sensitivity because platinum salts are DNA damaging agents, which cause DNA crosslinks, and are partially repaired by HR. DNA repair-deficient tumors are expected to be highly sensitive to both platinum and PARP-1. Therefore, clinical trials mainly focus on using PARP-1 as maintenance therapy in patients with ovarian cancer who respond to platinum-based chemotherapy. Study 19 was the key initial study performed to evaluate the efficacy of olaparib monotherapy as maintenance treatment in patients with platinum sensitive relapsed HGSOC compared with placebo. Results showed

a significantly prolonged PFS in patients with BRCA-mutated ovarian cancers (median PFS 11.2 vs. 4.3 months; HR = 0.18; $p < 0.0001$). However, no significant overall survival (OS) benefit was observed. Study 19 results led to the approval of olaparib as maintenance treatment for BRCA1/BRCA2-mutated patients in 2014. A phase III clinical trial, SOLO-2, expanded to all platinum-sensitive patients regardless of BRCA1/BRCA2 status (median PFS 19.1 vs. 5.5 months for olaparib and placebo, respectively). SOLO-1, a phase III clinical trial, established the role of olaparib in the first-line platinum based maintenance treatment of BRCA-mutated advanced ovarian cancer (FIGO stage III/IV). POALA-1 trial was a phase III trial of olaparib + bevacizumab versus bevacizumab alone in the first-line maintenance setting in advanced ovarian cancer patients. The trial met its primary endpoint with a statistically significant and clinically meaningful improvement in PFS, increasing the survival time for olaparib + bevacizumab group compared with those with bevacizumab patients (median PFS 22.1 vs. 16.6 months; HR = 0.59; $p < 0.0001$). Subgroup analysis based on the HRD status concluded that patients from the HRD-positive group had a median PFS of 37.2 versus 17.7 months, whereas patients from the HRD-negative group had a median PFS of 28.1 versus 16.6 months. Therefore, BRCA mutation status alone is an insufficient predictive biomarker for maintenance therapy with PARP-1; the detection of HRD is also important. Further research on platinum resistance in ovarian cancer obtained promising results. Study 42 revealed that olaparib could be used as maintenance therapy for patients with platinum resistance/refractory or platinum sensitivity but unsuitable for further platinum therapy with a response rate of 31.1% (CI: 24.6%–38.1%) for patients with BRCA1 or BRCA2 germ line mutations (gBRCA1/2 m) ovarian cancer. Further analysis of patients with gBRCA1/2 m ovarian cancer and who had received ≥3 prior lines of chemotherapy obtained a response rate of 34% and a median duration of response 7.9 months. CLIO (NCT02822157), a phase II clinical trial, was started to assess the efficacy and safety of olaparib monotherapy for recurrent platinum-resistant ovarian cancer with at least one prior line of therapy compared with single-agent non platinum agent chemotherapy. The overall response rate (ORR) was not statistically different between the groups ($p = 0.13$). Subgroup analysis of BRCA status concluded that olaparib is a viable treatment option for women with platinum-resistant ovarian cancer and BRCA-mutated tumors in platinum-resistant disease. SOLO-3 utilized the same design but

conducted in women with platinum-sensitive recurrent ovarian cancer with at least two prior lines of therapy. This study obtained an ORR of 72% compared with 51% in olaparib and chemotherapy arms. Olaparib is also being studied in a neoadjuvant chemotherapy, NEO (NCT02489006), to determine whether neoadjuvant chemotherapy settings for olaparib could achieve better survival rates compared with traditional platinum-based chemotherapy.

Niraparib

Niraparib obtained FDA approval in April 2017 for the maintenance treatment of patients with recurrent ovarian cancer who are in a CR/PR to platinum-based chemotherapy. Clinical trials of niraparib in ovarian cancer mainly concentrated on maintenance therapy. Niraparib was first approved on the basis of clinical trial ENGOT-OV16/NOVA (NCT01847274), which was a phase III trial for patients with platinumsensitive recurrent HGSOC to maintenance therapy compared with placebo after two lines or later line of platinum-based chemotherapy. This study clarified that the median duration of PFS for patients with niraparib were significantly longer than those receiving placebo, regardless of the presence or absence of gBRCA mutations or HRD status. A retrospective analysis of NOVA trial demonstrated that two risk factors that can predict myelosuppression are body weight (< 77 kg) and/or basal platelet count (< 150,000 μL) that require dose reduction. PRIMA (NCT02655016) was a setting for first-line maintenance treatment for patients with advanced ovarian cancer who respond to platinum-based chemotherapy. The PFS in patients with HRD was 21.9 months with niraparib and 10.4 months with placebo (HR: 0.43, CI: 0.31–0.59, $p < 0.001$). In the overall population, the median PFS was 13.8 months with niraparib and 8.2 months with placebo (HR: 0.62, CI: 0.50–0.76, $p < 0.001$). Cumulative myelosuppression, neurotoxicity, and allergy to platinum-based therapy limit the number of patients receiving multiple lines of treatment. The effectiveness of antiangiogenic agents and PARP-1 has been proved and they present the opportunity to develop chemotherapy-free combination regiments. AVANOVA2 (NCT02354131) compared niraparib and bevacizumab versus niraparib alone as a treatment strategy for platinum-sensitive recurrent ovarian cancer. Results showed that niraparib plus bevacizumab significantly improved PFS compared with niraparib with a median PFS of 11.9 months versus 5.5 months (HR: 0.35, CI: 0.21–

0.57, $p < 0.001$). Based on these results, a randomized phase III trial is needed to investigate niraparib plus bevacizumab versus chemotherapy plus bevacizumab in platinum-sensitive recurrent ovarian cancer to observe the efficacy of chemotherapy-free combination. QUADRA (NCT02354586) assessed the clinical benefit of niraparib monotherapy in late-line recurrent ovarian cancer treatment settings and achieved an ORR of 27.5% with a disease control rate (DCR) of 68.6% and a duration of response of 9.2 months.

Rucaparib

Rucaparib is an orally administered small molecule-based PARP1, PARP2, and PARP3 inhibitor approved by the FDA in December 2016 based on Study 10 and ARIEL2 clinical trials for the treatment of patients with deleterious BRCA mutation advanced ovarian carcinoma who receive two or more chemotherapy regiments. In part 1 of the ARIEL2 trial, rucaparib was efficacious not only in patients with relapsed, platinum-sensitive, and high-grade ovarian cancer with a BRCA mutation but also in those with BRCA wild-type carcinomas with high genomic loss of heterozygosity (LOH). ARIEL3 aimed to assess the efficacy and safety of rucaparib versus placebo to ≥2 lines of platinum sensitive ovarian patients and prospectively tested the genomic LOH cutoff discriminator to optimize the results of ARIEL2. PFS after rucaparib treatment was 16.6 months in the group with BRCA mutations (HR: 0.23, $p < 0.001$), 13.6 months in the HRD group (HR: 0.32, $p < 0.001$), and10.8 months in the intent-to-treat group (HR: 0.37, $p < 0.001$). By comparison, the median PFS was 5.4 months in the placebo group. ARIEL4 is an ongoing confirmatory study to assess the efficacy and safety of rucaparib in the treatment of relapsed ovarian cancer patients with BRCA mutation. In addition, clinical trial results of PARP-1 are also promising in other solid tumors harboring BRCA1 or BRCA2 mutations, and is expanding to HRR defect tumors, such as breast cancer, prostate cancer, gastric cancer, and pancreatic cancer.

Table 1. Clinical trials evaluating PARP-1 in clinical trials

Drug	Trial	Phase
Olaparib	SOLO-1 (NCT01844986)	III
	SOLO-2 (NCT01874353)	III
	Study 19 (NCT00753545)	II

	Study 42 (NCT01078662)	II
	PAOLA-1 (NCT02477644)	II
	SOLO-3 (NCT02282020)	II
	CLIO (NCT02822157)	II
	ICEBERG3 (NCT00628251)	II
	NEO (NCT02489006)	II
Niraparib	PRIMA (NCT02655016)	II
	NOVA (NCT01847274)	II
	AVANOVA2 (NCT02354131)	II
	QUADRA (NCT02354586)	I/II
Rucaparib	ARIEL3 (NCT01968213)	I/II
	ARIEL4 (NCT02855944)	II

1.2. Endometrial cancer

Endometrial cancer (EC) is the most common gynaecological malignancy in developed countries. While patients with early-stage and low-risk disease present an excellent prognosis with five-year survival rates of over 95%, women with advanced, recurrent and metastatic EC have extremely poor outcomes, owing to the low response rate to standard systemic chemotherapy. EC is a heterogeneous disease consisting of various histological subtypes with different pathogenesis, prognosis and sensitivity to therapeutic agents.3,4 Given the improved knowledge of cancer genetics and biology, in 2013, The Cancer Genome Atlas (TGCA) proposed a new endometrial cancer molecular classification, based on the following four groups: POLE-ultramutated, microsatellite instability hypermutated (MSI-H), copy-number low, and copy-number high.

1.2.1. Applications of PARP-1 in endometrial cancer

Currently, there are several Phase I and II clinical trials evaluating the role of PARP-1 (olaparib, niraparib, rucaparib, and talazoparib) in metastatic, advanced, and recurrent EC, alone or in combination with other drugs . Olaparib is under evaluation in many Phase I and II clinical trials. NCT02208375 is a Phase Ib/II to

evaluate the maximum tolerated dose (MTD) of olaparib and vistusertib (mTOR inhibitor) or olaparib and capivasertib (AKT kinase inhibitor) when given together in treating patients with recurrent endometrial cancer. ENDOLA trial is a Phase I/II study evaluating the safety and efficacy of olaparib in combination with metronomic cyclophosphamide plus metformin in recurrent/metastatic EC. The rationale behind this combined therapy is that metronomic cyclophosphamide may increase the anti-proliferative effect of olaparib and exert anti-angiogenic effects, while metformin can also increase the anti-proliferative effect of olaparib without further toxicity. The primary endpoint is the recommended Phase II trial (RP2D) dose of olaparib in combination with metformin and metronomic cyclophosphamide. DOMEC (NCT03951415) is a prospective, multicenter, Phase II study that aims to assess the efficacy of olaparib in combination with durvalumab (anti PD-L1) in advanced, recurrent and metastatic EC. Patients with prior chemotherapy failure, unwilling to undergo chemotherapy, or chemonaive not suitable for chemotherapy are enrolled in this trial and they receive olaparib tablets 300 mg twice daily and durvalumab 1500 mg intravenously (IV) every 28 days. The primary endpoint is the PFS.60 UTOLA (NCT03745950) is a multicenter, double-blind, randomized Phase II trial assessing the efficacy of olaparib as maintenance after platinum-based chemotherapy in advanced and recurrent EC patients. Patients randomized in the experimental arm will receive olaparib 300 mg orally twice daily as maintenance until progression disease according to RECIST 1.1 or unacceptable toxicity. Moreover, olaparib is also being tested in combination with cediranib, an anti-VEGF antibody, in a Phase II, randomized, three arms, open-label clinical trial. In COPELIA study (NCT03570437), patients with recurrent and advanced EC will be randomized in three arms: in cohort A, patients receive paclitaxel 80 mg/mq administered in days 1, 8 and 15 of a 28-day cycle up to 6 cycles; in cohort B, cediranib 20 mg orally daily for 28 days is added to the treatment with paclitaxel for 6 cycles; in cohort C, cediranib 20 mg orally is administered daily in combination with olaparib 300 mg orally twice daily for 28 days. Patients enrolled in cohort B and C with at least stable disease will be able to continue cediranib alone (cohort B) or cediranib/olaparib (cohort C) daily until disease progression. The primary endpoint is the PFS. NCT02684318 is a Phase I/II study to evaluate the efficacy and tolerability of PM01183 (Lurbinectedin) in combination with olaparib in patients with advanced or metastatic solid tumors,

including EC. The primary objective of Phase I is to establish the safety [dose limiting toxicity (DLT), MTD, and RP2D] of orally administered olaparib in combination with PM01183, whereas the primary objective of Phase II is to assess the efficacy of PM01183 in combination with olaparib in terms of tumor response rate according to RECIST 1.1 criteria. Furthermore, rucaparib is being tested in several Phase I/II clinical trials. NCT03572478 is a Phase I/II study to assess the safety (Phase I: DLT) and efficacy (Phase II: time to disease progression) of the combination of an immune checkpoint inhibitor (nivolumab) with a PARP inhibitor (rucaparib) in patients with metastatic or recurrent EC. NCT03552471 is a Phase I study to determine the recommended Phase II dose for the combination of mirvetuximabsoravtansine with rucaparib camsylate (rucaparib) in recurrent EC patients. Secondary objectives of this study are to determine the safety and tolerability of combining these drugs in the study population, to explore the objective antitumor activity (complete or partial response) according to RECIST criteria, to measure the PFS, and to evaluate the pharmacokinetics of mirvetuximabsoravtansine and rucaparib in combination.65 NCT03617679 is a Phase II, randomized, double-blind, clinical trial evaluating the efficacy of rucaparib as maintenance treatment in patients with metastatic and recurrent EC after the first-line chemotherapy. Patients within the experimental arm will receive rucaparib 600 mg orally twice daily until disease progression or other indications for discontinuation. The PFS is used as a primary endpoint. The efficacy of rucaparib is also tested in association with other drugs, such as bevacizumab and atezolizumab. ENDOBARR (NCT03694262) is an open-label, non randomized, Phase II clinical trial investigating the efficacy and safety of rucaparib in combination with atezolizumab and bevacizumab in recurrent, progressive EC patients. The rationale behind the combined use of PARP-1 and bevacizumab (anti-VEGF) can be explained through the results of some studies showing that the hypoxia induced by the antiangiogenic therapy causes a deficit in the HR pathway. Therefore, HR-deficient hypoxic tumor cells are sensitized to the action of PARPi.67 In the ENDOBARR trial patients will receive rucaparib 600 mg orally twice daily plus bevacizumab 15 mg/kg IV on day 1 of every 21- day cycle plus atezolizumab 1200 mg IV on day 1 of every cycle. The primary endpoint is the ORR.68 NCT03476798 is a Phase II clinical trial that aims to determine the PFS in recurrent EC patients who receive rucaparib 600 mg orally twice daily plus

bevacizumab 15mg/kg IV on day 1 of each 21-day cycle. NCT03586661 is a Phase I clinical trial to determine the MTD and RP2D of the combination of niraparib and copanlisib in patients with recurrent EC. Patients in the experimental arm will receive niraparib PO daily on days 1–28 and copanlisib IV on days 1,8 and 15. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. NCT03016338 and NCT04080284 are two Phase II clinical trials investigating the efficacy of nivolumab, alone or in combination with other drugs. The main goal of NCT03016338 is to assess whether combining niraparib with TSR-042 (dostarlimab, an anti PD-1) increases the clinical outcomes in recurrent EC. Patients in the experimental arm will receive niraparib 200 or 300 mg daily for a 21-day cycle and dostarlimab 500 mg IV on day 1 of every cycle followed by 1000 mg IV every 6 weeks for a maximum of 2 years. The primary endpoint is the clinical benefit rate. On the other hand, NCT04080284 is a clinical trial that analyzes the efficacy of niraparib as maintenance in patients with advanced or platinum sensitive recurrent uterine serous carcinoma. The primary endpoint is the PFS. Finally, talazoparib is an emerging PARP inhibitor under evaluation in several Phase I and II clinical trials. NCT03968406 is a Phase I to determine the safety, tolerability, and MTD of talazoparib combining talazoparib and fractionated radiotherapy in patients with refractory or recurrent EC.NCT02912572 is a Phase II, two-group, two-stage, open-label study of avelumab (an anti-PD-L1) in patients with MSS, MSI-H and POLE-ultramutated recurrent or persistent EC and of avelumab/talazoparib in patients with MSS recurrent or persistent EC. Talazoparib will be administered in cohort C MSS patients in combination with avelumab. The PFS is used as a primary endpoint. (Table 2)

1.3. Cervical cancer

While the incidence of cervical cancer in developed countries has decreased substantially, it remains the second most common cancer in women worldwide. At this time, the role of PARPi in the management of advanced cervical cancer remains in question. Michel’s and colleagues demonstrated constitutively hyper activated PARP1 and high levels of PAR in cisplatin resistant cancer cell lines,

including a cisplatin resistant cervical cancer cell lines. Additionally, the authors found that these cell lines were susceptible to PARP inhibition. These findings suggest a promising role for PARP inhibitors in the treatment of cisplatin resistant cervical cancer, though further investigation is needed.

1.3.1. Clinical applications of PARPi in cervical cancer

Clinically, few studies to date have investigated the use of PARP-1 in cervical cancer. GOG-76HH (NCT0126647) is a phase I/II trial assessing veliparib with cisplatin and paclitaxel in the setting of advanced, recurrent, or persistent cervical cancer. The results of the phase I portion of this study were presented at the ASCO annual meeting in 2015. This included 34 evaluable patients who had an overall response rate of 34% for all dose levels and 60% for the maximum dose level (ASCO 2015 annual meeting abstract 5600). GOG 127W (NCT01281852) investigates the use of veliparib and topotecan (with either filgrastim or pegfilgrastim) in recurrent or persistent cervical cancer of both squamous and non-squamous histologies. Results from these studies and future studies will hopefully reveal a promising role for PARP inhibitors in cervical cancer

1.3.2. Ongoing clinical trials of PPAR-1 in endometrial cancer

PARP-1	Combination with	Description	Setting	Primary Endpoint	Phase	Status	NCT Identifier	ECD
Olaparib	Cyclophosphamide and Metformin	Safety and efficacy of Metronomic Cyclophosphamide, Metformin and Olaparib in Endometrial Cancer Patients (ENDOLA)	Recurrent	RP2D	I/II	Active, not recruiting	NCT02755844	April, 2022
Olaparib	Durvalumab	Durvalumab and Olaparib in Metastatic or Recurrent Endometrial Cancer (DOMEC)	Metastatic/Locally Advanced/ Recurrent EC	PFS	II	Recruiting	NCT03951415	July, 2023
Olaparib	Monotherapy	UTOLA: UTerinOLAparib (UTOLA)	Advanced/ Metastatic EC	PFS	II	Not yet recruiting	NCT03745950	December, 2024
Olaparib	Cediranib	Does Cediranib with Paclitaxel, or Cediranib and Olaparib, Treat Advanced Endometrial Cancer Better than Paclitaxel? (COPELIA)	Advanced/ Recurrent EC	PFS	II	Recruiting	NCT03570437	September, 2021
Olaparib	Lurbinectedin	Study to evaluate PM01183 in combination with Olaparib in Advanced Solid Tumors	Advanced/ Metastatic and platinum refractory EC	DLT MTD	I/II	Unknow	NCT02684318	October, 2019

Olaparib	ATR inhibitor	ATR Inhibitor in combination with Olaparib in Gynecological Cancers with ARId1A Loss or no Loss (ATARI)	Progressive/ Recurrent gynecologic cancer, included EC	ORR	II	Recruiting	NCT04065269	March, 2023
Olaparib	Vistusertib or Capivasertib	mTORC1/2 Inhibitor AZD2014 or the Oral AKT Inhibitor AZD5363 for Recurrent Endometrial and Ovarian	Advanced/ Recurrent EC	MTD	I/II	Active, not recruiting	NCT02208375	November, 2021
Rucaparib	Monotherapy	Rucaparibvs Placebo Maintenance Therapy in Metastatic and Recurrent Endometrial Cancer	Metastatic/ Recurrent EC	PFS	II	Recruiting	NCT03617679	September, 2022
Rucaparib	Nivolumab	Rucaparib and Nivolumab in Patients with prostate or endometrial cancer	Metastatic EC	DLT	I/II	Recruiting	NCT03572478	December, 2021

2. FUTURE DIRECTIONS

As our understanding of the molecular biology and genetics of cancer continue to expand, we are learning of potential targets for anticancer treatment tailored to aberrancies specific to each malignancy. PARP-1 are an exciting class of agents that have demonstrated activity in gynaecologic malignancies and are already having a significant impact on ovarian cancer treatment. The exciting results obtained to date have led to several ongoing phase III trials that may be practice changing. Despite the rapid development and knowledge gained, many questions remain to be answered. Which patients should be treated with PARP-1. When is the best time to use a PARP-1 in the management of gynecologicmalignancies. How does the cost of PARP-1 therapy impact its utility.While it is clear that PARP-1 have activity in ovarian cancer, the timing of use remains in question. This has led to the development of several large clinical trials that are underway. These studies will elucidate the role of PARP-1 in adjuvant therapy, maintenance therapy and use in recurrent disease (alone or in combination with other agents). The use of other targeted agents (such as anti-angiogenic agents) may also have the potential to sensitize HR proficient tumours to PARP-1. While olaparib is currently only approved in gBRCAm recurrent ovarian cancer in patients treated with 3 or more lines of chemotherapy, these studies have the potential to greatly broaden its use. Lastly, cost is a clear barrier to use of PARP-1 in the treatment of gynaecologic malignancies. Recent cost-effective analyses suggest that PARP-1 may not be cost effective when accounting for BRCA testing and therapy.But there are many factors to consider. As genetic counselling and testing for hereditary cancer syndromes should be offered to all women diagnosed with invasive ovarian cancer according to the National Comprehensive Cancer Network and the Society of Gynaecologic Oncology's 2014 clinical practice statement, it seems reasonable to remove this factor from future cost analysis. It is very clear that further study in this arena is warranted. The application of PARP-1 in gynaecologic malignancies is an ideal example of the concept of personalized cancer care - identifying molecular and/or genetic aberrancies and exploiting them to ultimately improve the progression-free and overall survival of patients. Multiple studies have proven they are effective, tolerable agents; however moving forward, we have to further refine the most appropriate clinical setting and population for their use.

3. CONCLUSION

The poly (ADP-ribose) polymerase (PARP) family of enzymes is important in several DNA repair pathways. Drugs that inhibit these enzymes have been investigated in many types of cancer, but their application in the treatment of gynaecologic malignancies has rapidly evolved – as manifested by the 2014 FDA approval for olaparib in the treatment of recurrent ovarian cancer associated with a germline BRCA mutation (gBRCA). In efforts to broaden their efficacy, current clinical trials have demonstrated benefit of olaparib, and other PARP inhibitors (PARP-1), as single agents and in combination with cytotoxic chemotherapy and biologic agents, in wide ranging populations. Although the majority of data for PARP-1 in gynaecologic malignancies has been specifically regarding ovarian cancer, their role in the treatment of uterine and cervical cancer is currently being investigated. This review will serve as a synopsis of seminal trials to date, summarize the breadth of clinical application in on-going studies, query how these results may change future practice, and reflect on questions yet to be answered.

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