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R&D INSIGHT REPORT

Olaparib: First Global Approval

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Abstract Olaparib (Lynparza™) is an oral, small molecule, poly (ADP-ribose) polymerase inhibitor being developed by AstraZeneca for the treatment of solid tumours. The primary indication that olaparib is being developed for is *BRCA* mutation-positive ovarian cancer. A capsule formulation of the drug has received approval for use in this setting in the EU and USA, and a tablet formulation is in global phase III trials (including in the USA, EU, Australia, Brazil, Canada, China, Israel, Japan, Russia and South Korea). In addition, phase III trials in breast, gastric and pancreatic cancer are underway/planned, and phase I/II investigation is being conducted in other malignancies, including prostate cancer, non-small cell lung cancer, Ewing's sarcoma and advanced cancer. This article summarizes the milestones in the development of olaparib leading to this first approval for ovarian cancer.

1 Introduction

Patients with certain cancers, including those of the ovaries and breast, can carry mutations in the *BRCA1* and/or *BRCA2* gene and consequently have tumours that lack the homologous recombination (HR) pathway involved in error-free repair of DNA double-strand breaks (DSBs) [1–3]. As poly (ADP ribose) polymerase (PARP) is involved in the repair of single-strand DNA breaks, inhibiting PARP can result in replication-associated DSBs that require repair by HR. In HR-deficient cells (such as those of *BRCA1/2* tumours), these lesions can persist (which can be lethal) or are repaired via error-prone pathways (causing genetic instability) [3]. Thus, drugs that inhibit PARP are able to selectively kill BRCA-deficient tumour cells lacking HR and have consequently become a focus of therapy for such cancers [1, 3].

Olaparib is a PARP inhibitor being developed for the treatment of solid tumours, including *BRCA* mutation-positive ovarian cancer. In December 2014, the capsule formulation of olaparib, under the trade name Lynparza™, was approved in the EU [4] and USA [5] for the treatment of *BRCA*-mutated ovarian cancer (dosage: 400 mg twice daily). In the EU, there is a risk management plan for olaparib, involving a number of planned/ongoing studies, to ensure the drug is used as safely as possible [6]. Olaparib (tablet formulation) is also under phase III investigation in breast, gastric and pancreatic cancer and phase I/II investigation for other malignancies, including prostate cancer, non-small cell lung cancer (NSCLC), Ewing's sarcoma and advanced cancer.

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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Features and properties of olaparib

Alternative names	AZD 2281; AZD-2281; AZD2281; KU-0059436; KU-59436; Lynparza™
Class	Amides, Cyclopropanes, Fluorobenzenes, Phthalazines, Piperazines, Small-molecules
Mechanism of action	Poly (ADP-ribose) polymerase inhibitor
Route of administration	Oral
Pharmacodynamics	Displays anti-neoplastic activity in various cancer cell lines. Its benefits may be enhanced by other anti-cancer agents, according to preclinical studies
Pharmacokinetics	Rapidly absorbed and eliminated
Most frequent adverse events	Nausea, fatigue, vomiting, anaemia
ATC codes	
WHO	L01X-X (other antineoplastic agents)
EphMRA	L1X (all other antineoplastics)
Chemical name	4- [3- [4-(Cyclopropylcarbonyl)piperazin-1-ylcarbonyl] -4-fluorobenzyl] phthalazin-1(2H)-one

1.1 Company Agreements

In December 2005, AstraZeneca announced plans to acquire the UK biotechnology company KuDOS Pharmaceuticals Limited. KuDOS Pharmaceuticals had expertise in cancer therapies that exploit inhibition of DNA repair and had olaparib in phase I trials at the time of acquisition [7].

2 Scientific Summary

2.1 Pharmacodynamics

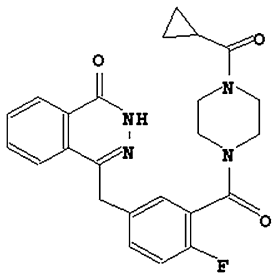
PARP inhibition may be high with olaparib in some instances. For example, PARP was inhibited >90 % with olaparib dosages of ≥60 mg twice daily in the mononuclear cells of patients with advanced solid tumours, including ovarian cancers, in a phase I trial [8]. Similarly, up to 80 % PARP inhibition was seen with olaparib 10–400 mg twice daily in tumour samples from breast cancer patients in another phase I study [9].

Olaparib displayed anti-neoplastic activity in various cancer cell lines, including ovarian [10], endometrial [11], gastric [12, 13], head and neck [14], colorectal (HR deficient due to MRE11 mutation or with microsatellite instability) [15], breast [including triple-negative cells; i.e. negative for estrogen and progesterone receptors and human epidermal growth factor receptor (HER) 2] [16] and mouse *BRCA2*-deficient mammary tumours [17]. Notably, sensitivity of gastric cancer cell lines to olaparib correlated with low-level expression of ataxia telangiectasia protein, which (like BRCA1/2) is involved in DSB repair [13].

Combining olaparib with agents that inhibit HR may enhance the effectiveness of olaparib in HR-proficient ovarian cancer cells according to in vitro and in vivo data [18, 19]. Further in vitro data suggest there may also be additional/synergistic anti-neoplastic activity in certain cancers when olaparib is used in combination with cyclin-dependent kinase or HER inhibition [16], standard chemotherapeutic agents [12, 17, 20–24] or irradiation [14]. Olaparib was radiosensitizing (independent of P53 status [25]) in colorectal cancer [25] and lung cancer [25, 26] cell lines, with stronger radiosensitization observed when in combination with the topoisomerase I inhibitor camptothecin [25].

Olaparib also demonstrated anti-tumour activity when used alone [27] or in combination with chemotherapeutic agents [27, 28] or radiotherapy [26] in preclinical models of cancer, including murine xenografts of patient-derived *BRCA2*-mutated ovarian cancer tissue [27] or lung cancer cells [26] and a murine model of hereditary *BRCA1*-deficient breast cancer [28]. Olaparib also displayed vasodilatory properties ex vivo and increased tumour perfusion [26].

In the EU, olaparib is not recommended for use in combination with other anti-cancer agents (as myelosuppressive activity may be potentiated/prolonged) and requires caution if coadministered with immunosuppressants or vaccines (as the potential pharmacodynamic interactions have not been assessed) [4].



Chemical structure of olaparib

Cancer cells deficient in RAD51C were highly sensitive to olaparib in vitro, indicating that this protein (which is essential for HR) may be a useful biomarker for olaparib benefit [29]. A seven-gene signature has been identified as a potential predictor of olaparib outcome, with some genes being associated with sensitivity (*CHEK2*, *MK2*) and others with resistance (*BRCA1*, *MRE11A*, *NBS1*, *TDG*, *XPA*) [30]. Additional mechanisms of olaparib resistance may involve drug efflux pump expression/upregulation [10, 28], although may be reversible with combined use of a p-glycoprotein inhibitor [28].

2.2 Pharmacokinetics

Absorption of olaparib is rapid after oral administration of the capsule formulation, with maximal plasma concentrations being achieved within 1–3 h post-dose in patients with cancer [5, 31]. In adults with advanced solid tumours, taking olaparib capsules with food reduced the rate at which the drug was absorbed relative to fasting administration, with the time taken to reach maximal concentrations delayed by ≈2 h [32]. In the EU, olaparib should be administered ≥1 h after food; patients should not eat for up to 2 h after taking the drug [4].

Olaparib had a mean apparent volume of distribution of 167 L after administration of a 400 mg capsule dose in patients with cancer [33], and the concentration of olaparib in breast tumours was ≈41 % that detected in plasma [9]. Olaparib-related material may bind to blood components, as the drug's concentration in blood versus plasma was 0.8 after a single 100 mg dose in patients with advanced solid tumours [31].

Olaparib is metabolized primarily via dehydrogenation and oxidation, as well as glucuronide and sulphide conjugation [34]. The cytochrome P450 enzyme CYP3A4 is predominant in the metabolism of olaparib in vitro [4, 5]. Excretion of the drug occurs largely via the faeces (42 %) and urine (44 %) [31], with unchanged drug being the main excreta component (accounting for ≈21 % of the dose) [34]. Plasma concentrations of olaparib were undetectable 16–24 h after administration of a single dose [31]. The drug had a mean terminal elimination half-life of 11.9 h and a mean apparent clearance of 8.64 L/h following a 400 mg capsule dose in patients with cancer [33].

Preliminary data suggest that mild renal impairment [creatinine clearance (CL_{CR}) 50–80 mL/min] may increase olaparib exposure versus normal renal function (mean 1.5-fold increase; however, the drug can be used in these patients in the USA [5] and EU [4], without adjustment of the starting dosage [5]. There are limited pharmacokinetic data for olaparib in patients with moderate/severe renal impairment (CL_{CR} < 50 mL/min) [4] and none in patients undergoing dialysis [5] or with hepatic impairment [4, 5]. Use of olaparib is not recommended in patients with hepatic impairment (serum bilirubin >1.5 times the upper limit of normal) or moderate/severe renal impairment in the EU [4].

2.2.1 Potential Drug Interactions

As olaparib is metabolized predominantly via CYP3A, drugs that inhibit or induce these enzymes may increase or decrease exposure to olaparib, respectively. Consequently, coadministration of olaparib with strong [4, 5] or moderate [5] CYP3A inhibitors/inducers is not recommended.

In vitro, olaparib inhibited CYP3A4 and induced CYP2B6 when used at concentrations higher than those achieved clinically; there was little, if any, inhibition of other CYP enzymes [5]. In the EU, caution is advised if administering olaparib in combination with CYP3A4 substrates, particularly those with a narrow therapeutic index [4].

Further in vitro data indicate that olaparib also inhibits breast cancer resistance protein [4, 5], organic anion-transporting polypeptide 1B1 [4, 5], organic cation transporters 1 and 2 [4, 5], organic anion transporter 3 [5], and multidrug and toxin extrusion proteins 1 and 2K [5], and is a substrate [4, 5] and inhibitor [4] of p-glycoprotein. It is not yet known if these findings are of clinical relevance [5], although caution is recommended in the EU if coadministering olaparib with a statin [4].

2.3 Therapeutic Trials

2.3.1 Ovarian Cancer

2.3.1.1 Monotherapy Maintenance treatment with oral olaparib 400 mg twice daily administered as capsules ($n = 136$) significantly prolonged median progression-free survival (PFS) (primary endpoint) relative to placebo ($n = 129$) in women with relapsed, platinum-sensitive ovarian cancer in a phase II trial (NCT00753545) (8.4 vs. 4.8 months; HR 0.35, 95 % CI 0.25–0.49; $p < 0.001$) [35], although no overall survival (OS) benefit was observed at the latest interim analysis (median OS was 29.8 vs. 27.8 months with placebo) [36]. This double-blind trial, known as Study 19, enrolled women with high-grade serous cancers (recurrent ovarian or fallopian tube cancer or primary peritoneal cancer) with or without germline *BRCA1/2* mutations who had already received ≥2 platinum-based chemotherapy regimens and had responded to the last.

In a predefined Study 19 subgroup analysis, a notable PFS benefit was observed with olaparib versus placebo in women with known *BRCA1/2* germline mutations (HR 0.11; 95 % CI 0.04–0.27; values estimated from a figure)

[35]. These findings were supported by a subsequent PFS analysis of total *BRCA1/2* status, in which the corresponding HR was 0.18 (95 % CI 0.10–0.31; $p < 0.0001$) in patients with a germline and/or tumor *BRCA1/2* mutation [37]. Significant ($p < 0.05$) benefit over placebo was also seen with olaparib for other clinical endpoints (including time to first or second subsequent therapy or death); as with PFS, the benefit was more pronounced in women with *BRCA* mutations [36].

In the phase II ICEBERG 3 trial in women with *BRCA1/2*-mutated advanced ovarian cancer (NCT00628251), oral olaparib (200 or 400 mg twice daily) did not differ significantly from intravenous pegylated liposomal doxorubicin (PLD) (the current standard of care) in terms of median PFS (primary endpoint; 6.5 and 8.8 vs. 7.1 months) or overall response rate (25 and 31 vs. 18 %) [38]. Patients in this randomized, open-label study had epithelial ovarian, primary peritoneal or fallopian tube carcinoma recurrence within 1 year of platinum-based chemotherapy and received olaparib 200 or 400 mg twice daily continuously as capsules ($n = 32$ in each group) or PLD 50 mg/m^2 via infusion every 28 days ($n = 33$).

An earlier phase II study (ICEBERG 2; NCT00494442) established the effectiveness of olaparib in women with *BRCA*-mutated recurrent ovarian cancer, with dosages of 400 and 100 mg twice daily being associated with objective response rates (primary endpoint) of 33 % (11 of 33 recipients) and 13 % (3 of 24 recipients) [39]. Clinical benefit was also seen with olaparib in ovarian cancer in other studies, including a non-randomized phase II trial (NCT00679783) that evaluated 400 mg twice daily (capsule formulation) in women with high-grade serous/poorly differentiated ovarian carcinoma ($n = 65$) or triple-negative breast cancer ($n = 26$) with/without *BRCA1/2* mutations [40], and the dose-escalation (40 mg daily for 2–3 weeks to 600 mg twice daily) and dose-expansion (200 mg twice daily) cohorts of a phase I trial in women with *BRCA1/2*-mutated ovarian cancer ($n = 50$) [41]. Another phase I trial (NCT00777582) in 77 ovarian or breast cancer patients with *BRCA1/2* mutations suggested the new tablet formulation of olaparib may have dose-dependent efficacy at 200–400 mg twice daily [42]. In an expansion of this trial ($n = 62$) [43], olaparib 300 mg twice daily was considered the best dosage for phase III trials.

2.3.1.2 Combination Therapy Administering olaparib capsules in combination with tablets of the anti-angiogenic agent cediranib (an inhibitor of vascular endothelial growth factor receptor kinases) showed promise as a treatment for recurrent ovarian cancer in a phase I dose-escalation study (NCT0116648), with an overall response rate of 44 % among the 18 women evaluable [44]. Women with metastatic triple-negative breast cancer were also included in the study, although none of the seven evaluable achieved a clinical response [44]. On the basis of this trial, olaparib 200 mg twice daily plus cediranib 30 mg daily was taken into the phase II open-label portion of the study and compared with olaparib alone in women with recurrent platinum-sensitive ovarian cancer [45]. In this trial, the dual regimen ($n = 44$) was associated with a significantly longer median PFS (17.7 vs. 9.0 months; $p = 0.005$) and a significantly greater objective response (79.6 vs. 47.8 % of patients; $p = 0.002$) than olaparib 400 mg twice daily as monotherapy ($n = 46$).

Olaparib (capsules [46] or tablets [47]) may also be effective in ovarian cancer when used in combination with either the phosphoinositide 3 kinase inhibitor buparlisib (NCT01623349; $n = 25$ treated to date) [47] or the alkylating agent carboplatin (NCT01445418; $n = 37$) [46], according to dose-escalating phase I/Ib trials (which also included patients with breast cancer; $n = 9$ [47] or 8 [46]).

Triple combination therapy with olaparib, carboplatin and paclitaxel is also under investigation for ovarian cancer in phase Ib/II trials. In the largest of these studies (NCT01081951; $n = 162$ randomized), olaparib capsules 200 mg twice daily plus carboplatin and paclitaxel, followed by olaparib maintenance monotherapy (400 mg twice daily) significantly prolonged PFS compared with carboplatin plus paclitaxel followed by no further treatment in women with platinum-sensitive recurrent serous ovarian cancer (12.2 vs. 9.6 months; hazard ratio 0.51, 95 % CI 0.34–0.77; $p = 0.0012$), with the benefit of triple versus dual therapy being greater in those with mutated *BRCA 1/2* (hazard ratio 0.21, 95 % CI 0.08–0.55; $p = 0.0015$) [48]. OS did not significantly differ between regimens in the overall population or the *BRCA* mutated subgroup at final analysis [48]. In another study in 14 women with advanced relapsed ovarian cancer (NCT01650376), half achieved a complete or partial response with olaparib tablets plus carboplatin and paclitaxel (four and three patients, respectively) and the rest had stable disease, progressive disease or were not evaluable (three, two and two patients) [49].

2.3.2 Other Malignancies

A noncomparative open-label phase II trial (NCT01078662) indicates that monotherapy with olaparib capsules 400 mg twice daily may have benefit in various advanced solid tumours (including ovarian, breast, pancreatic and prostate) with germline *BRCA1/2* mutations that are refractory to standard chemotherapy [50]. Among the patients in this study ($n = 298$), 26 % achieved a partial or complete response and 42 % had stable disease for ≥8 weeks. However, in a similarly designed phase II

trial in 12 patients with advanced Ewing sarcoma refractory to standard chemotherapy (NCT01583543), there were no objective tumour responses and only four patients achieved stable disease after treatment with olaparib tablets 400 mg twice daily for a median 5.7 weeks [51].

Several phase I/Ib trials also provide preliminary evidence of clinical benefit with olaparib (capsules [52–55] or tablets [56], where reported) used alone [8, 52] or in combination with conventional chemotherapy agents (including PLD [53], cisplatin [54] and carboplatin and/or paclitaxel [55, 56]), in patients with advanced solid tumours, some of which included only patients with *BRCA1/2* mutations [8]. Another phase I advanced solid tumour study (NCT00710268) showed the potential for olaparib capsules to be used in combination with bevacizumab [57], whereas similar studies assessing olaparib (capsules where specified [58]) in combination with cisplatin/gemcitabine [59], dacarbazine [58] or topotecan [60] in patients with advanced solid tumours were limited by haematological toxicities.

Additional phase I/Ib [61–65] or II [66, 67] trials have evaluated olaparib-based therapy specifically in patients with advanced breast cancer (*BRCA1/2*-mutated [67] or triple-negative [64, 65] disease), locally advanced head/neck cancer [61], relapsed glioblastoma [62], recurrent/metastatic gastric cancer [66] or epidermal growth factor receptor-positive advanced NSCLC [63]. Where specified, these studies used olaparib capsules [64, 65] or tablets [66].

Key clinical trials of olaparib

Drugs(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Olaparib + AZD2014 or AZD5363	Ovarian cancer	I/II	Recruiting	USA	NCT02208375	M.D. Anderson Cancer Center
Olaparib + cediranib	Ovarian or breast cancer	I/II	Recruiting	USA	NCT01116648	National Cancer Institute
Olaparib + carboplatin + paclitaxel	Ovarian or uterine cancer	I/II	Recruiting	USA	NCT01650376	Swedish Medical Center
Olaparib	Ovarian or breast cancer	II	Ongoing	Canada	NCT00679783	AstraZeneca
Olaparib + carboplatin + paclitaxel	Ovarian cancer	II	Ongoing	Multinational	NCT01081951	AstraZeneca
Olaparib	Ovarian cancer	II	Withdrawn	USA	NCT01661868	Dane-Faber Cancer Institute
Olaparib	Ovarian cancer	II	Ongoing	Multinational	NCT00628251 (ICEBERG 3)	AstraZeneca
Olaparib	Ovarian cancer	II	Ongoing	Multinational	NCT00494442 (ICEBERG 2)	AstraZeneca
Olaparib	Ovarian cancer	II	Completed	Multinational	NCT00753545 (Study 19)	AstraZeneca
Olaparib	Ovarian cancer	III	Recruiting	Multinational	NCT01844986 (SOLO 1; OSTRIA1)	AstraZeneca
Olaparib	Ovarian cancer	III	Ongoing	Multinational	NCT01874353 (SOLO2; OSTRIA2)	AstraZeneca
Olaparib	Ovarian cancer	III	Planned	Multicentre	NCT02282020 (SOLO 3)	AstraZeneca
Olaparib + paclitaxel	Breast cancer	I/II	Ongoing	Multinational	NCT00707707	AstraZeneca
Olaparib	Breast cancer	II	Ongoing	Multinational	NCT00494234 (ICEBERG 1)	AstraZeneca
Olaparib	Breast cancer	III	Recruiting	USA, Europe	NCT02000622	AstraZeneca
Olaparib	Breast cancer	III	Recruiting	Multinational	NCT02032823	AstraZeneca

continued

Drugs(s)	Indication	Phase	Status	Location(s)	Identifier	Sponsor
Olaparib + abiraterone	Prostate cancer	II	Recruiting	Multinational	NCT01972217 (EudraCT2013-003520-37)	AstraZeneca
Olaparib	Prostate cancer	II	Recruiting	UK	NCT01682772 (TOPARP)	Institute of Cancer Research, UK
Irinotecan + cisplatin + mitomycin C +/− olaparib	Pancreatic cancer	I/II	Ongoing	USA	NCT01296763	Sidney Kimmel Comprehensive Cancer Center
Olaparib	Pancreatic cancer	III	Planned	USA	NCT02184195	AstraZeneca
Olaparib + paclitaxel	Gastric cancer	II	Completed	Republic of Korea	NCT01063577	AstraZeneca
Olaparib + paclitaxel	Gastric cancer	III	Recruiting	Taiwan, Japan, China, Republic of Korea	NCT01924533	AstraZeneca
Olaparib	Colorectal cancer	II	Completed	USA	NCT00912743	AstraZeneca
Olaparib + gefitinib	Non-small cell lung cancer	I/II	Recruiting	Spain	NCT01513174	Spanish Lung Cancer Group
Olaparib	Non-small cell lung cancer	II	Recruiting	UK	NCT01788332	AstraZeneca
Olaparib	Ewing's sarcoma	II	Ongoing	USA	NCT01583543	Massachusetts General Hospital
Olaparib	Advanced cancer	II	Ongoing	Multinational	NCT01078662	AstraZeneca

2.4 Adverse Events

Oral olaparib 400 mg twice daily had acceptable tolerability when administered as maintenance monotherapy in women with relapsed ovarian cancer (with or without *BRCA1/2* mutations) responding to platinum-based therapy in the pivotal phase II trial (Study 19) [35]. Adverse events (AEs) reported in 10 % more olaparib than placebo recipients included nausea (68.4 vs. 35.2 %), fatigue (48.5 vs. 37.5 %), vomiting (31.6 vs. 14.1 %) and anaemia (16.9 vs. 4.7 %). AEs were generally mild or moderate in severity; however, olaparib was associated with a 1.7-fold higher incidence of grade 3 or 4 AEs than placebo (35.3 vs. 20.3 %), with the most common being fatigue (6.6 vs. 3.1 %) and anaemia (5.1 vs. 0.8 %). More olaparib than placebo recipients had dose interruptions (27.9 vs. 8.6 %) or reductions (22.8 vs. 4.7 %) because of AEs (most frequently vomiting, nausea and fatigue) [35].

Similarly, in the phase II ICEBERG 3 trial in women with *BRCA1/2*-mutated recurrent ovarian cancer, the most frequent AE was grade $\leq$2 nausea with oral olaparib 400 or 200 mg twice daily (72 and 56 vs. 50 % with PLD) and grade $\leq$2 stomatitis with PLD (53 vs. 0 % in each olaparib group) [38]. Two deaths occurred in the olaparib 200 mg twice daily group (as a result of cerebrovascular accident or myelodysplastic syndrome); both were considered possibly treatment related [38]. A similar adverse event profile was seen with olaparib (400 or 100 mg twice daily) in other phase II monotherapy studies in ovarian cancer [39, 40].

Use of olaparib plus cediranib in women with recurrent ovarian or triple-negative breast cancer in phase I [44] or II [45] studies was most commonly associated with fatigue, diarrhoea, nausea and hypertension, with these AEs occurring more frequently than with olaparib alone in the comparative trial [45]. However, when olaparib was used in combination with carboplatin and/or paclitaxel in phase Ib/II ovarian cancer trials [46, 49], the most common adverse events were consistent with those typical of chemotherapy (e.g. neutropenia, anaemia).

2.5 Companion Diagnostic

Myriad Genetics have developed BRCA gene testing for use as a companion diagnostic (BRACAnalysis CDx™) with PARP inhibitors, such as olaparib; all four modules of the premarket approval application for the test have been submitted to the US FDA [68]. The next-generation companion diagnostic, Tumour BRACAnalysis CDx™, detects

both germline and somatic *BRCA* mutations (and thus identifies up to 50 % more *BRCA* mutation carriers than conventional germline testing alone) and is launched in Europe [68]. Myriad Genetics have made an agreement with AstraZeneca to provide companion diagnostic BRCA testing for the olaparib phase III trial programme [69].

2.6 Ongoing Clinical Trials

AstraZeneca has initiated the phase III SOLO programme of olaparib maintenance monotherapy in patients with *BRCA*-mutated ovarian cancer with complete or partial response to first-line platinum-based chemotherapy [SOLO 1 (OSTRIA 1); NCT01844986] or after completing ≥2 lines of platinum-based chemotherapy [SOLO 2 (OSTRIA 2); NCT01874353] [70]. Each trial is double-blind, placebo-controlled and uses the tablet formulation of olaparib. Enrollment began in September 2013; by January 2014, 10 % of the target patient population of SOLO 1 and 2 had been recruited (≈344 and ≈264 patients randomized) [70]. AstraZeneca is planning to initiate SOLO 3, a randomized, open-label study comparing olaparib monotherapy with single-agent chemotherapy in patients with platinum-sensitive, *BRCA1/2* mutation-positive, relapsed ovarian cancer (NCT02282020). This study will include ≈411 patients who have received ≥2 lines of platinum-based chemotherapy. In addition, two phase III trials are planned to evaluate olaparib plus cediranib for the treatment of ovarian cancer [71], and a phase I/II trial (NCT02208375) designed to assess olaparib in combination with a mammalian target of rapamycin complex inhibitor or a kinase inhibitor is recruiting participants.

With regard to other indications, phase III *BRCA1/2*-mutated breast cancer trials are planning to compare olaparib with standard chemotherapy in metastatic disease (NCT02000622) and assess adjuvant olaparib in high-risk, HER2-negative primary disease following local treatment and adjuvant/neoadjuvant chemotherapy (NCT02032823). In addition, a phase III trial (NCT01924533) comparing olaparib plus paclitaxel with paclitaxel alone as second-line therapy in advanced gastric cancer has been initiated, and another phase III study (NCT02184195) is planned to evaluate olaparib monotherapy in patients with *BRCA*-mutated metastatic pancreatic cancer without progression on first-line platinum-based chemotherapy. Olaparib is also being assessed in combination with gemcitabine (NCT00515866) or irinotecan, cisplatin plus mitomycin C (NCT01296763) in advanced pancreatic cancer and in combination with radiotherapy in oesophageal cancer (NCT01460888) in phase I or I/II trials.

There are also phase II trials assessing olaparib in other indications, including advanced castration-resistant prostate cancer [as monotherapy (NCT01682772; TOPARP) or in combination with abiraterone (NCT01972217; EudraCT2013-003520-37] and advanced NSCLC [as monotherapy (NCT01788332) or in combination with gefitinib (NCT01513174)]. Other phase I/II trials are evaluating olaparib in combination with cisplatin-based chemoradiotherapy in advanced squamous cell carcinoma of the head and neck (ORCA; EudraCT2010-023599-24), olaparib plus radiotherapy (with or without cisplatin) in advanced NSCLC (NCT01562210) and olaparib plus radiotherapy in glioblastoma unsuitable for radical chemoradiation (PARADIGM; ISRCTN52658296). In addition, several phase I trials are investigating olaparib in patients with solid tumours [including those with renal (NCT01894256) or hepatic (NCT01894243) impairment].

3 Current Status

On the 18th December 2014, olaparib was approved in the EU for the maintenance treatment of adults with platinum-sensitive, relapsed, *BRCA* mutation-positive (germline and/or somatic), high-grade, serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy [4, 72]. On the 19th December, the drug received approval in the USA for use as monotherapy in patients with deleterious or suspected deleterious germline *BRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer treated with three or more prior lines of chemotherapy [5, 73].

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