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Olaparib: A Review of Its Use as Maintenance Therapy in Patients with Ovarian Cancer

James E. Frampton[1]

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Abstract Olaparib (Lynparza™) is a first-in-class, orally-active, small molecule, poly (ADP-ribose) polymerase inhibitor that induces synthetic lethality in homozygous *BRCA*-deficient cells. In the EU, the capsule formulation of olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, *BRCA*-mutated (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. This approval was based on the results of study 19, a randomized phase II trial in 265 patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer (HGSOC) who had received two or more platinum-based regimens and who had a partial or complete response to their most recent platinum-based regimen. Study 19 met its primary endpoint by demonstrating a significant improvement in progression-free survival in patients receiving olaparib compared with those receiving placebo. Moreover, a preplanned retrospective analysis identified those patients with a *BRCA* mutation (who comprised one-half of the overall study population) as being the subgroup that derived the greatest clinical benefit from olaparib. Single-agent olaparib was generally well tolerated, with the majority of adverse events being of mild to moderate severity and not requiring interruption of treatment. Fatigue, anaemia and neutropenia were the most frequently reported severe (grade ≥3) adverse events. An as yet unapproved tablet formulation of olaparib that has a lower pill burden than the capsule formulation is currently being investigated in phase III clinical studies.

Olaparib (capsule formulation) in Platinum-Sensitive, Relapsed, *BRCA*-Mutated, HGSOC in the EU: A Summary

Approved as monotherapy for maintenance treatment of patients in response to their most recent platinum-based regimen
Orally administered and generally well tolerated, making it suitable for long-term maintenance therapy
Treatment should commence ≤8 weeks after the last dose of platinum-based chemotherapy
Significantly prolongs progression-free survival, but not overall survival, according to analyses of the pivotal phase II trial that have been performed to date

1 Introduction

Epithelial ovarian cancer (OC) is the most common cause of death from gynaecological tumours in the Western world [1, 2]. The majority of women with OC present with advanced (stage III or IV) disease; currently, they have a 5-year survival rate of <30 % [3]. OC is a heterogeneous disease, with high-grade serous ovarian cancer (HGSOC)

The manuscript was reviewed by: ***M. Hall***, Department of Medical Oncology, Mount Vernon Cancer Centre, Northwood, UK; ***M. Markman***, Cancer Treatment Centers of America, Philadelphia, Pennsylvania, USA.

✉ James E. Frampton
demail@springer.com

[1] Springer, Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand

being both the most common (≈60–80 % of cases) and the most aggressive histological subtype [4].

The standard treatment for advanced OC includes both cytoreductive surgery and platinum-based chemotherapy [5]. Initial response rates are high, although most (≈70 %) patients experience recurrence within a 3-year period [5–7]. Re-treatment with a platinum-based doublet is the current treatment of choice for patients who are 'platinum sensitive' (i.e. those who relapse ≥6 months after an initial or subsequent course of platinum-based chemotherapy), although this approach is limited by cumulative toxicities and, ultimately, the development of chemoresistance [5, 8]. Patients are considered to be 'platinum resistant' if they experience recurrence or progression <6 months after an initial or subsequent course of platinum-based chemotherapy; they are considered to be 'platinum-refractory' if they experience recurrence or progression during or <1 month after an initial or subsequent course of platinum-based chemotherapy [5].

Greater understanding of the tumour biology of OC has led to the development of targeted anticancer medications that have the ability to improve tumour responses to platinum-based chemotherapy, thereby alleviating some of the limitations of the latter [3, 9]. The most advanced agents in this regard are bevacizumab, an intravenously-administered vascular endothelial growth factor inhibitor [10], and olaparib (Lynparza™), a first-in-class, orally-active, small molecule, poly (ADP-ribose) polymerase (PARP) inhibitor [11–13]. Regarding the latter, DNA damage is repaired via six primary pathways: four addressing single-strand breaks [base excision repair (BER), nucleotide excision repair, mismatch repair and translesional synthesis] and two addressing double-stranded breaks [homologous recombination (HR) and non-homologous end-joining) in an interactive and interdependent manner. PARP is an important component of the BER pathway; PARP inhibition, by blocking BER, leads to the formation of double-stranded DNA breaks, which cannot be accurately repaired in HR-deficient cells, such as cancer cells harbouring homozygous *BRCA* mutations, but can in HR-proficient cells, such as non-cancer cells in *BRCA* mutation carriers (which are heterozygous for the mutation and therefore produce sufficient functional BRCA proteins) [12, 14–16]. As such, PARP inhibition leading to the selective death of HR-deficient tumour cells provides the first clinical example of the concept of 'synthetic lethality' [17, 18]. Approximately one-half of patients with HGSOC may have HR-deficient tumour cells due to germline or somatically acquired *BRCA1* or *BRCA2* mutations, epigenetic inactivation of *BRCA1,* or *BRCA* mutation-independent defects in the HR repair pathway [6, 19]; approximately one-quarter have germline (≈17 %) or somatic (≈6 %) *BRCA* mutations [6, 20].

This article briefly summarizes the pharmacological properties of olaparib and, in line with the approved use of the drug in the EU [21], focuses on the efficacy and tolerability of monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, *BRCA*-mutated, HGSOC who are in complete or partial response to platinum-based chemotherapy.

2 Pharmacodynamic Properties

Olaparib is a potent inhibitor of PARP-1, the most important and best understood of the 17 PARP family members [22]. In several cell lines, including ovarian A2780 cancer cells, olaparib inhibited 50 % of PARP-1 activity at concentrations of 6–8 nmol/L; >90 % inhibition occurred at a concentration of ≈100 nmol/L [13]. In a phase I clinical trial [23], PARP in the mononuclear cells of patients with advanced solid tumours, including ovarian cancers, was inhibited >90 % with olaparib dosages of ≥60 mg twice daily.

Olaparib displayed antitumour activity as a single agent in a *BRCA*-mutated human ovarian cancer xenograft model [24]. Additional preclinical data, which suggest that HR-proficient ovarian cancer cells can be sensitized to olaparib by combining the drug with an agent that inhibits HR, such as 17-allylamino-17-demethoxygeldanamycin [25] or suberoylanilide hydroxamic acid [26], are also consistent with the concept of synthetic lethality [25, 26] (Sect. 1). Although carboplatin showed better single agent efficacy than olaparib in the aforementioned xenograft model, the best treatment response was seen with a combination of olaparib and carboplatin [24].

Olaparib demonstrated antitumour activity as monotherapy in several phase I or II multicentre trials in women with relapsed, germline *BRCA*-mutated, advanced OC (n = 17–193) [23, 27–30]. The objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines ranged from 31 to 41 % in heavily pretreated patients who received olaparib 400 mg twice daily in phase II studies [28–30]. Moreover, responses were observed in patients considered to be platinum-sensitive (e.g. 38 [28] and 60 [30] %) as well as those considered to be platinum-resistant (e.g. 30 [28] and 33 [30] %). Olaparib 400 mg twice daily also showed antitumour activity (ORR of 24 %) among a cohort of 46 patients with non-*BRCA*-mutated OC who were included in one phase II study; all 11 responders had HGSOC [30].

3 Pharmacokinetic Properties

Table 1 summarizes the pharmacokinetic parameters of olaparib, based on the capsule formulation, which has been used in the clinical studies discussed in Sects. 2 and 4.

Table 1 Key pharmacokinetic properties of oral olaparib (capsules). Data are from the EU summary of product characteristics [21]

General pharmacokinetic profile
Rapidly absorbed (t_{max} 1–3 h post-dose)
Steady-state exposure achieved within ≈3–4 days, with no marked accumulation
Food ↓ t_{max} by ≈2 h and ↑ exposure by ≈20 %; pts should take OLP ≥1 h after food and refrain from eating preferably for up to 2 h afterwards
Plasma protein binding is ≈82 % and apparent volume of distribution is 167 L after administration of OLP 400 mg twice daily
Unchanged drug accounts for majority (≈70 %) of circulating material in plasma
Extensively metabolized, mainly via oxidation, as well as glucuronide and sulphide conjugation
Excreted mainly via urine and faeces (44 and 42 % of administered dose; 15 and 6 % as unchanged drug)
Apparent plasma clearance is 8.6 L/h and terminal elimination half-life is 11.9 h after administration of OLP 400 mg twice daily
Special pt populations
No apparent effect of bodyweight or age on OLP exposure; no starting dose adjustment necessary in elderly pts
Effect of RI on OLP exposure not studied. Can be administered in pts with mild RI (CL_{CR} >50 mL/min); however, not recommended for use in pts with moderate (CL_{CR} <50 mL/min) or severe (CL_{CR} <30 mL/min) RI due to limited data availability
Effect of HI on OLP exposure not studied. Not recommended for use in pts with HI (serum bilirubin >1.5× upper limit of normal)
No evidence of marked inter-ethnic differences (Caucasian vs. Japanese pts); no dose adjustment necessary, based on ethnicity

CL_{CR} creatinine clearance, *HI* hepatic impairment, *OLP* olaparib, *pt(s)* patient(s), *RI* renal impairment, *t_{max}* time to peak plasma concentration, ↑ increased, ↓ decreased

Absorption of olaparib is rapid; similarly, elimination of the drug, mainly via the urine and faeces, is relatively rapid (Table 1).

Systemic exposure to olaparib increased in a less than dose-proportional fashion following administration of doses >100 mg in a phase I study in patients with advanced solid tumours, including those with OC carrying a *BRCA* mutation [23].

Cytochrome P450 (CYP) 3A4/5 are the isoenzymes primarily responsible for the metabolic clearance of olaparib; in the absence of relevant (drug-drug interaction) data, it is recommended that coadministration of olaparib with strong or moderate CYP3A inhibitors or inducers be avoided [21]. Moreover, olaparib may inhibit CYP3A4 in vitro; caution should be exercised if the drug is coadministered with a CYP3A4 substrate, particularly one with a narrow therapeutic margin [21].

Olaparib is a substrate for, and may also be an inhibitor of, the efflux transporter P-glycoprotein (P-gp) in vitro; caution should be exercised if the drug is coadministered with a statin, as exposure to the latter may be increased [21].

4 Therapeutic Efficacy

The efficacy of olaparib maintenance monotherapy in women with platinum-sensitive, relapsed, HGSOC, including those with a *BRCA* mutation, who are in response to platinum-based chemotherapy has been assessed in study 19, a randomized, double-blind, placebo-controlled, multicentre, phase II trial [8, 31].

Briefly, eligible patients were aged ≥18 years and had recurrent ovarian or fallopian tube cancer, or primary peritoneal cancer, with high-grade (grade 2 or 3) serous features or a serous component. They were required to have: (1) completed at least two previous courses of platinum-containing therapy, (2) demonstrated platinum sensitivity to the penultimate line of platinum-containing therapy and (3) shown an objective response to the most recent line of platinum-containing therapy, according to RECIST or Gynecologic Cancer Intergroup cancer antigen 125 criteria. Those recruited were randomized to receive olaparib 400 mg twice daily (capsules) or placebo within 8 weeks after completion of the last dose of platinum-based chemotherapy; study medications were continued until progression in the absence of unacceptable toxicity [8, 31].

Knowledge of *BRCA* mutation status was not necessary for study entry, but was established retrospectively for 254 (96 %) of the 265 trial participants. A prespecified exploratory analysis of all efficacy endpoints was done according to *BRCA* mutation status; patients who harboured a deleterious, or suspected deleterious, germline or somatic *BRCA* mutation were included in the *BRCA*-mutation subgroup ($n = 136$), while patients with no known or reported *BRCA* mutation and those with BRCA variants of unknown significance were included in the wild-type *BRCA* subgroup ($n = 118$). The *BRCA*-mutation and wild-type *BRCA* subgroups were generally well matched for demographic and baseline characteristics [8].

Compared with placebo, olaparib as maintenance monotherapy significantly increased investigator-assessed

progression-free survival (PFS), the primary endpoint of the trial [31]. According to the preplanned, retrospective analysis [8], the magnitude of the improvement over placebo in median PFS in the *BRCA*-mutation subgroup (6.9 months) was larger than that in the wild-type *BRCA* subgroup (1.9 months) and the overall study population (3.6 months) (Table 2). The hazard ratio for PFS in the *BRCA*-mutation subgroup based on blinded independent central review [0.22 (95 % CI 0.12–0.40); $p < 0.0001$) [8] was consistent with the investigator assessment (see Table 2).

Retrospective, exploratory analyses were conducted to determine the time to first subsequent therapy or death (TFST) as well as the time to second subsequent therapy or death (TSST) [31]. The aim of TFST was to assess PFS with additional maturity [at the time of the PFS analysis, 153 progression events had occurred (in 57.7 % of patients)]. The intention of TSST was to provide information about the treatment benefit beyond progression. Both analyses were performed in patients who had received at least one dose of study medication [31]. Compared with placebo, olaparib significantly prolonged TFST and TSST, regardless of *BRCA* mutation status (Table 2).

Overall survival (OS) did not differ significantly between olaparib and placebo recipients in the overall study population or the *BRCA*-mutation and wild-type *BRCA* subgroups, based on the second interim analysis of this secondary endpoint, which was performed at 58 % maturity (i.e. after 58 % of the patients had died) (Table 2). There was, however, no evidence of a survival detriment among patients with a *BRCA* mutation who received olaparib [8]. A further, final analysis of OS is planned at ≈85 % maturity [8].

Disease-related symptoms and health-related quality of life endpoints were also assessed; however, no statistically significant or clinically relevant differences were noted between olaparib and placebo recipients in the overall study population or the *BRCA*-mutation and wild-type *BRCA* subgroups [8].

Among the eight olaparib and 10 placebo recipients with a somatic *BRCA* mutation in the *BRCA*-mutation subgroup, three and six experienced progression events and four and six died [8].

5 Tolerability

Olaparib as maintenance monotherapy was generally well tolerated in women with platinum-sensitive, relapsed, HGSOC, including those with a *BRCA* mutation, who were in response to platinum-based chemotherapy in study 19 [31]. The majority of adverse events were of mild to moderate severity and did not require interruption of the treatment [31].

In the overall population, the most frequently reported adverse events of any grade in olaparib recipients were nausea (71 vs. 36 % for placebo), fatigue (52 vs. 39 %), vomiting (34 vs. 14 %), diarrhoea (27 vs. 24 %), abdominal pain (25 vs. 27 %), anaemia (21 vs. 5 %), headache (21 vs. 13 %), constipation (21 vs. 11 %) and decreased appetite (21 vs. 13 %) [8]. The most frequently reported severe adverse events (grade ≥3) in olaparib recipients were fatigue (7 vs. 3 % for placebo), anaemia (5 vs. <1 %) and neutropenia (4 vs. <1 %) [8]. Of the five olaparib recipients who experienced severe neutropenia, three experienced a grade 4 adverse event [8]. Small intestinal obstruction, the most common serious adverse event, occurred in 2 (1 %) of 136 olaparib-treated patients versus 3 (2 %) of 128 placebo-treated patients [8].

Twice as many olaparib than placebo recipients had dose interruptions (36 vs. 16 %) or reductions (42 vs. 22 %) because of adverse events (most frequently nausea, fatigue and vomiting) [8]. Discontinuations due to adverse events occurred in approximately three times as many olaparib recipients compared with placebo recipients (5.1 vs. 1.6 %) [8].

The adverse event profile of olaparib in the *BRCA*-mutation subgroup was consistent with that in the overall study population, with, for example, fatigue, anaemia and neutropenia being the most common severe adverse events (Fig. 1).

6 Dosage and Administration

In the EU, the recommended dosage of olaparib capsules for maintenance monotherapy is 400 mg twice daily [21]. Treatment should be commenced no later than 8 weeks after completion of the last dose of platinum-based chemotherapy; it is recommended that maintenance therapy be continued until progression of the underlying disease. Treatment may be interrupted and/or the dosage can be reduced (first to 200 mg twice daily and finally to 100 mg twice daily) in order to manage adverse events [21].

Local prescribing information should be consulted for full details of contraindications, special warnings and precautions, and drug interactions relating to the use of olaparib.

Table 2 Preplanned, retrospective analysis [8] of efficacy endpoints by *BRCA* mutation status in a pivotal phase II study [31]

Endpoint	Overall study population		*BRCA*-mutation subgroup		Wild-type *BRCA* subgroup	
	OLP[a] ($n = 136$)	PL ($n = 129$)	OLP[a] ($n = 74$)	PL ($n = 62$)	OLP[a] ($n = 57$)	PL ($n = 61$)
PFS[b]						
No. of events (% pts)	60 (44)	94 (73)	26 (35)	46 (74)	32 (56)	44 (72)
Median (months) (95 % CI)	8.4 (7.4–11.5)	4.8 (4.0–5.5)	11.2 (8.3–NC)	4.3 (3.0–5.4)	7.4 (5.5–10.3)	5.5 (3.7–5.6)
HR (95 % CI)	0.35 (0.25–0.49)***		0.18 (0.10–0.31)***		0.54 (0.34–0.85)**	
OS[c]						
No. of deaths (% pts)	77 (57)	77 (60)	37 (50)	34 (55)	36 (63)	41 (67)
Median (months) (95 % CI)	29.8 (27.2–35.7)	27.8 (24.4–34.0)	34.9 (29.2–NC)	31.9 (23.1–40.7)	24.5 (19.8–35.0)	26.2 (22.6–33.7)
HR (95 % CI)	0.88 (0.64–1.21)		0.73 (0.45–1.17)		0.99 (0.63–1.55)	
TFST						
No. of events (% pts)	95 (70)	118 (92)	46 (62)	54 (87)	45 (79)	59 (97)
Median (months) (95 % CI)	13.4 (11.3–15.7)	6.7 (5.7–8.2)	15.6 (12.3–28.2)	6.2 (5.3–9.2)	12.9 (7.8–15.3)	6.9 (5.7–9.3)
HR (95 % CI)	0.40 (0.30–0.52)***		0.33 (0.22–0.50)***		0.45 (0.30–0.67)***	
TSST						
No. of events (% pts)	88 (65)	108 (84)	42 (57)	49 (79)	42 (74)	55 (90)
Median (months) (95 % CI)	19.1 (16.6–22.3)	14.8 (14.0–16.7)	23.8 (17.7–NC)	15.2 (13.9–18.7)	17.1 (15.2–20.0)	14.7 (12.8–18.1)
HR (95 % CI)	0.53 (0.40–0.71)***		0.44 (0.29–0.67)***		0.64 (0.42–0.96)*	

HR hazard ratio, *NC* not calculable, *OLP* olaparib, *OS* overall survival, *PFS* progression-free survival, *PL* placebo, *pts* patients, *TFST* time (from randomization) to first subsequent therapy or death, *TSST* time (from randomization) to second subsequent therapy or death

* $p = 0.033$, ** $p = 0.0075$, *** $p \leq 0.00013$ vs. PL

[a] 400 mg twice daily (capsules)

[b] As assessed by local investigators. Primary endpoint

[c] Performed at 58, 51 and 65 % maturity (overall study population, *BRCA*-mutation subgroup and wild-type *BRCA* subgroup, respectively)

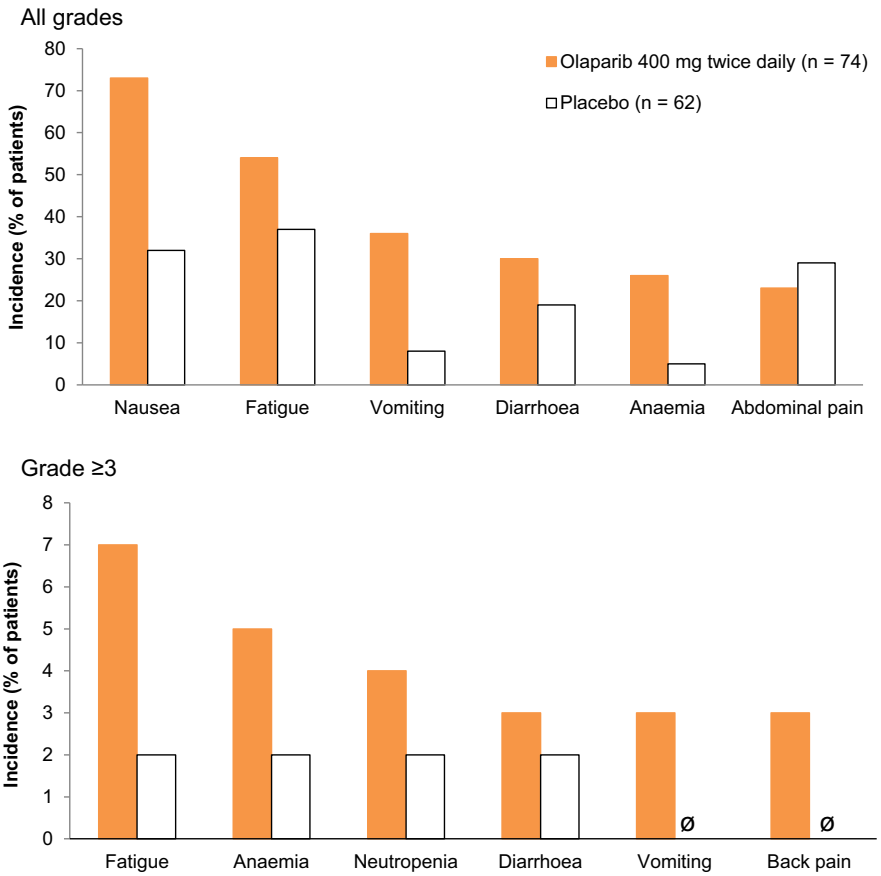

Fig. 1 Commonly occurring adverse events [i.e. incidence among olaparib-treated patients of >20 % (all grades) or ≥2 % (grade ≥3)] in the *BRCA*-mutation subgroup in a pivotal phase II study [8]. Ø = incidence of 0 %

7 Current Status of Olaparib in the Treatment of Ovarian Cancer

In the EU, the capsule formulation of olaparib (400 mg twice daily) is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, *BRCA*-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. *BRCA* mutation status should be determined by an experienced laboratory using a validated test method [21].

In the US, in contrast to the EU, the capsule formulation of olaparib (400 mg twice daily) is not indicated as maintenance therapy. Rather, it is indicated as monotherapy in patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced OC, as detected by an FDA-approved test (BRACAnalysis CDx^{TM}), who have completed at least three prior lines of chemotherapy [32]. This approval was based on the results of a single-arm, open-label, pivotal phase II study in which 34 % of 137 patients with germline *BRCA*-mutated advanced OC who had received three or more prior lines of chemotherapy experienced an objective response for a median duration of 7.9 months [32].

A tablet formulation of olaparib that requires fewer pills to be taken per day compared with the capsule formulation has been developed with the aim of improving patient convenience and compliance [13]. The comparative bioavailability, (antitumour) efficacy and tolerability of the two formulations has been assessed in studies in patients with advanced solid tumours [33–35]. According to the most recent study, in 62 patients with relapsed OC or primary peritoneal cancer and a *BRCA* mutation, a tablet dosage of 300 mg twice daily showed acceptable tolerability and, compared with the recommended capsule dosage (400 mg twice daily; Sect. 6), demonstrated similar efficacy, but with a much reduced total daily pill burden (4 vs. 16) [35].

The efficacy and tolerability of the tablet formulation of olaparib (300 mg twice daily) as maintenance monotherapy is being investigated in two ongoing, randomized, double-blind, placebo-controlled, multicentre, phase III trials in patients with *BRCA*-mutated HGSOC or high-grade endometrioid cancer who are in response to platinum-based chemotherapy (SOLO 1 and 2) [36]. SOLO 1 participants have newly diagnosed, advanced disease and have responded to first-line platinum therapy, whereas SOLO 2 participants have completed at least two prior lines of platinum therapy. The primary endpoint of both trials is PFS

(blinded independent central review of RECIST data); primary analyses will be performed at ≈60 % maturity [36].

Data selection sources: Relevant medical literature (including published and unpublished data) on olaparib was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) (searches last updated 7 April 2015), bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Olaparib, AZD2281, Lynparza
Study selection: Studies in patients with relapsed, high-grade serous ovarian cancer, including those carrying a *BRCA* mutation, who received olaparib. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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