

Olaparib (Lynparza) National Drug Monograph January 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis such as DNA transcription, cell cycle regulation, and DNA repair. Olaparib has been shown to have cytotoxicity and anti-tumor activity in select tumor cell lines with deficiencies in breast cancer susceptibility genes (BRCA).¹

Indication under Review in this document

Olaparib is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy¹

Dosage Form(s) Under Review

Capsules 50mg

REMS

REMS No REMS Postmarketing Requirements
See Other Considerations for additional REMS information

Pregnancy Rating

Category D

Executive Summary

Efficacy

- Olaparib received accelerated FDA approval based upon an unmet medical need among recurrent ovarian cancer patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) who have received multiple lines of chemotherapy and was approved based on a subgroup analysis report of a phase II prospective, multicenter, non-randomized, single-arm trial
- Olaparib provides a relatively well-tolerated treatment option for patients who have BRCA1/2 mutated ovarian cancer after ≥ 3 prior chemotherapy regimens who are platinum-resistant or not candidates for platinum therapy due to adverse effects or infusion reactions
- FDA approval was based on an ORR of 34%. ORR was higher in those who were platinum sensitive (46%) compared to those who were platinum resistant (30%). DoR was 7.9 months (95% CI 5.6-9.6)

Safety

- Common adverse effects include anemia, fatigue, and GI toxicities (nausea, vomiting, diarrhea, abdominal pain)
- Serious adverse effects include anemia, abdominal pain, intestinal obstruction, and pleural effusion
- Most common grade 3, 4 adverse reactions were anemia (18%) and lymphopenia (17%)
- Warnings/Precautions include the risk of MDS/AML, therefore CBC should be monitored at baseline and monthly thereafter ; ensure hematologic recovery from prior therapies before starting olaparib
- Warnings/Precautions include risk of pneumonitis, therefore monitor patients for new or worsening respiratory symptoms

Other Considerations

Outcome in clinically significant area	ORR, DoR
Effect Size	ORR 34% (95% CI 26-42) Median DoR 7.9 mos (95% CI, 5.6-9.6)

	Potential Harms	Grade 3: anemia (20%), abdominal pain (8%), fatigue (7%), dyspnea (4%), vomiting (3%), nausea (1%), diarrhea (1%), decreased appetite (1%), constipation (1%)
	Net Clinical Benefit	Not Available (accelerated approval)
	<ul style="list-style-type: none"> • Olaparib is the only agent available in relapsed ovarian cancer that targets those with BRCA1/2 mutations • Olaparib dose is 400 mg (eight 50 mg capsules) by mouth twice daily for a total daily dose of 800 mg. • Refer to Prescribing Information for full dosing information regarding dose adjustments due to adverse reactions and use with CYP3A inhibitors. • Olaparib was approved with a companion diagnostic test, BRCAAnalysis CDx™. The assay is for professional use only and is to be performed through Myriad Genetic Laboratories, Salt Lake City, Utah. 	
Projected Place in Therapy	<ul style="list-style-type: none"> • Olaparib’s FDA approval was based on a study in patients with germline BRCA1/2-mutated (gBRCA1/2m) advanced recurrent ovarian cancer who were platinum resistant (relapsed within 6 months of platinum therapy) or platinum sensitive (relapsed ≥ 6 months) but were not considered suitable for further platinum therapy due to toxicities or infusion reactions and who received ≥ 3 prior lines of chemotherapy • Olaparib had a 34% ORR in those with recurrent ovarian cancer with ≥ 3 prior chemotherapy regimens; response rates with current therapies in this setting are ~10-20%. • A higher ORR was seen in those with platinum-sensitive recurrence (who are unable to tolerate further platinum therapy due to toxicities or infusion reactions) compared to platinum-resistant disease (ORR 46% vs. 30% respectively), but a similar DoR was seen between the two groups (8.2 months vs. 8.0 months). • ORR was higher in those who received 3-5 prior lines of chemotherapy compared to those who received ≥ 6 prior lines of chemotherapy (31-57% vs. 13-20%). • Those considered to be the best candidates for this treatment include patients with recurrent ovarian cancer with BRCA1/2 mutations who are platinum-resistant or who are not able to tolerate further platinum therapy due to toxicities or infusion reactions; who have received 3-5 prior lines of chemotherapy and are able and willing to tolerate a large, oral pill burden twice daily. 	
Potential Impact	<ul style="list-style-type: none"> • Olaparib is a therapeutic option in patients with recurrent ovarian cancer with a BRCA 1 or 2 mutation who are platinum resistant or platinum sensitive but unable to tolerate further platinum-based chemotherapies • Olaparib was generally well tolerated in the studies 	

Background

Purpose for review

FDA-approval 12/2014

Issues to be determined:

- ✓ Evidence of need
- ✓ Does olaparib offer advantages to currently available alternatives?
- ✓ What safety issues need to be considered?
- ✓ Does olaparib have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options for recurrent platinum-resistant (relapse within 6 months of platinum-based chemotherapy) ovarian cancer.

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
Paclitaxel ²	ORR 25%	Recommended as 1 st line for platinum-resistant relapsed ovarian cancer

(For those who are platinum-sensitive, a combination platinum-based regimen is preferred.)	Topotecan ^{3,4}	ORR 17%, TTP 20 weeks, OS 56 weeks	
	Gemcitabine ⁵	ORR 9%, stable disease 55%, PFS 4 months, OS 13 months	
	Etoposide ⁶	ORR 27%	Not FDA approved for this indication
	Docetaxel ⁷	ORR 23%	Not FDA approved for this indication
	Non-formulary Alternative (if applicable)	Other Considerations	
	Pegylated liposomal doxorubicin ^{3,4}	ORR 20%, TTP 22 weeks, OS 66 weeks	Recommended as 1 st or 2 nd line for platinum-resistant relapsed ovarian cancer
	Nab-paclitaxel ⁹	ORR 23%, stable disease 36%	Not FDA approved for this indication
	Bevacizumab ⁸	ORR 16% (all PR), stable disease 61%	FDA-approved in conjunction with chemotherapy
	Pemetrexed ¹⁰	ORR 21%, stable disease 35%	Not FDA approved for this indication

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms olaparib and Lynparza. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Efficacy of Measures (see Appendix B: Approval Endpoints)

The following outcomes are commonly evaluated in the ovarian cancer trial setting:

- Objective response rate (ORR)
 - Complete response (CR), partial response (PR), stable disease (SD)
- Duration of response (DoR)
- Progression free survival (PFS)
- Overall survival (OS)

Summary of efficacy findings

The initial phase II study that led to the FDA approval study enrolled patients with germline BRCA1/2 mutation in a spectrum of recurrent cancers¹¹

- Patients were treated with olaparib 400mg PO BID
 - Dose interruptions and reductions to 200mg BID or 100mg BID were permitted for toxicity
- A total of 298 patients were enrolled
 - 193 patients with ovarian cancer
 - 62 patients with breast cancer
 - 23 patients with advanced pancreatic cancer
 - 8 patients with metastatic castrate resistant prostate cancer
 - 12 patients with other cancers: biliary tract cancer (n = 4), lung cancer (n = 3), bladder cancer (n = 2), colorectal cancer (n = 1), esophageal cancer (n = 1), endometrial cancer (n = 1)
- Patients enrolled with ovarian cancer were all heavily pre-treated with a mean number of prior regimens of 4.3 (range 1-14)
- All ovarian cancer patients were considered to be platinum resistant (relapse within 6 months) or not suitable for further platinum therapy due to significant toxicity or hypersensitivity to platinum
- Prior chemotherapy agents received were
 - Carboplatin (99.5%)
 - Paclitaxel (95%)
 - Liposomal doxorubicin (64%)
 - Gemcitabine (44%)
 - Cisplatin (28%)

Patients	ORR	Median DoR	PFS	OS
Total (n = 298)	26.2% (95%CI 21.3-31.6) CR 2%; PR 24% SD ≥ 8 wks 42%	208 days	--	--
Ovarian (n = 193)	31.1% (95%CI 24.6-38.1) CR 3%; PR 28% SD ≥ 8 wks 40%	225 days	7.0 months	16.6 months

A subgroup analysis report of the phase II, prospective, multicenter, non-randomized, single-arm trial focused on the ovarian cancer population. This study population included patients with known germline BRCA 1/2 mutated (gBRCA1/2m) ovarian cancer who had received ≥ 3 prior lines of chemotherapy¹²

- Patients included had either platinum-resistant disease (relapse within 6 months of platinum therapy) or platinum-sensitive disease (relapse ≥ 6 months) and considered not suitable for further platinum therapy due to significant toxicity or hypersensitivity to platinum
- The patients who were omitted from the Kaufman study was due to the number of prior regimens they received
- Patients were treated with olaparib 400mg PO BID. Dose reductions (to 200 or 100mg BID) and interruptions were permitted in the event of toxicity
- Average age of the study population was 58 years, most with ECOG PS 0 (55.5%) or 1 (38.0%)
- Number of prior chemotherapy regimens
 - 3 = 29.9% patients
 - 4 = 19.0% patients
 - 5 = 17.5% patients
 - 6-14 = 33.6% patients
- ORR and DoR were assessed by the investigator according to RECIST v1.1
- Tumor assessments were performed at baseline and at the end of every 2 cycles (28 days per cycle) up to and including the withdrawal visit
- Those with stable disease for a minimum of 16 weeks following start of treatment were considered to have stable disease (SD)
- The ORR, SD, and PFS were highest in patients considered platinum sensitive and not considered suitable to receive further platinum therapy
- Median DoR were similar for both platinum-sensitive and platinum-resistant patients
- When stratified by number of prior lines of chemotherapy received, ORR was highest for those who received < 6 prior lines of chemotherapy:
 - ORR 50-57% for platinum-sensitive with 3-5 prior lines of chemotherapy
 - ORR 31-39% for platinum-resistant with 3-5 prior lines of chemotherapy
 - ORR 20% for platinum-sensitive with ≥ 6 prior lines of chemotherapy
 - ORR 13% for platinum-resistant with ≥ 6 prior lines of chemotherapy

Platinum sensitivity	Confirmed responders	ORR	Median DoR	PFS	Prior lines of chemotherapy	ORR based upon prior chemo
Total (n = 137)	46 (33.6%)	34% (95%CI 26-42) CR = 2 (2%) PR = 44 (32%) SD = 23%	7.9 months (95%CI 5.6-9.6)	6.7 months (95%CI 5.5-7.6)	--	--
Platinum sensitive (n = 39)	18 (46.2%)	46% (95%CI 30-63) SD = 26%	8.2 months (95%CI 5.6-13.5)	9.4 months (95%CI 6.7-11.4)	3-5 ≥ 6	50-57% 20%
Platinum resistant (n = 81)	24 (29.6%)	30% (95%CI 20-41) SD = 24%	8.0 months (95%CI 4.8-14.8)	5.5 months (95%CI 4.2-6.7)	3-5 ≥ 6	31-39% 13%
Platinum refractory (n = 14)	2 (14.3%)	30% (95%CI 2-43) SD = 14%	6.4 months (95%CI 5.4-7.4)	--	--	--
Platinum status unknown (n = 3)	2 (66.7%)	67 (95%CI 9-99)	6.3 months (95%CI 4.7-7.9)	--	--	--

A study, conducted by Kaye et al., compared the efficacy of olaparib and pegylated liposomal doxorubicin (PLD) in a prospective, open-label, randomized, phase II trial¹³

- The patients included had ovarian cancer with BRCA1/2 deficiency and recurrence or progression within 12 months of the most recent platinum-based chemotherapy regimen
- Patients were randomized to receive olaparib 200mg PO BID, olaparib 400mg PO BID, or PLD 50mg/m² IV every 28 days
 - Dose reductions of olaparib from 400 to 200 to 100mg for permitted for toxicity
 - Dose reductions of PLD by 25% were allowed once
 - Patients were permitted to cross-over from PLD to olaparib after disease progression (25 patients)
- The study was not powered to detect a statistical difference between the 2 doses of olaparib
- Patients were stratified according to BRCA status and platinum sensitivity
 - Platinum sensitive (relapsed > 6 months)
 - Platinum resistant (relapsed ≤ 6 months)
- Disease assessments were performed at baseline and every 8 weeks until progression
- Centrally reviewed tumor assessments were used for sensitivity analysis
- PFS (primary outcome) was not statistically different between olaparib and PLD (HR 0.88; 95%CI 0.51-1.56; p=0.66)
- Responses seen in the PLD group were higher than expected and thus may have contributed to no difference seen when comparing olaparib to PLD

Tumor characteristic		Olaparib 200mg BID (n = 32)	Olaparib 400mg BID (n = 32)	PLD (n = 33)
BRCA status	BRCA 1	26 (81.3%)	28 (87.5%)	27 (81.8%)
	BRCA 2	6 (18.8%)	4 (12.5%)	6 (18.2%)
Platinum sensitivity	Sensitive	14 (43.8%)	15 (46.9%)	19 (57.6%)
	Resistant	18 (56.3%)	16 (50.0%)	14 (42.4%)
	Unknown	0	1 (3.1%)	0

No. of lines of previous cancer therapy at baseline	Olaparib 200mg BID (n = 32)	Olaparib 400mg BID (n = 32)	PLD (n = 33)
1	6 (18.8%)	1 (3.1%)	7 (21.2%)
2	7 (21.9%)	6 (18.8%)	9 (27.3%)
3	8 (25.0%)	15 (46.9%)	8 (24.2%)
4	7 (21.9%)	8 (25.0%)	6 (18.2%)
≥ 5	4 (12.5%)	2 (6.3%)	3 (9.1%)

Treatment Groups	PFS	ORR	DoR	OS
Olaparib 200mg BID (n = 32)	6.5 months (95%CI 5.5-10.1) Olaparib 200 BID vs. PLD HR 0.91 (95% CI, 0.48-1.74); p=0.78	25% OR 1.90(95%CI 0.55-7.01;p=0.31) SD ≥ 8wks 47%	6.0 months	9 deaths HR 0.66 (95%CI 0.27-1.55)
Olaparib 400mg BID (n = 32)	8.8 months (95%CI 5.4-9.2) Olaparib 400 BID vs. PLD HR 0.86 (95% CI, 0.45-1.62); p=0.63	31% OR 2.69 (95%CI 0.81-9.76;p=0.11) SD ≥ 8wks 59%	6.8 months	11 deaths HR 1.01 (95%CI 0.44-2.27)
PLD (n = 33)	7.1 months (95%CI 3.7-10.7)	18% OR 2.27 (95%CI 1.13-4.79;p=0.13) SD ≥ 8wks 52%	5.5 months	13 deaths

Potential Off-Label Use

- Metastatic castrate resistant prostate cancer¹⁴ (studied in those who received at least 2 prior regimens for CRPC)
- Recurrent breast cancer with BRCA1/2 mutation¹² (however a recent phase II trial did not show objective response in triple negative breast cancer patients¹⁵)
- Recurrent or metastatic gastric cancer in combination with paclitaxel after failure of first line therapy¹⁶
- Ongoing phase III trials:
 - Platinum-sensitive relapsed ovarian cancer with a BRCA1/2 mutation and who have previously received ≥ 2 lines of chemotherapy (SOLO3)
 - Advanced gastric cancer in combination with paclitaxel
 - gBRCA mutated pancreatic cancer not progressed on 1st line platinum-based chemotherapy
 - BRCA mutated high risk HER2 negative breast cancer as adjuvant treatment
 - Metastatic breast cancer with gBRCA1/2 mutations
 - Maintenance monotherapy in BRCA mutated ovarian cancer following first line platinum based chemotherapy

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	<ul style="list-style-type: none"> • None
Contraindications	<ul style="list-style-type: none"> • None
Warnings/Precautions	<ul style="list-style-type: none"> • Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) <ul style="list-style-type: none"> ○ Confirmed in 6 out of 298 (2%) patients enrolled in a single arm trial in patients with advanced germline BRCA mutated cancers ○ Occurred in 3 out of 136 (2%) patients in a randomized placebo controlled trial in patients with advanced ovarian cancer ○ Reported in 22 out of 2,618 (<1%) patients overall ○ Majority of cases (17 of 22 cases) were fatal ○ Duration of therapy with olaparib was between < 6 months to > 2 years ○ All patients had previous chemotherapy with platinum agents and/or other DNA damaging agents ○ Monitor CBC at baseline and monthly thereafter ○ Ensure hematologic recovery from previous treatment BEFORE starting olaparib ○ If hematologic toxicity is prolonged, interrupt olaparib and monitor CBC weekly until recovery; if blood levels have not recovered to \leq Grade after 4 weeks, refer patient to a hematologist for further investigation ○ Discontinue olaparib if MDS/AML is confirmed • Pneumonitis <ul style="list-style-type: none"> ○ Fatal cases occurred in < 1% of patients ○ Interrupt treatment if patients present with new or worsening respiratory symptoms (dyspnea, fever, cough, wheezing, radiological abnormalities) ○ Discontinue olaparib if pneumonitis is confirmed • Embryo-Fetal toxicity <ul style="list-style-type: none"> ○ Can cause fetal harm if administered to pregnant women based on mechanism of action and findings in animals ○ Occurred in rats at exposures below those in patients receiving the recommended human dose ○ Advise against becoming pregnant while taking olaparib and to use effective contraceptive methods during treatment and for at least 1 month after receiving the last dose of olaparib

Safety Considerations

- Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML) were confirmed in overall 22 out of 2,618

(<1%) patients receiving olaparib and 3 out of 136 (2%) with advanced ovarian cancer. Most incidences of MDS/AML were fatal, and duration of therapy with olaparib ranged from <6 months to > 2 years. All patients had prior chemotherapy with platinum agents and/or other DNA damaging agents

- The most common grade 3-4 adverse reactions were anemia (18%), lymphopenia (17%)
- Other common adverse reactions are mainly GI-related; nausea (64%), abdominal pain (43%), vomiting (43%), diarrhea (31%)
- The most common grade 3-4 non-hematologic lab abnormalities were elevations in LFTs
- In the trial that led to olaparib's FDA approval, the average daily dose of olaparib was 741 mg¹¹
 - Dose interruptions occurred in 83/193 (43%) patients
 - Dose reductions occurred in 41/193 (22%) patients
- Mean adherence was 93% (range 40-100%)¹¹
- Health-related quality of life (HRQoL) was measured by three scores of the Functional Assessment of Cancer Therapy-Ovarian Cancer (FACT-O) questionnaire (FACT-O Symptom Index, Trial Outcome Index, and total FACT-O score) in the study comparing olaparib to liposomal doxorubicin¹³
 - There were no significant differences in improvement or worsening rates between the olaparib and PLD treatment groups for the FACT-O Symptom Index and Trial Outcome Index scores
 - A higher improvement rate was noted for olaparib 400mg compared with PLD for the total FACT-O score (OR, 7.23;95% CI, 1.09-143.3; p = 0.039)
- The toxicity profile of olaparib is distinct from that of PLD¹³
 - Nausea, vomiting, fatigue, and anemia were more common in olaparib whereas stomatitis and palmar-plantar erythrodysesthesia were more common with PLD

Adverse Reactions

Common adverse reactions	All grades: any adverse event 151 (98%), nausea (60%), fatigue (55%), vomiting (44%), anemia (34%), abdominal pain (29%), diarrhea (30%), dysgeusia (19%), dyspepsia (21%), decreased appetite (20%), headache (14%), constipation (14%), cough (15%), dyspnea (15%)
Death/Serious adverse reactions	Grade \geq 3: any adverse event 84 (55%), anemia (20%), abdominal pain (8%), fatigue (7%), dyspnea (4%), vomiting (3%), nausea (1%), diarrhea (1%), decreased appetite (1%), constipation (1%) Serious adverse events 58/193 (30%) patients: anemia (12 patients, 6%), abdominal pain (10 patients (5%), intestinal obstruction (7, 4%), pleural effusion (4, 2%). 6 out of 193 (3%) patients experienced an adverse event with an outcome of death (myelodysplasia leading to acute leukemia, acute myeloid leukemia, cerebrovascular accident, chronic obstructive pulmonary disease, pulmonary embolism, wound dehiscence)
Discontinuations due to adverse reactions	Dose interruptions 83 (43%); dose reduction 42 (22%); discontinuation 9 (5%)

Drug Interactions

Drug-Drug Interactions

- Olaparib is primarily metabolized by CYP3A
 - Co-administering with a strong CYP3A4 inhibitor can potentially increase concentrations of olaparib by 2.7-fold
 - Co-administering with a moderate CYP3A4 inhibitor can potentially increase concentrations of olaparib by 2-fold
- Avoid concomitant use of strong and moderate CYP3A inhibitors and consider use of agents with less CYP3A4 inhibition.
- If a strong CYP3A inhibitor must be co-administered, reduce the dose of olaparib to 150mg twice daily; if a moderate CYP3A inhibitor must be co-administered, reduce the dose of olaparib to 200mg twice daily
 - Strong CYP3A inhibitors can include itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritonavir, lopinavir/ritonavir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir
 - Moderate CYP3A inhibitors can include amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil
- Avoid concomitant use of strong and moderate CYP3A4 inducers as they have been shown to significantly reduce the AUC of olaparib.
- If a strong or moderate CYP3A inducer must be co-administered, be aware for decreased efficacy of olaparib
 - Strong CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, St. John’s Wort) can potentially decrease concentrations of olaparib by 87%
 - Moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) can potentially decrease concentration olaparib by 50-60%
- Anticancer Agents
 - Studies indicate that the combination of olaparib with other myelosuppressive agents can lead to potentiated and prolonged bone marrow suppression

Drug-Food Interactions

- Avoid grapefruit and Seville oranges throughout treatment with olaparib (due to CYP3A inhibition)

Risk Evaluation

As of January 2016

	Comments				
Sentinel event advisories	<ul style="list-style-type: none"> • This medication is in a class the ISMP includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error • Sources: ISMP, FDA, TJC 				
Look-alike/sound-alike error potentials	NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
	!Olaparib 50mg cap Lynparza	Osimertinib Lenvima	None None	None None	Omalizumab Lopreeza Lopressor Lyrica Lysteda
	<ul style="list-style-type: none"> • !High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error. • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List) 				

Other Considerations

- Olaparib is the only agent available in relapsed ovarian cancer that targets those with BRCA1/2 mutations
- The drug was approved with a companion diagnostic test BRACAnalysis CDx™. The assay is for professional use only and is to be performed at Myriad Genetic Laboratories, Salt Lake City Utah.
- NCCN guidelines classify olaparib as a Category 2A recommendation for platinum-sensitive or platinum-resistant gBRCA1/2m ovarian cancer after 3 or more lines of chemotherapy¹⁹

Outcome in clinically significant area	ORR, DoR
Effect Size	ORR 34% (95% CI 26,42) Median DoR 7.9 mos (95% CI, 5.6-9.6)
Potential Harms	Grade 3: anemia (20%), abdominal pain (8%), fatigue (7%), dyspnea (4%), vomiting (3%), nausea (1%), diarrhea (1%), decreased appetite (1%), constipation (1%)
Net Clinical Benefit	Not Available

Dosing and Administration

- 400mg (eight 50mg capsules) by mouth twice daily for a total daily dose of 800mg.
- Continue treatment until disease has progressed or toxicity is unacceptable.
- If dose is missed, take next dose at its scheduled time
- Swallow capsule whole, do not chew, dissolve, or open capsule
- Refer to package insert for full dosing information regarding dose adjustments for:
 - Adverse reactions
 - Use with CYP3A inhibitors

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • In clinical studies enrolling patients with advanced tumors (69% with ovarian cancer), 148/735 (20%) were aged ≥ 65 years. Safety profile was similar irrespective of age with exception of adverse effects of Common Terminology Criteria for Adverse Events (CTCAE) ≥ 3 which were reported more frequently in patients ≥ 65 years (53.4%) than those < 65 years (43.4%)
Pregnancy	<ul style="list-style-type: none"> • Can cause fetal harm based on mechanism of action and findings in animals. Highly effective contraception should be used during treatment and for one month following the last dose.
Lactation	<ul style="list-style-type: none"> • Benefits of breastfeeding should be considered along with the mother's clinical need for olaparib, along with any potential adverse effects on the breastfed infant
Renal Impairment	<ul style="list-style-type: none"> • Preliminary data indicate a 1.5 fold increase in mean exposure (AUC) observed in patients with mild renal impairment (CrCl 50-80 ml/min). No dose adjustment required, but patients should be monitored closely for toxicity • No data in patients with moderate or severe renal impairment (CrCl < 50 ml/min) or patients on dialysis
Hepatic Impairment	<ul style="list-style-type: none"> • Effect of hepatic impairment has not been studied. Patients with bilirubin ≥ 1.5 x ULN and AST/ALT ≥ 2.5 x ULN (≥ 5 x ULN in the presence of liver metastases) were excluded from clinical trials
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified

Projected Place in Therapy

- Ovarian cancer represents 3% of cancers among women, the 2nd most common gynecologic malignancy, and leading cause of gynecologic cancer death. The American Cancer Society estimated 21,290 new diagnoses and 14,180 deaths in 2015.¹⁸ An ICD-9 code search of Veterans in FY15 indicate that 524 unique patients are coded with ovarian/fallopian tube cancer.
- Majority of patients (60-80%) with ovarian cancer develop persistent or recurrent disease despite high response rates to initial taxane-platinum-based chemotherapy
- Recurrences \geq 6 months of platinum therapy are considered platinum-sensitive and recurrences $<$ 6 months of platinum therapy are considered platinum resistant.
- For those who are platinum-sensitive, re-treatment with a combination platinum-based regimen is preferred unless the patient is unable to tolerate further platinum therapy due to toxicities or infusion reactions
- For those who are platinum-resistant, therapeutic options can include taxanes, anthracyclines, gemcitabine and/or topotecan. Paclitaxel, pegylated liposomal doxorubicin and topotecan have indirectly shown comparable efficacy with differing toxicity profiles.
- Patients with recurrent ovarian cancer often receive multiple lines of chemotherapy with time to progression shortening with consecutive therapies. Evidence from three randomized phase 3 trials, suggests that improvements in OS can be achieved with subsequent therapies (up to fourth-line) compared to no therapy.¹⁹
- BRCA1/2 mutations occur in up to 50% of patients with high-grade serous ovarian cancer
- Olaparib has been shown to have 34% ORR in those with recurrent ovarian cancer with \geq 3 prior chemotherapy regimens; response rates with current therapies in this setting are ~10-20%.
- A higher ORR was seen in those with platinum-sensitive recurrence (who are unable to tolerate further platinum therapy due to toxicities or infusion reactions) compared to platinum-resistant disease (ORR 46% vs. 30% respectively), but a similar DoR was seen between the two groups (8.2 months vs. 8.0 months).
- ORR was higher in those who received 3-5 prior lines of chemotherapy compared to those who received \geq 6 prior lines of chemotherapy (31-57% vs. 13-20%).
- Those considered to be the best candidates for this treatment include patients with recurrent ovarian cancer with BRCA1/2 mutations who are platinum-resistant or who are not able to tolerate further platinum therapy due to toxicities or infusion reactions who have received 3-5 prior lines of chemotherapy and are able and willing to tolerate a large oral pill burden twice daily.

References

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized studies essential • Blinding not essential 	<ul style="list-style-type: none"> • Universally accepted direct measure of benefit • Easily measured • Precisely measured 	<ul style="list-style-type: none"> • May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	<ul style="list-style-type: none"> • Randomized blinded studies 	<ul style="list-style-type: none"> • Patient perspective of direct clinical benefit 	<ul style="list-style-type: none"> • Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended 	<ul style="list-style-type: none"> • Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies 	<ul style="list-style-type: none"> • Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> • Randomized studies essential • Blinding preferred • Blinded review recommended 	<ul style="list-style-type: none"> • Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment 	<ul style="list-style-type: none"> • Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.