Canadian Association of Nurses in Oncology
Association canadienne des infirmières en oncologie

This program meets Canadian Association of Nurses in Oncology (CANO/ACIO) guidelines and is expected to support nurses in their understanding of PARP inhibitors for the treatment of ovarian, prostate, breast, and pancreatic cancers. Endorsement is provided by CANO/ACIO for a time period of two years, ending February, 2026.

PARP Inhibitor Clinical Resource: Breast, Ovarian, Pancreatic, and Prostate Cancers

LITERATURE REVIEW CURRENT THROUGH: MAY 2023

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OBJECTIVES

- To support oncology nurses and allied healthcare professionals in the routine clinical management of patients beginning or receiving a PARP inhibitor for the treatment of ovarian, prostate, breast, or pancreatic cancer
- To share the knowledge gained from the use of PARP inhibitors in ovarian cancer in order to optimize their use in the treatment of other solid tumours

1. Overview of PARP Inhibitors

PARP INHIBITORS IN BREAST, OVARIAN, PANCREATIC, AND PROSTATE CANCERS

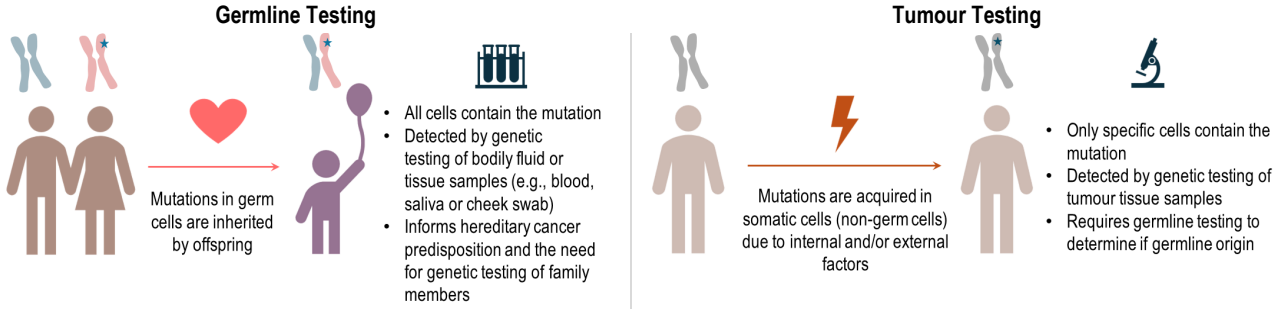
- PARP [poly (ADP-ribose) polymerase] enzymes play critical roles in the repair of single-strand DNA breaks; inhibition of PARP enzymes prevents proper repair of single-strand DNA breaks, leading to accumulation of double-strand DNA breaks.[1]
- In healthy cells, double-strand DNA breaks can be repaired through the homologous recombination repair (HRR) pathway.[2]
- However, in cancer cells with homologous recombination deficiency (HRD), such as *BRCA*-mutated ovarian, breast, prostate, and pancreatic cancer, double-strand DNA breaks accumulate, leading to genomic instability and cell death.[2]
- At the time of publication, three PARP inhibitors (PARPis), niraparib, olaparib, and talazoparib, have received Health Canada marketing authorizations for ovarian, breast, prostate and/or pancreatic cancers (drug-specific indications detailed below).
    - Note: at the time of publication of this resource, talazoparib is not currently accessible in Canada.

2. Genetic and Homologous Recombination Deficiency (HRD) Testing

- Clinically, HRD can present as a range of genomic changes that result in abnormal or loss of gene function, from deleterious mutations in individual HRR genes (*BRCA1/2* and non-*BRCA* such as *ATM*) to complex genomic scars.[3]
- Many PARPi indications for use require genetic testing to be eligible for therapy; some specifically require germline testing (see Table 2.1).

GENETIC TESTING

- Genetic testing can identify germline mutations and/or tumour (somatic) mutations:



- Genetic testing requirements for PARPi treatment differ depending on the drug and indication, as summarized in Table 2.1.

Table 2.1: Method of Genetic Mutation Detection by Tumour Site According to Health Canada Indications

	Niraparib	Olaparib
Breast Cancer	–	• Germline *BRCA*m
Ovarian Cancer: First-line Maintenance	• No genetic testing required	• Germline or tumour *BRCA*m
Ovarian Cancer: Relapsed	• No genetic testing required	• No genetic testing required[a]
Pancreatic Cancer	–	• Germline *BRCA*m
Prostate Cancer	–	• Germline or tumour *BRCA*m *or* • *ATM*m (may be germline or tumour)

[a] Germline or somatic *BRCA*m may be required in some jurisdictions to meet reimbursement criteria.

*ATM*m, *ATM* mutation; *BRCA*m, *BRCA* mutation.

HRD TESTING

- Commercial genetic tests such as the Myriad myChoice® test (Myriad Genetics, Inc.) or FoundationOne® CDx (Foundation Medicine) assess for genetic mutations and genomic instability through various measurements.
- Broader assessment of mutations in HRR genes other than *BRCA1/2* (i.e., larger gene panels) is not the same as HRD testing.
- In a pan-Canadian consensus statement, ovarian cancer experts advised that tumour HRD status is a predictive biomarker of treatment benefit from PARPis and commercially available HRD tests can help patients with *BRCA*-wild-type cancers make informed decisions regarding treatment.[4]
- At the time of publication of this document, HRD testing in Canada occurs primarily through clinical trials or patient support programs.

3. Health Canada Indications and Warnings

- The Health Canada indications in Table 3.1 are accurate at the time of publication.
  - Olaparib is indicated for multiple cancer types (breast, ovarian, pancreatic, and prostate).[5]
  - Talazoparib and niraparib monotherapies are each indicated for only one type of cancer (talazoparib for breast cancer[6] and niraparib for ovarian cancer).[7]
  - A combination tablet of niraparib plus abiraterone acetate is approved for prostate cancer.[8]
- Note that Health Canada has issued a risk communication for niraparib in the non-germline *BRCA*-mutated recurrent ovarian cancer setting;[9] niraparib should be used with caution until more data become available for this population [Clinical Opinion].
  - Refer to Table 3.1 for specific indications and warnings.

Table 3.1: Health Canada Indications and Warnings by Tumour Site

BREAST CANCER		KEY PATIENT AND DISEASE CHARACTERISTICS
LYNPARZA (olaparib)[5] Related trial: OlympiA (NCT02032823)	• Indicated for the adjuvant treatment of adult patients with deleterious or suspected deleterious g*BRCA*-mutated, HER2-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy – Patients must have confirmation of a g*BRCA* mutation before LYNPARZA treatment is initiated[a]	• HER2-negative early breast cancer (HR+ or TNBC) • g*BRCA*-mutated • High risk early breast cancer • Treated with neoadjuvant or adjuvant chemotherapy
LYNPARZA (olaparib)[5] Related trial: OlympiAD (NCT02000622)	• Indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*-mutated, HER2-negative metastatic breast cancer (mBC) who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting – Patients with hormone receptor (HR)-positive breast cancer should have progressed on or be considered inappropriate for endocrine therapy (ET) – g*BRCA* mutation must be confirmed before LYNPARZA treatment is initiated	• HER2-negative mBC (HR+ or TNBC) • Previously treated with chemotherapy • g*BRCA*-mutated • If HR+ progressed on or inappropriate for ET
TALZENNA (talazoparib)[6] Related trial: EMBRACA (NCT01945775)	• Indicated as monotherapy for the treatment of adult patients with a deleterious or suspected deleterious g*BRCA*-mutated HER2-negative locally advanced (not amenable to curative radiation or surgery) or metastatic breast cancer, who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting, unless patients were inappropriate for these treatments	• HER2-negative locally advanced or mBC (HR+ or TNBC) • g*BRCA*-mutated • Previously treated with chemotherapy unless inappropriate

Table continued.

Table 3.1: Health Canada Indications and Warnings by Tumour Site (continued)

OVARIAN CANCER[b]		KEY PATIENT AND DISEASE CHARACTERISTICS
ZEJULA (niraparib)[7] Related trial: PRIMA (NCT02655016)	• Indicated as monotherapy for the maintenance treatment of female adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy	• Advanced ovarian, fallopian tube or peritoneal cancer • In a complete or partial response to first-line platinum-based chemotherapy
ZEJULA (niraparib)[7] Related trial: NOVA (NCT01847274)	• Indicated as monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy – Note: niraparib should be used with caution in the non-g*BRCA*-mutated population. [CO] Health Canada is reviewing updated data for this population; see cautionary footnote.[b] Consider and share this information with patients to allow them to make an informed decision.[9]	• Recurrent ovarian, fallopian tube or peritoneal cancer • In a complete or partial response to platinum-based chemotherapy
LYNPARZA (olaparib)[5] Related trial: SOLO1 (NCT01844986)	• Indicated as monotherapy for the maintenance treatment of adult patients with advanced *BRCA*-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy – Patients must have confirmation of *BRCA* mutation (identified by either germline or tumour testing) before LYNPARZA treatment is initiated	• Advanced ovarian, fallopian tube or peritoneal cancer • g/t*BRCA*-mutated • In a complete or partial response to first-line platinum-based chemotherapy
LYNPARZA (olaparib)[5] Related trials: SOLO2 (NCT01874353), Study 19 (NCT00753545)	– Indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy[c,d,e]	• PSR ovarian, fallopian tube or peritoneal cancer • (*BRCA*-mutated or *BRCA*-wild-type) • In a complete or partial response to platinum-based chemotherapy
PANCREATIC CANCER		
LYNPARZA (olaparib)[5] Related trial: POLO (NCT02184195)	• Indicated as monotherapy for the maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*-mutated metastatic adenocarcinoma of the pancreas whose disease has not progressed on a minimum of 16 weeks of first-line platinum-based chemotherapy – g*BRCA* mutation must be confirmed before LYNPARZA treatment is initiated	• Metastatic pancreatic cancer • g*BRCA*-mutated • No progression on ≥ 16 weeks first-line platinum-based chemotherapy

Table continued.

Table 3.1: Health Canada Indications and Warnings by Tumour Site (continued)

PROSTATE CANCER		
LYNPARZA (olaparib)[5] Related trial: PROfound (NCT02987543)	• Indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic *BRCA*- or *ATM*-mutated metastatic castration resistant prostate cancer (mCRPC) who have progressed following prior treatment with a new hormonal agent – Examples of novel hormonal agents: abiraterone, apalutamide, darolutamide, enzalutamide – *BRCA* or *ATM* mutations must be confirmed before LYNPARZA treatment is initiated	• mCRPC • g/s*BRCA*-mutated or *ATM*-mutated • Progression on new hormonal agent
LYNPARZA (olaparib)[5] Related trial: PROpel (NCT03732820)	• Indicated with conditions: In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious germline and/or somatic *BRCA*-mutated mCRPC in whom chemotherapy is not clinically indicated – *BRCA* mutation must be confirmed before LYNPARZA treatment is initiated	• mCRPC • g/s*BRCA*-mutated • Chemotherapy not clinically indicated
AKEEGA (niraparib + abiraterone)[8] Related trial: MAGNITUDE (NCT03748641)	• Indicated as treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (germline and/or somatic) mCRPC, who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated – Patients must have confirmation of *BRCA* mutation before AKEEGA treatment is initiated	• mCRPC • g/s*BRCA*-mutated • Asymptomatic/mildly symptomatic • Chemotherapy not clinically indicated
NOTE	• AKEEGA (niraparib and abiraterone acetate tablets) received Health Canada approval in June 2023 – This resource does not provide further detail regarding clinical use of this combination product • TALZENNA (talazoparib) is not currently accessible in Canada for patients with breast cancer – This resource does not provide further detail regarding clinical use of this combination product	

[a] Marketing authorization with conditions issued based on invasive disease-free survival (IDFS) and distant disease-free survival (DDFS). [b] Data from the NOVA study is suggesting that median overall survival with ZEJULA may be lower than expected in the non-g*BRCA*-mutated patient population. GlaxoSmithKline will be submitting updated data to Health Canada. Consider and share this current information with patients to allow them to make an informed decision.[9] Consult the Health Canada website for updates: https://recalls-rappels.canada.ca/en. [c] Marketing authorization with conditions issued for ovarian cancer patients with *BRCA* wild-type status based on promising evidence of superior benefit in prolonging PFS of olaparib capsule versus placebo in a phase II trial (Study 19). [d] PSR is defined as disease progression occurring at least 6 months following completion of platinum chemotherapy. [e] [CO/NCCN[10]] Olaparib is the preferred PARPi for patients with *BRCA*-mutated PSR who did not receive prior olaparib;[10] olaparib may also be used for patients with *BRCA* wild-type PSR, depending on funding.

g*BRCA*, germline *BRCA*; CO, Clinical Opinion; HR+, hormone receptor positive; mCRPC, metastatic castration-resistant prostate cancer; NCCN, National Comprehensive Cancer Network; PSR, platinum-sensitive relapse; s*BRCA*, somatic *BRCA*; t*BRCA*, tumour *BRCA*; TNBC, triple negative breast cancer.

4. Dosing and Duration

NIRAPARIB

- The dosing and duration of niraparib depends on the patient's weight and/or platelet count as well as the line of therapy.
- Niraparib is available as 100 mg capsules and 100 mg tablets.[7]

Table 4.1: Niraparib Dosing and Duration of Treatment for Ovarian Cancer[7]

Ovarian Cancer	**First-line maintenance therapy for advanced ovarian cancer**		
	Timing of initiation	• Start niraparib ≤ 12 weeks after final dose of most recent platinum regimen	
	Recommended dose	• IF patient is < 77 kg OR platelets < 150,000/µL → 200 mg (2 x 100 mg capsule or tablet) daily • IF patient is ≥ 77 kg AND platelets ≥ 150,000/µL → 300 mg (3 x 100 mg capsule or tablet) daily	
	Duration	• Continue until disease progression or unacceptable toxicity – Some physicians/regions may follow the PRIMA trial protocol where the duration of niraparib therapy was 36 months or until disease progression[11] [CO]	
	Maintenance treatment of platinum-sensitive recurrent ovarian cancer		
	Timing of initiation	• Start niraparib ≤ 8 weeks after final dose of most recent platinum regimen	
	Recommended dose	• Per product monograph, 300 mg (3 x 100 mg capsule or tablet) daily – For patients < 58 kg, consider a starting dose of 200 mg daily • Per post-hoc analysis of the NOVA trial, patients weighing < 77 kg OR platelets < 150,000/µL may benefit from a starting dose of 200 mg daily	
	Duration	• Continue until disease progression or unacceptable toxicity	
	Precautions and dose adjustments		
	Hematologic recovery	• Ensure recovery of hematologic toxicities prior to starting (≤ CTCAE grade 1; see section 7 for toxicity grading) • Refer to section 7 for dose adjustments and interruptions for hematologic adverse events	
	Renal impairment	• Mild (CrCl 60-89 mL/min)[12] or moderate (CrCl 30-59 mL/min)[12]: no dose adjustment • Severe (CrCl < 30 mL/min)[12] or patients with end stage renal disease undergoing hemodialysis: safety unknown	
	Hepatic impairment	• Mild (total bilirubin ≤ 1.5 x ULN and any AST level, or bilirubin ≤ ULN and AST > ULN): no dose adjustment • Moderate (total bilirubin > 1.5–3.0 x ULN and any AST): 200 mg once daily – Monitor patients for hematologic toxicity and reduce dose further if needed • Severe (total bilirubin > 3.0 x ULN and any AST): safety unknown	
	Dose modifications for adverse events		
	• Consider interrupting treatment, reducing dose, or discontinuing dose as clinically indicated		
	First dose reduction	**Second dose reduction**	**Third dose reduction**
	• 200 mg → 100 mg (1 x 100 mg) daily • 300 mg → 200 mg (2 x 100 mg) daily	• 100 mg daily → Discontinue medication • 200 mg → 100 mg (1 x 100 mg) daily	• N/A • 100 mg → Discontinue

AST, aspartate transaminase; CO, Clinical Opinion; CrCl, creatinine clearance; CTCAE, common terminology criteria for adverse events; ULN, upper limit of normal.

OLAPARIB

- The timing of initiation and the duration of olaparib therapy differs by indication as described in the table below.

Table 4.2: Olaparib Dosing and Duration of Treatment by Cancer Type[5]

All Indications	**Precautions and baseline dose adjustments**			
	Hematologic recovery	• Prior to starting, ensure recovery of hematologic toxicities (to ≤ CTCAE grade 1; see section 7) caused by previous anti-cancer therapy		
	Renal impairment	• Mild (CrCl 51-80 mL/min): no dose adjustment • Moderate (CrCl 31-50 mL/min): reduce dose to 200 mg BID • Severe or end-stage renal disease (CrCl ≤ 30 mL/min): olaparib not recommended		
	Hepatic impairment	• Mild or moderate (Child-Pugh A or B)[a]: no dose adjustment • Severe (Child-Pugh C)[a]: olaparib not recommended		
	Co-administration with CYP3A4 inhibitors	• Concomitant use of strong or moderate CYP3A4 inhibitors not recommended; consider alternative agents – Refer to Drug Interaction Check for common strong or moderate CYP3A4 inhibitors – If co-administration is unavoidable, reduce dose of olaparib:		
		Moderate CYP3A4 inhibitor	• 150 mg BID	
		Strong CYP3A4 inhibitor	• 100 mg BID	
	Dose modifications for adverse events			
	• To manage adverse events, consider treatment interruption and dose reduction • For dose reductions, a 100 mg tablet is available			
	First dose reduction	**Second dose reduction**	**Third dose reduction**	**Fourth dose reduction**
	• 250 mg (1 x 150 mg tab AND 1 x 100 mg tab) BID	• 200 mg (2 x 100 mg tab) BID	• 150 mg BID	• 100 mg BID
Ovarian Cancer	**Maintenance treatment following first-line platinum-based chemotherapy in patients with *BRCA*m advanced ovarian cancer**			
	Recommended dose	• 300 mg (2 x 150 mg tablet) BID		
	Timing of initiation	• Following platinum-based chemotherapy, timing not specified in the product monograph – In the SOLO1 trial, patients were randomized within 8 weeks after their last chemotherapy infusion[13]		
	Duration	• Continue for 2 years or until disease progression • If complete response (no radiological evidence of disease) is achieved at 2 years, stop treatment – If evidence of disease is present at 2 years and further benefit can be derived from olaparib, treatment can be continued beyond 2 years		
	Maintenance treatment of platinum-sensitive relapsed (PSR) ovarian cancer			
	Timing of initiation	• Start treatment within 8 weeks after the final dose of platinum regimen		
	Duration	• Continue treatment until disease progression or unacceptable toxicity		
Breast Cancer	**Adjuvant treatment of g*BRCA*m HER2-negative high risk early breast cancer**			
	Recommended dose	• 300 mg (2 x 150 mg tablet) BID		
	Timing of initiation	• For patients with hormone receptor-positive breast cancer, given concurrently with endocrine therapy		
	Duration	• Continue treatment for 1 year or until disease recurrence or unacceptable toxicity		
	Treatment of g*BRCA*m HER2-negative metastatic breast cancer			
	Timing of initiation	• Not applicable in treatment setting (vs maintenance setting)		
	Duration	• Continue treatment until disease progression or unacceptable toxicity		
Pancreatic Cancer	**Maintenance treatment following response to first-line platinum-based chemotherapy in patients with g*BRCA*m metastatic adenocarcinoma of the pancreas**			
	Recommended dose	• 300 mg (2 x 150 mg tablet) BID		
	Timing of initiation	• Following platinum-based chemotherapy; timing not specified in the product monograph – In the POLO trial, the maintenance intervention was initiated 4-8 weeks after the last dose of first-line chemotherapy[14]		
	Duration	• Continue treatment until disease progression or unacceptable toxicity		

Table continued.

Table 4.2: Olaparib Dosing and Duration of Treatment by Cancer Type[5] (continued)

Prostate Cancer	**Treatment of patients with mCRPC and mutations in *BRCA* or *ATM* genes**	
	Recommended dose	• 300 mg (2 x 150 mg tablet) BID
	Timing of initiation	• Concurrently with gonadotropin-releasing hormone (GnRH) analog or following bilateral orchiectomy
	Duration	• Continue treatment until disease progression or unacceptable toxicity
	In combination with abiraterone and prednisone for the treatment of *BRCA*m mCRPC	
	Abiraterone dose	• 1000 mg orally once daily (when given in combination with olaparib) • Must be given with prednisone or prednisolone
	Prednisone or prednisolone dose	• 5 mg orally BID[5] or 10 mg once daily [CO]
	Timing of initiation	• Not specified in the product monograph
	Duration	• Continue treatment until disease progression or unacceptable toxicity

[a] Child-Turcotte-Pugh classification is a score based on the sum of 5 components (bilirubin, albumin, prothrombin time [or INR] and presence of ascites and hepatic encephalopathy); more information can be found at https://www.rxcirrhose.ca/child-pugh.[15]

BID, twice daily; *BRCA*m, *BRCA*-mutated; CO, Clinical Opinion; g*BRCA*m, germline *BRCA*-mutated; CrCl, creatinine clearance; CTCAE, common terminology criteria for adverse events; mCRPC, metastatic castration-resistant prostate cancer.

5. Baseline Evaluation

- Monitoring for hematologic toxicity is important before, during, and after PARPi therapy; cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been reported with both olaparib and niraparib.[5,7]
- Both PARPis can cause fetal harm if administered to a pregnant woman.[5,7]
- Hypertension and hypertensive crisis have been reported in patients with niraparib; ensure pre-existing hypertension is adequately controlled prior to initiating niraparib and monitor blood pressure and heart rate frequently (see Tables 6.1 and 6.2).[7]
- Rare but serious toxicities such as pneumonitis (olaparib), venous thromboembolic events (olaparib) and posterior reversible encephalopathy syndrome (niraparib) should be considered and related symptoms investigated (see Tables 6.2 and 6.4).

BASELINE ASSESSMENTS

- Before initiating PARPi treatment, ensure patients have recovered from hematologic toxicity (CTCAE ≤ grade 1) caused by previous anti-cancer therapy.[5,7]
- Refer to Tables 4.1 to 4.2 for precautions and dose adjustments recommended for renal or liver impairment and unavoidable co-administration of CYP3A4 inhibitors.

Table 5.1: Recommended Baseline Assessments and Patient Education Prior to PARPi Initiation

	Physical Examination	Laboratory Tests	Imaging And Other Assessments
All Tumour Sites	• Performance status (ECOG PS) • Weight, height • Blood pressure • Heart rate • Medical history including allergies, history of cardiovascular disease – Niraparib contains lactose and tartrazine[7]	• Complete blood count • Electrolytes • Renal function • Liver function	• CT chest/abdomen/pelvis, as clinically indicated for disease monitoring • Pregnancy test[5,7] • Review concomitant medications (e.g., hormonal birth control) and assess potential for interactions and/or adverse events (see Drug Interaction Check and below)
Tumour-Specific	• Staging and biomarker assessments per routine practice • Genetic testing (*BRCA*, *ATM*); refer to Table 2.1 • HRD testing if appropriate and available		

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRD, homologous recombination deficiency.

DRUG INTERACTION CHECK

- Before initiating PARPi therapy, the patient's best possible medication history should be obtained.
- Pharmacist assessment of drug interactions using a drug interaction database and clinical judgement is important for identifying the potential clinical implications of drug interactions and recommending possible management strategies.
- An overview of documented mechanisms of interaction and notable examples (as described in their respective product monographs) follows.

Table 5.2: Mechanisms of Drug Interaction and Clinical Considerations for Niraparib[7a]

DRUGS THAT MAY AFFECT NIRAPARIB EXPOSURE	EXAMPLES	CLINICAL CONSIDERATIONS
Strong inhibitors of Breast Cancer Resistance Protein (BCRP) [CO]	• Curcumin, cyclosporine, and elacridar [GF120918]	• May affect niraparib exposure [CO] • Not studied; avoid concomitant use [CO]
OTHER INTERACTIONS	**EXAMPLES**	**CLINICAL CONSIDERATIONS**
Pharmacodynamic Interactions [CO]	• Myelosuppressive anticancer agents, including DNA damaging agents	• Potentiation and prolongation of myelosuppressive toxicity

[a] Table includes interactions where caution was specifically advised. Additional mechanisms of interaction are described in the product monograph.

CO, Clinical Opinion.

Table 5.3: Mechanisms of Drug Interaction and Clinical Considerations for Olaparib[5]

DRUGS WHOSE EXPOSURE MAY BE AFFECTED BY OLAPARIB	EXAMPLES	CLINICAL CONSIDERATIONS
Substrates of CYP3A	• Cisapride, cyclosporine, ergot alkaloids, fentanyl, midazolam, pimozide, quetiapine, simvastatin, sirolimus, tacrolimus	• Olaparib may increase exposure to substrate • Exercise caution and closely monitor patients when co-administering as exposure to substrates may be increased – Drugs with a narrow therapeutic index should be monitored more closely [CO]
DRUGS THAT MAY AFFECT OLAPARIB EXPOSURE	**EXAMPLES**	**CLINICAL CONSIDERATIONS**
Strong inhibitors of CYP3A	• Boceprevir, clarithromycin, indinavir, itraconazole, nelfinavir, protease inhibitors boosted with ritonavir or cobicistat, saquinavir, telaprevir, telithromycin	• Shown to increase olaparib exposure • Co-administration is not recommended • If a strong CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced (see Table 4.2)
Strong inducers of CYP3A	• Rifampicin, phenobarbital, phenytoin, rifabutin, rifapentine, carbamazepine, nevirapine	• Shown to decrease olaparib exposure • Co-administration is not recommended • If a strong CYP3A inducer cannot be avoided, there is a potential for decreased efficacy of olaparib
Moderate inhibitors of CYP3A	• Aprepitant,[16] ciprofloxacin, diltiazem, erythromycin, fluconazole, fosnetupitant,[16] netupitant,[16] verapamil	• May increase olaparib exposure • Co-administration is not recommended • If a moderate CYP3A inhibitor must be co-administered, the dose of olaparib should be reduced
Moderate inducers of CYP3A	• Bosentan, efavirenz, etravirine, modafinil	• May decrease olaparib exposure • Co-administration is not recommended • If a moderate CYP3A inducer cannot be avoided, there is a potential for decreased efficacy of olaparib
OTHER INTERACTIONS	**EXAMPLES**	**CLINICAL CONSIDERATIONS**
Foods that are CYP3A inhibitors	• Grapefruit, star fruit, pomegranate and Seville oranges or their juices	• May increase olaparib plasma concentration • Patients should avoid these fruits during olaparib treatment
Pharmacodynamic Interactions	• Myelosuppressive anticancer agents, including DNA damaging agents	• Potentiation and prolongation of myelosuppressive toxicity • Olaparib monotherapy dose is not suitable for combination with myelosuppressive anticancer agents

CO, Clinical Opinion.

6. Recommended Monitoring

- Toxicity monitoring recommendations are outlined for each PARPi in the tables below; note that each PARPi has unique considerations.
- Monitoring of CBC should consider the risk for MDS/AML; clinically assess patients with hematologic toxicity.
- Note that some early symptoms in the maintenance setting (e.g., ovarian cancer) may be related to prior chemotherapy.[1]

MONITORING PATIENTS ON NIRAPARIB

Table 6.1: Suggested Routine Monitoring During Niraparib Therapy for Ovarian Cancer

	MONTH 1	MONTH 2	MONTH 3-12	REMAINDER OF THERAPY[a]	AFTER PARPi DISCONTINUATION
OVARIAN CANCER					
BP[b], HR[b]	≥ Weekly [PM][7] 3x per week [CO][c]	≥ Weekly [PM][7] 2x per week [CO][c]	Monthly [PM][7] 2x per month [CO][c]	Periodically [PM][7] 1x per month [CO][c]	Monitor and adjust antihypertensives as needed [CO][c]
CBC	Weekly [PM][7]	Monthly [PM][7]	Monthly [PM][7]	Monthly up to 24 mo, then at routine visit (q3-4mo)[CO][4]	At routine visit (q3-4mo)[4] [CO][d]
Creatinine/eGFR[e]			At routine visit (q3-4mo) [CO]	At routine visit (q3-4mo) [CO]	As clinically indicated [CO]

[a] More frequent monitoring may be required after the first year of treatment if any concerns arise [CO]. [b] Self-monitoring of blood pressure and heart rate: 3x per week for first month, then 2x per week for month 2, then 2x per month for months 3-12, then 1x per month after first year. Following niraparib discontinuation, adjust antihypertensives that may have been introduced/increased [CO]. [c] Patients with cardiovascular disorders (especially coronary artery disease, cardiac arrhythmias, and hypertension) may require more frequent monitoring.[17] [d] Risk of MDS/AML persists following PARPi discontinuation; continue to monitor CBC. [e] Some PARPi affect renal transporters, causing serum creatinine elevation without impacting renal function; consider alternative markers of renal function (see section 7).

AML, acute myeloid leukemia; BP, blood pressure; CBC, complete blood count; CO, Clinical Opinion; eGFR, estimated glomerular filtration rate; HR, heart rate; MDS, myelodysplastic syndrome; mo, months; PM, product monograph.

Table 6.2: Assessing for Rare but Serious Toxicities During Niraparib Therapy for Ovarian Cancer

POTENTIAL TOXICITY	ADDITIONAL MONITORING/INVESTIGATION
Cardiac arrest [CO] Hypertensive crisis [CO]	• Closely monitor patients with cardiovascular disorders, especially coronary artery disease, cardiac arrhythmias and hypertension[7] • Refer to section 7 Hypertension Management
Posterior Reversible Encephalopathy Syndrome (PRES), rare 0.09%[7]	• Signs and symptoms:[7] – Seizures, headache, altered mental status – Visual disturbance, or cortical blindness, with or without associated hypertension • PRES diagnosis requires confirmation by brain imaging (MRI preferred)[7] – If confirmed, treat specific symptoms (e.g., control of hypertension) and discontinue niraparib
Intestinal perforation [CO]	• Consider potential for intestinal perforation and investigate related symptoms: – Sudden and severe abdominal pain[18] – Nausea and vomiting[18] – Fever and chills[18] – Swelling and bloating of abdomen[18]

CO, Clinical Opinion; MRI, magnetic resonance imaging; PRES, posterior reversible encephalopathy syndrome.

MONITORING PATIENTS ON OLAPARIB

Table 6.3: Suggested Routine Monitoring During Olaparib Therapy

	MONTH 1[a]	MONTH 2-12	MONTH 13-24	BEYOND MONTH 24 & AFTER PARPi DISCONTINUATION
ALL TUMOUR TYPES				
CBC	Monthly [PM][5]	Monthly [PM][5]	Monthly [CO][4]	At routine visit [CO] (q3-4mo)[4b]
Creatinine/eGFR[c]		At routine visit (q3-4mo) [CO]	At routine visit (q3-4mo) [CO]	As clinically indicated [CO]

[a] Some experts recommend monitoring CBC weekly for the first month of PARPi therapy.[1] [b] Risk of MDS/AML persists following PARPi discontinuation; continue to monitor CBC. [c] Some PARPi affect renal transporters, causing serum creatinine elevation without impacting renal function; consider alternative markers of renal function (see section 7).

AML, acute myeloid leukemia; CBC, complete blood count; CO, Clinical Opinion; eGFR, estimated glomerular filtration rate MDS, myelodysplastic syndrome; PM, product monograph.

Table 6.4: Assessing for Rare but Serious Toxicities During Olaparib Therapy[5]

POTENTIAL TOXICITY	ADDITIONAL MONITORING/INVESTIGATION
Venous Thromboembolic Events	• A higher incidence of venous thromboembolic events was observed in patients treated with olaparib for metastatic castration-resistant prostate cancer (who also received ADT) compared with other approved indications • Monitor for clinical signs and symptoms of venous thrombosis and pulmonary embolism – Pulmonary embolism: shortness of breath, chest pain, more rapid breathing, fast heartbeat, coughing up blood – Thrombosis: swelling and pain in one part of the body (e.g., leg)
Pneumonitis, rare < 1%	• Investigate new or worsening respiratory symptoms such as dyspnea, cough and fever, or chest abnormality identified on radiographic testing

ADT, androgen-deprivation therapy.

7. Proactive and Reactive Management of Selected Toxicities

- PARPi therapy plays an important role in preventing/delaying disease progression.
- Anticipating and managing adverse events is critical to maintaining patients on therapy.
- Sections 7.1 to 7.6 review strategies for managing toxicities that commonly lead to PARPi discontinuation.
- Dose reductions for non-hematologic toxicities are listed in Table 7.0, by PARPi.
- Rule out other causes before discontinuing PARPi therapy [Clinical Opinion].

Table 7.0: Dose Reductions for Non-Hematologic Toxicities, by PARPi

PARPi	RECOMMENDATION
Niraparib[7]	• For non-hematologic CTCAE grade ≥ 3 adverse reactions that persist despite treatment/prophylaxis: – Interrupt niraparib – If grade ≥ 3 adverse reaction resolves within 28 days, resume niraparib at reduced dose (refer to Table 4.1) • If grade ≥ 3 adverse reaction persists > 28 days, discontinue niraparib
Olaparib[5]	• For adverse event management, olaparib may be interrupted and dose reduction considered (refer to Table 4.2)

CTCAE, common terminology criteria for adverse events.

HEMATOLOGIC TOXICITIES

CTCAE Grade[19]	1	2	3	4
Anemia	Hemoglobin (Hgb) < LLN - 100 g/L	Hgb < 100 - 80g/L	Hgb < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Neutrophil count decreased	< LLN - 1.5 x 10^9/L	< 1.5 - 1.0 x 10^9/L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9/L
Platelet count decreased	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9/L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9/L
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated
Leukemia secondary to oncology chemotherapy	-	-	-	Present

CTCAE, common terminology criteria for adverse events; Hgb, hemoglobin; LLN, lower limit of normal.

Table 7.1: Frequency of Hematologic Toxicities During PARPi Therapy

CANCER SITE AND SETTING	TRIAL	Anemia		Neutropenia		Thrombocytopenia		MDS/AML	
		Any Grade	Grade ≥ 3[a]	Any Grade	Grade ≥ 3[a]	Any Grade	Grade ≥ 3[a]	Any Grade	Grade ≥ 3[a]
EARLY BREAST CANCER	Olaparib (OlympiA)[5b]	23.8%	8.7%	16.5%	5.3%	4.2%	0.2%	--	0.1%[c]
METASTATIC BREAST CANCER	Olaparib (OlympiAD)[5b]	40.0%	16.1%	27.3%	9.3%	11.2%	3.9%	--	NR[d]
OVARIAN CANCER: 1L MAINTENANCE	Niraparib (PRIMA)[7e]	50%	23%	36%	15%	54%	21%	--	0.8%
	Olaparib (SOLO-1)[5f]	38.8%	21.5%	23.1%	8.5%	11.2%	0.8%	--	1.5%[20g]
OVARIAN CANCER: RELAPSED	Niraparib (NOVA)[7]	50%	25%	30%	20%	61%	29%	--	3.5%[h]
	Olaparib (SOLO-2)[5]	45.6%	21.0%	23.6%	7.2%	16.4%	2.1%	--	8.2%[i]
PANCREATIC CANCER	Olaparib (POLO)[5b]	32.2%	12.2%	15.6%	6.7%	15.6%	3.3%	--	NR[d]
PROSTATE CANCER	Olaparib (PROfound)[5j]	49.6%	22.7%	9.4%	5.9%	12.9%	5.5%	--	NR[d]

[a] Only grades 3-4 reported for niraparib. [b] g*BRCA*m population. [c] MDS/AML events are reported for AEs with an onset date between the date of first dose of continuous treatment and 30 days following the date of last dose of continuous treatment. [d] Number not reported for this clinical trial. In clinical studies, across all indications and formulations, MDS/AML occurred uncommonly in patients on treatment and during the 30-day safety follow up, and < 1.5% at any time after starting olaparib including cases actively solicited during the long term follow-up for overall survival.[5] [e] Incidence for patients receiving a starting dose of niraparib based on weight and platelet count. [f] *BRCA*m population. [g] Incidence reported after 7-year follow-up.[20] [h] Incidence reported at 5.6-year follow-up.[7] In g*BRCA*m and non-g*BRCA*m cohorts, the incidence of MDS/AML was 6.6% and 1.7%.[7] [i] Incidence reported after 5-year follow-up.[5] [j] HRR-mutated population.

1L, first line; AE, adverse event; AML, acute myeloid leukemia; *BRCA*m, *BRCA*-mutated; g*BRCA*m, germline *BRCA*-mutated; HRR, homologous recombination repair [gene]; MDS, myelodysplastic syndrome; NR, not reported.

Table 7.2: Hematologic Toxicity Management During PARPi Therapy

<table>
<tr><td rowspan="2">All PARPi</td><td colspan="2">PATIENT EDUCATION</td></tr>
<tr><td colspan="2">• Discuss risk of hematologic toxicities, including risk of MDS and AML, particularly in patients treated for ovarian cancer [CO]
• Reassure patients that treatment breaks and dose modifications may permit continued treatment despite myelosuppression [CO]
• Advise patients to monitor themselves and report any signs and symptoms of hematologic toxicities:[5]
– MDS/AML: fever, infection, breathlessness, bruising or bleeding easily, blood in urine or stool
– Neutropenia or leukopenia: fever or infection, aches and pains, fatigue, flu-like symptoms
– Thrombocytopenia: abnormal bruising or bleeding, weakness/fatigue
• Counsel patient on caution when considering use of NSAIDs, given the potential effect on platelets and bleeding risk; review with medical team for guidance [CO]</td></tr>
<tr><td rowspan="8">Niraparib</td><td colspan="2">PROACTIVE MEASURES</td></tr>
<tr><td colspan="2">Hematologic toxicity considerations
• Thrombocytopenia was a common adverse event reported in patients taking niraparib;[7] adhere to monitoring recommendations as described below and in Table 6.1
Baseline assessments and monitoring[7]
• Before initiating PARPi therapy, ensure patients have recovered from hematological toxicity caused by previous anti-cancer therapy (hemoglobin, platelet, and neutrophil levels should be ≤ CTCAE grade 1)[5]
• CBC weekly during the first month, monthly for the next 11 months and periodically thereafter
• Risk of MDS/AML persists following discontinuation of PARPi therapy; continue to monitor CBC at routine visits</td></tr>
<tr><td colspan="2">TOXICITY MANAGEMENT</td></tr>
<tr><td colspan="2">• NOTE: rule out other causes of anemia (e.g., deficiencies in iron, folate, or vitamin B12 and hypothyroidism)[1]
Hematological dose interruptions and reductions[7]
• If hematologic toxicities occur, interrupt niraparib, reduce dose (refer to Table 4.1) and perform additional hematological monitoring (see below for AE-specific requirements)
– If not resolved within 28 days after treatment interruption, discontinue niraparib and refer to hematologist for additional investigations (e.g., bone marrow analysis and blood sample for cytogenetics)</td></tr>
<tr><td>Adverse Event[a]</td><td>Action</td></tr>
<tr><td>Anemia[7]
Hgb < 80 g/L</td><td>• Interrupt dose
• Monitor weekly until levels return to ≥ 90 g/L
• If Hgb returns to acceptable levels within 28 days, resume at reduced dose (Table 4.1)
• If Hgb has not returned to acceptable levels within 28 days of interruption or if the patient has already undergone dose reduction to 100 mg once daily, discontinue niraparib</td></tr>
<tr><td>Neutropenia[7]
ANC < 1.0 x 10^9/L</td><td>• Interrupt dose
• Monitor weekly until ANC levels return to ≥ 1.5 x 10^9/L
• If ANC returns to acceptable levels within 28 days, resume at reduced dose (Table 4.1)
• If ANC have not returned to acceptable levels within 28 days of interruption or if the patient has already undergone dose reduce to 100 mg once daily, discontinue niraparib</td></tr>
<tr><td>Thrombocytopenia[7]
Platelets < 100 x 10^9/L</td><td>FIRST OCCURRENCE:
• Interrupt dose
• Monitor weekly until platelet counts return to ≥ 100 x 10^9/L
• If platelets return to acceptable levels within 28 days, resume at same or reduced dose (Table 4.1)
– If platelet count is < 75 x 10^9/L, resume at reduced dose
SECOND OCCURRENCE:
• Interrupt dose
• Monitor weekly until platelet counts return to ≥ 100 x 10^9/L
• If platelets return to acceptable levels within 28 days, resume at reduced dose as (Table 4.1)
• If platelet count has not returned to acceptable levels within 28 days of interruption or if patient has already undergone dose reduction to 100 mg once daily, discontinue niraparib</td></tr>
<tr><td>Hematologic AE requiring transfusion or hematopoietic growth factor support[7]</td><td>• If platelets ≤ 10 x 10^9/L, consider platelet transfusion
• If other risk factors for bleeding (e.g., co-administration of anticoagulation or antiplatelet drugs), consider interruption these drugs and/or transfusion at higher platelet count
• Resume niraparib at reduced dose</td></tr>
<tr><td>MDS/AML[7]</td><td>• If MDS/AML suspected, refer patient to hematologist for further evaluation[7]
• If confirmed, discontinue PARPi therapy and treat patient appropriately[7]</td></tr>
</table>

Table continued.

Table 7.2: Hematologic Toxicity Management During PARPi Therapy (continued)

Olaparib	**PROACTIVE MEASURES**
	Hematologic toxicity considerations • Anemia was the most common severe (CTCAE grade ≥ 3) adverse reaction reported in clinical studies; first onset was generally in the first 3 months of treatment[5] • The majority of MDS/AML reports in the SOLO2 relapsed ovarian cancer clinical trial occurred in g*BRCA*m carriers with some patients having a history of more than one primary malignancy or of bone marrow dysplasia; all patients had potential contributing factors having prior platinum-chemotherapy and many receiving other DNA damaging agents[5] **Baseline assessments and monitoring** • Before initiating PARPi therapy, ensure patients have recovered from hematological toxicity caused by previous anti-cancer therapy (hemoglobin, platelet, and neutrophil levels should be ≤ CTCAE grade 1)[5] • CBC at baseline and monthly for the first 12 months of treatment, then periodically thereafter to monitor for clinically significant changes in any parameter during treatment[5] – Some experts recommend monitoring CBC weekly for the first month of PARPi therapy[1] • Continue to monitor for MDS/AML following treatment completion [CO]
	TOXICITY MANAGEMENT
	• NOTE: rule out other causes of anemia (e.g., deficiencies in iron, folate, or vitamin B12 and hypothyroidism)[1] **Severe (grade 3/4) hematological toxicities** • If patient develops severe hematological toxicity or blood transfusion dependence, interrupt olaparib and initiate appropriate hematological testing[5] – Some experts recommend considering weekly blood work following a severe (grade 3 or 4) hematologic event until resolution[1] • After 4 weeks of dose interruption, if blood parameters remain clinically abnormal, perform bone marrow analysis and/or blood cytogenetic analysis[5] • If MDS/AML is confirmed, discontinue olaparib and treat appropriately[5]

[a] Values per product monograph, converted to Canadian units.

AE, adverse event; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CBC, complete blood count; CO, Clinical Opinion; CTCAE, common terminology criteria for adverse events; g*BRCA*m, germline *BRCA*-mutated; Hgb, hemoglobin; MDS, myelodysplastic syndrome; NSAIDs, non-steroidal anti-inflammatory drugs.

FATIGUE AND INSOMNIA

CTCAE Grade[19]	1	2	3	4
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-

ADL, activities of daily living.

Table 7.3: Frequency of Fatigue and Insomnia During PARPi Therapy

CANCER SITE AND SETTING	TRIAL	FATIGUE		INSOMNIA	
		Any Grade	Grade ≥ 3[a]	Any Grade	Grade ≥ 3[a]
EARLY BREAST CANCER	Olaparib (OlympiA)[5b]	42.5%	1.8%	NR	NR
METASTATIC BREAST CANCER	Olaparib (OlympiAD)[5b]	36.6%	3.9%	NR	NR
OVARIAN CANCER: 1L MAINTENANCE	Niraparib (PRIMA)[7c]	48%[d]	3%[d]	21%	0%
	Olaparib (SOLO-1)[5e]	63.5%	3.8%	0.4%[13f]	NR
OVARIAN CANCER: RELAPSED	Niraparib (NOVA)[7]	57%[g]	8%[g]	27%	0.3%
	Olaparib (SOLO-2)[5]	66.7%	5.6%	5.6%[21]	0%[21]
PANCREATIC CANCER	Olaparib (POLO)[5b]	63.3%	6.7%	NR	NR
PROSTATE CANCER	Olaparib (PROfound)[5h]	41.8%	3.1%	NR	NR

[a] Only grades 3-4 reported for niraparib. [b] g*BRCA*m population. [c] Incidence for patients receiving a starting dose of niraparib based on weight and platelet count. [d] Includes fatigue, asthenia, muscular weakness, malaise and somnolence. [e] *BRCA*m population. [f] Treatment-emergent adverse event leading to discontinuation. [g] Includes fatigue or asthenia. [h] HRR-mutated population.

1L, first line; *BRCA*m, *BRCA*-mutated; g*BRCA*m, germline *BRCA*-mutated; HRR, homologous recombination repair [gene]; NR, not reported.

Table 7.4: Fatigue and Insomnia Management During PARPi Therapy

PATIENT EDUCATION

- Counsel patients on adverse events they may experience such as fatigue and insomnia (particularly with niraparib)
- If experiencing fatigue, advise patient to use caution[7] or avoid driving or operating machinery[5,22]
- Encourage regular exercise (e.g., 20 min of sustained activity), a healthy diet, good sleep habits, and methods to reduce anxiety and stress[23]
- Advise patients to pace themselves (alternating between active and rest periods)[23]
- Provide patient information on cancer-related fatigue
  - E.g., Fatigue Patient Handout from BC Cancer: http://www.bccancer.bc.ca/health-info/coping-with-cancer/managing-symptoms-side-effects/fatigue-(tiredness)

TOXICITY MANAGEMENT

Insomnia

- Provide sleep hygiene education:[24]
  - Regular exercise, consistent bedtime, limiting naps to 1 hour no later than the early afternoon
  - Optimal sleep environment – dark, quiet, comfortable temperature
  - Relaxing activities before bedtime
  - Approaching bedtime, avoid the following: caffeine within 6 hours, other stimulants (nicotine, alcohol); going to bed hungry; heavy, spicy or sugary foods; fluids; stimulating activities (vigorous exercise within 2-4 hours)
- Consider cognitive behavioural treatment and/or pharmacologic methods for refractory insomnia[1]

Table continued.

Table 7.4: Fatigue and Insomnia Management During PARPi Therapy (continued)

TOXICITY MANAGEMENT
Fatigue • Reported to be worse initially and improve over time[1] • Rule out/treat other sources of fatigue such as: – Hypothyroidism, dehydration, nausea, anemia, uncontrolled pain, untreated depression/anxiety, medication, etc.[25] [CO] • Physical activity: – Use caution when determining appropriate level of activity if patient is experiencing concurrent treatment-related hematologic toxicities[1] – Emphasize importance of physical activity and protein intake for building muscle in cases of deconditioning post-chemotherapy [CO] • Address nutritional deficits/imbalance and sleep dysfunction[1] • Recommend massage therapy and/or psychosocial interventions[1] • Pharmacotherapy as clinically indicated (e.g., low dose steroids, stimulants, etc.) [CO] – CAUTION: avoid modafinil (CYP3A4 induction interaction with olaparib) • Consider dose interruption and reduction, as specified below **Dose interruptions and reductions for non-hematologic toxicities** • Refer to Table 7.0 for recommended dose interruptions and reductions by PARPi

BC, British Columbia; CO, Clinical Opinion.

NAUSEA AND VOMITING

CTCAE Grade[19]	1	2	3	4
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated

CTCAE, common terminology criteria for adverse events; TPN, total parenteral nutrition.

Table 7.5: Frequency of Nausea and Vomiting During PARPi Therapy

CANCER SITE AND SETTING	Trial	NAUSEA		VOMITING	
		Any Grade	Grade ≥ 3[a]	Any Grade	Grade ≥ 3[a]
EARLY BREAST CANCER	Olaparib (OlympiA)[5b]	57.1%	0.8%	22.6%	0.7%
METASTATIC BREAST CANCER	Olaparib (OlympiAD)[5b]	58.0%	0%	29.8%	0%
OVARIAN CANCER: 1L MAINTENANCE	Niraparib (PRIMA)[7c]	53%	1%	17%	0%
	Olaparib (SOLO-1)[5d]	77.3%	0.8%	40.0%	0.4%
OVARIAN CANCER: RELAPSED	Niraparib (NOVA)[7]	74%	3%	34%	2%
	Olaparib (SOLO-2)[5]	75.9%	3.1%	40.0%	2.6%
PANCREATIC CANCER	Olaparib (POLO)[5b]	48.9%	1.1%	25.6%	2.2%
PROSTATE CANCER	Olaparib (PROfound)[5e]	43.0%	1.6%	19.9%	2.3%

[a] Only grades 3-4 reported for niraparib. [b] g*BRCA*m population. [c] Incidence for patients receiving a starting dose of niraparib based on weight and platelet count. [d] *BRCA*m population. [e] HRR-mutated population.

1L, first line; *BRCA*m, *BRCA*-mutated; g*BRCA*m, germline *BRCA*-mutated; HRR, homologous recombination repair [gene].

Table 7.6: Nausea and Vomiting Management During PARPi Therapy

PATIENT EDUCATION
• Inform patients of the risk of nausea and vomiting, and offer reassurance that most nausea tends to be mild, manageable, and temporary, typically resolving after the first several weeks of treatment [CO] • Educate on the use of antiemetics:[1] – Antiemetic (metoclopramide, prochlorperazine, or olanzapine) 30 minutes before PARPi dose, especially near beginning of treatment – Eating 30-60 minutes before PARPi dose – Importance of adherence to avoid unnecessary interruptions in PARPi therapy • Promote good oral hygiene • To prevent nausea, advise patients to: – Try bedtime dosing where possible[7] – Drink plenty of fluids, avoid alcohol[22] – Eat and drink often in small amounts[22] • Provide resources for chemotherapy-related nausea and vomiting – E.g., video on PARPi for **ovarian cancer**: https://precare.ca/parp/
PROACTIVE MEASURES
• Generally, nausea and vomiting were reported early during treatment with olaparib and improved over time[5] • Risk factors for chemotherapy-induced nausea/vomiting:[23] – Female sex, < 50 years of age – History of low prior long-term alcohol intake – History of chemotherapy-induced nausea/vomiting with prior regimens • If patient experienced significant nausea during prior chemotherapy, tailor breakthrough antiemetic to patient history with chemotherapy [CO] • Bedtime dosing can help reduce nausea[7]
TOXICITY MANAGEMENT
Suggested treatment options for nausea and vomiting • Steroids, domperidone, olanzapine, haloperidol, prochlorperazine, or metoclopramide[1] [CO] – Ongoing use of 5-HT3 receptor antagonists (e.g., ondansetron) can increase constipation risk – Short-term use of steroids for acute cases; avoid long-term use (long-term dexamethasone use may cause CYP3A4 induction and interact with olaparib [CO]) • Olanzapine may be an effective option for refractory breakthrough nausea [CO] • Dimenhydrinate (Gravol) and haloperidol for refractory nausea/vomiting [CO] **Dietary modifications** • Advise patients to avoid strong tastes and to try flavouring food with spices and herbs or marinating to mask bitter taste • If patient complains of metallic taste, plastic utensils and food containers may help • Sugar-free gum or mints (without sorbitol) may reduce unpleasant taste • Provide reassurance and support; taste changes will improve over time **Dose interruptions and reductions for non-hematologic toxicities** • Refer to Table 7.0 for recommended dose interruptions and reductions by PARPi

CO, Clinical Opinion.

DIARRHEA AND CONSTIPATION

CTCAE Grade[19]	1	2	3	4
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

ADL, activities of daily living.

Table 7.7: Frequency of Diarrhea and Constipation During PARPi Therapy

CANCER SITE AND SETTING	Trial	DIARRHEA		CONSTIPATION	
		Any Grade	Grade ≥ 3[a]	Any Grade	Grade ≥ 3[a]
EARLY BREAST CANCER	Olaparib (OlympiA)[5b]	17.6%	0.3%	NR	0.2%[26c]
METASTATIC BREAST CANCER	Olaparib (OlympiAD)[5b]	20.5%	0.5%	12.7%	0.5%
OVARIAN CANCER: 1L MAINTENANCE	Niraparib (PRIMA)[7d]	14%	1%	33%[e]	1%[e]
	Olaparib (SOLO-1)[5f]	34.2%	3.1%	27.7%	0%
OVARIAN CANCER: RELAPSED	Niraparib (NOVA)[7]	20%	0.3%	40%	0.8%
	Olaparib (SOLO-2)[5]	34.4%	1.0%	20.5%[21]	0%[21]
PANCREATIC CANCER	Olaparib (POLO)[5b]	37.8%	1.1%	23%[14]	0%[14]
PROSTATE CANCER	Olaparib (PROfound)[5g]	21.5%	0.8%	18%[27]	0%[27]

[a] Only grades 3-4 reported for niraparib. [b] g*BRCA*m population. [c] Listed as AE leading to permanent discontinuation. [d] Incidence for patients receiving a starting dose of niraparib based on weight and platelet count. [e] Includes constipation, intestinal obstruction, and large intestinal obstruction. [f] *BRCA*m population. [g] HRR-mutated population.

1L, first line; AE, adverse event; *BRCA*m, *BRCA*-mutated; g*BRCA*m, germline *BRCA*-mutated; HRR, homologous recombination repair; NR, not reported.

Table 7.8: Diarrhea and Constipation Management During PARPi Therapy

PATIENT EDUCATION
• Inform patients about the risk of diarrhea and constipation as well as available prophylactic measures and OTC options[23]
• Educate patients regarding benefits of smaller, more frequent meals, soluble fibre, BRAT diet (bananas, rice, apples, toast), increased fluid intake[23], depending on patient's bowel function
• Advise patients to avoid sorbitol (e.g., dry fruits, chewing gum, diet beverages, sugar-free candies)[23]
• Counsel patients to have regular bowel movements
PROACTIVE MEASURES
• Prophylactic measures to minimize gastrointestinal toxicities: – Increase fluid intake[23] (1.5 - 3 L or 8 glasses of water per day) [CO] – Regular bowel movements
• If on opioid analgesics for pain, schedule bowel routine if experiencing constipation [CO]

Table continued.

Table 7.8: Diarrhea and Constipation Management During PARPi Therapy (continued)

TOXICITY MANAGEMENT
Diarrhea • Rule out other causes of diarrhea:[23] – E.g., infections, dietary or medication[a] causes, pancreatic insufficiency • Dietary modification can be used for uncomplicated symptoms[23] – Smaller, more frequent meals, avoid certain foods/beverages, adopt BRAT diet for mild cases (ensuring nutritional needs are met) • OTCs: – Loperamide[28] (if 4-6 loose stools per day or nocturnal diarrhea, 2 tablets immediately, then 1 tablet after each diarrhea episode until diarrhea-free for 12-24 hours) [CO] – Lomotil (diphenoxylate HCl/atropine sulfate [2.5 mg/0.025 mg]); usual initial dose is 5 mg (2 tab) 3 or 4 times per day,[29b] PRN (alternative to loperamide) [CO] **Constipation** • OTCs (PRN): Senna (BID) or polyethylene glycol 3350[28] • Utilize other antiemetics before 5-HT3 antagonists if patient is experiencing constipation[1] **Dose interruptions and reductions for non-hematologic toxicities** • Refer to Table 7.0 for recommended dose interruptions and reductions by PARPi

[a] E.g., antibiotics; [b] Refer to the LOMOTIL Product Monograph for complete dosing information.

BID, twice daily; BRAT, bananas, rice, apples, toast; CO, Clinical Opinion; OTC, over the counter treatment; PRN, as needed.

SERUM CREATININE ELEVATION

CTCAE Grade[19]	1	2	3	4
Creatinine increased	> 1 - 1.5 x baseline; > ULN - 1.5 x ULN	> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN	> 3.0 baseline; > 3.0 - 6.0 x ULN	> 6.0 x ULN

CTCAE, common terminology criteria for adverse events; ULN, upper limit of normal.

Table 7.9: Frequency of Serum Creatinine Elevation

CANCER SITE AND SETTING	Trial	Increased Serum Creatinine	
		Any Grade	Grade ≥ 3
EARLY BREAST CANCER	Olaparib (OlympiA)[5a]	2.0%	0%
METASTATIC BREAST CANCER	Olaparib (OlympiAD)[5a]	2.9%	0%
OVARIAN CANCER: 1L MAINTENANCE	Niraparib (PRIMA)[7b]	41%	0%
	Olaparib (SOLO-1)[5c]	8.1%	0%
OVARIAN CANCER: RELAPSED	Niraparib (NOVA)	NR	NR
	Olaparib (SOLO-2)[5]	10.8%	0%
PANCREATIC CANCER	Olaparib (POLO)[5a]	7.8%	0%
PROSTATE CANCER	Olaparib (PROfound)[5d]	3.9%	0%

[a] g*BRCA*m population.
[b] Incidence for patients receiving a starting dose of niraparib based on weight and platelet count.
[c] *BRCA*m population.
[d] HRR-mutated population.

1L, first line; *BRCA*m, *BRCA*-mutated; g*BRCA*m, germline *BRCA*-mutated; HRR, homologous recombination repair [gene]; NR, not reported.

Table 7.10: Management of Serum Creatinine Elevation During PARPi Therapy

PATIENT EDUCATION
• Inform patient of laboratory monitoring requirements during PARPi therapy • Educate patients on the importance of hydration during PARPi therapy: [CO] – Dehydration may cause increases in creatinine levels, which may lead to dose reductions
PROACTIVE MEASURES
• See section 4 for dose modifications for patients with renal impairment at baseline

Table continued.

Table 7.10: Management of Serum Creatinine Elevation During PARPi Therapy (continued)

TOXICITY MANAGEMENT
Background • Due to their direct impact on renal transporters (e.g., MATE-1, MATE-2, OCT-1, OCT-2) that secrete creatinine into the urine, some PARPis can cause elevated serum creatinine without affecting renal function[30] • Therefore, elevation of serum creatinine may not be associated with a true decrease in GFR or kidney dysfunction[28,31] – Use of the creatinine-derived eGFR can underestimate GFR in patients taking olaparib;[30] consider alternative renal markers (see below) **Management considerations for significantly elevated creatinine** • Consider alternative renal markers – Cystatin C (accurately calculate eGFR)[30] – Blood urea nitrogen (BUN) or urea (assess renal dysfunction) [CO] • Rule out other causes[1] – Encourage hydration to help distinguish between dehydration, pseudo-reduced GFR and true kidney failure [CO] • Consider renal scan[1] **Management of pseudo-reduced GFR** • If GFR remains appropriate (i.e., typical or not in agreement with elevated creatinine levels), dose reductions/interruptions can be avoided[28] **Management of truly reduced GFR** • Consider dose interruptions and reductions if CTCAE grade ≥ 3; refer to Table 7.0

BUN, blood urea nitrogen; CO, Clinical Opinion; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

HYPERTENSION

CTCAE Grade[19]	1	2	3	4
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg if previously WNL; monotherapy indicated	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

BP, blood pressure; mm Hg, millimetres of mercury; ULN, upper limit of normal; WNL, within normal limits.

Table 7.11: Frequency of Hypertension

CANCER SITE AND SETTING	Trial	HYPERTENSION	
		Any Grade	Grade ≥ 3[a]
EARLY BREAST CANCER	Olaparib (OlympiA)[b]	NR	NR
METASTATIC BREAST CANCER	Olaparib (OlympiAD)[b]	NR	NR
OVARIAN CANCER: 1L MAINTENANCE	Niraparib (PRIMA)[7c]	17%	5%
	Olaparib (SOLO-1)[d]	NR	NR
OVARIAN CANCER: RELAPSED	Niraparib (NOVA)[7]	20%	9%
	Olaparib (SOLO-2)[21]	2.6%	0%
PANCREATIC CANCER	Olaparib (POLO)[b]	NR	NR
PROSTATE CANCER	Olaparib (PROfound)[27e]	NR	1.2%

[a] Only grades 3-4 reported for niraparib.
[b] g*BRCA*m population.
[c] Incidence for patients receiving a starting dose of niraparib based on weight and platelet count.
[d] *BRCA*m population.
[e] HRR-mutated population.

*BRCA*m, *BRCA*-mutated; g*BRCA*m, germline *BRCA*-mutated; HRR, homologous recombination repair [gene]; NR, not reported.

Table 7.12: Management of Hypertension During PARPi Therapy

Niraparib

PATIENT EDUCATION

Patients starting niraparib

- Advise patients to report any signs and symptoms of hypertension:[7]
  - Shortness of breath, chest pressure or pain
  - Heart palpitations or racing pulse, dizziness or fainting
  - Swelling in ankles and legs, bluish colour in lips and skin
- Provide education on self-monitoring of blood pressure and heart rate, including optimal technique and timing[32]
  - Suggested home monitoring frequency for niraparib in patients with ovarian cancer: 3x per week for first month, then 2x per week for month 2, then 2x per month for months 3-12, then 1x per month after first year [CO]
  - More frequent blood pressure monitoring using home monitor is recommended if borderline hypertension [CO]
  - Blood pressure should be measured before breakfast and 2 hours after dinner, before taking medication[33]
- Educate patient on actions to take for hypertensive emergency and hypertensive urgency (see table below)[34]

HYPERTENSIVE CRISIS	SIGNS/SYMPTOMS	ACTION
Hypertensive emergency[34]	• BP ≥ 180/120 and patient is experiencing symptoms of target organ damage: – Chest and back pain, shortness of breath, vision changes, numbness/weakness, difficulty speaking or acute confusion[a]	• Patient should call 911; patient should NOT wait to see if pressure comes down on its own
Hypertensive urgency[34]	• BP ≥ 180/120 and patient is NOT experiencing symptoms of target organ damage: – Chest and back pain, shortness of breath, vision changes, numbness/weakness, difficulty speaking, or acute confusion[a]	• Patient should wait ~5 min and measure BP again • If second BP reading ≥ 180/120 and patient does NOT have symptoms of target organ damage, patient should contact healthcare provider for immediate management – Addition/adjustment of antihypertensive medications and niraparib dose may be required

PROACTIVE MEASURES

- In patients treated with niraparib, hypertension and hypertensive crisis have been reported[7]
- Pre-existing hypertension should be adequately controlled before starting niraparib[7]
- Closely monitor patients with cardiovascular disorders, especially coronary artery disease, cardiac arrhythmias, and hypertension[7]

Recommended monitoring of blood pressure and heart rate:[7]	Month 1-2: ≥ weekly[b]	Month 3-12: ≥ monthly[b]	Beyond Month 12: periodically for remainder of treatment with niraparib[b]

TOXICITY MANAGEMENT

Background

- Hypertension etiology is likely due to inhibition of dopamine, norepinephrine, and serotonin transporters[35]

Hypertension in patients with ovarian cancer on niraparib:[7]

- Medically manage with antihypertensive medications and adjust dose of niraparib if necessary
  - Choice of antihypertensive medications per routine care (refer to Canadian guidelines)[33]
  - CAUTION: avoid non-dihydropyridine calcium channel blockers ([CCBs], e.g., diltiazem and verapamil) with olaparib due to CYP3A4 inhibition and risk of increased drug exposure [CO]
- Management recommendations per Moore et al.[35]
  - For patients < 60 years, consider antihypertensive use for BP > 140/90
  - For patients ≥ 60 years, consider antihypertensive use for BP > 150/90
  - Recommended agents for non-black patients: thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or dihydropyridine CCBs such as amlodipine, felodipine, or nifedipine [CO]
  - For black patients, initial therapy should be a thiazide diuretic or a dihydropyridine CCB such as amlodipine, felodipine, or nifedipine [CO]
  - If the hypertension fails to respond to initial therapy at maximum doses or the hypertension worsens, add a second agent from a different class including non-specific beta blockers (e.g., labetalol) [CO]

Dose interruptions and reductions

- For non-hematologic CTCAE grade ≥ 3 adverse reactions that persist despite treatment/prophylaxis:[7]
  - Interrupt niraparib for maximum 28 days or until resolution of adverse reaction
  - Resume niraparib at reduced dose (refer to Table 4.1)
- Discontinue niraparib for hypertensive crisis or medically significant hypertension that cannot be adequately controlled with antihypertensive therapy

[a] Acute confusion may indicate PRES or stroke. [b] Optimal frequency: 3x per wk for first mo, 2x per wk for mo 2, 2x per mo for months 3-12, then monthly after first year [CO].

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CO, Clinical Opinion; CTCAE, common terminology criteria for adverse events; mo, month; PRES, posterior reversible encephalopathy syndrome.

8. Patient Education Checklist

☐ How to take niraparib/olaparib
- Instruct patients to swallow capsules and tablets whole with or without food;[5–7] bedtime administration or taking with food (if appropriate) may help manage nausea[7]
- If the patient vomits or misses a dose, an additional dose should NOT be taken; instruct them to take their next normal dose at the scheduled time[5–7]
- Ask the patient to repeat the number of tablets/capsules to take and the frequency to confirm their understanding

☐ Duration of treatment
- Prior to/during first-line treatment, inform patients of anticipated duration of therapy in order to minimize anxiety at treatment completion, for disease sites that have finite durations of PARPi treatment
  - Refer to Tables 4.1-4.2 for each PARPi duration by indication
- Provide counselling to patients completing treatment (consider involving a social worker):[36]
  - How to manage expectations
  - Follow-up care and checkups
  - Coping with stress, anxiety and other emotions
  - Dealing with physical changes
  - Healthy living, personal care and finding meaning after cancer treatment

☐ Drug interactions
- Review interactions with common foods and precautions regarding starting and stopping concomitant medications and alternative/complementary medicines (refer to Table 5.2)

☐ Pregnancy/sexual health, fetal harm
- PARPi therapy can cause fetal harm when administered to a pregnant woman;[6] niraparib may affect fertility[6,7]
- For all PARPi therapies, advise male and female patients of reproductive potential to use highly effective contraception (i.e., two reliable and complementary methods) during therapy and following the last dose; see below for duration of contraception following the last dose
- Pregnancy tests are recommended at baseline and at regular intervals during treatment and for the duration of contraception following the last dose [Clinical Opinion]

Duration of Contraception		
PARPi	**Females** ♀	**Males** ♂
Niraparib[7]	• ≥ 6 months after last dose	• ≥ 6 months after last dose [Clinical Opinion]
Olaparib[5]	• ≥ 6 months after receiving last dose • CAUTION: hormonal contraceptives – Olaparib may interact and reduce the efficacy of some hormonal contraceptives; consider additional non-hormonal contraceptives during olaparib therapy – For women with hormone-dependent cancer, consider two non-hormonal contraceptive methods	• 3 months after receiving the last dose – Male patients should not donate sperm during therapy and for 3 months after receiving last dose

☐ Breastfeeding
- Breastfeeding is not recommended during PARPi therapy and for ≥ 1 month after the last dose[5–7]

☐ Vaccinations
- Discuss vaccinations per local guidance

Checklist continued.

- ☐ Proactive approach to minimize common side effects (see section 7)
  - Low blood cell counts[5–7]
    - Importance of regular lab tests and monitoring for signs and symptoms (e.g., bruising, bleeding, fever, etc.)
  - Fatigue and asthenia (niraparib and olaparib) and insomnia (with niraparib)
    - Regular exercise, pace themselves, provide information on cancer-related fatigue
  - Nausea, vomiting, constipation, and diarrhea
    - Timing of doses
    - Prepare for potential need/use of antiemetics, laxatives, and anti-motility agents; practice oral hygiene, increase fluids, consume small, frequent meals
  - Skin care including liberal use of skin moisturizers at treatment initiation and use of sun protection[1,37]
- ☐ Blood pressure monitoring at home - for patients starting niraparib
  - Optimal frequency: 3x per week for the first month, 2x per week for month 2, 2x per month for months 2-12, then monthly beyond month 12 [CO]
  - Optimal technique and timing (before breakfast and 2 hours after dinner, before taking medication)[33]
  - Monitoring for signs/symptoms of hypertensive emergency vs urgency
- ☐ Notifying the oncology team early when they experience side effects
- ☐ Possible need for dose interruption and/or reduction may be required to manage side effects
  - Recent data on dose reductions and interruptions of olaparib in platinum-sensitive ovarian cancer suggests no impact on survival outcomes[38]
- ☐ Risk of serious adverse events and monitoring requirements (including frequency of tests)
  - Niraparib: hypertension; posterior reversible encephalopathy syndrome (e.g., seizures, headaches, visual disturbances)[7]; intestinal perforation (e.g., severe abdominal pain) [Clinical Opinion]
  - Olaparib: pneumonitis (e.g., new/worsening cough, dyspnea, fever)[5]; venous thromboembolic events (e.g., shortness of breath, chest pain, swelling/pain in leg)[5]
- ☐ Remind patients to monitor for progressive symptoms that may require a CT scan to rule out recurrent disease
  - Since progressive symptoms may appear as side effects, recurrent disease must be ruled out while managing symptoms, especially if the patient was tolerating the PARPi therapy for several months prior

PATIENT EDUCATION RESOURCES

- Links
  - Cancer Care Ontario (CCO): https://www.cancercareontario.ca/en/drugformulary/drugs
  - BC Cancer (Systemic Therapy): http://www.bccancer.bc.ca/our-services/patient-guide/systemic-therapy-teaching
  - Groupe d'étude en oncologie du Quebec (GEOQ): https://www.geoq.info/fr/pub/accueil
  - Canadian Cancer Society: Life after Cancer Treatment: https://cdn.cancer.ca/-/media/files/cancer-information/resources/publications/life-after-cancer/32060-life-after-cancer-treatment-en.pdf?rev=ad4b66e5184e460ead7d78e8e6875116&hash=8DC741A1D8B6F08AC362B524BAC96367

- Video on PARPi for **ovarian cancer**
  - Access with QR code or link: https://precare.ca/parp/

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10. Acronyms and Abbreviations

1L, first line
ACE, angiotensin converting enzyme
ADL, activities of daily living
ADT, androgen-deprivation therapy
AE, adverse event
AML, acute myeloid leukemia
ANC, absolute neutrophil count
ARB, angiotensin receptor blocker
AST, aspartate aminotransferase
*ATM*m, *ATM*-mutated
BC, British Columbia
BCRP, breast cancer resistant protein
BID, twice daily
BP, blood pressure
BRAT, bananas, rice, apples, toast
*BRCA*m, *BRCA*-mutated
BUN, blood urea nitrogen
Cap, capsule
CBC, complete blood count
CCB, calcium channel blocker
CO, Clinical Opinion
CrCl, creatinine clearance
CT, computed tomography
CTCAE, common terminology criteria for adverse events
ECOG-PS, Eastern Cooperative Oncology Group-Performance Status
eGFR, estimated glomerular filtration rate
g*BRCA*m, germline *BRCA*-mutated
GFR, glomerular filtration rate
HCP, healthcare professional
Hgb, hemoglobin
HR, heart rate
HR+, hormone receptor positive
HRD, homologous recombination deficiency
HRR, homologous recombination repair
LLN, lower limit of normal
mBC, metastatic breast cancer
mCRPC, metastatic castration-resistant prostate cancer
MDS, myelodysplastic syndrome
mm Hg, millimetres of mercury
mo, month
MRI, magnetic resonance imaging
NCCN, National Comprehensive Cancer Network
NIR, niraparib
NR, not reported
NSAIDs, non-steroidal anti-inflammatory drugs
OLA, olaparib
OTC, over the counter treatment
PARPi, PARP inhibitor
PM, product monograph
PRES, posterior reversible encephalopathy syndrome
PRN, as needed
PSR, platinum-sensitive relapsed
QID, four times daily
s*BRCA*, somatic *BRCA*
TNBC, triple negative breast cancer
TPN, total parenteral nutrition
ULN, upper limit of normal
WNL, within normal limits

11. References

1. Madariaga A, Bowering V, Ahrari S, Oza AM, Lheureux S. Manage wisely: poly (ADP-ribose) polymerase inhibitor (PARPi) treatment and adverse events. *Int J Gynecol Cancer*. 2020;30(7):903-915. doi:10.1136/ijgc-2020-001288

2. Sonnenblick A, de Azambuja E, Azim HA, Piccart M. An update on PARP inhibitors—moving to the adjuvant setting. *Nat Rev Clin Oncol*. 2015;12(1):27-41. doi:10.1038/nrclinonc.2014.163

3. Stewart MD, Merino Vega D, Arend RC, et al. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. *Oncologist*. 2022;27(3):167-174. doi:10.1093/oncolo/oyab053

4. Tinker AV, Altman AD, Bernardini MQ, et al. A Pan-Canadian Consensus Statement on First-Line PARP Inhibitor Maintenance for Advanced, High-Grade Serous and Endometrioid Tubal, Ovarian, and Primary Peritoneal Cancers. *Current Oncology*. 2022;29(6):4354-4369. doi:10.3390/curroncol29060348

5. AstraZeneca Canada Inc. LYNPARZA (olaparib) Product Monograph. Published online December 12, 2023. https://pdf.hres.ca/dpd_pm/00073774.PDF

6. Pfizer Canada ULC. TALZENNA (talazoparib) Product Monograph. Published online February 2, 2022. https://pdf.hres.ca/dpd_pm/00064613.PDF

7. GlaxoSmithKline Inc. ZEJULA (niraparib) Product Monograph. Published online August 17, 2023. https://pdf.hres.ca/dpd_pm/00072135.PDF

8. Janssen Inc. AKEEGA (niraparib and abiraterone acetate) Product Monograph. Published online June 7, 2023. Accessed August 14, 2023. https://pdf.hres.ca/dpd_pm/00071216.PDF

9. Government of Canada, Health Canada. ZEJULA (niraparib) - Update on the Maintenance Treatment in Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in the Second or Later Line Setting. Published February 16, 2023. Accessed March 17, 2024. https://recalls-rappels.canada.ca/en/alert-recall/zejula-niraparib-update-maintenance-treatment-recurrent-ovarian-fallopian-tube-or

10. National Comprehensive Cancer Network. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 2.2023. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)*. Published online June 2, 2023. Accessed June 5, 2023. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf

11. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine*. 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962

12. GlaxoSmithKline. ZEJULA (niraparib) Capsules Prescribing Information. Published online April 2023.

13. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *New England Journal of Medicine*. 2018;379(26):2495-2505. doi:10.1056/NEJMoa1810858

14. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *New England Journal of Medicine*. 2019;381(4):317-327. doi:10.1056/NEJMoa1903387

15. Child-Pugh score. RxCirrhosis. Accessed October 11, 2023. https://www.rxcirrhose.ca/child-pugh

16. UpToDate. Lexicomp® Drug Interactions. Accessed July 31, 2023. https://www.uptodate.com/drug-interactions/?source=responsive_home#di-document

17. Cancer Care Ontario. Drug Formulary: Niraparib. Cancer Care Ontario. Published June 2022. Accessed June 8, 2023. https://www.cancercareontario.ca/en/drugformulary/drugs/monograph/69561

18. Canadian Cancer Society. Bowel perforation. Canadian Cancer Society. Published June 2022. Accessed June 5, 2023. https://cancer.ca/en/treatments/side-effects/bowel-perforation

19. National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Published online June 14, 2010. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40

20. DiSilvestro P, Banerjee S, Colombo N, et al. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. *JCO*. 2022;41(3):609-617. doi:10.1200/JCO.22.01549

21. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(9):1274-1284. doi:10.1016/S1470-2045(17)30469-2

22. BC Cancer. Olaparib Patient Handout. Published June 1, 2022. Accessed June 6, 2023. http://www.bccancer.bc.ca/search?k=olaparib

23. Moore KN, Monk BJ. Patient Counseling and Management of Symptoms During Olaparib Therapy for Recurrent Ovarian Cancer. *Oncologist*. 2016;21(8):954-963. doi:10.1634/theoncologist.2015-0268

24. BC Cancer. Symptom Management Guidelines: Sleep-Wake Disturbances. Accessed June 6, 2023. http://www.bccancer.bc.ca/search?k=sleepwake

25. BC Cancer. Managing Fatigue (Tiredness). Published February 2020. Accessed June 6, 2023. http://www.bccancer.bc.ca/health-info/coping-with-cancer/managing-symptoms-side-effects/fatigue-(tiredness)

26. Geyer CE, Garber JE, Gelber RD, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Annals of Oncology*. 2022;33(12):1250-1268. doi:10.1016/j.annonc.2022.09.159

27. de Bono J, Mateo J, Fizazi K, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*. 2020;382(22):2091-2102. doi:10.1056/NEJMoa1911440

28. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol*. 2019;20(1):e15-e28. doi:10.1016/S1470-2045(18)30786-1

29. Pfizer Canada ULC. LOMOTIL (diphenoxylate hydrochloride and atropine sulfate) Product Monograph. Published online April 17, 2019.

30. Bruin MAC, Korse CM, van Wijnen B, et al. A real or apparent decrease in glomerular filtration rate in patients using olaparib? *Eur J Clin Pharmacol*. 2021;77(2):179-188. doi:10.1007/s00228-020-03070-0

31. Zibetti Dal Molin GZD, Westin SN, Msaouel P, Gomes LM, Dickens A, Coleman RL. Discrepancy in calculated and measured glomerular filtration rates in patients treated with PARP inhibitors. *International Journal of Gynecologic Cancer*. 2020;30(1). doi:10.1136/ijgc-2019-000714

32. American Heart Association. Monitoring Your Blood Pressure at Home. www.heart.org. Accessed August 3, 2023. https://www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings/monitoring-your-blood-pressure-at-home

33. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. *Canadian Journal of Cardiology*. 2020;36(5):596-624. doi:10.1016/j.cjca.2020.02.086

34. American Heart Association. Hypertensive Crisis: When You Should Call 911 for High Blood Pressure. www.heart.org. Accessed June 8, 2023. https://www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings/hypertensive-crisis-when-you-should-call-911-for-high-blood-pressure

35. Moore KN, Mirza MR, Matulonis UA. The poly (ADP ribose) polymerase inhibitor niraparib: Management of toxicities. *Gynecol Oncol*. 2018;149(1):214-220. doi:10.1016/j.ygyno.2018.01.011

36. Canadian Cancer Society. Life After Cancer Treatment. Published online 2018. Accessed July 18, 2023. https://cdn.cancer.ca/-/media/files/cancer-information/resources/publications/life-after-cancer/32060-life-after-cancer-treatment-en.pdf?rev=ad4b66e5184e460ead7d78e8e6875116&hash=8DC741A1D8B6F08AC362B524BAC96367

37. Friedlander M, Lee YC, Tew WP. Managing Adverse Effects Associated With Poly (ADP-ribose) Polymerase Inhibitors in Ovarian Cancer: A Synthesis of Clinical Trial and Real-World Data. *American Society of Clinical Oncology Educational Book*. 2023;(43):e390876. doi:10.1200/EDBK_390876

38. Francis KE, Kim SI, Friedlander M, et al. The impact of olaparib dose reduction and treatment interruption on treatment outcome in the SOLO2/ENGOT-ov21 platinum-sensitive recurrent ovarian cancer. *Annals of Oncology*. 2022;33(6):593-601. doi:10.1016/j.annonc.2022.02.222

12. Appendix: Quick Reference | PARP Inhibitor (PARPi) Therapy: Adverse Event Monitoring and Management (2 pages)

COMMON ADVERSE EVENT	PATIENT EDUCATION AND MONITORING	TOXICITY MANAGEMENT (Note: guidance below is derived from sources focused on experience in patients with ovarian cancer)
Hematologic – neutropenia, thrombocytopenia, anemia Grade 1 toxicity[1] • Neutrophils < LLN – 1.5 x 10^9/L • Hgb < LLN – 100 g/L • Plt < LLN – 75 x 10^9/L Grade 3 toxicity[1] • Neutrophils < 1.0 – 0.5 x 10^9/L • Hgb < 80 g/L; transfusion indicated Plt < 50 – 25 x 10^9/L	• Ensure recovery from prior hematologic toxicity (≤ grade 1) before starting PARPi therapy[2,3.] **Education** • Discuss possible low blood cell counts and risk of MDS/AML, particularly in patients treated for ovarian cancer [CO] • Advise patients to report fever, flu-like symptoms, infection, breathlessness, bruising, bleeding, blood in urine or stool[2] **Niraparib (note: weight and Plt count when dosing)[3]** • CBC weekly during the first month, monthly up to 24 months, then at routine visits (q3-4mo); continue to monitor following discontinuation[4] **Olaparib[2]** • CBC monthly for up to 24 months, then at routine visits (q3-4mo); continue to monitor following discontinuation[4]	• Rule out other causes of anemia (e.g., deficiencies in iron, folate, or vitamin B12 and hypothyroidism)[5] • If MDS/AML suspected, refer to Hematologist[3]; if counts abnormal > 4 wk, perform bone marrow analysis and/or blood cytogenetic analysis[2] **Niraparib[3]** • Interrupt niraparib if ≥ grade 3 anemia or neutropenia, or Plt < 100 • If counts return to acceptable levels within 28 days, may resume (use reduced dose if niraparib held for anemia, neutropenia, or second occurrence of thrombocytopenia); discontinue if toxicity > 28 days **Olaparib[2]** • Interrupt therapy and consider dose reductions as required
Fatigue and Insomnia	• Fatigue reported commonly with both PARPis, insomnia mostly with niraparib **Education** • Fatigue improves over time[5] • Encourage regular exercise (e.g., 20 min of sustained activity), healthy diet, good sleep habits, methods to reduce stress/anxiety, and to pace themselves[6] • Provide information on cancer-related fatigue	• Rule out other sources of fatigue: hypothyroidism, dehydration, nausea, anemia, uncontrolled pain, depression/anxiety, etc.[7] • Address nutritional deficits and sleep dysfunction[5] • Recommend massage therapy, psychosocial interventions[5] • Consider dose interruption and reduction • For insomnia: provide sleep hygiene education[8], consider pharmacologic methods for refractory insomnia[5]
Nausea and Vomiting	• Common, usually low grade **Education** • Eat 30-60 min before PARPi dose[5]; bedtime dosing with niraparib[3] • Eat small, more frequent meals, ↑ fluids, avoid alcohol[5,9] • Educate on use of antiemetics (e.g., 30 min before PARPi dose) • Generally improves over time[2]	• Interrupt therapy and consider dose reductions as required[2,3] • Steroids, domperidone, olanzapine, haloperidol, metoclopramide [CO], or prochlorperazine [CO][5] – Avoid long-term steroid use (long-term dexamethasone use may cause CYP3A4 induction and interact with olaparib)[5] • Olanzapine may be an effective option for refractory breakthrough nausea [CO] • Dimenhydrinate and haloperidol for refractory nausea/vomiting [CO]
Diarrhea and Constipation	**Education** • Inform patients regarding risk of diarrhea and constipation • Eat small, more frequent meals, soluble fibre, ↑ fluids, bland diet[6] • Avoid sorbitol (e.g., dry fruit, chewing gum, diet beverages, sugar-free candies)[6]	• Interrupt therapy and consider dose reductions as required[2,3] **Diarrhea** • Rule out other causes (e.g., infections, dietary, medication, pancreatic insufficiency)[6] • Loperamide, alternative – Lomotil (diphenoxylate/atropine) [CO] **Constipation** • E.g., Senna BID or polyethylene glycol 3350[10] • Use antiemetics other than 5-HT3 antagonists[5]

COMMON ADVERSE EVENT	PATIENT EDUCATION AND MONITORING	TOXICITY MANAGEMENT (Note: guidance below is derived from sources focused on experience in patients with ovarian cancer)
Increased Creatinine	• Monitor at routine visits • Remind patients of the importance of adequate hydration to help prevent elevated creatinine from dehydration [CO]	• ↑ serum creatinine may occur without true renal dysfunction; PARPis can impact renal transporters that secrete creatinine into the urine[11] • Consider alternative renal markers to avoid unnecessary dose interruption/reduction:[10] – Cystatin C[11], BUN or urea [CO], renal scan[5] • Consider dose interrupt/reduction if truly reduced GFR
Hypertension **(Cardiac arrest, hypertensive crisis – rare but serious)**	**Niraparib[3]** • Ensure pre-existing hypertension is controlled before starting niraparib • Closely monitor patients with cardiovascular disorders • Monitor BP/HR at least weekly x 2 months, at least monthly x 10 months, then periodically beyond month 12[a] – Monitor more frequently if borderline hypertension [CO] • Educate patients on self-monitoring BP and HR • Continue to monitor BP following discontinuation of niraparib and adjust antihypertensives as required [CO]	**Niraparib** • Management recommendations per Moore et al.[12] (see full document) – For patients < 60 y, consider antihypertensive use for BP > 140/90 – For patients ≥ 60 y, consider antihypertensive use for BP > 150/90 • Hypertensive Emergency: BP is ≥ 180/120 and patient is experiencing any symptoms of target organ damage such as chest pain, SOB, back pain, numbness/weakness, change in vision, or difficulty speaking ▶ Patient should call 911[13] • Hypertensive Urgency: BP is ≥ 180/120 at two measurements, 5 minutes apart but without symptoms of target organ damage ▶ Patient should contact HCP for immediate management[13]

RARE BUT SERIOUS ADVERSE EVENTS		
Posterior Reversible Encephalopathy Syndrome (PRES)[3]	**Niraparib**	• Monitor for seizure, headache, altered mental status, speech loss, visual disturbances, ± hypertension[3] • Hold niraparib, confirm PRES with brain imaging, preferably MRI; treat symptoms, control hypertension[3]
Intestinal Perforation [CO]	**Niraparib**	• Investigate related symptoms (sudden and severe abdominal pain, swelling/bloating of abdomen)[14]
Pneumonitis[2]	**Olaparib**	• Monitor for new/worsening respiratory symptoms and/or radiographic chest abnormality[2] • Hold olaparib and investigate; if pneumonitis confirmed, discontinue and treat pneumonitis appropriately[2]
Venous Thromboembolic Events[2]	**Olaparib (prostate cancer)**	• Monitor for signs and symptoms of venous thrombosis (swelling and pain in one part of the body) and pulmonary embolism (SOB, chest pain, more rapid breathing, fast heartbeat, coughing up blood)
MDS/AML	**Niraparib and Olaparib**	• Risk persists beyond treatment discontinuation; adhere to hematologic monitoring recommendations (Appendix Page 1/2) • If MDS/AML suspected, refer to Hematologist[3], if counts abnormal > 4 wk, perform bone marrow analysis and/or blood cytogenetic analysis[2]

- Sunscreen reminder (SPF ≥ 30)
- Patients/partners of child-bearing potential: review risks and contraception recommendations

[a] Optimal frequency: 3x per week for first month, 2x per week for month 2, 2x per month for months 3-12, then monthly beyond month 12 [CO].

BID, twice daily; BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; CO, Clinical Opinion; GFR, glomerular filtration rate; Hgb, hemoglobin; HR, heart rate; HCP, healthcare professional; LLN, lower limit normal; MDS/AML, myelodysplastic syndrome/acute myeloid leukemia; MRI, magnetic resonance imaging; NIR, niraparib; NR, not reported; OLA, olaparib; PARPi, poly (ADP-ribose) polymerase inhibitor; Plt, platelets; PRES, posterior reversible encephalopathy syndrome; q3-4mo, every 3 to 4 months; SOB, shortness of breath; wk, week; y, years of age.

Appendix to: PARP Inhibitor Clinical Resource: Breast, Ovarian, Pancreatic, and Prostate Cancers. Version 02.2024

REFERENCES: [1] National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events (CTCAE) v4.03. [2] LYNPARZA (olaparib) Product Monograph. Dec. 12, 2023. [3] ZEJULA (niraparib) Product Monograph. Aug. 17, 2023. [4] Tinker AV, et al. *Curr Oncol*. 2022;29(6):4354-4369. [5] Madariaga A, et al. *Int J Gynecol Cancer*. 2020;30(7):903-915. [6] Moore KN, Monk BJ. *Oncologist*. 2016;21(8):954-963. [7] BC Cancer. Managing Fatigue (Tiredness). Published February 2020. Accessed June 6, 2023. [8] BC Cancer. Symptom Management Guidelines: Sleep-Wake Disturbances. Accessed June 6, 2023. [9] BC Cancer. Olaparib Patient Handout. Published June 1, 2022. Accessed June 6, 2023. [10] LaFargue CJ, et al. *Lancet Oncol*. 2019;20(1):e15-e28. [11] Bruin M, et al. A real or apparent decrease in glomerular filtration rate in patients using olaparib? *Eur J Clin Pharmacol*. 2021;77(2):179-188. [12] Moore KN, et al. *Gynecol Oncol*. 2018;149(1):214-220. [13] Rabi DM, et al. *Canadian Journal of Cardiology*. 2020;36(5):596-624. [14] Canadian Cancer Society. Bowel perforation. Published June 2022. Accessed June 5, 2023. https://cancer.ca/en/treatments/side-effects/bowel-perforation.