CoLab Network

Observational Study

The Safety of Niraparib in Ovarian Cancer

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Key Messages

Niraparib, a poly-(adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibitor, is used as a maintenance therapy for patients with new or recurrent epithelial ovarian cancer who have had a complete or partial response to platinum-based chemotherapy. It was approved for use in Canada in 2019.

Clinical trials have shown that PARP inhibitors can cause hematological toxicity. A population-based, retrospective cohort study was conducted to evaluate the real-world toxicity of niraparib.

This study uses data from 4 provinces: Ontario, British Columbia, Alberta, and Quebec. Data access varied by province, and included administrative data, laboratory data, pharmaceutical dispensing data, data from electronic medical records, and registry data.

The study found that real-world administration of niraparib is given at lower doses than the recommendations provided in the product monograph. This may be 1 of several factors that could have contributed to the lower proportion of hematological toxicities observed in the real world.

More research is needed to understand why lower hematological toxicities were found in the real world.

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Abbreviations

ADP	adenosine diphosphate
CCRE	Canadian Cancer Real-world Evaluation Platform
CI	confidence interval
HRD	homologous recombination deficiency
PARP	poly-(ADP-ribose) polymerase
PFS	progression-free survival
PMT	personalize my treatment
SD	standard deviation

Background

Due to its nonspecific symptom presentation and rapid spread throughout the abdomen, many patients with epithelial ovarian cancers, fallopian tube cancers, and primary peritoneal cancers (collectively referred to as epithelial ovarian cancers throughout this report as these cancers are biologically alike) are diagnosed with advanced disease and therefore have poor prognosis.[1,2] It is estimated that approximately 3,000 females in Canada were diagnosed with ovarian cancer in 2022, and 1,950 died from the disease.[1,3] The 5-year survival rate for ovarian cancer is approximately 45%[4] and risk factors include familial history of ovarian cancer and identified genetic mutations (e.g., germline pathogenic variants in BRCA1 and BRCA2), older age, obesity, smoking, and endometriosis.[1,5]

The main treatment for ovarian cancer consists of cytoreductive surgery followed by platinum-based chemotherapy.[1,6] High-grade ovarian cancers (which represent the majority of cases) are particularly susceptible to the cytotoxicity of platinum-based drugs; however, up to 80% of patients will experience disease recurrence.[7]

In recent years, evidence has shown that the use of oral poly-(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors as a maintenance therapy after complete or partial response to platinum-based chemotherapy improves progression-free survival (PFS) when compared to placebo.[2,8] PARP inhibitors prevent the restoration of gene damage. Because of this, patients who have homologous recombination deficiency (HRD) and already have some dysregulation in their gene repair, tend to be more likely to respond to treatment with PARP inhibitors.[8,9]

Currently, there are 2 PARP inhibitors available in Canada for maintenance therapy in ovarian cancer: olaparib and niraparib. Olaparib was approved by Health Canada in 2019 for use as a maintenance therapy after complete or partial response to first-line platinum-based chemotherapy for patients with advanced, high-grade ovarian cancer who have germline pathogenic variants or somatic mutations in the BRCA1 or BRCA2 genes.[10] The approval for olaparib was limited to BRCA1 or BRCA2 where the evidence is strongest, although a gradient of benefits exists among other patients with HRD cancers without BRCA1 or BRCA2 to homologous recombination proficient cancers. However, evidence has shown potential benefits for PARP inhibitors among patients without BRCA1 or BRCA2 who have complete or partial response to platinum-based chemotherapy.[11]

Later in 2009, this led to Health Canada's approval of niraparib maintenance therapy for all patients with recurrent ovarian cancer who have complete or partial response to platinum-based chemotherapy, and subsequently, for all patients with newly diagnosed ovarian cancer after complete or partial response to platinum-based chemotherapy in 2020.[13]

Following Health Canada's approvals, CADTH's pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommended the reimbursement of niraparib as monotherapy for the maintenance treatment of platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer on September 3, 2020,[14] and platinum-sensitive newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer on April 29, 2021.[15] In Quebec, the Institut National d'Excellence en Santé et en Services

Sociaux (INESSS) recommended reimbursement for niraparib for the same indication on September 30, 2020.[16]

Niraparib was subsequently added to the provincial public drug formularies for both indications on December 1, 2021, in British Columbia;[17] December 21, 2021, in Ontario;[18] January 1, 2022 in Alberta;[19] and September 29, 2021, in Quebec.[20] Niraparib is administered orally for up to 3 years or until unacceptable toxicity or disease progression.[21] Additional dosing details are available in Table 1.

Table 1: Approved Indications, Suggested Regimens, and Key Funding Dates for Niraparib

Approved use	Dose	Public funding start date
Maintenance treatment of **recurrent** epithelial ovarian, fallopian tube, or primary peritoneal cancer	300 mg orally once daily for patients weighing ≥ 58 kg 200 mg for patients weighing < 58 kg may be considered Patients should start treatment with niraparib no later than 8 weeks after their most recent platinum-based chemotherapy.	Ontario: December 21, 2021[18] Alberta: January 1, 2022[19] BC: December 1, 2021[17] QC: September 29, 2021[20]
Maintenance treatment of **newly diagnosed** advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	300 mg once daily for patients weighing ≥ 77 kg with a platelet count ≥ $150x10^9$/L 200 mg once daily for patients < 77 kg or with a platelet count < $150x10^9$/L Patients should start treatment no later than 12 weeks after their most recent platinum-based chemotherapy.	Ontario: December 21, 2021[18] Alberta: January 1, 2022[19] BC: December 1, 2021[17] QC: September 29, 2021[20]

BC = British Columbia; QC = Quebec.

The previously mentioned approvals and recommendations were finalized based on results from 2 double-blind, placebo-controlled, phase III trials: the NOVA trial[11] and the PRIMA trial.[22] These trials enrolled patients with high-grade, platinum-sensitive recurrent and newly diagnosed ovarian cancer, respectively, with the purpose of evaluating the efficacy and safety of niraparib for maintenance therapy. Both trials reported that patients receiving niraparib (regardless of BRCA mutation status) experienced a statistically significant prolongation of PFS when compared to placebo. When assessing the safety profile of the treatment, both trials showed a substantially higher incidence of grade 3 or 4 adverse events among patients in the niraparib treatment group (74.1% of the niraparib group versus 22.9% of the placebo group in the NOVA trial; 65.3% of the niraparib group versus 6.6% of the placebo group in the PRIMA trial). Thrombocytopenia, anemia, neutropenia, fatigue, and hypertension were the most common toxicities. Among patients enrolled in the NOVA trial, grade 3 or 4 thrombocytopenia occurred in approximately 33.8% of the niraparib group (0.1% of the placebo group), grade 3 or 4 anemia in 25.3% of the niraparib group (0 in the placebo group), and grade 3 or 4 neutropenia in 19.6% of the niraparib group (1.7% of the placebo group).[11] In the PRIMA trial, grade 3 or 4 thrombocytopenia occurred in approximately 28.7% of the niraparib group (0.4% of the placebo group), grade 3 or 4 anemia in 31.0% of the niraparib group (1.6% in the placebo group), and grade 3 or 4 neutropenia in 12.8% of the niraparib group (1.2% in the placebo group).[22] Most patients required a dose interruption (66.5% in the NOVA trial and 79.5% in the PRIMA trial) or reduction (68.9% in the NOVA trial and 70.9% in the PRIMA

trial) to manage adverse events.[11] The PRIMA trial also evaluated individualized dosing (the starting dose was determined based on weight and platelet count) and found that those patients experienced a lower rate of all adverse events (except neutropenic sepsis) compared to patients on a standard dose (300 mg per day).

Purpose of This Report

The selection of participants for trials is highly restricted; therefore, the generalizability of adverse event burden from seminal trials to real-world patient populations can be limited. We aim to describe the clinical and demographic characteristics of patients treated with niraparib as well as the incidence of adverse events experienced by those receiving niraparib treatment in the real world. These results will be evaluated against the results from the seminal clinical trials and are intended to support clinicians and patients in joint decision-making that considers evidence-based information, the provider's knowledge and experience, and the patient's values and preferences.

Main Takeaway

Clinical trials have shown that niraparib can cause hematological toxicity (an adverse effect on blood or blood-forming tissues); however, event rates in clinical trials may differ from those in the real world. This study aims to determine whether the safety profile of niraparib in real-world patient populations differs from the clinical trial findings.

Policy Issues

Niraparib is reimbursed as a maintenance treatment for newly diagnosed and recurrent ovarian, fallopian tube, or primary peritoneal cancer, regardless of a patient's BRCA mutation or HRD status. Due to the high toxicity rates observed in clinical trials for PARP inhibitors, jurisdictions are seeking to further understand the risk profile of niraparib in the management of ovarian cancer in the real world, which could inform patient monitoring and toxicity management measures.

Policy Question

How does the safety and tolerability of niraparib in the real world compare with observations from the seminal clinical trials?

Research Question

What is the safety and tolerability of niraparib in patients with newly diagnosed and recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer?

Research Objectives

1. To characterize the patient population receiving niraparib for newly diagnosed or recurrent ovarian cancer.

2. To determine the proportion of these patients who experience adverse events in the real-world setting.

Methods

Population and Setting

We examined all individuals 18 years and older undergoing maintenance treatment for newly diagnosed or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer using publicly funded niraparib in Ontario, Alberta, and British Columbia, and all adult participants of the Personalize My Treatment (PMT) registry in Quebec treated with niraparib for the same indications. PMT is an active registry developed by Exactis Innovation that collects clinical and molecular patient data for patients with cancer at 16 sites across Canada.[23] For the purposes of this study, we are accessing PMT data for patients living in Quebec, which includes patient data from 1 hospital. Our study period ranged from June 27, 2019, to December 31, 2022, with each province having a different start date due to jurisdictional differences in data availability and different availability of niraparib due to variation in public funding approval and implementation dates. The accrual window started on June 27, 2019, for Ontario; January 1, 2020, for Quebec; December 1, 2021, for British Columbia; and January 1, 2022, for Alberta. Although public funding for niraparib started on December 21, 2021, in Ontario, the accrual period for this province began on the date of Health Canada approval (June 27, 2019) to include patients who were enrolled in patient support programs before receiving niraparib through the provincial funding program. This method of cohort creation is unique to Ontario in this study as it was the only site that relied on administrative data. We ascertained the exposure to publicly funded niraparib in Ontario using an administrative claims database (Ontario Drug Benefit), whereas exposure to niraparib in Alberta, British Columbia, and Quebec were ascertained using electronic medical records and/or pharmacy dispensing records. Because of this, it was pertinent to look back before the start date of Ontario's public funding for niraparib to ensure that we captured the correct start date for all patients in the cohort.

Study Design

We conducted a retrospective, single-arm, population-based cohort study to examine the safety of niraparib for maintenance therapy among patients with ovarian cancer who were treated with niraparib between 2019 and 2022 in 3 Canadian provinces: Ontario, Alberta, and British Columbia. This retrospective, single-arm, cohort design was replicated in Quebec using adults enrolled in the PMT registry.[23] The index date for each patient was the date of first niraparib prescription dispensed and we followed each patient until treatment discontinuation, death, or December 31, 2022, whichever came first. Refer to Table 2 for a summary of key dates in the study design and Figure 1 for a visual representation of the study design for each province.

Table 2: Key Dates for Study Design by Province

Study design details	Key date			
	Ontario	Alberta	British Columbia	Quebec
Accrual window for patients receiving maintenance therapy with niraparib	June 27, 2019, to December 31, 2022	January 1, 2022, to December 31, 2022	December 1, 2021, to December 31, 2022	January 25, 2021, to December 31, 2022
Index date	Earliest date is June 27, 2019	Earliest date is January 1, 2022	Earliest date is December 1, 2021	Earliest date is January 25, 2021
Look-back window	Up to 5 years before index, earliest date is June 27, 2014	Up to 5 years before index, earliest date is January 1, 2017	Up to 5 years before index, earliest date is December 1, 2016	Up to 5 years before index, earliest date is January 25, 2016
Observation window	Between index date and December 31, 2022			
Maximum follow-up date	December 31, 2022			

Figure 1: Study Design Diagram for Ontario

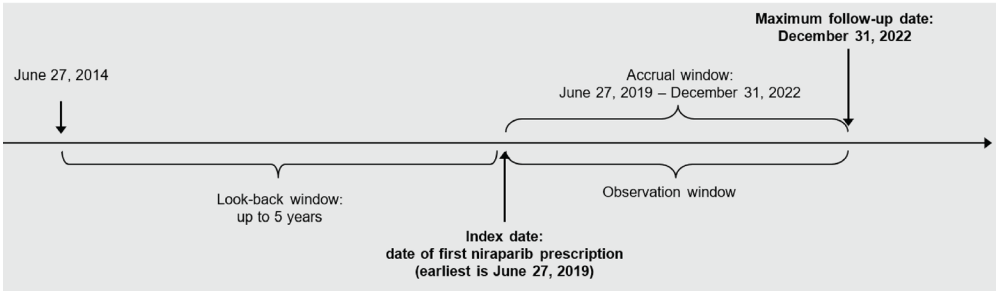


Figure 2: Study Design Diagram for Alberta

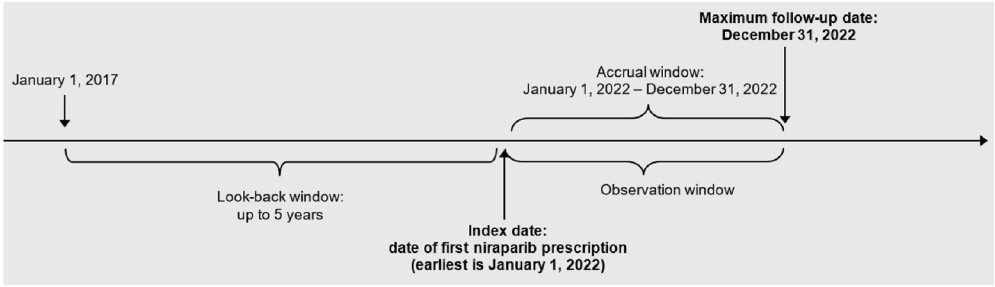


Figure 3: Study Design Diagram for British Columbia

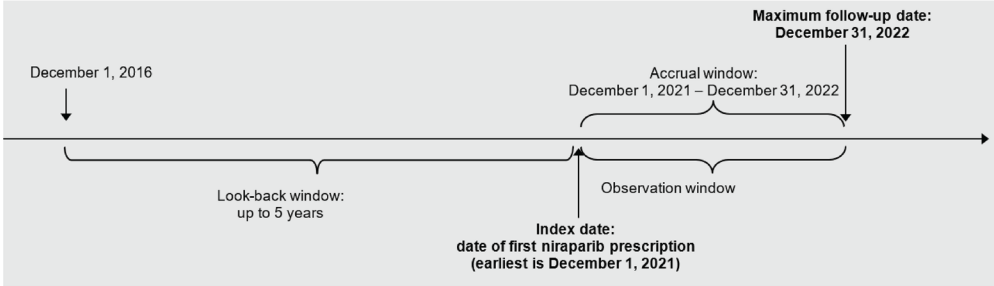
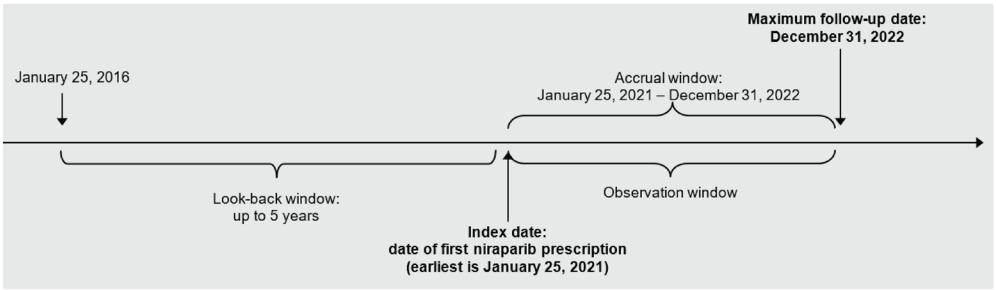


Figure 4: Study Design Diagram for Quebec



Eligibility Criteria

Our cohort included all adults who received maintenance treatment for ovarian cancer using publicly funded niraparib in Ontario, Alberta, and British Columbia, as well as all adults who received niraparib for ovarian cancer and were enrolled in the PMT registry in Quebec. Additional exclusion criteria for each province are outlined in Table 3.

Data Sources

We used a number of data sources to conduct this study, all of which are summarized in Table 4. The Canadian Cancer Real-World Evaluation (CCRE) Platform's access to data in Ontario is governed under section 45 of the province's Personal Health Information Protection Act and is not subject to additional review by an ethics review board. Access to data in Alberta is governed under the province's health information act. The Alberta site of the CCRE Platform was approved by the Health Research Ethics Board of Alberta – Cancer Committee. Data access was approved by the Alberta Data Stewards. The British Columbia site of the CCRE Platform was approved by the University of British Columbia — BC Cancer Research Ethics Board. Data access was approved by the BC Cancer Data Stewards. Ethics approval for the PMT registry in Quebec is provided by the Integrated University Health and Social Services Centres (CIUSSS) West-Central Montreal Research Ethics Board (Research Ethics Board number: MP-05-2016-321). Based on privacy policies to protect patient confidentiality set by each cancer agency, we only reported values larger than 5 in Ontario and British Columbia, and values greater than 9 in Alberta. We also suppressed small values (< 6) reported in Quebec to maintain consistency.

Table 3: Cohort Exclusion Criteria by Province

Province	Exclusion criteria
Ontario	Invalid patient identification number Invalid death date (death before index date) Invalid sex [from original source] Non-Ontario resident status on index date
Alberta	Invalid patient identification number Not referred (i.e., not in pharmacy or patient records) Invalid death date (death before index date) Non-Alberta resident on index date
British Columbia	Invalid patient identification number Not referred to BC Cancer (not in electronic medical record) Invalid death date (death before index date) Non-British Columbia resident on index date
Quebec	Invalid death date (death before index date) Invalid treatment date (missing date) Patient receiving niraparib in the context of a clinical trial Patient transferred to another hospital during treatment

Table 4: Data Sources by Province

Province	Data sources
Ontario	**Cohort creation (June 27, 2019, to December 31, 2022)** **ODB database:** all records of publicly funded medications in Ontario **ALR database:** records of visits to oncology centres in Ontario **OCR:** records of cancer diagnoses **RPDB:** demographics data
	Clinical and demographic characteristics (on index date or during look-back period) **Ontario Marginalization Index** • marginalization index specific to Ontario, developed based on geographical data • measures 4 dimensions: households and dwellings, material resources, age and labour force, racialized and newcomer populations **CIHI DAD:** all records of procedures and diagnoses that occur in an inpatient setting **CIHI SDS:** records of same day surgeries **OHIP:** all records of procedures and diagnoses that occur in an outpatient setting **NDFP:** all records of new and expensive injectable cancer drugs administered in hospital settings in Ontario **OCR** **ODB** **ALR** **RPDB**

Province	Data sources
	Outcomes (during observation window of June 27, 2019, to December 31, 2022) **OLIS database:** all laboratory records from hospital, community, and public health labs across Ontario **CIHI NACRS database:** all records of procedures and diagnoses that occur in the ambulatory setting **CIHI DAD** **OHIP** **CIHI SDS** **ODB** **RPDB**
Alberta	**Cohort creation (January 1, 2022, to December 31, 2022)** **PIN database:** all records of prescription medications dispensed in Alberta for all payers
	Clinical and/or demographic characteristics (on index date or during look-back period) and outcomes (during observation window of January 1, 2022, to December 31, 2022) **Electronic medical records**
British Columbia	**Cohort creation (December 21, 2021, to December 31, 2022)** **BC Provincial Systemic Therapy Program:** pharmacy dispensing records for all publicly funded systemic therapies **BC Cancer Registry:** records of patient demographics, cancer diagnosis, and mortality
	Clinical and/or demographic characteristics (on index date or during look-back period) and outcomes (during observation window of December 1, 2021, to December 31, 2022) **BC Provincial Systemic Therapy Program** **BC Cancer Registry** **Electronic medical records**
Quebec	**Cohort creation (January 25, 2021, to December 31, 2022), clinical and/or demographic characteristics (on index date or during look-back period), select outcomes (January 25, 2021, to December 31, 2022)** **PMT registry, Exactis Innovation:** all electronic medical records in patient charts of those enrolled in the PMT registry
	Hematological adverse events (January 25, 2021, to December 31, 2022) Electronic medical records

ALR = activity level reporting; BC = British Columbia; CIHI = Canadian Institute for Health Information; DAD = Discharge Abstract Database; NACRS = National Ambulatory Care Reporting System; NDFP = New Drug Funding Program; OCR = Ontario Cancer Registry; ODB = Ontario Drug Benefit; OHIP = Ontario Health Insurance Plan; OLIS = Ontario Laboratory Information System; PIN = Pharmaceutical Information Network; PMT = Personalize My Treatment; RPDB = Registered Persons Database; SDS = Same Day Surgery.

Key Study Measures

Exposures

The main exposure of interest in this study was the use of niraparib for maintenance treatment, ascertained in drug reimbursement records in Ontario, pharmacy dispensing records and electronic medical records in Alberta and British Columbia, and patient charts in Quebec (Drug Identification Number: 02489783).

Outcomes of Interest

The main outcomes of interest in this study were grade 3 or 4 thrombocytopenia, anemia, and neutropenia (as defined by platelet), and hemoglobin and neutrophil counts (respectively) listed in the Common Terminology Criteria for Adverse Events (Refer to Table 5).[24]

Table 5: Variable Definition for Main Outcomes of Interest

Variable	Definition
Thrombocytopenia	**Grade 1:** platelet count between 75 and 150 × 10^9/L **Grade 2:** platelet count between 50 and < 75 × 10^9/L **Grade 3:** platelet count between 25 and < 50 × 10^9/L **Grade 4:** platelet count < 25 × 10^9/L
Anemia	**Grade 1:** hemoglobin count between 100 g/L and 120 g/L **Grade 2:** hemoglobin count between 80 g/L and < 100 g/L **Grade 3:** hemoglobin count between 65 g/L and < 80 g/L **Grade 4:** hemoglobin count < 65 g/L
Neutropenia	**Grade 1:** neutrophil count between 1.5 and 2.0 × 10^9/L **Grade 2:** neutrophil count between 1.0 and < 1.5 × 10^9/L **Grade 3:** neutrophil count between 0.5 and < 1.0 × 10^9/L **Grade 4:** neutrophil count < 0.5 × 10^9/L

We also reported a number of secondary outcomes that occurred during the observation period in this study; these included febrile neutropenia, incident hypertension, blood transfusion (any, platelet, and red blood cell), hospitalizations, emergency department visits, time to niraparib discontinuation, median follow-up time, and overall survival. Additional details on variable definitions are provided in Appendix 1.

Covariates of Interest

We reported on a number of baseline variables defined on index date, including age, rurality (rural versus urban residence), marginalization index score (for Ontario), income quintile, year of niraparib treatment start, initial daily dose of niraparib, primary tumour location, and tumour histology. We also ascertained a number of baseline variables during the 5-year look-back period before the index date. These included the Charlson Comorbidity Index (for Ontario and Alberta),[25] prior hypertension diagnosis (for Ontario and Alberta),[26] prior platinum-based chemotherapy, and the number of cycles of prior platinum-based chemotherapy (refer to Table 9 in Appendix 1, for more detail). Certain covariates of interest are reported in select provinces due to differences in data availability.

Analyses

We used descriptive statistics to summarize the cohort's clinical and demographic characteristics in each province. We constructed cumulative incidence function curves for the primary outcomes accounting for the risk of death as well as treatment discontinuation plus 60 days (washout period) as competing risks and censoring on end of study period using the Fine-Gray model.[27] All analyses in Ontario and British Columbia

were conducted in SAS 9.4 (SAS Institute) and analyses conducted in Alberta and Quebec were conducted in R (v.4.2.2 in Alberta and v.4.3.0 in Quebec).

Results

Population Characteristics

Summary

Two-thirds of the cohort were 65 years of age or older.

More than half of the included patients were diagnosed with ovarian cancer between 2020 and 2022.

Most patients started niraparib treatment in 2022 after completing platinum-based chemotherapy.

The most common initial daily dose of niraparib was 200 mg/day, followed by 100 mg/day, and 300 mg/day.

Our study included patients undergoing maintenance treatment for newly diagnosed or recurrent ovarian cancer using publicly funded niraparib; there were a total of 483 patients across the CCRE jurisdictions, including 338 in Ontario, 45 in Alberta, and 100 in British Columbia. In Quebec, we identified 31 patients who were receiving niraparib for the same indications in the PMT registry (Table 6). Approximately two-thirds of the overall cohort were 65 years of age or older (N = 352; 68.5%), most patients started niraparib maintenance treatment in 2022 (N = 459 to 463; 89.3% to 90.1%), and the most common starting daily dose of niraparib was 200 mg/day (N = 288 to 292; 67.3% to 68.2%).

Table 6: Study Cohort Baseline Characteristics

Variable	All provinces N = 514	Ontario N = 338	Alberta N = 45	British Columbia N = 100	Quebec N = 31
Age on index date					
Mean ± standard deviation	66.8 ± 10.3	68.8 ± 9.7	67.0 ± 9.0	66.1 ± 10.4	65.3 ± 11.9
≥ 65 years, N (%)	352 (68.5)	254 (75.1)	29 (64.4)	51 (51.0)	18 (58.1)
Urban residence,[a] N (%)	396 to 402 (77.0 to 78.2)	280 (82.8)	24 (53.3)	92 to 98 (92.0 to 98.0)	NA
Marginalization Index Score,[a] N (%)					
1 (least marginalized)	NA	91 (26.9)	NA	NA	NA
2	NA	74 (21.9)	NA	NA	NA
3	NA	64 (18.9)	NA	NA	NA
4	NA	59 (17.5)	NA	NA	NA
5 (most marginalized)	NA	47 (13.9)	NA	NA	NA
Income Quintile,[a] N (%)					

Variable	All provinces N = 514	Ontario N = 338	Alberta N = 45	British Columbia N = 100	Quebec N = 31
1 (lowest)	51 to 65 (13.3 to 17.0)	56 (16.6)	< 10	NA	NA
2	103 (26.9)	72 (21.3)	31 (68.9)	NA	NA
3	73 to 81 (19.1 to 21.1)	72 (21.3)	< 10	NA	NA
4	62 to 70 (16.2 to 18.3)	61 (18.0)	< 10	NA	NA
5 (highest)	76 to 84 (19.8 to 21.9)	75 (22.2)	< 10	NA	NA
Charlson Comorbidity Index score, N (%)					
0	47 (12.3)	21 (6.2)	26 (57.8)	NA	NA
1	20 (5.2)	7 (2.1)	13 (28.9)	NA	NA
2	35 to 43 (9.1 to 11.2)	34 (10.1)	< 10	NA	NA
3+	94 to 102 (24.5 to 26.6)	93 (27.5)	< 10	NA	NA
No previous hospitalization	183 (47.8)	183 (54.1)	0	NA	NA
Prior hypertension	118 (28.5)	155 (45.9)	19 (42.2)	NA	13 (41.9)
Year of cancer diagnosis, N (%)					
2018 and earlier	89 (17.3)	81 (24.0)	< 10	< 6	< 6
2019	45 (8.8)	26 (7.7)	< 10	9 (9.0)	< 6
2020	78 (15.2)	60 (17.8)	< 10	< 6	10 (32.3)
2021	217 (42.2)	119 (35.2)	28 (62.2)	60 (60.0)	10 (32.3)
2022	86 (16.7)	52 (15.4)	< 10	25 (25.0)	< 6
Cancer stage at diagnosis, N (%)					
I to II	37 (7.2)	22 (6.5)	< 10	6 (6.0)	< 6
III	225 (43.8)	123 (36.4)	29 (64.4)	50 (50.0)	23 (74.2)
IV	89 to 101 (17.3 to 19.6)	56 (16.6)	< 10	27 (27.0)	5 to 9 (16.1 to 29.0)
Missing or unknown	155 to 163 (30.2 to 31.7)	137 (40.5)	< 10	17 (17.0)	0
Year of niraparib treatment, N (%)					
2020 to 2021	51 to 55 (9.9 to 10.7)	32 (9.5)	0	< 6	17 (54.8)

Variable	All provinces N = 514	Ontario N = 338	Alberta N = 45	British Columbia N = 100	Quebec N = 31
2022	459 to 463 (89.3 to 90.1)	306 (90.5)	45 (100.0)	94 to 98 (94.0 to 98.0)	14 (45.2)
Primary tumour location, N (%)					
Ovary	400 to 404 (77.8 to 78.6)	312 (92.3)	22 (48.9)	40 (40.0)	26 to 30 (83.9 to 96.8)
Fallopian tubes	78 to 86 (15.2 to 16.7)	12 (3.6)	13 to 21 (28.9 to 46.7)	53 (53.0)	0
Other	32 (6.2)	14 (4.1)	< 10	7 (7.0)	< 6
Tumour histology, N (%)					
Serous	453 to 461 (88.1 to 89.7)	292 (86.4)	41 (91.1)	94 to 98 (94.0 to 98.0)	26 to 30 (83.8 to 96.8)
Endometroid	9 to 17 (1.8 to 3.3)	8 (2.4)	< 10	0	0
Other	47 (9.1)	38 (11.2)	< 10	< 6	< 6
Presence of cancer antigen-125 > 35 units/mL	38 (21.6)	N/A	12 (26.7)	18 (19.0)	8 (25.8)
Prior platinum-based chemotherapy	505 (98.2)	336 (99.4)[b]	36 to 44 (80.0 to 97.8)	100 (100.0)	26 to 30 (83.9 to 96.7)
Mean number of cycles of prior platinum-based chemotherapy ± standard deviation	6.5 ± 2.9	8.8 ± 4.9	4 ± 2	6.4 ± 1.0	6.6 ± 1.9
Mean number of days between last platinum-based chemotherapy and index date ± standard deviation[c]	57.3 ± 25.9	55.3 ± 31.3	60.4 ± 27.0	55.1 ± 21.8	58.3 ± 22.2
Initial daily dose of niraparib[d]					
100 mg	103 (24.1)	58 (22.9)	17 (37.8)	28 (28.0)	0
200 mg	288 to 292 (67.3 to 68.2)	175 (69.2)	28 (62.2)	60 (60.0)	25 to 29 (83.3 to 96.7)
300 mg	33 to 37 (7.7 to 8.6)	20 (7.9)	0	12 (12.0)	< 6
Mean initial daily dose of niraparib ± standard deviation	172.3 ± 53.5	171 ± 49	162 ± 49	184 ± 61.5	NA

[a]This variable contains missing values; therefore, the categories do not add up to N = 338 for Ontario.

[b]The remaining cohort has missing data for this variable.

[c]Calculated for patients whose last dose of platinum-based chemotherapy occurred on or after the start of public funding for niraparib for each jurisdiction. This includes N = 287 overall, N = 166 in Ontario, N = 30 for Alberta, N = 76 for British Columbia, and N = 15 for Quebec.

[d]Using cohort of N = 253 for Ontario and N = 30 for Quebec.

Among patients in Ontario, the mean age was 68.8 years (standard deviation [SD] = 9.7), the majority of patients lived in urban settings (N = 280; 82.8%), and more than half of the group had no prior hospitalization for a comorbidity (N = 183; 54.1%) or had a Charlson Comorbidity Index score of 0 (N = 21; 6.2%), indicating the absence of noncancer comorbidities identified in inpatient data. Neighbourhood income was relatively evenly distributed throughout the Ontario cohort (approximately 20% in each income quintile). Approximately half of the Ontario cohort were diagnosed with ovarian cancer in 2021 (N = 119; 35.2%) and 2022 (N = 52; 15.4%) and the majority started niraparib maintenance treatment in 2022 (N = 306; 90.5%). The primary tumour location for patients in Ontario was in the ovaries (N = 312; 92.3%) and the most common tumour histology identified was serous (N = 292; 86.4%). Almost the entire Ontario cohort was treated with platinum-based chemotherapy before niraparib maintenance therapy (N = 336; 99.4%) and the mean number of cycles of prior chemotherapy was 8.8 (SD = 4.9). The mean number of days between last chemotherapy date and index date was 55.3 (SD = 31.3). The most common initial daily dose of niraparib was 200 mg per day (N = 175; 69.2%), followed by 100 mg per day (N = 58; 22.9%), and then 300 mg per day (N = 20; 7.9%).

In Alberta, the mean age was 67 years (SD = 9.0) and more than half of the cohort (N = 24; 53.3%) lived in an urban setting. More than half of the cohort had a Charlson Comorbidity Index score of 0 (N = 26; 58.8%). The majority of this cohort was diagnosed with ovarian cancer in 2021 (N = 28; 62.2%) and everyone initiated niraparib treatment in 2022 (N = 45; 100%). Almost half of the Alberta cohort had a primary tumour in the ovaries and the most common tumour histology was serous (N = 41; 91.1%). More than one-quarter of this group (N = 12; 26.7%) had a cancer antigen-125 level of more than 35 units/mL. In terms of characteristics relating to prior platinum-based chemotherapy, almost the entire cohort (N = 36 to 44; 80.0% to 97.8%; numbers are suppressed in alignment with privacy policies) were treated with platinum-based chemotherapy before initiating niraparib for maintenance therapy. The mean number of cycles for the Alberta cohort was 4 (SD = 2.0) and the mean number of days between last date of chemotherapy and start of niraparib was 60.4 days (SD = 27.0). The most common initial daily dose in Alberta was 200 mg per day (N = 28; 62.2%) followed by 100 mg per day (N = 17, 37.8%). There were no patients in the Alberta cohort who started at 300 mg per day.

In the British Columbia cohort, the mean age was 66.1 (SD = 10.4) and most patients (N = 92 to 98; 92.0% to 98.0%) lived in an urban setting. The proportion of individuals living in urban settings in the British Columbia cohort was substantially higher in British Columbia than in Ontario and Alberta because of the nature of the cohort development in this jurisdiction. We only included individuals who were referred to BC Cancer, which is less likely to include patients from rural areas who may have had their cancer care managed in community hospitals rather than with BC Cancer. The majority of the British Columbia cohort was diagnosed with ovarian cancer in 2021 (N = 60; 60.0%), with stage III (N = 50; 50.0%) or stage IV (N = 27; 27.0%) disease at diagnosis. All patients had previously received platinum-based chemotherapy, for a mean of 6.4 (SD = 1.0) cycles. The majority of patients initiated niraparib within 2 months of their last cycle of chemotherapy (mean = 55.1 days; SD = 21.8). Most patients initiated niraparib at a dose of 200 mg per day (N = 60; 60.0%). Only 12 patients (12.0%) started niraparib at 300 mg per day.

In Quebec, the cohort from PMT's mean age was 65.3 (SD = 11.9). Approximately two-thirds of the group (N = 20; 64.5%) were diagnosed with ovarian cancer in 2020 and 2021, and more than half (N = 17; 54.8%) started niraparib maintenance treatment during the same time frame. The remaining portion of the cohort (N = 14; 45.2%) started niraparib maintenance treatment in 2022. The most common primary tumour location for this group was ovaries (N = 26 to 30; 83.8% to 96.8%) and most patients had a serous tumour histology (N = 26 to 30; 83.8% to 96.8%). Approximately one-quarter (N = 8, 25.8%) of the Quebec cohort had a cancer antigen-125 level of more than 35 units/mL. Most patients in the Quebec cohort were previously treated with platinum-based chemotherapy (N = 26 to 30; 83.9% to 96.7%). The mean number of prior cycles of platinum-based chemotherapy was 6.6 (SD = 1.9) and the mean number of days between last platinum-based chemotherapy and index date was 58.3 (SD = 22.2). In terms of initial daily dose of niraparib, most of the Quebec cohort (N = 25 to 29; 83.3% to 96.7%) started on 200 mg per day, and fewer than 6 patients started on 300 mg per day. There were no patients in the Quebec PMT registry cohort who started at an initial daily dose of 100 mg per day.

Figure 5: CONSORT Diagram for Ontario

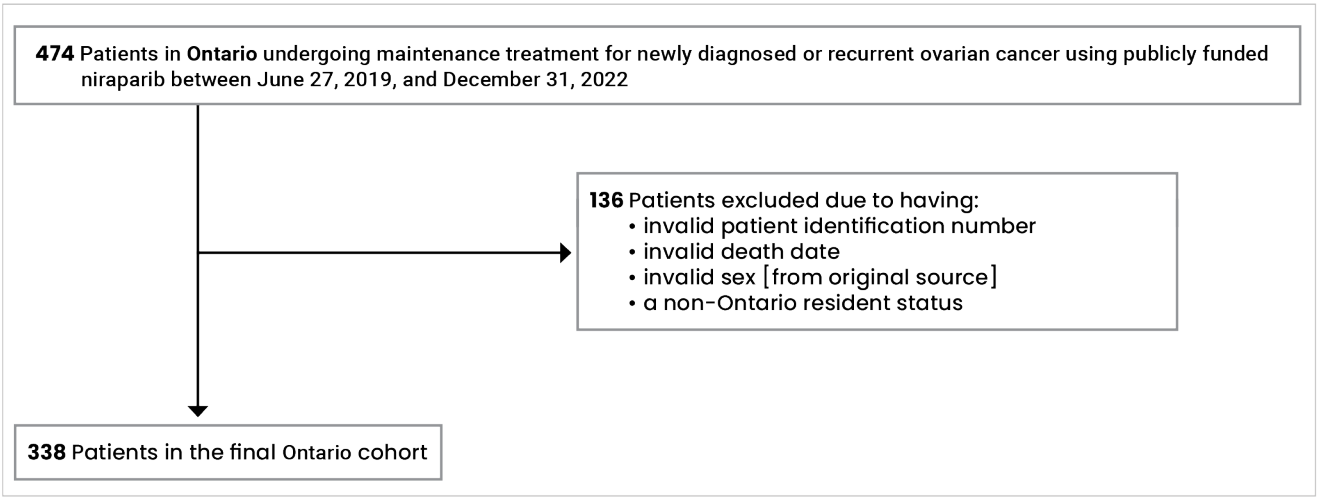


Figure 6: CONSORT Diagram for Alberta

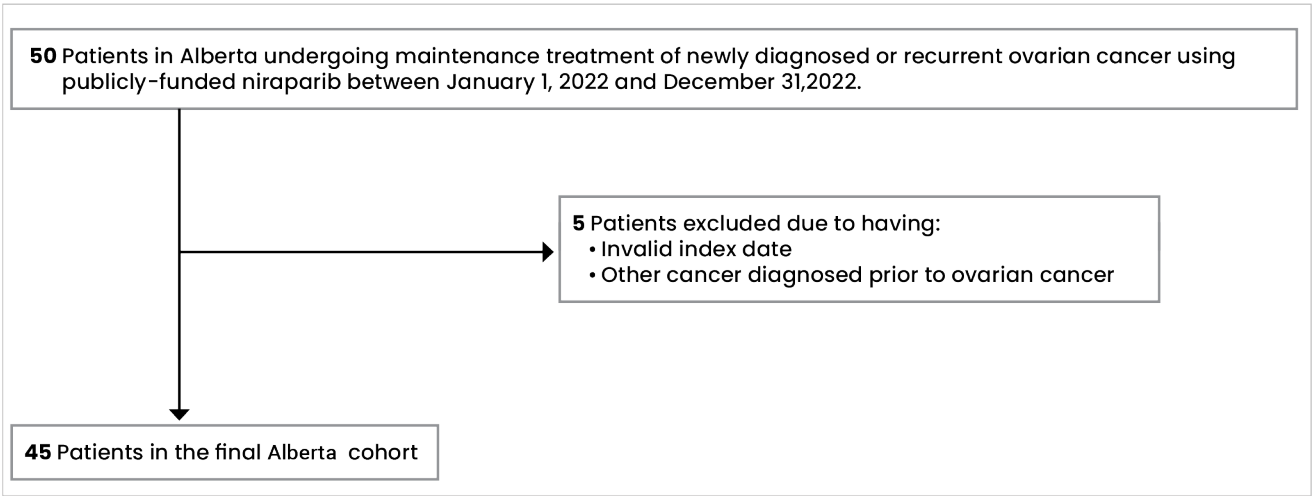


Figure 7: CONSORT Diagram for British Columbia

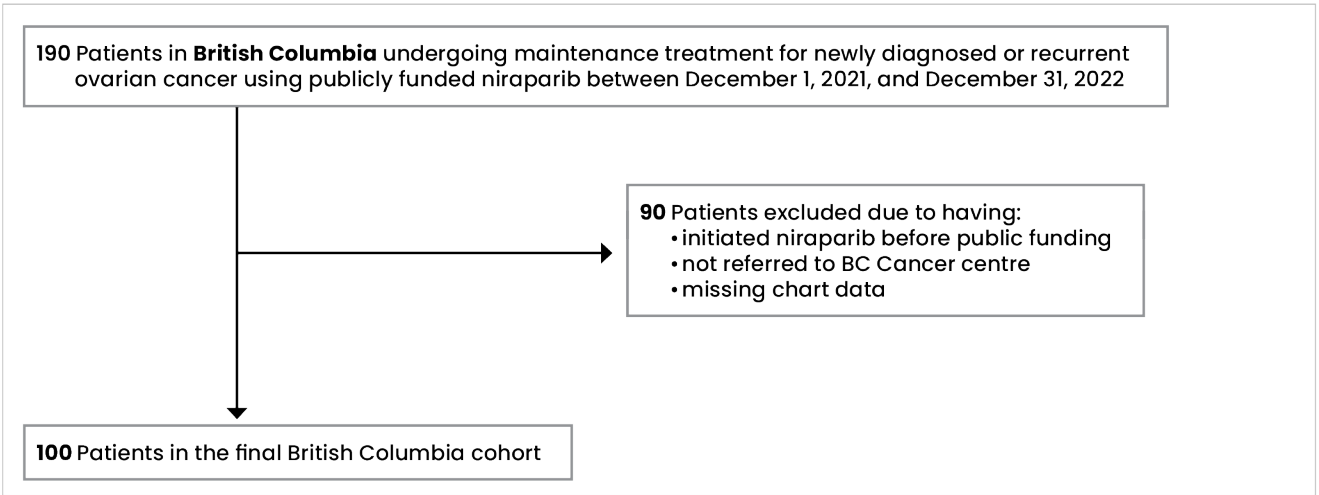
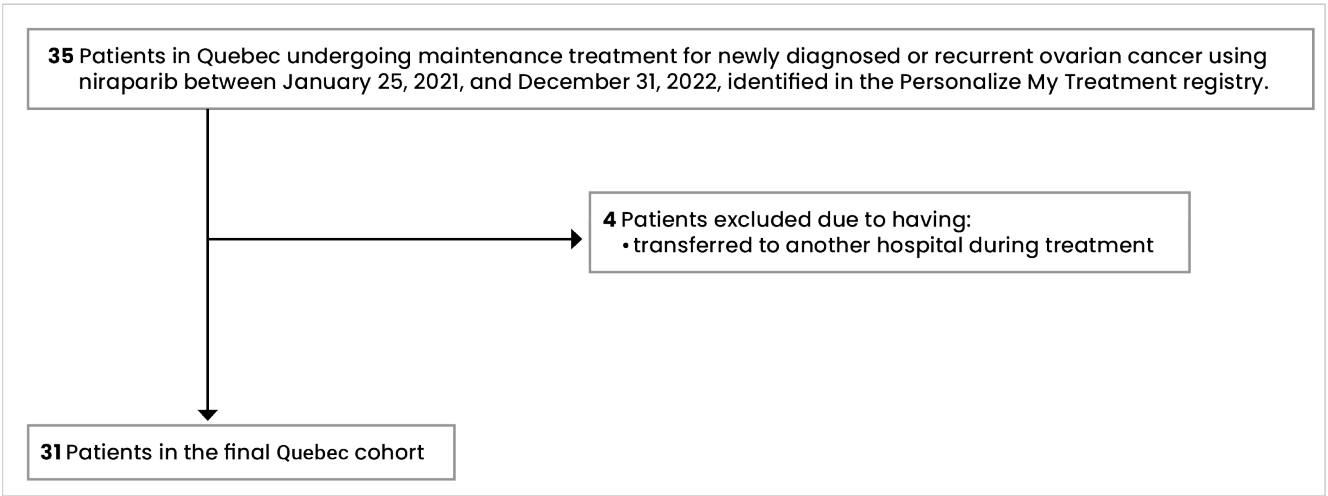


Figure 8: CONSORT Diagram for Quebec



Main Findings

Summary

Grade 3 or 4 hematological adverse events occurred in approximately 10% to 12% of the overall patient population, including thrombocytopenia (low blood platelet count), neutropenia (low white blood cell count), and anemia (low red blood cell count).

The occurrence of adverse events was lower in the real-world setting compared to what is reported in the clinical trials.

We reported the crude proportions of hematological adverse events (i.e., thrombocytopenia, neutropenia, and anemia) in Table 7. Overall, 76.8% of patients in all provinces experienced anemia of any grade during treatment. The proportion of any grade thrombocytopenia and neutropenia were lower, at 41.5% and 39.3%, respectively. When considering grade 3 or 4 hematological adverse events, the most common was anemia (N = 52; 12.2%), followed by thrombocytopenia (N = 50; 11.7%), and then neutropenia (N = 46; 10.8%).

Over the course of the observation period in Ontario (median follow-up time of 255 days [interquartile range, 241 to 267]), 40.6% of the cohort experienced thrombocytopenia of any grade (N = 104), 32.3% experienced neutropenia of any grade (N = 83), and 79.0% experienced anemia of any grade (N = 202). In terms of serious hematological adverse events, 10.9% of the Ontario cohort experienced grade 3 or 4 thrombocytopenia (N = 28), 8.9% experienced grade 3 or 4 neutropenia (N = 23), and 14.8% experienced grade 3 or 4 anemia (N = 38).

In British Columbia, 46.2% of the cohort experienced thrombocytopenia, 48.4% experienced neutropenia, and 76.3% experienced anemia of any grade. Thrombocytopenia and neutropenia were the most common grade 3 or 4 hematological adverse events (N = 13; 14.0% for both), followed by anemia (N = 8; 8.6%).

Due to the need to adhere to privacy policies and avoid potential identification of small sample sizes in Alberta and Quebec, we were unable to report exact numbers of grade 3 or 4 hematological toxicities for these jurisdictions; however, the proportions of thrombocytopenia and anemia of any grade in Alberta and Quebec remain similar to that of Ontario. The rate of neutropenia of any grade in British Columbia, Alberta, and Quebec are substantially higher than Ontario (British Columbia: N = 45 [48.4%]; Alberta: N = 23 [51.1%]; Quebec: N = 17 [54.8%]; Ontario: N = 83 [32.3%]).

At 3 months after starting niraparib, the cumulative incidence of grade 3 or 4 thrombocytopenia in Ontario was 9.0% (95% confidence interval [CI], 5.9% to 12.9%), grade 3 or 4 neutropenia was 5.8% (95% CI, 3.4% to 9.2%), and grade 3 or 4 anemia was 10.1% (95% CI, 6.8% to 14.2%) (Figure 3, Figure 4, and Figure 5). Cumulative incidence for all 3 outcomes in Ontario increased slightly with time, gradually plateauing by the 8 month after the index date. We observed a similar trend in the cumulative incidence of all 3 outcomes in Alberta, British Columbia, and Quebec (Figures 8 to 22 in Appendix 2).

In terms of secondary outcomes that occurred during the observation window, approximately 20% of those eligible among the overall cohort (i.e., without a diagnosis of hypertension before the index date) were newly diagnosed with hypertension (N = 44 to 52; 19.4% to 22.9% [value is an interval due to small cell suppression in compliance with privacy policies]) and very few (< 10 patients) experienced febrile neutropenia (Table 8). Approximately 12.8% of the overall cohort (N = 53) were given a transfusion, although the proportion in Ontario (N = 33; 9.8%) was substantially lower than those of Alberta (N = 11; 24.4%) and Quebec (N = 9; 29.0%). More than one-third of the overall cohort visited the emergency department (N = 153 to 157; 37.0% to 37.9%) and almost one-quarter of the overall cohort (N = 80; 19.3%) were hospitalized during the observation window. The cumulative incidence of treatment discontinuation at 3 months in Ontario was 24.6% (95% CI, 19.2% to 30.5%) (Figure 6), 25% (95% CI, 3% to 58%) in Alberta (Figure 11 in Appendix 2,), 27.5% (95% CI, 18.1% to 37.8%) in British Columbia (Figure 16 in Appendix 2,), and 10.7% (95% CI, 2.6% to 25.4%) in Quebec (Figure 21 in Appendix 2,). The overall survival in this study was high (Figure 7, and Figure 12, Figure 17, and Figure 22 in Appendix 2).

Table 7: Hematological Adverse Events

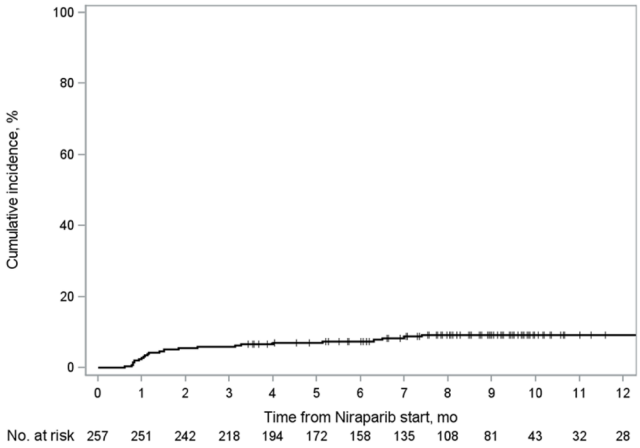
	All provinces N = 427		Ontario N = 257[a]		Alberta N = 45		British Columbia N = 93[b]		Quebec N = 31	
Hematological adverse event	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Thrombocytopenia, N (%)	177 (41.5)	50 (11.7)	104 (40.6)[c]	28 (10.9)[c]	16 (35.6)	< 10	43 (46.2)	13 (14.0)	14 (45.2)	< 6
Neutropenia, N (%)	168 (39.3)	46 (10.8)	83 (32.3)	23 (8.9)	23 (51.1)	< 10	45 (48.4)	13 (14.0)	17 (54.8)	< 6
Anemia, N (%)	328 (76.8)	52 (12.2)	202 (79.0)	38 (14.8)	34 (75.6)	< 10	71 (76.3)	8 (8.6)	21 (67.7)	< 6

[a]In total, 257 of the 338 patients in the Ontario cohort had records of laboratory tests.

[b]In total, 93 of the 100 patients in the British Columbia data had records of laboratory tests.

[c]The denominator for thrombocytopenia in Ontario is 256 instead of 257 due to additional missing data.

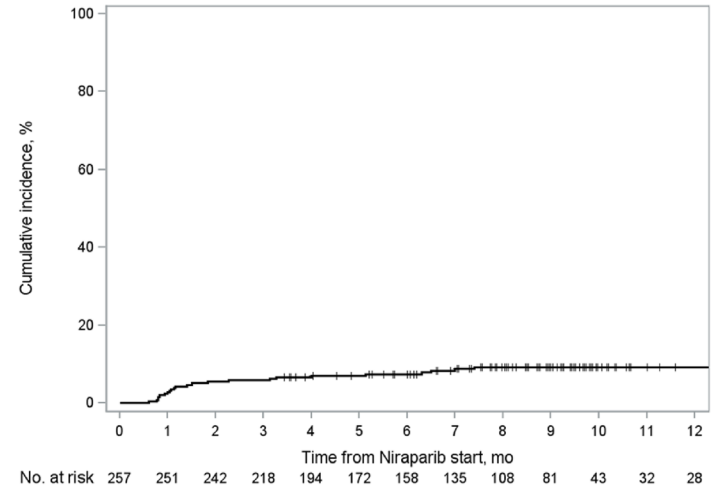
Figure 9: Cumulative Incidence of Grade 3 or 4 Thrombocytopenia in the Ontario Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
6.6% (4.0% to 10.1%)	9.0% (5.9% to 12.9%)	9.0% (5.9% to 12.9%)	10.2% (6.8% to 14.3%)	11.1% (7.6% to 15.3%)	11.1% (7.6% to 15.3%)

Figure 10: Cumulative Incidence of Grade 3 or 4 Neutropenia in the Ontario Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
2.7% (1.2% to 5.3%)	5.4% (3.1% to 8.7%)	5.8% (3.4% to 9.2%)	7.4% (4.6% to 11.1%)	9.2% (6.0% to 13.3%)	9.2% (6.0% to 13.3%)

Figure 11: Cumulative Incidence of Grade 3 or 4 Anemia in the Ontario Cohort

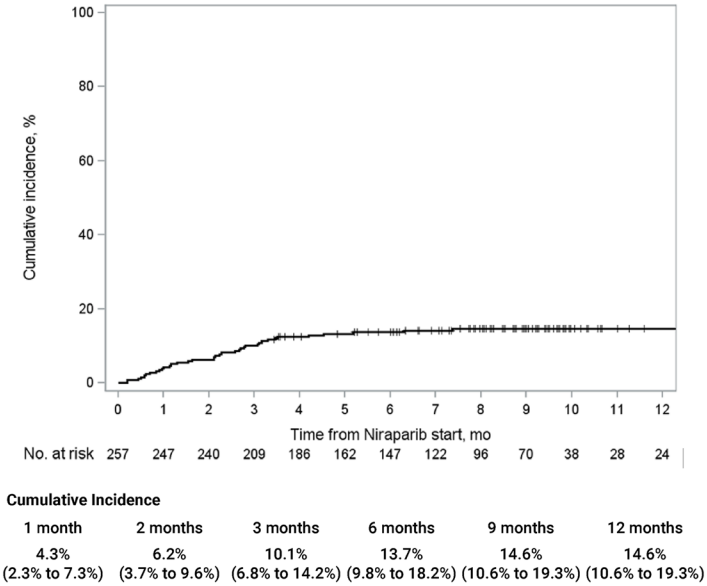


Table 8: Secondary Outcomes

Outcome of interest	All provinces N = 514	Ontario N = 338	Alberta N = 45	British Columbia N = 100	Quebec N = 31
Febrile neutropenia, N	< 10	< 6	< 10	NA	0
Incident hypertension,[a] N (%)	44 to 52 (19.4 to 22.9)	37 (20.2)	< 10	NA	6 (33.3)
Any transfusion, N (%)	53 (12.8)	33 (9.8)	11 (24.4)	NA	9 (29.0)
Platelet transfusion, N (%)	18 (4.3)	11 (3.3)	< 10	NA	< 6
Red blood cell transfusion, N (%)	32 (7.7)	22 (6.5)	< 10	NA	< 6
Emergency department visit, N (%)	153 to 157 (37.0 to 37.9)	134 (39.6)	18 (40.0)	NA	< 6
Hospitalization (any type), N (%)	80 (19.3)	63 (18.6)	17 (37.8)	NA	0
Hospitalization (unscheduled), N (%)	57 (15.4)	57 (16.9)	NA	NA	0
Niraparib treatment discontinuation,[b] N (%)	150 to 158 (35.0 to 36.9)	86 (34.0)	< 10	41 (41.0)	22 (73.3)
Mean time to niraparib treatment discontinuation in days (± standard deviation)[b]	163.6 ± 111.5	164.6 ± 64.1	135 ± 78	91 ± 53.9	263.8 ± 191.3

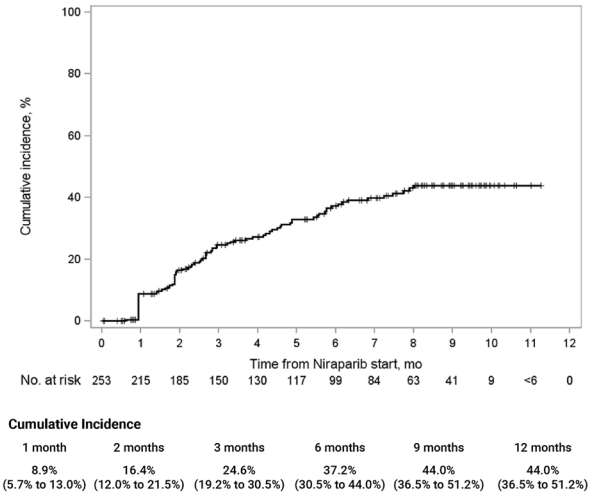
Outcome of interest	All provinces N = 514	Ontario N = 338	Alberta N = 45	British Columbia N = 100	Quebec N = 31
Median follow-up time in days, N (%)	NA[c]	255 (241 to 267)	229 (170 to 274)	250 (78 to 310)	411 (270 to 585)

[a]The number of patients eligible to ascertain this outcome (i.e., those who did not have prior hypertension) was 183 in Ontario, 26 in Alberta, and 18 in Quebec.

[b]Using a cohort of N = 253 for Ontario cohort and N = 30 for Quebec.

[c]Patient-level data are only available within each jurisdiction and we were therefore unable to calculate an aggregate median time to follow-up for all provinces.

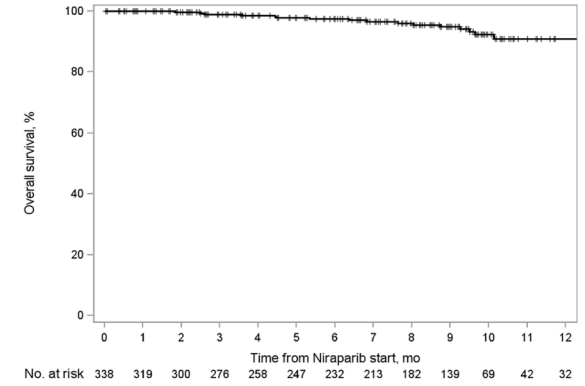
Figure 12: Cumulative Incidence of Discontinuation in Ontario



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
8.9% (5.7% to 13.0%)	16.4% (12.0% to 21.5%)	24.6% (19.2% to 30.5%)	37.2% (30.5% to 44.0%)	44.0% (36.5% to 51.2%)	44.0% (36.5% to 51.2%)

Figure 13: Kaplan-Meier Curve for Overall Survival in the Ontario Cohort



Overall Survival

1 month	2 months	3 months	6 months	9 months	12 months
100% (100% to 100%)	99.7% (97.7% to 100%)	99.0% (96.9% to 99.7%)	97.4% (94.7% to 98.8%)	94.4% (91.1% to 97.1%)	90.9% (84.6% to 94.7%)

Limitations

There are a number of limitations in this study that warrant discussion. First, although 3 of the 4 cohorts included in this study were population-based (Ontario, Alberta, and British Columbia), the generalizability of our findings may be impacted. The Ontario cohort consisted of patients who were treated with niraparib funded by the provincial government, the British Columbia cohort excluded patients not referred to a BC Cancer site for care, and the Quebec sample was limited to those enrolled in the PMT registry. Given that there may be some younger individuals in Ontario who paid for niraparib out of pocket or through private insurance, there is a small portion of patients in British Columbia who may have received treatment in a community hospital (i.e., outside of BC Cancer) and the selective enrolment in the PMT registry in Quebec (which only captures approximately 12% of patients with ovarian cancer in the province), our study cohort may have experienced different adverse outcome profiles compared to the broader ovarian cancer population in Canada eligible for treatment with niraparib. However, given that trends in our results are relatively consistent across provinces, it is possible that the use of data from a publicly funded cohort and registry only minimally limited generalizability. Second, the observation window for our study was limited for some patients because niraparib was only recently publicly funded in Canada. To capture as many patients on treatment as possible, the end of our accrual window coincided with the end of our observation window. While this method allows us to describe the baseline characteristics of more patients, it is possible that we may undercount the number of hematological adverse events for patients who started niraparib close to the end of our accrual period (in Ontario, this is approximately 17.5% of the cohort). The use of cumulative incidence functions allows us to provide unbiased time-dependent estimates despite this issue. Finally, we did not have access to data on patient weight, which affected our ability to ascertain whether the patients who started on 200 mg of niraparib per day represented those treated with an individualized dose based on patient weight and platelet count, or if they were treated with a dose that differed from recommendations. However, almost one-quarter of all patients in this study started on an initial daily dose of 100 mg. This is below the recommended initial daily dose on the drug's product monograph and may therefore be considered subtherapeutic dosing. It is unclear whether patients started with 100 mg per day in the first month and then subsequently titrated upward if they tolerated niraparib adequately or whether they were maintained on 100 mg per day without upward titration despite adequate tolerance.

Conclusions and Implications for Decision- or Policy-Making

Summary

In this cohort study, we found 338 patients in Ontario, 45 patients in Alberta, 100 patients in British Columbia, and 31 patients in Quebec who were 18 years and older and used niraparib for the maintenance treatment of ovarian cancer. The mean age for patients in our study was approximately 67 years and more than half of the group were diagnosed with ovarian cancer between 2020 and 2022. The ovaries were the most common primary tumour location, and the most common tumour histology was serous. The majority of the cohort started maintenance treatment with niraparib in 2022 after completing platinum-based chemotherapy. The

most common initial daily dose of niraparib was 200 mg per day, followed by 100 mg per day, and finally, 300 mg per day. In the analysis of hematological adverse events, we found that grade 3 or 4 thrombocytopenia, neutropenia, and anemia all occurred in approximately 10% to 12% of the overall cohort.

Comparison With Existing Literature

There are 3 published phase III trials that examine the efficacy and safety of niraparib for maintenance treatment.[11,22,28] The approval of niraparib for maintenance treatment of ovarian cancer in Canada was largely based on evidence reported in the NOVA[11] and PRIMA trials;[22] however, because of niraparib's approval in Canada, researchers in China have published an additional phase III study examining the efficacy and safety of individualized dosing of niraparib for the maintenance treatment of recurrent ovarian cancer among patients living in China (NORA trial).[28] The clinical and demographic characteristics of patients in all 3 trials were generally very similar to patients in our cohort, with the exception of age as patients in our cohort were slightly older.

Unlike the NOVA trial, which used standard dosing (300 mg per day), the PRIMA and NORA trials reported individualized dosing based on weight and platelet count. Based on the initial doses observed in our study, it is likely that clinicians have adopted the individualized dosing approach in practice as the most common observed dose was 200 mg per day. Similar to the trials, a very small portion of patients in our study received 300 mg per day as their starting dose. Of note, however, is the observation that approximately one-quarter of patients in our study initiated niraparib maintenance therapy at 100 mg per day, which is not a dose suggested by the product monograph nor one that is observed in the 3 trials. It is unknown at this time if the use of lower starting doses of niraparib in the real world has any general impact on drug effectiveness or whether this was only implemented briefly toward the beginning of treatment to assess drug tolerance.

Overall, we found that the proportion of hematologic adverse events in the real-world setting was lower in all participating Canadian jurisdictions than those reported in the clinical trials (refer to Table 10 in Appendix 3 for summary of results from the clinical trials). Given that the baseline characteristics between our cohort and the trial cohorts are generally similar (albeit slightly older in our study), there is no obvious difference accounting for this observation. We hypothesize that clinical experience and a cautious approach to dosing, monitoring, and management of adverse events may be underlying reasons rather than potential differences in baseline patient characteristics. The portion of patients starting on 100 mg per day may allude to this, providing evidence of clinicians being cautious and starting their patients on a lower dose than recommended. Hematological adverse events at any grade in our study are closer to those reported in the clinicals trials than grade 3 or 4 hematological toxicities, indicating that patients receiving niraparib maintenance treatment are not free of adverse events. Rather, this may be a signal showing clinicians being proactive in the management of hematologic adverse events, preventing them from progressing to grade 3 or 4. Li et al. observed that niraparib was well tolerated with intense follow-up and flexible management of adverse events.[29] Additionally, the authors also noted a significant association between the time from last chemotherapy to niraparib start and the rate of adverse events. Patients who started niraparib more than 20 days after their last chemotherapy treatment were less likely to experience adverse events than those who started niraparib soon after chemotherapy (< 21 days). This may be a contributing factor to the low

observed proportion of hematological adverse events in our cohort, as the mean number of days between last platinum-based chemotherapy and niraparib start date in our study was longer than 20 days. Although the median follow-up time in some jurisdictions in our study (i.e., Ontario, Alberta, and British Columbia) was slightly shorter than that of the seminal trials (ranging from a median of 229 days to 255 days in our study compared to approximately 400 days to 500 days in the trials), we speculate that this would likely not be a major contributing factor to the low proportion of primary outcomes. This is because our cumulative incidence curves showed that most events typically occurred shortly after treatment initiation. Additionally, although the median follow-up in the Quebec cohort of our study was 411 days, the observed proportion of primary outcomes in this jurisdiction was similar to that of the other study jurisdictions. Despite the small sample size in Quebec, this consistency observed across jurisdictions helps to reassure that follow-up time should not be a major contributing factor to the study results.

Main Takeaway

There is a lower proportion of hematological toxicities observed in the real world than in the clinical trial findings. The reason for this difference is not clear; however, we believe that it might be due to clinical experience, with clinicians taking a cautious dosing approach, as well as through proactive monitoring and management of adverse events.

Implications for Future Research

The identification of relatively low starting doses in our study translates to several implications for future research. First, it is important to examine the specific patient and clinician characteristics that are associated with starting niraparib at doses below those recommended in the product monograph. Additionally, it may be of interest to examine whether patients are receiving adequate laboratory monitoring when frequency aligning with the recommendations of the product monograph. Furthermore, the safety and effectiveness of lower individualized doses (e.g., 100 mg of niraparib per day) should be examined. If there are substantial impacts on safety and effectiveness of the medication for those starting on 100 mg per day, then it would be pertinent to develop clinician engagement activities to promote appropriate dosing while closely monitoring patients for adverse events. Finally, it may be useful to stratify this analysis based on disease status (i.e., patients who are newly diagnosed versus those with recurrent ovarian cancer) as patient outcomes may differ between these 2 populations.

Conclusion

In conclusion, the current analysis examining the use of niraparib for the maintenance treatment of newly diagnosed and recurrent ovarian cancer shows that this medication is used carefully and at low initial doses in 4 provinces across Canada, which should address the concerns raised by jurisdictions. It is possible that this, paired with close monitoring via regular bloodwork, has contributed to low rates of severe adverse events. Future work should examine the factors associated with starting niraparib at lower doses than recommended, as well as the effectiveness of starting patients on such low doses (i.e., 100 mg per day) to guide clinical decisions on the use of niraparib maintenance treatment.

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Authors and Contributors

Authors

Qi Guan led the conceptualization, design, analysis, interpretation of results and drafting of the report.

Suriya Aktar provided substantial contributions to the conception and design acquisition of data analysis and interpretation of the study results including the key messages and conclusions; contributed to the report draft and revision.

Reka Pataky planned the British Columbia arm of the analysis, acquired data, conducted data analysis, and contributed to the drafting of the report.

Mariet Mathew Stephen represented the CCRE-Alberta site and was responsible for data collection, data analysis and report generation as per the study protocol, concerning the site; involved in proofreading and editing multiple iterations of the study protocol and report.

Maud Marques identified Québec population in the PMT registry, data quality assessment for the QC cohort, data; anlayzed the QC cohort, provided results (tables and graphs) to CCRE for inclusion in the join report, and reviewed the report and the answers to stakeholder.

Karen Gambaro contributed to the Quebec cohort data acquisition, quality control, analysis, interpretation; reviewed and approved the final report.

Katharina Forster contributed to the methodology and interpretation of results; participated in drafting and revising the report with focus on the conclusions and implications.

Samara Strub contributed to conception, drafting key messages, revising report for content, reviewing for consistencies.

Winson Y Cheung contributed to study design, oversight for all analysis and interpretation, and revising Alberta specific sections of the report.

Stuart Peacock contributed to all aspects of study design, data collection, analysis, interpretation, and writing of reports.

Christie Farrer acquired Alberta data, revised Alberta specific sections of report, and coordinated legal agreements between Alberta and main centre.

Scott Gavura contributed to conception and design, draft and review of report including key messages and conclusions.

Mina Tadrous contributed to Methods and Design, review, and revisions.

Robert Grant participated in the study design and drafting the manuscript, providing context as a Gyn Med Onc

Kelvin KW Chan contributed to all aspects of the research, including study design, analysis and interpretation of results, drafting and revising entire report.

Contributors

Michael Waligora facilitated necessary data acquisition.

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Conflicts of Interest

These individuals disclosed the following conflicts of interest:

Mina Tadrous
Travel funding or payment
- Green Shield Canada: Data Analytics (2021)

Robert Grant
Personal education funding
- Pfizer: graduate award

Payment as Advisor or Consultant – General Advisory Board participation
- AstraZeneca: multiple drugs
- Eisai: Lenvatinib
- Incyte: Pemigatinib

Dr. Anna Tinker
Travel Funding or payment
- GSK: Niraparib 2020 to present; Dostarlimab

Speaking engagement and educational lectures
- AstraZeneca: Olaparib – 2015 to 2020
- Merck: Pembrolizumab 2020 to present

Payment as Advisory or Consultant
- Merck: pembrolizumab
- GSK: Niraparib and dostarlimab
- Eisai: Lenvatinib

Dr. Josee-Lyne Ethier
Payment as an Advisor or Consultant
- GSK: Niraparib

No other conflicts of interest were declared.

Appendix 1: Supplemental Materials for Methods

Note that this appendix has not been copy-edited.

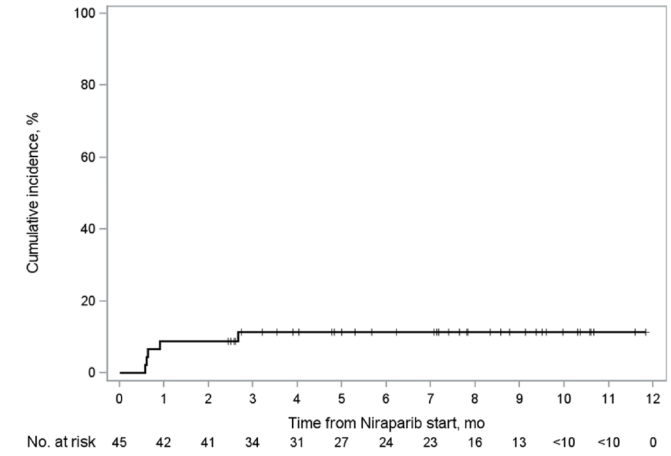
Table 9: Diagnosis Codes for Select Covariates Used in Study, by Province

Variable	Variable Definition			
	Ontario	Alberta	BC	Q uebec
Febrile neutropenia	Presence of the ICD-10 codes: D70 (most responsible diagnosis) **AND** R50.8 or R50.9 (any diagnosis) **during observation window**	Ascertained using EMR data during the observation window	N/A	Ascertained using EMR data during the observation window
Hypertension	1 hospital admission for hypertension (I10.x, I11.x, I12.x, I13.x, or I15.x in CIHI DAD) **OR** 2 physician claims for hypertension (401 to 405 in OHIP for Ontario, EMR in Alberta) **within 2 years for prior diagnosis of hypertension.** 1 hospital admission for hypertension (I10.x, I11.x, I12.x, I13.x, or I15.x in CIHI DAD) **OR** 2 physician claims for hypertension (401 to 405 in OHIP for Ontario, EMR in Alberta) **during the observation window for incident hypertension.**		N/A	Ascertained using EMR data during the observation window
Time to niraparib discontinuation	Patients are identified as having discontinued treatment if there are more than 60 days between the date of their last treatment (date of last prescription dispensing plus the days' supply of the prescription) and the study end date. This definition only applied to patients who started niraparib more than 60 days before the study end date.	Ascertained using EMR data during the observation window	Same as Ontario	Ascertained using EMR data during the observation window

Appendix 2: Cumulative Incidence and Kaplan-Meier Curves for Alberta, British Columbia, and Quebec

Note that this appendix has not been copy-edited.

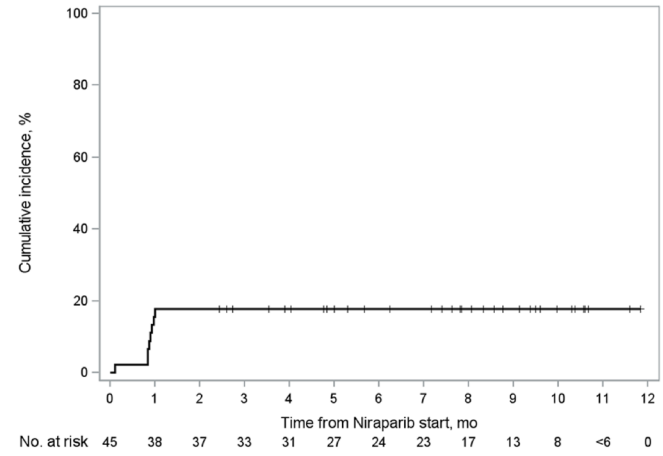
Figure 14: Cumulative Incidence of Grade 3 or 4 Thrombocytopenia in the Alberta Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
8.9% (2.8% to 19.5%)	8.9% (2.8% to 19.5%)	11.4% (4.1% to 22.7%)	11.4% (4.1% to 22.7%)	11.4% (4.1% to 22.7%)	NA

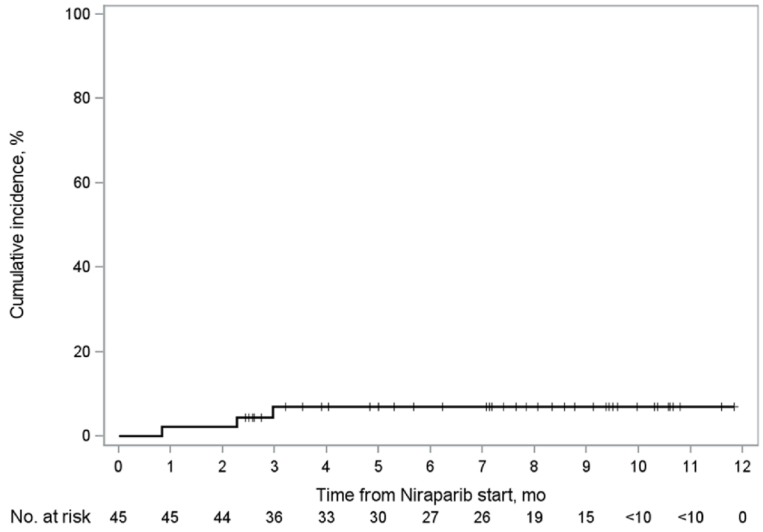
Figure 15: Cumulative Incidence of Grade 3 or 4 Neutropenia in the Alberta Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
17.8% (8.2% to 30.3%)	17.8% (8.2% to 30.3%)	17.8% (8.2% to 30.3%)	17.8% (8.2% to 30.3%)	17.8% (8.2% to 30.3%)	NA

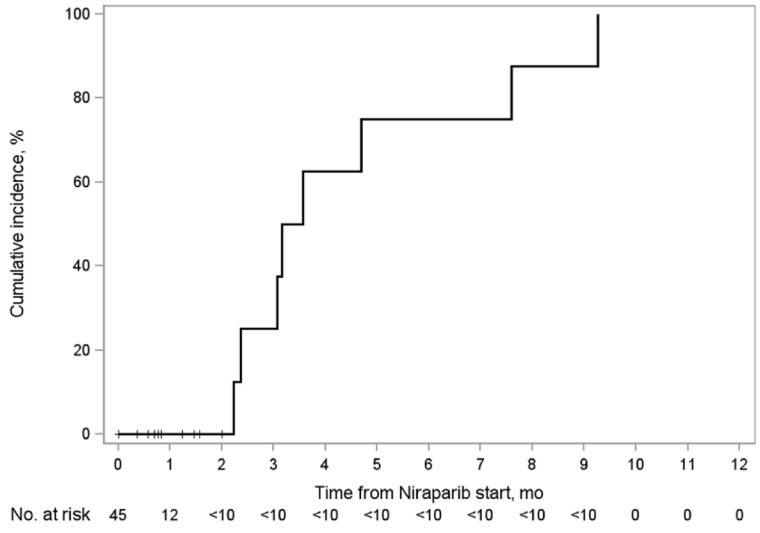
Figure 16: Cumulative Incidence of Grade 3 or 4 Anemia in the Alberta Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
2.2% (0.2% to 10.3%)	2.2% (0.2% to 10.3%)	7.0% (1.8% to 17.4%)	7.0% (1.8% to 17.4%)	7.0% (1.8% to 17.4%)	NA

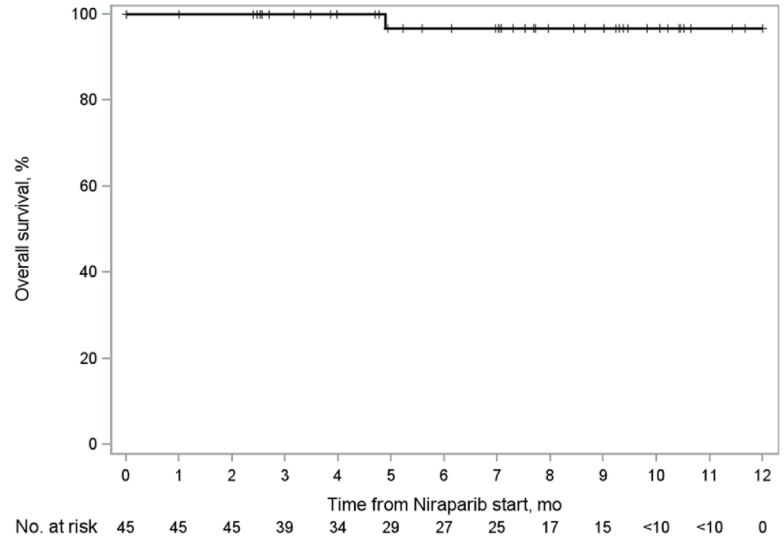
Figure 17: Cumulative Incidence of Niraparib Discontinuation in the Alberta Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
0%	0%	25.0% (3.0% to 57.9%)	75.0% (23.2% to 94.5%)	87.5% (17.2% to 99%)	NA

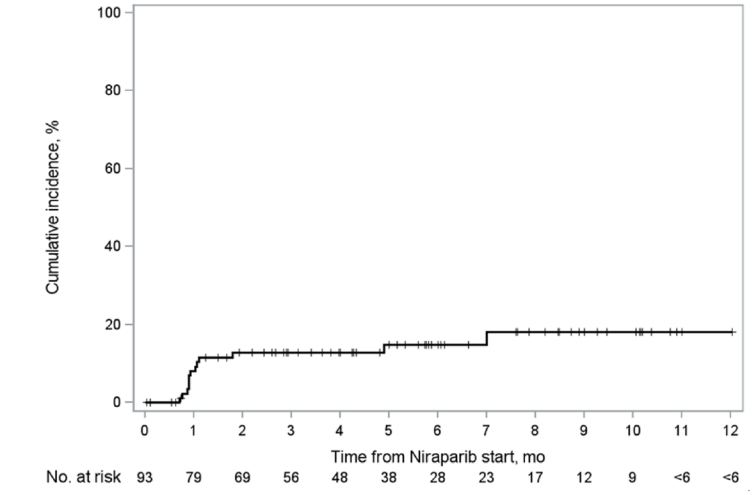
Figure 18: Kaplan-Meier Curve for Overall Survival in the Alberta Cohort



Overall Survival

1 month	2 months	3 months	6 months	9 months	12 months
100% (100% to 100%)	100% (100% to 100%)	100% (100% to 100%)	96.8% (90.8% to 100.0%)	96.8% (90.8% to 100.0%)	NA

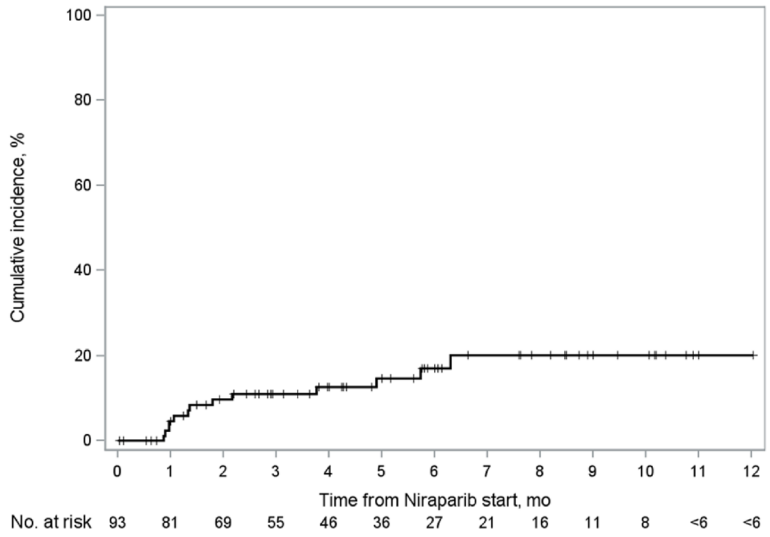
Figure 19: Cumulative Incidence of Grade 3 or 4 Thrombocytopenia in the British Columbia Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
8.1% (3.5% to 15.1%)	12.8% (6.8% to 20.9%)	12.8% (6.8% to 20.9%)	14.8% (8.0% to 23.7%)	18.0% (9.4% to 28.9%)	18.0% (9.4% to 28.9%)

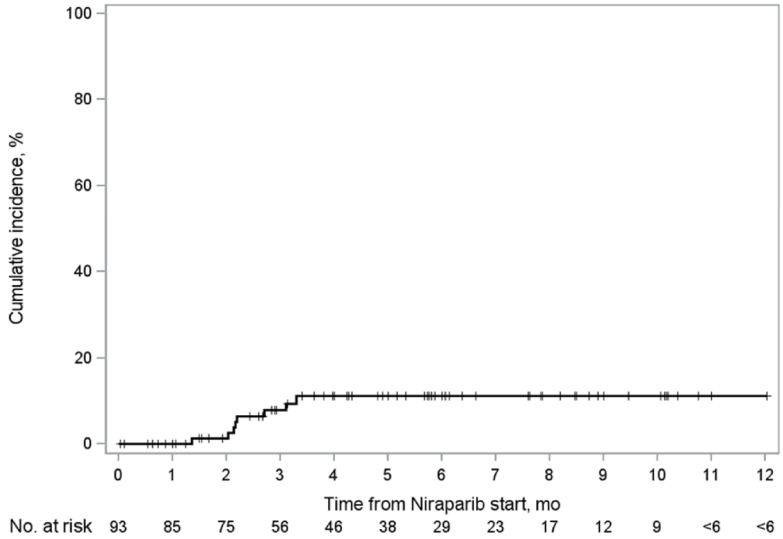
Figure 20: Cumulative Incidence of Grade 3 or 4 Neutropenia in the British Columbia Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
4.7% (1.5% to 10.7%)	9.6% (4.5% to 17.2%)	10.9% (5.3% to 18.8%)	17.1% (9% to 27.4%)	20.2% (10.6% to 31.9%)	20.2% (10.6% to 31.9%)

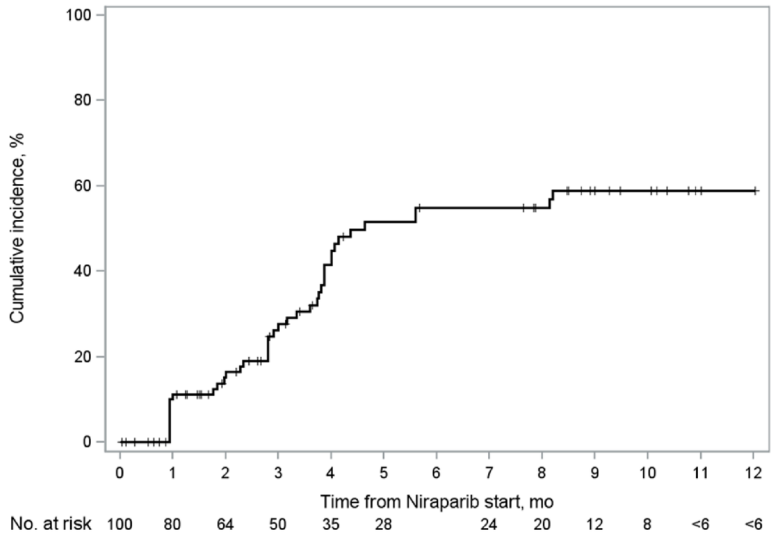
Figure 21: Cumulative Incidence of Grade 3 or 4 Anemia in the British Columbia Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
0%	1.2% (0.1% to 6.0%)	7.8% (3.2% to 15.2%)	11.1% (5.1% to 19.7%)	11.1% (5.1% to 19.7%)	11.1% (5.1% to 19.7%)

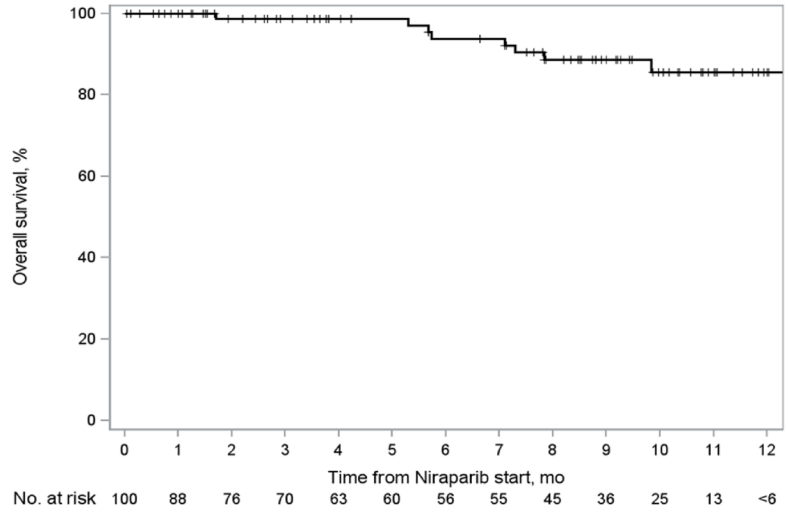
Figure 22: Cumulative Incidence of Niraparib Discontinuation in the British Columbia Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
11.2% (5.7% to 18.8%)	16.4% (9.4% to 25.1%)	27.5% (18.1% to 37.8%)	54.9% (41.9% to 66%)	58.9% (45.5% to 70%)	58.9% (45.5% to 70%)

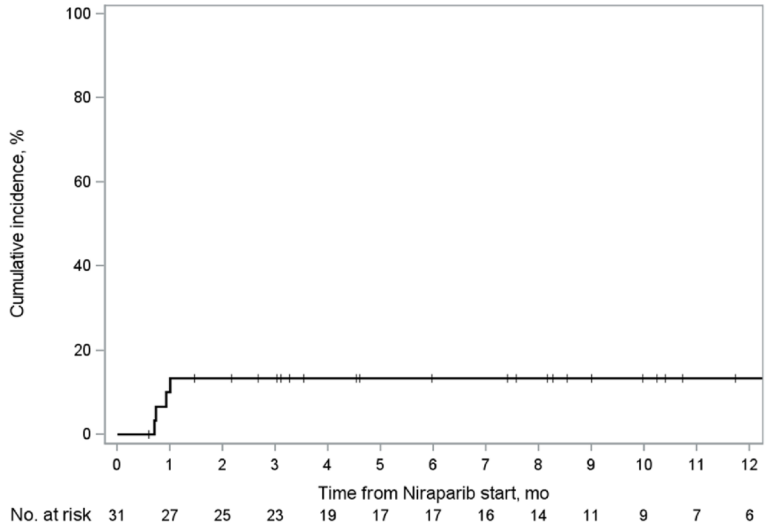
Figure 23: Kaplan-Meier Curve for Overall Survival in the British Columbia Cohort



Overall Survival

1 month	2 months	3 months	6 months	9 months	12 months
100% (100% to 100%)	98.7% (91.4% to 99.8%)	98.7% (91.4% to 99.8%)	93.9% (84.3% to 97.7%)	88.6% (77.4% to 94.4%)	85.6% (72.6% to 92.8%)

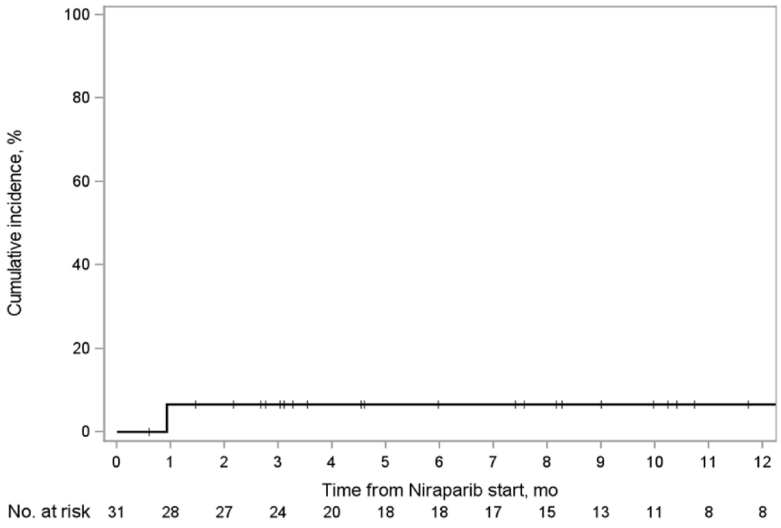
Figure 24: Cumulative Incidence of Grade 3 or 4 Thrombocytopenia in the Quebec Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
13.3% (4.1% to 28.1%)	13.3% (4.1% to 28.1%)	13.3% (4.1% to 28.1%)	13.3% (4.1% to 28.1%)	13.3% (4.1% to 28.1%)	13.3% (4.1% to 28.1%)

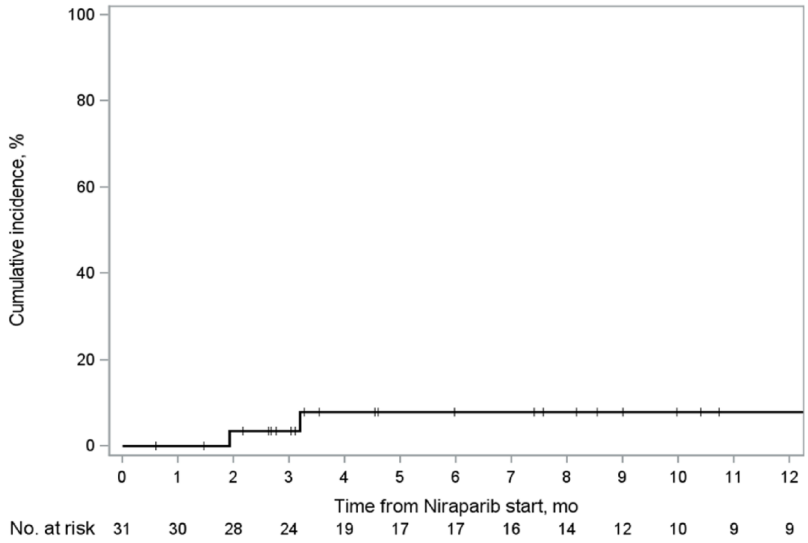
Figure 25: Cumulative Incidence of Grade 3 or 4 Neutropenia in the Quebec Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
6.7% (1.1% to 19.4%)	6.7% (1.1% to 19.4%)	6.7% (1.1% to 19.4%)	6.7% (1.1% to 19.4%)	6.7% (1.1% to 19.4%)	6.7% (1.1% to 19.4%)

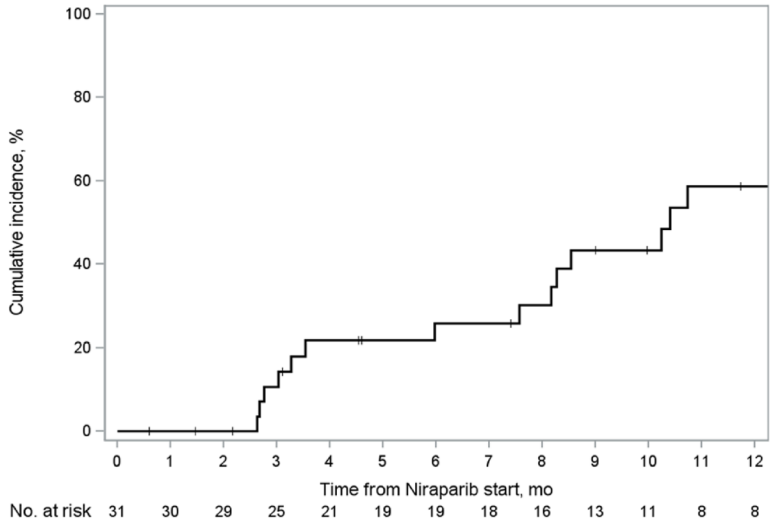
Figure 26: Cumulative Incidence of Grade 3 or 4 Anemia in the Quebec Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
0%	3.4% (0.2% to 15.2%)	3.4% (0.2% to 15.2%)	7.8% (1.3% to 22.6%)	7.8% (1.3% to 22.6%)	7.8% (1.3% to 22.6%)

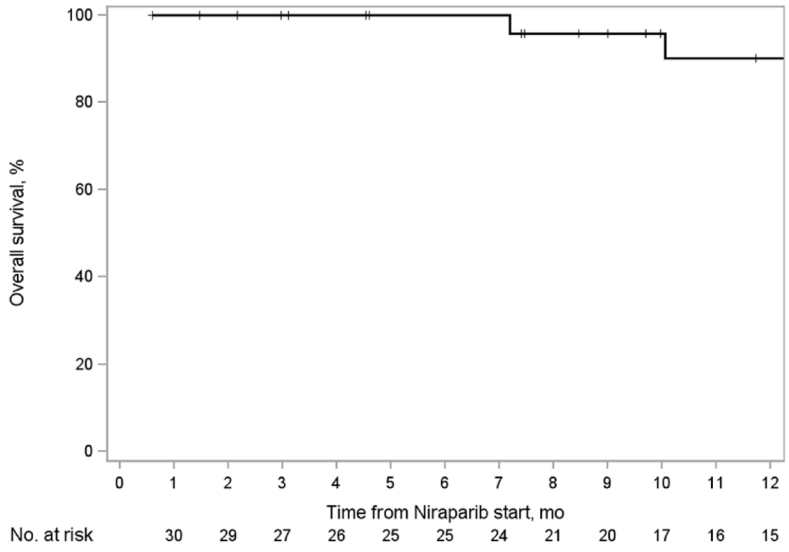
Figure 27: Cumulative Incidence of Niraparib Discontinuation in the Quebec Cohort



Cumulative Incidence

1 month	2 months	3 months	6 months	9 months	12 months
0%	0%	10.7% (2.6% to 25.4%)	25.9% (11.1% to 43.5%)	43.3% (23.2% to 61.9%)	58.8% (34.7% to 76.6%)

Figure 28: Kaplan-Meier Curve for Overall Survival in the Quebec Cohort



Overall Survival

1 month	2 months	3 months	6 months	9 months	12 months
100% (100% to 100%)	100% (100% to 100%)	100% (100% to 100%)	100% (100% to 100%)	95.8% (88.2% to 100.0%)	90.2% (78.0% to 100.0%)

Appendix 3: Summary Clinical Trial Results

Note that this appendix has not been copy-edited.

Table 10: Summary Table of Hematological Adverse Event Results From Seminal Clinical Trials

Adverse Event	Study Findings (all provinces)	PRIMA Trial	NOVA Trial	NORA Trial
Thrombocytopenia (grade 3/4)	11.7%	28.7%	33.8%	11.3%
Neutropenia (grade 3/4)	10.8%	12.8%	19.6%	20.3%
Anemia (grade 3/4)	12.2%	31.0%	25.3%	14.7%

For more information on CoLab and its work visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

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About CADTH: CADTH is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

About CoLab: CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with CADTH's Post-Market Drug Evaluation Program to produce credible and timely evidence on postmarket drug safety and effectiveness.