CADTH Observational Study

The Safety of Niraparib in Ovarian Cancer

Observational Study

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Abbreviations

ALR	Activity Level Reporting
BC	British Columbia
BRCA	Breast Cancer gene
CAP	BC Cancer Compassionate Access Program
CCRE	Canadian Cancer Real-world Evaluation Platform
CIF	Cumulative incidence function
CIHI-DAD	Canadian Institute for Health Information – Discharge Abstract Database
CIHI-NACRS	Canadian Institute for Health Information – National Ambulatory Care Reporting System
CIHI-SDS	Canadian Institute for Health Information – Same Day Surgery
CONSORT	Consolidated Standards of Reporting Trials
DIN	Drug identification number
ECOG	Eastern Cooperative Oncology Group
EMR	Electronic Medical Records
ESAS	Edmonton Symptom Assessment System
HRD	Homologous Recombination Deficiency
ICD-10	International Classification of Diseases, 10th edition
INESSS	Institut National d'Excellence en Santé et en Services Sociaux
IQR	Interquartile range
NDFP	New Drug Funding Program
OCR	Ontario Cancer Registry
ODB	Ontario Drug Benefits
OHIP	Ontario Health Insurance Plan
OLIS	Ontario Laboratory Information Systems
PARP	Poly (adenosine diphosphate [ADP]-ribose) polymerase
pCODR	pan-Canadian Oncology Drug Review
PIN	Pharmaceutical Information Network
PFS	Progression-Free Survival
PMT	Personalize My Treatment
PSP	Patient Support Program

RPDB	Registered Persons Database
SD	Standard deviation

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Key Messages

- Niraparib is used as a maintenance therapy after complete or partial response to platinum-based chemotherapy for patients with new or recurrent epithelial ovarian cancer, approved for use in Canada in 2020.
- There have been concerns that hematological toxicities occur more frequently in the real-world compared to what has been reported in clinical trials for niraparib.
- The Canadian Cancer Real-World Evaluation Platform and Exactis performed a population-based, retrospective cohort study using data from 4 provinces. Data access varied by province, but where possible, included administrative data, laboratory data, pharmaceutical dispensing data, and electronic medical record reviews.
- The study found that patients with ovarian cancer who were given niraparib had lower hematological toxicities in the real-world compared to the clinical trials. This could be because patients were administered lower doses of niraparib than what is recommended in the product monograph and used in the clinical trials (a quarter of patients started with 100 mg/day, compared to the recommended dose of 200-300 mg/day).
- More clinical research is required to understand why lower hematological toxicities were found in the real-world.

Background

Due to its non-specific symptom presentation and rapid spread throughout the abdomen, many patients with epithelial ovarian cancers, fallopian tube cancers, and primary peritoneal cancers (collectively referred to synonymously as epithelial ovarian cancers throughout the manuscript 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 women 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 majority of cases) are particularly susceptible to the cytotoxicity of platinum-based agents, 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 when compared to placebo.[2,8] PARP inhibitors disrupt the homologous recombination repair pathway and prevent the restoration of gene damage. Because of this, patients who have homologous recombination deficiency (HRD), who already have some dysregulation in their homologous recombination repair pathway, tend to be more likely to respond to treatment with to PARP inhibitors.[8,9] Currently, there are two PARP inhibitors available in Canada for maintenance therapy in ovarian cancer: olaparib and niraparib. Olaparib was approved in 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 *(BRCA1/2*).[10] The approval for olaparib was limited to *BRCA1/2,* where the evidence is strongest, although a gradient of benefits exists among other patients with HRD cancers without *BRCA1/2*, to homologous recombination proficient cancers. However, evidence has shown potential benefit for PARP inhibitors among patients without *BRCA1/2* who have complete or partial response to platinum-based chemotherapy.[11] 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 later in 2019[12] 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 (pCODR) Expert Review Committee 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 three years or until unacceptable toxicity or disease progression.[21] Additional dosing details are available in **Table 1** below.

Table 1. Approved indications, suggested regimens and key funding dates for niraparib.

Approved Use	Dose[1]	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 and have 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]

The above approvals and recommendations were finalized based on results from two double blind, placebo controlled, phase III trials: the NOVA trial[11] and 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 using niraparib (regardless of BRCA mutation status) experienced a statistically significant prolongation of progression free survival (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 niraparib group vs 22.9% of placebo group in NOVA; 65.3% of niraparib group vs 6.6% of placebo group in PRIMA). Thrombocytopenia, anemia, neutropenia, fatigue, and hypertension were the most common toxicities. Amongst patients enrolled in the NOVA trial, grade 3/4 thrombocytopenia occurred in approximately 33.8% of the niraparib group (0.1% of the placebo group), grade 3/4 anemia in 25.3% of the niraparib group (0 in placebo group), and grade 3/4 neutropenia in 19.6% of the niraparib group (1.7% of placebo group).[11] In the PRIMA trial, grade 3/4 thrombocytopenia occurred in approximately 28.7% of the niraparib group (0.4% of placebo group), grade 3/4 anemia in 31.0% of the niraparib group (1.6% in placebo), and grade 3/4 neutropenia 12.8% of the niraparib group (1.2% in placebo).[22] Most patients required a dose interruption (66.5% in NOVA, 79.5% in PRIMA) or reduction (68.9% in NOVA, 70.9% in PRIMA) to manage adverse events.[11] The PRIMA trial also evaluated individualized dosing (starting dose 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 on 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.

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. Jurisdictions raised concerns about anecdotal experience of significant hematological toxicity of the medication in the real world. Jurisdictions are seeking a more realistic picture of the risk profile of niraparib in the management of ovarian cancer, which could inform patient monitoring and toxicity management measures.

Policy Question(s)

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

Research Question(s)

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

Research Objective(s)

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 of 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 cancer patients at 16 sites across Canada.[23] For the purposes of this study, we are accessing PMT data for Quebec patients, which includes patient data from one 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 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) in order to include patients who were enrolled in patient support programs (PSPs) prior to 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 (ODB), 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 prior to the start date of Ontario's public funding for niraparib to ensure that we capture the correct start date for all patients in the cohort.

Study Design

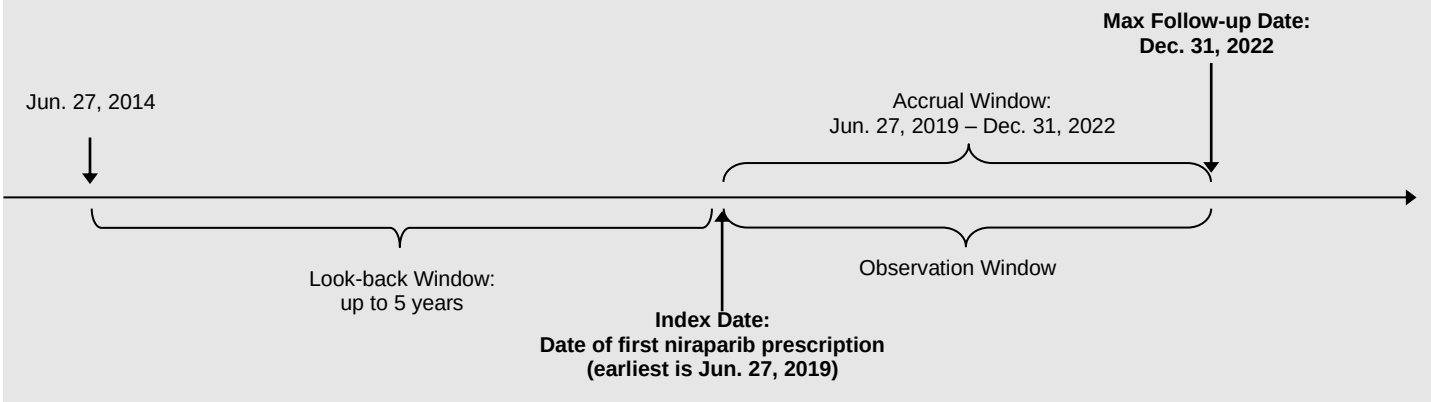
We conducted a retrospective, single-arm, population-based cohort study to examine the safety of niraparib for maintenance therapy among ovarian cancer patients treated with niraparib between 2019 and 2022 in three Canadian provinces: Ontario, Alberta, and British Columbia. This retrospective, single-arm, cohort design was replicated in Quebec using adult patients 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, December 31, 2022, whichever came first. See **Table 2** for a summary of key dates in the study design and **Figure 1** below 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 on Maintenance Therapy using Niraparib	June 27, 2019 – December 31, 2022	January 1, 2022 – December 31, 2022	December 1, 2021 – December 31, 2022	January 25, 2021 – December 31, 2022
Index Date	Earliest date is June 27, 2019	Earliest is January 1, 2022	Earliest is December 1, 2021	Earliest is January 25, 2021
Lookback Window	Up to 5 years prior to index, earliest is June 27, 2014	Up to 5 years prior to index, earliest is January 1, 2017	Up to 5 years prior to index, earliest is December 1, 2016	Up to 5 years prior to index, earliest is January 25, 2016
Observation Window	Between index date and December 31, 2022			
Max Follow-Up Date	December 31, 2022			

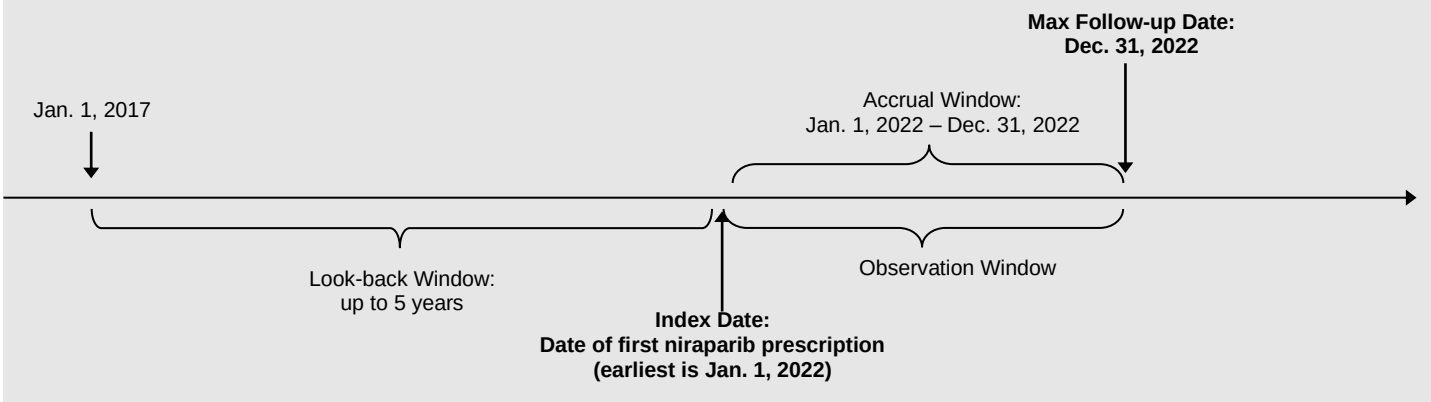
Figure 1. Study design diagrams for each province

Ontario



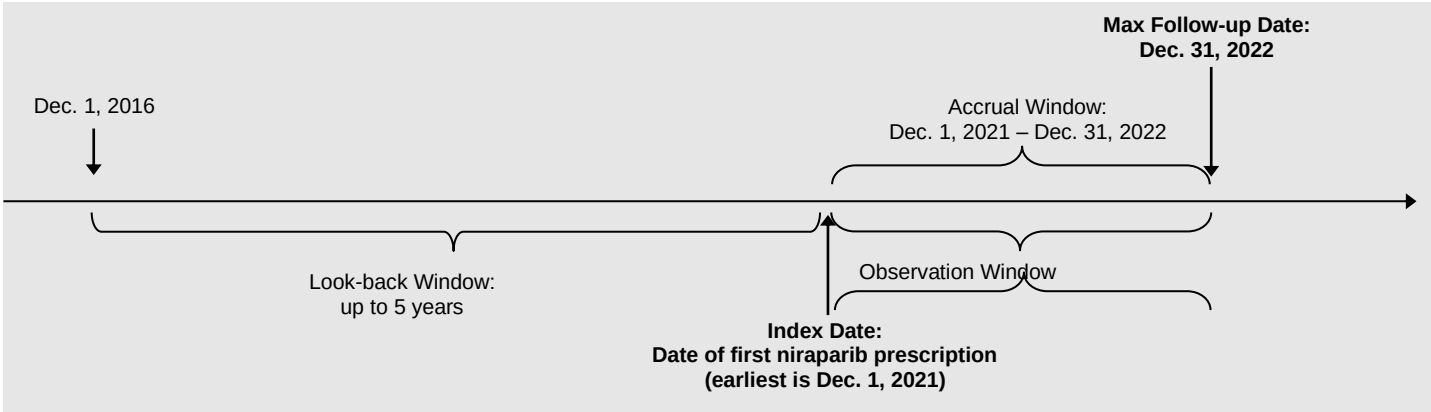
Alt text: This figure provides a visualization of study design timelines for the Ontario cohort. The index event date for each individual in the study will be the date of first niraparib prescription dispensed, and the accrual window for index events will be between June 27, 2019, and December 31, 2022. The lookback window for previously diagnosed comorbidities and instances of healthcare services utilization will be up to five years prior to the index date; for this cohort, the lookback window dates back to January 27, 2014. The observation window for study outcomes will range from the index date up to December 31, 2022.

Alberta



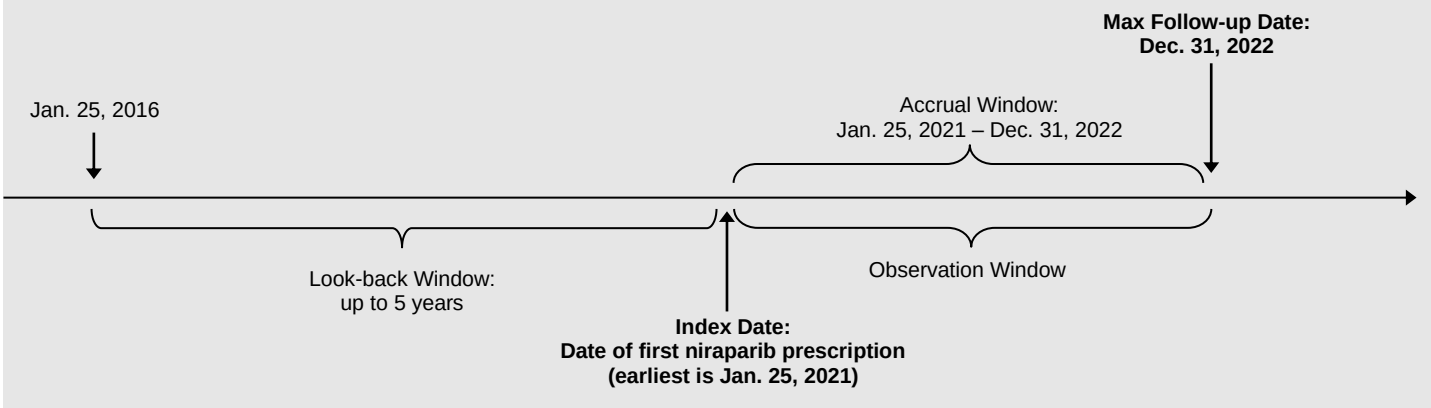
Alt text: This figure provides a visualization of study design timelines for the Alberta cohort. The index event date for each individual in the study will be the date of first niraparib prescription dispensed, and the accrual window for index events will be between January 1, 2022, and December 31, 2022. The lookback window for previously diagnosed comorbidities and instances of healthcare services utilitzation will be up to five years prior to the index date; for this cohort, the lookback window dates back to January 1, 2017. The observation window for study outcomes will range from the index date up to December 31, 2022.

British Columbia



Alt text: This figure provides a visualization of study design timelines for the British Columbia cohort. The index event date for each individual in the study will be the date of first niraparib prescription dispensed, and the accrual window for index events will be between December 1, 2021, and December 31, 2022. The lookback window for previously diagnosed comorbidities and instances of healthcare services utilization will be up to five years prior to the index date; for this cohort, the lookback window dates back to December 1, 2016. The observation window for study outcomes will range from the index date up to December 31, 2022.

Quebec



Alt text: This figure provides a visualization of study design timelines for the Quebec cohort. The index event date for each individual in the study will be the date of first niraparib prescription dispensed, and the accrual window for index events will be between January 25, 2021, and December 31, 2022. The lookback window for previously diagnosed comorbidities and instances of healthcare services utilitzation will be up to five years prior to the index date; for this cohort, the lookback window dates back to January 25, 2016. The observation window for study outcomes will range from the index date up to December 31, 2022.

Eligibility Criteria

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

Table 3. Cohort exclusion criteria by province

Province	Exclusion Criteria
Ontario	1. Invalid patient identification number 2. Invalid death date (death before index date) 3. Invalid sex 4. Non-Ontario resident status on index date
Alberta	1. Invalid patient identification number 2. Not referred (i.e., not in pharmacy or patient records) 3. Invalid death date (death before index date) 4. Non-Alberta resident on index date
BC	1. Invalid patient identification number 2. Not referred to BC Cancer (not in EMR) 3. Invalid death date (death before index date) 4. Non-British Columbia resident on index date
Quebec	1. Invalid death date (death before index date) 2. Invalid treatment date (missing date) 3. Patient receiving niraparib in the context of a clinical trial 4. Patient transferred to another hospital during treatment

Data Sources

We used a number of data sources to conduct this study, all of which are summarized in **Table 4** below. The Canadian Cancer Real-world Evaluation Platform's (CCRE'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 Control. Data access was approved by the Alberta Data Stewards. The BC 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 CIUSSS West-Central Montreal Research Ethics Board (REB 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 4. Data sources by province

Province	Data Sources
Ontario	*Cohort creation (Jun 27. 2019 – Dec 31. 2022):* **Ontario Drug Benefits (ODB) database** - all records of publicly funded medications in ON **Activity Level Reporting (ALR) database** - records of visits to oncology centres in Ontario **Ontario Cancer Registry (OCR)** - records of cancer diagnoses **Registered Persons Database (RPDB)** - demographics data
	Clinical and demographic characteristics (on index date or during lookback period): **ON-Marginalization Index** - marginalization index specific to Ontario, developed based on geographical data - measures four dimensions: households and dwellings, material resources, age and labour force, racialized and newcomer populations **Canadian Institute for Health Information (CIHI)-Discharge Abstract Database (DAD)** - all records of procedures and diagnoses that occur in an inpatient setting **CIHI-Same Day Surgery (SDS)** - records of same day surgeries **Ontario Health Insurance Plan (OHIP)** - all records of procedures and diagnoses that occur in an outpatient setting **New Drug Funding Program (NDFP)** - all records of new and expensive injectable cancer drugs administered in hospital settings in Ontario **OCR** **ODB** **ALR** **RPDB**
	Outcomes (during observation window: Jun 27, 2019 – Dec 31, 2022): **Ontario Laboratory Information System (OLIS) database** - all laboratory records from hospital, community, and public health labs across Ontario **CIHI-National Ambulatory Care Reporting System (NACRS) database** - all records of procedures and diagnoses that occur in the ambulatory setting

	CIHI-DAD **OHIP** **CIHI-SDS** **ODB** **RPDB**
Alberta	*Cohort creation (Jan 1, 2022 – Dec 31, 2022):* **Pharmaceutical Information Network (PIN) database** - all records of prescription medications dispensed in AB for all payers
	Clinical/demographic characteristics (on index date or during lookback period) and outcomes (during observation window: Jan 1,2022 – Dec 31, 2022): **Electronic Medical Records**
British Columbia	*Cohort creation (Dec 21, 2021 – Dec 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/demographic characteristics (on index date or during lookback period) and outcomes (during observation window: Dec 1, 2021 – Dec 31, 2022): **BC Provincial Systemic Therapy Program** **BC Cancer Registry** **Electronic Medical Records**
Quebec	*Cohort creation (Jan 25, 2021 – Dec 31, 2022), clinical/demographic characteristics (on index date or during lookback period), select outcomes (Jan 25, 2021 – Dec 31, 2022):* **Personalize My Treatment (PMT) registry, Exactis Innovation** - all electronic medical records in patient charts of those enrolled in the PMT registry
	Hematological adverse events (Jan 25, 2021 – Dec 31, 2022): **Electronic Medical Records**

Key Study Measures

Exposure(s)

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, as well as patient charts in Quebec (DIN: 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, hemoglobin, and neutrophil counts (respectively) listed in the Common Terminology Criteria for Adverse Events (see **Table 5** below).[24]

Table 5. Variable definition for main outcomes of interest

Variable	Definition
Thrombocytopenia	**Grade 1:** platelet count between 75 and150 x 10^9/L **Grade 2:** platelet count between 50 and <75 x 10^9/L **Grade 3:** platelet count between 25 and <50 x 10^9/L **Grade 4:** platelet count <25 x 10^9/L
Anemia	**Grade 1:** hemoglobin count between 100 and 120 g/L **Grade 2:** hemoglobin count between 80 and <100 g/L **Grade 3:** hemoglobin count between 65 and <80 g/L **Grade 4:** hemoglobin count <65 g/L
Neutropenia	**Grade 1:** neutrophil count between 1.5 and 2.0 x 10^9/L **Grade 2:** neutrophil count between 1.0 and <1.5 x 10^9/L **Grade 3:** neutrophil count between 0.5 and <1.0 x 10^9/L **Grade 4:** neutrophil count <0.5 x 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 vs 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 lookback period prior to index date. These included 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 (see Appendix 1, Table 9 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 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

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 patients in Alberta, and 100 patients in British Columbia. In Quebec, we identified 31 patients using 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=459-463, 89.3%-90.1%), and the most common starting daily dose of niraparib was 200 mg/day (N=288-292, 67.3%-68.2%).

Amongst patients in Ontario, the mean age was 68.8 years (standard deviation [SD] of 9.7), the majority of patients lived in urban settings (N=280, 82.8%), and over half of the group had no prior hospitalization for a comorbidity (N=183, 54.1%) or had a Charlson

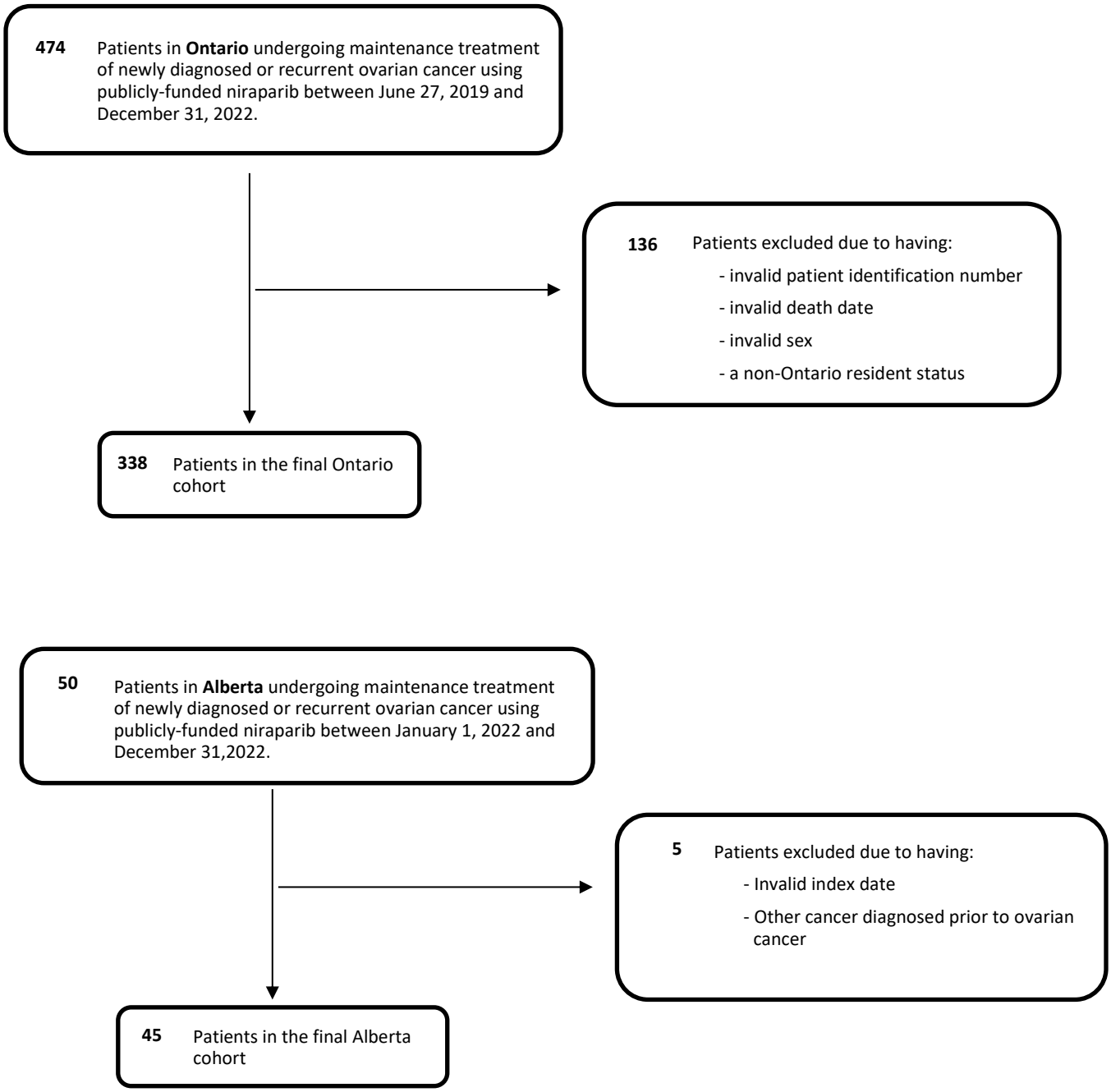
comorbidity index of 0 (N=21, 6.2%), indicating the absence of non-cancer comorbidities identified in inpatient data. Neighbourhood income was relatively evenly distributed throughout the Ontario cohort (approximately 20% in each income quintile). Approximately half of the Ontario cohort were diagnosed 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 prior to niraparib maintenance therapy 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 140.1 (SD 164.1). 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 an initial daily dose of 300 mg per day was the least common (N=20, 7.9%).

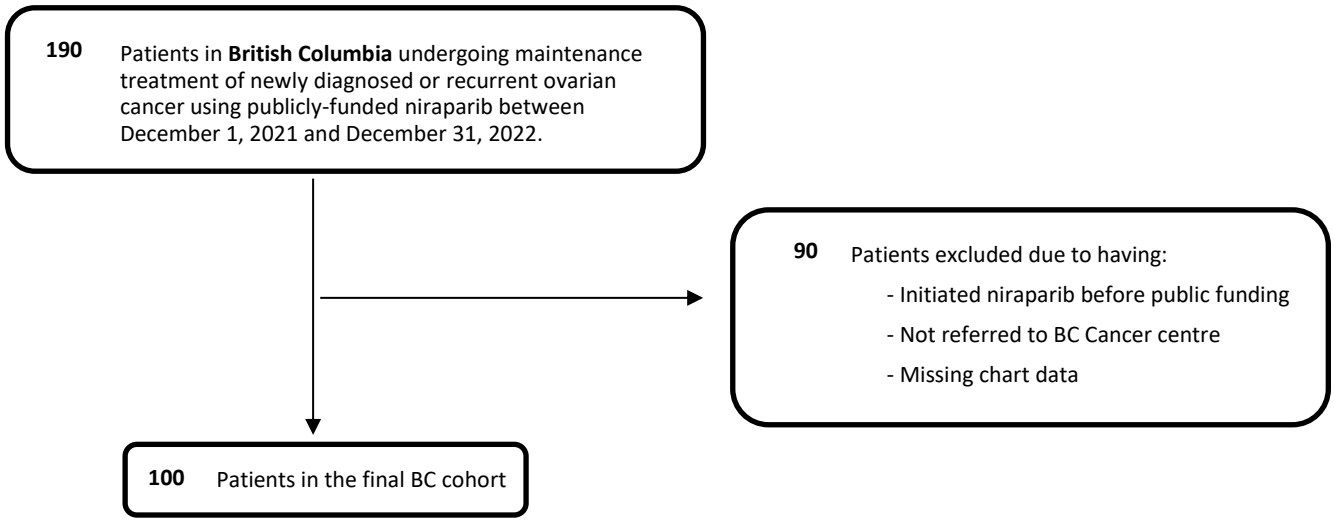
In Alberta, the mean age was 67 years (SD 9.0) and over half of the cohort (N=24, 53.3%) lived in an urban setting. More than half of the cohort had a Charlson Comorbidity Score of 0 (N=26, 58.8%). The majority of this cohort was diagnosed with ovarian cancer in 2021 (N=28, 62.2%) and everyone initiated 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%). Over one quarter of this group (N=12, 26.7%) had a cancer antigen-125 level of over 35 units/ml. In terms of characteristics relating to prior platinum-based chemotherapy, almost the entire cohort (N=36-44, 80.0-97.8%; 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 69 days (SD 36.0). The most common initial daily dose in Alberta was 200 mg (N=28, 62.2%) followed by 100 mg (N=17, 37.8%). No one in the Alberta cohort started at 300 mg per day.

In the British Columbia cohort, the mean age was 66.1 (SD 10.4) and most patients (N= 92-98, 92.0%-98.0%) lived in an urban setting. The proportion of individuals living in urban settings in the BC cohort is substantially higher in BC compared to Ontario and Alberta due to 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 rural patients who may have their cancer care managed in community hospitals rather than BC Cancer. The majority of the BC cohort was diagnosed with ovarian cancer in 2021 (N= 60, 60.0%), with Stage 3 (N= 50, 50.0%) or Stage 4 (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 two months of their last cycle of chemotherapy (mean 66.1 days, SD 39.1). 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 over half (N=17, 54.8%) started niraparib maintenance treatment during the same timeframe. 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=26-30, 83.8-96.8%) and most patients had a serous tumour histology (N=26-30, 83.8-96.8%). 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=26-30, 83.9%-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 90.8 (SD 108.1). In terms of initial daily dose of niraparib, most of the Quebec cohort (N=25-29, 83.3-96.7%) started on 200 mg, and less than 6 patients started on 300 mg. No one in the Quebec PMT registry cohort started at an initial daily dose of 100 mg.

Figure 2. CONSORT Diagrams for each province


474 Patients in **Ontario** undergoing maintenance treatment of newly diagnosed or recurrent ovarian cancer using publicly-funded niraparib between June 27, 2019 and December 31, 2022.
136 Patients excluded due to having:
- invalid patient identification number
- invalid death date
- invalid sex
- a non-Ontario resident status
338 Patients in the final Ontario cohort
50 Patients in **Alberta** undergoing maintenance treatment of newly diagnosed or recurrent ovarian cancer using publicly-funded niraparib between January 1, 2022 and December 31,2022.
5 Patients excluded due to having:
- Invalid index date
- Other cancer diagnosed prior to ovarian cancer
45 Patients in the final Alberta cohort


190 Patients in **British Columbia** undergoing maintenance treatment of newly diagnosed or recurrent ovarian cancer using publicly-funded niraparib between December 1, 2021 and December 31, 2022.
90 Patients excluded due to having:
- Initiated niraparib before public funding
- Not referred to BC Cancer centre
- Missing chart data
100 Patients in the final BC cohort

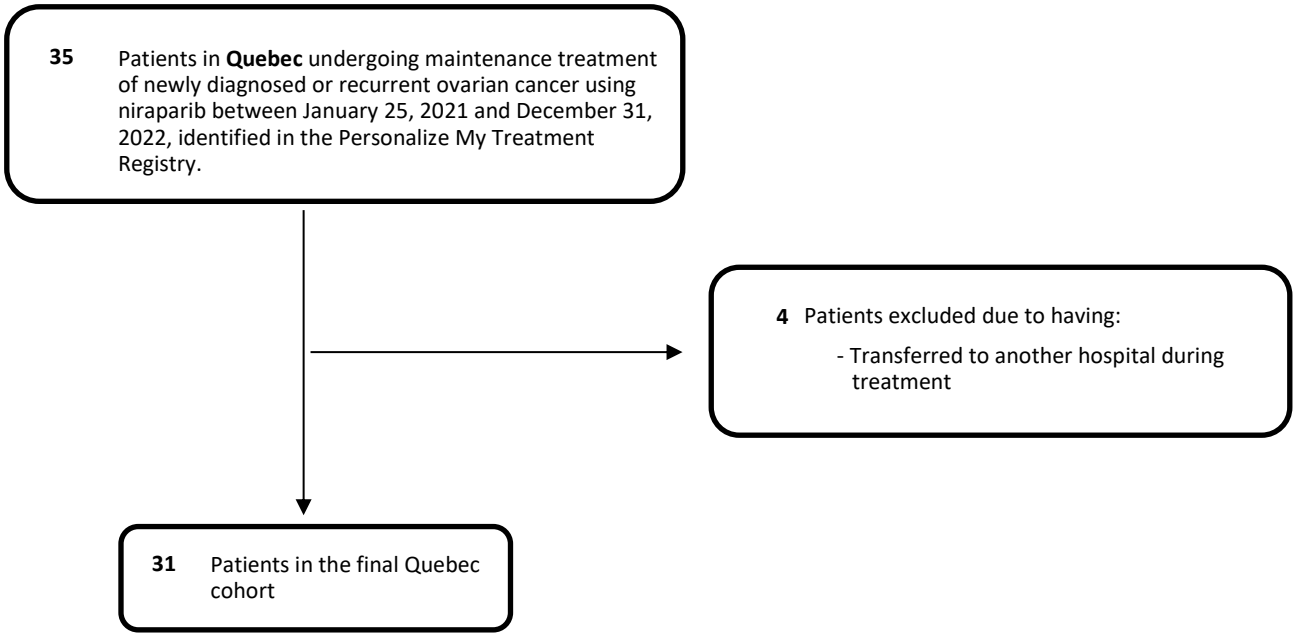

35 Patients in **Quebec** undergoing maintenance treatment of newly diagnosed or recurrent ovarian cancer using niraparib between January 25, 2021 and December 31, 2022, identified in the Personalize My Treatment Registry.
4 Patients excluded due to having:
- Transferred to another hospital during treatment
31 Patients in the final Quebec cohort

Table 6. Study Cohort Baseline Characteristics

Variables	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 ± 9	66.1±10.4	65.3 ± 11.9
≥ 65 years	352 (68.5)	254 (75.1)	29 (64.4)	51 (51.0)	18 (58.1)
Urban Residence[a]	396-402 (77.0-78.2)	280 (82.8)	24 (53.3)	92-98 (92.0-98.0)	N/A
Marginalization Index Score[a]					
1-least marginalized	-	91 (26.9)	N/A	N/A	N/A
2	-	74 (21.9)	N/A	N/A	N/A
3	-	64 (18.9)	N/A	N/A	N/A
4	-	59 (17.5)	N/A	N/A	N/A
5-most marginalized	-	47 (13.9)	N/A	N/A	N/A
Income Quintile[a]					
1-Lowest	51-65 (13.3-17.0)	56 (16.6)	<10	N/A	N/A-
2	103 (26.9)	72 (21.3)	31 (68.9)	N/A	N/A
3	73-81 (19.1-21.1)	72 (21.3)	<10	N/A	N/A
4	62-70 (16.2-18.3)	61 (18.0)	<10	N/A	N/A
5-Highest	76-84 (19.8-21.9)	75 (22.2)	<10	N/A	N/A
Charlson Comorbidity Score					
0	47 (12.3)	21 (6.2)	26 (57.8)	N/A	N/A
1	20 (5.2)	7 (2.1)	13 (28.9)	N/A	N/A
2	35-43 (9.1-11.2)	34 (10.1)	<10	N/A	N/A
3+	94-102 (24.5-26.6)	93 (27.5)	<10	N/A	N/A
No previous hospitalization	183 (47.8)	183 (54.1)	0	N/A	N/A
Prior Hypertension	118 (28.5)	155 (45.9)	19 (42.2)	N/A	13 (41.9)
Year of Cancer Diagnosis					
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					
I-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	89-101 (17.3-19.6)	56 (16.6)	<10	27 (27.0)	5-9 (16.1-29.0)
Missing/Unknown	155-163 (30.2-31.7)	137 (40.5)	<10	17 (17.0)	0
Year of Niraparib Treatment					
2020-2021	51-55 (9.9-10.7)	32 (9.5)	0	<6	17 (54.8)
2022	459-463 (89.3-90.1)	306 (90.5)	45 (100.0)	94-98 (94.0-98.0)	14 (45.2)
Primary Tumour Location					

Ovary		400-404 (77.8-78.6)	312 (92.3)	22 (48.9)	40 (40.0)	26-30 (83.9-96.8)
Fallopian Tubes		78-86 (15.2-16.7)	12 (3.6)	13-21 (28.9-46.7)	53 (53.0)	0
Other		32 (6.2)	14 (4.1)	<10	7 (7.0)	<6
Tumour Histology						
Serous		453-461 (88.1-89.7)	292 (86.4)	41 (91.1)	94-98 (94.0-98.0)	26-30 (83.8-96.8)
Endometroid		9-17 (1.8-3.3)	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)[c]	36-44 (80.0-97.8)	100 (100.0)	26-30 (83.9-96.7)
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)		91.5 ± 101.8	140.1 ± 164.1	69 ± 36	66.1 ± 39.1	90.8 ± 108.1
Initial Daily Dose of Niraparib[b]	**100 mg**	103 (24.1)	58 (22.9)	17 (37.8)	28 (28.0)	0
	200 mg	288-292 (67.3-68.2)	175 (69.2)	28 (62.2)	60 (60.0)	25-29 (83.3-96.7)
	300 mg	33-37 (7.7-8.6)	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	N/A

[a] Variable contains missing values therefore categories do not add up to N=338 for Ontario

[b]using cohort of N=253 for Ontario and N=30 for Quebec

[c] Remaining cohort has missing data for this variable

Main Findings

We reported crude proportion 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 3/4 hematological adverse events, the most common was anemia (N=52, 12.2%), followed by thrombocytopenia (N=50, 11.7%) and neutropenia (N=46, 10.8%).

Over the course of the observation period in Ontario (median follow-up time of 255 days [IQR 241-267]), 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 a grade 3/4 thrombocytopenia (N=28), 8.9% experienced grade 3/4 neutropenia (N=23), and 14.8% experienced grade 3/4 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 3/4 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 3/4 hematological toxicities for these jurisdictions, however proportion 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 three months after starting niraparib, the cumulative incidence of grade 3/4 thrombocytopenia in Ontario was 9.0% (95% confidence interval [CI], 5.9%-12.9%), grade 3/4 neutropenia was 5.8% (95% CI, 3.4%-9.2%), and grade 3/4 anemia was 10.1% (95% CI 6.8%-14.2%) (**Figures 3-5**). Cumulative incidence for all three outcomes in Ontario increased slightly with time, gradually plateauing by the 8th month after index date. We observed a similar trend in the cumulative incidence of all three outcomes in Alberta, BC, and Quebec (**Appendix 2, Figures 8-22**).

In terms of secondary outcomes that occurred during the observation window, approximately 20% of those eligible amongst the overall cohort (i.e., without a diagnosis of hypertension before index date) were newly diagnosed with hypertension (N=44-52, 19.4%-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 that of Alberta (N=11, 24.4%) and Quebec (N=9, 29.0%). Over one-third of the overall cohort visited the emergency department (N=153-157, 37.0%-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%-30.5%) (**Figure 6**), 25% (95% CI 3-58%) in Alberta **(Appendix 2, Figure 11),** 27.5% (95% CI 18.1-37.8%) in British Columbia **(Appendix 2, Figure 16),** and 10.7% (95% CI 2.6%-25.4%) in Quebec **(Appendix 2, Figure 21).** The overall survival in this study was high (**Figure 7, Appendix 2, Figures 12, 17** and **22**).

Table 7. Hematological Adverse Events

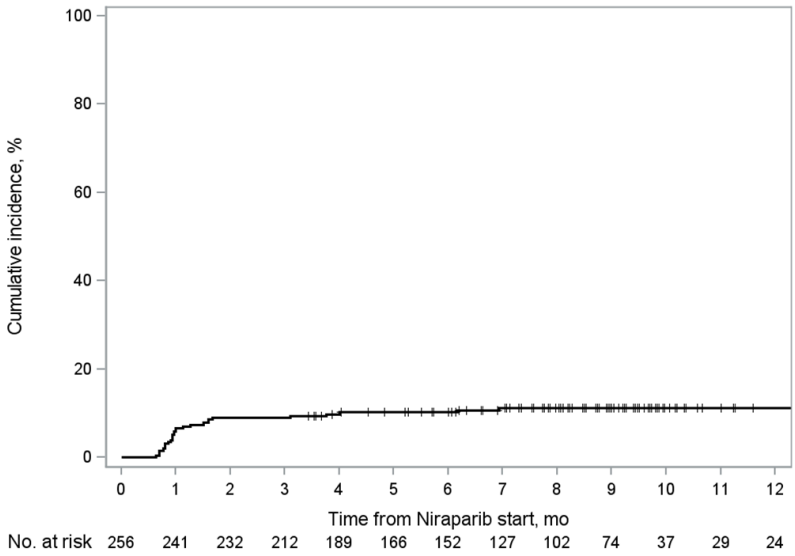
Hematological Adverse Event	All Provinces N= 427 (%)		Ontario N= 257 (%)[a]		Alberta N= 45 (%)		British Columbia N= 93 (%)[c]		Quebec N= 31 (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Thrombocytopenia	177 (41.5)	50 (11.7)	104 (40.6)[b]	28 (10.9)[b]	16 (35.6)	<10	43 (46.2)	13 (14.0)	14 (45.2)	<6
Neutropenia	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	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]257 of the 338 patients in the Ontario cohort had records of laboratory tests

[b]Denominator for thrombocytopenia in Ontario is 256 instead of 257 due to additional missing data

[c] 93 of the 100 patients in the British Columbia data had records of laboratory tests

Figure 3. Cumulative incidence of grade 3/4 thrombocytopenia in the Ontario cohort

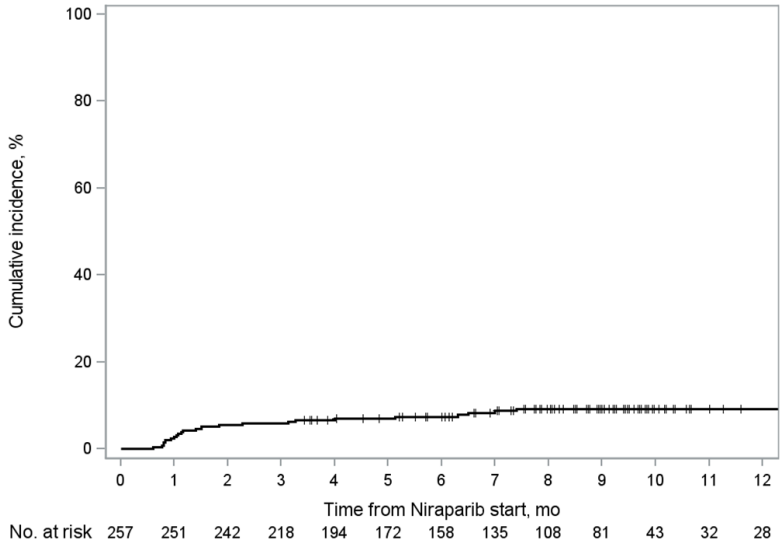


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
6.6% (4.0%-10.1%)	9.0% (5.9%-12.9%)	9.0% (5.9%-12.9%)	10.2% (6.8%-14.3%)	11.1% (7.6%-15.3%)	11.1% (7.6%-15.3%)

Alt text: Cumulative incidence of grade 3/4 thrombocytopenia in the Ontario cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 thrombocytopenia in percent is on the y-axis. Cumulative incidence in Ontario at 1 month is 6.6% (95% CI 4.0%-10.1%), at 2 months is 9.0% (95% CI 5.9%-12.9%), at 3 months is 9.0% (95% CI 5.9%-12.9%), at 6 months is 10.1% (95% CI 6.8%-14.3%), at 9 months is 11.1% (95% CI 7.6%-15.3%) and at 12 months is 11.1% (95% CI 7.6-15.3%).

Figure 4. Cumulative incidence of grade 3/4 neutropenia in the Ontario cohort

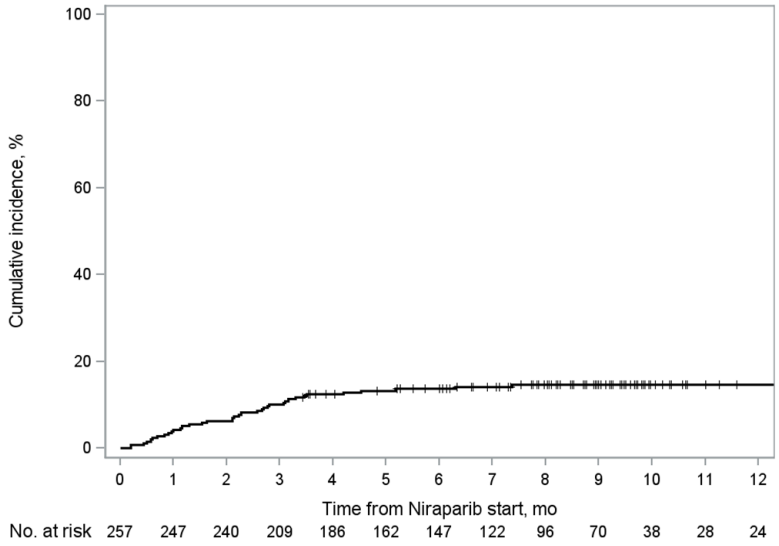


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
2.7% (1.2%-5.3%)	5.4% (3.1%-8.7%)	5.8% (3.4%-9.2%)	7.4% (4.6%-11.1%)	9.2% (6.0%-13.3%)	9.2% (6.0%-13.3%)

Alt text: Cumulative incidence of grade 3/4 neutropenia in the Ontario cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 neutropenia in percent is on the y-axis. Cumulative incidence in Ontario at 1 month is 2.7% (95% CI 1.2%-5.3%), at 2 months is 5.4% (95% CI 3.1%-8.7%), at 3 months is 5.8% (95% CI 3.4%-9.2%), at 6 months is 7.4% (95% CI 4.6%-11.1%), at 9 months is 9.2% (95% CI 6.0%-13.3%) and at 12 months is 9.2% (95% CI 6.0%-13.3%).

Figure 5. Cumulative incidence of grade 3/4 anemia in the Ontario cohort



Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
4.3% (2.3%-7.3%)	6.2% (3.7%-9.6%)	10.1% (6.8%-14.2%)	13.7% (9.8%-18.2%)	14.6% (10.6%-19.3%)	14.6% (10.6%-19.3%)

Alt text: Cumulative incidence of grade 3/4 anemia in the Ontario cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 anemia in percent is on the y-axis. Cumulative incidence in Ontario at 1 month is 4.3% (95% CI 2.3%-7.3%), at 2 months is 6.2% (95% CI 3.7%-9.6%), at 3 months is 10.1% (95% CI 6.8%-14.2%), at 6 months is 14.6% (95% CI 10.6%-18.2%), at 9 months is 14.6% (95% CI 10.6%-19.3%) and at 12 months is 14.6% (95% CI 10.6%-19.3%).

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	<10	<6	<10	N/A	0
Incident Hypertension[a]	44-52 (19.4-22.9)	37 (20.2)	<10	N/A	6 (33.3)
Any transfusion	53 (12.8)	33 (9.8)	11 (24.4)	N/A	9 (29.0)
Platelet Transfusion	18 (4.3)	11 (3.3)	<10	N/A	<6

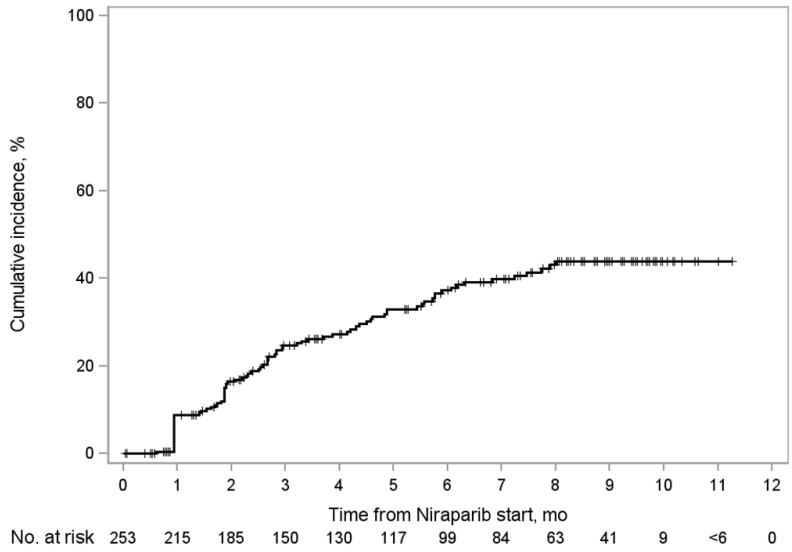
Red Blood Cell Transfusion	32 (7.7)	22 (6.5)	<10	N/A	<6
Emergency Department Visit	153-157 (37.0-37.9)	134 (39.6)	18 (40.0)	N/A	<6
Hospitalization (any type)	80 (19.3)	63 (18.6)	17 (37.8)	N/A	0
Hospitalization (unscheduled)	57 (15.4)	57 (16.9)	N/A	N/A	0
Niraparib Treatment Discontinuation[b]	150-158 (35.0-36.9)	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
Median Follow-up Time in Days	N/A[c]	255 (241.0-267.0)	229 (170-274)	250 (78.0-310.0)	411 (270-585)

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

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

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

Figure 6. Cumulative Incidence of Discontinuation in Ontario

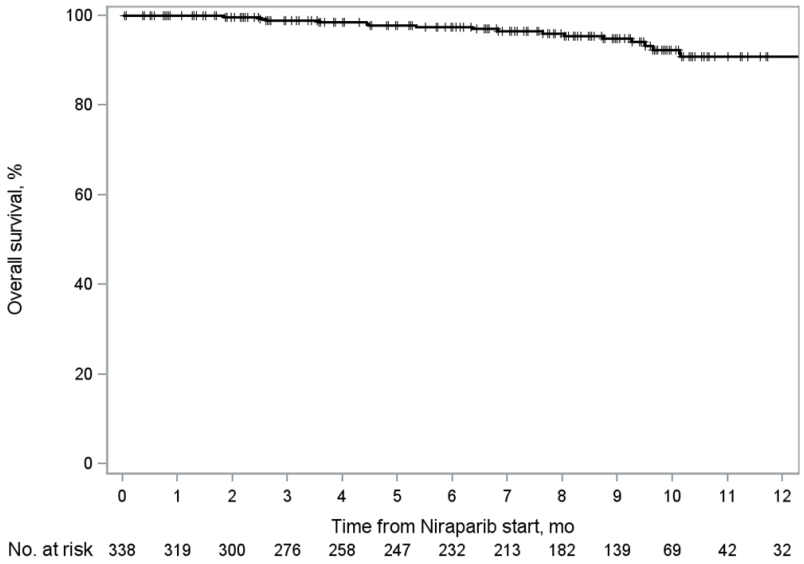


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
8.9% (5.7%-13.0%)	16.4% (12.0%-21.5%)	24.6% (19.2%-30.5%)	37.2% (30.5%-44.0%)	44.0% (36.5%-51.2%)	44.0% (36.5%-51.2%)

Alt text: Cumulative incidence of discontinuation in the Ontario cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of discontinuation in percent is on the y-axis. Cumulative incidence in Ontario at 1 month is 8.9% (95% CI 5.7%-13.0%), at 2 months is 16.4% (95% CI 12.0%-21.5%), at 3 months is 24.6% (95% CI 19.2%-30.5%), at 6 months is 37.2% (95% CI 30.5%-44.0%), at 9 months is 44.0% (95% CI 36.5%-51.2%) and at 12 months is 44.0% (95% CI 36.5%-51.2%).

Figure 7. Kaplan-Meier curve for overall survival in the Ontario cohort



Overall Survival

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
100.0% (100.0%-100.0%)	99.7% (97.7%-100%)	99.0% (96.9%-99.7%)	97.4% (94.7%-98.8%)	94.4% (91.1%-97.1%)	90.9% (84.6%-94.7%)

Alt text: Kaplan-Meier curve for overall survival in the Ontario cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability overall survival in percent is on the y-axis. Overall survival in Ontario at 1 month is 100% (95% CI 100%-100%), at 2 months is 99.7%

(95% CI 97.7%-100%), at 3 months is 99% (95% CI 96.9%-99.7%), at 6 months is 97.4% (95% CI 94.7%-98.8%), at 9 months is 94.9% (95% CI 91.1%-97.1%) and at 12 months is 90.9% (95% CI 84.6%-94.7%).

Limitations

There are a number of limitations in this study that warrant discussion. First, although three of the four cohorts included in this study were population-based (Ontario, Alberta, and British Columbia), 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 the fact 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 enrollment in the PMT registry in Quebec (which only captures approximately 12% of ovarian cancer patients in the province), our study cohort may have experienced different adverse outcome profiles compared to the broader Canadian ovarian cancer population 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. Secondly, the observation window for our study was limited for some patients because niraparib was only recently publicly funded in Canada, in particular for the first line maintenance indication. In order 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 allows us to describe baseline characteristics of more patients using this method, 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 potentially subtherapeutic dose. 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 dose. It is unclear whether patients started with 100 mg/day in the first month and then subsequently titrated upwards if they tolerated niraparib adequately or they were maintained on 100 mg/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 above, and used niraparib for the maintenance treatment of ovarian cancer. The mean age for patients in our study was approximately 67 years of age and over 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/day, followed by 100 mg/day, and finally, 300 mg/day. In the analysis of hematological adverse events, we found that grade 3/4 thrombocytopenia, neutropenia, anemia all occurred in approximately 10-12% of the overall cohort.

Comparison with Existing Literature

There are three 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, since 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 Chinese patients (NORA trial).[28] Clinical and demographic characteristics of patients in all three trials were generally very similar to patients in our cohort, with the exception of age; patients in our cohort were slightly older.

Both 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/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/day, which is not a dose suggested by the product monograph nor one that is observed in the three 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 towards 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 (see Table 10 in Appendix 3 for summary of results from clinical trials). Given that the baseline characteristics between our cohort and 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/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 3/4 hematological toxicities, indicating that patients on 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 twenty 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 that of the seminal trials. Patients in our cohort started niraparib, on average, approximately 91 days after last administration of platinum-based chemotherapy compared to within 56-84 days (depending on indication; patients should start within 84 days for maintenance therapy of newly diagnosed ovarian cancer and within 56 days for recurrent cancer)[21] in the trials.[11,22,28] Although the median follow-up time in some jurisdictions in our study (Ontario, Alberta, British Columbia) was slightly shorter than that of the seminal trials (ranging from a median of 229 to 255 days in our study compared to approximately 400-500 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.

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 recommendations 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.

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 four 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 doses less than recommended as well as the effectiveness of starting patients on such low doses (i.e., 100 mg/day) in order to guide clinical decisions on the use of niraparib maintenance treatment.

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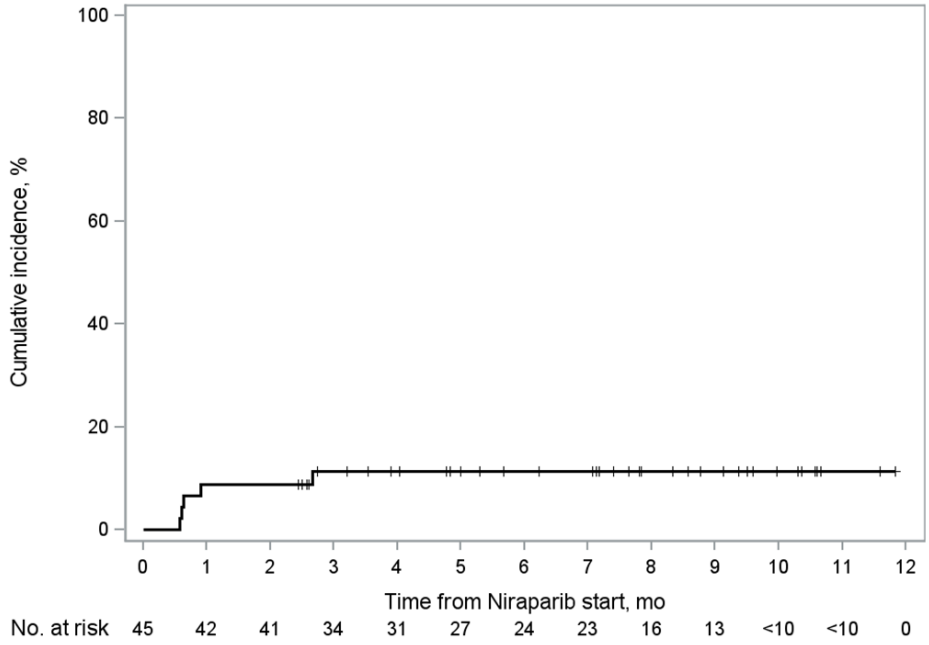
Appendix 1: Supplemental materials for methods

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

Variable	Variable Definition			
	Ontario	Alberta	BC	Quebec
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 (401-405 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 (401-405 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 study outcomes in Alberta, British Columbia, and Quebec

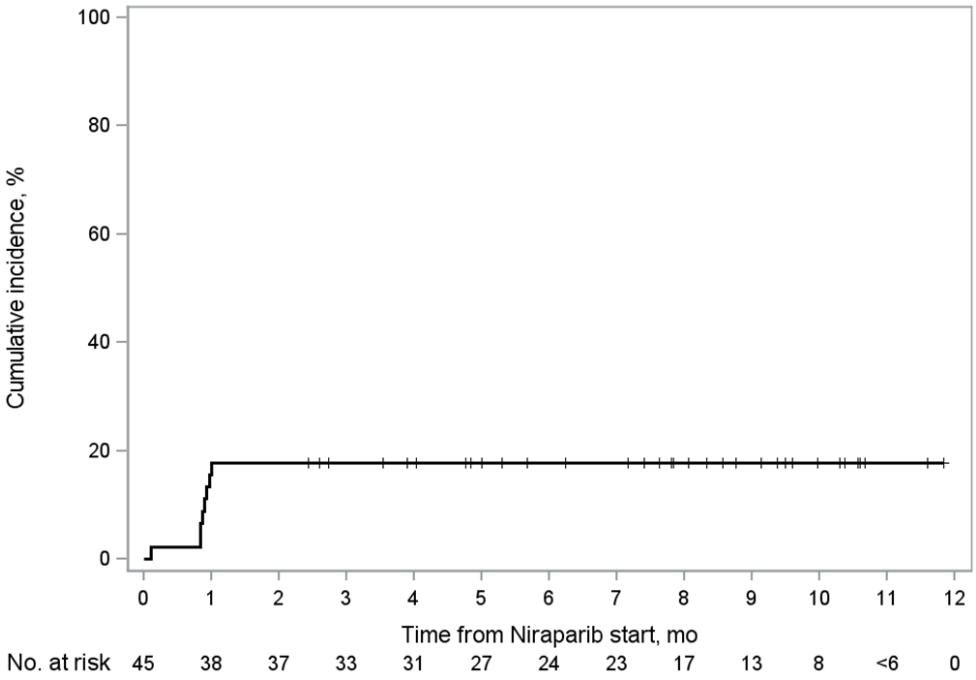
Figure 8. Cumulative incidence of grade 3/4 thrombocytopenia in the Alberta cohort



Cumulative Incidence					
1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
8.9% (2.8%-19.5%)	8.9% (2.8%-19.5%)	11.4% (4.1%-22.7%)	11.4% (4.1%-22.7%)	11.4% (4.1%-22.7%)	N/A

Alt text: Cumulative incidence of grade 3/4 thrombocytopenia in the Alberta cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 thrombocytopenia in percent is on the y-axis. Cumulative incidence in Alberta at 1 month is 8.9% (95% CI 2.8%-19.5%), at 2 months is 8.9% (95% CI 2.8%-19.5%), at 3 months is 11.4% (95% CI 4.1%-22.7%), at 6 months is 11.4% (95% CI 4.1%-22.7%), at 9 months is 11.4% (95% CI 4.1%-22.7%) and at 12 months is not available.

Figure 9. Cumulative incidence of grade 3/4 neutropenia in the Alberta cohort

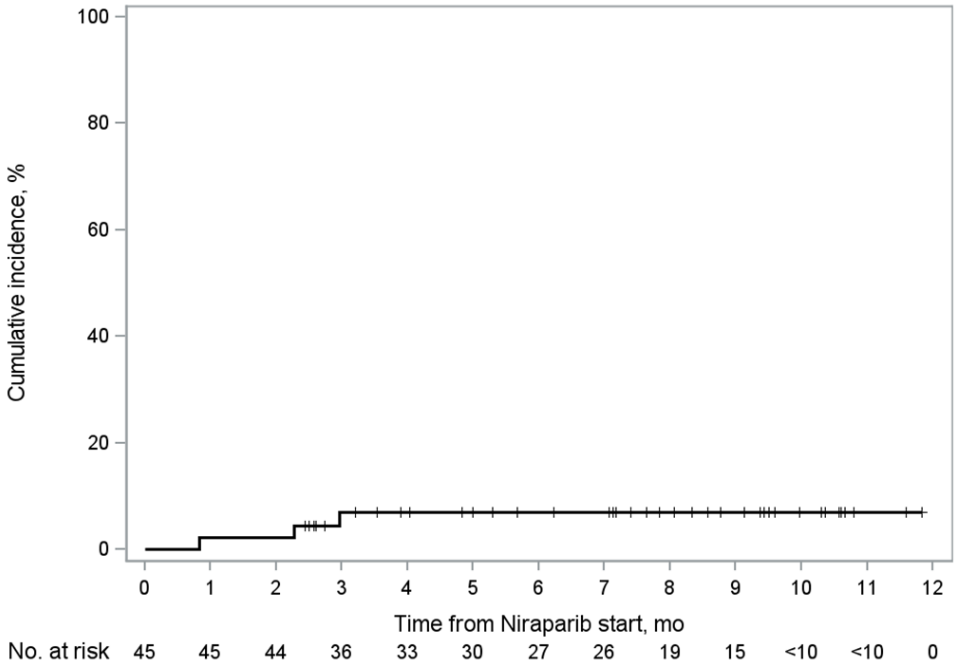


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
17.8% (8.2%-30.3%)	17.8% (8.2%-30.3%)	17.8% (8.2%-30.3%)	17.8% (8.2%-30.3%)	17.8% (8.2%-30.3%)	N/A

Alt text: Cumulative incidence of grade 3/4 neutropenia in the Alberta cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 neutropenia in percent is on the y-axis. Cumulative incidence in Alberta at 1 month is 17.8% (95% CI 8.2%-30.3%), at 2 months is 17.8% (95% CI 8.2%-30.3%), at 3 months is 17.8% (95% CI 8.2%-30.3%), at 6 months is 17.8% (95% CI 8.2%-30.3%), at 9 months is 17.8% (95% CI 8.2%-30.3%) and at 12 months is not available.

Figure 10. Cumulative incidence of grade 3/4 anemia in the Alberta cohort

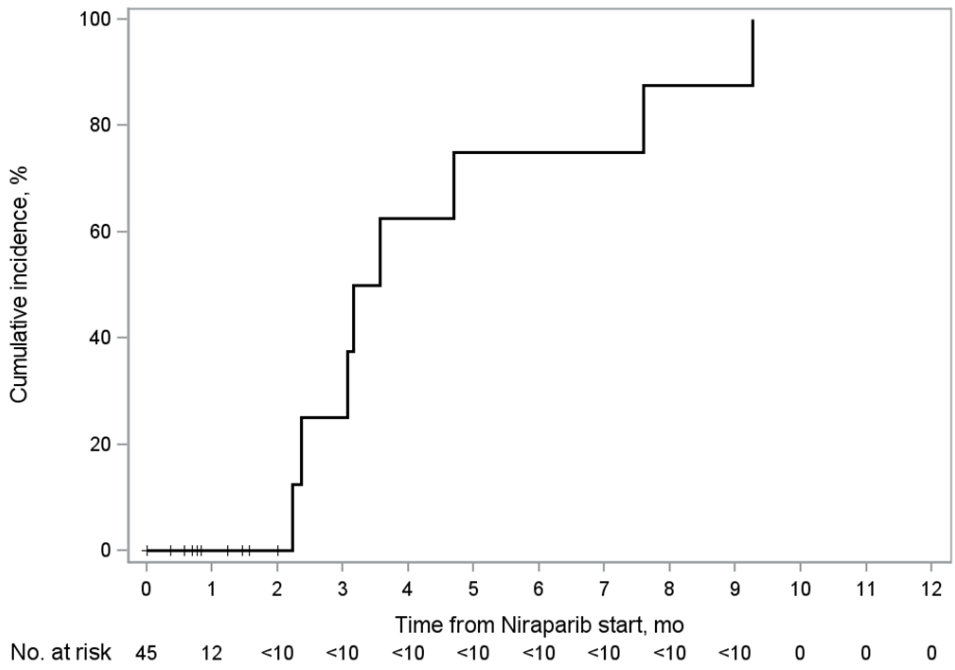


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
2.2% (0.2%-10.3%)	2.2% (0.2%-10.3%)	7.0% (1.8%-17.4%)	7.0% (1.8%-17.4%)	7.0% (1.8%-17.4%)	N/A

Alt text: Cumulative incidence of grade 3/4 anemia in the Alberta cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 anemia in percent is on the y-axis. Cumulative incidence in Alberta at 1 month is 2.2% (95% CI 0.2%-10.3%), at 2 months is 2.2% (95% CI 0.2%-10.3%), at 3 months is 7.0% (95% CI 1.8%-17.4%), at 6 months is 7.0% (95% CI 1.8%-17.4%), at 9 months is 7.0% (95% CI 1.8%-17.4%) and at 12 months is not available.

Figure 11. Cumulative incidence of niraparib discontinuation in the Alberta cohort

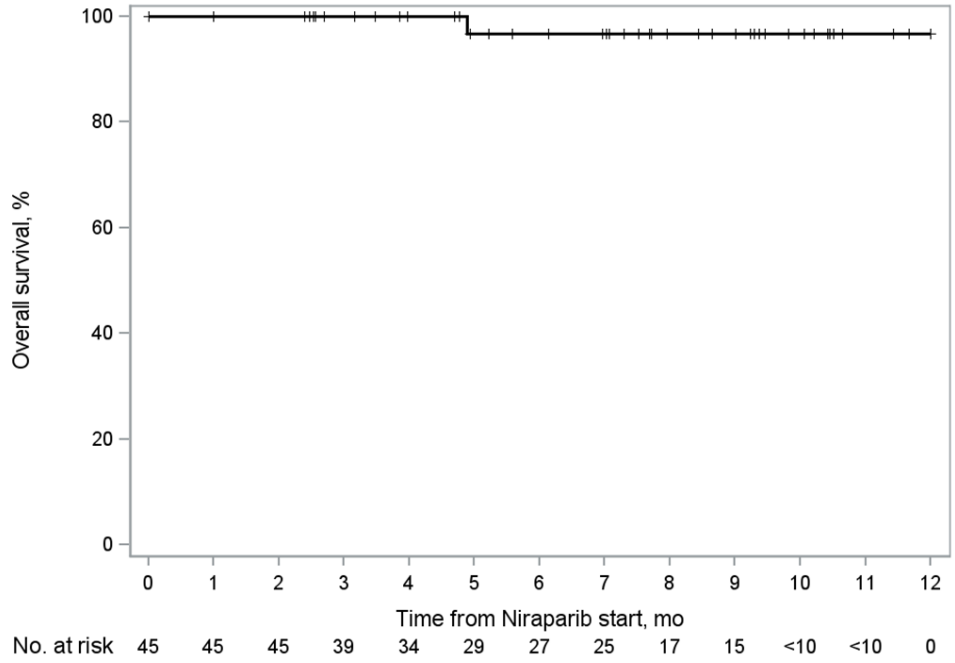


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
0%	0%	25.0% (3.0%-57.9%)	75.0% (23.2%-94.5%)	87.5% (17.2%-99%)	N/A

Alt text: Cumulative incidence of discontinuation in the Alberta cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of discontinuation in percent is on the y-axis. Cumulative incidence in Alberta at 1 month is 0%, at 2 months is 0%, at 3 months is 25.0% (95% CI 3.0%-57.9%), at 6 months is 75% (95% CI 23.2%-94.5%), at 9 months is 87.5% (95% CI 17.2%-99%) and at 12 months is not available.

Figure 12. Kaplan-Meier curve for overall survival in the Alberta cohort

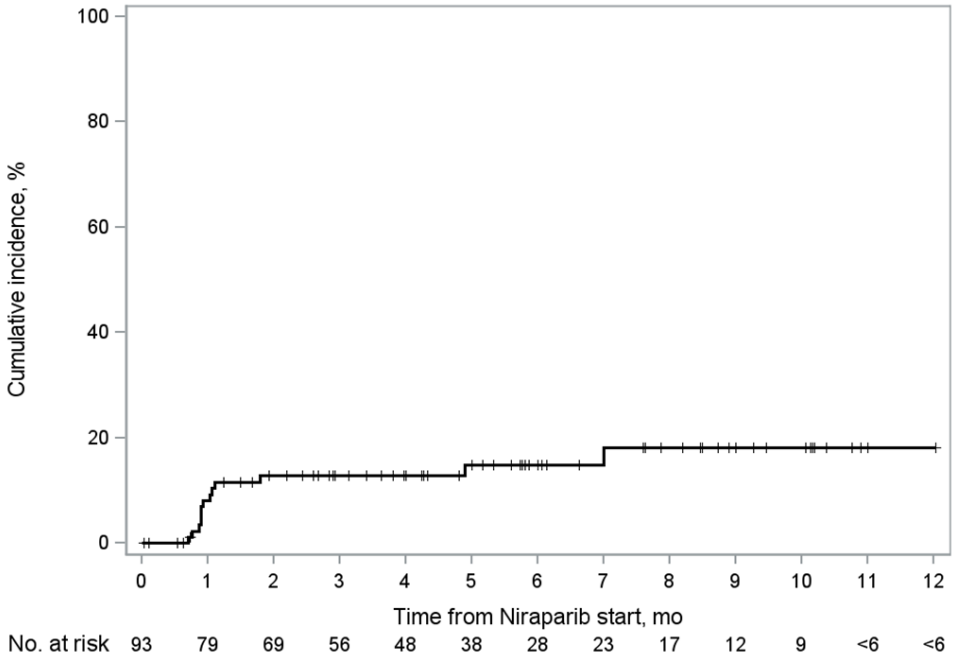


Overall Survival

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
100.0% (100.0%-100.0%)	100.0% (100.0%-100.0%)	100.0% (100.0%-100.0%)	96.8% (90.8%-100.0%)	96.8% (90.8%-100.0%)	N/A

Alt text: Kaplan-Meier curve for overall survival in the Alberta cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability overall survival in percent is on the y-axis. Overall survival in Alberta at 1 month is 100% (95% CI 100%-100%), at 2 months is 100% (95% CI 100%-100%), at 3 months is 100% (95% CI 100%-100%), at 6 months is 96.8% (95% CI 90.8%-100%), at 9 months is 96.8% (95% CI 90.8%-100%) and at 12 months is not available.

Figure 13. Cumulative incidence of grade 3/4 thrombocytopenia in the British Columbia cohort

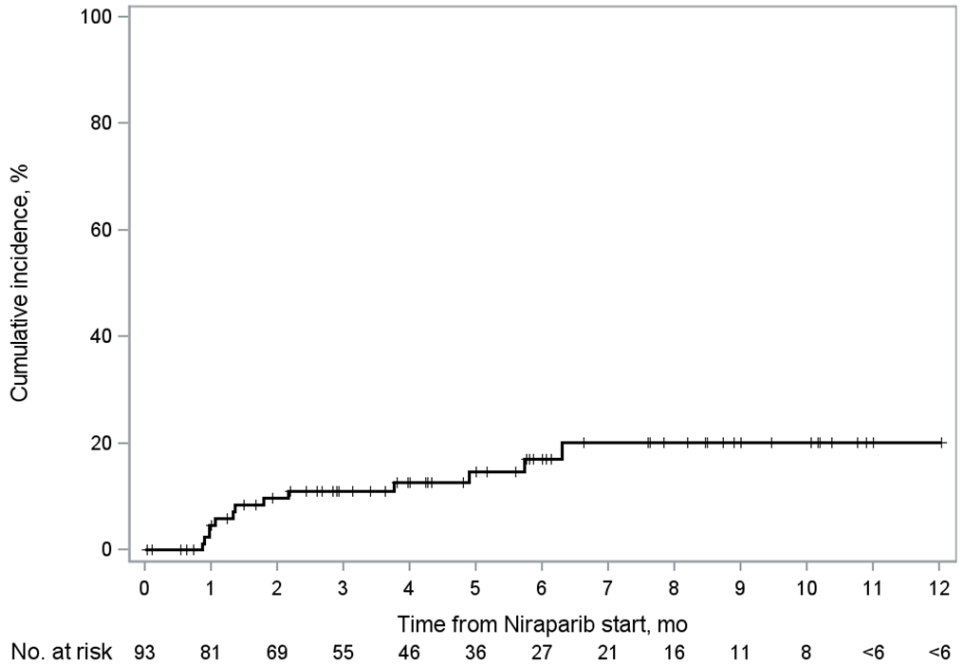


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
8.1% (3.5% -15.1%)	12.8% (6.8% -20.9%)	12.8% (6.8% -20.9%)	14.8% (8.0% -23.7%)	18.0% (9.4% -28.9%)	18.0% (9.4%-28.9%)

Alt text: Cumulative incidence of grade 3/4 thrombocytopenia in the BC cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 thrombocytopenia in percent is on the y-axis. Cumulative incidence in BC at 1 month is 8.1% (95% CI 3.5%-15.1%), at 2 months is 12.8% (95% CI 6.8%-20.9%), at 3 months is 12.8% (95% CI 6.8%-20.9%), at 6 months is 14.8% (95% CI 8.0%-23.7%), at 9 months is 18.0% (95% CI 9.4%-28.9%) and at 12 months 18.0% (95% CI 9.4%-28.9%).

Figure 14. Cumulative incidence of grade 3/4 neutropenia in the British Columbia cohort

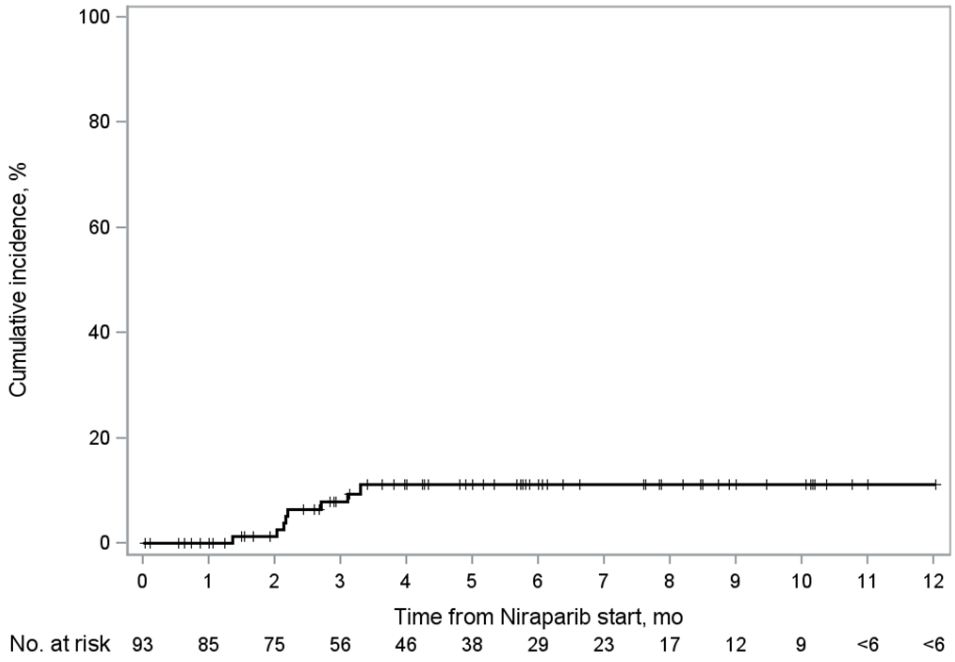


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
4.7% (1.5% -10.7%)	9.6% (4.5% -17.2%)	10.9% (5.3% -18.8%)	17.1% (9% -27.4%)	20.2% (10.6%-31.9%)	20.2% (10.6% -31.9%)

Alt text: Cumulative incidence of grade 3/4 neutropenia in the BC cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 neutropenia in percent is on the y-axis. Cumulative incidence in BC at 1 month is 4.7% (95% CI 1.5%-10.7%), at 2 months is 9.6% (95% CI 4.5%-17.2%), at 3 months is 10.9% (95% CI 5.3%-18.8%), at 6 months is 17.1% (95% CI 9%-27.4%), at 9 months is 20.2% (95% CI 10.6%-31.9%) and at 12 months 20.2% (95% CI 10.6%-31.9%).

Figure 15. Cumulative incidence of grade 3/4 anemia in the British Columbia cohort

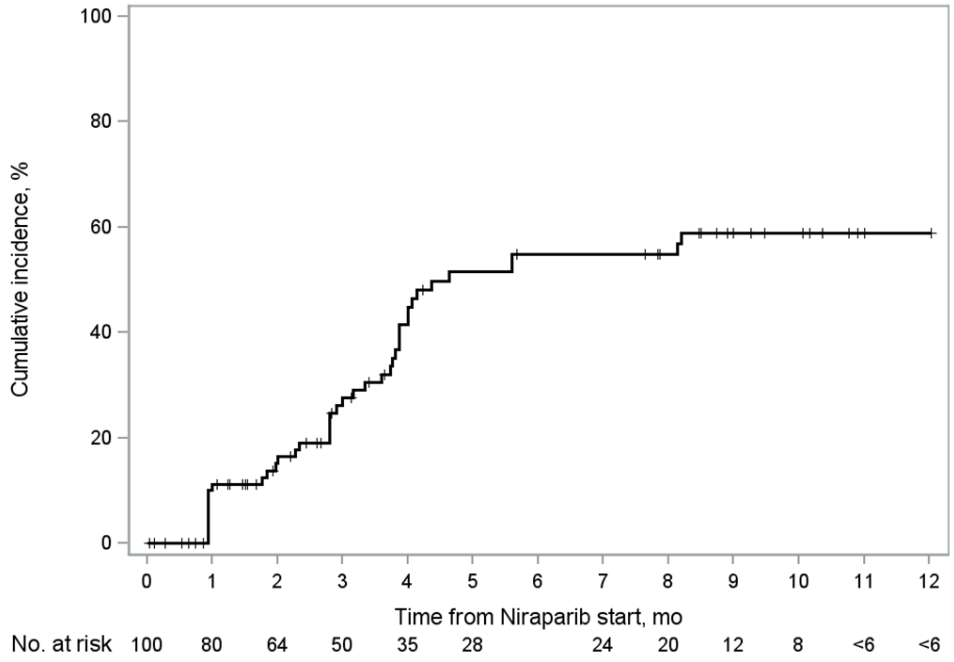


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
0%	1.2% (0.1%-6.0%)	7.8% (3.2% -15.2%)	11.1% (5.1% -19.7%)	11.1% (5.1% -19.7%)	11.1% (5.1% -19.7%)

Alt text: Cumulative incidence of grade 3/4 anemia in the BC cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 anemia in percent is on the y-axis. Cumulative incidence in BC at 1 month is 0%, at 2 months is 1.2% (95% CI 0.1%-6.0%), at 3 months is 7.8% (95% CI 3.2%-15.2%), at 6 months is 11.1% (95% CI 5.1%-19.7%), at 9 months is 11.1% (95% CI 5.1%-19.7%) and at 12 months 11.1% (95% CI 5.1%-19.7%).

Figure 16. Cumulative incidence of niraparib discontinuation in the British Columbia cohort

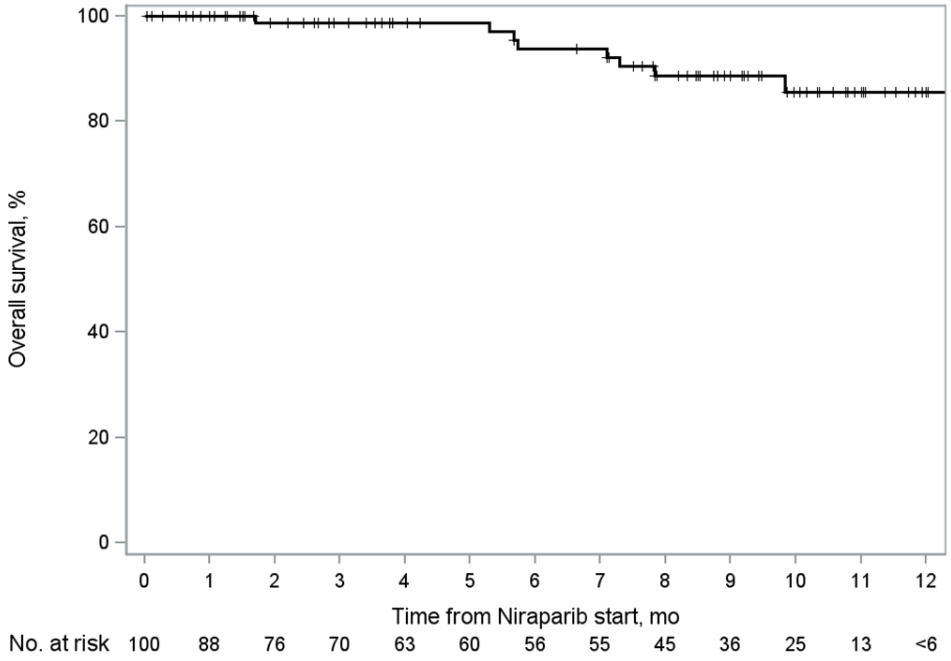


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
11.2% (5.7% -18.8%)	16.4% (9.4% -25.1%)	27.5% (18.1% -37.8%)	54.9% (41.9% -66.0%)	58.9% (45.5% -70.0%)	58.9% (45.5%-70.0%)

Alt text: Cumulative incidence of discontinuation in the BC cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of discontinuation in percent is on the y-axis. Cumulative incidence in BC at 1 month is 11.2% (95% CI 5.7%-18.8%), at 2 months is 16.4% (9.4%-25.1%), at 3 months is 27.5% (95% CI 18.1%-37.8%), at 6 months is 54.9% (95% CI 41.9%-66.0%), at 9 months is 58.9% (95% CI 45.5%-70.0%) and at 12 months 58.9% (95% CI 45.5%-70.0%).

Figure 17. Kaplan-Meier curve for overall survival in the British Columbia cohort

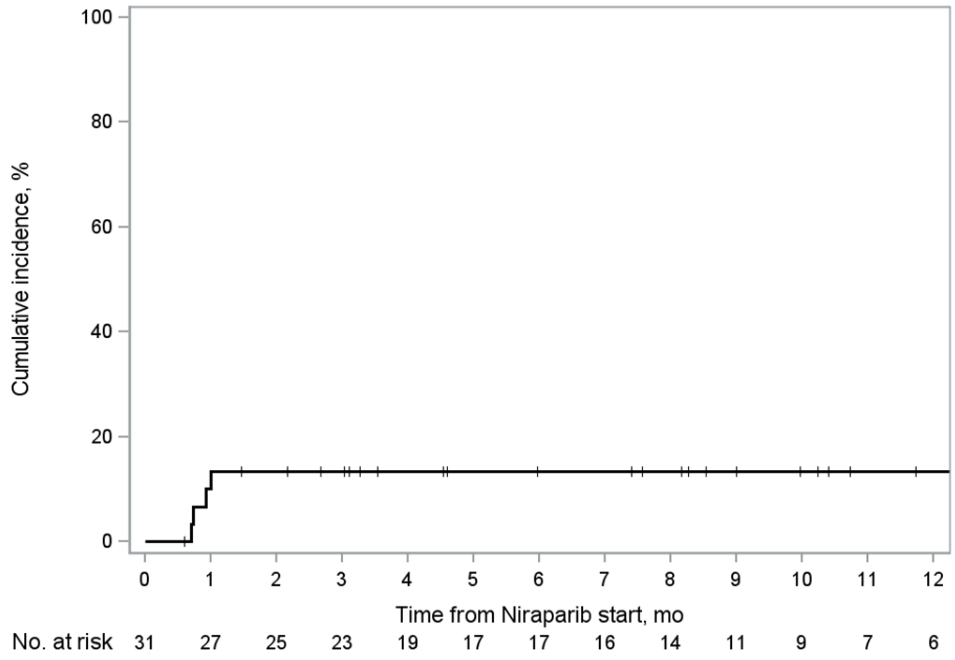


Overall Survival

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
100.0%	98.7%	98.7%	93.9%	88.6%	85.6%
(100.0%-100.0%)	(91.4%-99.8%)	(91.4% -99.8%)	(84.3% -97.7%)	(77.4% -94.4%)	(72.6% -92.8%)

Alt text: Kaplan-Meier curve for overall survival in the BC cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability overall survival in percent is on the y-axis. Overall survival in BC at 1 month is 100% (95% CI 100%-100%), at 2 months is 98.7% (95% CI 91.4%-99.8%), at 3 months is 98.7% (95% CI 91.4%-99.8%), at 6 months is 93.9% (95% CI 84.3%-97.7%), at 9 months is 88.6% (95% CI 77.4%-94.4%) and at 12 months 85.6% (95% CI 72.6%-92.8%).

Figure 18. Cumulative incidence of grade 3/4 thrombocytopenia in the Quebec cohort

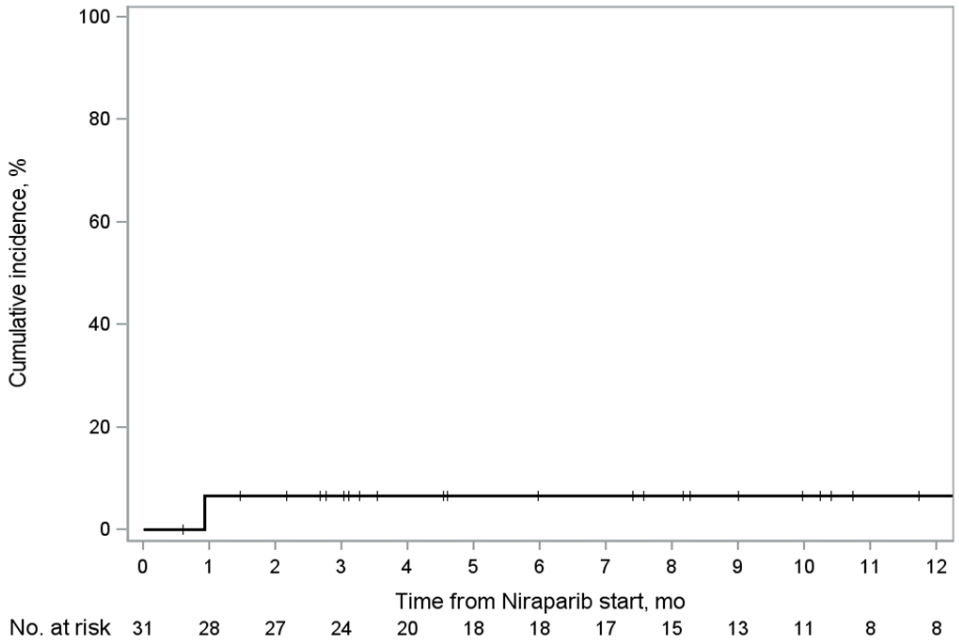


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
13.3% (4.1%-28.1%)	13.3% (4.1%-28.1%)	13.3% (4.1%-28.1%)	13.3% (4.1%-28.1%)	13.3% (4.1%-28.1%)	13.3% (4.1%-28.1%)

Alt text: Cumulative incidence of grade 3/4 thrombocytopenia in the Quebec cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 thrombocytopenia in percent is on the y-axis. Cumulative incidence in Quebec at 1 month is 13.3% (95% CI 4.1%-28.1%), at 2 months is 13.3% (95% CI 4.1%-28.1%), at 3 months is 13.3% (95% CI 4.1%-28.1%), at 6 months is 13.3% (95% CI 4.1%-28.1%), at 9 months is 13.3% (95% CI 4.1%-28.1%) and at 12 months 13.3% (95% CI 4.1%-28.1%).

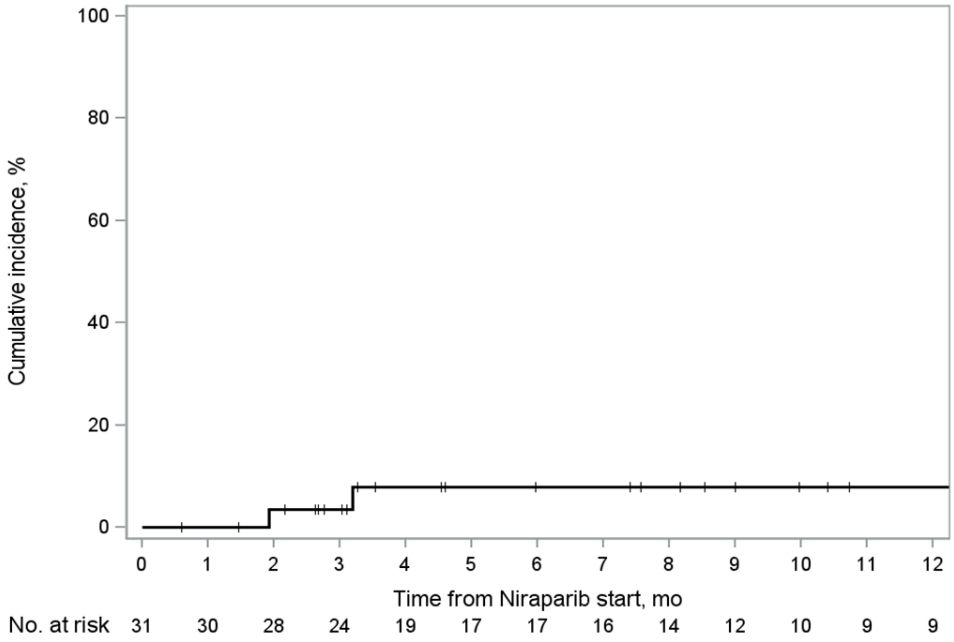
Figure 19. Cumulative incidence of grade 3/4 neutropenia in the Quebec cohort



Cumulative Incidence					
1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
6.7% (1.1%-19.4%)	6.7% (1.1%-19.4%)	6.7% (1.1%-19.4%)	6.7% (1.1%-19.4%)	6.7% (1.1%-19.4%)	6.7% (1.1%-19.4%)

Alt text: Cumulative incidence of grade 3/4 neutropenia in the Quebec cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 neutropenia in percent is on the y-axis. Cumulative incidence in Quebec at 1 month is 6.7% (95% CI 1.1%-19.4%), at 2 months is 6.7% (95% CI 1.1%-19.4%), at 3 months is 6.7% (95% CI 1.1%-19.4%), at 6 months is 6.7% (95% CI 1.1%-19.4%), at 9 months is 6.7% (95% CI 1.1%-19.4%) and at 12 months 6.7% (95% CI 1.1%-19.4%).

Figure 20. Cumulative incidence of grade 3/4 anemia in the Quebec cohort

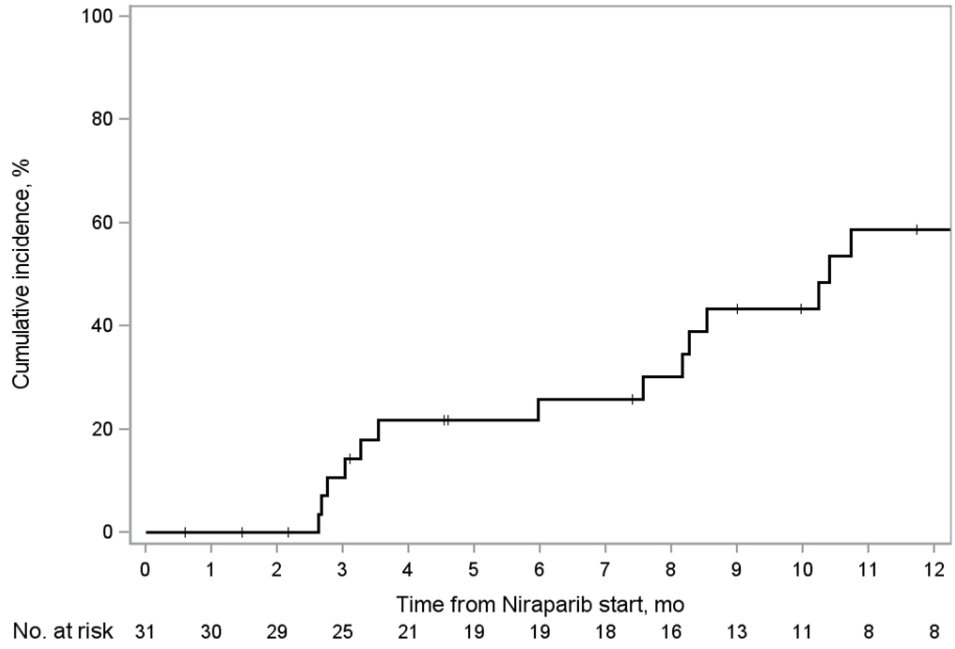


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
0%	3.4% (0.2%-15.2%)	3.4% (0.2%-15.2%)	7.8% (1.3%-22.6%)	7.8% (1.3%-22.6%)	7.8% (1.3%-22.6%)

Alt text: Cumulative incidence of grade 3/4 anemia in the Quebec cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of grade 3/4 anemia in percent is on the y-axis. Cumulative incidence in Quebec at 1 month is 0%, at 2 months is 3.4% (95% CI 0.2%-15.2%), at 3 months is 3.4% (95% CI 0.2%-15.2%), at 6 months is 7.8% (95% CI 1.3%-22.6%), at 9 months is 7.8% (95% CI 1.3%-22.6%) and at 12 months 7.8% (95% CI 1.3%-22.6%).

Figure 21. Cumulative incidence of niraparib discontinuation in the Quebec cohort

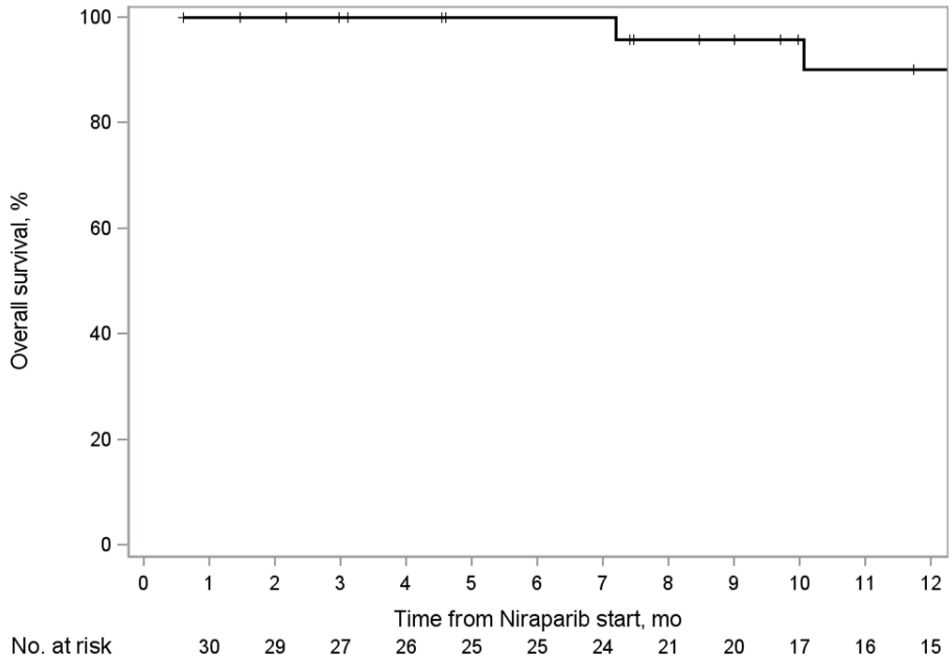


Cumulative Incidence

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
0%	0%	10.7% (2.6%-25.4%)	25.9% (11.1%-43.5%)	43.3% (23.2%-61.9%)	58.8% (34.7%-76.6%)

Alt text: Cumulative incidence of discontinuation in the Quebec cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability of discontinuation in percent is on the y-axis. Cumulative incidence in Quebec at 1 month is 0%, at 2 months is 0%, at 3 months is 10.7% (95% CI 2.6%-25.4%), at 6 months is 25.9% (95% CI 11.1%-43.5%), at 9 months is 43.3% (95% CI 23.2%-61.9%) and at 12 months 58.8% (95% CI 34.7%-76.6%).

Figure 22. Kaplan-Meier curve for overall survival in the Quebec cohort



Overall Survival

1 Month	2 Months	3 Months	6 Months	9 Months	12 Months
100.0% (100.0%-100.0%)	100.0% (100.0%-100.0%)	100.0% (100.0%-100.0%)	100.0% (100.0%-100.0%)	95.8% (88.2%-100.0%)	90.2% (78.0%-100.0%)

Alt text: Kaplan-Meier curve for overall survival in the Quebec cohort over the course of 12 months starting at index date (date of niraparib maintenance treatment start). Time is in months on the x-axis, and probability overall survival in percent is on the y-axis. Overall survival in Quebec at 1 month is 100% (95% CI 100%-100%), at 2 months is 100% (95% CI 100%-100%), at 3 months is 100% (95% CI 100%-100%), at 6 months is 100% (95% CI 100%-100%), at 9 months is 95.8% (95% CI 88.2%-100%) and at 12 months 90.2% (95% CI 78%-100%).

Appendix 3: Summary Clinical Trial Results

Table 10. Summary table of hematological adverse event results from seminal clinical trials

Adverse Event	PRIMA Trial	NOVA Trial	NORA Trial
Thrombocytopenia (grade 3/4)	28.7%	33.8%	11.3%
Neutropenia (grade 3/4)	12.8%	19.6%	20.3%
Anemia (grade 3/4)	31.0%	25.3%	14.7%