Observational Study

The Safety of Niraparib in Ovarian Cancer

Protocol

CoLab

Table of Contents

Project Team

Canadian Cancer Real-World Evaluation Team

Ontario

Platform Lead — Kelvin KW Chan
Site Lead — Mina Tadrous
Platform Manager — Katharina Forster
Operations Lead — Samara Strub
Team Lead-Decision Scientist — Qi Guan
Senior Analyst — Suriya Aktar

Alberta

Site Lead — Winson Y Cheung
Program Manager — Christie Farrer Rogers
Analyst — Mariet Mathew Stephen

British Columbia

Site Lead — Stuart Peacock
Health Data Research Network Liaison — Kimberlyn McGrail
Analyst — Reka Pataky

Exactis Innovation Team

Quebec

Analyst — Maud Marques
Analyst — Karen Gambaro
PMT Manager — Rosa Christodoulopoulos
Data Manager — Cyrielle Beaubois

Post-Market Drug Evaluation Staff

Director — Tarry Ahuja
Program Development Officer — Louis de Léséleuc
Scientific Advisor — David Stock

Abbreviations

CCRE	Canadian Cancer Real-World Evaluation
HR	homologous recombination
HRD	Homologous Recombination Deficiency
PARP	poly-(adenosine diphosphate [ADP]-ribose) polymerase

Amendments and Updates

Table 1: Protocol Version Tracking

Final version	Version date	Location	Amendment description and rationale
V2	June 8, 2023	Study variables	• Clarified definitions for exploratory variables, removed dose outcome variables • Performed by Qi Guan • Amendment to version 1
V3	August 1, 2023	Study variables	• Updated heme laboratory value units for thrombocytopenia, anemia, and neutropenia to SI units (no change in variable categories, just a conversion to SI units) • Updated details on CIF curves (death as competing risk) • Updated detail on categorizing initial dose (round to the nearest 100 mg, 200 mg, or 300 mg) • Performed by Qi Guan • Amendment to version 2
V4	August 2, 2023	Study variables	• Added the number of days between last date of platinum-based chemotherapy and index date • Altered the format of reporting for niraparib discontinuation — median

Final version	Version date	Location	Amendment description and rationale
			time to discontinuation was used instead of reporting a binary variable • Performed by Qi Guan • Amendment to version 3
V5	September 15, 2023	Study variables	• Added discontinuation (plus 60 days washout period) to cumulative incidence curves as a competing risk for all provinces • Update heme toxicities to only include events that happen while on treatment (i.e., before discontinuation date plus 60 days washout) for all provinces • Performed by Qi Guan • Amendment to version 4

CIF = cumulative incidence function; SI = International System of Units.

Abstract

Niraparib is a poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitor that was recently introduced into public formularies in Canada as a maintenance treatment for ovarian cancer among patients who respond to platinum-based chemotherapy. PARP inhibitors have demonstrated high rates of hematological toxicity in clinical trials; therefore, the Canadian Cancer Real-world Evaluation (CCRE) Platform was tasked by CADTH to examine niraparib's safety profile in the real-world setting.

We will conduct a population-based, retrospective cohort study using data from 4 provinces: Ontario, Alberta, British Columbia, and Quebec. Our cohort will consist of adults undergoing maintenance treatment for newly diagnosed or recurrent ovarian cancer using niraparib between June 2019 and December 2022. We will describe the cohort's baseline clinical and demographic characteristics and identify the first instance of thrombocytopenia, neutropenia, and anemia during treatment using administrative data in Ontario, a combination of administrative data and electronic medical records in British Columbia and Alberta, and registry data in Quebec from the Personalize My Treatment Registry. We will summarize baseline characteristics using descriptive statistics and reported outcomes using cumulative incidence in the presence of competing risks.

Background and Rationale

Ovarian cancer may present in the ovaries, the fallopian tubes, or the peritoneum. Epithelial ovarian cancer is the most common, accounting for 90% of cases[1,2] and most females will present with advanced disease.[3] In Canada, the 5-year survival for ovarian cancer is 45%.[4] In 2022, it is estimated that 2,500 females will be diagnosed with ovarian cancer and 2,400 will die from it.[5] Risk factors include older age, genetics (for example *BRCA* mutation is present in 15% to 18% of females with advanced disease[3]), family history of ovarian cancer, obesity, smoking, and endometriosis.[6]

Epithelial ovarian cancer is classified in multiple epithelial subtypes, the most common being high-grade serous.[1,2] Approximately 50% of patients with ovarian cancer are classified as homologous recombination (HR) deficient,[7] which is a mutation present within the tumour cells.[8] Of those who are HR deficient (HRD), 25% will have the *BRCA1* or *BRCA2* mutation.[8] Patients with *BRCA1* or *BRCA2* mutated tumours have a better prognosis than those with *BRCA* wild type tumours (tumours without the *BRCA* mutation).[9]

Niraparib is a PARP inhibitor with efficacy as a first-line treatment and for recurrent disease. Patients with a *BRCA1* or *BRCA2* mutation are most likely to benefit, followed by those with HRD positive and *BRCA* wild type cancers. Minimal benefit is seen in tumours in patients who are HR proficient (HRD negative).[9] Adverse events such as nausea, vomiting, fatigue, anemia, thrombocytopenia, neutropenia, insomnia, hypertension, tachycardia, and palpitations have been reported by patients taking niraparib.[10]

Policy Issue

Niraparib is administered as maintenance treatment (first line or after platinum-based chemotherapy) for recurrent ovarian, fallopian tube, or primary peritoneal cancer, regardless of *BRCA* mutation or HRD status.

For both CADTH reimbursement reviews, clinicians raised concerns with including patients with *BRCA* wild type or who are HRD positive in the recommendations. This was based on the potential significant toxicity and high cost of the drug, as well as its perceived low efficacy in these groups.

A systematic review of 3 phase III trials (NOVA, PRIMA, and NORA), including 1,539 females with endothelial cell ovarian cancer who completed and responded to platinum-based chemotherapy, concluded that niraparib management was efficacious (longer progression-free survival in treatment arms compared to placebo) and relatively well tolerated.[11] In the included metanalysis of adverse events, statistically significantly more frequent events in the treatment arm comprised the hematological toxicities of thrombocytopenia, anemia, and neutropenia, as well as the gastrointestinal toxicities of nausea, vomiting, and constipation were reported. Fatigue, insomnia, and headache were also

statistically significantly more likely in patients receiving maintenance niraparib. Other identified adverse events from treatment arms in individual trials were found to be more likely to occur in the placebo arm in the metanalysis combining all 3 trials. The authors additionally noted a high degree of heterogeneity across the 3 trials for many adverse effects. Notably, although more severe (grade 3 or 4; i.e., medically significant or life threatening or disabling) adverse effects were less common, patients in the treatment arms were 35 times more likely to present with grade 3 or 4 thrombocytopenia and at 13 times higher risk of grade 3 or 4 anemia.[11] Due to the heterogeneity and much greater risk of select severe adverse events identified from these trials, real-world data on safety is warranted.

Policy Question

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

Policy Impact

The findings of the query will be used to support a risk-benefit analysis of the use of niraparib in patients with ovarian cancer given the reported toxicity.

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?

Objectives

Table 2: Objective 1

Criteria	Description
Objective	To characterize the patient population receiving niraparib
Hypothesis	We hypothesize that the cohort baseline characteristics will differ by province (Ontario, Alberta, BC, Quebec)
Population	Individuals 18 years and older who start niraparib for the maintenance treatment of newly diagnosed or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
Exposure	Treatment with publicly funded niraparib (DIN: 02489783)
Comparator	NA (This is a single-arm population-based cohort study.)

Criteria	Description
Outcome and/or end point	Descriptive — clinical and demographic characteristics
Time	December 1, 2021 — December 31, 2022 (BC) January 1, 2022 — December 31, 2022 (Alberta) June 27, 2019 — December 31, 2022 (Ontario) January 1, 2020 — December 31, 2022 (Quebec) Patients are followed until death, end treatment (+90 days), or end of study period (December 31, 2022).
Intercurrent events	NA
Setting	The care settings relevant to this study are outpatient, ambulatory, emergency department, and inpatient.
Main measure of effect	Proportion of cohort receiving niraparib

BC = British Columbia; DIN = Drug Identification Number; NA = not applicable.

Table 3: Objective 2

Criteria	Description
Objective	To determine the proportion of patients receiving niraparib who experience adverse events in the real-world setting
Hypothesis	We hypothesize that proportions of hematological toxicities in our cohorts (in the real world) will be higher than those of the seminal trials conducted
Population	Individuals 18 years and older who start niraparib for the maintenance treatment of newly diagnosed or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
Exposure	Treatment with publicly funded niraparib (DIN: 02489783)
Comparator	NA (This is a single-arm population-based cohort study.)
Outcome and/or end point	Primary: grade 3 and 4 hematological toxicities (thrombocytopenia, neutropenia, and anemia) Secondary: febrile neutropenia, platelet transfusion, red blood cell transfusion, emergency department visits, unplanned hospitalizations, incident hypertension, overall survival, and niraparib treatment discontinuation
Time	December 1, 2021 — December 31, 2022 (BC) January 1, 2022 — December 31, 2022 (Alberta) June 27, 2019 — December 31, 2022 (Ontario) January 1, 2020 — December 31, 2022 (Quebec) Patients are followed until death, end treatment (+90 days), or end of study period (December 31, 2022).

Criteria	Description
Intercurrent events	Competing risks such as niraparib treatment discontinuation and death during the observation period for adverse events
Setting	The care settings relevant to this study are outpatient, ambulatory, emergency department, and inpatient.
Main measure of effect	Proportion of cohort with the outcomes of interest

BC = British Columbia; DIN = Drug Identification Number; NA = not applicable.

Research Methods

Study Design

The study design was a retrospective single-arm population-based cohort study.

Figure 1: Study Design Diagram

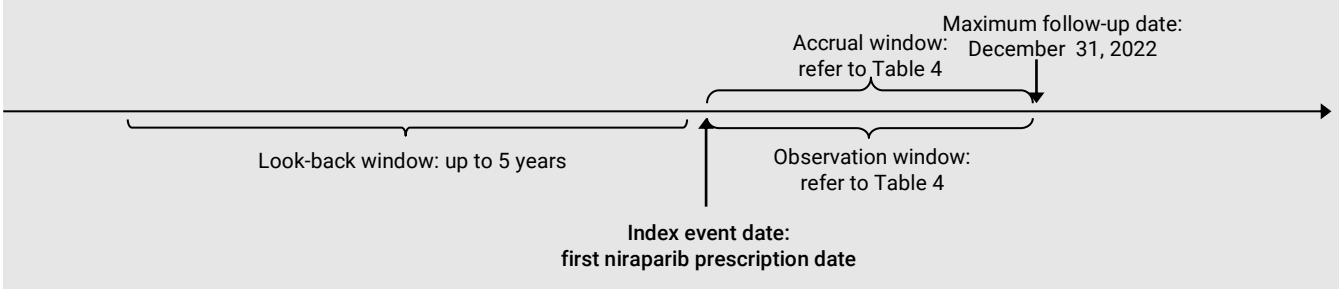

Table 4: Key Dates for Study Design by Province

Study design details	Key dates			
	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 is June 27, 2019	Earliest is January 1, 2022	Earliest is December 1, 2021	Earliest is January 25, 2021
Look-back 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 the index date and December 31, 2022			
Maximum follow-up date	December 31, 2022			

Study Population and Setting

Table 5: Study Population

Term	Criteria	Definition
Index date (and rationale)	The index date in this study will be the first date of niraparib dispensing. This date was chosen because the objective of this study is to characterize patients who receive niraparib treatment and to determine the proportion of them who experience adverse events. Therefore, it is pertinent for the patients of this study to enter the cohort on the first day they receive niraparib treatment.	
Ontario cohort	Inclusion criteria	The cohort will consist of patients with ovarian cancer in Ontario who received publicly funded maintenance treatment with niraparib following completion of chemotherapy treatment. This will include those who started treatment on public drug funding as well as those who started treatment on compassionate funding and then transitioned to public drug funding once the policy was implemented. The follow are steps for cohort creation: **Step A:** Identify patients (and their treatment start dates) in the ODB Database (public drug funding database). • Identify patients from ODB who received niraparib (DIN = 02489783) between January 1, 2022n and December 31, 2022. **Step B:** Identify patients (and their treatment start dates) using the ALR database to identify patients who may have started niraparib before it was added to the public drug formulary. • Identify patients from the systemic ALR who received niraparib using DIN = 02489783 between June 27, 2019, and December 31, 2022. **Step C:** Merge ODB and ALR patient groups, flag patients who were only identified in the ALR group (likely patients on compassionate funding who did not transition into publicly funded niraparib). • Exclude any patients from Step A or B with abnormal morphology code (morphology codes typically not used for ovarian cancer, determined based on clinical expert input). **Step D (final cohort):** Remove patients who only show up in the ALR group to obtain a final cohort of patients who started on publicly funded niraparib or compassionate funding and then transitioned to publicly funded niraparib.

Term	Criteria	Definition
	Exclusion criteria	1. Invalid patient identification number 2. Invalid death date (death before index date; RPDB) 3. Invalid sex (i.e., sex = M or missing; RPDB) 4. Non-Ontario resident status on index date
	Anticipated sample size	300
Alberta cohort	Inclusion criteria	The cohort will consist of patients with ovarian cancer in Alberta who received maintenance treatment with publicly funded niraparib following completion of chemotherapy treatment. This will include those who started treatment on public drug funding as well as those who started treatment on compassionate funding and then transitioned to public drug funding once the policy was implemented. The follow are steps for cohort creation: **Step A:** Extract list of patients treated with niraparib. • Obtain list of patients newly exposed to niraparib between January 1, 2022, and December 31, 2022. • Narrow list of patients to those also exposed to ovarian cancer–specific chemotherapy prior to receipt of niraparib. **Step B:** Verify patients who were diagnosed with ovarian cancer. • Based on sample size, corroborate with patient records to confirm that there was a preceding ovarian cancer diagnosis before niraparib treatment. • If available, corroboration may be done with the use of the cancer registry.
	Exclusion criteria	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
	Anticipated sample size	50 to 75
British Columbia cohort	Inclusion criteria	The cohort will consist of patients with ovarian cancer in BC who have been referred to BC Cancer for treatment, and who received maintenance treatment with niraparib following completion of chemotherapy treatment. In BC, requests for niraparib must be approved by the BC Cancer CAP. The follow are steps for cohort creation: **Step A:** Pull BC Cancer Systemic Therapy Program patient list.

Term	Criteria	Definition
		• Obtain list of unique patient IDs (BC Cancer Agency ID) from Pharmacy for patients with dispensed prescription for niraparib. • Limit to dispensing date between December 1, 2021, and December 31, 2022. **Step B:** Verify ovarian cancer diagnosis and referral status. • Link patient IDs to BC Cancer Registry. • Limit to patients with a confirmed diagnosis of primary ovarian, fallopian tube, or peritoneal cancer, and referred to BC Cancer. **Step C:** Verify dispensing date. • From dispensing records and notes in BC Cancer EMR, verify first dispensing date of niraparib for each patient. • Limit cohort to patients with first dispensing date between December 1, 2021, and December 31, 2022.
	Exclusion criteria	1. Invalid patient identification number 2. Not referred to BC Cancer (not in EMR) 3. Invalid death date (death before index date) 4. Non-BC resident on index date
	Anticipated sample size	40
Quebec cohort	Inclusion criteria	The cohort will consist of patients with ovarian cancer who received maintenance treatment with niraparib following completion of chemotherapy treatment. The follow are steps for cohort creation: 1. Pull patient list. 2. Obtain list of unique patient IDs (PMT ID) from the PMT registry. 3. Limit to treatment date start between January 1, 2020, and December 31, 2022.
	Exclusion criteria	1. Invalid death date (death before index date) 2. Invalid treatment date (incomplete date) 3. Patient receiving Niraparib in the context of a clinical trial
	Anticipated sample size	40

ALR = activity-level reporting; BC = British Columbia; CAP = BC Cancer Compassionate Access Program; DIN = Drug Identification Number; EMR = electronic medica record; ODB = Ontario Drug Benefit; PMT = Personalize My Treatment; RPDB = Registered Persons Database.

Study Variables

Table 6: Baseline Variables

Variable	Variable definition	Variable output
Age on index date	**Definition:** Mean of age in years **Assessment period:** Index date **Database:** RPDB (Ontario), EMRs (Alberta, BC, and Quebec)	1 continuous variable
Age on index date	**Definition:** Age categorized as greater than or equal to 65 years and younger than 65 years **Assessment period:** Index date **Database:** RPDB (Ontario), EMRs (Alberta, BC, and Quebec)	1 categorical variable
Rurality	**Definition:** Residential geography variable **Assessment period:** Index date **Database:** RPDB (Ontario), EMRs (Alberta and BC)	1 categorical variable
Marginalization index score	**Definition:** • Material deprivation in ON-Marg (Ontario) • CAN-Marg summary score (BC) **Assessment period:** Index date **Database:** ON-Marg (Ontario), CAN-Marg (BC)	1 categorical variable. • reported in quintiles from 1 to 5 (1 meaning least marginalized and 5 meaning most marginalized, missing)
Income quintile	**Definition:** Income variable based on residential geography **Assessment period:** Index date **Database:** RPDB (Ontario), postal code linkage (BC), census tract (Alberta)	1 categorical variable with 6 quintiles (1 meaning lowest and 5 meaning highest, missing)
Charlson comorbidity index	**Definition:** • Charlson program (Ontario and Alberta) • Excluded incident cancer and metastatic cancer comorbidities from calculations **Assessment period:** 2 years before index date **Database:** CIHI DAD, CIHI SDS (Ontario and Alberta)	1 categorical variable with 4 levels. • reported as categories from 0 (no previous hospitalization) to 3+

Variable	Variable definition	Variable output
Prior hypertension	**Definition:** • 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 **Assessment period:** 2 years before index date **Database:** CIHI DAD and OHIP (Ontario), CIHI DAD and EMRs (Alberta and Quebec) **Source:** Validation of a Case Definition to Define Hypertension Using Administrative Data	1 binary variable • flagged as 1 if patient has a diagnosis of hypertension during the look-back period
Year of cancer diagnosis	**Definition:** Year of ovarian cancer diagnosis **Assessment period:** Look-back window **Database:** OCR (Ontario), EMRs (Alberta, BC, and Quebec)	1 categorical variable (each province may have a different number of levels depending on the patient population)
Cancer stage	**Definition:** • Best cancer stage (OCR for Ontario) • Cancer stage listed in EMRs (BC, Alberta, Quebec) **Assessment period:** Look-back window **Database:** OCR (Ontario), EMRs (Alberta, BC, and Quebec)	1 categorical variable with 4 levels
Year of niraparib treatment start	**Definition:** Year of Niraparib treatment start **Assessment period:** Index date **Database:** ODB (Ontario), PIN (Alberta), EMRs (BC and Quebec)	1 categorical variable with 2 levels
Primary tumour location	**Definition:** Primary tumour topography ICD-10 codes (Ontario) • C569 (ovary) • C570 (fallopian tube) • All other codes (others)	1 categorical variable with 3 levels (i.e., ovary, fallopian, others) • Based on feasibility analyses conducted by the Ontario site, it is possible that this variable

Variable	Variable definition	Variable output
	Primary tumour location in EMR (Alberta, BC, and Quebec) **Assessment period:** Index date **Database:** OCR (Ontario), EMR (Alberta, BC, and Quebec)	may be susceptible to small-cell suppression.
Tumour histology	**Definition:** Tumour histology based on morphology codes (Ontario) • 84413, 84603, 84613 (serous) • 83803 (endometrioid) • All other codes (other) Tumour histology in EMRs (Alberta, BC, Quebec) **Assessment period:** Index date **Database:** OCR (Ontario), EMR (Alberta, BC, and Quebec)	1 categorical variable with 3 levels (i.e., serious, endometrioid, others) • Based on feasibility analyses conducted by the Ontario site, it is possible that this variable may be susceptible to small-cell suppression.
Presence of cancer antigen-125	**Definition:** Presence of CA-125 > 35 units/mL (Alberta, BC, Quebec) **Assessment period:** Between diagnosis date and index date **Database:** OLIS (Ontario), EMR (Alberta, BC, Quebec)	1 binary variable to identify a level of CA-125 > 35 units/mL
Prior platinum-based chemotherapy	**Definition:** Carboplatin or cisplatin administered **Assessment period:** Between diagnosis date and index date **Database:** ALR, NDFP (Ontario), EMRs (Alberta and BC), EMRs (Quebec)	1 binary variable • flagged as 1 if patient received prior platinum-based chemotherapy between diagnosis date and index date
Mean number of cycles of prior platinum-based chemotherapy	**Definition:** Mean of the number of prior cycles of platinum-based chemo (cisplatin or carboplatin), defined as number of dispensing days (each dispensing day is 1 cycle) **Assessment period:** Between diagnosis date and index date	1 continuous variable

Variable	Variable definition	Variable output
	Database: ALR, NDFP (Ontario), EMRs (Alberta and BC), EMRs (Quebec)	
Mean number of days between last platinum-based chemotherapy and index date	**Definition:** Mean number of days between the date of last platinum-based chemotherapy on or after the niraparib funding date in each jurisdiction and index date **Assessment period:** Between diagnosis date and index date **Database:** ALR and ODB (Ontario), EMRs (Alberta, BC, Quebec)	1 continuous variable

Initial daily dose of niraparib	**Definition:**
	• Ontario:
	  ○ For each patient, the daily dose in mg for the initial niraparib prescription using the following formula:
	  ▪ daily dose = (quantity/days supply) × 100 mg
	• Alberta, BC, Quebec:
	  ○ For each patient, initial daily dose in EMRs
	Assessment period: Index date
	
	Databases: ODB (Ontario), PIN and EMRs (Alberta), BC Cancer pharmacy records and EMRs (BC), EMRs (Quebec)
		1 categorical variable
		• If there are daily doses that are not 100 mg, 200 mg, or 300 mg, then rounded to the nearest 100 mg, 200 mg, or 300 mg.

Mean initial daily dose of niraparib	**Definition:** Mean value of the initial daily dose of niraparib
	• Ontario:
	  ○ For each patient, the daily dose in mg for the initial niraparib prescription using the following formula:
	  ▪ daily dose = (quantity/days supply) × 100 mg
	• Alberta, BC, Quebec:
	  ○ For each patient, identify initial daily dose in EMRs
	
	Assessment period: Index date
		1 continuous variable

Variable	Variable definition	Variable output
	Databases: ODB (Ontario), PIN and EMRs (Alberta), BC Cancer pharmacy records and EMRs (BC), EMRs (Quebec)	

ALR = activity-level reporting; CAN-MARG = Canadian Marginalization Index; CIHI = Canadian Institute for Health Information; DAD = Discharge Abstract Database; EMR = electronic medical records; ICD-10 = International Classification of Diseases, 10th edition; NDFP = New Drug Funding Program; OCR = Ontario Cancer Registry; ODB = Ontario Drug Benefit; OHIP = Ontario Health Insurance Plan; OLIS = Ontario Laboratory Information Systems; ON-MARG = Ontario Marginalization Index; PIN = Pharmaceutical Information Network; RPDB = Registered Persons Database; SDS = Same Day Surgery.

Table 7: Outcomes of Interest

Outcome	Variable definition	Variable output
Primary outcome		
Thrombocytopenia	**Definition:** • Grade 1: platelet count between 75 and 150 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 **Assessment period:** Observation window **Database:** OLIS (Ontario), EMRs (BC, Alberta, Quebec) **Definition source:** Common Terminology Criteria for Adverse Events v5.0	2 binary variables and up to 1 date variable. • For each patient, the first instance of the highest grade of thrombocytopenia (3, or 4) that occurs during the observation period flagged as grade 3/4) • For each patient, "any grade" of thrombocytopenia that occurs before death, discontinuation date+60 days, or end of study period • Time to first instance of grade 3 or 4 thrombocytopenia (1 combined event) to plot cumulative incidence curves with death and (discontinuation+60 days) as a competing risk and censoring on end of observation period.
Neutropenia	**Definition:** • 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	2 binary variables and up to 1 date variable. • For each patient, the first instance of the highest grade of neutropenia (3, or 4) that occurs during the observation period flagged as grade 3)

Outcome	Variable definition	Variable output
	• Grade 4: neutrophil count <500/L **Assessment period: O**bservation window **Database:** OLIS (Ontario), EMRs (BC, Alberta, Quebec) **Definition source:** Common Terminology Criteria for Adverse Events v5.0(2)	• For each patient, "any grade" of neutropenia that occurs before death, discontinuation date+60 days, or end of study period • Time to first instance of grade 3 or 4 neutropenia (1 combined event) to plot cumulative incidence curves with death and (discontinuation+60 days) as a competing risk and censoring on end of observation period.
Anemia	**Definition:** • 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 (life-threatening consequences; urgent intervention indicated) **Assessment period:** Observation window **Database:** OLIS (Ontario), EMRs (BC, Alberta, Quebec) **Definition source:** Common Terminology Criteria for Adverse Events v5.0[12]	2 binary variables and up to 1 date variable. • For each patient, the first instance of the highest grade of anemia (3, or 4) that occurs during the observation period flagged as grade 3) • For each patient, "any grade" of anemia that occurs before death, discontinuation date+60 days, or end of study period • Time to first instance of grade 3 or 4 anemia (1 combined event) to plot cumulative incidence curves with death and (discontinuation+60 days) as a competing risk and censoring on end of observation period.
Secondary outcome		
Febrile neutropenia	**Definition (using ICD-10 codes):** D70 (most responsible diagnosis) AND R50.8 or R50.9 (any diagnosis) **Assessment period:** Observation window **Database:** CIHI DAD and CIHI NACRS (Ontario), EMRs (Alberta, Quebec)	1 binary variable • Flagged if patient is diagnosed with febrile neutropenia during the observation period

Outcome	Variable definition	Variable output
	Source: "Can Chemotherapy-Related Acute Care Visits Be Accurately Identified in Administrative Data?"[13]	
Incident hypertension	**Definition:** • 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). NOTE: This outcome is ascertained in a subcohort of individuals who were not previously diagnosed with hypertension **Assessment period:** Observation window **Database:** CIHI DAD and OHIP (Ontario), EMRs (Alberta, Quebec) **Source:** Validation of a Case Definition to Define Hypertension Using Administrative Data[14]	1 binary variable • Among individuals who were not previously diagnosed with hypertension, flagged patient is diagnosed with hypertension during the observation period
Any transfusion	**Definition:** Blood transfusion indicator in CIHI databases **Assessment period:** Observation window **Database:** CIHI DAD and CIHI NACRS (Ontario), EMRs (Alberta, Quebec)	1 binary variable • Flagged if patient received a platelet transfusion during the observation period
Platelet transfusion	**Definition:** Platelet transfusion indicator in CIHI databases **Assessment period:** Observation window **Database:** CIHI DAD and CIHI NACRS (Ontario), EMRs (Alberta, Quebec)	1 binary variable • Flagged if patient received a platelet transfusion during the observation period
Red blood cell transfusion	**Definition:** Red blood cell transfusion indicator in CIHI databases **Assessment period:** Observation window **Database:** CIHI DAD and CIHI NACRS (Ontario), EMRs (Alberta, Quebec)	1 binary variable • Flagged if patient received a red blood cell transfusion during the observation period

Outcome	Variable definition	Variable output
Emergency department visits	**Definition:** Number of patients who had at least 1 unscheduled emergency department visit **Assessment period:** Observation window **Database:** CIHI NACRS (Ontario and Alberta), EMRs (Quebec)	1 binary variable Flagged if patient had emergency visits
Hospitalization (any type)	**Definition:** Number of patients who had at least 1 hospitalization **Assessment period:** Observation window **Database:** CIHI DAD and CIHI SDS (Ontario and Alberta), EMRs (Quebec)	1 binary variable • Flagged if patient was hospitalized for any reason
Hospitalization (unscheduled)	**Definition:** Number of patients with unplanned hospitalizations **Assessment period:** Observation window **Database:** CIHI DAD and CIHI SDS (Ontario and Alberta), EMRs (Quebec)	1 binary variable • Flagged if patient had unscheduled hospitalization

Niraparib treatment discontinuation	**Definition:**
	• Ontario and BC:
	  ○ For the subset of patients with a niraparib supply, identify the last niraparib prescription in the observation window and calculate the last date of treatment (serve date of last prescription plus number of days supply). If there are > 60 days between this date and the end of the observation window, flag as a discontinuation.
	• Alberta and Quebec:
	  ○ Based on treatment discontinuations in EMR data
	
	Assessment period: Observation window
	
	Databases: ODB (Ontario), PIN and EMRs (Alberta), BC Cancer pharmacy records and EMRs (BC), EMRs (Quebec)
		1 continuous variable and 1 date variable
		• Discontinuation date for Ontario/BC listed as the last date of treatment (date of last prescription plus days supplied)
		• Discontinuation date for Alberta and Quebec listed in EMR

Outcome	Variable definition	Variable output
Median follow-up time in days	**Definition:** Median time to death date (event) or maximum follow-up date (censored) **Assessment period:** Observation window **Database:** RPDB (Ontario), EMRs (Alberta, BC, Quebec)	1 continuous variable
Overall survival	**Definition:** Time to death date (event) or maximum follow-up date (censored) **Assessment period:** Observation window **Database:** RPDB (Ontario), EMRs (Alberta, BC, Quebec)	1 date variable

BC = British Columbia; CIHI = Canadian Institute for Health Information; DAD = Discharge Abstract Database; EMR = electronic medical record; ICD-10 = International Classification of Diseases, 10th edition; NACRS = National Ambulatory Care Reporting System; ODB = Ontario Drug Benefits; OHIP = Ontario Health Insurance Plan; OLIS = Ontario Laboratory Information Systems; PIN = Pharmaceutical Information Network; RPDB = Registered Persons Database; SPS = Same Day Surgery.

Data Analysis

Statistical Analysis Plan

Table 8: Descriptive Analyses

Criteria	Description
Hypothesis	We hypothesize that the cohort baseline characteristics will differ by province (Ontario, Alberta, BC, Quebec)
Exposure	Treatment with niraparib (DIN: 02489783)
Measures of interest	Proportion of cohort receiving niraparib
Analytic software	SAS 9.4 (Ontario, BC) R (v.4.2.2 in Alberta and v.4.3.0 in Quebec)
Sampling and weighting	NA
Missing data methods	NA
Bias due to loss to follow-up	NA
Subgroup analyses	NA

BC = British Columbia; DIN = Drug Identification Number; NA = not applicable.

Table 9: Primary and Secondary Analysis

Criteria	Description
Hypothesis	We hypothesize that proportions of hematological toxicities in our cohorts (in the real-world) will be higher than that of the seminal trials conducted.
Exposure	Treatment with niraparib (DIN: 02489783)
Outcomes	Primary and secondary outcomes
Measures of interest	Proportion of cohort with the outcomes of interest
Analytic software	SAS 9.4 (Ontario, BC) R (v.4.2.2 in Alberta and v.4.3.0 in Quebec)
Models	NA (as all analyses are descriptive); we have provided details on the descriptive analyses in the following. **Primary:** For grade 3 or 4 hematological toxicities (thrombocytopenia, neutropenia, anemia) • Determine the proportions • Plot CIF in the presence of death and treatment discontinuation (plus 60 days) as competing risks; time scale in intervals of months with risk set displayed • Calculate cumulative incidences and 95% confidence intervals at 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months, including death and treatment discontinuation (plus 60 days) as a competing risk • Report proportions with mean (± SD) and median (IQR) follow-up time for all primary outcomes **Secondary:** For febrile neutropenia, platelet transfusion, red blood cell transfusion, emergency department visits, unplanned hospitalizations, incident hypertension, overall survival, and niraparib treatment discontinuation • Determine the proportions • Calculate treatment discontinuation cumulative incidences and 95% confidence intervals at 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months • Plot Kaplan-Meier curve for overall survival; time scale in intervals of months with risk set displayed • Calculate overall survival estimates and 95% confidence intervals at 1 month, 2 months, 3 months, 6 months, 9 months, and 12 months • Report proportions with mean (± SD) and median (IQR) follow-up time for all secondary outcomes
Method of confounding adjustment	NA (as all analyses are descriptive)

BC = British Columbia; CIF = Cumulative incidence function; DIN = Drug Identification Number; IQR = interquartile range; NA = not applicable; SD = standard deviation.

Data Sources

Table 10: Data Sources by Province

Province	Data sources
Ontario	**Cohort creation (June 27, 2019 – 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
	  ○ all 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

	Outcomes (during observation window: June 27, 2019 – 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

Province	Data sources
Alberta	**Cohort creation (January 1, 2022 – 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: January 1, 2022 – December 31, 2022): Electronic medical records

British Columbia	**Cohort creation (December 21, 2021 – December 31, 2022):**
	• BC 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: December 1, 2021 – December 31, 2022): • BC Systemic Therapy Program • BC Cancer Registry • Electronic medical records
Quebec	**Cohort creation (January 25, 2021 – December 31, 2022), clinical and/or demographic characteristics (on index date or during look-back period), and select outcomes (January 25, 2021 – 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 – 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 Benefits; OHIP = Ontario Health Insurance Plan; OLIS = Ontario Laboratory Information Systems; PIN = Pharmaceutical Information Network; PMT = Personalize My Treatment; RPDB = Registered Persons Database; SDS = Same Day Surgery.

Data Management

All data used in this study, except those for Quebec, are housed within the local cancer agencies of each CCRE province (Ontario Health, Alberta Health Services, and BC Cancer). Data are managed, stored, and protected under the policies of each health authority. Data for patients in Quebec are accessed via the Personalize My Treatment Registry developed by Exactis Innovation, which includes patient data from one Quebec hospital. Preliminary data analysis for the Quebec cohort are to be performed at Exactis, with aggregate data to be shared with CCRE for the report.

Quality Control

All data used in this study are assessed for reliability during the initial feasibility assessment and protocol development phase of CCRE work to ensure minimal missingness of reported results. Data checkpoints are built into the protocol to ensure that variable definitions are suitable and clinically relevant, and validated definitions of variables are used when available.

Study Size and Feasibility

Table 11: Power to Detect a 10% Increase in Risk in Hematological Toxicities Compared to Results From the PRIMA Trial[4]

Outcome of interest	Province			
	Ontario N = 300	Alberta N = 50 to 75	British Columbia N = 40	Quebec N = 40
Grade 3 or 4 thrombocytopenia NOVA trial proportion: 33.8%[15] PRIMA trial proportion: 28.7%[16]	0.976	0.366 to 0.546	0.366	0.366
Grade 3 or 4 neutropenia NOVA trial proportion: 19.6%[15] PRIMA trial proportion: 12.8%[16]	0.998	0.608 to 0.663	0.43	0.43
Grade 3 or 4 anemia NOVA trial proportion: 25.3%[15] PRIMA trial proportion: 31.0%[16]	0.974	0.384 to 0.521	0.359	0.359

Limitations

There are a number of anticipated limitations in this study. First, data availability varies across all participating provinces; therefore, several key results will not be pooled. However, access to data relevant for this query (i.e., linked data from laboratory tests and hospital visits) is complete in Ontario, which has the largest cohort of patients among the 3 provinces. Additionally, niraparib was added to the public funding programs at the end of 2021. Because of this, patients included in the analysis will have variable follow-up windows (up to 1 year) depending on their treatment start date. However, it is anticipated that most hematological adverse events will occur within the first 3 months of treatment; therefore, it should be possible to capture most of the cohort's hematological toxicities. Finally, CCRE is only accessing records of publicly funded niraparib; therefore, patients who have private insurance or are paying for treatment out of pocket will not be captured. Although this results in a smaller sample size, it should not affect the final proportion estimates for adverse events (and therefore, generalizability to other populations) because differences in accessing regular bloodwork and emergency acute care services are not anticipated between those receiving public drug funding and those who do not.

References

1. Dumitru A, Dobrica EC, Croitoru A, Cretoiu SM, Gaspar BS. Focus on PD-1/PD-L1 as a Therapeutic Target in Ovarian Cancer. *IJMS*. 2022;23(20):12067. doi:10.3390/ijms232012067
2. Nag S, Aggarwal S, Rauthan A, Warrier N. Maintenance therapy for newly diagnosed epithelial ovarian cancer– a review. *J Ovarian Res*. 2022;15(1):88. doi:10.1186/s13048-022-01020-1
3. Guy H, Hawkes C, Walder L, Malinowska IA, Gupta D. Systematic literature review of efficacy and safety of first-line maintenance therapy trials in advanced ovarian cancer. *Future Oncology*. 2022;18(30):3435-3447. doi:10.2217/fon-2022-0578
4. Canadian Cancer Society. Survival statistics for ovarian cancer. Published 2023. Accessed July 23, 2023. https://cancer.ca/en/cancer-information/cancer-types/ovarian/prognosis-and-survival/survival-statistics
5. Canadian Cancer Society. *Cancer-Specific Stats 2022*.; 2022. Accessed July 23, 2023. https://cdn.cancer.ca/-/media/files/research/cancer-statistics/2022-statistics/2022_cancer-specific-stats.pdf
6. Sambasivan S. Epithelial ovarian cancer: Review article. *Cancer Treatment and Research Communications*. 2022;33:100629. doi:10.1016/j.ctarc.2022.100629
7. Colombo N, Sessa C, Du Bois A, et al. ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Annals of Oncology*. 2019;30(5):672-705. doi:10.1093/annonc/mdz062
8. MyChoice® CDx Product Overview. Accessed November 10, 2022. https://myriad.com/oncology/mychoice-cdx/
9. Miller RE, Elyashiv O, El-Shakankery KH, Ledermann JA. Ovarian Cancer Therapy: Homologous Recombination Deficiency as a Predictive Biomarker of Response to PARP Inhibitors. *OTT*. 2022;Volume 15:1105-1117. doi:10.2147/OTT.S272199
10. Xie T, Dickson KA, Yee C, et al. Targeting Homologous Recombination Deficiency in Ovarian Cancer with PARP Inhibitors: Synthetic Lethal Strategies That Impact Overall Survival. *Cancers*. 2022;14(19):4621. doi:10.3390/cancers14194621
11. Pagkali A, Mamais I, Michalinos A, Agouridis AP. Safety Profile of Niraparib as Maintenance Therapy for Ovarian Cancer: A Systematic Review and Meta-Analysis. *Current Oncology*. 2022;29(1):321-336. doi:10.3390/curroncol29010029
12. National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0*.; 2017. Accessed July 23, 2023. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf
13. Krzyzanowska MK, Enright K, Moineddin R, et al. Can Chemotherapy-Related Acute Care Visits Be Accurately Identified in Administrative Data? *JOP*. 2018;14(1):e51-e58. doi:10.1200/JOP.2017.023697
14. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. *Hypertension*. 2009;54(6):1423-1428. doi:10.1161/HYPERTENSIONAHA.109.139279
15. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med*. 2016;375(22):2154-2164. doi:10.1056/NEJMoa1611310
16. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962

Appendix 1: Results Summary Templates

Note that this appendix has not been copy-edited.

Table 12: Study Cohort Baseline Characteristics

Variables	All provinces N= (%)	Ontario N= (%)	Alberta N= (%)	British Columbia N= (%)	Quebec N= (%)
Age on index date					
Mean (± standard deviation)					
≥ 65 years					
Urban Residence					
Marginalization Index Score					
1-least marginalized					
2					
3					
4					
5-most marginalized					
Income Quintile					
1-Lowest					
2					
3					
4					
5-Highest					
Charlson Comorbidity Score					
0					
1					
2					
3+					
No previous hospitalization					
Prior Hypertension					
Year of Cancer Diagnosis					
2018 and earlier					
2019					
2020					
2021					

Variables	All provinces N= (%)	Ontario N= (%)	Alberta N= (%)	British Columbia N= (%)	Quebec N= (%)
2022					
Cancer Stage at Diagnosis					
I-II					
III					
IV					
Missing/Unknown					
Year of Niraparib Treatment					
2020-2021					
2022					
Primary Tumour Location					
Ovary					
Fallopian Tubes					
Other					
Tumour Histology					
Serous					
Endometroid					
Other					
Presence of Cancer Antigen-125 >35 units/mL					
Prior Platinum-Based Chemotherapy					
Mean number of Cycles of Prior Platinum-Based Chemotherapy (± standard deviation)					
Mean Number of Days Between Last Platinum-Based Chemotherapy and Index Date (± standard deviation)					
Initial Daily Dose of Niraparib	100 mg				
	200 mg				
	300 mg				
Mean Initial Daily Dose of Niraparib (± standard deviation)					

Table 13: Hematological Adverse Events

Hematological Adverse Event	All provinces N= (%)		Ontario N= (%)		Alberta N= (%)		British Columbia N= (%)		Quebec N= (%)	
	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										
Neutropenia										
Anemia										

Table 14: Secondary Outcomes

Outcome of interest	All provinces N = (%)	Ontario N = (%)	Alberta N = (%)	British Columbia N = (%)	Quebec N = (%)
Febrile Neutropenia					
Incident Hypertension					
Any transfusion					
Platelet Transfusion					
Red Blood Cell Transfusion					
Emergency Department Visit					
Hospitalization (any type)					
Hospitalization (unscheduled)					
Niraparib Treatment Discontinuation					
Mean Time to Niraparib Treatment Discontinuation in Days (± standard deviation)					
Median Follow-up Time in Days					

Appendix 2: Additional Information

Note that this appendix has not been copy-edited.

Table 15: 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	NA	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.		NA	Ascertained using EMR data during the observation window
	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.			
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

This work was supported by CADTH and its Post-Market Drug Evaluation Program, through funding provided by Health Canada.