CADTH Observational Study

# The Safety of Niraparib in Ovarian Cancer: Draft Project Protocol

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Protocol

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**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

# Table of Contents

## List of Tables



## List of Figures

## Abbreviations

| | |
|---|---|
| **CIHI** | Canadian Institute for Health Information |
| **ED** | emergency department |

# Background

## Ovarian Cancer and Niraparib

Ovarian cancer may present in the ovaries, the fallopian tubes, or the peritoneum. Epithelial ovarian cancer is the most common type, accounting for 90% of cases.[1,2] In Canada, the 5-year survival rate for ovarian cancer is 45%.[3]

Niraparib is a poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitor. It is used as a maintenance treatment after platinum-based chemotherapy for ovarian, fallopian tube, or primary peritoneal cancer in the first line, as well as the recurrent setting.

# Rationale

Clinicians have raised concern about the safety and tolerability of niraparib in treating certain patient populations with ovarian cancer.

A systematic review of 3 phase III trials (NOVA, PRIMA, and NORA) concluded that disease management with niraparib after platinum-based chemotherapy was effective (offered longer progression-free survival) and relatively well tolerated.[4] The review included 1,539 women with endothelial ovarian cancer. Those receiving niraparib had significantly more frequent hematological toxicities (thrombocytopenia, anemia, and neutropenia) and significantly more gastrointestinal toxicities (nausea, vomiting, and constipation). Fatigue, insomnia, and headache were also more likely in patients receiving niraparib. Other adverse events were found to be more common in those not receiving niraparib. The authors noted that the adverse events differed across all 3 trials.

Real-world evidence on safety is warranted because of the differences observed and because of the higher risk of select severe adverse events from these trials. This evidence will help to identify if the safety profile of niraparib in real-world patient populations with ovarian cancer is significantly different from findings reported in these clinical trials.

# Policy Question

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

# Policy Impact

The findings will assist decision-making when considering niraparib for managing ovarian cancer.

# 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

There are 3 objectives for this study:

- to characterize the patient population receiving niraparib maintenance treatment (following chemotherapy) for epithelial ovarian, fallopian tube, or primary peritoneal cancer in the first line and recurrent settings
- to determine the proportions of these patients who experience grade 3 and grade 4 hematological adverse outcomes (i.e., thrombocytopenia, neutropenia, and anemia)
- to determine the proportions of these patients with onset of secondary adverse outcomes (i.e., febrile neutropenia, incident hypertension, transfusions, overall survival, niraparib treatment interruption, and emergency department [ED] visits).

# Deliverables

The following deliverables are planned:

- protocol
- scientific report
- summary and/or visual tool to aid knowledge dissemination.

# Methods

## Population

Individuals aged 18 years and older who start niraparib for the maintenance treatment of newly diagnosed or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in 4 participating provinces: Ontario, Quebec, Alberta, and British Columbia.

## Study Design

- A cohort design, done in parallel across the 4 provinces (refer to Appendix 1 for study design figures).
- The accrual periods to capture individuals starting niraparib are June 27, 2019, to December 31, 2022, for Ontario; January 1, 2020, to December 31, 2022, for Quebec; January 1, 2022, to December 31, 2022, for Alberta; and December 1, 2021, to December 31, 2022, for British Columbia.

- The follow-up period (i.e., eligibility for adverse outcomes) ends December 31, 2022, in all provinces.

## Inclusion Criteria

Patients who start maintenance treatment with niraparib after chemotherapy, including those who started treatment via public and/or compassionate funding programs, and then transitioned to public funding programs (e.g., Ontario Drug Benefit Program).

## Data Sources

The 4 participating provinces will access administrative data and/or electronic medical records, where available:

- provincial public health insurance databases for eligibility and demographic data (Alberta, British Columbia, Ontario)
- provincial cancer registries for eligibility criteria and covariate status (Alberta, British Columbia, Ontario)
- provincial drug dispensation databases (public insurance and compassionate cancer treatment funding sources) for exposure and covariate status (Alberta, British Columbia, Ontario)
- Canadian Institute for Health Information (CIHI) inpatient hospital discharge abstract (ED visit and day surgery records) to determine covariates and outcomes (Alberta and Ontario)
- electronic medical records to determine covariates and outcomes (Alberta, British Columbia, Quebec)
- laboratory data to determine outcomes (Ontario and British Columbia*).

The ability to derive covariates and outcome measures from these data will vary by province.

*Note: British Columbia will have laboratory data available through electronic medical records for the majority of its cohort.

## Exposure

The observation window is from treatment start until December 31, 2022 (maximum follow-up date due to data availability), treatment discontinuation, or death, whichever comes first.

## Outcomes of Interest

### Primary Study End Point

- Grade 3 and grade 4 hematological toxicities (thrombocytopenia, neutropenia, and anemia) defined (when data availability permits) using blood cell count thresholds from the Common Terminology Criteria for Adverse Events.[5]

Rationale: Patients who start niraparib are monitored closely with frequent outpatient bloodwork because of the potential risk of severe hematological toxicities. Interventions such as blood transfusions or changes to niraparib treatment (e.g., dose reduction, pause, or discontinuation) may be used when blood cell counts meet adverse event thresholds. This is done to avoid complications that may lead to health care encounters such as ED visits and/or hospitalization. We will use blood cell counts from lab test records (where available) to ensure we capture all instances of hematological adverse events. The seminal niraparib phase III trials defined hematological adverse events using blood cell counts. Given that the purpose of this query is to generate real-world evidence to compare to trial results, it is important to define outcomes in a similar manner.

### Secondary Study End Points

We will report on a number of secondary study end points to further characterize the safety of niraparib. The reporting of these end points will depend on data availability in each province. These end points include:

- febrile neutropenia
- any blood transfusion, platelet transfusion, or red blood cell transfusion
- ED visits; unplanned hospitalization
- overall survival
- niraparib treatment interruption
- incident hypertension.

## Analyses Overview

We will use descriptive statistics to characterize the baseline patient cohort in each of the 4 provinces. We will report the proportion of patients who experience adverse events including hematological toxicities, hospital visits, ED visits, and unplanned hospitalizations. We will also show overall survival as well as treatment disruption (including dose decrease, treatment pause, and discontinuation). When data permits, we will pool results between provinces using a random-effects, variance-weighted meta-analysis.

## Limitations

There are 3 anticipated limitations in this study:

- Data availability varies across the 4 provinces. All estimated statistics cannot be pooled because of this variation. However, access to data relevant for this query (i.e., linked data from lab tests and hospital visits) is complete in Ontario, which has the largest cohort of patients across the 4 provinces.
- Niraparib was added to Canadian public funding programs at the end of 2021, restricting follow-up and potentially limiting ability to fully characterize adverse outcome burden. Patients included

in the analysis will have variable follow-up windows depending on their treatment start date. However, it is expected that most hematological adverse events occur within the first 3 months of treatment. As such, we expect to be able to estimate the main outcome (i.e., hematological toxicities) for the majority of the study cohort.

- We are mainly accessing records of publicly funded niraparib. Patients who have private insurance or are paying for treatment out-of-pocket may not be fully captured. This may result in a smaller sample size than expected. It should not affect the final proportion estimates for adverse events because accessing regular bloodwork and emergency acute care services should not differ between those receiving public funding and those who do not.

## Opportunities for Stakeholder Feedback

Stakeholders — including patient groups, medical associations, clinicians, clinical experts and/or peer reviewers, and industry — will be given the opportunity to provide feedback on the proposed protocol and the draft report through public postings on the CADTH website.

## Areas for Potential Amendments

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report.

# References


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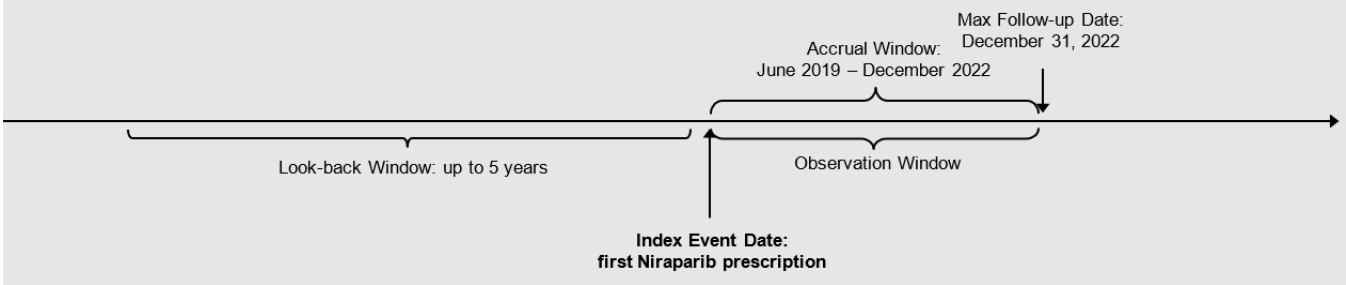
5. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [Internet]. 2017 [cited 2023 May 5]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

# Appendix 1: Additional Study Design Descriptions

Note that this appendix has not been copy-edited.

## Figure 1: Niraparib Observational Study Design Timelines




## Table 1: Key Dates for Study Design Described in Figure 1

| Study elements | Key dates |
|---|---|
| **Accrual window** | December 1, 2021, to December 31, 2022 (British Columbia)<br>January 1, 2022, to December 31, 2022 (Alberta)<br>June 27, 2019, to December 31, 2022 (Ontario)<br>January 1, 2020, to December 31, 2022 (Quebec) |
| **Index date** | Date of first niraparib dispensing |
| **Observation window** | Between index date and December 31, 2022 |
| **Lookback window** | • Up to 5 years prior to and including index date (earliest date: December 1, 2016, for British Columbia; June 27, 2014, for Ontario and Alberta; January 1, 2015, for Quebec)<br>• Lookback window is used in this study to identify previous comorbidities and original diagnosis dates |