NON-INTERVENTIONAL STUDY REPORT

TITLE PAGE

Division: Research and Development

Information Type: Non-Interventional PASS Report

Title:	Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)
Compound Number:	GSK3985771
Effective Date:	04 Dec 2024
Subject:	Safety
Author(s):	PPD
Indication Studied:	ZEJULA® maintenance treatment for epithelial ovarian, fallopian tube, or primary peritoneal cancer

STUDY INFORMATION

Title	Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)
Report version identifier	213705
Date of last version of report	Final: 04 Dec 2024
EU PAS (ENCEPP) register number	EUPAS29407
Active substance	Niraparib
Medicinal product	ZEJULA®
Product reference	Not applicable
Procedure number	EMEA/H/C/004249/MEA/002
Marketing authorisation holder(s)	GlaxoSmithKline (Ireland) Limited 12 Riverwalk Citywest Business Campus Dublin 24 Ireland
Research question and objectives	To determine the risk of developing myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) in patients administered niraparib in the routine clinical setting. **Primary objective:** To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients with: • Advanced epithelial (International Federation of Gynecology and Obstetrics [FIGO] Stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,

	• Platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy. **Secondary objective:** To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts.
Country(-ies) of study	European countries with approved use of ZEJULA®
Author	PPD PhD MPH 1250 S Collegeville Rd, Collegeville, PA 19426 United States

MARKETING AUTHORISATION HOLDER(S)

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STUDY DETAILS

UNIQUE IDENTIFIER	213705
TITLE	Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)
STUDY ACCOUNTABLE PERSON	PPD Real World Study Delivery
CONTRIBUTING AUTHORS	PPD Syneos Health
ASSET ID	GSK3985771
GSK ASSET	Niraparib (ZEJULA®)
EFFECTIVE DATE	04 Dec 2024
INDICATION	ZEJULA® maintenance treatment for epithelial ovarian, fallopian tube, or primary peritoneal cancer

REPORT REVISION HISTORY

Date	Version	Change(s) since last version
04 Dec 2024	Original	N/A

SPONSOR SIGNATORY

Title:	Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)
Compound Number:	GSK3985771

Tirza Boyle, PhD, MPH
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Date (DD Month YYYY)

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Date (DD Month YYYY)

Note: Not applicable if an eSignature process is used to get the sponsor approval.

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LIST OF ABBREVIATIONS

1LM	First-line maintenance group
2LM+	Second or later line maintenance group
ADP	Adenosine diphosphate
ADR	Adverse drug reaction
AE	Adverse Event
ALT	Alanine transaminase
AML	Acute myeloid leukemia
AST	Aspartate transferase
AT	Adjuvant chemotherapy
BICR	Blinded independent central review
BMI	Body Mass Index
BRCA	Breast cancer susceptibility gene
CBC	Complete blood cell count
CI	Confidence interval
CML	Chronic myeloid leukemia
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EAP	Expanded Access Program
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EHR	Electronic health record

EMA	European Medicines Agency
EU	European Union
FIGO	International Federation of Gynecology and Obstetrics
g*BRCA*mut	Germline breast cancer susceptibility gene mutation
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practices
Hb	Hemoglobin
HR	Hazard ratio
HRD	Homologous recombination deficiency
HR-deficient	Homologous recombination deficient
HR-proficient	Homologous recombination proficient
HR-unknown	Homologous recombination unknown
ICDS	Integrated Coding Dictionary System
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDS	Interval debulking surgery
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
Max	Maximum
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum

NAT	Neoadjuvant chemotherapy
NCI	National Cancer Institute
NOVA	Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer
NTF	Note to file
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PASS	Post-authorization safety study
PDS	Primary debulking surgery
PFS	Progression-free survival
PT	Preferred Term
Q1	First quarter
Q2	Second quarter
Q3	Third quarter
Q4	Fourth quarter
RMP	Risk management plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SIR	Standardized incidence ratio
SmPC	Summary of product characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure

SPM	Second primary malignancy
TEAE	Treatment-emergent adverse event
UAT	User Acceptance Testing
US	United States
WBC	White blood cells
WHO	World Health Organization

TRADEMARK INFORMATION

Trademarks of the GSK group of companies
ZEJULA

Trademarks not owned by the GSK group of companies
MarketScan
PankoMab (anti-MUC1mAb)
SAS

1. RESPONSIBLE PARTIES

A list of principal investigators for each participating site is available (refer to ANNEX 1 for a list of available stand-alone documents).

1.1. Study Advisory Committee

There is a dedicated Steering Committee that provided oversight of the conduct of this study, with a focus on the progress of the study, results review and interpretation, and consideration of new information relevant to the risk of developing MDS/AML and other SPMs in patients administered niraparib in the routine clinical setting. Following review of the final analysis, the Steering Committee prepared a Consensus Statement (refer to ANNEX 1 for a list of available stand-alone documents).

2. SYNOPSIS

Title Post-authorization safety study (PASS) to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)

Keywords

Niraparib, Ovarian cancer, PARP inhibitor, MDS/AML, SPM

Rationale and background

Niraparib is a poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. A decision to grant marketing authorization for niraparib was adopted by the European Commission on 16 November 2017 with the indication of monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy, based on results from the Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer (NOVA) clinical trial. On 17 September 2020, following the PRIMA clinical trial, GlaxoSmithKline (GSK) received European Commission approval of niraparib as first-line monotherapy maintenance treatment of adult patients with advanced epithelial (International Federation of Gynecology and Obstetrics [FIGO] Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) have been observed in the context of systemic therapies including platinum-based chemotherapy and PARP inhibitor treatments [Ricks, 2015; Shenolikar, 2018; Marmouset, 2022]. While the mechanism of action of PARP inhibition suggests that there may be a risk of MDS/AML and other SPMs associated with the use of PARP inhibitors, results from Phase 3 clinical studies using niraparib (NOVA), olaparib (SOLO2), or rucaparib (ARIEL3) did not show any statistically significant correlation between the use of PARP inhibitors and the incidence of MDS/AML or other SPMs at the time of initiating this PASS.

A PASS (European Union [EU] risk management plan [RMP] Category 3) was agreed with the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use to characterize the potential risk of MDS/AML and other SPMs associated with niraparib for the approved recurrent (second or later line maintenance group [2LM+]) ovarian cancer setting in 2017. Following the decision to grant market authorization to niraparib as first-line maintenance (1LM) treatment, the study protocol was amended in 2020 to incorporate the 1LM indication. Since this PASS commitment was agreed upon, MDS/AML has been recategorized from an important potential risk to an important identified risk based on comprehensive signal assessment and added to the Zejula (niraparib) Global Data Sheet in 2021 and the EU summary of product characteristics (SmPC) in 2022.

In March 2024, the EMA endorsed the early termination of this niraparib PASS based on results from the 2023 interim analysis and post hoc precision analysis.

Research questions and objectives

The objective of this PASS was to determine the risk of developing MDS/AML and SPMs in patients administered niraparib in the routine clinical setting.

Primary objective: To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients with:

- Advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
- Platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy

Secondary objective: To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts.

Study design

This PASS was a prospective, non-interventional, single-arm observational study including patients who received niraparib through the European Expanded Access Program (EAP), in the control arm of a clinical trial (other than a GSK/TESARO sponsored or supported niraparib trial), and patients treated post-approval in routine clinical practice.

Setting

Patients were enrolled from 4 European countries (Germany, Italy, Netherlands, Spain).

Subjects and study size

Overall, 797 patients were enrolled from 94 sites. Enrollment in the study closed on 17 January 2023 when the *a priori* patient-years threshold (1000 patient-years) had been surpassed.

Enrolled patients that met all eligibility criteria and received at least 1 dose of niraparib with sufficient clinical information available to classify line of therapy were included in the Safety Population for analysis. This cohort was stratified by niraparib line of therapy: 1LM or 2LM+.

Note that at the time of the interim analysis, there were multiple open queries with sites. As these queries were resolved, additional data were available which resulted in the recategorization of some patients and an adjustment in the patient counts of the overall Safety Population, 1LM, and 2LM+ cohorts for the final analysis.

Variables and data sources

Data were sourced from the patients' electronic health records (EHR) and collected at 2 different time periods as follows: 1) baseline data and 2) follow-up data (quarterly during a maximum of 5 years of routine clinical follow-up of the patient after niraparib initiation). Baseline data were collected relative to date of enrollment or niraparib initiation. For patients who started niraparib prior to enrollment, some follow-up data were collected retrospectively.

The baseline data collected included patient demographic characteristics, tumor characteristics, medical and treatment history. Follow-up data were collected on treatment, adverse events (AEs) and study outcomes (MDS/AML and other SPMs).

Results

The Safety Population included 745 patients, with the majority in the 2LM+ group (181 1LM; 564 2LM+). Nearly 90% of patients were FIGO stage III (n=498) or IV (n=169) high-grade serous at ovarian cancer diagnosis, with a median age at index (niraparib initiation) of 65.0 years (interquartile range [IQR] 58.0, 72.0). Most patients (72.9% [n=543]) were enrolled after they had received their first dose of niraparib, with a median of 30.1 months (IQR 18.0, 47.5) from ovarian cancer diagnosis to niraparib initiation.

The median number of lines of platinum-based chemotherapy received prior to niraparib was 2.0 (IQR 2.0, 2.0) in the 2LM+ cohort. Less than 10% of patients (8.2%, n=61) received radiation prior to niraparib initiation, while nearly all patients received cytoreductive surgery (95.6%; n=712). Over half of surgical patients (57.6%; n=410) received primary debulking surgery (PDS).

Overall, 78.5% (n=585) of patients were tested for breast cancer susceptibility gene (*BRCA*) mutations, of whom 86 patients (14.7%) were *BRCA* mutant (n=54 germline, n=23 somatic, n=9 not specified). In total, 30.2% of patients (n=225) were tested for homologous recombination deficiency (HRD), of whom 68 patients (30.2%) were HR-proficient. Biomarker status was derived from available HRD and *BRCA* test results: 113 patients (15.2%) were HR-deficient.

Approximately 86% of the safety population completed 1-year of follow-up (n=638), 53.7% completed 2-years of follow-up (n=400), 29.3% (n=218) completed 3-years of follow-up, 14.8% completed 4-years of follow-up (n=110), and 6.7% (n=50) completed 5-years of follow-up, with follow-up more limited among 1LM patients. Death was the main reason for study discontinuation (47.1%), mainly due to disease progression (84.4%; n=276). The median duration of niraparib treatment was 11.0 months (IQR 5.1, 20.0) in the 1LM cohort and 10.4 months (IQR 4.8, 22.9) in the 2LM+ cohort. Dose modifications occurred in 50.5% (n=376) of the safety population, most commonly because of thrombocytopenia (34.6%) or other (38.8%) reasons. Niraparib treatment was discontinued by 72.9% (n=132) of 1LM patients and 78.9% (n=445) of 2LM+patients mostly due to disease progression.

As of the database lock date of 11 July 2024, 1762.6 patient-years were accumulated (322.9 patient-years 1LM and 1439.6 patient-years 2LM+). A total of 9 (1.2%) patients had reported events of MDS/AML (11 total events; 2 patients had 2 events of MDS/AML), with 88.9% (n=8) of patients having MDS/AML events deemed related to niraparib. All patients with MDS/AML were *BRCA* tested, of whom 77.8% (n=7) were *BRCA* wild type. Time at-risk specific to first onset of MDS/AML was 1767.6 patient-years (324.1 patient-years 1LM and 1443.4 patient-years 2LM+). The overall incidence rate of MDS/AML was 0.51 (95% confidence interval [CI]: 0.23, 0.97) per 100 patient-years (0.0 [95% CI: not evaluable [NE], 1.14] per 100 patient-years 1LM; 0.62 [95% CI: 0.29, 1.18] per 100 patient-years 2LM+). The median time from niraparib initiation to MDS/AML onset was 32.7 months (IQR 22.6, 36.3). Six patients (0.8%) were newly diagnosed with other SPMs (7 total events; 1 patient had 2 diagnoses of basal cell carcinoma, 2 had breast cancer, 1 had chronic myeloid leukemia (CML), 1 had head and neck cancer, and 1 had squamous cell carcinoma of the oral cavity), with 1 patient having an other SPM event deemed related to niraparib. Time at-risk specific to first onset of other SPM was 1767.6 patient-years (322.9 patient-years 1LM and 1444.7 patient-years 2LM+). The overall SPM incidence rate was 0.34 (95% CI: 0.12, 0.74) per 100 patient-years (0.31 [95% CI: 0.01, 1.73] per 100 patient-years 1LM; 0.35 [95% CI: 0.11, 0.81] per 100 patient-years 2LM+). Time from niraparib initiation to other SPM onset was 9.5 months for the one patient in the 1LM cohort and the median time from niraparib initiation to other SPM onset was 20.0 months (IQR 10.8, 32.1) in 2LM+ cohort. All patients with MDS/AML events and 5 of 6 patients with other SPMs events occurred in the 2LM+ cohort. The limited number of observed MDS/AML and other SPMs (combined total of 15 patients) precluded an assessment on patterns across risk factors.

In total, 389 patients (52.2%) experienced at least 1 treatment-emergent adverse event (TEAE), 138 patients (18.5%) experienced a TEAE grade 3 or higher, and 69 patients (9.3%) experienced a serious TEAE. Overall, 49 patients (6.6%) experienced a TEAE that lead to the discontinuation of niraparib and 3 patients (0.4%) experienced TEAEs that lead to death (all 2LM+ patients), 1 of which was reported as related to niraparib.

Discussion

The overall incidence of MDS/AML (1.2%, 0.51 per 100 patient-years) was consistent with the incidence observed in long-term safety updates for the NOVA and PRIMA clinical trials. In the NOVA clinical trial (median follow-up >75 months), there were 14 MDS/AML cases observed in 367 niraparib-treated patients (3.8%; CCI [redacted] and 3 observed in 179 placebo patients (1.7%) [Matulonis, 2023; GSK Document Number: CCI [redacted]. In the PRIMA clinical trial (median follow-up 73.9 months), there were 11 cases of MDS/AML observed in 484 niraparib-treated patients (2.3%; CCI [redacted] and 4 observed in 244 placebo patients (1.6%) [Monk, 2024; GSK Study Report Document CCI [redacted]. Additionally, few other SPMs were reported overall (0.8%), comparable to that observed in both NOVA CCI [redacted] and PRIMA CCI [redacted] with event types not unexpected in this population [GSK Document Number: CCI [redacted]; GSK Study Report Document CCI [redacted].

The percent of TEAEs reported in this real-world, non-interventional study were lower than those reported for niraparib-treated subjects from the NOVA trial (100.0% experienced any TEAE; TEAE ≥ grade 3, 76.6%; [Matulonis, 2023]) and the PRIMA trial (any TEAE, 99.0%; TEAE ≥ grade 3, 73.8%; [Monk, 2024]). Similarly, the percent of patients experiencing a serious TEAE was lower than that observed for both the niraparib-treated arm (34.6%; 40.9%) and placebo-arm (16.2%, 17.6%) in NOVA [Matulonis, 2023] and PRIMA [Monk, 2024], respectively. Niraparib discontinuation due to TEAEs was also lower in this study than in the NOVA and PRIMA clinical trials (18.3% and 16.3%, respectively).

Conclusions

The final study results were consistent with the current risk-benefit profile for niraparib: the incidence of MDS/AML in patients treated with niraparib in the routine clinical setting is aligned with the incidence reported in the label and the incidence of MDS/AML and other SPMs is aligned with that observed in niraparib clinical trials, specifically the Phase 3 clinical trials NOVA and PRIMA. Results were consistent with the niraparib known safety profile; no new safety signals were detected. See Steering Committee Consensus Statement (refer to ANNEX 1 for a list of available stand-alone documents).

Marketing authorization holder

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
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Names and affiliations of principal investigators

Please refer to ANNEX 1 for a list of available stand-alone documents, including a List of Principal and sub-Investigators.

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study report	Amendment or update	Reason
1	*7 December 2020*	*Title*	• *Platinum sensitive relapsed, high grade serous has been removed from the title*	• *The study population has been updated to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy due to the EMA approval for use of niraparib as first line maintenance therapy. The title has been revised to include the new study population*
2	*7 December 2020*	*Pass Information*	• *Revised the contact Details for the Market Authorisation Holder, author, and names for the sponsor signature page* • *Research question and objectives have been updated to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy due to the EMA approval for use of niraparib as first line maintenance therapy*	• *Revised to most current contact details for GSK following transition from Legacy Tesaro* • *To include the new indication for niraparib approved by the EMA*

Amendment or update no	Date	Section of study report	Amendment or update	Reason
3	*7 December 2020*	*Section 3.1-3.10*	• *Most of the text that was included in the abstract was also included in the main protocol. Therefore, the text that was repeated in the main protocol has been deleted in the abstract* • *The study population has also been updated to include patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy*	• *The abstract was revised to streamline the protocol to allow sites to easily follow the protocols to improve site adherence to protocol procedures* • *To include the new indication for niraparib approved by the EMA*
4	*7 December 2020*	*Section 4*	• *The list of amendments to the protocol*	• *Included the list of amendments implemented in the protocol*
5	*7 December 2020*	*Section 5*	• *Some of the text that was included in primary data collection section was also included in the other sections of the protocol (study setting and sample size calculation). This text has now been deleted* • *The end of enrollment period has been extended to Q4 2021*	• *The protocol was revised to be more streamlined to allow sites to easily follow the protocols to improve on adherence to protocol procedures* • *This is account for the impact of COVID on the recruitment*

Amendment or update no	Date	Section of study report	Amendment or update	Reason
6	*7 December 2020*	*Section 6*	• *Updated background information on the occurrence of study outcomes using more recent data and added background information on the new population that will be included in the study i.e., patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy*	• *To include the new indication for niraparib approved by the EMA*
7	*7 December 2020*	*Section 7*	• *Updated the study objectives to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy*	• *To include the new indication for niraparib approved by the EMA*
8	*7 December 2020*	*Section 8.1 – Section 8.8*	• *The text in the methods section has been revised. This includes removing text that was repeated in multiple sections or moving texts to more relevant sections. Details for the revisions in each section are provided below*	• *The revisions were implemented to streamline the protocol to allow sites to easily follow the protocols to improve adherence to study procedures*

Amendment or update no	Date	Section of study report	Amendment or update	Reason
		Section 8.2.1	• *Inclusion of patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in the selection criteria.* • *Inclusion criteria providing clarification that patients who are part of a clinical trial arm will be excluded if this is GSK trial*	• *To include the new indication for niraparib approved by the EMA* • *To avoid duplication in the reporting of adverse events*
		Section 8.2.3	• *Weight to be collected within 3 months of study enrollment* • *To collect data on Homologous Recombination Deficiency (HRD) status* • *Collect the latest complete blood count data prior to niraparib initiation*	• *To ensure that the weight reflects that weight the time of niraparib initiation* • *The HRD status data will be used to characterize the patient population* • *This is to ensure the baseline data reflects the status of the patient at the time of niraparib initiation*
		Section 8.6	• *Data analysis to include stratification of data analysis by the two ovarian cancer populations based on the use of niraparib either as first-line or second-line maintenance therapy*	• *This is due to the inclusion of the study population with the new indication for niraparib approved by the EMA*

Amendment or update no	Date	Section of study report	Amendment or update	Reason
		Section 8.7.3	• *Updating the duration of archiving study documents from 2 years to 10 years after finalization of the study report*	• *Updated to align with the GSK archiving processes*
		Section 8.7.7	• *Study monitoring included additional information on how the study monitoring will be implemented and considering the COVID-19 pandemic*	• *To ensure compliance with study procedures*
		Section 10	• *Management and reporting of adverse events/adverse reactions: Hospitalizations for planned elective treatment for pre-existing conditions will not be considered a severe adverse event, deleted pneumonitis as an AE of special interest and will now be reported as an AE, updated the sponsor contact details from Tesaro to GSK and included the COVID-19 infection assessment form*	• *To align with the GSK pharmacovigilance processes*
9	*7 December 2020*	*Annex 1*	• *Deleted*	• *This information is already included in the protocol Section 8.2.1*
10	*12 April 2024*	*Section 3.3 – Section 3.9*	• *Removal of Exploratory Objective and any text related to the study population, data collection, data source, and analysis relevant to the Exploratory Objective only*	• *To align with EMA approval of early termination of study*

Amendment or update no	Date	Section of study report	Amendment or update	Reason
11	*12 April 2024*	*Section 5*	• *Removal of milestones related to Exploratory Objective* • *Update of end of primary data collection/start of analysis and final report of study results milestones*	• *To align with EMA approval of early termination of study*
12	*12 April 2024*	*Section 7*	• *Removal of Exploratory Objective*	• *To align with EMA approval of early termination of study*
13	*12 April 2024*	*Section 8.1, Section 8.2.1, Section 8.2.2, Section 8.2.4, Section 8.3.1, Section 8.5, Section 8.6*	• *Removal of study design description, inclusion/exclusion criteria, secondary data collection, secondary data sources, and secondary data analysis relevant to the Exploratory Objective*	• *To align with EMA approval of early termination of study*
14	*12 April 2024*	*Section 8.8*	• *Removal of limitations relevant to the Exploratory Objective only*	• *To align with EMA approval of early termination of study*
15	*12 April 2024*	*Section 10.4*	• *Removal of safety reporting requirements relevant to the Exploratory Objective*	• *To align with EMA approval of early termination of study*

4. MILESTONES

Data collection began at the time of enrollment of the first patient on 06 November 2019. Enrollment in the study closed on 17 January 2023 when the *a priori* patient-years threshold (1000 patient-years) had been surpassed. End of data collection was originally planned for Q3 of 2026, however, in March 2024 the EMA endorsed early termination based on results from the 2023 interim analysis and post hoc precision analysis.

The date of database lock for the final analysis was 11 July 2024.

Milestone	Planned date	Actual Date	Comments
Registration in the EU PASS register	*Q2 2019*	*07 June 2019*	-
Start of data collection	*Q4 2019*	*06 November 2019*	-
End of enrollment	*Q3/4 2021*	*17 January 2023*	-
Interim report (primary data)	*Q3 2023*	*28 August 2023*	Interim report v1.0
End of primary data collection and start of final analysis	*Q3 2026*	*11 July 2024*	Database lock
Final report of study results	*Q1 2027*	04 Dec 2024	Final report v1.0

5. RATIONALE AND BACKGROUND

Niraparib is a potent, orally active PARP1 and PARP2 inhibitor. Prior niraparib clinical trials were instrumental in gaining market authorization of niraparib (NOVA and PRIMA) based on efficacy results and tolerability and were necessary to demonstrate the niraparib safety profile.

In the randomized, double-blind, Phase 3 NOVA clinical trial, a total of 553 patients were randomized at 107 centers worldwide [Mirza, 2016; Matulonis 2023]. Patients were categorized according to the presence or absence of a germline *BRCA* mutation (g*BRCA*mut cohort and a non-g*BRCA*mut cohort) and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily. In the non-g*BRCA*mut cohort, testing for HRD was performed using an HRD test on tumor tissue obtained at the time of initial diagnosis or at the time of recurrence. The primary endpoint was PFS. The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were identified as HR-deficient, and 134 had tumors that were HR-proficient. HRD tumor status was not determined for 54 patients.

In the primary efficacy analysis, demographic and baseline characteristics were well balanced. Table 1 shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (i.e., g*BRCA*mut cohort, overall non-g*BRCA*mut cohort, HR-deficient cohort). CCI [redacted] [GSK Document Number: CCI [redacted]].

In an updated long-term safety analysis (median follow-up >75 months), the final OS as of the 31 March 2021 data cut-off for these 3 populations (i.e., g*BRCA*mut cohort, overall non-g*BRCA*mut cohort, HR-deficient cohort) was reported (Table 1) [Matulonis, 2023]. Median OS in patients with HR-proficient tumors was 27.9 months (95% CI: 22.6, 32.8) in the niraparib arm and 27.9 months (95% CI: 19.2, 44.0) in the placebo arm, with a HR

of 0.93 (95% CI: 0.61, 1.41). It was noted that analyses were confounded by imbalances in post-progression therapy, including subsequent PARP inhibitors, in all treatment arms. Secondary endpoints, including chemotherapy-free interval, time to first subsequent therapy, time to second subsequent therapy, and time to second progression or death, demonstrated a persistent treatment effect favoring niraparib in both the g*BRCA*mut and non-g*BRCA*mut cohorts [Matulonis, 2023].

Table 1 Progression-Free Survival and Overall Survival in Ovarian Cancer Patients in NOVA

	g*BRCA*mut Cohort		Non-g*BRCA*mut Cohort (regardless of HRD status)		HR-deficient (within non-g*BRCA*mut Cohort)	
	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=234)	Placebo (n=116)	Niraparib (n=106)	Placebo (n=56)
Median PFS[1], months (95% CI)	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.6)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	<0.001		<0.001		<0.001	
HR (niraparib: placebo) (95% CI)	0.26 (0.170, 0.406)		0.45 (0.338, 0.609)		0.38 (0.243, 0.586)	
Median OS[2], months (95% CI)	40.9 (34.9, 52.9)	38.1 (27.6, 47.3)	31.0 (27.8, 35.6)	34.8 (27.9, 41.4)	35.6 (28.3, 43.4)	41.4 (33.9, 57.6)
HR (niraparib: placebo) (95% CI)	0.85 (0.606, 1.198)		1.06 (0.813, 1.369)		1.29 (0.849, 1.949)	

Sources [GSK Document Number: CCI [redacted]; Matulonis, 2023].
Abbreviations: CI = confidence interval; g*BRCA*mut = germline breast cancer gene mutation; HR = hazard ratio; HRD = homologous recombination deficiency; HR-deficient = homologous recombination deficient; NE = not estimable; NOVA = Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer; OS = overall survival; PFS = progression free survival.
[1]NOVA primary efficacy analysis
[2]NOVA updated final OS and long-term safety analysis

All 367 patients who received niraparib and 172 (96.1%) of 179 patients who received placebo experienced at least 1 TEAE. The high percentage of TEAEs stresses the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib and placebo treatment arms, the incidence of Grade 3 or 4 TEAEs (76.6% and 24.0%), SAEs (34.6% and 16.2%), TEAEs leading to dose interruption (69.5% and 15.1%), TEAEs leading to dose reduction (69.2% and 5.0%), and TEAEs leading to treatment discontinuation (18.3% and 2.2%), respectively, were higher for niraparib than for placebo [Matulonis, 2023].

In the primary NOVA analysis, the most commonly observed TEAEs (all grades) in niraparib-treated and placebo-treated patients were nausea CCI [redacted] anemia CCI [redacted] fatigue CCI [redacted] thrombocytopenia CCI [redacted] constipation CCI [redacted] vomiting CCI [redacted] headache CCI [redacted], and decreased appetite CCI [redacted] respectively [GSK Document Number: CCI [redacted]]. The majority of the nonhematologic TEAEs were mild to moderate in severity. Although Grade 3 or 4 hematologic laboratory TEAEs were

common at the initiation of study treatment, no severe clinical sequelae were observed, and relatively few patients discontinued study treatment due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these AEs beyond Cycle 3. In the NOVA clinical trial, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (i.e., Cycle 3) of treatment [Mirza, 2016].

The efficacy results in the PRIMA (PR-30-5017-C) randomized, double-blind, placebo-controlled, Phase 3 clinical trial demonstrated a statistically significant and clinically meaningful benefit of niraparib treatment in the overall population of patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) who had responded to front-line platinum-based therapy [González-Martín, 2019; González-Martín, 2023; Monk, 2024]. The primary endpoint was PFS by BICR analyzed in both the HR-deficient and the overall (intended to treat) populations per prespecified hierarchical testing [González-Martín, 2019]. Median PFS was significantly longer in subjects who received niraparib compared to those who received placebo, with corresponding favorable HR. The PRIMA clinical trial met the primary endpoint in subjects with HR-deficient tumors; median PFS as determined by BICR based on Response Evaluation Criteria in Solid Tumors (version 1.1) was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43; [95% CI: 0.31, 0.59]; p<0.001) [González-Martín, 2023; Monk, 2024]. For the overall population, median PFS for subjects randomized to niraparib was 13.8 months versus 8.2 months on placebo (HR 0.62 [95% CI: 0.50, 0.76]; p<0.001). A reduction of risk to progression of disease or death during study was demonstrated for subjects in the niraparib arm compared to subjects in placebo arm, for subjects with HR-proficient tumors (HR 0.65; 95% CI: 0.49, 0.87) [González-Martín, 2023]. Furthermore, the 5-year PFS rate numerically favored niraparib in both the overall (22% niraparib, 12% placebo) and the HR-deficient (35% niraparib, 16% placebo) populations [Monk, 2024].

Safety outcomes were consistent with those seen in the NOVA clinical trial, specifically thrombocytopenia of any grade and grade ≥3. Initiation of the individualized starting dose of niraparib in the PRIMA clinical trial (i.e., initial starting dose of 200 mg or 300 mg based on the subject's baseline body weight and/or baseline platelet count) decreased the incidence of TEAEs, with the largest reductions seen in any grade and grade ≥3 events of anemia, thrombocytopenia, and neutropenia (which were found to most often occur during the first month of treatment), and the incidence of TEAEs leading to dose interruptions and reductions [González-Martín, 2023]. Safety findings after a longer study follow-up time (median follow-up 73.9 months) were consistent with those in the primary analysis, and no new safety signals were identified [Monk, 2024; GSK Study Report Document CCI [redacted]].

A decision to grant marketing authorization for niraparib was adopted by the European Commission on 16 November 2017 with the indication of monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy.

On 17 September 2020, GSK received European Commission approval of Zejula (niraparib) as first-line monotherapy maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

While marketing authorization has made novel therapies available outside of a clinical trial setting, gaining access may often be time consuming and cumbersome for patients with life-threatening, debilitating diseases [Balasubramanian, 2016]. Early access programs, such as the EAP or compassionate use program, have created opportunities for patients to gain access to critical treatments in a real-world setting.

A PASS (EU RMP Category 3) was agreed with the EMA/Committee for Medicinal Products for Human Use to characterize the potential risk of MDS/AML and other SPMs associated with niraparib for the approved recurrent (2LM+) ovarian cancer setting in 2017. Following the decision to grant market authorization to niraparib as first-line maintenance treatment, the study protocol was amended in 2020 to incorporate the 1LM indication. Since this PASS commitment was agreed upon, MDS/AML has been recategorized from an important potential risk to an important identified risk based on comprehensive signal assessment and added to the Zejula (niraparib) Global Data Sheet in 2021 and the EU SmPC in 2022.

5.1. MDS/AML

MDS is a group of bone marrow failure disorders characterized by ineffective hematopoiesis in 1 or more of the lineages of the bone marrow [Corey, 2007]. MDS can evolve from a refractory anemia to AML, which is associated with a decrease in intramedullary apoptosis and a block in myeloid differentiation. The incidence of MDS is 4 per 100 000 and increases to 25 per 100 000 among persons aged 65 years and older [Sekeres, 2022]. The association of MDS with age suggests genetic damage caused by hazardous exposure or inherited susceptibility. This study utilized the diagnostic classification used by the WHO in 2016, which recognized 6 distinct entities of MDS based on morphologic quantitative and qualitative evaluation of the peripheral blood and bone marrow using basic hematological techniques [Arber, 2016]. In 2022, the WHO definition of real disease entities was updated, including the introduction of new entities and refined criteria for existing diagnostic categories, to facilitate diagnosis and prognostication of these neoplasms [Arber, 2022].

5.1.1. Reported Cases of MDS/AML with PARP Inhibitors

MDS/AML, including cases with fatal outcome, have been reported in patients who received niraparib monotherapy in clinical trials. In 851 patients treated with niraparib in the PRIMA and NOVA clinical trials, MDS/AML occurred in 25 patients (2.9%). Of these 25 patients, 11 patients were treated in PRIMA and 14 patients in NOVA. The duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to >5 years. The cases were typical of secondary, cancer therapy related MDS/AML. All patients had received platinum-containing chemotherapy regimens, and many had also received other DNA damaging agents and radiotherapy [Matulonis, 2023;

GSK Document Number: CCI [redacted]; Monk, 2024; GSK Study Report Document CCI [redacted].

A Phase 3, randomized, double-blind, placebo-controlled, multicenter clinical trial (SOLO1), found the incidence of MDS/AML in patients with newly diagnosed *BRCA* mutant advanced (FIGO Stage III-IV) ovarian cancer who were treated with olaparib in the first-line setting, was 1.9% in olaparib treated patients and 0.8% in placebo patients [Lynparza package insert, 2023]. In patients with *BRCA* mutant platinum-sensitive relapsed ovarian cancer who had received at least 2 prior lines of platinum chemotherapy (SOLO2), the incidence of MDS/AML was 8% in olaparib treated patients and 4% in placebo patients at a follow-up of 5 years [Lynparza package insert, 2023].

In a Phase 3, randomized, double-blind clinical trial (ARIEL3), 3.8% of patients with high-grade ovarian carcinoma who had received 2 or more previous platinum-based chemotherapy regimens and were treated with rucaparib experienced an MDS/AML event compared to 3.2% of placebo patients. All cases had developed after completion of study drug [Coleman, 2022].

5.1.2. Risk Factors Associated with MDS/AML

Risk factors for MDS/AML include age, chemotherapy and/or radiation therapy, family history of MDS/AML, smoking, alcohol use, autoimmune diseases, genetic syndromes, and exposure to certain chemicals and heavy metals [Nisse, 1995; Philpott, 1996; Pasqualetti, 1997; Travis, 1999; Nisse, 2001; Strom, 2005; Strom, 2008; Ma, 2009; Anderson, 2009; Frost, 2011; Kaplan, 2011; Morton, 2013; Dinmohamed, 2014; Jin, 2014; Madry, 2015; Sun, 2015; Komrokji, 2016; Vogt, 2017]. In addition, the incidence of MDS/AML was found to be associated with gender (more common in the male population), weight, platelet transfusions, anemia, renal and/or hepatic insufficiency, history of cytopenia, elevated MC, and CBC abnormalities [Balducci, 2006; Kantarjian, 2007; Wang, 2010; Triantafyllidis, 2012; Li, 2017].

The mechanism of action of PARP inhibitors suggests that these agents may induce development of MDS/AML [Ricks, 2015]. Results from Phase 3 clinical studies using niraparib (NOVA), olaparib (SOLO2), or rucaparib (ARIEL3) have failed to show any statistically significant correlation between the use of PARP inhibitors and the incidence of MDS/AML. It is important to note that all patients who received either niraparib, olaparib, or rucaparib had previously received chemotherapy with DNA-damaging agents and/or radiotherapy, the use of which is known to be a risk factor associated with MDS/AML [Coleman, 2022; Matulonis, 2023; DiSilvestro, 2023].

Patients treated with chemotherapy have an increased risk for MDS/AML. This has been shown in a study using information from the US SEER database collected between 1975 and 2008 [Morton, 2013]. In this study, among 23 180 adult patients with ovarian cancer who received initial chemotherapy, 72 cases of AML occurred. The SIRs were calculated as the ratio of the observed-to-expected incidence of AML. The expected incidence of AML was computed considering age-, race-, sex-, and calendar year specific-incidence rates of AML from the general SEER population, multiplied by the appropriate patient-years. For the SIRs, 2-sided Poisson-based 95% CIs were also calculated. The overall

SIR for treatment-related AML in this cohort was 8.68 (95% CI: 6.79, 10.94). The SIR increased to 12.07 (95% CI: 8.77, 16.20) during the 4.9 years following the administration of chemotherapy. The cohort included in this study did not receive treatment with a PARP inhibitor. Therefore, it is likely that the incidence of MDS/AML is elevated in patients with ovarian cancer who have been previously treated with chemotherapy compared with the general population.

This is supported by a study analyzing the US claims database MarketScan for the incidence of MDS/AML in 23 862 patients diagnosed with ovarian cancer between January 2000 and June 2014 [Shenolikar, 2018]. The study reports that the incidence of MDS and AML was higher among patients exposed to DNA-damaging therapy, such as alkylating agents, antimetabolites, platinum-based antineoplastic agents, and topoisomerase inhibitors, and that duration of exposure to these agents was a significant risk factor for developing MDS and AML [Shenolikar, 2018].

5.2. Secondary Primary Malignancies

The mechanism of action of PARP inhibitors suggests that these agents may induce development of SPMs [EMA, 2014]. SPMs are cancers that develop after a primary cancer was diagnosed and treated in the same individual. Based on a study using information from the US SEER database collected from 1992 to 2012, among 41 073 women with a diagnosis of a histologically confirmed primary ovarian malignancy, a total of 1831 women (4.5%) developed an SPM [Kanninen, 2017]. The overall SIR for this cohort as compared to the general population was 0.978 (99% CI: 0.992, 1.036). Patients with a history of multiple cancers are often genetically more likely to develop SPMs following diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer. Furthermore, race and age of diagnosis may impact the subsequent risk of developing SPMs. Studies have shown that women could be at risk of developing subsequent cancers including breast, gastrointestinal, lung, and, gynecological cancers, as well as leukemia [Levi, 2009; Hung, 2015; Kanninen, 2017].

5.2.1. Reported SPMs in Patients Treated with Niraparib

Among 367 patients treated with niraparib in the NOVA clinical trial, SPMs other than MDS/AML occurred in [redacted] [GSK Document Number: [redacted]]. [redacted] [GSK Study Report Document [redacted]]. The types of other SPMs reported included, but were not limited to, basal cell carcinoma, squamous cell carcinoma, breast cancer, and thyroid cancer.

6. RESEARCH QUESTION AND OBJECTIVE(S)

The objective of this PASS was to determine the risk of developing MDS/AML and SPMs in patients administered niraparib in the routine clinical setting.

The objectives were as follows:

Primary objective: To estimate the incidence rate of MDS/AML, and the distribution of these events across risk factors for MDS/AML, among a cohort of adult patients with:

- Advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
- Platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy

Secondary objective: To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts.

7. RESEARCH METHODS

7.1. Study Design

This PASS was a prospective, non-interventional, single-arm study to estimate the incidence rate of MDS/AML and other SPMs in ovarian cancer patients (as described in Section 6) who received niraparib through the EAP, in the control arm of a clinical trial (other than a GSK/TESARO sponsored or supported niraparib trial), or in routine clinical practice.

Patients were followed for up to 5 years from index date, defined as niraparib treatment initiation. Baseline characteristics of the patients were collected relative to date of study enrollment or niraparib initiation. During the follow-up period, data were collected on treatment, study outcomes (MDS/AML and other SPMs), and other AEs.

7.2. Study Population/Subjects and Setting

Patients were enrolled from 4 European countries (Germany, Italy, Netherlands, Spain), all of which have niraparib treatment approved for reimbursement in the 1LM and 2LM+ settings. A total of 96 sites were selected for inclusion in the study and activated based on the following parameters:

1. Site using niraparib per EU SmPC guidelines
2. Number of patients visiting the site with the correct indication for use of niraparib as maintenance treatment
3. Sites with an organized and compliant infrastructure for global clinical research

4. Sites participating in the EAP were preferred to collect outcome of patients participating in this early treatment program

Two of the activated sites were closed due to lack of enrollment, leaving 94 sites with at least 1 patient enrolled. Patients were identified and notified of the study by their treating physician. Signed consent from interested patients was then obtained by the physician or a designated representative. The baseline characteristics, study outcomes, and other relevant data were recorded in an EDC system by the physician or study staff at the time of enrollment and quarterly thereafter for a maximum period of 5 years (Table 2).

7.2.1. Study Discontinuation

Specific reasons for discontinuation from the study included the following:

- Withdrawal of consent by the patient, who was at any time free to discontinue participation in the study, without prejudice to further treatment
- Lost to follow-up
- Death from any cause
- Sponsor decision to terminate study

If a patient was thought to be lost to follow-up, or discontinued the study (i.e., if the patient missed at least 3 of the expected visits for management based on standard clinical practice guidelines), attempts were made to contact the patient to determine the reason for discontinuation. For patients who were thought to be lost to follow-up, at least 3 attempts, including 1 attempt via certified mail, were made to contact the patient before being deemed lost to follow-up.

7.2.2. Eligibility Criteria

7.2.2.1. Inclusion Criteria

Patients were eligible for the study if they fulfilled ALL of the following criteria at the time of study enrollment:

1. Patient was female, aged 18 years or older
2. Patient had a diagnosis of:
    a. Advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
    b. Platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
3. Patient received niraparib:
    a. As part of the EAP, regardless of whether the patient was receiving niraparib at the time of enrollment

b. As part of clinical practice, within 4 weeks of enrollment and regardless of whether the patient was receiving niraparib at the time of enrollment

c. As part of the control arm of a clinical trial (other than TESARO/GSK sponsored or supported niraparib trial [see Exclusion Criteria]), regardless of whether the patient was receiving niraparib at the time of enrollment

4. Patient was able and agreed to sign an ICF

7.2.2.2. Exclusion Criteria

Patients were excluded from the study if they fulfilled ANY of the following criteria:

1. Patient was receiving niraparib for use that is not according to the approved EU SmPC guidelines

2. Patient was receiving or had received niraparib in the past as part of TESARO or GSK clinical trial, where they were still participating in active follow-up to reduce the risk of double reporting of safety events

3. Patient was enrolled into a GSK Investigator Supported Study or Supported Collaborative Study

7.3. Variables

7.3.1. Data Collection

Data were collected at 2 different time periods, as follows:

1. Baseline data (relative to date of enrollment or niraparib initiation)

2. Follow-up data (quarterly during a maximum 5-year clinical follow-up of the patient after study enrollment)

Most baseline data were collected relative to the time when niraparib treatment was initiated. Some baseline characteristics were collected relative to study enrollment date, e.g., family cancer history, smoking history and alcohol use, patient's exposure to oncogenic chemicals/heavy metals, *BRCA*/HRD genetic assessments, and target medical history.

Follow-up data were collected prospectively at participating sites using an eCRF that was developed specifically for this non-interventional study. For patients who initiated niraparib prior to enrollment, some follow-up data was collected retrospectively. The schedule of data collection is provided in Table 2.

Table 2 Schedule of Data Collection

Data Collection and study assessments	Patient Baseline Assessment Day 0	Interval Data Collections Quarterly Every 3 months (+/-) 10 working days	Unscheduled Intervals During Observation Period (up to 5 years from start date of niraparib)	Lost to follow up	End of Study Period
ICF	X				
Inclusion and exclusion check	X				
Year of birth	X				
Weight	X	X			
Height	X				
Family Cancer History	X				
BRCA/HRD Status	X				
Auto-immune history	X				
Ovarian cancer diagnosis	X				
Other cancer diagnosis	X	X		X	X
Cancer treatment	X	X		X	X
Radiotherapy Treatment	X	X		X	X
Risk Factors	X			X	X
Complete blood cell counts	X			X	X
MDS/AML and other SPM summary	X	X	X	X	X
AE reporting	X	X	X	X	X
Pregnancy Reporting and Outcomes	X	X	X	X	X
COVID-19 infection assessment			X		

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; *BRCA* = breast cancer susceptibility gene; COVID-19 = coronavirus disease 2019; HRD = homologous recombination deficiency; ICF = informed consent form; MDS = myelodysplastic syndrome; SPM = second primary malignancy.
Notes: Weight was collected at baseline or within 3 months; Refer to Protocol version 9 for the management and reporting timeframes of adverse events/adverse reactions (please refer to ANNEX 1 for a list of available stand-alone documents, including Protocol version 9).
The overall follow-up time for a patient was defined as the start date of niraparib treatment initiation until earliest occurrence of date of death, study discontinuation, completion of 5 years maximum follow-up, or database lock date of 11 July 2024 for final analysis.

7.3.2. Study Variables

7.3.2.1. Baseline Study Variables

Baseline data collected were as follows:

- Age at index (years, derived from year of birth until date of niraparib initiation)
- Age group at index (<50 years, 50-64 years, 65-74 years, ≥75 years)
- Height (cm), at index

- Weight (kg), at index
- Weight group at index (<58 kg, ≥58 kg, or missing)
- BMI (kg/m^2), at index
- BMI group at index (<25 kg/m^2, 25-29.9 kg/m^2, ≥30 kg/m^2, or missing)
- Age at ovarian cancer diagnosis (years, derived from year of birth until date of diagnosis)
- Age group at ovarian cancer diagnosis (<50 years, 50-64 years, 65-74 years, ≥75 years)
- Niraparib exposure prior to enrollment (yes, no)
- Family cancer history at enrollment (yes, no, unknown)
- Smoking status at enrollment (never smoked, former smoker, current smoker, unknown, or missing)
- Smoking duration at enrollment (years), measured among current or former smokers at enrollment
- Average number of cigarettes smoked per day, measured among current or former smokers at enrollment
- Exposure to oncogenic factors at enrollment (yes, no, unknown, or missing; type of oncogenic factors for those exposed)
- Average number of alcoholic drinks (drinks per week) before ovarian cancer diagnosis (1-2, 3-6, 7-12, 13-24, >24, unknown, or missing), restricted to only patients who reported drinking alcohol at enrollment
- Average number of alcoholic drinks (drinks per week) after ovarian cancer diagnosis (1-2, 3-6, 7-12, 13-24, >24, unknown, or missing), restricted to only patients who reported drinking alcohol at enrollment
- Autoimmune disease history prior to niraparib initiation (yes, no, or unknown; if yes, on-going, or not on-going)
- *BRCA* tested (yes, no)
- *BRCA* test results (mutant, wild type, or missing; if mutant status, germline, somatic, or missing), percentage is based on patients who were *BRCA* tested
- HRD tested (yes, no)
- HRD test results (HR-deficient, HR-proficient, or missing), percentage is based on patients who were HRD tested
- Biomarker status (derived from HRD test results and *BRCA* test results; HR-deficient, HR-proficient, HR-unknown/*BRCA* wild type, no results available for *BRCA* or HRD)

Baseline disease characteristic data collected were as follows:

- Time from ovarian cancer diagnosis to niraparib initiation (months)
- Histological classification at enrollment (high-grade serous, high-grade endometrioid, other)
- FIGO stage at ovarian cancer diagnosis (Stage I, II, III, IV, or missing)
- Other cancer diagnosis prior to niraparib initiation (yes, no; if yes, type of cancer)
- Received chemotherapy and radiation therapy for any cancer prior to niraparib initiation (yes, no)
- Received chemotherapy for any cancer prior to niraparib initiation (yes, no)
- Received radiotherapy for any cancer prior to niraparib initiation (yes, no)
- Received radiotherapy for other cancer prior to niraparib initiation (yes, no), percentage based on patients who had other cancer diagnosis prior to niraparib initiation
- Received other therapy for other cancer prior to niraparib initiation (yes, no), percentage is based on patients who had other cancer diagnosis prior to niraparib initiation

The following characteristics on therapy for ovarian cancer were collected:

- Total lines of therapy prior to niraparib initiation
- Total lines of platinum-based chemotherapy prior to niraparib initiation, including cisplatin, oxaliplatin, and carboplatin
- Total number of platinum-based chemotherapy cycles for ovarian cancer prior to niraparib initiation, including cisplatin, oxaliplatin, and carboplatin
- Other PARP inhibitor received prior to niraparib initiation (yes, no; if yes, olaparib, rucaparib, talazoparib, other)
- Cytoreductive surgery performed prior to niraparib initiation (yes, no; if yes, type of debulking surgery: PDS, IDS, more than 1 surgery)
- Residual disease status post-cytoreductive surgery performed prior to niraparib initiation (no visible residual disease including no gross residual disease or residual disease less than or equal to 1 cm, visible residual disease including residual disease greater than 1 cm, unknown, not applicable)
- NAT for ovarian cancer received prior to niraparib initiation (yes, no; if yes, best response to NAT [complete response, partial response, progressive disease, stable disease, not evaluable, unknown]; if yes, primary reason for stopping treatment [treatment completed, progressive disease, toxicity, other])
- AT for ovarian cancer received prior to niraparib initiation (yes, no; if yes, best response to AT [complete response, partial response, progressive disease, stable disease, not evaluable, unknown]; if yes, primary reason for stopping treatment [treatment completed, progressive disease, toxicity, other])

- Received radiotherapy for ovarian cancer prior to niraparib initiation (yes, no)
- Received chemotherapy for ovarian cancer prior to niraparib initiation (alkylating agents, topoisomerase inhibitors, antimetabolites, antineoplastic – platinum complexes, taxanes, other)

Additionally, the following baseline risk factors associated with MDS/AML and other SPMs were summarized:

- Overweight/obesity (BMI ≥25 kg/m^2) (yes, no, or missing)
- Other PARP inhibitor received prior to niraparib initiation (olaparib, rucaparib, talazoparib, other)
- Targeted medical history at enrollment including thrombocytopenia, platelet transfusions, anemia, renal insufficiency, hepatic insufficiency, and neutropenia (yes, no, unknown, or missing)
- CBC abnormalities prior to niraparib initiation including Hb, WBC, blasts (%), absolute blasts count, platelets, absolute neutrophil count, neutrophils (%), absolute lymphocytes count, lymphocytes (%), and MCV (normal, abnormal, unknown, or missing)
- Average number of alcoholic drinks before ovarian cancer diagnosis (≤24 drinks per week, >24 drinks per week, unknown, or missing), restricted to only patients who reported drinking at enrollment
- Average number of alcoholic drinks after ovarian cancer diagnosis (≤24 drinks per week, >24 drinks per week, unknown, or missing), restricted to only patients who reported drinking at enrollment

7.3.2.2. Follow-up Study Variables

Follow-up data collected were as follows:

- Relevant concomitant medication/therapy (indication, dose, start and stop date, suspected as causal, ongoing medication)
- Chemotherapy/radiotherapy and/or other cancer treatments (indication, dose, start and stop date, best response [complete response, partial response, progressive disease, stable disease, not evaluable, unknown], and primary reason for stopping treatment [treatment completed, progressive disease, toxicity, other])
- Niraparib exposure (starting dose, dates of first dose modification [reason for first dose modification: thrombocytopenia, anemia, fatigue, nausea, other], subsequent dose modification [reason for subsequent dose modification: thrombocytopenia, anemia, fatigue, nausea, other], dose interruptions [reason for dose interruption: thrombocytopenia, anemia, fatigue, nausea, other], and date of discontinuation and reason [disease progression, patient request, investigator discretion, patient became pregnant, patient passed away, AE ≥ grade 3, or other])
- New occurrence of MDS/AML and other SPM events (type of event, date of first onset, relationship to niraparib [related, not related])

- Other PARP inhibitors (PARP inhibitor [olaparib, rucaparib, talazoparib, other] dose, start date and end date)
- End of treatment CBC, platelet transfusion, renal and hepatic insufficiency with all PARP inhibitor treatment
- CBC associated with all SAEs

Additional AEs and SAEs observed during the study were collected through GSK standard pharmacovigilance processes and reported as summarized in Section 7.3.3. Full details are provided in Protocol version 9 (please refer to ANNEX 1 for a list of available stand-alone documents, including Protocol version 9).

7.3.2.3. Derived Study Variables of Interest

Details on derived study variables of interest are available in ANNEX 2.

7.3.3. Safety Variables

All AEs, serious and non-serious, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, reported by patient), were collected and recorded in the eCRF for each patient from the signing of the ICF through 30 days after the last dose of niraparib, or the patient's death for any cause, whichever occurred first. However, if there was reasonable belief that a SAE that occurred after the 30 days window was related to study drug, it was also reported to the safety database.

Exceptions to the reporting requirements were as follows:

- MDS/AML and other SPM as the study endpoints were collected and reported to the Sponsor from first dose of niraparib until death, or the patient was lost to follow-up, whichever occurred first
- Embryo fetal toxicity was reported as outlined in Protocol version 9 Section 10.5 (ANNEX 1 for a list of available stand-alone documents, including Protocol version 9)

Concomitant illnesses that existed prior to study enrollment were not considered AEs unless the illness worsened during the treatment period. For patients who experienced a SAE, pre-existing conditions were collected on the SAE form and recorded as medical history in the eCRF.

Disease progression was an efficacy criterion and was therefore not considered an AE or SAE (even if fatal) and was not reported. If AEs or SAEs occurred in relation to disease progression that were not consistent with the natural progression of the patient's disease, these AEs/SAEs were reported per AE/SAE reporting requirements.

The safety database collected narratives for SAEs and ADRs, including all events of MDS/AML and other SPM. It was the responsibility of the Investigator to provide case narrative in the dedicated eCRF field. All AEs experienced by a patient, regardless of causality, were monitored until the AE or SAE resolved, until any abnormal laboratory values returned to baseline or normal levels, until stabilized with a satisfactory

explanation for the changes observed, until the patient was lost to follow-up, or until the patient died. Full details of reporting and submission requirements of AEs, SAEs, and ADRs can be found in Protocol version 9 Section 10 (please refer to ANNEX 1 for a list of available stand-alone documents, including Protocol version 9).

7.3.4. COVID-19 Infection Assessment

This PASS took place during the COVID-19 pandemic. GSK took steps to provide ongoing support for studies amidst the concerns related to the COVID-19 outbreak and its potential impact on patient safety monitoring.

A COVID-19 infection assessment form was completed for all COVID-19 cases identified during the study. COVID-19 cases were evaluated as to whether they met SAE criteria as defined in the protocol. SAEs and AEs were submitted following usual study procedures and timelines. The COVID-19 assessments included diagnosis, whether a COVID-19 test was performed, and results of the COVID-19 test. Additionally, data were collected on:

- History of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset
- Visits to any health care facility in the 14 days prior to symptom onset
- Contact with a confirmed or probable case in the 14 days prior to symptom onset
- Concomitant medications taken by the patient, including experimental medications, to treat COVID-19
- Home quarantine or isolation requirements

7.4. Data sources

Data were collected from EHRs of patients enrolled into the study. All data were entered by the staff at each clinical site into a password-protected eCRF.

Data collection started at the time of each patient enrollment. For each patient, data continued to be collected quarterly until maximum 5 years of follow-up from the first dose of niraparib was achieved, until lost to follow-up, patient's death, or Sponsor termination of the study, whichever occurred first.

7.5. Bias

Patients could have initiated niraparib prior to the time of enrollment. For these patients, some follow-up data was collected retrospectively, which may have introduced information bias. Additionally, some of these patients terminated niraparib treatment prior to enrollment but were still considered eligible for the study.

All AEs, serious and non-serious, were collected and recorded in the eCRF for each patient starting from the signing of the ICF, with the exception of MDS/AML and other SPMs and embryo fetal toxicity (see Section 7.3.3), which were captured from niraparib initiation. This introduced immortal time bias as patients who started niraparib prior to

the time of signing the ICF contributed person-time to the analysis, but no safety events other than MDS/AML (primary objective), other SPMs (secondary objective), and embryo fetal toxicity were reported between the date of niraparib initiation and date of ICF signing. Thus, this immortal time bias may have been introduced in the reporting of safety events but did not impact the capture of MDS/AML and other SPMs.

7.6. Study size

CCI [redacted] Thus, the minimum data required to achieve a quantifiable number of MDS/AML and other SPM events was 1000 patient-years with approximately 2.5 years of average follow-up.

To allow for the necessary time required for development of a SPM, patients were followed for up to 5 years from niraparib treatment initiation. Data from a clinical trial that evaluated survival in patients treated with olaparib maintenance therapy suggested that with maximum 5-years follow-up from treatment initiation it was possible to achieve an average of approximately 2.5 years of follow-up per patient, which was consistent with the NOVA clinical trial follow-up acquired [Ledermann, 2014].

Given the high risk for missing data and for losing patients to follow-up in a non-interventional study within a real-world setting, it was planned to recruit up to 800 patients for 1000 patient-years collected over a maximum of 5 years of follow-up per patient. This sample size would allow adequate patient data to compensate for a large incidence of missing data given that it was expected to observe a significant incidence of MDS/AML and other SPMs when 1000 patient-years were reached.

The sample size was not revised following the addition to the study population patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who were in response (complete or partial) following completion of first-line platinum-based chemotherapy. It was anticipated that the exposure to niraparib would be similar in the 2 populations based on the data from the NOVA and PRIMA clinical trials.

Table 3 provides the 95% CIs for different numbers of observed events of MDS/AML during this follow-up period.

Table 3 Confidence Intervals for Observed Events of MDS/AML for 100 Patient-Years

Observed Number of Events	Rate (per 100 patient-years)	Lower 95% Confidence Limit (per 100 patient-years)	Upper 95% Confidence Limit (per 100 patient-years)
5	0.5	0.16	1.2
10	1.0	0.48	1.8
15	1.5	0.84	2.5
20	2.0	1.2	3.1
25	2.5	1.6	3.7

Enrollment in the study closed on 17 January 2023 when the *a priori* patient-years threshold (1000 patient-years) had been surpassed. A total of patients 797 were enrolled across 94 sites.

7.7. Data analysis

This was an observational, non-interventional prospective study to characterize the risk of MDS/AML and other SPMs in niraparib-treated patients. The study did not evaluate the efficacy of the drug. No comparisons of the incidence of events of interest were planned between patient groups.

Unless otherwise stated, the analysis population for all final analyses completed was the Safety Population, defined as all patients who enrolled, met all eligibility criteria, and received at least 1 dose of niraparib, with sufficient clinical information to classify their niraparib line of therapy.

Analyses were descriptive; no hypotheses were tested. Summary statistics, including the number and percentage for categorical variables and the number of patients, mean, SD, Q1, median, Q3, minimum, and maximum for continuous variables were provided. Patient and tumor characteristics were summarized for the overall Safety Population and stratified by patients who received niraparib in the 1LM or 2LM+ setting.

For a detailed description of all planned data analyses please refer to the latest SAP version 2.0, dated 17 May 2024 (please refer to ANNEX 1 for a list of available stand-alone documents, including the SAP).

7.7.1. Patient Characteristics

7.7.1.1. Patient Disposition

Patient disposition was summarized overall and by 1LM and 2LM+ cohorts, based on the Enrolled Population. Within the subset of the patients included in the Safety Population, follow-up years were provided cumulatively. The cumulative number and percentage of patients in the Safety Population were described, along with the cumulative number and percentage of the Safety Population who completed less than 1-year of follow-up, 1-year of follow-up, 2-years of follow-up, 3-years of follow-up, 4-years of follow-up, and 5-years of follow-up after niraparib initiation. The number and percentage of patients in the

Safety Population who discontinued the study along with primary reason for study discontinuation were also described.

Primary reason for study discontinuation was summarized by category:

- Withdrawal of consent
- Lost to follow-up
- Death from any cause
- Sponsor decision to terminate study
- Other

If the primary reason for study discontinuation was death, the main cause of death was also provided.

7.7.1.2. Protocol Deviations

Study protocol deviations and important protocol deviations were identified and assessed by the clinical research physician or designee following the SOP on collection, evaluation, and reporting of protocol deviations and important protocol deviations. Major protocol deviations were presented as important protocol deviations.

7.7.1.3. Background and Demographic Characteristics

Demographic and clinical baseline characteristics of patients were summarized overall and by 1LM and 2LM+ cohorts. Baseline study variables are provided in Section 7.3.2.1.

7.7.1.4. Treatment Exposure and Compliance

The extent of exposure to niraparib was evaluated by duration of exposure (months), calculated as total time from start date of niraparib to niraparib end date (i.e., the last dose on drug), or, for patients who did not discontinue niraparib or who did not have a dose interruption, to the date of database lock. For patients who had a dose interruption and did not restart niraparib treatment at the time of database lock, the last non-missing niraparib administration date was used as the end date.

Descriptive statistics of duration of niraparib exposure, duration of niraparib treatment prior to development of MDS/AML or other SPMs, and niraparib starting dose were summarized overall and by 1LM and 2LM+ cohorts.

Dose modifications were summarized for the same cohorts as follows:

- Number and percentage of patients with at least 1 dose modification, patients with starting dose modified, reason for dose modification (Thrombocytopenia, Anemia, Fatigue, Nausea or Other)
- Number and percentage of patients with a subsequent dose modification, reason for dose modification (Thrombocytopenia, Anemia, Fatigue, Nausea or Other)

- Number and percentage of patients with dose interrupted, reason for dose interruption (Thrombocytopenia, Anemia, Fatigue, Nausea or Other)
- Number and percentage of patients with niraparib administration discontinued, reason for discontinuation (Disease progression, Patient request, Investigator discretion, Patient become pregnant, Patient passed away, AE [grade 3 or higher], or Other)

Patients could have experienced multiple dose modifications during the treatment period.

7.7.1.5. Prior and Concomitant Medications and Therapies

Relevant medications/therapies were collected and coded into Anatomical Therapeutic Chemical classification levels and PT according to the corresponding GSK Drug Synonym.

7.7.2. Primary Analysis

7.7.2.1. Main Analytical Approach

Incidence rates of MDS/AML and/or other SPMs and their respective 95% CIs per 100 person-time units were estimated overall and by 1LM and 2LM+ cohorts. Time to onset of MDS/AML and/or other SPMs was also provided.

Time at-risk, provided as patient-years, was calculated as the total time from start date of niraparib to either the first onset of MDS/AML or other SPM, or, for patients who had no events of MDS/AML or other SPM, to the earliest occurrence of date of study discontinuation, death, or date of database lock for final analysis. Table 4 describes the start date and end date for each patient-years calculation.

Table 4 Patient-years Start and End Dates (Time at-risk)

	Patient-years start date	Patient-years end date
Overall patient-years	Start date of niraparib (Index date)	Developed event: Earliest onset date of MDS or AML or SPM Did not develop event: Earliest date of study discontinuation, death, or date of database lock
Incidence rate of MDS/AML patient-years	Start date of niraparib (Index date)	Developed event: Earliest onset date of MDS or AML (not including SPM) Did not develop event: Earliest date of study discontinuation, death, or date of database lock
Incidence rate of SPMs patient-years	Start date of niraparib (Index date)	Developed event: Earliest onset date of SPM (not including MDS or AML) Did not develop event: Earliest date of study discontinuation, death, or date of database lock

	Patient-years start date	Patient-years end date
Incidence rate of MDS/AML and SPMs patient-years	Start date of niraparib (Index date)	Developed event: Earliest onset date of MDS or AML or SPM Did not develop event: Earliest date of study discontinuation, death, or date of database lock Note: This is the same as overall patient-years.

All analyses were performed using SAS statistical software version 9.4 or later. The SAS Programming and Validation Plan describing project-specific requirements, SOP for executing and documenting the validation of outputs and deliverables is listed in ANNEX 1, available stand-alone documents.

7.7.2.2. Data Handling Conventions/Data Transformations

Retrospective data were based on historical dates in which some data might be missing or incomplete. Outcomes dates, which are the dates corresponding to study endpoints such as MDS/AML or other SPM start or end dates, were not imputed. Milestone dates, which are dates of protocol milestones (e.g., informed consent date, start date of niraparib, niraparib termination date, etc.), should not be missing if the milestone occurred for a patient. When necessary, sites were queried for incomplete or missing date for protocol milestones.

Incomplete dates for study treatment, prior anticancer therapies, and radiotherapy

Start and stop dates of niraparib were imputed by assigning the first day of the month when only the day part of the date was missing. Otherwise, incomplete dates were treated as missing. The other treatment dates (e.g., start date of anticancer treatment including PARP and non-PARP inhibitors, and radiotherapy treatment) were imputed by the earliest possible date given the non-missing field(s) of the date, e.g., 01 January. Incomplete date with missing year was treated as missing.

Incomplete dates for disease history

Incomplete date of ovarian cancer diagnosis was imputed by the earliest possible date given the non-missing field(s) of the date (e.g., 01 January) in the analysis, such as calculation of age at ovarian cancer diagnosis. Incomplete start and end dates of other disease history were not imputed, including autoimmune diseases history and other cancer diagnosis. However, for the analysis of baseline disease characteristics such as to determine prior autoimmune diseases history (yes or no), the incomplete date was compared with the first dose date of niraparib by using the same imputation rule as incomplete date of ovarian cancer diagnosis, i.e. if the day of the disease start date was missing, the first day of month was used; if both the day and month of the disease start date were missing, 01 January was used for the missing parts to compare with niraparib first dose date.

Incomplete dates for prior concomitant medications and surgeries

Incomplete start and end date of relevant concomitant medications/therapies and date of surgery were not imputed. However, the incomplete date was compared with the first dose date of niraparib by using the same approach as described for incomplete dates for disease history for the analysis of baseline disease characteristics such as to determine prior surgery history (yes or no).

Missing or incomplete dates for adverse events

Queries were issued to the site for missing or incomplete start dates for AEs. When necessary, dates were imputed in the analysis dataset for AEs. The AE was assumed as treatment emergent if it could not be definitively shown that the AE did not occur or worsen during the treatment-emergent period, from start date of niraparib to 30 days after the end date of niraparib (worst case approach). The following rules were applied:

- For missing start day only: Day was imputed as the first day of the month (i.e., 01) with the following exception: if the partial date fell in the same month and year as niraparib start date, then the partial date was imputed to equal niraparib start date
- For missing start day and month: Day and month were imputed as the first day of the year (i.e., 01 January) with the following exception: if the partial date fell in the same year as niraparib start date, then the partial date was imputed to equal niraparib start date
- For complete missing: Date was imputed to equal niraparib start date
- Imputed start dates had to be prior to niraparib discontinuation date or completion date

7.7.2.3. Sensitivity Analyses

A sensitivity analysis was performed on the group of patients who initiated niraparib prior to study enrollment and those who initiated niraparib on or after enrollment.

7.7.3. Secondary Analysis

The distribution of MDS/AML and/or other SPM events was summarized across various risk factors for these events: age, anticancer chemo- and radiotherapy received, history of other cancers, family history of cancers, presence of autoimmune disorders, use of alcohol and/or tobacco, exposure to certain chemicals and heavy metals, other non-DNA damaging anti-cancer treatments, use of other PARP inhibitors, weight, prior history of cytopenia, and MCV (for a complete explanation of variables analyzed during the study, see Section 7.3).

7.7.4. Safety Analyses

All AEs were coded into SOC and PT according to MedDRA Version 27.0. TEAEs were summarized descriptively using number and percentage by MedDRA SOC/PT. A patient was counted only once at the Dictionary Synonym level. Each AE was graded using NCI CTCAE version 5.0. If a patient experienced the same TEAE more than once with different CTCAE grade, the event with the highest grade was considered for the table summary by intensity.

All AE listings included the date of onset, date of resolution (if AE was resolved) and investigator's assessment of severity and relationship to study drug. Missing (partial) start/stop dates appear as missing (partial) in the patient data listings but start dates were imputed to permit proper tabulation of AE data (see Section 7.7.2.2).

AEs were summarized descriptively by number and percentage (%) of patients with an event (n [%]), and number of events [e], by MedDRA SOC/PT and CTCAE grade.

A patient was counted once at the SOC level and once at PT level. For summaries by SOC, PT, and severity, a patient was counted only once at the maximum CTCAE grade. Summaries by relatedness were handled similarly to the summaries by intensity. Summaries by SOC and PT were ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. Summaries of PT were ordered in descending frequency of PT.

Summaries of TEAEs were generated for each of the following:

- Overview of Patients with AEs (Table 14.3.01)
- MDS/AML and other SPM events by PT (Table 14.3.02)
- MDS/AML and other SPM events related to niraparib by PT (Table 14.3.03)
- TEAEs by SOC and PT (Table 14.3.04)
- Related to niraparib TEAEs by SOC and PT (Table 14.3.05)
- TEAEs by SOC and PT and maximum NCI CTCAE grade (Table 14.3.06)
- Related to niraparib TEAEs by SOC and PT and maximum NCI CTCAE grade (Table 14.3.07)
- Serious TEAEs by SOC and PT (Table 14.3.08)
- Related to niraparib serious TEAEs by SOC and PT (Table 14.3.09)
- Serious TEAEs by SOC and PT (Number of patients and occurrences) (Table 14.3.10)
- TEAEs leading to drug withdrawn by SOC and PT (Table 14.3.11)
- Related to niraparib TEAEs leading to drug withdrawn by SOC and PT (Table 14.3.12)
- TEAEs with death outcome by SOC and PT (Table 14.3.13)

- Related to niraparib TEAEs with death outcome by SOC and PT (Table 14.3.14)
- Common (≥5%) TEAEs by overall frequency (Table 14.3.15)
- Related to niraparib non-serious TEAEs by Overall Frequency (Table 14.3.16)
- Serious fatal and non-fatal related to niraparib TEAEs by Overall Frequency (Table 14.3.17)

The following by-patient listings are also available:

- All AEs (Listing 15.26.0)
- MDS/AML and Other SPM events (Listing 15.27.0)
- AEs leading to drug withdrawn (Listing 15.26.0)
- AEs Grade 3 or higher by maximum NCI CTCAE grade (Listing 15.28.0)
- Serious TEAEs (Listing 15.29.0)
- Reasons for considering as a SAE (Listing 15.30.0)
- TEAEs with death outcome (Listing 15.31.0)
- All deaths (Listing 15.34.0)
- Patients with MDS/AML events (Listing 15.35.0)
- Patients with SPM events (Listing 15.36.0)

7.7.5. Amendments to Statistical Plan

The criteria utilized to identify the Safety Population was updated to restrict inclusion to patients that met all eligibility criteria, with sufficient clinical information to classify their niraparib line of therapy, as this information was not directly collected on the eCRF. Line of therapy was also refined and definitions for follow-up and patient-years were added.

Baseline variables measured in a subset of the population were reported as proportions with the relevant subset as the denominator (e.g., smoking duration measured among current or former smokers only).

Furthermore, the need to derive additional variables of interest was identified, including "*BRCA* Tested" (yes, no) and "HRD Tested" (yes, no), biomarker status, line of therapy, total lines of platinum-based chemotherapy, total cycles of prior platinum-based chemotherapy, PDS, IDS, NAT for ovarian cancer, AT, and dose modifications (please refer to the latest SAP version 2.0, dated 17 May 2024, and Derived Study Variables of Interest in ANNEX 2).

Lastly, to align with the EMA approval of early study termination, the exploratory objective and any related text and analyses were removed. Furthermore, due to low volume of events, stratum-specific sample sizes, and removal of exploratory objectives, some analyses were not feasible and could not be performed.

7.8. Quality Control and Quality Assurance

7.8.1. Data Quality Assurance

Investigators were responsible for preparing and maintaining adequate and accurate records of all observations and other data pertinent to the study for each study participant. The Investigator was also responsible for making all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor had the ability to review safety information as it became available throughout the study.

All aspects of the study were carefully monitored with respect to SOPs for compliance with applicable government regulations. Furthermore, a data management quality review was performed on an ongoing basis throughout the project, once data entry and remote data review were complete, queries were resolved, associated manual listings were reviewed with issues resolved for each patient and clinical coding was complete. This was performed on critical safety and efficacy fields and included the review of query responses for manually raised queries on defined fields within the eCRF to ensure the responses were appropriate. All findings from the data management quality review were documented in a quality review log and followed through to resolution.

7.8.2. Access to Source Data/Documents

An EDC system to manage data collection was utilized during this study. The EDC system is a software tool designed to ensure quality assurance and facilitate data capture during non-interventional studies.

The Investigator ensured the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures were reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail of all data changes was maintained. The Investigator or designee cooperated with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each remote monitoring call or on site monitoring visit.

Electronic consistency checks and manual reviews were used to identify any errors or inconsistencies in the data. This information was provided to the respective study sites by means of electronic or manual queries.

The Sponsor and the Investigators followed the EU General Data Protection Regulation that replaces the Data Protection Directive 95/46/EC and that was designed to harmonize data privacy laws across Europe, to protect and empower all EU citizens' data privacy, and to reshape the way organizations across the region approach data privacy.

The Investigator allowed Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB to have direct access to all documents pertaining to the study.

7.8.2.1. Data Management

Data were entered by the staff at each clinical site into the study-specific eCRF. Access to the eCRF was only granted once the system-specific user role training had been successfully completed. All coding was performed by a clinical coder, using ICDS GlaxoSmithKline Ltd system. Data entry was expected within 10 working days of a site becoming aware of a reportable event or with 24 hours in the case of a SAE. Every data entry and every data change were automatically provided with a user and date (audit trail). System queries were triggered by data entry and required either a change in data or in an entered response (e.g., no blanks could appear in the eCRF where data was expected).

Missing data were identified via a standard listing in the clinical database called the Missing Page Report. The study database was designed to capture forms and visits per the defined schedule in the protocol. If a visit or form was available for entry in the database but not completed by the site, it was identified as missing in the Missing Page Report.

Once all edit/validation checks applicable to the study protocol were identified and approved by the clinical study team, they were programmed to help identify any missing data and data discrepancies. Queries were placed on the discrepant data within the EDC system for the site to respond and make any necessary corrections to the data. All derivation and validation procedures were fully tested and documented in UAT scripts. Details regarding the edit checks are listed in the Data Validation Specifications, an appendix of the Data Management Plan (please refer to ANNEX 1 for a list of available stand-alone documents, including the Data Management Plan).

In addition, a site management plan was established, which addressed the handling of any missing data with the sites (see Section 7.8.6).

7.8.3. Archiving Study Documents

Essential clinical documents were maintained to demonstrate the validity of the study, and the integrity of the data collected. Master files were established at the beginning of the study and were maintained for the duration of the study and retained according to the appropriate regulations.

Study documents will be archived by participating investigator sites and GSK for a minimum of 10 years following the finalization of this final study report.

7.8.4. Regulatory Guidelines

This study was conducted in accordance with the Declaration of Helsinki (version 2008), as well as with the guideline on GVP – Module VIII EMA/813938/2011 Rev 3 [EMA, 2017] and the Module VIII Addendum I EMA/395730/2012 Rev 3 [EMA, 2020]. The study was also carried out in accordance with national and local regulatory requirement(s).

7.8.5. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents were approved by the responsible IRB/IEC/Competent Authorities, in accordance with local legal requirements. The Sponsor ensured that all ethical and legal requirements had been met before the first patient was enrolled in the study.

7.8.6. Study Monitoring

A site management plan was established to include scheduled monitoring calls biannually with each site. Any missing data were addressed during these interactions with the sites. The plan also included the option of additional ad hoc calls and/or site visits where data collection presented persistent problems. A risk-based monitoring approach was followed and adapted as required in consultation with the Clinical Research Organization overseeing the implementation of the plan.

A monitor commissioned by the Sponsor could randomly check the data collection by matching the data stored in the eCRF with the medical records. Patients were informed about this aspect before participation in this non-interventional study and asked for their consent. Only patients who had given their informed consent could be observed in the non-interventional study.

All study materials were returned to the Sponsor upon study completion.

7.8.7. Audits and Inspections

Responsible IRB/IEC/Competent Authorities and/or the Sponsor’s clinical quality assurance group, or its designee, could request access to all source documents, CRFs, and other study documentation for on-site audits or inspections. Direct access to these documents was guaranteed by the Investigator, who provided support at all times for these activities.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical Approval and Subject Consent

This study was conducted in accordance with the ethical principles founded in the Declaration of Helsinki (version 2008). The IRB/IEC reviewed all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study was only conducted at sites where IRB/IEC approval had been obtained.

8.1.1. Informed Consent

Before each patient was enrolled in this safety study, written informed consent was obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator had to explain orally and in writing the nature, duration, and purpose of the study, in such a manner that the patient

was aware of the potential risks and inconveniences. The patient was informed that she was free to withdraw from the study at any time. The patient then received all information that was required by regulatory authorities and ICH guidelines. The Investigator or designee provided the Sponsor with a copy of the IRB/IEC-approved ICF, as required by each country's regulatory agency, prior to the start of the study.

The ICF had to be signed and dated; 1 copy was given to the patient, and the Investigator retained 1 copy as part of the study records. The Investigator did not undertake any investigation specifically required for the study until written consent had been obtained. The terms of the consent and when it was obtained also had to be documented.

8.2. Patient Confidentiality

The Sponsor, parties working with or on behalf of the Sponsor, the ethics committee responsible for approving the conduct of the study, local regulatory authorities and regulatory authorities in other countries where the Sponsor may seek approval for Zejula (niraparib), such as the US Food and Drug Administration, may access patient medical records to make sure the study has been done properly, and may be able to identify patients. Medical records will be reviewed only at the study site.

The personal data collected on patients may include sensitive information, as such, each participant was required to sign an ICF prior to study enrollment (see Section 8.1.1).

9. RESULTS

9.1. Participants

9.1.1. Patient Disposition

On 17 January 2023, enrollment in the study closed when the *a priori* patient-years threshold (1000 patient-years) had been surpassed. A total of 797 patients were enrolled from 94 sites.

Patient status and disposition for all patients enrolled are presented in Table 5. Of the Enrolled Population, 44 patients were deemed ineligible and were not included in the Safety Population (see Table 14.1.02 for a detailed summary of eligibility criteria deviations). An additional 8 patients were eligible, however excluded from the Safety Population with insufficient clinical information to classify their niraparib line of therapy (see Derived Study Variables of Interest in ANNEX 2). The remaining 745 patients met all eligibility criteria and received at least 1 dose of niraparib with sufficient clinical information to be included in the Safety Population.

The Safety Population cohort was stratified by niraparib line of therapy: 1LM or 2LM+ setting, with majority of patients receiving niraparib in the 2LM+ setting:

- First-line maintenance group: 181 patients
- Second or later line maintenance group: 564 patients

Note that at the time of the interim analysis, there were multiple open queries with sites. As these queries were resolved, additional data were available which resulted in the recategorization of some patients and an adjustment in the patient counts of the overall Safety Population, 1LM, and 2LM+ cohorts for the final analysis. Additionally, 1 patient included in the Safety Population during the interim analysis (Patient PPD), was marked as a screen failure on 15 January 2024 and therefore ineligible for the final analysis. Previous interim analysis counts were as follows: 798 patients enrolled, with 740 patients included in the Safety Population (174 1LM patients, 566 2LM+ patients).

Follow-up was more limited among 1LM patients. Approximately 86% (n=638) of the safety population completed 1-year of follow-up (84.0% [n=152] 1LM patients, 86.2% [n=486] 2LM+ patients), 53.7% (n=400) completed 2-years (35.9% [n=65] 1LM patients, 59.4% [n=335] 2LM+ patients), 29.3% (n=218) completed 3-years (6.1% [n=11] 1LM patients, 36.7% [n=207] 2LM+ patients), 14.8% (n=110) completed 4-years (0% [n=0] 1LM patients, 19.5% [n=110] 2LM+ patients), and 6.7% (n=50) completed the maximum 5-years of routine clinical follow-up (0% [n=0] 1LM patients, 8.9% [n=50] 2LM+ patients) (Table 5).

All patients who had not achieved the maximum 5-years of routine clinical follow-up milestone, were classified by reason for discontinuation from the study. Reasons for discontinuation included withdrawal of consent, lost to follow-up, death from any cause, Sponsor decision to terminate study, and other. Overall, death was the main reason for study discontinuation (47.1% [n=327]), mainly due to disease progression (84.4% [n=276]) (Table 5). An additional 40.4% (n=281) discontinued the study due to the EMA endorsed Sponsor decision to terminate the study early. By-patient listings of patient disposition for the Safety Population are provided in Listing 15.1.0.

Table 5 Patient Status and Patient Disposition (Enrolled Population)

	Enrolled Population		
	1LM	2LM+	Overall
Enrolled Population[1]			797
Ineligible Patients			44
Eligible with Insufficient Clinical Information			8
Safety Population[2], n (%)	181	564	745
Completed Less than 1-year Follow-up	29 (16.0%)	78 (13.8%)	107 (14.4%)
Completed 1-year Follow-up	152 (84.0%)	486 (86.2%)	638 (85.6%)
Completed 2-year Follow-up	65 (35.9%)	335 (59.4%)	400 (53.7%)
Completed 3-year Follow-up	11 (6.1%)	207 (36.7%)	218 (29.3%)
Completed 4-year Follow-up	0	110 (19.5%)	110 (14.8%)
Completed 5-year Follow-up	0	50 (8.9%)	50 (6.7%)
Discontinued	181 (100%)	514 (91.1%)	695 (93.3%)
Primary Reason Study Discontinuation[3], n (%)			
Withdrawal of Consent	3 (1.7%)	8 (1.6%)	11 (1.6%)
Lost to Follow-up[4]	17 (9.4%)	49 (9.5%)	66 (9.5%)
Death from Any Cause	42 (23.2%)	285 (55.4%)	327 (47.1%)
Sponsor Decision to Terminate Study	115 (63.5%)	166 (32.3%)	281 (40.4%)
Other	4 (2.2%)	6 (1.2%)	10 (1.4%)
If Death, Main Cause of Death[5], n (%)			

	Enrolled Population		
	1LM	2LM+	Overall
Disease Progression	37 (88.1%)	239 (83.9%)	276 (84.4%)
Adverse event	0	6 (2.1%)	6 (1.8%)
Unknown	5 (11.9%)	31 (10.9%)	36 (11.0%)
Other	0	9 (3.2%)	9 (2.8%)

Source: Table 14.1.01
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group.
[1]Enrolled Population are all patients who signed the informed consent form (ICF).
[2]Safety Population includes patients who enrolled, met inclusion/exclusion criteria, and received at least 1 dose of niraparib, with sufficient clinical information to classify their niraparib line of therapy. The percentage is based on the number of patients in Safety population.
[3]The percentage is based on the number of patients who are discontinued in Safety population.
[4]Patients are lost to follow-up after having 3 consecutive Interval Data Collections where PI has entered '*no*' to the question *'has the patient been seen since the last data collection?'*
[5]The percentage is based on the number of patients who discontinued from study due to death from any cause.

As of the database lock date of 11 July 2024, 1762.6 patient-years were accumulated (322.9 patient-years accumulated in 1LM patients and 1439.6 patient-years accumulated in 2LM+ patients) (see Section 7.7.2.1). Time at-risk specific to first onset of MDS/AML was 1767.6 patient-years (324.1 patient-years in 1LM and 1443.4 patient-years in 2LM+) and time at-risk specific to other SPM was 1767.6 patient-years (322.9 patient-years in 1LM and 1444.7 patient-years in 2LM+) (see Section 9.4.1).

9.1.2. Protocol Deviations

This PASS took place during the COVID-19 pandemic, as a result of which some of the study data may have been impacted in terms of missing visits and/or assessments. No protocol deviations related to COVID-19 occurred.

Overall, there were 143 enrolled patients with at least 1 important protocol deviation (17.9%), of whom 102 patients (71.3%) were kept for analysis in the Safety Population (n=58 1LM patients; n=44 2LM+ patients) as the protocol deviation did not impact their eligibility but rather involved treatment start date, an outdated form, a pending protocol amendment or the reporting of SAEs.

Eligibility criteria deviations made up the majority of protocol deviations overall (n=98; 68.5%) and in the 1LM setting (n=50; 86.2%). Due to the real-world nature of the study, sites were guided by the EU SmPC guidelines when considering patients eligible for inclusion, which were updated to include first-line maintenance therapy after the study had started. Prior to the approval of an amended protocol and associated ICF, sites were working and enrolling patients under the new SmPC guidelines, thereby deviating from the eligibility criteria outlined in the available ICF version. Additionally, there were 24 protocol deviations regarding the ICF in the overall Enrolled Population, of which 20 were in the Safety Population. There have been multiple versions of the ICF since study start up. Despite several reminders and re-trainings, some sites continued to use older ICF versions after the new versions became available.

Furthermore, on 18 February 2021, a NTF was issued to begin excluding patients with non-indicated histology. Prior to this date, there were 14 patients kept in the study with a non-indicated histology, who otherwise met all study eligibility criteria. Each of these were recorded as eligibility criteria protocol deviations.

There were 29 SAEs or safety follow-up reports not reported or reported late in the overall Enrolled Population, and 27 in the Safety Population. Most of these (n=23) were for 2LM+ patients.

Summaries of the SAEs reported outside the required timeline are as follows:

- Patient PPD experienced thrombocytopenia on PPD and hydronephrosis on PPD These events were reported to the Sponsor on PPD and PPD respectively.
- Patient PPD experienced MDS on PPD and was hospitalized on PPD . This event was reported to the Sponsor on PPD PPD
- Patient PPD experienced dyspnea on PPD requiring hospitalization. This event was reported to the Sponsor on PPD
- Patient PPD experienced a platelet count decrease reported in the patient's chart on PPD This event was not reported to the Sponsor until PPD PPD
- Patient PPD experienced thrombocytopenia on PPD This event was reported to the Sponsor on PPD
- Patient PPD experienced events of asthenia from PPD to PPD and from PPD to PPD as well as insomnia from PPD to PPD . These events were not reported to the Sponsor within the required timeframe.
- Patient PPD experienced MDS on PPD This event was reported to the Sponsor on PPD
- Patient PPD experienced ileal obstruction and myelotoxicity on PPD These events were reported to the Sponsor on PPD
- Patient PPD experienced dyspnea on PPD This event was reported to the Sponsor on PPD
- Patient PPD experienced episodes of constipation on PPD and again on PPD These events were reported to the Sponsor on PPD and PPD respectively.
- Patient PPD experienced a bowel obstruction on PPD The site was notified of this event on PPD and it was reported to the Sponsor on PPD PPD
- Patient PPD experienced pancytopenia. This event was reported late to the Sponsor.

- Patient PPD experienced ileus. This event was not reported to the Sponsor.
- Patient PPD experienced a cerebral infarction on PPD The event was reported to the Sponsor on PPD
- Patient PPD experienced a SAE that was reported late to the Sponsor on PPD
- Patient PPD experienced a SPM (breast cancer diagnosis) in PPD. This event occurred after study enrollment on PPD and niraparib treatment initiation on PPD. This event was reported late to the Sponsor.
- Patient PPD experienced a SAE of anemia that led to hospitalization on PPD. The event was reported to the Sponsor on PPD
- Patient PPD was hospitalized due to thrombocytopenia; however the event was not reported until 1 month later.
- Patient PPD experienced a SPM (head and neck cancer diagnosis) on PPD and it was reported to the Sponsor on PPD
- Patient PPD experienced a platelet count decrease (grade 4) that was not reported as a serious event at the time.
- Patient PPD experienced a platelet count decrease (grade 4) that was not reported as a serious event at the time.
- Patient PPD required a Custom Safety Report follow-up report which was not sent to the Sponsor safety team within 24 hours as expected.
- Patient PPD experienced bronchopneumonia reported in the patient's chart on PPD This event was not reported to the Sponsor until PPD
- Patient PPD experienced kidney congestion of the left side requiring hospitalization on PPD. This event was not reported to the Sponsor until PPD
- Patient PPD experienced two SAEs of thrombocytopenia that were reported late to the Sponsor.
- Patient PPD experienced ileal obstruction and myelotoxicity reported in the patient's chart on PPD These events were reported to the Sponsor on PPD
- Patient PPD was hospitalized due to bowel occlusion and the event was not reported to the Sponsor until 3 months after.
- Patient PPD was hospitalized due to suspected spondylodiscitis and the event was not reported to the Sponsor until 2 months after.
- Patient PPD experienced dyspnea and streptococcus pneumoniae grade 3 that were not reported within the required 24 hours.

- Patient PPD experienced acute leukemia that was not reported within the required 24 hours.

A high-level summary of protocol deviations is provided in Table 14.1.03. Additionally, details by patient are provided in Listing 15.4.0.

Of note, there were 6 patients marked as screen failures who were excluded from the study before any data were collected (e.g., signatures on the ICF acquired after enrollment had closed):

- Patient PPD
- Patient PPD
- Patient PPD
- Patient PPD
- Patient PPD
- Patient PPD

These 6 patients are not included in Listing 15.4.0 of important protocol deviations; however, they are included in Listing 15.2.0 of patients who did not meet eligibility criteria.

9.2. Descriptive data Including Baseline Characteristics

9.2.1. Demographics and General Characteristics

A summary of patient demographics and general characteristics for the Safety Population overall, and by 1LM patients and 2LM+ patients are provided in Table 6. The median age at index (niraparib initiation) was 65.0 years (IQR 58.0, 72.0 years). The median BMI (derived from patients' height and weight at index) was 24.6 kg/m^2 (IQR 21.8, 28.1 kg/m^2) (Table 6). By category, the 1LM cohort had a higher percentage of patients with a BMI <25 kg/m^2 (55.8% and 50.9%) and a lower percentage of patients with a BMI ≥30 kg/m^2 (11.0% and 17.2%) than 2LM+ patients, respectively. Demographics are listed by patient in Listing 15.3.0.

Table 6 Demographics and General Characteristics

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Age at Index (niraparib Initiation) (years)			
n	181	564	745
Mean	65.5	64.4	64.7
SD	10.80	9.49	9.83
Q1	59.0	58.0	58.0
Median	66.0	65.0	65.0
Q3	74.0	72.0	72.0
Min	23	39	23
Max	84	88	88
Age Group at Index, n (%)			
<50 Years	14 (7.7%)	35 (6.2%)	49 (6.6%)
50-64 Years	68 (37.6%)	244 (43.3%)	312 (41.9%)
65-74 Years	57 (31.5%)	197 (34.9%)	254 (34.1%)
≥75 Years	42 (23.2%)	88 (15.6%)	130 (17.4%)
Weight Group at Index, n (%)			
<58 kg	46 (25.4%)	135 (23.9%)	181 (24.3%)
≥58 kg	129 (71.3%)	415 (73.6%)	544 (73.0%)
Missing	6 (3.3%)	14 (2.5%)	20 (2.7%)
BMI at Index (kg/m^2)			
n	172	545	717
Mean	24.73	25.59	25.38
SD	4.763	4.914	4.889
Q1	21.40	22.00	21.80
Median	24.05	24.70	24.60
Q3	27.15	28.40	28.10
Min	16.0	16.0	16.0
Max	45.9	46.4	46.4
BMI Group at Index, n (%)			
<25 kg/m^2	101 (55.8%)	287 (50.9%)	388 (52.1%)
25 – 29.9 kg/m^2 (Overweight)	51 (28.2%)	161 (28.5%)	212 (28.5%)
≥30 kg/m^2 (Obese)	20 (11.0%)	97 (17.2%)	117 (15.7%)
Missing	9 (5.0%)	19 (3.4%)	28 (3.8%)

Source: Table 14.1.04

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; BMI = Body mass index; kg = kilogram; m = meter; Max = Maximum; Min = Minimum; Q1 = First quartile; Q3 = Third quartile; SD = Standard deviation.

The median age at ovarian cancer diagnosis was 62.0 years (IQR 54.0, 69.0 years) (Table 7). More than half of patients (52.3%; n=390) reported any family cancer history at enrollment (45.3% of the 1LM cohort [n=82]; 54.6% of the 2LM+ cohort [n=308]). Most patients (72.9%) had niraparib exposure prior to study enrollment (61.9% of 1LM patients [n=112]; 76.4% 2LM+ patients [n=431]). A total of 20 patients (2.7%) had history of an autoimmune disease prior to initiation of niraparib, of whom 90.0% (n=18) had ongoing disease. Baseline characteristics are listed by patient in Listing 15.6.0, Listing 15.8.0, and Listing 15.16.0.

Table 7 Baseline Characteristics

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Age at Ovarian Cancer Diagnosis (years)			
n	181	564	745
Mean	64.7	60.4	61.5
SD	10.68	9.88	10.24
Q1	58.0	53.0	54.0
Median	65.0	61.0	62.0
Q3	73.0	68.0	69.0
Min	22	19	19
Max	83	86	86
Age Group at Ovarian Cancer Diagnosis, n (%)			
<50 Years	15 (8.3%)	90 (16.0%)	105 (14.1%)
50-64 Years	73 (40.3%)	264 (46.8%)	337 (45.2%)
65-74 Years	56 (30.9%)	173 (30.7%)	229 (30.7%)
≥75 Years	37 (20.4%)	37 (6.6%)	74 (9.9%)
Niraparib Exposure prior to Enrollment, n (%)			
Yes	112 (61.9%)	431 (76.4%)	543 (72.9%)
No	69 (38.1%)	133 (23.6%)	202 (27.1%)
Family Cancer History at Enrollment, n (%)			
Yes	82 (45.3%)	308 (54.6%)	390 (52.3%)
No	68 (37.6%)	173 (30.7%)	241 (32.3%)
Unknown	31 (17.1%)	83 (14.7%)	114 (15.3%)
Autoimmune Disease History Prior to niraparib Initiation, n (%)			
Yes	7 (3.9%)	13 (2.3%)	20 (2.7%)
No	172 (95.0%)	547 (97.0%)	719 (96.5%)
Unknown	2 (1.1%)	4 (0.7%)	6 (0.8%)
If yes (Autoimmune Disease History), Ongoing[1], n (%)			
Yes	6 (85.7%)	12 (92.3%)	18 (90.0%)
No	1 (14.3%)	1 (7.7%)	2 (10.0%)

Source: Table 14.1.05

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; Max = Maximum; Min = Minimum; Q1 = First quartile; Q3 = Third quartile; SD = Standard deviation.

Note: "Unknown" are those who have "Unknown" checked on eCRF. "Missing" are those with no reported data.

[1]The percentage is based on the number of patients who have history of an autoimmune disease.

Behavioral and environmental factors collected at study enrollment included smoking and alcoholic drink habits, as well as exposures to oncogenic factors such as solvents (including benzene, gasoline, oil, ammonia), agricultural chemicals (including pesticides, fertilizer, herbicide), contact with poultry or livestock, infective risks (e.g., activities involving sick people or animals, occupations including garbage collectors, cleaners, etc.), fumes and dust (including metal or textiles), asbestos, heavy metals, or 'other'. Behavioral and environmental factors by-patient listings are available in Listing 15.12.0.

Most patients reported to have never smoked (66.3%; n=494), with 22.7% (n=169) reporting former smoking, and 7.1% (n=53) reporting to be current smokers (Table 8). Smoking status was unknown ("unknown" marked on the eCRF) for 3.8% (n=28) and missing (data not reported) for 0.1% (n=1) of patients. Of current and former smokers (n=222), data on the duration in years of smoking at study enrollment was available for 131 patients (59.0%) (median 20.0 years; IQR 13.0, 37.0 years) and data on the average number of cigarettes smoked per day was available for 158 patients (71.2%) (mean 12 cigarettes; SD 8.86; range 0 to 40 cigarettes).

Table 8 Baseline Behavioral and Environmental Factors

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Smoking Status at Enrollment, n (%)			
Never Smoked	124 (68.5%)	370 (65.6%)	494 (66.3%)
Former Smoker	37 (20.4%)	132 (23.4%)	169 (22.7%)
Current Smoker	15 (8.3%)	38 (6.7%)	53 (7.1%)
Unknown	5 (2.8%)	23 (4.1%)	28 (3.8%)
Missing	0	1 (0.2%)	1 (0.1%)
Smoking Duration at Enrollment[1] (years)			
n	34	97	131
Mean	26.8	22.9	23.9
SD	13.60	14.28	14.16
Q1	15.0	10.0	13.0
Median	30.0	20.0	20.0
Q3	40.0	32.0	37.0
Min	3	1	1
Max	48	57	57
Average Number of Cigarettes Smoked Per Day[1]			
n	39	119	158
Mean	11.3	12.2	12.0
SD	8.16	9.10	8.86
Q1	4.0	5.0	5.0
Median	10.0	10.0	10.0
Q3	20.0	20.0	20.0
Min	1	0	0
Max	30	40	40
Alcohol Use at Enrollment, n (%)			
Yes	39 (21.5)	97 (17.2)	136 (18.3)
No	134 (74.0)	439 (77.8)	573 (76.9)
Unknown	8 (4.4)	25 (4.4)	33 (4.4)
Missing	0	3 (0.5)	3 (0.4)
Average Number of Alcoholic Drinks Before Ovarian Cancer Diagnosis[2] (drinks per week), n (%)			
1-2	30 (76.9%)	52 (53.6%)	82 (60.3%)
3-6	3 (7.7%)	21 (21.6%)	24 (17.6%)
7-12	3 (7.7%)	10 (10.3%)	13 (9.6%)
13-24	0	3 (3.1%)	3 (2.2%)
>24	0	2 (2.1%)	2 (1.5%)
Unknown	1 (2.6%)	4 (4.1%)	5 (3.7%)
Missing	2 (5.1%)	5 (5.2%)	7 (5.1%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Average Number of Alcoholic Drinks After Ovarian Cancer Diagnosis[2] (drinks per week), n (%)			
1-2	29 (74.4%)	57 (58.8%)	86 (63.2%)
3-6	0	10 (10.3%)	10 (7.4%)
7-12	3 (7.7%)	6 (6.2%)	9 (6.6%)
13-24	1 (2.6%)	3 (3.1%)	4 (2.9%)
>24	0	0	0
Unknown	3 (7.7%)	14 (14.4%)	17 (12.5%)
Missing	3 (7.7%)	7 (7.2%)	10 (7.4%)
Exposure to Oncogenic Factors at Enrollment, n (%)			
Yes	0	4 (0.7%)	4 (0.5%)
No	109 (60.2%)	447 (79.3%)	556 (74.6%)
Unknown	72 (39.8%)	110 (19.5%)	182 (24.4%)
Missing	0	3 (0.5%)	3 (0.4%)

Source: Table 14.1.05, Listing 15.12.0
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second line or later maintenance group; Max = Maximum; Min = Minimum; Q1 = First quartile; Q3 = Third quartile; SD = Standard deviation.
Note: "Unknown" are those who had "unknown" checked on eCRF. "Missing" was when the eCRF field was left blank.
[1]Measured among current or former smokers at enrollment. There was 1 patient who reported being a former smoker and smoked <1 cigarette per day. Due to non-conformant data rules, this was reflected as 0 cigarettes per day.
[2]Restricted to only patients who reported drinking alcohol at enrollment.

A total of 136 (18.3%) patients reported drinking alcohol at enrollment. Approximately 60% of these patients (n=82) reported consuming an average of 1 to 2 drinks per week prior to being diagnosed with ovarian cancer, with an additional 17.6% (n=24) reporting an average of 3 to 6 drinks per week, 9.6% (n=13) reporting an average of 7 to 12 drinks per week, 2.2% (n=3) reporting an average of 13 to 24 drinks per week, and 1.5% (n=2) reporting an average >24 drinks per week prior to ovarian cancer diagnosis (Table 8). Drinking behavior prior to ovarian cancer diagnosis was unknown ("unknown" marked on the eCRF) for 3.7% (n=5) and missing (data not reported) for 5.1% (n=7) of patients.

After being diagnosed with ovarian cancer, 63.2% (n=86) reported consuming an average of 1 to 2 drinks per week, 7.4% (n=10) reported an average of 3 to 6 drinks per week, 6.6% (n=9) reported an average of 7 to 12 drinks per week, and 2.9% (n=4) reported an average of 13 to 24 drinks per week post-diagnosis (Table 8). No patients reported consuming an average >24 drinks per week after ovarian cancer diagnosis. Drinking behavior post-ovarian cancer diagnosis was unknown ("unknown" marked on the eCRF) for 12.5% (n=17) and missing (data not reported) for 7.4% (n=10) of patients who reported alcohol use.

Of note, the eCRF lacked an option of reporting an average of zero drinks per week prior to and after ovarian cancer diagnosis.

Furthermore, 4 patients (0.5%) reported exposure to oncogenic factors at enrollment. Of these, 1 patient had been exposed to heavy metals, 1 had been exposed to infective risks (activities involving sick people/animals, occupations including garbage collectors, cleaners, etc.), and 2 had been exposed to 'other' factors (Listing 15.12.0).

Demographics and baseline characteristics were consistent across patients who received niraparib prior to or on/after enrollment (see Table 14.1.06).

9.2.2. Biomarker Characteristics

Overall, 78.5% (n=585) of patients had been tested for *BRCA* (67.4% of 1LM patients [n=122]; 82.1% of 2LM+ patients [n=463]) (Table 9). The majority of those tested were *BRCA* wild type (84.8% [n=496] overall; 88.5% [n=108] 1LM patients; 83.8% [n=388] 2LM+ patients), while 14.7% (n=86) of patients were *BRCA* mutant (10.7% [n=13] 1LM patients, 15.8% [n=73] 2LM+ patients).

In total, 30.2% of patients (n=225) were tested for HRD (28.7% of 1LM patients [n=52]; 30.7% of 2LM+ patients [n=173]), with 54.2% of those tested having unspecified results (i.e., missing) (Table 9). Approximately 16% (n=35) were HRD test-positive (HR-deficient) and 30.2% (n=68) were HRD test-negative (HR-proficient).

Biomarker status was derived from available HRD and *BRCA* test results for 80.4% (n=599) patients: 15.2% (n=113) patients were HR-deficient (14.9% [n=27] 1LM patients; 15.2% [n=86] 2LM+ patients), 9.1% (n=68) patients were HR-proficient (15.5% [n=28] 1LM patients; 7.1% [n=40] 2LM+ patients), and 56.1% (n=418) patients were HR-unknown/*BRCA* wild type (43.1% [n=78] 1LM patients; 60.3% [n=340] 2LM+ patients) (Table 9).

By-patient listings of biomarker characteristics are available in Listing 15.7.0.

Table 9 Summary of Biomarker Characteristics

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
BRCA Tested, n (%)			
Yes	122 (67.4%)	463 (82.1%)	585 (78.5%)
No	59 (32.6%)	101 (17.9%)	160 (21.5%)
BRCA Test Results[1]			
Mutant	13 (10.7%)	73 (15.8%)	86 (14.7%)
Germline[2]	7 (53.8%)	47 (64.4%)	54 (62.8%)
Somatic[2]	4 (30.8%)	19 (26.0%)	23 (26.7%)
Missing[2]	2 (15.4%)	7 (9.6%)	9 (10.5%)
Wild Type	108 (88.5%)	388 (83.8%)	496 (84.8%)
Missing	1 (0.8%)	2 (0.4%)	3 (0.5%)
HRD Tested[3], n (%)			
Yes	52 (28.7%)	173 (30.7%)	225 (30.2%)
No	129 (71.3%)	391 (69.3%)	520 (69.8%)
HRD Test Results[4]			
HR-deficient	15 (28.8%)	20 (11.6%)	35 (15.6%)
HR-proficient	28 (53.8%)	40 (23.1%)	68 (30.2%)
Missing	9 (17.3%)	113 (65.3%)	122 (54.2%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Biomarker Status[5]			
HR-deficient	27 (14.9%)	86 (15.2%)	113 (15.2%)
BRCA Mutant[6]	13 (48.1%)	73 (84.9%)	86 (76.1%)
BRCA Wild Type[6]	13 (48.1%)	11 (12.8%)	24 (21.2%)
BRCA Unknown[6]	1 (3.7%)	2 (2.3%)	3 (2.7%)
HR-proficient	28 (15.5%)	40 (7.1%)	68 (9.1%)
HR-Unknown/*BRCA* Wild Type	78 (43.1%)	340 (60.3%)	418 (56.1%)
No Results Available for *BRCA* or HRD	48 (26.5%)	98 (17.4%)	146 (19.6%)

Source: Table 14.1.05, Ad hoc Table – Biomarker Status run on 17 October 2024
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; *BRCA* = Breast cancer susceptibility gene; HR-deficient = Homologous recombination deficient; HRD = Homologous recombination deficiency; HR-proficient = Homologous recombination proficient.
Note: "Unknown" are those who have "Unknown" checked on eCRF. "Missing" are those with no reported data.
[1]The percentage is based on the number of patients who were *BRCA* tested.
[2]The percentage is based on the number of patients who have *BRCA* status as Mutant.
[3]HRD testing status and results for 14 patients who did not sign ICF V8 and were alive were excluded from analysis.
[4]The percentage is based on the number of patients who were HRD tested.
[5]Numbers across *BRCA* and HRD test results may not sum to Biomarker status groups due to inconsistencies in testing for individual biomarkers.
[6]The percentage is based on the number of patients who were HR-deficient when deriving biomarker status from available *BRCA* and HRD test results.

Findings were consistent across patients who received niraparib prior to or on/after enrollment (see Table 14.1.06).

9.2.3. Baseline Disease Characteristics

The median time from ovarian cancer diagnosis to niraparib initiation was 30.1 months (IQR 18.0, 47.5 months) (Table 10). The time from diagnosis to start of niraparib was shorter among 1LM patients (median 7.4 months; IQR 6.7, 8.6 months) than 2LM+ patients (median 36.3 months; IQR 27.2, 55.1 months). There was 1 patient in the 1LM group with a time difference of 308.9 months between ovarian cancer diagnosis and niraparib initiation (patient level dates provided in Listing 15.11.0 and Listing 15.16.0). The treatment pattern for this patient was reviewed by a GSK board-certified gynecologic oncologist and the 1LM line of therapy designation was confirmed.

Baseline disease characteristics and other cancer diagnoses are provided in by-patient listings in Listing 15.11.0 and Listing 15.19.0.

Table 10 Baseline Disease Characteristics

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Time from Ovarian Cancer Diagnosis to niraparib Initiation (Months)			
n	181	564	745
Mean	10.616	47.988	38.909
SD	24.8416	37.0602	38.0244
Q1	6.669	27.203	18.004
Median	7.359	36.337	30.127
Q3	8.608	55.129	47.507
Min	3.65	6.93	3.65
Max	308.90	359.59	359.59
Histological Classification at Enrollment, n (%)			
High-grade Serous	179 (98.9%)	556 (98.6%)	735 (98.7%)
High-grade Endometrioid	2 (1.1%)	2 (0.4%)	4 (0.5%)
Other	0	6 (1.1%)	6 (0.8%)
FIGO Stage at Ovarian Cancer Diagnosis, n (%)			
I	1 (0.6%)	17 (3.0%)	18 (2.4%)
II	1 (0.6%)	43 (7.6%)	44 (5.9%)
III	113 (62.4%)	385 (68.3%)	498 (66.8%)
IV	62 (34.3%)	107 (19.0%)	169 (22.7%)
Missing	4 (2.2%)	12 (2.1%)	16 (2.1%)
Other Cancer Diagnosis Prior to niraparib Initiation, n (%)			
Yes	17 (9.4%)	42 (7.4%)	59 (7.9%)
No	164 (90.6%)	522 (92.6%)	686 (92.1%)
If Yes, Type of Cancer[1]			
Brain Cancer	0	1 (2.4%)	1 (1.7%)
Breast Cancer	11 (64.7%)	24 (57.1%)	35 (59.3%)
Carcinoid Cancer	0	2 (4.8%)	2 (3.4%)
Endometrial Cancer	0	1 (2.4%)	1 (1.7%)
Gastrointestinal Stromal Tumor	0	1 (2.4%)	1 (1.7%)
Head and Neck Cancer	0	1 (2.4%)	1 (1.7%)
Malignant Melanoma	1 (5.9%)	3 (7.1%)	4 (6.8%)
Sarcoma	0	1 (2.4%)	1 (1.7%)
Skin Cancer	0	2 (4.8%)	2 (3.4%)
Other	5 (29.4%)	8 (19.0%)	13 (22.0%)

Source: Table 14.1.07

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; FIGO = International Federation of Gynecology and Obstetrics; Max = Maximum; Min = Minimum; SD = Standard deviation; Q1 = First quartile; Q3 = Third quartile.

[1]Patients may have been diagnosed with multiple types of cancer. The percentage is based on patients who had other cancer diagnosis prior to niraparib initiation.

Patients were predominantly FIGO stage III or IV at ovarian cancer diagnosis (Table 10). Approximately 99% (n=735) were high-grade serous at study enrollment (98.9% of 1LM patients [n=179]; 98.6% of 2LM+ patients [n=556]). Patients with 'other' histological classification included clear cell ovarian carcinoma (n=2), mixed serous-endometroid (n=1), invasive poorly differentiated serous adenocarcinoma (n=1), high-grade

adenocarcinoma (n=1), and transitional non-Brenner (n=1) (Listing 15.11.0). Patients enrolled with non-indicated histology were included in the analysis as protocol deviations (see Section 9.1.2). Less than 10% of patients reported other cancer diagnosis prior to niraparib initiation (9.4% of 1LM patients [n=17]; 7.4% of 2LM+ patients [n=42]). Of the 59 total patients (7.9%) who had other cancer diagnoses prior to starting niraparib, breast cancer was most commonly reported (59.3%).

Less than 10% of patients received radiation therapy for any type of cancer prior to niraparib initiation (6.1% of 1LM patients [n=11]; 8.9% 2LM+ patients [n=50]) (Table 11). By-patient listings of other cancer therapies and radiotherapy treatments is available in Listing 15.19.0 and Listing 15.20.0.

Table 11 Prior Chemotherapy and Radiation Therapy

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Received Chemotherapy and Radiation Therapy Prior to niraparib Initiation[1], n (%)			
Yes	11 (6.1%)	50 (8.9%)	61 (8.2%)
No	170 (93.9%)	514 (91.1%)	684 (91.8%)
Received Chemotherapy Prior to niraparib Initiation[1], n (%)			
Yes	181 (100%)	564 (100%)	745 (100%)
No	0	0	0
Received Radiation Therapy Prior to niraparib Initiation[1], n (%)			
Yes	11 (6.1%)	50 (8.9%)	61 (8.2%)
No	170 (93.9%)	514 (91.1%)	684 (91.8%)
Received Radiotherapy for Other Cancer Prior to niraparib Initiation[2], n (%)			
Yes	10 (58.8%)	16 (38.1%)	26 (44.1%)
No	7 (41.2%)	26 (61.9%)	33 (55.9%)
Received Other Therapy for Other Cancer Prior to niraparib Initiation[2], n (%)			
Yes	11 (64.7%)	19 (45.2%)	30 (50.8%)
No	6 (35.3%)	23 (54.8%)	29 (49.2%)

Source: Table 14.1.07
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group.
[1]Capturing receipt of chemotherapy or radiation therapy for any cancer.
[2]The percentage is based on patients who had other cancer diagnosis prior to niraparib initiation.

Findings were consistent across patients who received niraparib prior to or on/after enrollment (see Table 14.1.08).

9.2.4. Prior Ovarian Cancer Therapies

Prior ovarian cancer therapies are presented in Table 12. Less than 4% of patients had received other PARP inhibitors prior to niraparib initiation (1.7% of 1LM patients [n=3]; 3.5% of 2LM+ patients [n=20]), with the most common being olaparib (91.3%). The median lines of any therapy prior to niraparib was 2.0 (IQR 2.0, 3.0) in the 2LM+ cohort;

more specifically, the median lines of platinum-based chemotherapy prior to niraparib initiation was 2.0 in the 2LM+ cohort (IQR 2.0, 2.0).

By-patient listings of prior ovarian cancer therapies are provided in Listing 15.15.0, Listing 15.16.0, and Listing 15.18.0.

Table 12 Prior Ovarian Cancer Therapies

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Total Lines of Therapy Prior to niraparib Initiation[1]			
n	181	564	745
Mean	1.0	2.4	2.1
SD	0.00	0.88	0.98
Q1	1.0	2.0	2.0
Median	1.0	2.0	2.0
Q3	1.0	3.0	2.0
Min	1	2	1
Max	1	9	9
Total Lines of Platinum-based Chemotherapy Prior to niraparib Initiation[1,2]			
n	181	564	745
Mean	1.0	2.3	2.0
SD	0.00	0.63	0.77
Q1	1.0	2.0	2.0
Median	1.0	2.0	2.0
Q3	1.0	2.0	2.0
Min	1	1	1
Max	1	6	6
Total Number of Platinum-based Chemotherapy Cycles Prior to niraparib Initiation[2,3]			
n	181	562	743
Mean	6.4	13.4	11.7
SD	1.94	4.53	5.02
Q1	6.0	12.0	8.0
Median	6.0	12.0	12.0
Q3	6.0	14.0	12.0
Min	3	3	3
Max	18	62	62
Other PARP Inhibitor Received Prior to niraparib Initiation, n (%)			
Yes	3 (1.7%)	20 (3.5%)	23 (3.1%)
No	178 (98.3%)	544 (96.5%)	722 (96.9%)
Other PARP Inhibitor Received[4], n (%)			
Olaparib	3 (100%)	18 (90.0%)	21 (91.3%)
Rucaparib	0	3 (15.0%)	3 (13.0%)
Talazoparib	0	0	0
Other	0	0	0

Source: Table 14.1.09
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; Max = Maximum; Min = Minimum; PARP = Poly (ADP-ribose) polymerase; SD = Standard deviation; Q1 = First quartile; Q3 = Third quartile.

[1]Total lines of therapy prior to niraparib initiation is a derived variable, as line of therapy data was not directly reported by sites for any treatment.
[2]Platinum compounds include cisplatin, oxaliplatin, and carboplatin.
[3]Patients may have received more than 1 platinum-based chemotherapy drug.
[4]The percentage is based on the number of patients who received other PARP inhibitor prior to niraparib initiation. There was 1 patient who received more than 1 PARP inhibitor prior to niraparib initiation.

Over 95% of patients received cytoreductive surgery prior to niraparib initiation (90.1% of 1LM patients [n=163]; 97.3% of 2LM+ patients [n=549]), with over one-half (57.6%) receiving PDS (Table 13). In the 1LM cohort, 41.7% (n=68) of patients received PDS, 58.3% (n=95) received IDS, and 3.1% (n=5) received more than 1 surgery. In the 2LM+ cohort, 62.3% (n=342) of patients received PDS, 37.7% (n=207) received IDS, and 1.1% (n=6) received more than 1 surgery.

More than half (53.5%) of all patients receiving cytoreductive surgery prior to niraparib initiation had no gross residual disease (residual=0: no gross residual disease) (48.5% 1LM patients [n=79]; 55.0% 2LM+ patients [n=302]). Residual disease status was unknown for approximately one quarter of patients. If a patient had more than 1 surgery performed, it was not specified whether the residual disease status provided was related to the first or secondary surgery.

Table 13 Cytoreductive Surgery Prior to niraparib Initiation

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Cytoreductive Surgery Performed Prior to niraparib Initiation, n (%)			
Yes	163 (90.1%)	549 (97.3%)	712 (95.6%)
No	18 (9.9%)	15 (2.7%)	33 (4.4%)
Primary Debulking Surgery (PDS) Performed[1], n (%)			
Yes	68 (41.7%)	342 (62.3%)	410 (57.6%)
No	95 (58.3%)	207 (37.7%)	302 (42.4%)
Interval Debulking Surgery (IDS) Performed[1], n (%)			
Yes	95 (58.3%)	207 (37.7%)	302 (42.4%)
No	68 (41.7%)	342 (62.3%)	410 (57.6%)
More than 1 Surgery Performed[1], n (%)			
Yes	5 (3.1%)	6 (1.1%)	11 (1.5%)
No	158 (96.9%)	543 (98.9%)	701 (98.5%)
Residual Disease Status Post Cytoreductive Surgery Performed Prior to niraparib Initiation[1], n (%)			
R=0 (no gross residual disease)	79 (48.5%)	302 (55.0%)	381 (53.5%)
R ≤1 (residual disease ≤1 cm)	19 (11.7%)	62 (11.3%)	81 (11.4%)
R >1 residual disease >1 cm)	20 (12.3%)	49 (8.9%)	69 (9.7%)
Unknown	45 (27.6%)	136 (24.8%)	181 (25.4%)
Not Applicable	0	0	0

Source: Table 14.1.09
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; cm = centimeter; R = Residual.
[1]The percentage is based on the number of patients with cytoreductive surgery performed prior to niraparib initiation.

Prior chemotherapy and radiation therapy for ovarian cancer are presented in Table 14. Approximately 41% (n=302) of the Safety Population received NAT for ovarian cancer prior to niraparib initiation (52.5% 1LM patients [n=95]; 36.7% 2LM+ patients [n=207]), most with partial response (62.3%). More than 88% (n=658) of the Safety Population received AT for ovarian cancer prior to niraparib initiation (80.1% 1LM patients [n=145]; 91.0% 2LM+ patients [n=513]), nearly one-half (46.2%) with complete response. Less than 5% of patients (n=35) received prior radiation therapy for ovarian cancer (0.6% 1LM patients [n=1]; 6.0% 2LM+ patients [n=34]).

Table 14 Prior Chemotherapy and Radiation for Ovarian Cancer

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Neoadjuvant Chemotherapy for Ovarian Cancer Prior to niraparib Initiation, n (%)			
Yes	95 (52.5%)	207 (36.7%)	302 (40.5%)
No	86 (47.5%)	357 (63.3%)	443 (59.5%)
If Yes, Best Response to Neoadjuvant Therapy			
Complete Response (CR)	12 (12.6%)	20 (9.7%)	32 (10.6%)
Partial Response (PR)	66 (69.5%)	122 (58.9%)	188 (62.3%)
Progressive Disease (PD)	0	1 (0.5%)	1 (0.3%)
Stable Disease (SD)	5 (5.3%)	15 (7.2%)	20 (6.6%)
Not Evaluable (NE)	2 (2.1%)	10 (4.8%)	12 (4.0%)
Unknown	10 (10.5%)	39 (18.8%)	49 (16.2%)
If Yes, Primary Reason for Stopping Treatment[1]			
Treatment Completed	84 (88.4%)	175 (84.5%)	259 (85.8%)
Progressive Disease	0	2 (1.0%)	2 (0.7%)
Toxicity	4 (4.2%)	6 (2.9%)	10 (3.3%)
Other	11 (11.6%)	31 (15.0%)	42 (13.9%)
Adjuvant Chemotherapy for Ovarian Cancer Prior to niraparib Initiation, n (%)			
Yes	145 (80.1%)	513 (91.0%)	658 (88.3%)
No	36 (19.9%)	51 (9.0%)	87 (11.7%)
If Yes, Best Response to Adjuvant Therapy			
Complete Response (CR)	67 (46.2%)	237 (46.2%)	304 (46.2%)
Partial Response (PR)	61 (42.1%)	84 (16.4%)	145 (22.0%)
Progressive Disease (PD)	0	12 (2.3%)	12 (1.8%)
Stable Disease (SD)	4 (2.8%)	49 (9.6%)	53 (8.1%)
Not Evaluable (NE)	4 (2.8%)	45 (8.8%)	49 (7.4%)
Unknown	9 (6.2%)	86 (16.8%)	95 (14.4%)
If Yes, Primary Reason for Stopping Treatment[1]			
Treatment Completed	141 (97.2%)	473 (92.2%)	614 (93.3%)
Progressive Disease	0	40 (7.8%)	40 (6.1%)
Toxicity	12 (8.3%)	34 (6.6%)	46 (7.0%)
Other	4 (2.8%)	12 (2.3%)	16 (2.4%)
Received Radiotherapy for Ovarian Cancer Prior to niraparib Initiation, n (%)			
Yes	1 (0.6%)	34 (6.0%)	35 (4.7%)
No	180 (99.4%)	530 (94.0%)	710 (95.3%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Received Chemotherapy for Ovarian Cancer Prior to niraparib Initiation[2], n (%)			
Alkylating Agents	181 (100%)	564 (100%)	745 (100%)
Topoisomerase Inhibitors	0	5 (0.9%)	5 (0.7%)
Antimetabolites	2 (1.1%)	208 (36.9%)	210 (28.2%)
Antineoplastic – Platinum Complexes[3]	181 (100%)	564 (100%)	745 (100%)
Taxanes	175 (96.7%)	549 (97.3%)	724 (97.2%)
Other	2 (1.1%)	262 (46.5%)	264 (35.4%)

Source: Table 14.1.09
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group.
[1]Patients may have received multiple chemotherapy drugs, and therefore, may report more than 1 reason for stopping treatment.
[2]Patients may have received more than 1 prior chemotherapy medication.
[3]Platinum compounds include cisplatin, oxaliplatin, and carboplatin.

Cytoreductive surgery prior to niraparib initiation and neoadjuvant and adjuvant treatment are available by-patient listing in Listings 15.11.0 and Listing 15.14.0. Non-PARP Inhibitor ovarian cancer treatments are available by-patient listing in Listing 15.15.0 and Listing 15.20.0.

Prior ovarian cancer therapies findings were consistent across patients who received niraparib prior to or on/after enrollment (see Table 14.1.10).

9.2.5. Summary of Risk Factors Associated with MDS/AML and Other SPM

Overall, 44.2% (n=329) of patients were overweight or obese prior to niraparib initiation (Table 15). At enrollment, 20.1% (n=150) of patients had a history of thrombocytopenia, 5.4% (n=40) had a history of platelet transfusions, 32.3% (n=241) had a history of anemia, 7.0% (n=52) had a history of renal insufficiency, 2.4% (n=18) had a history of hepatic insufficiency, and 25.2% (n=188) had a history of neutropenia.

Table 15 Risk Factors Associated with MDS/AML and Other SPMs

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Overweight/Obesity (BMI ≥25 kg/m^2), n (%)			
Yes	71 (39.2%)	258 (45.7%)	329 (44.2%)
No	101 (55.8%)	287 (50.9%)	388 (52.1%)
Missing	9 (5.0%)	19 (3.4%)	28 (3.8%)
Targeted Medical History at Enrollment[1]			
Thrombocytopenia, n (%)			
Yes	31 (17.1%)	119 (21.1%)	150 (20.1%)
No	136 (75.1%)	371 (65.8%)	507 (68.1%)
Unknown	14 (7.7%)	71 (12.6%)	85 (11.4%)
Missing	0	3 (0.5%)	3 (0.4%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Platelet Transfusions, n (%)			
Yes	10 (5.5%)	30 (5.3%)	40 (5.4%)
No	155 (85.6%)	459 (81.4%)	614 (82.4%)
Unknown	16 (8.8%)	72 (12.8%)	88 (11.8%)
Missing	0	3 (0.5%)	3 (0.4%)
Anemia, n (%)			
Yes	47 (26.0%)	194 (34.4%)	241 (32.3%)
No	118 (65.2%)	290 (51.4%)	408 (54.8%)
Unknown	16 (8.8%)	77 (13.7%)	93 (12.5%)
Missing	0	3 (0.5%)	3 (0.4%)
Renal Insufficiency, n (%)			
Yes	13 (7.2%)	39 (6.9%)	52 (7.0%)
No	156 (86.2%)	463 (82.1%)	619 (83.1%)
Unknown	12 (6.6%)	59 (10.5%)	71 (9.5%)
Missing	0	3 (0.5%)	3 (0.4%)
Hepatic Insufficiency, n (%)			
Yes	4 (2.2%)	14 (2.5%)	18 (2.4%)
No	163 (90.1%)	483 (85.6%)	646 (86.7%)
Unknown	14 (7.7%)	64 (11.3%)	78 (10.5%)
Missing	0	3 (0.5%)	3 (0.4%)
Neutropenia, n (%)			
Yes	33 (18.2%)	155 (27.5%)	188 (25.2%)
No	132 (72.9%)	331 (58.7%)	463 (62.1%)
Unknown	16 (8.8%)	75 (13.3%)	91 (12.2%)
Missing	0	3 (0.5%)	3 (0.4%)

Source: Table 14.1.11
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group, BMI = Body mass index.
Note: "Unknown" are those who have "Unknown" checked on eCRF. "Missing" are those with no reported data.
[1]Targeted medical history questions apply to the patient's lifetime prior to informed consent.

A by-patient listing of targeted medical history is available in Listing 15.7.0.

A summary of CBC parameters at index (niraparib initiation), i.e., Hb, WBC, blasts (%), absolute blasts count, platelets, absolute neutrophil count, neutrophils (%), absolute lymphocytes count, lymphocytes (%) and MCV, is provided in Table 16. The following parameters were most frequently available for patients: Hb, WBC, platelets, absolute neutrophil count and MCV. Abnormal parameter test results were most frequently observed for Hb (n=356, 47.8%) followed by MCV (n=253, 34.0%), WBC (n=202; 27.1%), absolute neutrophil count (n=127, 17.0%), and platelets (n=108, 14.5%).

Table 16 CBC Abnormalities Prior to niraparib Initiation

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Hemoglobin (Hb), n (%)			
Normal	70 (38.7%)	198 (35.1%)	268 (36.0%)
Abnormal	90 (49.7%)	266 (47.2%)	356 (47.8%)
Unknown	0	20 (3.5%)	20 (2.7%)
Missing	21 (11.6%)	80 (14.2%)	101 (13.6%)
White Blood Cells (WBC), n (%)			
Normal	104 (57.5%)	313 (55.5%)	417 (56.0%)
Abnormal	54 (29.8%)	148 (26.2%)	202 (27.1%)
Unknown	2 (1.1%)	23 (4.1%)	25 (3.4%)
Missing	21 (11.6%)	80 (14.2%)	101 (13.6%)
Blasts %, n (%)			
Normal	14 (7.7%)	79 (14.0%)	93 (12.5%)
Abnormal	2 (1.1%)	16 (2.8%)	18 (2.4%)
Unknown	143 (79.0%)	389 (69.0%)	532 (71.4%)
Missing	22 (12.2%)	80 (14.2%)	102 (13.7%)
Absolute Blasts Count, n (%)			
Normal	18 (9.9%)	82 (14.5%)	100 (13.4%)
Abnormal	0	7 (1.2%)	7 (0.9%)
Unknown	141 (77.9%)	395 (70.0%)	536 (71.9%)
Missing	22 (12.2%)	80 (14.2%)	102 (13.7%)
Platelets, n (%)			
Normal	132 (72.9%)	382 (67.7%)	514 (69.0%)
Abnormal	28 (15.5%)	80 (14.2%)	108 (14.5%)
Unknown	0	22 (3.9%)	22 (3.0%)
Missing	21 (11.6%)	80 (14.2%)	101 (13.6%)
Absolute Neutrophil Count, n (%)			
Normal	109 (60.2%)	305 (54.1%)	414 (55.6%)
Abnormal	27 (14.9%)	100 (17.7%)	127 (17.0%)
Unknown	24 (13.3%)	79 (14.0%)	103 (13.8%)
Missing	21 (11.6%)	80 (14.2%)	101 (13.6%)
Neutrophils, n (%)			
Normal	51 (28.2%)	174 (30.9%)	225 (30.2%)
Abnormal	11 (6.1%)	64 (11.3%)	75 (10.1%)
Unknown	98 (54.1%)	246 (43.6%)	344 (46.2%)
Missing	21 (11.6%)	80 (14.2%)	101 (13.6%)
Absolute Lymphocytes Count, n (%)			
Normal	75 (41.4%)	259 (45.9%)	334 (44.8%)
Abnormal	12 (6.6%)	67 (11.9%)	79 (10.6%)
Unknown	73 (40.3%)	158 (28.0%)	231 (31.0%)
Missing	21 (11.6%)	80 (14.2%)	101 (13.6%)
Lymphocytes, n (%)			
Normal	48 (26.5%)	178 (31.6%)	226 (30.3%)
Abnormal	14 (7.7%)	58 (10.3%)	72 (9.7%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Unknown	98 (54.1%)	248 (44.0%)	346 (46.4%)
Missing	21 (11.6%)	80 (14.2%)	101 (13.6%)
Mean Corpuscular Volume (MCV), n (%)			
Normal	85 (47.0%)	187 (33.2%)	272 (36.5%)
Abnormal	54 (29.8%)	199 (35.3%)	253 (34.0%)
Unknown	21 (11.6%)	83 (14.7%)	104 (14.0%)
Missing	21 (11.6%)	95 (16.8%)	116 (15.6%)

Source: Table 14.1.11
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; CBC = Complete blood cell count.
Note: "Unknown" are those who have "Unknown" checked on eCRF. "Missing" are those with no reported data.

By-patient listings of CBC differential parameter results with niraparib treatment are available in Listing 15.22.0.

9.3. Outcome data

9.3.1. Treatment Exposure

Niraparib treatment was discontinued by 72.9% of 1LM patients (n=132) and 78.9% of 2LM+ patients (n=445) (Table 17). Niraparib was most often discontinued due to disease progression (83.0% overall [n=479]; 76.5% [n=101] of 1LM patients who discontinued niraparib; 84.9% [n=378] of 2LM+ patients who discontinued niraparib).

The median duration of niraparib treatment was 11.0 months (IQR 5.1, 20.0 months) in the 1LM cohort and 10.4 months (IQR 4.8, 22.9 months) in the 2LM+ cohort.

Table 17 Extent of niraparib Exposure

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Patients with niraparib Dose Discontinued, n (%)			
Yes	132 (72.9%)	445 (78.9%)	577 (77.4%)
No	49 (27.1%)	119 (21.1%)	168 (22.6%)
Reason for Discontinuation[1], n (%)			
Disease progression	101 (76.5%)	378 (84.9%)	479 (83.0%)
Patient request	12 (9.1%)	19 (4.3%)	31 (5.4%)
Investigator discretion	4 (3.0%)	17 (3.8%)	21 (3.6%)
Patient became pregnant	0	0	0
Patient passed away	0	2 (0.4%)	2 (0.3%)
Adverse event (grade 3 or higher)	7 (5.3%)	19 (4.3%)	26 (4.5%)
Other	8 (6.1%)	10 (2.2%)	18 (3.1%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Niraparib Treatment Duration (months)			
N	181	564	745
Mean	13.18	16.97	16.05
SD	9.516	16.675	15.328
Q1	5.13	4.75	4.80
Median	11.04	10.35	10.71
Q3	20.01	22.93	21.13
Min	0.7	0.1	0.1
Max	41.2	60.9	60.9

Source: Table 14.1.12
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; Max = Maximum; Min = Minimum; SD = Standard deviation; Q1 = First quartile; Q3 = Third quartile.
[1]The percentage is based on the number of patients with dose discontinued.

Patients predominantly started on a 200 mg dose of niraparib (66.2%; Table 18). Overall, one-half (50.5%) of patients had at least 1 dose modification (52.5% of the 1LM patients [n=95]; 49.8% of the 2LM+ patients [n=281]), with at least 1 subsequent dose modification reported for 9.8% (n=73) of patients. Approximately 45% (n=332) of patients had a dose interruption (49.2% of the 1LM patients [n=89]; 43.1% of the 2LM+ patients [n=243]). Thrombocytopenia and 'other' were the most commonly reported reasons for first dose modification (34.6% and 38.8%, respectively) and dose interruption (38.9% and 46.7%, respectively). Anemia and 'other' were the most commonly reported reasons for subsequent dose modifications (24.7% and 58.9%, respectively). Reports of 'other' reasons included, but were not limited to, AEs (e.g., neutropenia, pancytopenia, hypertension, headache, etc.), patient request, and physician decision.

Table 18 Niraparib Starting Dose and Dose Modifications

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Starting Dose of niraparib, n (%)			
100 mg	8 (4.4%)	17 (3.0%)	25 (3.4%)
200 mg	142 (78.5%)	351 (62.2%)	493 (66.2%)
300 mg	31 (17.1%)	196 (34.8%)	227 (30.5%)
Patients with at least One Dose Modification, n (%)	95 (52.5%)	281 (49.8%)	376 (50.5%)
Reason for First Dose Modification[1]			
Thrombocytopenia	34 (35.8%)	96 (34.2%)	130 (34.6%)
Anemia	16 (16.8%)	51 (18.1%)	67 (17.8%)
Fatigue	6 (6.3%)	12 (4.3%)	18 (4.8%)
Nausea	6 (6.3%)	9 (3.2%)	15 (4.0%)
Other	33 (34.7%)	113 (40.2%)	146 (38.8%)
Patients with Subsequent Dose Modification, n (%)	12 (6.6%)	61 (10.8%)	73 (9.8%)
Reason for Subsequent Dose Modification[1]			
Thrombocytopenia	0	14 (23.0%)	14 (19.2%)
Anemia	2 (16.7%)	16 (26.2%)	18 (24.7%)
Fatigue	1 (8.3%)	5 (8.2%)	6 (8.2%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Nausea	1 (8.3%)	0	1 (1.4%)
Other	10 (83.3%)	33 (54.1%)	43 (58.9%)
Patients with Dose Interruption, n (%)	89 (49.2%)	243 (43.1%)	332 (44.6%)
Reason for Dose Interruption[1]			
Thrombocytopenia	33 (37.1%)	96 (39.5%)	129 (38.9%)
Anemia	23 (25.8%)	57 (23.5%)	80 (24.1%)
Fatigue	3 (3.4%)	7 (2.9%)	10 (3.0%)
Nausea	5 (5.6%)	4 (1.6%)	9 (2.7%)
Other	39 (43.8%)	116 (47.7%)	155 (46.7%)

Source: Table 14.1.12
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; mg = milligram.
[1]Patients may have more than 1 reason for dose modification or interruption. The percentage is based on the number of patients who had at least 1 dose modification, subsequent dose modification or dose interruption.

By-patient listings of study treatment exposure are available in Listing 15.17.0.

9.4. Results of Primary Analyses

9.4.1. MDS/AML and/or Other SPM Incidence Rates

There were a total of 9 (1.2%) patients with MDS/AML events observed over 1767.6 patient-years with a corresponding MDS/AML incidence rate of 0.51 (95% CI: 0.23, 0.97) per 100 patient-years (Table 19). Two patients had two events, for a total of 11 MDS/AML events. All events occurred in the 2LM+ population (incidence rate 0.62 [95% CI: 0.29, 1.18] per 100 patient-years).

By-patient listings of MDS/AML and other SPMs are available in Listing 15.27.0.

Table 19 Incidence Rate of MDS/AML and Other SPM per 100 Patient-years

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Incidence of New MDS/AML[1], n (%)	0	9 (1.60%)	9 (1.21%)
Total New MDS/AML events	0	11	11
PY	324.1	1443.4	1767.6
Incidence Rate of MDS/AML per 100 PY[2]	0	0.62	0.51
(95% CI)	(NE, 1.14)	(0.29, 1.18)	(0.23, 0.97)
Incidence of New Other SPMs[1], n (%)	1 (0.55%)	5 (0.89%)	6 (0.81%)
Total New Other SPM events	1	6	7
PY	322.9	1444.7	1767.6
Incidence Rate of Other SPMs per 100 PY[2]	0.31	0.35	0.34
(95% CI)	(0.01, 1.73)	(0.11, 0.81)	(0.12, 0.74)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Incidence of New MDS/AML and Other SPMs[1], n (%)	1 (0.55%)	14 (2.48%)	15 (2.01%)
Total New MDS/AML and Other SPM events	1	17	18
PY	322.9	1439.6	1762.6
Incidence Rate of MDS/AML and Other SPMs per 100 PY[2]	0.31	0.97	0.85
(95% CI)	(0.01, 1.73)	(0.53, 1.63)	(0.48, 1.40)

Source: Table 14.2.01, Table 14.2.06, Table 14.2.11, Table 14.3.02

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; AML = Acute myeloid leukemia; CI = Confidence Interval; MDS = Myelodysplastic syndrome; NE = Not evaluable; PY = Patient-years; SPM = Second primary malignancy.

Note: There was 1 additional patient in the Enrolled Population who was diagnosed with an SPM. Due to insufficient clinical information to classify the patient's niraparib line of therapy, despite site queries, this patient was excluded from the Safety Population. This patient initiated niraparib on PPD and was diagnosed with breast cancer on PPD

[1]n reflects the number of patients with event, 1 patient may have had more than 1 event in this category; 2 patients had 2 events of MDS/AML, 1 patient had 2 events of SPM.

[2]The number of patients with occurrence of an event (e.g., MDS/AML, other SPM, or MDS/AML and other SPM) divided by PY, multiplied by 100. Patient-years are calculated as the total time from the start date of niraparib to the first onset date of event of MDS/AML or other SPM, or, for patients who have no events of MDS/AML or other SPM, to the earliest occurrence of date of study discontinuation, death or date of database lock for final analysis.

A total of 6 (0.8%) patients with other SPMs were observed over 1767.6 patient-years; the SPM incidence rate was 0.34 (95% CI: 0.12, 0.74) per 100 patient-years (Table 19). One patient had 2 basal cell carcinomas, for a total of 7 SPM events in 6 patients. One patient with other SPM was in the 1LM population (incidence rate 0.31 [95% CI: 0.01, 1.73] per 100 patient-years) and 5 patients were in the 2LM+ population (incidence rate 0.35 [95% CI: 0.11, 0.81] per 100 patient-years).

There was 1 additional patient in the Enrolled Population who initiated niraparib on PPD and was diagnosed with a SPM of breast cancer on PPD Despite additional queries to the site, there was insufficient clinical information to assign the patient to a niraparib cohort. Therefore, the patient did not meet inclusion criteria for the Safety Population.

Overall, there were a total of 15 (2.0%) patients with MDS/AML and/or other SPM events observed over 1762.6 patient-years; the MDS/AML and other SPM incidence rate was 0.85 (95% CI: 0.48, 1.40) per 100 patient-years (Table 19).

All cases of MDS/AML occurred in patients who initiated niraparib prior to enrollment (see Table 14.2.02). Five out of 6 patients who experienced other SPM events had initiated niraparib prior to enrollment (see Table 14.2.07).

9.4.2. MDS/AML and Other SPMs by Preferred Term

All events of MDS/AML and other SPMs are presented by PT in Table 20. Combined, MDS/AML or other SPMs occurred in 15 out of 745 (2.0%) total patients, for a total of 18 events (2 patients had 2 events of MDS/AML; 1 patient had 2 events of basal cell carcinoma). Additionally, 2 patients had breast cancer, 1 patient had CML, 1 patient had head and neck cancer, and 1 patient had squamous cell carcinoma of the oral cavity.

Table 20 MDS/AML and Other SPM Events by Preferred Term

	Safety Population		
Preferred Term[1]	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
All Events (MDS/AML and Other SPMs)	1	17	18
Patients with Any Event, n (%)	1 (0.6%)	14 (2.5%)	15 (2.0%)
Myelodysplastic Syndrome, n (%) [events]	0	6 (1.1%) [6]	6 (0.8%) [6]
Acute Myeloid Leukemia, n (%) [events]	0	5 (0.9%) [5]	5 (0.7%) [5]
Breast Cancer, n (%) [events]	0	2 (0.4%) [2]	2 (0.3%) [2]
Basal Cell Carcinoma, n (%) [events]	0	1 (0.2%) [2]	1 (0.1%) [2]
Chronic Myeloid Leukemia, n (%) [events]	0	1 (0.2%) [1]	1 (0.1%) [1]
Head And Neck Cancer, n (%) [events]	1 (0.6%) [1]	0	1 (0.1%) [1]
Squamous Cell Carcinoma Of The Oral Cavity, n (%) [events]	0	1 (0.2%) [1]	1 (0.1%) [1]

Source: Table 14.3.02

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; AML = Acute myeloid leukemia; MDS = Myelodysplastic syndrome; SPM = Second primary malignancy.

Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.

Note: There was 1 additional patient in the Enrolled Population who was diagnosed with an SPM. Due to insufficient clinical information to classify their niraparib line of therapy, despite site queries, they were excluded from the Safety Population. This patient initiated niraparib on PPD and was diagnosed with breast cancer on PPD

Note: Percentage is calculated based on the number of patients in each group (N). For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Events are sorted by descending frequency of preferred term of the overall column.

[1]Adverse events are classified into preferred term using MedDRA Version 27.0.

Seven of the 18 MDS/AML and other SPM events were reported to be not related to niraparib treatment: 1 case of MDS, 2 cases of breast cancer, 2 cases of basal cell carcinoma, 1 case of head and neck cancer, and 1 case of squamous cell carcinoma of the oral cavity (Listing 15.27.0). MDS/AML and other SPM events reported as related to niraparib treatment are presented in Table 21.

Table 21 MDS/AML and Other SPMs Related to Niraparib by Preferred Term

Preferred Term[1]	Safety Population 1LM (N=181)	2LM+ (N=564)	Overall (N=745)
All Events (MDS/AML and Other SPMs) Related to niraparib	0	11	11
Patients with Any Event Related to niraparib, n (%)	0	9 (1.6%)	9 (1.2%)
Acute Myeloid Leukemia, n (%) [events]	0	5 (0.9%) [5]	5 (0.7%) [5]
Myelodysplastic Syndrome, n (%) [events]	0	5 (0.9%) [5]	5 (0.7%) [5]
Chronic Myeloid Leukemia, n (%) [events]	0	1 (0.2%) [1]	1 (0.1%) [1]

Source: Table 14.3.03

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; AML = Acute myeloid leukemia; MDS = Myelodysplastic syndrome; SPM = Second primary malignancy.

Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.

Note: There was 1 additional patient in the Enrolled Population who was diagnosed with an SPM. Due to insufficient clinical information to classify their niraparib line of therapy, despite site queries, they were excluded from the Safety Population. This patient initiated niraparib on PPD and was diagnosed with breast cancer on PPD

Note: Percentage is calculated based on the number of patients in each group (N). For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Events are sorted by descending frequency of preferred term of the overall column.

[1]Adverse events are classified into preferred term using MedDRA Version 27.0.

9.4.3. Narratives of MDS/AML

A detailed listing of the 9 patients with MDS/AML events is presented in Table 22. Narratives for all 9 patients with MDS/AML events (11 total events) are provided below, in Section 9.4.3.1 and Section 9.4.3.2, organized by whether events were reported to be related to niraparib (n=8 patients; 10 events) or reported to not be related to niraparib treatment (n=1 patient; 1 event), respectively. One patient was on a niraparib dose of 150 mg prior to development of MDS/AML (a non-marketed dose), achieved by switching every other day between taking 1 capsule of 100 mg or 2 capsules of 100 mg. All 9 patients received chemotherapy for any cancer prior to niraparib initiation.

Table 22 Patients with MDS/AML Events

Pat. ID	Age[1] (yrs)	Niraparib dose (mg) prior to MDS/ AML	Niraparib duration (days)	PT	Time from niraparib initiation to event onset (days)	Radiation therapy for any cancer/other PARP inhibitor received prior to niraparib	*BRCA*/HRD test result[2]
2LM+ Patients, MDS/AML Related to niraparib							
PPD	PPD	100	993	MDS	986	No/No	Wild Type/-
PPD				AML	1131	No/No	Wild Type/-
		100	525	AML	531	No/No	Wild Type/-
		150	1001	MDS	994	Yes/No	Mutant Som./NP
		100	161	MDS	689	No/No	Wild Type/-
				AML	884	No/No	Wild Type/-
		100	217	MDS	256	No/No	Mutant Germ./NP
	PP	300	763	AML	1038	No/No	Wild Type/-
	PPD	100	1800	AML	1729	No/No	Wild Type/HRDp
		200	75	MDS	1363	No/No	Wild Type/NP
2LM+ Patients, MDS/AML Not Related to niraparib							
PPD	PPD	300	36	MDS	1106	No/No	Wild Type/-

Source: Listing 15.35.0

Abbreviations: 2LM+ = Second or later line maintenance group; AML = Acute myeloid leukemia; *BRCA* = Breast cancer susceptibility gene; Germ. = Germline; HRDp = Homologous recombination deficiency – proficient (negative); MDS = Myelodysplastic syndrome; NP = Not performed; PARP = Poly (ADP-ribose) polymerase; Pat. ID = Patient Identification; PT = Preferred Term; Som. = Somatic; SPM = Second primary malignancy.

Note: All 9 patients received chemotherapy for any cancer prior to niraparib initiation.

[1]Age was calculated from year of birth to year of niraparib initiation.

[2]Symbol "-" means no data was provided in the database.

9.4.3.1. Narratives of MDS/AML Related to Niraparib

Narratives for patients who experienced MDS/AML reported as related to niraparib during the study are provided below:

Patient PPD

Patient PPD a PPD year-old obese woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* wild type on PPD Patient received PDS on PPD with unknown gross residual disease after surgery. Her prior medical/surgical history included thrombocytopenia and neutropenia. Patient never smoked, had no history of alcohol use, and no history of known exposures to oncogenic factors.

Patient completed 3 first line chemotherapy treatments prior to study enrollment including 15 cycles of bevacizumab, 6 cycles of carboplatin, and 6 cycles of paclitaxel from PPD (study day -540) to PPD (study day -432), with complete response. Second-line chemotherapy treatments received prior to study enrollment included 4 cycles of carboplatin (terminated due to an allergic response) and 4 cycles of gemcitabine from PPD (study day -87) to PPD (study day -15).

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. On PPD study day 27), patient's dose of niraparib was interrupted and on PPD (study day 45), niraparib treatment was restarted with a modified dose of 100 mg.

On PPD (study day 986; day -7 since last dose), patient was hospitalized with life-threatening, grade 4 MDS event that was considered medically significant. One week later, on PPD (study day 993), patient discontinued treatment with niraparib. This event was reported to be related to niraparib treatment and resolved with a status of recovering with sequelae on PPD (duration of event 146 days).

On PPD (study day 1131; day 139 since last niraparib treatment dose), patient experienced signs and/or symptoms of life-threatening AML reported to be related to niraparib treatment, with a diagnosis date of PPD (study day 1147). Patient was treated with decitabine combined with venetoclax but died on PPD (study day 1200; duration of event 70 days).

Patient PPD

Patient PPD, a PPD-year-old obese woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* wild type on PPD Patient received PDS on PPD with no gross residual disease after surgery (R=0). Her prior medical/surgical history included ablation by vaporization of diaphragmatic nodules (PPD), bilateral hysterectomy PPD laparotomy (PPD omentectomy PPD pelvic and para-aortic lymphadenectomy PPD and pelvic peritonectomy PPD Smoking status and history of alcohol use were unknown at initiation of niraparib. Patient had no known exposures to oncogenic factors.

Patient completed 2 first line chemotherapy treatments after debulking surgery including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -3548) to PPD (study day -3436), with complete response. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -2561) to PPD study day -2452), unknown response. Third-line chemotherapy treatments received prior to study enrollment included 6 cycles of pegylated liposomal doxorubicin and 6 cycles of carboplatin from PPD (study day -1854) to PPD (study day -1714), unknown response. Fourth-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of gemcitabine from PPD (study day -1343) to PPD (study day -1217), unknown

response. From PPD (study day -1084) to PPD (study day -923) patient received 6 cycles of paclitaxel, unknown response.

Furthermore, patient received 10 cycles of 1700 mg of PPD (anti-MUC1mAb) or placebo from PPD (study day -885) to PPD (study day -661), after which her disease progressed. From PPD (study day -650) to PPD (study day -293) patient received 16 cycles of trabectedin with a report of stable disease upon stopping due to toxicity. On PPD (study day -192) patient started carboplatin, receiving 2 cycles before stopping on PPD (study day -147) due to toxicity. Cisplatin was started on PPD (study day -140) and treatment was completed following 5 cycles on PPD (study day -56), with partial response.

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. On PPD (study day 404), patient's dose of niraparib was interrupted and on PPD (study day 432), niraparib treatment was restarted with a modified dose. On PPD (study day 492), patient had a second dose interruption. Treatment with niraparib 100 mg was discontinued on PPD (study day 525).

Patient experienced 3 AEs of thrombocytopenia, the first was a non-serious grade 2 event with an onset of PPD (study day 411) which lasted 7 days, leading to patient's first dose interruption. This event was reported to be related to niraparib treatment. The second was a non-serious grade 1 event of thrombocytopenia diagnosed on PPD (study day 418) lasting for 8 days, leading to an extended dose interruption. This event was reported to be related to niraparib treatment. The third thrombocytopenia event was a non-serious grade 2 event diagnosed on PPD (study day 432) and lasting 75 days. This event led to patient's first dose modification, restarting her on a reduced dose. This event was reported to be related to niraparib treatment. Additionally, patient experienced non-serious grade 1 headaches (ongoing up until time of death) with an onset on PPD (study day 431). These headaches were reported to be not related to niraparib treatment.

On PPD (study day 531; day 7 since last niraparib treatment dose), patient was hospitalized with life-threatening AML that was considered medically significant, reported to be related to niraparib treatment. Patient required a platelet transfusion that same day. Patient died on PPD (study day 759; duration of event 229 days).

Patient PPD

Patient PPD, a PPD-year-old obese woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage IV) ovarian cancer with somatic *BRCA* mutation on PPD. Patient received IDS on PPD with no gross residual disease after surgery (R=0). Patient never smoked, and had no history of alcohol use, and no known exposures to oncogenic factors.

Patient completed front-line chemotherapy prior to debulking surgery including 4 cycles of carboplatin and 4 cycles of paclitaxel from PPD (study day -1397) to PPD (study day -1334), with partial response. Patient then completed 2 chemotherapy treatments (after IDS) prior to study enrollment including 2 cycles of carboplatin and 2 cycles of paclitaxel from PPD (study day -1229) to

PPD (study day -1212), with complete response. Second-line chemotherapy treatments received prior to study enrollment included 3 cycles of carboplatin and 3 cycles of gemcitabine from PPD (study day -262) to PPD (study day -213), with complete response. Patient received third-line chemotherapy including 1 cycle of gemcitabine on PPD (study day -77), with partial response. Patient also completed second-line radiation therapy for her ovarian cancer from PPD (study day -25) to PPD (study day -11).

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. On PPD (study day 12), patient's dose of niraparib was interrupted and on PPD (study day 46), niraparib treatment was restarted with a modified dose of 150 mg, achieved by switching every other day between taking 1 capsule of 100 mg or 2 capsules of 100 mg. Treatment was discontinued on PPD (study day 1001).

Patient experienced 2 AEs of thrombocytopenia, the first was a serious grade 3 event with onset of PPD (study day 12) lasting 32 days and leading to patients first dose interruption. This event was reported to be related to niraparib treatment. The second was a serious grade 4 event of thrombocytopenia, secondary to MDS, with onset of PPD (study day 994) lasting 121 days and leading to treatment discontinuation. This event was reported to be related to niraparib treatment.

On PPD (study day 994; day -7 since last niraparib treatment dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 4 MDS that was considered medically significant. The event duration was 121 days and was reported as recovering with sequelae on PPD. The event was reported to be related to niraparib treatment. Patient also suffered thrombocytopenia based on secondary therapy related to MDS diagnosed on PPD (study day 994). On PPD (study day 1370), patient discontinued participation in the study by withdrawing her consent.

Patient PPD

Patient PPD, a PPD-year-old overweight woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage IV) ovarian cancer with *BRCA* wild type on PPD. Patient received IDS on PPD with no gross residual disease after surgery (R=0). Her prior medical/surgical history included thrombocytopenia, platelet transfusions, renal insufficiency, hepatic insufficiency, and neutropenia. Patient was a current smoker, smoking an average of 10 cigarettes a day. Patient reported no history of alcohol use, and no known exposures to oncogenic factors. Concomitant medications included ongoing use of omeprazole with an unknown start date.

Patient completed front-line chemotherapy prior to debulking surgery including 3 cycles of carboplatin and 3 cycles of paclitaxel from PPD (study day -728) to PPD (study day -686), with partial response. After IDS, patient completed 2 chemotherapy treatments including 3 cycles of carboplatin and 3 cycles of paclitaxel from PPD (study day -603) to PPD (study day -543). Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of doxorubicin from PPD (study day -216) to

PPD (study day -62), with complete response. Third-line chemotherapy treatments received after study enrollment included 6 cycles of carboplatin and 6 cycles of gemcitabine from PPD (study day 176) to PPD (study day 325), before stopping due to toxicity.

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. On PPD (study day 29), patient's dose of niraparib was interrupted and on PPD (study day 43), niraparib treatment was restarted with a modified dose of 100 mg. Treatment was discontinued on PPD (study day 161).

CBC assessments were completed for start of treatment on PPD (study day 57), indicating that patient required platelet transfusions and had hepatic toxicity.

On PPD (study day 689; day 529 since last niraparib treatment dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a life-threatening, grade 4 MDS event that was considered medically significant. The event duration was 196 days and was reported as recovering with sequelae on PPD This event was reported to be related to niraparib treatment.

Patient received red blood cell transfusions and platelet transfusions for pancytopenia on PPD (study day 876) and PPD (study day 884), respectively. Then, on PPD (study day 884; day 724 since last niraparib treatment dose), patient was hospitalized with grade 3 AML. This event was reported to be related to niraparib treatment and was still ongoing when the patient was lost to follow-up on PPD (study day 1052).

Patient PPD

Patient PPD , a PPD -year-old obese woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with germline *BRCA* mutation on PPD . Patient received PDS on PPD with no gross residual disease after surgery (R=0). Her prior medical/surgical history included thrombocytopenia, anemia, and neutropenia with a known diagnosis of breast cancer since PPD . Patient was never a smoker and reported no history of alcohol use, and no known exposures to oncogenic factors.

In PPD , patient received chemotherapy for breast cancer treatment including 4 cycles of cyclophosphamide, 4 cycles of docetaxel, and 4 cycles of epirubicin.

After her ovarian cancer diagnosis, patient received 2 first line chemotherapy treatments prior to study enrollment including 8 cycles of carboplatin, and 8 cycles of paclitaxel from PPD (study day -1904) to PPD (study day -1745), with complete response. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of paclitaxel along with 6 cycles of bevacizumab and 6 cycles of atezolizumab from PPD (study day -1208) to PPD (study day -1100), with partial response. Patient received second-line therapy with 31 cycles of bevacizumab and atezolizumab from PPD (study day -1074) to PPD (study day -351), stopping due to disease progression with partial response. Third-line chemotherapy treatments received prior to study

enrollment included 6 cycles of pegylated liposomal doxorubicin and 6 cycles of carboplatin from PPD 1 (study day -282) to PPD (study day -99), with partial response.

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. On PPD (study day 34), the treatment dose was modified to 100 mg. Treatment was discontinued on PPD (study day 217).

Patient experienced an AE of non-serious grade 1 thrombocytopenia with onset of PPD (study day 217) leading to niraparib treatment discontinuation. This event was reported to be related to niraparib treatment and was considered ongoing at the time patient discontinued from the study due to death.

On PPD study day 256; day 40 since last niraparib treatment dose), patient was hospitalized with life-threatening MDS that was considered medically significant. The event was reported to be related to niraparib treatment. Patient died on PPD (study day 327; duration of event 72 days).

Patient PPD

Patient PPD, a PPD-year-old overweight woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* wild type on PPD. Patient received IDS on PPD with no gross residual disease after surgery (R=0). Patient never smoked and reported no known exposures to oncogenic factors. Patient had a history of alcohol use, averaging 3 to 6 per week before ovarian cancer diagnosis and 1 to 2 drinks per week after ovarian cancer diagnosis.

Patient completed front-line chemotherapy prior to IDS including 4 cycles of carboplatin and 4 cycles of paclitaxel from PPD (study day -1218) to PPD (study day -1142), with partial response. After IDS, patient completed front-line chemotherapy treatments including 4 cycles of carboplatin and 4 cycles of paclitaxel from PPD (study day -1075) to PPD (study day -986), with partial response. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of doxorubicin from PPD (study day -225) to PPD (study day -78), with complete response. Third-line chemotherapy treatments received after study enrollment included 2 cycles of carboplatin and 2 cycles of doxorubicin from PPD (study day 935) to PPD (study day 994), discontinued due to toxicity.

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. Treatment was discontinued on PPD (study day 763).

Patient had a COVID-19 assessment completed following a confirmed diagnosis.

On PPD (study day 1038; day 276 since last niraparib treatment dose), patient was hospitalized with life-threatening AML that was considered medically significant. The event was reported to be related to niraparib treatment. Patient died on PPD (study day 1097; duration of event 60 days).

Patient PPD

Patient PPD, a PPD-year-old woman with a BMI of PPD kg/m^2, was diagnosed with high-grade serous carcinoma (FIGO stage I) ovarian cancer with HR-proficient and *BRCA* wild type on PPD. Patient received PDS on PPD with no gross residual disease after surgery (R=0). Patient never smoked, reported no history of alcohol use and no known exposures to oncogenic factors.

Patient completed first-line chemotherapy prior to study enrollment, including 4 cycles of carboplatin and 4 cycles of paclitaxel from PPD (study day -2060) to PPD (study day -1992), with complete response. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -1137) to PPD (study day -1029), with complete response. Third-line chemotherapy treatments received before study enrollment included 6 cycles of carboplatin and 6 cycles of doxorubicin liposome from PPD (study day -268) to PPD (study day -81), with complete response.

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. On PPD (study day 379), this dose was interrupted and on PPD (study day 404), niraparib treatment was restarted with a modified dose of 100 mg. Treatment was discontinued on PPD (study day 1800).

On PPD (study day 1729; day -71 since last niraparib treatment dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 4 AML event that was considered medically significant. The event was reported to be related to niraparib treatment. Patient received red blood cell transfusions on PPD (study day 1763), PPD (study day 1782) and PPD (study day 1793), before niraparib treatment was discontinued. The AML event was considered ongoing at the time patient discontinued from the study after completing 5-years of follow-up on PPD (study day 1827).

Patient PPD

Patient PPD, a PPD-year-old overweight woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage IV) ovarian cancer with *BRCA* wild type on PPD. Patient received IDS on PPD with no gross residual disease after surgery (R=0). Her prior medical/surgical history included thrombocytopenia, anemia, and neutropenia. Patient was a former smoker, smoking an average of 15 cigarettes a day. Patient reported no history of alcohol use and no known exposures to oncogenic factors. Relevant concomitant medications during the study period included corticosteroids from PPD (study day 1482) until PPD (study day 1608) and epoetin alfa from PPD (study day 1521) until PPD (study day 1563).

Patient completed front-line chemotherapy prior to debulking surgery including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -1970) to PPD (study day -1859), with partial response. After IDS, patient completed front-line chemotherapy treatments including 6 cycles of carboplatin and 6 cycles of

paclitaxel from PPD (study day -1393) to PPD (study day -1287), with partial response. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -766) to PPD (study day -656), with partial response. Third-line chemotherapy treatments received before study enrollment included 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -172) to PPD (study day -67), with partial response.

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. On PPD (study day 61), this dose was modified to 200 mg, and on PPD (study day 75), treatment was discontinued.

Subsequently, patient received chemotherapy including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day 283) to PPD (study day 388), 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day 596) to PPD (study day 701), 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day 862) to PPD (study day 967), and 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day 1170) to PPD (study day 1279), all with partial response.

On PPD (study day 1363; day 1289 since last niraparib treatment dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 3 MDS event that was considered medically significant. The event was reported to be related to niraparib treatment. The MDS event was considered ongoing at the time patient discontinued from the study due to death from ovarian cancer progression on PPD (study day 1608).

9.4.3.2. Narratives of MDS/AML Not Related to Niraparib

The narrative for 1 patient who experienced MDS/AML reported to be not related to niraparib during the study is provided below:

Patient PPD

Patient PPD, a PPD-year-old overweight woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* wild type on PPD. Patient received IDS on PPD with no gross residual disease after surgery (R=0). Her prior medical/surgical history included thrombocytopenia. Patient was a former smoker and reported no history of alcohol use and no known exposures to oncogenic factors.

Patient completed front-line chemotherapy prior to debulking surgery including 3 cycles of carboplatin and 3 cycles of paclitaxel from PPD (study day -1205) to PPD (study day -1163), with partial response. After IDS, patient completed front-line chemotherapy treatments including 3 cycles of carboplatin and 3 cycles of paclitaxel from PPD (study day -1094) to PPD (study day -1052). Second-line chemotherapy treatments received prior to study enrollment included 7

cycles of doxorubicin and 7 cycles of carboplatin from PPD (study day -268) to PPD (study day -72), with complete response.

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. On PPD (study day 36) treatment was discontinued.

Subsequently, patient received chemotherapy including 6 cycles of carboplatin and 6 cycles of gemcitabine from PPD (study day 475) to PPD (study day 588), with complete response, 6 cycles of carboplatin and 6 cycles of gemcitabine from PPD (study day 825) to PPD (study day 930), with partial response.

On PPD (study day 1106; day 1071 since last niraparib treatment dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 5 MDS event that was considered medically significant. This event was reported to be not related to niraparib treatment. Patient was treated with 6 cycles of azacitidine from PPD (study day 1111) to PPD (study day 1280), with progressive disease. The duration of MDS was 183 days, with an outcome of death due to ovarian cancer progression on PPD (study day 1288).

9.4.4. Narratives of Other SPMs

A detailed listing of the 6 patients with other SPM events is presented in Table 23. Narratives for all 6 patients with other SPM events (7 total events) are provided below, in Section 9.4.4.1 and Section 9.4.4.2, organized by whether events were reported to be related to niraparib (n=1 patient; 1 event) or reported to not be related to niraparib treatment (n=5 patients; 6 events), respectively. One patient was on a niraparib dose of 150 mg prior to development of SPM (a non-marketed dose), achieved by switching every other day between taking 1 capsule of 100 mg or 2 capsules of 100 mg. All 6 patients received chemotherapy for any cancer prior to niraparib initiation.

Table 23 Patients with Other SPM Events

Pat. ID	Age[1] (yrs)	Niraparib dose (mg) prior to SPM	Niraparib duration (days)	PT	Time from niraparib initiation to event onset (days)	Radiation therapy for any cancer/other PARP inhibitor received prior to niraparib	*BRCA*/HRD test result[2]
2LM+ Patients, Other SPM Related to niraparib							
PPD	PPD	150	340	CML	330	No/No	Wild Type/-
1LM Patients, Other SPM Not Related to niraparib							
PPD	PPD	200	49	HNC	290	No/No	Mutant/NA
2LM+ Patients, Other SPM Not Related to niraparib							
PPD	PPD	200	195	BC	127	No/Yes	Wild Type/-
PPD	PPD	300	546	SCC of the oral cavity	1008	No/No	Wild Type/-
	PPD	100	259	BCC	610	No/No	Wild Type/NP
				BCC	757	No/No	Wild Type/NP
PPD	PPD	200	242	BC	978	No/No	Wild Type/HRDp

Source: Listing 15.36.0

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; BC = Breast cancer; BCC = Basal cell carcinoma; *BRCA* = Breast cancer susceptibility gene; CML = Chronic myeloid leukemia; HNC = Head and neck cancer; HRDp = Homologous recombination deficiency – proficient (negative); NA = Not available; NP = Not performed; PARP = Poly (ADP-ribose) polymerase; Pat. ID = Patient Identification; PT = Preferred Term; SCC = Squamous cell carcinoma; SPM = Second primary malignancy.

Note: All 6 patients received chemotherapy for any cancer prior to niraparib initiation.

Note: There was 1 additional patient in the Enrolled Population who was diagnosed with an SPM. Due to insufficient clinical information to classify their niraparib line of therapy, despite site queries, they were excluded from the Safety Population. This patient initiated niraparib on PPD and was diagnosed with breast cancer on PPD

[1]Age was calculated from year of birth to year of niraparib initiation.
[2]Symbol "-" means no data was provided in the database.

9.4.4.1. Narratives of Other SPMs Related to Niraparib

The narrative for the 1 patient who experienced other SPMs reported to be related to niraparib during the study is provided below:

Patient PPD

Patient PPD, a PPD-year-old woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* wild type on PPD. Patient received PDS on PPD with no gross residual disease after surgery (R=0). Patient was a former smoker, with no history of alcohol use and no known exposures to oncogenic factors.

Patient completed 2 first line chemotherapy treatments prior to study enrollment including 8 cycles of carboplatin and 8 cycles of paclitaxel from PPD (study day -780) to PPD (study day -638), with complete response. Additionally, patient completed 31 cycles of bevacizumab from PPD (study day -780) to PPD (study day -116), with treatment stopping due to disease progression. Second-line chemotherapy treatments received prior to study enrollment included 4 cycles of carboplatin and 4 cycles of gemcitabine from PPD (study day -106) to PPD (study day -37). Each second-line treatment was completed with complete response.

Patient received her first dose of niraparib on PPD at a dose of 100 mg per day. On PPD (study day 76), patient's dose of niraparib was interrupted and on PPD (study day 84), niraparib treatment was restarted with a modified dose of 150 mg, achieved by switching every other day between taking 1 capsule of 100 mg or 2 capsules of 100 mg. Treatment was discontinued on PPD (study day 340).

Subsequently, patient received third-line chemotherapy, including 9 cycles of carboplatin from PPD (study day 411) toPPD (study day 491), which was stopped due to disease progression. A fourth-line chemotherapy treatment included 5 cycles of pegylated liposomal doxorubicin from PPD (study day 505) to PPD (study day 564), which was also stopped due to disease progression.

On PPD (study day 330; day -10 since last niraparib treatment dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 4 SPM event of CML that caused a dose interruption, ultimately leading to niraparib treatment discontinuation. The event was reported to be related to niraparib treatment. CML was considered ongoing at the time patient discontinued from the study due to death from ovarian cancer progression on PPD (study day 590).

9.4.4.2. Narratives of Other SPMs Not Related to Niraparib

The narratives for the 5 patients who experienced other SPMs reported to be not related to niraparib during the study are provided below:

Patient PPD

Patient PPD, a PPD-year-old overweight woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* mutation on PPD. Patient received IDS on PPD with an unknown gross residual disease status after surgery. Her prior medical/surgical history included anemia, renal insufficiency, and neutropenia. Patient never smoked and had unknown exposure to oncogenic factors. Patient had a history of alcohol use, averaging 1 to 2 drinks per week before ovarian cancer diagnosis and 1 to 2 drinks per week after ovarian cancer diagnosis. Concomitant medications included omeprazole (study day 10), macrogol (study day 10), and other multiple ingredient medications for constipation (study day 10, and study day 39).

Patient completed front-line chemotherapy prior to IDS including 4 cycles of carboplatin and 4 cycles of paclitaxel from PPD (study day -191) to PPD (study day -128), with partial response. After IDS, patient completed front-line chemotherapy treatments including 3 cycles of carboplatin and 3 cycles of paclitaxel from PPD (study day -70) to PPD (study day -28), with complete response.

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. On PPD (study day 49), treatment was discontinued.

CBC assessments completed for start of treatment on PPD (study day -8), indicated that patient had renal insufficiency. CBC assessments completed at the end of treatment on PPD (study day 52), indicated that patient required platelet transfusions and had renal insufficiency.

Patient experienced gastrointestinal disorders including grade 1 stomach pain and constipation from PPD (study day 10; -39 days since last niraparib treatment dose) to PPD (duration 21 days), with a full recovery. These events were reported to be related to niraparib treatment. On PPD (study day 24; -25 days since last niraparib treatment dose), patient experienced grade 1 events of increased ALT, AST, and LDH enzymes, as well as grade 1 anemia and a decrease in platelet counts; each reported to be related to niraparib treatment and resolved with status of recovered on PPD (duration 29 days). Also, on PPD (study day 24; -25 days since last niraparib dose), patient experienced onset of grade 1 chronic kidney disease, which resolved with status of recovering with sequelae on PPD (duration of 53 days). This event was reported to not be related to niraparib treatment.

On PPD (study day 30), patient began to experience grade 1 night sweats (resolving after a duration of 50 days) followed by constipation on PPD (study day 36; resolved after a duration of 17 days). These events were reported to be related to niraparib treatment. On PPD (study day 49), patient developed a grade 1 cough

with grade 2 dyspnea, reported to be related to niraparib treatment and the latter leading to treatment discontinuation. Both events resolved with recovery on PPD after a duration of 31 days. On PPD (study day 52; 4 days since last niraparib treatment dose), patient experienced grade 2 anemia, reported to be related to niraparib treatment, and grade 1 hypercalcemia, reported to not be related to niraparib treatment. These events resolved with a status of recovered on PPD (duration 9 days). On PPD (study day 60; 12 days since last niraparib treatment dose), patient experienced another event of anemia (grade 3) reported to be related to niraparib treatment, for which the patient received red blood cell transfusions on PPD (study day 62). This event resolved on PPD (duration 17 days).

On PPD (study day 290; 242 days since last dose of niraparib treatment), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 2 SPM of head and neck cancer that was considered medically significant. The event was not related to niraparib treatment. Patient was reported to have recovered from the event on PPD (duration 406 days).

Patient discontinued study on PPD (study day 737) when the Sponsor decision was made to terminate study.

Patient PPD

Patient PPD, a PPD-year-old woman with a BMI of PPD kg/m^2, was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* wild type in PPD (full date unknown). Patient received PDS on PPD with residual disease less than or equal to 1 cm after surgery (R≤1). Her prior medical/surgical history included anemia and neutropenia. Patient never smoked and reported no history of alcohol use and no known exposures to oncogenic factors. Prior to study enrollment, patient received another PARP inhibitor, olaparib 600 mg from PPD (study day -21) toPPD (study day -20).

Patient completed first-line chemotherapy after to debulking surgery including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -952) to PPD (study day -847) along with 5 cycles of bevacizumab from PPD (study day -931) to PPD (study day -847), treatment completed with stable disease. Patient received an additional 17 cycles of bevacizumab from PPD (study day -826) to PPD (study day -483), treatment completed with stable disease. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of doxorubicin and 6 cycles of carboplatin from PPD (study day -204) to PPD (study day -63), treatment completed with stable disease.

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. On PPD (study day 111), treatment was interrupted. On PPD (study day 125), treatment was restarted with a modified dose of 200 mg. On PPD (study day 195), treatment was discontinued.

On PPD (study day 127; day -68 since last niraparib treatment dose), patient was hospitalized with a grade 3 SPM of mammary carcinoma breast cancer, diagnosed on PPD (study day 129). The event was not related to niraparib treatment. On PPD , patient had breast-conserving surgery with sentinel node biopsy. Patient then underwent radiotherapy and received an aromatase inhibitor (letrozole) at a dose of 2.5 mg from PPD (study day 196) to PPD (full date unknown), with complete response.

Subsequently, patient received chemotherapy including 6 cycles of trabectedin and 6 cycles of doxorubicin from PPD (study day 288) to PPD (study day 414), with progressive disease.

The other SPM event was ongoing when the patient died on PPD (study day 584) from ovarian cancer progression.

Patient PPD

Patient PPD , a PPD -year-old obese woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage IV) ovarian cancer with *BRCA* wild type onPPD . Patient received IDS on PPD unknown status of gross residual disease after surgery. Patient never smoked and reported no history of alcohol use and no known exposures to oncogenic factors.

Patient completed front-line chemotherapy prior to debulking surgery including 8 cycles of carboplatin and 8 cycles of paclitaxel from PPD (study day -3937) to PPD (study day -3790), with partial response. Patient then received front-line chemotherapy after IDS including 8 cycles of carboplatin and 8 cycles of pegylated liposomal doxorubicin from PPD (study day -3561) to PPD (study day -3364), with a non-evaluable response. Patient received a second-line treatment of chemotherapy prior to study enrollment that included 6 cycles of cisplatin and 6 cycles of cyclophosphamide from PPD (study day -2775) to 27 March 2013 (study day -2670), with complete response. Third-line chemotherapy treatment received prior to study enrollment included 6 cycles of bevacizumab and 6 cycles of topotecan from PPD study day -2388) to PPD (study day -2168), with complete response. From PPD (exact date unknown) to PPD (exact date unknown), patient received 8 cycles of bevacizumab and 8 cycles of paclitaxel, stopping due to disease progression. From PPD (exact date unknown) to PPD (study day -40), patient received 40 cycles of pegylated liposomal doxorubicin and 40 cycles of carboplatin, stopping due to toxicity.

Patient received her first dose of niraparib on PPD at a dose of 300 mg per day. On PPD (study day 153) treatment was interrupted. On PPD (study day 181), treatment was restarted with a modified dose. A second dose modification occurred on PPD (study day 329). On PPD (study day 546), treatment of niraparib 300 mg was discontinued.

Subsequently, patient received chemotherapy including 10 cycles of pegylated liposomal doxorubicin and 10 cycles of carboplatin from PPD (study day 553) to PPD (study day 938), with complete response. From PPD (study

day 1099) to PPD (study day 1204), patient received 4 cycles of carboplatin, stopping to be treated for squamous cell carcinoma of the oral cavity.

Patient had a COVID-19 assessment completed following a confirmed diagnosis.

On PPD (study day 1008; 463 days since last niraparib dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 3 SPM of squamous cell carcinoma of the oral cavity that was considered medically significant. The event was not related to niraparib treatment. The event resolved on PPD (duration 32 days).

Patient discontinued study on PPD (study day 1370) when the Sponsor decision was made to terminate study.

Patient PPD

Patient PPD, a PPD year-old obese woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer with *BRCA* wild type on PPD. Patient received PDS on PPD with no gross residual disease after surgery (R=0). Her prior medical/surgical history included thrombocytopenia, platelet transfusions, anemia, and neutropenia. Relevant medical history included PPD disorder (prior to niraparib initiation) and arterial hypertension, heart failure, and hydronephrosis, all with onset after niraparib initiation. Patient was a former smoker, smoking for PPD years at an average of 2 cigarettes per day. Patient reported no history of alcohol use and no known exposures to oncogenic factors.

Relevant concomitant medications included olanzapine (study day -2989), nebivolol (study day 34), hydrochlorothiazide (study day 34), nimodipine (study day 58), imidapril (study day 148), doxazosin (study day 195), enoxaparin (study day 290), bisoprolol (study day 290), amlodipine (study day 290), furosemide (study day 300), digoxin (study day 344), and rosuvastatin (study day 401).

Patient completed first-line chemotherapy after debulking surgery including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -541) to PPD (study day -429), with partial response. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -183) to PPD (study day -29), with partial response.

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. On PPD (study day 195) treatment was interrupted. On PPD (study day 217), treatment was restarted with a modified dose of 100 mg. On PPD (study day 259), treatment was discontinued.

Subsequently, patient received chemotherapy including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day 265) to PPD (study day 401), with partial response. From PPD (study day 517) to PPD (study day 759), patient received 9 cycles of pegylated liposomal doxorubicin, with

progressive disease. On PPD (study day 791), patient received 1 cycle of bevacizumab and 1 cycle of paclitaxel, reason for stopping listed as death.

On PPD (study day 610; 352 days since last niraparib dose), patient experienced signs and/or symptoms that led to a subsequent diagnosis of a grade 4 SPM of eyelid basal cell carcinoma that was considered medically significant. The event was not related to niraparib treatment. On PPD, the eyelid basal cell carcinoma resolved (duration 48 days). On PPD (study day 757; 499 days since last niraparib dose), patient had second SPM of grade 4 forehead basal cell carcinoma that was considered medically significant. The event was not related to niraparib treatment. On PPD the forehead basal cell carcinoma resolved (duration 17 days), after patient underwent a surgical procedure to remove the basal cell carcinoma.

On PPD (study day 801), patient died from ovarian cancer progression.

Patient PPD

Patient PPD, a PPD-year-old woman with a BMI of PPD kg/m^2, was diagnosed with high-grade serous carcinoma (FIGO stage IV) ovarian cancer with HR-proficient and *BRCA* wild type in PPD (full date unknown). Patient received IDS on PPD with no gross residual disease after surgery (R=0). Patient never smoked and reported no history of alcohol use and no known exposures to oncogenic factors.

Patient completed front-line chemotherapy prior to debulking surgery including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -860) to PPD (study day -727), with partial response. Patient received a second-line treatment of chemotherapy prior to study enrollment that included 4 cycles of carboplatin and 4 cycles of doxorubicin from PPD (study day -185) to PPD (study day -41), with complete response, stopping due to toxicity.

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. On PPD (study day 26) treatment was interrupted. While no restart date was known, patient had a second dose interruption on PPD (study day 208). On PPD (study day 242), treatment was discontinued.

Subsequently, patient received chemotherapy including 3 cycles of carboplatin from PPD (study day 254) to PPD (study day 306), stopped due to toxicity, along with 5 cycles of gemcitabine from PPD (study day 254) to PPD (study day 355), with progressive disease. From PPD (study day 383) to PPD (study day 551), patient received 6 cycles of paclitaxel with partial response, along with 15 cycles of maintenance therapy bevacizumab from PPD (study day 383) to PPD (study day 796) with disease progression. From PPD (study day 841) to PPD (study day 922), patient received 4 cycles of paclitaxel, stopping due to other SPM diagnosis of breast cancer.

On PPD (study day 978; 737 days since last niraparib dose), patient experienced signs and/or symptoms of a grade 4 SPM of breast cancer that was considered medically significant and was diagnosed on PPD (study day 971). The event was not related to niraparib treatment. Patient received 2 cycles of

doxorubicin from PPD (study day 983) to PPD (study day 1013), reason for stopping listed as death.

On PPD (study day 1086), patient died from ovarian cancer progression. The SPM event of breast cancer was considered ongoing at the time of death.

9.4.5. COVID-19

A COVID-19 infection assessment was completed for all COVID-19 cases identified during the study (see Section 7.3.4 and Table 2). There were 118 patients (15.8%) with a suspected, probable, or confirmed COVID-19 case diagnosis (Table 24).

Table 24 Suspected, Probable, or Confirmed COVID-19 Case Diagnosis

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
COVID-19 Case Diagnosis[1], n (%)	24 (13.3%)	94 (16.7%)	118 (15.8%)
Confirmed	19 (10.5%)	77 (13.7%)	96 (12.9%)
Probable	6 (3.3%)	9 (1.6%)	15 (2.0%)
Suspected	0	8 (1.4%)	8 (1.1%)

Source: Table 14.3.18
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group.
[1]COVID-19 Case Diagnosis is based on WHO definition. Patients may have multiple COVID-19 case diagnosis events.

Additional COVID-19 assessments completed for patients with a suspected, probable, or confirmed COVID-19 diagnosis are summarized and provided in Table 14.3.19. A full by-patient listing of AEs is available in Listing 15.26.0 and a by-patient listing of assessments for patients with COVID-19 AEs is available in Listing 15.33.0.

9.5. Results of Secondary Analyses

9.5.1. MDS/AML and/or Other SPM Incidence by Potential Risk Factors

With an overall MDS/AML and other SPM incidence rate of 0.85 (95% CI: 0.48, 1.40) per 100 patient-years based on 15 patients with 18 MDS/AML and other SPM events over 1762.6 patient-years (Table 19), there were too few cases to observe any patterns in potential risk factors for MDS/AML and other SPMs.

Details of MDS/AML and other SPM incidence by potential risk factors and other factors are provided in Table 14.2.04, Table 14.2.05, Table 14.2.09, Table 14.2.10, Table 14.2.14, and Table 14.2.15.

Critical risk factors among patients who experienced events of MDS/AML or other SPMs are described in Section 9.5.1.1 and Section 9.5.1.2, respectively.

9.5.1.1. Critical Risk Factors Among MDS/AML Patients

All MDS/AML events occurred among 2LM+ patients. A detailed listing of the 9 patients with MDS/AML events is presented in Table 22, followed by patient narratives (Section 9.4.3). An aggregate summary of critical risk factors among patients with MDS/AML events is presented in Table 25. Most patients (88.9%) with MDS/AML events had events that were reported to be related to niraparib treatment. The median time from niraparib initiation to MDS/AML event onset was 32.7 months (IQR 22.6, 36.3 months). *BRCA* test results were available for all 9 of these patients, 7 (77.8%) were *BRCA* wild type, and 2 (22.2%) were *BRCA* mutant (n=1 germline, and n=1 somatic). All 9 patients had received platinum-based chemotherapy prior to niraparib initiation, with a median of 14.0 cycles (IQR 12.0, 20.0).

Table 25 Critical Risk Factors Among Patients with MDS/AML Events

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Total Patients with MDS/AML Events, n	0	9	9
Total Patients with MDS/AML Events Related to niraparib, n (%)	0	8 (88.9%)	8 (88.9%)
Time from niraparib Initiation to Event Onset (months)[1]			
n	0	9	9
Mean		31.7	31.7
SD		14.40	14.40
Q1		22.6	22.6
Median		32.7	32.7
Q3		36.3	36.3
Min		8	8
Max		57	57
BRCA Tested, n (%)			
Yes	0	9 (100%)	9 (100%)
No	0	0	0
BRCA Test Results[2]			
Mutant	0	2 (22.2%)	2 (22.2%)
Germline[3]	0	1 (50.0%)	1 (50.0%)
Somatic[3]	0	1 (50.0%)	1 (50.0%)
Missing[3]	0	0	0
Wild Type	0	7 (77.8%)	7 (77.8%)
Missing	0	0	0
Received Chemotherapy and Radiation Therapy Prior to niraparib Initiation, n (%)[4]			
Yes	0	1 (11.1%)	1 (11.1%)
No	0	8 (88.9%)	8 (88.9%)
Total Number of Platinum-based Chemotherapy Cycles Prior to niraparib Initiation[5]			
n	0	9	9
Mean		16.6	16.6
SD		7.21	7.21
Q1		12.0	12.0
Median		14.0	14.0

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Q3		20.0	20.0
Min		9	9
Max		31	31

Source: Table 14.2.16

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; AML = Acute myeloid leukemia; *BRCA* = breast cancer susceptibility gene; Max = Maximum; MDS = Myelodysplastic syndrome; Min = Minimum; SD = Standard deviation; Q1 = First quartile; Q3 = Third quartile.

Note: For categorical factors, summaries are presented as number and percentage of patients with event in each group. The percentage is based on the number of patients with MDS/AML events.

Note: "Unknown" are those who have "Unknown" checked on eCRF. "Missing" are those with no reported data.

[1]The time from niraparib initiation to MDS/AML event onset is calculated as the time in months from the start date of niraparib to the onset of the first occurrence of MDS/AML.

[2]The percentage is based on the number of patients with MDS/AML events and *BRCA* testing performed.

[3]The percentage is based on the number of patients who have *BRCA* status as Mutant.

[4]Capturing receipt of chemotherapy or radiation therapy for any cancer.

[5]Platinum compounds include cisplatin, oxaliplatin, and carboplatin.

More than one-half (55.6% [n=5]) of the patients were between the ages of 65 years to 74 years at index date (niraparib initiation), the other 44.4% (n=4) were between the ages of 50 years to 64 years at index date (niraparib initiation) (see Table 14.2.16). No patients were exposed to oncogenic factors at the time of enrollment and 5 patients (55.6%) reported never smoking. A full summary of critical risk factors among patients with MDS/AML events is available in Table 14.2.16.

9.5.1.2. Critical Risk Factors among Other SPM Patients

Five out of 6 patients who experienced other SPM events were in the 2LM+ cohort. A detailed listing of the 6 patients with other SPM events is presented in Table 23, followed by patient narratives (Section 9.4.4). An aggregate summary of critical risk factors among patients with other SPM events is presented in Table 26. One patient (16.7%) with other SPM events had an event that was reported to be related to niraparib treatment. Time from niraparib initiation to other SPM event onset was 9.5 months for the one patient in the 1LM cohort and the median time from niraparib initiation to other SPM event onset was 20.0 months (IQR 10.8, 32.1) in the 2LM+ cohort. *BRCA* test results were available for all 6 of these patients; the 1LM patient was *BRCA* mutant, while all 5 2LM+ patients were *BRCA* wild type. All 6 patients had received platinum-based chemotherapy prior to niraparib initiation, with a median of 12.0 cycles (IQR 10.0, 12.0).

Table 26 Critical Risk Factors among Patients with Other SPM Events

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Total Patients with SPM Events, n	1	5	6
Total Patients with SPM Events Related to niraparib, n (%)	0	1 (20.0%)	1 (16.7%)
Time from niraparib Initiation to Event Onset (months)[1]			
n	1	5	6
Mean	9.5	20.1	18.3
SD	NE	12.78	12.22
Q1	9.5	10.8	9.5
Median	9.5	20.0	15.4
Q3	9.5	32.1	32.1
Min	10	4	4
Max	10	33	33
BRCA Tested, n (%)			
Yes	1 (100%)	5 (100%)	6 (100%)
No	0	0	0
BRCA Test Results[2]			
Mutant	1 (100%)	0	1 (16.7%)
Germline[3]	0	0	0
Somatic[3]	0	0	0
Missing[3]	1 (100%)	0	1 (100%)
Wild Type	0	5 (100%)	5 (83.3%)
Missing	0	0	0
Received Chemotherapy and Radiation Therapy Prior to niraparib Initiation, n (%)[4]			
Yes	0	0	0
No	1 (100%)	5 (100%)	6 (100%)
Total Number of Platinum-based Chemotherapy Cycles Prior to niraparib Initiation[5]			
n	1	5	6
Mean	7.0	21.6	19.2
SD	NE	22.60	21.08
Q1	7.0	12.0	10.0
Median	7.0	12.0	12.0
Q3	7.0	12.0	12.0
Min	7	10	7
Max	7	62	62

Source: Table 14.2.17

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; *BRCA* = Breast cancer susceptibility gene; Max = Maximum; Min = Minimum; NE = Not evaluable; SD = Standard deviation; SPM = Second primary malignancy; Q1 = First quartile; Q3 = Third quartile.

Note: There was 1 additional patient in the Enrolled Population who was diagnosed with an SPM. Due to insufficient clinical information to classify their niraparib line of therapy, despite site queries, they were excluded from the Safety Population. This patient initiated niraparib on PPD and was diagnosed with breast cancer on PPD

Note: For categorical factors, summaries are presented as number and percentage of patients with event in each group. The percentage is based on the number of patients with SPM events.

Note: "Unknown" are those who have "Unknown" checked on eCRF. "Missing" are those with no reported data.

[1]The time from niraparib initiation to SPM event onset is calculated as the time in months from the start date of niraparib to onset of the first occurrence of SPM.
[2]The percentage is based on the number of patients with SPM events and *BRCA* testing performed.
[3]The percentage is based on the number of patients who have *BRCA* status as Mutant.
[4]Capturing receipt of chemotherapy or radiation therapy for any cancer.
[5]Platinum compounds include cisplatin, oxaliplatin, and carboplatin.

One-half (50.0% [n=3]) of patients who experienced other SPM events were between the ages of 50 years to 64 years at index date (niraparib initiation) (see Table 14.2.17). Five patients reported no exposure to oncogenic factors at the time of enrollment (exposure unknown for 1 patient) and 4 patients (66.7%) reported never smoking. A full summary of critical risk factors among patients with other SPM events is available in Table 14.2.17.

9.6. Adverse Events/Adverse Reactions

9.6.1. Brief Summary of Adverse Events

An overview of the number of patients with at least 1 TEAE is presented in Table 27. A TEAE was defined as an AE with a start date on or after the start date of niraparib and within 30 days of last dose. In total, 389 patients (52.2%) experienced at least 1 TEAE (60.8% of 1LM patients [n=110]; 49.5% of 2LM+ patients [n=279]), 138 patients (18.5%) experienced a TEAE with grade 3 or higher by maximum NCI CTCAE grade (19.9% of 1LM patients [n=36]; 18.1% of 2LM+ patients [n=102]), and 69 patients (9.3%) experienced a serious TEAE (10.5% of 1LM patients [n=19]; 8.9% of 2LM+ patients [n=50]). Overall, 49 patients (6.6%) experienced a TEAE that lead to the discontinuation of niraparib (8.3% of 1LM patients [n=15]; 6.0% of 2LM+ patients [n=34]), and 3 patients (0.4%) experienced a TEAE with outcome of death (all 2LM+ patients).

Table 27 Overview of Patients with Treatment-Emergent Adverse Events

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Any Treatment-Emergent Adverse Event (TEAE) During Study, n (%)	110 (60.8%)	279 (49.5%)	389 (52.2%)
TEAEs Related to niraparib, n (%)	79 (43.6%)	180 (31.9%)	259 (34.8%)
TEAEs with Grade 3 or Higher by Maximum NCI CTCAE Grade	36 (19.9%)	102 (18.1%)	138 (18.5%)
TEAEs Related to niraparib with Grade 3 or Higher by Maximum NCI CTCAE Grade, n (%)	24 (13.3%)	67 (11.9%)	91 (12.2%)
Serious TEAEs, n (%)	19 (10.5%)	50 (8.9%)	69 (9.3%)
Serious TEAEs Related to niraparib, n (%)	14 (7.7%)	21 (3.7%)	35 (4.7%)
TEAEs Leading to Drug Withdrawn, n (%)	15 (8.3%)	34 (6.0%)	49 (6.6%)

	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
TEAEs with Death Outcome, n (%)	0	3 (0.5%)	3 (0.4%)
TEAEs Related to niraparib with Death Outcome, n (%)	0	1 (0.2%)	1 (0.1%)

Source: Table 14.3.01

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group; AML = Acute myeloid leukemia; CTCAE = Common Terminology Criteria for Adverse Events; MDS = Myelodysplastic syndrome; NCI = National Cancer Institute; SPM = Second primary malignancy; TEAE = Treatment-Emergent Adverse Event.

Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.

Note: Number of patients with event are counted in each category. One patient may have had more than 1 event in the category.

9.6.2. All TEAEs by SOC and PT

A summary of all TEAEs by SOC and PT is provided in Table 14.3.04. Note that AE numbers decrease as Tables begin to focus on TEAEs, as not all TEAEs were reported to be related to niraparib. By-patient TEAEs are provided in Listing 15.26.0.

9.6.2.1. Common TEAEs by Overall Frequency

A summary of all common (≥5% in either cohort) TEAEs is presented by overall frequency in Table 28. By-patient TEAEs are provided in Listing 15.26.0.

Table 28 Common (≥5%) Treatment-Emergent Adverse Events by Overall Frequency

	Safety Population		
Preferred Term (PT)[1]	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Any Common Adverse Event, n (%)	89 (49.2%)	192 (34.0%)	281 (37.7%)
Anemia, n (%)	31 (17.1%)	62 (11.0%)	93 (12.5%)
Nausea, n (%)	24 (13.3%)	50 (8.9%)	74 (9.9%)
Thrombocytopenia, n (%)	23 (12.7%)	48 (8.5%)	71 (9.5%)
Constipation, n (%)	23 (12.7%)	40 (7.1%)	63 (8.5%)
Fatigue, n (%)	19 (10.5%)	37 (6.6%)	56 (7.5%)
Asthenia, n (%)	12 (6.6%)	40 (7.1%)	52 (7.0%)
Dyspnea	10 (5.5%)	18 (3.2%)	28 (3.8%)
Insomnia	10 (5.5%)	13 (2.3%)	23 (3.1%)

Source: Table 14.3.15

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group.

Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.

Note: Common Adverse Event refers to the adverse events with ≥5% in either cohort. Percentage is calculated based on the number of patients in each group (N).

Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

9.6.2.2. All TEAEs by SOC and PT and Maximum Grade

A summary of (≥2%) TEAEs for the overall patient population is presented in Table 29. A summary of all TEAEs by SOC and PT and maximum grade is provided in Table 14.3.06. By-patient TEAEs are provided in Listing 15.26.0.

Table 29 Treatment-Emergent Adverse Events (≥2%) by Overall System Organ Class, Preferred Term, and Maximum Grade

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population (Overall N=745)			
	Grade 1	Grade 2	Grade ≥3	Total
Patients with Any Event, n (%)	107 (14.4%)	144 (19.3%)	138 (18.5%)	389 (52.2%)
Gastrointestinal Disorders, n (%)				
Any Event[2]	115 (15.4%)	57 (7.7%)	22 (3.0%)	194 (26.0%)
Nausea	55 (7.4%)	19 (2.6%)	0	74 (9.9%)
Constipation	42 (5.6%)	18 (2.4%)	3 (0.4%)	63 (8.5%)
Abdominal Pain	20 (2.7%)	7 (0.9%)	4 (0.5%)	31 (4.2%)
Vomiting	16 (2.1%)	7 (0.9%)	0	23 (3.1%)
Abdominal Pain Upper	13 (1.7%)	4 (0.5%)	1 (0.1%)	18 (2.4%)
Diarrhea	13 (1.7%)	2 (0.3%)	1 (0.1%)	16 (2.1%)
Blood and Lymphatic System Disorders, n (%)				
Any Event[2]	25 (3.4%)	59 (7.9%)	80 (10.7%)	164 (22.0%)
Anemia	16 (2.1%)	35 (4.7%)	42 (5.6%)	93 (12.5%)
Thrombocytopenia	17 (2.3%)	27 (3.6%)	27 (3.6%)	71 (9.5%)
Neutropenia	3 (0.4%)	9 (1.2%)	17 (2.3%)	29 (3.9%)
General Disorders and Administration Site Conditions, n (%)				
Any Event[2]	81 (10.9%)	48 (6.4%)	6 (0.8%)	135 (18.1%)
Fatigue	27 (3.6%)	26 (3.5%)	3 (0.4%)	56 (7.5%)
Asthenia	38 (5.1%)	13 (1.7%)	1 (0.1%)	52 (7.0%)
Nervous System Disorders, n (%)				
Any Event[2]	63 (8.5%)	14 (1.9%)	4 (0.5%)	81 (10.9%)
Headache	32 (4.3%)	2 (0.3%)	0	34 (4.6%)
Dizziness	9 (1.2%)	6 (0.8%)	0	15 (2.0%)
Musculoskeletal and Connective Tissue Disorders, n (%)				
Any Event[2]	49 (6.6%)	11 (1.5%)	2 (0.3%)	62 (8.3%)
Arthralgia	22 (3.0%)	3 (0.4%)	1 (0.1%)	26 (3.5%)
Investigations, n (%)				
Any Event[2]	24 (3.2%)	12 (1.6%)	14 (1.9%)	50 (6.7%)
Platelet Count Decreased	6 (0.8%)	5 (0.7%)	9 (1.2%)	20 (2.7%)
Respiratory, Thoracic and Mediastinal Disorders, n (%)				
Any Event[2]	29 (3.9%)	17 (2.3%)	3 (0.4%)	49 (6.6%)
Dyspnea	13 (1.7%)	13 (1.7%)	2 (0.3%)	28 (3.8%)

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population (Overall N=745)			
	Grade 1	Grade 2	Grade ≥3	Total
Psychiatric Disorders, n (%)				
Any Event[2]	24 (3.2%)	10 (1.3%)	3 (0.4%)	37 (5.0%)
Insomnia	16 (2.1%)	6 (0.8%)	1 (0.1%)	23 (3.1%)
Vascular Disorders, n (%)				
Any Event[2]	13 (1.7%)	16 (2.1%)	6 (0.8%)	35 (4.7%)
Hypertension	8 (1.1%)	12 (1.6%)	6 (0.8%)	26 (3.5%)
Metabolism and Nutrition Disorders, n (%)				
Any Event[2]	21 (2.8%)	9 (1.2%)	4 (0.5%)	34 (4.6%)
Decreased Appetite	15 (2.0%)	1 (0.1%)	0	16 (2.1%)

Source data: Table 14.3.06
Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.
Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.
[2]The 'Any event' row within the system organ class is a calculation of the number of unique patients who had an adverse event within the system organ class. For each patient in this row, the maximum grade across the system organ class was chosen.

9.6.2.3. All TEAEs Leading to Drug Withdrawn by SOC and PT

A summary of (≥1%) TEAEs that lead to niraparib being withdrawn by SOC and PT for the overall patient population is presented in (Table 30). A summary of all TEAEs that lead to niraparib being withdrawn is provided for SOC and PT in Table 14.3.11. By-patient listings of all TEAEs are provided in Listing 15.26.0.

Table 30 Treatment-Emergent Adverse Events (≥1%) Leading to Drug Withdrawn by Overall System Organ Class and Preferred Term

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population		
	1LM (N=181)	2LM+ (N=564)	Overall (N=745)
All Events	22	41	63
Patients with Any Event Leading to Drug Withdrawn, n (%)	15 (8.3%)	34 (6.0%)	49 (6.6%)
Blood And Lymphatic System Disorders, n (%) [event]	5 (2.8%) [6]	10 (1.8%) [10]	15 (2.0%) [16]
Anemia	4 (2.2%) [4]	5 (0.9%) [5]	9 (1.2%) [9]

Source data: Table 14.3.11
Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.

Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

9.6.2.4. All TEAEs with Death Outcome by SOC and PT

A summary of all TEAEs with a death outcome are presented by SOC and PT in Table 31, followed by a brief narrative in Section 9.6.2.4.1. By-patient AEs with death outcome are provided in Listing 15.31.0. Please note, to be included in the TEAE table below, the AE from Listing 15.31.0 had a start date on or after the niraparib initiation and within 30 days of last niraparib dose, per the TEAE study definition.

Table 31 Treatment-Emergent Adverse Events with Death Outcome by Overall System Organ Class and Preferred Term

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population 1LM (N=181)	 2LM+ (N=564)	 Overall (N=745)
All Events	0	3	3
Patients with Any Event with Death Outcome, n (%)	0	3 (0.5%)	3 (0.4%)
Gastrointestinal Disorders, n (%) [event]	0	1 (0.2%) [1]	1 (0.1%) [1]
Ascites	0	1 (0.2%) [1]	1 (0.1%) [1]
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps, n (%) [event]	0	1 (0.2%) [1]	1 (0.1%) [1]
Acute Myeloid Leukemia	0	1 (0.2%) [1]	1 (0.1%) [1]
Nervous System Disorders, n (%) [event]	0	1 (0.2%) [1]	1 (0.1%) [1]
Cerebral Infarction	0	1 (0.2%) [1]	1 (0.1%) [1]

Source data: Table 14.3.13
Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.
Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

9.6.2.4.1. Narratives of TEAEs with Death Outcome

Patient PPD

Patient PPD, a PPD-year-old woman with a BMI of PPD kg/m^2, was diagnosed with high-grade serous carcinoma (FIGO stage II) ovarian cancer in PPD (full date unknown), somatic *BRCA* mutation. Patient received PDS on PPD with

no residual disease after surgery (R=0). Her prior medical/surgical history included neutropenia. Patient's smoking status, history of alcohol use, and exposure to oncogenic factors was unknown. Prior to study enrollment, patient received another PARP inhibitor, olaparib 600 mg from PPD (study day -399) to PPD (full date unknown). During this time, patient had 1 dose modification, decreasing from 600 mg olaparib to 300 mg olaparib on PPD (study day -393).

Patient completed first-line chemotherapy after debulking surgery including 6 cycles of carboplatin and 6 cycles of paclitaxel from PPD (study day -3003) to PPD (study day -2884), treatment completed with unknown response. Second-line chemotherapy treatments received prior to study enrollment included 6 cycles of pegylated liposomal doxorubicin and 6 cycles of carboplatin from PPD (study day -581) to PPD study day -441), complete response. Third-line chemotherapy treatments received prior to study enrollment included 6 cycles of carboplatin and 6 cycles of gemcitabine from PPD (study day -149) to PPD (study day -30), partial response.

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. Treatment was discontinued on PPD (study day 160).

Subsequently, patient received chemotherapy including 3 cycles of carboplatin from PPD (study day 174) to PPD (study day 209), stopping for toxicity. From PPD (study day 210) to PPD (study day 337), patient received 7 cycles of topotecan, with disease progression.

During the study period, patient was confirmed positive with asymptomatic COVID-19 resulting in home quarantine/isolation.

On PPD (study day 30), patient experienced a serious grade 2 PPD and a serious grade 2 PPD requiring inpatient hospitalization and resolving on PPD with a duration of 49 days. These events were reported to be not related to niraparib treatment. On PPD (study day 60), patient experienced a grade 3 skin ulceration on herPPD resolving on PPD with a duration of 32 days. This event was reported to be not related to niraparib treatment. On PPD (study day 79), patient experienced grade 1 worsening of lymphedema on her PPD This event was reported to be not related to niraparib treatment and was ongoing at time of death. On PPD (study day 129), patient experienced grade 2 worsening of hyperthyroidism. This event was reported to be not related to niraparib treatment and was ongoing at time of death. On PPD (study day 146), patient experienced a grade 1 headache, which resolved with a status of recovered on PPD (duration 63 days). This event was reported to be not related to niraparib treatment. On PPD (study day 174), patient experienced a grade 2 infusion related reaction resolving on PPD with a duration of 37 days. This event was reported to be not related to niraparib treatment.

On PPD (study day 160), patient experienced ascites requiring inpatient hospitalization with an outcome of death due to disease progression on PPD (study day 411; duration 252 days). This event was reported to be not related to niraparib treatment.

Patient PPD

The narrative for Patient PPD is provided in Section 9.4.3.1.

Patient PPD

Patient PPD, a PPD year-old overweight woman (BMI of PPD kg/m^2), was diagnosed with high-grade serous carcinoma (FIGO stage III) ovarian cancer on PPD, *BRCA* wild type. Patient received IDS on PPD with unknown residual disease after surgery. Her prior medical/surgical history included ongoing Crohn disease diagnosed on PPD. Patient's smoking status and history of alcohol use was unknown. Patient reported no known exposures to oncogenic factors.

Patient completed front-line chemotherapy before debulking surgery including 3 cycles of carboplatin and 3 cycles of paclitaxel from PPD (study day -1597) to PPD (study day -1554), unknown response. Patient then completed AT after debulking surgery including 3 cycles of paclitaxel from PPD to PPD, and 3 cycles of carboplatin and 3 cycles of paclitaxel from PPD (study day -1492) to PPD (study day -1422), unknown response. Second-line chemotherapy treatments received prior to study enrollment included 4 cycles of carboplatin and 4 cycles of paclitaxel from PPD (study day -713) to PPD (study day -643), stopping due to toxicity with stable disease. Third-line chemotherapy treatments received prior to study enrollment included 6 cycles of cisplatin and 6 cycles of paclitaxel from PPD (study day -132) to PPD (study day -13), partial response.

Patient received her first dose of niraparib on PPD at a dose of 200 mg per day. Patient remained on niraparib treatment until her death on PPD (study day 584).

On PPD (study day 578; 6 days before last niraparib dose), patient experienced a serious life-threatening cerebral infarction with an outcome of death on PPD (study day 584; duration 7 days). This event was reported to be not related to niraparib treatment.

9.6.3. TEAEs Related to Niraparib by SOC and PT

All TEAEs reported to be related to niraparib treatment and occurring in 2% or more of the overall population are presented in Table 32. A full summary of all TEAEs related to niraparib treatment is provided in Table 14.3.05. By-patient TEAEs reported to be related to niraparib treatment are provided in Listing 15.26.0.

Table 32 Treatment-Emergent Events (≥2%) Overall Related to niraparib by System Organ Class and Preferred Term

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population 1LM (N=181)	2LM+ (N=564)	Overall (N=745)
All Events Related to niraparib	230	504	734
Patients with Any Event Related to niraparib, n (%)	79 (43.6%)	180 (31.9%)	259 (34.8%)
Blood And Lymphatic System Disorders, n (%) [event]	42 (23.2%) [66]	96 (17.0%) [182]	138 (18.5%) [248]
Anemia	22 (12.2%) [32]	51 (9.0%) [80]	73 (9.8%) [112]
Thrombocytopenia	20 (11.0%) [22]	45 (8.0%) [62]	65 (8.7%) [84]
Neutropenia	7 (3.9%) [8]	15 (2.7%) [32]	22 (3.0%) [40]
Gastrointestinal Disorders, n (%) [event]	38 (21.0%) [55]	59 (10.5%) [98]	97 (13.0%) [153]
Nausea	20 (11.0%) [22]	38 (6.7%) [44]	58 (7.8%) [66]
Constipation	14 (7.7%) [15]	11 (2.0%) [15]	25 (3.4%) [30]
General Disorders and Administration Site Conditions, n (%) [event]	23 (12.7%) [27]	45 (8.0%) [53]	68 (9.1%) [80]
Fatigue	12 (6.6%) [14]	21 (3.7%) [25]	33 (4.4%) [39]
Asthenia	7 (3.9%) [9]	19 (3.4%) [20]	26 (3.5%) [29]
Investigations, n (%) [event]	15 (8.3%) [34]	20 (3.5%) [43]	35 (4.7%) [77]
Platelet Count Decreased	9 (5.0%) [16]	10 (1.8%) [18]	19 (2.6%) [34]
Nervous System Disorders, n (%) [event]	8 (4.4%) [10]	20 (3.5%) [27]	28 (3.8%) [37]
Headache	3 (1.7%) [4]	13 (2.3%) [14]	16 (2.1%) [18]
Vascular Disorders, n (%) [event]	5 (2.8%) [8]	18 (3.2%) [21]	23 (3.1%) [29]
Hypertension	5 (2.8%) [8]	15 (2.7%) [18]	20 (2.7%) [26]
Psychiatric Disorders, n (%) [event]	6 (3.3%) [7]	10 (1.8%) [13]	16 (2.1%) [20]
Insomnia	6 (3.3%) [6]	9 (1.6%) [9]	15 (2.0%) [15]

Source: Table 14.3.05

Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group.

Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.

Note: Percentage is calculated based on the number of patients in each group (N).

Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.

[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

Furthermore, a summary of all non-serious TEAEs reported to be related to niraparib treatment is provided by overall frequency for the Safety Population in Table 14.3.16. By-patient TEAEs are provided in Listing 15.26.0.

9.6.3.1. TEAEs Related to Niraparib by SOC and PT and Maximum Grade

A summary of (≥2%) TEAEs reported to be related to niraparib treatment for the overall patient population is presented in Table 33. A summary of all reported niraparib-related TEAEs by SOC and PT and maximum grade for the Safety Population is provided in Table 14.3.07. By-patient TEAEs are provided in Listing 15.26.0.

Table 33 Treatment-Emergent Adverse Events (≥2%) Related to niraparib by Overall System Organ Class, Preferred Term, and Maximum Grade

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population (Overall N=745)			
	Grade 1	Grade 2	Grade ≥3	Total
Patients with Any Event Related to niraparib, n (%)	73 (9.8%)	95 (12.8%)	91 (12.2%)	259 (34.8%)
Blood and Lymphatic System Disorders Any Event[2], n (%)	22 (3.0%)	47 (6.3%)	69 (9.3%)	138 (18.5%)
Anemia	13 (1.7%)	24 (3.2%)	36 (4.8%)	73 (9.8%)
Thrombocytopenia	15 (2.0%)	24 (3.2%)	26 (3.5%)	65 (8.7%)
Neutropenia	3 (0.4%)	7 (0.9%)	12 (1.6%)	22 (3.0%)
Gastrointestinal Disorders Any Event[2], n (%)	65 (8.7%)	31 (4.2%)	1 (0.1%)	97 (13.0%)
Nausea	43 (5.8%)	15 (2.0%)	0	58 (7.8%)
Constipation	15 (2.0%)	10 (1.3%)	0	25 (3.4%)
General Disorders and Administration Site Conditions Any Event[2], n (%)	37 (5.0%)	28 (3.8%)	3 (0.4%)	68 (9.1%)
Fatigue	14 (1.9%)	17 (2.3%)	2 (0.3%)	33 (4.4%)
Asthenia	19 (2.6%)	6 (0.8%)	1 (0.1%)	26 (3.5%)
Investigations Any Event[2], n(%)	15 (2.0%)	8 (1.1%)	12 (1.6%)	35 (4.7%)
Platelet Count Decreased	6 (0.8%)	4 (0.5%)	9 (1.2%)	19 (2.6%)
Nervous System Disorders Any Event[2], n (%)	21 (2.8%)	7 (0.9%)	0	28 (3.8%)
Headache	15 (2.0%)	1 (0.1%)	0	16 (2.1%)
Vascular Disorders Any Event[2], n (%)	7 (0.9%)	11 (1.5%)	5 (0.7%)	23 (3.1%)
Hypertension	5 (0.7%)	10 (1.3%)	5 (0.7%)	20 (2.7%)
Psychiatric Disorders Any Event[2], n (%)	10 (1.3%)	6 (0.8%)	0	16 (2.1%)
Insomnia	10 (1.3%)	5 (0.7%)	0	15 (2.0%)

Source data: Table 14.3.07

Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.

Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.

Note: Percentage is calculated based on the number of patients in each group (N).

Note: For each row category, a patient with 2 or more adverse events in that category is counted only once. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.

[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

[2]The 'Any event' row within the system organ class is a calculation of the number of unique patients who had an adverse event within the system organ class. For each patient in this row, the maximum grade across the system organ class was chosen.

9.6.3.2. TEAEs Related to Niraparib Leading to Drug Withdrawn by SOC and PT

A summary of (≥1%) TEAEs reported to be related to niraparib treatment that led to treatment being withdrawn by SOC and PT for the overall patient population is presented in Table 34. A summary of all reported niraparib-related TEAEs in the Safety Population that lead to niraparib being withdrawn is provided by SOC and PT in Table 14.3.12. By-patient listings of all TEAEs are provided in Listing 15.26.0.

Table 34 Treatment-Emergent Adverse Events (≥1%) Related to niraparib Leading to Drug Withdrawn by Overall by System Organ Class and Preferred Term

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population 1LM (N=181)	2LM+ (N=564)	Overall (N=745)
All Events	19	29	48
Patients with Any Event Related to niraparib Leading to Drug Withdrawn, n (%)	12 (6.6%)	22 (3.9%)	34 (4.6%)
Blood And Lymphatic System Disorders, n (%) [event]	5 (2.8%) [6]	9 (1.6%) [9]	14 (1.9%) [15]
Anemia	4 (2.2%) [4]	5 (0.9%) [5]	9 (1.2%) [9]

Source data: Table 14.3.12
Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.
Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

9.6.3.3. TEAEs Related to Niraparib with Death Outcome by SOC and PT

Out of the 3 TEAEs with death outcome, 1 was reported to be related to niraparib (Table 35). Patient PPD had a life-threatening TEAE of AML. The patient narrative is provided in Section 9.4.3.1.

By-patient AEs with death outcome are provided in Listing 15.31.0. Please note, to be included in the TEAE table below, the AE from Listing 15.31.0 had a start date on or after the niraparib initiation and within 30 days of last niraparib dose, per the TEAE study definition, and be reported as related to niraparib treatment.

Table 35 Treatment-Emergent Adverse Events Related to niraparib with Death Outcome by System Organ Class and Preferred Term

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population 1LM (N=181)	 2LM+ (N=564)	 Overall (N=745)
All Events	0	1	1
Patients with Any Event Related to niraparib with Death Outcome, n (%)	0	1 (0.2%)	1 (0.1%)
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps), n (%) [event]	0	1 (0.2%) [1]	1 (0.1%) [1]
Acute Myeloid Leukemia	0	1 (0.2%) [1]	1 (0.1%) [1]

Source data: Table 14.3.14
Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.
Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

9.6.4. All Serious TEAEs by SOC and PT

A summary of (≥1%) serious TEAEs by SOC and PT for the overall population is presented in Table 36. A summary of all serious TEAEs by SOC and PT is provided in Table 14.3.08. By-patient listings of all serious TEAEs are provided in Listing 15.29.0.

Table 36 Serious Treatment-Emergent Adverse Events (≥1%) by Overall System Organ Class and Preferred Term

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population 1LM (N=181)	 2LM+ (N=564)	 Overall (N=745)
All Events	30	74	104
Patients with Any Serious Event, n (%)	19 (10.5%)	50 (8.9%)	69 (9.3%)
Blood And Lymphatic System Disorders, n (%) [event]	11 (6.1%) [15]	14 (2.5%) [17]	25 (3.4%) [32]
Anemia	8 (4.4%) [10]	5 (0.9%) [5]	13 (1.7%) [15]
Thrombocytopenia	4 (2.2%) [4]	8 (1.4%) [9]	12 (1.6%) [13]

Source data: Table 14.3.08
Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.
Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

A summary of all serious TEAEs by SOC and PT, including number of patients and occurrences, is provided in Table 14.3.10. By-patient listings of all serious TEAEs are provided in Listing 15.29.0.

9.6.5. All Serious TEAEs Related to Niraparib by SOC and PT

All serious TEAEs reported to be related to niraparib treatment and occurring in 1% or more of the overall patient population are presented in Table 37. A full summary of all serious TEAEs reported to be related to niraparib treatment is provided in Table 14.3.09. By-patient listings of all serious TEAEs are provided in Listing 15.29.0.

Table 37 Serious Treatment-Emergent Events (≥1%) Related to niraparib by System Organ Class and Preferred Term

System Organ Class (SOC) Preferred Term (PT)[1]	Safety Population 1LM (N=181)	2LM+ (N=564)	Overall (N=745)
All Events	19	29	48
Patients with Any Serious Event Related to niraparib, n (%)	14 (7.7%)	21 (3.7%)	35 (4.7%)
Blood And Lymphatic System Disorders, n (%) [event]	11 (6.1%) [15]	14 (2.5%) [17]	25 (3.4%) [32]
Anemia	8 (4.4%) [10]	5 (0.9%) [5]	13 (1.7%) [15]
Thrombocytopenia	4 (2.2%) [4]	8 (1.4%) [9]	12 (1.6%) [13]

Source: Table 14.3.09
Abbreviations: 1LM = First line maintenance group; 2LM+ = Second or later line maintenance group.
Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of system organ class and then, within a system organ class, by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

9.6.5.1. Serious Fatal TEAEs Related to Niraparib by Overall Frequency

A summary of the 1 serious fatal TEAE reported to be related to niraparib treatment is presented in Table 38. Patient PPD had a life-threatening TEAE of AML. The patient narrative is provided in Section 9.4.3.1. By-patient TEAEs are provided in Listing 15.26.0.

Table 38 Serious Fatal Treatment-Emergent Adverse Events Related to niraparib by Overall Frequency

Preferred Term (PT)[1]	Safety Population 1LM (N=181)	2LM+ (N=564)	Overall (N=745)
Patients with Any Serious Fatal Event Related to niraparib, n (%)	0	1 (0.2%)	1 (0.1%)
Acute Myeloid Leukemia	0	1 (0.2%)	1 (0.1%)

Source data: Table 14.3.17
Abbreviation: 1LM = First line maintenance group, 2LM+ = Second or later line maintenance group.
Note: MDS/AML/SPMs were collected from niraparib start (retrospectively if prior to ICF signing) until death or lost to follow-up, whichever occurred first. All other treatment-emergent adverse events (TEAEs) were collected from signing of ICF through 30 days after the last dose of niraparib or death, whichever occurred first.
Note: Percentage is calculated based on the number of patients in each group (N).
Note: For each row category, a patient with 2 or more adverse events in that category is counted only once for the patient count. Adverse Events are sorted by descending frequency of preferred term of the overall column.
[1]Adverse events are classified into system organ class and preferred term using MedDRA Version 27.0.

10. DISCUSSION

This prospective, non-interventional, single-arm observational study to collect real-world data on the risks of developing MDS/AML and other SPM in adult patients with ovarian cancer receiving maintenance treatment with niraparib in the routine clinical setting was conducted in 4 European countries. The first patient was enrolled on 06 November 2019. Enrollment in the study closed on 17 January 2023 when the *a priori* patient-years threshold (1000 patient-years) had been surpassed. In March 2024, the EMA endorsed an early termination of this PASS based on the results from the 2023 interim analysis and post hoc precision analyses. This report represents the final analysis for this study, following database lock on 11 July 2024.

In total, 797 patients were enrolled into the study from 94 sites. Of the Enrolled Population, 745 patients were included in the Safety Population. This cohort met all eligibility criteria and received at least 1 dose of niraparib with sufficient clinical information to be stratified by niraparib line of therapy: 1LM or 2LM+. Most patients included were 2LM+ (181 1LM and 564 2LM+), as expected with enrollment of 1LM beginning with the SmPC update after the study had started. Please note, these final cohort counts vary from those presented in the interim analysis report. At the time of the interim report, there were multiple open queries with sites. As these queries were resolved, additional data were available which resulted in the recategorization of some patients and an adjustment in the patient counts of the overall Safety Population, 1LM, and 2LM+ cohorts for this final report.

Important protocol deviations were mostly the result of eligibility criteria deviations (68.5% of deviations in the Enrolled Population; 86.2% of deviations in 1LM cohort), no reporting or late reporting of SAEs (20.3% in the Enrolled Population; 45.5% in the 2LM+ cohort), or the use of outdated or unacceptable ICFs (16.8% of deviations in the Enrolled Population; 38.6% of deviations in the Safety Population 2LM+ cohort). These

protocol deviations were considered minor regarding their potential impact on the completeness, accuracy, and reliability of the study data.

More than one-half (53.7%) of the Safety population completed 2-years of follow-up, with 29.3% going on to complete 3-years of follow-up. Follow-up was more limited in the 1LM cohort. Approximately 93% of patients discontinued from the study, mainly due to death from any cause (47.1%; predominantly due to disease progression [84.4%]), followed by Sponsor decision to terminate the study (40.4%).

Patients were predominately FIGO stage III or IV high-grade serous at diagnosis and showed variability in the time from ovarian cancer diagnosis to niraparib initiation (median 30.1 months; IQR 18.0, 47.5 months). Radiation therapy for any cancer prior to niraparib initiation was received by <10% of patients. More than 95% of patients received cytoreductive surgery prior to niraparib initiation, as expected as this is commonly used alongside chemotherapy as the first line of treatment for ovarian cancer. Furthermore, 2LM+ patients had received a median of 2.0 (IQR 2.0, 2.0) lines of platinum-based chemotherapy prior to niraparib initiation.

The proportion of patients who had biomarker testing was low, and lower for HRD (30.2%) than for *BRCA* (78.5%). Of those with *BRCA* test results, 14.7% (n=86) were *BRCA* mutant (n=54 germline, n=23 somatic, n=9 not specified), lower than expected for an advanced ovarian cancer population, but reflective of the real-world utilization of niraparib. Biomarker status was derived from available HRD and *BRCA* test results for 599 patients; 68 were HR-proficient and 113 were HR-deficient.

Approximately three-quarters of the Safety Population discontinued niraparib treatment (72.9% 1LM and 78.9% 2LM+), mostly due to disease progression (83.0%), which was observed to be higher among 2LM+ patients than 1LM (84.9% and 76.5%, respectively). This result was expected as niraparib clinical trials found 1LM patients treated with niraparib have a longer median PFS than 2LM+ patients (13.8 months and 9.3 months, respectively) [Mirza, 2016; Monk, 2024;]. CCI [redacted] [GSK Study Report Document CCI [redacted].

A total of 18 MDS/AML and other SPM events (9 patients with 11 MDS/AML events and 6 patients with 7 other SPM events) occurred in 15 out of 745 (2.0%) total patients. Of these 18 events, 11 events reported in 9 patients (1.2%) were reported to be related to niraparib. Over the duration of the study, 1762.6 patient-years were accumulated to assess the time-at-risk for MDS/AML and other SPM events. The overall MDS/AML or other SPM incidence rate was 0.85 per 100 patient-years (0.31 per 100 patient-years 1LM; 0.97 per 100 patient-years 2LM+). The incidence rate was 0.51 per 100 patient-years for MDS/AML only (0.0 per 100 patient-years 1LM; 0.62 per 100 patient-years 2LM+) and 0.34 per 100 patient-years for other SPMs only (0.31 per 100 patient-years 1LM; 0.35 per 100 patient-years 2LM+).

MDS/AML incidence results are aligned with niraparib treatment arm findings from the long-term safety updates from the NOVA [redacted]; median follow-up >75 months) and PRIMA [redacted] median follow-up 73.9 months) clinical trials as shown in Table 39. While SPMs other than MDS/AML were not reported in the published updated OS and long-term safety results for NOVA, results aligned with both the niraparib treatment arm [redacted]) and the placebo arm [redacted] in the updated clinical study report for the NOVA clinical trial [GSK Document Number: [redacted]] and with both the niraparib treatment arm [redacted]) and the placebo arm ([redacted] in the updated clinical study report for the PRIMA clinical trial [GSK Study Report Document [redacted].

Table 39 Niraparib Trial MDS/AML and Other SPMs

	Niraparib Treatment Arm			Placebo Arm		
	NOVA (N=367)	PRIMA (N=484)		NOVA (N=179)	PRIMA (N=244)	
		3.5 years[a]	6.2 years[b]		3.5 years[a]	6.2 years[b]
Patients with New MDS/AML[1], n (%)	14 (3.8%)	6 (1.2%)	11 (2.3%)	3 (1.7%)	3 (1.2%)	4 (1.6%)
Incidence Rate of MDS/AML per 100 Patient-years	[redacted]					
Patients with New Other SPMs[2,3], n (%)						

Sources: [Matulonis, 2023; González-Martín, 2023; GSK Document Number: [redacted]; Monk, 2024; GSK Study Report Document [redacted]].

Abbreviations: AML = Acute myeloid leukemia; MDS = Myelodysplastic syndrome; SPM = Second primary malignancy.

[1]n reflects the number of patients with any MDS/AML event.

[2]n reflects the number of patients with any SPM event other than MDS/AML.

[3]Collected in NOVA as TEAE under system organ class 'neoplasms benign, malignant and unspecified' which included MDS/AML events. For this calculation MDS/AMLs events were removed, leaving only 'other SPMs.'

[a]Results from the PRIMA analysis at 3.5 years of follow-up [González-Martín, 2023]

[b]Results from the PFS analysis at 6.2 years of follow-up [Monk, 2024; GSK Study Report Document [redacted]]

Although a direct comparison cannot be made between the niraparib clinical trials and this real-world, non-interventional study, the clinical trial data provides insight and context. Given the rigors of monitoring in the clinical trial setting, the percentage of any TEAE (52.2%) and TEAEs ≥ grade 3 (18.5%) were expectedly lower than what were observed for niraparib-treated subjects from the NOVA trial (any TEAE, 100.0%; TEAE ≥ grade 3, 76.6%; [Matulonis, 2023]) and the PRIMA trial (any TEAE, 99.0%; TEAE ≥ grade 3, 73.8%; [Monk, 2024]) (Table 40). Similarly, the percent of patients experiencing a serious TEAE (9.3%) was lower than that observed for both the niraparib-treated arm (34.6%; 40.9%) and placebo-arm (16.2%; 17.6%) in NOVA [Matulonis, 2023] and PRIMA [Monk, 2024], respectively. Niraparib treatment discontinuation due to TEAEs was also lower in this study (6.6%) than in the NOVA and PRIMA clinical trials (18.3% and 16.3%, respectively). All TEAEs reported aligned with previous findings. No new safety signals were detected.

Table 40 Niraparib Trial Treatment-Emergent Adverse Events (TEAEs)

	Niraparib Treatment Arm	
	NOVA (N=367)	PRIMA (N=484)
Any TEAE During the Study, n (%)	367 (100.0%)	479 (99.0%)
Any Serious TEAE	127 (34.6%)	198 (40.9%)
TEAE grade 3 or higher by maximum NCI CTCAE	281 (76.6%)	357 (73.8%)
TEAEs Leading to Drug Withdrawn, n (%)	67 (18.3%)	79 (16.3%)
TEAEs Leading to Death, n (%)	5 (1.4%)	12 (2.5%)

Sources: [Matulonis, 2023; Monk, 2024].
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; TEAE = Treatment-Emergent Adverse Event.

10.1. Key Results

The incidence of MDS/AML and other SPMs reflect the safety profile reported in the niraparib label and from niraparib clinical trials and support the current benefit-risk profile for niraparib. The limited number of observed MDS/AML and other SPMs (combined total of 15 patients) precluded an assessment on patterns across risk factors.

- A total of 9 patients (1.2%) had MDS/AML events, for overall incidence rate of MDS/AML of 0.51 (95% CI: 0.23, 0.97) per 100 patient-years.
- A total of 6 patients (0.8%) had other SPMs, for an overall SPM incidence rate of 0.34 (95% CI: 0.12, 0.74) per 100 patient-years.
- Overall, a total of 15 patients (2.0%) had 18 MDS/AML and/or other SPM events. The overall MDS/AML and other SPM incidence rate was 0.85 (95% CI: 0.48, 1.40) per 100 patient-years.
- All events of MDS/AML and 5 out 6 patients who experienced events of other SPMs occurred in the 2LM+ cohort.

No new safety signals have been detected. All TEAEs were consistent with the known safety profile for niraparib.

10.2. Limitations

Due to the real-world nature of the study, patient eligibility criteria were affected when the EU SmPC guidelines for niraparib were updated to include 1LM therapy after enrollment started. Prior to the approval of an amended study protocol and associated ICF, sites were working and enrolling patients under the new SmPC guidelines, thereby deviating from the eligibility criteria outlined in the available ICF version. This led to a high proportion of protocol deviations linked to eligibility criteria. Upon review, these protocol deviations were considered minor regarding their potential impact on the completeness, accuracy, and reliability of the study data.

Furthermore, patient demographics, disease characteristics, and prior cancer therapies were documented in a study-specific eCRF at baseline enrollment. When the EU SmPC guidelines for niraparib were updated to include 1LM therapy, the study protocol was amended but the eCRF was not. As a result, line of niraparib maintenance therapy for the Safety Population was not collected by the site and had to be derived using a therapy designation algorithm. Identified outliers (e.g., extended time periods between ovarian diagnosis and start of niraparib) were reviewed by a GSK board-certified gynecologic oncologist to confirm patient cohorts prior to final analysis.

Biomarker testing rates were lower for HRD (30.2%) than for *BRCA* (78.5%), as observed in real-world practice. Biomarker status was a derived variable that used known *BRCA* and HRD test results to fully highlight data availability with HR-deficient tumors identified as HRD test-positive and *BRCA* mutant. Due to the real-world nature of this study and other PARP inhibitors approved as maintenance treatment for *BRCA*-mutated ovarian cancer, such as olaparib, the proportion of *BRCA*-mutated ovarian cancer patients treated with niraparib may be lower than expected for an advanced ovarian cancer population. As patients with *BRCA* mutations are at higher risk of MDS/AML events, this may have contributed to an underestimated risk of MDS/AML. This imbalance, however, reflects the real-world utilization of niraparib.

The majority of patients were enrolled after they had initiated niraparib and therefore had some follow-up data collected retrospectively, which may have impacted data quality and completeness. Furthermore, retrospective data collection for patients who initiated niraparib prior to enrollment may have introduced immortal time bias in the assessment of TEAEs, as they may be underreported for the period of time between date of niraparib initiation and a subsequent date of enrollment when those with serious TEAEs initiating niraparib prior to enrollment did not make it into the study. While this would not have affected the primary or secondary endpoints, as these data were collected regardless of when niraparib treatment was initiated, a stratified sensitivity analysis was conducted to evaluate the impact of this bias on patients who received niraparib prior to enrollment and those who received niraparib on or after enrollment. Findings from the sensitivity analysis were consistent across both groups and aligned with the primary analyses.

Lastly, the median duration of niraparib treatment observed was 11.0 months (IQR 5.1, 20.0 months) in the 1LM cohort and 10.4 months (IQR 4.8, 22.9 months) in the 2LM+ cohort. Notably, the leading cause of niraparib discontinuation overall was disease progression (83.0%). The majority of patients in this study were *BRCA* wild type and Stage III/IV at diagnosis, reflective of the real-world utilization of niraparib, and consistent with a high-risk patient population as described in the NOVA and PRIMA clinical trials.

10.3. Interpretation of Results

All MDS/AML events and 5 out 6 other SPM events were observed in 2LM+ niraparib-treated patients who had received previous chemotherapy with platinum agents, which is a known risk factor for developing MDS/AML or other SPMs. The median prior lines of platinum-based chemotherapy treatment among the 2LM+ patient cohort was 2.0 (IQR 2.0, 2.0) before niraparib initiation, with a median of 12.0 (IQR 12.0, 14.0) cycles

received. One patient (out of 15 patients) received another PARP inhibitor prior to event. Furthermore, many of these patients had also received other DNA-damaging agents before niraparib initiation.

When summarizing TEAEs by descending order of SOC, gastrointestinal disorders, followed by blood and lymphatic systems disorders were the most prevalent. Approximately 10% of patients experienced TEAEs of anemia and approximately 9% experienced TEAEs of thrombocytopenia related to niraparib. This SOC was also the most prevalent of serious TEAEs. Serious TEAEs of anemia and/or thrombocytopenia occurred in approximately 2% of the Safety Population. These results align with clinical trials and the niraparib label, which report hematologic adverse reactions, including grade ≥3 anemia and grade ≥3 thrombocytopenia, in approximately 25% to 39% of trial subjects [Zejula, 2024].

10.4. Generalisability

The results from this final analysis regarding the incidence rates of MDS/AML and other SPMs and the niraparib safety profile are consistent with the known safety profile for niraparib from clinical trials (Table 39). In the 851 patients that were treated with niraparib in clinical trials (NOVA [median follow-up >75 months], PRIMA [median follow-up 73.9 months]), MDS/AML occurred in 25 (2.9%) patients; an incidence rate of 1.12 per 100 patient-years in NOVA and 0.62 per 100 patient-years in PRIMA. All these patients had received prior platinum-containing chemotherapy regimens. Additionally, few SPMs were reported overall (0.8%), comparable to that observed in both NOVA CCI and PRIMA CCI with event types not unexpected in this population [GSK Document Number: CCI; GSK Study Report Document CCI].

11. OTHER INFORMATION

Not applicable.

12. CONCLUSIONS

The final study results were consistent with the current risk-benefit profile for niraparib: the incidence of MDS/AML in patients treated with niraparib in the routine clinical setting is aligned with the incidence reported in the label and the incidence of MDS/AML and other SPMs is aligned with that observed in niraparib clinical trials, specifically the Phase 3 clinical trials NOVA and PRIMA. Results were consistent with the niraparib known safety profile; no new safety signals were detected. See Steering Committee Consensus Statement (refer to ANNEX 1 for a list of available stand-alone documents).

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14. TABLES AND FIGURES

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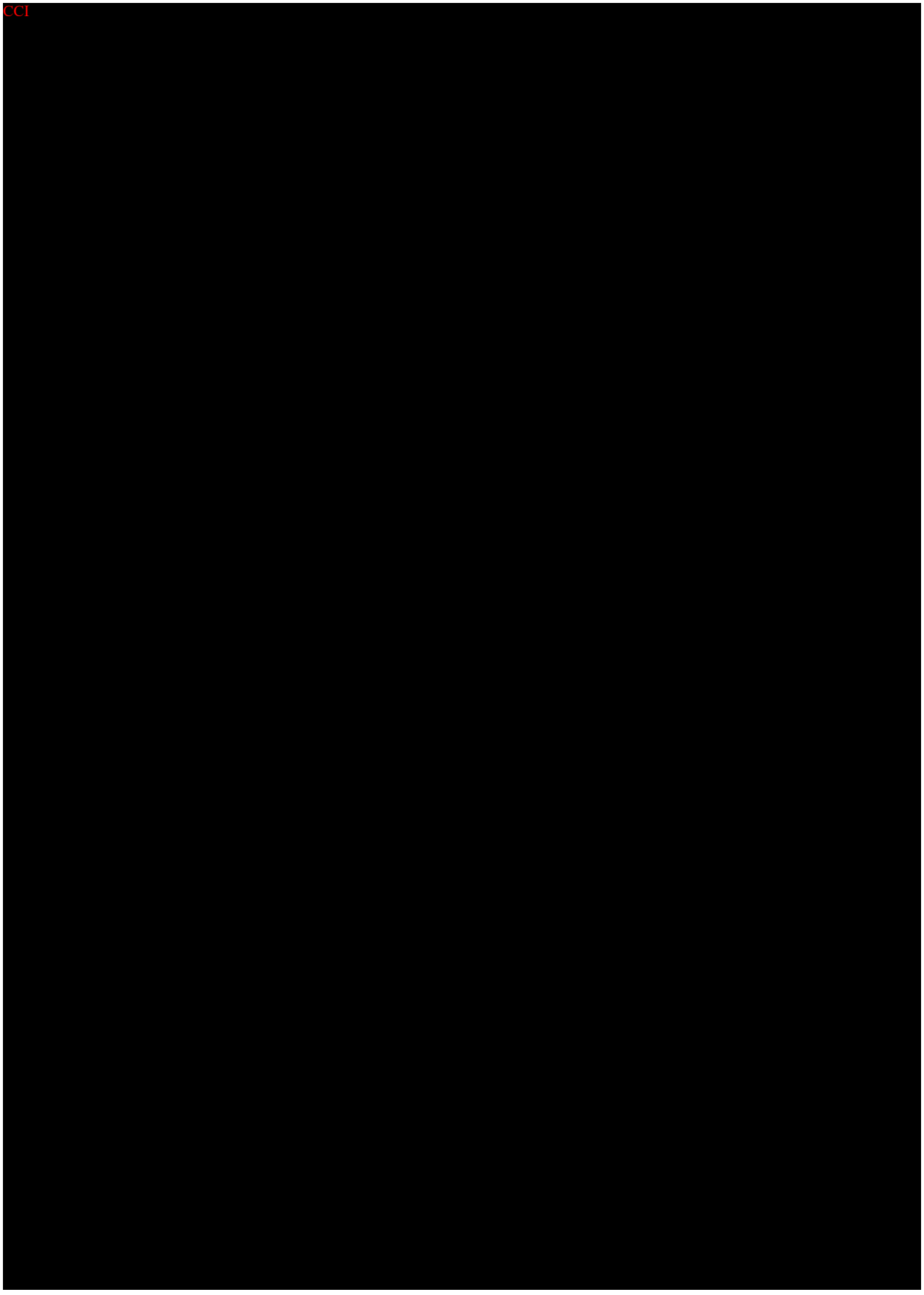
15. PATIENT DATA LISTINGS

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

CCI



ANNEX 2 ADDITIONAL INFORMATION

Derived Study Variables of Interest

In addition to standard derived variables (e.g., calculation of age in years at a point in time based on the birth date and the date of interest, duration in months converted from number of days/30.4375), algorithms were developed and implemented to derive more complex variables, including line of therapy, NAT and AT for ovarian cancer, PDS and IDS. Derived line of therapy was also used to classify the Safety Population cohort assignment.

As line of therapy and cohort assignment were not directly reported from the site, these variables were derived. Outliers in each cohort (1LM and 2LM+) were reviewed by a GSK board-certified gynecologic oncologist to confirm appropriateness of derived designation (e.g., two patients in 2LM+ cohort who initiated niraparib ≤15 months after initial ovarian cancer diagnosis). The Safety Population cohort represents the findings of this adjudication evaluation.

Line of therapy was derived by combining all reported ovarian cancer therapies for a patient from the CRF, using therapy start dates, therapy end dates, and line of therapy type (maintenance treatment, non-maintenance treatment, and line of therapy assignment where available), accounting for NAT, AT, non-PARP inhibitor, and PARP inhibitor start and end dates.

Safety Population cohort assignment definition for derivation:

- If a patient was treated with niraparib maintenance therapy as 1LM following first-line chemotherapy, and typically, cytoreductive surgery, they were included in the 1LM cohort
- If a patient was treated with niraparib maintenance therapy as 2LM+, following second-line (or third-line, fourth-line, etc.) chemotherapy they were included in the 2LM+ cohort

For a detailed description of the algorithm and rules utilized to identify 1LM and 2LM+ cohorts, please refer to the latest SAP version 2.0, dated 17 May 2024.

Type of first-line chemotherapy (i.e., neoadjuvant and/or adjuvant treatment) and type of cytoreductive surgery (i.e., PDS or IDS) was not consistently or systematically reported across sites. Patients who had a cytoreductive surgery date prior to or within 30 days of their first-line chemotherapy initiation date were considered to have received PDS. Patients who received first-line chemotherapy following PDS were considered to have received adjuvant therapy. Those who had a cytoreductive surgery date more than 30 days from the start of first-line chemotherapy were considered to have received IDS. These patients would have also received NAT and may have also received AT. The earliest surgery date was considered for patients with more than one documented surgery.

Derived variables that were defined post-SAP development, including lines of therapy, PDS, IDS, NAT, and AT are documented in the analysis dataset specifications (refer to ANNEX 1 for a list of available stand-alone documents).

Signature Page for 213705 TMF-20171095 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 04-Dec-2024 16:13:46 GMT+0000

Reason for signing: Approved	Name:PPD Role: Author Date of signature: 04-Dec-2024 16:30:52 GMT+0000

Signature Page for TMF-20171095 v1.0

PASS information

Title	**Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)**
Protocol version identifier	**3000-04-001 (GSK 213705) Version 9**
Date of last version oprotocol	**06 Oct 2021**
Sponsor	**Tesaro (GlaxoSmithKline company)** 1250 South Collegeville Road Collegeville, PA 19126
EU PAS register number	**EUPAS29407**
Active substance	**Niraparib**
Medicinal product	**ZEJULA®, 100 mg hard capsules**
Product reference	**Not applicable**
Procedure number	**EMEA/H/C/004249/MEA/002**
Marketing authorisation holder(s)	**GlaxoSmithKline (Ireland) Limited** **12 Riverwalk** **Citywest Business Campus** **Dublin 24** **Ireland**
Joint PASS	**Not applicable**
Research question and objectives	**To determine the risk of developing myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) in patients with:** **- epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy** **or**

	- platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial to platinum-based chemotherapy **To whom niraparib is administered in the routine clinical setting.** **The objectives are as follows:** • **Primary:** To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients: 1) with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy or 2) with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy, treated with niraparib • **Secondary:** To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts
Country(ies) of study	**European countries with approved use of ZEJULA®**
Author	PPD **PhD, MPH** PPD **Epidemiology, Oncology** **GSK** **1250 S. Collegeville Rd,** **Collegeville, PA 19426** **USA**

SPONSOR SIGNATURE PAGE

Declaration of Sponsor

Title (Study Number): Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib) (3000-04-001; GSK 213705)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Pharmacovigilance Practice.

_____ _____

Linda Kalilani
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USA
GSK

Date

_____ _____

Heather Stein

Vice President, Head of Oncology Clinical Safety & Pharmacovigilance

Waltham MA 1000 Winter Street, UNITED STATES

Date

INVESTIGATOR'S AGREEMENT

I have received and read the European Union (EU) summary of product characteristics (SmPC) released by the European Medicines Agency (EMA). I have read Protocol 3000-04-001(GSK 213705) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF MAIN ABBREVIATIONS USED IN THE STUDY PROTOCOL

Table 1 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADR	adverse drug reaction
AE	adverse event
AML	acute myeloid leukemia
BICR	Blinded independent central review
BRCA	breast cancer susceptibility gene
CBC	complete blood cell count
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
EAP	Expanded Access Program
eCRF	electronic case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FIGO	International Federation of Gynecology and Obstetrics
g*BRCA*mut	germline breast cancer susceptibility gene mutation
GVP	Good Pharmacovigilance Practices
HA	Health authority
HRD	homologous recombination deficiency
HRDneg	homologous recombination deficiency negative
HRDpos	homologous recombination deficiency positive
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intended to treat
MAA	Marketing Authorisation Application
MCV	mean corpuscular volume

Abbreviation or Specialist Term	Explanation
MDS	myelodysplastic syndrome
NCI	National Cancer Institute
NIH	National Institutes of Health
NOVA	Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer
PARP	poly(ADP-ribose) polymerase
PASS	post-authorization safety study
PFS	progression-free survival
Q1	first quarter
Q2	second quarter
Q3	third quarter
Q4	fourth quarter
RECIST	Response Evaluation Criteria in Solid Tumours
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio
SmPC	summary of product characteristics
SPM	second primary malignancy
TEAE	treatment-emergent adverse event
UAT	User Acceptance Testing
US	United States

Trademarks of the GlaxoSmithKline group of companies
Zejula

Trademarks not owned by the GlaxoSmithKline group of companies
Lynparza
MarketScan
Rubraca
SAS

3. ABSTRACT

3.1. Title

Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)

3.2. Rationale and Background

Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor. A decision to grant marketing authorization for niraparib was adopted by the European Commission on 16 November 2017 with the indication of monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy.

On 17 September 2020 GSK received European Commission approval of Zejula (niraparib) as first-line monotherapy maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) have been observed in the context of PARP inhibitor treatments. However, results from Phase 3 clinical studies using niraparib, olaparib, or rucaparib did not show any statistically significant correlation between the use of PARP inhibitors and the incidence of MDS/AML or SPMs. The mechanism of action of PARP inhibition suggests that there may be a risk of MDS/AML and SPM associated with the use of PARP inhibitors. Therefore, the specific evaluation of this potential risk has been included in the Risk Management Plan for niraparib.

To better characterize the risks of MDS/AML and SPMs associated with niraparib treatment, a post-authorization safety study (PASS) in patients receiving maintenance treatment with niraparib was agreed with the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use.

3.3. Research Question and Objectives

The objective of this PASS is to determine the risk of developing MDS/AML and SPMs in patients administered niraparib in the routine clinical setting.

The objectives are as follows:

- **Primary Objective**: To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients with:
  - advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR

- platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy

- **Secondary Objective**: To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts.

3.4. Study Design

This PASS will be conducted as a prospective (referred as primary data), noninterventional, single-arm study including patients who have received or are receiving niraparib through the European Expanded Access Program (EAP) and patients treated post-approval in routine clinical practice.

3.5. Population

Cohort for primary data collection: Adult patients diagnosed with:

- advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy or,
- platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy

3.6. Data Collected

Primary data cohort: Data will be collected at 2 different time periods: 1) baseline data (at initiation of niraparib treatment) and 2) follow-up data (collection occurs quarterly during a maximum 5-year clinical follow-up of the patient after niraparib initiation). For patients who start niraparib treatment before being enrolled in the study, the baseline data will be collected retrospectively from the time when niraparib treatment was initiated. For patients who start niraparib treatment at time of enrollment, baseline data will be collected prospectively at time of enrollment. The baseline data will include patient demographic characteristics, tumor characteristics, medical and treatment history. During the follow-up period, data will be collected on treatment with chemotherapeutic agents, adverse events and study outcomes (MDS, AML and SPM).

3.7. Data Sources

This primary cohort will prospectively collect data from patients who have received or are receiving niraparib through the European Expanded Access Program (EAP), in a clinical trial, and patients treated post-approval in routine clinical practice. Primary data will be sourced from patients' electronic health records. The participating physicians will document the measures taken in the web-based documentation sheet (eCRF) of this noninterventional study on a quarterly basis.

3.8. Study Size

CCI [redacted]

CCI [redacted] Thus, the minimum data required to achieve a quantifiable number of MDS/AML and SPM events is 1,000 patient years with approximately 2.5 years of average follow-up.

The sample size was not revised following the addition to the study population patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. It is anticipated that the exposure to Niraparib will be similar in the two populations based on the data from the NOVA and PRIMA clinical studies. Given the high risk for missing data and for losing patients to follow-up in a non-interventional study in a real world setting, it is planned to recruit up to 800 patients for a maximum of 5 years of follow-up per patient so that up to 2,000 patient-years of observation data can be reached. This sample size allows adequate patient data to compensate for a large incidence of missing data given that we expect to observe a significant incidence of MDS/AML and SPMs when data for 1,000 patient-years are collected over a maximum follow-up period of 5 years and an overall average follow-up of 2.5 years.

3.9. Data Analysis

The study population for all analyses is the safety population, defined as all patients who receive any amount of niraparib (at least 1 dose). All analyses will be performed using SAS statistical software v9.4 or later and will include summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Further details will be provided in the statistical analysis plan (SAP).

Analyses will be descriptive; no hypothesis will be tested. Distributions of patient and tumor characteristics will be summarized. Incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be estimated. For the primary data, a sensitivity analysis will be performed on the group of patients who have never received PARP inhibitor treatments prior to study enrollment. In addition, a descriptive comparison on baseline characteristics of those patients who did not receive/initiate niraparib after initial enrollment versus those who did receive the treatment will be performed.

3.10. Milestones

Detailed milestones are listed Section 5 below.

4. TABLE OF AMENDMENTS AND UPDATES

Table 2 Table of Revisions

Number	Date	Section of the study protocol	Amendment or update	Reason
1	7 December 2020	Title	Platinum sensitive relapsed, high grade serous has been removed from the title	The study population has been updated to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy due to the EMA approval for use of niraparib as first line maintenance therapy. The title has been revised to include the new study population
2	7 December 2020	Pass Information	• Revised the contact Details for the Market Authorisation Holder, author and names for the sponsor signature page • Research question and objectives have been updated to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy due to the EMA approval for use of niraparib as first line maintenance therapy.	• Revised to most current contact details for GSK following transition from Legacy Tesaro • To include the new indication for niraparib approved by the EMA
3	7 December 2020	Section 3.1-3.10	• Most of the text that was included in the abstract was also included in the main protocol. Therefore, the text that was repeated in the	• The abstract was revised to streamline the protocol to allow sites to easily follow the protocols to

Number	Date	Section of the study protocol	Amendment or update	Reason
			main protocol has been deleted in the abstract • The study population has also been updated to include patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy • The data source for the secondary data cohort has been revised to a non-claims EU healthcare database	improve site adherence to protocol procedures • To include the new indication for niraparib approved by the EMA • The secondary data source has been revised to identify a data source that will enable creation of a more comparable cohort to the primary data cohort, due to availability of more granular details to define the characteristics of the patient population, and to allow for a similar follow up period to measure study outcomes as the average follow-up period in MarketScan approximately 2 years.
4	7 December 2020	Section 4	• The list of amendments to the protocol	• Included the list of amendments implemented in the protocol
5	7 December 2020	Section 5	• Some of the text that was included in primary data collection section was also included in the other sections of the protocol (study setting and sample size calculation). This text has now been deleted. • The text has been revised for the secondary data collection due to	• The protocol was revised to be more streamlined to allow sites to easily follow the protocols to improve on adherence to protocol procedures.

Number	Date	Section of the study protocol	Amendment or update	Reason
			changes proposed data secondary data source and the study period • The end of enrollment period has been extended to Q4 2021	• The proposed secondary data source has been revised to include a data source that will identify a more comparable cohort to the primary data cohort and to allow for a similar follow up period to measure study outcomes • This is account for the impact of COVID on the recruitment
6	7 December 2020	Section 6	• Updated background information on the occurrence of study outcomes using more recent data and added background information on the new population that will be included in the study i.e. patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy	• To include the new indication for niraparib approved by the EMA
7	7 December 2020	Section 7	• Updated the study objectives to include patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy	• To include the new indication for niraparib approved by the EMA

Number	Date	Section of the study protocol	Amendment or update	Reason
8	7 December 2020	Section 8.1-Section 8.8	• The text in the methods section has been revised. This includes removing text that was repeated in multiple sections or moving texts to more relevant sections. Details for the revisions in each section are provided below.	The revisions were implemented to streamline the protocol to allow sites to easily follow the protocols to improve on adherence to study procedures
		Section 8.2.1	• Inclusion of patients with epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in the selection criteria • Inclusion criteria providing clarification that patients who are part of a clinical trial arm will be excluded if this is GSK trial	• To include the new indication for niraparib approved by the EMA • To avoid duplication in the reporting of adverse events
		Section 8.2.2	• The selection criteria for the second data collection has also been updated	• To include the new indication for niraparib approved by the EMA and to ensure the study population is similar to the primary data collection cohort
		Section 8.2.3	• Weight to be collected within 3 months of study enrolment • To collect data on Homologous Recombination Deficiency (HRD) status • Collect the latest complete blood count data prior to niraparib initiation	• To ensure that the weight reflects that weight the time of niraparib initiation • The HRD status data will be used to characterize the patient population • This is to ensure the baseline data reflects the status of the patient at the time of niraparib initiation

Number	Date	Section of the study protocol	Amendment or update	Reason
		Section 8.3.2	• Replacing the secondary data source from MarketScan database to either a non-claims European healthcare database	• The secondary data source has been revised to identify a data source that will enable creation of a more comparable cohort to the primary data cohort, due to availability of more granular details to define the characteristics of the patient population, and to allow for a similar follow up period to measure study outcomes as the average follow-up period in MarketScan approximately 2 years.
		Section 8.5	• The data management for the secondary data has been updated	• This is to provide more details on how the secondary data will be managed
		Section 8.6	• Data analysis to include stratification of data analysis by the two ovarian cancer populations based on the use of niraparib either as first-line or second-line maintenance therapy	• This is due to the inclusion of the study population with the new indication for niraparib approved by the EMA
		Section 8.7.3	• Updating the duration of archiving study documents from 2 years to 10 years after finalization of the study report	• Updated to align with the GSK archiving processes
		Section 8.7.7	• Study monitoring included additional information on how the study monitoring will be implemented and considering the COVID-19 pandemic	• To ensure compliance with study procedures

Number	Date	Section of the study protocol	Amendment or update	Reason
		Section 8.8	• Limitation of the research methods: deleted the limitations associated with the MarketScan databases and updated with information on the new proposed secondary data sources	• This is due to changes in the proposed data source for the secondary data collection
		Section 10	• Management and reporting of adverse events/adverse reactions: Hospitalizations for planned elective treatment for pre-existing conditions will not be considered a severe adverse event, Deleted pneumonitis as an AE of special interest and will now be reported as an AE, , updated the sponsor contact details from Tesaro to GSK and included the COVID-19 infection assessment form	• To align with the GSK pharmacovigilance processes
9	7 December 2020	Annex 1	• Deleted	• This information is already included in the protocol Section 8.2.1
10	12 Apr 2024	Section 3.3-Section 3.9	• Removal of Exploratory Objective and any text related to the study population, data collection, data source and analysis relevant to the Exploratory Objective only	• To align with EMA approval of early termination of study
11	12 Apr 2024	Section 5	• Removal of milestones related to Exploratory Objective • Update of end of primary data collection/start of analysis and final report of study results milestones	• To align with EMA approval of early termination of study
12	12 Apr 2024	Section 7	• Removal of Exploratory Objective	• To align with EMA approval of early termination of study

Number	Date	Section of the study protocol	Amendment or update	Reason
13	12 Apr 2024	Section 8.1, Section 8.2.1., Section 8.2.2., Section 8.2.4., Section 8.3.1., Section 8.5, Section 8.6	• Removal of study design description, inclusion/exclusion criteria, secondary data collection, secondary data sources, and secondary data analysis relevant to the Exploratory Objective only	• To align with EMA approval of early termination of study
14	12 Apr 2024	Section 8.8	• Removal of limitations relevant to the Exploratory Objective only	• To align with EMA approval of early termination of study
15	12 Apr 2024	Section 10.4.	• Removal of safety reporting requirements relevant to the Exploratory Objective only	• To align with EMA approval of early termination of study

5. MILESTONES

Primary data collection: Data collection will start at the time of enrolment of the first patient into the study in fourth quarter (Q4) 2019. Data collection will continue until fulfillment of the target observation period of at least 1,000 patient-years and maximum 5 years of follow-up for those patients who achieve this survival milestone, with an expected average patient follow-up of 2.5 years.

Details of the key study milestones are provided in Table 3 below.

Table 3 Detailed Study Milestones

Milestone	Planned Date
Start of data collection (primary data)	Q4 2019
End of enrollment	Q3/4 2021
Interim report (primary data)	Q3 2023
End of primary data collection and start of analysis	Q2 2024
Registration in the EU PAS register	Q2 2019
Final report of study results	Q4 2024

Abbreviations: EU = European Union; PAS = Post-Authorization Studies; Q1= first quarter; Q2 = second quarter; Q3 = third quarter; Q4 = fourth quarter.

6. RATIONALE AND BACKGROUND

Niraparib is a potent, orally active poly (ADP-ribose) polymerase (PARP)1 and PARP2 inhibitor.

In the randomized, double-blind, Phase 3 NOVA (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer) study,[5] a total of 553 patients were randomized at 107 centers worldwide. Patients were categorized according to the presence or absence of a germline breast cancer susceptibility gene (*BRCA*) mutation (g*BRCA*mut cohort and a non-g*BRCA*mut cohort) and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily. In the non-g*BRCA*mut cohort, testing for HRD was performed using an HRD test on tumor tissue obtained at the time of initial diagnosis or at the time of recurrence. The primary endpoint was progression-free survival (PFS). The study enrolled 203 patients in the g*BRCA*mut cohort and 350 patients in the non-g*BRCA*mut cohort. Among the 350 patients in the non-g*BRCA*mut cohort, 162 had tumors that were identified as HRD positive (HRDpos), and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined for 54 patients.

Demographic and baseline characteristics were well balanced. Table 4 below shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (i.e. g*BRCA*mut cohort, HRDpos cohort, and overall non-g*BRCA*mut cohort). In addition, median PFS in patients with HRDneg tumors was 6.9 months (95% CI: 5.6, 9.6) in the niraparib arm versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a hazard ratio (HR) of 0.58 (95% CI: 0.361, 0.922) (p = 0.0226).

Table 4 Progression-Free Survival in Ovarian Cancer Patients in NOVA[5]

	g*BRCA*mut Cohort		**Non-g*BRCA*mut Cohort (regardless of HRD status)**		**HRDpos (within non-g*BRCA*mut cohort)**	
	Niraparib (n = 138)	**Placebo (n = 65)**	**Niraparib (n = 234)**	**Placebo (n = 116)**	**Niraparib (n = 106)**	**Placebo (n = 56)**
Median PFS, months (95% CI)	21.0 (12.9, NE)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	< 0.0001		< 0.0001		< 0.0001	
HR (niraparib: placebo) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Abbreviations: CI = confidence interval; g*BRCA*mut = germline breast cancer gene mutation; HR=hazard ratio; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NE = not estimable; PFS = progression-free survival; US=United States.
Note: PFS is defined as the time in months from the date of first dose to progression or death.
Source: ZEJULA US Prescribing Information.

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidence of Grade 3 or 4 TEAEs (74% versus 23%), SAEs (30% versus 15%), TEAEs leading to treatment interruption (67% versus 15%), TEAEs leading to dose reduction (69% versus 5%), and

TEAEs leading to treatment discontinuation (15% versus 2%) were higher for niraparib than for placebo. There were no on-treatment deaths reported.

The most commonly observed nonhematologic TEAEs (all grades) in niraparib-treated compared with placebo-treated patients were nausea (74% versus 35%), fatigue (46% versus 32%), constipation (40% versus 20%), and vomiting (34% versus 16%). The majority of the nonhematologic TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) in niraparib-treated compared with placebo-treated patients were anemia (49% versus 7%), thrombocytopenia (46% versus 3%), decreased platelet count (20% versus 2%), and neutropenia (18% versus 3%). Although Grade 3 or 4 hematologic laboratory AEs were common at the initiation of study treatment, no severe clinical sequelae were observed, and relatively few patients discontinued study treatment due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these AEs beyond Cycle 3. In the NOVA study, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (ie, Cycle 3) of treatment.

The efficacy results in the PRIMA (PR-30-5017-C) study demonstrated a statistically significant and clinically meaningful benefit of niraparib treatment in the overall population of patients with Stage III or IV ovarian cancer (including fallopian and peritoneal cancers) who had responded to front-line platinum-based therapy. Median progression free survival (PFS) was significantly longer in subjects who received niraparib compared to those who received placebo, with corresponding favourable hazard ratio (HR). The PRIMA study met the primary endpoint in subjects with HRD tumours; median PFS as determined by Blinded independent central review (BICR) based on Response Evaluation Criteria in Solid Tumours (RECIST) (version 1.1) was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43; [95% CI: 0.310,0.588]; p<0.0001). For the overall population, median PFS for subjects randomised to niraparib was 13.8 months versus 8.2 months on placebo (HR 0.62 [95% CI: 0.50 to 0.76]; p<0.0001). A reduction of risk to progression of disease or death during study was demonstrated for subjects in the niraparib arm compared to subjects in placebo arm, for subjects with homologous recombination proficient tumors (HR 0.68 [95% CI: 0.492,0.944]; p=0.0203) as well. Safety outcomes were consistent with those seen in the NOVA study, specifically thrombocytopenia of any grade and grade≥3. Initiation of the individualised starting dose of niraparib in the PRIMA study (i.e. initial starting dose of 200 mg or 300 mg based on the subject's baseline body weight and/or baseline platelet count) decreased the incidence of myelosuppression events.

On 17 Sep 2020 GSK received European Commission approval of Zejula (niraparib) as first-line monotherapy maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

6.1. MDS/AML

Myelodysplastic syndrome (MDS) is a group of bone marrow failure disorders characterized by ineffective hematopoiesis in one or more of the lineages of the bone marrow.[12] MDS can evolve from a refractory anemia to acute myeloid leukemia (AML), which is associated with a decrease in intramedullary apoptosis and a block in myeloid differentiation. The incidence of MDS is 5 per 100,000 and increases to 21 per 100,000 among persons aged 70 or older.[13] The association of MDS with age suggests genetic damage caused by hazardous exposure or

inherited susceptibility. The diagnostic classification currently in use by the World Health Organization recognizes 6 distinct entities of MDS based on morphologic quantitative and qualitative evaluation of the peripheral blood and bone marrow using basic hematological techniques.[14]

6.1.1. Reported Cases of MDS/AML With PARP Inhibitors

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received niraparib monotherapy in clinical trials. In 1,785 patients treated with niraparib in clinical trials, MDS/AML occurred in 15 patients (0.8%). Of these 15 patients, 1 patient was treated in PRIMA, 11 patients in NOVA, and 3 patients in QUADRA. The duration of niraparib treatment in patients prior to developing MDS/AML varied from 1 month to > 4 years. The cases were typical of secondary, cancer therapy related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia. Additional cases of MDS/AML have been documented in patients treated with Zejula in combination studies and in post-marketing reports. (according to Niraparib General Datasheet Version 2.0 Version Date: 14 SEP 2020; also in USPI 2020)
According to the Lynparza® (olaparib) Product Information, the incidence of MDS/AML in patients treated with olaparib monotherapy in clinical studies, including long-term follow-up, was 1.08% (30 out of 2783 patients).[3] All of these patients had received previous chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Some patients also had a history of previous cancer or bone marrow dysplasia.[3]According to the Rubraca® (rucaparib) Product Information, MDS/AML was reported in 1.7% (20 out of 1146) of patients with ovarian cancer treated with rucaparib. Patients who experienced MDS/AML after treatment with rucaparib had all received prior treatment with platinum agents and other DNA-damaging agents.[4]

6.1.2. Risk Factors Associated With MDS/AML

Risk factors for MDS/AML include age, chemotherapy and/or radiation therapy, family history of MDS/AML, smoking, alcohol use, autoimmune diseases, genetic syndromes, and exposure to certain chemicals and heavy metals.[6,13,15-30] In addition, the incidence of MDS/AML was found to be associated with gender (more common in the male population), weight, platelet transfusions, anemia, renal and/or hepatic insufficiency, and mean corpuscular volume (MCV) abnormalities.

The mechanism of action of PARP inhibitors suggests that these agents may induce development of MDS/AML.[31] Results from Phase 3 clinical studies using niraparib, olaparib, or rucaparib have failed to show any statistically significant correlation between the use of PARP inhibitors and the incidence of MDS/AML or SPMs. It is important to note that all patients who received either niraparib, olaparib, or rucaparib had previously received chemotherapy with DNA-damaging agents and/or radiotherapy,[1-4] the use of which is known to be a risk factor associated with MDS/AML.

Patients treated with chemotherapy have an increased risk for MDS/AML. This has been shown in a study using information from the US SEER database collected between 1975 and 2008.[6] In this study, among 23,180 adult patients with ovarian cancer who received initial chemotherapy, 72 cases of AML occurred. The standardized incidence ratios (SIRs) were calculated as the ratio of the observed-to-expected incidence of AML. The expected incidence of AML was computed considering age-, race-, sex-, and calendar year specific-

incidence rates of AML from the general SEER population, multiplied by the appropriate patient-years at risk. For the SIRs, 2-sided Poisson-based 95% CIs were also calculated. The overall SIR for treatment-related AML in this cohort was 8.68 (95% CI: 6.79, 10.94). The SIR increased to 12.07 (95% CI: 8.77, 16.20) during the 4.9 years following the administration of chemotherapy. The cohort included in this study did not receive treatment with a PARP inhibitor. Therefore, it is likely that the incidence of MDS/AML is elevated in patients with ovarian cancer who have been previously treated with chemotherapy compared with the general population.

This is supported by a study by Shenolikar et al[7] through analysis of the US claims database MarketScan for the incidence of MDS/AML in 23,862 patients diagnosed with ovarian cancer between January 2000 and June 2014. The study reports that the incidence of MDS and AML was higher among patients exposed to DNA-damaging therapy, such as alkylating agents, antimetabolites, platinum-based antineoplastic agents, and topoisomerase inhibitors, and that duration of exposure to these agents was a significant risk factor for developing MDS and AML.[7]

6.2. Second Primary Malignancies

The mechanism of action of PARP inhibitors suggests that these agents may induce development of SPMs.[32] SPMs are cancers that develop after a primary cancer was diagnosed and treated in the same individual. Based on a study using information from the US SEER database collected from 1992 to 2012,[8] among 41,073 women with a diagnosis of a histologically confirmed primary ovarian malignancy, a total of 1,831 women (4.5%) developed an SPM. The overall SIR for this cohort as compared to the general population was 0.978 (99% CI: 0.992, 1.036). Race and age of diagnosis may impact the subsequent risk of developing SPM. Studies have shown that women could be at risk of developing subsequent cancers including breast, gastrointestinal, lung, and gynecological cancers, as well as leukemia.[8,33,34]

6.2.1. Reported SPMs in Patients Treated With Niraparib

In 1357 patients treated with niraparib in ovarian cancer monotherapy clinical trials (NOVA, PRIMA, QUADRA), SPM other than MDS/AML occurred in 17 patients (1.25%). (Niraparib Investigator Brochure v.11, 17 June 2020). The types of SPMs reported were undifferentiated sarcoma, intestinal carcinoma, lymphocytic leukemia, basal cell carcinoma, squamous cell carcinoma of skin, invasive ductal breast carcinoma, intraductal proliferative breast carcinoma, breast cancer, thyroid cancer, papillary thyroid cancer (RMP v.5 26 Aug 2020). There were additional cases of SPM documented in patients treated with Zejula in combination studies and in post-marketing reports.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this PASS is to determine the risk of developing MDS/AML and SPMs in patients administered niraparib in the routine clinical setting.

The objectives are as follows:

- **Primary Objective**: To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients with:
  - Advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
  - Platinum-sensitive, relapse, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with niraparib who are in a complete or partial response to platinum-based chemotherapy
- **Secondary Objective**: To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts

8. RESEARCH METHODS

8.1. Study Design

This PASS will be conducted as a prospective, noninterventional, single-arm study will estimate the incidence rate of MDS/AML and SPMs in patients with advanced (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy or patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy, that have received or are receiving niraparib through the expanded access program (EAP), a clinical trial and in routine clinical practice.

To allow for the necessary time required for development of a secondary malignancy, patients will be followed for up to 5 years from niraparib treatment initiation. Baseline characteristics of the patients will be collected at study enrollment. During the follow-up period, data on treatment with niraparib and other chemotherapeutic agents, and study outcomes (MDS/AML and SPMs) and AEs will be collected.

8.2. Setting

Primary Data Collection Cohort

Patients will be enrolled in up to 5 European countries, all of which will have niraparib treatment approved for reimbursement by the time local enrollment will start. A total of 100 to 120 sites will be engaged to reach the targeted sample size within a period of 5 years. The sites will be selected for inclusion in the study based on the following parameters:

1. Sites using niraparib per EU SmPC guidelines
2. Number of patients visiting the site with the correct indication for use of niraparib as maintenance treatment.
3. Sites with an organized and compliant infrastructure for global clinical research
4. Sites participating in the EAP will be preferred to collect the outcome of patients participating in this early treatment program, but sites that did not participate in the EAP will also be included to meet the enrollment goal for this project.

Patients will be identified and notified of the study by their treating physician. Signed consent from interested patients will then be obtained by the physician or a designated representative. The baseline characteristics, the study outcomes of MDS/AML and SPMs and any other relevant data variables will be recorded in an electronic data capture (EDC) system by the physician or study staff at the time of enrollment and quarterly thereafter for a maximum period of 5 years (Table 5). For patients who were exposed to niraparib treatment before being enrolled in the study, retrospective data starting from the beginning of niraparib treatment will be collected.

Discontinuation from the study

Specific reasons for discontinuing from the study include the following:

- Withdrawal of consent by the patient, who is at any time free to discontinue participation in the study, without prejudice to further treatment
- Loss to follow-up

- Death from any cause
- Sponsor decision to terminate study

If a patient is thought to be lost to follow-up, or discontinues the study (i.e., if the patients miss at least 3 of the expected visits for management based on standard clinical practice guidelines), attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are thought to be lost to follow-up, at least 3 documented attempts, including 1 attempt via certified mail, should be made to contact the patient before the patient is deemed lost to follow-up.

8.2.1. Inclusion/Exclusion Criteria

Patients will be eligible for enrolment into this cohort if they fulfill ALL of the following criteria at the time of enrollment into the study:

1. Patient must be a female, aged 18 years or older.
2. Patient must have a diagnosis of:
   - advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
   - platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
3. The patient received niraparib:
   a. as part of the EAP, regardless of whether the patient is receiving niraparib at the time of enrollment.
   b. as part of clinical practice, within 4 weeks of enrollment regardless of whether the patient is receiving niraparib at the time of enrollment.
   c. as part of the control arm of a clinical trial (other than TESARO/GSK sponsored or supported niraparib trial please see exclusions below), regardless of whether the patient is receiving niraparib at the time of enrollment.
4. Patient must be able and agree to sign a consent form.

Exclusion criteria

Patients who fulfil ANY of the following criteria will be excluded from the study:

1. Patient is receiving niraparib for use that is not according to the approved EU SmPC.
2. Patient is receiving or received Zejula in the past as part of TESARO or GSK clinical trial, where there are still participating in active follow-up to reduce the risk of double reporting of safety events.
3. Patients enrolled into a GSK Investigator Supported Study or Supported Collaborative Study.

8.2.2. Data Collection

Previous publications have shown that exposure to DNA-damaging therapies and the length of exposure to these therapies are critical risk factors to developing secondary malignancies in this population [6,7]. Generation of a new malignancy is a complex and lengthy process that is observed more frequently in an elderly population[13,15] and over a longer follow-up period after treatment with DNA-damaging agents. Data relating to both of these risk factors will be captured by describing the age of the patient at diagnosis, all cancer treatments received by the patient at specific dates, exposure time to each cancer treatment, and the follow-up period (derived from date of diagnosis until 1 of the following events, whichever comes first: patient death, loss to follow-up, or end of study). Patients who have a history of multiple cancers are often genetically more likely to develop secondary malignancies following diagnosis of relapsed epithelial ovarian, fallopian tube, or primary peritoneal cancer. The anticancer treatment history to which each patient has been exposed will also provide the individual history of cancers that have occurred in each patient before enrollment into the study.

To determine the risk of developing MDS/AML and SPMs in this patient population following exposure to niraparib, the following variables were described to be critical or moderate risk factors for MDS/AML or SPM, or simply associated with early stage of MDS/AML development:

- Critical risk factors for MDS/AML and other SPMs

1. **Age:** It is well established that both MDS and other SPMs are more likely to occur in the elderly. The incidence of MDS is 5 per 100,000 and increases to 21 per 100,000 among persons aged 70 or older.[13,15]
2. **Prior chemotherapy medications and radiation:** Patients who receive a certain type of chemotherapy and radiation treatment for cancers are at increased risk of developing MDS, AML, and/or SPMs.[6,7,16-18] Three groups of chemotherapy agents are known to cause treatment-related MDS/AML, including alkylating agents, topoisomerase II inhibitors, and antimetabolites.[6] In addition, cisplatin chemotherapy has been shown to increase the risk for MDS/AML.[19] Combining these agents with radiation therapy further increases the risk of MDS and AML.
3. **Smoking:** An association between smoking and MDS and/or SPM risk was found to be significant in most studies.[20-22,30] The risk seems to be related to intensity and duration of smoking with a greater risk of MDS being observed among former and current smokers who smoked more than 1 pack of cigarettes per day.[21-23]
4. **Chemicals and other environmental hazards:** Patients exposed to occupational and environmental chemicals are at increased risk of developing MDS. Solvents, including benzene, and agricultural chemicals[20,21,29] are classes of chemicals most often reported as linked with MDS.[27,28,30]

- Moderate risk factors for MDS/AML and other SPMs

5. **Alcohol use:** Daily alcohol consumption may be associated with increased risk of MDS and/or SPM.[30] Data indicated an increased risk for MDS in individuals who consumed ≥10 g/day versus those who consumed <10 g/day.[24]
6. **Patient's history of autoimmune diseases:** Recent studies suggest an increased risk of MDS or AML among patients with autoimmune diseases. Specifically, AML was associated with rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, hemolytic anemia, systemic vasculitis, ulcerative colitis, pernicious anemia, and giant cell arthritis.[25] MDS is associated with hypothyroidism, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, polymyalgia rheumatica, chronic rheumatic heart disease, polyarteritis nodosa, discoid lupus erythematosus, pernicious anemia, and psoriasis.[25,26]

- Factors associated with MDS/AML and SPMs but that are not considered risk factors for these malignancies

7. **Weight:** An association between increased weight and AML risk was found, including overweight (25 to 29.9 kg/m^2) and obese (≥30 kg/m^2) patients.[38]
8. **Prior history of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia:** Anemia, thrombocytopenia, and neutropenia are common cytopenias associated with MDS[40,41] and are prognostic factors for diagnosing MDS.[44]
9. **Complete blood count (CBC) abnormalities:** Elevated MCV is associated with early stages of MDS[39] and can be evaluated by conducting a CBC with leukocyte differentials.

   To determine whether the occurrence of MDS/AML and SPMs is associated with niraparib treatment and not with other potential risk factors, 3 types of data will be collected in the primary data cohort:

   1) Data for variables that are critical and moderate risk factors for MDS/AML and SPMs as described in Section 8.2.3
   2) Data for variables that are not described as risk factors for MDS/AML and other SPMs, but that are described as associated with early stages of development of these events as well as with adverse events related to treatment with niraparib as described in Section 8.2.3.
   3) Data to confirm use the of niraparib according to EU SmPC guidelines.

Primary Data Collection

For the primary data cohort, data will be collected at 2 different time periods as follows:

1) Baseline data (at initiation of niraparib treatment)
2) Follow-up data (collection will occur quarterly during a maximum 5-year clinical follow-up of the patient after enrollment into the study).

For patients who start niraparib treatment before being enrolled in the study, the baseline data will be collected retrospectively from the time when niraparib treatment was initiated. For patients who start niraparib treatment at time of enrollment, baseline data will be collected prospectively at time of enrollment.

The participating physicians will document the measures in a web-based documentation sheet (eCRF) that has been develop for this noninterventional study. The schedule of data collection for all study variables is provided in Table 5.

8.2.3. Study Variables

Baseline data for the primary data cohort will include the following:

- Tumor diagnosis (histological type, grade, FIGO stage, primary location)
- Age at diagnosis (derived from year of birth until date of diagnosis)
- Age at study entry (derived from year of birth until date of enrollment)
    - Height
    - Weight within 3 months of study enrollment (initiation of niraparib)
    - If available: germline and/or somatic breast cancer susceptibility gene (*BRCA*) status
    - If available: Homologous recombination deficiency (HRD) status
    - Prior chemotherapy medications and radiations (indication, dose, and duration of treatment)
    - Other treatment received for cancer (indication, dose, and duration of treatment)
    - Niraparib exposure: dose and duration (start and stop dates and interruptions)
    - Other PARP inhibitor use: dose and duration (specify which PARP inhibitor, start and stop dates, and interruptions)
    - Patient's history of other cancers (type of cancer and date at diagnosis)
    - Patient's family history of cancer (type of cancer and family member)
    - Smoker (no/yes–frequency/quantity)
    - Patient's exposure to oncogenic chemicals/heavy metals
    - Alcohol use (no/yes–frequency/quantity)
    - Patient's history of autoimmune diseases
    - Prior history of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia
    - CBC (the latest before initiation of niraparib)
    - MCV (the latest before initiation of niraparib)
    - MDS/AML and SPM events (type of event and date of diagnosis)

Follow-up data for the primary data cohort will include the following:

- Weight
- Chemotherapy/radiotherapy and/or other cancer treatments (indication, dose, and duration of treatment)
- Niraparib exposure (dose, dates of dose changes and interruptions, and date of discontinuation and reason)
- Use of other PARP inhibitors (specify which PARP inhibitor, dose, and duration)

- Patient's exposure to oncogenic chemicals/heavy metals
- New occurrence of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia
- New occurrences of MDS/AML and SPMs (type of event and date of diagnosis)
- CBC

Additional AEs and SAEs observed during the study will be collected through GSK standard pharmacovigilance processes and reported as described in Section 10.

Table 5 Schedule of Data Collection for the Primary Data Cohort

Data Collection and study assessments	Patient Baseline Assessment Day 0	Interval Data Collections Quarterly Every 3 months (+/-) 10 working days	Unscheduled Intervals During Observation Period (up to 5 years from start date of niraparib)	Lost to follow up	End of Study Period	Notes
Informed consent form (ICF)	X					
Inclusion and exclusion criteria check	X					
Year of birth	X					
Weight	X	X				At baseline or within last 3 months.
Height	X					
Family Cancer History	X					
BRCA/HRD status	X					
Auto-immune history	X					
Ovarian cancer diagnosis	X					
Other cancer diagnosis	X	X		X	X	
Cancer treatment	X	X		X	X	
Radiotherapy Treatment	X	X		X	X	
Risk Factors	X			X	X	
Complete blood cell counts	X			X	X	
Myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) and other secondary primary malignancies (SPM) Summary at Enrollment	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes

Data Collection and study assessments	Patient Baseline Assessment Day 0	Interval Data Collections Quarterly Every 3 months (+/-) 10 working days	Unscheduled Intervals During Observation Period (up to 5 years from start date of niraparib)	Lost to follow up	End of Study Period	Notes
Adverse Events (AE) reporting	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes
Pregnancy Reporting and Outcomes	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes
COVID-19 infection assessment			X			

Abbreviations: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; Q1 = first quarter; Q3 = third quarter; SPM = second primary malignancy

8.3. Data Sources

8.3.1. Primary Data Collection

This primary data collection will include patients who have received or are receiving niraparib through the EAP), in a clinical trial (other than TESARO/GSK sponsored or supported niraparib trial, GSK investigator sponsored studies or supported collaborative studies), and patients treated post-approval in routine clinical practice. Data will be collected from electronic medical records of patients enrolled into the study. The data will be entered by the staff at each clinical site into a web-based, password-protected documentation system (eCRF).

Data collection will start at the time of each patient enrollment. For each patient, data will be collected quarterly until 5 years of follow-up from the first dose of niraparib is achieved or until loss to follow-up or the patient's death, whichever occurs first.

Termination of data collection will occur once sufficient data are gathered to fulfill the target observation plan for 1,000 patient-years and when data for 5 years of follow-up are collected for patients who reach this milestone, with an anticipated overall average follow-up of 2.5 years.

8.4. Study Size

CCI [redacted]. Thus, the minimum data required to achieve a quantifiable number of MDS/AML and SPM events is 1,000 patient years with approximately 2.5 years of average follow-up.

To allow for the necessary time required for development of a secondary malignancy, patients will be followed for up to 5 years from treatment initiation. Data from a clinical trial that evaluated survival in patients treated with olaparib maintenance therapy suggest that with maximum 5-years follow-up from treatment initiation it is possible to achieve an average of approximately 2.5 years of follow-up per patient.[11] CCI [redacted]

Given the high risk for missing data and for losing patients to follow-up in a non-interventional study within a real world setting, this study plans to recruit up to 800 patients for a maximum of 5 years of follow-up per patient so that up to 2,000 patient-years of observation data can be reached. This sample size allows adequate patient data to compensate for a large incidence of missing data given that it is expected to observe a significant incidence of MDS/AML and SPMs when 1,000 patient-years are reached over a maximum follow-up period of 5 years and an overall average follow-up of 2.5 years.

The sample size was not revised following the addition to the study population patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. It is anticipated that the exposure to Niraparib will be similar in the two populations based on the data from the NOVA and PRIMA clinical studies.

Table 6 below provides the 95% CIs for different numbers of observed events of MDS/AML during this follow-up period.

Table 6 Confidence Intervals for Observed Events of MDS/AML for 1,000 Patient-Years

Observed Number of Events	Rate (per 100 patient-years)	Lower 95% Confidence Limit (per 100 patient-years)	Upper 95% Confidence Limit (per 100 patient-years)
5	0.5	0.16	1.2
10	1.0	0.48	1.8
15	1.5	0.84	2.5
20	2.0	1.2	3.1
25	2.5	1.6	3.7

8.5. Data Management

Primary Data Collection

The data are entered by the staff at each clinical site into the data input mask of a web-based, password-protected documentation system (eCRF). The data entered manually for each patient are validated online and stored via a secure internet connection (https) in the central study database in the secure computer center of the contract research organization (see Section 8.7.1 for complete data quality assurance). Every data entry and every data change are automatically provided with a user and date (audit trail). De-identified data collected for each patient will be accessible through a secure web system.

Missing data will be identified via a standard listing in the clinical database called the Missing Page Report. The study database is designed to capture forms and visits per the defined schedule in the protocol. If a visit or form is available for entry in the database but not completed by the site, it will be identified as missing in the Missing Page Report.

Once all edit/validation checks applicable to the study protocol are identified and approved by the clinical study team, they are programmed to help identify any missing data and data discrepancies. Queries are placed on the discrepant data within the electronic data capture (EDC) system for the site to respond and make any necessary corrections to the data. All derivation and validation procedures are fully tested and documented in User Acceptance Testing (UAT) scripts. Details regarding the edit checks are listed in the Data Validation Specifications, an appendix of the Data Management Plan.

In addition, a clinical monitoring plan has been established to include scheduled monitoring calls biannually with each site. Any missing data will be addressed during these interactions with the sites. The plan also includes the option of having additional ad hoc calls and/or site visits where data collection presents persistent problems.

A full midterm report will be prepared and distributed to the competent local agencies where the study is performed and to the EMA. All statistical analyses will be performed on variables listed in Section 8.3 as well as additional adverse reactions that will be identified during the study. All adverse reactions will be reported both in the study analysis and in the safety database (see also Section 10). Analysis will be performed using SAS statistical software v9.4 or later, unless otherwise noted.

8.6. Data Analysis

Details of the statistical analyses presented below will be provided in the study's SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol.

The analysis population for all analyses is the safety population, defined as all patients who receive any amount of niraparib (at least 1 dose). All analyses will be performed using SAS statistical software v9.4 or later and will include summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Further details will be provided in the SAP.

Analyses will be descriptive; no hypothesis will be tested. Distributions of patient and tumour characteristics will be summarized. Incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be estimated. For the primary data, a sensitivity analysis will be performed on the group of patients who have never received PARP inhibitor treatments prior to study enrollment. In addition, a descriptive comparison on baseline characteristics of those patients who did not receive/initiate niraparib after initial enrollment versus those who did receive the treatment will be performed.

The primary analysis on the primary cohort will be performed using all events of either MDS/AML or other SPMs without considering the risk factors associated with these events.

This initial analysis will then be followed by an evaluation of how MDS/AML and SPM events detected in the primary data cohort are distributed with respect to the variables collected for each group.

For the primary data cohort, standardized incidence of MDS/AML and SPMs will be performed across various critical and moderate risk factors for MDS/AML and SPMs, such as age, anticancer chemo- and radio-therapy received, history of other cancers, family history of cancers, presence of autoimmune disorders, use of alcohol and/or tobacco, exposure to certain chemicals and heavy metals, other non-DNA damaging anti-cancer treatments, and use of other PARP inhibitors (for a complete explanation of variables analyzed during the study, see Section 8.2.3).

The primary analysis will also be stratified by the indication used niraparib treatment i.e., by the following cohorts:

- advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
- platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy

If sufficient data is available, secondary analyses will be conducted, stratifying the study population by HRD and BRCA status.

8.7. Quality Control

To ensure compliance with all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 8.7.8 for more details regarding the audit process.

8.7.1. Data Quality Assurance

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to standard operating procedures for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Investigator or designee.

8.7.2. Access to Source Data/Documents

An electronic data capture system to manage data collection will be utilized during this study. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail of all data changes will be maintained. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Sponsor and the Investigators will follow the EU General Data Protection Regulation that replaces the Data Protection Directive 95/46/EC and that was designed to harmonize data privacy laws across Europe, to protect and empower all EU citizens' data privacy, and to reshape the way organizations across the region approach data privacy.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the Institutional Review Board (IRB) to have direct access to all documents pertaining to the study.

8.7.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

Study documents will be archived by participating investigator sites and GSK for a minimum of 10 years following the finalization of a study report.

8.7.4. Regulatory Guidelines

This study will be conducted in accordance with the Declaration of Helsinki (version 2008), as well as with the guideline on Good Pharmacovigilance Practices (GVP) – Module VIII

EMA/813938/2011 Rev 3.[45] The clinical study will also be carried out in keeping with national and local regulatory requirement(s).

8.7.5. Informed Consent

Before each patient is enrolled in this safety study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, in such a manner that the patient is aware of the potential risks and inconveniences. The patient should be informed that she is free to withdraw from the study at any time. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/Independent Ethics Committee (IEC)-approved informed consent form (ICF), as required by each country's regulatory agency, prior to the start of the study.

If an ICF is required, the ICF must be signed and dated; 1 copy will be given to the patient, and the Investigator will retain 1 copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

8.7.6. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the responsible IRB/IEC/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

8.7.7. Study Monitoring

A site management plan has been established to include scheduled monitoring calls biannually with each site. Any missing data will be addressed during these interactions with the sites. The plan also includes the option of having additional ad hoc calls and/or site visits where data collection presents persistent problems. A risk-based monitoring approach will be followed and adapted as required in consultation with the Clinical Research Organisation overseeing the implementation of the plan.

Travel limitations, quarantine and shutdowns caused by the COVID –19 pandemic may lead to difficulties in the implementation of agreed monitoring activities. This will be kept under review until normal activities can commence.

A monitor commissioned by the Sponsor can randomly check the data collection by matching the data stored in the eCRF with the medical records. Patients are informed about this aspect before participation in this noninterventional study and asked for their consent. Only patients who have given their informed consent can be observed in the noninterventional study.

All study materials will be returned to the Sponsor after the study has been completed.

8.7.8. Audits and Inspections

Responsible IRB/IEC/Competent Authorities and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

8.7.9. Ethical Considerations

The study will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki (version 2008). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

8.8. Limitations of the Research Methods

This is an observational, noninterventional prospective study aimed at collecting specific AEs that may be associated with niraparib. The study does not address efficacy of the drug. In addition, no comparisons of the incidence of events of interest are planned. Lack of randomization does not allow establishing causality between niraparib and MDS/AML and SPM incidence.

To increase the chances of detecting events of MDS/AML or SPM, attempts will be made to follow-up with patients for up to 5 years from first dose exposure to niraparib and accrue data for an average of 2.5 years follow-up. However, due to the poor prognosis of the disease, it is expected that such an observational time frame will be applicable to less than 30% of patients enrolled, as per historical data reporting overall survival from diagnosis of high-grade, advanced stage ovarian cancer. In addition, while in a clinical trial setting it was possible to achieve an average follow-up of 2.5 years with approximately 400 patients receiving niraparib, in the real world setting the risk for losing the patients to follow-up is much greater. It is expected that up to 17 events will be observed of MDS/AML and up to 3 events of SPM at up to 2,000 patient-years of observation that can be achieved through this extended research design, which is twice as much the minimum data collection required to observe a quantifiable number of MDS/AML and other SPM events, which is 1,000 patient years for up to 5-years follow-up and 2.5 years of average follow up.

The treating physician may not be able to collect exposure to environmental factors, such as heavy metals and other polluters known to be associated with various malignancies. Finally, not all risk factors that could be associated with the diverse SPMs are known and/or can be accurately captured by this study.

The current study also aims at including patients who have been exposed to niraparib before the time of enrollment. Some of these patients may have terminated niraparib treatment but will still be considered eligible for the study. The observation period for incidence of MDS/AML or SPMs in these patients will include the time from the beginning of niraparib treatment, thus providing a time advantage in assessing safety of niraparib treatment. However, inclusion of this patient population may introduce a potential bias of patient selection by leaving aside those who have received niraparib and died before the study start. The incidence of this bias should be minimal as this patient population includes patients who

participate in the EAP and for whom it is known that no mortality has occurred. Thus, the potential bias is accepted to provide patients a safety assessment of niraparib treatment in a shorter time.

8.9. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Definitions

10.1.1. Adverse Event

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including clinically significant laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. For a marketed Medicinal Product this can also include those related to a deficiency occurring with a medical device. GSK defines a Medical Device Incident as any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health and a Serious Adverse Device Effect (SADE).

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the signing of the informed consent.

10.1.2. Adverse Drug Reaction

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

10.1.3. Serious Adverse Events

An SAE is any untoward medical occurrence, that, at any dose

- Results in death
- Is life-threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization* or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event**

* Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered SAEs; an important medical event may not be immediately life-threatening, result in death, or require hospitalization but may jeopardize the patient or require intervention to prevent 1 of the above outcomes. Examples of such events are allergic

bronchospasm, blood dyscrasias, convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug.

10.1.4. Treatment-Emergent Adverse Events

A TEAE is any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

10.1.5. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** The persistent or sporadic, intentional excessive use of the study treatment, which is accompanied by harmful physical or psychological effects.
- **Misuse:** The medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** Any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, or systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** A deliberate or accidental administration of study treatment to a study patient at a dose greater than that assigned to the patient per the study protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as described in Section 10.5.2.
- **Accidental/Occupational Exposure:** The unintentional exposure to a study treatment as a result of one's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (ie, study product given to wrong patient).

10.2. Assessment of Adverse Events

10.2.1. Severity Assessment

All AEs must be assessed by the Investigator for severity* according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0, 27 November 2017, National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity Grades 1 through 5 provide unique clinical descriptions of the severity of each AE. The CTCAE v5.0 is available on the NCI/NIH website.

*Note that there is a distinction between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the SAE criteria in Section 10.1.3. For example, a mild degree of gastrointestinal bleeding requiring a hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

10.2.2. Relationship to the Study Product

The Investigator must provide a causality assessment regarding the relationship of the event with the niraparib treatment prescribed for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product. Positive rechallenge/dechallenge is supportive.
- Not related: A causal relationship between the medicinal product and AE is not a reasonable possibility. There is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

10.3. Collecting and Recording Adverse Events

AEs may be volunteered spontaneously by the study patient, discovered by the study staff during physical examinations, or by asking an open, nonleading question such as, “How have you been feeling since your last study visit?” The Investigator will document the nature of the AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All AEs, serious and non-serious, regardless of the source of identification (eg, physical examination, laboratory assessment, electrocardiogram, reported by patient), will be collected and recorded in the eCRF for each patient from the signing of the ICF for this study through 30 days after the last dose of niraparib or patient’s death for any cause, whichever comes first. However, if there is reasonable belief that an SAE that occurred after the 30 days window is related to study drug, it will be reported to the safety database.

Exceptions to the reporting requirements detailed above are as follows:

- MDS/AML and SPM as the study endpoint should be collected and reported to the Sponsor from first dose of niraparib until death or loss to follow-up, whichever comes first.
- Embryo fetal toxicity should be reported as outlined in Section 10.5.1.

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the treatment period. Pre-existing conditions will be recorded as medical history in the eCRF.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal) and should not be reported. If AEs or SAEs occur in relation to disease

progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 10.4.

The safety database will collect narratives for SAEs and ADRs, including all events of MDS/AML and SPM. It is the responsibility of the Investigator to provide case narrative in the dedicated eCRF field.

10.3.1. Follow-Up of Adverse Events

All AEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

10.4. Reporting to Sponsor

The Investigator must report all SAEs (related and nonrelated) including follow-up information to the Sponsor's safety database through the eCRF-generated Safety Form within 24 hours of becoming aware of the initial event or follow-up information. Further, non-serious ADRs should be reported to the Sponsor within five (5) days of awareness of the quarterly interval data collections through the Safety Form

It is the responsibility of the Investigator to review source documentation, describe pertinent information, and then print and sign the Safety Form before sending to the contact information below. If supporting documentation is requested (eg, hospital reports, consultant reports, death certificates, autopsy reports), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including medical record number) are removed, and submit the documents to the Sponsor. The Sponsor (or designee) will return a confirmation of receipt within 1 business day. If no acknowledgment of receipt is received, the Investigator or designee should resubmit the Safety Form or query the Sponsor to confirm the reporting route.

After receipt of the Safety Form, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information. The Investigator must promptly respond to queries from the Sponsor.

Any queries and/or follow-up communication from Investigator to the Sponsor regarding safety reporting should be addressed to:

- Email: OAX37649@gsk.com or Fax: +44(0) 208754 7822

10.5. Sponsor Submission and Distribution of Adverse Drug Reactions

Per regulatory requirements, if an event is assessed as an adverse drug reaction (ADR) (serious or non-serious), it is the responsibility of the Sponsor, and not of the Investigator, to report the ADR to Regulatory Authorities according to applicable regulations.

If any ADRs are observed related to **any other products of the Sponsor**, the Investigator should report the ADRs to the Sponsor's safety database within 24 hours. If any ADRs are observed related to drug product(s) not related to the Sponsor, the Investigator should report the ADRs to the appropriate marketing authorisation application of the product(s) or Health Authority per local regulations.

All AEs and SAEs including all MDS/AML and SPM events and embryo fetal toxicity, collected through primary data collection will be reported through the study interim safety

analyses as well as in the final study report to the competent authority of each country where the study is being conducted. The study progress will be reported through the product periodic safety update reports.

10.5.1. Pregnancy

The Investigator must report all pregnancies that occur from the signing of the ICF up to 180 days after last dose of niraparib treatment using the Initial Pregnancy Notification Report Form and forward it to the Sponsor (or designee) within 24 hours of first awareness of the pregnancy. The details of the pregnancy outcomes or other associated event (eg, elective abortion) must be reported to the Sponsor using the Pregnancy Outcome Report Form.

Pregnancy is not an AE and therefore does not need to be reported as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. The Investigator must follow up all pregnancies, document the course and the outcome, and report this information to the Sponsor within 24 hours of awareness—even if the patient was withdrawn from the study or the study has finished.

Pregnancy is not considered an SAE unless there is an associated serious outcome that must be recorded on the Pregnancy Outcome Report Form, and reported as an SAE on the SAE Report Form (e.g., maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor within 24 hours in accordance with the procedure for reporting SAEs.

10.5.2. Special Situations

All occurrences of abuse, misuse, medication error, overdose, accidental, or occupational exposure with the study product must be reported through the Special Situation Report Form provided by the Sponsor regardless of whether an AE or SAE has occurred. The form must be submitted as soon as possible, and if there is no AE or SAE, it should be indicated that “no AE has occurred.” If the abuse, misuse, medication error, overdose, or accidental/occupational exposure is associated with an SAE, an SAE must be submitted to the Sponsor within 24 hours of awareness through the eCRF.

10.5.3. Covid-19 Infection Assessment

A COVID-19 infection assessment form should be completed for ALL cases of COVID-19 cases identified during the study.

COVID 19 cases should be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The noninterventional PASS will be registered in the EU PASS register via the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website (www.encepp.eu) before the study commences.

The study protocol will be uploaded after finalization and prior to the start of data collection (EMA/613603/2012 EU PAS Register Guide).

An annual progress report (including status of patients' enrollment, eventual protocol deviations, and/or other problems encountered) and a midterm interim report of data analysis will be submitted to the competent authority of each country where the study is being conducted. A final study report will be submitted to the EMA and to the competent authority of each country where the study is being conducted.

The interim and final report will include descriptive statistical analysis, performed as described in Section 8.6, of variables collected as described in Section 8and other eventual adverse reactions collected during the study and reported in the safety database.

TESARO (A GSK company) retains the right to publish the results from this study.

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ANNEX 1. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the Investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer "N/A" (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the GVPs)

Study title:

Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)

Study reference number:
3000-04-001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5 and 8
1.1.3 Study progress report(s)	☐	☐	☒	5 and 8
1.1.4 Interim progress report(s)	☒	☐	☐	5 and 8
1.1.5 Registration in the EU PAS register	☒	☐	☐	5 and 8
1.1.6 Final report of study results.	☒	☐	☐	5 and 8

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	3.2 and 7
2.1.2 The objective(s) of the study?	☒	☐	☐	3.3 and 7
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3.5 and 8.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is not a hypothesis-driven study. This type of safety data collection was not done before

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	3.4 and 8

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
.3.2 Does the protocol specify whether the study is based on primary, second or combined data collection?	☒	☐	☐	3.4 and 8.2
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	3.8 and 8.5
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	3.5, 3.7, and 8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	5.0 and 8.2
4.2.2 Age and sex?	☒	☐	☐	3.5 and 8.2
4.2.3 Country of origin?	☒	☐	☐	3.5 and 8.2
4.2.4 Disease/indication?	☒	☐	☐	3.5 and 8.2
4.2.5 Duration of follow-up?	☒	☐	☐	3.5 and 8.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	3.5, 3.7, and 8.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	3.7 and 8.2

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	3.7, 3.8, and 8.2
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	3.7, 3.8, and 8.2
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and second (if applicable) outcome(s) to be investigated?	☒	☐	☐	3.9 and 8.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	3.6 and 8.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	8.2 and 8.3
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	8.9
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	8.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☐	8.2, 8.3, and 8.9

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	3.7, 8.2, 8.3, and 8.9

Comments:

The rationale for study covariates is justified from published literature

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	3.7 and 8.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	3.6, 8.2, and 8.3
9.1.3 Covariates?	☒	☐	☐	3.6, 8.2, and 8.3
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	3.7 and 8.4
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	3.6, 8.2, and 8.3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	3.6, 8.2, and 8.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.6

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	3.9 and 8.7
10.2 Are descriptive analyses included?	☒	☐	☐	3.9 and 8.7
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	3.9, 8.7, and 8.9
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.6
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	3.8 and 8.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6 and 8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias?	☒	☐	☐	8.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	8.9
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.1

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8.8
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	8.8
13.3 Have data protection requirements been described?	☒	☐	☐	8.8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: PPD

Date:

Signature: _____

Signature Page for 213705 TMF-13993422 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 12-Apr-2024 14:36:53 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 12-Apr-2024 16:15:16 GMT+0000

Signature Page for TMF-13993422 v2.0

Statistical Analysis Plan for Real World Research Studies

Statistical Analysis Plan (SAP) Text Version Number: V2.0
SAP Text Date: 17-May-2024

Sponsor Name: Tesaro (GlaxoSmithKline company)

Protocol Number: PASS 3000-04-001 (GSK 213705)
Protocol Title: Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with ZEJULA® (niraparib)

Protocol Version and Date: Version 9: 12-Apr-2024

Syneos Health Project Code: 1012514

Authors: PPD Sr. Principle Biostatistician

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date	Document Owner	Revision Summary
0.1	21-DEC-2022	PPD	Initial Release Version
0.2	25-Jan-2023		Address the comments from v0.1
0.3	09-Feb-2023		Address the comments from v0.2
1.0	10-Feb-2023		Final stable draft
1.1	16-May-2023		Incorporate the comments from IA first draft
1.1	24-May-2023		Incorporate the comments from IA second draft
1.1	25-Aug-2023		Incorporate the comments post final IA delivery updates: - section 4: adding follow-up time definition - section 6.1.5: adding a sentence regarding the unplanned derivied variables per sponsor comments - section 6.2.3: remove sentence “Stratification by HRD and BRCA status will be implemented when sufficient data is available.”. - section 6.3: adding sponsor shared table on PY definition. - section 6.2.7: adding clarification for medical history regarding the data collection and data reporting
2.0	02-May-2024		To align with protocol amendment 9 (dated on 12-Apr-2024): - Cover page: updated protocol version and date - Section 3: removal of exploratory objective - Section 4: removal of exploratory objective related text - Removal section 6.3.3 exporatory analysis - Section 6.2.5, date of study drug end date is updated by incorporating database lock for final report.
2.0	17-May-2024		Updates per 10-May-2024 GSK comments: - Updated GSK approval’s title on Approval page - Time to onset of MDS/AML and/or other SPMs analysis is added into section 6.3.1. - Section 4 and 6.4 added text for final analysis

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

PPD Sr. Principle Biostatistician	PPD lectronically signed by: PPD eason: I am the author ate: May 17, 2024 14:05 EDT		May 17, 2024
Lead Biostatistician	Signature		Date
PPD	PPD Electronically signed by: PPD Reason: I am the approver Date: May 17, 2024 13:24 CDT		May 17, 2024
Senior Reviewing Biostatistician	Signature		Date

Tesaro (GlaxoSmithKline company) Approval

PPD PPD Oncology Epidemiology	PPD Electronically signed by: PPD Reason: I am the approver Date: May 17, 2024 15:08 EDT		May 17, 2024
	Signature		Date
PPD PPD Oncology Epidemiology	PPD Electronically signed by PPD Reason: I am the approver Date: May 17, 2024 15:23 EDT		May 17, 2024
	Signature		Date

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
ADR	Adverse Drug Reaction
AE	Adverse Event
AML	Acute Myeloid Leukemia
AT	adjuvant chemotherapy
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
BRCA	Breast Cancer Susceptibility Gene
CBC	Complete Blood Count
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
EAP	Expanded Access Program
ECG	Electrocardiogram
EMA	European Medicines Agency
eCRF	Electronic Case Report Form
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
HRD	homologous recombination deficiency
ICF	informed consent form
ICH	International Conference on Harmonization
IDS	Interval debulking surgery
Max	Maximum
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NAT	neoadjuvant chemotherapy
N/A	Not Applicable

Abbreviation	Description
OR	Observational Research
PASS	Post Authorization Safety Study
PARP	poly (ADP-ribose) polymerase
PDS	Primary debulking surgery
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SPM	Second Primary Malignancies
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure, and Listing
WHO	World Health Organization

2. Introduction

Zejula is a poly (ADP-ribose) polymerase (PARP) inhibitor. A decision to grant marketing authorization for Zejula was adopted by the European Commission on 16 November 2017 with the indication of monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer after response (complete or partial) to platinum-based chemotherapy.

On 17 September 2020 GSK received European Commission approval of Zejula (niraparib) as first-line monotherapy maintenance treatment of adult patients with advanced epithelial (International Federation of Gynecology and Obstetrics (FIGO) Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and other second primary malignancies (SPMs) have been observed in the context of PARP inhibitor treatments. However, results from Phase 3 clinical studies using Zejula, olaparib, or rucaparib did not show any statistically significant correlation between the use of PARP inhibitors and the incidence of MDS/AML or SPMs. The mechanism of action of PARP inhibition suggests that there may be a risk of MDS/AML and SPM associated with the use of PARP inhibitors. Therefore, the specific evaluation of this potential risk has been included in the Risk Management Plan for Zejula. During PASS study conduct the company revised the position and MDS/AMLs are currently upgraded to important identified risk (ADR), while SPMs are still important potential risk in Risk Management Plan.

To better characterize the risks of MDS/AML and SPMs associated with Zejula treatment, a post-authorization safety study (PASS) in patients receiving maintenance treatment with Zejula was agreed with the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use.

This statistical analysis plan (SAP) describes the analyses and data presentations for protocol GSK 213705 “Post-authorization safety study to evaluate the risks of myelodysplastic syndrome/acute myeloid leukemia and second primary malignancies in adult patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula® (niraparib)” version no. 8 dated on 08 June 2021. The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

3. Study Objectives

The objective of this PASS is to determine the risk of developing MDS/AML and SPMs in patients administered Zejula in the routine clinical setting.

The objectives are as follows:

- **Primary Objective**: To estimate the incidence rate of MDS/AML, and the distribution of these events across different risk factors for MDS/AML, among a cohort of adult patients with:
  - Advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy OR,
  - Platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with Zejula who are in a complete or partial response to platinum-based chemotherapy

- **Secondary Objective:** To estimate the incidence rate of SPMs, and the distribution of these events across different risk factors for SPMs, in the same cohorts

4. Study Design

This PASS is conducted as a prospective (referred to as primary data), noninterventional, single-arm study including patients who have received or are receiving Zejula through the European Expanded Access Program (EAP) and patients treated post-approval in routine clinical practice.

To allow for sufficient patient follow-up time to capture the majority of secondary malignancy events, patients will be followed for up to 5 years from Zejula maintenance treatment initiation. Baseline characteristics of the patients are collected at study enrollment. Patients may have initiated Zejula prior to study enrollment or on or after study enrollment. Data on treatment with Zejula and other anticancer therapy will be collected retrospectively and prospectively. During the follow-up period, study outcomes (MDS/AML and SPMs) and AEs will be collected.

Following enrollment, data is prospectively collected from patients who have received or are receiving Zejula through the EAP, in a clinical trial, and patients treated post-approval in routine clinical practice. Primary data is sourced from patients' electronic health records.

Data are collected at two different time periods as follows:

1) Baseline data (at initiation of Zejula treatment, which may have occurred prior to or on or after enrollment into the study)
2) Follow-up data (collection occurs quarterly during a maximum 5-year clinical follow-up of the patient after enrollment into the study).

Most baseline data are collected relative to the time when Zejula treatment was initiated. Some baseline characteristics are collected relative to study enrollment date, e.g. family cancer history, smoking history and alcohol use, patient's exposure to oncogenic chemicals/heavy metals, BRCA/HRD genetic assessments and target medical history.

The overall study follow-up time for a patient will start from initiation of Zejula treatment until the earliest date of death, study discontinuation or completion of 5 years maximum follow-up (or data cutoff date for interim analysis/date of database lock for final analysis).

5. Analysis Sets

Enrolled Population: The Enrolled Population includes all patients who signed the informed consent form (ICF).

Safety Population: The Safety Population includes patients who enrolled, met all eligibility criteria and received at least one dose of Zejula, with sufficient clinical information to classify their Zejula line of therapy. Patients may have received Zejula in the first or second line maintenance setting. The Safety Population will be used for all analyses and data listings. And, the data will be presented overall and by whether patients received Zejula in the first-line maintenance (1LM) or second-line maintenance or beyond (2LM+) setting, unless otherwise specified.

The study cohort includes adult patients diagnosed with:

- Advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy and treated with Zejula maintenance therapy [**1LM**]

  or
- Platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and treated with Zejula maintenance therapy [**2LM+**]

6. Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

Analyses will be descriptive; no hypotheses will be tested. Summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, first quartile (Q1), median, third quartile (Q3), minimum, and maximum for continuous variables will be provided. Distributions of patient and tumor characteristics will be summarized in the overall patient cohort and stratified by 1LM and 2LM+.

Incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be estimated. Sensitivity analysis will be performed on the group of patients who received Zejula prior to study enrollment versus those who received Zejula on or after enrollment. All analyses will be performed using SAS statistical software v9.4 or later.

6.1.2 Bias and Confounding

This is an observational, non-interventional prospective study aimed at collecting AE data in patients treated with Zejula. The study does not evaluate the efficacy of the drug. No comparisons of the incidence of events of interest are planned between patient groups.

The current study includes patients who initiated Zejula prior to the time of enrollment. Some of these patients may have terminated Zejula treatment prior to enrollment, but were still considered eligible for the study. There is potential for bias with patients who started Zejula prior to enrollment having some data collected retrospectively and those who initiate on or after enrollment having all data collected prospectively. Additionally, all AEs, serious and non-serious, are collected and recorded in the electronic Case Report Form (eCRF) for each patient from the signing of the ICF for this study, with the exception of MDS/AML and SPMs and embryo fetal toxicity. This introduces immortal time bias as patients who have started Zejula prior to enrollment are contributing person-time to the analysis, but have no safety events other than MDS/AML, SPMs and embryo fetal toxicity reported.

Previous publications have shown that exposure to DNA-damaging therapies and the length of exposure to these therapies are critical risk factors to developing secondary malignancies in this population[3,4]. Generation of a new malignancy is a complex and lengthy process that is observed more frequently in an elderly population and over a longer follow-up period after treatment with DNA-damaging agents. Data relating to both of these risk factors will be captured by describing demographic and clinical risk factors, all anticancer treatments received, and exposure time to each anticancer treatment. Patients who have a history of multiple cancers are often genetically more likely to develop secondary malignancies following diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer. The anticancer treatment history to which each patient has been exposed and individual and familial history of cancers are captured.

To assess whether the occurrence of MDS/AML and SPMs is associated with Zejula treatment and not with other potential risk factors, data for variables that are described to be critical and moderate risk factors for MDS/AML and SPMs, or data for variables that are not described as risk factors for MDS/AML and other SPMs, but that are described as associated with early stages of development of these events as well as with adverse events related to treatment with Zejula have been described in section 6.2.3.

6.1.3 Handling of Dropouts and Missing Data

The reason patients discontinue from the study will be summarized with patient disposition section 6.2.1. For this study, retrospective data will be based on historical dates in which some date might be missing or incomplete. Outcomes dates, which are the dates corresponding to study endpoints such as MDS/AML or SPMs start or end dates, will not be imputed. Milestone dates which are dates of protocol milestones, such as informed consent date, start date of Zejula, Zejula termination date, study closure date, etc., should not be missing if the milestone occurs for a patient. They are not supposed to be imputed unless otherwise

specified, given that some data are collected retrospectively. However, in listings, the dates will be shown as recorded without imputation.

Incomplete dates for study treatment, prior anticancer therapies and radiotherapy

Start and stop dates of Zejula will be imputed by assigning the first day of the month when only the day part of the date is missing. Otherwise, incomplete dates will be treated as missing. The other treatment dates (e.g. start date of anticancer treatment including PARP and non-PARP inhibitors, and radiotherapy treatment) will be imputed by the earliest possible date given the non-missing field(s) of the date, e.g. January 1. Incomplete date with missing year will be treated as missing.

Incomplete dates for disease history

Incomplete date of ovarian cancer diagnosis will be imputed by the earliest possible date given the non-missing field(s) of the date, e.g. January 1 in the analysis such as calculation of age at ovarian cancer diagnosis. Incomplete start and end dates of other disease history will not be imputed, including autoimmune diseases history and other cancer diagnosis. However, for the analysis of baseline disease characteristics such as to determine prior autoimmune diseases history (yes or no), the incomplete date will be compared with the first dose date of Zejula by using the same imputation rule as incomplete date of ovarian cancer diagnosis, i.e. if the day of the disease start date is missing, the first day of month will be used; if both the day and month of the disease start date are missing, January 1 will be used for the missing parts to compare with Zejula first dose date. For example, a patient autoimmune diseases start date is UNUNK2020, imputed date of 01Jan2020 will be used to compare with the first dose date of Zejula to determine if the disease started prior to Zejula initiation.

Incomplete dates for prior/concomitant medications and surgeries

Incomplete start and end date of relevant concomitant medications/therapies and date of surgery will not be imputed. However, the incomplete date will be compared with the first dose date of Zejula by using the same approach as described for incomplete dates for disease history for the analysis of baseline disease characteristics such as to determine prior surgery history (yes or no).

Missing or incomplete dates for adverse events

Missing or incomplete start dates for Adverse Events (AE) will be imputed in the analysis dataset for AEs. The AE will be assumed as treatment emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period, from start date of Zejula to 30 days after the end date of Zejula (worst case approach). The following rules will be applied:

- For missing start day only: Day will be imputed as the first day of the month (i.e., 01) with the following exception: if the partial date falls in the same month and year as Zejula start date, then the partial date will be imputed to equal Zejula start date.
- For missing start day and month: Day and month will be imputed as the first day of the year (i.e., 01 January) with the following exception: if the partial date falls in the same year as Zejula start date, then the partial date will be imputed to equal Zejula start date.
- For complete missing: Date will be imputed to the Zejula start date.
- Imputed start dates must be prior to the Zejula discontinuation date or completion date.

All dates will be present in the listings as collected.

6.1.4 Determination of Sample Size

CCI

[redacted]

CCI [redacted] Thus, the minimum data required to achieve a quantifiable number of MDS/AML and SPM events is 1000 patient-years with approximately 2.5 years of average follow-up per patient.

The sample size or follow-up time threshold was not revised following the addition of patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy (1LM) to the study population. It is anticipated that the exposure to Zejula will be similar in the two populations based on the data from the NOVA and PRIMA (A Study of Niraparib Maintenance Treatment in Participants with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy; PR-30-5017-C) clinical studies. Given the high risk for missing data and for losing patients to follow-up in a non-interventional study in a real-world setting, up to 800 patients are recruited with a maximum of 5 years of follow-up per patient so that up to 2000 patient-years of observation data may be reached. This sample size allows adequate patient data to compensate for a potentially large incidence of missing data given that we expect to observe a significant incidence of MDS/AML and SPMs when data for 1000 patient-years are collected over a maximum follow-up period of 5 years and a per-patient average follow-up of 2.5 years.

Table 1 Confidence Intervals for Observed Events of MDS/AML for 1000 Patient-Years1 provides the 95% CIs for different numbers of observed events of MDS/AML during this follow-up period.

Table 1 Confidence Intervals for Observed Events of MDS/AML for 1000 Patient-Years

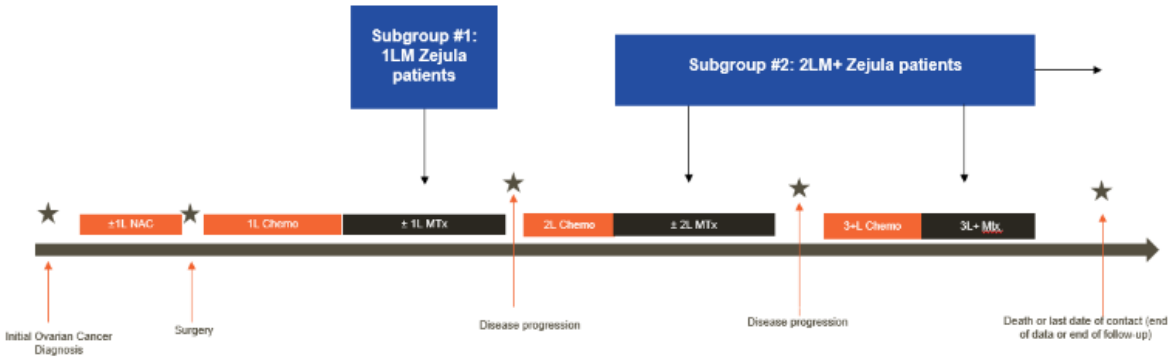
Observed Number of Events	Rate (per 100 patient-years)	Lower 95% Confidence Limit (per 100 patient-years)	Upper 95% Confidence Limit (per 100 patient-years)
5	0.5	0.16	1.2
10	1.0	0.48	1.8
15	1.5	0.84	2.5
20	2.0	1.2	3.1
25	2.5	1.6	3.7

6.1.5 Determination of Maintenance Line of Therapy Subgroup

Patients who received Zejula in the 1LM and 2LM+ settings will be identified by following the typical treatment journey for ovarian cancer (Figure 1). A patient treated with 1LM Zejula receives their first dose of Zejula following complete or partial response to front-line chemotherapy treatment, and typically, cytoreductive surgery. A patient may receive primary debulking surgery (PDS), followed by adjuvant chemotherapy. Alternatively, front-line chemotherapy treatment may comprise of both neoadjuvant chemotherapy (NAT), for patients who receive interval debulking surgery (IDS), followed by adjuvant chemotherapy (AT). Patients with relapsed ovarian cancer who receive 2LM+ Zejula receive their first dose of Zejula following complete or partial response to their second or later (or third, etc.) line of chemotherapy treatment.

Figure 1

Ovarian cancer: Treatment journey



NAC: Neoadjuvant chemotherapy

GSK

09 November 2022

Ovarian cancer patients receiving Zejula in the 1LM and 2LM+ settings will be identified by approaches described below:

CCI

[redacted]

CCI

[redacted]

Patients identified as 1LM via the above-specified algorithm and whose index date is >15 months following their initial ovarian cancer diagnosis will be clinically reviewed by a GSK board-certified gynecologic oncologist for cohort assignment.

Any unplanned derived variables defined post-SAP development will be documented in the analysis dataset specifications, e.g. total lines of therapy prior to Zejula initiation, total lines of platinum-based chemotherapy prior to Zejula initiation.

6.1.6 Time Windows

Data will be collected during two different time periods: 1) baseline data (index date is initiation of Zejula treatment where possible; some baseline characteristics are assessed at date of study enrollment) and 2) follow-up data (a maximum 5-year clinical follow-up after Zejula initiation). For each patient, data will be collected quarterly until 5 years of follow-up from the first dose of Zejula is achieved or until the earliest occurrence of loss to follow-up or death.

Baseline is defined as the last non-missing assessment prior to the first dose date of Zejula. Some baseline characteristics which were otherwise specified below in section 6.2.3 were assessed at the study enrollment, e.g. family cancer history, smoking history and alcohol use, patient's exposure to oncogenic chemicals/heavy metals, BRCA/HRD genetic assessments and target medical history. The baseline data includes patient demographic characteristics, tumor characteristics, medical and treatment history. During the follow-up period, data will be collected on anticancer treatment, adverse events and study outcomes of interest (MDS/AML and SPMs).

There is no plan to re-assign visits based on actual visit dates. The analysis will be based on nominal visit/time points collected, e.g. Beginning of Treatment, End of Treatment.

6.2 Patient Characteristics

6.2.1 Patient Disposition

The patient disposition will be summarized overall and by 1LM or 2LM+ subgroup, based on the Enrolled Population. The number and percentage of patients who were screened but deviated from the inclusion or exclusion criteria will be summarized.

The total number of patients who enrolled into the study will be provided. The number and percentage of patients who are in the Safety Population, who have completed 5-year follow-up after Zejula initiation, and who do not complete study along with primary reason for study discontinuation will be described as well.

Primary reason for study discontinuation will be summarized with the following categories:

- Withdrawal of consent
- Loss to follow-up
- Death from any cause
- Sponsor decision to terminate study
- Other

Patients disposition will be provided in a listing for all who are enrolled. A listing of the inclusion/exclusion criteria deviation record for patients with deviations will be produced.

6.2.2 Protocol Deviations

Clinical Trial Management System (CTMS) is utilized for entry of subject level protocol deviations and site level non-compliances. Study protocol deviations and important protocol deviations (PD/IPD) defined as part of the protocol deviation management plan for the study will be identified and assessed by the clinical research physician or designee following standard operational procedure on collection, evaluation and reporting of PD/IPD. The severity (major, minor) of PD will be determined in CTMS. The major PD will be presented as IPD in the table and listing. The number and percentage of patients who entered into the study, and had IPD will be summarized by categories using frequency tabulations on the Enrolled Population. The protocol deviations categories will be sorted in descending order based on total incidence and within category the protocol deviations coded terms are sorted in descending order based on total incidence.

A patient listing of PD/IPD, the category and coded term for the deviation will be produced.

In addition, a summary of IPDs related to COVID-19 will be included as applicable.

6.2.3 Background and Demographic Characteristics

Demographics and clinical baseline characteristics of patients will be summarized by 1LM patients, 2LM+ patients and the overall primary patient cohort.

Definition of baseline is provided in section 6.1.6.

All descriptive analyses will generate summary statistics, including the number of patients and percentage for categorical variables and the number of patients, mean, standard deviation, Q1, median, Q3, minimum, and maximum for continuous variables.

The following baseline data for the primary data cohort will be summarized:

- Age at index (derived from year of birth until date of Zejula initiation)
- Age group at index (< 50 years, 50-64 years, 65-74 years, ≥ 75 years)
- Age group at ovarian cancer diagnosis (derived from year of birth until date of diagnosis) (< 50 years, 50-64 years, 65-74 years, ≥ 75 years)
- Any family cancer history at enrollment (yes, no)
- Current smoking status at enrollment (never smoked, former smoker or current smoker)
- Smoking duration at enrollment (years) measured among current or former smokers at enrollment
- Average number of cigarettes smoked per day measured among current or former smokers at enrollment
- Exposure to oncogenic factors at enrollment (yes, no, or unknown); Type of oncogenic factors for those exposed
- Average number of alcoholic drinks before ovarian cancer diagnosis (drinks per week) (1-2, 3-6, 7-12, 13-24, > 24) measured among those who report drinking alcohol before ovarian cancer diagnosis
- Average number of alcoholic drinks after ovarian cancer diagnosis (drinks per week) (1-2, 3-6, 7-12, 13-24, > 24) measured among those who report drinking alcohol after ovarian cancer diagnosis
- Autoimmune disease history prior to Zejula initiation (yes, no) (any assessment prior to index)
  - If yes, ongoing or not ongoing
- BRCA testing performed (yes, no) (assessed at enrollment only)
  - Yes, defined as non-missing BRCA test results (mutant, wild type) plus missing which are patients with eCRF question “BRCA/HRD genetic testing performed at enrollment” checked “Yes” but missing BRCA status
  - No, defined as BRCA test results (not performed, not available) plus patients who had eCRF question “BRCA/HRD genetic testing performed at enrollment” checked “No”
- BRCA test results among patients with BRCA testing performed (mutant, wild type and missing as applicable)
  - If BRCA mutant status, germline or somatic mutation
- HRD testing performed (yes, no) (assessed at enrollment only)
  - Yes, defined as HRD test result (HR-deficient, HR-proficient) plus missing which are patients with eCRF question “BRCA/HRD genetic testing performed at enrollment” checked “Yes” but missing HRD test results
  - No, defined as HRD test result (not performed, not available) plus patients who had eCRF question “BRCA/HRD genetic testing performed at enrollment” checked “No”
- HRD test results among patients with HRD testing performed (HR-deficient, HR-proficient and missing as applicable)
- Biomarker status (HR-deficient, HR-proficient, HR unknown/BRCA wild type, no results available for BRCA or HRD) (derived from HRD test results and BRCA test results assessed at enrollment)
  - HR-deficient, defined as BRCA test results are mutated or HRD results are HR deficient
  - HR-proficient, defined as HRD results are HR proficient and BRCA results are not equal to mutant

  - HR unknown/BRCA wild type, defined as HRD results are not tested/missing and BRCA results are wild type
  - No results available for BRCA or HR, if both HRD and BRCA tests are not tested/missing
- Height (cm) (continuous) (latest assessment prior to index)
- Weight (kg) (latest assessment prior to index)
- BMI (kg/m^2) (latest assessment prior to index)
- Overweight and obesity (BMI ≥ 25 kg/m^2) (latest assessment prior to index)
- Prior history of thrombocytopenia, platelet transfusions, anemia, renal insufficiency, hepatic insufficiency, and neutropenia (yes, no, or unknown) (assessed at enrollment only)

The following baseline cancer-related medical history data will be summarized:

- Time to Zejula initiation (since ovarian cancer diagnosis, calculated as the date of first dose of Zejula minus date of ovarian cancer diagnosis. If only month and year are provided, the day=1 will be assumed. If only year is provided, month=1 and day=1 will be assumed.)
- Histological classification (high-grade serous, high-grade Endometrioid, other) (assessed at enrollment only)
- International Federation of Gynecology and Obstetrics (FIGO) stage at ovarian cancer diagnosis (1998 and 2014, combined) (Stage I, II, III, IV)
- Other cancer diagnosis prior to Zejula initiation (yes, no); Type of cancer if other prior cancer diagnosed.
- Received radiotherapy for other cancer prior to Zejula initiation (yes, no)
- Received any other therapy for other cancer prior to Zejula initiation (yes, no)

Additionally, the following characteristics on therapy for ovarian cancer will be included in summary:

- Total lines of therapy prior to Zejula initiation
- Total lines of platinum-based chemotherapy prior to Zejula initiation
- Total number of platinum-based chemotherapy cycles prior to Zejula initiation
- Zejula exposure prior to enrollment (yes, no)
- Other PARP inhibitor received prior to Zejula initiation (Olaparib, Rucaparib, Talazoparib, Other)
- Cytoreductive surgery performed prior to Zejula initiation, if yes, type of debulking surgery (PDS, IDS, more than one surgery)
- Residual disease status post-cytoreductive surgery (no visible residual disease including residual disease less than or equal to 1 cm, visible residual disease defined as residual disease greater than 1 cm, unknown, no surgery)
- Neoadjuvant chemotherapy for ovarian cancer received prior to Zejula initiation (yes, no)
  - If yes, best response to neoadjuvant chemotherapy (complete response, partial response, progressive disease, stable disease, not evaluable, unknown)
  - If yes, primary reason for stopping treatment (treatment completed, progressive disease, toxicity, other)
- Adjuvant chemotherapy for ovarian cancer received prior to Zejula initiation (yes, no)
  - If yes, best response to adjuvant chemotherapy (complete response, partial response, progressive disease, stable disease, not evaluable, unknown)
  - If yes, primary reason for stopping treatment (treatment completed, progressive disease, toxicity, other)
- Received radiotherapy for ovarian cancer prior to Zejula initiation (yes, no)
- Chemotherapy received prior to Zejula initiation for ovarian cancer and for all types of cancer, respectively:
  - Alkylating agents
  - Topoisomerase II inhibitors
  - Antimetabolites
  - Antineoplastic - Platinum Complexes

- Taxanes
- Other

Any unplanned derived variables defined post-SAP development will be documented in the analysis dataset specifications.

In addition, baseline characteristics of patients who initiated Zejula prior to and after enrollment will be described.

All demographic and baseline data will be presented in listings.

All cancer history, history of surgery for cancer, and history of prior therapy for cancer (radiation, chemotherapy, and other therapy) will be presented in listings.

6.2.4 Risk Factors Associated with MDS/AML and other SPMs

Risk factors associated with MDS/AML and other SPMs include three categories: critical risk factors, moderate risk factors and other factors, described in detail below.

To determine the risk of developing MDS/AML and other SPMs in this patient population following exposure to Zejula, the following variables were described to be critical or moderate risk factors for MDS/AML or other SPMs, or simply associated with early stages of MDS/AML development.

- Critical risk factors for MDS/AML and other SPMs
  - Age group at index (< 50 years, 50-64 years, 65-74 years, ≥ 75 years)
  - Received chemotherapy and radiation therapy for any cancer prior to Zejula initiation (yes vs. no)
  - Received radiation therapy only for any cancer prior to Zejula initiation (yes vs. no)
  - Received chemotherapy only for any cancer prior to Zejula initiation (yes vs. no)
  - Chemotherapy received for any cancer prior to Zejula initiation
    - Alkylating agents
    - Topoisomerase II inhibitors
    - Antimetabolites
    - Antineoplastic - Platinum Complexes
    - Taxanes
    - Other
  - Smoking status at enrollment (current smoker, former smoker or never smoked)
  - Exposure to oncogenic factors at enrollment (yes, no, or unknown), if yes, type of oncogenic factor
  - Total number of platinum-based chemotherapy cycles for ovarian cancer prior to Zejula initiation
  - BRCA testing performed (yes, no) and BRCA test results among patients with BRCA testing performed (mutant, wild type and missing as applicable; germline or somatic mutation if BRCA test result is mutant) (assessed at enrollment only)
  - HRD testing performed (yes, no) and HRD test results among patients with HRD testing performed (HR-deficient, HR-proficient and missing as applicable) (assessed at enrollment only)
  - Biomarker status (derived from HRD test results and BRCA test results assessed at enrollment) (HR-deficient, HR-proficient, HR unknown/BRCA wild type, no results available for BRCA or HRD)

- Moderate risk factors for MDS/AML and other SPMs

- Average number of alcoholic drinks before ovarian cancer diagnosis (≤ 24 drinks per week, > 24 drinks per week, unknown)
- Average number of alcoholic drinks after ovarian cancer diagnosis (≤ 24 drinks per week, > 24 drinks per week, unknown)
- Autoimmune disease history prior to Zejula initiation (yes, no, unknown)

- Factors associated with MDS/AML and other SPMs but that are not considered risk factors for these malignancies

  - PARP inhibitor received (Zejula, Olaparib, Rucaparib, Talazoparib, Other), length of exposures and dose received prior to development of MDS/AML and other SPMs
  - Overweight and obesity (BMI ≥ 25 kg/m^2) (latest assessment prior to index)
  - Prior history of thrombocytopenia, platelet transfusions, anemia, renal insufficiency, hepatic insufficiency, and neutropenia (yes, no, or unknown) (assessed at enrollment only)
  - Complete blood cell count (CBC) abnormalities prior to Zejula initiation
    - Haemoglobin (Hb) (g/dL) (normal vs. abnormal)
    - White blood cells (WBC) (g/dL) (normal vs. abnormal)
    - Blasts (%) (normal vs. abnormal)
    - Absolute Blasts Count (normal vs. abnormal)
    - Platelets (normal vs. abnormal)
    - Absolute Neutrophil Count (normal vs. abnormal)
    - Neutrophils (%) (normal vs. abnormal)
    - Absolute Lymphocytes Count (normal vs. abnormal)
    - Lymphocytes (%) (normal vs. abnormal)
    - Mean corpuscular volume (MCV) (normal vs. abnormal)

6.2.5 Treatment Exposure and Compliance

The extent of exposure to Zejula will be evaluated by duration of exposure (months), which will be calculated as:

Duration of exposure (months) = (Date of study drug end date – Date of first dose +1) /30.4375.

The study drug end date is the date of the last dose on drug. For patients whose Zejula is not discontinued or interrupted at the time of clinical cut-off for interim report, the clinical cut-off date will be used as the end date. For patients whose Zejula is not discontinued or interrupted at the time of database lock for final report, the date of database lock will be used as the end date. For patients whose Zejula administration was interrupted and not restarted at the time of clinical cut-off for interim report or database lock, the last non-missing Zejula administration will be used as the end date.

Descriptive statistics of duration of Zejula exposure, duration of Zejula treatment prior to development of MDS/AML or other SPMs and Zejula starting dose will be provided for 1LM patients, 2LM+ patients and the overall patient cohort.

Dose modifications will be summarized for the same cohorts as follows:

- Number and percentage of patients with at least 1 dose modification, patients with starting dose modified, reason for dose modification (Thrombocytopenia, Anemia, Fatigue, Nausea or Other)
- Number and percentage of patients with a second dose modification, reason for dose modification (Thrombocytopenia, Anemia, Fatigue, Nausea or Other)
- Number and percentage of patients with dose interrupted, reason for dose interruption (Thrombocytopenia, Anemia, Fatigue, Nausea or Other)
- Number and percentage of patients with Zejula administration discontinued, reason for discontinuation (Disease progression, Patient request, Investigator discretion, Patient become pregnant, Patient passed away, Adverse event (grade 3 or higher), or Other)

Note that a patient may experience multiple dose modifications during treatment period.

By-patient listing of Zejula administration will be provided to support the data summaries in the table.

6.2.6 Prior and Concomitant Medications and Therapies

Relevant medication/therapy will be coded into Anatomical Therapeutic Chemical (ATC) classification levels and preferred term (PT) according to the corresponding GSK Drug Synonym.

By-patient listings will be provided for following medication/therapies:

- Relevant concomitant medication/therapies, including name of the medication, indication, dosing information (dose per administration, frequency, route), start date, ongoing at study entry, end date if not ongoing and if suspected as cause.
- Neoadjuvant chemotherapy treatment (frontline chemotherapy prior to debulking surgery) and adjuvant chemotherapy treatment (frontline chemotherapy after debulking surgery) will be listed, including type of therapy both reported term and coded term, number of cycles, dose per administration, start date, end date, primary reason for stropping treatment and the best response.
- Any chemotherapy or other therapy that does not include a PARP inhibitor to treat ovarian cancer at enrollment and during study, including line of therapy, type of therapy both reported term and GSK drug synonym, number of cycles, dose per administration, start date, end date, primary reason for stropping treatment and the best response.
- Any other PARP inhibitor administered to patient at enrollment and during study, including PARP inhibitor both reported term and GSK drug synonym, dose administered, start date, end date, any dose modification, date of dose modification and modified dose if any, if interrupted, date of interruption if any and date of restarted.

6.2.7 Medical Histories

Pre-existing conditions will be recorded as relevant medical history in eCRF. Relevant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.1, which provides the dictionary synonym System Organ Class (SOC) and preferred term (PT). Medical History, only collected among patients who experience serious AE, will not be reported in aggregate tabular form; only listings will be reported.

Relevant medical history will be listed which includes medical conditions, event start date, condition ongoing at study entry, end date if not ongoing, suspected as causal and if prior to Zejula initiation.

In addition, relevant surgical history will be listed for those who had surgery including details of the relevant surgical history, date of the surgery, if suspected as causal and if prior to Zejula initiation.

6.3 Statistical Analysis

All analyses will be descriptive; no hypotheses will be tested.

Incidence rates of MDS/AML and/or other SPMs and their respective 95% CIs per 100 person-time units will be estimated for 1LM patients, 2LM+ patients and the overall patient cohort.

The incidence rate per 100 patient-years is defined as 100 times the number of patients who experienced the event divided by the total person time (in years) among all patients included in the analysis (whether or not they experienced the event), as defined below:

Incidence rate of per 100 patient-years = $100 * \frac{\mathrm{D}}{\mathrm{PY}}$

95% CI of the incidence rate per 100 patient-years: $\left(\frac{\chi^2_{2D,\frac{\alpha}{2}}}{2*\left({}^{PY}/_{100}\right)} \ , \ \frac{\chi^2_{2(D+1),(1-\frac{\alpha}{2})}}{2*\left({}^{PY}/_{100}\right)} \right)$

where,

α: Type 1 error

D: Numbers of patients with an new incidence of MDS/AML (and/or other SPMs)
PY: Patient-years which will be calculated as the total time from the start date of Zejula to either the first onset date of MDS/AML or other SPM, or, for subjects who have no events of MDS/AML or other SPM, to the earliest occurrence of date of study discontinuation, death or date of data cutoff. The start date and end date for patient-years calculation are described in table below.

	PY start date	**PY end date**
Overall PYs	Start date of Zejula (Index date)	**Developed event:** Earliest onset date of MDS or AML or SPM **Did not develop event:** Earliest date of study discontinuation, death or date of data cutoff
Incidence rate of MDS/AML PYs	Start date of Zejula (Index date)	**Developed event:** Earliest onset date of MDS or AML (not including SPM) **Did not develop event:** Earliest date of study discontinuation, death or date of data cutoff
Incidence rate of SPMs PYs	Start date of Zejula (Index date)	**Developed event:** Earliest onset date of SPM (not including MDS or AML) **Did not develop event:** Earliest date of study discontinuation, death or date of data cutoff
Incidence rate of MDS/AML and SPMs PYs	Start date of Zejula (Index date)	**Developed event:** Earliest onset date of MDS or AML or SPM **Did not develop event:** Earliest date of study discontinuation, death or date of data cutoff **Note: This is the same as overall PYs, as specified above.**

6.3.1 Primary Analysis

The incidence rate of MDS/AML and/or other SPMs, and the distribution of these events across different risk factors for MDS/AML and/or other SPMs will be provided by 1LM patients, 2LM+ patients and the overall patient cohort.

The primary analysis will use all events of MDS/AML and/or other SPMs without considering the risk factors associated with these events. This initial analysis will then be followed by an evaluation of how MDS/AML and/or other SPMs events are distributed with respect to risk factors collected for each group.

The incidence of MDS/AML and/or other SPMs will be summarized by various critical and moderate risk factors, such as age at diagnosis, anticancer chemo- and radio-therapy received, history of other cancers, family history of cancers, presence of autoimmune disorders, use of alcohol and/or tobacco, exposure to certain chemicals and heavy metals, other non-DNA damaging anti-cancer treatments, and use of other PARP inhibitors (see Section 6.2.4 for the list of variables for risk factors).

Time to onset of MDS/AML and/or other SPMs will also be summarized.

6.3.2 Secondary Analysis

The incidence of MDS/AML and/or other SPMs will be summarized by factors associated with MDS/AML and SPMs but that are not considered risk factors for these malignancies (PARP inhibitor received, overweight and obese, prior history of thrombocytopenia, platelet transfusions, anemia, renal and/or hepatic insufficiency, and neutropenia, and prior CBC abnormalities).

6.3.3 Adverse Events

All adverse events (AEs) will be collected and recorded in the eCRF for each patient from the signing of the ICF for this study through 30 days after the last dose of Zejula or patient's death for any cause, whichever comes first. However, if there is reasonable belief that a serious AE (SAE) that occurred after the 30 days window is related to study drug, it will be reported to the safety database. MDS/AML and SPMs are collected and reported from the first dose of Zejula.

All AEs and SAEs including all MDS/AML and SPM events and embryo fetal toxicity, collected through primary data collection will be reported through the study interim safety analyses as well as in the final study report to the competent authority of each country where the study is being conducted. The study progress will be reported through the product periodic safety update reports.

A treatment-emergent adverse event (TEAE) is any event that was not present prior to the initiation of Zejula or any event already present that worsens in either intensity or frequency following exposure to Zejula. If AE onset date is missing or incomplete, the onset date will be imputed according to section 6.1.3.

All AEs will be coded into system organ class (SOC) and preferred term (PT) according to MedDRA Version 25.1 or later. TEAEs will be summarized descriptively using number and percentage by MedDRA SOC/PT. A patient will be counted only once at the Dictionary Synonym level. Each AE will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. If a patient experiences the same TEAE more than once with different CTCAE grade, the event with the highest grade will be considered in table of summary by intensity.

All AE listings will include the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity and relationship to study drug. Missing (partial) start/stop dates will appear as missing (partial) in the subject data listings but will be imputed to permit proper tabulation of AE data (See Section 6.1.3).

AEs will be summarized descriptively by number and percentage (%) of subjects with an event (n [%]), and number of events [e], by MedDRA SOC/PT and CTCAE grade.

A patient will be counted once at the SOC level and once at PT level. For summaries by SOC, PT, and severity, a patient will be counted only at the maximum CTCAE grade. Summaries by relatedness would be handled similarly to the summaries by intensity. Summaries by SOC and PT will be ordered by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. Summaries of PT will be ordered in descending frequency of PT.

Summaries of TEAEs will be generated for each of the following:

- Overview of TEAEs
- MDS/AML and other SPM events by overall frequency
- MDS/AML and other SPM events related to Zejula by overall frequency
- TEAEs by SOC and PT
- Related to Zejula TEAEs by SOC and PT
- TEAEs by SOC and PT and maximum NCI CTCAE grade
- Related to Zejula TEAEs by SOC and PT and maximum NCI CTCAE grade
- Serious TEAEs by SOC and PT

- Related to Zejula serious TEAEs by SOC and PT
- Serious TEAEs by SOC and PT (the number and percentage of subjects and the number of occurrences of serious, drug-related serious, fatal serious, and drug-related fatal serious adverse events)
- TEAEs leading to drug withdrawn by SOC and PT
- Related to Zejula TEAEs leading to drug withdrawn by SOC and PT
- TEAEs with death outcome by SOC and PT
- Related to Zejula TEAEs with death outcome by SOC and PT
- Common (>=5%) TEAEs by overall frequency
- Related to Zejula non-serious TEAEs by Overall Frequency
- Serious fatal and non-fatal related to Zejula TEAEs by Overall Frequency

The following by-patient listings will be provided:

- All AEs
- MDS/AML and Other SPM events
- AEs leading to drug withdrawn
- AEs Grade 3 or higher by maximum NCI CTCAE grade
- Serious TEAEs
- TEAEs with death outcome
- All deaths

6.3.4 Analysis of Other Assessments

6.3.5.1 CBC Assessments

CBC differential parameters values with PARP inhibitor treatment are collected at the beginning of PARP inhibitor treatment and at the end of PARP inhibitor treatment. For patients who had Zejula treatment, CBC differential parameters, i.e. haemoglobin (Hb), white blood cells (WBC), blasts (%), absolute blasts count, platelets, absolute neutrophil count, neutrophils (%), absolute lymphocytes count, lymphocytes (%) and MCV are collected at the beginning of Zejula treatment and at the end of Zejula treatment.

All the CBC assessment result will be listed. Additionally, abnormal CBC differential parameters values with Zejula will be listed separately.

6.3.5.2 Pregnancy Reporting and Outcomes

The Investigator must report all pregnancies that occur from signing the ICF up to 180 days after the last dose of Zejula treatment using the Initial Pregnancy Notification Report Form and forward it to the Sponsor (or designee) within 24 hours of first awareness of the pregnancy. The details of the pregnancy outcomes or other associated event will be presented in a listing.

6.3.5.3 COVID-19 infection assessment

A COVID-19 infection assessment form will be completed for all COVID-19 cases identified during the study. Also, COVID 19 cases will be evaluated as to whether they meet SAE criteria as defined in the protocol. SAEs and AEs will be submitted following usual study procedures and timelines. A summary of the number and percentage of patients for the COVID-19 assessments will be provided including diagnosis, COVID-19 test performed, and results of the COVID-19 test. A summary of the following COVID-19 additional assessments may be produced as applicable: does the subject have a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset? did the subject visit any health care facility in the 14 days prior to symptom onset? did the subject have contact with a confirmed or probable case in the 14 days prior to symptom

onset? were any concomitant medications taken by the subject, including experimental medications, to treat COVID-19? was the subject in home quarantine or isolation?

The COVID-19 infection assessments and symptoms will be provided in a listing.

6.4 Interim and Final Analysis

A midterm interim report and final report of data analysis have been planned for this study. The interim report and final study report will be submitted to the competent authority of each country where the study is being conducted. All AEs and SAEs including all MDS/AML and SPM events and embryo fetal toxicity, collected through primary data collection will be reported. In addition, all other statistical analysis in this SAP will be performed.

7. Tables, Figures and Listings

Table of contents is provided in a separate document.

8. References

1. European Medicines Agency (EMA). ZEJULA® - Summary of Product Characteristics. 2020; https://www.ema.europa.eu/documents/productinformation/zejula-epar-product-information_en.pdf.

2. ZEJULA® [package insert]. Waltham, MA: TESARO, Inc.; 2020.

3. Morton LM, Dores GM, Tucker MA, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood. 013;121(15):2996-3004.

4. Shenolikar R, Durden E, Meyer N, Lenhart G, Moore K. Incidence of secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients with ovarian or breast cancer in a real-world setting in the United States. Gynecol Oncol. 2018;151(2):190-195.

9. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). The general programming convensions will be stated in the TLF shells document.

10. Quality Control

SAS programs are developed to produce output such as analysis datasets, summary tables, figures, and data listings, or statistical analyses. An overview of the development of programs is detailed in Developing Statistical Programs SOP (3922).

The Developing Statistical Programs and Conducting the Transfer of Biostatistical Deliverables SOP (3922) and the SAS Programming and Validation Plan (3920A) describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

11. Shells

Table, figure and listing shells will be provided as a separate document.

12. Appendix

Schedule of Data Collection for the Primary Data Cohort:

Data Collection and study assessments	Patient Baseline Assessment Day 0	Interval Data Collections Quarterly Every 3 months (+/-) 10 working days	Unscheduled Intervals During Observation Period (up to 5 years from start date of niraparib)	Lost to follow up	End of Study Period	Notes
Informed consent form (ICF)	X					
Inclusion and exclusion criteria check	X					
Year of birth	X					
Weight	X	X				At baseline or within last 3 months.
Height	X					
Family Cancer History	X					
BRCA/HRD status	X					
Auto-immune history	X					
Ovarian cancer diagnosis	X					
Other cancer diagnosis	X	X		X	X	
Cancer treatment	X	X		X	X	
Radiotherapy Treatment	X	X		X	X	
Risk Factors	X			X	X	
Complete blood cell counts	X			X	X	
Myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML) and other secondary primary malignancies (SPM) Summary at Enrollment	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes
Adverse Events (AE) reporting	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes

Data Collection and study assessments	Patient Baseline Assessment Day 0	Interval Data Collections Quarterly Every 3 months (+/-) 10 working days	Unscheduled Intervals During Observation Period (up to 5 years from start date of niraparib)	Lost to follow up	End of Study Period	Notes
Pregnancy Reporting and Outcomes	X	X	X	X	X	Refer to protocol section 10.0 for reporting timeframes
COVID-19 infection assessment			X			

Abbreviations: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; Q1 = first quarter; Q3 = third quarter; SPM = second primary malignancy.

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