Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database

Pierre-Marie Morice, Alexandra Leary, Charles Dolladille, Basile Chrétien, Laurent Poulain, Antonio González-Martín, Kathleen Moore, Eileen Mary O'Reilly, Isabelle Ray-Coquard, Joachim Alexandre

Lancet Haematol 2021; 8: e122–34

Published Online December 18, 2020 https://doi.org/10.1016/S2352-3026(20)30360-4

See Comment page e97

This online publication has been corrected. The corrected version first appeared at thelancet.com/haematology on January 26, 2021

Normandie Univ, UNICAEN, INSERM U1086, Interdisciplinary Research Unit for Cancers Prevention and Treatment, Biology and Innovative Therapeutics for Ovarian Cancers Team, Caen, France (P-M Morice PhD, L Poulain PhD); UNICANCER, Cancer Center François Baclesse, Caen, France (P-M Morice, L Poulain); Department of Medical Oncology, Gustave Roussy Cancer Center, University Paris Saclay, Villejuif, France (A Leary MD); Inserm U981 Gynaecological Tumours, Gustave Roussy Cancer Center, University Paris Saclay, Villejuif, France (A Leary); Department of Pharmacology, Pharmacoepidemiology Unit, Caen University Hospital, Caen, France (C Dolladille MD, Prof J Alexandre MD); Normandie Univ, UNICAEN, EA4650, Signalisation, Électrophysiologie et Imagerie des Lésions d'Ischémie-Reperfusion Myocardique, Caen, France (C Dolladille, Prof J Alexandre); Pharmacovigilance Regional Center, Caen University Hospital, Caen, France (B Chrétien PharmD, Prof J Alexandre); Department of Medical Oncology, Clínica Universidad de Navarra, Madrid, Spain (A González-Martín MD); Division of Gynecologic

Summary

Background Poly(ADP-ribose) polymerase (PARP) inhibitors have shown efficacy and acceptable safety in a range of neoplasms, particularly in ovarian cancers. However, some concerns have emerged regarding rare and delayed adverse events including cases of myelodysplastic syndrome and acute myeloid leukaemia, for which data are scarce. The aim of this study was to estimate the risk of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitors, via a systematic review and safety meta-analysis, and to describe clinical features of PARP inhibitor-related myelodysplastic syndrome and acute myeloid leukaemia cases reported in WHO's pharmacovigilance database (VigiBase).

Methods We systematically reviewed randomised controlled trials (RCTs) comparing PARP inhibitor therapy versus control treatments (placebo and non-placebo) in adults (age ≥18 years) treated for cancer in MEDLINE, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov registry with ongoing surveillance up to May 31, 2020. The date range for included studies was not restricted. By a stepwise method to capture all available adverse events, we first extracted data on myelodysplastic syndrome and acute myeloid leukaemia cases from ClinicalTrials.gov. If cases were not available, we extracted them from published manuscripts, or subsequently contacted corresponding authors or sponsors to provide data. RCTs without available data from ClinicalTrials.gov, publications, or corresponding authors or sponsors were excluded. The primary outcome was the summary risk of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibition versus placebo treatment in RCTs. We used a fixed-effects meta-analysis to obtain Peto odds ratios (ORs) with 95% CIs. In a separate observational, retrospective, cross-sectional pharmacovigilance study of VigiBase, cases of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor therapy were extracted on May 3, 2020, and clinical features summarised with a focus on median duration of PARP inhibitor exposure, median latency period between first drug exposure and diagnosis, and proportion of cases resulting in death. Our systematic review and safety meta-analysis were registered with PROSPERO, CRD42020175050. Our retrospective pharmacovigilance study was registered on ClinicalTrials.gov, NCT04326023.

Findings For our safety meta-analysis, initial searches identified 1617 citations, and 31 RCTs were systematically reviewed for eligibility. 28 RCTs with available adverse events were analysed (18 placebo and ten non-placebo RCTs), with 5693 patients in PARP inhibitor groups and 3406 patients in control groups. Based on the 18 placebo RCTs (n=7307 patients), PARP inhibitors significantly increased the risk of myelodysplastic syndrome and acute myeloid leukaemia compared with placebo treatment (Peto OR 2·63 [95% CI 1·13–6·14], p=0·026) with no between-study heterogeneity (I^2=0%, χ^2 p=0·91). The incidence of myelodysplastic syndrome and acute myeloid leukaemia across PARP inhibitor groups was 0·73% (95% CI 0·50–1·07; I^2=0%, χ^2 p=0·87; 21 events out of 4533 patients) and across placebo groups was 0·47% (0·26–0·85; I^2=0%, χ^2 p=1·00; three events out of 2774 patients). All 28 RCTs were rated as having unclear risk of bias. In VigiBase, 178 cases of myelodysplastic syndrome (n=99) and acute myeloid leukaemia (n=79) related to PARP inhibitor therapy were extracted. In cases with available data, median treatment duration was 9·8 months (IQR 3·6–17·4; n=96) and median latency period since first exposure to a PARP inhibitor was 17·8 months (8·4–29·2; n=58). Of 104 cases that reported outcomes, 47 (45%) resulted in death.

Interpretation PARP inhibitors increased the risk of myelodysplastic syndrome and acute myeloid leukaemia versus placebo treatment. These delayed and often lethal adverse events should be studied further to improve clinical understanding, particularly in the front-line maintenance setting.

Funding None.

Research in context

Evidence before this study

Cases of myelodysplastic syndrome and acute myeloid leukaemia have been reported in randomised controlled trials (RCTs) evaluating poly(ADP-ribose) polymerase (PARP) inhibitors in patients with cancer. Before initiation of this study, no meta-analysis addressing the association of PARP inhibitors with myelodysplastic syndrome and acute myeloid leukaemia, nor their incidence or clinical features, had been published. To be exhaustive concerning these adverse events, we identified RCTs assessing PARP inhibitors in MEDLINE, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov registry, with search terms "randomized controlled trial" AND "olaparib" OR "rucaparib" OR "niraparib" OR "talazoparib" OR "veliparib", with ongoing surveillance up to May 31, 2020. Only RCTs with available adverse event data were selected for a safety meta-analysis. We also did a retrospective pharmacovigilance study on May 3, 2020, of WHO's pharmacovigilance database. Myelodysplastic syndrome and acute myeloid leukaemia cases were identified by searches for "Leukaemias" (High Level Group Term) and "Myelodysplastic syndromes" (High Level Term), and cases assessed were those notified as suspected to be caused by PARP inhibitors.

Added value of this study

Our meta-analysis showed that occurrence of secondary myelodysplastic syndrome and acute myeloid leukaemia in patients with cancer was related to PARP inhibitor regimens across 28 RCTs. Furthermore, clinical features recorded in WHO's real-world pharmacovigilance database highlighted that myelodysplastic syndrome and acute myeloid leukaemia occurred several months after PARP inhibitor administration, with a high frequency of death and co-reported cytopenia in confirmed cases.

Implications of all the available evidence

Despite previous studies showing improved progression-free survival, PARP inhibitors also increase the risk of myelodysplastic syndrome and acute myeloid leukaemia versus placebo treatment. These delayed adverse events need further research to improve understanding, and clinicians should be aware of these potentially fatal haematological toxicities, particularly in the front-line maintenance setting.

Oncology, Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA (K Moore MD); **Memorial Sloan Kettering Cancer Center, New York City, NY, USA** (E M O'Reilly MD); **Cancer Center Léon Bérard, Lyon, France** (Prof I Ray-Coquard MD); **and University Claude Bernard Lyon 1, Lyon, France** (Prof I Ray-Coquard)

Correspondence to:
Prof Joachim Alexandre, Department of Pharmacology, Pharmacoepidemiology Unit, Caen University Hospital, F-14000 Caen, France
alexandre-j@chu-caen.fr

Introduction

Oral poly(ADP-ribose) polymerase (PARP) inhibitors provide clinical benefit in a range of cancers with or without deleterious mutations in homologous recombination genes involved in DNA repair (eg, *BRCA1*/*BRCA2*). PARP inhibitors have mainly shown clinically significant improvements in progression-free survival in both recurrent and primary ovarian cancers.[1,2] The ability of the drugs to provide such benefit led to the approval of four PARP inhibitors by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) between 2014 and 2018 in various clinical indications for patients with ovarian, breast, pancreatic, or prostate cancers. In randomised controlled trials (RCTs), the most common adverse events of PARP inhibitors were fatigue and haematological and gastrointestinal toxicities.[3] Adverse events with PARP inhibitors generally occurred during the first 3 months of treatment. A potential risk of developing myelodysplastic syndrome or acute myeloid leukaemia has not yet been confirmed, but the few reported cases from RCTs found that myelodysplastic syndrome and acute myeloid leukaemia could be a delayed adverse event following treatment initiation.[4–7] In these conditions, isolated RCTs might be underpowered to assess the association of PARP inhibitor treatment with the development of myelodysplastic syndrome and acute myeloid leukaemia. Additionally, the clinical features of myelodysplastic syndrome and acute myeloid leukaemia associated with PARP inhibitors and their incidence remain unknown. In this study, we did a systematic review and safety meta-analysis of placebo RCTs to estimate the risk of developing myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitors. Subsequently, we assessed the incidence and risk of PARP inhibitor-related myelodysplastic syndrome and acute myeloid leukaemia in placebo and non-placebo RCTs. Furthermore, we describe clinical features of myelodysplastic syndrome and acute myeloid leukaemia cases related to PARP inhibitors reported in VigiBase, the WHO pharmacovigilance database.

For **VigiBase** see https://www.who-umc.org/vigibase/vigibase/

Methods

Study design and participants

The study protocol for our systematic review and safety meta-analysis of RCTs was prospectively registered with PROSPERO, CRD42020175050. The study protocol for our observational, retrospective, cross-sectional pharmacovigilance study of VigiBase (myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitors [MyeloRIB]) was registered on ClinicalTrials.gov, NCT04326023. No ethics committee approval or informed consent was sought since these were retrospective analyses of publicly available data.

VigiBase is the unique WHO pharmacovigilance database of individual case safety reports with more than 21 million anonymised cases of adverse events from 130 countries, managed by the Uppsala Monitoring Centre (Uppsala, Sweden). Reports include administrative information and patient characteristics, and adverse events and drug information according to the latest version of the Medical Dictionary for Regulatory Activities terms (MedDRA, version 22.1), with adverse events characterised as serious or non-serious according to definitions of the Cancer Therapy Evaluation Program Adverse Event

See Online for appendix

Reporting System (CTEP-AERS; appendix p 1). Reports of suspected medicine-related adverse events have been submitted to VigiBase since 1968.

Systematic review strategy and selection criteria

This work is reported according to the PRISMA harms checklist, which contains additional items for harms reporting (appendix pp 2–3).[8] A systematic review of the literature was done in MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the ClinicalTrials.gov register. The search strategy included key words (eg, medical subject heading terms in MEDLINE) and free-text words related to PARP inhibitors up to March 14, 2020 (MEDLINE) and April 6, 2020 (Cochrane CENTRAL; ClinicalTrials.gov searched in the intermediate period) with language restricted to English (appendix p 4). We did not seek to translate studies that were not published in English. Available safety data reported on ClinicalTrials.gov without a corresponding publication were eligible for inclusion. Ongoing surveillance was done up to May 31, 2020, to identify newly published studies (MEDLINE) or posted results (ClinicalTrials.gov) that might affect the findings of the review. Terms related to PARP inhibitors (olaparib, rucaparib, niraparib, talazoparib, and veliparib) in the title or abstract (or both) were considered as the sole research domain, and the search strategy included the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE (appendix p 4). Two authors (P-MM and JA) independently screened references for eligibility of data extraction and consulted a third author (CD) to resolve disagreements. RCTs comparing PARP inhibitors versus placebo or non-placebo controls in adult patients (age ≥18 years) with cancer were eligible for inclusion. Case reports or case series, case-control studies, observational studies, single-arm studies, and non-randomised trials were excluded. To be exhaustive concerning rare and delayed adverse events, we used a stepwise method to comprehensively capture all available myelodysplastic syndrome and acute myeloid leukaemia cases. Firstly, all available myelodysplastic syndrome and acute myeloid leukaemia events classified according to the CTEP-AERS in RCTs on PARP inhibitors reported on ClinicalTrials.gov were extracted.[9,10] Secondly, if reported adverse events were not available on ClinicalTrials.gov, all graded myelodysplastic syndrome and acute myeloid leukaemia events according to the Common Terminology Criteria for Adverse Events (CTCAE versions 3 and 4) definition were extracted from published RCTs. Lastly, regarding RCTs for which we had neither available adverse events on ClinicalTrials.gov nor available adverse events in publications, corresponding authors or sponsors of the study were contacted by e-mail to provide the required information. We checked each RCT identified to avoid double counting, and only RCTs for which adverse events were available were retained in our final analyses. RCTs without data related to the adverse events of interest were not included. Additional data from eligible studies were collected, including PARP inhibitor regimen, control arm regimen, median age (years), previous lines of chemotherapy, intervention model, masking, median follow-up (months), overall number of patients analysed, and number of myelodysplastic syndrome and acute myeloid leukaemia events related to PARP inhibitor (or control) treatment. All results including follow-up data posted on ClinicalTrials.gov were collected at the time of searches.

For **VigiLyze** see https://www.who-umc.org/vigibase/vigilyze

Pharmacovigilance study procedures

We did our retrospective pharmacovigilance study on May 3, 2020, using VigiLyze, the web interface to VigiBase. Myelodysplastic syndrome and acute myeloid leukaemia cases were identified by searches with the MedDRA (version 22.1) preferred terms "Leukaemias" (High Level Group Term) and "Myelodysplastic syndromes" (High Level Term); cases notified as suspected to be caused by PARP inhibitors were specifically considered in the analysis. When available, we also collected administrative and clinical characteristics of cases: reporting year, reporter to the database (health-care professional or non-health-care professional), sex, age at onset, geographical location, previous lines of chemotherapy, PARP inhibitor treatment (regimen, start and end date, exposure duration, and dose modifications), myelodysplastic syndrome and acute myeloid leukaemia characteristics (date of diagnosis, last follow-up, and outcome), malignant neoplasm progression (present or absent), and co-reported cytopenias (type and time from PARP inhibitor initiation to onset). Each case was checked to avoid double counting.

Statistical analysis

The primary outcome of our meta-analysis was the summary risk of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibition versus placebo treatment in RCTs in patients with cancer. Secondary outcomes were: the summary incidence of myelodysplastic syndrome and acute myeloid leukaemia cases related to PARP inhibition or control treatment in placebo RCTs, non-placebo RCTs, and all RCTs (placebo and non-placebo); and the summary risk of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibition versus all control treatments (placebo and non-placebo) in RCTs. In addition, we used subgroup analyses to explore possible sources of heterogeneity or inconsistency in placebo RCTs in the primary analysis. Prespecified subgroup analyses were done according to previous systemic therapy, to the PARP inhibitor used, to whether trials were restricted to *BRCA1/2* mutation carriers or recruited patients regardless of mutation status, to PARP inhibitor treatment setting (eg, first-line, front-line maintenance, recurrent disease), and to PARP inhibitor assignation (alone or in combination with non-PARP inhibitor

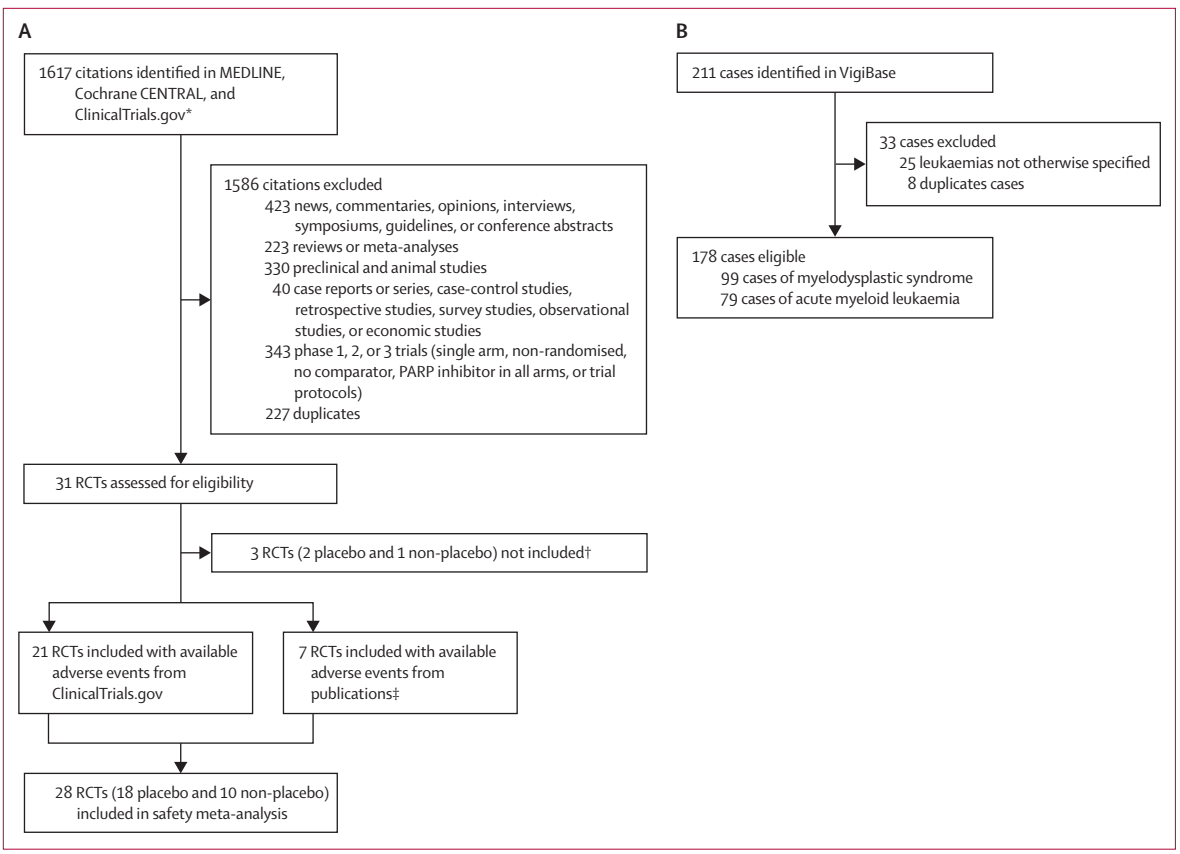

Figure 1: **Study flow diagrams**
(A) PRISMA diagram of our systematic review and safety meta-analysis of RCTs on PARP inhibitors in adult patients with cancer, available in MEDLINE, Cochrane CENTRAL, and the ClinicalTrials.gov registry (ongoing surveillance up to May 31, 2020). (B) Flow diagram of our observational, retrospective, cross-sectional pharmacovigilance study of cases of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor treatment reported in VigiBase up to May 3, 2020. RCTs=randomised controlled trials. PARP=poly(ADP-ribose) polymerase. CENTRAL=Central Register of Controlled Trials. *Studies were searched in MEDLINE (n=833) followed by Cochrane CENTRAL (n=744) and ClinicalTrials.gov (n=40). †RCTs without safety data related to myelodysplastic syndrome or acute myeloid leukaemia from ClinicalTrials.gov, publications, or corresponding authors or sponsors. ‡Data were provided by corresponding authors or sponsors (n=6) and extracted from the publication (n=1).

therapy). Post-hoc subgroup analyses were according to median follow-up duration and to PARP inhibitor treatment duration. Cases of myelodysplastic syndrome that progressed to acute myeloid leukaemia were counted only once as acute myeloid leukaemia. Two authors (P-MM and JA) evaluated the risk of bias in individual studies using the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (also known as PROTECT) checklist tool specially designed to assess bias in safety meta-analyses.[11] In case of disagreements, a third author (CD) was consulted. Publication bias was assessed graphically by constructing a funnel plot. Quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

We did a fixed-effects meta-analysis to compute Peto odds ratios (ORs) with 95% CIs, which has been described as the most accurate method for binary studies with rare events (<1%) by Morton and colleagues[12] and exemplified previously.[13] Assuming myelodysplastic syndrome and acute myeloid leukaemia were rare events (incidence <10%), we interpreted OR as a measure of the risk.[14,15] Median latency period in months with IQR and range, defined as the interval between PARP inhibitor initiation and diagnosis of myelodysplastic syndrome or acute myeloid leukaemia, was calculated with available data from placebo RCTs. The incidence of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor therapy was computed with the logit transformation and inverse variance weighting. Prespecified sensitivity analyses of the primary outcome were computed to assess the robustness of results, by recalculating the combined Peto OR with ClinicalTrials.gov data only, and independently with published RCT data only. If some of these studies had available data from both sources, we independently included each set of reported results in the two sensitivity analyses. Post-hoc sensitivity analyses were computed after removing trials with a sample size of less than 100 patients per arm and after excluding trials which had a follow-up shorter than 17 months on reviewer request. We assessed

between-study heterogeneity using the inconsistency index I^2 statistic and the χ^2 test with its p value. Substantial between-study heterogeneity was defined by an I^2 value of greater than 50%, and significant heterogeneity was defined by a χ^2 p value of less than 0·10 per the Cochrane Handbook for Systematic Reviews of Interventions.[16] Data management and meta-analysis of the pooled data (Peto method) were done with R (version 3.5.3) and the R package meta, and presented in forest plots. A two-sided p value of less than 0·05 in Z-tests (for overall effect) or χ^2 tests (for overall subgroup comparison) in all analyses was considered statistically significant.

In our descriptive assessment of cases in VigiBase, duration of PARP inhibitor exposure and latency period

	PARP inhibitor	Patient groups (n=7307)	All patients or biomarker selected	Cancer type	Median age, years	Previous lines of chemotherapy	Intervention model	Masking	Median follow-up
Ledermann et al (2012);[21] NCT00753545	Olaparib*	Olaparib 400 mg bid (n=136) versus placebo (n=128)	All patients	Ovarian	58 years (PARP inhibitor group) versus 59 years (placebo group)	Two (platinum-based chemotherapy)	Parallel assignment	Quadruple	78·0 months
Bang et al (2015);[35] NCT01063517	Olaparib†	Olaparib 100 mg bid plus paclitaxel (n=61) versus placebo plus paclitaxel (n=62)	All patients	Gastric	63 years (PARP inhibitor group) versus 60 years (placebo group)	One (platinum-based or fluorouracil, capecitabine, tegafur, gimeracil, and oteracil chemotherapy)	Parallel assignment	Quadruple	8·4 months
Middleton et al (2015);[42] NCT00804908	Veliparib†	Veliparib 20 mg bid plus temozolomide (n=116) versus veliparib 40 mg bid plus temozolomide (n=115) versus placebo plus temozolomide (n=113)	All patients	Melanoma	60 years (PARP inhibitor 20 mg group) versus 63 years (PARP inhibitor 40 mg group) versus 59 years (placebo group)	One to five (type not specified)	Parallel assignment	Quadruple	12·0 months
Mirza et al (2016);[4] NCT01847274	Niraparib*	Niraparib 300 mg qd (n=367) versus placebo (n=179)	All patients	Ovarian	57 years (g*BRCA*m PARP inhibitor group) versus 58 years (g*BRCA*m placebo group) and 63 years (non-g*BRCA*m PARP inhibitor group) versus 61 years (non-g*BRCA*m placebo group)	Two (platinum-based chemotherapy)	Parallel assignment	Quadruple	24·0 months
Bang et al (2017);[36] NCT01924533	Olaparib†	Olaparib 100 mg bid plus paclitaxel (n=263) versus placebo plus paclitaxel (n=262)	All patients	Gastric	58 years (PARP inhibitor group) versus 59 years (placebo group)	One (platinum-based and 5-fluorouracil-based chemotherapy)	Parallel assignment	Quadruple	11·1 months (PARP inhibitor group) versus 9·9 months (placebo group)
Chabot et al (2017);[32] NCT01657799	Veliparib†	Brain radiation plus veliparib 50 mg bid (n=103) versus brain radiation plus veliparib 200 mg bid (n=102) versus brain radiation plus placebo (n=101)	All patients	Non-small-cell lung cancer	60 years (PARP inhibitor 50 mg group) versus 62 years (PARP inhibitor 200 mg group) versus 60 years (placebo group)	None	Parallel assignment	Double	36·0 months
Coleman et al (2017);[5] NCT01968213	Rucaparib*	Rucaparib 600 mg bid (n=372) versus placebo (n=189)	All patients	Ovarian	61 years (PARP inhibitor group) versus 62 years (placebo group)	Two (platinum-based chemotherapy)	Parallel assignment	Double	Ongoing (>24 months)
Pujade-Lauraine et al (2017);[23] NCT01874353	Olaparib*	Olaparib 300 mg bid (n=195) versus placebo (n=99)	Patients with *BRCA* mutations	Ovarian	56 years (PARP inhibitor group) versus 56 years (placebo group)	Two (platinum-based chemotherapy)	Parallel assignment	Quadruple	66·0 months (PARP inhibitor group) versus 64·8 months (placebo group)
Clarke et al (2018);[39] NCT01972217	Olaparib†	Olaparib 300 mg bid plus abiraterone (n=71) versus placebo plus abiraterone (n=71)	All patients	Prostate	70 years (PARP inhibitor group) versus 67 years (placebo group)	One (taxane-based or hormone antagonist-based chemotherapy)	Parallel assignment	Double	15·9 months (PARP inhibitor group) versus 24·5 months (placebo group)
Gorbunova et al (2018);[41] NCT02305758	Veliparib†	Veliparib 200 mg bid plus FOLFIRI ± bevacizumab (n=65) versus placebo plus FOLFIRI ± bevacizumab (n=65)	All patients	Colorectal	59 years (PARP inhibitor group) versus 64 years (placebo group)	Naive	Parallel assignment	Double	23·8 months

(Table 1 continues on next page)

	PARP inhibitor	Patient groups (n=7307)	All patients or biomarker selected	Cancer type	Median age, years	Previous lines of chemotherapy	Intervention model	Masking	Median follow-up, months
(Continued from previous page)									
Loibl et al (2018);[28] NCT02032277	Veliparib‡	Carboplatin–paclitaxel plus veliparib 50 mg bid (n=313) versus carboplatin–paclitaxel plus placebo (n=158) versus paclitaxel plus placebo (n=157)	Patients with *BRCA* mutations	Breast	51 years (PARP inhibitor group) versus 49 years (carboplatin–paclitaxel plus placebo group) versus 50 (paclitaxel plus placebo group)	Naive	Parallel assignment	Quadruple	Ongoing (>48 months)
Moore et al (2018);[22] NCT01844986	Olaparib§	Olaparib 300 mg bid (n=260) versus placebo (n=131)	Patients with *BRCA* mutations	Ovarian	53 years (PARP inhibitor group) versus 53 years (placebo group)	One (platinum-based chemotherapy)	Parallel assignment	Quadruple	57·6 months (PARP inhibitor group) versus 60·0 months (placebo group)
Pietanza et al (2018);[34] NCT01638546	Veliparib†	Veliparib 40 mg bid plus temozolomide (n=52) versus placebo plus temozolomide (n=45)	All patients	Small-cell lung cancer	63 years (PARP inhibitor group) versus 62 years (placebo group)	One to three (platinum-based chemotherapy)	Parallel assignment	Quadruple	8·2 months (PARP inhibitor group) versus 7 months (placebo group)
Coleman et al (2019);[6] NCT02470585	Veliparib§	Carboplatin–paclitaxel plus veliparib followed by placebo maintenance (n=383) versus carboplatin–paclitaxel plus veliparib followed by veliparib maintenance (n=382) versus carboplatin–paclitaxel plus placebo followed by placebo maintenance (n=375)	All patients	Ovarian	62 years (PARP inhibitor followed by placebo group) versus 62 years (PARP inhibitor group) versus 62 years (placebo group)	Concomitantly or after first-line platinum-based chemotherapy	Parallel assignment	Double	28·0 months
Golan et al (2019);[37] NCT02184195	Olaparib†	Olaparib 300 mg bid (n=92) versus placebo (n=62)	Patients with *BRCA* mutations	Pancreatic	57 years (PARP inhibitor group) versus 57 years (placebo group)	One (platinum-based chemotherapy)	Parallel assignment	Quadruple	9·1 months (PARP inhibitor group) versus 3·8 months (placebo group)
González-Martín et al (2019);[20] NCT02655016	Niraparib§	Niraparib 300 mg qd (n=484) versus placebo (n=244)	All patients	Ovarian	62 years (PARP inhibitor group) versus 62 years (placebo group)	One (platinum-based chemotherapy)	Parallel assignment	Quadruple	Ongoing (>24 months)
Owonikoko et al (2019);[33] NCT01642251	Veliparib‡	Cisplatin–etoposide plus veliparib 100 mg bid (n=66) versus cisplatin–etoposide plus placebo (n=66)	All patients	Small-cell lung cancer	66 (PARP inhibitor group) versus 64 years (placebo group)	Naive	Parallel assignment	Double	18·1 months (PARP inhibitor group) versus 21·5 months (placebo group)
Ray-Coquard et al (2019);[7] NCT02477644	Olaparib§	Olaparib 300 mg bid plus bevacizumab (n=535) versus placebo plus bevacizumab (n=267)	All patients	Ovarian	61 years (PARP inhibitor group) versus 60 years (placebo group)	One (platinum-based chemotherapy)	Parallel assignment	Triple	35·5 months (PARP inhibitor group) versus 36·5 months (placebo group)

PARP=poly(ADP-ribose) polymerase. bid=twice a day. qd=once a day. g*BRCA*m=germline *BRCA* mutation. FOLFIRI=fluorouracil, folinic acid, and irinotecan. *Maintenance therapy, second-line, and subsequent lines. †For recurrent cancer. ‡First-line. §Front-line maintenance.

Table 1: **Characteristics of placebo randomised controlled trials**

were computed as median duration in months with IQR and range. For cases with data available after diagnosis of myelodysplastic syndrome or acute myeloid leukaemia, the median follow-up in months (with IQR and range) and outcome of the event were also collected (appendix p 5). The proportion of cases resulting in death were calculated as the number of fatal cases divided by total available cases.

Role of the funding source

There was no funding source for this study. The funding sources of all RCTs played no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results

Overall, 1617 citations were identified by the search strategy for our systematic review (figure 1A). After screening, we excluded 1586 citations that did not fulfil the inclusion criteria. We included 31 eligible RCTs published between March 27, 2012, and April 28, 2020, in the systematic review. Three RCTs (NCT01506609, NCT01560104, and

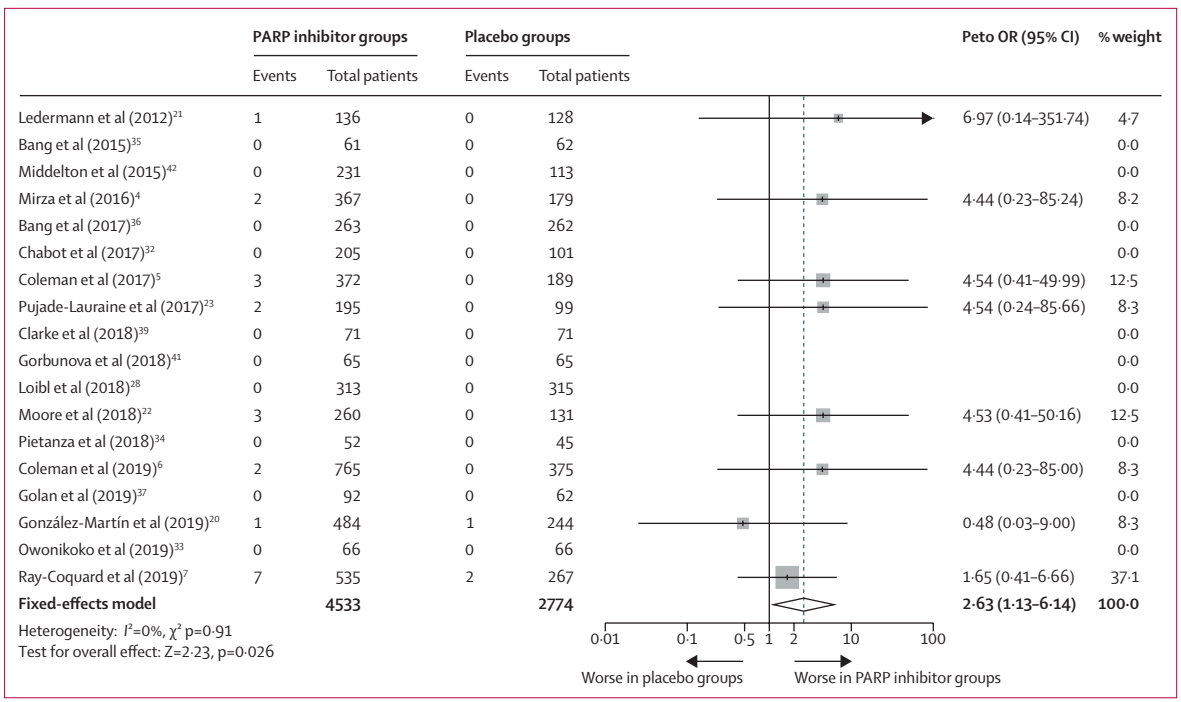

Figure 2: **Pooled analysis forest plot on the risk of therapy-related myelodysplastic syndrome and acute myeloid leukaemia with PARP inhibitors versus placebo in randomised controlled trials**

ORs are not shown for studies with no events in either arm. PARP=poly(ADP-ribose) polymerase. OR=odds ratio.

NCT01576172)[17–19] did not have data available on adverse events and were not included. 28 RCTs met the predefined criteria and were included in our safety meta-analysis. 18 studies were placebo RCTs (table 1) and 10 were non-placebo RCTs (appendix p 6), enrolling 9099 patients, of whom 5693 (62·6%) were in PARP inhibitor treatment groups and 3406 (37·4%) in control groups. 12 (42·9%) of the 28 studies were in patients with ovarian cancers,[4–7,20–27] five (17·9%) were in patients with breast cancers[28–31] including one unpublished study (NCT01818063), three (10·7%) were in patients with lung cancers,[32–34] two (7·1%) each were in patients with gastric cancers,[35,36] pancreatic cancers,[37,38] and prostate cancers,[39,40] and one (3·6%) each was in patients with colorectal cancer[41] and melanoma.[42] Olaparib was being studied in 13 (46·4%) RCTs, veliparib in 11 (39·2%), niraparib in two (7·1%), rucaparib in one (3·6%), and talazoparib in one (3·6%). Median follow-up ranged from 3·8 to 78·0 months.

Based on the 18 placebo RCTs (n=7307 patients), PARP inhibitors significantly increased the risk of myelodysplastic syndrome and acute myeloid leukaemia versus placebo treatment (Peto OR 2·63 [95% CI 1·13–6·14], p=0·026), with no heterogeneity across studies (I^2=0%, χ^2 p=0·91; figure 2). All myelodysplastic syndrome and acute myeloid leukaemia cases were reported in RCTs in ovarian cancers. Overall, six cases of acute myeloid leukaemia in two placebo RCTs were informative regarding the latency period.[7,22] The median latency period was 20·3 months (IQR 18·7–22·1) and ranged from 18·4 to 26·6 months. The incidence of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor treatment across placebo RCTs was 0·73% (95% CI 0·50–1·07; I^2=0%, χ^2 p=0·87; 21 events out of 4533 patients), across non-placebo RCTs was 1·22% (0·62–2·37; I^2=0%, χ^2 p=0·59; five events out of 1160 patients), and across all RCTs (placebo and non-placebo) was 0·83% (0·59–1·15; I^2=0%, p=0·84; 26 events out of 5693 patients; appendix p 7). PARP inhibitor therapy significantly increased the risk of myelodysplastic syndrome and acute myeloid leukaemia versus all control treatments (Peto OR 2·25 [1·07–4·75], p=0·033), with no heterogeneity across studies (I^2=0%, χ^2 p=0·80; appendix p 9). The incidence of myelodysplastic syndrome and acute myeloid leukaemia related to control treatment across placebo RCTs was 0·47% (0·26–0·85; I^2=0%, χ^2 p=1·00; three events out of 2774 patients), across non-placebo RCTs was 1·21% (0·54–2·67; I^2=0%, χ^2 p=0·90; two events out of 632 patients), and across all RCTs was 0·66% (0·41–1·05; I^2=0%, χ^2 p=1·00; five events out of 3406 patients; appendix p 8). The inverted funnel plot for the primary outcome did not suggest publication bias (appendix p 10). Risk of bias assessments for each of the included studies are summarised in the appendix (p 11; presented for individual studies on pp 12–177). According to the GRADE scale, certainty of evidence was high for both placebo RCTs and non-placebo RCTs (appendix p 178). Subgroup analyses did not show significant differences with regard to previous systemic therapy, PARP inhibitor

used, biomarker specificity, PARP inhibitor treatment setting, PARP inhibitor assignation, and, post-hoc, follow-up and PARP inhibitor treatment duration (table 2). Available data on PARP inhibitor duration are presented in the appendix (p 179). The association of PARP inhibitor therapy with myelodysplastic syndrome and acute myeloid leukaemia remained significant in sensitivity analyses with data only from ClinicalTrials.gov (Peto OR 4·79 [95% CI 1·11–20·63], p=0·035; I^2=0%, χ^2 p=1·00) and data only from published RCTs (Peto OR 1·90 [1·04–3·46], p=0·037; I^2=0%, χ^2 p=0·93; appendix p 180). Post-hoc sensitivity analyses based on trials with at least 100 patients per group and trials with at least 17 months of follow-up were also consistent with the primary result (in both analyses, Peto OR 2·63 [95% CI 1·13, 6·14], p=0·026; I^2=0%, χ^2 p=0·91; appendix pp 181). In both analyses, no events of myelodysplastic syndrome or acute myeloid leukaemia were reported in the studies removed.

On May 3, 2020, our search in VigiBase identified 178 cases of myelodysplastic syndrome (n=99) and acute myeloid leukaemia (n=79) related to PARP inhibitor therapy (figure 1B). All cases were considered serious. Patient characteristics are summarised in table 3. Median age was 64 years (IQR 58–69) and ranged from 38 to 81 years. The most common indications for PARP inhibitor use were ovarian cancer (119 [85%] of 140 patients with available data), prostate cancer (ten [7%]), and breast cancer (seven [5%]). Cases were mainly reported in Europe (89 [50%] of 178) and the Americas (79 [44%]). The number of patients diagnosed with myelodysplastic syndrome or acute myeloid leukaemia increased during the 2015–20 period, with 71 (40%) cases reported in 2019.

Duration of PARP inhibitor exposure was available in 96 of 178 cases, with a median treatment duration of 9·8 months (IQR 3·6–17·4), ranging from 0·2 to 66·8 months. The latency period of myelodysplastic syndrome and acute myeloid leukaemia from first exposure to a PARP inhibitor was available in 58 of 178 cases, for which median latency period was 17·8 months (IQR 8·4–29·2), ranging from 0·6 to 66·8 months (appendix p 182). Myelodysplastic syndrome occurred after a median of 17·8 months (IQR 8·6–27·9) from first PARP inhibitor exposure, and acute myeloid leukaemia after 20·6 months (8·4–29·7). In this cohort, acute myeloid leukaemia was reported as progressing from myelodysplastic syndrome in 14 (8%) of 178 patients (here counted as acute myeloid leukaemia) and primary neoplasm progression was reported in 13 (15%) of 85 patients with available data.

Overall, cytopenia was co-reported with myelodysplastic syndrome and acute myeloid leukaemia in 71 (40%) of the 178 cases, with the most frequent type being anaemia (24 [34%] cases; table 3). Available data (18 [25%] of 71 cases) suggested that patients experienced a cytopenia at a median of 7 months (IQR 1·4–27·0; range 0·4–40·6) after PARP inhibitor initiation. Information on previous lines of therapy before PARP inhibitor exposure were available in 13 of 178 cases and consisted mainly of platinum-based and taxane-based chemotherapy (appendix p 183).

	Peto odds ratio (95% CI)	I^2 (%); χ^2 p value	χ^2 p value for subgroup differences
Previous systemic therapy			
Naive or first line	1·93 (0·68–5·49)	0%; 0·63	..
≥Two lines	4·79 (1·11–20·63)	0%; 1·00	..
Various*	No event reported	NA	0·32
Follow-up duration, months			
<24	No event reported	NA	..
≥24	2·63 (1·13–6·14)	0%; 0·91	NA
PARP inhibitor duration, months			
0 to <12	No event reported	NA	..
12 to <18	4·54 (0·41–49·99)	NA‡	..
18 to <24	1·98 (0·56–6·98)	0%; 0·55	..
≥24†	3·03 (0·82–11·21)	0%; 0·75	0·80
PARP inhibitor			
Niraparib	1·45 (0·18–11·61)	9%; 0·29	..
Olaparib	2·58 (0·88–7·53)	0%; 0·80	0·89
Rucaparib	4·54 (0·41–49·99)	NA	..
Veliparib	4·44 (0·23–85·00)	NA	..
Biomarker specificity			
BRCA mutations	4·54 (0·71–29·15)	0%; 1·00	..
All patients	2·28 (0·88–5·91)	0%; 0·80	0·52
PARP inhibitor treatment settings			
First-line	No event reported	NA	..
Front-line maintenance	1·93 (0·68–5·49)	0%; 0·63	..
Maintenance therapy, second-line and beyond	4·79 (1·11–20·63)	0%; 1·00	0·32
Recurrent disease	No event reported	NA	..
PARP inhibitor assignation			
Monotherapy	3·33 (1·05–10·49)	0%; 0·85	..
In combination with non-PARP inhibitor therapy	1·98 (0·56–6·98)	0%; 0·55	0·55

PARP=poly(ADP-ribose) polymerase. RCT=randomised controlled trial. NA=not applicable. *Chabot et al,[32] Pietanza et al,[34] and Middleton et al.[42] †Including RCTs with ongoing treatment and unpublished data. ‡Only one study in the subgroup.

Table 2: **Subgroup analyses on the risk of therapy-related myelodysplastic syndrome and acute myeloid leukemia with PARP inhibitors versus placebo in RCTs (n=18)**

Median follow-up was 5·6 months (IQR 3·2–9·5) after diagnosis of myelodysplastic syndrome or acute myeloid leukaemia in 34 cases with available data (including one case of acute myeloid leukaemia that progressed from myelodysplastic syndrome). Outcomes were available in 104 cases, among which nine (9%) were reported as recovered or recovering, 48 (46%) were ongoing, and 47 (45%) resulted in death (table 3).

Discussion

To our knowledge, this large-scale analysis is the first to show an increased risk of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor

versus placebo treatment, and provides data on the incidence and clinical features of these rare, delayed, and life-threatening adverse events.

	All cases (n=178)	Myelodysplastic syndrome (n=99)	Acute myeloid leukaemia (n=79)
Reporting year			
Total data	178	99	79
2020	14 (8%)	5 (5%)	9 (11%)
2019	71 (40%)	45 (45%)	26 (33%)
2018	53 (30%)	23 (23%)	30 (38%)
2017	22 (12%)	15 (15%)	7 (9%)
2016	14 (8%)	8 (8%)	6 (8%)
<2015	4 (2%)	3 (3%)	1 (1%)
Reporter			
Total data	159	89	70
Health-care professional	137 (86%)	77 (87%)	60 (86%)
Non-health-care professional	22 (14%)	12 (13%)	10 (14%)
Sex			
Total data	164	89	75
Female	153 (93%)	89 (100%)	64 (85%)
Male	11 (7%)	0	11 (15%)
Age at onset, years			
Total data	117	62	55
Median (IQR)	64 (58–69)	62 (56–71)	66 (60–69)
Range	38–81	38–80	45–81
Location			
Total data	178	99	79
Americas	79 (44%)	43 (43%)	36 (46%)
Asia	5 (3%)	4 (4%)	1 (1%)
Australia	5 (3%)	3 (3%)	2 (3%)
Europe	89 (50%)	49 (49%)	40 (51%)
Indication			
Total data	140	77	63
Breast cancer	7 (5%)	5 (6%)	2 (3%)
Ovarian cancer	119 (85%)	69 (90%)	50 (79%)
Pancreatic cancer	3 (2%)	2 (3%)	1 (2%)
Prostate cancer	10 (7%)	0	10 (16%)
Vulval cancer	1 (1%)	1 (1%)	0
PARP inhibitor			
Total data	178	99	79
Niraparib	32 (18%)	18 (18%)	14 (18%)
Olaparib	133 (75%)	75 (76%)	58 (73%)
Rucaparib	10 (6%)	4 (4%)	6 (8%)
Talazoparib	1 (1%)	1 (1%)	0
Veliparib	2 (1%)	1 (1%)	1 (1%)
Primary neoplasm progression			
Total data	85	47	38
Yes	13 (15%)	11 (23%)	2 (5%)
No	72 (85%)	36 (77%)	36 (95%)
Latency period, months			
Total data	58	30	28
Median (IQR)	17·8 (8·4–29·2)	17·8 (8·6–27·9)	20·6 (8·4–29·7)
Range	(0·6–66·8)	(0·6–42·1)	(2·8–66·8)

(Table 3 continues on next page)

The efficacy of PARP inhibitors was shown in several RCTs, primarily in newly diagnosed or relapsed ovarian cancers following complete or partial response to platinum-based chemotherapy.[4–7,20,21,23,43] Since the first approval of olaparib in 2014, PARP inhibitors have become routine care for some patients with ovarian, breast, pancreatic, or prostate cancers. Additionally, data from placebo RCTs showed that a subgroup of patients without *BRCA1/2* mutation or homologous recombination deficiencies clinically benefit from PARP inhibitor maintenance treatment, even if this benefit is lower than in patients with *BRCA* mutation or homologous recombination deficiencies.[4,21,44,45] These data highlight that patients without clearly identified biomarkers could be eligible for PARP inhibitor therapies, and require a case-by-case risk–benefit assessment. Early RCTs, particularly those with short follow-up, did not identify any concerning safety signals. A small number of myelodysplastic syndrome and acute myeloid leukaemia cases were reported with longer follow-up.[45] However, due to the rare incidence of these adverse events, no causal association of PARP inhibitor therapy with myelodysplastic syndrome and acute myeloid leukaemia could be established.

All myelodysplastic syndrome and acute myeloid leukaemia cases in our meta-analysis were reported in RCTs in ovarian cancers, assessing PARP inhibitors in platinum-sensitive maintenance and front-line maintenance settings. This exclusivity for ovarian cancer might be explained by the difference in median follow-up across studies, with ovarian cancer RCTs having the longest follow-up in completed trials (around 2–6 years), thus increasing the likelihood of detecting these rare and delayed adverse events. The short follow-up in many of the RCTs might have led to an underestimation of the true incidence of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor therapy. Final analysis of the SOLO2 placebo RCT[46] (first analysis reported in Pujade-Lauraine et al[23]) in platinum-sensitive, relapsed ovarian cancer with a *BRCA1/2* mutation showed for the first time that maintenance olaparib improved median overall survival (51·7 months with olaparib *vs* 38·8 months with placebo; hazard ratio for death 0·74 [95% CI 0·54–1·00]; p=0·054). Aside from this clinical benefit, long-term follow-up of the trial (>5 years in each group) reported 16 cases of myelodysplastic syndrome or acute myeloid leukaemia in the PARP inhibitor group and four cases in the placebo group.[46]

The significant risk of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor versus placebo treatment in our safety meta-analysis, and the occurrence of these adverse events in first-line maintenance RCTs, suggest that these events might be a toxicity specific to PARP inhibitors.[6,7,20] However, due to the clinical gain in overall survival in SOLO2, we cannot exclude a competitive bias between death and myelodysplastic syndrome or acute myeloid leukaemia occurrence, and therefore we cannot exclude that these

adverse events could have a stronger association with previous lines of chemotherapy than with PARP inhibition. In 2020, data from Bolton and colleagues[47] suggested that PARP inhibitor therapy could select for acquired mutations in clonal haematopoiesis within the DNA damage response (DDR) pathway, and more so than conventional chemotherapeutic drugs. This inhibitor-driven expansion of DDR-mutated clonal haematopoiesis could increase the risk of secondary myelodysplastic syndrome and acute myeloid leukaemia. PARP inhibitor exposure could also lead to off-target epigenetic modifications, resulting in transformation of clonal haematopoiesis of indeterminate potential and subsequent myelodysplastic syndrome or acute myeloid leukaemia, given that myelodysplastic syndrome and acute myeloid leukaemia are observed with platinum-based chemotherapy and irradiation.[48] Mechanistically, the PARP and BRCA proteins are involved in the repair of DNA strand damages. Researchers also hypothesise that inherited risk factors, such as germline *BRCA1/2*, *TP53*, or *PALB2* mutations in women with ovarian or breast cancer, are associated with therapy-related myelodysplastic syndrome and acute myeloid leukaemia.[49,50] However, to date, results from the PAOLA-1 trial[7] olaparib group (four cases of myelodysplastic syndrome or acute myeloid leukaemia in *BRCA* wild-type patients and one case in *BRCA*-mutated patients) and the ARIEL-3 trial[5] rucaparib group (one case in *BRCA* wild-type patients and two cases in *BRCA*-mutated patients) do not seem to support this hypothesis. Furthermore, our subgroup analyses showed no significant difference in the risk of myelodysplastic syndrome and acute myeloid leukaemia between trials restricted to *BRCA1/2* mutation carriers and trials open to all patients. Analyses based on individual patient data and long-term follow-up data from front-line maintenance RCTs are now required to fully understand and confirm or refute these preliminary results.

We also provided the largest description of clinical features of myelodysplastic syndrome and acute myeloid leukaemia related to PARP inhibitor therapy, based on 178 cases in WHO's pharmacovigilance database. In cases with available data, median latency period from first PARP inhibitor exposure was 17·8 months and median exposure duration was 9·8 months. Our findings are in line with case reports from the PAOLA-1 trial,[7] in which two women (without *BRCA* mutation) who received olaparib for 6·9 months and 12·4 months developed acute myeloid leukaemia at 13·7 months and 6·0 months after treatment discontinuation. Unfortunately, information on latency period in other RCTs is absent.

These delays to onset of myelodysplastic syndrome and acute myeloid leukaemia are shorter than typically described with conventional chemotherapeutic drugs. A study based on records of the Surveillance, Epidemiology, and End Results (SEER) Program with a systematic long-term follow-up (2000–13) reported that 113 (0·3%) of 32 662 patients with ovarian cancers developed therapy-related myelodysplastic syndrome, with a mean latency period of 5·3 years, or acute myeloid leukaemia, with a mean latency period of 4·5 years.[51] In patients with breast cancer previously exposed to alkylating-based treatment, these periods were similar at 5·1 years for myelodysplastic syndrome and 3·8 years for acute myeloid leukaemia. Prognosis of therapy-related myelodysplastic syndrome and acute myeloid leukaemia is often poor compared with de novo cases, and influenced by disease-related and patient-related factors such as age, karyotype, comorbidities, and previous therapies.[48,52] Following diagnosis of 1619 therapy-related cases of myelodysplastic syndrome and acute myeloid leukaemia, the SEER study reported a median overall survival of 7 months and 1270 (78%) patients died. In cases of myelodysplastic syndrome and acute myeloid leukaemia in VigiBase, median age at diagnosis was 64 years, similar to published data;[51–53]

	All cases (n=178)	Myelodysplastic syndrome (n=99)	Acute myeloid leukaemia (n=79)
(Continued from previous page)			
PARP inhibitor duration, months			
Total data	96	56	40
Median (IQR)	9·8 (3·6–17·4)	9·8 (3·6–17·4)	9·4 (3·4–19·6)
Range	(0·2–66·8)	(0·2–41·6)	(0·4–66·8)
Treatment modifications			
Total data	104	64	40
Reduction	6 (6%)	3 (5%)	3 (8%)
Discontinuation	98 (94%)	61 (95%)	37 (93%)
Outcomes			
Total data	104	54	50
Recovered or recovering	9 (9%)	9 (17%)	0
Not recovered	48 (46%)	25 (46%)	23 (46%)
Deaths	47 (45%)	20 (37%)	27 (54%)
Last follow-up since case onset, months			
Total data	34	20	14
Median (IQR)	5·6 (3·2–9·5)	6·0 (3·7–9·4)	4·8 (2·0–11·2)
Range	(0·9–23·9)	(1·1–18·4)	(0·9–23·9)
Co-reporting of cytopenias*			
Total data	71	45	26
Thrombocytopenias	17 (24%)	12 (27%)	5 (19%)
Anaemias	24 (34%)	18 (40%)	6 (23%)
Neutropenias	13 (18%)	6 (13%)	7 (27%)
Pancytopenias	12 (17%)	7 (16%)	5 (19%)
Leucopenias	5 (7%)	2 (4%)	3 (12%)
Cytopenia onset from PARP inhibitor initiation, months			
Total data	18	12	6
Median (IQR)	7·0 (1·4–27·0)	7·0 (1·1–23·1)	14·6 (2·3–29·3)
Range	(0·4–40·6)	(0·4–40·6)	(0·8–29·9)

Data collection was on May 3, 2020. Cases with available data are shown in the first row for each characteristic. Percentages might not add to 100% due to rounding. PARP=poly(ADP-ribose) polymerase. *Cases of cytopenia were co-reported (before or concomitantly) with the onset of myelodysplastic syndrome and acute myeloid leukaemia.

Table 3: **Characteristics of patients diagnosed with myelodysplastic syndrome and acute myeloid leukaemia from WHO's pharmacovigilance database**

however, almost half of patients died (47 [45%] of 104 cases with available outcomes; related or unrelated to myelodysplastic syndrome or acute myeloid leukaemia), and these results are likely to be underestimated due to a short follow-up after diagnosis (5·6 months in 34 cases with available data) compared with previous studies.[51,53]

To conclude, the main adverse events related to PARP inhibition in RCTs were haematological, but usually transient and occurring during the first 3 months.[3,54] In the NOVA trial by Mirza and colleagues,[4] grade 3 or 4 thrombocytopenia, anaemia, and neutropenia were reported in 124 (34%), 93 (25%), and 72 (20%) of 367 patients with ovarian cancer receiving niraparib.[4] In a long-term efficacy, tolerability, and overall survival analysis of one RCT (first analysis reported in Ledermann et al[21]) two delayed pancytopenia events were reported in two patients in the olaparib maintenance group, which subsequently developed into myelodysplastic syndrome and lethal acute myeloid leukaemia, respectively (no pancytopenia in the placebo group).[45] In our real-world setting pharmacovigilance cohort, the most frequent co-reported cytopenia associated with the diagnosis of myelodysplastic syndrome or acute myeloid leukaemia was anaemia, followed by thrombocytopenia, neutropenia, and pancytopenia. FDA and EMA labels and RCT study protocols recommend complete blood count monitoring before and monthly after starting a PARP inhibitor. If patients have not recovered within 28 days or have persistent cytopenia following dose modification, further investigation including bone marrow analysis and blood sample for cytogenetics must be done in addition to monthly monitoring, and consideration given as to whether to discontinue the PARP inhibitor. PARP inhibitor must be discontinued if myelodysplastic syndrome or acute myeloid leukaemia, or secondary cancers are confirmed. However, this close monitoring is particularly challenging in patients who undergo long periods of PARP inhibitor therapy, as reported in the SOLO2 study, with 43 (22%) of 196 patients potentially cured after more than 5 years of olaparib treatment.[46]

The present study has three main limitations. First, rare or delayed adverse events are not comprehensively captured during a short follow-up as in some RCTs in our meta-analysis, and could be affected by treatment duration and survival data. This limitation is inherent to the design of RCTs that cannot provide long-term follow-up and might only accrue a small number of patients, as compared with the real-world target population size of the treatment. In this situation, the Peto OR is the most accurate method to detect rare adverse events,[12,13] and we were able to show an association. However, the true incidence of myelodysplastic syndrome and acute myeloid leukaemia might be underestimated in our study, and long-term prospective cohorts of patients treated with PARP inhibitors are warranted to improve accuracy. Second, adverse events from RCTs can be accessed from a variety of sources and discrepancies might exist between them. We chose to prioritise events from the ClinicalTrials.gov registry as it comprehensively reports all serious adverse events, as opposed to published data, and we assumed that online safety data represent a more powerful tool due to regular updates and completeness of serious adverse event reporting even after publication.[10] Furthermore, our sensitivity analysis of each source showed consistency in our findings, possibly explained by myelodysplastic syndrome and acute myeloid leukaemia being considered as serious conditions in almost every case (eg, myelodysplastic syndrome and acute myeloid leukaemia are always grade 3 or higher according to the CTCAE classification). Finally, adverse events are under-reported to VigiBase despite it covering more than 21 million reports of adverse events, and data come from heterogeneous sources (both health-care and non-health-care practitioners). In addition, detailed clinical information such as *BRCA1/2* status or last follow-up outcome since myelodysplastic syndrome or acute myeloid leukaemia onset are missing.

Aside from improving progression-free survival, and, as recently observed, overall survival, PARP inhibitors increased the risk of myelodysplastic syndrome and acute myeloid leukaemia versus placebo in our safety meta-analysis. Myelodysplastic syndrome and acute myeloid leukaemia cases related to PARP inhibitor therapy appear to be rare and delayed adverse events, associated with a substantial proportion of deaths. Further research and individual patient data are needed to improve understanding and define patient-specific risk factors and susceptibility to these adverse events, particularly in the front-line maintenance setting. Clinicians need to remain vigilant in evaluating delayed haematological toxicities in patients treated with PARP inhibitors.

Contributors

P-MM, AL, CD, and JA conceived and designed the study. P-MM and JA did the literature search. P-MM, AL, CD, and JA drafted the manuscript. All authors acquired, analysed, or interpreted data. P-MM, CD, and JA had access to and verified the data. All authors critically revised the manuscript for intellectual content. CD, BC, AL, and JA provided administrative, technical, or material support.

Declaration of interests

AL reports reports fees to her institution for consulting from AstraZeneca, Clovis, GlaxoSmithKline, Biocad, Ability Pharma, Merck Serono, Tesaro, Merck Sharp & Dohme, Seattle Genetics, GamaMabs Pharma, and Gritstone Oncology, grants from Inivata and Sanofi, personal fees for consulting from Biocad, Gridstone Oncology, and Seattle Genetics, and non-financial support from AstraZeneca, Roche, Clovis, and Tesaro, outside the submitted work. KM reports personal fees from AstraZeneca, Genentech/Roche, Immunogen, Clovis, Tesaro, Janssen, Aravive, VBL Therapeutics, OncoMed Pharmaceuticals, Samumed, Eisai, Vavotar, AbbVie, and Tarveda, and grants from Lilly, outside the submitted work. EMO'R reports grants and personal fees from AstraZeneca, Celgene, and Polaris, personal fees from Merck, Ipsen, Rafael Therapeutics, CytomX Therapeutics, Sobi, Eisai, and Bayer, and grants from BioAtla and Silenseed, outside the submitted work. IR-C reports personal fees from Clovis and Amgen, and grants and personal fees from

AstraZeneca, Roche, and GlaxoSmithKline, outside the submitted work. AG-M reports personal fees from AstraZeneca, PharmaMar, Roche, and Tesaro for speaker and advisory roles, from Clovis, GenMab, ImunoGen, Merck Sharp & Dohme, and Oncoinvent for advisory roles, financial support from Roche and Tesaro (for the ANITA/GEICO trial), and non-financial support from Tesaro (for the PRIMA study), outside the submitted work. All other authors declare no competing interests.

Data sharing

Data from the safety meta-analysis are freely and publicly available on ClinicalTrials.gov. At this time, data from VigiBase (the WHO global pharmacovigilance database of individual case safety reports) are only available for national pharmacovigilance centres and the Uppsala Monitoring Centre. Public access to overview statistics from VigiBase can be gained via the VigiAccess website.

Acknowledgments

We thank the custom searches team at the Uppsala Monitoring Centre research section for providing data from VigiBase, without whom this study would not have been possible. The information presented in this study does not represent the opinion of the Uppsala Monitoring Centre or WHO. P-MM was supported by the Cancer Institut Thématique Multi-Organisme of the French National Alliance for Life and Health Sciences Plan Cancer 2014–2019 (doctoral grant).

References

1 Mateo J, Lord CJ, Serra V, et al. A decade of clinical development of PARP inhibitors in perspective. *Ann Oncol* 2019; **30:** 1437–47.

2 Ruscito I, Bellati F, Ray-Coquard I, et al. Incorporating PARP-inhibitors in primary and recurrent ovarian cancer: a meta-analysis of 12 phase II/III randomized controlled trials. *Cancer Treat Rev* 2020; **87:** 102040.

3 LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol* 2019; **20:** e15–28.

4 Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016; **375:** 2154–64.

5 Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **390:** 1949–61.

6 Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. *N Engl J Med* 2019; **381:** 2403–15.

7 Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med* 2019; **381:** 2416–28.

8 Zorzela L, Loke YK, Ioannidis JP, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016; **352:** i157.

9 National Cancer Institute. NCI guidelines: adverse event reporting requirements. Sept 16, 2013. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf (accessed Dec 8, 2020).

10 Hartung DM, Zarin DA, Guise J-M, McDonagh M, Paynter R, Helfand M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Ann Intern Med* 2014; **160:** 477–83.

11 Faillie J-L, Ferrer P, Gouverneur A, et al. A new risk of bias checklist applicable to randomized trials, observational studies, and systematic reviews was developed and validated to be used for systematic reviews focusing on drug adverse events. *J Clin Epidemiol* 2017; **86:** 168–75.

12 Morton S, Murad M, O'Connor E, et al. Methods guide for effectiveness and comparative effectiveness reviews. Quantitative synthesis—an update. Agency for Healthcare Research and Quality. Feb 23, 2008. https://www.ncbi.nlm.nih.gov/books/NBK519365/ (accessed March 18, 2020).

13 Guirguis-Blake JM, Beil TL, Senger CA, Coppola EL. Primary care screening for abdominal aortic aneurysm: updated evidence report and systematic review for the US preventive services task force. *JAMA* 2019; **322:** 2219–38.

14 Sedgwick P. Relative risks versus odds ratios. *BMJ* 2014; **348:** 7.

15 Ranganathan P, Aggarwal R, Pramesh CS. Common pitfalls in statistical analysis: odds versus risk. *Perspect Clin Res* 2015; **6:** 222–24.

16 Deeks JJ, Higgins JPT, Altman DG, on behalf of the Cochrane Statistical Methods Group. In: Higgins J, Thomas J, eds. Cochrane handbook for systematic reviews of interventions. Version 6.1, 2020. https://training.cochrane.org/handbook/current/chapter-10#section-10-10-2 (accessed Dec 4, 2020).

17 Han HS, Diéras V, Robson M, et al. Veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with *BRCA1/2* locally recurrent/metastatic breast cancer: randomized phase II study. *Ann Oncol* 2018; **29:** 154–61.

18 Ramalingam SS, Blais N, Mazieres J, et al. Randomized, placebo-controlled, phase II study of veliparib in combination with carboplatin and paclitaxel for advanced/metastatic non-small cell lung cancer. *Clin Cancer Res* 2017; **23:** 1937–44.

19 Hussain M, Daignault-Newton S, Twardowski PW, et al. Targeting androgen receptor and DNA repair in metastatic castration-resistant prostate cancer: results from NCI 9012. *J Clin Oncol* 2018; **36:** 991–99.

20 González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2019; **381:** 2391–402.

21 Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012; **366:** 1382–92.

22 Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018; **379:** 2495–505.

23 Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; **18:** 1274–84.

24 Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. *Lancet Oncol* 2015; **16:** 87–97.

25 Kaye SB, Lubinski J, Matulonis U, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly(ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer. *J Clin Oncol* 2012; **30:** 372–79.

26 Kummar S, Oza AM, Fleming GF, et al. Randomized trial of oral cyclophosphamide and veliparib in high-grade serous ovarian, primary peritoneal, or fallopian tube cancers, or *BRCA*-mutant ovarian cancer. *Clin Cancer Res* 2015; **21:** 1574–82.

27 Penson RT, Valencia RV, Cibula D, et al. olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline *BRCA1/2* mutation (SOLO3): a randomized phase III trial. *J Clin Oncol* 2020; **38:** 1164–74.

28 Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol* 2018; **19:** 497–509.

29 Kummar S, Wade JL, Oza AM, et al. Randomized phase II trial of cyclophosphamide and the oral poly (ADP-ribose) polymerase inhibitor veliparib in patients with recurrent, advanced triple-negative breast cancer. *Invest New Drugs* 2016; **34:** 355–63.

30 Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation. *N Engl J Med* 2018; **379:** 753–63.

31 Robson M, Im S-A, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. *N Engl J Med* 2017; **377:** 523–33.

32 Chabot P, Hsia T-C, Ryu J-S, et al. Veliparib in combination with whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer: results of a randomized, global, placebo-controlled study. *J Neurooncol* 2017; **131:** 105–15.

33 Owonikoko TK, Dahlberg SE, Sica GL, et al. Randomized phase II trial of cisplatin and etoposide in combination with veliparib or placebo for extensive-stage small-cell lung cancer: ECOG-ACRIN 2511 study. *J Clin Oncol* 2019; **37:** 222–29.

34 Pietanza MC, Waqar SN, Krug LM, et al. Randomized, double-blind, phase II study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. *J Clin Oncol* 2018; **36:** 2386–94.

For **VigiAccess** see http://www.vigiaccess.org/

35 Bang Y-J, Im SA, Lee KW, et al. Randomized, double-blind phase II trial with prospective classification by ATM protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer. *J Clin Oncol* 2015; **33:** 3858–65.

36 Bang Y-J, Xu R-H, Chin K, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; **18:** 1637–51.

37 Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. *N Engl J Med* 2019; **381:** 317–27.

38 O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline *BRCA/PALB2* mutation. *J Clin Oncol* 2020; **38:** 1378–88.

39 Clarke N, Wiechno P, Alekseev B, et al. Olaparib combined with abiraterone in patients with metastatic castration-resistant prostate cancer: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2018; **19:** 975–86.

40 de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med* 2020; **28:** 2091–102.

41 Gorbunova V, Beck JT, Hofheinz R-D, et al. A phase 2 randomised study of veliparib plus FOLFIRI±bevacizumab versus placebo plus FOLFIRI±bevacizumab in metastatic colorectal cancer. *Br J Cancer* 2019; **120:** 183–89.

42 Middleton MR, Friedlander P, Hamid O, et al. Randomized phase II study evaluating veliparib (ABT-888) with temozolomide in patients with metastatic melanoma. *Ann Oncol* 2015; **26:** 2173–79.

43 Tomao F, Bardhi E, Di Pinto A, et al. PARP inhibitors as maintenance treatment in platinum sensitive recurrent ovarian cancer: an updated meta-analysis of randomized clinical trials according to *BRCA* mutational status. *Cancer Treat Rev* 2019; **80:** 101909.

44 González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2019; **381:** 2391–402.

45 Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer* 2018; **119:** 1075–85.

46 Poveda A, Floquet A, Ledermann JA, et al. Final overall survival (OS) results from SOLO2/ENGOT-ov21: a phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a *BRCA* mutation. *Proc Am Soc Clin Oncol* 2020; **38** (suppl)**:** 6002 (abstr).

47 Bolton KL, Moukarzel LA, Ptashkin R, et al. The impact of poly ADP ribose polymerase (PARP) inhibitors on clonal hematopoiesis. *Proc Am Soc Clin Oncol* 2020; **38** (suppl)**:** 1513 (abstr).

48 Short NJ, Rytting ME, Cortes JE. Acute myeloid leukaemia. *Lancet* 2018; **392:** 593–606.

49 McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. *Nat Rev Cancer* 2017; **17:** 513–27.

50 Churpek J, Marquez R, Neistadt B, et al. Inherited mutations in cancer susceptibility genes are common among breast cancer survivors who develop therapy-related leukemia. *Cancer* 2016; **122:** 304–11.

51 Morton LM, Dores GM, Schonfeld SJ, et al. Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. *JAMA Oncol* 2019; **5:** 318–25.

52 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:** 190–95.

53 Takeyama K, Seto M, Uike N, et al. Therapy-related leukemia and myelodysplastic syndrome: a large-scale Japanese study of clinical and cytogenetic features as well as prognostic factors. *Int J Hematol* 2000; **71:** 144–52.

54 Musella A, Bardhi E, Marchetti C, et al. Rucaparib: an emerging PARP inhibitor for treatment of recurrent ovarian cancer. *Cancer Treat Rev* 2018; **66:** 7–14.