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Risk of secondary myelodysplastic syndromes and acute myeloid leukaemia following poly(ADP-ribose) polymerase inhibitor treatment for advanced-stage recurrent ovarian cancer: A retrospective cohort study in England

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ABSTRACT

Background: Poly(ADP-ribose) polymerase inhibitors (PARPi) maintenance therapies are used to treat advanced ovarian cancer in first line and recurrent settings. Because of concerns about associations between PARPi therapy and secondary cancers myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML), a meta-analysis of clinical trials was conducted, reporting MDS/AML incidence of 0.73 %; however, clinical trial populations are highly selective and may not reflect incidence in the wider population.
Methods: This retrospective cohort study calculated incidence of MDS/AML within five years of completing first-line chemotherapy + /- PARPi maintenance for recurrent, advanced-stage ovarian cancer. Absolute and relative risks were calculated and compared to meta-analysis.
Results: Of 11,531 included patients, 1529 received PARPi and 10,002 chemotherapy only. Absolute risk of MDS/AML was 0.3 % (n = 5/1529) for chemotherapy + PARPi maintenance therapy versus 0.1 % (n = 10/10,002) for chemotherapy alone. Relative risk was 2.97 (95 % CI 1.02, 8.68, p = 0.046) in patients receiving PARPi maintenance versus chemotherapy alone.
Discussion: Relative risk of MDS/AML was greater in patients treated with PARPi; however, absolute risk was low in both treatment groups and lower than in the meta-analysis of trials. This analysis suggests small increased relative risk of MDS/AML associated with PARPi maintenance versus chemotherapy only, but not increased absolute risk.

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1. Background

Ovarian cancer cause around 4100 deaths in the UK annually [1]. Most patients are diagnosed at advanced stages of disease, with poor prognosis. Despite best practice treatment of optimal debulking surgery and platinum-based neo/adjuvant chemotherapy, around 75 % of patients will relapse within 18 months following completion of first-line platinum-based chemotherapy [2].

Poly(ADP-ribose) polymerase inhibitors (PARPi) are a novel class of systemic anti-cancer therapy used as maintenance treatment for patients with advanced-stage OC who have responded to their most recent line of chemotherapy, defined as control of disease for at least six months [3]. Approved PARPi drugs olaparib, niraparib and rucaparib have revolutionised ovarian cancer treatment, providing a novel treatment modality in first-line and recurrent settings and improving progression-free survival by up to 73 % [4].

Common toxicities associated with PARPi include fatigue, cytopaenias, nausea, vomiting, diarrhoea, indigestion and cough [4] [5]. Despite the potential for adverse events, PARPi toxicity profiles are generally favourable compared to cytotoxic chemotherapy, allowing PARPi to be taken for long periods as maintenance therapies. Due to their relatively recent introduction, understanding of long-term toxicity is limited. In particular, concerns about potential associations between PARPi use and serious haematological conditions, including myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been a focus of clinical trial safety follow-up. MDS is often diagnosed following low peripheral blood cells counts and confirmed by bone marrow sampling and genetic testing [6]. Patients may exhibit symptoms of fatigue and shortness of breath, or experience frequent, recurrent infections often associated with low blood cell counts. For these patients, outcomes are poor, with median survival reported as 4–8 months from diagnosis [7] [8].

Clinical trial safety follow-up suggests greater MDS/AML incidence in patients treated with PARPi than chemotherapy alone [9]. A meta-analysis of trials found a 0.73 % incidence (95 % CI 0.5,1.07) of MDS or AML in patients receiving PARPi, compared to 0.47 % (95 % CI 0.26–0.85) in those receiving placebo following first-line chemotherapy [9]. This meta-analysis found greater risk for patients treated with PARPi maintenance in recurrent settings, with an odds ratio of 4.79 (95 % CI 1.11, 20.63) in the recurrent setting versus 1.93 (95 % CI 0.68, 5.49) in the front-line.

BReast-CAncer mutant status [10] and previous treatment with cytotoxic chemotherapy are known to be associated with secondary haematological cancer incidence [11]. However, there are difficulties in assessing risks associated with chemotherapy and PARPi in patients who have received both treatments.

The availability of national, population-level data for cancer patients treated in England provides the opportunity to study incidence of these secondary cancers in the routine care population, and compare findings to the published meta-analysis to assess whether clinical trial follow-up accurately represents true incidence in the "real-world" population.

2. Methods

2.1. Data sources

National Cancer Registration Dataset (Cancer Registry) [12], Systemic Anti-Cancer Therapy (SACT) Dataset [13] and Hospital Episode Statistics (HES) [14] were used, containing diagnostic and treatment data for cancer patients in England. Reporting of systemic treatment data from National Health Service cancer treating hospitals in England has been mandatory since 2014, and is clinically coded by specialist Cancer Registration Officers. The Cancer Registry contains patient-level demographic information and tumour-specific information such as cancer diagnosis, defined by International Classification of Diseases (ICD-10) codes [15]), diagnosis date, stage, tumour morphology and other data. The SACT Dataset records systemic treatments and secondary MDS/AML diagnosis are recorded in the Cancer Registry and HES data. Patient-level data, systemic treatment data and hospital appointment and admission data were linked using common pseudonymised identifiers, with almost all patients are represented in each data source. The datasets contained information for patients diagnosed with cancer up to and including 31/12/2019.

MDS/AML diagnoses were identified from Cancer Registry and HES records, specified by ICD-10 codes D46 (MDS) and C92 (AML) including subcategories. This method was used to identify any record of secondary MDS or AML diagnosis in the data sources available. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [16].

2.2. Study design, setting and population

This retrospective cohort study was conducted in the period 01/01/2014–31/12/2019 to match the period when PARPi began to be used in clinical practice. The start date of 01/01/2014 was defined to exclude patients treated before chemotherapy data reporting became mandatory to minimise missing data issues [13]. Line of therapy was assigned algorithmically using a period of $>$ 120 days between treatments as initiation of a new line of therapy, based upon clinical guidance from oncologists involved in the study design. Duration of PARPi was defined as time from initiation to final PARPi treatment, including a standard cycle length of 28 days.

2.3. Eligibility criteria

Women $\geq$ 18 years of age with a primary diagnosis of ovarian, fallopian tube or primary peritoneal cancer (ICD-10 codes C56, C57 or C48 respectively) and advanced-stage III-IV disease according to International Federation of Gynaecology (FIGO) staging criteria were eligible. Borderline ovarian tumours and ovarian sarcomas were excluded.

Patients were required to initiate first-line treatment chemotherapy (+/- bevacizumab maintenance) within 90 days of diagnosis. Patients receiving PARPi were included only if they had a record of $\geq$ 2 cycles of PARPi therapy to ensure that included patients were not prescribed one cycle only, which may not have been dispensed or taken. Patients who switched PARPi therapy (i.e. received two different PARPi in the same line of therapy) were also excluded. Each new record of PARPi treatment was assumed to be a new cycle of therapy [17]. Patients in the control group (chemotherapy only) may have received first-line and recurrent chemotherapy treatment.

2.4. Study outcome

The primary outcome was secondary diagnosis of MDS or AML within 5-years of completion of first-line chemotherapy (defined as 8 weeks after the final carboplatin/paclitaxel treatment), based on the eligibility period for PARPi maintenance therapy [3]. A five-year follow-up period was selected as MDS/AML usually occurs within 2 years of treatment initiation [18]; therefore this period allowed for comparison within a standard follow-up period. The background rate of secondary MDS/AML in the advanced ovarian cancer population was calculated for all patients regardless of treatment strategy for comparison. The event rate was also investigated in patients who received 1 cycle of PARPi only; however, these patients were not included in the primary analysis cohort.

2.5. Statistical analysis plan

Absolute risk was calculated as the proportion of patients with an MDS or AML diagnosis within 5 years of completing first-line chemotherapy. Relative risk was calculated as the ratio of MDS/AML in the PARPi treatment group compared to chemotherapy alone, according to

standard formula [19]. Relative risk was unadjusted and compared by treatment strategy only. Time to diagnosis from the index date to was calculated and reported as median time in days with interquartile range. Patients treated with PARPi for recurrent disease were identified by algorithmic assignment of lie of therapy using systemic treatment dates. Incidence of secondary MDS/AML was then compared to the meta-analysis of clinical trial safety follow-up data.

2.6. Missing data handling

For patients with missing cancer stage data, treatment with bevacizumab or PARPi was used to assign an 'advanced-stage' status to allow for inclusion in the study. Other incomplete data fields such as height, weight and performance status were not considered pivotal to conduct this descriptive study, as the main exposure of interest was chemotherapy + /- PARPi, and the primary outcome was secondary MDS/AML diagnosis. No multiple imputation or other missing data handling methods were therefore employed. BRCA status and platinum sensitivity are not routinely recorded in the datasets available; therefore these patient factors could not be incorporated into the analysis.

3. Results

11,531 patients were included in the study. 1529 patients were treated with chemotherapy + PARPi, and 10,002 were treated with chemotherapy alone. 8384 (73 %) patients received first-line carboplatin/doublet chemotherapy, 2975 (26 %) first-line carboplatin single agent, and 172 (1 %) with other combinations including cisplatin. Median follow-up time was 5.87 years (IQR 3.95, 7.06). Exclusion criteria are illustrated in Fig. 1.

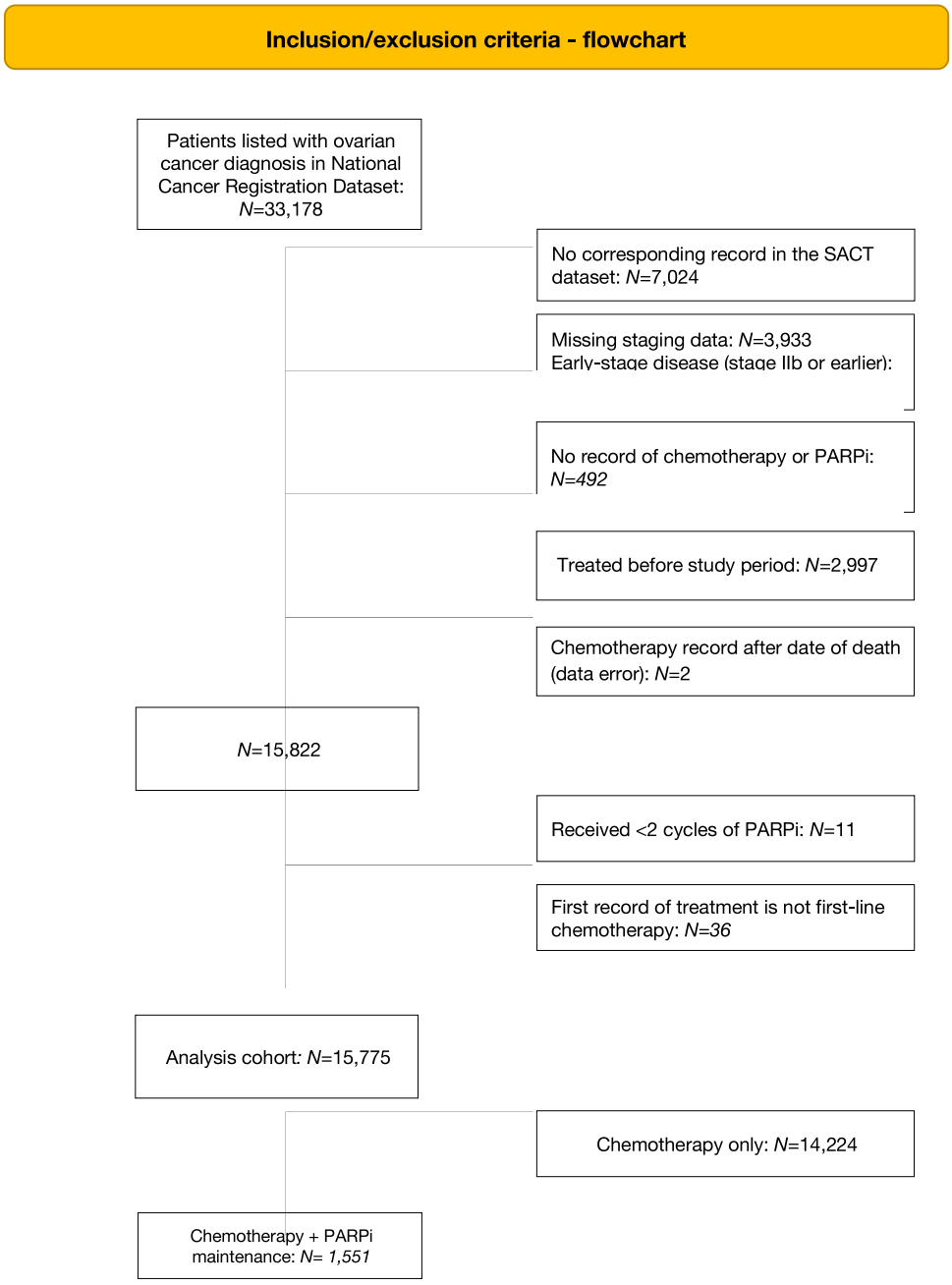

Fig. 1. Flowchart showing specification of study population by exclusion criteria.

Median age at start of treatment was 68 years (IQR 59, 75), with lower median age in the PARPi treatment group (63, IQR 55, 70) compared to chemotherapy alone (69, IQR 60, 76). Median duration of PARPi therapy for recurrent disease was 205 days (IQR 112, 395). Table 1 summarises the baseline characteristics of the study cohort.

Table 1
Baseline characteristics of the study cohort by chemotherapy only and chemotherapy + poly(ADP-ribose) polymerase inhibitor treatment groups.

Characteristic, *n*, (%)	Overall N = 11,531[a]	Chemotherapy only N = 10,002[a]	Chemotherapy + PARPiN = 1529[a]
Age at start of treatment, median, years (IQR)	68 (59, 75)	69 (60, 76)	63 (55, 70)
< 50	1057 (9.2 %)	857 (8.6 %)	200 (13 %)
50–60	2122 (18 %)	1687 (17 %)	435 (28 %)
60–70	3593 (31 %)	3048 (30 %)	545 (36 %)
> 70	4759 (41 %)	4410 (44 %)	349 (23 %)
Cancer stage, n (%)			
3	694 (6.0 %)	621 (6.2 %)	73 (4.8 %)
3A	638 (5.5 %)	562 (5.6 %)	76 (5.0 %)
3B	715 (6.2 %)	616 (6.2 %)	99 (6.5 %)
3C	5188 (45 %)	4477 (45 %)	711 (47 %)
4	2503 (22 %)	2237 (22 %)	266 (17 %)
4A	594 (5.2 %)	531 (5.3 %)	63 (4.1 %)
4B	954 (8.3 %)	824 (8.2 %)	130 (8.5 %)
Advanced (unspecified)	245 (2.1 %)	134 (1.3 %)	111 (7.3 %)
Body mass index, median (IQR)	26.0 (22.8, 30.1)	25.9 (22.7, 29.8)	26.8 (23.2, 31.2)
Index of multiple deprivation			
1 - most deprived	1728 (15 %)	1543 (15 %)	185 (12 %)
2	2085 (18 %)	1826 (18 %)	259 (17 %)
3	2496 (22 %)	2166 (22 %)	330 (22 %)
4	2591 (22 %)	2260 (23 %)	331 (22 %)
5 - least deprived	2631 (23 %)	2207 (22 %)	424 (28 %)
Ethnicity			
Asian	418 (3.6 %)	356 (3.6 %)	62 (4.1 %)
Black	178 (1.5 %)	151 (1.5 %)	27 (1.8 %)
Mixed Race	42 (0.4 %)	37 (0.4 %)	5 (0.3 %)
Other	148 (1.3 %)	120 (1.2 %)	28 (1.8 %)
Unknown	328 (2.8 %)	280 (2.8 %)	48 (3.1 %)
White	10,417 (90 %)	9058 (91 %)	1359 (89 %)
Region			
East of England	1359 (12 %)	1176 (12 %)	183 (12 %)
London	1551 (13 %)	1290 (13 %)	261 (17 %)
Midlands	1771 (15 %)	1611 (16 %)	160 (10 %)
North East & Yorkshire	2059 (18 %)	1793 (18 %)	266 (17 %)
North West	1467 (13 %)	1246 (12 %)	221 (14 %)
South East	1877 (16 %)	1633 (16 %)	244 (16 %)
South West	1446 (13 %)	1252 (13 %)	194 (13 %)
Missing/Unknown	1	1	-
Chemotherapy regimen (first-line)			
Carboplatin + paclitaxel	8384 (73 %)	6997 (70 %)	1387 (90 %)
Carboplatin single agent	2975 (26 %)	2845 (28 %)	130 (9 %)
Other first-line chemotherapy regimen	172 (1 %)	160 (2 %)	12 (1 %)
PARPi treatment			
Niraparib	53 (4 %)	-	53 (4 %)
Olaparib	368 (24 %)	-	368 (24 %)
Rucaparib	1108 (72 %)	-	1108 (72 %)

[2] Fisher's exact test; Wilcoxon rank sum exact test; Wilcoxon rank sum test; Pearson's Chi-squared test
[a] n (%); Median (IQR)

3.1. Risk of MDS or AML

Absolute risk of MDS *or* AML diagnosis within 5 years of first-line chemotherapy completion was 0.33 % (n = 5/1529) in patients treated with PARPi and < 0.1 % in patients treated with platinum-based chemotherapy only (n = 10/10,002). Absolute risk was greater in the PARPi treatment group, but was not statistically significant in each case (p = 0.13 MDS, p = 0.14 AML, Pearson's Chi-squared test, Table 2). Relative risk of MDS or AML diagnosis was 2.97 (95 % CI 1.02, 8.68, p = 0.046) in patients treated with PARPi versus chemotherapy alone. The background rate of MDS/AML for ovarian cancer patients treated with any systemic therapy was 0.28 % (n = 94/33,737). The median time from completion of first-line chemotherapy to secondary MDS or AML diagnosis was 1377 days (IQR 709, 1554) in patients treated with PARPi and 525 days (IQR 215, 875) in patients treated with chemotherapy alone. Time to diagnosis did not differ significantly between treatment groups (p = 0.2). No cases of secondary MDS/AML were identified for patients who received only one cycle of PARPi (N = 171, Supplementary Table 1). Risk of MDS/AML diagnoses is summarised in Table 2.

3.2. Comparison of incidence to RCTs

MDS/AML incidence was 0.5 % (N = 2/368) in patients treated with olaparib in the recurrent setting, compared to 2.25 % in SOLO3. MDS/AML incidence was 0.3 % (N = 3/1108) for patients treated with niraparib in the recurrent setting, compared 1.36 % in the NOVA trial. No events occurred in patients treated with rucaparib for recurrent disease. Comparison to clinical trial safety follow-up data are shown in Table 3.

3.3. Missing data handling

245 patients with missing cancer stage data were identified as advanced-stage by a record of treatment with PARPi or bevacizumab and were included in the study cohort. 94.2 % of patients (N = 10,865) in the study cohort had corresponding HES records for diagnoses made in outpatient, admitted care, or A&E settings. BMI data were complete for 82.2 % of patients.

4. Discussion

In this real-world analysis, absolute risk of MDS or AML was low in both treatment groups. 0.33 % of patients treated with PARPi (n = 5/1529) developed MDS or AML, a small but significantly greater risk than in patients treated with chemotherapy alone (0.1 %, n = 10/10,002, p = 0.039). Relative risk was significantly greater in the PARPi treatment group versus chemotherapy alone (2.97, 95 % CI 1.02, 8.68 p = 0.046). Median time to diagnosis did not differ significantly between treatment groups, suggesting PARPi therapy was not associated with faster development of secondary disease.

The low absolute risk of secondary MDS or AML across both treatment groups (<0.1 %, n = 15/11,531) suggests that these conditions occur infrequently in patients treated with chemotherapy + /- PARPi maintenance therapy, in concordance with other publications examining this issue [20]. MDS/AML incidence in the English population was lower than the overall 0.73 % value identified in the meta-analysis conducted by Morice et al. for patients receiving chemotherapy either with or without PARPi [9].

Whilst absolute risk for MDS/AML was low in the routine care population, the relative risk of 2.97 supports an increased risk of secondary MDS/AML associated with PARPi therapy versus chemotherapy alone, in agreement with Morice et al. [9] and other observational analyses [21] [22]. Incidence in patients treated with PARPi was also greater than incidence in the background patient population, further supporting an association between PARPi and increased relative risk of secondary MDS/AML. We do however acknowledge that the sample size

Table 2
Myelodysplastic syndrome and acute myeloid leukaemia diagnoses compared between chemotherapy only and chemotherapy + poly(ADP-ribose) polymerase (PARPi) inhibitor treatment groups.

Characteristic, *n*, (%)	Overall N = 11,531	Chemotherapy only N = 10,002	PARPi + chemotherapyN = 1529[b]	p-value[c]
Myelodysplastic syndrome	5 (0.04 %)	3 (0.03 %)	2 (0.13 %)	0.13
Acute myeloid leukaemia	10 (0.09 %)	7 (0.07 %)	3 (0.2 %)	0.14
Time to diagnosis, median, days (IQR)	709 (215, 1377)	524 (215, 875)	1377 (709, 1554)	0.2

[b] n (%); Median (IQR)
[c] Fisher's exact test; Wilcoxon rank sum exact test; Wilcoxon rank sum test; Pearson's Chi-squared test

Table 3
Comparison of myelodysplastic syndrome and acute myeloid leukaemia incidence in the National Cancer Registration Dataset compared to safety follow-up reporting from key RCTs for poly(ADP-ribose) polymerase (PARPi) inhibitors; SOLO3 (olaparib, recurrent setting) [25], NOVA (niraparib, recurrent setting) [28], ARIEL3 (niraparib, recurrent setting) [5].

PARP-inhibitor	Recurrent (N = 1529)		
	N	MDS/AML incidence (N), Cancer Registry	Incidence (RCT)
Olaparib	368	0.5 % (N = 2)	2.25 % (SOLO3)
Niraparib	1108	0.3 % (N = 3)	1.36 % (NOVA)
Rucaparib	53	0 %	3.7 % (ARIEL3)

of patients treated with PARPi and the event rate for MDS/AML diagnosis in the national patient population were low due to period of data coverage available for study, limiting the conclusions that can be drawn from this analysis.

This analysis allowed for comparison of MDS/AML incidence in routine care to RCT safety follow-up data. In SOLO3 [23], (olaparib, recurrent disease), MDS or AML incidence was 2.25 % compared to 0.5 % in the observational cohort. Comparing these findings to the NOVA [24] (niraparib, recurrent setting), our analysis observed MDS/AML incidence of 0.2 % in the real-world cohort compared to 1.36 % in trial follow-up. No patients diagnosed with MDS or AML treated with rucaparib were identified in this analysis, the sample size of 53 patients treated with rucaparib was very small and therefore limited comparison to RCTs. In summary, these findings do not suggest findings suggest that incidence is greater in the English routine care population than clinical trial safety follow-up.

Survival outcomes for patients diagnosed with advanced-stage OC are poor, and the clinical significance of a small risk of MDS/AML must be weighed against the survival benefit from PARPi therapy. With significant reductions in disease progression and death following PARPi maintenance therapy for recurrent disease (38 % in SOLO3 [25], 73 % in NOVA [4] and 77 % in ARIEL3 [26]), the 0.5 % incidence rate in this analysis is unlikely to represent a significant risk for patients undergoing systemic treatment for ovarian cancer. It is important to acknowledge however that outcomes are poor for OC patients diagnosed with secondary MDS/AML.

5. Strengths and limitations

The major strength of this study is the near-total population coverage of the cancer patient population in England. As far as we are aware, this is the largest observational study of its kind to assess MDS/AML incidence in the national, routine care OC population in England. There were, however, limitations owing to the use of observational data. Due to the availability of data in the SACT Dataset for patients diagnosed with cancer up to 31/12/2019, and the relatively recent introduction of PARPi (2014 onwards for recurrent disease, 2019 for front-line), the sample size for patients treated with PARPi was limited. This limited our ability to investigate incidence in the first-line setting, and led to the decision to investigate patients treated for recurrent disease only. There was also the potential for some secondary diagnoses of MDS/AML in the NCRD not being recorded, due to the known reporting lag previously been described [27]. To account for this, we designed our study to identify secondary diagnoses within 5 years of completion of first-line chemotherapy to compare equal lengths of follow-up in each treatment arm. We acknowledge that the limited sample size and low event rate for these conditions limited the statistical power needed to compare incidence rates and time to diagnosis, guiding this work to be presented as a descriptive study. Despite these limitations, the analysis supports greater relative risk of MDS or AML in patients treated with PARPi maintenance compared to chemotherapy alone. We believe that these results have high external validity, as we used population-based registries to address this research question.

6. Conclusions

Relative risk of developing MDS or AML was greater in patients treated with PARPi maintenance than with chemotherapy alone; however, absolute risk in both groups was low. This analysis of observational data did not suggest greater MDS/AML incidence in English patients compared to the RCT population, acknowledging the limitations discussed. These findings suggest low incidence of secondary MDS/AML in patients treated with PARPi maintenance therapy; however, clinicians should remain vigilant for patients at high risk of developing these conditions.

Ethics approval and consent to participate

Ethical approval for use of pseudonymised National Cancer Registration Dataset, Systemic Anti-Cancer Therapy and Hospital Episode Statistics datasets for research into risks and benefits of cancer treatment was given favourable opinion given 10/06/2019 by Research Ethics Committee, reference 19/NS/0057. There were no human participants in this data-only study and therefore no consent to participate was required.

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Author contributions

LS: study inception, protocol development, programming and data analysis, manuscript writing, article submission; SN; project supervision and clinical oversight, manuscript editing, PC; project supervision and clinical oversight, manuscript editing, KM; project supervision, development of protocol, data analysis, manuscript editing, DD; project supervision and clinical oversight, manuscript editing, ZW; assistance with data analysis, manuscript editing, AP; clinical oversight, manuscript editing, BPS; clinical oversight, manuscript editing, LW; project supervision, development of protocol, manuscript editing

CRediT authorship contribution statement

Steventon Luke: Writing – review & editing, Project administration,

Formal analysis, Data curation, Conceptualization. **Nicum Shibani:** Writing – review & editing, Supervision. **Chambers Pinkie:** Writing – review & editing, Supervision, Conceptualization. **Man Kenneth:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Pickwell-Smith Ben:** Writing – review & editing, Supervision. **Wei Li:** Writing – review & editing, Supervision, Conceptualization. **Dodwell David:** Writing – review & editing. **Wang Zhe:** Writing – review & editing. **Patel Apini:** Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PC has declared research funding from Pfizer and Gilead, consultancy around patient advocacy with GSK within the last three years. KM reports grants from the Hong Kong Research Grant Council, the CW Maplethorpe Fellowship, UK National Institute for Health and Care Research, European Commission Framework Horizon 2020, Korea Ministry of Food and Drug Safety, Innovation and Technology Commission of the Government of the Hong Kong Special Administrative Region, and personal fees from IQVIA Ltd. SN reports personal fees for advisory board membership from AstraZeneca and GSK; personal fees as an invited speaker from AstraZeneca, Clovis and GSK; personal fees for Scientific Committee membership from GSK; ownership of stocks/shares of GSK; and institutional funding from AstraZeneca. LS, DD, ZW, AP, LW declare no COI.

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Consent for publication

No individual data is contained within this manuscript and publication is allowed under the terms of agreement for the European Journal of Cancer.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115472.

Data availability

Data will not be made available due to the restricted nature of the datasets used for the study.

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