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Original research

Olaparib as maintenance therapy in non resectable pancreatic adenocarcinoma associated with homologous recombination deficiency profile: A French retrospective multicentric AGEO real-world study

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis. The POLO trial showed that olaparib (PARP inhibitor) improved progression-free survival (PFS) but not overall survival (OS), when used as maintenance therapy after ≥ 16 weeks of disease control with first-line platinum-based chemotherapy in patients with germline (g) *BRCA 1* or *2* pathogenic variants (PV) metastatic PDAC. However, real-world data on the effectiveness of olaparib are missing.

Methods: Patients with unresectable PDAC associated with somatic (s) or (g)*BRCA1/2* and (g)*non-BRCA-HRD* PV (*i.e.* other homologous recombination deficiency/HRD genes) who were treated with olaparib between 2020–2023 were included. The primary objective was to describe treatment patterns. Secondary exploratory objectives included OS and PFS in patients treated with olaparib according to the POLO trial or not, OS and PFS

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in patients with (g)HRD PV-associated PDAC *versus* (s)PVs, olaparib safety profile and factors associated with olaparib poor outcomes.
Results: Among 85 patients, 45.9 % received olaparib as defined by the POLO trial. No difference in OS and PFS was observed between patients who received olaparib according to the POLO trial *versus* not. Patients with (g)HRD PV-associated PDAC had better OS compared to others (22.3 *versus* 10.5 months, p = 0.038). Factors associated with olaparib poor outcomes included a high neutrophil-to-lymphocyte ratio and the use of olaparib outside the recommendations of the POLO trial. Few grade ≥ 3 adverse events were reported (9.4 %).
Conclusion: Patients with (g)HRD PV-associated PDAC had longer OS than those with (s)HRD PV. Olaparib use beyond the scope of the POLO trial was associated with poor outcomes.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with a poor prognosis. It is the seventh most common cause of cancer death worldwide, especially in high-income regions[1,2]. PDAC incidence is projected to increase and become the third leading cause of cancer-related death in Europe[3] and the second leading cause in the United States[4,5] by 2030–2040, also related to the fact that other cancer-related deaths are expected to decrease (*i.e.* breast and prostate cancers). With a non-resectable disease at diagnosis in more than 80 % of patients[6] and an overall survival (OS) rate, all stages combined, being still < 10 % at 5 years[7], PDAC remains a major challenge in gastrointestinal oncology[2].

Among all PDAC cases, a small proportion (5–7 %) occurs in the context of a genetic predisposition due to the presence of a germline (g) pathogenic variant (PV, also known as unclassified variant class 5/UV5) or probably pathogenic (UV4), located in some tumor suppressor genes [8], the most well-known being *BRCA1* and *BRCA2*, associated with the hereditary breast and ovarian cancer (HBOC) syndrome. It is essential to identify those patients as soon as PDAC is diagnosed, in order to define the optimal treatment strategy. Indeed, according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) classification, only germline *BRCA1/2* (g*BRCA1/2*) pathogenic variants, microsatellite instability and *NRTK* fusion tests are currently recommended with a high level of evidence in PDAC[9]. Focusing on g*BRCA1* or g*BRCA2* PV, the presence of such germline alteration confers to the tumor cells an altered profile of DNA break repair by homologous recombination (homologous recombination deficiency, HRD) and a high sensitivity to platinum salts as well as to poly ADP ribose polymerase (PARP) inhibitors. Olaparib, a PARP inhibitor, is now used as maintenance therapy after at least 16 weeks of PDAC control (*i.e.* non-progressive disease) with first line platinum-based chemotherapy, for patients with g*BRCA* PV-associated metastatic PDAC (UV5 and UV4). In the POLO phase III trial, the use of olaparib as maintenance therapy was associated with improved progression-free survival (PFS) in that specific population compared with placebo (PFS = 7.4 months *versus* 3.8 months, hazard ratio (HR) 0.53; p = 0.004). There was no difference in overall survival (OS) between the two groups (median OS 19.0 *versus* 19.2 months; (HR) 0.83; 95 % CI, 0.56–1.22; p = 0.3487)[10]. In that study, grade 3 or higher adverse events have been reported in approximately 40 % of patients and may have an impact on patients' quality of life. Furthermore, recent data have demonstrated that olaparib was not a cost-effective maintenance option[11]. Combined with the lack of benefit in terms of OS, some physicians do not offer olaparib to their patients. In addition, there is a lack of available data regarding the use of olaparib in daily practice, especially its prescription in cases of somatic or other germline *non-BRCA-HRD* PV tumor profile (*i.e.* other HRD genes as *PALB2, ATM, ATR, ATRX, BAP1, BARD1, BRIP1, CHEK1, CHEK2, RAD50, RAD51, RAD51B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG* or *FANCL*).

The aim of this study was to describe the patterns of use of olaparib in France, in real-world setting, its safety profile and to analyze PFS and OS as well as predictive factors of poor outcomes with olaparib in patients with unresectable PDAC. Following progression on olaparib, the (re) introduction of a platinum salt based-chemotherapy was also assessed.

2. Patients and methods

2.1. Patients

We performed a retrospective observational[11] study which involved French centers under the auspices of AGEO (Association des Gastro-Entérologues Oncologues).

We included all patients with histologically or cytologically proven unresectable PDAC (*i.e.* locally advanced according to the MD Anderson Cancer Center criteria[12] or metastatic), treated with olaparib whether within the scope of the marketing authorization for this drug in France (*i.e.* in accordance with the prescription conditions defined by the POLO study[13]: maintenance therapy after at least 16 weeks of non-progressive *gBRCA1/2* PV-associated metastatic PDAC with platinum-based first line chemotherapy) or not, between January 2020 and June 2023. When olaparib was prescribed outside the scope of the marketing authorization in France, its indication was approved by the tumor molecular board of the affiliated center.

We excluded patients for whom no radiological assessment of PDAC was available under olaparib treatment and for whom there was no follow-up data or no data on therapeutic sequences.

2.2. Data collection

We collected all relevant data regarding patient and tumor characteristics, somatic (s) or germline (g) variants (*i.e.* UV1 = benign, UV2 = probably benign, UV3/VUS = unknown significance, UV4 or UV5) in *BRCA 1/2* and *non-BRCA-HRD* involved genes that justified the prescription of olaparib by the referent oncologist, PDAC treatments, follow-up and survival data.

We also collected data related to the patterns of use of olaparib, olaparib safety profile according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 5.0[14], the best observed radiological response, the date of PDAC surgery or ablation of metastases if any, the date of progression, subsequent treatment after olaparib (if any), date of last follow up and date/cause of death. Radiological response rate (defined as progressive disease, stable disease, partial response and complete response) was assessed according to RECIST 1.1 criteria. Radiological tumor assessments using computed tomography scans were done every 2 to 3 months in each participating center.

Anonymous data were obtained from electronic review according to strict privacy standards.

The study was conducted in accordance with the French regulatory requirements (Commission Nationale Informatique et Libertés, CNIL) and the Declaration of Helsinki. All patients alive at the time of the study received appropriate verbal information or an information note and gave their consent for anonymous data collection. In accordance to French national laws and Clinical research Guidelines, this retrospective observational study did not require formal ethical committee approval.

2.3. Objectives

Our main objective was to describe the patterns of use of olaparib. No sample size was calculated as no formal hypothesis was done. Exploratory secondary objectives were 1) to compare the outcomes (OS and PFS) of patients corresponding to the inclusion criteria of the POLO trial or not, 2) to compare OS and PFS between patients with gHRD PV-associated PDAC *versus* sHRD PV, 3) to describe olaparib safety profile in the whole cohort, and 4) to explore predictive factors of poor outcomes with olaparib. Notably, we explored the role of olaparib prescription according to POLO trial or not [13] and other factors previously identified in previous studies: a CA 19–9 level $\leq$ or $>$ 200 ui/mL[12,15], a neutrophil-to-lymphocyte ratio (NLR) $\leq$ or $>$ 3.74[16], Eastern cooperative oncology group Performans status[17] (ECOG PS) of 0–1 *versus* $\geq$ 2 and the presence of liver metastases at olaparib initiation. Following progression on olaparib, the type of chemotherapy regimen and survival data were also assessed in patients with gHRD PV-associated PDAC.

2.4. Statistical analyses

Continuous variables were described as medians with their 25–75 interquartile range (IQR) and were compared using the Student's test or Wilcoxon test. Categorical variables were described as frequencies and percentages and were compared using the Chi2 test or the Fisher exact test, wherever most appropriate.

Follow-up time for OS was defined as the time elapsed between olaparib introduction and death from any cause, patients alive were censored at their last follow up.

Follow-up time for PFS was defined as the time elapsed between olaparib introduction and the diagnosis of radiological progressive disease (defined as progressive disease on tomodensitometry following RECIST 1.1 criteria).

Median OS and PFS were estimated by the Kaplan-Meier method and compared by the log-rank test.

Duration of response was defined as the time elapsed between the best radiological response observed under olaparib treatment and a radiological progressive disease.

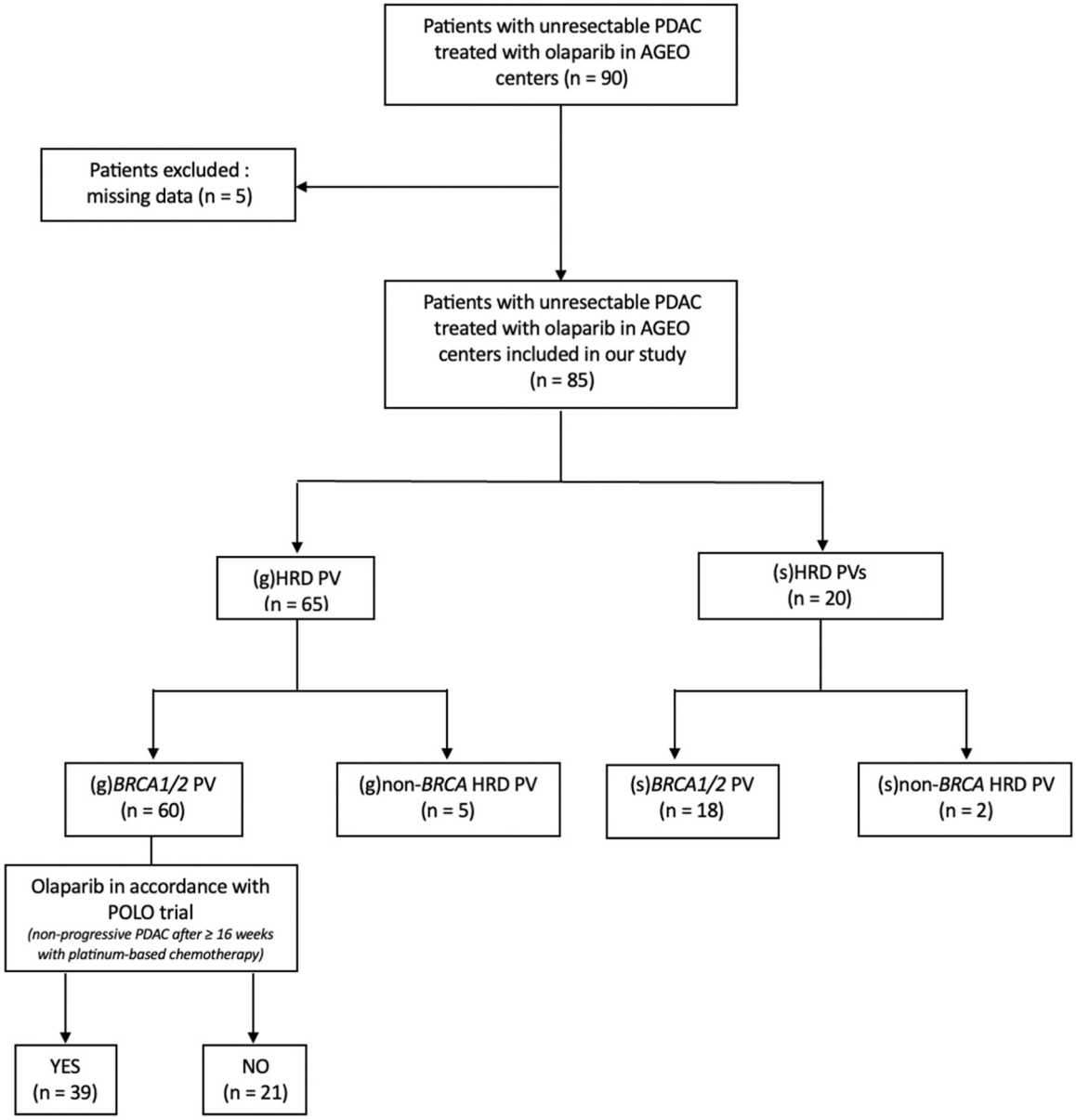

Fig. 1. Flow chart of patients with unresectable PDAC treated with olaparib in AGEO French centers. *Abbreviations: (g)HRD = germline homologous recombination deficiency; (g)BRCA = germline BRCA; (s)BRCA = somatic BRCA; PDAC = pancreatic ductal adenocarcinoma; PV = pathogenic variant.*

Survival curves were calculated using Kaplan-Meier method and were compared between groups using a Log Rank test.

The factors associated with olaparib poor outcomes, which was defined as a progressive disease according to RECIST 1.1 criteria at first radiological evaluation, were identified with a bivariate logistic regression model. Variables with a p-value < 0.2 in the bivariable model were eligible for the multivariable model. A stepwise selection procedure was applied. The significance threshold was set at 5 %. Analyses were performed using SAS 9.4 (SAS Inst., Cary, NC, USA).

3. Results

3.1. Patients characteristics

Ninety patients with unresectable PDAC treated with olaparib were identified among 14 French centers. Eighty-five patients met inclusion criteria (5 patients were excluded due to missing follow-up data, Fig. 1).

In the whole cohort, 51 were female (60.0 %) and median age at PDAC diagnosis was 58 years (IQR 50–67). Most of patients (93.0 %) were in a clinical good condition with an Eastern Cooperative Oncology Group Performance status (ECOG PS) 0–1, 7.0 % were ECOG PS 2.

PDAC was mainly located in the head of the pancreas (47.1 %), and was considered as unresectable at diagnosis in most of cases (94.1 %; 76 had metastatic PDAC, 4 had locally advanced PDAC). The most frequent metastatic sites were the liver (73.8 %), the peritoneum (21.2 %) and distant lymph node extension (16.2 %).

Germline PVs were detected in 65 patients (76.5 %) and were distributed as follows: *BRCA1* (n = 10); *BRCA2* (n = 50); *RAD51C* (n = 2); *ATM* (n = 1); *PALB2* (n = 1) and *FANCA* (n = 1) genes. Among them, 21 patients (32.3 %) had a personal history of cancer and 16 (24.6 %) were in the HBOC spectrum (breast (n = 13), ovary (n = 2), prostate (n = 1)). PDAC diagnosis led to the discovery of a *BRCA*-related cancer predisposition syndrome in 46/65 (70.8 %) of patients. In the remaining cases, g*BRCA* PV was already identified because of a personal history of cancer presented by the patient or because of a known familial g*BRCA* PV, with previous presymptomatic genetic testing performed.

Twenty patients received olaparib but had no germline PV. In this setting, olaparib prescription was proposed or approved by a molecular tumor board because of the detection of a somatic *BRCA* pathogenic variant (s*BRCA1* (n = 5), s*BRCA2* (n = 13) or in *non-BRCA-HRD* genes (n = 2)).

3.2. Olaparib use patterns

In our cohort, 39 patients (45.9 %) received olaparib in accordance with the indications of the POLO trial[13]. For the remaining 46 patients, olaparib prescription was justified as follows: maintenance therapy after a second or third line of chemotherapy not containing platinum salts (n = 13, among 11 g*BRCA1* or g*BRCA2* patients), maintenance therapy in patients with no response to first line platinum-based therapy (n = 5, among 5 g*BRCA1* or g*BRCA2* patients), maintenance therapy in patients after a non-platinum-based first line chemotherapy or < 16 weeks platinum-based chemotherapy (n = 6, among 5 g*BRCA1* or g*BRCA2* patients), the detection of somatic PV in *BRCA1/BRCA2* genes (n = 15), somatic PV in *non-BRCA-HRD* genes (n = 2), germline PV in *non-BRCA-HRD* genes (n = 5). These 2 groups of patients had similar characteristics. However, it should be noted that patients who received olaparib according to the POLO recommendations were most often diagnosed with metastatic PDAC. Their main characteristics are described in Table 1.

3.3. Survival and prognosis data

In the whole cohort, median follow-up was 24.0 months (IQR 17–39) from the date of unresectable PDAC diagnosis and 15.0 months (IQR 7.8–24) from the date of olaparib introduction. Considering the date of olaparib initiation, median PFS was 5.6 months [95 %CI = 4.5; 8.9] and median OS was 20.6 months [95 %CI = 14.8; 25.2].

There was no significant difference in survival outcomes between patients who received olaparib according to the POLO trial and those who received olaparib outside the indications of the study (median OS: 23.9 months [95 %CI = 15.2; 37.2] *versus* 18.1 months [95 %CI = 6.3; 22.3, p = 0.1572, Fig. 2A; median PFS: 6.0 months [95 %CI = 5.2; 9.4] *versus* 4.6 months [95 %CI = 2.8; 10.1], p = 0.9393, Fig. 2B).

There was a significant difference in OS between patients with gHRD-associated PDAC and those without gHRD PV. Median OS was 22.3 months [95 %CI = 15.1; 31.9] in patients with gHRD-associated PDAC *versus* 10.5 months [95 %CI = [4.7; 21.2] in others (p = 0.038, Supplementary material 1A). No significant difference in PFS was noticed between those two groups (6.0 months [95 %CI = 4.9; 9.7] *versus* 3.9 months [95 %CI = 1.6; 10.1] respectively; Supplementary material 1B).

In univariate analysis, CA 19–9 level > 200 ui/mL, NLR > 3.74,

Table 1
Clinical characteristics of patients at PDAC diagnosis in the AGEO cohort.

	Total (n = 85)n(%)/median (Q1-Q3)	Olaparib according to POLO trial (n = 39)n (%)/median(Q1-Q3)	Olaparib outside POLO trial (n = 46)n (%)/median(Q1-Q3)	p-value[a]
Sex				0.2863
Male	34 (40.0)	18 (46.2)	16 (34.8)	
Female	51 (60.0)	21 (53.8)	30 (65.2)	
ECOG PS at PDAC diagnosis				0.9434
0	37 (43.5)	16 (41.0)	21 (45.7)	
1	42 (49.4)	20 (51.3)	22 (47.8)	
2	6 (7.1)	3 (7.7)	3 (6.5)	
Age (years) at PDAC diagnosis	58.0 (50.0 −67.0)	57.0.8 (50.0 −67.0)	59.5 (52.0 −67.0)	0.9694
PDAC staging at diagnosis				**0.0092**
Resectable	4 (4.7)	0 (0.0)	4 (8.7)	
Borderline	1 (1.2)	0 (0.0)	1 (2.2)	
Locally advanced	4 (4.7)	4 (10.3)	0 (0.0)	
Metastatic	76 (89.4)	35 (89.7)	41 (89.1)	
Liver metastasis at diagnosis				0.6471
No	17 (22.4)	7 (20.0)	10 (24.4)	
Yes	59 (77.6)	28 (80.0)	31 (75.6)	

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; Q1 = 1st quartile; Q3 = 3rd quartile
[a] Chi-2 test or Fisher's exact test for qualitative variables, Student's test for quantitative variables

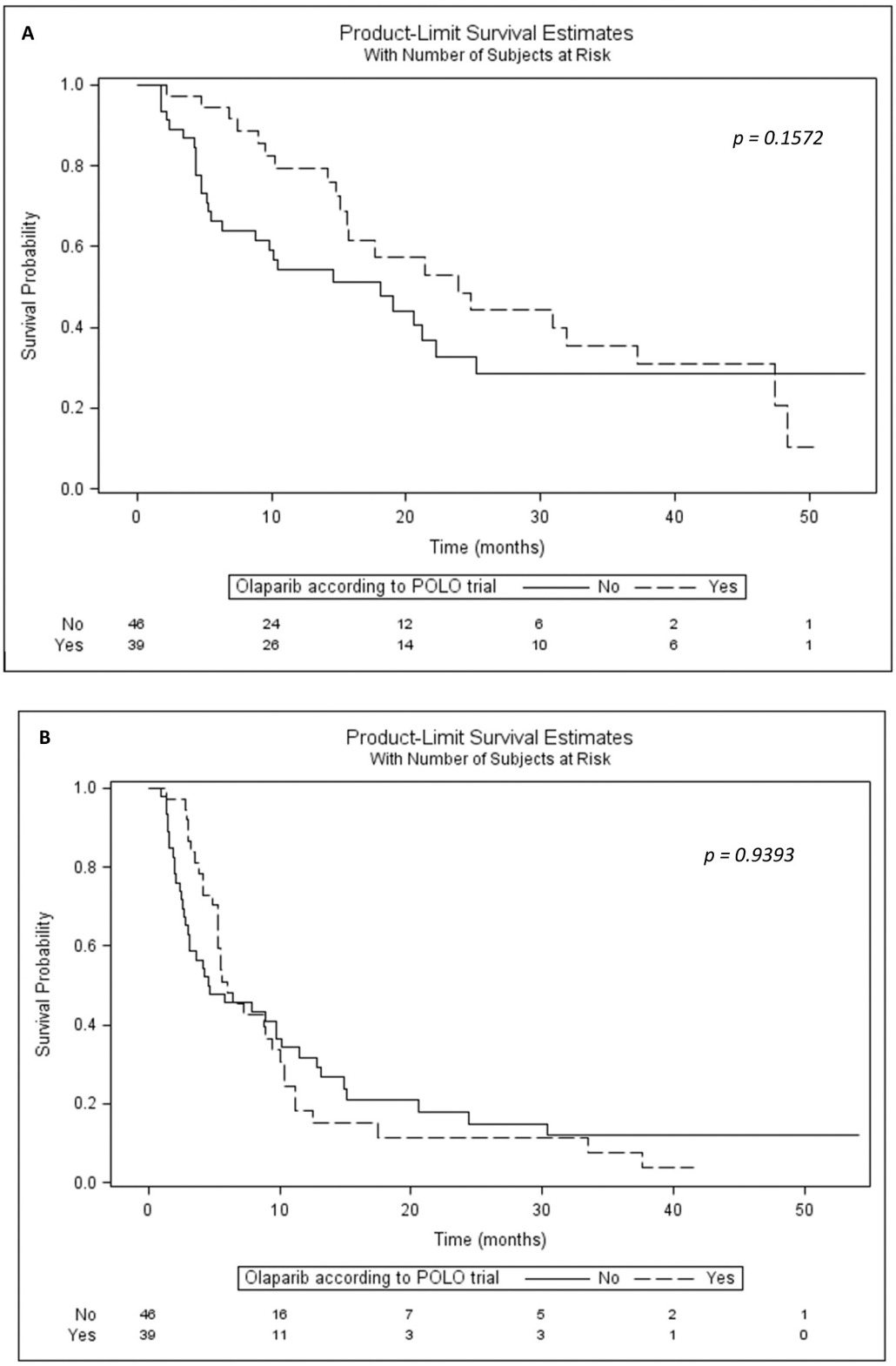

Fig. 2. Overall survival (**A**) and progression-free survival (**B**) curves in patients who received olaparib according to POLO trial *versus* not. *Abbreviations:* gHRD PV = *germline homologous recombination deficiency pathogenic variant; PDAC = pancreatic ductal adenocarcinoma.*

prescription of olaparib outside the recommendations defined by the POLO trial and the absence of gHRD PV were associated olaparib poor outcomes. In multivariate analysis, the factors that remained associated with olaparib poor outcomes were a NLR > 3.74 (Odds ratio (OR) = 9.8, [95 %CI = 2.3–42.7], p = 0.002) and prescription of olaparib outside the recommendations defined by the POLO trial (OR = 5.6, [95 %CI = 1.2–26.7], p = 0.03) (Table 2).

In patients who responded to olaparib, the median duration of response was similar between patients with gHRD or sHRD PV-associated PDAC (4 months *versus* 3.5 months respectively). After progression on olaparib, 44 patients (51.8 %) with gHRD PV-associated PDAC were able to continue a systemic treatment, including 29 with

Table 2
Clinical and biological factors associated with non-response to olaparib in the AGEO cohort.

	All patients (n = 85), (n,%)	PD at fist olaparib evaluation (n, %)	Univariate regression p-value	Multivariate analysis p-value
ECOG PS at olaparib initiation			**0.888**	
0	37 (43.5)	9 (24.3)	1	
1	41 (48.2)	10 (24.4)	1; 95 %CI (0.4 −2.8)	
2	6 (7.0)	2 (33.43)	1.6; 95 %CI (0.2 −10.0)	
Liver metastasis			**0.412**	
No	17[20]	3 (17.6)	1	
Yes	58 (68.2)	16 (27.6)	1.8; 95 %CI (0.5 −7.0)	
CA 19 −9			**0.083**	
≤ 200 ui/mL	41 (48.2)	7 (17.1)	1	
> 200 ui/mL	28[33]	10 (35.7)	2.7; 95 %CI (0.9 −9.3)	
NLR			**0.005**	**0.002**
≤ 3.74	51 [60]	9 (17.6)	1	1
> 3.74	19 (22.3)	10 (52.6)	5.2; 95 %CI (1.6 −16.4)	9.8; 95 %CI (2.3 −42.7)
Missing data	15 (17.6)			
gHRD PV			**0.082**	
No	20 (23.5)	11 [44]	1	
Yes	65 (76.5)	10 (16.6)	0.4; 95 %CI ((0.1 −1.1)	
Olaparib prescription in accordance with POLO trial[12]			**0.028**	**0.031**
No	46 (54.1)	16 (34.8)	3.5; 95 %CI ((1.1 −10.8)	5.6; 95 %CI (1.2 −26.7)
Yes	39 (45.9)	5 (12.8)	1	1

Abbreviations: EGOS PS = Eastern cooperative oncology group Performans status; IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio; PD = progression disease; gHRD PV = germline homologous recombination deficiency pathogenic variant, sHRD PV = somatic homologous recombination deficiency pathogenic variant

platinum salts. There was no significant difference in terms of survival, whether or not the chemotherapy treatment following olaparib was platinum-based chemotherapy (median OS = 21.4 months, *versus* 18.4 months in those not receiving a platinum-based chemotherapy, p = 0.3557).

Six patients (7 %) of the cohort had a complete radiological response to olaparib treatment. Among those cases, 3 had locally advanced PDAC and 3 had liver metastasis. All of them had g*BRCA2* PV-associated PDAC. Olaparib was prescribed in accordance with POLO trial for 3 patients, as maintenance treatment after second line chemotherapy without platinum salts (n = 2) and as maintenance therapy after first line chemotherapy containing a platinum salt for < 16 weeks. Three patients underwent surgical resection, all of them had liver metastasis. Pathological analysis revealed ypT2N2Mx (hepatic metastases not found perioperatively) and 2 were ypT0N0M0 (complete pathological response) PDACs. No recurrence was observed postoperatively at the end of data collection (*i.e.* after 9, 12 and 6 months, respectively). For the 3 non-operated PDAC patients with a complete radiological response to olaparib, treatment was still ongoing at the end of data collection, for 48 months, 36 months and 15 months and no recurrence was reported.

3.4. Safety and tolerability

In our cohort, grade 1–2 adverse events were the most common and mainly consisted of asthenia (20.0 %), nausea (10.6 %) and anemia (11.8 %) (Table 3). Few patients reported grade 1–2 side effects such as abdominal pain, diarrhea or anorexia (5.9 %; 3.5 % and 2.3 % respectively). Grade 3–4 adverse events were only reported in 7 patients (9.4 %, anemia (n = 4), diarrhea (n = 2), hepatitis (n = 1)), which led to a dosage adjustment. No toxic deaths attributable to olaparib had been reported and no discontinuation of treatment due to toxicity/intolerance was noticed.

4. Discussion

Pancreatic adenocarcinoma, whose incidence rate is rising steadily in industrialized countries[18], remains one of the cancers with the worst prognosis, despite intensive research.

According to the ESCAT classification[9], identifying patients with g*BRCA1/2* PV-associated PDAC is crucial (ESCAT score IA) as PARP inhibitors are an alteration-drug match associated with improved outcome with evidence from the POLO[10] randomized phase III clinical trial.

However, although the POLO study has extended the therapeutic prospects in a selected population, its results should be interpreted with caution due to its limitations[19], especially i) the primary endpoint (PFS as a primary endpoint in a highly lethal condition has limited justification), ii) the choice of the control arm (patients in the control arm received a placebo, while standard of care would rather correspond to continued chemotherapy or 5-fluorouracil monotherapy) and iii) the extent to which olaparib offers high-value care to the patients (not a cost-effective maintenance option).

In this context, we report here a retrospective real-world series of olaparib prescriptions in France. To our knowledge, this is the largest real-world series reporting the cases of those patients[20–22], including those who received olaparib for metastatic PDAC with somatic PV in HRD genes. Indeed, others cohorts focused either on multi-tumors or on PDAC with matched therapy[20,21] or other reports were limited to case reports[23–26]. That topic was one of the subject of a French multicentre study, which was however stopped early due to futility (MAZEPPA D19–02 PRODIGE-72, NCT04348045[27]).

In our cohort, olaparib was prescribed in more of 75 % of cases in patients with gHRD PV but complied with the recommendations of the POLO trial in less than half of cases (45.9 %). The referent oncologist and molecular tumor boards also justified olaparib prescription in other cases, notably in the presence of sHRD PV. Among the various clinical

Table 3
Summary of main adverse events.

	n = 85 (n, %)
Any grade	
Any	47 (55.3)
Asthenia or fatigue	17 (20.0)
Nausea	9 (10.6)
Anemia	10 (11.8)
Abdominal pain	5 (5.9)
Diarrhea	3 (3.5)
Decreased appetite	2 (2.3)
Constipation	0 (0.0)
Vomiting	2 (2.3)
Arthralgia	2 (2.3)
Grade ≥ 3	
Any	8 (9.4)
Asthenia or fatigue	1 (1.2)
Nausea	0 (0.0)
Anemia	3 (3.5)
Abdominal pain	0 (0.0)
Diarrhea	1 (1.2)
Decreased appetite	0 (0.0)
Constipation	0 (0.0)
Vomiting	0 (0.0)
Arthralgia	0 (0.0)

and biological factors that we analyzed, the factors associated with olaparib poor outcomes were its use outside the recommendations of the POLO trial and a NLR > 3.74. NLR might act as a prognostic factor in patients with unresectable pancreatic cancer[16]. The prescription of olaparib beyond the scope of the POLO trial does not seem to offer any a benefits.

In the whole cohort, median PFS was 5.6 months and was not statistically different between patients presenting gHRD PV-associated PDAC or not. However, our numbers remain small and our population is heterogeneous, enabling us to confirm this. The median PFS we observed was shorter than that observed in the POLO trial[10] (7.4 months), which may be explained by the strict setting of a phase III trial with a highly selected population with only g*BRCA1* or g*BRCA2* PV.

Survival outcomes between patients who received olaparib according to the POLO trial and those who received olaparib outside the indications of the study were similar, but with a different tumor stage at diagnosis between the 2 groups. We observed a difference in terms of OS in gHRD PV-associated PDAC patients (22.3 months *versus* 10.5 months in patients with sHRD PV-associated PDAC), which might be explained by the greater sensitivity to platinum salts in that specific population. Another hypothesis could be a better prognosis for PDAC in this g*BRCA*-PV subgroup, but we are unable to state this, especially as the data in the scientific literature remain discordant[28–30]. This presumed platinum-sensitivity feature[31], due to the deficiency in the repair of DNA double-strand breaks, which might increase chemotherapy sensitivity to DNA-damaging agents[32], also led us to investigate whether immediate post-olaparib treatment with platinum-based chemotherapy would provide benefit in the gHRD PV-associated PDAC population. We found no evidence of a difference in terms of OS, whether or not the patient received a platinum salt after olaparib therapy (median OS = 21.4 months *versus* 18.4 months respectively, p = 0.3557), which is discordant with recent published data[33].

In this real-world study, it is also important to underline that 6 patients (7 %) had a complete clinical and radiological response to olaparib, three of whom underwent surgery (2 had a complete pathological response). No recurrence was reported for these patients at the end of data collection, with an encouraging follow-up period (range 6–48 months). All had a germline PV in *BRCA2* gene. Nevertheless, we cannot exclude that these objective responses were related to previous chemotherapy. At this time, as these observations are uncommon (2 patients in POLO trial), no genotype-phenotype correlation could be established.

More specifically, with regard to hereditary predisposition syndromes, this retrospective study also highlights the fact that syndromes predisposing to pancreatic cancer are still poorly understood and investigated too late in patients with PDAC. In fact, none of the patients identified as having g*BRCA1* or g*BRCA2* PV (30 %) were screened for pancreatic cancer, which might be the only effective way of preventing PDAC[8,34]. In addition, a significant number of patients were prescribed olaparib beyond first-line of treatment (n = 13, *i.e.* 21.7 % of the gHRD PV-associated PDAC population). This illustrates the fact that genetic and molecular biological analyses are initiated too late, whereas it is crucial that they be carried out as soon as unresectable PDAC is diagnosed. Indeed, identifying potentially actionable therapeutic target that can derive long-term clinical benefit in their management[35] should be assessed early in the patient's care plan (*i.e.* g*BRCA* PV[10,13], microsatellite instability[36], *KRAS* wild type PDAC[37,38]). A multidisciplinary management approach involving an expert center is recommended for those patients.

4.1. Limitations

Our study presents some limitations. As all patients were treated with olaparib, and given the retrospective nature of the study, it was not possible to conclude to what extent the differences in outcomes seen between different populations were due to differences in olaparib effectiveness between those groups or merely due to different prognoses driven by differing biological factors among those groups. Moreover, a lack of statistical power may be observed due to the small numbers in the analysis of some patient subgroups. Similarly, we also reported better tolerability of olaparib than reported in the POLO trial (we observed 9.4 % of grade 3 or more side effects whereas there were reported in 40 % of patients in POLO trial[13]): this is linked to the retrospective nature of this study and the likely under-reporting of adverse events. These observations should therefore be treated with caution. In addition, it was not possible to conduct radiological reviews and more particularly to make a centralized decision on the time to progression/early failure after introduction of olaparib, which may have generated selection bias. Moreover, patients treated with olaparib who did not have a radiological assessment of PDAC were excluded, which may also have introduced a selection bias, although they were limited (n = 5).

5. Conclusion

In this retrospective French real-world study, olaparib prescriptions complied with the recommendations of the POLO trial in 45.9 % of cases. Among patients with advanced PDAC treated with olaparib, there was no significant difference in survival outcomes between those who met the POLO criteria or not.

We observed a better OS in patients with gHRD PV-associated PDAC compared to other mutations, suggesting better efficacy of olaparib in these patients, although this may also indicate different prognoses due to different biological factors. A NLR > 3.74 and olaparib prescription outside the POLO trial recommendations were the 2 factors associated with PARP inhibitor poor outcomes and could help in the decision-making process.

A multidisciplinary management approach involving an expert center is recommended for patients with g*BRCA1* or g*BRCA2*-associated PDAC.

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Author contributions

Data collection: JM, DT, AB, RG, MBA, AD, AT, SQ, JFB, PA, CT, IT, AP, YT, JP, FXCB, JT, SD, OB, ALV, LDM, MM. Data acquisition and analysis: EJ, MM. Manuscript writing: JM, EJ, LDM, MM. Project supervision: LDM, MM. Review and approval of the manuscript: all authors.

CRediT authorship contribution statement

Elodie Jeanbert: Writing – review & editing, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Clémence Toullec:** Validation, Investigation. **David Tougeron:** Writing – review & editing, Validation, Investigation. **Anna Pellat:** Writing – review & editing, Validation, Investigation. **Alice Boilève:** Writing – review & editing, Validation, Investigation. **Yann Touchefeu:** Writing – review & editing, Validation, Investigation. **Julien Taieb:** Writing – review & editing, Validation, Investigation. **Alice Durand:** Writing – review & editing, Validation, Investigation. **Solène Doat:** Writing – review & editing, Validation, Investigation. **Anthony Turpin:** Writing – review & editing, Validation, Investigation. **Julien Pinot:** Writing – review & editing, Validation, Investigation. **Rosine Guimbaud:** Writing – review & editing, Validation, Investigation. **François-Xavier Caroli-Bosc:** Writing – review & editing, Validation, Investigation. **Maher Ben Abdelghani:** Writing – review & editing, Validation, Investigation. **Louis De Mestier:** Writing – review & editing, Validation, Supervision,

Conceptualization. **Pascal Artru:** Writing – review & editing, Validation, Investigation. **Marie Muller:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Isabelle Trouilloud:** Writing – review & editing, Validation, Investigation. **Jeannie M'Baloula:** Writing – original draft, Validation, Investigation. **Olivier Bouché :** Writing – review & editing, Validation, Investigation. **Stanislas Quesada:** Writing – review & editing, Validation, Investigation. **Anne Laure Vedie:** Writing – review & editing, Validation, Investigation. **Jean-Frédéric Blanc:** Writing – review & editing, Validation, Investigation.

Declaration of Competing Interest

APe declares speaker's engagement from Servier; consulting/advisory role for Amgen; travel grant from Ipsen, Merk and Servier.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115051.

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