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REVIEW

The Landscape of PARP Inhibitors in Solid Cancers

Marta Muzzana[1], Massimo Broggini[2], Giovanna Damia[2]

[1]Oncology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2]Experimental Oncology Department, Istituto Di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy

Correspondence: Massimo Broggini, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, via Mario Negri, Milan, 2 20156, Italy, Email massimo.broggini@marionegri.it

Abstract: PARP inhibitors are a class of agents that have shown significant preclinical activity in models defective in homologous recombination (HR). The identification of synthetic lethality between HR defects and PARP inhibition led to several clinical trials in tumors with known HR defects (initially mutations in *BRCA1/2* genes and subsequently in other genes involved in HR). These studies demonstrated significant responses in breast and ovarian cancers, which are known to have a significant proportion of patients with HR defects. Since the approval of the first PARP inhibitor (PARPi), olaparib, several other inhibitors have been developed, expanding the armamentarium available to clinicians in this setting. The positive results obtained in breast and ovarian cancer have expanded the use of PARPi in other solid tumors with HR defects, including prostate and pancreatic cancer in which these defects have been identified. The clinical trials have demonstrated responses to PARPi which are now also available for the subset of patients with prostate and pancreatic cancer with HR defects. This review summarizes the results obtained in solid tumors with PARPi and their potential use when combined with other agents, including immune checkpoint inhibitors that are likely to further increase the survival of these patients which still needs a dramatic improvement.

Keywords: DNA damage, homologous recombination, PARP inhibitors, solid tumors, BRCA

Introduction

Poly-ADP-ribose polymerase inhibitors (PARPi) represent one of the first example of synthetic lethality approach in oncology.[1] Synthetic lethality refers to a genetic interaction in which inactivation of either gene individually has no effect on cell viability, while their concomitant loss of function causes cell death. Importantly, the inactivation can be a gene deletion, an inactivating mutation or a pharmacological treatment. PARPi were shown to be in synthetic lethality with *BRCA1/2* (breast-related cancer antigen protein 1 and 2) mutations, which favored their clinical use in cancers harboring these mutations. However, their use was later extended to a broader clinical context, in tumors with deficiency in homologous recombination (HR) repair. Deficiency in HR (condition known as *BRCAness* or HRD) is due to functional inactivation of mutation/deletion and/or lack of expression (due to hypermethylation) of genes involved in the HR repair pathway.[2] HR is a pathway that repairs the DNA double-strand breaks (DNA-DSBs) in an error-free manner because it uses the sister chromatid as a template with no genetic loss/alteration. The accuracy and fidelity of DNA-DSBs is of paramount importance as these are the most deleterious DNA lesions and can result in chromosomal aberrations, insertions and deletions and many other mutagenic outcomes that promote tumorigenesis.[3]

Treatment of HRD cells with inhibitors of PARPi results in cell death, with an almost 100-fold difference in sensitivity between HR-proficient and HR-deficient cells.[4,5] The basis of the synthetic interaction is not fully understood and may be based on the inability of PARPi-treated cells to process DNA single strands, generating DNA-DSBs, that are highly toxic in HR-deficient cells; on the ability of PARPi to trap PARP1 on DNA with the subsequent accumulation of DNA damage,[6] replication fork stalling and cell death,[7] and on the accumulation of replication gaps.[8] In addition, the single-strand DNA breaks in HRD cells treated with PARPi cause replication fork collapse and the resulting DNA-DSBs, which cannot be repaired by HR, are processed by error-prone non-homologous end joining (NHEJ), with the accumulation of genetic damage ultimately leading to cell death.

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BRCA1 and *BRCA2* are tumor suppressor genes that are mutated in breast, ovarian, pancreatic and prostate cancers. Germline mutations in the *BRCA1/2* genes significantly increase the lifetime risk of developing breast (up to 85%) and ovarian cancer (15–56%),[9] pancreatic cancer (2–7%)[10] and prostate cancer,[11] usually by inactivating the second allele, resulting in almost complete loss of protein function. BRCA1/2 proteins play a key role in HR and their functional inactivation results in HRD with increased levels of unrepaired DNA-DSBs that promote tumorigenesis.[12] Since HR is a multi-step process involving many other proteins, HR deficiency has been reported to be caused by mutations in other genes (eg, *PALB2, RAD51C, BRIP1*, etc.) found in several cancers.[13]

Four PARPi (olaparib, rucaparib, niraparib and talazoparib) are now approved in the clinic with different indications (Figure 1) mainly in *BRCA1/2* mutated/HRD tumors, including ovarian carcinoma, breast, and pancreatic with very interesting results. Even PARPi activity has also been reported in HD proficient (HRP) tumors,[14] suggesting that other defects not detectable by HRD tests may contribute to their anticancer activity, the highest activity has been reported in HRD tumors and HRD is indeed considered the most important predictive biomarker of response to PARPi. In the last decades, a number of HRD tests have been developed that have been the companion tests for the development of PARPi in the clinical setting (recently reviewed in).[15]

We will summarize the most important clinical data of PARPi in ovarian, breast, pancreatic and prostate cancer alone or in combination therapy. Specifically, we will describe and discuss the trials in these different tumor types that lead to the approval of the different PARPi in specific settings. We will also discuss the possible mechanism of PARPi resistance and the new emerging PARPi, designed to be more specific, more potent and potentially less toxic that are now being tested in clinical trials.

Clinical Results in Ovarian Cancer

PARPi were first tested in ovarian cancer (OC), based on the evidence that 50% of the high-grade serous ovarian carcinomas are HRD[2] and at least 17 Phase III clinical trials have been published (recently reviewed in).[16] Table 1 shows the different PARPi and their current FDA and EMA approved indications in OC.

Table 2 reports the results of the most important trials of PARPi in OC. Olaparib was approved as maintenance therapy for newly diagnosed OC based on the results of the SOLO1 trial, which showed that 2-years olaparib treatment

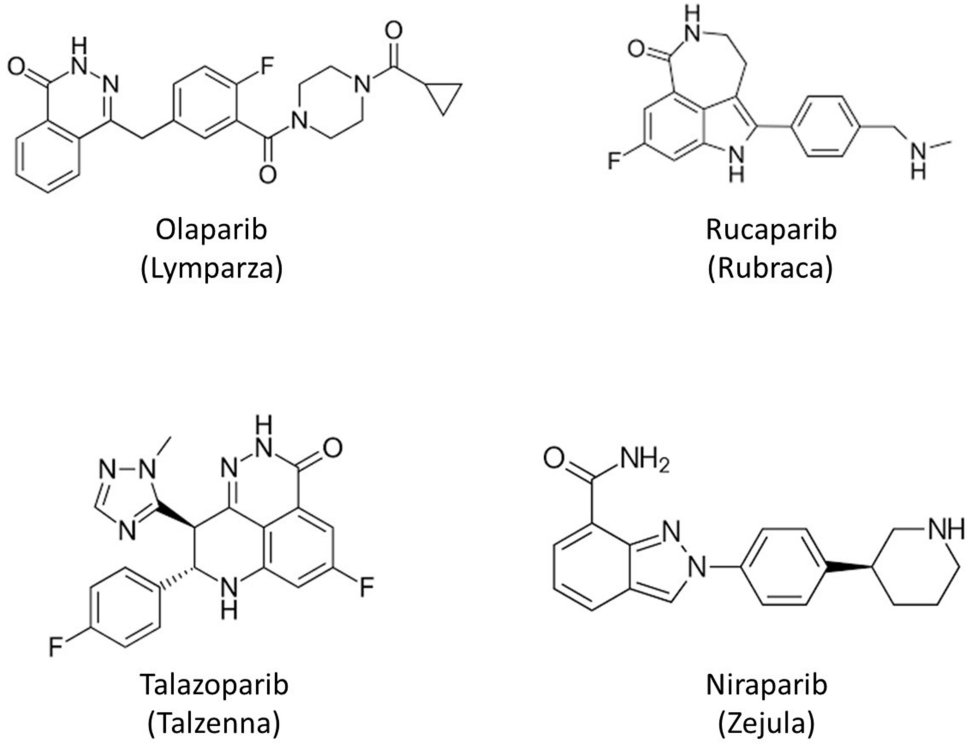

Figure 1 Structure of the four FDA and EMA-approved PARPi.

Table 1 PARP I Approved by FDA and EMA in Ovarian and Breast Cancer

Drug	Ovarian Carcinoma		Breast Carcinoma	
Olaparib	**FDA***	**EMA****	**FDA***	**EMA****
	Maintenance treatment of patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.	Maintenance treatment of adult patients with advanced BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.	Adjuvant treatment of patients with deleterious or suspected deleterious gBRCAm human epidermal growth factor receptor 2 (HER2)-negative early breast cancer treated with neoadjuvant or adjuvant chemotherapy.	Monotherapy or in combination with endocrine therapy for the adjuvant treatment of patients with germline BRCA1/2-mutations who have early HER2-negative breast cancer treated with neoadjuvant or adjuvant chemotherapy
	Maintenance treatment of patients with deleterious or suspected deleterious germline or somatic BRCA-mutated recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.	Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	Treatment of patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.	Monotherapy in patients with germline BRCA1/2-mutations, who have HER2 negative locally advanced or metastatic breast cancer.
	In combination with bevacizumab for the maintenance treatment of ì patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status.	Maintenance treatment in patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency		
Rucaparib	Maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.	Maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.		

(*Continued*)

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Table 1 (Continued).

Drug	Ovarian Carcinoma		Breast Carcinoma	
Olaparib	**FDA***	**EMA****	**FDA***	**EMA****
Niraparib	Maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy	Maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.		
		Maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy		
Talazoparib			Monotherapy in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative locally advanced or metastatic breast cancer.	Monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer.

Abbreviations: *FDA, Food and Drug Administration; **EMA, European Medicines Agency.

extended the progression-free survival (PFS) in patients with *BRCA1/2* mutations and that the PFS benefit was maintained 3 years after discontinuation of olaparib treatment.[17] Similar results were obtained with niraparib in the PRIMA trial,[18] which further extended the activity of niraparib not only in patients with *BRCA1/2* mutations but also in patients with HRD, and with rucaparib in the ATHENA-MONO trial.[19]

The PAOLA-1 trial evaluated the addition of olaparib maintenance to bevacizumab after first-line platinum-taxane therapy and demonstrated a statistically significant increase in PFS in the olaparib+bevacizumab (22.1 months) versus placebo+bevacizumab (16.6 months) and this effect appeared to be greater in HRD patients;[22] however, no survival benefit was later observed.

In the setting of recurrent platinum-sensitive OC, olaparib as maintenance therapy in patients with gBRCAmut (*BRCA* germline mutation) was associated with a statistically significant increase in PFS in the SOLO2[31] and in the Study 19 trials.[32] The ARIEL3 trial evaluated the effect of rucaparib treatment versus placebo as maintenance therapy in platinum-sensitive relapsed OC with a significant improvement in PFS benefit independent of *BRCA* mutations or HRD status.[29] However, no overall survival (OS) benefit was demonstrated.[33] In the same setting, niraparib was tested versus placebo in both patients with gBRCAmut and non-gBRCAmut and again a significant PFS improvement was observed regardless of *BRCA* mutation or HRD tumor status.[34] All of these studies support the indication of these drugs as maintenance monotherapy in relapsed-sensitive OC, establishing a new standard of care; interestingly, for some of the drugs, the effect was independent of the *BRCA* mutation and HRD status.

Table 2 Summary of the Phase III Trials Assessing the Use of PARPi in Patients with Ovarian Cancer

Trial	Study population	Treatment	Outcome	Results	Ref
SOLO1	Stage III/IV high-grade EOC. Prior cytoreductive surgery for stage III or biopsy/surgery for stage IVBRCA1/2m	Olaparib vs placebo	PFS, months	All comers: 56 vs 13.8 hR95% CI 0.33 (0.25–0.43)	[17,20,21]
				pts with BRCAm:41.4 vs13.8	
			OS, months	NR vs 75.2 hR95% CI 0.55 (0.40–0.76); p=0.004	
PAOLA-1	Stage III/IV high-grade EOC. No evidence of disease or CR or PR on 1L treatment with platinum–taxaneCT plus bevacizumab	Olaparib/ bevacizumab vs placebo/bevacizumab	PFS, months	All comers: 22 vs 16.6 hR95% CI 0.63 (0.53–0.74)	[22–24]
				pts with BRCAm: 60.7 vs 21.7 hR95% CI 0.41 (0.32–0.54)	
				pts with HDR: 46.8 vs 17.6 hR95% CI 0.55 (0.40–0.76); p=0.004	
			OS, months	56.5 vs 51.4 hR95% CI 1.92 (0.76–0.12); p=0.4118	
PRIMA	Stage III/IV high-grade EOC. Visible residual tumor after primary debulking surgery or inoperable stage IIICR or PR on 1L platinum-based CT	Niraparib vs placebo	PFS, months	All comers: 13.8 vs 8.2 hR95% CI 0.66 (0.56–0.79)	[18,25]
				pts with BRCAm: 31.5 vs 11.5 hR95% CI 0.45 (0.32–0.64)	
				pts with HDR: 24.5 vs 11.2 hR95% CI 0.52 (0.40–0.68)	
SOLO2	Relapsed, high-grade EOC ≥2L of platinum-based CT and platinum-sensitive diseaseBRCA1/2 mutations	Olaparib vs placebo	PFS, months	19.5 vs 5.5 hR95% CI 0.30 (0.22–0.1);p<0.0001	[26,27]
			OS, months	52.4 vs 37.4 hR95% CI 0.71 (0.52–0.97); p=0.031	
NOVA	EOC with high-grade histologic features ≥2L of platinum-based CT and platinum-sensitive disease	Niraparib vs placebo	PFS, months	pts with BRCAm: 21.0 vs 5.5 hR95% CI 0.27 (0.17–0.41); p<0.001	[28]
				pts with HDR: 12.9 vs 3.8 hR95% CI 0.38 (0.24–0.59); p<0.001	
			OS, months	pts with BRCAm: 40.9 vs 38.1 hR95% CI 0.85 (0.61–1.20)	
				pts with HDR: 35.6 vs 41.4 hR95% CI 1.29 (0.85–1.95)	
ARIEL3	High-grade EOC≥2L of platinum-based CT and platinum-sensitive disease	Rucaparib vs placebo	PFS, months	All comers: 10.8 vs 5.4 hR95% CI 0.36 (0.30–0.45); p<0.001	[29,30]
				pts with BRCAm: 16.6 vs 5.4 hR95% CI 0.23 (0.16–0.34); p<0.001	
				pts with HDR: 13.6 vs 5.4 hR95% CI 0.32 (0.24–0.42); p<0.001	
			OS, months	All comers: 36 vs 43.2 hR95% CI 1.0 (0.81–1.22); p=0.96	
				pts with BRCAm: 45.3 vs 47.9 hR95% CI 0.83 (0.59–1.19); p=0.32	
				pts with HDR: 40.5 vs 47.8 hR95% CI 1.01 (0.77–1.32); p=0,.97	

Abbreviations: PFS, progression free survival; OS, overall survival.

The SOLO3 trial compared olaparib (single agent) versus non-platinum-based chemotherapy (PDL, gemcitabine or topotecan) in platinum-sensitive gBRCAmut who had already received ≥2 prior platinum-based chemotherapies. While in the primary analysis an increase in OS and PFS in the olaparib arm compared to single-agent chemotherapy was reported, in the final analysis, the OS was similar, and only the time to second objective disease progression (PFS2) was longer in the olaparib arm.[35] The efficacy of rucaparib was evaluated in a phase III trial in OC patients with germline and somatic *BRCA* mutations, who had already received ≥2 prior lines of chemotherapy, with varying degrees of platinum sensitivity compared to standard chemotherapy (ARIEL4).[36] Despite the PFS advantage of rucaparib over chemotherapy (7.4 months −95% Confidence Interval – CI-: 7.3–9.1 versus 5.7 months 95% CI: 5.5–7.3), the median OS was 19.4 months and 25.4 months, respectively. Although these data could be inferred from the high crossover rate (69%), Clovis Oncology voluntarily withdrew rucaparib in this setting.[16]

PARPi have also been studied in recurrent and platinum-resistance settings, although very few trials considered the possible common mechanism of resistance between platinum and PARPi.[37] In the CLIO trial, olaparib monotherapy was comparable to chemotherapy in platinum-resistant OC, including patients with gBRCA wild-type.[38] An overall response rate of 28% (95% CI: 15.6–42.6; p=0.00053) was observed in the QUADRA trial evaluating niraparib monotherapy (as ≥4 lines of therapy) and was evaluated in 463 patients with disease recurrence within 6 months of last platinum-based therapy.[39] The effect was more pronounced in HRD, platinum-sensitive disease. Olaparib monotherapy was found to have activity in patients with gBRCAmut advanced OC who had received more than three prior lines of chemotherapy (overall response rate – ORR – 34%; CI: 26–42).[40]

The introduction of PARPi in the treatment of OC has clearly changed the therapeutic approach in this tumor type. However, the updated long-term OS data in the recurrent setting (both as maintenance therapy after completion of chemotherapy and as monotherapy) did not correlate with the longer PFS survival reported in various studies. Final OS data from ARIEL4 were 19.4 months in the rucaparib arm versus 25.4 months with standard of care.[36] Similar data were seen in the SOLO3 trial, with the *post-hoc* subgroup analysis showing a potential detrimental effect of olaparib compared to standard of care. Concerns have been raised in the relapse maintenance setting. Long-term follow-up data from the phase III NOVA trial, which evaluated the role of niraparib versus placebo in 553 patients with platinum-sensitive recurrent ovarian cancer (gBRCAmut and non-gBRCAmut cohorts) after standard platinum therapy, reported no difference in OS, although a trend over increased OS was observed in the niraparib-treated gBRAmut cohort versus placebo-treated patients (43.8 versus 34.1 months; Hazard Ratio HR, 0.66, CI95%: 0.44–0.99).[41] Similar OS data were reported in the primary analysis of ARIEL3 trial in the intention to treat population (ITT), the mOS in patients treated with rucaparib was 36 months versus 43.2 months in the placebo group (HR 0.995, 95% CI: 0.809–1.223) despite the significant improvement in PFS.[33] There could be several reasons for the lack of a clear OS benefit, including the fact that OS was a secondary end-point in many of the trials and these trials were underpowered for this endpoint, the high crossover rate between arms and the recent advances in the treatment of OC that have increased the mOS in these patients.

Nevertheless, the mature OS data from the first-line maintenance setting are positive. A clear OS benefit was reported after 7 years of follow-up in the SOLO1 trial, which had a median follow-up time of 88 months, with an OS HR of 0.55 in the olaparib maintenance group versus placebo and a substantial proportion of the olaparib patients not receiving subsequent lines of chemotherapy compared with placebo patients.[20] Again, the PAOLA 1 5-year OS data clearly showed a benefit in favor of the combination of olaparib plus bevacizumab (OS at 5 years 65.5% versus 48.4%, HR: 0.62, 95% CI; 0.45–0.85) in the HRD patient cohort.[22]

There are few trials of PARPi in combination with immune-checkpoint inhibitors (ICIs), including anti-PD-1 and antiPD-L1 antibodies, in advanced OC. The clinical efficacy of ICIs in OC is limited and is considered a post-treatment option. However, emerging preclinical evidence suggests that PARPi have immunomodulatory effects, being able to activate the cGAS/STING pathway, to upregulate PD-L1 expression through the ATM/ATR/chk1 pathway, and to induce INF-1 release and expression of the chemokines CCL5 and CXCL10. Finally, PARPi treatment increases genomic instability, potentially leading to a higher tumor mutation burden and immune responsiveness.[42] Given this background, the combination of PARPi and ICI may be a viable approach. Olaparib and durvalumab (an anti-PD-L1) combination in platinum-sensitive recurrent gBRCAmut OC patients showed a good safety profile and promising efficacy. The results of this Phase II trial have been recently published[43] with an ORR was 92.2% and more than 40% patients presenting a complete response (CR). Based on these results, the DUO-O phase II trial was activated with the aim to compare in newly diagnosed OC patients the following schedules: Arm a) chemotherapy +

bevacizumab + placebo followed by bevacizumab + placebo maintenance treatment; Arm b) chemotherapy + bevacizumab + durvalumab followed by bevacizumab + durvalumab + placebo maintenance treatment; or arm c) chemotherapy + bevacizumab + durvalumab followed by bevacizumab + durvalumab + olaparib maintenance treatment. Enrollment began in January 2019, and the updated final PFS, interim OS and updated safety were recent.[44] A clinically meaningful PFS was observed for Arm 3 versus Arm 1 in the non-tBRCAm HRD population: HR 0.46 (95% CI: 0.33–0.65), with a mPFS of 45.1 versus 23.3 months, and a PFS rate at 24 months of 72.9% versus 46.5%, respectively. In the non-tBRCAm ITT population for Arm 3 versus Arm 1 an HR 0.61 (95% CI: 0.51–0.73), with mPFS of 25.1 versus 19.3 months, and PFS rate at 24 months of 53.0% versus 33.2%, respectively, have been found. The mPFS of 45.1 months observed in patients with HRD-positive disease treated with the triplet (Arm 3) is the longest ever reported in this setting. Although the interim OS analysis was not statistically significant in the ITT population, a favorable trend in overall survival was also observed in the *BRCA* wild-type, HRD-positive population. In the HRD-negative population, Arm 3 demonstrated an improvement in mPFS with a HR of 0.68 compared with Arm 1, even if the interim OS analysis did not show a significant difference between the treatment arms.[44]

The TOPACIO/KEYNOTE-162, a phase III study, evaluated the combination of niraparib and pembrolizumab in relapsed platinum-resistant OC. Among the 62 patients treated, the ORR was 18% (90% CI, 11–29%), with a disease control rate of 65% (90% CI, 54–75%). Interestingly, higher than expected responses were observed in patients without tumor BRCA mutations or non-HRD cancers.[45] Many other studies are ongoing (recently reviewed in[42]), and data on efficacy are awaited.

The unraveling of the molecular characteristic of high-grade serous OC (HRD and its synthetic interaction with inhibition of PARPi greatly foster their clinical development with very positive results and a change in the therapeutic management of OC. The positive data from SOLO-1, PRIMA, and ATHENA trial have led to the approval of olaparib as for first-line maintenance treatment of advanced OC with *BRCA* mutated OC and niraparib regardless of HRD status. Recently, the PAOLA-1 data granted the approval of olaparib in combination with bevacizumab as first-line maintenance therapy in HRD OC; in addition, the long-term follow-up results are awaited from the DUO-O study to possibly include ICI in combination with PARPi and bevacizumab.

Clinical Results in Breast Cancer

The unraveling of the molecular characteristics of breast cancer (BC) has made it possible to define that nearly 10% of this type of tumor carries mutations in DNA repair genes (mainly *BRCA1* and *2* genes) with the acquisition of an HDR phenotype. These tumors tend to be triple-negative and of high-grade and are generally more aggressive than the sporadic BCs.[46] As HRD, they could benefit from a PARPi therapy. Indeed, two PARPi have been approved in BC: olaparib and talazoparib (Table 1). The specific indications were granted based on the results obtained in the OlympAD and EMBRACA trials[47,48] (Table 3).

Table 3 Summary of the OlympiA, OlympiAD, EMBRACA, and BROCADE3 Phase III Trials Assessing the Use of PARPi in Patients with Breast Cancer

Trial	Study Population	Treatment	Outcome	Results	Ref
OlympiA	High-risk, HER2-negative, early BC gBRCA mutations- Prior definitive local treatment	Olaparib vs placebo	PFS, months	85.9 vs 77.1 hR95% CI 0.58 (0.41–0.82); p<0.001	[48,49]
			OS, months	89.8 vs 86.5 hR95% CI 0.68 (0.47–0.97); p=0.009	
OlympiAD	HER2-negative BC gBRCA mutation. Prior progression on two or less CT regimens	Olaparib vs physician's choice of CT (capecitabine, eribulin, or vinorelbine)	PFS, months	7.0 vs 4.2 hR95% CI 0.58 (0.43–0.80); p<0.001	[47,50]
			OS, months	19.3 vs 17.1 hR95% CI 0.90 (0.66–1.23); p=0.513	
EMBRACA	HER2-negative, locally advanced or metastatic BC gBRCA mutations. Prior progression on three or less CT regimens	Talazoparib vs physician's choice of CT (capecitabine, eribulin, gemcitabine, or vinorelbine)	PFS, months	8.6 vs 5.6 hR95% CI 0.54 (0.41–0.71); p<0.001	[51,52]
			OS, months	19.3 vs 19.5 hR95% CI 0.85 (0.67–1.07); p=0.17	

Abbreviations: PFS, progression free survival; OS, overall survival.

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The phase III OlympAD trial, compared olaparib monotherapy with investigator's choice (capecitabine, eribulin, or vinorelbine- standard) therapy in metastatic BC patients with a g*BRCA* mutation and human epidermal growth factor receptor type 2 (HER2)-negative, who had received no more than two prior chemotherapy regimens.[50] The mPFS was 2.8 months longer in patients treated with olaparib than in patients treated with standard therapy; in addition, the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy. The final survival data did not show a statistically significant improvement in OS with olaparib compared to standard therapy; however, a significant OS benefit was observed in patients who had not received chemotherapy for metastatic disease.[47] In an extended further analysis, the 3-year survival was 27.9% for olaparib versus 21.2% for standard of care, 8.8% of patients received olaparib treatment for ≥3 years versus none with chemotherapy treated patients.[53] Following these results, a phase III trial patients with (HER2)-negative early breast cancer with *BRCA1* or *BRCA2* germline pathogenic or likely pathogenic variants and high-risk clinicopathologic factors who had received local treatment and neoadjuvant or adjuvant chemotherapy were randomized to receive olaparib or placebo for 1 year.[48] At 3-year follow-up, invasive disease-free survival was 85.9% in the olaparib group versus 77.1% in the placebo group (HR 0.58; 99.5% CI; 0.41 to 0.82; p<0.001) and the distant disease-free survival was 87.5% versus 80.4%, respectively (HR 0.57; 99.5% CI; 0.39 to 0.83; p<0.001).

Similar results were observed in the EMBRACA trial in which patients with g*BRCA1/2*-mutated HER2-negative advanced BC patients were randomized to receive talazoparib or physician's choice of chemotherapy[51] The EMBRACA trial randomized 431 patients to receive talazoparib versus single-agent chemotherapy of physician's choice and is the largest PARP monotherapy trial to date in this setting. Significant increase in PFS was observed in talazoparib treated patients versus chemotherapy treated patients: HR: 0.542 (95% CI: 0.413–0.711; p < 0.0001) with mPFS of 8.6 months versus 5.6 months. The results from the patient-reported outcomes (PRO) favored talazoparib, with significant overall improvement and significant delay in time to clinically meaningful deterioration of the global health status/quality of life (GHS/QoL) and breast symptom scales.[52,54] Safety profile was similar to other PARPi treatment and could be managed by supportive care and dose modification. However, the final results of the OS,[51] evaluated as a key secondary endpoint in this trial, did not show any statistically significant difference between arms, the HR was 0.848 (95% CI 0.670–1.073; p = 0.17); it was suggested that subsequent treatments the patients have undergone may have impacted results. Overall, these data supported the incorporation of talazoparib in clinical practice as a treatment option for patients with advanced BC with a g*BRCA1/2* mutation. Clinical trials evaluating the role of rucaparib and niraparib in triple negative BC are ongoing, and results are awaited.[55]

All these data have suggested that patients with high-risk, HER2-negative early BC harboring g*BRCA1/2* mutations can receive olaparib in the adjuvant setting after neoadjuvant or adjuvant chemotherapy. In addition, patients with HER-negative, gBRCA1/2 mutation locally advances or metastatic BC can receive talazoparib or olaparib in the metastatic setting after prior exposure to chemotherapy.

PARPi Inhibitors in Tumors Different from Breast and Ovarian Cancer

PARPi have been shown to have activity in other solid tumors besides breast and ovarian cancer, particularly in prostate cancer and pancreatic cancer where their use is approved as reported in Table 4.

Prostate Cancer

Prostate cancer (PC) is the second most commonly diagnosed cancer and the fifth leading cause of cancer death in men in Western countries.[56] While early-stage PC is generally responsive to antiandrogen therapy, advanced-stage and metastatic PC (metastatic Castration-Resistant Prostate Cancer, mCRPC) is a very heterogeneous disease with poor response to therapy[57] and with a very dismal prognosis (median OS of about 2 years).[58] The molecular characterization of PC revealed that approximately 10% of localized tumors and up to 30% of mCRCP show defects in DNA damage response (DDR) for mutations in *BRCA1*, BRCA2, *CDK12, ATM*, and *CHK2* genes leading to their loss of function and impairment of HR.[59,60] For this reason, all patients with PC should undergo germline testing, and somatic testing is recommended in patients with recurrent and metastatic disease.[58] The presence of HR defects has opened up the way for the use of PARPi, particularly in mCRPC, changing the standard of care for these patients.[61]

Table 4 PARP Inhibitors Approved by FDA and EMA in Prostate and Pancreatic Cancer

Drug	Pancreatic Adenocarcinoma		Prostate Carcinoma	
Olaparib	**FDA***	**EMA****	**FDA***	**EMA****
	Maintenance treatment in patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen	Maintenance treatment of adult patients with germline BRCA1/2-mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen.	Monotherapy for the treatment of adult patients with (mCRPC) and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.	As monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.
			In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated	In combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated
Rucaparib			Treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated mCRPC who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy.	
Talazoparib			In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated mCRPC	

Abbreviations: *FDA, Food and Drug Administration; **EMA, European Medicines Agency.

PARPi were first evaluated in phase II trials as monotherapy in mCRPC.[57] In all these studies, patients with mCRPC progressing after taxane or after taxane and androgen receptor signaling inhibitors (ARSi) with DDR alterations, directly or indirectly related to HR, were treated with olaparib (TORAP-B),[62] rucaparib (TRITON2),[63] talazoparib (TALAPRO-1)[64] and niraparib (GALAHAD).[65] The objective response rate (ORR) in patients with DDR alterations was the primary endpoint in all the phases II except for the GALAHAD trials, where the primary endpoint was the ORR in patients with biallelic inactivation of *BRCA1/2*. The ORRs were, respectively, 39.1 and 54.3% (for the 300 and 400mg olaparib twice-daily doses), 43%, 29.8% and 34.2%. Interestingly, all the studies reported higher response rates in the BRCA1/2 cohorts of patients than in other cohorts of patients with DDR genomic alterations.

These exciting results prompted the implementation of phase III clinical trials: the PROfound[60] and TRITON3[66] trials, the positive results of which led to the approval of olaparib and rucaparib in mCRPC patients with alteration in DDR gene alterations (Table 5).

The TRIOTON 3 is a phase III trial that enrolled mCRPC with *BRCA1/2* or *ATM* alterations that progressed after treatment with a second-generation androgen receptor pathway inhibitor (APRi). A total of 4855 patients were screened and 270 were assigned to the rucaparib arm (600mg twice daily) and 135 to the physician's choice of docetaxel or

Table 5 Summary of the Phase III Trials Assessing the Role of PAPRi in Monotherapy or in Combination in mCRPC

Trial	Study population	Treatment	Outcome	Results	Ref
PROfound	1L mCRPC with prior progression on an ARPi	Olaparib vs physician's choice of abiraterone or enzalutamide	rPFS, months	pts with HRRm: 5.8 vs 3.5 hR95% CI 0.49 (0.38–0.63); p<0.001	[60,76]
				pts with BRCAm: 9.8 vs 3.0 hR95% CI 0.22 (0.15–0.32)	
			OS, months	pts with HRRm: 17.3 vs 14 hR95% CI 0.79 (0.61–1.03)	
				pts with BRCAm: 19.1 vs 15.1 hR95% CI 0.61 (0.37–1.01)	
			ORR, %	21.7 vs 4.5	
TRITON 3	1L mCRPC with prior progression on an ARPi	Rucaparib vs physician's choice of docetaxel or abiraterone or enzalutamide	rPFS, months	pts with HRRm: 10.2 vs 6.4 hR95% CI 0.61 (0.47–0.80); p<0.001	[66]
				pts with BRCAm: 11.2 vs 6.4 hR95% CI 0.50 (0.36–0.69); p<0.001	
			OS, months	pts with HRRm: 23.6 vs 20.9 hR95% CI 0.94 (0.72–1.23)	
				pts with BRCAm: 24.3 vs 20.8 hR95% CI 0.81 (0.58–1.12)	
			ORR, %	45.1 vs 17.1	
PROpel	1L mCRPC (prior docetaxel allowed)	Abiraterone/olaparib vs abiraterone/ placebo	rPFS, months	all comers: 15 vs 16.5 hR 95% CI 0.68 (0.57–0.79)	[73,77]
				pts with HRRm: NRvs 13.9 hR95% CI 0.50 (o.34–0.73)	
				pts with HHR unknown: 24.1 vs 19 hR95% CI 0.76 (0.60–0.97)	
				pts with BRCAm: NR vs 8.4 hR95% CI 0.23 (0.12–043)	
			OS, months	all comers: 42.1 vs 34.7 hR 95% CI 0.81 (0.67–1.00); p=0.054	
				pts with HRRm: NR vs 28.5 hR95% CI 0.66 (0.45–0.95)	
				pts with HHR unknown: 42.1 vs 38.9 hR95% 0.89 (0.70–1.14)	
				pts with BRCAm: NR vs 23 hR95% CI 0.29 (0.14–0.56)	
			ORR, %	58.4 vs 48.1	

(*Continued*)

Table 5 (Continued).

Trial	Study population	Treatment	Outcome	Results	Ref
Magnitude	1L mCRPC (prior systemic therapy)	Abiraterone/niraparib vs abiraterone/ placebo	PFS, months	rPFS in pts with HRRm: 16.7 vs 13.7 hR95% CI 0.76 (0.6–0.97); p =0.028	[74,78,79]
				rPFS in pts with BRCAm: 19.5 vs 10.9 hR95% CI 0.55 (0.39–078); p =0.007	
			OS, months	pts with HRRm: 29.3 vs 32.2 hR95% CI 0.70 (0.49–0.99); p =0.0414	
				pts with BRCAm: 30.4 vs 28.6 hR95% CI 0.66 (0.46–0.95); p =0.024	
			ORR, %	59.7 vs 28.1	
TALAPRO-2 cohort 1	1L mCRPC (prior ARPi and docetaxel)	Enzalutamide/talazoparib vs enzalutamide/placebo	rPFS, months	all comers: NR vs 21.9 hR 95% CI 0.63 (0.51–0.78); p <0.001	[75]
				pts with HRRm: 27.9 vs 16.4 hR95% CI 0.46 (0.30–0.70); p=0.0003	
				pts with HHR unknown: NR vs 22.5 hR95% 0.70 (0.54–0.89); p=0.0039	
				pts with BRCAm: NR vs 8.4 hR95% CI 0.23 (0.12–043)	
			OS, months	all comers: NR vs 36.4 hR 95% CI 0.89 (0.69–1.14); p=0.35	
			ORR, %	61.7 vs 43.9	
TALAPRO-2 cohort 2	1L mCRPC (prior ARPi and docetaxel) in pts with mutation in HRR genes	Enzalutamide/talazoparib vs enzalutamide/placebo	rPFS, months	pts with HRRm: NR vs 16.4 hR95% CI 0.45 (0.33–0.61); p<0.0001	
				pts with BRCAm: NR vs 11.0 hR95% CI 0.20 (0.11–0.36); p<0.0001	
			OS, months	pts with HRRmNR vs 33.7 hR 95% CI 0.69 (0.46–1.03); p=0.07	
				pts with BRCAm: NR vs 11.0 hR95% CI 0.61 (0.31–1,23); p=0.16	
			ORR, %	61.7 vs 43.9	

Abbreviations: rPFS, radiological progression free survival; PFS, progression free survival; OS, overall survival; ORR%, percentage of overall response rate.

a second-generation ARPi (abiraterone acetate or enzalutamide) arm. Patients with *BRCA1* alterations comprised 75% of both groups. In the control arm, 56% of the patients received docetaxel. The primary endpoint was the median duration of imaging-based progression-free survival, and at 62 months follow-up, it was significantly longer in the rucaparib group than in the control group both in the *BRCA* subgroup (median, 11.2 months vs 6.4 months, HR: 0.50, 95% CI:

0.36–0.69, p < 0.001) and in the intention to-treat group (median, 10.2 months and 6.4 months, HR: 0.61, 95% CI: 0.47–0.80, p < 0.001). No difference was observed in the *ATM* mutated patients with a median duration of imaging-based progression-free survival of 8.1 months (95% CI, 5.5 to 8.3) in the rucaparib group and of 6.8 months (95% CI, 4.0 to 10.4) in the control group (HR 0.95; 95% CI, 0.59–1.52). OS data are awaited.

The PROfound study is a randomized, open-label, biomarker-driven phase III trial in mCRPC that has progressed while receiving enzalutamide or abiraterone to evaluate the efficacy of olaparib. Only patients with alterations in prespecified genes directly or indirectly associated with HR were enrolled in two cohorts: cohort A (245 patients) with alterations in *BRCA1, BRCA 2* and *ATM* and cohort B (142 patients) with alterations on other prespecified DDR genes. Primary end point was radiological PFS (rPFS) of olaparib compared to androgen receptor signaling inhibitors (ARSi) in the BRCA cohort and in the overall population. Olaparib treatment significantly improved rPFS in cohort A (median,7.4 months vs 3.6 months; HR 0.39 95% CI 0.34; 95% CI, 0.25 to 0.47; p<0.001) and in the overall population (median, 5.8 versus 3.5 months; HR, 0.49; 95% CI, 0.38 to 0.63; p<0.001). In addition, in cohort A the OS interim analysis shows a benefit in the olaparib-treated arm that did not reach a statistical significance (19.1 versus 14.7 months, HR: 0.69, 95% CI: 0.50–0.97, p=0.02); these latter data could be inferred from the 80% of crossover to olaparib arm. The main criticism of these data was the fact that the treatment in the control arm was ARSi after prior ARSi therapy, which has been reported to have limited efficacy in mCRPC due to cross-resistance mechanisms,[67,68] and a taxane-based chemotherapy would probably have been a better control arm.

Preclinical evidence strongly suggests a synergistic effect between PARPi and ARSi. Indeed, the androgen receptor (AR) has been shown to enhance the expression of DNA damage repair (DDR) genes[69] and PARP1 supports the AR-X transcriptional activity,[70,71] suggesting that androgen receptor blockade could induce a BRCAness phenotype. With this in mind, the efficacy and tolerability of olaparib and abiraterone were evaluated in 142 mCRPC patients randomized to receive olaparib/abiraterone and placebo/abiraterone.[72] The rPFS was 13.8 in the olaparib group versus 8.2 in the placebo group (HR 065, 95% CI0.11–0.97, p=0.034). Based on these results, the combination of PARPi and ARSi was evaluated as a first-line therapy in mCRPC in three randomized, double-blind, placebo-controlled prospective Phase 3 trials: PROpel,[73] MAGNITUDE,[74] and TALAPRO-2[75] (Table 5).

The PROpel study[73] enrolled 796 mCRPC patients, regardless of HRR gene mutation status, to receive abiraterone/olaparib versus abiraterone/placebo in the first-line setting. The primary endpoint (rPFS) was met with a median rPFS of 24.8 months observed in the combination group versus 16.6 months in the placebo-combination arm (HR: 0.66, 95% CI: 0.54–0.81, p < 0.001). In patients with the HRR gene mutations, rPSF was not yet reached in the olaparib group compared to 13.9 months in the control combo group. However, at 36.5 months of follow-up, no difference was observed between the two treatment arms in the prespecified analysis of mOS (42.1 vs 34.7 months, HR: 0.81, 95% CI: 0.67–1.00, p = 0.054). However, in a *post-hoc* exploratory subgroup analysis, the combination of abiraterone/olaparib reduced the risk of death by 71% of in *BRCA1/2* patients (mOS: not reached vs 23.0 months, HR: 0.29, 95% CI: 0.14–0.56) and by 34% in patients with HRR gene mutations (mOS: not reached vs 28.5 months, HR: 0.66, 95% CI: 0.45–0.95).

In the MAGNITUDE[74] trial evaluated the combination of niraparib/abiraterone versus placebo/abiraterone as the first-line treatment of mCRPC with a defined HRR status. Patients with HRR alteration (423 patients) and without HRR alteration (247 patients) were randomized 1:1 to receive niraparib or placebo. rPFS, assessed by central review, was the primary endpoint and was assessed first in the BRCA1/2 mutated cohort and then in the HRR deficient cohort. Median rPFS in the BRCA1/2 subgroup was significantly longer in the niraparib combination arm compared to the placebo control arm compared with the placebo group (16.6 vs 10.9 months; HR: 0.53; 95% CI, 0.36 to 0.79; p=0.001). When considering the entire HRR-deficient cohort, again rPFS was significantly longer in the niraparib than in with the placebo group (16.5 vs 13.7 months; HR, 0.73; 95% CI, 0.56 to 0.96; p=0.022). The OS data were immature in this first initial analysis.

The TALAPRO-2[75] trial compared the combination of talazoparib/enzalutamide (402 patients) was compared to placebo/enzalutamide (403 patients) as the first-line treatment of mCRPC (regardless of HRR gene alterations). Patients were stratified at randomization by HRR gene alteration status and prior treatment with life-prolonging therapy. A statistically significant improvement in rPFS was observed in the talazoparib and enzalutamide at the planned primary analysis, with a median rPFS not reached in the PARPi combination versus 21.9 months in the placebo group (HR: 0.63, 95% CI: 0.51–0.78; p < 0.0001). In addition, subgroup analysis using HRR gene alteration status showed an HR for rPFS

of 0.46 (95% CI 0.30–0.70; p=0.0003) in patients with HRD and of 0.70 (0.54–0.89; p=0.0039) in patients with a status of non-deficient or unknown in favor of talazoparib/enzalutamide combination versus placebo.

In all these studies, the combination treatments were well tolerated with a manageable safety profile consistent with the reported side effects of the individual drugs.

Given these very positive results, evaluating the synergistic effect of ARSi and PARPi in early-stage disease will be of great value, and indeed clinical trials are ongoing to evaluate evaluating the combination of niraparib/abiraterone (ARSiAMPLITUDE)[80] and talazoparib/enzalutamide (TALAPRO-3)[81] in metastatic hormone-sensitive PC patients with HRR alterations to potentially prolong the duration of hormone sensitivity and modify the disease course.

PARPi are also being studied in combination with other drugs in metastatic PC.

The combination of PARPi with immune checkpoint inhibitors (ICI) has been proposed based on the genomic instability caused by the HR and DDR defects, which may trigger neoantigen production and T-cell activation.[82] However, the phase III Keylink-010 trial[83] showed no significant improvement in outcomes with the combination of pembrolizumab and olaparib in biomarker-unselected, heavily pretreated mCRPC, suggesting that further patient selection is critical for this approach. The combination of PARPi with radioligand therapies, such as lutetium-177 (177Lu)-PSMA-617 and radium-223 dichloride, shows potential due to the synergy between radiation-induced DNA damage and PARPi. Early studies have tested these combinations with ARSi with positive safety profiles, suggesting that they could be further explored also in combination with PARPi.[84–86]

Other combinations of PARPi with targeted therapies, such as AKT inhibitors and VEGFR inhibitors, are also being studied.[87,88] While some studies have shown good safety, others have shown improved PFS but with increased adverse events, highlighting the need for further research to identify biomarkers for treatment tailoring.

Summing up, enzalutamide/talazoparib combination is a valid first-line option in mCRPC patients with HRR mutations; abiraterone/olaparib and abiraterone/niraparib are available in patients with *BRCA1/2* mutations. In patients with advanced relapses, disease and mutations in any of the prespecified HRR gene olaparib can be used, while rucaparib is available for patients with BRCA1/2 alterations after therapy with ARPi and docetaxel.

Pancreatic Cancer

Pancreatic cancer, and in particular, pancreatic ductal adenocarcinoma (PDAC), remains one of the deadliest tumor with a 5-year survival rate of 10% in the metastatic setting. In the recent years, with the increasing number of molecular characterizations, a significant percentage of PDAC tumors have shown HRD defects, thus offering new potential therapeutic patients in selected population. It is estimated that approximately 15–20% of PDAC are HRD (mostly due to mutations in BRCA1/2 and PALB2 genes).[89,90] These patients represent a subset for whom the use of PARPi may help improve their outcomes. Back in 2019, olaparib was approved in PDAC following the results of Phase III trials that evaluated the use of this PARPi versus placebo in PDAC patients who had a response or stabilization to prior platinum therapy. The primary endpoint (PFS) was met with a PFS of 7.4 months in the olaparib arm vs 3.8 months in the placebo arm (resulting in a statistically significant HR of 0.53).[91,92] The overall impact of the study was somewhat limited by the fact that the comparison was to placebo and most importantly because the secondary endpoint of the study (OS) did not show an advantage in the olaparib group.

The efficacy of rucaparib in PDAC in two studies has been evaluated. In one study, the drug was tested in patients with defined mutations in *BRCA1/2* and *PALB2* genes as maintenance after platinum, while in the second study, the prior response to platinum was not mandatory.[93,94] The first maintenance study after response to platinum-based therapy gave positive results in terms of ORR (42%) PFS and OS (13 and 23.5 months, respectively).[93] Interestingly, of the 42 patients evaluable in the phase II trial, 3 had complete response and 12 had a partial response. Enrollment in the second study was stopped due to a low response rate in the first patients.[94] In this study, prior response to platinum was not mandatory, and patients with platinum-resistant tumor did not achieve an objective response. This suggested that platinum sensitivity may be a useful biomarker for PARPI efficacy.

Interestingly, trials are testing PARPi in the early setting of pancreatic cancer; in particular, the APOLLO trial is comparing olaparib versus placebo in patients with no evidence of recurrent disease following perioperative chemotherapy in patients with mutations in the *BRCA1/2* or *PALB2* genes.[95]

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Finally, new PARPi such as veliparib have been tested in phase II trials with no positive results.[96] In this Phase II, the safety and efficacy of velarapib were evaluated in BRCAm PDAC patients, with progressive disease with 1–2 prior chemotherapy regimens; no confirmed radiographic responses were observed, although a stable disease >8 weeks was seen in one-fourth of patients. One possible explanation for the lack of positive results could be that, as mentioned above, several enrolled patients were resistant to platinum.

Finally, several trials are testing the combination of PARPi and immune checkpoint inhibitors based on the positive preclinical results.[97] Hopefully, this will also translate into benefits also at the clinical level.

In conclusion, patients with *BRCA1/2* mutations, platinum sensitive (not progression after ≥ 16 weeks), and metastatic pancreatic cancer can receive olaparib as maintenance.

Other Tumors

PARPi have been and are currently being tested in tumors other than the four in which these drugs are approved.

In NSCLC, a systemic review analyzing 12 trials in which PARPi were used mostly in combination with chemotherapy found a slight improvement in OS (with an HR of 0.9 (0.83–0.97)) but a nonsignificant difference in PFS.[98] A randomized phase II trial comparing olaparib with placebo as maintenance in patients responding to platinum therapy (PIPSeN trial) was stopped due to lack of improvement.[99] Given the evidence that HR defects predict the response to immune checkpoint inhibitors in NSCLC patients,[100] it is likely that there could be a potential benefit, in this subset of patients from the use of a combination of PARPi and ICI.

In HCC, there is evidence of a potential sensitization by the use of PARPi and shown in a patient with HCC presenting a mutation in the FANC A gene (belonging to HR).[101] Recent results from a tumor-agnostic phase II trial showed varying degrees of response in different tumors with germline of somatic mutations in genes belonging to HR.[102]

Acquired or Intrinsic Resistance to PARPi

Although the introduction of PARPi has significantly improved patient survival, a significant percentage of HRD-patients do not respond to these drugs. In addition to the intrinsic resistance, as is reported for almost all drugs used in oncology, drug resistance also occurs in patients who initially respond to treatment with PARPi. Several studies have been conducted to elucidate the mechanisms of resistance and possible ways to overcome it. Based on preclinical studies, the mechanisms of resistance reported to date include some that are generally observable mechanisms (such as increased expression of P-glycoprotein mediating drug efflux from cells or activation of epithelial-to-mesenchymal transition-EMT) some that are related to alteration of the target (such as reduced levels of DNA trapped PARP1, or reduced expression of the poly-ADP-ribose glycohydrolase) and some that specifically related to the mechanism of action and/or of synthetic lethality. The latter are particularly relevant as they are among those seen clinically.

The ABCB1 (ATP-binding cassette superfamily B member 1) gene encodes a P-glycoprotein (P-gp) that belongs to a family of protein pumps (ABC proteins) found in the cells' membrane. The ABC protein acts by removing drugs from the cells, thereby controlling their intracellular levels. It is well known that ABC protein expression is associated with resistance to those drugs that are substrates of the glycoprotein. Doxorubicin and etoposide are two examples of drugs whose intracellular levels are regulated by ABC protein. Olaparib is a substrate of P-gp, and it has been shown that repeated treatment with these drugs induces an upregulation of the ABCB1 gene conferring resistance to the drug. To confirm the role of this mechanism in the resistance to olaparib, treatments with ABC inhibitors are able to restore the sensitivity to olaparib in preclinical models.[103–105]

EMT is a well-known mechanism by which epithelial cells acquire a more malignant and invasive phenotype that is associated with metastasis and drug resistance.[106–109] Using transgenic mouse models and patient-derived xenografts (PDX), three independent groups have found that PARPi resistance can also be associated with an enhanced mesenchymal phenotype,[110–112] although other mechanisms have been found to be associated with resistance in these models (including increased drug efflux).

Another mechanism of resistance observed for several DNA damaging agents (cisplatin, etoposide, trabectedin, topotecan) is the loss of expression of the DNA/RNA helicase SLFN11. This helicase acts normally or when overexpressed by preventing tumor replication. In fact, SLFN11 is recruited early to stressed replication forks, thereby

inducing replication arrest and controlling tumor growth.[113] In many cancer cells, SLFN11 expression is low and, when treated with DNA damaging agents SLFN11, is further inactivated mostly due to hypermethylation of its promoter. This has been associated with resistance to many DNA damaging agents and more recently for PARPi.[110,114–117] However, it should be noted, however, that, in a retrospective study of ovarian cancer patients treated with olaparib, there was a positive trend between high SLFN11 expression and better PFS, although this was not observed when overall survival was considered.[118] Olaparib and other PARPi are able to exert anticancer activity not only because of their ability to inhibit the enzymatic activity of PARP but also because they trap PARP into DNA. In fact, the trapping activity is considered to be a relevant factor in the overall activity of the inhibitors.[6,119] There is evidence that the basal levels of PARP correlate positively with the response to PARPi.[120,121] Although this has not been clinically demonstrated, it is important to note that the different PARPi clinically available have a different ability and potency to trap PARP, and therefore, their use could potentially be selected based on PARP levels.

The most important and clinically relevant mechanisms of resistance to date are those associated with restoration of BRCA function and, more generally, to restoration of HR.

Indeed, reversion mutations in the *BRCA1/2* genes have been found in different patients with different tumors that were in progression after PARPi.[122,123] The importance of mutation reversion is further corroborated by the evidence that in long responders to PARPi there is an enrichment of BRCA mutations that cannot be reversed by secondary mutations.[124] Additional mutations have recently been found in patients-derived xenografts derived from PARPi resistant patients and confirmed clinically in a cohort of patients with ovarian cancer.[125] Interestingly, splice site mutations are able to remove the entire exon (in this case exon 11) carrying the mutation, thus resulting in the production of a truncated protein with functional (albeit reduced) activity.

Methylation of the BRCA promoter resulting in loss of protein expression is another mechanism leading to HR deficiency and PARPi activity.[126,127] It has been reported that promoter demethylation in epigenetically silenced *BRCA1* tumors represents an additional mechanism of resistance to PARPi by restoring HR function.[128]

Finally, the mechanisms proposed for mutation reversion and promoter demethylation in the *BRCA* genes, have also been found in other genes acting in the HR repair such as *RAD51C, RAD51D* and *PALB2*.[129–134]

Conclusions and Future Perspectives

The introduction of PARPi into clinical practice has significantly and positively changed the scenario for patients with defects in HR. This is true not only for breast and ovarian cancer that, which were the first tumors in which these drugs were tested but also for other solid tumors such as prostate and pancreatic cancer in which PARPi are being tested on an ongoing basis. In recent years, other clinical trials have been implemented assessing these agents in different oncologic settings, including small cell lung cancer and metastatic colon cancer. Their efficacy is associated with the presence of HRD (ie mutation in HHR genes, including BRCA1/2) and the response of a platinum-based therapy, even if hints of activity have also been observed in HRP tumors. The increasing availability of tests to determine the status of HR beyond *BRCA1/2* and other known gene mutations, together with the introduction of functional tests that can easily identify defective tumors, will certainly increase the number of patients (and likely tumors) that could potentially benefit from the use of PARPi.

Given the positive results of PARPi in different settings, they have been introduced earlier and earlier in the management of cancer patients and still open is the optimal duration of adjuvant PARPi. While in the OC setting PARPi have been used for up to 2 years, in the OlympiA trial olaparib has been administered for one year and this could be different for the different PARPi and in early stage cancers (ie gBRCAm carriers with early-stage breast cancer). Another important issue relates to the safety of PARPi, especially the long-term effects, including their impact of the quality of life in cancer patients considering the long treatment duration. Hematological toxicities and higher risk of developing myelodysplastic syndrome and acute myeloid leukemia are among the reported adverse effects of these agents. As most of these effects appear to be due to the inhibition of PARP2, as new PARPi more selective and less toxic are being studied at the preclinical and clinical levels. Some are already in phase III trial (iniparib, veliparib, senaparib), some in phase II (INO-1001, nesuparib, saruparib, stenoparib, atamparib, vendaparib, CEP-9722, BGP-15, TSL-1502SC10914, HWH340) and several others in early clinical trials.

Further research should be focused not only on a better patient stratification using more biomarkers as outlined above but also to explore through biologically driven approach to implement new combination of PARPi and both cytotoxic and non-cytotoxic agents, including immunotherapy.

Lastly, as for other anticancer agents, also for this class of agents, resistance to therapy has been observed in the clinic. There is the strong need for preclinical models that recapitulate human tumors in which to evaluate the resistance mechanism and ways to overcome it. Resistance to treatment is still one of the reasons for treatment failure despite an initial response. Although some mechanisms have been highlighted (such as reversion mutations in *BRCA* genes), additional studies on well-defined models are urgently needed to unleash the full potential of this class of drugs to induce durable responses and thus a strong benefit for patients.

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Disclosure

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