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PARP inhibitors in older patients with ovarian and breast cancer: Young International Society of Geriatric Oncology review paper

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ABSTRACT

Breast and ovarian cancer are common malignancies among older adults, causing significant morbidity and mortality. Although most cases of breast and ovarian cancer are sporadic, a significant proportion is caused by mutations in cancer susceptibility genes, most often breast cancer susceptibility genes (BRCA) 1 and 2. Furthermore, some breast and ovarian tumors are phenotypically similar to those with BRCA mutations, a phenomenon known as "BRCAness". BRCA mutations and "BRCAness" lead to defects in DNA repair, which may be a target for therapeutic agents such as Poly ADP-Ribose Polymerase (PARP) inhibitors. PARP inhibitors are novel medications which lead to double-strand breaks resulting in cell death due to synthetic lethality, and which have been shown to be effective in patients with advanced breast and ovarian cancers with or without BRCA mutations. Three different PARP inhibitors (olaparib, niraparib, and rucaparib) have been approved for the treatment of ovarian cancer and one (olaparib) for breast cancer harboring BRCA mutations. Here, we review the currently available evidence regarding the use of PARP inhibitors for the treatment of patients with breast and ovarian cancer, with a particular focus on the inclusion of older adults in clinical trials of these therapies. Additionally, we provide an overview of currently ongoing studies of PARP inhibitors in breast and ovarian cancer, and include recommendations for increasing the evidence-base for using these medications among older patients.

Contents

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1. Breast and Ovarian Cancer in Older Women

Breast cancer is the most common cancer in women in the United States, with an estimated 266,120 new cases in 2018 [1]. Ovarian cancer, on the other hand, is less common, with an estimated 22,240 cases in 2018 [2]. However, their age distribution is similar, with approximately 44% new breast and ovarian cancer cases and 60-66% of breast and ovarian cancer-related deaths occurring in adults aged ≥65 [1,2]. Aging is a risk factor for cancer and, with the demographic shift of the population, the number and proportion of adults aged ≥65 will increase, along with the incidence of both breast and ovarian cancer [3]. Although randomized controlled trials (RCTs) are the gold standard guiding the management of patients with cancer, older adults are frequently under-represented [4–7], and those who are enrolled are typically not representative of older patients seen in everyday clinical practice, who are less fit and have more comorbidities [6] (Fig. 1). Outcomes in older women with ovarian cancer is known to be worse, overall survival rates at one year are significantly lower than in younger patients. The probability of receiving standard treatment, in accordance with recommendations, is reduced by 50% in older patients [8,9].

In recent years, Poly ADP-Ribose Polymerase (PARP) inhibitors have shown to be effective in patients with advanced breast and ovarian cancer, particularly those harboring mutations in breast cancer susceptibility genes (BRCA) 1 and 2. BRCA1 and 2 proteins are important in the process of homologous recombination repair (HRR), and thus BRCA-mutated breast and ovarian tumors are more likely to respond to PARP inhibitors. In this review, we summarize the latest available clinical evidence on the use of PARP inhibitors in breast and ovarian cancer, with a focus on older adults.

2. BRCA Mutation Carriers and "BRCAness"

Although most cases of breast and ovarian cancer are sporadic, a significant proportion is caused by mutations in cancer susceptibility genes, most often BRCA1 and BRCA2 [10]. BRCA1 and 2 are essential for repairing double-strand DNA breaks (DSB) by HRR, and alterations in these genes can lead to carcinogenesis in several human tissues [11]. At age 70, the risk of developing a breast or ovarian cancer is 57% and 49%, respectively, for deleterious BRCA1 germline mutation carriers, and of 40% and 18%, respectively, for those with BRCA2 mutations [12]. BRCA mutations are common in certain subtypes of breast and ovarian cancer, with up to 20% of women with triple negative breast cancer (TNBC) [13] and 15% of women with high-grade serous ovarian carcinoma (HGSOC) harboring germline BRCA mutations [14].

Additionally, HRR defects may occur in sporadic cancers, leading to tumors which are phenotypically similar to those with BRCA mutations, a phenomenon known as "BRCAness" [15]. Tumors exhibiting "BRCAness" show dysfunction or inactivation of genes involved in HRR, and harbor characteristics such as TP53 mutations, loss of RAD-51 focus formation, and extreme genomic instability [16]. Such characteristics make these tumors potential targets for DNA-crosslinking agents and other therapies targeting DNA-repair defects, and thus "BRCAness" could have therapeutic implications. In a study examining "BRCAness" characteristics in TNBC, two-thirds of tumors were shown to have BRCA1-like profiles, and 40% showed BRCA1 promoter methylation [17]. In ovarian cancer, this proportion is even higher, with 82% of tumor harboring genetic alterations in BRCA1, BRCA2, or both [18–20].

Some women with breast and ovarian cancer are candidates for genetic cancer risk assessment and testing [21] (Fig. 2). While women with ovarian cancer are candidates for genetic testing regardless of age [22,23], those with breast cancer are only considered candidates if they are aged ≤50 or aged ≤60 with TNBC. Therefore, many older adults with breast cancer are excluded from genetic cancer risk assessment. However, a recent report from the United States and Latin America showed that among 1035 women with breast cancer aged ≥65, 10.4% carried breast cancer-associated germline mutations (42% BRCA2, 37% BRCA1), suggesting that older patients should not be excluded from genetic testing [24]. Likewise, a recent report from Scotland showed that

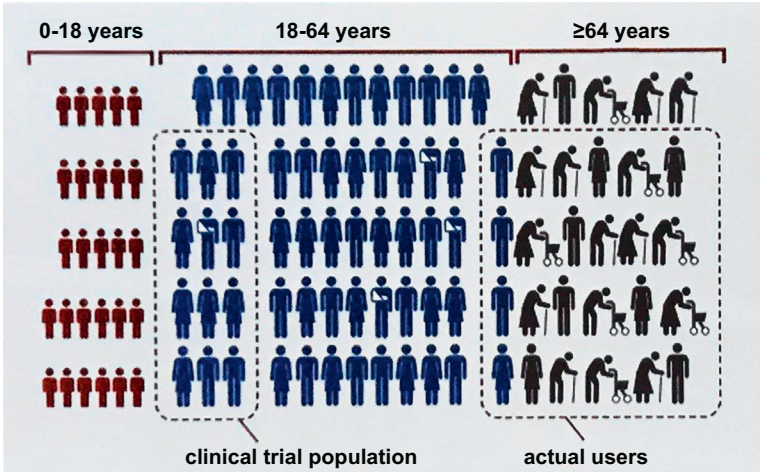

Fig. 1. Comparison between older adults seen in everyday clinical practice and those enrolled in randomized clinical trials of cancer therapies. Adapted from Erna Beers: Information for rational drug prescribing to older patients. Written permission has been given by Erna Beers.

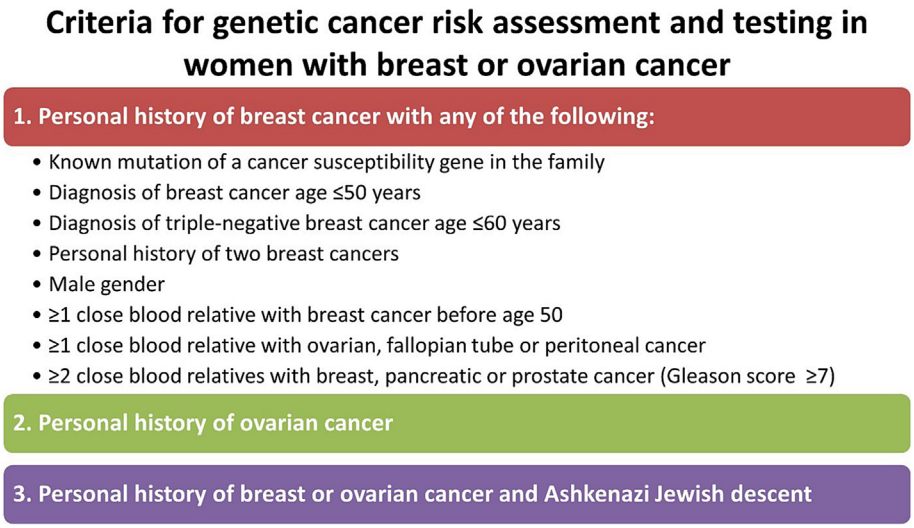

Fig. 2. Criteria for genetic cancer risk assessment and testing in women with breast or ovarian cancer.

the prevalence of germline BRCA1/2 mutations in patients aged >70 with ovarian cancer was 8.2% [22].

For women with BRCA mutations, risk-reducing bilateral salpingo-oophorectomy (rrBSO) is recommended regardless of age [21], as rrBSO is associated with a reduction in the risk of breast and ovarian cancers [25] as well as all-cause mortality [26]. However, the utility of rrBSO in post-menopausal women without a family history of ovarian cancer or BRCA2 mutation is unclear. Risk-reducing mastectomy, on the other hand, should not necessarily be recommended for older women with BRCA mutations, since it may have little effect on life expectancy [21,27].

While germline mutations are easily detectable, there is a lack of biomarkers to identify "BRCAness", and therapeutic decisions are based on the assumption that "BRCAness" is intrinsically present in some tumor types, such as TNBC and HGSOC [15,16]. Biomarkers of HRR deficiency and other hallmarks of "BRCAness" are therefore needed to determine which patients could benefit the most from drugs targeting these pathways [15].

3. Synthetic Lethality

Synthetic lethality refers to cell death that occurs as a result of deficient expression of two or more genes, but does not occur if only one of these genes is deficient [28]. This concept was explored in cancer cells which often have DNA repair defects, and therefore targeting an additional DNA repair pathway has been of interest in the development of chemotherapeutic agents [29]. HRR and non-homologous end joining (NHEJ) are cellular repair mechanisms involved in repairing double-strand breaks [30,31]. HRR uses the undamaged sister chromatin, or homologous chromosome, as a template for DNA repair, whereas NHEJ re- joins two break ends of DNA without a template [30,31]. For

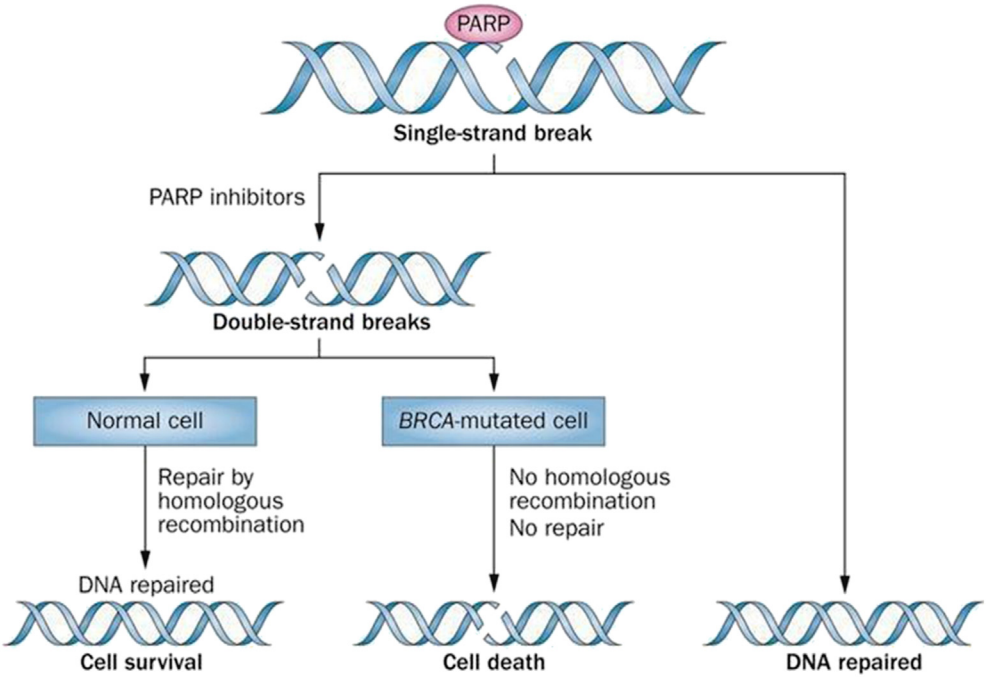

Fig. 3. Mechanism of action of PARP inhibitors and synthetic lethality. Adapted from Sonnenblick A et al. An update on PARP inhibitors–moving to the adjuvant setting. Nat Rev Clin Oncol. 2015 Jan;12(1):27-41. doi: 10.1038/nrclinonc.2014.163. Written permission has been given by Springer Nature. License number: 4381210949123.

single-strand breaks, nucleotide and base excision repair and DNA mismatch repair are involved [32].

Deficiency of either BRCA1 or 2 leads to defects in HRR and, in combination with an additional DNA pathway defect induced by therapeutic agents, can lead to synthetic lethality [33] (Fig. 3). One of these examples is the use of Poly ADP-ribose Polymerase (PARP) inhibitors [34]. PARP enzymes are best known for their involvement in DNA repair, but also play an important role in various cellular processes, including transcription, recombination, remodeling of chromatin, cell proliferation, and cell death. To date, seventeen members of the PARP family have been identified, of which PARP1, 2, and 3 are the most widely studied. PARP 1 and 2 share complementary but non-overlapping repair mechanisms (nucleotide excision repair, single-strand break repair, and NHEJ), chromatin modulation, and programmed cell death. PARP3 is important in cellular response to DSBs and in the stabilization of the mitotic spindle and telomere integrity [35–37]. Therefore, the inhibition of PARP enzymes can lead to subsequent DSBs during replication, which in turn may lead to synthetic lethality, particularly in BRCA-mutated tumors [34]. Of note, beyond the synthetic lethality, PARP inhibitors also have several other mechanisms of action through which they exert their antitumor effects, such as PARP1 trapping, impaired BRCA1 recruitment and activation of NHEJ [38].

4. Poly ADP-Ribose Polymerase (PARP) Inhibitors

Since 2016, four different PARP inhibitors have been approved by the United States Food and Drug Administration (FDA). Olaparib, niraparib, and rucaparib are approved for maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or peritoneal cancer responding to platinum-based chemotherapy (PBC). In the relapsed setting, olaparib and rucaparib are approved for the treatment of patients with BRCA-mutated epithelial ovarian cancer after ≥2 lines of chemotherapy. Additionally, olaparib is approved for the treatment of patients with BRCA-mutated human epidermal growth factor receptor 2 (HER2)-negative breast cancer previously treated with chemotherapy. Two other PARP inhibitors—talazoparib and veliparib—are currently undergoing evaluation in phase III trials in breast cancer. In the following sections, we review the most relevant studies of PARP inhibitors in ovarian and breast cancer, with a focus on the inclusion of older adults in clinical trials.

4.1. Olaparib

4.1.1. Ovarian Cancer

Olaparib is the most extensively evaluated PARP-1/2/3 inhibitor in ovarian cancer, and it is approved for use both as a maintenance therapy and for treatment of BRCA-mutated advanced disease. In patients with BRCA-mutated, treatment-refractory ovarian tumors, 63% derived a clinically meaningful benefit from treatment with olaparib [39]. Two subsequent phase 2 study further confirmed the clinical activity of olaparib, showing a 34% overall response rate (ORR) with a median duration of response of 7.9 months, including patients who had received ≥3 prior lines of chemotherapy [40,41].

A randomized phase 2 study (Study 19) evaluated olaparib versus placebo maintenance in 265 women with ovarian cancer who responded to PBC, of which 51.3% (n=136) had BRCA mutations. Median age in the olaparib cohort was 58 (range 21-89). Progression-free survival (PFS) was 8.4 months in the olaparib arm versus 4.8 months in the placebo arm (HR 0.35; p<0.001) [42]. OS also increased with the use of olaparib: 29.8 versus 27.8 months (Hazard Ratio (HR) 0.73; p= 0.025) in the entire population, and 34.9 versus 30.2 months (HR 0.62; p=0.025) among patients with BRCA-mutated tumors [43]. Age-specific subgroup analysis for PFS showed that the upper limit of the 95% CI was crossed in patients aged ≥65 (i.e. not statistically significant, p-value is not provided), which may be related to the small proportion of older adults in the trial. Toxicities were mild, although grade 3/4 fatigue and anemia were reported in 6.6% and 5.1% of patients, respectively [42]. Dose reduction due to toxicity was required in 24% of the patients, and there was no difference in health-related quality of life (HRQoL) between the two groups [44]. Notably, age-specific data regarding both safety and HRQoL are not available.

SOLO-2 was a phase 3 RCT that assessed olaparib versus placebo as a maintenance therapy for patients after at least ≥2 lines of PBC (n = 295) [45]. Median age in the olaparib group was 56 years (range 51-63), and all patients had Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. PFS was 19.1 months in the olaparib group versus 5.5 months in the placebo group (HR 0.30, p<0.0001), without significant differences in HRQoL. Toxicities were similar to Study 19, albeit at higher rates. Although 2% of patients in the olaparib group and 4% of patients receiving placebo developed myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), it remains unclear whether PARP inhibitors directly lead to secondary malignancies. Older adult-specific data were not reported in SOLO-2.

A pooled analysis of older adults that included eight phase 1/2 studies of olaparib in ovarian cancer ($n = 78$) showed no significant difference in toxicity between patients aged <65 and ≥65 (Table 1) [46]. However, most of the older patients included were aged 65-75 (n = 61); only a very small proportion were older than 75 (n = 17), none were >85, and almost all had an ECOG PS of 0 or 1 [46]. Although the findings may seem reassuring, the applicability of these results among older adults, particularly those aged >75 and/or with poor functional status, remains unclear and requires further investigation. Furthermore, the impact of comorbidities such as renal impairment, which are more common in the older population, on the toxicity of olaparib is currently under investigation. At present, olaparib is not recommended for patients with severe renal impairment [47].

The currently recommended dose of olaparib for older adults with ovarian cancer is 300 mg twice daily as monotherapy in tablet form [48]. It is important to mention that olaparib tablets and capsules are neither bioequivalent nor interchangeable due to differences in dosing and bioavailability. However, the tablet form of olaparib may be more convenient for older patients, since it requires taking only 4 tablets per day instead of 16 capsules, which may be particularly burdensome for patients with cognitive impairment and/or poor social support [49]. When using olaparib, concomitant administration of CYP3A inhibitors or inducers should be avoided [47].

4.1.2. Breast Cancer

Olaparib may play an important role in the treatment of breast cancer, particularly in TNBC and in tumors harboring BRCA mutations. In a phase 1 study, 62 heavily pre-treated patients with BRCA-mutated tumors (median age 48, range 29-73) were treated with olaparib and the clinical benefit rate (CBR) was 59.9%. A subsequent phase 2 study in 58 women reported an ORR of 33%, and 36% of patients had stable disease (SD) [50]. Reported toxicities in both of these studies were consistent with data from ovarian cancer trials [39,50].

The OlympiAD RCT evaluated olaparib versus physician's choice of chemotherapy in 302 patients with germline BRCA mutations and HER2-negative breast cancer [51]. Median age was 44 years (range 22-76). In the olaparib group, ORR was 59.9% [95% Confidence Interval (CI), 52.0 to 67.4] compared to 28.8% (95% CI 18.3 to 41.3) in the chemotherapy group. PFS was 7.0 months in the olaparib group versus 4.2 months in the chemotherapy group (HR 0.58, p<0.001). No difference in OS was noted. Due to the small number of older adults included in the trial (n = 15), subgroup analyses for PFS in the older patients could not be performed. However, of the eleven patients aged ≥65 in the olaparib group, 81.8% (n = 9) experienced events affecting PFS. Overall, the toxicity profile of olaparib was similar to that seen in ovarian cancer trials [41–43]. HRQoL was better in the olaparib group; the time to a clinically meaningful decrease in HRQoL was not reached in the olaparib group compared to 15.3 months in the chemotherapy group.

Table 1
Age-specific data on toxicities associated with olaparib and niraparib in clinical trials.

	Olaparib – pooled data from eight phase 1/2 trials								Niraparib – phase 3 NOVA			
Age group (n)	< 65 years ($n = 320$)		65–69 years ($n = 38$)		70–74 years ($n = 23$)		≥75 years ($n = 17$)		< 65 years ($n = 240$)		≥ 65 years ($n = 132$)	
Adverse events n (%)	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Anemia	84 (26%)	40 (13%)	14 (37%)	5 (13%)	5 (22%)	2 (9%)	7 (41%)	4 (24%)	*	65 (27%)	*	26 (20%)
Nausea	223 (70%)	7 (2%)	16 (42%)	1 (3%)	12 (52%)	1 (4%)	13 (76%)	0 (0%)	*	*	*	*
Fatigue	183 (57%)	22 (7%)	25 (66%)	2 (5%)	14 (61%)	2 (9%)	11 (65%)	4 (24%)	*	*	*	*
MDS/AML	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	n/a	n/a	n/a	n/a

Abbreviations: MDS/AML: myelodysplastic syndrome/acute myeloid leukemia; n/a: not available.
* Similar incidence – not otherwise specified.

4.2. Niraparib

Niraparib is an orally bioavailable, highly selective PARP-1/2 inhibitor used in maintenance therapy for patients with recurrent ovarian cancer who achieved objective response to PBC [52,53]. Its antitumor activity was demonstrated in a phase 1 study of 100 patients (median age 59, range 39-75) with advanced solid tumors [54], and the maximum tolerated dose (MTD) established at 300mg daily.

In the phase 3 NOVA RCT, 553 patients with platinum-sensitive, recurrent ovarian cancer were randomized in a 2:1 fashion to niraparib maintenance or placebo upon completion of PBC. Patients were stratified according to the presence of germline BRCA mutations [55]. Included patients were aged 33-84; 29.3% (n=160) were aged 65-74 and 5.7% (n=31) were aged ≥75. Compared to placebo, niraparib improved PFS in all subgroups: in the germline BRCA-mutated cohort, 21.0 versus 5.5 months (HR 0.27, p<0.001); in the overall non- germline BRCA mutated cohort, 9.3 versus 3.9 months (HR 0.45, p<0.001); and in the non- BRCA cohort with HRR deficiency, 12.9 versus 3.8 months (HR 0.38, p<0.001). These results suggest that niraparib may benefit all patients with platinum-sensitive recurrent ovarian cancer. Pre-specified subgroup analyses documented consistency of the PFS benefit in patients aged ≥65. The most commonly reported grade 3-4 toxicities were hematologic, including thrombocytopenia (34%), anemia (25%), neutropenia (20%), and myelodysplastic syndromes (1.4%). The most common grade 3-4 non-hematologic toxicities were hypertension (8%) and fatigue (8%). HRQoL was similar in both groups. Combined phase 1 and phase 3 studies suggest that age has no impact on the pharmacokinetics of niraparib, although data in patients aged ≥75 are limited [54–57].

The safety and efficacy of niraparib among older patients enrolled in the NOVA study has recently been reported (Table 2) [56]. In both the BRCA and non-BRCA mutated cohorts, efficacy was similar in patients aged ≥65 and their younger counterparts (BRCA-mutated: <65 years, HR 0.27; ≥65 years, HR=0.27; non-germline BRCA mutated: <65 years, HR 0.54; ≥65 years, HR 0.38). Outcomes were also comparable between patients <70 and ≥70 (BRCA-mutated: <70 years, HR 0.30; ≥70 years, HR 0.09; non-germline BRCA mutated: <70 years, HR 0.47; ≥70 years, HR 0.35). Grade 3-4 toxicities occurring in >10% of patients were similar in those aged <65 and ≥65 (thrombocytopenia, 27% versus 31%; anemia, 27% versus 20%; neutropenia 12% versus 10%, respectively), suggesting a favorable safety profile for niraparib among older patients. No treatment-related deaths were reported in either subgroup. A subsequent retrospective analysis of patients included in NOVA identified two risk factors for myelosuppression [57]: body weight <77 kilograms and/or basal platelet count <150,000/μL. Approximately 25% of patients weighed less than 58kg, and approximately 25% of patients weighed more than 77kg. The incidence of grade 3 or 4 AEs was greater in the former compared to the latter group (78% versus 53%). Only a small percentage of patients (13%) remained at a dose of 300 mg beyond cycle three. This analysis therefore suggests a starting dose of 200mg for patients weighing less than 58kg. Nonetheless, even at 200mg, platelet count should be monitored weekly in the first month after initiating niraparib treatment due to the significant risk of thrombocytopenia.

4.3. Rucaparib

Rucaparib is a potent small-molecule inhibitor of PARP-1/2/3. The efficacy of rucaparib was investigated in two clinical trials, the phase 1/2 Study 10 and the phase 2 ARIEL2 [58,59]. Both studies included previously treated women with relapsed BRCA-mutated ovarian cancer who were treated with 600mg of rucaparib twice daily as monotherapy. A pooled analysis of the 106 patients included in both trials showed an ORR of 53.8% (95% CI 43.8-63.5); 8.5% and 45.3% of patients achieved CR and PR, respectively (median duration of response 9.2 months, 95% CI 6.6-11.6) [58,59]. The median PFS was 10.0 months (95% CI, 7.3-12.5 months).

The phase 3 ARIEL3 RCT included 564 patients with ovarian cancer (median age 61 years, range 36-85) [60]. All patients had received ≥2 prior PBC lines and were in CR/PR. Patients were randomized 2:1 to receive rucaparib or placebo maintenance therapy until unacceptable toxicity or progression. The primary endpoints were investigator-assessed PFS in 3 subgroups: patients with BRCA mutations, patients with HRR deficiency, and all patients. Rucaparib treatment led to an improvement of PFS in all groups. Median PFS was 16.6 months in the rucaparib group

Table 2
Age-specific data on efficacy of selected trials of PARP inhibitors (when available).

Drug/Study	Progression-Free Survival by age group (Hazard Ratio, 95% Confidence Interval)			
	All patients	Aged < 65 years	Aged 65–74 years	Aged ≥ 75 years
Olaparib Phase 3 SOLO2	0.30 (0.22–0.41)	0.30 (0.22–0.41)	No patients were included in these age groups	
Niraparib Phase 3 NOVA	Germline BRCA mutations: 0.27 (0.17–0.41) Non-germline BRCA mutations: 0.45 (0.34–0.61)	Germline BRCA mutations: 0.27 (0.16–0.44) Non-germline BRCA mutations: 0.54 (0.37–0.80)	Germline BRCA mutations: 0.27 (0.09–0.81) Non-germline BRCA mutations: 0.38 (0.23–0.61)	
Rucaparib Phase 3 ARIEL3	0.36 (0.30–0.45)	0.33 (0.25–0.43)	0.43 (0.29–0.64)	0.47 (0.16–1.35)
Olaparib Phase 3 OlympiAD	0.58 (0.43–0.80)	0.66 (0.49–0.88)	Not calculated, only 11 were included patients in these age groups	

Abbreviations: BRCA: breast cancer susceptibility genes.

versus 5.4 months in the placebo group among patients with BRCA mutations (HR: 0.23, p<0·0001); 13.6 months versus 5.4 months among patients with HRR deficiency (HR: 0.32, p<0.0001); and 10.8 months versus 5.4 months among all patients (HR: 0.36, p<0.0001). Similar to ARIEL2, rucaparib appears to benefit patients without BRCA mutations. Thirty-eight percent (n = 138) of rucaparib-treated patients in ARIEL3 were aged ≥65, and 7% (n = 25) were aged ≥75. Subgroup analyses of PFS in patients aged 65-74 showed a survival benefit for rucaparib versus placebo (aged 65-74: HR 0.43, p<0.001). However, for patients aged ≥75, the HR was non-significant (HR 0.47, p=0.16) [60].

Patients in all three trials (Study 10, ARIEL2, ARIEL3) were highly selected and had ECOG PS of 0 or 1. As with other PARP inhibitors, nausea, vomiting, asthenia, fatigue, and myelosuppression were the most common toxicities leading to treatment interruption (13.4%) or dose reduction (54.6%). In contrast with other PARP inhibitors, grade ≥3 liver transaminase elevations requiring dose reduction were reported in 10% of rucaparib-treated patients. However, these elevations were transient, self-limiting, and not associated with other signs of liver toxicity. Rucaparib also caused elevations in serum creatinine in 17% of the patients, which were mostly grade 1-2 and self-limiting. Grade 3-4 toxicity occurred in 65% of patients aged ≥65 and in 63% of patients aged >75. Data on HRQoL are not yet available.

4.4. Talazoparib

Talazoparib is a highly potent oral dual-mechanism PARP inhibitor with significant PARP- DNA trapping activity. The MTD of talazoparib has been established at 1mg once daily. In the phase 2 ABRAZO study [61], i84 patients with advanced BRCA-mutated breast cancer were included (median age 50 years, range 31-75). ORR was 24% in patients with BRCA1 mutation, 34% with BRCA2 mutation, 26% with TNBC, and 29% with HR+ disease. Commonly reported all-grade toxicities included anemia (52%), fatigue (45%), nausea (42%), diarrhea (33%), thrombocytopenia (33%), and neutropenia (27%). Grade ≥3 toxicities were exclusively hematological. Drug discontinuation occurred in 3 patients (4%), and there were no treatment-related deaths.

Talazoparib versus physician's choice of chemotherapy among 431 patients (median age 46 years) with HER2-negative metastatic breast cancer harboring BRCA1/2 mutations was evaluated in the phase 3 EMBRACA RCT [62]. PFS was 8.6 months in the talazoparib arm versus 5.6 months in the chemotherapy arm (HR 0.542, p≤0.0001). ORR was higher in the talazoparib arm: 62.6% versus 27.2% (HR=4.99, p≤ 0.0001). Significant PFS and QoL benefits were seen in all pre-defined subgroups. Grade 3-4 hematologic toxicities were observed in 55% of patients in the talazoparib arm versus 38% of those in the chemotherapy arm, while grade 3-4 non-hematologic toxicities were higher in the chemotherapy arm. Treatment-related deaths occurred in 2.1% and 3.2% of patients in the talazoparib and chemotherapy arm, respectively. While talazoparib may represent a potential option for the treatment of patients with BRCA-mutated breast cancer, age-specific data are not yet available, and making recommendations for older adults is currently not possible.

4.5. Veliparib

Veliparib is an oral PARP-1/2 inhibitor with a MTD of 400 mg twice daily as monotherapy. The efficacy of veliparib has been investigated in patients with TNBC in the neoadjuvant phase 2 I-SPY2 trial [63]. Veliparib produced high pathologic complete response (pCR) rates when combined with carboplatin, although it is unclear whether these were primarily driven by carboplatin, since platinum compounds have led to increased pCR when added to standard chemotherapy regimens [64–67]. A subsequent phase 2 study (NCT01506609) [68] and the phase 3 BrighTNess trial [69] unfortunately failed to show any benefit of adding veliparib to a platinum containing regimen compared to a platinum containing regimen alone.

5. Future Directions

Immune escape and DNA repair deficiency are two of the key hallmarks of cancer [70,71]. Immune checkpoint inhibitors play an evolving role in cancer treatment, and recent analyses on biomarkers of response to checkpoint inhibitors have highlighted a link between genomic instability, mutational load, and response to treatment [72,73]. PARP inhibitors show intrinsic immunomodulatory activity [75], and are able to induce PD-L1 expression in both DNA repair-proficient and DNA repair-deficient tumors [74–76]. Results of the first phase I trial evaluating the combination of olaparib and an anti-PD-L1 monoclonal antibody durvalumab reported an encouraging safety profile: no dose limiting toxicity, 8% grade 3 anemia, and 25% grade 1 thrombocytopenia. The combination had no overlapping toxicities, with a trend for efficacy (83% CBR), regardless of PD-L1 status [77].

Overall, there is a strong scientific rationale for combining a PARP inhibitor and an anti-PD-1 inhibitor in patients with DNA repair-deficient or platinum-sensitive cancer. Combinations may improve the durability of PARP inhibitors by inducing an immunological memory response and enhance response rate to PD-1 inhibitors. These strategies are appealing in older patients because of the non-overlapping toxicities and the induced immune memory response. However, data on toxicities with these combination drugs in older patients needs to be further evaluated. Table 3 summarizes some of the ongoing clinical trials evaluating PARP inhibitors in combination with various targeted agents.

Table 3
Ongoing clinical trials with PARP inhibitors in combination with targeted agents.

PARP inhibitor	Targeted Agent	Phase	Clinicaltials.gov identifier
Olaparib	Durvalumab (PD-L1 inhibitor)	2	NCT03167619
	Onalespib (HSP90 inhibitor)	1	NCT02898207
	Adavosertib (WEE1 inhibitor)	2	NCT03579316
		1/2	NCT02485990
	Tremelimumab (CTLA-4 inhibitor)	1/2	NCT02571725
	BKM120 or BYL719 (PI3K inhibitor)	1	NCT01623349
	Atezolizumab (PD-L1 inhibitor)	2	NCT02849496
	Cediranib (VEGF inhibitor)	1	NCT02855697
		2	NCT02889900
		1/2	NCT01116648
	Bevacizumab (VEGF inhibitor)	1	NCT00710268
	AZD5363 (AKT Inhibitor)	1	NCT02338622
	Selumetinib (MEK1/2 inhibitor)	1/2	NCT03162627
	Prexasertib (CHK1/2 inhibitor)	1	NCT03057145
	AZD2014 (mTORC1/2 Inhibitor) or AZD536 (AKT Inhibitor)	1b	NCT02208375
	Endocrine treatment (Tamoxifen or NSAIs)	1	NCT02093351
Niraparib	Trastuzumab (anti-HER2)	1b/2	NCT03368729
	Everolimus (mTOR inhibitor)	1	NCT03154281
	Pembrolizumab (PD-1 inhibitor)	1/2	NCT02657889
	Bevacizumab (VEGF inhibitor)	2	NCT03326193
		1/2	NCT02354131
Rucaparib	Atezolizumab (PD-L1 inhibitor)	1	NCT03101280
	Nivolumab (PD-1 inhibitor)	3	NCT03522246
Talazoparib	Avelumab (PD-1 inhibitor)	1b/2	NCT03330405
Veliparib	Lapatinib (anti-HER2)	Not applicable	NCT02158507
	Dinaciclib (CDK1/2/5/9 inhibitor)	1	NCT01434316

Abbreviations: PD-L1: programmed death-ligand 1; HSP90: heat shock protein 90; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; PI3K: phosphatidylinositide 3-kinase; VEGF: vascular endothelial growth factor; mTORC: mammalian target of rapamycin complex; HER2: human epidermal growth factor receptor 2; mTOR: mammalian target of rapamycin; PD-1: programmed cell death protein 1; CDK: cyclin-dependent kinases; NSAI: non-steroidal aromatase inhibitors; WEE1: WEE1 kinase; AKT: RAC-beta serine/threonine-protein kinase; MEK: mitogen-activated protein kinase kinase; CHK: checkpoint kinase

6. Clinical Use of PARP Inhibitors in Older Adults

Currently, the main use of PARP inhibitors is in the maintenance setting, following objective response to PBC in platinum-sensitive advanced ovarian cancer. While patients with tumors harboring BRCA mutations or "BRCAness" derive the most benefit, patients with normal BRCA status seem to obtain benefit as well. Additionally, patients with advanced ovarian cancer who have received ≥3 prior lines of chemotherapy and have BRCA mutations may derive benefit from PARP inhibitors. Finally, heavily pre-treated patients with HER2-negative advanced BRCA-mutated breast cancer achieve longer PFS with olaparib. Although the reported side effects in trials are manageable without any decline in HRQoL, the lack of age- specific data makes it difficult to make recommendations for a significant proportion of older adults with breast and ovarian cancer, particularly those who are vulnerable or frail.

The toxicity profile of PARP inhibitors appears to be acceptable based on available data from RCT, although the occurrence of clinically significant toxicity is likely to be higher in "real- world" settings. Older patients included in RCTs were highly selected, had a good performance status (ECOG 0-1), and adequate organ functions. On the other hand, those treated in daily clinical practice often have organ dysfunctions and are on multiple medications, and may lead to clinically significant drug interactions affecting the efficacy and toxicity of PARP inhibitors. Therefore, there is a need to enroll more vulnerable or frail older patients into RCT of PARP inhibitors. In addition, the inclusion of a geriatric assessment into these trials should be encouraged in order to adequately risk-stratify older patients [78–83] and to help balance the potential benefits and side-effects of treatment [84–89]. A geriatric assessment is a multidimensional tool that evaluates several domains, including functional status, comorbidities, cognition, psychological status, social functioning and support, nutritional status, and concomitant medications [79–81,83,90–92]. The geriatric assessment can categorize older patients into fit, vulnerable, or frail categories, and may guide treatment modifications or patient stratification in clinical trials.

Another potential strategy to increase the evidence for the use of PARP inhibitors in older adults is the design of older adult-specific phase II clinical trials that include geriatric assessment tools when evaluating the efficacy and safety of these therapies among older patients [93]. Although BRCA-mutated ovarian and breast cancers are typically considered a disease of young women, about 8-10% of cases occur in patients aged ≥65, and "BRCAness" is common in TNBC and HGSOC among older women [17,18]. Overall, currently available evidence suggests that fit older patients derive the same benefit and experience similar toxicities than younger patients from PARP inhibitors. Therefore, although data regarding the efficacy and toxicity of PARP inhibitors in vulnerable and frail older patient are lacking, this treatment option remains attractive, and should be the subject of further investigation.

7. Conclusions

Although there is a lack of age-specific data, available evidence suggests that fit older patients with ovarian cancer with or without BRCA mutations may benefit from PARP inhibitors in the maintenance setting. Older patients with advanced ovarian and HER-2 negative breast cancer with BRCA mutations who are heavily pre-treated may also benefit from PARP inhibitors in the relapsed setting. Nevertheless, there is a need to increase the representation of older adults who are vulnerable or frail in clinical trials evaluating the use of PARP inhibitors.

Conflicts of Interest

Gabor Liposits, Lucy Dumas, Kah Poh Loh, Enrique Soto-Perez-de-Celis, Nicolò Matteo Luca Battisti, Sindhuja Kadambi, Capucine Baldini and Stuart L. Lichtman have no conflicts of interest to disclose. Dr. Banerjee serves advisory boards and received honoraria from AstraZeneca, Clovis and Tesaro.

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