Role of PARP in TNBC

Subjects: Biochemistry & Molecular Biology

Contributor: Dharmendra Yadav

Triple-negative breast cancer is a combative cancer type with a highly inflated histological grade that leads to poor theragnostic value. Gene, protein, and receptor-specific targets have shown effective clinical outcomes in patients with TNBC. Cells are frequently exposed to DNA-damaging agents. DNA damage is repaired by multiple pathways; accumulations of mutations occur due to damage to one or more pathways and lead to alterations in normal cellular mechanisms, which lead to development of tumors. Advances in target-specific cancer therapies have shown significant momentum; most treatment options cause off-target toxicity and side effects on healthy tissues. PARP (poly(ADP-ribose) polymerase) is a major protein and is involved in DNA repair pathways, base excision repair (BER) mechanisms, homologous recombination (HR), and nonhomologous end-joining (NEJ) deficiency-based repair mechanisms. DNA damage repair deficits cause an increased risk of tumor formation. Inhibitors of PARP favorably kill cancer cells in BRCA-mutations. For a few years, PARPi has shown promising activity as a chemotherapeutic agent in BRCA1- or BRCA2-associated breast cancers, and in combination with chemotherapy in triple-negative breast cancer.

breast cancer PARP (poly(ADP-ribose) polymerase) TNBC therapeutic target DNA damage repair signaling pathway

1. Introduction

Breast cancer (BC) is the most common cancer that occurs in women worldwide [1]. BC is caused by accumulation of somatic mutations in breast cells, which impair cell division and DNA repair mechanisms, resulting in irregular cell growth proliferation, differentiation, and ultimately, progression of tumorigenesis [2][3]. Triple-negative breast cancer is more belligerent and has a poorer prognosis than other types of breast cancer. Triple-negative breast cancer (TNBC) accounts for approximately 15% of all BC, and lacks human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and estrogen receptor (ER) expression and amplification. If we compare it with another type of BC, TNBC exhibits inherently aggressive clinical symptoms and poorer clinical outcomes [4][5][6][7]. Presently, the clinical targeted drugs for BC include poly-(ADP)-ribose polymerase (PARP) inhibitors (PARPi), CDK4/6 inhibitors (CDK4/6i), PI3K inhibitors, and AKT inhibitors—but none of these drugs alone are very effective against TNBC [8]. There is an urgent need for the rational exploration of drug compatibility and potential targets for TNBC [7][8]. PARP1 (poly (ADP-ribose) polymerase 1) was discovered approximately 50 years ago and is involved in gene transcription, DNA repair, and cell death [9]. PARP1 has acceptable therapeutic importance against cancer, as shown in **Figure 1** and **Figure 2** [10]. PARP inhibitors have emerged as effective treatments in clinical trials for sporadic TNBC and *BRCA*-associated cancers [11]. There are various types of PARP inhibitors under clinical trial

such as olaparib, BSI-201, talazoparib, rucaparib veliparib, and niraparib [10][11]. Inhibition of the PARP-1 and PARP-2 enzymes is believed to be attained mainly via binding of the NAD+ catalytic domain side chain, extending out of the NAD catalytic site of the PARP inhibitor [12]. It also thought that the PARP enzyme locks on to the site of DNA damage, preventing its usual release from DNA molecules [10][11][12][13][14][15]. PARP-1 binds to the damaged site through its zinc-finger domains in the presence of SS (single-stranded)-DNA breaks [13]. PARP-1 and poly (ADP) polymerization recruits and binds other DNA-repair proteins, leading under normal cell physiology to an increasingly negative charge on the enzyme, and eventual dissociation from the DNA [14]. Some clinical investigations have shown the need for HRD (homologous recombination DNA repair) in facilitating PARP inhibition, via loss of *BRCA* function [16][17]. Researchers from the field have suggested that PARP inhibition is associated with the induction of DNA damage by chemotherapy in the more general cohort of TNBC.

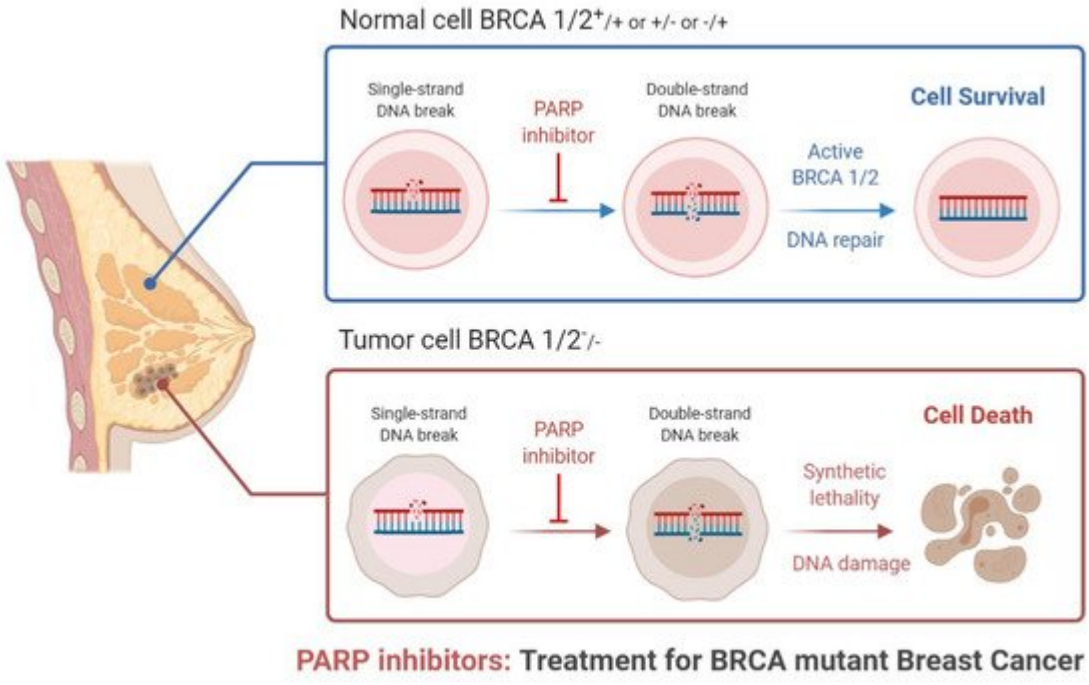


Figure 1. Role of PARP inhibitors in treatments for *BRCA* mutant breast cancer.

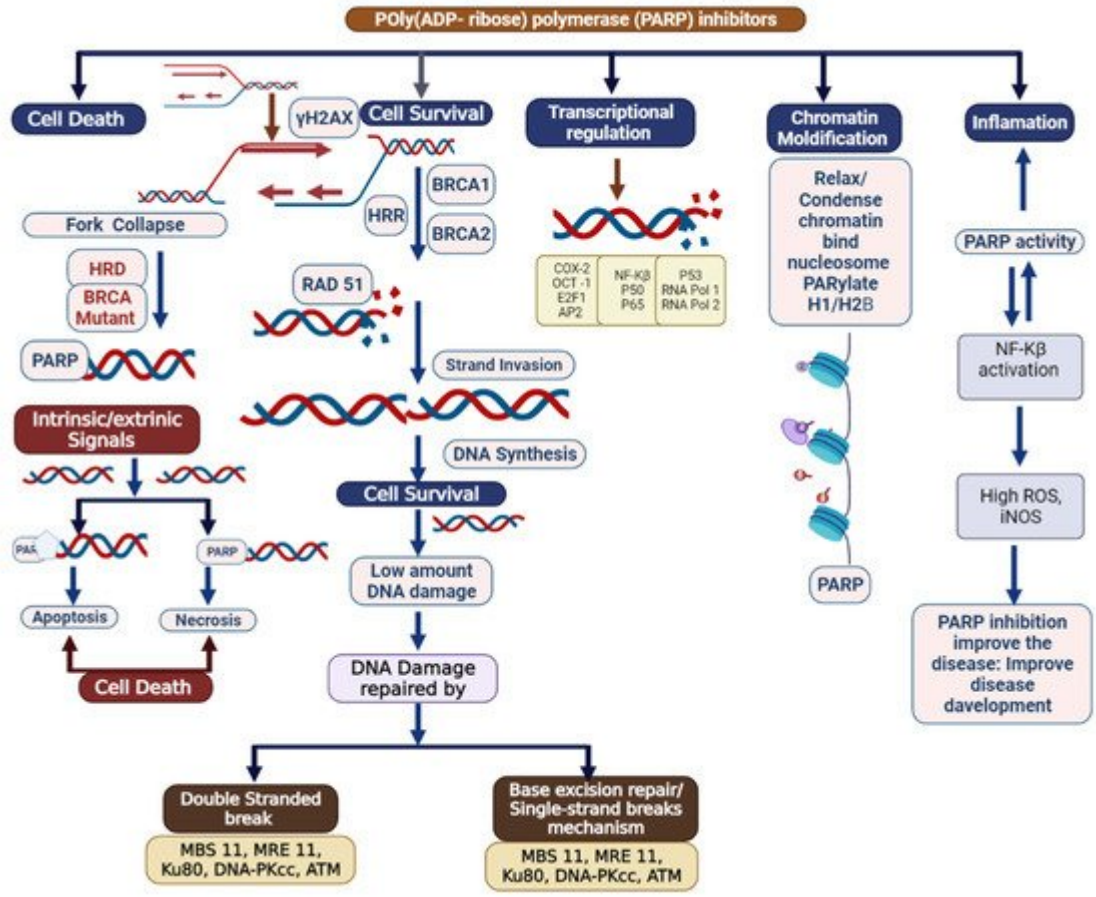
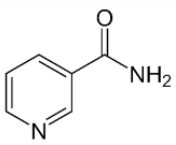


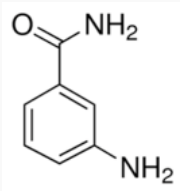
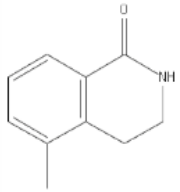
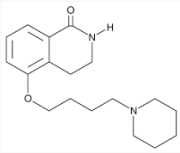
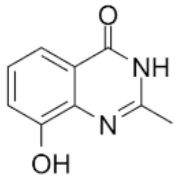
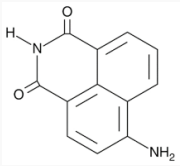
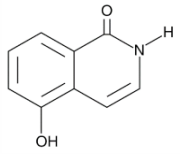
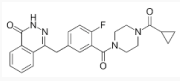
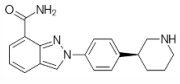
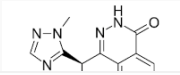
Figure 2. Schematic delineating the multifaceted nature of poly (ADP) ribose polymerase (PARP): DNA repair, chromatin modification, inflammation, transcriptional regulation, and cell death. Potential role of elevated PARP-1 in tumorigenesis. After DNA damage, PARP-1 activates DNA repair. However, PARP-1 also acts as a co-activator of NFkB signaling, which can propagate inflammatory signaling and lead to more DNA damage, including the formation of oxidatively clustered DNA lesions (OCDLs). The formation of OCDLs is elevated in numerous tumor types. PARP-1 activity could potentially be beneficial or harmful in the repair of ROS-induced DNA lesions.

2. Clinical Applications of PARP Inhibitors in TNBC

PARP inhibitors have been shown to have effective clinical outcomes against different types of cancer. There are various clinical trials registered investigating PARPi therapies (**Table 1**, **Table 2** and **Table 3**).

Table 1. List of PARP inhibitors.

Compound Name	Compound Structure	Efficacy	IC_{50}
Nicotinamide		PARP inhibitor and by-product of the PARP reaction; many pharmacological actions other than that of inhibiting PARP	210 μM

Compound Name	Compound Structure	Efficacy	IC_{50}
3-aminobenzamide		Benzamides are free radical scavengers, among other pharmacological actions	33 μM
PD128763		Cytoprotective agent, chemosensitizer, and radiosensitizer; adverse effect of compound causes hypothermia	420 nM
DPQ		A commonly used Warner–Lambert PARP inhibitor compound based on an isoquinoline core	1 μM
NU1025		Potentiators of anticancer agent cytotoxicity	400 nM
4-ANI		PARP in DNA repair and cell death	180 nM
ISO		PARP in DNA repair and cell death	390 nM
Olaparib (Lynparza)		Use in a *BRCA1*-positive patient with metastatic triple-negative breast cancer, without the initial use of platinum-based chemotherapy, showed significant rapid near-resolution of large liver metastasis while patient experienced gout-like symptoms	1 nM
Niraparib (Zejula)		Niraparib in combination with pembrolizumab in patients with triple-negative breast cancer	4 nM
Talazoparib		Ferm line *BRCA*-mutant, *HER2*-negative locally advanced or	0.6

Name of the Molecules	T_{max} (h)	t (h)	AUC (lgh/mL)	C_{max} (lg/mL)	CL/F (L/h)	V_z/F	References
Olaparib capsule formulation 300 mg	1.49 (0.57–3.05)	13.02 (8.23)	55.20 (67.4)	8.05 (24.3)	6.36 (3.47)	112.1 (59.84)	[18]

Name of the Molecules	T_{max} (h)	t (h)	AUC (lgh/mL)	C_{max} (lg/mL)	CL/F (L/h)	V_z/F	References
Olaparib tablet formulation 300 mg single dose (fasted)	1.50 (0.50–5.85)	12.2 (5.31)	43.6 (54.3) [AUC_t] 43.0 (55.2) [AUC]	7.00 (35.0)	7.95 (4.23)	146 (142)	[19]
Olaparib tablet formulation 300 mg single dose (fed)	4.00 (1.00–12.0)	12.2 (5.31)	46.0 (56.6) [AUC_t] 45.4 (57.1) [AUC]	5.48 (40.5)	7.55 (3.99)	127 (107)	[19]
Veliparib monotherapy 40 mg (10 mg, fasting)	1.2 ± 0.8	5.9 ± 1.3	2.23 ± 0.82 [AUC_t] 2.43 ± 1.07 [AUC]	0.36 ± 0.13	19.0 ± 7.36	NA	
Veliparib monotherapy 40 mg (10 mg, fed)	1.2 ± 0.7	5.8 ± 1.2	2.45 ± 0.93 [AUC_t] 2.65 ± 1.17 [AUC_t]	0.37 ± 0.12	17.3 ± 6.41	NA	[20][21]
Veliparib monotherapy 40 mg (40 mg, fasting)	1.3 ± 0.9	5.8 ± 1.3	2.24 ± 0.98 [AUC_t] 2.45 ± 1.24 [AUC_t]	0.34 ± 0.12	19.5 ± 7.66	NA	
Veliparib monotherapy 40 mg (40 mg, fed)	2.5 ± 1.1	5.8 ± 1.4	2.14 ± 0.80 [AUC_t] 2.35 ± 1.06 [AUC_t]	0.28 ± 0.09	19.7 ± 7.51	NA	
Veliparib metabolite M8	2.4 (3.5–9.8)	–	0.3–1.9 [AUC_{int}]	0.011 (0.007–0.014)	NA	NA	[20][21]
Niraparib 300 mg/day	3.1 (2.0–6.1)	a	14.117 (AUC24)b	1.921	NA	NA	[12]
Niraparib metabolite: unlabeled M1 plasma	9.02	78.4	41.2 (AUC_t)	476	NA	NA	[15]

Table 3. Clinical Trials of PARP Inhibitors in TNBC.

Name of Drug	Types of Inhibitors	Prior Treatment	Type of Population	Status	ClinicalTrials.gov Identifier
AZD1775 in patent with	PARP Inhibitor, patent with TNBC	Olaparib in combination with	Inhibitor of Ataxia-Telangiectasia and *WEE1* inhibitor	Phase II	NCT03330847

Name of Drug	Types of Inhibitors	Prior Treatment	Type of Population	Status	ClinicalTrials.gov Identifier
TNBC LYNPARZATM		AZD6738 mutated (ATM)			
AZD1775 in patent with TNBC LYNPARZATM	PARP Inhibitor, patent with TNBC	Olaparib with radiation therapy, after chemotherapy	Inhibitor of ataxia-telangiectasia	Phase I	NCT03109080
AZD1775, LYNPARZATM	Patent with TNBC	Olaparib with atezolizumab	Inhibitor of *PD-L1*	Phase II	NCT02849496
AZD1775, LYNPARZATM	Patent with TNBC	Oolaparib with paclitaxel and carboplatin	Inhibitor of germline *BRCA* mutated	Phase II/III	NCT03150576, NCT02789332
AZD1775, LYNPARZATM	Patent with TNBC	Olaparib with AZD2171 orally	Inhibitor of *VEGFR* tyrosine kinase	Phase I/II	NCT01116648
AZD1775, LYNPARZATM	Patent with TNBC	Olaparib with PI3K inhibitor, BKM120	Inhibitor of BKM120	Phase I	NCT01623349
AZD1775, LYNPARZATM	Patent with TNBC	Olaparib with onalespib	Inhibitor of heat shock protein 90	Phase I	NCT02898207
AZD1775, LYNPARZATM	Patent with TNBC	Olaparib with AZD2014	mTORC1/2 or Oral AKT inhibitor	Phase I/II	NCT02208375
PARP1/2 inhibitor Veliparib	Patent with TNBC	Veliparib in combination with cyclophosphamide	Inhibitor of *EGFR*, *HER2*, *BRCA*, and tyrosine kinase	Phase II and failed in phase III trials	NCT01306032
PARP1/2 inhibitor Veliparib	Inhibitor of tyrosine kinase, *HER2*, and *BRCA*	Veliparib in combination with carboplatin	Patients with TNBC	Completed phase I study	NCT01251874
PARP1/2 inhibitor Veliparib	Inhibitor of *EGFR*, *BRCA*, and tyrosine kinase	Veliparib with vinorelbine	Patients with TNBC	Completed phase I	NCT01281150
PARP1/2 inhibitor Veliparib	Inhibitor of *EGFR*, *HER2*, *BRCA*, and tyrosine kinase	Veliparib with cisplatin	Patients with TNBC	Completed phase I	NCT01104259
PARP1/2 inhibitor	Inhibitor of *EGFR*, *HER2*, *BRCA*,	Veliparib with pegylation	Patients with TNBC	Completed phase I	NCT01145430

Name of Drug	Types of Inhibitors	Prior Treatment	Type of Population	Status	ClinicalTrials.gov Identifier
Veliparib	and tyrosine kinase				
PARP1/2 inhibitor Veliparib	Inhibitor of *EGFR*, *HER2*, *BRCA*, and tyrosine kinase	Veliparib with pegylation	Patients with TNBC	Completed phase I	NCT01145430
PARP1/2 inhibitor Veliparib	Inhibitor of *EGFR*, *HER2*, *BRCA*, and tyrosine kinase	Veliparib with lapatinib	Patients with TNBC	Phase I	NCT02158507
PARP1/2 inhibitor Veliparib	Inhibitor of *EGFR*, *HER2*, *BRCA*, and tyrosine kinase	Veliparib in combination with irinotecan HCl	Patients with TNBC	Phase I I	NCT00576654
PARP1/2 inhibitor Veliparib	Inhibitor of *EGFR*, *HER2*, *BRCA*, and tyrosine kinase	Veliparib with cisplatin	Patients with TNBC	Phase II	NCT02595905
AZD2281 and Ku-0059436 PARP1/2 inhibitor (Selective)	PARP inhibitor; *BRCA* Mutated	Olaparib alone, or in combination with durvalumab MEDI4736 against PD-L1	*HER2*-negative treated mTNBC	Phase-II	NCT00679783 NCT03544125 NCT02484404 NCT03167619 NCT02681562 NCT02484404
PARP1/2 inhibitor Veliparib	Inhibitor of *EGFR*, *HER2*, *BRCA*, and tyrosine kinase	Veliparib plus carboplatin	Patients with TNBC	Phase III	NCT02032277
Iniparib BSI-201 and SAR240550	Competitive PARP inhibitor; ability to form adducts with many cysteine-containing proteins	Combination with gemcitabine and carboplatin	Patients with TNBC	Phase II	NCT00813956 NCT01045304 NCT01130259
Iniparib BSI-201 and SAR240550	Competitive PARP inhibitor; ability to form adducts with many	Combination of iniparib with paclitaxel for	Patients with TNBC	Competed phase II	NCT01204125

Name of Drug	Types of Inhibitors	Prior Treatment	Type of Population	Status	ClinicalTrials.gov Identifier
	cysteine-containing proteins	TNBC compared to paclitaxel alone			
Iniparib BSI-201 and SAR240550	Competitive PARP inhibitor; ability to form adducts with many cysteine-containing proteins	Iniparib with irinotecan	Patients with TNBC	Phase II trial	NCT01173497
Niraparib	≥1 anti-*HER2* treatment; PARP inhibitor	Niraparib plus trastuzumab IV	Metastatic *HER2*+ breast cancer	Phase Ib/II (recruiting)	NCT03368729
Niraparib	PARP inhibitor	One anthracycline and/or taxane in the (neo-) adjuvant or Niraparib	Advanced/metastatic *BRCA1*-like	Phase-II, Active, not recruiting	NCT02826512
Niraparib	PARP inhibitor	≥1 line of therapy Niraparib plus everolimus	Patients with TNBC	Phase I Recruiting	NCT03154281
Niraparib	Germline *BRCA* mutation-positive (PARP inhibitors)	≤2 prior cytotoxic regimens and Niraparib versus physician's choice	Advanced or metastatic breast cancer	Phase III Active, not yet recruiting	NCT01905592 (BRAVO)
Niraparib	Metastatic TNBC inhibitors (PARP inhibitors)	≤2 lines of cytotoxic therapy, Niraparib plus pembrolizumab	Advanced or metastatic TNBC	Phase I/II Active, not yet recruiting	NCT02657889 (KEYNOTE-162)
veliparib	Metastatic TNBC inhibitors (PARP inhibitors)	≤2 lines of cytotoxic Chemotherapy, Carboplatin, and paclitaxel with or without veliparib [36][37]	Locally advanced unresectable *BRCA* associated	Phase III Recruiting	NCT02163694 [34]
veliparib	Metastatic TNBC inhibitors (PARP inhibitors)	Veliparib with temozolomide versus veliparib with carboplatin and paclitaxel versus placebo	Metastatic TNBC [2]	Randomized phase II, Ongoing	NCT01506609 [36][38]

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and PFS were analyzed further in a phase III clinical trial; the trial did not find successful treatment of patients [38].

2.3. Niraparib

Niraparib is a PARP1 and PARP1 inhibitor. Niraparib is indicated as a maintenance treatment for recurrent cancer patients, mainly with HR deficiency (HRD) with positive status [35][39]. HRD has been linked to deleterious *BRCA* mutations in patients, with disease development occurring more than six months later following platinum-based chemotherapy [35][39]. Niraparib was extended for use in the care treatment of adults following first-line platinum-based chemotherapy [29][35].

Name of Drug	Types of Inhibitors	Prior Treatment	Type of Population	Status	ClinicalTrials.gov Identifier
		with carboplatin and paclitaxel ≤2 lines of cytotoxic chemotherapy [38][39][40][41]	[38][39][40][41]		
veliparib	Metastatic TNBC inhibitors (PARP inhibitors)	Veliparib versus atezolizumab versus veliparib plus atezolizumab	Stage III–IV TNBC [38][39][40][41]	Randomized phase II Ongoing	NCT02849496
veliparib	Metastatic TNBC inhibitors PARP inhibitors) [42][43]	Cisplatin and placebo versus cisplatin and veliparib ≤1 line of cytotoxic chemotherapy for metastatic disease	Metastatic TNBC and/or *BRCA* mutation-associated breast cancer [42]	Phase II Active, not recruiting	NCT02595905
veliparib	Metastatic TNBC inhibitors PARP inhibitors)	Temozolomide and veliparib ≥1 chemotherapy regimen	Metastatic TNBC and/or *BRCA* mutation-associated breast cancer [44][45]	Phase II, Active, not recruiting	NCT01009788
Talazoparib	Neoadjuvant therapy	None	Primary breast cancer ≥1 cm with a deleterious BRCA mutation [43][44][45]	Phase II, Active, not recruiting	NCT02282345
Talazoparib [43][44][45]	Advanced TNBC and HR deficiency and advanced *HER2*-negative breast cancer or other solid tumors with a mutation in HR pathway genes	≥1 line of therapy	Talazoparib	Phase II, Recruiting	[43][44][45] NCT02401347
Talazoparib	Metastatic TNBC inhibitors PARP inhibitors [45]	Platinum-containing regimen with disease progression > 8 weeks	Metastatic breast cancer with *BRCA* mutation	Phase II Terminated (Primary Analysis and study completed Not stopped	[45] NCT02034916 (ABRAZO)

stage II–III TNBC with no previous therapy for potentially curative surgery—they were randomly assigned to two groups; group I was treated with 50 mg veliparib orally twice a day, with 12 weekly doses of 80 mg/m^2 intravenous paclitaxel, and carboplatin administered every 3 weeks, for 4 cycles [43][44][45]. Patients with a germline *BRCA* mutation were then allocated to group II and administered cyclophosphamide and doxorubicin every 2–3 weeks for 4 rounds [44]. Effective clinical outcomes were observed to be higher in 53% of patients with combined therapies in comparison to patients who received paclitaxel alone (31%). No significant toxicity was observed against Veliparib. [43][44][45].

2.5. Talazoparib (BMN-673)

Name of Drug	Types of Inhibitors	Prior Treatment	Type of Population	Status	ClinicalTrials.gov Identifier
Talazoparib [46][47]	Metastatic TNBC inhibitors PARP inhibitors	≤3 chemotherapy-inclusive regimens Talazoparib versus physician's choice	Locally advanced and/or metastatic breast cancer with germline *BRCA* mutations [46][47]	Phase III Completed	NCT01945775 (EMBRACA) [46]
Rucaparib	Metastatic TNBC inhibitors PARP inhibitors	≤5 prior chemotherapy Rucaparib regimens in the last 5 years	Patients presenting with metastatic breast cancer (MBC)	Phase II, Completed [46][47][48]	NCT00664781 [47] [46][47][48]
Rucaparib	Metastatic TNBC inhibitors PARP inhibitors	≥1 line of chemotherapy, Rucaparib	Patients with a *BRCA*ness genomic signature	Phase II Completed	NCT02505048 (RUBY) [47][48]
Rucaparib [46]	Stage I–III patients with TNBC or inhibitors PARP inhibitors [46][47][48]	Neoadjuvant chemotherapy Cisplatin with rucaparib	*ER/PR+*, *HER2-* negative breast cancer with known *BRCA1/2* mutations	Phase II Completed	NCT01074970
Rucaparib	TNBC inhibitors [47][48]	≥3 prior chemotherapy regimens, Rucaparib	Patients with advanced solid tumors with evidence of germline	Phase I/II Active, not recruiting	NCT01482715
Rucaparib	TNBC inhibitors	≤5 prior chemotherapy regimens in the last 5 years, Rucaparib	Patients with MBC carriers of a *BRCA1/2* [47]	Phase II Completed	NCT00664781
Rucaparib	TNBC inhibitors	≥1 line of chemotherapy Rucaparib	Patients with a *BRCA*ness genomic signature	Phase II Completed	NCT02505048 (RUBY)
Rucaparib	TNBC inhibitors	Neoadjuvant chemotherapy Cisplatin with rucaparib	Advanced solid tumors with evidence of germline or somatic *BRCA* mutation	Completed [49]	NCT01074970
Rucaparib	TNBC inhibitors [50]	≥3 prior chemotherapy regimens	Advanced solid tumors with evidence of germline or somatic *BRCA* mutation	Phase I/II Active, not recruiting	NCT01482715

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concentrations [51]. Efficacy and safety levels were evaluated, such as pharmacodynamics, pharmacokinetic dose-limiting toxic effects, and tolerability [52]. Intravenous rucaparib was given and the objective response rate was analyzed: 41% of patients showed an ongoing response for at least 12 weeks [53]. The efficacy and safety of rucaparib in patients with *HER2*-negative metastatic breast cancer were associated with *BRCA*ness phenotype and/or a somatic *BRCA* mutations [49][50][51][52][53]. Patients received 600 mg rucaparib orally for 21 days or up to the development of the disease. The main endpoint was the clinical benefit rate and secondary endpoints, including PFS, overall survival, safety, and the prognostic value of the *BRCA*ness signature [49][50][51][52][53]. An additional study determined the quantity of sporadic TNBC patients likely to benefit from rucaparib treatment [49][50][51][52][53].

2.1. Olaparib
2.7. Checkpoint Inhibitors

TNBC is subject to important ongoing questions regarding biomarkers of response, defining the utility of novel approaches, and exploring potential combinations of checkpoint inhibitors and PARP inhibitors. The FDA approved the nab-paclitaxel (Abraxane) with atezolizumab (Tecentriq) for patients with metastatic PD-L1-positive TNBC. The approval was based on the phase III IMpassion130 trial (NCT02425891), which established a 38% decrease in the risk of disease development or death compared to placebo plus nab-paclitaxel in this patient population. Pembrolizumab is a second approved checkpoint inhibitor drug, approved by the FDA in Nov 2020, for patients with metastatic TNBC whose tumors express PD-L1 (combined positive score (CPS) of 10 or higher, as determined by an FDA-approved test. Pembrolizumab also demonstrated proof of concept as a neoadjuvant in TNBC patients. In phase II I-SPY2 trial (NCT01042379), pembrolizumab was neoadjuvant plus chemotherapy, improving pathologic complete response (pCR) rates by 13.6 percentage points compared with chemotherapy alone for patients with early TNBC (95% CI, 5.4–21.8; p < 0.001).

Olaparib is a potent oral PARP inhibitor effective against *BRCA1* and *BRCA2* mutations [22]. A multicentric clinical evaluation of olaparib was carried out, using it as monotherapy for patients with germline *BRCA1/2* mutations [23][24][25]. Olaparib was administered to the patient twice a day at a dose of 400 mg. The clinical trial was performed with 298 patients, in which an effective clinical response was observed, with adverse effects including nausea and fatigue observed [26][27][28][29][30]. Another study was performed to optimize the drug concentration and determine its maximum dose and minimum dose. In patients with *BRCA1* and *BRCA2* mutations, an ORR (overall response rate) of 11 (41%) was observed in 27 patients with a 400 mg dose twice daily. An ORR of 6 (22%) was observed in 27 patients with 100 mg doses twice daily; the ORR was observed to be 7/13 (54%) with higher doses and 4/16 (25%) with lower doses in TNBC patients. In the highest dose-tested patients, some adverse effects were observed, such as anemia, vomiting, nausea, and fatigue. Olaparib was approved by the FDA based on the clinical outcomes of the phase 3 clinical trial [27][28][29][30]. A phase 3 clinical trial employed olaparib monotherapy in germline *BRCA* mutations with *HER2* negativity and, at minimum, previous chemotherapy therapy [29]. A total of 300 patients were selected randomly in a 2:1 ratio into two groups; group one was administered 300 mg olaparib twice daily, and 92 patients in group two were administered vinorelbine or capecitabine and eribulin in 21-day cycles. Out of 300, 49.8% of the TNBC patients were included in the olaparib group and 49.5% of the TNBC patients received standard therapy [3][26][27][28]. Median PFS was significantly longer in the olaparib group than in the standard therapy group (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% CI, 0.43 to 0.80; $p < 0.001$). In the subgroup analysis, the hazard ratio for PFS was 0.43 (95% CI, 0.29–0.63) for patients with TNBC [3][28][29][30]. The response rate was 59.9% in the olaparib group and 28.8% in the standard therapy group, while the rate of grade 3 or higher adverse events was 36.6% in the olaparib group and 50.5% in the standard therapy group; the rate of treatment discontinuation due to toxic effects was 4.9% and 7.7%, respectively [28][29][30][31]. Metabolism of olaparib occurs via oxidation and dehydrogenation and does so progressively via the use of other factors such as sulfate conjugate and glucuronide [27][28]. Olaparib is mainly excreted through urine (44%) and feces (42%) [28].

OlympiAD was a randomized open clinical phase III trial (NCT02000622) assessing the daily administration of 600 mg olaparib tablets. A total of 302 patients who had received two or fewer prior treatments were randomized in a 2:1 ratio to olaparib or chemotherapy. The results showed significantly prolonged PFS with olaparib versus standard therapy (7.0 vs. 4.2 months; hazard ratio (HR), 0.58; 95% CI, 0.43–0.80; $p < 0.001$). Response rates were observed to be 59.9% vs. 28.8% (olaparib vs. standard group) [26]. Olaparib was the first PARP inhibitor to establish higher efficacy and tolerability than standard chemotherapy in g*BRCA*-mutated advanced BC [27][28][29][30]. According to earlier results, the FDA approved olaparib as the first PARP inhibitor for the treatment of this patient subgroup. However, in the interim analysis, no differences in overall survival (OS) were observed between the two groups [30][31][32]. The 3-year OS was 40.8% versus 12.8% in the two groups, respectively, in patients with TNBC. Currently, research on PARP inhibitors for adjuvant therapy and neoadjuvant therapy, as well as for the prevention of BC, is ongoing—including the OlympiA (phase III) and GeparSixto studies; in the future, the results of these studies will evaluate adjuvant therapy with olaparib for *HER-2-*/g*BRCA*m BC and explore the value of a PARP inhibitor in neoadjuvant therapy, respectively [33][34][35]. Various remarkable drugs have been approved to benefit patients with TNBC, including the PARP inhibitors olaparib and talazoparib for germline *BRCA* mutation-associated

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