

# The Role of PARP Inhibitors in the Treatment of Triple Negative Breast Cancer

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## Abstract

Triple Negative Breast Cancer (TNBC) is a particular subtype of breast cancer accounting for 15% to 20% of all breast cancer. It is defined on immunohistochemistry (IHC) by negative estrogen receptor (ER) and progesterone receptors (PR) and negative human epidermal growth factor receptor 2 (HER2) and characterized by aggressive nature, distinct metastatic patterns, lack of targeted therapies and poor outcomes. Cytotoxic chemotherapy was the mainstay of treatment for long decades and the development of new treatments for selected patients was complicated because of the heterogeneity of TNBC. The good understanding of molecular and genomic mechanisms of TNBC has allowed the development of new targeted therapies more efficient. Although the heterogeneity of genetic alterations in TNBCs based on the ethnicity and the age, BRCA mutations are found in around 20% to 25% of patients and especially in those of the basal-like immune-phenotype. Thus, targeting the defects in the DNA repair pathway becomes a promising field of research for this selected category of TNBC patients. Poly (ADP-ribose) polymerase (PARP) inhibitors exploit this DNA defects through synthetic lethality and therefore represent a promising treatment especially in BRCA1/ BRCA2 mutation carriers. These findings have finally allowed bringing personalized treatment to this orphan disease. In this work we tried to explain the rationale and mechanisms of targeting the immune system in TNBC, to report the results from recent clinical trials that put immunotherapy as a new standard of care in TNBC.

**Keywords:** Triple negative breast cancer • DNA repair • BRCA • PARP inhibitors

## Introduction

### Overview on DNA damaging and DNA repair targets

The Cancer Genome Atlas (TCGA) Research Network analyzed primary breast cancers using different genomic tools and has found that most frequent genetic alterations in DNA damage-repair genes, including loss of TP53, RB1 and BRCA1 in addition to activation of the PI3K pathway [1]. Around 75%-80% of TNBCs display a basal like (BL) molecular phenotype on gene expression arrays, characterized by a basal epithelial cell gene expression cluster [2].

DNA repair mechanisms play a major role in maintaining the integrity and stability of the genome. The BRCA1 or BRCA2 mutations are found in 10% and 20% TNBC and these mutations have a crucial role in DNA repair as tumor suppressor genes [3]. They are implicated in homologous recombination-mediated repair of double-stranded breaks. Defects in BRCA1 or BRCA2 genes result in impaired DNA repair by homologous recombination and subsequent genomic instability. This instability opens the door to interesting therapeutic opportunities in TNBC [4].

## Literature Review

Breast cancers arising in BRCA1 germ-line mutation carriers display

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a triple-negative phenotype in more than 75% of cases. A better knowledge about DNA repair mechanism defects leads to higher sensitivity to DNA-damaging agents such as PARP inhibitors [5].

However, even sporadic breast cancers may also display different genetic and epigenetic disruptions to BRCA function. This concept is called 'BRCAness' [6]. PARP enzymes play a crucial role in DNA repair mechanisms, specifically in homologous recombination-mediated repair of double-stranded breaks. Therefore, the inhibition of PARP enzymes is important to target in cancers with specific DNA-repair deficiency, including TNBC with BRCA1/2 mutations and TNBC with BRCAness phenotype.

### Clinical trials with PARP inhibitors

There is a particular vulnerability of BRCA-mutant cancers to the cytotoxicity of PARP enzymatic inhibition. Therefore, PARP inhibitors have a high cytotoxicity in cells with BRCA1/2 dysfunction, while they have no therapeutic effect in BRCA normal cells [7,8].

Several trials have investigated the role of PARP inhibitors in breast cancer alone or in association with chemotherapy in different settings. Initially, many trials were disappointing with negative results but more recently, the findings were very promising that they allowed to PARP inhibitors to integrate the standard of care in a selected patients.

Iniparib, was evaluated in an open-label, phase II trial of 123 patients with metastatic TNBC who were randomly assigned to receive gemcitabine/carboplatin with or without iniparib. Results showed significant improvement in clinical benefit rate (CBR) with iniparib (55.7% vs. 33.9%) and ORR (52.5% vs. 32.3%) in addition to a survival benefit: PFS from 3.6 to 5.9 months (HR 0.59; p=0.012) and OS from 7.7 to 12.3 months (HR 0.57; p=0.014) [9].

Unfortunately, the phase III trial with iniparib didn't meet its endpoint in terms of PFS and OS. These disappointing were attributed to the fact that iniparib lacked PARP activity [10]. In the neo-adjuvant setting, a single-arm phase II trial has demonstrated promising results with iniparib in terms of high response retain BRCA1/BRCA2 carriers [11].

Veliparib another PARP inhibitor was evaluated in neo-adjuvant setting

in combination with carboplatin and has shown an improvement in pCR for patients with TNBC from 26% to 52%, but it is difficult to distinguish between the benefit of veliparib and the benefit of carboplatin [12].

Veliparib was also assessed in a phase II trial in patients with metastatic BRCA1/BRCA2-mutant breast cancer, from which 42.4% had TNBC. The study studied veliparib in combination with carboplatin and paclitaxel vs. placebo. The ORR was 77.8% (95% CI 66.4-86.7) with veliparib versus 61.3% (95% CI 49.7-71.9) in the placebo arm. There was not significant improvement of PFS with veliparib (14.1 vs. 12.3 months) [13].

## Discussion

Phase III trials were conducted with different PARP inhibitors (Table 1). BROCADE 3 is a phase III trial that has evaluated veliparib (120 mg twice daily) Plus Carboplatin/Paclitaxel in Patients with HER2-negative, germline BRCA-mutated advanced breast cancer (48% had TNBC) [14].

Median PFS per investigator assessment in 337 patients treated with veliparib plus carboplatin/paclitaxel was 14.5 months vs. 12.6 months in 172 patients receiving placebo/chemotherapy. At the interim analysis, median OS was 33.5 months with veliparib/chemotherapy compared to 28.2 months with placebo/chemotherapy. Moreover, veliparib, demonstrated a durable benefit compared to the control group, with 26% of patients treated with veliparib remaining alive and progression-free at 3 years compared to just 11% of patients receiving only chemotherapy [14].

Olaparib and talazoparib are two other orally active PARP inhibitors that have an impressive response rate and favorable toxicity in metastatic breast cancer harboring gBRCA mutations. Results had reported an ORR of 41% and 50% with these two agents, respectively. after phase I and II trials, two phase III studies (OlympiAD and EMBRACA) have evaluated the efficacy and

safety of olaparip and talazoparib in comparison to treatment of physician choice in HER2-negative metastatic breast cancer patients with germline BRCA mutations (Table 1). In the OlympiAD trial (N=302), 50% of patients had TNBC, and patients in the arm of Olaparib reached a median PFS (mPFS) of 7.0 months vs. 4.2 months for control arm (HR: 0.58; p<0.001). For PFS in TNBC patients, the HR was 0.43 (95% CI 0.29 to 0.63). Olaparib has improved significantly the ORR compared to control arm (59.9% vs. 28.8%, respectively). For the subgroup of TNBC patients the ORR was 54.7% vs. 21.2% [15] in the EMBRACA trial (N=431), 46% had triple-negative breast cancer; BRCA1 and BRCA2 mutations were split at 45% and 55%, respectively.

Talazoparib has led to better mPFS compared to control arm (8.6 months vs. 5.6 months, respectively; HR: 0.54; p<0.001) and a markedly higher ORR (62.6% vs. 27.2%, respectively). In the subset of TNBC the ORR was 61.8% vs. 12.5% for 11.89 (95% CI 4.5-41.3). The PFS in the subgroup of TNBC was also significantly improved, HR 0.596 (95% CI 0.406-0.874) [16].

After 2 years of median follow-up, Olaparib didn't show a significant improvement in OS, but interestingly, in the subgroup analysis, Olaparib has shown significant benefit in OS benefit compared to control arm in the group of patients with no prior chemotherapy for their mBC (mOS of 22.6 and 14.7 months, respectively; p=0.02).

Regarding talazoparib, EMBRACA study has revealed the mOS in patients treated by Talazoparib and TPC was 22.3 and 19.5 months, respectively (p=0.11). Interestingly, both agents were almost equally effective in patients with TNBC or HR + HER2-disease, which confirmed the hypothesis that PARP inhibitors are typically genotype-specific rather than phenotype-specific therapy. Regarding quality-of-life, results revealed a prolonged time to deterioration of overall health with both agents compared to chemotherapy arm.

Talazoparib and Olaparib were generally well-tolerated with no new safety

**Table 1.** The phase III studies of PAPR inhibitors in the treatment of metastatic breast cancer with gBRCA mutations including TNBC patients (OlympiAD, EMBRACA and BROCADE-3).

Trial	OlympiAD Olaparib vs. TPC (N = 302)	EMBRACA Talazoparib vs. TPC (N = 431)	BROCKADE 3 VCP vs. Pla-CP (N = 512)
TNBC population	50%	45%	48%
Primary end point	PFS	PFS	PFS
PFS (ITT)	7.0 mo vs. 4.2 mo HR 0.58 (95% CI 0.43-0.80) p<0.001	8.6 mo vs. 5.6 mo HR 0.54 (95%CI 0.41-0.71) p<0.001	14.5 mo vs. 12.6 mo HR 0.71 (95% CI 0.57, 0.88) p=0.002
PFS (HR + patients)	HR 0.82 (95% CI 0.55 to 1.26)	HR 0.474 (95% CI 0.318-0.708)	mPFS2: 21.3 mo vs. 17.4 mo HR 0.76 (95% CI 0.60, 0.96)
PFS (TNBC)	HR 0.43 (95% CI 0.29 to 0.63)	HR 0.596 (95% CI 0.406-0.874)	
PFS (Priorplatinum)	HR 0.67 (95% C 0.41-1.14)	HR 0.76 (95% CI 0.4-1.45)	26% of patients in the v arm and 11% in the Pla arm were alive and progression free at 3 y
PFS (No priorplatinum)	HR 0.60 (95% CI 0.43-0.84)	HR 0.52 (95% CI 0.39-0.71)	
OS	19.3 mo vs. 17.1 mo HR: 0.90 (95% CI: 0.66-1.23) p=0.513	22.3 mo vs. 19.5 mo HR 0.76 (95%CI 0.55-1.06) p=0.105	33.5 mo vs. 28.2 mo HR 0.95 (95% CI 0.73, 1.2) p=0.67
ORR (ITT)	59.9% vs. 28.8% [OR and p value NR]	62.6% vs. 27.2% [OR 5 (95% CI 2.9-8.8)] p<0.001	75.8% vs. 74% CBR at 24 wks: 90.7% vs. 93.2%
ORR (HR + patients)	65.4% vs. 36.4	63.2% vs. 37.9% [OR 2.89 (95% CI 1.43-5.8)]	NR
ORR (TNBC)	54.7% vs. 21.2%	61.8% vs. 12.5% [OR 11.89 (95% CI 4.5-41.3)]	NR
ORR (Priorplatinum)	46.0% vs. 26.7%	50% vs. 24% [OR 3.16 (95% CI 0.88, 15.67)]	NR
ORR (No priorplatinum)	65.8% vs. 29.4%	65.2% vs. 28.1% [OR5.36 (95% CI 2.89, 9.89)]	NR
TTR	47 days vs. 45 days (p value NR)	2.6 mo vs. 1.7 mo (p value NR)	NR
DOR	6.2 mo vs. 7.1 mo. [HR NA]	5.4 mo vs. 3.1 mo [HR=0.43 (95% CI: 0.27-0.70)]	14.7 mo vs. 11.0 mo

TTDQoL	Not reached vs. 15.2 mo HR: 0.44 (95% CI: 0.25-0.77) p=0.0043	24.3 mo vs. 6.3 mo HR 0.38 (95% CI: 0.26-0.55) p<0.0001	NR
D/C: Treatment Discontinuation; DOR: Duration of Response; HR: Hazard Ratio; HR+: Hormone Receptor Positive; mo: Months; Mpfs: Median Progression Free Survival; mOS: Median Overall Survival; NR: Not Reported; ORR: Overall Response Rate; P: Paclitaxel(P: 80 mg/m <sup>2</sup> /wk); Pla: Placebo; OR: Odd Ratio; TNBC: Triple Negative Breast Cancer; wks: Weeks; TPC: Treatment of Physician Choice; TTDQoL: Time to Deterioration in Global Health Related Quality of Life; TTR: Time to Response			

signals (Table 1). According to these findings, these two agents have already changed the treatment landscape of TNBC patients and brought this disease into the era of personalized therapy.

## Conclusion

PARP inhibitors have shown great efficacy with acceptable toxicity, which make olaparib and talazoparib new standards of care for BRCA-mutant TNBC patients. More knowledge about the role of PARP inhibitors in BRCA wild-type TNBC patients is needed and new strategies including combination with conventional chemotherapy and other targeted therapies and also immune checkpoint inhibitors are under investigation.

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