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**Review Article**

# Homologous Repair Deficiency Status and Response to Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer: The Best Current Biomarker to Select the Most Appropriate Treatment?

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## Abstract

Despite recent discoveries regarding the genomic characterization of triple-negative breast cancer (TNBC), the neoadjuvant treatment of TNBC is focused on the anthracycline- and taxane- (AT) based chemotherapy regimens. Clinical studies have highlighted the role of platinum in the neoadjuvant setting, because its addition to AT-based neoadjuvant chemotherapy (NACT) increases the

rate of pathological complete response (pCR). Retrospective analysis showed that the pCR rate is not influenced by the BRCA mutational status in relation to platinum use, while promising data found homologous repair deficiency (HRD) status as a potential predictive factor of response to platinum based neoadjuvant treatment. We will look specifically at the role of HRD status in platinum response prediction for two reasons: first, to understand whether the anthracycline use can be avoided in some TNBC subpopulations, sparing toxicity; second, to understand if it is possible, through the modulation of known oncogenic pathways, to make a TNBC from HRD-low to HRD-high phenotype and to exploit its sensitivity to DNA-damaging agents.

**Keywords:** Triple-negative breast cancer; Neoadjuvant chemotherapy; Platinum agents; BRCA status; HRD score

## 1. Background

Triple-negative breast cancer (TNBC) accounts for 15-20% of breast cancers (BCs) [1, 2]. It is a heterogeneous disease, characterized by the lacking expression of the estrogen and progesterone receptors and human epidermal growth factor receptor 2 [3]. The recent comprehensive genomic analysis of TNBCs, conducted by Jiang YZ et al., show that four transcriptional subtypes can be identified, with distinct genomic drivers and potential therapeutic targets: the immunomodulatory subtype, with up-regulation of immune-related genes, the mesenchymal subtype, enriched with genes related to the epithelium-mesenchymal transition and growth factors, the luminal androgen receptor subtype, with up-regulation of the androgen pathway, and the basal-like immune-suppressed (BLIS) subtype, characterized by the elevated cell cycle and DNA damage gene expression with down-regulation of the immune response [4]. These transcriptional TNBC subtypes are strongly concordant with those defined in a series of other studies [5-8]. Notably, TNBC subtypes significantly differ in response to similar neoadjuvant chemotherapy (NACT) [7].

Chemotherapy represents the cornerstone of TNBC treatment; in recent years DNA-damaging agents and immunomodulating drugs have been investigated, both in the early and metastatic setting [9-11]. Considering the prognostic role of the complete pathological response (pCR) after NACT [12], clinical trials focused on the combination of experimental drugs with standard chemotherapy with the aim to increase pCR. Approximately 30% of TNBCs achieves a pCR after an anthracycline and taxane-(AT) based NACT [12]. Therapeutics that target DNA damage repair system such as platinum agents and poly (ADP ribose) polymerase (PARP) inhibitors have been tested also in the neoadjuvant setting [13-15]. The rationale for their use derives from the genomic substrate of TNBCs [16] and, overall, platinum addiction to NACT increases pCR rate by about 15% [17]. Considering the crucial role of the tumor microenvironment in the development of drug resistance, immunomodulating agents have been tested in association with chemotherapy [18]. In the KEYNOTE-522, the immune checkpoint inhibitor pembrolizumab has been shown to increase pCR by an additional 15% when added to a sequential regimen of NACT including anthracycline, cyclophosphamide, taxane and carboplatin [11].

In the neoadjuvant setting, one of the most studied biomarkers of response to immunotherapy is the anti-programmed cell death ligand-1 (PD-L1), which in the KEYNOTE-522 does not seem to correlate with the response to pembrolizumab [11], while according to a multivariate analysis, PD-L1 expression correlates with the response to atezolizumab in the NeoTRIP trial [19].

Analyses on the relationship between tumor infiltrating lymphocytes (TILs) pre-NACT and pCR to immunotherapy are available for the GeparNuevo trial, which showed that high stromal TILs (sTILs) levels before therapy predict a higher pCR rate in both therapy groups, durvalumab plus chemotherapy and chemotherapy alone. However, sTILs were not specifically predictive for durvalumab response [20].

## 2. BRCA and HRD Status in TNBC

Up to 20% of TNBCs harbor a breast cancer susceptibility gene 1 or 2 (BRCA1/2) mutation [21, 22] and up to 50-75% have a BRCAness phenotype [23, 24]. The BRCA1/2 genes code for two tumor suppressor proteins involved in the homologous recombination (HR) system, activating after a double-strand break and ensuring genomic stability [25, 26]. Breast cancers that harbor BRCA1/2mutations are sensitive to platinum salts, as they covalently bind to DNA to form DNA-platinum adducts with intra- and inter-strand cross-links [26], that cannot be repaired in cells with BRCA mutation, leading to cell death. Sporadic BRCA-wild-type (wt) TNBCs can harbor DNA repair defects, such as epigenetic inactivation of BRCA, mutations in other genes or post-translational modifications of other proteins involved HR system. These genetic signatures identify the BRCAness phenotype, with a clinical behavior and treatment response similar to BRCA-mutated (mBRCA) patients. [26]. A combined score called homologous repair deficiency (HRD) was developed to evaluate the genomic instability resulting from HR repair defects: HRD-loss of heterozygosity score, HRD-large-scale state transition and HRD-allelic imbalance extending to the telomeric end of a chromosome [23, 24, 27, 28]. This biomarker facilities the identification of patients (including but not restricted to germline BRCA1/2 mutation carriers) who might benefit from DNA-damaging agents [4]. In the neoadjuvant setting, the HRD cut-off of 42 showed its ability to predict pCR to platinum containing therapy [29], thus, the HR deficiency is defined by a threshold of HRD score equal or over 42 [23].

### 2.1 BRCA mutational status in predicting platinum response

A series of studies have retrospectively evaluated the role of BRCA1/2 mutational status and HRD score in predicting platinum response in the neoadjuvant setting [9, 17]. The BRCA1/2 mutation does not increase pCR rate with platinum addition to NACT [17], but it predisposes to a greater response to chemotherapy in general and, more specifically, to DNA-targeting agents [17, 30]. However, randomized prospective data comparing response to platinum-based regimen with response to a standard AT-based NACT are not available in mBRCA patients.

The phase II INFORM trial compared pCR after neoadjuvant cisplatin vs doxorubicin-cyclophosphamide (AC) in 118 germline mBRCA carriers with early stage BC, of which 82 with TN subtype. The pCR rate was not higher with cisplatin than with AC in BRCA carriers (18% with cisplatin vs 26% with AC, risk ratio 0.70; 90% CI: 0.39-1.2) [30]. These results are consistent with those reported from the Geparsixto and BrighTNess studies, that evaluated platinum addition to an AT-based regimen in TNBCs. Both studies reported that, in contrast to BRCA-wt, among BRCA carriers, platinum addition did not improve the pCR rate [15, 31]. A potential explanation is that mBRCA tumors are more sensitive to DNA-damaging agents, whether cisplatin or AC compared to BRCA-wt tumors and that the higher sensitivity of mBRCA tumors to anthracycline and cyclophosphamide may hide the benefit from platinum addiction [30]. Therefore, cisplatin activity on a mBRCA tumor may have been recovered by the

combination of cyclophosphamide, an alkylating agent, and doxorubicin, that targets DNA replication.

Sharma P, et al. explored the efficacy of docetaxel and carboplatin as NACT among 190 TNBCs, of which only 16% mBRCA; the pCR rate was 55%. According to germline BRCA, pCR was 56% in BRCA-wt and 59% in mBRCA tumors ($p=0.83$) [32]. These pCR rates, obtained with an anthracycline-free NACT, are comparable to those with AT-based NACT including platinum on an unselected for biomarkers TNBC population, but with a significant saving in toxicity. Regarding the survival outcome, the disease-free survival (DFS) reported with carboplatin and docetaxel are consistent with those of the GeparSixto and CALGB 40603 trials, which included anthracyclines in NACT regimens [32]. Furthermore, in the Geparsixto study platinum addition led to a survival improvement only for BRCA-wt patients; in mBRCA patients the DFS was higher compared to BRCA-wt patients, independently from platinum addiction [33].

Overall, these data suggest that mBRCA tumors could perhaps be spared of the platinum, since they experience high levels of chemotherapy response and survival with sequential anthracycline/cyclophosphamide and taxane regimens [15, 24, 33, 34]. The INFORM trial may represent the proof of concept that platinum-based neoadjuvant regimens, without anthracyclines, could be further explored in the BRCA carriers.

### 2.2 HRD status in predicting platinum response

The genomic and transcriptomic characterization of TNBCs, conducted by Jang YZ et al. reported that the majority of these tumors belonging to BLIS subtype have a mutational signature HRD. They showed that BLIS subtype can be distinguished in HRD-high score tumors, with better prognosis and better response to platinum, and HRD-low score tumors, with worse prognosis [4].

The TBCRC 030, a randomized phase II study of cisplatin vs paclitaxel in BRCA-wt TNBCs, showed a pCR of 15% in cisplatin arm and 13% in paclitaxel arm; no association was observed between HRD score and pCR to either cisplatin or paclitaxel (Table 1). However, in this study the HRD status was considered positive if higher than 33 and the HRD evaluation was performed only on 95 samples of 140 enrolled patients [35].

A pooled analysis of five phase II studies, including 161 TNBCs treated with platinum-based, without anthracycline, NACT, concluded that the HRD score, evaluated on pre-NACT samples, is significantly associated with the pCR rate (Table 1) [36-41]. The HRD score seems to correlate with platinum response also when added to AT-based NACT [9]. Retrospective analyses have shown that, among BRCA-wt TNBCs, HRD-high tumors benefit more in terms of pCR from platinum addition to AT-based NACT compared to HDR-low (Table 1) [9, 31, 37]. The BSMO 2014-01, a phase II study that evaluated the efficacy of AT-based NACT, including carboplatin, in 63 TNBCs, has shown a pCR rate of 54%. Out of the 52 investigated patients, the HRD status due to germline mutations predicted the pCR (Table 1). Importantly, this is the first study to demonstrate that a germline mutation in any of the HR genes predicts a pCR on sequential NACT including platinum in TNBCs [42].

The increasing pCR rate from platinum addition in TNBCs could concern BRCA-wt HRD-high tumors. Unfortunately, no large randomized trials, stratified for HRD score, have compared AT-based NACT, with and without platinum. The Neostop phase II trial, designed to evaluate the activity

of neoadjuvant regimens based on carboplatin and paclitaxel followed by AC compared to carboplatin and docetaxel in TNBCs, showed a pCR of 54% in anthracycline-based arm and 52% in docetaxel and carboplatin arm (*p=0.84*) [43]. Sixteen percent of the 100 enrolled patients carried a BRCA1/2 mutation. A trend towards higher pCR rates have been found among BRCA carriers compared to BRCA-wt (75% *vs* 50% respectively; *p=0.10*), while no HRD data are available. Therefore, we do not know whether, among BRCA-wt, HRD-high tumors, more sensitive to platinum, have improved the pCR in the overall population and in particular in the anthracycline-free arm.

Taken together, these findings suggest that the impairment of the HR system induced by BRCA1/2 mutations in TNBCs contributes to the tumor response to DNA-damaging agents, including anthracycline, cyclophosphamide or platinum.

| **Study** | **Trial arms** | **pCR rate in HRD-low (N)** | **p-value** | **pCR rate in HRD-high (N)** | **p-value** |
|---|---|---|---|---|---|
| **TBCRC 030** [35] | CDDP<br>TXL | 18.7% (3/16) (*)<br>45.4% (5/11) (*) | | 39.4% (15/38) (*)<br>44.8% (13/29) (*) | |
| **GeparSixto** [31] | TXL + M + BEV + CB<br>TXL + M + BEV | 29.6% (7/27)<br>20% (6/30) | *0.540* | 63.5% (46/74)<br>33.9% (21/62) | *0.001* |
| **PrECOG 0105** [37] (**) | CB + GMZ + INIPARIB | 20% (3/15) | | 66% (33/50) | |
| **NCT0137257** [40] (**) | CB + E | 14.2% (2/14) | | 75% (9/12) | *0.0012* |
| **BSMO 2014-01** [42] (***) | EC à CB + TXL | 40.5% (15/37) | | 86.6% (13/15) | *0.003* |

* This rate refers to the pathologic response evaluated as Residual Cancer Burden 0-1 and not as pCR; ** These are two studies included in the pooled analysis of *Telli ML et al*., for which pCR data are available in relation to the HRD score; *** In this study the HRD status was defined in relation to the presence of an HR gene germline mutation.

pCR, pathological complete response; N, number; HRD, homologous recombination deficiency; CDDP, cisplatin; TXL, paclitaxel; M, non-pegylated lyposomal doxorubicin; BEV, bevacizumab; CB, carboplatin; GMZ, gemcitabine; EC, epirubicin and cyclophosphamide; E, eribulin.

**Table 1:** Pathological complete response rate based on the HRD score in triple-negative breast cancer patients treated with platinum-based neoadjuvant chemotherapy.

## 3. Future Perspectives

Considering the potential similar pCR rate with an AT regimen including platinum and a platinum based-,

anthracycline-free, NACT in TNBCs, carboplatin and taxane regimes should be explored with the aim to de-escalate the chemotherapy backbone at least in a subset of TNBCs. We hypothesize that in the neoadjuvant setting, both in the mBRCA and in the HRD-high TNBCs, omitting anthracycline in a carboplatin-based regimen could represent an alternative to AT-based regimens including platinum. In contrast, the best chemotherapy backbone for HRD-low tumors still seems to be AT-based, also with platinum. Currently, the decision of the chemotherapy regimen as NACT, without validated biomarkers, should weigh the potential benefits and the risks in terms of toxicity and delay in treatment cycles.

The previous hypotheses need to be confirmed in future prospective trials. It would be interesting to conduct randomized trials of TNBCs in the neoadjuvant setting, stratified by HRD status and tested for the BRCA1/2 mutation, with the aim to compare the activity in terms of pCR of a taxane and platinum regimen vs a sequential AT-based NACT, including platinum. These trials should clarify the role of HRD in predicting response to sequential platinum-based NACT in general and to platinum-based regimes, without anthracycline, in particular. Clarified the best treatment regimen, according to TNBC subgroup, the chemotherapy backbone could be used for treatment escalation, testing additional drugs. The most studied agents in this setting are the immune checkpoint inhibitors.

The phase III KEYNOTE-522 trial demonstrated that the addition of pembrolizumab, an anti-PD-1 antibody, to carboplatin and paclitaxel followed by anthracycline and cyclophosphamide improved pCR from 51.2% to 64.8% (*p=00055*) [11]. Another phase III trial, the NeoTRIP, evaluated the addition of an anti-PD-L1 antibody, atezolizumab, to carboplatin and nab-paclitaxel. The pCR rates were not different between the study arms (43.5% vs 40.8% in the experimental and standard arm, respectively; *p=0.66*) [19]. Among other factors, also the different chemotherapy backbone (with and without anthracycline in KEYNOTE-522 and NeoTRIP trial, respectively) may have contributed to these different results [44].The TONIC trial showed that doxorubicin, more than other chemotherapeutics, may prime tumors for response to anti-PD-1, upregulating immune-related gene and T cell infiltration [45]. In this regard, the randomized phase III IMpassion031 trial, evaluating the efficacy of atezolizumab vs placebo with a platinum-free NACT including anthracycline (nab-paclitaxel followed by AC) in TNBCs, met its co-primary endpoint of improved pCR with atezolizumab in all-randomized patients, showing a numerically but not statistically significant increase in the pCR rate in the PD-L1 positive population (other co-primary endpoint of the study) [46]. Results are expected from the GeparDouze study, the design of which is similar to that of the KEYNOTE-522 study. This randomized phase III, placebo-controlled trial, is testing whether adding atezolizumab to an anthracycline and taxane-based NACT, containing carboplatin, could improve pCR rate and event-free survival [47].

Finally, innovative strategies can enhance the efficacy of drugs used in clinical practice. Preclinic data showed the possibility of making a TNBC from HRD-low to HRD-high, modulating the DNA damage response pathway [48]. The cyclin-dependent kinase 12 (CDK12) controls the transcription of a series of BRCAness genes, involved in the DNA damage repair. Quereda V, et al. have shown that the CDK12 inhibition weakens the expression of these genes, leading the TNBC to a BRCAness phenotype. The tumor, becoming HRD-high, develops a greater sensitivity to DNA-targeting agents, such platinum, cyclophosphamide,

anthracyclines and PARP inhibitors [48]. Future researches in the neoadjuvant setting of TNBCs could focus on the exploration of HRD as a platinum response predictor, in order to de-escalate chemotherapy in a TNBC subpopulation, and on the modulation of known targets and oncogenic pathways, in order to tailor the use of effective therapeutics, such as platinum agents and PARP inhibitors.

## Declaration of Competing Interests

E.B. received speakers' and travels' fee from MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche. E.B re- ceived consultant's fee from Roche, Pfizer. E.B. received institutional research grants from Astra-Zeneca, Roche.

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