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Platinum salts in the treatment of *BRCA*-associated breast cancer: A true targeted chemotherapy?

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ABSTRACT

Germline pathogenic mutations in breast cancer (BC) susceptibility genes (g*BRCA1/2*) are the most frequent inherited alterations in BC and are involved in the homologous recombination pathway, the principal mechanism of DNA double strand break repair. Platinum salts which act as DNA cross-linking agents are therefore more likely to be active in *BRCA*-deficient tumors.

Women with *gBRCA*-associated tumors, particularly with triple negative BC, receiving neoadjuvant platinum containing regimens achieved higher pCR rates as compared to wild-type BC. However in two large randomized trials the addition of carboplatin significantly increased pCR rate only in wild-type tumors.

On the contrary, the randomized TNT trial showed a significant benefit for carboplatin vs docetaxel in terms of response rate and PFS specifically in patients with advanced *gBRCA* -associated tumors.

Biomarkers of sensitivity to DNA damaging agents beyond *gBRCA* mutations predicting activity of platinum salts have been proposed and should be validated prospectively.

1. Introduction

Breast cancer (BC) represents the most frequent cancer and the second leading cause of cancer death in female population worldwide. Among all BCs, up to 7–8% is related to the presence of a specific genetic predisposition. Germline pathogenic mutations in BC susceptibility genes type 1 and 2 (*BRCA*1 and 2) are the most frequent inherited alterations. They are responsible of the Hereditary Breast and Ovarian Cancer Syndrome (HBOCS), indeed women harboring such mutations have a meaningfully higher lifetime risk of developing these cancers in comparison with general population. The impact of either gene is dramatically significant: *BRCA1* mutations increase the lifetime risk for BC by age 70 up to 65%, *BRCA2* mutations up to 45%. Furthermore, if family history is positive for BC (Antoniou et al., 2003; Easton et al., 1995; Ford et al., 1998), this risk increases up to 85% and 84%, respectively. *BRCA*1 and 2 genes can be inactivated in sporadic cancers as well. These cancers, caused by epigenetic alterations or an impairment of RAD51 complex, share some traits with the inherited ones and are referred, in general terms, to *BRCAness* (Turner et al., 2004; Boulton, 2006).

Women carriers of *BRCA* germline (g*BRCA*) pathogenic mutations usually develop cancers at a younger age, with a more aggressive behavior and subsequently poorer prognosis *versus* those carriers of somatic mutations (Musolino et al., 2007). Additionally, 75% of BCs containing germline mutations in *BRCA* genes show a triple negative (TN) phenotype, with *BRCA1* dysfunction frequently as one of the main drivers (Badve et al., 2011). This phenotype is characterized by the absence of hormonal receptors and no amplification of Human Epidermal growth factor Receptor-2 (HER2) gene (Nielsen et al., 2004) and, compared with any other subtype of BC, presents a more aggressive clinical course and a higher capacity to metastasize in the first 3–5 years after diagnosis (Foulkes et al., 2010).

2. Role of *BRCA* 1 and *BRCA* 2 genes in DNA repair process

DNA in cells can undergo a wide range of damage, partially in response to extracellular agents, like ionizing radiation, ultraviolet light and environmental chemicals, but largely as a result of endogenous mechanism, including depurination, deamination, intracellular interaction with reactive oxygen groups and errors in replication and

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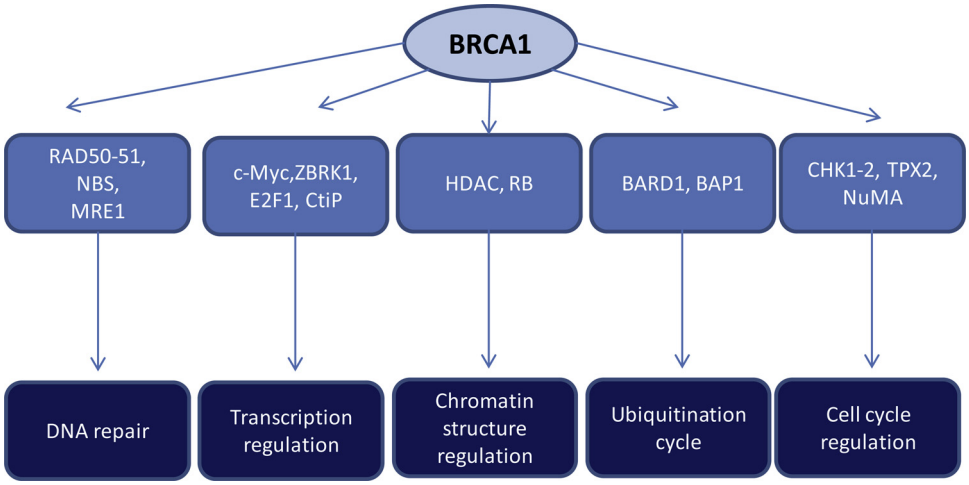

Fig. 1. Functions of *BRCA1* gene in DNA stability.

recombination. To overcome all these damages the human cell is capable of at least five types of DNA repair: Base Excision Repair (BER), using glycosidase enzymes to remove abnormal bases; Nucleotide Excision Repair (NER), removing thymine dimers and large chemical adducts; Mismatch repair, correcting mismatched base pairs caused by mistake in DNA replication; double-strand break (DSB) repair, which includes both homologous recombination (HR) and non-homologous end joining (NHEJ) (Altieri et al., 2008). Human genes involved in the HR pathway include the BRCA1 and 2 breast cancer susceptibility genes, which therefore play a crucial molecular role in the maintenance of the genome integrity and stability (Fig. 1). Every pathogenic mutation that causes functional impairment of these proteins is deleterious, leading to genomic instability and potentially to cancer development and progression (Roy et al., 2011).

3. Platinum salts: mechanism of action in *BRCA*-deficient breast cancer cells

Lack of HR mechanism is a perfect target for therapies that lead to DSBs during the DNA replication process, when homologous recombination is the principal DSB repair mechanism. Platinum drugs, like cisplatin and carboplatin, are commonly used in the treatment of breast and ovarian cancers. They act as DNA cross-linking agents forming intra-strand crosslinks. The formation of these DNA adducts inhibits DNA synthesis, function and transcription (Dasari and Tchounwou, 2014) (Fig. 2). In absence of functional *BRCA* proteins complex, like in *BRCA* mutation carriers, tumor cells are more sensitive to platinum salts, because inefficient in repairing their damage and in avoiding apoptotic death (Fig. 3). Nevertheless, despite a favorable initial response, *BRCA*-deficient cancer cells can frequently become resistant to platinum salts. They can indeed activate multiple mechanisms of resistance: reduced platinum accumulation as a result of defective expression of transporters and lower expression of the cytoskeletal system of endocytosis; cisplatin inactivation by thiol-containing biomolecules; enhanced DNA repair; decreased apoptosis. Even if only one mechanism could lead to platinum resistance, it is more likely that a combination of different mechanisms induces this condition, resulting in an important obstacle to a long-term successful treatment.

Purpose of this paper is to critically review and compare the results of the major clinical trials where platinum salts have been used in *BRCA*-associated BC patients in all the settings of disease.

4. Platinum salts and early breast cancer

Based on this preclinical rationale in the late 2000s the activity of platinum salts was sporadically investigated in the preoperative treatment of *gBRCA*-associated early BC (EBC). Silver et al treated 28 women with triple negative (TN) EBC, 2 of whom were *gBRCA1* mutation carriers with 4 cycles of preoperative cisplatin 75 mg/sqm. After surgery standard anthracycline and taxane-based adjuvant chemotherapy was administered. Principal endpoint was pathological complete response (pCR). Overall 6/28 patients achieved a pCR and both *gBRCA* mutation carriers were among them. Data from a translational exploratory analysis suggested that also a subset of basal-like BC, with intact *BRCA1,* who shared some fundamental molecular defects (low *BRCA*1 mRNA expression, *BRCA*1 promoter methylation) with *BRCA1*-deficient tumors, were more likely to respond to cisplatin (Silver et al., 2010).

Data from a retrospective cohort were published by Byrski et al. (2010), who reviewed the outcome of 103 patients with *gBRCA*-associated EBC treated with several preoperative regimens (Dasari and Tchounwou, 2014). pCR was obtained in 2 (8%) of 25 women treated with doxorubicin and docetaxel and in 11 (22%) of 51 women treated with doxorubicin based regimens. On the other hand, 10 out of 12 (83%) women treated with 4 cycles of cisplatin achieved a pCR (Byrski et al., 2010).

In a large retrospective cohort of Chinese women, among TN EBC, *gBRCA1* carriers exhibited a higher pCR rate than did non-carriers (53.8% vs 29.7%) and *BRCA1* mutation status remained a favorable independent predictor of pCR, after adjusting for other characteristics (Wang et al., 2015). Moreover, *gBRCA1* mutation carriers were more likely to respond to anthracycline-based neoadjuvant regimens than non-carriers. Differently from previous reports, pCR rate was inferior with taxane plus carboplatin as compared with anthracycline based regimens (40 vs 57.1%, respectively), while response to carboplatin was not different among *gBRCA1* mutation carriers vs non carriers (Wang et al., 2015).

One of the larger prospective studies investigating the role of neoadjuvant carboplatin is the GeparSixto trial (Von Minckwitz et al., 2014). This multicentric phase II randomized study included stage II-III TN and HER2-positive BC who received weekly paclitaxel and pegylated liposomial doxorubicin for 18 weeks associated with 3-week bevacizumab, in TNBC, and 3-week trastuzumab and lapatinib, in HER2-positive BC. Patients were randomized to receive weekly carboplatin at a dose of 2 area under the curve (AUC) which was reduced to 1.5 AUC after an interim safety analysis including 329 patients. Among the 315 TN EBC, pCR rate (defined as absence of tumor both in breast and axilla, ypT0/ypN0) was 53.2 vs 36.9% ($p = 0.005$) in patients receiving and not receiving carboplatin, respectively. The advantage of carboplatin was maintained also when carboplatin dose was reduced to 1.5 AUC (pCR rate = 45.8% vs 30.5% $p = 0.016$) (Von Minckwitz

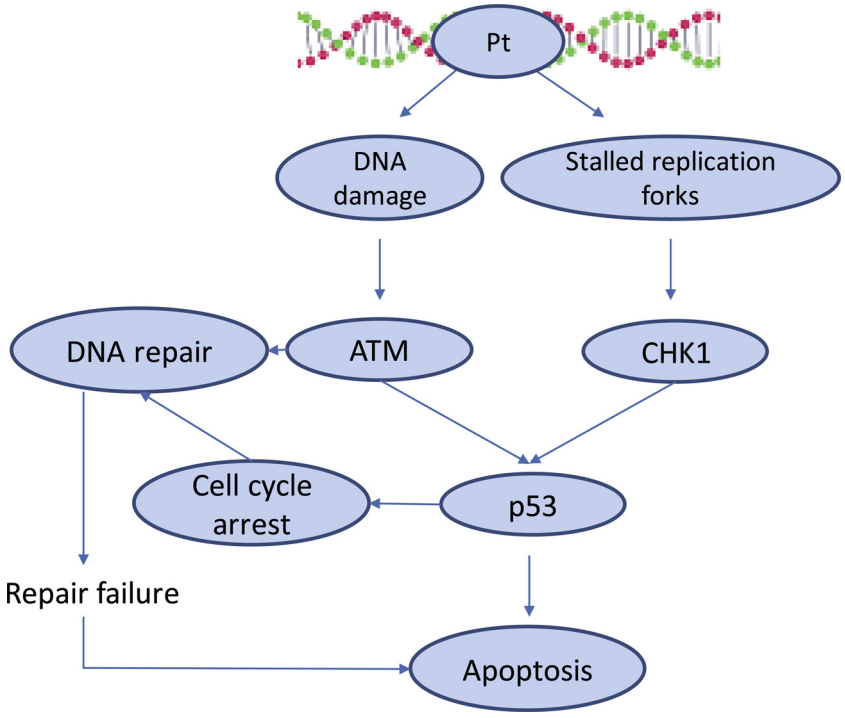

Fig. 2. Outcome of platinum-induced DNA damage: repair or cell apoptosis.

et al., 2014). The most relevant result of this study was that the advantage in pCR rate translated also in a superior disease-free survival (DFS) rate at 3 years (85.8% vs 76.1% HR = 0.56 95%CI 0.33-0.96 p = 0.035) (von et al., 2016).

In the TN EBC cohort, 291 patients with available DNA sample were tested for *gBRCA 1/2* mutations and 50 were *gBRCA1/2* mutation carriers. Analysis for pCR rate and DFS were performed in this population and results were compared between the *BRCA* wild type and the

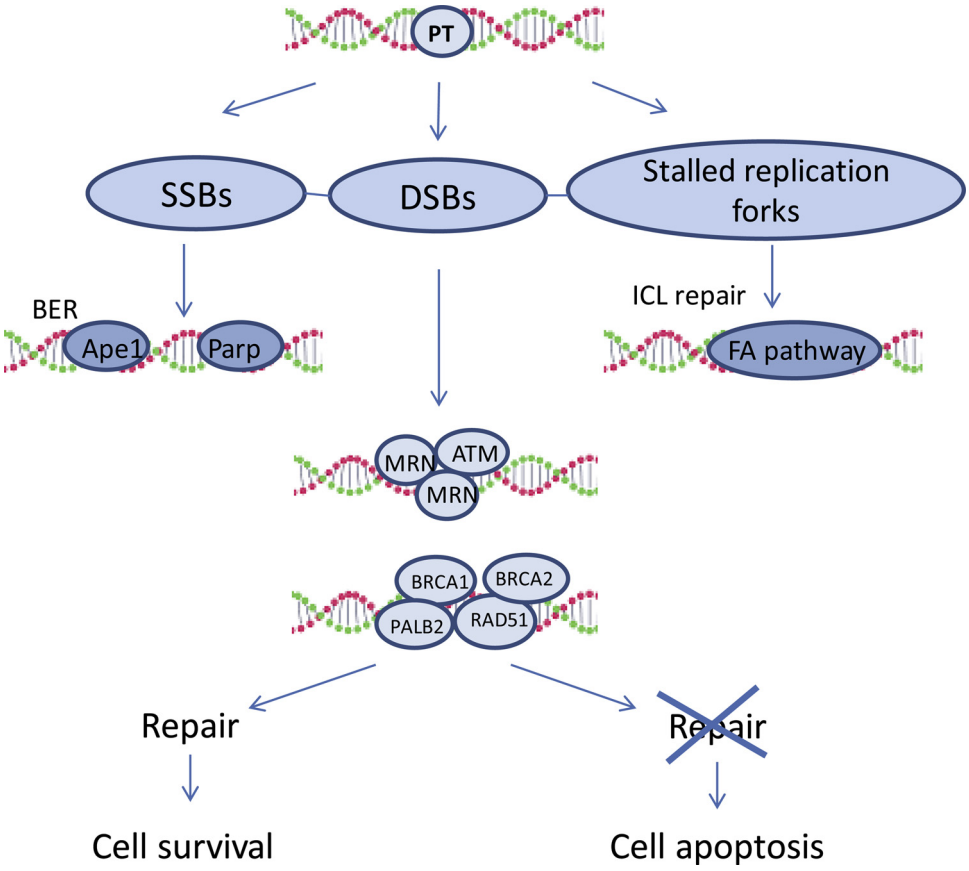

Fig. 3. Mechanisms of repair in platinum-induced DNA damage repair.

mutant cohorts. pCR rate, according to the less stringent definition of ypT0/is ypN0 was the primary endpoint and was obtained in 83/146 (56.4%) and in 60/145 (41.4%) of carboplatin-treated and untreated patients, respectively (OR 1.87, 95%CI 1.17–2.97, p = .009) (Hahnen et al., 2017).

When pCR rate was evaluated according to *BRCA* status, the addition of carboplatin did not increase pCR rate in mutation carriers (65.4% vs 66.7% in treated vs untreated patients, respectively), while, in the wild type population, neoadjuvant carboplatin significantly increased it (55% vs 36.4%, OR 2.14, 95%CI 1.28–3.58, p = .004). Thus, this study confirmed that *gBRCA1/2* mutation carriers are at higher likelihood of achieving pCR, irrespective of the addition of carboplatin. Similar findings were reaffirmed in the DFS analysis, although the study was not powered to address such subgroup differences. With a median follow up of 35 months, treatment with carboplatin improved DFS in the whole population (HR, 0.55; 95% CI, 0.32-0.95; p = .03), but this difference was attributable mainly to the wild type cohort in which DFS increased from 73.5% to 85.3% in the carboplatin group (HR, 0.53; 95% CI, 0.29- 0.96; p = .04). *gBRCA 1/2* carriers experienced a better DFS which was not significantly improved by the addition of carboplatin (82.5% vs 86.3% in carboplatin-treated vs untreated patients, respectively). A correlation between pCR and DFS was observed regardless of *BRCA* status. The authors suggested that the higher rate of pCR observed in the *gBRCA 1/2* mutation carriers, which was not increased by carboplatin, was due to the sensitivity to other cytotoxic agents such as doxorubicin, which ultimately promotes the formation of single-stranded and double-stranded DNA breaks, thus hampering the effect of another DNA damaging agents (Hahnen et al., 2017).

Conflicting results on the benefit of carboplatin in the neoadjuvant treatment of TN EBC have been reported in other two large randomized studies (GEICAM 2006-03 and CALGB 40603) in terms of impact of carboplatin on pCR rate (negative the first trial and positive the second), but separate results in *gBRCA* mutation carriers are not available for these studies (Sikov et al., 2015; Alba et al., 2012).

After the encouraging results of their pilot retrospective experience, Byrski et al. (2014) prospectively treated, with 4 cycles of preoperative cisplatin, a cohort of 107 *gBRCA1* mutation carriers, irrespective of tumor subtype, although 76% were TN. Fourteen patients had been previously treated with chemotherapy for prior breast and/or ovarian cancer. The vast majority of patients received 4 cycles of standard AC after surgery. pCR rate was 61% overall and it was unexpectedly high also in the small proportion of patients with positive estrogen receptors (ER) (9/16, 56%) suggesting that *BRCA* defect is highly sensitive to chemotherapy. Data on long term outcome are lacking, but since nearly all patients received adjuvant anthracyline and half of them underwent oophorectomy, impact of platinum salts on survival is not assessable (Byrski et al., 2014).

More recently, Wunderle et al. (2018) reported the results of a large cohort of 355 patients treated with neoadjuvant therapy at a single German Institution and who had been tested for *BRCA1/2* status. Mutations were found in 59 patients, with a higher frequency in TN (24.6%). Chemotherapy regimens included epidoxorubicin and cyclophosphamide or carboplatin plus weekly paclitaxel (the latter regimen administered in about one third of *gBRCA 1/2* mutated patients and in almost one half of patients with TNBC). Overall, pCR rate was greater in *gBRCA* mutation carriers irrespective of tumor subtype (54.3% vs 22.6%). The addition of carboplatin yielded higher pCR rates either in wild type and *gBRCA* mutated patients, with higher rates observed in patients with TNBC (58.5% and 73.3% in wild type and *gBRCA* mutated patients, respectively). Despite in *BRCA* mutated patients the addition of carboplatin increased pCR rates across all tumor subtypes, no significant interaction between *BRCA* status and type of therapy was observed (Wunderle et al., 2018).

Data on pCR rates after neoadjuvant therapy in other smaller retrospective cohorts of patients with *gBRCA* mutation associated tumors are reported in Table 1 (Byrski et al., 2010; Wang et al., 2015; Von Minckwitz et al., 2014; von et al., 2016; Hahnen et al., 2017; Byrski et al., 2014; Wunderle et al., 2018; Sharma et al., 2017; Arun et al., 2011; Sæther et al., 2018; Sella et al., 2018; Paluch-Shimon et al., 2016; Telli et al., 2015; Loibl et al., 2018).

5. Platinum salts and PARP inhibitors in early breast cancer

Last generation neoadjuvant trials have investigated the addition of a PARP inhibitor (PARPi) to carboplatin based neoadjuvant regimens.

The PreECOG 0105 is a phase II open label study which enrolled 80 patients with stage I-III TN (although the threshold for ER and PR negativity was 5%) or *BRCA1/2* mutation-related BC to receive 6 cycles of neoadjuvant combination of carboplatin, gemcitabine and iniparib (Telli et al., 2015). The study was designed to assess the efficacy and safety of iniparib, formerly considered as a PARP1-inhibitor, but which was subsequently demonstrated to not possess characteristics typical of the PARPi class (Patel et al., 2012). The principal endpoint was pCR rate, defined as ypT0/is ypN0. Secondary endpoint was residual cancer burden (RCB) scored from 0 to III, assessed in surgical specimen. Nineteen out of 80 patients (24%) had deleterious *gBRCA* mutations, mostly associated with TNBC, except for 3 patients who had ER and/or PR positive BC. Among the whole population, 29 pts (36.3%) achieved a pCR; pCR rate was higher in *BRCA* associated vs wild- type BC (47% vs 33%). In *BRCA*-associated TNBC, pCR rate increased to 56%. When differences were assessed by RCB, a score of 0 and 1 was obtained in 81% of *BRCA* associated and 47% of wild type breast cancers (Telli et al., 2015).

The combination of a true PARPi (veliparib) with carboplatin in addition to standard neoadjuvant therapy with paclitaxel was explored in a phase III randomized placebo controlled trial: the BrighTNess trial (Loibl et al., 2018). Patients with stage II-III TNBC were randomized to receive paclitaxel plus carboplatin/placebo and veliparib/placebo or paclitaxel plus carboplatin plus veliparib/placebo or paclitaxel plus carboplatin and veliparib. All patients received, subsequently, standard chemotherapy with doxorubicin and cyclophosphamide for 4 cycles. *gBRCA* mutational status was one of the stratification factors. Among the 634 patients, 15% were *gBRCA 1/2* mutation carriers. The addition of both carboplatin and veliparib increased pCR rate in both *gBRCA* mutation carriers (57%) and wild type patients (53%), with no significant differences in pCR rate observed in patients who received only carboplatin (50% and 59%, respectively). Similarly to GeparSixto results, in patients treated with standard chemotherapy, pCR rate was higher in mutated patients compared with non mutated patients (41% vs 29%), confirming that tumors in *gBRCA* mutation carriers are particularly chemosensitive (Narod et al., 2013). The failure of veliparib in improving pCR rate might be attributed to less than optimal dose administered and to the schedule of the PARPi.

Very few data with platinum salts in *gBRCA* associated BC are available in the adjuvant setting. The only study which has published preliminary results is the HOCN BRE-0146 which randomized 128 patients with TN EBC who had residual disease after anthracycline and taxane-based neoadjuvant therapy, to receive 4 cycles of cisplatin 75 mg/sqm, with or without the PAPRPi rucaparib. The primary endpoint was 1-year DFS which, in such a high-risk subset of patients, may adequately predict long term outcome. Overall DFS was completely identical between the two arms (76%) and was not significantly different between patients with *BRCA*-associated and sporadic tumors (85% vs 79%, respectively) (Dwadasi et al., 2014). Notably, none of the 8 patients with *gBRCA*-associated BC receiving the combination relapsed.

A number of studies are ongoing in *BRCA*-associated EBC investigating platinum salts in comparison and in combination with PARPi and they are summarized in Table 2 (Anon., 2018a, b; Anon., 2018c, d; Anon., 2018e, f; Anon., 2018g).

Table 1
Studies of neoadjuvant therapy in cohorts of patients with *BRCA* associated breast cancer.

Study	N pts/BRCAmut	Study design	Tumor subtype	CT regimen	Platinum regimens pCR rate%		Non platinum regimens pCR rate%	
					BRCA carriers	BRCA wildtype	BRCA carriers	BRCA wildtype
Birsky[14]	102	Retro	Any	Cis; AT; AC; FAC;CMF	83%	–	15.6%	–
Arun[24]	317/80	Retro	Any	AT, AC	–	–	36%	22% ^
Wang [15]	956/90	Retro	TN	various	40%	32.9%	57.1%	29% ^
Saether[25]	12	Retro	TN	Cis + doxo	83%	–	–	–
Sella[26]	43/14	Retro	TN	ddAC→wPCb	64.3%	44.8%*	67%	38%*
Paluch-Shimon[27]	80	Retro	TN	ddAC→ wP	–	–	68%	37%
Wunderle [22]	355/59	Obs	Any	EC; CbwP	81%	56%	39.5%	13%
Birsky [11]	107	Phase II	Any	Cis	61%	–	–	–
Sharma [23]	183/30	Phase II	TN	Cb + Doc	59%	56%	–	–
GeparSixto [16–18]	291/50	Phase II R	TN	wP + NPLD + /-Cb + /- Bev	65%	55%	66.7%	36.4% ^
PrECOG0105[28]	80/19	Phase II	Any	Cb + Gem + iniparib	47%	33%	–	–
BrighTNess[29]	634/93	Phase III R	TN	wP + /-Cb + /-veliparib	50%‡	59%‡	41%	29%

CT chemotherapy; pCR pathological complete response; Retro retrospective; Cis cisplatin; AT doxorubicin and docetaxel; AC doxorubicin and cyclophosphamide; FAC fluorouracil, doxorubicin cyclophosphamide; CMF cyclophosphamide methotrexate fluorouracil; ddAC dose dense doxorubicin cyclophosphamide; wPCb weekly paclitaxel carboplatin; Obs observational; EC epidoxorubicin cyclophosphamide ; doc docetaxel; NPLD non pegylated liposomial doxorubicin; Bev bevacizumab; Gem gemcitabine.

^ $p < .05$ vs BRCA carriers.

**historical color.

* only BRCA1 carriers.

‡ only carboplatin + paclitaxel.

Table 2
Platinum-based treatment in early-stage and advanced breast cancer with *BRCA* mutation: ongoing clinical trials.

Study	phase	Population	Treatment	Primary endpoint	Status
Neoadjuvant setting					
NCT03150576 [33] (PARTNER trial)	III	TNBC and/or germline BRCA	Arm A: paclitaxel + carboplatin + olaparib Arm B: paclitaxel + carboplatin	pCR	Currently recruiting
NCT01670500 [34] (INFORM trial)	II	Newly diagnosed HER2 negative BC in BRCA mutation carriers	Arm A: Doxorubicin-Cyclophospamide Arm B: Cisplatin	pCR	Currently recruiting
NCT02413320 [35] (NeoSTOP trial)	II	Subjects with germline BRCA associated and BRCA wild type TNBC	Arm A: Carboplatin + Paclitaxel then Doxorubicin + Cyclophosphamide Arm B: Carboplatin + Docetaxel	pCR	Active, not recruiting
NCT02789332 [36] (GeparOla trial)	II	HER2-negative BC with homologous recombination deficiency (HRD patients with deleterious BRCA1/2 tumor or germline mutation and/or HRD score high)	Arm A: paclitaxel + olaparib followed by epirubicin + cyclophosphamide Arm B: paclitaxel + carboplatin followed by epirubicin + cyclophosphamide	pCR	Currently recruiting
NCT01982448 [37]	II	TNBC with and without homologous recombination deficiency (defined as a high HRD score or a BRCA mutation)	Arm A: Paclitaxel Arm B: Cisplatin	pCR	Active, not recruiting
NCT01057069 [38] (neo-TN trial)	II/III	TNBC with and without deficient homologous recombination	Arm A: Carboplatin and Paclitaxel Arm B: Doxorubicin, cyclophosphamide Arm C: Doxorubicin, cyclophosphamide, carboplatin, thiotepa, cyclophosphamide	Average Neoadjuvant Response Index (NRI)	Active, not recruiting
Adjuvant setting					
NCT02488967 [39] (NRG-BR003 trial)	III	High-risk node-negative or node-positive TNBC with or without a germline BRCA mutation (stratification according to BRCA mutational status)	Arm A: carboplatin + anthracycline/taxane-based regimen Arm B: anthracycline/taxane-based regimen	Invasive DFS	Currently recruiting
Advanced setting					
NCT01898117 [49]	II	TNBC with or without a germline BRCA mutation	Arm A: Carboplatin-cyclophosphamide Arm B: Carbo/cyclo + atezolizumab Arm C: Paclitaxel Arm D: Paclitaxel + Atezolizumab	Validation of a BRCA-like test PFS	Currently recruiting
NCT02393794 [50]	I-II	TNBC or BRCA 1/2 mutation (regardless of BC subtype)	Romidepsin + Cisplatin +/- Nivolumab	Evaluating recommended dose of Romidepsin ORR	Currently recruiting
NCT02595905 [51] (SWOG 1416 trial)	II	Recurrent or metastatic TNBC and/or BRCA mutation-associated BC with or without brain metastases	Arm A: Cisplatin Arm B: Cisplatin + Veliparib	PFS	Currently recruiting
NCT02163694 [52]	III	HER2-negative BRCA-associated BC	Arm A: Carboplatin and Paclitaxel Arm B: Veliparib + Carboplatin + Paclitaxel	PFS	Active, not recruiting

TNBC: triple-negative breast cancer; pCR: pathological complete response; BC: breast cancer; HRD: homologous recombination deficiency; DFS: disease-free survival; PFS: progression-free survival; ORR: objective response rate.

Table 3
Studies with platinum salts alone or in combination with PARP inhibitors in *BRCA* associated metastatic breast cancer.

Study	N pts/BRCAm	Tumor type	Prior CT	CT regimen	ORR%		PFS/OS (mos)	
					BRCA carriers	BRCA wildtype	BRCA carriers	BRCA wildtype
Birsky[40]	20	TN (15) Other(5)	Any	Cis	80%	–	12/30	–
Isakoff [42]	86/11	TN	≤1	Cis/Cb	54.5%	25.6%	3.3/13.7	2.8/10.9
Tutt [43–44]	376/67	TN	No	Cb vs DX	68% ^ 33.3%	28% 34.5%	6.8 ^/NR 4.4 /NR	3.1/NR 4.6/NR
Somlo [45]	28 phase I	Any	Any	Vel + Cb	53%	–	8.7/18.8	–
	44 phase II			Vel→Cb	50%		5.2/14.5	
Han [46]	284	Any	≤2	PCb vs	61.3%	–	12.3/25.9	–
				Vel + PCb	77.8%^		14.1/28.3	

CT chemotherapy; ORR: objective response rate; PFS progression free survival; OS overall survival.
TN triple negative; Cis cisplatin; Cb Carboplatin; DX docetaxel; Vel: veliparib; P paclitaxel.
^ $p < .05$.

6. Platinum salts and metastatic breast cancer

The activity of platinum salts in *BRCA*-associated advanced breast cancer (ABC) has been less investigated than in the neoadjuvant setting with partially inconsistent results (Table 3)

Byrski et al. extended their experience with single agent cisplatin in 20 patients with g*BRCA1* associated ABC. Objective response rate (ORR) was obtained in 80% of patients (45% complete response and 35% partial response) with no relevant difference between 1st line or subsequent lines of treatment (89% vs 73%) and between TNBC and luminal cancers (80% for both), although complete response was higher in TNBC. Treatment was administered for 6 cycles and all patients progressed with a median time to progression (TTP) of 12 months which was extended to 17 months in patients achieving a complete response. Median overall survival (OS) was 30 months and was exceptionally prolonged beyond 4 years in 4 patients (Byrski et al., 2012). The results of this study are consistent with the high activity shown by cisplatin monotherapy in the neoadjuvant setting and favorably compare with results obtained in historical controls of a larger cohort of *gBRCA1* mutation carriers treated with CMF and anthracycline containing regimens who achieved a ORR of 66%, a median PFS of 7.6 months and a OS of 15 months (Kriege et al., 2009). However these results should be considered very cautiously because of the small sample size, the lack of a central radiological confirmation and, as the authors conclude, the impossibility of separating the impact of cisplatin from that of the subsequent lines of treatment which jeopardizes OS results. However this study was the first to clearly show a substantial activity of platinum salts in *BRCA*1 associated ABC (Byrski et al., 2012).

Isakoff et al. (2015) investigated in another phase II study (TBCRC009) the activity of platinum salts monotherapy (cisplatin and carboplatin) as 1st or 2nd line in 86 ABC patients. Response rate was 29% in patients treated as 1st line and only 12% in patients treated as 2nd line and was higher in patients treated with cisplatin compared to those treated with carboplatin (32.6 % vs 18,6%). Eleven patients had a *gBRCA1*- (Foulkes et al., 2010) and *gBRCA2*-mutation (Easton et al., 1995) and obtained a RR of 54.5%. However, PFS and OS were not different between carriers and non carriers (3.3 vs 2.8 months, and 13.7 vs 10.9 months respectively) (Isakoff et al., 2015).

The largest randomized trial investigating platinum salts in TN ABC is the recently published TNT trial (Tutt et al., 2018). In this study, 376 unselected patients with TN ABC were randomized to carboplatin AUC 6 *versus* standard docetaxel for 6–8 cycles with a preplanned cross over at progression. Only 10% of patients had received prior treatment for ABC and 32%–35% had received taxanes in the adjuvant setting. *gBRCA1/2* mutation carriers were only 55 (43 *BRCA1* and 12 *BRCA2* mutation carriers respectively). Since patients with known *gBRCA* mutation were allowed, irrespectively of ER status, 11 patients had ER-positive disease. Overall, no difference in ORR, which was the principal endpoint, was observed (34% vs 31% in docetaxel and carboplatin arm, respectively). Centrally reviewed response rate was similar (29.3% vs 25.5%). No difference was observed also in terms of median PFS and OS, although precise estimation of OS attributable to single drug was not feasible, because of the cross over design. On the other hand, subjects with *gBRCA1/2* mutation had a significant better ORR with carboplatin than with docetaxel (68% vs 33.3%, p = .03) with a significant interaction between treatment and *BRCA* status (p = .01) which remained significant also after adjustment for other prognostic factors. Median PFS, as well, was significantly prolonged by carboplatin in the BRCA mutated cohort (6.8 vs 4.4 months) but not in the *BRCA* wild type, while no difference in OS was observed (Tutt et al., 2018, 2014).

7. Platinum salts and PARP inhibitors in metastatic breast cancer

As for neoadjuvant treatment, more recent trials design included PARPi in addition or in comparison with platinum salts (Table 3).

In a phase I/II study, patients with *BRCA*-associated ABC were treated with carboplatin plus escalating doses of veliparib. The phase I study enrolled 28 patients, mostly with ER/PR-positive BC (68%). The established maximum tolerated dose (MTD) for the phase II study for veliparib was 150 mg BID in combination with carboplatin AUC5. Median number of prior therapies for ABC was 1 (range 0–5). Overall ORR was 56% and 63% and 53% in TNBC and ER/PR-positive BC, respectively. Median PFS was 8.7 months (95% CI 7.3–10.6). In the phase II study, patients started treatment with veliparib as single agent, with the addition of carboplatin at progression. Forty-four patients were evaluable for response, half of whom had ER/PR-positive tumors. Median PFS on veliparib was 5.2 months. Both ORR and PFS were higher in *BRCA2* as compared to *BRCA1*-associated BC (36% vs 14% and 6.6 months vs 3.3 months), although the difference was significant only for PFS. Among the 30 progressing patients who added carboplatin, ORR was observed only in 1 patient and PFS was 1.8 month (Somlo et al., 2017).

Although a comparison between the two different cohorts is not reliable, the combination was far more active than the PARPi as single agent; moreover, resistance to PARPi, when established, appeared to be extended also to platinum salts.

The recently published BROCADE 2 is a phase II, placebo controlled, randomized study which compared standard chemotherapy with 3-weekly paclitaxel and carboplatin AUC 6 plus veliparib/placebo *versus* veliparib plus temozolamide in 290 women with known *BRCA1/2*-associated ABC (Han et al., 2018). Prior treatments did not include platinum salts or PARPi, but about 70% of patients were chemotherapy naive for ABC. More than a half of patients (167/290) had ER and/or PR-positive BC, while 120/290 were TNBC. *gBRCA1* and *gBRCA2* mutations were present in 163 and 133 patients, respectively. No difference in PFS was observed between chemotherapy/placebo and chemotherapy/veliparib arm (12.3 months and 14.1 months, respectively). On the contrary, ORR was significantly improved by the addition of veliparib (78% vs 61.3%, p = 0.027). Subgroup analyses consistently

favored, although not significantly, the chemotherapy/veliparib arm (Han et al., 2018).

Independently from the comparison with the addition of the PARPi, results obtained with the chemotherapy arm alone were particularly interesting when compared with other trials with the same combination in non *BRCA* carriers patients, particularly considering that more than half of the patients in this study were non TNBC (Egger et al., 2017; Yardley et al., 2018).

However, the lack of a randomized comparison and the generic increased sensitivity of *BRCA*-associated tumors to chemotherapy might undermine the relevance of these findings.

The ongoing studies investigating platinum salts in metastatic BC are summarized in Table 2 (Anon., 2018h, i; Anon., 2018j, k).

8. Beyond germline *BRCA* mutation

The term "BRCAness" describes tumors that have not originated from a germline *BRCA1* or *BRCA2* pathogenic mutation. Nonetheless they share certain phenotypes with these hereditary cancers, in particular an HR defect and subsequent sensitiveness to DNA damages (Rigakos and Razis, 2012).

Other DNA repair genes that may be altered by germline or somatic mutations, rearrangements, DNA methylation, or dysregulated mRNA expression are hypothesized to result in impairment of the HR pathway (Xu et al., 2013; Lord and Ashworth, 2016).

Beyond germline testing for *BRCA1/2* mutation, at present, no standardized assay for detecting HRD or *BRCAness* is clinically available. However, a number of assays has been developed in order to identify and score HRD as a marker of sensitivity to DNA damaging agents.

Currently, there are 3 prominent scoring systems for HRD: HRD-large-scale transition (HRD-LST), which identifies chromosome breaks (translocations, inversions and deletions) resulting in adjacent segments of at least 10 Mb; HRD-loss-of-heterozygosity (HRD-LOH), which allows for the detection of HRD, regardless of etiology or mechanism, as measured by levels of genomic LOH; HRD-telomeric allelic imbalance (HRD-TAI) (Popova et al., 2012; Abkevich et al., 2012; Birkbak et al., 2012). All these assays have been investigated as predictive markers of platinum salts sensitiveness (Tung and Garber, 2018).

In the TBCRC009 trial the *BRCA 1/2* pathway was further characterized in terms of *BRCA* somatic mutation and of *BRCA*-associated genomic instability, using, in addition to the HRD-LOH assay, the HRD-LST assay. As expected, the two markers were higher in *BRCA* mutation carriers *versus* non carriers (mean HRD-LST plus HRD-LOH 13.81 vs 6.52, p = .0089), but, interestingly, they were higher also in patients lacking *gBRCA* mutation and responding to platinum (mean HRD-LST plus HRD-LOH 12.68 vs 5.11, p = .0318). The authors concluded suggesting that platinum sensitivity may be largely or wholly a result of a defect in a *BRCA1/2*-related pathway for abnormal DNA repair (Isakoff et al., 2015).

The HRD-LOH was assessed in the 77 tumor specimens with sufficient extracted DNA in the PrECOG 0105 study (Telli et al., 2015). Among the 65 evaluable patients, mean HRD-LOH scores were higher in responders compared with non responders (15.7 vs 12.5, p = 0.020), while no difference was observed according to mutation status. HRD-LOH score ≥ 10 was also predictive of RCB 0 to I (66% vs 20%) and of pCR. In an attempt to clarify the underlying mechanisms relating HRD and response, in 25 of 45 *BRCA1/2* wild type patients with HRD-LOH data, *BRCA1* promoter methylation was investigated and detected in 15 samples, all of whom had an HRD-LOH score ≥ 10. Nine out of 15 (60%) were responders. The authors underscored that an elevated HRD-LOH assay was able to identify patients other than *gBRCA* mutation carriers who benefited from carboplatin and appeared as a powerful diagnostic tool for assessing DNA repair capacity of tumors.

Telli et al. (2016) assessed a combined HRD score defined as the unweighted numeric sum of LOH, TAI, and LST and tested the predictive power of a HRD score threshold, obtained by analyzing the 3 HRD scores in a training cohort of 497 breast and 561 ovarian chemotherapy-naive tumors with known *BRCA1/2* status. A cutoff with 95% sensitivity was identified to detect those tumors with *BRCA1/2* mutations or *BRCA1* promoter methylation (Telli et al., 2016).

The HRD, defined as HRD score ≥ 42 and/or tumor with *BRCA1/2* mutation, was tested for its ability to identify which tumors responded to neoadjuvant platinum-containing chemotherapy in 3 studies of patients with TNBC (Silver et al., 2010; Telli et al., 2016; Ryan et al., 2009). Patients in these 3 trials were unselected for *BRCA* mutation status. An HRD score ≥ 42 correctly identified 96% of *BRCA1 /2* mutated tumors. *BRCA* mutation status was significantly associated with response to neoadjuvant platinum salts in the PrECOG 0105, but not in the other 2 trials due to the limited number of mutation-associated tumors in these studies. HRD was significantly associated with RCB 0/I and with pCR also in BRCA wild type tumors. The authors concluded that HRD test might be useful to identify sporadic TN EBC patients likely to respond to DNA-damaging therapy beyond those identified by *BRCA1/2* mutation screening.

More recently, the same authors tested the predictive power of this HRD score in a cohort of 47 patients with unselected EBC treated with neoadjuvant anthracycline and taxane-based chemotherapy (Telli et al., 2018). TNBC represented the vast majority (45/47) and only 2 patients had known *gBRCA1/2* associated EBC. *BRCA* mutations were found in 12/47 patients and were not significantly associated with either RCB 0/I and pCR. On the contrary, HRD score ≥ 42 was significantly associated with increased likelihood of achieving both endpoints, irrespectively of tumor *BRCA* mutation status (Telli et al., 2018).

The TNT study prespecified subgroup analyses according to the presence of other features of *BRCAness* as *BRCA1* promoter methylation, HRD assessed by a Myriad assay, *BRCA* somatic mutations, low *BRCA1* mRNA and basal-like phenotype (Tutt et al., 2018). Differently from what hypothesized, subjects with *BRCA1* promoter methylation did not respond better to carboplatin than to docetaxel (21.4% vs 42.1%, p = 0.28), as did patients with low *BRCA1* mRNA (28.76% vs 64.7%, p = .07). A correlation between high HRD score and presence of *gBRCA* mutations was observed, but differently from the preoperative setting, it was not associated with higher response to carboplatin as compared to docetaxel (38.2% vs 40.4%, p = 1.0). On the other hand, patients with somatic *BRCA* mutation had a numerically greater ORR with carboplatin (66.7% vs 35.7%), but numbers were too small to reach statistical significance. The authors hypothesized that epigenetic *BRCAness* is different from genetic mutation of the *BRCA* locus at least in predicting response to therapies. A possible selective reversion of HR after adjuvant therapies might explain the different results obtained with platinum salts in subgroups classified by HRD score in the neoadjuvant and the metastatic setting (Tutt et al., 2018).

Another tool, called HRDetect, a weighed model based on 6 HRD associated distinguishing mutational signatures, was developed as a predictor of *BRCA1* and *BRCA2* deficiency. HRDetect identified *BRCA1/2*-deficient tumors with 98.7% sensitivity. In a cohort of 560 BC, HRDetect identified 22 tumors with somatic loss-of-*BRCA1/2* and 47 tumors with functional *BRCA1/2* deficiency, none of which had germline mutations (Davies et al., 2017).

In an observational study of patients with ABC an elevated HRDetect score was associated with response to platinum chemotherapy but not to PARP inhibitors (Zhao et al., 2017).

Domagala et al. investigated the predictive value of a set of 120 genes associated with the major DNA damage repair pathways in pretreatment biopsies of 43 patients with *BRCA1*-associated TN EBC receiving neoadjuvant therapy with cisplatin and compared their expression between patients achieving pCR and non pCR. The main finding was a different expression of genes involved in the NER pathway which were downregulated in tumors with pCR and increased in tumors not achieving a pCR. When the analyses were performed splitting node positive and node negative tumors, in the former group a

downregulation of other DNA damage repair pathways, as non homologous end joining (NHEJ) and BER, was observed in the pCR group, while, conversely, PARP 1 and PARP3 were upregulated in the other group. These findings suggest that more complex mechanisms other than *gBRCA1*-associated HRD are involved in response to platinum salts and, on the other hand, provide a rationale for the activity of PARPi in platinum resistant tumors (Domagala et al., 2016).

The clinical implication of somatic *BRCA* mutations, mutations that can be found in the tumor tissue, is not fully understood. The percentage of somatic *BRCA* mutations in BC is much lower than in ovarian cancer (3% vs 19%) and it has been shown that only 3% of *gBRCA* negative BC carries somatic tumor mutations as compared to 8–9% in ovarian cancer (Nik-Zainal et al., 2016; Winter et al., 2016; Hennessy et al., 2010; Moschetta et al., 2016).

An ongoing phase III trial is testing the activity of PARPi in BC carrying only somatic BRCA mutations (NCT03344965). It is unknown whether results might be extended also to platinum salts although the results of the TNT trial showed encouraging activity of carboplatin in the small sample of patients with somatic mutations (Tutt et al., 2018).

9. Conclusions

An improved knowledge of DNA repair mechanisms has provided the molecular basis of the putative sensitiveness of *BRCA1/2* associated tumors to DNA damaging agents. Results of clinical studies have undoubtedly confirmed a substantial activity of platinum salts, despite partially inconsistent results have been observed raising a number of issues.

In the advanced setting the only randomized study clearly showed an increased benefit of carboplatin in *BRCA* associated cancers but not in sporadic TNBC.

On the other hand, in the neoadjuvant setting the addition of carboplatin did not consistently increase pCR rates in *gBRCA1/2*-associated TN EBC, while a clear benefit was observed in sporadic TN EBC. This discrepancy was particularly evident in randomized trials which included a relatively larger number of carriers. A comparison across trials due to different drugs, schedules, comparison arms and study populations would be biased. On the other hand, it can be hypothesized that, as can be inferred from results reported in Table 1, *gBRCA1/2*-associated EBC have intrinsically a greater likelihood to respond to chemotherapy which is not significantly affected by the addition of carboplatin.

A recent meta-analysis of 2 randomized trials including *gBRCA* carriers did not show any significant increase in pCR rate with the addition of carboplatin in *BRCA* mutated patients, differently from what observed in *BRCA* wild type tumors (OR 1.17, 95% CI 0.51–2.67, $p = 0.711$ and OR 2.72, 95% CI 1.71–4.32, $p < 0.001$, respectively) (Poggio et al., 2018).

Waiting for the results of ongoing studies, the net benefit of the addition of platinum salts in *BRCA* mutation associated cancers should be weighed in light of the high chemo-sensitiveness of this cancer subset and the increased toxicity with higher rates of discontinuations and dose reductions associated with the addition of carboplatin (Sikov, 2015).

International guidelines and recommendations reflect this inconsistency of the activity of platinum salts in *BRCA*-associated ABC and EBC, respectively. In fact, in the *BRCA*-associated ABC the 2017 St Gallen Consensus, the 4th ABC consensus conference and the ESO-ESMO guidelines for treatment of BC in young women support platinum salts as a ***preferred*** option for treatment, according to the results of the TNT trial (Curigliano et al., 2017; Cardoso et al., 2018; Paluch-Shimon et al., 2017). On the other hand, in the 2017 St Gallen Consensus the panel was splitted about the use of carboplatin in EBC, recommending, in this setting, the use of standard anthracyclines and taxanes in combination with alkylating agents (Curigliano et al., 2017). The 2017 ESMO guidelines state that, in the neoadjuvant setting, addition of platinum is just an ***acceptable*** option (Cardoso et al., 2018; Paluch-Shimon et al., 2017; Appendix, 2019).

Another open question is the role of platinum salts in combination or in sequence to PARPi. Despite a strong rationale for a synergistic effect of the combination provided from preclinical models (Donawho et al., 2007; Rottenberg et al., 2008), the results deriving from the few completed studies, both in EBC and ABC, do not seem to confirm an addictive effect of the two drugs. A partial overlap between the mechanisms of action is a plausible explanation for this finding. A number of studies are ongoing to better clarify this issue, as well as the right sequence of treatments. In the OlympiaD study the benefit of olaparib was limited to the subgroup of patients who had not received platinum salts (Robson et al., 2017). In fact, resistance mechanisms to PARPi may involve HRD restored and thus may be extended also to platinum salts and *viceversa* (Fojo and Bates, 2013). Translational investigations within ongoing clinical trials will hopefully shade light on molecular markers of resistance and then to putative residual sensitiveness to platinum salts after PARPi.

Finally, the search for predictive markers including assays to score HRD and *BRCAness* in *BRCA* wild type cancers will help to identify those sporadic TNBC which are more likely to benefit from platinum salts therapy with the aim to optimize treatment efficacy and spare useless toxicity.

Conflict of interest

Rosalba Torrisi participation to Advisory Board and fees as speaker for : Celgene, MSD, Pfizer, Novartis, Lilly.

Armando Santoro: participation to Advisory Board and fees as speaker for: Sandoz, Servier, EISAI, Roche, Novartis, Gilead, Pfizer, BMS

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Appendix 2: advanced breast cancer: MCBS eUpdate published online 25 April 2017. Ann. Oncol. 28 (suppl_4) iv145–6. www.esmo.org/Guidelines/Breast-Cancer.