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REVIEW ARTICLE

Dissecting the Heterogeneity of Triple-Negative Breast Cancer

Otto Metzger-Filho, Andrew Tutt, Evandro de Azambuja, Kamal S. Saini, Giuseppe Viale, Sherene Loi, Ian Bradbury, Judith M. Bliss, Hatem A. Azim Jr, Paul Ellis, Angelo Di Leo, José Baselga, Christos Sotiriou, and Martine Piccart-Gebhart

Otto Metzger-Filho, Evandro de Azambuja, Kamal S. Saini, Sherene Loi, Hatem A. Azim Jr, Christos Sotiriou, and Martine Piccart-Gebhart, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; Andrew Tutt and Paul Ellis, King's College London, Guy's Campus, London; Judith M. Bliss, Institute of Cancer Research, Sutton; Ian Bradbury, Frontier Science, Kincraig, Scotland, United Kingdom; Giuseppe Viale, European Institute of Oncology, University of Milan, Milan; Angelo Di Leo, Hospital of Prato, Prato, Italy; and José Baselga, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

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Corresponding author: Martine Piccart-Gebhart, MD, PhD, Institut Jules Bordet, Université Libre de Bruxelles, Blvd de Waterloo, 121, 1000 Brussels, Belgium; e-mail: martine.piccart@bordet.be.

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ABSTRACT

Triple-negative breast cancer (TNBC) accounts for 15% to 20% of breast cancers. It is a heterogeneous disease, not only on the molecular level, but also on the pathologic and clinical levels. TNBC is associated with a significantly higher probability of relapse and poorer overall survival in the first few years after diagnosis when compared with other breast cancer subtypes. This is observed despite its usual high sensitivity to chemotherapy. In the advanced setting, responses observed with chemotherapy lack durability. Early-stage clinical studies suggested impressive potential when a poly (ADP-ribose) polymerase (PARP) inhibitor is given for the treatment of advanced TNBC with *BRCA* gene dysfunction. The molecular complexity of TNBC has led to proposed subclassifications, which will be of great value for the development of targeted therapies. In this review, we discuss the biology of TNBC at the pathologic and the molecular levels. We also elaborate on the role of systemic therapies and the results of the first phase III clinical trial evaluating the addition of iniparib, a novel investigational anticancer agent that does not possess characteristics typical of the PARP inhibitor class, in combination with chemotherapy in advanced TNBC.

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INTRODUCTION

Triple-negative breast cancer (TNBC) is defined by the lack of estrogen receptors (ERs) and progesterone receptors (PRs) and by human epidermal growth factor receptor 2 (HER2) –negative status and accounts for 15% to 20% of newly diagnosed breast cancer (BC) cases.[1] It has a distinct epidemiology, histologic features, and clinical behavior. Defining TNBC through the absence of predictive biologic markers is suboptimal and could explain its increasingly recognized heterogeneity. Subclassifications of TNBC based on the presence of biomarkers, gene signatures, and BRCA dysfunction have been proposed, as detailed in Figure 1.

This article provides an overview of relevant clinical and translational research findings in the field of TNBC, aiming to translate relevant findings to clinical practice. Therapeutic developments and the utility of known cytotoxics, such as platinum, are discussed in the context of TNBC heterogeneity. Specific focus is put on a new class of targeted drugs with the ability to modulate the DNA damage repair machinery, namely the poly (ADP-ribose) polymerase (PARP) inhibitors. Iniparib, a novel investigational anticancer agent that does not possess characteristics typical of PARP inhibitors and for which investigations into its real mechanism of action are still ongoing, is also discussed.

References for this review were identified by conducting searches of Medline and selecting references from relevant articles using the terms "basal" or "triple negative" and "breast neoplasm" without restrictions for date. Only articles in English were used. Proceedings from conferences of the American Society of Clinical Oncology and San Antonio Breast Cancer Symposium were also manually searched for relevant abstracts.

EPIDEMIOLOGY AND CLINICAL CHARACTERISTICS

TNBC is associated with African American ethnicity,[1-5] younger age,[1,6,7] advanced stage at diagnosis, and poorer outcome when compared with other BC subtypes.[2,8-11] Different population-based studies have demonstrated a higher prevalence of TNBC among women of African American or black ethnicity.[1-5] A clear correlation has been made between young age at diagnosis and TNBC. In a large population-based study involving 6,370 patients, women with TNBC were significantly more likely to be under the age of 40 years.[1] TNBC is known to have an early peak of recurrence between the first

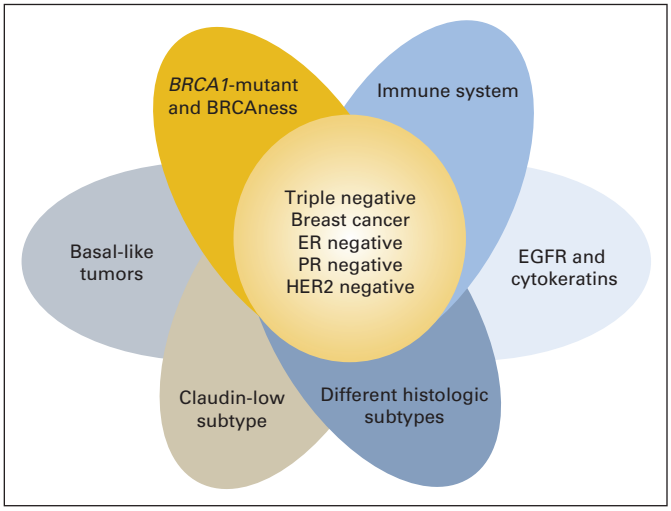

Fig 1. Heterogeneities in the nomenclature and classification of triple-negative breast cancer. EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

and third year after diagnosis followed by a sharp decrease in the recurrence rate in subsequent years and virtually no relapse after 8 years.[6] Worse survival outcomes have been reported for TNBC tumors when compared with hormone receptor–positive tumors in several series.[1,2,8,12,13] Additionally, TNBCs have a site-specific distribution of recurrence. In a retrospective analysis of 1,608 patients, a greater proportion of TNBCs had visceral metastasis as first site of disease recurrence when compared with other types of BC (84% *v* 61%, respectively; $P < .001$).[12] In a recent analysis including 2,033 patients with BC with a 12.7-year median follow-up, a higher visceral relapse rate was observed in the TNBC subset over the first 5 years, but with longer follow-up, the subset of patients with hormone receptor–positive BC (highly proliferative subset) had the same incidence of visceral metastasis as TNBC.[14]

HOW SHOULD TNBC BE DEFINED IN CLINICAL PRACTICE?

In clinical practice, patients are selected for treatment based on clinical stage, tumor histology, and biomarkers with the ability to predict response to treatment. HER2 receptor assessment follows a standardized definition according to guidelines,[15] but hormone receptor assessment varies across different countries, and different immunohistochemistry (IHC) cutoffs are used to define positivity. The American Society of Clinical Oncology/College of American Pathologists guidelines for IHC testing for ERs and PRs recommend that ER and PR assays be considered positive if there is at least 1% of positive tumor cells in the sample.[16] The adoption of a standardized definition for hormone receptor positivity worldwide would enable better definition of patients with TNBC and thus improve the quality of research conducted on this patient subset.

In this respect, the need for an accurate and reproducible assessment of triple-negative status by pathologists cannot be overemphasized. Every effort must be made to improve the accuracy and reproducibility of the assays by fostering compliance with the existing recommendations and guidelines. This will optimize the preanalytic and analytic phases of the testing procedures and the interpretation and scoring of the test results.[15,16]

Although the definition of TNBC depends strongly on pathology, the term basal-like (B-L) BC is derived from gene expression studies.[8] In their seminal article, Perou et al[8] described distinct BC molecular subtypes, with gene expression patterns resembling luminal epithelial cells (luminal), basal and/or myoepithelial cells (B-L), and a subtype showing amplification of high expression of the *Erb-B2* (*HER2*) gene. Further studies using independent data sets have shown similar clusters, with prognostic associations.[8,17-23]

The complexity and costs of gene expression profiling limit its use in clinical practice. Different research groups have proposed IHC-based surrogates to diagnose the genomically defined B-L subtype. Basal cytokeratins (CKs; CK5/6 and/or CK17) correctly identified B-L BCs defined by gene expression profiling in early studies.[8,17] The IHC variables most commonly used in IHC-based surrogates to identify the B-L subtype in subsequent studies were the triple negativity definition (ER negative, PR negative, and HER2 negative), basal CKs (ie, CK5/6, CK14, and CK17), epidermal growth factor receptor (EGFR), and C-kit (CD117).[10,24,25] Nielsen et al[10] evaluated 21 breast tumors defined as B-L by gene expression profiling and demonstrated CK5/6, EGFR, and C-kit expression in 62%, 57%, and 29%, respectively. Rakha et al[26] subsequently proposed a similar IHC surrogate characterized as ER, PR, and HER2 negative and CK5/6, CK14, and CK17 positive, or EGFR positive. The presence of such a B-L surrogate within a group of TNBCs was associated with shorter survival when compared with the remaining TNBCs.[26]

The heterogeneity in the staining patterns of CKs and the absence of defined cutoffs are factors limiting the use of such IHC-based surrogates.[27] At present, there is no standardization for a panel of IHC markers to identify B-L cancers, limiting their applicability in clinical practice.[28-31] The lack of a consensus definition for stratifying TNBCs into subtypes attests to the molecular complexity of basal tumors, underscoring the need for comprehensive translational research efforts in this field.

At the morphology level, TNBC and B-L tumors share similar characteristics.[26] Larger tumor size, higher grade, presence of geographic necrosis, pushing borders of invasion, and stromal lymphocytic infiltrate are characteristics commonly reported across different series.[6,25,32] The majority of TNBCs are invasive ductal carcinoma, but less common histologic subtypes (ie, medullary, metaplastic, and adenoid cystic) share the TNBC phenotypic characteristics.[25,33-35] However, caution should be used when stratifying risk among patients with TNBC with special histologic subtypes because tumor types such as classically defined medullary carcinoma and adenoid cystic carcinoma have an inherently favorable prognosis despite being classified as TNBCs.[36-39]

An important phenotypic overlap is present between *BRCA1*-associated tumors and TNBC/B-L cancers. Initial attempts to classify *BRCA1* mutation carriers at a genomic level classified all 18 *BRCA1*-mutant tumors as basal.[18,40] IHC-based studies also classify 80% to 90% of *BRCA1*-associated tumors as TNBC and/or B-L.[41-45] Subsequent studies have demonstrated the importance of *BRCA1* dysfunction in this group of tumors, as further detailed later. In contrast to *BRCA1*, no association with TNBC is present for *BRCA2* carriers.

GENE EXPRESSION PROFILING IN TNBC

Advances in the field of gene expression profiling have resulted in the development of different signatures aiming to provide better prognostic and predictive tools than classical clinicopathologic parameters. The first generation of signatures, including the 21-recurrence score,[46] gene-70,[40] genomic grade index,[23] and others,[47] was found to be useful for determining the risk of relapse in the ER-positive subgroup, yet was much less informative for basal and HER2-positive subtypes, which were assigned to the high-risk category in almost all cases.[48]

A recent effort to identify biologically distinct TNBC subgroups using the transcriptome data set from 21 independent BC studies identified different clusters defined by mesenchymal features, immune system–related genes, DNA damage response genes, and activated androgen receptor signaling.[49] Interestingly, previous research groups have demonstrated the importance of individual components of these TNBC clusters.[48,50-60]

The first cluster, the claudin-low BC subtype, is characterized by mesenchymal features, low expression of cell-cell junction proteins (ie, claudin, E-cadherin), and intense immune infiltrate.[50] Clinically the majority of claudin-low tumors are TNBCs. From a biologic perspective, the claudin-low subtype represents the most primitive tumors, on a scale of epithelial cell differentiation.[51,52]

With respect to the second cluster, different research groups have demonstrated that genes involved in the immune system can provide prognostic information about TNBC and ER-negative BC. A pooled analysis of microarray studies with more than 2,000 patients with BC observed that high expression of an immune response gene module was significantly associated with better outcome among patients with TNBC.[48] Similar findings were observed among patients with ER-negative BC.[54,55] An immune response seven-gene module[54] and a 14-gene signature[55] linked to immune/inflammatory chemokine regulation were capable of identifying a subgroup of patients with ER-negative BC with reduced risk of distant relapse. In addition, tumor lymphocyte infiltration was associated with better prognosis among patients with TNBC.[61] Finally, immune-related metagenes have also shown ability to predict response to therapy; in the Trial of Principle (TOP) study where patients with ER-negative BC were treated with single-agent epirubicin, an immune response gene module was directly correlated with pathologic complete response (pCR).[59]

With regard to the third TNBC cluster, a gene signature based on DNA repair genes identified patients with TNBC responding to a neoadjuvant anthracycline, which could arguably be attractive for further validation in the context of prediction of response to DNA repair targeting agents.[53] DNA damage response genes have direct implications for drug development as detailed later.

The final TNBC cluster identified highlights the importance of androgen signaling. Specifically, in silico experiments have demonstrated that a subset of TNBC has gene expression that closely matches that of ER-positive tumors, and this subset was found to have androgen receptor expression.[60]

As the heterogeneity of TNBC is better defined, potential therapeutic targets are likely to emerge. A better understanding of the immune system is likely to foster new therapies designed to modulate immune response. For the time being, studies in TNBC are focused on evaluating the role of novel cytotoxics or available cytotoxics in combination with known target agents, as detailed in the next section.

TARGETING TNBC

The lack of identified molecular targets in the majority of TNBCs implies that chemotherapy remains the treatment of choice for patients with TNBC. Neoadjuvant studies have shown that TNBC is highly chemotherapy sensitive.[9,62-64] A retrospective analysis demonstrated twice the pCR rate in TNBC versus non-TNBC (22% *v* 11%, respectively; odds ratio, 1.53; 95% CI, 1.03 to 2.26; $P = .034$).[9] Despite the high chemotherapy sensitivity, treatment of TNBC remains challenging, and on recurrence, patients with TNBC have worse survival outcomes than patients with hormone receptor–positive BC subtypes.[65,66]

In the adjuvant setting, no clear distinction can be made regarding the benefit of particular regimens according to BC subtypes. A decline in the use of anthracyclines for women with BC has been observed in the United States in the recent past.[67] Nevertheless, anthracyclines remain an important class of drugs for treating TNBC. Retrospective exploratory analyses evaluating anthracycline benefit in patients with TNBC should be carefully evaluated. In the MA.5 phase III clinical trial, which compared cyclophosphamide, methotrexate, and fluorouracil (CMF) with cyclophosphamide, epirubicin, and fluorouracil (CEF), a superiority of CMF over CEF was demonstrated in a subset of 35 patients with B-L BC (IHC definition)[68] and, subsequently, in a subset of 94 B-L tumors (reverse transcriptase polymerase chain reaction definition).[69] However, the lack of a statistically significant interaction between treatment and B-L BC subtype and the small number of patients limit definitive conclusions.[68,69] In a combined analysis of five adjuvant trials comparing anthracycline-containing regimens to CMF, anthracycline-containing regimens seemed to be more active than CMF in the TNBC subgroup.[70] Moreover, when epirubicin was added to CMF versus CMF alone, the results of a randomized phase III study demonstrated superior 5-year disease-free survival (85% *v* 59%, respectively; $P = .002$) and 5-year overall survival (OS; 91% *v* 73%, respectively; $P = .002$) in patients with TNBC.[71]

With regard to the use of taxanes in the adjuvant setting, a meta-analysis has shown that the addition of a taxane to an anthracycline-based regimen improves disease-free survival and OS independently of ER expression.[72] Hence, an anthracycline/taxane-based regimen currently seems to be the most suitable option for TNBC outside of the context of a clinical trial.

Ongoing adjuvant clinical trials aiming to improve the outcomes of patients with early-stage TNBC are listed in Table 1.[73-77] The epothilone B analog ixabepilone, which has been shown to have activity in highly pretreated advanced TNBC, is being compared with classical taxanes.[78] Exploratory analysis in a subset of 202 patients with TNBC enrolled onto the FinXX study showed improved efficacy when capecitabine was added to an anthracycline/taxane-based regimen.[79] Capecitabine is also being evaluated as a maintenance therapy after standard adjuvant therapy in two phase III studies.[74,75] However, the addition of capecitabine to a chemotherapy backbone without a comparator limits the evaluation of a specific interaction between capecitabine and TNBC.

In advanced TNBC, responses to chemotherapy lack durability. In a retrospective series of 3,726 patients with 14.8 years of median follow-up, the median survival of patients with metastatic TNBC was only 6 months.[65] Bevacizumab, an anti–vascular endothelial growth

Table 1. Ongoing Adjuvant Phase III Clinical Trials for the Treatment of Triple-Negative Breast Cancer

ClinicalTrials.gov Identifier	Estimated Enrollment (No. of Patients)	Study Design
BEATRICE NCT00528567[73]	2,430	adj ct + bev → bev up to 1 year *v* adj ct
CIBOMA NCT00130533[74]	876	adj ct → capecitabine 1 year *v* adj ct
SYSCBS-001 NCT01112826[75]	684	adj ct → capecitabine 1 year *v* adj ct
TITAN NCT00789581[76]	1,800	AC x 4 → ixabepilone × 4 *v* AC × 4 → paclitaxel every week × 12
PACS08 NCT00630032[77]	2,500	FEC × 3 → ixabepilone *v* FEC × 3 → docetaxel

Abbreviations: AC, anthracycline cyclophosphamide; adj ct, adjuvant chemotherapy; BEATRICE, A Study of Avastin (Bevacizumab) Adjuvant Therapy in Triple-Negative Breast Cancer; bev, bevacizumab; CIBOMA, Iberoamerican Coalition for Breast Oncology Research; FEC, fluorouracil, epirubicin, and cyclophosphamide; PACS08, Combination Chemotherapy Followed by Docetaxel or Ixabepilone in Treating Patients Who Have Undergone Surgery for Nonmetastatic Breast Cancer; SYSCBS-001, Efficacy of Capecitabine Metronomic Chemotherapy to Triple-Negative Breast Cancer; TITAN, Randomized Trial of Ixabepilone Versus Taxol in Adjuvant Therapy of Triple-Negative Breast Cancer.

factor monoclonal antibody, was evaluated for the treatment of advanced BC across five phase III studies.[80-84] The grouped analysis of data from the three first-line bevacizumab studies demonstrated progression-free survival (PFS) benefit in the subset of TNBC (PFS 4.7 *v* 10.2 months; hazard ratio [HR], 0.45; 95% CI, 0.33 to 0.61), but no OS gain.[85] Bevacizumab is under evaluation in a large adjuvant phase III study, as detailed in Table 1.[73] Another therapeutic option explored is the EGFR monoclonal antibody cetuximab, given the relatively high expression of EGFR in TNBC.[86] In a phase II study, cetuximab in combination with carboplatin was associated with 18% overall response rate (ORR).[87] A parallel randomized phase II study compared cisplatin with cisplatin plus cetuximab.[88] The combination arm was associated with increased ORR compared with cisplatin alone (20% *v* 10%, respectively; odds ratio, 2.13; 95% CI, 0.81 to 5.59; $P = .11$).[88] However, the evidence available about the role of EGFR as a driver of BC oncogenesis has not been convincing thus far. It is likely that multilevel downstream activation of EGFR and parallel signaling pathways may have reduced the efficacy of a single-target therapeutic approach.[89,90]

Scientific evidence linking defective DNA repair machinery and sensitivity to DNA-damaging agents in TNBC has been considered as a potentially important factor that might influence therapeutic development. A number of clinical studies have evaluated the role of platinum salts in this population, as detailed in Table 2.[91-97] In the subset of patients with *BRCA1* mutations, striking pCR rates have been demonstrated with single-agent cisplatin.[91-93] However, the role of platinums in non–*BRCA*-mutant advanced TNBC requires further validation. The Triple-Negative Breast Cancer Trial (TNT) is an ongoing randomized phase III study comparing carboplatin with docetaxel for the treatment of advanced TNBC.[98] In addition, the Cancer and Leukemia Group B 40603 neoadjuvant study is evaluating weekly paclitaxel followed by dose-dense anthracycline-cyclophosphamide with or without the addition of carboplatin and/or bevacizumab in early TNBC.[99] Results from both studies are awaited.

DNA Damage Repair Modulation: PARP Inhibitors and Iniparib

A range of DNA repair pathways are organized to maintain stability and integrity of the genome.[100,101] Targeting mechanisms of DNA damage repair (DDR) is an innovative approach being developed for TNBC. Cancer cells are known to acquire DNA mutations over time, and failures in the mechanisms of DDR favor genetic instability and tumorigenesis.[102] The remaining DNA repair mechanisms (those that were not lost during tumor progression) are upregulated and may be involved in resistance to DNA-damaging agents.

DNA repair mechanisms can be classified into categories repairing either single- or double-stranded damage. When one DNA strand is affected and the complementary strand is intact, direct

Table 2. Reported Studies Evaluating Cisplatin or Carboplatin for the Treatment of Patients With *BRCA*-Mutant Breast Cancer and/or TNBC

Study	Study Design	Population	No. of Patients	Treatment	Results
Byrski et al[92]	Retrospective-neoadjuvant	*BRCA1* mutant	102	CMF, n = 14; AC, n = 23; FAC, n = 28; AT, n = 25; cisplatin, n = 12	pCR: CMF, 7%; AC, 22%; FAC, 21%; AT, 8%; cisplatin, 83%
Byrski et al[93]	Pilot neoadjuvant	*BRCA1* mutant	10	Cisplatin	pCR: 90%
Gronwald et al[91]	Neoadjuvant phase II	*BRCA1* mutant	25	Cisplatin	pCR: 72%
Silver et al[94]	Neoadjuvant phase II	TNBC, n = 2 *BRCA1* mutant	28	Cisplatin	pCR: 22% (95% CI, 9% to 43%)
Alba et al[97]	Neoadjuvant randomized phase II	TNBC	94	EC × 4 → T *v* EC × 4 → T + carbo	pCR: EC × 4 → T, 30%; EC × 4 → T + carbo, 30%
Advanced setting					
Wang et al[95]	Phase II	First-line advanced TNBC	45	Cisplatin + gem	ORR: 62% (95% CI, 47.5% to 77%)
Bhattacharyya et al[96]	Randomized phase II	Second-line advanced TNBC	126	Metronomic CM (n = 66) *v* metronomic CM + cisplatin (n = 60)	ORR: metronomic CM, 30%; metronomic CM + cisplatin, 62%

Abbreviations: A, doxorubicin; C, cyclophosphamide; carbo, carboplatin; E, epirubicin; F, fluorouracil; gem, gemcitabine; M, methotrexate; ORR, overall response rate; pCR, pathologic complete response; T, docetaxel; TNBC, triple-negative breast cancer.

repair, base excision repair, nucleotide excision repair, and mismatch repair are activated to correct it. For damage leading to breaks in both DNA strands (double-stranded breaks [DSBs]), the following two main repair pathways are available: nonhomologous end joining, which can induce mutagenic deletion or inappropriate rejoining between DSBs, and the potentially more accurate homologous recombination repair.

Deficiencies in the *BRCA1* gene pathway are important for understanding the sensitivity of drugs targeting DDR in TNBC. The *BRCA1* gene is essential for maintaining genomic stability by promoting repair of DSBs, particularly where these arise at arrested DNA replication forks.[41] The majority of BCs arising in *BRCA1* germline mutation carriers display a triple-negative phenotype determined by IHC or genomic techniques.[18,41,44] In contrast, the frequency of *BRCA1/2* mutations observed in an unselected population (n = 77) was 19.5%.[103] Although the majority of TNBCs are sporadic and lack *BRCA1* mutations, phenotypic analysis and mechanistic studies show similarities between TNBC and *BRCA1*-mutant tumors.[104,105] This has suggested a concept referred to as BRCAness, which describes the phenotype that some sporadic TNBCs share with *BRCA*-associated tumors.[105] Therefore, drugs blocking single-stranded DNA repair and encouraging repair using error-prone nonhomologous end joining that lead to chromosome aberrations when homologous recombination repair is defective could be selectively lethal to tumor cells lacking functional *BRCA1* (*BRCA*-mutant tumors and BRCAness tumors).[106-108]

Concerted attempts have been made to describe *BRCA* dysfunction not associated with *BRCA1* mutation in TNBC. Methylation of the promoter region of the *BRCA1* gene and overexpression of *BRCA1* counter-regulators are proposed as mechanisms leading to *BRCA* dysfunction, but their exact prevalence in larger data sets and a common consensus on how to identify this state are not available.[104,109-113]

PARPs are a large family of multifunctional enzymes, with PARP1 as the most abundant.[114] PARP1 and PARP2 are involved in the mechanism of single-stranded DNA repair called base excision repair and may also stimulate early phases of DNA replication fork repair by homologous recombination repair.[115] PARP inhibition is known to have selective anticancer activity in *BRCA1*- and *BRCA2*-deficient cancers with 100 to 1,000 times greater killing power in *BRCA1*-deficient tumors than in *BRCA*-proficient cells.[116,117] This represents a classic example of synthetic lethality in which two genes are said to be in a synthetic lethal relationship if a mutation in either gene alone is not lethal, but mutations or inactivation of both cause cell death.[118]

Several PARP inhibitors are being evaluated for the treatment of TNBC, as detailed in Table 3. The in vitro findings of PARP inhibitor selectivity against *BRCA*-mutant tumors has also been observed in the clinical setting, as detailed in Table 4.[119-122] A phase I study with olaparib (AZD2281), an oral PARP inhibitor, demonstrated an impressive 47% ORR among patients with *BRCA*-mutant tumors (19 evaluable patients).[123] Later, a proof-of-concept trial with two different doses of olaparib was successfully conducted with 54 patients with *BRCA1*- or *BRCA2*-mutated tumors previously treated with a median of three lines of chemotherapy.[119] ORRs of 41% (95% CI, 25% to 59%) and 22% (95% CI, 11% to 41%) were observed for the higher and lower doses, respectively. Adding chemotherapy to PARP inhibitors has potential advantages for the treatment of TNBC, whereas PARP inhibitor monotherapy might have significant activity for a TNBC subpopulation with nonfunctional *BRCA* genes. Partial and, to a lesser extent, non-BRCAness forms of TNBC might still benefit from PARP inhibitors because many chemotherapeutic agents cause DNA damage that PARP acts to repair and PARP inhibition may act as a chemotherapy sensitizer to these agents.[124]

Table 3. PARP Inhibitors and Phase of Development

Name	Company	Phase of Development
Iniparib (BSI-201)	BiPar/sanofi-aventis	III
BSI-401	BiPar/sanofi-aventis	Preclinical
Olaparib (AZD2281)	KuDOS/AstraZeneca	III
Veliparib (ABT-888)	Abbot	II
CO-338	Clovis	II
INO-1001	Inotek	II
CEP-9722	Cephalon	I
MK-4827	Merck	II
E7016	Eisai	I
BMN-673	BioMarin	I

NOTE. Recent preclinical and clinical data indicate that iniparib does not possess characteristics typical of PARP inhibitor class.
Abbreviation: PARP, poly (ADP-ribose) polymerase.

Iniparib (BSI-201) was initially thought to be a PARP inhibitor, but recent data indicate that iniparib does not possess characteristics typical of this class.[125] Iniparib induces γ-H2AX (a marker of DNA damage) and potentiates cell cycle effects of chemotherapy in tumor cell lines.[126] However, the molecular mechanism accounting for the observed cellular effects has yet to be elucidated, and the relevance of these cellular effects for clinical anticancer activity is not known. In this regard, O'Shaughnessy et al[121] have conducted a randomized phase II trial in which a total of 123 patients with locally defined TNBC (< 10% ER/PR immunoreactive cells and HER2 negative) were randomly assigned to receive the combination of gemcitabine and carboplatin (GC) or GC plus iniparib (GCI) but were allowed to cross over on centrally confirmed progression of disease. GCI, compared with GC, resulted in an increased clinical benefit rate (56% *v* 34%, respectively; $P = .01$), ORR (52% *v* 32%, respectively; $P = .02$), PFS (5.9 *v* 3.6 months, respectively; HR, 0.59; $P = .01$), and OS (12.3 *v* 7.7 months, respectively; HR, 0.57; $P = .01$). This was achieved with no significant increase in the rate of adverse events.

The same group of researchers then conducted a phase III study with PFS and OS as coprimary end points and randomly assigned 519 patients with TNBC to GCI or GC. The coprimary end points of PFS (HR, 0.79; 95% CI, 0.65 to 0.98; $P = .027$ [prespecified P for significance = .01]) and OS (HR, 0.88; 95% CI, 0.69 to 1.12; $P = .28$ [prespecified P for significance = .04]) suggested modest effects for GCI but did not reach the level of statistical significance prespecified in the trial's analysis plan.[122] The fact that the PFS and OS benefit for GCI was restricted to patients treated in second and third line is likely to be misleading because of the significant imbalance in various baseline characteristics; moreover, the differences in estimated treatment effect size between patients with first-line and second/third-line treatment seem less extreme once appropriate adjustment has been made for these factors in the multivariate analysis. For example, the disease-free interval in the first-line treatment strata has a shorter time from diagnosis to metastasis in the GCI arm versus GC arm

Table 4. Reported Results of Phase II and Phase III Studies With PARP Inhibitors in Breast Cancer

Author	Study Design	Population	Treatment Regimens	Efficacy	Toxicity
Tutt et al[119]	Phase II, two cohorts	54 patients with BC with ≥ 1 CT regimen; all with *BRCA1/2* mutation	Olaparib 400 mg twice daily PO, every 28 days, n = 27 Olaparib 100 mg twice daily PO, every 28 days, n = 27	Olaparib 400 mg: RR, 41% (95% CI, 25% to 59%); CR, 4% (95% CI, 1% to 18%); PR, 37% (95% CI, 22% to 56%); SD, 44% (95% CI, 28% to 63%) Olaparib 100 mg: RR, 22% (95% CI, 11% to 41%); CR, 0%; PR, 22% (95% CI, 11% to 41%); SD, 44% (95% CI, 28% to 63%)	Grade 3 or 4: olaparib 400 mg: nausea, 15%; vomiting, 11%; fatigue, 15%; anemia, 11%; olaparib 100 mg: nausea, 0%; vomiting, 0%; fatigue, 4%; anemia, 7%
Isakoff et al[120]	Phase II, single arm	41 patient with BC with ≥ 1 CT regimen; 8 patient with *BRCA1/2* mutation (efficacy results)	TMZ 150 mg/m^2 PO on days 1-5; veliparib 40 mg twice daily PO on days 1-7, every 28 days (dose reduced to 30 mg twice daily)	ORR, 37%; CBR, 62%; PFS, 5.5 months	Grade 3: thrombocytopenia, 22%; neutropenia, 19%; hypophosphatemia, 2% Grade 4: thrombocytopenia, 22%; neutropenia, 7%; hypophosphatemia, 5%
O'Shaughnessy et al[121]	Phase II, randomized	123 patients with TNBC with ≤ 2 CT regimens, *BRCA* unknown	Carboplatin AUC 2 IV days 1 and 8; gemcitabine 1,000 mg/m^2 IV days 1 and 8, every 21 days; n = 62 Carboplatin AUC 2 IV days 1 and 8; gemcitabine 1,000 mg/m^2 IV days 1 and 8; iniparib 5.6 mg/kg IV days 1, 4, 8, and 11, every 21 days; n = 61	Carboplatin/gemcitabine: ORR, 32%; CBR, 34%; PFS, 3.6 months (95% CI, 2.6 to 5.2 months); OS, 7.7 months (95% CI, 6.5 to 13.3 months) Carboplatin/gemcitabine/iniparib: ORR, 52%; CBR, 56%; PFS, 5.9 months (95% CI, 4.5 to 7.2 months); OS, 12.3 months (95% CI, 9.8 to 21.5 months)	Carboplatin/gemcitabine: grade 3: neutropenia, 36%; anemia, 15%; thrombocytopenia, 10%; fatigue, 17% Carboplatin/gemcitabine: grade 4: neutropenia, 27%; anemia, 0%; thrombocytopenia, 17%; fatigue, 2% Carboplatin/gemcitabine/iniparib: grade 3: neutropenia, 44%; anemia, 23%; thrombocytopenia, 18%; fatigue, 7% Carboplatin/gemcitabine/iniparib: grade 4: neutropenia, 23%; anemia, 0%; thrombocytopenia, 19%; fatigue, 0%
O'Shaughnessy et al[122]	Phase III, randomized	519 patients with TNBC with ≤ 2 CT regimens; 57% first line; 43% second or third line; *BRCA* unknown	Carboplatin AUC 2 IV days 1 and 8; gemcitabine 1,000 mg/m^2 IV days 1 and 8, every 21 days; n = 258 Carboplatin AUC 2 IV days 1 and 8; gemcitabine 1,000 mg/m^2 IV days 1 and 8; iniparib 5.6 mg/kg IV days 1, 4, 8, and 11, every 21 days; n = 261	Carboplatin/gemcitabine: ORR, 30% (95% CI, 25% to 36%); CBR, 36%; PFS, 4.1 months (95% CI, 3.1 to 4.6 months); OS, 11.1 months (95% CI, 9.2 to 12.1 months) Carboplatin/gemcitabine/iniparib: ORR, 34% (95% CI, 28% to 40%); CBR, 41%; PFS, 5.1 months (95% CI, 4.2 to 5.8 months); OS, 11.8 months (95% CI, 10.6 to 12.9 months)	Carboplatin/gemcitabine: grade 3 or 4: neutropenia, 53%; anemia, 22%; thrombocytopenia, 24%; fatigue, 6% Carboplatin/gemcitabine/iniparib: grade 3 or 4: neutropenia, 61%; anemia, 18%; thrombocytopenia, 28%; fatigue, 8%

Abbreviations: AUC, area under the concentration-time curve; BC, breast cancer; CBR, clinical benefit rate; CR, complete response; CT, chemotherapy; IV, intravenously; ORR, overall response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival; PO, oral; PR, partial response; RR, objective response rate; SD, stable disease; TMZ, temozolomide; TNBC, triple-negative breast cancer.

(median, 9.5 *v* 15.9 months, respectively). In concordance with phase II data, no increase in grade 3 or 4 toxicities was observed.

Despite this trial's failure to meet the prespecified statistical criteria for the use of coprimary end points, it did show a signal of efficacy for GCI within this heterogeneous group of patients. What is not clear is where the signal is coming from within the population and whether this relates to the degree of prior treatment or a biologic subgroup. The relatively limited understanding of the mechanism of action of iniparib currently compounds the challenges associated with resolving this issue.[125]

The results obtained with PARP inhibitors so far represent a real milestone in managing patients with *BRCA*-associated TNBC. However, there is still a critical need to identify patients without *BRCA* mutations likely to benefit from PARP inhibitors. In addition, more information about differences among PARP inhibitors and clarification of the exact mechanism of action of iniparib are needed. In vitro findings have shown that when a *BRCA1*-defective BC cell line was treated with veliparib, olaparib, or iniparib, DSBs increased in a dose- and time-dependent fashion.[125] However, only veliparib and olaparib were able to inhibit PARP1/2. In contrast, iniparib was able to suppress genes involved in telomere function, which the authors suggest may be a result of blockade of other PARP family members.[125]

CONCLUSION

TNBC is a challenging disease that has lacked a standardized treatment approach both in the early and advanced settings. Available evidence suggests that among patients with TNBC, prognosis seems to vary according to factors such as age and pathologic subtype. Several research groups have provided important insights into TNBC heterogeneity. Genes related to immune response have been shown to be of prognostic and predictive value, but validation is needed. PARP inhibitors have demonstrated impressive results in studies in the *BRCA1/2* BC subpopulation, but the identification of nonmutant TNBC likely

to derive the same magnitude of benefit remains challenging. Prospective clinical trials coupled with integrated adequately powered translational research questions are likely to improve the outcome of patients with TNBC and should be our priority.

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AUTHOR CONTRIBUTIONS

Conception and design: Otto Metzger-Filho, Andrew Tutt, Evandro de Azambuja, Kamal S. Saini, Giuseppe Viale, Sherene Loi, Judith M. Bliss, Hatem A. Azim Jr, Paul Ellis, Angelo Di Leo, José Baselga, Christos Sotiriou, Martine Piccart-Gebhart
Collection and assembly of data: Otto Metzger-Filho, Andrew Tutt, Martine Piccart-Gebhart
Data analysis and interpretation: Ian Bradbury, Judith M. Bliss, Otto Metzger-Filho
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Bauer KR, Brown M, Cress RD, et al: Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California Cancer Registry. Cancer 109: 1721-1728, 2007
2. Carey LA, Perou CM, Livasy CA, et al: Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295:2492-2502, 2006
3. Morris GJ, Naidu S, Topham AK, et al: Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: A single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Cancer 110:876-884, 2007
4. Stead LA, Lash TL, Sobieraj JE, et al: Triple-negative breast cancers are increased in black women regardless of age or body mass index. Breast Cancer Res 11:R18, 2009
5. Lund MJ, Trivers KF, Porter PL, et al: Race and triple negative threats to breast cancer survival: A population-based study in Atlanta, GA. Breast Cancer Res Treat 113:357-370, 2009
6. Dent R, Trudeau M, Pritchard KI, et al: Triple-negative breast cancer: Clinical features and patterns of recurrence. Clin Cancer Res 13:4429-4434, 2007
7. Anders CK, Fan C, Parker JS, et al: Breast carcinomas arising at a young age: Unique biology or a surrogate for aggressive intrinsic subtypes? J Clin Oncol 29:e18–e20, 2011
8. Perou CM, Sorlie T, Eisen MB, et al: Molecular portraits of human breast tumours. Nature 406: 747-752, 2000
9. Liedtke C, Mazouni C, Hess KR, et al: Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 26:1275-1281, 2008
10. Nielsen TO, Hsu FD, Jensen K, et al: Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 10:5367-5374, 2004
11. Cancello G, Maisonneuve P, Rotmensz N, et al: Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer. Ann Oncol 21:1974-1981, 2010
12. Dent R, Hanna WM, Trudeau M, et al: Pattern of metastatic spread in triple-negative breast cancer. Breast Cancer Res Treat 115:423-428, 2009
13. Rodriguez-Pinilla SM, Sarrio D, Honrado E, et al: Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. Clin Cancer Res 12:1533-1539, 2006
14. Metzger O, Sun Z, Viale G, et al: Patterns of breast cancer relapse according to breast cancer subtypes in lymph node-negative breast cancer: Results from International Breast Cancer Study Group trials VIII and IX. Cancer Res 70:24s, 2010 (suppl; abstr P5-13-01)
15. Wolff AC, Hammond ME, Schwartz JN, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 131:18-43, 2007
16. Hammond ME, Hayes DF, Dowsett M, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28:2784-2795, 2010
17. Sorlie T, Perou CM, Tibshirani R, et al: Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98:10869-10874, 2001
18. Sorlie T, Tibshirani R, Parker J, et al: Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 100:8418-8423, 2003
19. Calza S, Hall P, Auer G, et al: Intrinsic molecular signature of breast cancer in a population-based cohort of 412 patients. Breast Cancer Res 8:R34, 2006
20. Ihemelandu CU, Leffall LD Jr, Dewitty RL, et al: Molecular breast cancer subtypes in premenopausal African-American women, tumor biologic factors and clinical outcome. Ann Surg Oncol 14:2994-3003, 2007
21. Hu Z, Fan C, Oh DS, et al: The molecular portraits of breast tumors are conserved across microarray platforms. BMC Genomics 7:96, 2006
22. Yu K, Lee CH, Tan PH, et al: Conservation of breast cancer molecular subtypes and transcriptional patterns of tumor progression across distinct ethnic populations. Clin Cancer Res 10:5508-5517, 2004
23. Sotiriou C, Neo SY, McShane LM, et al: Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci U S A 100:10393-10398, 2003
24. Rakha EA, El-Sayed ME, Green AR, et al: Breast carcinoma with basal differentiation: A proposal for pathology definition based on basal cytokeratin expression. Histopathology 50:434-438, 2007
25. Livasy CA, Karaca G, Nanda R, et al: Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol 19:264-271, 2006
26. Rakha EA, Elsheikh SE, Aleskandarany MA, et al: Triple-negative breast cancer: Distinguishing between basal and nonbasal subtypes. Clin Cancer Res 15:2302-2310, 2009
27. Moinfar F: Is 'basal-like' carcinoma of the breast a distinct clinicopathological entity? A critical review with cautionary notes. Pathobiology 75:119-131, 2008
28. Jumppanen M, Gruvberger-Saal S, Kauraniemi P, et al: Basal-like phenotype is not associated with patient survival in estrogen-receptor-negative breast cancers. Breast Cancer Res 9:R16, 2007
29. Kim MJ, Ro JY, Ahn SH, et al: Clinicopathologic significance of the basal-like subtype of breast cancer: A comparison with hormone receptor and Her2/neu-overexpressing phenotypes. Hum Pathol 37:1217-1226, 2006

30. Potemski P, Kusinska R, Watala C, et al: Prognostic relevance of basal cytokeratin expression in operable breast cancer. Oncology 69:478-485, 2005

31. Fulford LG, Reis-Filho JS, Ryder K, et al: Basal-like grade III invasive ductal carcinoma of the breast: Patterns of metastasis and long-term survival. Breast Cancer Res 9:R4, 2007

32. Fulford LG, Easton DF, Reis-Filho JS, et al: Specific morphological features predictive for the basal phenotype in grade 3 invasive ductal carcinoma of breast. Histopathology 49:22-34, 2006

33. Jacquemier J, Padovani L, Rabayrol L, et al: Typical medullary breast carcinomas have a basal/myoepithelial phenotype. J Pathol 207:260-268, 2005

34. Bertucci F, Finetti P, Cervera N, et al: Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers. Cancer Res 66:4636-4644, 2006

35. Rodriguez-Pinilla SM, Rodriguez-Gil Y, Moreno-Bueno G, et al: Sporadic invasive breast carcinomas with medullary features display a basal-like phenotype: An immunohistochemical and gene amplification study. Am J Surg Pathol 31:501-508, 2007

36. Huober JB, Gelber S, Thürlimann B, et al: Prognosis of medullary breast cancer: Analyses of 13 International Breast Cancer Study Group (IBCSG) trials. J Clin Oncol 28:99s, 2010 (suppl; abstr 630)

37. Ellis P, Schnitt SJ, Sastre-Garau X, et al: Invasive breast carcinoma, in Tavassoli FA, Devilee P (eds): WHO Classification of Tumours Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyon, France, IARC Press, 2003

38. McClenathan JH, de la Roza G: Adenoid cystic breast cancer. Am J Surg 183:646-649, 2002

39. Weigelt B, Horlings HM, Kreike B, et al: Refinement of breast cancer classification by molecular characterization of histological special types. J Pathol 216:141-150, 2008

40. van't Veer LJ, Dai H, van de Vijver MJ, et al: Gene expression profiling predicts clinical outcome of breast cancer. Nature 415:530-536, 2002

41. Foulkes WD, Stefansson IM, Chappuis PO, et al: Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 95:1482-1485, 2003

42. Arnes JB, Brunet JS, Stefansson I, et al: Placental cadherin and the basal epithelial phenotype of BRCA1-related breast cancer. Clin Cancer Res 11:4003-4011, 2005

43. Laakso M, Loman N, Borg A, et al: Cytokeratin 5/14-positive breast cancer: True basal phenotype confined to BRCA1 tumors. Mod Pathol 18: 1321-1328, 2005

44. Lakhani SR, Reis-Filho JS, Fulford L, et al: Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 11:5175-5180, 2005

45. Pathology of familial breast cancer: Differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases—Breast Cancer Linkage Consortium. Lancet 349:1505-1510, 1997

46. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351: 2817-2826, 2004

47. Sotiriou C, Pusztai L: Gene-expression signatures in breast cancer. N Engl J Med 360:790-800, 2009

48. Desmedt C, Haibe-Kains B, Wirapati P, et al: Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. Clin Cancer Res 14:5158-5165, 2008

49. Lehmann BD, Bauer JA, Chen X, et al: Transcriptome analysis of triple negative breast cancers identifies six distinct biological subgroups and reveals therapeutic strategies. Cancer Res 70:24s, 2010 (suppl; abstr PD01-07)

50. Prat A, Parker JS, Karginova O, et al: Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. Breast Cancer Res 12:R68, 2010

51. Lim E, Vaillant F, Wu D, et al: Aberrant luminal progenitors as the candidate target population for basal tumor development in BRCA1 mutation carriers. Nat Med 15:907-913, 2009

52. Prat A, Perou CM: Mammary development meets cancer genomics. Nat Med 15:842-844, 2009

53. Rodriguez AA, Makris A, Wu MF, et al: DNA repair signature is associated with anthracycline response in triple negative breast cancer patients. Breast Cancer Res Treat 123:189-196, 2010

54. Teschendorff AE, Miremadi A, Pinder SE, et al: An immune response gene expression module identifies a good prognosis subtype in estrogen receptor negative breast cancer. Genome Biol 8:R157, 2007

55. Yau C, Esserman L, Moore DH, et al: A multigene predictor of metastatic outcome in early stage hormone receptor-negative and triple-negative breast cancer. Breast Cancer Res 12:R85, 2010

56. Rody A, Karn T, Liedtke C, et al: Identification of a clinically relevant gene signature in triple negative and basal-like breast cancer. Cancer Res 70:24s, 2010 (suppl; abstr S5-5)

57. Denkert C, Loibl S, Noske A, et al: Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 28:105-113, 2010

58. Farmer P, Bonnefoi H, Anderle P, et al: A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. Nat Med 15:68-74, 2009

59. Desmedt C, Di Leo A, de Azambuja E, et al: Multifactorial approach to predicting resistance to anthracyclines. J Clin Oncol 29:1578-1586, 2011

60. Gucalp A, Traina TA: Triple-negative breast cancer: Role of the androgen receptor. Cancer J 16:62-65, 2010

61. Kreike B, van Kouwenhove M, Horlings H, et al: Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast Cancer Res 9:R65, 2007

62. Rouzier R, Perou CM, Symmans WF, et al: Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 11:5678-5685, 2005

63. Parker JS, Mullins M, Cheang MC, et al: Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 27:1160-1167, 2009

64. Carey LA, Dees EC, Sawyer L, et al: The triple negative paradox: Primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res 13:2329-2334, 2007

65. Kennecke H, Yerushalmi R, Woods R, et al: Metastatic behavior of breast cancer subtypes. J Clin Oncol 28:3271-3277, 2010

66. Kassam F, Enright K, Dent R, et al: Survival outcomes for patients with metastatic triple-negative breast cancer: Implications for clinical practice and trial design. Clin Breast Cancer 9:29-33, 2009

67. Giordano SH, Lin Y, Kuo Y, et al: Anthracycline (A) use among women with breast cancer (BC). J Clin Oncol 29:84s, 2011 (suppl; abstr 1019)

68. Cheang M, Chia SK, Tu D, et al: Anthracyclines in basal breast cancer: The NCIC-CTG trial MA5 comparing adjuvant CMF to CEF. J Clin Oncol 27:11s, 2009 (suppl; abtr 519)

69. Cheang M, Voduc D, Tu D, et al: The responsiveness of intrinsic subtypes to adjuvant anthracyclines versus nonanthracyclines in NCIC.CTG MA.5 randomized trial. J Clin Oncol 29:88s, 2011 (suppl; abstr 1032)

70. Di Leo A, Desmedt C, Bartlett JM, et al: Final results of a meta-analysis testing HER2 and topoisomerase IIalpha genes as predictors of incremental benefit from anthracyclines in breast cancer. J Clin Oncol 28:72s, 2010 (suppl; abstr 519)

71. Rocca A, Paradiso A, Sismondi P, et al: Benefit from CMF with or without anthracyclines in relation to biologic profiles in early breast cancer. J Clin Oncol 29:87s, 2011 (suppl; abstr 1031)

72. De Laurentiis M, Cancello G, D'Agostino D, et al: Taxane-based combinations as adjuvant chemotherapy of early breast cancer: A meta-analysis of randomized trials. J Clin Oncol 26:44-53, 2008

73. ClinicalTrials.gov: BEATRICE study: A study of Avastin (bevacizumab) adjuvant therapy in triple negative breast cancer. http://clinicaltrials.gov/ct2/show/NCT00528567

74. ClinicalTrials.gov: Maintenance treatment with capecitabine versus observation in breast cancer patients. http://clinicaltrials.gov/ct2/show/NCT00130533

75. ClinicalTrials.gov: Efficacy of capecitabine metronomic chemotherapy to triple-negative breast cancer (SYSCBS-001). http://clinicaltrials.gov/ct2/show/NCT01112826

76. ClinicalTrials.gov: A randomized trial of Ixempra versus Taxol in adjuvant therapy of triple negative breast cancer (TITAN). http://clinicaltrials.gov/ct2/show/NCT00789581

77. ClinicalTrials.gov: Combination chemotherapy followed by docetaxel or ixabepilone in treating patients who have undergone surgery for nonmetastatic breast cancer. http://clinicaltrials.gov/ct2/show/NCT00630032

78. Perez EA, Patel T, Moreno-Aspitia A: Efficacy of ixabepilone in ER/PR/HER2-negative (triple-negative) breast cancer. Breast Cancer Res Treat 121:261-271, 2010

79. Lindman H, Kellokumpu-Lehtinen P-L, Huovinen R, et al: Integration of capecitabine into anthracycline- and taxane-based adjuvant therapy for triple-negative early breast cancer: Final subgroup analysis of the FinXX Study. Cancer Res 70:24s, 2010 (suppl; abstr PD01-02)

80. Miller KD, Chap LI, Holmes FA, et al: Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 23:792-799, 2005

81. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-2676, 2007

82. Miles DW, Chan A, Dirix LY, et al: Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 28:3239-3247, 2010

83. Robert NJ, Dieras V, Glaspy J, et al: RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 27:42s, 2009 (suppl; abstr 1005)

84. Brufsky A, Bondarenko IN, Smirnov V, et al: RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer. Cancer Res 69:24s, 2009 (suppl; abstr 42)

85. O'Shaughnessy J, Dieras V, Glaspy J, et al: Comparison of subgroup analyses of PFS from three phase III studies of bevacizumab in combination with chemotherapy in patients with HER2-negative metastatic breast cancer (MBC). Cancer Res 69:24s, 2009 (suppl; abstr 207)

86. Viale G, Rotmensz N, Maisonneuve P, et al: Invasive ductal carcinoma of the breast with the "triple-negative" phenotype: Prognostic implications of EGFR immunoreactivity. Breast Cancer Res Treat 116:317-328, 2009

87. Carey LA, Rugo HS, Marcom PK, et al: TBCRC 001: EGFR inhibition with cetuximab added to carboplatin in metastatic triple-negative (basal-like) breast cancer. J Clin Oncol 26:43s, 2008 (suppl; abstr 1009)

88. Baselga J, Gomez P, Awada A, et al: The addition of cetuximab to cisplatin increases overall response rate (ORR) and progression-free survival (PFS) in metastatic triple-negative breast cancer (TNBC): Results of a randomized phase II study (BALI-1). Ann Oncol 21:8s, 2010 (suppl; abstr 274)

89. Moyano JV, Evans JR, Chen F, et al: AlphaB-crystallin is a novel oncoprotein that predicts poor clinical outcome in breast cancer. J Clin Invest 116:261-270, 2006

90. Albeck JG, Brugge JS: Uncovering a tumor suppressor for triple-negative breast cancers. Cell 144:638-640, 2011

91. Gronwald J, Byrski T, Huzarski T, et al: Neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. J Clin Oncol 27:7s, 2009 (suppl; abstr 502)

92. Byrski T, Gronwald J, Huzarski T, et al: Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol 28:375-379, 2010

93. Byrski T, Huzarski T, Dent R, et al: Response to neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. Breast Cancer Res Treat 115:359-363, 2009

94. Silver DP, Richardson AL, Eklund AC, et al: Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. J Clin Oncol 28:1145-1153, 2010

95. Wang Z, Hu X, Chen L, et al: Efficacy of gemcitabine and cisplatin (GP) as first-line combination therapy in patients with triple-negative metastatic breast cancer: Preliminary results report of a phase II trial. J Clin Oncol 28:138s, 2010 (suppl; abstr 1100)

96. Bhattacharyya GS, Basu S, Agarwal V, et al: Single institute phase II study of weekly cisplatinum and metronomic dosing of Endoxan and methotrexate in second line metastatic breast cancer triple-negative. Eur J Cancer Suppl 7:18, 2009 (abstr 41)

97. Alba E, Chacon J, Lluch A, et al: Chemotherapy (CT) with or without carboplatin as neoadjuvant treatment in patients with basal-like breast cancer: GEICAM 2006-03-A multicenter, randomized phase II study. J Clin Oncol 29:83s, 2011 (suppl; abstr 1015)

98. ClinicalTrials.gov: Triple negative breast cancer trial (TNT). http://www.clinicaltrial.gov/ct2/show/NCT00532727

99. ClinicalTrials.gov: Paclitaxel with or without carboplatin and/or bevacizumab followed by doxorubicin and cyclophosphamide in treating patients with breast cancer that can be removed by surgery. http://clinicaltrials.gov/ct2/show/NCT00861705?term=NCT00861705&rank=1

100. Hoeijmakers JH: Genome maintenance mechanisms for preventing cancer. Nature 411:366-374, 2001

101. Ashworth A: A synthetic lethal therapeutic approach: Poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 26:3785-3790, 2008

102. DePinho RA, Polyak K: Cancer chromosomes in crisis. Nat Genet 36:932-934, 2004

103. Gonzalez-Angulo AM, Timms KM, Liu S, et al: Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 17:1082-1089, 2011

104. Turner NC, Reis-Filho JS, Russell AM, et al: BRCA1 dysfunction in sporadic basal-like breast cancer. Oncogene 26:2126-2132, 2007

105. Turner N, Tutt A, Ashworth A: Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4:814-819, 2004

106. Patel AG, Sarkaria JN, Kaufmann SH: Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. Proc Natl Acad Sci U S A 108:3406-3411, 2011

107. Vollebergh MA, Lips EH, Nederlof PM, et al: An aCGH classifier derived from BRCA1-mutated breast cancer and benefit of high-dose platinum-based chemotherapy in HER2-negative breast cancer patients. Ann Oncol 22:1561-1570, 2010

108. Treszezamsky AD, Kachnic LA, Feng Z, et al: BRCA1- and BRCA2-deficient cells are sensitive to etoposide-induced DNA double-strand breaks via topoisomerase II. Cancer Res 67:7078-7081, 2007

109. Catteau A, Harris WH, Xu CF, et al: Methylation of the BRCA1 promoter region in sporadic breast and ovarian cancer: Correlation with disease characteristics. Oncogene 18:1957-1965, 1999

110. Esteller M, Silva JM, Dominguez G, et al: Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. J Natl Cancer Inst 92:564-569, 2000

111. Magdinier F, Ribieras S, Lenoir GM, et al: Down-regulation of BRCA1 in human sporadic breast cancer; analysis of DNA methylation patterns of the putative promoter region. Oncogene 17:3169-3176, 1998

112. Rice JC, Ozcelik H, Maxeiner P, et al: Methylation of the BRCA1 promoter is associated with decreased BRCA1 mRNA levels in clinical breast cancer specimens. Carcinogenesis 21:1761-1765, 2000

113. Grushko TA, Nwachukwu C, Charoenthammaraksa S, et al: Evaluation of BRCA1 inactivation by promoter methylation as a marker of triple-negative and basal-like breast cancers. J Clin Oncol 28:725s, 2010 (suppl; abstr 10510)

114. Ame JC, Spenlehauer C, de Murcia G: The PARP superfamily. Bioessays 26:882-893, 2004

115. Bryant HE, Petermann E, Schultz N, et al: PARP is activated at stalled forks to mediate Mre11-dependent replication restart and recombination. Embo J 28:2601-2615, 2009

116. Bryant HE, Schultz N, Thomas HD, et al: Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 434:913-917, 2005

117. Farmer H, McCabe N, Lord CJ, et al: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917-921, 2005

118. Iglehart JD, Silver DP: Synthetic lethality: A new direction in cancer-drug development. N Engl J Med 361:189-191, 2009

119. Tutt A, Robson M, Garber JE, et al: Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof-of-concept trial. Lancet 376:235-244, 2010

120. Isakoff SJ, Overmoyer B, Tung NM, et al: A phase II trial of the PARP inhibitor veliparib (ABT888) and temozolomide for metastatic breast cancer. J Clin Oncol 28:118s, 2010 (suppl; abstr 1019)

121. O'Shaughnessy J, Osborne C, Pippen JE, et al: Iniparib plus chemotherapy in metastatic triple-negative breast cancer. N Engl J Med 364:205-214, 2011

122. O'Shaughnessy J, Schwartzberg LS, Danso MA, et al: A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). J Clin Oncol 29:81s, 2011 (suppl; abstr 1007)

123. Fong PC, Boss DS, Yap TA, et al: Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. N Engl J Med 361:123-134, 2009

124. Ljungman M: Targeting the DNA damage response in cancer. Chem Rev 109:2929-2950, 2009

125. Ji J, Lee MP, Kadota M, et al: Pharmacodynamic and pathway analysis of three presumed inhibitors of poly (ADP-ribose) polymerase: ABT-888, AZD2281, and BSI201. Proc Am Assoc Cancer Res 1:71, 2011 (abstr 4527)

126. Ossovskaya V, Lim C, Schools G, et al: Cell cycle effects of iniparib, a PARP inhibitor, in combination with gemcitabine and carboplatin in the MDA-MB-468(-) triple-negative breast cancer (TNBC) cell line. Cancer Res 70:24s, 2010 (suppl; abstr P5-06-09)

