Triple-negative breast cancer: treatment challenges and solutions

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Abstract: Triple-negative breast cancers (TNBCs) are defined by the absence of estrogen and progesterone receptors and the absence of HER2 overexpression. These cancers represent a heterogeneous breast cancer subtype with a poor prognosis. Few systemic treatment options exist besides the use of chemotherapy (CT). The heterogeneity of the disease has limited the successful development of targeted therapy in unselected patient populations. Currently, there are no approved targeted therapies for TNBC. However, intense research is ongoing to identify specific targets and develop additional and better systemic treatment options. Standard adjuvant and neoadjuvant regimens include anthracyclines, cyclophosphamide, and taxanes. Platinum-based CT has been proposed as another CT option of interest in TNBC. We review the role of this therapy in general, and particularly in patients carrying BRCA1/2 germ-line mutations. Available data concerning the role of platinum-based CT in TNBC were acquired primarily in the neoadjuvant setting. The routine use of platinum-based CT is not yet recommended by available guidelines. Many studies have reported the molecular characterization of TNBCs. Several actionable targets have been identified. Novel therapeutic strategies are currently being tested in clinical trials based on promising results observed in preclinical studies. These targets include androgen receptor, EGFR, PARP, FGFR, and the angiogenic pathway. We review the recent data on experimental drugs in this field. We also discuss the recent data concerning immunologic checkpoint inhibitors.

Keywords: triple-negative breast cancer, molecular subtype, platinum-based chemotherapy, targeted therapy, androgen receptor, BRCA1/2 mutation

Introduction

In 2012, 1.7 million women worldwide were diagnosed with breast cancer (BC), and 521,900 women died from it.1 These statistics include all subtypes of BC, but it is well known that BC is not a homogeneous disease. Four major intrinsic subtypes have been identified by genomic studies: the luminal subtypes A and B, which express hormone receptor-related genes, basal-like (BL) BC, and HER2-positive BC.2,3

Triple-negative BC (TNBC) is a heterogeneous group characterized by the lack of expression of hormonal receptors and the absence of HER2 overexpression. The definition of negative estrogen receptor (ER) status by immunohistochemistry (IHC) is not concordant in the literature, with some definitions considering ER expression to be significant only if at least 10% of tumor cells express the receptors. However, the St Gallen guidelines,4 the American Society of Clinical Oncology,5 and the American College of Pathology5 have defined TNBC as BC with less than 1% of tumor cells expressing the ER and progesterone receptors via IHC.
We first review the available data on molecular heterogeneity and BRCA1-associated TNBC/BL BC. Thereafter, we discuss the current treatment options and some promising new treatment approaches that include targeted treatments.

**Understanding TNBC heterogeneity**

Before molecular profiling confirmed the important heterogeneity in the biology of TNBC, clinical data had already indicated the existence of heterogeneous treatment responses and long-term outcomes. Some patients respond very well to neoadjuvant CT and present a pathologic complete response (pCR) at the time of surgery. Other patients present no response to neoadjuvant CT and suffer from early relapse after surgery.\(^6\)\(^7\)\(^8\)\(^9\) Unfortunately, predictive factors that allow the identification of patients who will present a pCR and those who will not benefit from CT at the time of diagnosis do not exist.

The vast majority of TNBCs are high-grade invasive ductal carcinomas, but some rare cases are histologically different, such as adenoid cystic carcinoma, secretory carcinoma, medullary carcinoma, and metaplastic carcinoma. The prognosis depends on the TNBC pathological subtype.\(^10\)\(^11\)\(^12\)

The Cancer Genome Atlas Research Network used six methods to analyze primary BCs: genomic DNA copy-number arrays, DNA methylation, exome sequencing, messenger-RNA arrays, microRNA sequencing, and reverse-phase protein arrays.\(^21\) Only in three genes did somatic mutations occur at a frequency higher than 10% across all BCs: TP53, PIK3CA, and GATA3. Specific mutations are more frequent in some BC subtypes. In TNBC/BL cancers, the most frequent findings were the loss of TP53, RB1, BRCA1, and PIK3CA.\(^23\) Known drivers, such as P53, PIK3CA, and PTEN, have the highest clonal frequencies, but at the time of diagnosis, some patients present low clonality, while others have a more extensive clonal evolution, illustrating further important heterogeneity in TNBC.\(^24\)

**Subtyping TNBC: clinical implications**

More recently, gene expression profiling of 587 TNBCs identified six different subtypes: BL1 and BL2, an immunomodulatory (IM) subtype, a mesenchymal subtype, a mesenchymal stem like (MSL) subtype, and a luminal androgen receptor (LAR) subtype.\(^25\) The strengths of this study were to identify further the molecular drivers in corresponding cell-line models to provide preclinical platforms for the development of effective therapies (Table 1). For example, the authors showed that BL1 lines were the most sensitive...
to cisplatin and that the mesenchymal and MSL lines were most sensitive to the Abl/Src inhibitor dasatinib.20

The same group used the intrinsic subtype tool to examine the composition of each TNBC subtype. The authors showed that all TNBC subtypes except MSL and LAR were composed primarily of the BL intrinsic subtype (BL1 [99%], BL2 [95%], IM [84%] and mesenchymal [97%]). The LAR subtype is classified as HER2 (74%) and luminal B (14%), and the MSL subtype includes BL (50%), normal-like (28%), and luminal B (14%).20

Other gene expression analyses have also defined a claudin-low tumor subtype.26 Molecular characterization showed that these tumors are enriched in epithelial-to-mesenchymal transition, immune system response, and stem-like features, but show low expression of luminal and proliferation-associated genes.27

Another group used genomic profiling of 198 TNBCs to identify four TNBC subtypes: LAR, mesenchymal, BL immunosuppressed, and BL immunoactivated.28 If compared with the results reported by Lehmann et al.,25 LAR and mesenchymal tumors fall into the LAR and MSL subtypes.

The comprehensive analysis of TNBC can lead to the improved selection of study populations that have the highest probability of responding to specific treatments. For example, TNBC molecular subtypes may respond differently to CT. The clinical validity of the genomic classification was indeed confirmed by a retrospective analysis of the response to neoadjuvant CT. The overall pCR in this study was 28%. In the BL1 subtype, the pCR was the highest (51%), in comparison to 0 in the BL2 subtype and 10% in the LAR subtype, clearly showing the need to develop alternative treatments for some subgroups.

In the future, the evaluation of heterogeneity in TNBC and subtyping may lead to different therapeutic strategies. Potential targets and approaches include DNA damage and repair, immunomodulation, hormone receptor modulation, and signaling pathway inhibition.

Prospective trials will help us better understand the role of subtyping in the prediction of not only pCR but also long-term patient outcomes. New therapeutic strategies are needed for subgroups with the poorest therapeutic responses to standard CT.

### DNA-damaging chemotherapy and DNA repair targets

**BRCA1** mutation and “BRCAness”

Many external or internal agents, such as ultraviolet light, ionizing radiation, CT, and chemical substances

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**Table 1 Genomic TNBC subtypes and potential therapeutic targets**

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Genetic abnormalities</th>
<th>Potential therapeutic target</th>
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<tbody>
<tr>
<td>BL1</td>
<td>Cell cycle gene expression</td>
<td>PARP inhibitors</td>
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<td></td>
<td>DNA repair gene (ATR–BRCA pathway)</td>
<td>Genotoxic agents</td>
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<td>Proliferation genes</td>
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<td>BL2</td>
<td>Growth factor signaling pathways (EGFR, MET, NGF, Wnt/β-catenin, IGF-1R)</td>
<td>mTOR inhibitors</td>
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<td></td>
<td>Glycolysis, gluconeogenesis</td>
<td>Growth-factor inhibitors</td>
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<td>Expression of myoepithelial markers</td>
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<td>Immunomodulatory</td>
<td>Immune cell processes (CTLA4, IL12, IL7 pathways, antigen processing/presentation)</td>
<td>PD1/PDL1 inhibitors</td>
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<td>Gene signature for medullary BC (rare TNBC with a favorable prognosis)</td>
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<tr>
<td>Mesenchymal-like</td>
<td>Cell motility</td>
<td>mTOR inhibitors</td>
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<td>Cell differentiation</td>
<td>EMT- and CSC-targeted treatment</td>
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<td>Growth factor signaling</td>
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<td></td>
<td>EMT</td>
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<tr>
<td>Mesenchymal stem-like</td>
<td>Similar to M+</td>
<td>PI3K inhibitors</td>
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<td></td>
<td>Low proliferation</td>
<td>Antiangiogenic therapy</td>
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<td></td>
<td>Angiogenesis genes</td>
<td>Src antagonist</td>
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<td>Luminal androgen receptor</td>
<td>Androgen receptor gene</td>
<td>Antiandrogen therapy</td>
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<td></td>
<td>Luminal gene expression pattern</td>
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<td>Molecular apocrine subtype</td>
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</table>

**Note:** Data from Lehmann et al.25

**Abbreviations:** BC, breast cancer; BL, basal-like; CSC, cancer stem cells; DNA, deoxyribonucleic acid; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; IGF-1R, insulin-like growth factor 1 receptor; IL, interleukin; IM, immunomodulatory; LAR, luminal androgen receptor; M, mesenchymal-like; MET, hepatocyte growth factor; mTOR, mammalian target of rapamycin; MSL, mesenchymal stem-like; NGF, nerve growth factor; PARP, poly ADP ribose polymerase; PD1, programmed cell death 1; PDL1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; TNBC, triple negative breast cancer.
or products of normal cellular metabolism, including oxidation and hydrolysis, affect double-stranded DNA. DNA repair mechanisms are important for maintaining the stability and integrity of the genome, and include nucleotide- and base-excision repair, homologous recombination, end joining, mismatch repair, and telomere metabolism. Inherited defects in one of these important genes can lead to cancer, as observed in the **BRCA1**/2 syndrome. DNA repair mechanisms are classified as the repair of single- or double-stranded damage. **BRCA1** and **BRCA2** are important proteins in the homologous recombination process when damage leads to breaks in both DNA strands. The proteins have also been implicated in other fundamental cellular processes, such as cell cycle control and transcription.

**BC in BRCA1** germ-line mutation carriers most often displays a TN phenotype, as indicated by IHC and genomic studies. Due to the similarity between sporadic TNBC and familial **BRCA1** cancers, the concept of **BRCAness** has been developed. In sporadic cancers, **BRCA1** is inactivated by an epigenetic mechanism: the aberrant methylation of cytosine residues in CpG dinucleotides. Aberrant methylation of the **BRCA1** promoter is found in 11%–14% of sporadic BCs. In contrast, **BRCA2** tumors lack a clear pathological phenotype.

Knowledge of DNA repair mechanism defects leads to some specific treatment approaches in TNBC. These tumors present potentially higher sensitivity to DNA-damaging agents, such as platinum salts. The concept of “synthetic lethality” is also tested in the clinic, with the development of drugs (poly ADP-ribose polymerase [PARP] inhibitors) that target single-stranded DNA repair when homologous recombination is defective in **BRCA**-mutant tumors or in **BRCAness** tumors. Several studies have attempted to find a biomarker of homologous recombination deficiency (HRD) with the aim of better predicting responders to PARP inhibitors and DNA-damaging chemotherapies.

**Platinum-based chemotherapy**

**Metastatic TNBC**

The use of platinum compounds in metastatic BC was evaluated many years ago. Objective responses have been reported in ABC. Some retrospective analyses have also suggested the occurrence of increased survival with platinum-based CT in patients with advanced TNBC.

A prospective Phase II study showed activity of platinum agents, including cisplatin (75 mg/m²/3 weeks) and carboplatin (area under the curve 6/3 weeks), in patients with metastatic TNBC, especially in patients with germ-line **BRCA1/2** (g**BRCA1/2**) mutations. A total of 86 patients were enrolled. The overall response rate was 25.6%, but in patients with germ-line **BRCA1/2** mutations, the response rate increased to 54.5%. Interestingly, using a measure of DNA repair function, those authors also identified patients without mutations who had the potential to benefit from platinum therapy. They used two HRD assays to characterize **BRCA**-like genomic instability: the HRD large-scale state transition assay and the HRD loss of heterozygosity assay. They observed that patients who presented higher values in these assays also responded better to platinum-based treatments, even in the absence of germ-line mutations.

A prospective randomized trial comparing docetaxel with carboplatin in patients suffering from TNBC was presented at the 2014 San Antonio Breast Cancer Symposium (SABCS). Those authors observed similar results for unselected TNBC, but patients with **BRCA1/2** mutations experienced a significantly higher response rate and improved progression-free survival (PFS) when receiving carboplatin in comparison to docetaxel.

**Early TNBC**

The rate of pCR after anthracycline- and taxane-based neoadjuvant CT is higher in TNBC (±30%) than in luminal BC. In addition, patients presenting pCR after neoadjuvant CT generally have a better prognosis compared to patients who do not present pCR at the time of surgery. Unfortunately, patients suffering from TNBC who present residual disease after neoadjuvant CT have very poor outcomes. New therapies should be evaluated in patients who present residual disease after neoadjuvant CT. Retrospective research has suggested improved outcomes in terms of pCR when cisplatin is added to the neoadjuvant treatment. Byrski et al published a retrospective analysis of 6,903 patients, including 102 patients with the germ-line **BRCA1** mutation. The highest pCR rate was reported in germ-line **BRCA1**-mutation carriers who received neoadjuvant cisplatin therapy: 24% of the **BRCA1**-mutation carriers had pCR, but in the subgroup that received cisplatin, a much higher rate of 83% pCR rate was observed.

Five randomized studies evaluated the addition of carboplatin to standard neoadjuvant therapy (Table 2). Experimental arm 1 from the I-SPY 2 trial showed an increased rate of pCR in patients with TNBC if standard CT (paclitaxel/anthracycline–cyclophosphamide) was
combined with carboplatin and the PARP inhibitor veliparib. A confirmatory Phase III trial is underway.\textsuperscript{55} The GeparSixto\textsuperscript{52} and CALGB 40603\textsuperscript{53} trials showed increased rates of pCR with carboplatin, but toxicities were also more frequent and more significant if carboplatin was added. More dose reductions and early study discontinuations occurred due to these toxicities. The incidence of grade 3–4 hematological toxicities almost doubled. Data on late toxicities are missing, because the median follow-up period was only 3 years. Recently, at the 2015 SABCS, improved overall survival for patients receiving carboplatin was reported in the GeparSixto trial.\textsuperscript{56} A subsequent Phase III trial evaluating two dose-dense regimens is recruiting participants (GeparOcto, NCT02125344).\textsuperscript{57} In contrast, in the CALGB 40603 trial, despite significantly higher pCR rates, neither carboplatin nor bevacizumab showed improved event-free or overall survival. In addition, not all Phase II trials evaluating the use of carboplatin have shown improvements in pCR.\textsuperscript{54}

Currently, platinum compounds are not included in the guidelines for the treatment of early TNBC, but their role should be discussed in some specific cases, such as patients with a higher risk of relapse or requiring rapid disease control. Some recommend the use of carboplatin only for patients with BRCA mutations, but the available data are conflicting, as illustrated by the GeparSixto trial, which showed better outcomes when using carboplatin in patients with TNBC, independently of germ-line BRCA status. Interestingly, the GeparQuinto trial showed a statistically higher pCR rate with a classical sequential anthracycline–taxane regimen and a trend for better disease-free survival (hazard ratio 0.64, \( P=0.06 \)) in the subgroup of patients with \textit{BRCA} mutations (82 of 471 patients).\textsuperscript{58} These results suggest higher chemosensitivity and

### Table 2: Carboplatin-based chemotherapy in neoadjuvant treatment: randomized Phase II results

<table>
<thead>
<tr>
<th>Phase II trials</th>
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<th>Standard chemotherapy</th>
<th>Standard chemotherapy + carboplatin</th>
<th>Toxicity</th>
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</thead>
<tbody>
<tr>
<td>GeparSixto\textsuperscript{52} TNBC subgroup</td>
<td>315</td>
<td>pCR: 36.9% (ypT0N0) 3-year EFS 76.1%</td>
<td>pCR: 53.2% (ypT0N0) 3-year EFS 85.8%</td>
<td>Increased with carboplatin (AUC 2) More grade 3/4 anemia More grade 3/4 neutropenia More grade 3/4 thrombopenia More grade 3/4 diarrhea Reduction of carboplatin AUC to 1.5 Reduced hematological events (from 82% to 70%) and nonhematological events (78% to 59%)</td>
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<td>Weekly paclitaxel and liposomal doxorubicin ×18 weeks + bevacizumab every 3 weeks ×6 cycles ± weekly carboplatin AUC 2×18 weeks</td>
<td>CALGB 40603, only TNBC\textsuperscript{53}</td>
<td>pCR 41% (ypT0/TisN0) 3-year EFS 71.6%</td>
<td>pCR 54% (ypT0/TisN0) 3-year EFS 76.5%</td>
<td>Increased with carboplatin More grade 3/4 neutropenia More grade 3/4 thrombopenia</td>
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<td>Weekly paclitaxel ×12 weeks ± carboplatin AUC 6 every 3 weeks ×4 cycles/dose-dense anthracycline–cyclophosphamide ×4 cycles</td>
<td>GEICAM/2006-03\textsuperscript{54}</td>
<td>pCR 35% (ypT0N0)</td>
<td>pCR 30% (ypT0N0)</td>
<td>No difference in grade 3/4 toxicity</td>
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<tr>
<td>Epirubicin–cyclophosphamide every 3 weeks ×4 cycles/ docetaxel every 3 weeks ×4 cycles ± carboplatin AUC 6 every 3 weeks ×4 cycles</td>
<td>I-SPY arm I\textsuperscript{55}</td>
<td>pCR 26% (ypT0N0)</td>
<td>pCR 52% (ypT0N0)</td>
<td>More toxicity with carboplatin/ veliparib ≥ Hematological grade 3 events: 26.4% versus 4.5%</td>
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<tr>
<td>Weekly paclitaxel ×12 weeks/ dose-dense doxorubicin– cyclophosphamide ×4 cycles ± veliparib and carboplatin</td>
<td>Paclitaxel plus carboplatin versus paclitaxel plus epirubicin as neoadjuvant treatment in locally advanced TNBC\textsuperscript{56}</td>
<td>pCR: 14% (ypT0/TisN0) 4-year RFS 52.8%</td>
<td>pCR: 38.6% (ypT0/TisN0) 4-year RFS 71.1%</td>
<td>No difference in grade 3/4 toxicity</td>
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<tr>
<td>Paclitaxel–carboplatin AUC 5 every 3 weeks ×4–6 cycles or epirubicin– paclitaxel every 3 weeks ×4–6 cycles</td>
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**Abbreviations:** AUC, area under curve; EFS, event-free survival; is, in situ; pCR, pathologic complete response; RFS, relapse-free survival; TNBC, triple-negative breast cancer.

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<th>Phase, design</th>
<th>Treatment</th>
<th>Primary outcome</th>
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<td><strong>Neoadjuvant studies</strong></td>
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<td>Two consequent chemotherapy regimens as induction preoperative therapy for patients with locally advanced TNBC</td>
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<td>Single-arm Open-label</td>
<td>P + carboplatin/AC + capecitabine</td>
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<td>Single-arm Open-label</td>
<td>Neoadjuvant olaparib/olaparib + carboplatin (if lack of response to olaparib alone)</td>
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<td>Identification of BRCA1-associated DNA-repair dysfunction in patients with early TNBC treated with neoadjuvant platinum-based chemotherapy</td>
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<td>Effect of neoadjuvant platinum-based chemoradiation therapy for locally advanced TNBC: clinical outcomes and correlation to biological parameters</td>
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<td>Impact of an additional four cycles of cisplatin in patients with TNBC not achieving clinical CR after four cycles of neoadjuvant adriamycin plus cyclophosphamide</td>
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<td>II</td>
<td>Single-arm Open-label</td>
<td>Adriamycin + cyclophosphamide/ cisplatin</td>
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<td>NCT01057069</td>
<td>ii/iii</td>
<td>Randomized Open-label</td>
<td>Platinum-based chemotherapy, but variable schedule based on HRD status and response</td>
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<td>Neoadjuvant carboplatin plus docetaxel or carboplatin plus P followed by AC in stage I–III TNBC NCT02413320</td>
<td>III Randomized Open-label</td>
<td>Carboplatin + docetaxel/AC versus carboplatin + P/AC</td>
<td>pCR rates</td>
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<td>Two dose-dense, dose-intensified approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto) NCT02125344</td>
<td>III Randomized Open-label</td>
<td>Carboplatin + Myocet + P versus epirubicin + P + cyclophosphamide</td>
<td>pCR rates</td>
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<td>Safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy in subjects with early stage TNBC NCT02032277</td>
<td>III Randomized Double-blind</td>
<td>Veliparib + carboplatin + P followed by AC versus placebo + carboplatin + P followed by AC versus 2 placebos + P followed by AC</td>
<td>pCR rates</td>
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<td>Neoadjuvant or adjuvant study</td>
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<td>Anthracyclines followed by taxane versus anthracyclines followed by taxane plus carboplatin as (neo)adjuvant therapy in patients with TNBC (PEARLY trial) NCT02441933</td>
<td>III Randomized Open-label</td>
<td>AC/taxol versus AC/taxol + carboplatin</td>
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<td>Adjuvant studies, if residual disease after neoadjuvant chemotherapy</td>
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<td>PARP inhibition after preoperative chemotherapy in patients with TNBC or ER/PR+, HER2– with known BRCA1/2 mutations NCT01074970</td>
<td>II Randomized Open-label</td>
<td>Cisplatin versus cisplatin + rucaparib</td>
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<td>Everolimus plus cisplatin in TNBC patients with residual disease after standard chemotherapy (NECTAR trial) NCT01931163</td>
<td>II Single-arm Open-label</td>
<td>Cisplatin + everolimus</td>
<td>Tumor response</td>
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<td>Postoperative trial of platinum-based chemotherapy versus observation in patients with residual TN basal-like breast cancer following neoadjuvant chemotherapy NCT02445391</td>
<td>III Randomized Open-label</td>
<td>Platinum-based chemotherapy (cisplatin or carboplatin) versus observation</td>
<td>IDFS</td>
</tr>
<tr>
<td>Carboplatin as adjuvant chemotherapy versus observation in TNBC with pathologic residual cancer after neoadjuvant chemotherapy: POST-neoadjuvant study NCT01752686</td>
<td>III Randomized Open-label</td>
<td>Carboplatin versus observation</td>
<td>DFS</td>
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<tr>
<td>Adjuvant studies</td>
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<td></td>
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</tr>
<tr>
<td>NRG BR-003: adjuvant therapy comparing AC followed by weekly P with or without carboplatin for node-positive or high-risk node-negative triple-negative invasive breast cancer NCT02488967</td>
<td>II Randomized Open-label</td>
<td>Sequential treatment AC/P versus AC/P + carboplatin</td>
<td>IDFS</td>
</tr>
<tr>
<td>EC followed by docetaxel given every 3 weeks, weekly P or weekly P plus carboplatin in TNBC (TPPC) NCT02455141</td>
<td>II Randomized Open-label</td>
<td>3 arms: EC/docetaxel versus EC/P versus EC/carboplatin + P</td>
<td>3-year DFS</td>
</tr>
<tr>
<td>Efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germ-line BRCA1/2 mutations and high-risk HER2-negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy (Olympia) NCT02032823</td>
<td>III Randomized Double-blind</td>
<td>Olaparib versus placebo</td>
<td>IDFS</td>
</tr>
</tbody>
</table>

**Abbreviations:** AC, doxorubicin + cyclophosphamide; CR, complete response; CRR, clinical response rate; DFS, disease-free survival; EFS, event-free survival; ETC, epirubicin–paclitaxel–cyclophosphamide; HRD, homologous recombination deficiency; IDFS, invasive DFS; PARP, poly ADP ribose polymerase; P, paclitaxel; pCR, pathologic complete response; PM(Cb), paclitaxel–Myocet (carboplatin); TNBC, triple-negative breast cancer.

Better prognosis in patients with germ-line *BRCA* mutations, even without platinum compounds. Participation in clinical trials is recommended in the neoadjuvant and postneoadjuvant setting in the absence of pCR to better define the optimal standard systemic therapy for TNBC (Table 3).

**The potential role of PARP inhibitors in TNBC**

Based on the synthetic lethality concept, PARP inhibitors were developed for the treatment of cancers with specific DNA-repair deficits, such as TNBC with *BRCA1*/*2*...
Table 4 Results of trials with PARP inhibitors in triple-negative breast cancer

<table>
<thead>
<tr>
<th>Study, ClinicalTrials.gov identifier</th>
<th>Phase, design</th>
<th>Drug</th>
<th>Primary objective</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic and biological evaluation of a small molecule inhibitor of PARP1 (KU-0059436) in patients with advanced tumors&lt;sup&gt;40&lt;/sup&gt; NCT00516373</td>
<td>I</td>
<td>Open-label</td>
<td>Olaparib</td>
<td>Safety, tolerability, dose-limiting toxicity, and maximum tolerated dose of olaparib</td>
</tr>
<tr>
<td>AZD2281 in patients with known BRCA mutation status or recurrent high-grade ovarian cancer or patients with known BRCA mutation status/TNBC&lt;sup&gt;61&lt;/sup&gt; NCT00679783</td>
<td>II</td>
<td>Open-label</td>
<td>Olaparib 400 mg</td>
<td>Objective response rate (ORR) Complete response (CR)</td>
</tr>
<tr>
<td>Efficacy and safety of KU-0059436 (olaparib) given orally twice daily in patients with advanced BRCA1- or BRCA2-associated breast cancer&lt;sup&gt;61&lt;/sup&gt; NCT00494234</td>
<td>II</td>
<td>Open-label</td>
<td>Olaparib 100 mg twice daily, 400 mg twice daily</td>
<td>Confirmed objective tumor response CR Overall response (OR) = CR + PR</td>
</tr>
<tr>
<td>Efficacy and safety of olaparib given orally twice daily in patients with advanced cancers who have a confirmed genetic BRCA1 and/or BRCA2 mutation&lt;sup&gt;62&lt;/sup&gt; NCT01078662</td>
<td>II</td>
<td>Open-label</td>
<td>Olaparib 400 mg twice daily</td>
<td>Tumor-response rate</td>
</tr>
</tbody>
</table>

Abbreviation: TNBC, triple-negative breast cancer.

mutations and BRCAness TNBC.<sup>35</sup> The first drug of this class, olaparib, was approved by the US Food and Drug Administration in December 2014 as a single-agent treatment for patients with deleterious or suspected deleterious germ-line BRCA1-mutated advanced ovarian cancer who were treated with three or more prior lines of CT. In BC, several Phase I and II trials have shown antitumor activity in BRCA1-mutated patients (Table 4).<sup>60–63</sup> In the proof-of-concept Phase II study, Tutt et al<sup>61</sup> reported on two cohorts of patients with BRCA1/2-mutated ABC. In the first cohort (27 patients), which was assigned 400 mg twice daily, the objective response rate was 41% compared to 22% in the cohort (27 patients) treated with a lower dose (100 mg twice daily). Toxicities were mild, and included nausea and fatigue. Clinical trials are ongoing in patients with high-risk BRCA1-mutated primary BC in the neoadjuvant and adjuvant settings.<sup>64</sup>

Androgen receptor and TNBC

The LAR subtype is characterized by luminal gene expression and is driven by the AR.<sup>25</sup> The AR is expressed in normal and malignant breast tissue, and its prevalence is variable according to the subtype of BC. Approximately 10%–15% of TNBCs express the AR.<sup>65,66</sup> The LAR subtype demonstrates some similarities with the apocrine subtype. Indeed, in this histologic subtype, the gene expression profile is highly correlated with the LAR subtype. These findings indicate that the LAR subtype includes BCs with apocrine histology.<sup>67,68</sup>

The function of the AR is less well understood in BC than in prostate cancer. In a paper by Doane et al,<sup>69</sup> a cell line that recapitulated the molecular profile of the LAR subtype was identified. This cell line was used in preclinical models, and androgen-dependent growth was demonstrated in an estrogen-independent manner. This growth was inhibited by an AR antagonist (flutamide). This study was the first proof of concept for androgen blockade in the LAR subtype.<sup>67,69</sup>

At present, results from two Phase II studies have been presented and showed a benefit for androgen blockade in this LAR subtype. The first study was conducted by Gucalp et al.<sup>70</sup> That was a multicenter Phase II study that investigated the use of bicalutamide at a dose of 150 mg daily in AR-positive, ER- and PgR-negative metastatic BC (26 patients). The majority of patients were HER2-negative. The AR was expressed in 12% of patients with ER/PgR-negative BC. This study showed a clinical benefit rate (CBR; = CR + partial response [PR] + stable disease >6 months) of 19% for bicalutamide. The median PFS was 12 weeks (comparable to single-agent or combination CT in TNBC). The treatment was well tolerated, with the most common
side effects including fatigue, hot flashes, limb edema, and transaminase elevations.70

The second study evaluated the activity of the next-generation antiandrogen enzalutamide in advanced AR-positive TNBC. That study was a multicenter Phase II trial conducted in two stages. In stage 1, 26 patients were evaluated for the primary end point of the CBR at 16 weeks (CBR_{16} = CR + PR + stable disease at 16 weeks). These patients received enzalutamide at a dose of 160 mg orally daily. The stage 1 result was a CBR_{16} of 42% (95% confidence interval 24%–62%), including one CR and one PR.71 For the stage 2 study, 165 patients were screened, and 75 patients had AR IHC ≥10% and more than one postbaseline evaluation. Patients with TNBC had a median of one line of prior therapy. The data were presented at the American Society of Clinical Oncology’s 2015 meeting and showed a CBR_{16} of 35% and a median PFS of 14.7 weeks.72 Because of these results, interest in androgen blockade therapy in the LAR subtype is growing. A number of different trials are in the recruitment stage or are waiting for results (Table 5).

| Table 5 First results with antiandrogen therapy in TNBC and studies in progress |
|---------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------------------|
| **Study, ClinicalTrials.gov identifier**   | **Phase, design**                | **Drug**                        | **Primary outcome**             | **Status**                                | **Results**                                |
| Bicalutamide for the treatment of AR+, ER+, PR+ metastatic BC patients70 NCT00468715 | II Open-label Single-arm        | Bicalutamide 150 mg once daily  | CBR at 6 months (CR, PR, stable disease) | Closed                                    | 26 patients CBR 19% Median PFS 12 weeks |
| **Clinical activity and safety of enzalutamide in patients with advanced, AR+ TNBC, stage 1** NCT01899238 | II Open-label Single-arm        | Enzalutamide 160 mg once daily  | CBR at 16 weeks (CR, PR, stable disease) | Not recruiting                            | 75 patients CBR 35% Median PFS 14.7 weeks |
| **Clinical activity and safety of enzalutamide in patients with advanced, AR+ TNBC, stage 2** NCT01899238 | II Open-label Single-arm        | Enzalutamide 160 mg once daily  | CBR at 16 weeks (CR, PR, stable disease) | Not recruiting                            | Not available |
| **Activity of abiraterone acetate plus prednisone in patients with a molecular apocrine HER2-locally advanced or metastatic BC** NCT01842321 | II Open-label Single-arm        | Abiraterone acetate 160 mg once daily | CBR at 6 months (CR, PR, stable disease) | Not recruiting                            | Not available |
| **Orteronel as monotherapy in patients with metastatic BC that expresses the AR** NCT01990209 | II Open-label Single-arm        | Orteronel 300 mg twice daily    | Response rate at 36 months Disease control rate at 36 months | Recruiting                                | Not available |
| **Bicalutamide as a treatment in AR-positive metastatic triple-negative breast cancer (mTNBC) patients** NCT02348281 | II Open-label Single-arm        | Bicalutamide 150 mg once daily  | CBR at 6 months (CR, PR, stable disease) | Recruiting                                | Not available |
| **AR inhibitor bicalutamide in treating patients with TNBC** NCT02353988 | II Open-label Single-arm        | Bicalutamide 150 mg once daily  | CBR at 6 months (CR, PR, stable disease) | Recruiting                                | Not available |
| **Efficacy and safety of GTx-024 in patients with AR+ TNBC** NCT02368691 | II Open-label Single-arm        | GTx-024 18 mg once daily        | CBR at 6 months (CR, PR, stable disease) | Recruiting                                | Not available |
| **Safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of VT-464 in patients with advanced BC** NCT02580448 | III Open-label Single-arm       | VT-464 18 mg once daily         | CBR at 6 months (CR, PR, stable disease) | Recruiting                                | Not available |

**Abbreviations:** BC, breast cancer; CBR, clinical benefit rate; CBR_{16}, clinical benefit rate at 16; CBR_{24}, clinical benefit rate at 24; CR, complete response; mTNBC, metastatic triple-negative breast cancer; PFS, progression-free survival; PR, partial response; TNBC, triple-negative breast cancer; AR, androgen receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR+, progesterone receptor positive.
be considered as a new validated treatment option. Future challenges related to the LAR subtype include understanding the role of the AR in tumorigenesis, understanding the escape mechanisms in AR-directed therapy, and discovering predictive biomarkers. 

**Immune subtype and role of immunotherapy**

BC was not previously considered to be an “immunogenic” malignancy. Nevertheless, accumulating evidence indicates the prognostic and predictive values of tumor-infiltrating lymphocytes (TILs) in BC. The degree of immune infiltration differs among BC subtypes. TIL levels are significantly higher in TNBC and HER2-positive BC. Hormone receptor-positive disease is the subtype associated with the least robust number of TILs. Recently, several studies confirmed the prognostic value of TILs in TNBC. The lymphocyte-predominant BC subtype, which contains high levels of TILs (>50%), is associated with improved disease-free and overall survival and pCR in the neoadjuvant setting.

These findings suggest that immunomodulation could represent a new approach in the treatment of these aggressive BC subtypes. Our current understanding suggests that the immunogenic potential of TNBC is derived at least in part from its genetic instability and high mutation rate. Tumors from patients with TNBC are more likely than tumors from patients with other subtypes to exhibit chromosomal instability and potential mutations.

TNBC is the subtype that is most frequently associated with TILs, but only a minority of TNBCs demonstrate a high number of TILs, suggesting that IM therapy could be necessary to promote immunorecognition and increase the adaptive immune infiltrate to levels adequate for a survival benefit in the majority of patients with this BC subtype. Patients with high levels of TILs at the time of diagnosis might benefit from the use of drugs that can enhance antitumoral immune responses.

Monoclonal antibodies have been developed to block specific immune-checkpoint proteins. Some of these antibodies have already been approved by the Food and Drug Administration for the treatment of metastatic melanoma. Three categories of these antibodies exist: antibodies that block CTLA4, PD1, or PDL1.

CTLA4 was the first immune checkpoint receptor to be targeted clinically. Two antibodies are known: ipilimumab and tremelimumab. Normally, after T-cell activation, CTLA4 is upregulated on the plasma membrane, where its function is to downregulate T-cell function through a variety of mechanisms, including preventing costimulation via CD28 and its ligand – B7. CTLA4 plays an essential role in maintaining normal immunologic homeostasis. Ipilimumab blocks CTLA4, and does not allow the T cell to interact with the receptor via CD28 on its cell surface.

PD1 is also a negative regulator of T-cell activity that limits the activity of T cells at a variety of stages of the immune response when it interacts with its two ligands: PDL1 and PDL2. Unlike CTLA4, which is primarily believed to regulate immune responses early in T-cell activation, PD1 is primarily believed to inhibit effector T-cell activity in the effector phase within tissues and tumors.

Targeting PDL1 is a similarly promising approach to targeting PD1. However, targeting PDL1 may result in different biologic effects than targeting PD1. In addition to binding PD1, PDL1 is also believed to exert negative signals on T cells by interacting with B7. PDL1-blocking antibodies prevent this interaction, but PD1-blocking antibodies do not. Another slight difference is that PDL1 antibodies do not prevent PD1 from interacting with PDL2, although the effect of this interaction remains unknown. Nivolumab and pembrolizumab are antibodies that block PD1 on the surface of T cells and prevent those T cells from interacting with PDL1. Monoclonal antibodies that block PDL1 are being evaluated in clinical trials.

Investigations evaluating the presence of PD1 on TILs and PDL1 on tumor cells in BC found that immune checkpoint proteins are upregulated in many BCs, particularly the TN subtype. The reported incidence of expression is highly variable. TILs expressing PD1 appear to be found more frequently in the TN subtype than in the other subtypes. In addition, the same pattern appears to occur for PDL1. These data support the study of immune checkpoint inhibitors in TNBC.

**Clinical trials of immunotherapy in TNBC**

One of the first completed clinical trials of a PD1 monoclonal antibody (pembrolizumab) in TNBC was reported at the 2014 SABCS by Nanda et al. That was a Phase IB study that enrolled 32 patients with TNBC who had recurrent or metastatic disease (47% of whom had had more than three lines of previous CT). The participants were all PDL1-positive. Pembrolizumab was administered intravenously at a dose of 10 mg/kg every 2 weeks, and treatment could continue indefinitely as long as the patients were stable and their disease was not clearly progressing, as assessed by Response Evaluation
Table 6 Immunotherapy trials in breast cancer

<table>
<thead>
<tr>
<th>Study, ClinicalTrials.gov identifier</th>
<th>Phase, design</th>
<th>Drug</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant/adjuvant</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MEDi4736 (anti-PDL1 antibody)</td>
<td>Phase I/II, Single-arm</td>
<td>Anti-PDL1 (MEDi4736) concomitant with Nab-paclitaxel and doxorubicin + cyclophosphamide</td>
<td>pCR</td>
</tr>
<tr>
<td>concomitant with weekly Nab-paclitaxel and dose-dense doxorubicin-cyclophosphamide chemotherapy for clinical stage I–III TNBC</td>
<td>Open-label</td>
<td></td>
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<tr>
<td>NCT02489448</td>
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<tr>
<td>Triple-negative first-line study:</td>
<td>Phase II, Single-arm</td>
<td>Anti-PDL1 (MPDL3280A) in combination with Nab-paclitaxel</td>
<td>pCR</td>
</tr>
<tr>
<td>neoadjuvant trial of Nab-paclitaxel and MPDL3280A, a PDL1 inhibitor, in patients with TNBC</td>
<td>Open-label</td>
<td></td>
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<tr>
<td>NCT02530489</td>
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<tr>
<td>Safety and clinical activity of</td>
<td>Phase I, Randomized</td>
<td>Anti-PD1 (MK-3475, pembrolizumab) + chemotherapy versus MK-3475 + chemotherapy + carboplatin</td>
<td>DLT, pCR</td>
</tr>
<tr>
<td>pembrolizumab (MK-3475) in</td>
<td>Single-arm, Open-label</td>
<td></td>
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<tr>
<td>combination with chemotherapy as</td>
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<tr>
<td>neoadjuvant treatment for TNBC</td>
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<tr>
<td>NCT02622074</td>
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<tr>
<td>Metastatic</td>
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<tr>
<td>Single-agent pembrolizumab (MK-3475)</td>
<td>Phase III, Randomized</td>
<td>Anti-PD1 (MK-3475, pembrolizumab) versus chemotherapy</td>
<td>PFS</td>
</tr>
<tr>
<td>versus single-agent chemotherapy as per physician’s choice for metastatic TNBC</td>
<td>Single-arm, Open-label</td>
<td></td>
<td>OS</td>
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<tr>
<td>NCT02555657</td>
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<tr>
<td>Pembrolizumab (MK-3475) as</td>
<td>Phase II, Single-arm</td>
<td>Anti-PD1 (MK-3475, pembrolizumab) monotherapy</td>
<td>ORR safety</td>
</tr>
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<td>monotherapy for metastatic TNBC</td>
<td>Open-label</td>
<td></td>
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<tr>
<td>NCT02447003</td>
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<tr>
<td>Nivolumab after induction treatment in TNBC patients: TONiC trial</td>
<td>Phase II, Randomized</td>
<td>Anti-PD1 (nivolumab) after induction treatment (four arms: radiotherapy, doxorubicin, cisplatin, cyclophosphamide) or noninduction treatment</td>
<td>PFS</td>
</tr>
<tr>
<td>NCT02499367</td>
<td>Single-arm, Open-label</td>
<td></td>
<td></td>
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<tr>
<td>Atezolizumab (MPDL3280A) (anti-PDL1 antibody) in combination with Nab-paclitaxel compared with placebo with Nab-paclitaxel for patients with previously untreated metastatic TNBC</td>
<td>Phase III, Randomized</td>
<td>Anti-PDL1 (MPDL3280A, atezolizumab) with Nab-paclitaxel compared with placebo and Nab-paclitaxel</td>
<td>PFS</td>
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<tr>
<td>NCT02425891</td>
<td>Double-blind</td>
<td></td>
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<tr>
<td>Tremelimumab monotherapy in</td>
<td>Phase, Single-arm</td>
<td>Anti-CTLA4 (tremelimumab) monotherapy with the option to be sequenced to MEDi4736 monotherapy or MEDi4736 + tremelimumab after progressive disease</td>
<td>ORR</td>
</tr>
<tr>
<td>patients with advanced solid tumors</td>
<td>Open-label</td>
<td></td>
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<tr>
<td>NCT02527434</td>
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<tr>
<td>Safety and efficacy of PDR001</td>
<td>Phase I/II, Single-arm</td>
<td>Anti-PD1 (PDR001) monotherapy Safety</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>administered to patients with advanced malignancies</td>
<td>Open-label</td>
<td></td>
<td>ORR</td>
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<tr>
<td>NCT02404441</td>
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<tr>
<td>Immuno-PET imaging with 89Zr-MPDL3280A in patients with locally advanced or metastatic non-small cell lung cancer, bladder cancer, or TNBC prior to MPDL3280A treatment</td>
<td>Phase I, Single-arm</td>
<td>89Zr-MPDL3280A (anti-PDL1)</td>
<td>Description of 89Zr-MPDL3280A PK by measuring SUV on the 89Zr-MPDL3280A-PET scans → to evaluate the uptake of the tracer in tumor lesions and its use as a complementary tool for patient selection</td>
</tr>
<tr>
<td>NCT02453984</td>
<td>Open-label</td>
<td></td>
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<td>MPDL3280A treatment in patients</td>
<td>Phase II, Single-arm</td>
<td>Anti-PDL1 (MPDL3280A)</td>
<td>ORR</td>
</tr>
<tr>
<td>with locally advanced or metastatic non-small cell lung, bladder, and TNBC after investigational imaging</td>
<td>Open-label</td>
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<tr>
<td>NCT02478099</td>
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</tbody>
</table>

(Continued)
Criteria in Solid Tumors version 1.1 every 8 weeks. Treatment with PD1 blockade was tolerable, with 56% of patients reporting an adverse event, but only 16% reporting grade 3–5 toxicity. Toxicity was essentially low-grade joint and muscle pain, fatigue, and nausea. One treatment-related death was caused by disseminated intravascular coagulation. Overall, 18.5% of 27 evaluable patients responded to pembrolizumab, with one (4%) CR, four (15%) PRs, and seven patients (26%) with stable disease. The median time to response was 18 weeks. The median PFS was just under 2 months. Three patients remained on pembrolizumab for at least 11 months.

At the same meeting, initial data from a Phase I study of an anti-PDL1 monoclonal antibody (MPDL3280A, atezolizumab) in metastatic TNBC were also reported. Emens et al. showed results from 12 patients with PDL1-positive disease. Grade 3–4 toxicities occurred in 8% of patients. Although immune-related adverse events have been reported with the use of immune checkpoint inhibitor agents, only one patient in this study demonstrated grade 2 pyrexia that was potentially attributable to immune activation. In general, immune-related adverse events occurred in a minority of patients. There were no toxicity-related deaths. Although over 90% of patients had been previously treated with more than two prior regimens and one-third of those enrolled had visceral metastases, the overall response rate was 33% in the nine patients who were evaluable for efficacy (one CR and two PRs). All responses were seen within the first 6 weeks of treatment.

Recently, data presented at SABCS 2015 encouraged the evaluation of another anti-PDL1 agent (avelumab). The trial showed promising results in a subgroup of TNBC. For those patients with TNBC and PDL1 expression on immune cells, the clinical response with avelumab was 44.4% versus 2.6% in the absence of expression.

All of these preliminary results are promising for the use of immuno-oncology agents in TNBC. The future challenge will be the identification of tumoral immune microenvironments that improve prognosis in BC. In this way, we hope to promote efficacious antitumoral immunity for all BCs. For example, in TNBC, controlling tumor growth with conventional chemotherapies in combination with immune checkpoint inhibitors could increase response rates. For patients with limited T-cell infiltration, vaccine priming before or concurrent with immune checkpoint inhibitors may also result in additional clinical benefits. Many studies of further immunotherapy in BC are ongoing or planned. We hope that the best is still to come with respect to this therapy in the field of TNBC (Table 6).

**Growth factor overexpression in TNBC**

Different growth factors are overexpressed in TNBC, such as vascular endothelial growth factor (VEGF) and EGFR. Targeting these pathways showed only limited activity in unselected TNBC. For the VEGF pathway, different trials in patients with ABC and in the adjuvant setting did not show any benefit in overall survival, even in trials dedicated to TNBC, such as the BEATRICE trial. Similarly, for the EGFR pathway, the results have been disappointing. EGFR is overexpressed in more than 50% of TNBCs, but the rate of mutation is low (10%) and is found only in Asian populations. Trials with anti-EGFR therapies have suggested that EGFR overexpression is not correlated with the activity of anti-EGFR agents in TNBC. FGFRs may be a better target. FGFRs are expressed on many different cells, and regulate cell growth, survival, migration, and differentiation. In many cancer types, FGFR signaling is implicated in oncogenic behavior. Targeting this pathway is a current area of drug development.
not only primarily with tyrosine-kinase inhibitors but also with monoclonal antibodies that target FGFRs and the FGFR-ligand trap. In BC, only 9% of tumors have FGFR1 amplification and 4% have FGFR2 amplification. These tumors represent a very small population, but FGFRs could be an interesting target. Participation in clinical trials is crucial for improved evaluation of the potential of new treatment strategies according to specific FGFR alterations.224

Conclusion and perspectives

Progress in the treatment of TNBC remains an important challenge. In clinical practice, we still use standard CT (anthracyclines and taxanes). Some data in favor of the use of platinum-based CT in TNBC are now available, particularly in BRCA-mutation carriers. Clinical research is focused on two main axes in the neoadjuvant setting: how to increase pCR and how to improve outcomes in patients with residual disease. New targeted treatments and immunotherapeutic drugs are under development. The challenge is to drive studies on more selected patient populations due to the importance of heterogeneity in TNBC. The most promising new approaches include immunotherapy with checkpoint inhibitors, PARP inhibitors, and AR inhibitors. Furthermore, active research to discover additional specific targets in TNBC is ongoing.225

Disclosure

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References


