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Breast Cancer (Carla I. Falkson, Section Editor)

How do I Treat "Triple-Negative" Disease

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Abbreviations ASCO · American Society of Clinical Oncology · *BRCA1* · Breast cancer 1 early onset · *BRCA2* · Breast cancer 2 early onset · CAP · College of American Pathologists · DNA · Deoxyribonucleic acid · EGFR · Epidermal growth factor receptor · ER · Estrogen receptor · Her2 (ERBB2) · Epidermal growth factor receptor 2 · mTOR · Mammalian target of rapamycin · PARP · Poly (Adenosine Diphosphate–Ribose) Polymerase · pCR · Pathologic complete response · PI3K · Phosphatidylinositol 3-kinase · PR · Progesterone receptor · RNA · Ribonucleic acid · TBCRC · Translational Breast Cancer Research Consortium · TRAIL · Tumor necrosis factor-related apoptosis inducing ligand · VEGF · Vascular endothelial growth factor

Level of Evidence
I: Evidence comes from multiple well-designed clinical trials conducted in representative populations with consistent results.
II: Evidence comes from at least one well-designed clinical study. Strength of evidence limited by the number, quality, or consistency of the individual studies.
III: Evidence comes from well-designed nonrandomized single-group or single-cohort studies or case–control studies. Evidence also comes from retrospective analyses of prospective clinical trials.
IV: Evidence comes from well-designed nonexperimental studies such as comparative correlational, and descriptive studies.
V: Evidence comes from case reports or case series and therefore, is insufficient for recommendations.

Opinion statement

Over the recent years, there has been an increasing recognition that triple-negative breast cancer constitutes a separate, albeit heterogeneous, entity arising from distinct oncogenic pathways. Despite its aggressive clinical behavior, triple-negative disease responds favorably to cytotoxic chemotherapy resulting in high response rates. Nonetheless, the relapse rates are high and, in the absence of targeted therapies to significantly alter its natural history, the prognosis can be poor. Most of the trials conducted in the past that led to the formulation of the current guidelines have indiscriminately lumped triple-negative disease with receptor-positive subtypes. Therefore, there are relatively scant data regarding how standard approaches specifically apply for triple-

negative disease. By virtue of its chemosensitive nature and high probability of achieving a complete pathologic response, neoadjuvant chemotherapy in early-stage/operable and locally-advanced/inoperable triple-negative disease is highly recommended. The indications for adjuvant chemotherapy are the same as in receptor-positive tumors, although endocrine therapies or agents targeting Her2 signaling have no established role in triple-negative disease. The optimal chemotherapy is not entirely clear; however, by virtue of their efficacy in breast cancer in general, anthracycline-containing regimens are the most widely used. The incorporation of taxanes in the regimen is supported by retrospective analyses. There is scant evidence to recommend any particular agent in the metastatic setting, although the combination of ixabepilone with capecitabine was shown to be active specifically in triple-negative disease. Given the uncertainty in the optimal management of triple-negative disease, the shortcomings of contemporary regimens, and the strong rationale of novel therapies, participation in clinical trials should be strongly considered at any stage of the disease.

Introduction

Breast cancer constitutes the most common malignancy in women in developed countries. In 2010, in the United States, an estimated 208,000 women were diagnosed with breast cancer with an estimated 40,000 deaths attributed to the disease [1]. Gene expression analysis of primary breast tumors has led to the recognition of five distinct subtypes: the estrogen receptor (ER) positive luminal A and B, the human epidermal growth factor receptor 2 (HER2)-overexpressing/enriched, the normal breast tissue-like, and the basal-like subtype [2–4]. Recently, another subtype has been described, "claudin-low", which appears to be enriched for stem cell markers [5].

Triple-negative breast cancer is characterized by the lack of expression of ER, progesterone receptor (PR), and HER2. It represents approximately 12–17% of all breast cancers [6] and encompasses a heterogeneous group of tumors including, but not limited to, those classified as basal-like. It expresses cytokeratins 5/6/17 and has upregulation of epidermal growth factor receptor (EGFR). As ER, PR, and HER2 represent known targets in breast cancer therapeutics, patients with triple-negative disease do not derive any benefit from endocrine therapies or agents targeting HER2 signaling, a fact that may in part account for the unfavorable clinical outcomes in this subgroup of patients. However, over the recent years, there has been a considerable effort to elucidate the molecular underpinnings of triple-negative disease, identify new treatment targets, and refine the therapeutic approaches.

Definitions

The identification of a triple-negative phenotype has important clinical implications. In an attempt to overcome the variability in reporting and interpretation of the receptor status of a tumor, the American Society of Clinical Oncology jointly with the College of American Pathologists have proposed guidelines for testing and interpretation [7, 8]. In triple-negative disease, less than 1% of tumor cells stain positive for ER and PR by immunohistochemistry [7]. These cells also stain ≤2+ on immunohistochemistry for HER2 or carry fewer than 6 *HER2* gene copies per nucleus or have a fluorescence in situ hybridization ratio of less than 2.2 (*HER2* signals to chromosome 17 signals) [8]. We recommend abiding by the ASCO/CAP recommendations as even low levels of receptor expression are associated with clinical benefit from targeted therapies.

Basal-like breast cancer is a classification based on gene expression profile and not on immunohistochemistry. Triple-negative and basal-like breast cancer are not synonymous despite the significant overlap.

Under the immunohistochemical definition of "triple-negative disease" other intrinsic subtypes, such as Her2-enriched, may be represented as well [9].

Epidemiology

Premenopausal and African-American women seem to be disproportionately afflicted by the disease [10] which is clinically associated with an unfavorable prognosis [10, 11]. Nonetheless, the disease-related mortality seems to be higher among white premenopausal and particularly postmenopausal women compared with their African-American counterparts [12].

Deleterious *BRCA1* mutations are associated with an exceptionally high risk for developing triple-negative/basal-like breast cancer [4, 13, 14]. Single-nucleotide polymorphisms specific for triple-negative disease have been identified in a locus on 19p13 and their association with triple-negative disease was shown to be particularly strong in the context of germline *BRCA1* mutations [15•].

Pathologic and molecular characteristics

Pathologically, triple-negative tumors are usually high-grade invasive ductal carcinomas of no special type with high mitotic indices [16]. Pushing borders, central necrotic areas, lymphocytic infiltration, medullary and metaplastic differentiation constitute other histologic hallmarks of triple-negative disease.

At the molecular level, gene-expression studies have unveiled the significant heterogeneity within the triple-negative disease. This was illustrated in a recent analysis that identified six distinct subtypes within triple-negative disease with unique gene-expression patterns and distinct "driver" signaling pathways [17••]. On cell line models, these subtypes showed differential sensitivities to cisplatin, bicalutamide (an androgen receptor antagonist used in prostate cancer), and PI3K/mTOR inhibition [17••].

Clinical characteristics

Triple-negative tumors are usually larger at diagnosis and more likely to be detected on physical examination [18] compared with the other subtypes. Basal-like breast cancers also constitute the majority of cancers detected in the interval between screening mammograms [19]. Although studies have shown that basal-like breast cancer tends to be node-negative at presentation [20], its risk for nodal and regional recurrence is high and appears to be similar to the other subtypes [21].

Another distinctive feature of triple-negative disease is its metastatic pattern in terms of location and time. Compared with the other subtypes, basal-like breast cancer has a high risk of visceral and central nervous involvement; skeleton is frequently spared [22]. The risk for distant recurrence was shown to peak at approximately 2 to 3 years after diagnosis and to remain high for the first 5 years, whereas the risk among patients with other subtypes remains constant throughout the years of follow-up [18]. Upon metastatic recurrence, the median survival in triple-negative disease is significantly shorter compared with the other subtypes [23].

Treatment

- In deciding the optimal approach to treat triple-negative disease, the general principles of breast cancer therapeutics still apply. Distinct differences, however, when compared to the management of other subtypes, are the absence of response to endocrine therapies and HER2 targeted agents, and the high chemosensitivity especially in the neoadjuvant setting. Despite the high response rates, the risk of relapse in triple-negative disease remains high, especially if residual tumor is present resulting in inferior clinical outcomes (hence the term "triple-negative paradox") [24].
- The clinical trials conducted over the years that led to the formulation of the current guidelines have indiscriminately lumped triple-

negative disease with receptor-positive subtypes. Therefore, there are relatively scant data regarding how standard approaches specifically apply for triple-negative disease. Given the uncertainty in the optimal management of triple-negative disease, the shortcomings of contemporary regimens, and the strong rationale of novel therapies, participation in clinical trials should be highly preferred at any stage of the disease.

Surgery

Surgery for local disease

- Surgery represents the optimal modality for local control of triple-negative disease. Large randomized trials have demonstrated the equivalent outcomes between mastectomy and breast conserving surgery followed by moderate-dose radiation therapy in early breast cancer [25]. [Class I] Triple-negative disease is usually unifocal with smooth radiographic margins, and, hence, a good candidate for breast conserving surgery with negative resection margins.
- Although not uniformly shown in studies, triple-negative disease and basal-like breast cancer in particular, have been associated with high rates of locoregional recurrence [21]. However, locoregional relapse-free survival rates among women who underwent mastectomy and those who underwent breast-conserving surgery were overlapping [21], advocating in favor of less invasive interventions in early breast cancer. [Class III]
- Positive or indeterminate resection margins should prompt reexcision, as these patients have a high risk of local recurrence even with adjuvant radiation therapy. The importance of achieving negative margins in triple-negative disease is underscored by the high frequency of residual tumors identified in the reexcision specimens [26], which in the context of neoadjuvant chemotherapy, may represent chemoresistant disease responsible for early relapse. [Class I]
- There is no consensus definition for "close margins"; however, in most studies the latter was defined as ≤2 mm. Although the clinical implications of lumpectomy in close margins are not clear-cut, we recommend reexcision following the same rationale as in excisions performed in positive margins. If reexcision in negative margins cannot be performed, radiation boost of 16 Gray to the primary tumor bed, in addition to the usual postoperative radiation treatment, should be considered [27]. [Class II]

Surgery for metastatic disease

- Surgery in the metastatic setting is recommended for palliation of symptoms or impending complications. In view of the aggressive nature of triple-negative disease, surgery can be undertaken only if complete resection of the tumor is anticipated. Otherwise, radiation therapy constitutes a reasonable alternative. Also, as the patient will

not be eligible for chemotherapy in the perioperative period, other sites of disease should not pose a threat for growth.

- Although there is evidence to recommend excision of the primary tumor in the metastatic setting [28], this evidence comes from retrospective studies and this recommendation should be applied with caution in triple-negative disease. [Class IV] A protocol of the Translational Breast Cancer Research Consortium (TBCRC) is exploring prospectively the role of mastectomy in the metastatic setting.

Pharmacologic treatments

Neoadjuvant chemotherapy

- The primary rationale of neoadjuvant chemotherapy is to downstage inoperable, locally advanced tumors so as to facilitate locoregional control by means of surgery and/or radiation therapy. In this setting, a significant benefit in progression-free and overall survival has been shown among patients who achieve a pathologic complete response (pCR) [29]. [Class I] In operable, early stage breast cancer, neoadjuvant chemotherapy has resulted in a higher rate of successful breast-conserving surgeries among women who would otherwise require mastectomy; no benefit in overall survival, disease progression, and distant disease recurrence was seen in the clinical trials comparing identical regimens in the adjuvant versus neoadjuvant setting [30]. [Class I]
- Triple-negative disease constitutes a particularly chemosensitive entity, especially in the neoadjuvant setting. This has been illustrated in 2 studies conducted on prospectively collected clinical databases where patients with triple-negative disease achieved significantly higher response rates compared with their counterparts with other subtypes [23, 24]. These high response rates, however, did not translate into better clinical outcomes, primarily due to the high recurrence rates among patients with residual disease [23, 24]. The importance of achieving pCR in triple-negative disease with neoadjuvant chemotherapy was underscored by the significantly better outcomes among patients who achieved pCR; their prognosis was similar to that of patients with other subtypes who achieved pCR. [23] Improving the pCR rates in triple-negative disease appears to be an important stepping stone in improving the overall clinical outcomes. The TBCRC012 study is addressing if exercise, diet, metronomic chemotherapy and bevacizumab can improve the prognosis of patients with less than a pCR in the neoadjuvant setting [31].
- Support regarding the importance of achieving pCR is also provided by insightful research that showed the selective survival of resistant clones after the administration of chemotherapy [32, 33•]. Overcoming the intrinsic resistance of these cells by identifying the most relevant therapeutic targets is anticipated to bend the high recurrence rate in triple-negative disease.

- Anthracycline- and taxane-based regimens have been extensively evaluated in clinical trials and constitute the most widely used regimens in the neoadjuvant setting. Multiple trials have shown the improvement in the response rate conferred by adding a taxane concurrently or sequentially to an anthracycline-based regimen, although the benefit in overall survival has been less clear. [Class I] In the largest trial of neoadjuvant chemotherapy in breast cancer conducted by the National Surgical Adjuvant Breast and Bowel Project, the sequential addition of docetaxel improved the overall response rate and, most importantly, the pCR rate over adriamycin and cyclophosphamide alone [34]. Although no differences in disease-free and overall survival were seen, the clinical outcomes among patients who achieved a pCR were significantly superior [34].
- Dose-dense chemotherapy constitutes an appealing option and has been made possible with the concurrent administration of hematopoietic growth factors. Its clinical benefit was clearly shown in the adjuvant setting [35]. Although many neoadjuvant trials have included a dose-dense arm, differences in the regimens between arms besides intervals of administration, preclude clear conclusions. In fact, in a clinical trial that compared identical regimens administered in a standard versus dose-dense fashion, no differences in the response rates and clinical outcomes were seen [36]. Nonetheless, dose-dense chemotherapy remains a promising option as illustrated by the higher (but not statistically significant) pCR rates in triple-negative disease in a recent neoadjuvant trial comparing similar regimens [37•]. [Class II]
- Clinical trials have shown that changing regimen in the neoadjuvant setting based on response did not confer any benefit [38]; however, it is unclear whether this applies to triple-negative disease as these trials did not discriminate for receptor status. In the absence of clinical response, we recommend transition to locoregional treatments and systemic therapies under clinical trials.
- The optimal length of neoadjuvant chemotherapy has not been clearly established. Although prolonging neoadjuvant chemotherapy from 3 to 6 cycles improved significantly the pCR rate [39], no further improvement was seen by prolonging chemotherapy to 8 cycles [40]. In a pooled analysis of neoadjuvant trials, adding more cycles of chemotherapy did not confer a clear benefit in triple-negative disease [41]. In the same analysis, higher response rates in triple-negative disease were associated with higher cumulative doses of anthracyclines and taxanes and the administration of capecitabine [41]. Most experts would recommend, in the absence of progressive disease, the administration of four to six cycles of neoadjuvant chemotherapy. [Class II]
- By virtue of its high chemosensitivity, and consequently the high probability of achieving favorable long-term outcomes, we recommend neoadjuvant chemotherapy in early-stage/operable and locally-

advanced/inoperable triple-negative disease. An anthracycline-containing regimen should generally be preferred as there is scant data with nonanthracycline-containing regimens. Taxanes improve significantly the response rate and therefore should be incorporated in the regimen. It is unclear whether a dose-dense schedule is superior to a conventional one.

Adjuvant chemotherapy

- The principal rationale of adjuvant chemotherapy is the elimination of clinically inapparent micrometastases that are thought to give rise to recurrent disease after locoregional treatment. Multiple trials have demonstrated the benefit of adjuvant chemotherapy in recurrence rate and disease-specific mortality [42] but most of them did not prospectively stratify for receptor status. Nonetheless, retrospective analyses of those studies have shown that patients with receptor-negative disease have derived the most benefit from adjuvant chemotherapy [43, 44]. [Class III]
- Overall, the regimens and the indications for adjuvant cytotoxic chemotherapy in triple-negative disease are the same as in receptor-positive tumors with poor prognostic features. Although tumors >1 cm and/or metastatic to the lymph nodes require adjuvant chemotherapy, the recommendations for smaller tumors with or without micrometastases to the lymph nodes are unclear. In a retrospective analysis of 965 patients with T1a/bN0M0 tumors who did not receive cytotoxic chemotherapy, the 5-year survival and recurrence rates in triple-negative disease were statistically worse compared to hormone-receptor positive disease [45]. Another retrospective study that included T1c tumors, showed a higher recurrence rate and an inferior disease-free survival among patients with T1N0 triple-negative disease compared to hormone-receptor positive counterparts, even with adjuvant chemotherapy [46]. As the benefit of adjuvant chemotherapy in this subgroup is unclear, we recommend an individualized approach weighing the potential benefit against the anticipated toxicities [47]. [Class III]
- Numerous regimens have been investigated in phase III clinical trials and can be considered in the adjuvant setting. Anthracycline-containing regimens were shown to achieve better reductions in the recurrence rates compared to cyclophosphamide plus methotrexate plus 5-fluorouracil although the benefit in the mortality was marginal [48]. Moreover, it has been suggested that the superiority of anthracycline-containing regimens may be limited to Her2-positive disease [49] rendering their use in other subtypes, including triple-negative disease, controversial. The benefit of incorporating a taxane to the regimen specifically in triple-negative disease was shown in retrospective analyses of adjuvant trials with docetaxel, paclitaxel, and weekly paclitaxel, respectively [50–52]. As the superiority of

anthracycline- and taxane-based regimens in triple-negative disease [53] has been challenged, participation in clinical trials is highly recommended to identify the optimal regimens. [Class III]

- The benefit of incorporating capecitabine in an anthracycline-taxane containing regimen in triple-negative disease was shown in an exploratory subgroup analysis of a prospective clinical trial [54]. The incorporation of capecitabine resulted in a significant improvement in relapse-free and overall survival after 5 years [54]. [Class III]
- The clinical benefit of dose-dense chemotherapy in the adjuvant setting was shown in a prospective clinical trial that compared identical chemotherapies administered in a conventional versus dose-dense schedule [35]. The preference for a dose-dense schedule in triple-negative disease is supported by a retrospective analysis where, compared to other subtypes, triple-negative disease was shown to derive the most benefit from a dose-dense regimen [55]. [Class II]
- In the absence of adjuvant trials specifically for triple-negative disease, we recommend participation in clinical trials for eligible patients. If none available or the patient declines participation, an anthracycline-taxane containing regimen, preferably administered in a dose-dense schedule should be considered. We also favor weekly paclitaxel given the benefit in disease-free and overall survival with the weekly regimen [52, 56]. Extension of chemotherapy beyond 6 months has been associated with a nonsignificant benefit in recurrence rate without reflection on overall survival, and, therefore is not recommended [48].

Chemotherapy in metastatic disease

- In the metastatic setting, chemotherapy constitutes the primary therapeutic modality. As its principal goals are palliation of symptoms and prolongation of life, efficacy and toxicity should be equally considered. Selection of the optimal regimen should be individualized considering performance status, prior treatments, extent of disease, presence of disease-related symptoms, toxicity profile, and goals of care.
- Although combination chemotherapy has shown superior response rates and progression-free intervals compared to single-agent regimens, the benefit in overall survival has been modest [57] and inconsistent [58]. [Class II] As combination chemotherapy comes with the cost of significant toxicities, it is generally reserved for cases where rapid control of the disease is required. Otherwise, sequential single-agent regimens are preferred.
- There is scant evidence to recommend any particular regimen in triple-negative disease. The use of anthracyclines and taxanes is generally limited by prior exposure to these agents. Ixabepilone plus

capecitabine represents one of the few combinations shown to be active specifically in triple-negative disease with an improvement of progression-free and overall survival compared to capecitabine alone [59]. [Class III]

Emerging therapies

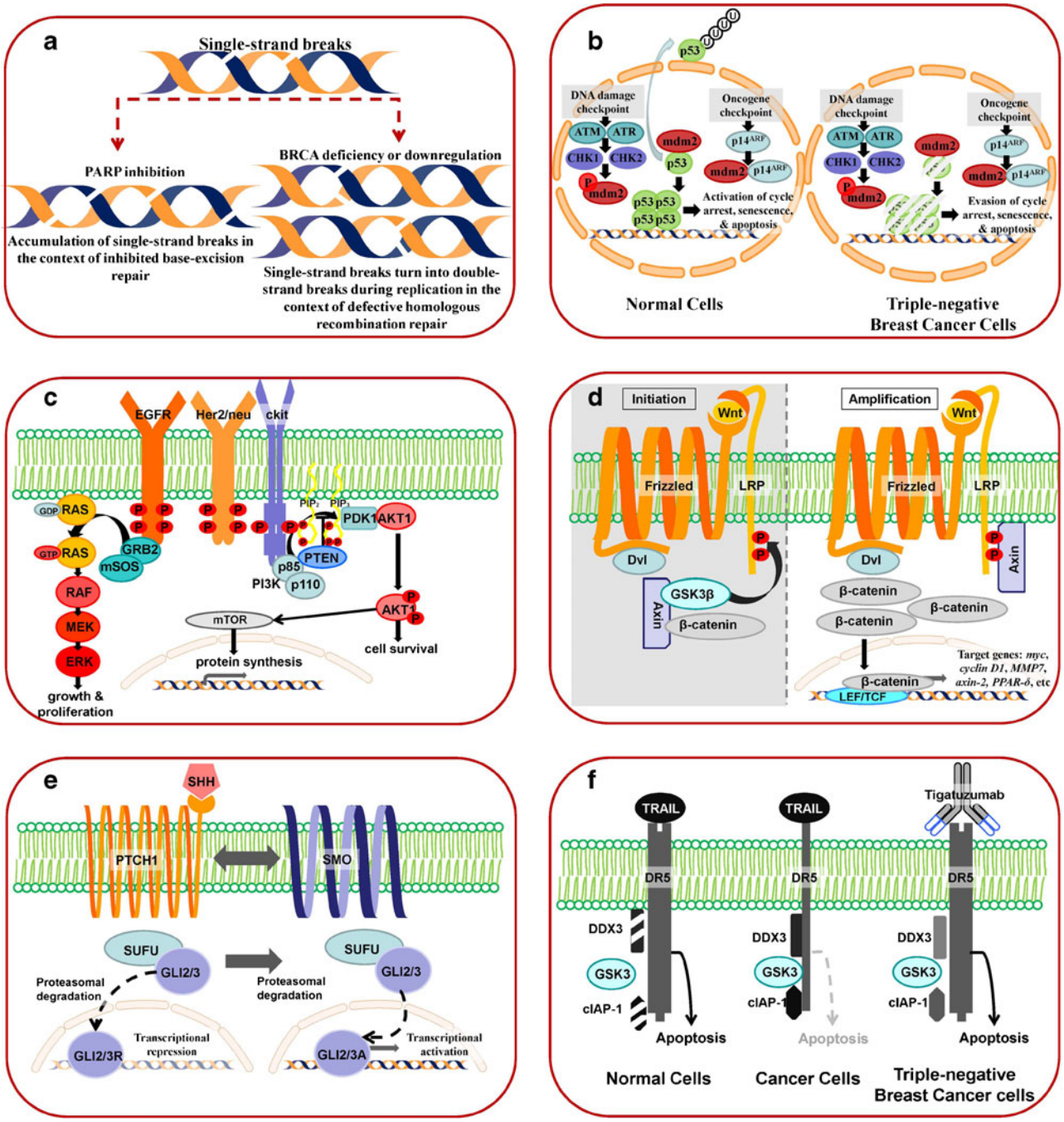
Multiple pathways amenable to therapeutic targeting (Fig. 1) have been shown to be operational in triple-negative disease providing a strong rationale for investigational therapies and supporting the preference for participation in clinical trials.

Platinum agents

- There has been a renewed interest in platinum compounds, partly because of improvements in the management of their toxicities as well as preclinical evidence of increased sensitivity to cisplatin of BRCA1-deficient cell lines [60].
- In early-phase clinical trials, platinum compounds have shown variable activity depending on the setting, population, and use in combination or alone (Table 1). The results of two trials are anticipated to clarify the role of the platinum compounds in triple-negative disease: a randomized phase II trial investigating the benefit of incorporating carboplatin and/or bevacizumab in the neoadjuvant setting (Cancer and Leukemia Group B 40603) [61] and a randomized trial comparing the efficacy of cisplatin or carboplatin in the metastatic setting (TBCRC009) [62].

Antiangiogenic agents

- Preclinical data has shown significantly higher intra-tumoral vascular endothelial growth factor (VEGF) levels in triple-negative [63] and basal-like breast cancers [64] compared to other subgroups rendering VEGF signaling a rational therapeutic target in triple-negative disease [63].
- Despite the significant improvements in the response rate and progression-free survival with bevacizumab, no significant improvements in overall survival were achieved [65, 66, 67•]. A recent combined analysis of three major randomized trials with bevacizumab showed a significant increase in progression-free survival in patients with triple-negative disease receiving anti-angiogenic therapy but no improvement in overall survival [68]. Thus, the clinical utility of bevacizumab remains undefined.
- Tyrosine kinase inhibitors targeting angiogenesis have also been clinically investigated. One such inhibitor, sunitinib, has been evaluated alone or in combination with chemotherapy but the results have been disappointing [69–71]. Subset analyses of patients with triple-negative disease in these studies suggested a benefit and led to trials of sunitinib in combination with chemotherapy in the neoadjuvant setting [72].



PolyADP-ribose Polymerase (PARP) inhibitors

- As *BRCA*-deficient tumor cells cannot repair double-strand DNA breaks by homologous recombination, they rely heavily on PARP to maintain the integrity of DNA by engaging the mechanism of base-excision repair [73]. In the setting of PARP inhibition, an over-

◀ **Figure 1.** Illustration of selected pathways found to be operational in triple-negative disease. **a**. As *BRCA*-deficient tumor cells cannot repair double-strand DNA breaks by homologous recombination, they rely heavily on PARP to maintain the integrity of DNA by engaging the mechanism of base-excision repair. In the setting of PARP inhibition, an overwhelming accumulation of double-strand breaks during replication occurs selectively in *BRCA*-deficient tumor cells, leading to death, whereas normal tissues are spared. In sporadic triple-negative tumors, *BRCA1* may be epigenetically silenced, or downregulated by means of microRNA-182 overexpression. Abbreviations: BRCA, breast cancer 1 early onset; PARP, PolyADP-ribose Polymerase. **b**. Under normal conditions, p53 binds with mdm2 and is shuttled out of the nucleus where is undergoes degradation by ubiquitination. In response to stimuli such as DNA damage, p53 and mdm2 are phosphorylated by the ATM and ATR serine/threonine kinases, and the immediate downstream checkpoint kinases, CHK1 and CHK2. As a result, p53 dissociates from mdm2, forms tetramers, and leads to upregulation of genes involved in cell cycle arrest and apoptosis. p53 is also activated by oncogenes such as Myc, which promote aberrant G1/S transition. Under these conditions, $p14^{ARF}$ is upregulated, binds to mdm2, and rescues p53 from degradation. p53 is mutated in 44% of triple-negative breast cancers [14] leading to aberrant cell cycle progression. Tumors with mutated p53 may be amenable to a "synthetic lethality" approach, as different molecular pathways may be operational in cells with mutated p53 compared to normal tissues. Abbreviations: ATM, ataxia-telangiectasia mutated; ATR, ataxia telangiectasia and Rad3 related; CHK1, checkpoint 1; CHK2, checkpoint 2; mdm2, murine double minute 2; P, phosphoryl group; $p14^{ARF}$, p14 alternate open reading frame; U, ubiquitine. **c**. Receptor tyrosine kinases and downstream signaling pathways in triple-negative disease. Receptor tyrosine kinases such as EGFR, ckit, Insulin-like Growth Factor 1 Receptor (IGF1R), and Fibroblast Growth Factor Receptor 2 (FGFR2) activate downstream signaling pathways by phosphorylation of specific tyrosine residues in their intracellular domains. One pathway involves the protooncogene RAS which is activated by the Grb2/mSOS guanine nucleotide exchange factor as it cycles between the inactive GDP- and active GTP-bound state. RAS-GTP recruits and activates RAF leading to subsequent activation of MEK and ERK. Another pathway involves the kinase PI3K which phosphorylates the membrane lipid PIP_2 to PIP_3. PIP_3 in turn acts as a docking site for serine/threonine kinases PDK1 and AKT1 which have numerous downstream cellular targets, including mTOR. The end effect of the activation of these pathways is upregulation of protein synthesis and upregulation of genes involved in cell survival, growth, and proliferation. A small subgroup of triple-negative breast tumors have a Her2-enriched molecular signature. Abbreviations: AKT1, protein kinase B; ckit, stem cell factor receptor; EGFR, epidermal growth factor receptor; ERK, mitogen-activated protein kinase 1; GDP/GTP, guanosine diphosphate/ triphosphate; GRB2, growth factor receptor-bound protein 2; Her2/neu, epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase kinase 1; mTOR, mammalian target of rapamycin; mSOS, son of sevenless homolog 1; P, phosphoryl group; p85 and p110, p85 [regulatory] and p110[catalytic] subunits of the PI3K, respectively; PDK1, 3- phosphoinositide-dependent protein kinase 1; PI3K, phosphatidyl inositol-3 kinase; PIP_2, phosphatidyl inositol 4, 5 diphosphate; PIP_3, phosphatidyl inositol 3,4,5 triphosphate; PTEN, phosphatase and tensin homolog ; RAF, Raf-1 serine/threonine kinase ; RAS, rat sarcoma viral oncogene homolog. **d**. The Wnt/β-Catenin pathway. In the absence of Wnt, cytoplasmic β-catenin forms a complex with Axin, adenomatous polyposis coli gene product (APC), casein kinase 1 (CK1), and glycogen synthase kinase 3 beta (GSK3β). In this complex, β-catenin undergoes phosphorylation followed by proteasomal degradation. The Wnt-ligand is a secreted glycolipoprotein that binds to Frizzled receptor and LRP leading to the recruitment of Dishevelled to the Frizzled receptor. Disheveled in turn, recruits axin and GSK3β away from the β-catenin degradation complex, thereby leading to the stabilization of β-catenin. β-catenin translocates to the nucleus and associates with LEF/ TCF DNA-binding factors where it acts as an activator of transcription. GSK3β phosphorylates critical sites on LRP which serve as docking sites for axin allowing for the stabilization of β-catenin. Abbreviations: Dvl, Dishevelled; GSK3β, glycogen synthase kinase 3 beta; LRP, low-density lipoprotein receptor related protein; *MMP7*, matrix metallopeptidase 7; *PPAR-δ*, peroxisome proliferator-activated receptor delta; TCF/LEF, T cell factor/lymphoid enhancer factor; Wnt, Wnt ligand. **e**. The hedgehog signaling pathway may be operational in cancer stem cells. In normal cells, the PTCH1 receptor binds to the SMO receptor, blocking hedgehog signaling. In the absence of ligand, the GLI family zinc finger transcription factors GLI2 and GLI3, are bound by the SUFU and undergo proteasomal cleavage into the repressor forms, GLI2R and GLI3R. In cancer cells, the binding of hedgehog ligands, such as SHH, to PTCH1 releases SMO, whereby GLI2 and GLI3 evade proteasomal degradation, translocate to the nucleus and act as activating transcription factors (GLI2A and GLI3A) for genes such as BCL2 and Cyclin D1. (Abbreviations: GLI1/2, glioma-associated oncogene homolog 1 and 2; PTCH1, patched; SHH, Sonic hedgehog homolog; SMO, smoothened; SUFU, suppressor of fused). **f**. The Death Receptor 5 is the target of the agonistic monoclonal antibody, tigatuzumab. An antiapoptotic protein complex consisting of GSK3, DDX3, and cIAP-1 is associated with death receptors. Normal cells overcome the antiapoptotic complex upon stimulation of the death receptors by causing GSK3 inactivation and cleavage of DDX3 and cIAP-1. The antiapoptotic complex, however, remains functional in cancer cells rendering them resistant to death receptor stimulation. Triple-negative breast cancer cell lines were shown to contain low levels of DR5-associated DDX3 and cIAP-1 rendering them susceptible to DR5-mediated cytotoxicity. (Abbreviations: cIAP-1, cellular inhibitor of apoptosis protein-1; DDX3, DEAD {Asp-Glu-Ala-Asp} box polypeptide 3; DR5, TNT-related apoptosis-inducing ligand receptor-2; GSK3; glycogen synthase kinase-3; TRAIL, TNF-related apoptosis-inducing ligand).

Table 1. Selected clinical studies in triple-negative disease with novel regimens

Author	Regimen	Population	Response	Remarks
Platinum Compounds				
Silver DP, et al. [87]	Neoadjuvant cisplatin	TNBC *n*=28	pCR 12%, good response (Miller-Payne score [88] 3–5) 50%	14% experienced clinical progression. The low pCR rate compared to multiagent chemotherapy argues against single-agent cisplatin for unselected TNBC.
Ryan PD, et al. [89]	Neoadjuvant cisplatin+ bevacizumab	TNBC *n*=51	pCR 15%, good response (Miller-Payne score [88] 4–5) 37%	2% experienced progressive disease, 9% discontinued due to toxicity. Completion of chemotherapy limited by significant toxicities.
Frasci P, et al. [90]	Neoadjuvant cisplatin+ epirubicin+paclitaxel (8 weekly cycles with GCSF support)	TNBC *n*=74	pCR 62%	A regimen of 8 weekly cycles of cisplatin+ epirubicin+paclitaxel is highly effective in TNBC. Patients who achieved pCR faired significantly better compared to those with residual disease.
Torrisi R, et al. [91]	Neoadjuvant epirubicin+ cisplatin+5-fluorouracil continuous infusion followed by paclitaxel	TNBC* *n*=30	pCR 40%, objective response 86%	16% experienced progression on paclitaxel. The combination of cisplatin with anthracyclines and taxanes may enhance the pCR rate. Long-term outcomes with this regimen are unknown.
Byrski T, et al. [92]	Neoadjuvant cisplatin	*BRCA1*-mutated *n*=10	pCR 90%, partial response 10%	Neoadjuvant cisplatin achieved a high pCR rate in *BRCA1*-associated breast cancer (not necessarily TNBC).
Carey LA, et al. [80]	Randomized phase II, cetuximab +/− carboplatin	Metastatic TNBC *n*=71	Clinical benefit 27% (in the combination arm)	The low response rate in the cetuximab arm prompted its closure. The results from the combination arm were deemed encouraging.
Baselga J, et al. [93]	Randomized phase II, cisplatin +/− cetuximab	Metastatic TNBC *n*=173	Overall response rate 10.3% (cisplatin alone) & 20% (combination)	Adding cetuximab to cisplatin increased the overall response rate compared with cisplatin alone and improved significantly the progression-free survival.
Maisano R, et al. [94]	Phase II, carboplatin+ gemcitabine	Metastatic TNBC *n*=31	Overall response rate 32%	Carboplatin+gemcitabine is a reasonable option in pretreated metastatic TNBC. High rates of dose reductions, delays, omissions, neutropenia, and febrile neutropenia

Staudacher L, et al. [95]	Retrospective, various platinum containing regimens	Metastatic TNBC *n*=93	Partial response 33.3%	Higher but nonsignificant response rate of TNBC to platinum-containing regimens compared to non-TNBC. Progression-free and overall survival no different compared to other subtypes.
Sirohi B, et al. [96]	Retrospective, multiple platinum-containing regimens	TNBC *n*=62	Clinical CR 88% (neoadjuvant) Clinical benefit 65% (metastatic)	Clinical response rates were significantly higher in TNBC compared to other subtypes in the neoadjuvant setting. Although a benefit in outcomes was seen in TNBC, this is compounded by the retrospective nature of the study.
Byrski T, et al. [97]	Retrospective neoadjuvant	*BRCA1*-mutated *n*=12	pCR 83%	Among 102 patients with *BRCA1*-associated breast cancer, 12 patients received cisplatin. The pCR with cisplatin was 83%, whereas the pCR with other regimens ranged between 7 and 22%.
PARP inhibitors				
Tutt A, et al. [98•]	Phase II, olaparib (100 or 400 mg PO twice daily)	*BRCA1 or BRCA2* mutated *n*=54	pCR 4% (400 mg) overall response rate 22% (100 mg), 47% (400 mg)	Positive proof-of-concept for PARP inhibition in *BRCA1* or *BRCA2* deficient tumors with favorable therapeutic index.
O'Shaughnessy J, et al. [74]	Open label phase II carboplatin+ gemcitabine +/– iniparib	Metastatic TNBC *n*=123	Overall response rate 56% (vs 32% in chemotherapy alone arm)	The addition of iniparib to cytotoxic chemotherapy improved all measures of efficacy (response rate, progression-free and overall survival) without significant additional toxicities.
Isakoff SJ, et al. [76]	Phase II veliparib+ temozolomide	Metastatic TNBC *n*=15	Overall response rate 37.5% (*BRCA*-mutants)	The clinical activity observed is likely attributable to the combination (rather veliparib alone). Clinical activity appeared to concentrate among *BRCA*-mutated tumors.

BRCA1 Breast cancer 1 early onset; *BRCA2* Breast cancer 2 early onset; *CR* Complete response; *GCSF* Granulocyte colony stimulating factor; *pCR* Pathologic complete response; *TNBC* Triple-negative breast cancer

* Definition of triple-negative disease did not conform with the ASCO/CAP guidelines

whelming accumulation of double-strand breaks during replication occurs selectively in *BRCA*-deficient tumor cells, leading to death, whereas normal tissues are spared [73]. This concept of synthetic lethality has borne out nicely in early-phase clinical trials (Table 1, Fig. 1a) especially among patients with germline *BRCA* mutations.

- Based on the observation that sporadic triple-negative tumors have impaired DNA repair capabilities similar to BRCA1-deficient tumors, O'Shaughnessy et al. have conducted clinical trials evaluating whether the addition of the PARP inhibitor iniparib, to DNA-damaging chemotherapy could improve outcomes in triple-negative disease. Although the randomized phase II study showed that iniparib added to carboplatin and gemcitabine conferred a significant benefit in response rate, progression-free and overall survival [74], preliminary negative results from the phase III confirmatory trial [75] imply that the benefit may not be uniform in sporadic triple-negative disease.
- Other PARP inhibitors such as veliparib [76] and PF-01367338 [77] are currently evaluated in clinical trials with patients with *BRCA*-mutated or sporadic triple-negative breast cancer. Results of these trials will further clarify the role of PARP inhibition in triple-negative disease.

Targeting the epidermal growth factor receptor

- Preclinical studies have shown that basal-like breast cancer depends on the EGFR pathway for proliferation, rendering EGFR a rational target (Fig. 1c) [78, 79]. Two classes of agents target EGFR signaling: monoclonal antibodies, such as cetuximab and panitumumab; and small molecule tyrosine kinase inhibitors, such as gefitinib and erlotinib.
- Carey et al. conducted a clinical trial of cetuximab with or without carboplatin in patients with metastatic triple-negative disease (TBCRC001) [80]. Patients who received cetuximab alone had a clinical benefit ratio of 10%. Although this ratio was raised to 31% when cetuximab was combined with carboplatin, the progression-free survival was only 2 months in both arms [80].
- Clinical trials with gefitinib and erlotinib alone or in combination with chemotherapy have been conducted in breast cancer but the results were not encouraging [81–83].

Targeting Death-Receptor 5 (DR5)

- Targeting death receptors on cancer cells with agonistic monoclonal antibodies (Fig. 1f) may represent a new generation of targeted therapy as these antibodies can directly induce apoptosis of malignant cells [84]. Monoclonal antibodies may be superior to the natural ligand (tumor necrosis factor-related apoptosis inducing ligand; TRAIL) as TRAIL targets multiple receptors including functional and decoy receptors as well as has a shorter plasma half-life affecting dose

and schedule parameters. Daiichi Sankyo has developed an agonistic humanized monoclonal antibody (Tigatuzumab) specific for the human DR5 receptor. Unlike cell lines of other subtypes, basal-like breast cancer cell lines were sensitive to agonistic DR5 targeting and, when the anti-DR5 antibody was combined with chemotherapy, an additive or synergistic effect was seen. The in vivo efficacy of the anti-DR5 antibody plus Abraxane (or doxorubicin) exceeded the efficacy of either agent alone [85, 86]. A protocol involving treatment with Abraxane±Tigatuzumab will be activated in 2011 (TBCRC019).

Several other potential therapeutic targets have been identified and are currently clinically investigated. Given the strong rationale and promising activity of new agents in triple-negative disease, participation in clinical trials is strongly encouraged at any stage of the disease. Studies have indicated that in order to optimize the benefit from novel agents, a refined patient selection based on genomic profiling of the tumor may be necessary, as different "driver" pathways may be activated among the triple-negative subsets [17••].

Disclosure

The authors have no conflicts of interest relevant to this manuscript to declare.

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