Abstract
Unlike estrogen receptor (ER)-positive and HER2-positive breast cancer, triple-negative breast cancer (TNBC) lacks a repertoire of targeted therapies. Hence, chemotherapy is the only available systemic option in current clinical practice. In general, survival of patients with TNBC is worse than that for those with ER-positive and HER2-positive breast cancer, especially for advanced-stage disease. Thus, a great unmet need exists. Conventional chemotherapeutic agents such as platinum-salts have been examined for specific benefit in TNBC; however, no one agent has yet been shown to offer a differential incremental benefit in metastatic TNBC. The hope is that ongoing research in targetable molecular pathways will lead to new therapeutic options for TNBC. Because these patients are likely to be increasingly subcategorized using potentially targetable molecular alterations, investigators will need to be mindful of the challenges in designing and conducting clinical trials in smaller subpopulations. The successful incorporation of targeted therapies in routine clinical practice for TNBC, which mirrors the success achieved by anti-HER2 and endocrine therapies, is awaited. (J Natl Compr Canc Netw 2015;13:(e8–e18)

Heterogeneity of TNBC
Because the utilitarian definition of TNBC is simply based on the exclusion of ER/PR/HER2 expression, it is not unexpected that this clinical subtype remains biologically heterogeneous. Studies examining tumor characteristics have found correlations between TNBC and certain molecular genomic features, such as basal cytokeratin (eg, CK5/6) and epidermal growth factor receptor (EGFR) expression, checkpoint kinase (Chk1), p53 alterations, and BRCA1 germline mutations.8–13 TNBC has also been shown to have overlapping features with the basal-like subtype (intrinsic breast cancer classification),14,15 including a high frequency of poorly differentiated tumors, expression of cytokeratins and EGFR, and p53 mutations. Although the basal-like–subtypes are most often triple-negative, they are not equivalent groups.16,17 In a gene expression study of 579 TNBCs, 73% of TNBCs showed basal-like characteristics.18
The Cancer Genome Atlas (TCGA) project reporting of breast cancer molecular analysis also showed significant overlap between TNBC and basal-like features and similarity to high-grade serous ovarian cancer.\textsuperscript{19} The TCGA basal-like subanalysis and the primary TNBC analysis identified several involved pathways that included PTEN, PI3K/PTEN, cell cycle, and growth factors, and highlighted the heterogeneity of TNBC.\textsuperscript{19,20} Recently a large meta-analysis of 587 TNBC gene expression profiles from 21 data sets described 7 TNBC subtypes with 6 potentially targetable pathways.\textsuperscript{21} Those subtypes consist of 2 basal-like types (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), and unstable (UNS). The BL1 subtype was characterized by cell cycle/cell division and DNA damage response pathways (and association with the BRCA deficiency). The BL2 subtype was typified by growth factor signaling such as via the EGFR pathway. The IM subtype was named for a cluster that contained immune-related processes. The M and MSL types were both associated with motility and epithelial to mesenchymal transition (EMT), but the MSL had more stem cell–like features. The LAR subtype contained the genes involved in androgen and steroid pathways. In addition, various cell lines were classified into these TNBC subtypes and evaluated for responses to therapy designed to match to the appropriate representative subtype.\textsuperscript{21} A Web-based subtyping tool was also created that allowed normalized gene expression data to be analyzed for TNBC subtypes.\textsuperscript{22}

**Treating TNBC: Where Are We Now?**

Currently, cytotoxic chemotherapy is the standard therapeutic approach for TNBC. TNBC is relatively chemosensitive, as evidenced by relatively higher pathologic complete response (pCR) rates compared with other subtypes, such as ER-positive/HER2-negative.\textsuperscript{23} This may be explained partially by the fact that TNBC is often associated with a high grade and proliferative rate. However, despite higher response rates, they have an inferior outcome with respect to time to recurrence and overall survival (OS) after chemotherapy.\textsuperscript{4} Preclinical studies and subgroup analyses within clinical trials have suggested that certain chemotherapeutic agents have differential antitumor activity in TNBC compared with non-TNBC. Thus, certain classes of chemotherapeutic agents have been preferentially evaluated in patients with TNBC.

**Microtubule-Targeting Agents**

Based on the TNBC subtypes, the basal-like types are postulated to respond well to taxanes because of their expression of proliferation genes.\textsuperscript{21} Efficacy of paclitaxel specifically for TNBC (compared with non-TNBC) has been observed in subtype analyses within clinical trials.\textsuperscript{24,25} However, these associations between TNBC and taxanes have not been consistent; a meta-analysis has shown benefit for taxane in the adjuvant setting independent of ER status.\textsuperscript{26}

Ixabepilone is an epothilone B analogue that stabilizes microtubules and has activity in patients with TNBC as a monotherapy.\textsuperscript{27} In a phase III study of ixabepilone and capecitabine versus capecitabine, improvements in response rate and median progression-free survival (PFS) were noted for the combination regimen in the TNBC subset compared with the ER-positive subset (response rate, 27% vs 9%, and median PFS, 4.1 vs 2.1 months, respectively).\textsuperscript{28} However, no significant benefit was noted in terms of median OS for patients with TNBC (hazard ratio [HR], 0.83; \(P < .05\)).\textsuperscript{29}

Eribulin is a halichondrin B analogue that perturbs microtubule dynamics. It demonstrated a survival benefit in heavily pretreated metastatic breast cancer (MBC) compared with the treatment of physician’s choice in the EMBRACE trial.\textsuperscript{30} The phase III “301” trial compared eribulin with capecitabine in 1102 pretreated patients with MBC, and reported a significant improvement in median OS associated with eribulin among the subset of patients with TNBC in an exploratory analysis (14.4 vs 9.4 mo; HR, 0.7; \(P = .01\)).\textsuperscript{31} However, in the published version of this study, the authors did not report any significant difference in benefit among the subgroups.\textsuperscript{32} Given that patients with metastatic TNBC often require multiple lines of chemotherapy, eribulin and capecitabine are both likely to remain useful. Eribulin is also being evaluated in combination with carboplatin (neoadjuvant) and everolimus (metastatic) for the treatment of for TNBC.\textsuperscript{33,34}

**Platinum Salts**

TNBCs have been associated with BRCA mutation status. BRCA-mutated tumors have defects in their...
The neoadjuvant use of platinum salts has been evaluated in BRCA-mutated and unselected TNBC. A recent meta-analysis of 28 neoadjuvant studies showed a pooled pCR rate of 45% (95% CI, 40%–49%) for platinum-containing regimens. The inclusion of a platinum seemed to be associated with a higher proportion of pCRs compared with non-platinum-containing regimens (response rate, 1.45; 95% CI, 1.25–1.68; P <.001). The GeparSixto study evaluated the addition of carboplatin to paclitaxel and pegylated liposomal doxorubicin (plus bevacizumab in TNBC) in the neoadjuvant setting. The addition of carboplatin was associated with a significant increase in pCR for TNBC (37.9% vs 58.7%; P <.05), although a high rate of discontinuation (39%) was noted for the regimen that included carboplatin.

In the CALGB 40603 trial in which carboplatin and/or bevacizumab was added to anthracycline/paclitaxel chemotherapy in 454 patients with TNBC, the breast pCR rate improved with the addition of carboplatin (from 46% to 60%; P = .018), with more marrow suppression noted in the carboplatin group: grade 3/4 neutropenia (56% vs 20%) and thrombocytopenia (22% vs 4%). The available evidence suggests that platinum can improve the pCR rate. Patients with TNBC who experience a pCR have significantly better survival than those who do not. However, an association between platinum use and relapse-free survival and OS still needs to be elucidated (ie, does the incremental improvement in pCR translate to fewer “downstream” events). The NeoALTO and ALTO trials recently reported that the addition of lapatinib, which improves pCR from 29.5% to 51.0% in the neoadjuvant setting, did not translate into a significant benefit in disease-free survival or OS when used as adjuvant therapy. At the time of this writing, whether...
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#### Table 1: Selected Chemotherapy Regimens With TNBC-Specific Outcomes in the Metastatic Setting

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study Design</th>
<th>Total Patients</th>
<th>Patients With TNBC</th>
<th>Study Population</th>
<th>TNBC RR</th>
<th>TNBC TTP/PFS</th>
<th>TNBC OS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (doc) vs carboplatin (carb)</td>
<td>Phase III</td>
<td>376</td>
<td>376</td>
<td>No previous taxane or platinum in metastatic setting</td>
<td>31% (carb) vs 36% (doc)</td>
<td>3.1 (carb) vs 4.5 mo (doc)</td>
<td>12.4 (carb) vs 12.3 mo (doc)</td>
<td>Tutt et al, 2012</td>
</tr>
<tr>
<td>Gemcitabine and carboplatin arm (gemcitabine and carboplatin+/- iniparib)</td>
<td>Phase III, gemcitabine and carboplatin-only arm</td>
<td>519</td>
<td>519</td>
<td>Prior 0–2 lines</td>
<td>30%</td>
<td>4.1 mo</td>
<td>11.1 mo</td>
<td>O'Shaughnessy et al, 2011</td>
</tr>
<tr>
<td>Gemcitabine and cisplatin</td>
<td>Phase II</td>
<td>144</td>
<td>144</td>
<td>Relapsed after 1 adjuvant/NAC regimen or first-line metastatic regimen with anthracycline</td>
<td>33%</td>
<td>5.1 mo</td>
<td>73% at 1 y</td>
<td>Kohail et al, 2012</td>
</tr>
<tr>
<td>Gemcitabine and cisplatin</td>
<td>Phase II</td>
<td>38</td>
<td>38</td>
<td>Second-line, anthracycline and taxane pretreated</td>
<td>42%</td>
<td>5.4 mo</td>
<td>13.9 mo</td>
<td>Wang et al, 2012</td>
</tr>
<tr>
<td>Gemcitabine and cisplatin</td>
<td>Retrospective review</td>
<td>33</td>
<td>33</td>
<td>Prior anthracycline and taxane</td>
<td>27%</td>
<td>5 mo</td>
<td>14 mo</td>
<td>Ozkan et al, 2012</td>
</tr>
<tr>
<td>Gemcitabine and cisplatin</td>
<td>Retrospective review</td>
<td>36</td>
<td>17</td>
<td>Prior taxane</td>
<td>5.3 mo</td>
<td></td>
<td></td>
<td>Koshly et al, 2010</td>
</tr>
<tr>
<td>Gemcitabine and carboplatin</td>
<td>Phase II</td>
<td>31</td>
<td>31</td>
<td>Prior anthracycline and taxane</td>
<td>32%</td>
<td>5.5 mo</td>
<td>11 mo</td>
<td>Maisano et al, 2011</td>
</tr>
<tr>
<td>Gemcitabine and carboplatin</td>
<td>Phase II</td>
<td>47</td>
<td>15</td>
<td>First-line</td>
<td>20%</td>
<td></td>
<td></td>
<td>Yardley et al, 2008</td>
</tr>
<tr>
<td>Gemcitabine and carboplatin</td>
<td>Phase II</td>
<td>150</td>
<td>30</td>
<td>Prior taxane or no prior taxane</td>
<td>30%</td>
<td></td>
<td></td>
<td>Loesch et al, 2008</td>
</tr>
<tr>
<td>Gemcitabine and paclitaxel</td>
<td>Phase II</td>
<td>56</td>
<td>14</td>
<td>First-line</td>
<td>35.7%</td>
<td>6 mo</td>
<td></td>
<td>Aogi et al, 2011</td>
</tr>
<tr>
<td>Cisplatin (cis) arm (cisplatin +/- cetuximab)</td>
<td>Randomized phase II</td>
<td>115</td>
<td>115</td>
<td>No more than 1 prior</td>
<td>10% (cis)</td>
<td>1.5 mo (cis)</td>
<td></td>
<td>Baselga et al, 2013</td>
</tr>
<tr>
<td>Cisplatin or carboplatin</td>
<td>Phase II</td>
<td>87</td>
<td>87</td>
<td>First- or second-line</td>
<td>25.6%</td>
<td>2.9 mo</td>
<td>11 mo</td>
<td>Isakoff et al, 2014</td>
</tr>
<tr>
<td>Cisplatin (cis) and irinotecan (iri) arm (cisplatin, irinotecan +/- cetuximab)</td>
<td>Randomized phase II</td>
<td>154</td>
<td>72</td>
<td>Prior 0–1 line</td>
<td>30% (cis/iri)</td>
<td>5.1 mo (cis/iri)</td>
<td>12.8 mo (cis/iri)</td>
<td>O'Shaughnessy et al, 2014</td>
</tr>
<tr>
<td>Docetaxel/cisplatin vs docetaxel/capecitabine</td>
<td>Randomized phase II</td>
<td>53</td>
<td>53</td>
<td>First-line</td>
<td>63% vs 15.4%; P&lt;.002</td>
<td>10.9 vs 4.8 mo HR, 0.29; P&lt;.001</td>
<td>32.8 vs 21.5 mo HR, 0.41; P=.027</td>
<td>Fan et al, 2013</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Retrospective review</td>
<td>162</td>
<td>28</td>
<td>First-line</td>
<td>0% at 2 y</td>
<td>37.8% at 2 y</td>
<td>3.6 mo</td>
<td>Gonçalves et al, 2009</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Retrospective review</td>
<td>75</td>
<td>15</td>
<td>Prior anthracycline and taxane</td>
<td>0%</td>
<td></td>
<td></td>
<td>Gilabert et al, 2011</td>
</tr>
<tr>
<td>ixabepilone</td>
<td>Retrospective subanalysis</td>
<td>11–42</td>
<td></td>
<td>Prior anthracycline, taxane, capecitabine</td>
<td>6%–55%</td>
<td>1.6–4.6 mo</td>
<td></td>
<td>Perez et al, 2010</td>
</tr>
<tr>
<td>ixabepilone</td>
<td>Phase II</td>
<td>52</td>
<td>16</td>
<td>Prior anthracycline and taxane</td>
<td>6.3%</td>
<td></td>
<td></td>
<td>Aogi et al, 2013</td>
</tr>
<tr>
<td>Ixabepilone + capcitabine vs capecitabine</td>
<td>Phase III subanalysis</td>
<td>752</td>
<td>71</td>
<td>Prior anthracycline and taxane</td>
<td>27% (iri + cis) vs 9% (cis)</td>
<td>4.1 vs 2.1 mo HR, 0.68; P&lt;.05</td>
<td></td>
<td>Pivot et al, 2009</td>
</tr>
<tr>
<td>Oral vinorelbine and capecitabine</td>
<td>Phase II</td>
<td>54</td>
<td>9</td>
<td>First-line</td>
<td>22.2%</td>
<td>4 mo</td>
<td></td>
<td>Tubiana-Mathieu et al, 2009</td>
</tr>
<tr>
<td>Metronomic oral cyclophosphamide and capecitabine</td>
<td>Phase II</td>
<td>51</td>
<td>10</td>
<td>No more than 1 prior line and no prior 5-FU, capcitabine, or cyclophosphamide</td>
<td>44.4%</td>
<td>10.7 mo</td>
<td></td>
<td>Yoshimoto et al, 2012</td>
</tr>
<tr>
<td>Oral cyclophosphamide and capcitabine</td>
<td>Phase II</td>
<td>45</td>
<td>12</td>
<td>No more than 1 prior line</td>
<td>41.7%</td>
<td>220.5 d</td>
<td></td>
<td>Tanaka et al, 2010</td>
</tr>
<tr>
<td>Eribulin vs capcitabine</td>
<td>Phase III subanalysis</td>
<td>1102</td>
<td>284</td>
<td>Prior anthracycline and taxane</td>
<td>14.4 vs 9.4 mo HR, 0.7; P=.05</td>
<td></td>
<td></td>
<td>Kaufman et al, 2012</td>
</tr>
<tr>
<td>Eribulin</td>
<td>Phase II</td>
<td>56</td>
<td>12</td>
<td>First-line</td>
<td>16.7%</td>
<td>3.4 mo</td>
<td></td>
<td>McIntyre et al, 2014</td>
</tr>
<tr>
<td>Anthracycline and cyclophosphamide</td>
<td>Retrospective review</td>
<td>110</td>
<td>25</td>
<td>First-line</td>
<td>56.5%</td>
<td>8.1 mo</td>
<td>25.4 mo</td>
<td>Yi et al, 2010</td>
</tr>
<tr>
<td>Paclitaxel arm (from paclitaxel +/- bevacizumab)</td>
<td>Phase III, paclitaxel-only arm</td>
<td>722</td>
<td>233</td>
<td>First-line</td>
<td>4.6 mo</td>
<td></td>
<td></td>
<td>Miller et al, 2007</td>
</tr>
</tbody>
</table>

**Abbreviations:** HR, hazard ratio; NAC, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; RR, response rate; TNBC, triple-negative breast cancer; TTP, time to progression.

*Median, unless otherwise noted.*
platinum agents deserve routine inclusion in regimens for TNBC of any stage remains uncertain.

Based on a mechanistic rationale and efficacy in nonrandomized trials, platinum is perhaps a reasonable choice for a subset of patients with TNBC who are more likely to have a DNA-repair deficiency. Several studies have reported biomarkers that may be helpful in selecting an appropriate population. For example, a homologous recombination deficiency assay is currently being evaluated as a biomarker in sporadic TNBC, with a primary end point of correlation with pCR (ClinicalTrials.gov identifier: NCT01982448).

Treating TNBC: Where Are We Going?
As knowledge of TNBC molecular features expands, several potential therapeutic targets have emerged, which include “the hallmarks of cancer”: DNA repair and damage checkpoint mechanism, proliferation and growth, angiogenesis, and invasion/metastases. Whether disease can successfully be controlled through targeting a single pathway in a subpopulation of TNBC (as in the case of some HER2-driven tumors) is unclear. It is likely that a rational combination of systemic agents will need to be found, which may include conventional chemotherapy (eg, platinum drug and poly(ADP-ribose) polymerase [PARP] inhibitor). The following are selected examples of biologic and immunologic agents currently under investigation.

PARP Inhibition
Molecular genomic analyses have identified potentially targetable pathways and areas of drug development for TNBC (Table 2). In addition to the platinum drugs, PARP inhibitors have been evaluated in TNBC to target their BRCA-ness. PARP1 is a DNA repair enzyme involved in single-strand break (SSB). When used in a setting of BRCA-related repair deficiency, it is thought to facilitate “synthetic lethality,” wherein SSB repair deficiency leads to double-strand breaks that cannot be repaired by homologous recombination. Preclinical and clinical studies have shown a particular sensitivity to PARP inhibition in BRCA-mutated tumors.

Initially, the investigational drug iniparib was thought to be a PARP inhibitor and was initially evaluated in a randomized phase II study with gemcitabine and carboplatin. Despite the promising initial data, a larger phase III trial did not show significant benefit for iniparib when added to chemotherapy. Additional studies showed that the drug demonstrated poor PARP inhibition. However, other PARP inhibitors are being evaluated in patients with BRCA-mutated and sporadic TNBC. Olaparib as a monotherapy did not show any confirmed objective response in a phase II study for TNBC, although modest efficacy was noted in patients with a BRCA mutation. It is currently being evaluated in combination with chemotherapy or other biologic agents, such as cediranib (anti–vascular endothelial growth factor [VEGF]).

Veliparib in combination with carboplatin (V+C) was evaluated in the I-SPY-2 neoadjuvant trial. There was a 92% predictive probability (Bayesian) that the addition of V+C would be statistically superior to the standard anthracycline/taxane-based therapy alone based on the observed pCR rates: 52% (28%–67%) for V+C and 26% (9%–43%) in the control arm. Finally, perturbation of the PI3K/AKT and cell cycle pathways (eg, CDK1 inhibition) have been shown to sensitize cells to PARP inhibition even in BRCA-proficient tumors in preclinical models, and clinical studies of combination therapy with PARP and PI3K inhibitors are underway (ClinicalTrials.gov identifier: NCT01623349).

Other efforts to target DNA damage repair and cell cycle checkpoint mechanisms include use of histone deactylase (HDAC), heat-shock protein 90 (Hsp90), and Chk1 inhibition. Although a phase II study of Chk1 inhibition in combination with irinotecan demonstrated limited activity in TNBC (response rate, 4%), preclinical studies have suggested that these strategies may be particularly relevant in TNBC associated with p53 mutation and BRCA mutation and await further clinical evaluation.

Anti-VEGF Therapy
VEGF is frequently expressed in TNBC and is a potential therapeutic target. Anti-VEGF therapy, particularly bevacizumab, has been studied with modest and inconsistent improvements in response rate and PFS but not for OS in the metastatic setting. Recently the phase III BEATRICE trial examined the addition of bevacizumab to standard adjuvant chemotherapy in TNBC and failed to show a benefit in DFS or OS. In CALGB 40603, the addition of neoadjuvant bevacizumab was associated with a significant improvement in breast-only pCR but not for
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breast and axillary nodes (36% increase with P=.06 for breast and axilla). On the other hand, the TNBC subset analysis of GeparQuinto showed improvement in pCR (breast and lymph nodes): 27.9% to 39.3% with addition of bevacizumab (P=.003). Again, as with platinums, it is unclear (perhaps unlikely) that this incremental improvement is clinically meaningful and will translate to an improvement in DFS or OS. In addition, biomarker studies (eg, MERIDIAN trial) are being conducted to better select patients who may derive greater benefit from bevacizumab therapy.

Small molecule anti-VEGF drugs, such as sunitinib and sorafenib, have been also evaluated and have shown unclear benefit. Sunitinib failed to show benefit as a monotherapy or in combination with chemotherapy in HER2-negative MBC, whereas sorafenib in combination with chemotherapy has shown a modest association with PFS improvement in phase II studies, although results of the phase III trial are currently awaited.

**Growth Factor Signaling Pathway**

EGFR is another receptor frequently expressed in TNBC and associated with the BL2 subtype. The EGFR-targeting antibody cetuximab has been evaluated in otherwise unspecified TNBC, with a suggestion of either modest benefit or improved response rate but not PFS or OS. Ongoing studies for EGFR targets include panitumumab with platinum-containing chemotherapy (ClinicalTrials.gov identifiers: NCT00894504 and NCT01009983). Other growth factor pathways identified as potential targets include the fibroblast growth factor receptor (FGFR) pathway. Preclinical studies have shown antitumor activity with anti-FGFR treatment, but a clinical trial examining the FGFR inhibitor dovitinib in breast

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Potentially Targetable Pathways and Selected Examples of Drugs Being Preferentially Evaluated in TNBC *</th>
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<tbody>
<tr>
<td>Pathway</td>
<td>Drugs</td>
</tr>
<tr>
<td>DNA repair</td>
<td>Veliparib, Olaparib</td>
</tr>
<tr>
<td>TP53 mutation/checkpoint</td>
<td>UCN-01, P276-00, Ganetespiib, Dinaciclib</td>
</tr>
<tr>
<td>Growth factor pathway</td>
<td>MM-121, Panitumumab</td>
</tr>
<tr>
<td>Anti-VEGF</td>
<td>Cabozantinib, Sorafenib</td>
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<td>AR pathway</td>
<td>Enzalutamide</td>
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<tr>
<td>Notch pathway</td>
<td>RO4929097, LDE225</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>LCL161</td>
</tr>
<tr>
<td>PI3K/Akt pathway</td>
<td>GDC-0941, BKM120</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>PD-1 antibody, MUC1 peptide vaccine, Autologous cMet-redirection T cells</td>
</tr>
</tbody>
</table>

Abbreviations: AR, androgen receptor; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; PARP, poly(ADP-ribose) polymerase; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

*Active on ClinicalTrials.gov as of June 1, 2014.
cancer did not report any responses, although the difference in the proportion of patients experiencing stable disease and a minor reduction in tumor size suggested that patients with FGFR amplification may benefit from this strategy.\textsuperscript{72}

Recently, DUSP4 loss, a negative regulator of the Ras-ERK pathway, was reported as a potential prognostic biomarker for basal-like breast cancer after neoadjuvant chemotherapy and MEK as a potential target in this setting.\textsuperscript{73} Phase I and pharmacodynamics studies with MEK inhibitors are ongoing in patients with TNBC (ClinicalTrials.gov identifiers: NCT01467310, NCT01155453, and NCT01363232).

**Cell Motility and EMT Features**
Characteristics of the M-like subtype include cell motility and EMT features. Steroid receptor coactivator (SRC) is thought to play a role in migration and invasion.\textsuperscript{21} Dasatinib, an oral SRC inhibitor, has shown antitumor activity in preclinical TNBC studies. In a phase II trial of dasatinib monotherapy conducted among 44 patients with metastatic TNBC, dasatinib showed modest antitumor activity (overall response rate, 4.7% with median PFS of 8.3 weeks; 95% CI, 7.3–15.3).\textsuperscript{74} Dasatinib is currently being studied in combination with chemotherapy (weekly paclitaxel) for MBC (ClinicalTrials.gov identifier: NCT00820170).

**The LAR Subtype**
Although its prevalence is higher in ER-positive breast cancer, androgen receptor (AR) is expressed in approximately 30% of TNBC and thought to be another potential target, especially for the LAR subtype.\textsuperscript{21,75,76} AR-targeted drugs, such as bicalutamide and enzalutamide, approved for prostate cancer, are currently being evaluated in breast cancer, including TNBC (ClinicalTrials.gov identifier: NCT 011889238).\textsuperscript{76} In the study evaluating bicalutamide, 150 mg/d orally in ER/PR-negative breast cancer, 14% were AR-positive with no confirmed complete response or partial response, but with 19% stable disease.\textsuperscript{76} In the TNBC subtype analysis, it is interesting to note that LAR subtype cell lines had a PI3K mutation and were sensitive to PI3K inhibition.\textsuperscript{21}

**PI3K/AKT Pathway**
PTEN loss is commonly noted in basal-like breast cancer and is a negative regulator of the PI3K/AKT pathway.\textsuperscript{12} mTOR inhibition with everolimus has antitumor activity in a basal-like breast cancer xenograft model.\textsuperscript{73} In the TNBC preclinical study, cell lines with PIK3CA mutations and PTEN deficiency were highly sensitive to dual PI3K/mTOR inhibition.\textsuperscript{21} An intact PI3K/AKT/mTOR pathway has been shown to also contribute to DNA damage repair preclinically, and pathway inhibition sensitizes cells to PARP inhibition.\textsuperscript{78} PI3K/AKT pathway inhibition is currently being evaluated as monotherapy (ClinicalTrials.gov identifiers: NCT01629615 and NCT01790932) or in combination with other agents (ClinicalTrials.gov identifiers: NCT01918306, NCT01623349, and NCT01939418).

**Immunotherapy**
TNBC has been associated with various characteristics in which immunotherapy would be a rational and attractive mode of therapy. Tumor-infiltrating lymphocytes (TILs) have been associated with a better prognosis among patients with TNBC.\textsuperscript{77} An analysis of stromal TILs in TNBC from the ECOG 2197 and 1199 adjuvant therapy trials reported that for every 10% incremental increase in stromal TILs there was an associated 18% reduction in the risk for distant recurrence ($P=0.04$) and 19% reduction in risk of death ($P=0.01$).\textsuperscript{80} A higher programmed death-ligand 1 (PD-L1) expression has been reported for TNBC compared with other breast cancer subtypes, and immune checkpoint therapy with a PD-L1 inhibitor is now being evaluated in breast cancer\textsuperscript{81} (ClinicalTrials.gov identifiers: NCT011714739 and NCT01375842). Pembrolizumab, an anti–PD-1 antibody, was reported to have single-agent activity in the phase I Keynote-012 trial.\textsuperscript{82} MUC1 is a tumor antigen highly expressed in early-stage basal-like breast cancer,\textsuperscript{83} and an MUC1 peptide vaccine trial is ongoing (ClinicalTrials.gov identifier: NCT00986609). With success reported in hematologic malignancies, adoptive T-cell therapy is also being evaluated in breast cancer (ClinicalTrials.gov identifier: NCT01837602).

Ideally, molecularly directed studies would be conducted among specific subgroups of TNBC with targetable pathways. Because TNBC represent approximately 20% of all breast cancer, further subsetting leads to smaller source populations for clinical trials. Examples of TNBC and subtype prevalence are shown in Figure 1. In a recent sobering report, a molecular genomic alteration screening process was used for patient accrual into targeted therapeutic trials for breast cancer. Of 423 patients, rational targeted therapy was identified and offered in only
13% of patients. If appropriate biomarkers are used to select the study population (ie, subset of TNBC), the hope is that the strength of the therapeutic effect would be strong enough to detect significant and clinically meaningful antitumor activity, even with a modest number of patients. Therefore, the concurrent development of reliable and validated biomarkers with novel targeted therapeutics is critical.

Conclusions

Although the amount of molecular genomic information informing potentially targetable pathways is expanding, additional predictive biomarkers and associated treatment options have not been incorporated into clinical practice to improve the outcomes in TNBC. Conventional cytotoxic chemotherapy is still standard treatment for TNBC. An incremental benefit of platinum therapy for TNBC is demonstrated by neoadjuvant studies, but the impact of platinums on outcomes other than pCR is uncertain, limiting their incorporation into standard clinical practice. Whether the gain from the incremental improvement in pCR rates will translate to improved relapse-free survival or OS is unclear. The discovery of many candidate targetable pathways may provide more rational treatment options and approaches for TNBC. The efficiency of clinical trial design for tar-
targeted therapy evaluation will be enhanced by the use of appropriate biomarkers; however, validation of new biomarkers and their clinical utility remain to be established. Ongoing research in TNBC will hopefully lead to practice-changing findings similar to or greater than those witnessed for ER-positive and HER2-positive breast cancer, and ultimately contribute to improved survival for TNBC; to this end, enrollment of such patients into clinical trials remains a high priority.

References


Review

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