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Capecitabine in Combination with Novel Targeted Agents in the Management of Metastatic Breast Cancer: Underlying Rationale and Results of Clinical Trials

Debu Tripathy

Komen/University of Texas Southwestern Breast Cancer Research Program, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Key Words. Capecitabine • Breast neoplasm • Biological response modifiers • Antineoplastic agents

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Provide the biological basis for using capecitabine in combination therapy.
2. Describe the results of trials assessing capecitabine in combination with the biological response modifiers trastuzumab and bevacizumab in the setting of metastatic breast cancer.
3. Detail the other molecularly targeted agents that are being studied in combination with capecitabine in this setting and the rationale for these investigations.

ABSTRACT

At present there is no established standard of care for metastatic breast cancer and prognosis remains poor, although the use of newer chemotherapeutic regimens has led to modest improvements in survival. Capecitabine, an oral prodrug of 5-fluorouracil, is a promising addition to these approaches, having already shown single-agent activity against metastatic breast cancer. Following a pivotal trial demonstrating that capecitabine confers increased survival when used in combination with docetaxel, it is being investigated intensively in combined regimens using other standard chemotherapeutic agents, as well as with novel molecularly targeted therapies.

Among the novel agents, the most intensively studied in combination with capecitabine is trastuzumab. Despite preclinical data suggesting that these two agents might not show additive effects, clinical trials have been very encouraging for both heavily pretreated patients and for patients receiving first-line therapy in the metastatic setting. This work is being further extended in an ongoing trial in the neoadjuvant setting. An initial trial in combination with bevacizumab, enrolling heavily pretreated patients, was less successful, but following the example of the E2100 trial, this combination is being re-examined in less heavily treated patients. In addition, this review discusses ongoing trials with an array of newer molecularly targeted agents. Significant improvement in time to progression has already been demonstrated in the combination of lapatinib and capecitabine compared with capecitabine monotherapy; for the most part, however, these trials are still in early stages. The Oncologist 2007;12:375–389

Disclosure of potential conflicts of interest is found at the end of this article.
INTRODUCTION
Despite improvements in survivability of nonmetastatic breast cancer over the past 25 years, particularly for both estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER-2)-positive disease, metastatic disease remains largely incurable, causing the great majority of the approximately 41,000 disease-associated deaths in the U.S. annually [1]. While several chemotherapeutic agents, including taxanes, anthracyclines, vinorelbine, gemcitabine, and capecitabine, have demonstrated single-agent activity in the metastatic breast cancer setting, treatment is aimed primarily at prolonging progression-free survival and overall survival time as well as maintaining quality of life [2].

Recent analyses of decadal survival rates have reported a trend toward modest improvements in survival [3, 4] or improvements in disease-free interval and reductions in both relapse ratio and intensity of chemotherapy [5]. A large meta-analysis of data from 189 trials published between 1975 and 1997 that included more than 31,000 patients found that combination chemotherapy regimens conferred a survival advantage when compared with single-agent approaches [6]. Similar trends also have been observed in randomized controlled trials initiated in the last few years, several of which have included a taxane in combination with either targeted biologicals such as trastuzumab [7] or cytotoxic agents including gemcitabine [8] and capecitabine [9]. Capcitabine is the only therapy specifically approved for anthracycline- and taxane-exposed patients, a setting that is becoming increasingly important as more patients have recurrent metastatic disease after receiving adjuvant anthracycline and taxane therapy. Moreover, capcitabine is being included in other promising combination regimens, especially with novel agents. This review examines new developments involving capcitabine-based combinatorial approaches with a particular focus on its use with molecularly targeted therapies.

RATIONALE FOR USING CAPECITABINE IN COMBINATION THERAPY
Capcitabine is currently indicated as a treatment for metastatic breast cancer, both as monotherapy [10] and in combination with docetaxel [9, 11], is effective in the treatment of colorectal cancer, and is one of the few agents with activity against pancreatic cancer [12]. Its general pharmacological properties make it an attractive option in combinatorial therapy. Capcitabine is an orally administered fluoropyrimidine carbamate prodrug of 5-fluorouracil (5-FU) whose therapeutic effects are attributed to misincorporation of fluoronucleotides into DNA and RNA, as well as to inhibition of the enzyme thymidylate synthase and resultant disruption of nucleotide pools [13, 14]. Oral administration provides the advantages of convenience and thus lower cost. Capcitabine has a good tolerability profile, with major side effects being hand–foot syndrome and diarrhea, both usually overcome by dose interruptions or dose reductions [15].

At least two mechanisms are likely to contribute to the efficacy of capcitabine and to its potential utility in combination therapy. First, thymidine phosphorylase, the final enzyme in the conversion of capcitabine to 5-FU, is generally upregulated in tumor cells relative to healthy tissue so that overall systemic toxicity is reduced [15]. Numerous studies on tumor cells have reported that thymidine phosphorylase activity is further increased by some standard cancer therapies, including paclitaxel [16], mitomycin C [16], radiation [17], cyclophosphamide [18], docetaxel [19], and combined anthracycline–cyclophosphamide regimens [19].

Second, recent in vitro gene expression studies have shown that capcitabine has the potential to affect numerous molecular pathways that may provide opportunities for developing combinatorial regimens with other agents. Li et al. [20] found that exposure of prostate cancer cells to 5′-deoxy-5-fluorouridine (5′-DFUr), the penultimate metabolite in the pathway between capcitabine and 5-FU [14], led to changes in the expression of dozens of genes, many of which are involved in diverse pathways related to cell cycle regulation, apoptosis, oncogenesis, invasiveness, metastasis, and resistance to chemotherapeutic agents. Additional changes in gene expression occur in prostate cancer cells exposed to a combination of 5′-DFUR and docetaxel, including downregulation of a variety of genes essential for cell proliferation, cell cycle progression, and oncogenesis, with corresponding upregulation of certain genes involved in apoptosis, cell cycle arrest, differentiation, and chemotherapeutic resistance [20].

CLINICAL TRIALS INVOLVING COMBINATION THERAPY WITH CAPECITABINE
The interest in using capcitabine in combination with other therapies is reflected in the large number of completed and ongoing clinical trials. (Tables 1–4 [9, 21–44] provide an overview of trials involving capcitabine.) Combinations of capcitabine with standard chemotherapeutic regimens are still being actively investigated (Table 1 [9, 21–27] provides a summary of data from randomized clinical trials involving capcitabine with other chemotherapeutic agents) along with an increasing number of studies examining the use of capcitabine with newer targeted therapies (Table 2 [28–40] provides summaries of data from such trials). In addition,
there are a number of ongoing studies for which results are either preliminary or not yet available. Table 3 [41] presents a summary of ongoing trials investigating the use of capecitabine in combination with monoclonal antibody therapies, and Table 4 [41–44] describes ongoing trials with capecitabine in combination with other novel agents.

**Table 1. Results of randomized trials evaluating the efficacy of combination therapy with capcitabine and chemotherapeutic agents in the treatment of locally advanced or metastatic breast cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n of patients</th>
<th>ORR (%)</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Shaughnessy et al. [9]</td>
<td>Docetaxel</td>
<td>256</td>
<td>30</td>
<td>4.2</td>
<td>11.5</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Capcitabine/docetaxel</td>
<td>255</td>
<td>42</td>
<td>6.1</td>
<td>14.5</td>
<td>NR</td>
</tr>
<tr>
<td>von Minckwitz et al. [21]</td>
<td>Docetaxel/doxorubicin/cyclophosphamide</td>
<td>242</td>
<td>59.9b</td>
<td>NR</td>
<td>NR</td>
<td>6.6 (n = 311)</td>
</tr>
<tr>
<td></td>
<td>Capcitabine/vinorelbine</td>
<td>233</td>
<td>63.5</td>
<td>NR</td>
<td>NR</td>
<td>6.2 (n = 291)</td>
</tr>
<tr>
<td>Lee et al. [22]</td>
<td>Doxorubicin/cyclophosphamide</td>
<td>101</td>
<td>67</td>
<td>NR</td>
<td>NR</td>
<td>10c</td>
</tr>
<tr>
<td></td>
<td>Capcitabine/docetaxel</td>
<td>103</td>
<td>84</td>
<td>NR</td>
<td>NR</td>
<td>23</td>
</tr>
<tr>
<td>Mavroudis et al. [23]</td>
<td>Epirubicin/docetaxel</td>
<td>112</td>
<td>49</td>
<td>11.1</td>
<td>32</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Capcitabine/docetaxel</td>
<td>109</td>
<td>49</td>
<td>9.8</td>
<td>35</td>
<td>NR</td>
</tr>
<tr>
<td>Chan et al. [24]</td>
<td>Gemcitabine/docetaxel</td>
<td>153</td>
<td>32</td>
<td>NRd</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Capcitabine/docetaxel</td>
<td>152</td>
<td>32</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lueck et al. [25]</td>
<td>Epirubicin/paclitaxel</td>
<td>144</td>
<td>51</td>
<td>NR</td>
<td>24.0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Capcitabine/paclitaxel</td>
<td>145</td>
<td>52</td>
<td>NR</td>
<td>25.6</td>
<td>NR</td>
</tr>
<tr>
<td>Soto et al. [26]</td>
<td>Capcitabine/paclitaxel</td>
<td>95</td>
<td>65</td>
<td>NR</td>
<td>33.1</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Capcitabine/docetaxel</td>
<td>91</td>
<td>74</td>
<td>NR</td>
<td>28.6</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Capcitabine → taxane</td>
<td>91</td>
<td>46f</td>
<td>NR</td>
<td>31.5</td>
<td>NR</td>
</tr>
<tr>
<td>Beslija et al. [27]</td>
<td>Capcitabine/docetaxel</td>
<td>50</td>
<td>68</td>
<td>9.3</td>
<td>22.0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Capcitabine → docetaxel</td>
<td>50</td>
<td>40</td>
<td>7.7</td>
<td>19.0</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Note:** ORR = objective response rate; OS = overall survival; median TTP and OS are presented as months unless otherwise stated.

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**Established Combinations—Taxane-based Chemotherapy**

While the principal focus of this review is the use of capecitabine together with newer molecularly targeted therapies, several studies with standard chemotherapies have helped to inform protocols employing the newer biological...
agents. Although evaluation of combinations of standard chemotherapeutic agents is continuing and wide ranging, with more than two dozen such trials ongoing [41], the present discussion reviews in detail only the completed pivotal trials for the established combination with docetaxel, together with some recent developments in taxane-based combination therapy. A list of other completed randomized trials evaluating capecitabine and chemotherapeutic agents in combination is presented in Table 1 [9, 21–27]. (For additional reviews of this topic, see O’Shaughnessy [2] and Fumoleau and Cameron [45].)

Currently, a regimen of capecitabine plus docetaxel is indicated for the treatment of patients with progressive metastatic breast cancer who have received prior treatment with anthracycline-based chemotherapy [11]. The pivotal trial leading to U.S. Food and Drug Administration approval of this regimen was a multinational, multicenter, open-label, randomized phase III study (Table 1) [9]. In all, 511 patients

### Table 2. Results of randomized controlled trials and phase II trials evaluating the efficacy of combination therapy with capecitabine and molecularly targeted agents in the treatment of locally advanced or metastatic breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n of patients</th>
<th>ORR (%)</th>
<th>Median TTP (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller et al. [28]</td>
<td>Capecitabine versus capecitabine/bevacizumab</td>
<td>230</td>
<td>9.1</td>
<td>4.17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>232</td>
<td>19.8</td>
<td>4.86</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;i&gt;p = .001&lt;/i&gt;</td>
<td></td>
</tr>
<tr>
<td>Geyer et al. [29]</td>
<td>Capecitabine versus capecitabine/lapatinib</td>
<td>161</td>
<td>14</td>
<td>4.4</td>
<td>NR–35 deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td>163</td>
<td>22</td>
<td>8.4</td>
<td>NR–36 deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;i&gt;p = .09&lt;/i&gt;</td>
<td>&lt;i&gt;p &lt; .001&lt;/i&gt;</td>
</tr>
<tr>
<td>Wardley et al. [30]</td>
<td>Trastuzumab/docetaxel versus trastuzumab/docetaxel/capecitabine</td>
<td>110</td>
<td>73</td>
<td>13.8</td>
<td>38.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>112</td>
<td>71</td>
<td>18.2</td>
<td>40.5</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;i&gt;p = .717&lt;/i&gt;</td>
<td>&lt;i&gt;p = .045&lt;/i&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;i&gt;p = .72&lt;/i&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Phase II trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schaller et al. [31, 32]</td>
<td>Capecitabine/trastuzumab</td>
<td>23</td>
<td>52</td>
<td>NR&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20.7</td>
</tr>
<tr>
<td>Yamamoto et al. [33]</td>
<td>Capecitabine/trastuzumab</td>
<td>27</td>
<td>41</td>
<td>5.2</td>
<td>16.1</td>
</tr>
<tr>
<td>Xu et al. [34]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Capecitabine/trastuzumab</td>
<td>43</td>
<td>63</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chew et al. [35]</td>
<td>Capecitabine/imatinib</td>
<td>19</td>
<td>21</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lybaert et al. [36]</td>
<td>Capecitabine/docetaxel/trastuzumab</td>
<td>25</td>
<td>100&lt;sup&gt;e&lt;/sup&gt;</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Miller et al. [37]</td>
<td>Capecitabine/bevacizumab (XCalibr)</td>
<td>103</td>
<td>34</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Perez et al. [38]</td>
<td>Capecitabine/docetaxel/bevacizumab</td>
<td>45</td>
<td>53</td>
<td>8.4</td>
<td>NR</td>
</tr>
<tr>
<td>Bunnell et al. [39]</td>
<td>Capecitabine/ixabepilone (BMS-247550)</td>
<td>50</td>
<td>30</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pusztai et al. [40]</td>
<td>Capecitabine/exisulind</td>
<td>31</td>
<td>16</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup> If response times were given in weeks in the original report, conversion to months was based on 1 month = 4.345 weeks.

<sup>b</sup> The principal endpoint, progression-free survival, was not met (4.17 months for capecitabine and 4.86 months for the combination; hazard ratio, 0.98).

<sup>c</sup> The median progression-free survival time was 6.4 months.

<sup>d</sup> Overall survival follow-up is ongoing, with further assessment to be made in 12 months.

<sup>e</sup> ORR was 91% in HER-2–negative patients (not given trastuzumab). Pathological complete response rates were 9 of 20 evaluable HER-2–positive patients (45%), who received all three drugs, and 4 of 46 evaluable HER-2–negative patients (9%), receiving capecitabine and docetaxel.

Abbreviations: HER-2, human epidermal growth factor receptor 2; NR, not reported; ORR, objective response rate; OS, overall survival; TTP, time to progression.
Table 3. Ongoing trials evaluating the efficacy of combination therapy with capecitabine and monoclonal antibody agents in the treatment of patients with locally advanced or metastatic breast cancer

<table>
<thead>
<tr>
<th>Agents</th>
<th>Trial design</th>
<th>Patient eligibility</th>
<th>Regimen</th>
<th>Trial identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine, docetaxel, trastuzumab</td>
<td>Phase II, neoadjuvant,</td>
<td>Newly diagnosed breast cancer; no metastatic disease except ipsilateral lymph nodes; no previous systemic or local primary treatment</td>
<td>HER-2–negative patients, capecitabine/docetaxel; HER-2–positive patients, capecitabine/docetaxel/trastuzumab</td>
<td>NCT00127933 (XeNA) [41]</td>
</tr>
<tr>
<td></td>
<td>stratified by HER-2 status,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>open label</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine, trastuzumab</td>
<td>Phase II</td>
<td>HER-2–positive metastatic disease refractory to taxanes and anthracyclines</td>
<td>Trastuzumab/capecitabine</td>
<td>NCT00107393 [41]</td>
</tr>
<tr>
<td>Capecitabine, trastuzumab</td>
<td>Phase III, randomized, active</td>
<td>HER-2–positive metastatic breast cancer having progressed after trastuzumab</td>
<td>Trastuzumab/capecitabine versus capecitabine alone</td>
<td>NCT00148876 [41]</td>
</tr>
<tr>
<td>Capecitabine, cyclophosphamide,</td>
<td>Phase III, randomized, active</td>
<td>Stage I–III primary breast cancer</td>
<td>Epirubicin/cyclophosphamide (4 cycles) followed by randomization to docetaxel (4 cycles), or</td>
<td>NCT00288002 [41]</td>
</tr>
<tr>
<td>docetaxel, epirubicin, trastuzumab</td>
<td>control</td>
<td></td>
<td>docetaxel/capcitabine (4 cycles), or docetaxel (1 cycle)/capcitabine (4 cycles); HER-2–positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>patients also receive trastuzumab throughout</td>
<td></td>
</tr>
<tr>
<td>Capecitabine, trastuzumab, vinorelbine</td>
<td>Phase II, randomized, active</td>
<td>Nonoperable locally advanced or metastatic HER-2–positive breast cancer; previous</td>
<td>Capcitabine/vinorelbine versus capcitabine/vinorelbine/trastuzumab as second-line therapy</td>
<td>NCT00130507 [41]</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>treatment with taxanes plus trastuzumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine, trastuzumab, vinorelbine</td>
<td>Phase II</td>
<td>HER-2–positive metastatic breast cancer; prior taxane or anthracycline adjuvant therapy or for metastatic disease</td>
<td>Capcitabine/vinorelbine/trastuzumab</td>
<td>NCT00093808 [41]</td>
</tr>
<tr>
<td>Capecitabine, paclitaxel,</td>
<td>Phase I/II, dose escalating</td>
<td>HER-2–positive metastatic breast cancer; no prior trastuzumab; no prior chemotherapy for metastatic disease</td>
<td>Capcitabine (dose-escalating)/paclitaxel/trastuzumab</td>
<td>NCT0006108 [41]</td>
</tr>
<tr>
<td>trastuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab, chemotherapy (capecitabine or</td>
<td>Phase III, randomized, placebo</td>
<td>HER-2–negative metastatic breast cancer; no prior chemotherapy for locally recurrent or metastatic disease; no adjuvant or neoadjuvant chemotherapy within the last 12 months</td>
<td>Chemotherapy (with capecitabine being option/bevacizumab versus chemotherapy/placebo</td>
<td>NCT00262067 [41] (RIBBON 1)</td>
</tr>
<tr>
<td>taxane or anthracycline)</td>
<td>control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab, chemotherapy (capecitabine or</td>
<td>Phase III, randomized, placebo</td>
<td>HER-2–negative metastatic breast cancer; progression of disease during or following</td>
<td>Chemotherapy (with capecitabine being option/bevacizumab versus chemotherapy/placebo</td>
<td>NCT00281697 [41] (RIBBON 2)</td>
</tr>
<tr>
<td>taxane or gemcitabine or vinorelbine)</td>
<td>control</td>
<td>one chemotherapy regimen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: HER-2, human epidermal growth factor receptor 2.
were randomized to 21-day cycles, receiving either capecitabine (1,250 mg/m² twice daily) on days 1–14 of each cycle plus i.v. docetaxel (75 mg/m²) on day 1 or i.v. docetaxel alone (100 mg/m²) on day 1 of each cycle.

The combined treatment was proven to be superior for the primary efficacy endpoint, time to disease progression (6.1 versus 4.2 months; \( p = .001 \)), as well as for secondary endpoints, including median survival (14.5 versus 11.5 months; \( p = .0126 \)) and tumor response rate (42% versus 30%; \( p = .006 \)). Median times to treatment failure also favored the combined group (4.0 versus 2.8 months; \( p = .0002 \)). Higher proportions of patients in the combined

**Table 4.** Ongoing trials of nonantibody novel agents in combination with capecitabine

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mode of action</th>
<th>Trial design</th>
<th>Primary inclusion criterion</th>
<th>Trial identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>Phase I, dose escalating</td>
<td>Metastatic breast cancer previously treated with taxanes and/or anthracyclines</td>
<td>Schmid et al. [42]</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Cyclooxygenase 2 inhibitor</td>
<td>Phase I, dose escalating</td>
<td>Metastatic breast cancer having progressed after at least 1 prior chemotherapy regimen</td>
<td>Fabi et al. [43]</td>
</tr>
<tr>
<td>GTI-2040</td>
<td>Antisense oligonucleotide against ribonucleotide reductase subunit mRNA</td>
<td>Phase II</td>
<td>Metastatic breast cancer having progressed after 1 or 2 prior chemotherapy regimens; no prior capcitabine or fluorouracil</td>
<td>NCT00068588 [41]</td>
</tr>
<tr>
<td>Indisulam (E7070)</td>
<td>Cell cycle inhibitor</td>
<td>Phase II randomized, active control</td>
<td>Metastatic breast cancer previously treated with a taxane and an anthracycline</td>
<td>NCT00165880 [41]</td>
</tr>
<tr>
<td>Ispinesib</td>
<td>Kinesin spindle protein inhibitor</td>
<td>Phase I dose escalating</td>
<td>Advanced solid tumors, including breast cancer, progressing on standard therapy or lacking standard therapy</td>
<td>NCT00119171 Calvo et al. [44]</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Microtubule stabilizing agent</td>
<td>Phase III, randomized, active control</td>
<td>Metastatic breast cancer previously treated with a taxane and an anthracycline</td>
<td>NCT00082433 [41]</td>
</tr>
<tr>
<td>Pegylated interferon-α2a</td>
<td>Pleiotropic cytokine</td>
<td>Phase II</td>
<td>Brain metastases secondary to breast cancer; no progressive systemic cancer</td>
<td>NCT00227656 [41]</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Immunomodulatory agent; antiangiogenic agent</td>
<td>Phase II</td>
<td>Metastatic breast cancer; maximum of 3 prior chemotherapeutic regimens in metastatic setting</td>
<td>NCT00193102 [41]</td>
</tr>
<tr>
<td>Tipifarnib (R115777)</td>
<td>Farnesyl transferase inhibitor</td>
<td>Phase Ib/II</td>
<td>Taxane-resistant metastatic breast cancer; prior anthracyline therapy; no prior capcitabine or fluorouracil</td>
<td>NCT00077363 [41]</td>
</tr>
<tr>
<td>Tipifarnib/docetaxel</td>
<td>Farnesyl transferase inhibitor/stabilizer of microtubules</td>
<td>Phase Ib/II neoadjuvant</td>
<td>Locally advanced or metastatic breast cancer or stage IIIA or IIIB disease; no prior capcitabine/docetaxel</td>
<td>NCT00070252 [41]</td>
</tr>
</tbody>
</table>
group suffered gastrointestinal side effects and hand–foot syndrome, while patients receiving docetaxel monotherapy were more likely to experience myalgia, arthralgia, and neutropenic fever/sepsis [9].

There have been several other trials employing varying dosing regimens and taxane combinations in the metastatic setting. Gradishar et al. [46] and Blum et al. [47] combined capecitabine with paclitaxel in small-scale phase II studies involving 47 and 55 patients, respectively; both trials used a lower dose of capecitabine (825 mg/m² twice daily for 2 weeks per 3-week cycle) together with paclitaxel dosed at 175 mg/m² on day 1 [46] or 80 mg/m² on days 1 and 8 [47]. In both trials, the treatment proved to be highly active, with objective response rates of 51% and 59%, respectively, together with favorable tolerability profiles. The lower capecitabine dose resulted in marked reductions in gastrointestinal complications over those seen in the pivotal trial [9].

Another recent study of capecitabine plus taxane therapy [22] (Table 1) has yielded favorable response rates in the neoadjuvant setting. In a phase III trial involving 204 patients, Lee et al. [22] demonstrated that the capecitabine–docetaxel combination (capecitabine, 1,000 mg/m² twice daily, and docetaxel, 75 mg/m², in a 3-week cycle) was superior to standard regimens of doxorubicin plus cyclophosphamide given preoperatively for locally advanced disease. The taxane–capecitabine combination resulted in an objective response rate of 84%, versus 67% for the standard regimen (p = .0047), and the pathological complete response rates were 23% versus 10%; comparable tolerability and quality-of-life assessments were seen for the two treatment regimens.

**Biological Response Modifiers**
The encouraging results of combinatorial approaches involving capecitabine and established chemotherapeutic regimens have prompted a variety of initiatives to examine the efficacy of capecitabine in combination with the newer biological response modifiers. These include the monoclonal antibody agents trastuzumab and bevacizumab as well as novel agents directed at molecular targets. Ideally, these studies would contain correlative tissue-based studies to identify the patients most likely to respond to combination therapy, as is now standard in establishing ER status and HER-2 expression levels. To date, however, the available tumor profile or host pharmacogenomic data do not permit making such assignments for treatments with pyrimidine antagonists [14, 48]. Accordingly, the identification of optimal partners for capecitabine will involve recourse to data from preclinical models as well as straightforward empiricism in the clinic.

Typically, preclinical studies evaluating drug effects on proliferation of cultured breast cancer cell lines are followed by assessment of tumor xenograft growth in immunocompromised mice. In addition to providing basic data regarding antiproliferative effects of different drugs, these investigations can provide valuable insights into the mode of action of given agents, the extent of crosstalk between molecular pathways under study, and the control of synthesis and degradation of key molecular constituents [49]. However, these models are not fully representative of human disease, because cell lines harbor distinct genetic and biochemical abnormalities not seen in human cancer, and the interactions between tumor and host cells are not mirrored fully. Recently, these approaches have been supplemented by large-scale analyses of tumor gene expression as in the previously described studies by Li et al. [20].

**Trastuzumab**
Trastuzumab, the monoclonal antibody against the HER-2 protein whose overexpression characterizes some 20%–25% of breast cancers, has been the most intensively studied in regard to its interactions with other agents in combination therapies. Pegram et al. [50, 51], following on earlier preclinical investigations with trastuzumab, doxorubicin, and cisplatin [52], conducted systematic examinations of combinations of various classes of cytotoxic drugs with trastuzumab. A range of interactions was observed, including synergy, straightforward additivity, and antagonism. Two of the fluoropyrimidine metabolites of capecitabine, 5-FU [50] and 5′-dFUrd [51], provided an example of antagonistic interactions, with the combination less potent on cultured cells than the individual agents. Tests on xenograft volume in inoculated mice also indicated that the combination of trastuzumab with 5-FU [50] or capecitabine [51, 52] did not produce additive effects. In contrast, Fujimoto-Ouchi et al. [53] reported paradoxical outcomes in their in vitro and in vivo studies. While they also observed antagonistic interactions between trastuzumab and either 5-FU or 5′-dFUrd, when examining the antiproliferative effect on HER-2–expressing breast cancer cell lines, the combination of trastuzumab with either capecitabine, 5′-dFUrd, or 5-FU led to highly potent synergy in depressing tumor growth, even reducing tumor volumes.

The reasons for the discrepancies in the findings on tumor volume are unclear, but may reflect differing administration regimens or experimental protocols as well as differences in the cellular models. Another possible rationale for a potential in vivo synergistic effect is the ability of antiangiogenic therapies to improve the delivery of cytotoxic agents by a mechanism that involves pruning and normalizing tumor vasculature [54]. These effects are not
restricted to therapies that are explicitly designed to be antiangiogenic, such as bevacizumab, but also are observed in response to trastuzumab [55], whose target, the HER-2 protein, is associated with elevated expression of vascular endothelial growth factor (VEGF) [56].

Irrespective of the equivocal nature of the preclinical studies, results of clinical trials examining the combination of trastuzumab and capcitabine have been very encouraging. Schaller et al. [31, 32] conducted a phase II study of 23 patients with HER-2–overexpressing metastatic breast cancer who had received extensive prior treatment with anthracyclines, taxanes, or both (Table 2) [28–40]. Patients were given an i.v. loading dose of 4 mg/kg trastuzumab followed by 2 mg/kg weekly while capcitabine was given at 1,250 mg/m² twice daily on days 1–14 on a 3-week cycle; treatment continued until disease progression. The treatment was proven to be active, with eight partial responses (35%), nine cases of stable disease (39%), and four complete remissions (17%) lasting for at least 3 years. Principal grade 3 and 4 adverse events were nausea and vomiting (12% each), general pain (28%), motor dysfunction (20%), and hand–foot syndrome (16%); there were two instances (8%) of grade 3 or 4 anemia and one each (4%) of leukopenia and thrombocytopenia. Qualitatively similar efficacy results, and a more favorable toxicity profile, were reported in another small phase II trial with 27 patients [33] who had received prior therapy for metastatic disease, using the same trastuzumab loading but a smaller capcitabine dosage (1,657 mg/m² per day from day 1–21 on a 4-week cycle). There were 11 partial responses (41%) and nine cases of stable disease (33%). The median time to progression was 5.2 months, and overall survival was 16.1 months. There were no reports of grade 3 or higher adverse events (Table 2).

Using the same treatment regimen, Xu et al. [34] reported early results on the first 43 evaluable patients of an ongoing phase II study (Table 2), with five complete responses (12%), 22 partial responses (51%), and 10 cases of stable disease (23%) observed. Safety outcomes were excellent, with no grade 4 toxicities, four cases of grade 3 hand–foot syndrome, and one case of leukopenia; there were no cases of cardiac dysfunction, or of grades 3 and 4 diarrhea or vomiting. If these efficacy and toxicity data are maintained in appropriately powered phase III trials, the capcitabine–trastuzumab combination could provide an attractive option as first-line metastatic therapy in HER-2–positive disease with minimal expected cardiotoxicity.

In another combinatorial regimen, Wardley et al. [30] assessed the efficacy of trastuzumab and docetaxel, with or without capcitabine, in treating HER-2–positive locally advanced or metastatic breast cancer. While overall response rates were virtually identical between the two treatment arms (71% and 73%, with and without capcitabine, n = 112 and 110, respectively), the median time to progression was significantly longer with the inclusion of capcitabine (18.2 versus 13.8 months; p = .045), and the median progression-free survival time was also longer, with the difference almost reaching significance (14.8 versus 12.8 months; p = .060). Side effects were tolerable, with hand–foot syndrome (16%), diarrhea (11%), and vomiting (5%) being the principal grade 3 or 4 toxicities that increased with the addition of capcitabine.

These encouraging results in advanced disease have prompted a trial to employ the capcitabine–trastuzumab combination in the neoadjuvant setting. The ongoing XeNA trial (Table 3; [41]), projected to recruit approximately 140 patients, is an open-label study to establish the rate of pathological complete response in the primary tumor at the time of definitive surgery. Four cycles of capcitabine and docetaxel will be administered to HER-2–negative patients, with trastuzumab added for patients whose tumors are HER-2–positive and therapy continued for 1 year. Secondary objectives include assessments of overall clinical response, local recurrence, and disease-free and overall survival, as well as toxicity profiles. Blood and tumor samples also will be taken to establish whether the presence of specific tumor molecular indices and germline pharmacogenomic markers can be correlated with the frequency of pathological complete responses and toxicities, respectively. This trial allows additional postoperative chemotherapy at the discretion of the patient and physician, but a response rate of >20% may provide a basis for more definitive trials using a much briefer and well-tolerated regimen than the 16- to 24-week prevailing therapies. Also, the potential for a minimally cardiotoxic trastuzumab-based regimen for HER-2–positive disease is attractive. A number of other similar studies examining the use of trastuzumab and capcitabine as part of various combinatorial regimens, many with standard chemotherapeutic agents such as epirubicin, docetaxel, vinorelbine, paclitaxel, and oxaliplatin (Table 3) [41], are under way.

**Bevacizumab**

Several studies have reported that the extent of breast tumor vascularization is associated with unfavorable disease parameters, including the likelihood of metastasis [57] and survival [58]. (For a review see Schneider and Miller [59].)

However, a phase II trial with i.v. bevacizumab, the anti-VEGF monoclonal antibody already used as part of chemotherapy regimens for colorectal cancer, revealed limited activity as monotherapy for metastatic breast cancer, with
an overall response rate of 9.3% in previously treated patients [60].

In a phase III combination trial with capecitabine involving 462 patients, Miller et al. [28] compared capecitabine alone with capecitabine plus bevacizumab (Table 2). These patients were heavily pretreated, having received one or two prior chemotherapeutic regimens for metastatic disease. Capecitabine was given at 1,250 mg/m² twice daily on days 1–14 of a 3-week cycle, alone or accompanied by 15 mg/kg bevacizumab on day 1. Therapy continued for a maximum of 35 cycles or until unacceptable toxicities were experienced.

The combination regimen produced a significantly greater response rate (19.8% versus 9.1%; p = .001), but did not affect the primary endpoint of progression-free survival (4.86 versus 4.17 months, hazard ratio = 0.98) or overall survival (15.1 versus 14.5 months). The tolerability was good, with grade 3 hypertension being the only adverse event occurring at a significantly greater frequency with the addition of bevacizumab (17.9% versus 0.5%) [28].

However, the results were more promising in the first-line E2100 trial involving 680 patients that compared paclitaxel alone with paclitaxel plus bevacizumab for locally recurrent or metastatic breast cancer [61]. Patients were randomly assigned to receive paclitaxel (90 mg/m²) on days 1, 8, and 15 every 4 weeks alone or in combination with bevacizumab (10 mg/kg) on days 1 and 8. The overall response rate was dramatically higher in the bevacizumab arm (29.9% versus 13.8% for all patients, p < .0001, and 37.7% versus 16% for those with measurable disease, p < .0001), and progression-free survival was impressively longer (11.4 versus 6.11 months; p < .0001). Hypertension, proteinuria, and neuropathy were among the adverse events that were observed more frequently in the combined therapy arm.

The reasons for the difference in response to the combinations of capecitabine with bevacizumab and paclitaxel are unclear. Several factors may have contributed to the failure to meet the designated endpoint with bevacizumab. First, it is not yet possible to use molecular markers to identify those patients who are most likely to respond to bevacizumab treatment, in the manner now well established for trastuzumab; in fact, it is still unclear as to whether the principal cellular targets for bevacizumab are endothelial cells, tumor cells, or both [28, 62]. This lack of definition extends even to the molecular species targeted by bevacizumab. Bates et al. [63] and Woolard et al. [64] have identified an entire nonangiogenic VEGF family whose members act as competitive inhibitors of the proangiogenic isoforms; because these inhibitory isoforms are also bound by bevacizumab [65], the impact of bevacizumab therapy may well depend on the particular VEGF isoform profile of a given tumor. Additionally, breast cancer tumors express a plethora of angiogenic factors [66], and the biology of angiogenesis may change over time as tumors progress. Finally, the low number of responders typical of any late-line therapy trial makes it difficult to detect an overall improvement in the primary endpoint of time to progression, yet this trial did show a nearly doubling of the response rate. Thus, it is possible that earlier intervention with antiangiogenic drugs could be more effective.

Based on a similar premise, the ongoing XCalibr trial will assess the effect of adding bevacizumab (15 mg/kg on day 1) to capecitabine (1,000 mg/m² on days 1–14) as first-line therapy for metastatic breast cancer, essentially the same group of patients as in the E2100 trial. Patients will be allowed to continue bevacizumab after initial progression, either with vinorelbine or paclitaxel, at the discretion of patients and investigators (Table 2). Interim safety and efficacy data for the XCalibr trial have recently been presented [61]. With a mean duration of 6.1 months of follow-up of 103 patients who had received at least one dose of bevacizumab plus capecitabine, the overall response rate was 34%, with another 38% showing stable disease. To date the combination treatment has been well tolerated, with hand–foot syndrome (13%) and pain (10%) being the most common grade 3 adverse events; the only grade 4 events were two cases of pulmonary embolism.

In another phase II trial of first-line chemotherapy for metastatic disease, Perez et al. [38] evaluated the combination of bevacizumab, docetaxel, and capecitabine in 45 patients, with a median follow-up of 7.5 months. The overall response rate was 53%, while the progression-free survival and overall survival rates at 6 months were 74% and 95%, respectively. The median time to progression was 8.4 months. However, dose reductions or holds were frequent for both capecitabine and docetaxel, and the authors state that continuation of this regimen would require growth factor supplementation to maintain dose intensity.

Finally, two other randomized, placebo-controlled phase III trials, designated RIBBON 1 [41] and RIBBON 2 [41], are currently recruiting, with accrual targets of 1,050 and 630 patients, respectively. In the RIBBON 1 trial, patients will be randomized to receive either chemotherapy plus placebo or chemotherapy plus bevacizumab given as first-line therapy; after disease progression, patients will continue on the initial regimen, with the exception that chemotherapy will be administered at the investigator’s discretion, and patients who have not received bevacizumab will have the option of crossing over to the bevacizumab arm. In the RIBBON 2 trial, patients who have progressed after first-line chemotherapy will be randomized to receive a tax-
ane, gemcitabine, vinorelbine, or capecitabine, together with bevacizumab; in the control arm, bevacizumab will be replaced by a placebo. These and other ongoing trials are summarized in Table 3 [41].

**Novel Molecularly Targeted Agents**
A variety of new agents is currently being evaluated in combination with capecitabine, the majority in phase I or phase II trials along with one important phase III trial for which early results recently have been reported (Tables 2 and 4) [28–40, 41–44]. All of the trials are open label, and most are ongoing or in the process of data analysis; each is discussed briefly below, with an outline of supporting preclinical data and preliminary results where available.

**Lapatinib**
Lapatinib is a small-molecule, reversible inhibitor of the intracellular tyrosine kinase domain of two members of the HER family, HER-1 (epidermal growth factor receptor) and HER-2 [67]. Preclinical studies have shown that some HER-2–positive breast cancer cell lines that are resistant to trastuzumab are sensitive to lapatinib [68]. Lapatinib is being investigated in clinical trials involving a variety of cancers [67, 69].

Very encouraging results have been released comparing the combination of lapatinib plus capecitabine with capecitabine alone in a phase III trial of HER-2–positive metastatic breast cancer patients whose cancers had not responded to trastuzumab or to other therapies (Table 2) [29]. An interim analysis of 324 patients revealed that the primary endpoint, a 50% increase in median time to progression, had been achieved, crossing the statistical significance threshold for early reporting (8.4 months in the combined group versus 4.4 months in patients receiving capecitabine alone; \( p < .001 \)). The incidence of central nervous system metastases was also lower in the combined group (2.5% versus 6.8%), although this difference did not reach statistical significance (\( p = .10 \)). Toxicity profiles were similar in the two groups. Trial enrollment has been halted, and all participants in the capecitabine-alone arm are being offered the option of crossing over to the combined regimen.

**Imatinib**
Imatinib is active against several tyrosine kinases, including the Abelson gene (ABL), ABL-related fusion gene product, c-kit, and the platelet-derived growth factor receptor (PDGFR) [70], and is used in treating chronic myeloid leukemia. In breast cancer, one likely focus of potential imatinib action is PDGFR-α, as overexpression of this receptor has been associated with tumor progression [71]. Moreover, although c-kit is downregulated in some invasive breast cancers, it is correlated with high tumor grade and aggressivity in those tumors that express it [72]. A trial of imatinib monotherapy in heavily pretreated patients showed little activity [73]. Also, in a phase II trial of patients with metastatic breast cancer who had progressed on previous therapy, the combination of imatinib and capecitabine was well tolerated, but the response rate of 21% (4/19 evaluable patients) was not superior to previous experience with single-agent capecitabine. Studies are continuing to assess whether or not clinical benefits can be correlated with the expression of c-kit, PDGFR, or ER (Table 2) [35].

**Tipifarnib**
Tipifarnib is an orally administered inhibitor of the enzyme farnesyl transferase whose function is important in the Ras signal induction pathway as well as in other intracellular signaling processes [74, 75]. Preclinical studies have shown growth inhibitory effects on breast cancer cell lines, including synergistic effects in combination with paclitaxel [76] and tamoxifen [77], while clinical activity has been reported in metastatic breast cancer when used as monotherapy [78] or in combinations with tamoxifen [79] or doxorubicin plus cyclophosphamide [80]. Currently, the efficacy of combining tipifarnib with capecitabine in pretreated patients with metastatic breast cancer, and as neoadjuvant therapy in a combination with docetaxel in locally advanced metastatic disease, is being evaluated (Table 4).

**GTI-2040**
GTI-2040 is a 20-base phosphorothioate oligonucleotide that is complementary to a coding region in the mRNA of the R2 small subunit component of human ribonucleotide reductase [81]. Preclinical studies have demonstrated that GTI-2040 inhibits the growth of a variety of cancer cell lines and tumors in breast cancer models; it also has been shown to reduce metastasis of melanoma to the lungs [81]. A trial examining its use together with capecitabine in heavily pretreated metastatic breast cancer patients is under way (Table 4).

**Pegylated Interferon-α2a**
Interferon-α2a is a multifunctional cytokine; addition of a 40-kDa polyethylene glycol moiety greatly improves its pharmacological properties. It has been proven to be effective in preclinical models, leading to significant inhibition of melanoma cell lines and tumor growth in mice [82], with concomitant impacts on the expression of dozens of genes [82, 83]. In addition, it has shown activity in treating can-
cers such as chronic myelogenous leukemia [84] and metastatic melanoma [85]. In a current trial, pegylated interferon α-2a is being employed in combination with capecitabine for the treatment of brain metastases secondary to breast cancer (Table 4).

**Ispinesib**

Ispinesib (SB-715992) is a kinesin spindle protein inhibitor. Kinesin spindle proteins are essential in mediating centrosome separation and formation of the bipolar mitotic spindle during mitosis [45, 86, 87]. Ispinesib inhibits growth and causes major changes in gene expression in prostate cancer cells in vitro [87]. An ongoing phase I study (Table 4) [41–44] is examining its use in conjunction with capecitabine in the treatment of intractable solid tumors, including breast cancer. Experiments involving tumor xenografts in mice, carried out as part of this study, showed that the combined administration of capecitabine and ispinesib led to greater inhibition than with either agent given alone [45]. Preliminary findings from the trial indicate that the combination has an acceptable tolerability profile, and 8 of 16 patients experienced stable disease for 2–6.5 months [45].

**Bortezomib**

Bortezomib is a first-in-class inhibitor of the proteasome, an intracellular organelle whose proteolytic functions are essential for maintaining cellular homeostasis [88]. Because the actions of several proteins that inhibit cell survival and cell cycling are mediated by proteasomal degradation, drugs such as bortezomib have pleiotropic antineoplastic effects. Currently, bortezomib is indicated in the treatment of multiple myeloma [88], although it has been found to have limited activity as a single agent in refractory breast cancer [89]. Preliminary results from a phase I trial of its use together with capecitabine in metastatic breast cancer suggest that an acceptable tolerability profile could be achieved at doses with moderate antitumor activity in heavily pretreated patients, with 2 of 17 (12%) patients demonstrating partial responses and 5 of 17 (29%) having stable disease (Table 4).

**Indisulam**

The sulfonamide indisulam (E7070) inhibits cell-cycle progression, although its precise molecular target is unclear. Some identified effects include induced expression of the tumor suppressor gene p53, inhibition of phosphorylation of the tumor suppressor retinoblastoma protein (Rb), and reduced expression of cyclins and cyclin-dependent kinases [90]; recently, it has also been found to inhibit carbonic anhydrase IX [91], a hypoxia-inducible protein associated with a poor outcome in several cancer types [92, 93]. As monotherapy, indisulam has been shown to have moderate activity in a phase II trial (6 of 15 evaluable patients with stable disease) [94]. A trial comparing the combination of E7070 and capecitabine with capecitabine alone in heavily pretreated metastatic breast cancer (Table 4) is ongoing.

**Epothilones**

The epothilones, originally identified as macrolide fungi- cides isolated from the myxobacterium Sorangium cellulo- sum [95], have been found to act as microtubule-stabilizing agents in a manner similar to taxanes [96]. Some of these agents have the advantage that they are not multiple drug resistance efflux pump substrates [96] and also can penetrate the blood–brain barrier [97, 98]. The epothilones have been shown to inhibit the growth of cancer cell lines and tumor xenografts, and the epothilone BMS247550 (ixabepilone) has also been shown to have activity in several phase I and phase II trials, including those involving patients with metastatic breast cancer [96]. Recently, in a phase I/II study in patients previously treated with an anthracycline and a taxane, Bunnell et al. [39] examined the effects of combined ixabepilone/capecitabine therapy (Table 2). Two dosing regimens for ixabepilone were employed, either a single 3-hour infusion on day 1 or 1-hour infusions given on three successive days. Capecitabine was administered on days 1–14 of the 21-day cycle. Of 50 evaluable patients receiving the 3-hour infusion, the overall response rate was 30%, with a median response duration of 6.9 months. Currently, an ongoing, large, phase III study aiming at an enrollment of 1,200 patients is comparing the combination of BMS247550 plus capecitabine with capecitabine alone in the treatment of metastatic breast cancer in patients having received prior taxane and anthracycline chemotherapy (Table 4).

**Thalidomide**

Thalidomide is an oral drug with antiangiogenic, immunomodulatory, and other properties believed to underlie its activity in treating myeloma [99]; it has been evaluated for activity against prostate cancer [100]. Previous trials of thalidomide as monotherapy against heavily pretreated metastatic breast cancer patients showed little or no activity [101, 102]. An ongoing trial in combination with capecitabine, involving patients with no more than three regimens of previous therapy, is based on the premise that the nonoverlapping mechanisms of action between the two drugs may lead to a more effective regimen (Table 4).
**Celecoxib**

Celecoxib is an inhibitor of cyclooxygenase 2 (COX-2), an enzyme whose expression is associated with several cancers, including breast cancer. Preclinical data indicate that COX-2 inhibition can suppress tumor growth [103], and epidemiological studies indicate that exposure to COX-2 inhibitors is associated with a reduction in the risk for breast cancer [104]. Fabi et al. [43] have reported on a pilot study of combined capecitabine–celecoxib therapy in patients pretreated with anthracyclines and/or taxanes. Toxicity was negligible, and of 20 patients evaluable for response, there were two partial responses and 15 cases of stable disease (Table 4).

**Exisulind**

Exisulind is a metabolite of sulindac, a nonsteroidal anti-inflammatory drug that promotes apoptosis by inhibiting cyclic guanosine monophosphate phosphodiesterases [40]. In a phase I/II study involving 35 heavily pretreated patients with metastatic breast cancer, exisulind was given orally in combination with capecitabine for 14 days of each 21-day cycle (Table 2). The combination was well tolerated and the response rate was 16%, the same magnitude as with capecitabine alone in this patient population [40].

**CONCLUSIONS**

The interest in employing capecitabine together with other agents suggests that we may expect that there will not only be a range of new combinations being evaluated but also further refinements of promising combinations. An area of particular relevance likely to inform these studies is the application of cancer genomics and pharmacogenomics to better select patients most likely to respond to capecitabine and biological combination therapies. Pharmacogenomic data from clinical trials should aid in these determinations; the ongoing XeNA trial, for example (see above), includes such sampling as part of its protocol.

Although biologically targeted agents have shown encouraging activity against breast cancer, responses have typically been seen in only a fraction of patients, with very limited activity in the setting of heavy pretreatment. Given the multiplicity of molecular and cellular aberrations exhibited by most tumors, it is not surprising that intrinsic or acquired resistance is often seen with single-agent therapies. Future success is critically dependent on developing combination therapies that provide quantum leaps in clinical effectiveness. Capecitabine affects multiple pathways by affecting DNA and RNA synthesis and, in turn, activating several cellular pathways involved in the cell cycle, apoptosis, and DNA repair. As an active drug in its own right, combinations of capecitabine with novel targeted agents merit further study and are already showing potential with drugs such as trastuzumab and lapatinib. Given the limitations of preclinical models, a strategy of integrated laboratory, clinical, and correlative studies holds the best promise for the next generation of combinatorial regimens tailored to individuals based on tumor and host characteristics.

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**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

D.T. has acted as a consultant for Roche and Genentech and has performed contract work for Roche, Genentech, AstraZeneca, and GlaxoSmithKline.

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