Use of the gemcitabine (Gemzar) plus docetaxel (Taxotere) combination in metastatic breast cancer is motivated by the different mechanisms of action of the drugs, partially nonoverlapping toxicity profiles, and good single-agent activities of both drugs in treatment-naive and anthracycline-pretreated patients. In phase II trials, combinations of gemcitabine at 900 or 1,000 mg/m² on days 1 and 8 and docetaxel at 75 to 100 mg/m² on either day 1 or day 8 every 3 weeks, or gemcitabine at 800 mg/m² on days 1, 8, and 15 and docetaxel at 35 mg/m² on days 1, 8, and 15 or 100 mg/m² on day 1 every 4 weeks, have produced response rates of 36% to 79% in patients receiving primarily second-line treatment; response rates were greater than 50% in five of six studies. In phase II trials using every-2-week regimens of gemcitabine at 1,500 or 2,000 mg/m² on day 1 and docetaxel at 50 or 65 mg/m² on day 1 or 55 mg/m² on day 8, response rates were 50% in pretreated patients and 66% in treatment-naive patients. Neutropenia is the primary toxicity of the combination; in phase II studies performed with or without growth factor support, rates of grade 3/4 neutropenia ranged from 29% to 79% and rates of febrile neutropenia ranged from 0% to 18%. An ongoing phase III trial is comparing gemcitabine at 1,000 mg/m² on days 1 and 8 plus docetaxel at 75 mg/m² on day 1 every 21 days, vs capecitabine at 1,000 mg/m² twice daily for 14 days plus docetaxel at 75 mg/m² on day 1 every 21 days in patients with metastatic breast cancer. Results of this trial will help to determine optimal use of taxane-based combinations in patients with advanced disease. Several factors provide the rationale for combining gemcitabine (Gemzar) with docetaxel (Taxotere) in metastatic breast cancer. Use of the gemcitabine/docetaxel combination for treatment of metastatic breast cancer is supported by the different mechanisms of action of the two drugs, partially nonoverlapping toxicity profiles, and high single-agent response rates in this setting. Results of phase II trials investigating this combination have encouraged performance of a phase III trial comparing gemcitabine/docetaxel with capecitabine (Xeloda)/docetaxel in previously untreated and pretreated patients with metastatic breast cancer. There has been some concern, however, about hematologic toxicity, primarily neutropenia, which is a common toxicity of both drugs. This concern has prompted evaluation of different doses and schedules of the combination. Single-agent docetaxel has produced response rates of 40% to 68% as first-line treatment and 30% to 42% in anthracycline-pretreated patients with metastatic breast cancer,[1-3] with comparative data indicating clinical effectiveness at least comparable to that of doxorubicin.[4] Response rates with single-agent gemcitabine treatment have ranged from 14% to 42%[5,6] and from 18% to 23% in anthracycline- and taxane-refractory disease.[7-9] At the 2004 meeting of the American Society of Clinical Oncology (ASCO), Albain et al reported the initial findings of overall survival in an international phase III study (JHQG study; n = 529) of gemcitabine plus paclitaxel vs paclitaxel as front-line therapy for metastatic breast cancer.[ 10] Patients received either paclitaxel at 175 mg/m² in a 3-hour infusion followed by gemcitabine at 1,250 mg/m² given over 30 minutes on days 1 and 8 or paclitaxel at 175 mg/m² on day 1 every 3 weeks.
The overall survival hazard ratio (HR) was 0.775, significantly in favor of gemcitabine plus paclitaxel (P = .018), with median overall survival increased in patients in the gemcitabine plus paclitaxel arm (18.5 vs 15.8 months). One-year survival was significantly increased for the gemcitabine plus paclitaxel arm (70.7% vs 60.9%; P = .019). The HR in favor of gemcitabine plus paclitaxel persisted in Cox regression after adjusting for baseline covariates: 0.740 (P = .006). Thirty-eight percent of patients receiving gemcitabine plus paclitaxel stopped therapy due to disease progression, compared with 55% on paclitaxel; therapy ended due to adverse events in 6.7% of patients in the gemcitabine plus paclitaxel arm vs 5.0% of those receiving paclitaxel.[10] These data demonstrate the superiority of the gemcitabine plus paclitaxel regimen over paclitaxel and also bolster significantly the rationale for the use of docetaxel plus gemcitabine. This trial did not compare the sequential use of these two agents to the combination. Phase II Studies of Gemcitabine/Docetaxel Phase II studies of the gemcitabine/ docetaxel combination have included six trials in which gemcitabine was administered.

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Gemcitabine Dose (mg/m²)</th>
<th>Docetaxel Dose (mg/m²)</th>
<th>G-CSF</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavroudik[12] 1999</td>
<td>52</td>
<td>900 d 1, 8</td>
<td>100 d 8</td>
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<td>54%</td>
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<tr>
<td>Fountzilas[11] 2000</td>
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<td>1,000 d 1, 8</td>
<td>75 d 1</td>
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<td>36%</td>
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<tr>
<td>Brandl[13] 2001</td>
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<td>1,000 d 1, 8</td>
<td>80 d 8</td>
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<tr>
<td>Laufman[14] 2001</td>
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<td>800 d 1, 8, 15</td>
<td>100 d 1</td>
<td>Yes</td>
<td>79%</td>
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<tr>
<td>Brugnatelli[15] 2002</td>
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<td>800 d 1, 8, 15</td>
<td>35 d 1, 8, 15</td>
<td>No</td>
<td>58%</td>
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<tr>
<td>Lenz[16] 2003</td>
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<td>1,000 d 1, 8</td>
<td>75 d 1</td>
<td>No</td>
<td>54%</td>
</tr>
</tbody>
</table>

G-CSF = granulocyte colony-stimulating factor.

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Gemcitabine Dose (mg/m²)</th>
<th>Docetaxel Dose (mg/m²)</th>
<th>G-CSF</th>
<th>Response Rate</th>
</tr>
</thead>
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<td><strong>Second-Line Treatment</strong></td>
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<tr>
<td>Ishmael[17] 2001</td>
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<td>2,000 d 1</td>
<td>55 d 8</td>
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<tr>
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<td>1,500 d 1</td>
<td>50 d 1</td>
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<td>43%</td>
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<td><strong>First-Line Treatment</strong></td>
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<td>38</td>
<td>1,500 d 1</td>
<td>50 d 1</td>
<td>Yes</td>
<td>60%</td>
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<tr>
<td>Pelegri[19] 2001 [20] In press</td>
<td>48</td>
<td>2,000 d 1</td>
<td>65 d 1</td>
<td>No</td>
<td>71%</td>
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</tbody>
</table>

G-CSF = granulocyte colony-stimulating factor.

The overall survival hazard ratio (HR) was 0.775, significantly in favor of gemcitabine plus paclitaxel (P = .018), with median overall survival increased in patients in the gemcitabine plus paclitaxel arm (18.5 vs 15.8 months). One-year survival was significantly increased for the gemcitabine plus paclitaxel arm (70.7% vs 60.9%; P = .019). The HR in favor of gemcitabine plus paclitaxel persisted in Cox regression after adjusting for baseline covariates: 0.740 (P = .006). Thirty-eight percent of patients receiving gemcitabine plus paclitaxel stopped therapy due to disease progression, compared with 55% on paclitaxel; therapy ended due to adverse events in 6.7% of patients in the gemcitabine plus paclitaxel arm vs 5.0% of those receiving paclitaxel.[10] These data demonstrate the superiority of the gemcitabine plus paclitaxel regimen over paclitaxel and also bolster significantly the rationale for the use of docetaxel plus gemcitabine. This trial did not compare the sequential use of these two agents to the combination. Phase II Studies of Gemcitabine/Docetaxel Phase II studies of the gemcitabine/ docetaxel combination have included six trials in which gemcitabine was administered.
on days 1 and 8 every 3 weeks or days 1, 8, and 15 every 4 weeks[11-16] and three trials in which
gemcitabine was given every 14 days.[17-20] Findings from the trials using 3- or 4-week schedules
are summarized in Table 1.[11-16] Most patients in these studies were receiving second-line or
subsequent treatment, and most had received previous anthracycline treatment. In the
every-3-week regimens, gemcitabine doses were 900 or 1,000 mg/m² on days 1 and 8, and
docetaxel doses were 75 to 100 mg/m² on either day 1 or day 8. In the every-4-week regimens,
gemcitabine doses were 800 mg/m² on days 1, 8, and 15, and the docetaxel dose was 35 mg/m² on
days 1, 8, and 15 or 100 mg/m² on day 1. Some of the studies employed routine granulocyte
colony-stimulating factor (G-CSF [Neupogen]) support. Response rates ranged from 36% to 79% and
were greater than 50% in five of the six trials. In the second-line setting, there was a 51% overall
response rate (107 of 207 total patients). Table 2 shows findings from three trials using an
every-2-week administration schedule of gemcitabine/docetaxel in the first-line or second-line and
subsequent settings.[17-20] Dos- es consisted of 1,500 to 2,000 mg/m² of gemcitabine on day 1 and
50 or 65 mg/m² of docetaxel on day 1 or 55 mg/m² on day 8. Response rates with the combination
as second-line or subsequent treatment were 43% and 57%, and response rates as first-line
treatment were 60% and 71%. Overall, response rates on an every-2-week schedule were 50% (14 of
28) in pretreated patients and 66% (57 of 86) in patients receiving first-line treatment. Notably, the
trial reported by Pelegr et al[19,20] did not include routine G-CSF support. An interim report on the
first 32 evaluable patients showed an objective response rate of 66%, including a complete response
in 12.5% of patients. These patients had received a median of 10 treatment cycles, with 91% of
treatment being delivered as planned. Despite the absence of G-CSF, grade 3/4 neutropenia
occurred in only 46% and febrile neutropenia in 6% of patients. Grade 3/4 toxicities in seven trials
examining the gemcitabine/docetaxel combination using various doses and schedules are shown in
Table 3.[11-14,16,18-20] Rates of neutropenia ranged from 29% to 79%, and rates of grade 3/4
febrile neutropenia ranged from 0% to 18%. Grade 3/4 thrombocytopenia was seen in 0% to 21% of
patients; most studies with available data showed low rates of this effect. In summary, the
gemcitabine/docetaxel combination has been evaluated in phase II trials involving nearly 300
patients. Efficacy has been promising in patients receiving first-line treatment and in pretreated
patients. The predominant toxicities with the combination are hematologic effects, the frequency
and severity of which may be modifiable through altering the dose and schedule and use of growth
factor support.

Phase III

**Trial: Gemcitabine/Docetaxel vs Capecitabine/Docetaxel** In a recent phase III trial reported by O'Shaughnessy et al.[21] 511 anthracycline-pretreated patients with metastatic breast cancer received oral capecitabine at 1,250 mg/m² twice daily for 14 days plus docetaxel at 75 mg/m² on day 1 every 3 weeks or docetaxel alone at 100 mg/m² every 3 weeks. The capecitabine/docetaxel doublet...
was associated with a significantly higher objective response rate (42% vs 30%) and significant improvements in median overall survival (14.5 vs 11.5 months) and 1-year survival rates (57% vs 47%). Analyses of delivered treatment indicated that early in the trial, capecitabine doses were reduced to approximately 1,000 mg/m$^2$ twice daily due to poor tolerability (diarrhea and hand-foot syndrome) and were maintained at that level throughout treatment. These results suggest that the capecitabine/docetaxel combination should be considered a standard of treatment in the setting of metastatic breast cancer. Accordingly, we have designed and instituted a phase III trial comparing gemcitabine/docetaxel and capecitabine/docetaxel in patients with metastatic breast cancer (study B9EUS-S188). Accrued patients consist of chemotherapy-naive patients and patients who have received one or two previous chemotherapy courses. Stratification at baseline is based on first- and second-line or second- and third-line treatment of metastatic breast cancer, including anthracycline adjuvant therapy as a stratifying criterion. A target population of 442 patients is being randomly assigned to receive gemcitabine at 1,000 mg/m$^2$ on days 1 and 8 plus docetaxel at 75 mg/m$^2$ on day 1 every 21 days or oral capecitabine at 1,000 mg/m$^2$ twice daily for 14 days plus docetaxel at 75 mg/m$^2$ on day 1 every 21 days (Figure 1). Patients are allowed to receive G-CSF support, but it is not a requirement. When disease progression or intolerable toxicity occurs, patients are designated by protocol design to cross over in a balanced fashion from the assigned treatment arm to the alternate single-agent therapy with capecitabine at 1,000 mg/m$^2$ twice daily for 14 days every 3 weeks or gemcitabine at 1,000 mg/m$^2$ on days 1 and 8 every 3 weeks. The target population provides 80% power to detect (with type I error rate $\alpha = 0.05$) a 2-month difference in time to disease progression. In addition to time to disease progression, study outcome measures include response rate, overall survival, and quality of life as assessed by the Rotterdam Symptom Checklist. Results of this trial will help to identify optimal taxane-based combination therapy and to define further the role of gemcitabine in combination treatment in metastatic breast cancer. Summary The rationale for using gemcitabine and docetaxel combinations in metastatic breast cancer consists of good single-agent activity of both agents in treatment-naive and anthracycline-pretreated patients, different mechanisms of action, and partially nonoverlapping toxicity profiles. Phase II trials of this combination given every 3 or 4 weeks, primarily in patients receiving second-line treatment, have resulted in response rates of 36% to 79%. In phase II trials using every-2-week regimens of gemcitabine and docetaxel, response rates were 50% in pretreated patients and 66% in treatment-naive patients. Currently, a phase III trial is comparing the gemcitabine plus docetaxel combination administered every 3 weeks and the capecitabine (2 weeks on, 1 week off) plus docetaxel combination given every 3 weeks to patients with metastatic breast cancer. Data from this trial may help to define further the role of taxane-based combinations in breast cancer patients with advanced disease.

Disclosures:
Dr. Seidman has been a member of the speakers' bureau for, received honoraria from, and consulted for Aventis, Eli Lilly, Amgen, and Genentech. He has consulted for Ortho, and has been a member of the speakers' bureau for/received honoraria from Bristol-Myers Squibb, Novartis, and Pfizer.

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