Ixabepilone plus capecitabine in advanced breast cancer patients with early relapse after adjuvant anthracyclines and taxanes: A pooled subset analysis of two phase III studies

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Abstract
Background: Metastatic breast cancer (MBC) patients with rapid disease relapse after neo/adjuvant chemotherapy including anthracyclines and taxanes have limited treatment options and their efficacy is marginal. Two phase III studies compared ixabepilone plus capecitabine vs. capecitabine alone as first-line treatment in MBC patients pretreated with anthracyclines and taxanes in the neo/adjuvant setting. Here we report the efficacy and safety of these treatments in a prespecified subset of patients whose disease relapsed within 12 months.

Patients and methods: Of 1973 patients across two studies, 293 relapsed within 12 months of neo/adjuvant treatment and received ixabepilone plus capecitabine (n = 149) or capecitabine alone (n = 144) as first-line chemotherapy for MBC. Analysis included progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and toxicity.

Results: In 293 patients, ixabepilone plus capecitabine, as compared to capecitabine alone, increased PFS (median: 5.6 months vs. 2.8 months; hazard ratio, 0.58; p < 0.0001), ORR (46% vs. 24%) and OS (median: 15.1 months vs. 12.5 months; hazard ratio, 0.84; p = 0.208). Major toxicities of this regimen included neuropathy, neutropenia and hand-foot syndrome, but were manageable.

Conclusions: Patients with breast cancer with early relapse following neo/adjuvant treatment with anthracyclines and taxanes may benefit from ixabepilone plus capecitabine. (ClinicalTrials.gov identifiers: NCT00080301 and NCT00082433.)

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Introduction

Breast cancer is the most common cancer among women with 1.4 million new cases and 458,000 deaths estimated to have occurred worldwide in 2008.1 Nearly 30% of patients diagnosed with early breast cancer recur locally or develop distant metastases following initial treatments.2 In locally recurrent or metastatic breast cancer (MBC), taxanes and anthracyclines are the most active cytotoxic agents but relapse occurs in a substantial number of patients. In patients with long relapse-free intervals after adjuvant anthracyclines and taxanes, re-treatment with the same agents is often attempted.3 In contrast in patients with early relapse, the prognosis is exceptionally grim and the efficacy of available treatment options is marginal. Only a few agents have been formally tested in phase III studies in this setting4 and until recently, single-agent capecitabine was the only approved therapy.5 There is, therefore, an obvious need for more effective treatments for patients whose disease relapses early within 12 months from treatment with anthracyclines and taxanes in the neo/adjuvant setting.

Ixabepilone (IXEMPRA®, Bristol-Myers Squibb), an epothilone B derivative with potent microtubule-stabilizing activity, inhibits the growth of a variety of taxane-sensitive and taxane-resistant tumor types in preclinical tumor models.6–8 A series of phase II studies showed single-agent efficacy of this agent in MBC patients refractory to previous chemotherapies including anthracyclines and
Ixabepilone is an approved treatment in the United States and in a number of other countries but not the European Union, as monotherapy for MBC resistant to anthracyclines, taxanes and capcitabine, and in combination with capcitabine for MBC progressing after treatment with anthracyclines and taxanes. The approval of ixabepilone in combination with capcitabine was based on a large phase III study comparing the combination with capcitabine alone in 752 MBC patients previously treated with anthracyclines and taxanes. In that study, the combination showed significant improvements in progression-free survival (PFS) and objective response rate (ORR) compared with capcitabine alone. A subsequent, similarly designed phase III study in 1221 patients confirmed these results.

Each of these studies included prespecified patient subsets. One such subset, termed post-adjuvant rapidly relapsing (PARR) patients, had disease that relapsed within 12 months after adjuvant or neoadjuvant treatment with anthracyclines and taxanes. Thus, these patients received study treatments as first-line chemotherapy in the metastatic setting. Here for the first time, we assess the efficacy and safety of the combination vs. capcitabine alone in this subset of patients. Since both studies were similar in design and patient characteristics, a pooled analysis was performed for more precise estimates of the efficacy and safety.

Methods

Study design and treatment

CA163-046 (study 046) and CA163-048 (study 048) were international, randomized, open-label, phase III studies that used a similar study design as previously described. Briefly, MBC patients pretreated or resistant to anthracyclines and taxanes were randomly assigned to receive, in a 21-day cycle, ixabepilone 40 mg/m² as a 3-h intravenous infusion on day 1, plus oral capcitabine 1000 mg/m² twice daily on days 1 through 14, or capcitabine alone 1250 mg/m² twice daily on days 1 through 14. Treatment was continued until disease progression or unacceptable toxicity. Doses were reduced, delayed or discontinued based on tolerability, as described. There were only minor differences in eligibility criteria between the two studies. Resistance to taxanes, a prerequisite for study 046, was not mandated for study 048. Resistance in 046 was defined as tumor progression during treatment or within 4 months of last dose in the metastatic setting, or recurrence within 12 months in the neoadjuvant or adjuvant setting. Further, up to 3 lines of prior chemotherapy including neoadjuvant/adjuvant treatments were permitted in study 046, whereas study 048 permitted up to 2 lines. Finally, measurable disease was a requirement in 046, whereas patients with either measurable or non-measurable disease were allowed in study 048.

Both studies were conducted in accordance with the declaration of Helsinki and related amendments. The protocols were approved by the institutional review boards of participating institutions and all patients provided written informed consent before enrollment.

Patients

A total of 1973 patients with MBC was enrolled in the two studies: 752 in study 046 and 1221 in study 048. The PARR subset was prospectively defined as patients who relapsed within 6 months of prior anthracycline treatment and within 12 months of prior taxane treatment in the neoadjuvant or adjuvant settings. PARR criteria were met by a total of 293 patients: 55 out of 752 patients (7.3%) in study 046 and 238 out of 1221 patients (19.5%) in study 048. The smaller proportion of PARR patients in study 046 can be attributed to a more stringent inclusion criterion of relapse within 6 months for both taxanes and anthracyclines in this study, which was later amended to be identical to that in study 048.

Efficacy measurements

All randomized patients in study 046 and patients with measurable disease at randomization in study 048 were assessed for PFS and ORR. Overall survival (OS) was analyzed for all randomized patients in both studies. The primary endpoints were PFS in study 046 and OS in study 048. The secondary endpoints were OS and ORR in study 046, and PFS and ORR in study 048. PFS and tumor response rates were assessed by both independent radiology review committee and investigators in study 046, and only by investigators in study 048. Data from independent radiology review committee were consistent with those from investigator assessments. For consistency, only investigator-assessed data were presented in this report.

Safety evaluation

All patients who received study drug were evaluated for safety. Adverse events and laboratory abnormalities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.

Data analyses

PFS, tumor responses and OS were analyzed for the PARR subset in each study and for the pooled PARR subset, and for the pooled overall population. Adverse events were analyzed for the pooled PARR subset and the pooled overall population. Tumor response rates along with 95% confidence intervals (CI) were presented. PFS, OS and reversibility of peripheral neuropathy were analyzed using Kaplan–Meier product limit method. A two-sided 95% CI for the medians was computed by the Brookmeyer and Crowley method. A Cox proportional hazards model, stratified by study, was used to calculate hazard ratios (HR) for PFS and OS along with two-sided 95% CI. Nominal log-rank p values presented were not adjusted for multiple comparisons and should be interpreted with caution. All PFS analyses were based on the investigator assessment.

Results

Patients

PARR patients (n = 293) receiving ixabepilone plus capcitabine or capcitabine alone as first-line metastatic treatment accounted for 15% of the pooled overall population. Baseline demographics and clinical characteristics between the two treatment groups were well matched in both the pooled PARR subset and the pooled overall population (Table 1). The PARR subset included more patients with triple-negative tumors, i.e. tumors lacking epidermal growth factor receptor-2 (HER2), estrogen receptor (ER) and progesterone receptor (PR) as compared to the pooled overall population (40% and 22%, respectively). As prospectively defined, all PARR patients were taxane-resistant in that their disease had recurred within 12 months of receiving taxane therapy in the adjuvant setting. Fifty percent of PARR patients had lung and/or liver visceral metastases, and nearly 15% expressed HER2. Compared to the PARR subset, the overall population had more patients with ER-positive tumors or with Karnofsky’s performance status of 70–80.
Consistent improvements in PFS were observed in population (median, 5.6 months vs. 4.2 months; HR, 0.80; HER2, epidermal growth factor receptor-2; ER, estrogen receptor; PR, progesterone receptor.

In pooled PARR patients, the addition of ixabepilone to capecitabine increased median OS by 2.6 months compared to capecitabine alone (15.1 months vs. 12.5 months; Table 4), corresponding to a 16% reduction of the estimated risk of death (HR, 0.84; p = 0.208) (see also Fig. 1B). Consistent results were observed in the PARR subset from study 046 (median, 13.8 months vs. 8.6 months; HR, 0.65; p = 0.1758), study 048 (median, 15.6 months vs. 13.6 months; HR, 0.89; p = 0.4529) and in the pooled overall population (median, 14.6 months vs. 13.6 months; HR, 0.92; p = 0.0861).

Safety

The safety profiles of ixabepilone plus capecitabine or capecitabine alone were similar between the pooled PARR subset and the pooled overall population (Table 5). The most frequent grade 3/4 hematologic events in patients treated with ixabepilone plus capecitabine were neutropenia (PARR, 74%; overall, 71%) and leukopenia (PARR, 65%; overall, 61%) with infrequent febrile neutropenia (PARR, 5%; overall, 5%). Hematologic toxicity was generally manageable by dose reduction or delay.

Non-hematologic adverse events were more frequent in the combination arm in both PARR subsets and in the overall population (Table 5). Two most common grade 3/4 non-hematologic adverse events were hand-foot syndrome (in the combination and capecitabine alone arms) and peripheral sensory neuropathy (in the combination arm). The frequency of hand-foot syndrome, a known side-effect of capecitabine, was similar between the combination and capecitabine alone arms (22% and 19%, respectively). Peripheral neuropathy was predominantly sensory, and grade 3/4 events (23%) occurred only in the two-drug arm, with similar frequencies between the PARR patients (23%) and the overall population (24%). No grade 4 neuropathy event occurred in PARR patients, and 7 out of 964 patients (0.7%) experienced grade 4 neuropathy in the pooled overall population.

Peripheral neuropathy resolved in most cases following dose reduction or interruption. Resolution was defined as time from worst grade neuropathy to baseline or grade 1. Of the 32 PARR patients with grade 3 events, 28 (88%) had a symptom resolution with a median duration of 5.6 weeks (95% CI, 3.9–7.6 weeks). Of 72 PARR patients with grade 2/3 events, 63 (88%) had a symptom resolution with a median duration of 5.1 weeks (95% CI, 4.1–6.9) in the pooled overall population, median resolution times for grade 3/4 and grade 2/3 events were 6.0 weeks (95% CI: 5.0–7.4) and 5.1 weeks (95% CI: 4.9–6.0), respectively. For the PARR population, there were 32 Grade 3 neuropathy events, 28 of which did and 4 (13%) did not resolve and 72 Grade 2/3 neuropathy events 63 of which and 9 (13%) did not resolve. For the overall population, there were 219 Grade 3 neuropathy events of which 191 did and 28 (13%) did not resolve, and 475 Grade 2/3 neuropathy events 420 of which did and 55 (12%) did not resolve.

In PARR patients, the median treatment cycles were 6 (range, 1–44) for the combination and 4 (range, 1–30) for capecitabine alone (Table 6). In the pooled overall population, the corresponding values were 6 (range, 1–44) for the combination and 5 for capecitabine alone (range, 1–50). Frequencies of dose reductions were similar between PARR patients and the overall population. Peripheral neuropathy was the most frequent cause of ixabepilone dose reduction in both the PARR (14.8%) and the overall (17.7%)
populations. Non-hematologic toxicity was a common cause for dose reduction in the capecitabine alone treatment.

Discussion

The present analysis explored the efficacy and safety of ixabepilone plus capecitabine vs. capecitabine alone in the PARR population, a subset of patients with particularly poor prognosis. These patients were prospectively defined in studies 046 and 048 comparing the combination with capecitabine alone in MBC patients previously treated with anthracyclines and taxanes, where the combination was more effective than the monotherapy in terms of PFS and ORR.15,17

Our analyses showed that the PARR population experienced superior PFS and ORR with the ixabepilone combination compared to capecitabine alone. Results in PARR patients were similar to those observed in the pooled overall population. Taken together, these results indicate that patients who relapsed within 12 months of adjuvant anthracyclines and taxanes may benefit from the addition of ixabepilone to capecitabine.

In this analysis, PFS after capecitabine monotherapy was shorter in the PARR population than in the overall population (2.8 months vs 4.2 months), a finding consistent with the unfavorable outcome typically experienced by PARR patients. However, treatment with the combination was associated with the same PFS in both populations (5.6 months). Consequently, the PFS prolongation by the two-drug therapy over capecitabine alone and the associated HR were numerically greater in the PARR population than in the overall population (PFS, 2.8 months vs 1.4 months; HR, 0.58 vs 0.80). These results may further confirm the effectiveness of the ixabepilone
combination in this patient population. Interestingly, ORR after capecitabine alone was similar between the PARR patients and the overall population (24% vs 25%), raising the possibility that the tumor response to capecitabine monotherapy lasts for a shorter period in the PARR patients, thus contributing to the poorer PFS.

Tumor responses.a

Table 3

<table>
<thead>
<tr>
<th>Response</th>
<th>Pooled PARR subset</th>
<th>Pooled overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ixa + Cape</td>
<td>Cape</td>
</tr>
<tr>
<td></td>
<td>n = 123</td>
<td>n = 111</td>
</tr>
<tr>
<td>Objective response rate, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>(37–56)</td>
<td>24</td>
</tr>
<tr>
<td>Best response, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Partial response</td>
<td>39</td>
<td>23</td>
</tr>
<tr>
<td>Stable response</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Not determined</td>
<td>7</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviations: PARR, post-adjuvant rapidly relapsing; Ixa, ixabepilone; Cape, capecitabine.
a Computed using investigator assessment data on all randomized patients in study 046 and on randomized patients with measurable disease in study 048.

A major limitation of the present analysis is that, although the PARR population was prespecified, the analysis was not, raising the possibility of bias toward an overestimation of the benefit. PARR patients constituted only 15% of the overall population; but still represented a reasonably large series. It is notable, however, that results were consistent across the analyses performed here and elsewhere in the overall population from studies 046 and 048.5,16,23 Prospective studies are clearly needed to confirm the benefit of the ixabepilone combination in the PARR population. Studies are also needed to determine if the sequential use of capecitabine and ixabepilone as monotherapy would yield similar results.

In conclusion, breast cancer patients experiencing a rapid relapse following adjuvant anthracyclines and taxanes may benefit from the first-line use of ixabepilone plus capecitabine in the metastatic setting. Increased toxicity associated with the combination remains an important, yet generally manageable concern.

Table 4

Overall survival.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Treatment (n)</th>
<th>Median, mo (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
<th>Log-rank p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled PARR</td>
<td>Ixa + Cape (149)</td>
<td>15.1 (12.4–17.8)</td>
<td>0.84 (0.65–1.10)</td>
<td>0.2081a</td>
</tr>
<tr>
<td></td>
<td>Cape (144)</td>
<td>12.5 (10.0–15.9)</td>
<td>0.65 (0.35–1.21)</td>
<td>0.1758a</td>
</tr>
<tr>
<td>PARR in study 046</td>
<td>Ixa + Cape (25)</td>
<td>13.8 (10.7–22.5)</td>
<td>0.90 (0.53–1.51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cape (30)</td>
<td>8.6 (5.4–14.9)</td>
<td>0.87 (0.48–1.62)</td>
<td></td>
</tr>
<tr>
<td>PARR in study 048</td>
<td>Ixa + Cape (124)</td>
<td>15.6 (11.8–17.4)</td>
<td>0.89 (0.67–1.20)</td>
<td>0.4529a</td>
</tr>
<tr>
<td></td>
<td>Cape (114)</td>
<td>13.6 (10.8–17.7)</td>
<td>0.82 (0.53–1.28)</td>
<td></td>
</tr>
<tr>
<td>Pooled overall</td>
<td>Ixa + Cape (984)</td>
<td>14.6 (13.9–15.8)</td>
<td>0.92 (0.83–1.01)</td>
<td>0.0861</td>
</tr>
<tr>
<td></td>
<td>Cape (989)</td>
<td>13.6 (12.7–14.9)</td>
<td>0.91 (0.82–1.01)</td>
<td></td>
</tr>
</tbody>
</table>

a Not adjusted for multiple comparisons.

Table 5

Selected Grade 3/4 Adverse Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Pooled PARR subset</th>
<th>Pooled overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ixa + Cape</td>
<td>Cape</td>
</tr>
<tr>
<td></td>
<td>n = 142</td>
<td>n = 140</td>
</tr>
<tr>
<td>Hematologic adverse event, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>74</td>
<td>9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>65</td>
<td>9</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Non-hematologic adverse event, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any PN</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Sensory PN</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Motor PN</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: PARR, post-adjuvant rapidly relapsing; Ixa, ixabepilone; Cape, capecitabine.
a No grade 4 event.
b Seven (0.7%) grade 4 events.

range of 0%–33% reported for other microtubule-stabilizing agents including taxanes,20 and is comparable to those reported for weekly paclitaxel (24%) and albumin-bound paclitaxel (17%).21,22

A major limitation of the present analysis is that, although the PARR population was prespecified, the analysis was not, raising the possibility of bias toward an overestimation of the benefit. PARR patients constituted only 15% of the overall population; but still represented a reasonably large series. It is notable, however, that results were consistent across the analyses performed here and elsewhere in the overall population from studies 046 and 048.5,16,23 Prospective studies are clearly needed to confirm the benefit of the ixabepilone combination in the PARR population. Studies are also needed to determine if the sequential use of capecitabine and ixabepilone as monotherapy would yield similar results.

In conclusion, breast cancer patients experiencing a rapid relapse following adjuvant anthracyclines and taxanes may benefit from the first-line use of ixabepilone plus capecitabine in the metastatic setting. Increased toxicity associated with the combination remains an important, yet generally manageable concern.
Further studies should identify PARR patients most likely to benefit from ixabepilone combination.

Conflict of interest

Jacek Jassem has provided advisory service to Bristol-Myers Squibb. Luis Fein has received research funding from Bristol-Myers Squibb. Mark Karwal has received honoraria from Bristol-Myers Squibb, Genentech, Novartis and GlaxoSmithKline; and research funding from Bristol-Myers Squibb, Genentech and Novartis. Mario Campone has no conflict to declare. Ronald Peck and Valerie Poulart are employees of Bristol-Myers Squibb and own shares of Bristol-Myers Squibb. Linda Vahdat has provided consultancy or advisory service to Bristol-Myers Squibb; and has received honoraria and research funding from Bristol-Myers Squibb.

Ethical approval

Both studies were conducted in accordance with the declaration of Helsinki and related amendments. The protocols were approved by the institutional review boards of participating institutions and all patients provided written informed consent before enrollment.

Acknowledgments

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Appendix. Supplementary material

The supplementary data associated with this article can be found in the on-line version at doi:10.1016/j.jbreast.2011.09.003.

References