CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-065

MEDICAL REVIEW

Date	October 11, 2007
From	Ramzi Dagher, MD
Subject	Medical Team Leader Memo
NDA #	22065
Drug	ixabepilone (ixempra)
Indications	as monotherapy and in combination with capecitabine in advanced, metastatic breast cancer
Recommendation	Approval

Recommendations

I agree with the medical reviewers' recommendation for regular approval of ixabepilone for the following indications:

TRADENAME is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

TRADENAME is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

Post Marketing Commitments

The following post-marketing commitments have been proposed by FDA and agreed to by the sponsor:

1. To submit the complete study report and datasets for the ongoing clinical study CA163048 entitled " A Phase 3 Trial of Novel Epothilone BMS-247550 plus Capecitabine versus Capecitabine Alone in Patients with Advanced Breast Cancer Previously Treated with An Anthracycline and a Taxane" with a primary endpoint of overall survival following the collection of data for a prespecified number of events (deaths), or earlier if recommended by the independent data monitoring committee.

2. To submit the final study report and datasets for the study CA163046 "A Phase III Trial of Novel Epothilone BMS-247550 Plus Capecitabine Versus Capecitabine Alone in Patients With Advanced Breast Cancer Previously Treated With or Resistant To an Anthracycline and Who are Taxane Resistant" after collection of overall survival data following the prespecified number of deaths for a mature analysis.

3. Submit the completed report for the rifampin drug-drug interaction evaluation and datasets for study CA163102.

4. An *in-vitro* assessment to determine if ixabepilone is a P-glycoprotein substrate or inhibitor needs to be conducted.

5. To design, conduct and submit the completed study report and datasets for a study to assess the potential for ixabepilone to prolong the QT interval in patients.

Clinical Database

Combination Therapy

The clinical data supporting the combination indication is derived from an open-label, multicenter, multinational, randomized trial of 752 patients with metastatic or locally advanced breast cancer. The efficacy and safety of ixabepilone (40 mg/m^2 every 3 weeks) in combination with capecitabine (at 1000 mg/m^2 twice daily for 2 weeks followed by 1 week rest) were assessed in comparison with capecitabine as monotherapy (at 1250 mg/m^2 twice daily for 2 weeks followed by 1 week rest). Patients were previously treated with anthracyclines and taxanes. Patients were required to have demonstrated tumor progression or resistance to taxanes and anthracyclines as follows:

- tumor progression within 3 months of the last anthracycline dose in the metastatic setting or recurrence within 6 months in the adjuvant or neoadjuvant setting, and
- tumor progression within 4 months of the last taxane dose in the metastatic setting or recurrence within 12 months in the adjuvant or neoadjuvant setting.

For anthracyclines, patients who received a minimum cumulative dose of 240 mg/m^2 of doxorubicin or 360 mg/m^2 of epirubicin were also eligible. Sixty-seven percent of patients were White, 23% were Asian and 3% were Black. Both arms were evenly matched with regards to race, age, baseline Karnofsky performance status, receipt of prior adjuvant or neo-adjuvant chemotherapy, hormone receptor status and HER2 expression.

The primary endpoint of the study was progression-free survival (PFS) defined as time from randomization to radiologic progression as determined by Independent Radiologic Review (IRR), clinical progression of measurable skin lesions or death from any cause. Other study endpoints included objective tumor response based on Response Evaluation Criteria in Solid Tumors (RECIST), time to response, response duration, and overall survival. At an interim overall survival analysis, no difference was observed between the two treatment arms. This analysis was not pre-planned and was conducted at the request of FDA to assure that there was no negative trend in overall survival. Approximately 60% of death events had occurred at the time of this analysis.

Ixabepilone in combination with capecitabine resulted in a statistically significant improvement in PFS compared to capecitabine monotherapy. The results of the study are presented in Table 1.

Table 1: Efficacy of TRADENAME in Combination with Capecitabine vs Capecitabine Alone - Intent-to-Treat Analysis

Efficacy Parameter	**TRADENAME with Capecitabine n=375**	**Capecitabine n=377**
PFS		
Number of events[c]	242	256
Median	5.7 months	4.1 months
(95% CI)	(4.8 - 6.7)	(3.1 - 4.3)
Hazard Ratio[a] (95% CI)	0.69 (0.58 - 0.83)	
p-value[b] (Log rank)	<0.0001	
Objective Tumor Response Rate (95% CI)	34.7% (29.9 - 39.7)	14.3% (10.9 - 18.3)
Duration of Response, Median (95% CI)	6.4 months (5.6 - 7.1)	5.6 months (4.2 - 7.5)

a Patients were censored for PFS at the last date of tumor assessment prior to the start of subsequent therapy. In patients where independent review was not available PFS was censored at the randomization date.

b For the hazard ratio, a value less than 1.00 favors combination treatment, CI adjusted for interim analysis.

c Stratified by visceral metastasis in liver/lung, prior chemotherapy in metastatic setting, and anthSracycline resistance.

d Cochran-Mantel-Haenzel test

Monotherapy

Ixabepilone was evaluated as a single agent in a multicenter single-arm study in 126 women with metastatic or locally advanced breast cancer. The study enrolled patients whose tumors had recurred or had progressed following two or more chemotherapy regimens including an anthracycline, a taxane, and capecitabine. Patients who had received a minimum cumulative dose of 240 mg/m^2 of doxorubicin or 360 mg/m^2 of epirubicin were also eligible. Tumor progression or recurrence were prospectively defined as follows:

- Disease progression while on therapy in the metastatic setting (defined as progression while on treatment or within 8 weeks of last dose),
- Recurrence within 6 months of the last dose in the adjuvant or neoadjuvant setting (only for anthracycline and taxane),
- HER2 positive patients must also have progressed during or after discontinuation of trastuzumab.

In this study the median age was 51 years (range, 30-78), and 79% were White, 5% Black, and 2% Asian, Karnofsky performance status was 70-100%, 88% had received two or more prior chemotherapy regimens for metastatic disease, and 86% had liver and/or lung metastases. Tumors were ER-positive in 48% of patients, ER-negative in 44%, HER2-positive in 7%, HER2-negative in 72%, and ER-negative, PR-negative, HER2-negative in 33%.

Ixabepilone was administered at a dose of 40 mg/m^2 intravenously over 3 hours every 3 weeks. Patients received a median of 4 cycles (range 1 to 18) of therapy.

Objective tumor response was determined by independent radiologic review and investigator review using RECIST. Efficacy results are presented in Table 2.

Table2: Efficacy in Metastatic and Locally Advanced Breast Cancer

	Treated Patients n=126
Objective tumor response rate (95% CI)	
IRR Assessment (N = 113)	12.4 % (6.9 – 19.9)
Investigator Assessment (N=126)	18.3% (11.9-27.0)
Time to response* (N = 14)	
Median, weeks (min - max)	6.1 (5 - 54.4)
Duration of response* (N = 14)	
Median, months (95% CI)	6.3 (5.0 - 7.6)

Two smaller supportive single-arm trials were conducted in patients with advanced metastatic breast cancer. In one study with a population similar to that evaluated in the study described above, a partial response rate of 12% was observed. In a less refractory population of patients who received ixabepilone as first line treatment of metastatic disease, an objective response rate of 40% was observed.

Safety

Peripheral neuropathy was the major non-hematological toxicity related to ixabepilone, occurring in 70% of patients treated. In the randomized trial, 23% of patients in the combination arm had grade 3 or 4 neuropathy compared to none in the capecitabine alone arm. In the monotherapy trial, grade 3 / 4 peripheral neuropathy occurred in 14% of patients.

Myelosuppression occurred in the majority of patients. Sixty-eight percent of patients receiving combination therapy experienced grade 3 or 4 neutropenia compared to 12% in the capecitabine alone arm. Over half the patients experienced thrombocytopenia, with grade 3 or 4 thrombocytopenia occurring in 9% of patients.

An unacceptable risk of death was found in patients with moderate or severe hepatic impairment treated with ixabepilone in combination with capecitabine. Five of sixteen patients with moderate or severe hepatic insuffiecinecy treated with the combination died, compared with 7 of 353 patients with normal hepatic function or mild insufficiency. Ixabepilone should not be used in combination with capecitabine in the presence of moderate or severe hepatic insufficiency. The agreed upon labeling includes a box warning contraindicating the use of ixabepilone in combination with capecitabine in patients moderate or severe hepatic insufficiency defined by AST / ALT / bilirubin.

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/s/

Ramzi Dagher
10/11/2007 08:51:43 AM
MEDICAL OFFICER
medical team leader

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-065
Submission Code	0000, SU
Letter Date	April 16, 2007; August 7, 2007
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Reviewer Name	Robert J. Lechleider, M.D. Edvardas Kaminskas, M.D.
Review Completion Date	October 2, 2007
Established Name	Ixabepilone for injection
(Proposed) Trade Name	Ixempra
Therapeutic Class	Anti-neoplastic
Applicant	Bristol-Myers Squibb
Priority Designation	P
Formulation	Lyophilized powder
Dosing Regimen	40 mg/m^2 IV every 3 weeks
Indication	Ixabepilone is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further

	anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting. Ixabepilone is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes and capecitabine.
Intended Population	Patients in whom an anthracycline and a taxane have failed (combination therapy), or who have progressed on capecitabine after failure of an anthracycline and a taxane (monotherapy)

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LIST OF ABBREVIATIONS

List of Abbreviations is from the Sponsor's NDA submission. Not all are used in the review.

ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil counts
AST	Aspartate aminotransferase
BMS	Bristol-Myers Squibb
BP	Blood pressure
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed Tomography
CTC	Common Terminology Criteria
CYP3A4	Cytochrome P450 3A4
DCR	Disease control rate
ECG	Electrocardiogram
ER	Estrogen receptor
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Gramulocyte-macrophage colony-stimulating factor
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor-2
HSR	Hypersensitivity reaction
HR	Heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IHC	Immunohistochemistry
IRB	Institutional Review Board
IRRC	Independent Radiology Review Committee
IV	Intravenously
IVRS	Interactive Voice Response System
KPS	Karnofsky Performance Status
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Objective response rate
PD	Progressive disease
PE	Physical examination
PET	Positron Emission Tomography
PFS	Progression-free survival
PR	Partial response
PR (+ or -)	Progesterone receptor
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SDR	Stable disease rate
uPR	Unconfirmed partial response
US	The United States
WBC	White blood cells
WOCBP	Women of childbearing potential

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The reviewers recommend on the basis of this review of NDA 22-065 that ixabepilone (Ixempra™) receive regular approval for the following indications:

- In combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane-resistant and for whom further anthracycline therapy is contraindicated. Anthracycline resistance is defined as progression while on therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.
- As monotherapy for the treatment of metastatic or locally advanced breast cancer patients whose tumors are resistant or refractory to an anthracycline, a taxane, and capecitabine.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

The Sponsor should provide periodic safety reporting and continue post-marketing surveillance activities. This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. Commonly observed toxicities with ixabepilone include peripheral neuropathy, myelosuppression, gastrointestinal toxicities, myalgia/arthralgia and fatigue/asthernia.

1.2.2 Required Phase 4 Commitments

The following Phase 4 commitments are requested by the clinical review team:

- To submit the complete study report and datasets for the ongoing clinical study CA163048 "A Phase 3 Trial of Novel Epothilone BMS-247550 plus Capecitabine versus Capecitabine Alone in Patients with Advanced Breast Cancer Patients Previously Treated with An Anthracycline and a Taxane" with a primary endpoint of overall survival following the collection of data for a prespecified number of events (deaths), or earlier if recommended by the independent data monitoring committee.

- To submit the final study report and datasets for the study CA163046 "A Phase III Trial of Novel Epothilone BMS-247550 Plus Capecitabine Versus Capecitabine Alone in

Patients With Advanced Breast Cancer Previously Treated With or Resistant To an Anthracycline and Who are Taxane Resistant" after collection of overall survival data following the prespecified number of deaths for a mature analysis.

The following commitments were requested by the Clinical Pharmacology review team:

- To submit the completed report for the rifampin drug-drug interaction evaluation and datasets for study CA163102.

- To perform an *in vitro* assessment to determine if ixabepilone is a P-glycoprotein substrate or inhibitor.

- To design, conduct and submit the completed study report and datasets for a study to assess the potential for ixabepilone to prolong the QT interval in patients.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Ixabepilone for intravenous injection is a cytotoxic chemotherapeutic agent that inhibits microtubule function leading to cell death. There are two indications sought in this application. The first is for use in combination with capecitabine in patients with metastatic or locally advanced breast cancer who have previously received chemotherapy with an anthracycline and a taxane and in whom those therapies have failed. The second is for monotherapy in patients with metastatic or locally advanced breast cancer who have received an anthracycline, a taxane and capecitabine and in whom those therapies have failed. The intended population is adult women, as this disease is rare in men and not found in pediatric populations.

The pivotal trial for the combination therapy regimen is a 752 patient trial with a primary endpoint of progression free survival (PFS) comparing capecitabine plus ixabepilone ("combination") to capecitabine alone ("capecitabine"). This trial is supported by a single arm trial of 62 patients treated with the combination at the same dose and schedule. The monotherapy indication is supported by a trial of 126 patients with a primary endpoint of objective tumor response rate. This trial is supported by two other similar trials with different dosing and slightly different patient populations.

The safety database consists of 369 patients treated with combination therapy at a dose of ixabepilone of 40 mg/m2 every three weeks in the pivotal trial and a second trial of 62 patients

for a total of 431 patients treated with combination therapy. For monotherapy, 240 patients were treated at the same dose and schedule.

1.3.2 Efficacy

Combination Therapy

The pivotal efficacy trial is trial CA163046 (Study 046) which is an open label, randomized trial that compared combination therapy to capecitabine alone in patients with advanced breast cancer. The primary endpoint of this trial was PFS, defined as radiological or quantifiable clinical progression or death from any cause. Radiological progression was adjudicated by an independent radiological review committee (IRRC) using Response Criteria in Solid Tumors (RECIST). Secondary endpoints included overall survival, PFS determined by investigator assessment, tumor response rate, response duration, time to response and patient reported outcomes. Trial CA163031 (Study 031) was a dose-finding trial that compared single day administration at a dose of 40 mg/m^2 to a dose of 8 mg/m^2 administered daily for three days, both in combination with various doses of capecitabine. The primary efficacy endpoint was objective tumor response rate. Based on Study 031 and other studies the dose of 40 mg/m^2 in a single infusion once every three weeks was chosen. Study 031 is supportive of Study 046 and contributes to the safety database.

The primary endpoint of PFS has been used previously in approval of drugs for advanced breast cancer. The clinical endpoint of PFS is not of certain clinical benefit, as it may not be in and of itself of benefit, and may not be a surrogate for a benefit in overall survival (OS), which is of clear clinical benefit. PFS is also subject to bias, particularly in unblinded trials, as the assessment of radiological progression dependent on operator selection and measurement of target lesions. The sponsor in this case has attempted to minimize the effect of bias on determination of PFS. The definition of PFS was appropriate, and radiological progression was determined by independent review that was blinded to the treatment arm.

In this multinational, multicenter study, patients were adult women with metastatic or locally advanced breast cancer who had previously received therapy with an anthracycline and a taxane, and whose disease was resistant to such therapy or who had received a maximal dose. Capecitabine monotherapy is an approved and accepted therapy in such patients. Study arms were balanced with respect to race, age, extent of disease, previous therapies, hormone receptor status and HER2 expression. Three hundred seventy-seven patients were randomized to receive capecitabine and 375 patients were randomized to receive combination therapy. Tumor assessments were performed every two cycles (six weeks) by high resolution computed tomography, standard computed tomography or magnetic resonance imaging. Skin lesions were acceptable as measurable disease if photographed with a ruler in place. The first patient was enrolled on September 4, 2003 and database lock occurred on December 1, 2006.

The study was conducted well, the patient population was clearly defined and clinically relevant, and the results are statistically significant. Patients in the capecitabine arm received a median of four cycles of chemotherapy, while those in the combination arm received a median of five

cycles. Using the intent to treat population and data from the independent radiologic review, patients in the capecitabine alone arm had a median PFS point estimate of 4.17 months while for the combination arm it was 5.85 months with a hazard ratio of 0.75 (95% CI: 0.64, 0.88) and stratified log-ranked p-value of 0.0003 (Sponsor's analysis). Multiple sensitivity analyses, including an analysis of patients as treated and censoring patients with unevaluable disease yielded similar, statistically significant results. Similarly, PFS analysis using data generated by the investigators yielded a median PFS point estimate of 3.81 and 5.26 months for capecitabine and combination respectively, with a HR of 0.78 (95% CI: 0.67, 0.91) and a stratified log-ranked p-value of 0.0011. Analysis of efficacy data by this reviewer concurred with the Sponsor's results.

Analysis of the secondary endpoint of overall survival (OS) is premature. Interim analysis by the data monitoring committee as requested by the FDA did not necessitate study cessation. The final OS analysis of Study 046 will be conducted when 631 patients have died. Four hundred eighty-three patients had died as of database lock. The objective response rate (ORR) for capecitabine was 14.3% (95% CI: 10.9, 18.3) and for combination therapy it was 34.7% (95% CI: 29.9, 39.7) as determined by the IRRC. The median time to response was similar in both groups at approximately twelve weeks, and the duration of response was 5.6 and 6.4 months for capecitabine and combination respectively. This difference was not statistically significant. Analyses using the investigators' assessments were similar. Analysis by the reviewer concurs with the sponsor's findings.

Monotherapy

A second indication for use as monotherapy in advanced breast cancer after the failure of an anthracycline, a taxane and capecitabine is supported by pivotal trial CA163081 (Study 081). The primary endpoint for this trial was tumor response (objective response rate (ORR) comprising partial responses (PRs) and complete responses (CRs)) assessed by computerized tomography. RECIST was used as the criteria to determine radiological response. An independent radiological review was also used in this trial. Use of ORR to support regulatory approval is somewhat problematic, as it is unclear what clinical benefit is derived from tumor response in the absence of a prolongation of survival or improvement in symptoms. An attempt by the sponsor to seek regulatory approval for ixabepilone based solely on this endpoint in a single arm trial was discouraged by the Agency. Determination of ORR harbors some of the same difficulties as does determination of PFS. Again, the sponsor has used independent review to help minimize these problems.

In Study 081, ixabepilone was administered every 3 weeks at 40 mg/m^2 to 126 patients with metastatic or locally advanced breast cancer who had previously received an anthracycline, a taxane and capecitabine, and who had received maximal amounts of those therapies or had experienced disease progression. Patients were evaluated for tumor response by CT scan every two cycles (six weeks). IRRC adjudication identified an ORR of 12%. Median time to response was two cycles and the median duration of response was 6.3 months. Median PFS was 3.2 months, but no comparator arm is available. There were no subgroups identified who had significantly different response rate.

Two smaller trials support the findings from Study 081. Study 163010 examined ixabepilone therapy in patients previously treated with an anthracycline in the adjuvant setting. Study 163009 examined therapy in the metastatic setting in patients whose tumors were resistant to taxanes. There are slight differences in the patient populations studied and the conduct of these trials compared to Study 081, but the results support the findings of Study 081 that ixabepilone has activity in patients with advanced breast cancer who have received previous cytotoxic chemotherapies.

Conclusions

The findings from the two pivotal trials (046 and 081) support the use of ixabepilone in advanced breast cancer, both in combination with capecitabine and as monotherapy. The trials were well-conducted, met their primary endpoints and demonstrate activity of this drug against tumors that are largely resistant to available therapies. It is not certain whether the increase in PFS seen in Study 046 will translate into an increase in OS, but final findings from this trial, and another ongoing trial (CA163048) should answer that question definitively. There are few options for patients with advanced breast cancer who have received maximal useful therapy with a taxane and an anthracycline. Gemcitabine is an approved agent but its utility in second- or third-line settings is unclear. Other agents used include vinorelbine, carboplatin and cisplatin, but there is little evidence that they are of significant benefit. The studies presented in this application demonstrate that there is clear activity of ixabepilone in patients who have been extensively treated and who have experienced disease progression.

1.3.3 Safety

The safety of ixabepilone was analyzed both in combination with capecitabine and as monotherapy.

Combination Therapy

Study 046, in which 369 patients were treated with combination therapy and 368 were treated with capecitabine (of a total of 752 randomized) is the primary basis for analysis of safety in combination therapy as it enables a direct comparison to capecitabine therapy and should identify those adverse reactions and toxicities that are related to ixabepilone therapy. Study 031, in which 62 patients were treated at the same dose and schedule as in Study 046, is used for support of the findings in 046. Patients receiving combination therapy in Study 046 received a median of 5 cycles of ixabepilone therapy, and 5 cycles of capecitabine therapy, while those in the capecitabine arm received a median of 4 cycles of therapy. This difference is largely due to earlier progression on capecitabine monotherapy. Most patients discontinued therapy for disease progression. This relatively short duration of exposure limits the ability to identify adverse reactions that may only be found with prolonged therapy.

There were more deaths within 30 days of study drug administration on the combination arm than on the capecitabine arm. Twelve patients receiving combination therapy in Study 046 died from a toxicity related to study drug. The comparable number for capecitabine therapy is two. Five of these twelve patients had moderate or severe hepatic insufficiency. The rate of death in patients with moderate or severe hepatic insufficiency (5 of 16 patients) is significantly higher than in patients with normal hepatic function or mild insufficiency (7 of 353). All but one of the drug-related deaths can reasonably be attributed to complications from neutropenia. The remaining death may also be related to neutropenia, but hepatic and/or cardiac insufficiency may have contributed.

The major non-hematological adverse events associated with ixabepilone combination therapy are peripheral neuropathy, palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), fatigue/asthenia, myalgias/arthralgias and gastrointestinal disturbances including pain, constipation, nausea and vomiting. The major (≥5%) hematological and non-hematological grade 3 or 4 adverse reactions reported on the combination arm were febrile neutropenia, peripheral neuropathy (both sensory and motor), diarrhea, palmar-plantar erythrodysesthesia syndrome, myalgia/arthralgia and fatigue/asthenia.

Of the 369 patients treated in the combination arm in Study 046, 163 (44%) discontinued one or both medications due to adverse events. Of these, 136 were deemed to be treatment related. Seventy-nine (21%) discontinued ixabepilone for treatment related neuropathy after a median of 6 cycles. Forty-four of these patients continued on capecitabine for at least one cycle. Thus, neuropathy was the biggest single cause of discontinuation due to drug toxicity.

Peripheral neuropathy was the major non-hematological toxicity related to ixabepilone. Seventy percent of patients had a treatment-emergent neuropathy, and 68% had a neuropathy deemed to be related to treatment. Twenty-four percent of patients in the combination arm had Grade 3 or 4 neuropathy. In the capecitabine arm, 17% of patients developed peripheral neuropathy, and there were no Grade 3 or 4 events. Analysis by the sponsor demonstrated that dose and diabetes were the only factors of those examined that predicted development of neuropathy. The majority of patients with severe (Grade 3 or 4) neuropathy had resolution of their symptoms to Grade 1 or better following cessation of ixabepilone therapy.

Myelosuppression was a major hematological toxicity. Sixty-eight percent of patients receiving combination therapy experienced Grade 3 or 4 neutropenia, and 5% had febrile neutropenia. In the capecitabine arm 12% of patients had Grade 3 or 4 neutropenia. As noted above, the majority of deaths related to ixabepilone therapy were due to infection with neutropenia. Thrombocytopenia was also common, with 55% pf patients experiencing thrombocytopenia that was Grade 3 or 4 in 9.2% of patients. Bleeding was not a noticeable consequence of thrombocytopenia. Anemia was common but not debilitating. Neutropenia, thrombocytopenia and anemia were all increased in combination therapy compared to capecitabine monotherapy.

Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) was common in the combination and capecitabine arms. There is a slightly higher (two percent) increase in the

combination arm (64% vs. 62% for capecitabine alone), but this is unlikely to be significant. No dose reduction for hand-foot syndrome is necessary for ixabepilone.

Cardiac toxicities were rare, but appeared to be increased with combination therapy. These included myocardial infarction, ischemia and ventricular dysfunction. Arrhythmias were also more common. Two deaths occurred from cardiac causes within ten days of administration of ixabepilone. These were not attributed to study drug by the investigators. Further study is required to determine the precise relationship between ixabepilone and cardiac toxicity.

Other toxicities were common, as would be expected with a cytotoxic drug. These include gastrointestinal toxicities, myalgias and arthralgias, fatigue and asthenia. Hepatic toxicity does not appear to be a concern with ixabepilone combination therapy. Other laboratory abnormalities did not appear to be increased with ixabepilone combination therapy. The majority of adverse reactions were Grade 1 or 2 and easily managed.

Analysis of Study 031 did not reveal any additional adverse reactions. No direct comparison with capecitabine monotherapy is possible with Study 031.

Conclusions (Ixabepilone in combination with capecitabine)

- Ixabepilone combination therapy is associated with major toxicities, especially myelosuppression and peripheral neuropathy.

- Ixabepilone should not be used in combination with capecitabine in the presence of moderate or severe hepatic insufficiency. An unacceptable risk of death was found in patients treated with combination therapy in the presence of moderate or severe hepatic insufficiency.

- Ixabepilone does not appear to increase the incidence or severity of palmar-plantar erythrodysesthesia syndrome caused by capecitabine.

Monotherapy

A total of 126 metastatic breast cancer patients who had failed prior therapies with an anthracycline, a taxane and capecitabine were treated with ixabepilone monotherapy at the above dose for a median of 4 cycles. Most patients discontinued treatment with ixabepilone because of disease progression. Virtually all patients in the study reported one or more drug-related adverse event. There was one drug-related death due to sepsis in a severely neutropenic patient. About one-third of the patients experienced an SAE and 40% of patients had a Grade 3 or 4 drug-related toxicity. The most problematic adverse events related to ixabepilone therapy were peripheral neuropathy and neutropenia. Peripheral neuropathy affected about two-thirds of patients. Peripheral neuropathy, mostly sensory, affected patients with baseline neuropathy slightly more frequently than patients without neuropathy at baseline. Neuropathy was managed with dose delays, dose reductions and drug discontinuation. Neuropathy resolved to baseline or Grade 1 in most (88%) patients. The second most important toxicity was neutropenia, which at

its worst was severe or moderately severe (Grades 3 and 4) in one-half of the patients. A minority of neutropenic patients (2%) had infections, one of which resulted in death. Neutropenia usually resolved within one cycle of treatment, and was not an important cause of dose delays, dose reductions and drug discontinuations. Patients were pre-medicated for prevention of hypersensitivity reactions, which nevertheless occurred in 6% of patients. Gastrointestinal disorders, anorexia, asthenia, fatigue, myalgias, arthralgias and alopecia occurred in approximately 40-50% of patients. Although they were of mild to moderate severity, they contributed to 19% of discontinuations from the study. The major limitations of these data are the limited exposure of patients to ixabepilone, mainly because of disease progression, and the lack of a comparator arm. In summary, ixabepilone therapy is associated with a high incidence of adverse events and with risk of death. The potential benefit and the attendant discomforts and risks need to be considered when choosing ixabepilone to treat patients with advanced breast cancer.

1.3.4 Dosing Regimen and Administration

The recommended ixabepilone regimen is 40 mg/m^2 given over a three hour intravenous infusion once every three weeks. When used in combination with capecitabine, the dose of capecitabine should be 1000 mg/m^2 per day for fourteen days beginning on the day of ixabepilone infusion. Ixabepilone should be administered until disease progression or intolerable toxicity.

1.3.5 Drug-Drug Interactions

Ixabepilone is primarily metabolized by the liver via CYP3A4. The use of concomitant strong CYP4A4 inhibitors should be avoided. Grapefruit juice should also be avoided.

1.3.6 Special Populations

Based on a population pharmacokinetic analysis, age, gender and race do not have meaningful effects on the pharmacokinetics of ixabepilone. Ixabepilone AUC increases progressively with hepatic impairment. Renal excretion of ixabepilone is minimal. No controlled pharmacokinetic studies were conducted with ixabepilone in renal impairment patients.

Age

Combination therapy: An analysis of patients greater than 65 years old compared to those 65 or less showed that there was no difference in efficacy findings between the two groups. Adverse reactions were greater in the above 65 group for both capecitabine monotherapy and ixabepilone combination therapy. No specific dose adjustments for age are made. No studies have been performed in pediatric populations.

Monotherapy: The response rate was lower in patients 65 years (1/15 or 7%) or older than in patients younger than 65 (12/98 or 12%). The small number of patients aged $\geq$ 65 years makes

this statistic of a lower response rate unreliable. Treatment-related adverse events data in patients aged < 50 years (N = 103) and 50 years and older (N = 137) show similar percentages of patients with all drug-related AEs, Grades 3/4 AEs, AEs leading to discontinuation from the study, and on-study deaths. No specific dose adjustments for age are recommended.

Race

Combination therapy: Patients in Studies 046 and 031 were predominantly white (71%) or Asian (19%). Blacks accounted for 3% and other races 6%. No differences were seen between whites and Asians in efficacy or safety, except for the rate of severe hand-foot syndrome, which may be an artifact of different grading scales for palmar-plantar erythrodysesthesia between the U.S.-based Study 031 and the multinational Study 04. (No such difference is seen when only Study 046 is analyzed.) There can be no conclusions drawn about other races because of small sample sizes.

Monotherapy: Response rate analyses for races other than White are unreliable because of low numbers enrolled in the monotherapy trial (5% Black, 2% Asian, and 10% Other).

Hepatic impairment

Combination therapy: Ixabepilone in combination with capecitabine should not be used in the setting of moderate or severe hepatic impairment.

Monotherapy: More than 50% of patients had hepatic metastases at enrollment into the study; 84% to 95% had normal or Grade 1 liver function parameters. During study treatment, liver function worsened in about 15% of patients and remained stable or improved in the remainder. There was no instance of hepatotoxicity that could be attributed to ixabepilone.

Renal impairment

Ixabepilone may be used with mild renal insufficiency. Ixabepilone has not been tested in patients with moderate or severe renal insufficiency.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

- Ixabepilone for Injection
- The established name is ixabepilone (BMS-247550). The proposed trade name is Ixempra.
- Ixabepilone is a new molecular entity. Ixabepilone is a semi-synthetic epothilone, a class of anti-neoplastic agents that bind to tubulins in a mode distinct from that of other microtubule-stabilizing agents and result in microtubule stabilization, cell cycle arrest during mitosis, and tumor cell death by apoptosis.
- The proposed indications are
    - Ixabepilone is indicated in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline and a taxane.
    - Ixabepilone is indicated as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to cytotoxic chemotherapy. Previous therapy should have included an anthracycline, a taxane, and capecitabine.
- The recommended dosage of ixabepilone is 40 mg/m^2 administered IV over 3 hours every 3 weeks.

2.2 Currently Available Treatment for Indications

For patients with advanced breast cancer who have received maximal therapy with an anthracycline and a taxane, approved agents are capecitabine and gemcitabine. Other drugs used in this population are vinorelbine, bevacizumab plus paclitaxel, cisplatin, carboplatin, etoposide, vinblastine, and rarely continuous infusion fluorouracil.

There are no approved alternatives for patients with metastatic or locally advanced breast cancer in whom therapy with an anthracycline, a taxane, and capecitabine has failed.

Other drugs used in this patient population include gemcitabine, vinorelbine and the combination of bevacizumab and paclitaxel. Other active agents include cisplatin, carboplatin, etoposide, vinblastine and continuous infusion fluorouracil.

2.3 Availability of Proposed Active Ingredient in the United States

Ixabepilone is not marketed in the United States.

2.4 Important Issues With Pharmacologically Related Products

There are other microtubule associating agents available. They include the taxanes--paclitaxel and docetaxel--and the vinca alkaloids--vincristine, vinblastine, vinorelbine and vindesine. Ixabepilone, the first member of a class of agents called epothilones to seek approval in the United States for use in cancer chemotherapy, has a mechanism of action distinct from these other drugs. Both taxanes and vinca alkaloids have peripheral neuropathy and myelosuppression as significant adverse effects.

2.5 Presubmission Regulatory Activity

- IND submission: June 30, 1999.
- EOP2 meeting: March 26, 2003. Designs of trials CA163046, CA163048 and CA163081 were discussed. Trial CA163046 was to be sized for OS; expectation of 37.5% greater median TTP in the experimental arm was thought to be optimistic. In CA163048 a 3.5-month increment in OS in the experimental arm was thought to be overly optimistic. The sponsor will base the sample size on a 3-month increment. In CA163081, ORR as primary endpoint was discouraged. A proposed hepatic impairment study (CA163040) was discussed, as well as the designs of the proposed ketoconazole interaction study (CA163042) and the PK study (CA163550).
- CA163046 (randomized trial) SPA: August 21, 2003. Agreement between the Agency and the Sponsor on 1) primary (Time to Progression) and secondary endpoints (OS, ORR, TTR, and response duration, safety, FACT-B PRO) in support of subpart H approval of ixabepilone, 2) sample size and proposed stratification factors, 3) Independent Radiological Review, 4) doses of capecitabine, 5) accounting of missing data, 6) dose modification schema, and 7) CRFs.
- CA163081 (pivotal monotherapy trial) SPA: December 18, 2003. Agreement between the Sponsor and the Agency to consider an uncontrolled Phase II trial in the specified population, which has no approved therapeutic options, with ORR as primary endpoint and duration of response as secondary endpoint to support a subpart H approval of ixabepilone. Eligibility criteria were agreed upon, except that hormonal status and prior trastuzumab therapy needed to be defined. The Agency suggested that the primary analysis of response was to be by the IRRC and secondary, by the investigators, rather than the reverse as proposed by the Sponsor. The IRRC charter was requested. Sponsor proposed an indication based on the results of this study.
- Pre-NDA monotherapy meeting: March 6, 2006. 1) The proposed data package for ixabepilone monotherapy (results from trials CA1630481, CA163009 and CA163010) is sufficient for accelerated approval of ixabepilone as monotherapy. 2) Statistical Analysis Plan is acceptable. The Agency urged the Sponsor to submit a planned OS analysis at the time of the final PFS analysis. 3) The Sponsor will request a Pediatric Studies Waiver, since breast cancer is not reported to occur under the age of 20. 4) The proposed format and content of the NDA is acceptable. Pooled summaries of deaths, SAEs and discontinuations due to AEs will be provided. 5) Population PK report will be included in the NDA.

- Pre-NDA CMC pre-NDA meeting: May 9, 2006. 1) Drug product stability data to be provided in the NDA is reasonable. 2) Manufacturing overages are unacceptable. 3) Approach to use period limits appears reasonable. 4) The Agency strongly recommends that all CMC data be submitted in the original submission. The format of the CMC section is acceptable. 5) The Sponsor to provide statement in the NDA that all manufacturing, etc. sites are ready for pre-approval inspection.
- Pre-NDA for combination therapy and monotherapy meeting: February 15, 2007. 1) FDA requested that the Sponsor conduct a planned interim OS analysis at the time of the final PFS analysis in study CA163046. The sponsor responded that an "unscheduled interim analysis" on survival data from CA163046 would be conducted by the DMC who would have sole access to these interim data. The DMC would determine whether the interim data are conclusive, the data would be released to the sponsor; if the data are not conclusive, the DMC would provide a letter to BMS VP Dr. Donna Murray (unconnected to the ixabepilone project) for transmittal to the FDA. These data would indicate whether survival data indicate that ixabepilone poses a safety risk. The Sponsor plans to submit this information at the time of the 120-day Safety Update. 2) Submission of both combination therapy and monotherapy trials together, not separately, was encouraged. 3) eCTD format for submission was stated to be acceptable. 4) Safety analysis plan was acceptable. 5) The Sponsor will request a Pediatric Studies Waiver. 6) A Post-Marketing Commitment for QT/QTc interval prolongation studies may be requested. 7) No Risk Management Plan is planned for this NDA. 8) A trade name was submitted by the Sponsor on March 25, 2005.

2.6 Other Relevant Background Information

This drug product is not marketed in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The IXEMPRA™ drug product will be supplied as a **kit** containing a — vial of IXEMPRA (ixabepilone) for injection as lyophilized drug substance and a — vial of DILUENT for IXEMPRA, which is used to constitute the lyophilized drug substance. Configurations containing two strengths of the drug product are proposed. In one configuration a 15 mg vial of IXEMPRA (ixabepilone) for injection (in 10 cc — vial) will be co-packaged with a 8 ml DILUENT for IXEMPRA, also in 10 mL — vial. In the second configuration 45 mg vial of IXEMPRA (ixabepilone) for injection in 50 cc — vial will be co-packaged with 23.5 ml DILUENT for IXEMPRA in 30 mL — vial.

Ixabepilone has very poor water solubility. The aqueous solution degrades following first order kinetics over a pH range of 2.5 and 10.5. The maximum stability for ixabepilone in aqueous solution is between pH 6 and 10. Ixabepilone drug substance will be manufactured at the BMS

facility in Swords, Ireland. IXEMPRA (ixabepilone) for Injection vials will be manufactured at Baxter Oncology, Halle, Germany. Ixabepilone for injection is a single-use, sterile, lyophilized powder for intravenous (IV) infusion following constitution with supplied diluent and further dilution with Lactated Ringer's Injection, USP. Adequate CMC information has been provided for the manufacture and control of ixabepilone drug substance and ixabepilone for injection. Adequate data are provided to support the requested expiration dating period of 24 month when stored in a refrigerator at 2°-8°C (36°-46°F) and retained in the original package to protect from light. [redacted]. The product is required to have the statement "Protect from light" on the label. The DILUENT to constitute ixabepilone for injection consists of a 50/50 (v/v) mixture of purified polyoxyethylated castor oil (also known as Cremophor, or Polyoxyl 35 castor oil, NF) and dehydrated alcohol, USP.

The contents of the DILUENT vial are cloudy at refrigerator temperature. The solution, however, becomes clear when warmed to room temperature. This risk to human subject is minimal from this product attribute, as the product undergoes two manipulations (constitution and dilution) and filtration before entering the patient. The constituted ixabepilone solution should be used within 1-hour and should be stored in the original vial during this period. Total impurities in the constituted solution (2 mg/mL ixabepilone concentration) increase by as much as [redacted] over 24 hours when stored at room temperature, exposed to room light. Prior to intravenous (IV) administration the constituted solution must be further diluted with Lactated Ringer's Injection, USP. Lactated Ringer's Injection, USP is the only IV fluid that has been qualified for making dilutions of constituted ixabepilone for injection. Since it is known that the mixture of purified polyoxyethylated castor oil and dehydrated alcohol extracts the plasticizer DEHP, only DEHP-free bags and sets must be used to administer dilutions of ixabepilone for injection. The dilution of ixabepilone in Lactated Ringer's Injection, USP is to be administered over 3 hours using an infusion set equipped with an in-line or final filter with a microporous membrane size of 0.2 to 1.2 microns. The ixabepilone solution in Lactated Ringer's Injection, USP has a shelf life of 6 hours at room temperature and room light, and the infusion should be completed within this 6-hour period.

Conclusions from CMC review:

- Ixempra for injection (ixabepilone for injection) will be marketed as a kit with a dedicated diluent
- Ixabepilone must be stored at refrigerator temperature and protected from light
- Ixabepilone is unstable after constitution and should be rapidly diluted in Lactated Ringer's Injection, USP.
- Only DEHP-free administration sets should be used with Ixempra for injection due to the presence of cremaphore.
- Manufacturing standards for Ixempra are found to be acceptable for marketing.

3.2 Animal Pharmacology/Toxicology

Ixabepilone is a microtubule stabilizing agent with a mechanism of action that differs from other such agents approved for clinical use. Ixabepilone showed activity in 5-paclitaxel-resistant tumors (3 human tumor xenografts and one murine tumor). As monotherapy, ixabepilone has antitumor activity against a total of 35 human nonclinical *in vivo* cancer models representing a broad spectrum of tumor types. Ixabepilone showed enhanced activity with capecitabine, cetuximab, bevacizumab, or trastuzumab. The drug showed modest efficacy enhancement when combined with irinotecan. The drug showed no enhancement when combined with gefitinib, gemcitabine or paclitaxel. In nonclinical studies, ixabepilone showed low susceptibility to multiple tumor resistance mechanisms including efflux transporters, such as MRP-1 and P-glycoprotein.

Metabolism primarily involves the P450 isozymes CYP3A4 and CYP3A5. Ixabepilone showed moderate to high clearance in mouse, rat, and dog. In both animals and humans, ixabepilone was extensively metabolized and eliminated mainly through fecal excretion. In humans, the unchanged parent drug represents approximately 2% of the dose in feces and approximately 6% of the dose in urine. In studies with lactating rats, ixabepilone-derived radioactivity was excreted in milk following an IV dose. Tissue distribution studies in rats have shown the drug is extensively distributed. The cerebellum, spinal cord, and testes had small but significant amounts of ixabepilone suggesting that the drug-derived radioactivity crossed the blood/brain and blood/testes barriers. In the rat placenta, high concentrations of radiolabeled-ixabepilone were distributed in fetal tissues indicating the drug crossed the placenta.

A full battery of toxicology studies has been conducted with ixabepilone in nonclinical models. The primary toxicities of ixabepilone involve tissues having rapid cell division and include the GI, hematopoietic and lymphoid systems, and the male reproductive system. Dose-dependent decreases in neutrophils were observed in both rodents and non-rodents. In mice and rats, peripheral neuropathy was also a prominent effect. Ixabepilone-induced toxicities were generally reversible following a 1-month, post dose recovery period, except for delayed testicular effects in rats and dogs and peripheral neuropathy in rats and mice. Rodents, lagomorphs and canines were more sensitive to ixabepilone-induced toxicity than human subjects. *In vitro* and *in vivo* cardiovascular safety pharmacology studies indicate that ixabepilone is unlikely to affect electrocardiographic parameters at anticipated plasma concentrations in patients. The general toxicology program has adequately addressed the safety of ixabepilone with appropriate animal models and dosing ranges and regimens.

In the battery of genotoxicity studies, ixabepilone was not mutagenic or clastogenic *in vitro*. However, ixabepilone was clastogenic (induction of micronuclei) in the *in vivo* rat micronucleus study. The genotoxicity profile of ixabepilone was consistent with its pharmacological mechanism of action on microtubules and was similar to the genotoxicity profiles of docetaxel and paclitaxel.

Ixabepilone did not affect mating or fertility. It was not teratogenic in either the rat or the rabbit. Embryo-fetal toxicity (resorptions, abortions, decreased fetal body weights) in rats and rabbits

occurred only at doses that also caused maternal toxicity. Therefore, since clinical administration of ixabepilone occurs at doses associated with minimal to mild clinical side effects, administration during pregnancy may pose a risk for fetal toxicity.

Conclusions from Pharmacology/Toxicology review

- Ixabepilone stabilizes microtubules leading to cell death
- Ixabepilone is active in multiple nonclinical anti-cancer models
- Ixabepilone has been adequately studied for nonclinical toxicology in the mouse, rat, rabbit and dog
- Ixabepilone has a large volume of distribution, is excreted in the feces and is excreted in the milk of lactating rats
- Major toxicities from ixabepilone observed in nonclinical studies were found in hematological, gastrointestinal, neurological and reproductive (male) organ systems
- Myelosuppression and peripheral neuropathy were both evident during nonclinical testing of ixabepilone
- Ixabepilone may pose a risk during pregnancy as evidenced by observed embryo-fetal toxicity.
- Nonclinical toxicological findings predict the major clinical toxicities of ixabepilone

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

- CA163046. A Phase III Trial of Novel Epothilone BMS-247550 Plus Capecitabine Versus Capecitabine Alone in Patients With Advanced Breast Cancer Previously Treated With or Resistant To an Anthracycline and Who are Taxane Resistant
- CA163031 A Phase 1/2 Study of Ixabepilone (BMS-247550) in Combination With Capecitabine in Patients With Metastatic Breast Cancer Previously Treated With a Taxane and an Anthracycline
- CA163081. A Phase 2 Trial of Novel Epothilone BMS-247550 in Patients with Advanced Breast Cancer Who Are Resistant to an Anthracycline, a Taxane, and Capecitabine
- CA163009. A Phase 2 Study of the Epothilone B Analog BMS-247550 in Patients with Taxane-resistant Metastatic Breast Cancer
- CA163010. A Phase 2 Study of the Epothilone B Analog BMS-247550 in Patients With Metastatic Breast Cancer Previously Treated with an Anthracycline

A summary of the trials supporting this application are shown in Tables 1 and 2 (Sponsor Tables 1 and 2)

Table 1.

Table 1: Studies Supporting the Combination of Ixabepilone plus Capecitabine in MBC

Study No	Design	N (Enrolled/ Treated)	Treatment[a]	Population	Primary Efficacy Endpoint
CA163046	Phase 3, open-label, randomized multinational	752[b]/737	Ixabepilone 40 mg/m^2 on Day 1 + capecitabine oral 2000 mg/m^2/day on Days 1-14, Q3 weeks vs capecitabine 2500 mg/m^2/day on Days 1 - 14, Q3 weeks	• Anthracycline resistant or minimum cumulative dose • Taxane resistant	PFS[c] (IRRC)
CA163031	Phase 1/2, open-label, multicenter, dose-escalation	64/62[d]	Ixabepilone 40 mg/m^2 Q3 weeks + capecitabine 2000 mg/m^2/day Q3 weeks (Phase 2 expansion)	Taxane and anthracycline-pretreated	ORR

Source: 29, 26

NA = not available; PFS = progression-free survival; ORR = objective response rate; IRRC = independent radiology review committee

[a] Ixabepilone was administered by intravenous (IV) infusion over 3 hours. Capecitabine was administered orally on Days 1-14 of each cycle

[b] Randomized

[c] Time to progression or death (TTP) in protocol

[d] Subset of patients treated with 40 mg/m^2 ixabepilone/2000 mg/m^2 capecitabine

Table 2

Table 2: Studies Supporting Ixabepilone Monotherapy in Breast Cancer

Study No	Design	Setting/Population	Number (Enrolled/Treated)	Response Criteria[a]	Efficacy Endpoints
CA163081	Phase 2, single-arm, multinational	Advanced breast cancer - anthracycline resistant or minimum cumulative dose, taxane-resistant, and capecitabine resistant	128/126	Tumor response evaluated by RECIST criteria every other cycle	**Primary**: ORR by IRRC **Secondary**: duration of overall response, time to response, duration of SD, month 6 SD rate, PFS, and OS
CA163009	Phase 2, open-label, multinational	Advanced breast cancer - taxane-resistant	49/49[b]	Tumor response evaluated by modified WHO criteria every other cycle	**Primary**: ORR **Secondary**: duration of overall response, PFS, and OS
CA163010	Phase 2, open-label, multinational	Advanced breast cancer - anthracycline pretreated in the adjuvant setting	65/65[b]	Tumor response evaluated by modified WHO criteria every other cycle	**Primary**: ORR **Secondary**: duration of overall response, PFS, and OS

[a] Lesions are measured in 1 dimension using RECIST criteria or in 2 dimensions using WHO criteria

[b] Subset of patients treated with 40 mg/m2 ixabepilone

ORR = objective response rate; IRRC = independent radiology review committee; SD = stable disease; PFS = progression-free survival; OS = overall survival; pCR = pathologic complete response; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

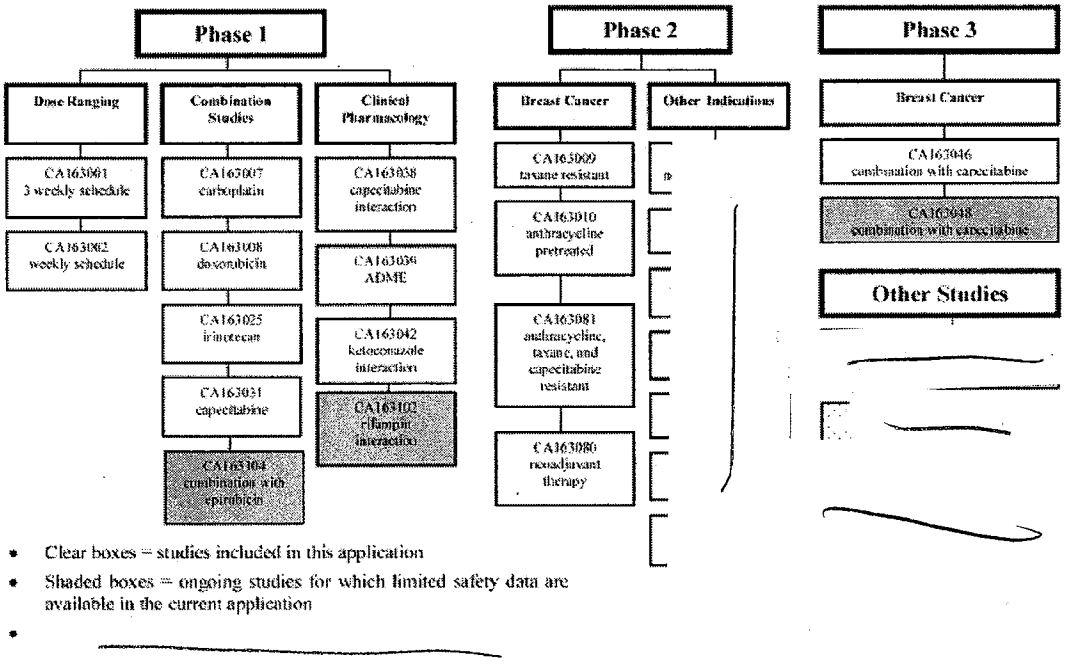
Source: [30,31,32,33]

4.2 Tables of Clinical Studies

The complete clinical development plan for ixabepilone is shown below in Figure 1 (Sponsor Figure 3)

Figure 1

Figure 3: Ixabepilone Clinical Development Program - BMS-sponsored Studies



4.3 Review Strategy

Both the efficacy and safety reviews were divided according to indication. For combination therapy, the pivotal trial was trial 046, with support from trial 031. Safety findings in combination therapy are also derived from these two trials. For monotherapy, the pivotal trial is 081, with support from trials 009 and 010. Again, safety findings for monotherapy are derived from these trials. Other trials are not used to analyze safety since doses differed as did disease indication. The electronic submission, with the Clinical Study Reports, Summary of Clinical Safety, Summary of Clinical Efficacy, and other relevant portions were reviewed. Major efficacy and safety analyses were reproduced using raw or derived datasets in JMP. No literature sources were used.

The efficacy and safety review of combination therapy was performed by Dr. Robert Lechleider. The efficacy and safety review of monotherapy was performed by Dr. Edvardas Kaminskas. Drs. Lechleider and Kaminskas drafted and edited the final review document.

4.4 Data Quality and Integrity

The Division of Scientific Integrity was asked to audit two study sites, based on the volume of patients enrolled. Since both Study 046 and Study 081 were multinational, one U.S. and one foreign site were chosen. For the U.S., Drs. Nuhad Ibrahim and Eva Thomas were the Principal Investigators at UT MD Anderson Cancer Center, Department of Breast Medical Oncology, Houston, TX. For the foreign site, [redacted] Dr. Rubi Khaw Li, Principal Investigator at St. Luke's Medical Center, Quezon City, Philippines, [redacted]. The Philippines site was chosen for inspection.

At the time of this review a report from the inspections has not been finalized. There have not been any reported significant concerns. No FDA 483 was issued.

4.5 Compliance with Good Clinical Practices

From the Study Report for Study 046:

The laws and regulatory requirements of all countries participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study protocol and amendments were reviewed by the Protocol Review Committee of Bristol-Myers Squibb Company (BMS). The protocol, amendments, and patient informed consent received appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion prior to initiation at study sites.

Investigators were to ensure that patients, or, in those situations where consent could not be given by patients, their legally acceptable representatives, were clearly informed about the purpose, potential risks, and other critical issues regarding this study. Prior to the beginning of the study, the investigator must have had the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the patients. Freely given written informed consent was obtained from each patient, or, in those situations where consent could not be given by the patient, their legally acceptable representatives, prior to study participation.

This study was conducted in accordance with the ethical principles in the Declaration of Helsinki. The rights, safety, and well-being of patients were the most important consideration and prevailed over the interests of science and society.

Similar language was presented for Study 081. There are no concerns regarding compliance with Good Clinical Practices.

4.6 Financial Disclosures

According to the Applicant, for no study was there any financial arrangement with the study clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Each investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in the product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). Two investigators disclosed such relationships. One sub-investigator [redacted], and one investigator [redacted] disclosed holdings of >$50,000 in Bristol Myers-Squibb stock. These sites enrolled [redacted] patients respectively. Applicant determined that the participation of these individuals did not introduce significant bias into the study results. In 4 other cases, three for study 046 and one for study 009 there was no response to requests for financial disclosure. A total of fourteen patients were treated at the sites in study 046 where these investigators practiced. There is no apparent bias introduced by these investigators. No patients were treated by the investigator who did not report in study 009.

Financial disclosure was also required from the investigators at [redacted] who performed the independent radiological review. This was reported only for studies 081 and 046. No financial information was required to be disclosed. No compensation related to study outcome was provided to [redacted] investigators.

There are no concerns regarding the integrity of the data as influenced by financial considerations.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The Tmax of ixabepilone typically occurs at the end of infusion, and following administration the concentrations of ixabepilone decreased in a multiexponential manner with a half-life of approximately 52 hours after a 40 mg/m2 IV dose infused over 3 hours. The pharmacokinetics of ixabepilone are dose proportional in the dosage range of 15 to 57 mg/m2. After administration of radio-labeled ixabepilone, 65% of the total radioactivity was eliminated in the feces with 1.6% recovered as unchanged drug. Ixabepilone is metabolized by CYP3A4/5 to form several oxidative metabolites. None of the metabolites were present in human plasma in significant amounts. The known chemical degradants of ixabepilone (BMS-249798, BMS-326412 [redacted] were detected in the plasma of humans but their exposures were <4% that of ixabepilone. In addition their cytotoxicities were 174 to 312 fold less than that of ixabepilone and therefore their plasma concentrations were only characterized in the initial first-in-man trial.

Co-administration of ixabepilone with ketoconazole increased the exposure (AUC) of ixabepilone by 79% (Cmax increased by 7%). The interaction potential with the potent CYP3A4 inducer, rifampin, is on-going. *In-vitro*, ixabepilone was not an inhibitor or inducer of CYP enzymes therefore ixabepilone is not expected to alter the plasma concentrations of other drugs.

In-vitro P-glycoprotein screens were not completed. To support the combination therapy, a phase 1 study was conducted to investigate the pharmacokinetics of ixabepilone and capecitabine co-administration. Results suggest that that capecitabine does not have any clinically relevant effects on the PK of ixabepilone, and ixabepilone does not affect the PK of capecitabine or 5-flurouracil.

The addition of the population PK data to support hepatic dosing was not considered to be robust, therefore, dose recommendations were based on the dedicated hepatic study and will be added to the Dosage and Administration section of the label for moderate and mild hepatic impairment.

5.2 Pharmacodynamics

Results from one phase 1 study in patients with advanced solid tumors suggested that 50 mg/m2 administered IV over 1-hour was a feasible phase 2 dose. However, peripheral neuropathy was reported with this dose and schedule early during the initial supportive phase 2 studies for monotherapy. Based on these reports the infusion duration was extended to 3-hours and the dose was reduced to 40 mg/m2 after the observation of gastrointestinal events in a phase 1 trial. A dose escalation trial in combination with capecitabine (1650 mg/m2 & 2000 mg/m2) was conducted with fixed dose ixabepilone (40 mg/m2). The 2000 mg/m2 dose of capecitabine when co-administered with ixabepilone had an acceptable safety and efficacy profile and this dose was chosen for investigation in further trials. No information regarding the potential to prolong the QT or QTc interval was submitted.

5.3 Exposure-Response Relationships

Exposure-response analyses were performed for neutropenia and neuropathy. Concentration dependent inhibition of absolute neutrophil count (ANC) with a time delay in the effect was observed. A semi-mechanistic non-linear mixed effects model for inhibition of neutrophil progenitor formation in the bone marrow by ixabepilone was developed. The model provided adequate description of the ANC-time profiles as shown in Figure 1. The parameters of the final model are shown in Table 3. The estimated EC_{50} is 14 ng/mL. The highest peak concentrations of ixabepilone in the patient population is about 100-fold higher than the EC50 value, suggesting a strong suppression of bone marrow function immediately after ixabepilone administration. Even 2 days after dosing, approximately 50% of plasma concentration values observed in the patients were still higher than the EC_{50}, indicating a sufficient suppression of bone marrow function. Ixabepilone-associated neutropenia is not dependent on age, baseline ANC value, ECOG performance score, or study (taxane-refractory or anthracycline pre-treated subjects). Model based simulations suggest that risk of neutropenia does not change dramatically over 30 – 50 mg/m2 despite dose-dependent increase in neutropenia. Analyses to predict time-to-first neuropathy did not show any exposure-response relationship.

6 INTEGRATED REVIEW OF EFFICACY

Two indications are being sought in this application.

Proposed Indication 1: Ixabepilone in combination with capecitabine is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.

This indication is supported by the randomized phase III trial CA163046 of capecitabine plus ixabepilone versus capecitabine alone in patients with locally advanced or metastatic breast cancer. Secondary support for this indication is found in study CA163031, which is a phase 1/2 trial of ixabepilone with capecitabine in a similar patient population. These studies and their outcomes are described in **Section 6.1**

Proposed Indication 2: Ixabepilone as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.

The pivotal study to support this indication is CA163081. This study and supportive studies are described in **Section 6.2**

6.1 Indication-Combination Therapy

Ixabepilone in combination with capecitabine is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.

6.1.1 Methods

Study CA 163031

Study CA163031 is a Phase 1/2 study designed to determine the dose and initial efficacy of the combination of ixabepilone with capecitabine in advanced breast cancer. Reference is made to this study for adequacy in determination of dose for the pivotal Phase III study.

Study CA 163046

The phase III, randomized trial of ixabepilone plus capecitabine versus capecitabine alone, study CA163046, is the primary study used to support efficacy. This is a large, 752 patient, multicenter, international study in women with locally advanced or metastatic breast cancer who have received prior anthracycline and taxane therapy.

6.1.2 General Discussion of Endpoints

Primary Endpoint: Progression Free Survival

The primary endpoint for study CA163046 is progression free survival (PFS) although this is referred to as time to progression (TTP) in the study protocol. In TTP deaths are not included, whereas they are in PFS. PFS is an established regulatory endpoint for breast cancer trials, the most recent example being the approval of lapatinib for use in HER2 expressing tumors. A thorough discussion of PFS and other endpoints in cancer trials can be found at http://www.fda.gov/cder/guidance/7478fnl.pdf. In general, PFS is preferred over TTP. Use of PFS as a regulatory endpoint requires regularly scheduled assessments, high quality data with few missing datapoints, prospectively assigned criteria for progression and minimization of bias in assessments. Bias may be minimized through several mechanisms. When possible, patients and treating physicians should be blinded to treatment arm. This is often not possible, practical or ethical, and this study was conducted as an open label study. A blinded assessment of response by a centralized review committee helps to insure the validity of the data, as does review by an entity other than the sponsor. Both of these approaches were taken to minimize bias in the conduct of study CA163046.

Secondary Endpoints

Overall Survival: Overall survival (OS) is a hard, easily measurable endpoint. It is an acceptable endpoint for cancer therapy trials. The relationship between PFS and OS in breast cancer has been reasonably well established. It is presumed that a benefit in PFS will be reflected in OS. This may be confounded by several factors, however, including subsequent therapies received. OR will be evaluated in CA163046 after the pre-specified number of events have occurred.

Objective Response Rate: Objective response rate (ORR) is not generally acceptable as a primary regulatory endpoint. ORR is the combination of complete responses (CRs) and partial responses (PRs). It is a direct measure in most cases of antitumor activity. Included in ORR should be an analysis of duration and extent, i.e. the number of CRs obtained. ORR, time to response and duration of response will be supportive analyses for CA163046.

ORR may be used to support a new indication when there are other therapies unavailable for treatment and the magnitude and duration of the response is significantly large. In this application, ORR is used to support the monotherapy indication. In this case there is a large amount of supporting data from multiple studies, and an advantage in PFS found with the combination therapy trial. See Section 6.2.N for a more detailed discussion of ORR to support a labeling claim.

Symptomatic Benefit: The measurement of symptomatic benefit is among the most difficult endpoints to quantify. Proper measurement of symptomatic benefit requires use of an instrument that has been validated in the disease setting studied and frequent assessments without bias. If properly measured and validated, determination of symptomatic benefit can be used as a

Reviewer's Comment: PFS is an acceptable endpoint in this patient population. OS should be supportive, but may be confounded by subsequent therapies. The secondary endpoints are all deemed exploratory.

regulatory endpoint. Study 163046 incorporated a measurement of symptomatic benefit using the FACT-B instrument.

6.1.3 Study Design

CA163031

Study CA163031 is a non-randomized Phase 1/2 study designed to determine the optimum dose and initial efficacy of ixabepilone in combination with capecitabine in advanced breast cancer. It will be discussed briefly here to determine the adequacy of dose finding for the pivotal study CA163046

Objectives:

Primary: Determine the recommended Phase 2 and Phase 3 dose of ixabepilone when given in combination with capecitabine to treat patients with breast cancer who have previously received an anthracycline and taxane.

Secondary: Safety assessment, determine preliminary antitumor activity, determine preliminary clinical activity as assessed by tumor response

Treatment Plan

This was a two arm Phase 1 study with two schedules of ixabepilone (daily for three days starting at 8 mg/m2/day or as a single bolus at 40 mg/m2 on the first day) in 21 day cycles in combination with capecitabine, BID for 14 days. The single administration of 40 mg/m2 of ixabepilone on day one was chosen to go forward, based on convenience and data from monotherapy studies. Two doses of capecitabine, 1650 mg/m2/day and 2000 mg/m2/day were tested with expansion to 30 patients in each cohort. The 2000 mg/m2/day dose in combination with ixabepilone 40 mg/m2/day was chosen for phase 2 studies.

The Phase 2 portion of this study consists of the 30 patients evaluated in the phase 1 dose finding portion described above, plus additional patients for a total of 64 patients, 62 of whom received ixabepilone 40 mg/m2 on day one and capecitabine 2000 mg/m2/day in twice daily doses on days 1-14 of each 21 day cycle. This is the dose that was carried forward to trial CA163046 to determine efficacy of the combination. The study was non-randomized, open label trial to determine preliminary efficacy.

Patient population

Women with advanced breast cancer who had previously received treatment with an anthracycline and taxane in the adjuvant, neo-adjuvant or metastatic setting were enrolled. Initially patients with non-evaluable (by RECIST) disease were enrolled, however Amendment 3 of this study restricted enrollment to only those patients with evaluable disease. Two patients did not receive any study drug, one for non-compliance before initiation, the other for unknown reasons.

Results:

Analysis was of overall response rate of patients who had evaluable disease (N=50) for patients treated with 40 mg/m2 ixabepilone plus 2000 mg/m2/day capecitabine as described above. Response was determined radiologically using RECIST. The ORR (Complete response (CR) plus partial response (PR)) was 30% (95% CI, 17.9%, 44.6%). All responders had significant metastases and all but 2 had lung and or liver involvement. Among responders, median time to response was 6 weeks. Median duration of response was 6.9+ months. Median PFS was 3.8 months (95%CI, 2.7, 5.6 months). Analysis of the lower dose capecitabine arm (1650 mg/m2/day) from the phase 1 study demonstrated a ORR of 47% (95% CI, 43.4%, 71.1%)

Reviewer's comments: These results supported the initiation of the Phase III study to determine efficacy of ixabepilone in combination with capecitabine in patients with metastatic or locally advance breast cancer. The patient population is essentially identical to that studied in the Phase III trial. These results have not been analyzed independently by the reviewer. Efficacy results for this study are not included in the proposed label. Safety data from this study are included in the proposed label.

CA163046

Study CA163046 is a randomized, unblinded active control trial comparing the combination of capecitabine plus ixabepilone to capecitabine alone in patients with metastatic or recurrent breast cancer. Patients should have received an adequate dose of an anthracycline and be resistant to taxane therapy. The original protocol was modified by 6 amendments, listed below. No peer-reviewed publications from this study have been forthcoming, however the findings have been presented in abstract form at the 2007 American Society of Clinical Oncology (ASCO) Annual Meeting. The description of the protocol found below reflects incorporation of the amendments and is the final version used in the study. The study was performed in 160 centers in 22 countries.

Protocol Landmarks

Study Initiation Date: 04 September 2003
First patient randomized: 04 September 2003
Last patient randomized: 12 January 2006
Database lock: 01 December 2006

Objectives:

Primary:

- Compare time to progression (TTP) of patients treated with ixabepilone plus capecitabine to those treated with capecitabine alone.

Secondary:

- Compare overall survival (OS) in the same population
- Compare objective response rate (ORR) in the same population
- Estimate time to response and response duration
- Compare the safety of the combination ixabepilone plus capecitabine to capecitabine alone in patients with breast cancer
- Compare the impact of each therapy on symptoms using the FACT-B instrument

Reviewer Comment: The protocol as originally written proposed to analyze time to progression, which typically does not include death as an endpoint. As performed, the trial included death from any cause or radiographic progression as the primary endpoint. Clinically evaluable lesions that could be quantified, such as skin lesions measurable with a ruler, were allowed. Thus, the trial in fact used PFS as its primary endpoint.

Patient Population:

Women with advanced breast cancer who had previously received treatment with an anthracycline and taxane in the metastatic setting were initially enrolled. Initially patients with non-evaluable (by RECIST) disease were able to be enrolled, however Amendment 1 of this study restricted enrollment to only those patients with evaluable disease. Further amendments expanded the population to include patients who had previously received adjuvant or neo-adjuvant therapy but subsequently progressed.

Main Entry Criteria (includes both Inclusion and Exclusion criteria):

- Metastatic or locally advanced incurable adenocarcinoma of the breast
- Maximum of three chemotherapeutic regimens. Hormonal and biotherapeutic (e.g. trastuzumab) regimens excluded.
- Previous radiation therapy to less then 30% of bone marrow acceptable
- Anthracycline therapy required, minimum 240 mg/m2 doxorubicin or 360 mg/m2 epirubicin, or progression on therapy or within 3 months when used in metastatic setting, or within 6 months in adjuvant setting
- Taxane resistance defined as recurrence within 4 months following therapy in the metastatic setting or 12 months in the adjuvant setting (see below)
- Adequate organ function
- Neuropathy $\leq$ CTC Grade 2 acceptable

- No brain metastases
- No other concurrent therapies
- No concurrent cardiac disease
- No concurrent inhibitors of CYP3A4

Randomization

Patients were randomized to either arm in a 1:1 ratio. Patients were stratified according to:

- Presence of visceral metastases (yes/no)
- Cumulative dose of anthracycline: ≥240 mg/m2 doxorubicin, ≥360 mg/m2 epirubicin, relapsed>6 months after adjuvant therapy (yes/no)
- Prior chemotherapy for metastatic disease (yes/no) (see Amendment 4 below)
- Study site

Reviewer Comment: The Eligibility Criteria defined a patient population with advanced disease with no accepted alternative therapies. The criteria also defined a population based on current practices regarding adjuvant and neo-adjuvant therapies. Stratification criteria are reasonable and take major possible confounding factors into account.

Treatment Plan:

Combination Arm:

- Ixabepilone 40 mg/m^2 IV Day 1 every 21 days plus oral capecitabine 1000 mg/m^2 BID for 14 days beginning Day 1

Capecitabine alone Arm;

- Capecitabine 1250 mg/m^2 BID for 14 days every 21 days.

Efficacy analysis performed every 6 weeks until progression or death. Patients removed from study for reasons other than progression assessed every 6 weeks until 24 weeks post study entry, then every 3 months until progression. Toxicities evaluated continuously.

Dose Modification:

The dose modification scheme for both ixabepilone and capecitabine as presented in the protocol are replicated in Table 3 (Sponsor table 6.3.4a) below. Note that the grading scheme for hand-foot syndrome is based on a scale of 3, not 4 as per other toxicities. The modified grading criteria were included in the protocol.

Table 3

Table 6.3.4a: Dose Modification - Study Drug Related Non-Hematologic Toxicities

Toxicity	Treatment Arm A		Treatment Arm B
	BMS-247550	Capecitabine	Capecitabine
Grade 2			
Grade 2 except Gr 2 Neuropathy lasting ≥ 7 days[a]	No change	1st appearance - interrupt until resolved to Grade 0 - 1 then maintain dose level[b] 2nd and 3rd appearance - interrupt until resolved to Grade 0 - 1 then decrease 1 dose level 4th appearance - discontinue capecitabine	1st appearance - interrupt until resolved to Grade 0 - 1 then maintain dose level[b] 2nd and 3rd appearance - interrupt until toxicity resolved to Grade 0 - 1 then decrease 1 dose level 4th appearance - discontinue capecitabine
Grade 2 Neuropathy lasting ≥ 7 days	Decrease 1 dose level[c,d]	No change	

Appears This Way
On Original

Toxicity	Treatment Arm A		Treatment Arm B
	BMS-247550	Capecitabine	Capecitabine
Grade 3			
Grade 3 except Gr 3 Hand-Foot-Syndrome and Neuropathy[e]	Decrease 1 dose level[c,d]	1st and 2nd appearance - interrupt until resolved to Grade 0 - 1 then decrease 1 dose level with each appearance 3rd appearance - discontinue capecitabine	1st and 2nd appearance - interrupt until resolved to Grade 0 - 1 then decrease 1 dose level with each appearance 3rd appearance - discontinue capecitabine
Grade 3 Hand-foot-Syndrome	No change		
Grade 3 Neuropathy lasting < 7 days	Decrease 1 dose level[c,d]	No change	
Grade 3 Neuropathy lasting ≥ 7 days	Discontinue BMS-247550[f]		
Grade 4			
Grade 4 except Gr 4 Neuropathy	Discontinue BMS-247550[f]	1st appearance - discontinue capecitabine (if treating physician considers it to be in the patient's best interest to continue with capecitabine, interrupt until toxicity resolved to Grade 0 - 1 then decrease 2 dose levels)	1st appearance - discontinue capecitabine (if treating physician considers it to be in the patient's best interest to continue with capecitabine, interrupt until toxicity resolved to Grade 0 - 1 then decrease 2 dose levels)
Grade 4 Neuropathy	Discontinue BMS-247550	No change	

[a] Also excludes Grade 2 alopecia, fatigue/asthenia, arthralgia, and myalgia.

[b] For Grade 2 hand and foot syndrome and diarrhea reducing one dose level may be considered upon first appearance (based on investigator's clinical judgment)

[c] Delay until toxicity resolved to baseline or ≤ Grade 1 (see Section 6.3.6)

[d] Patients requiring more than two dose reductions will discontinue BMS-247550 except those who appear to be benefiting from treatment in which case treatment can be continued after consultation with and approval by the Sponsor.

[e] Excludes Grade 3 fatigue/asthenia and transient arthralgia/myalgia for which no dose reduction is required

[f] Responding patients who have sufficiently recovered from toxicity during previous cycle may be considered for retreatment after dose reduction only after discussion with and agreement by Sponsor

Table 6.3.4b: Dose Modification - Hematologic Toxicities

Toxicity	Treatment Arm A		Treatment Arm B
	BMS-247550	Capecitabine	Capecitabine
Grade 3:			
Grade 3 Platelets with: significant bleeding or requiring platelet transfusion	Decrease 1 dose level[a,b]	Interrupt for any coexisting diarrhea or stomatitis until platelet count ≥ 50,000/mm^3 then maintain dose level	1st and 2nd appearance - interrupt until resolved to Grade 0 - 1 then decrease 1 dose level with each appearance 3rd appearance - discontinue capecitabine
Grade 4			
Grade 4 Platelets	Decrease 1 dose level[a,b]	Interrupt for any coexisting diarrhea or stomatitis until platelet count ≥ 50,000/mm^3 then maintain dose level	1st appearance - discontinue capecitabine (if treating physician considers it to be in the patient's best interest to continue with capecitabine, interrupt until toxicity resolved to Grade 0 - 1 then decrease 2 dose levels)
Grade 4 Neutrophils lasting ≥ 7 days	Decrease 1 dose level[a,c]	Interrupt for any coexisting diarrhea or stomatitis until neutrophil count ≥ 1000/mm^3 then maintain dose level	
Febrile Neutropenia any grade	Decrease 1 dose level[a,c]	Interrupt for any coexisting diarrhea or stomatitis until neutrophil count ≥ 1000/mm^3 then maintain dose level	

[a] Patients requiring more than 2 dose reductions will discontinue BMS-247550 except those who appear to be benefiting from treatment in which case treatment can be continued after consultation with and approval by the Sponsor.

[b] Delay until platelet count ≥ 100,000/mm^3 (see Section 6.3.6).

[c] Delay until neutrophil count ≥ 1,500/mm3 (see Section 6.3.6).

Study Evaluations

Radiographic: Patients were evaluated by radiography every 6 weeks from study entry. Preferred method was spiral or helical CT with a 5 mm reconstruction algorithm. Acceptable alternatives were MRI or standard CT. Ultrasound was acceptable for superficial lesions. Bone scan was performed when clinically indicated but could not be used to determine progression. Confirmation of bone lesions by radiographic means was required to document disease progression.

Clinical: Patients were evaluated clinically prior to each cycle of chemotherapy. Clinical evidence of disease progression required radiologic confirmation. Skin lesions were allowable for ascertaining disease status. If skin lesions were the sole evaluable site of disease, digital photography with a ruler were required. FACT-B was completed at each visit.

Laboratory: Hematology was measured each week for cycles 1-4, then at each cycle. Other laboratory values were determined at each cycle.

All studies were repeated at the off study visit.

Evaluation Criteria

Progression was determined at a central facility ———, using scans obtained at local sites. In addition to determination of radiographic progression by evaluation of scans, a medical oncology review was performed to evaluate progression based on clinical criteria, such as appearance of new skin lesions, findings from physical exam or adverse events. Data for oncology review was supplied to ——— from BMS. For determination of radiological progression, RECIST was used. Progression was determined when the sum of the longest diameters of target lesions exceeded the best response by 20%. New lesions also indicated progression. The following exceptions to published criteria were included in the charter

- Bone scans were required at baseline, but were only repeated if clinically indicated, even if disease was present at baseline.
- Clinically measured lesions other than skin lesions were considered non-target.
- Photographed skin lesions could be considered target
- Chest x-ray was not allowed to evaluate target lesions
- Measurable lesions must be at least twice the slice thickness at baseline.
- Tumor markers were not used for evaluation
- Histological confirmation of a solitary metastatic lesion was not required
- Non-target lesions were evaluated for progression, not only presence or absence

Statistical Analysis:

The primary endpoint as defined in the protocol is TTP, however the analysis presented is of PFS. Patients who died without documented progression were considered to have progressed on

the date of death. Patients who did not progress or die were censored on the date of the last IRRC assessment.

Reviewer's Comments: The overall design of the protocol is sound. Biases should be eliminated by the randomization scheme, and there are a minimal number of strata. The study protocol consistently describes TTP as the primary efficacy endpoint. Traditionally, TTP includes only progression, and patients are censored if they die without evidence of progression. In this study, death or radiographic progression were the primary time to event endpoints, if no previous progression was documented. Thus, this is in fact a PFS analysis. Use of the IRRC should minimize bias in assessment of disease progression.

Protocol Amendments

Amendment 1 (2 patients enrolled)
Date: 23 September 2003

- Defined measurable lesions measured by other than CT scan as ≥ 20 mm in diameter
- Required radiographic confirmation of bone lesions
- Defined CR as complete clinical and radiographic disappearance of lesions
- Modified inclusion criteria to insure at least one measurable lesion
- Charged DMC with monitoring safety as well as efficacy
- Clarified dose modifications scheme for capecitabine

Amendment 2 (3 patients enrolled)
Date: 24 September 2003

- Allowed for collection of blood samples for pharmacogenetic research

Amendment 3 (77 patients enrolled)
Date: 06 April 2004

- Allowed for collection of tissue samples to be used for biomarker research

Amendment 4 (320 patients enrolled)
Date: 03 February 2005

- Increased the disease free interval following prior taxane therapy from 6 to 12 months in the adjuvant setting
- Increased the disease free interval following prior taxane therapy for metastatic disease from 3 to 4 months
- Eliminated the requirement for one prior metastatic regimen. Patients who received adjuvant taxane and anthracycline, and have received maximal anthracycline and have recurred within the window defined above will be considered eligible.
- Introduced a new stratification factor of previous therapy for metastatic disease. All patients randomized before this amendment will be considered as having received therapy for metastatic disease.
- Expanded inclusion criteria to include skin lesions without other radiographic lesions

- Revised exclusion criteria to exclude patients with grade 2 or greater elevations in AST or ALT
- Permits dose reduction of capecitabine upon first appearance of grade 2 hand-foot syndrome and diarrhea.

Amendment 5 (482 patients enrolled)
Date: 05 July 2005

- Allowed for collection of blood samples for PK analysis in China

Amendment 6 (527 patients enrolled)
Date: 11 August 2005

- Recommended no co-administration of ixabepilone with strong inhibitors of CYP3A4
- Clarified the use of filters for administration

Reviewer's comments: Amendments 2, 3 and 5 are not expected to influence the interpretation of either safety or efficacy. Amendment 1 which modifies criteria for entry and measurement was instituted near the start of the trial (2 patients enrolled) and is not expected to influence study outcome. Amendment 4 expands the patient population eligible for the trial to include patients who have had disease progression within 12 months following adjuvant taxane therapy, from those who had progression within 6 months. Similarly it expands the population eligible in the metastatic setting. This may have the effect of slightly increasing the apparent efficacy of ixabepilone therapy if there is overlapping activity with taxanes. The introduction of a new stratification scheme will not affect interpretation of the primary endpoint. The exclusion criteria for liver disease, based on the observation of significant toxicity, has the effect of increasing patient safety and will be addressed in the safety section. Under half of the total study population was enrolled by this point. The population definition probably more accurately reflects current clinical practice.

6.1.4 Efficacy Findings

Study CA163046

Primary Analysis Population

The population used for the analysis of the primary endpoint of PFS is the set of all patients who enrolled on the trial and received a randomization assignment. This is the intention to treat (ITT) population. 752 patients were enrolled on the trial (target was 750). 375 patients were randomized to combination and 377 to capecitabine only. 369 patients in the combination arm received at least one dose of therapy, and 368 in the capecitabine received therapy. 93% and 97% of patients in the combination and capecitabine arms respectively received their first dose of therapy within 5 days of therapy. One patient was randomized twice to the combination arm but is counted only once for analysis purposes. One patient who was randomized to combination received only capecitabine. A total of fifteen patients were never treated; 5 (1.3%) in the combination arm and 10 (2.7%) in the combination arm.

Demographics

The baseline demographics as derived by the reviewer from dataset **demodb.xpt** are shown in Reviewer Table N. All but one patient was female (the male patient was a protocol violation). The majority of patients were white, with a significant minority of Asian patients. The two arms were balanced for racial make up. There were slightly more patients under 65 in the combination arm, but this is balanced by the slight preponderance of patients at the age of 65 in the capecitabine arm. Performance status was balanced with an equal number of patients on both arms having a Karnofsky score of greater than 70. Patients did not differ across arms in menopausal status, and 76.7 % of patients overall were reported as post-menopausal.

Table 4. Baseline demographics Study 046

RANDOMIZED ARM	CAPECITABINE n total=377 n (%)	CAPECITABINE PLUS IXABEPILONE n total=375 n (%)
RACE		
American Indian Native Alaskan	0 (0)	1 (0)
Asian	87 (23)	83 (22)
Black/African American	11 (3)	11 (3)
Other	32 (8)	23 (6)
White	247 (66)	257 (69)
TREATMENT RECEIVED		
Not treated	10 (3)	5 (1)
Capecitabine	367 (97)	1 (0)
Ixabepilone + Capecitabine	0	369 (99)
AGE GROUP		
Not Reported	1 (0)	0 (0)
< 65	322 (85)	336 (90)
>= 65	54 (15)	39 (10)
ER STATUS		
Negative	161 (43)	164 (44)
Not Reported	38 (10)	37 (10)
Positive	178 (47)	173 (46)
Unknown	0	1 (0)
ERPR STATUS		
ER or PR Status Not Reported	53 (14)	52 (14)
ER+, PR+	126 (33)	126 (34)
ER+, PR-	39 (10)	41 (11)
ER-, PR+	19 (5)	10 (3)
ER-, PR-	140 (37)	146 (39)
HER2 STATUS		
Negative	238 (63)	220 (59)
Not Reported	72 (19)	80 (21)

Positive	53 (14)	59 (16)
Unknown	14 (4)	16 (4)
TRIPLE NEGATIVE		
No	281 (75)	284 (76)
Yes	96 (25)	91 (24)
PRIOR ANTHRACYCLINE		
Yes	374 (99)	373 (99)
No	3 (1)	2 (1)

Disease Characteristics

The population studied had extensive disease. 89.6% of patients in the combination arm and 91% in the capecitabine arm had two or more disease sites as assessed by the IRRC. (Table N shows the extent and sites of disease as evaluated by the IRRC.) Investigator assessment had 83.7% and 83.8% in the combination and capecitabine arms respectively with two or more sites. Most patients had soft tissue or visceral disease, with only a handful (five or fewer in any group) with bone only disease. This may be a consequence of the requirement to have measurable disease for study entry.

Table 5. Baseline disease sites

Table 8.4.1A: Summary of IRRC Tumor Assessments at Baseline (All Lesions) - Randomized Patients

	Number of Subjects (%)		
	Ixabepilone + Capecitabine N = 375	Capecitabine N = 377	Total N = 752
Presence of all Lesions			
Subjects with at least one lesion	371 (98.9)	375 (99.5)	746 (99.2)
Disease Sites (a)			
Ascites	14 (3.7)	14 (3.7)	28 (3.7)
Bone	168 (44.8)	162 (43.0)	330 (43.9)
Breast	61 (16.3)	63 (16.7)	124 (16.5)
Chest Wall	53 (14.1)	53 (14.1)	106 (14.1)
Effusion	57 (15.2)	55 (14.6)	112 (14.9)
Lymph Node	250 (66.7)	249 (66.0)	499 (66.4)
Other	20 (5.3)	18 (4.8)	38 (5.1)
Peritoneum	7 (1.9)	14 (3.7)	21 (2.8)
Pleura	29 (7.7)	35 (9.3)	64 (8.5)
Skin/Soft Tissue	60 (16.0)	62 (16.4)	122 (16.2)
Visceral, Liver	245 (65.3)	228 (60.5)	473 (62.9)
Visceral, Lung	180 (48.0)	174 (46.2)	354 (47.1)
Visceral, Other	34 (9.1)	28 (7.4)	62 (8.2)
Number of Disease sites			
1	39 (10.4)	34 (9.0)	73 (9.7)
2	85 (22.7)	98 (26.0)	183 (24.3)
3	110 (29.3)	121 (32.1)	231 (30.7)
4	79 (21.1)	69 (18.3)	148 (19.7)
>= 5	58 (15.5)	53 (14.1)	111 (14.8)

[a] Patients may have had lesions at more than 1 site

Patients were evaluated for hormone and growth factor receptor status at baseline and were well balanced. The number of HER2 positive patients was 15.7% in the combination arm and 14.1% in the capecitabine arm. The number of ER-/PR-/HER2- (triple negative) patients was 24.3% and 25.5% in the combination and capecitabine arms respectively. The patient population was heavily pre-treated. All but 5 patients total received at least one prior regimen (2 in the

combination arm, 3 in the capecitabine arm). The number of prior regimens is shown in sponsor table A. Approximately half of all patients in both arms received hormonal therapy, while 67% of combination patients and 71% of capecitabine patients received previous radiation therapy. The characteristics of patients with regards to previous chemotherapeutic regimens is shown in Table 6 (Sponsor Table 8.4.3.1)

Table 6. Prior chemotherapeutic regimens

Table 8.4.3.1: Number of Prior Chemotherapy Regimens - Randomized Patients

	Number of Subjects (%)		
	Ixabepilone + Capecitabine N = 375	Capecitabine N = 377	Total N = 752
Number of subjects receiving prior chemotherapy (a)	373 (99.5)	374 (99.2)	747 (99.3)
Number of prior chemotherapy regimens			
0	2 (0.5)	3 (0.8)	5 (0.7)
1	22 (5.9)	24 (6.4)	46 (6.1)
2	202 (53.9)	215 (57.0)	417 (55.5)
3	132 (35.2)	119 (31.6)	251 (33.4)
>3	17 (4.5)	16 (4.2)	33 (4.4)
Number of prior chemotherapy regimens - Neo adjuvant/Adjuvant setting			
0	93 (24.8)	92 (24.4)	185 (24.6)
1	213 (56.8)	227 (60.2)	440 (58.5)
2	63 (16.8)	49 (13.0)	112 (14.9)
3	5 (1.3)	9 (2.4)	14 (1.9)
>3	1 (0.3)	0	1 (0.1)

Baseline Measurements

The majority of patients had normal hematological measurements. Protocol amendment 4 dated 3 February 2005 altered the entry criteria for liver function test abnormalities. Prior to this date, patients with grade 2 or greater ALT or bilirubin or with ALT grade 3 or greater in the presence of metastases were excluded. After institution of this amendment because of safety concerns, patients with grade 2 or greater AST, ALT or bilirubin elevations were excluded, regardless of metastases. Prior to this, 33 patients (15 combination, 18 capecitabine) with moderate to severe hepatic dysfunction were treated. After implementation, 9 (1 combination, 8 capecitabine) were treated. At study end, 16 (4%) patients in the combination arm had moderate or severe hepatic dysfunction and 26 (7%) of patients in the capecitabine alone arm had moderate severe hepatic dysfunction. The overwhelming majority had normal renal function at baseline. One patient in the combination arm had grade 2 creatinine elevation and no patients had grade 3.

Missing Data

In the primary PFS analysis, patients who at the end of the study had not had progression and were still alive were censored on the date of their last assessment. It is not clear whether this includes patients who were lost to follow-up, although presumably this group would be included as not having progressed or died. In a sensitivity analysis performed by the sponsor, two

additional restrictions were applied. The first concerns patients who died at an extended time after the last tumor assessment. Patients who died more than three months after their last tumor assessment were censored at the date of the last tumor assessment (and not counted as a death on the date of death). To account for unscheduled assessments, three restrictions were used. Patients who had progression while on treatment or who were off treatment but had received less than 30 weeks of therapy and were assessed at an interval of greater than 48 days were presumed to have progressed at 48 days. Patients who had progression off treatment and were treated for more then 30 weeks were presumed to have progressed at 97 days from the last assessment. In the later case the assumption is that assessment occurred at greater than or equal to 98 days after the previous assessment.

Protocol Violations

There were significant protocol violations in both arms of the trial.

In the combination (ixabepilone plus capecitabine) arm, there were 31 significant eligibility violations that affected 24 patients. In the capecitabine arm, 44 violations affected 33 patients. Table N lists the violations. There were 25 significant protocol violations affecting 23 subjects during treatment in the combination arm, and 14 violations affecting 13 patients in the capecitabine arm. The primary reasons for violation during treatment were improper dose adjustment following toxicity for either capecitabine or ixabepilone. The number of violations for improper adjustment of the capecitabine dose was roughly even between the two arms (12 and 9 for combination and capecitabine alone, respectively) but there were 13 instances of improper adjustment of the ixabepilone dose in the combination arm, which accounts for the increase in violations in the combination arm. Three patients in the capecitabine arm received other anti-cancer agents and one patient had been randomized to combination therapy but only received capecitabine. (This patient is included in the combination arm in the ITT analysis.) Of note, all patients had a correct diagnosis of adenocarcinoma of the breast. Eligibility violations are summarized in Table 7, Sponsor Table S.7.8.

Table 7.

Table S.7.8:
Significant Eligibility Deviations - Randomized Subjects

	Number of Subjects (%)		
	Ixabepilone + Capecitabine N = 375	Capecitabine N = 377	Total N = 752
Subjects with at least one significant eligibility deviation	24 (6.4)	33 (8.8)	57 (7.6)
Significant eligibility Deviations:			
Wrong cancer diagnosis	0	0	0
Non-measurable disease (as per investigator)	5	8	13
No Taxane Resistance	8	14	22
No Anthracycline resistance/minimum cumulative dose	10	12	22
More than 3 prior chemotherapy regimens	6	7	13
No prior chemotherapy regimen	2	3	5

Exposure

The median number of cycles received was 5 in the combination arm and 4 in the capecitabine alone arm. Fifty-one percent of patients required reduction of ixabepilone and 45% required reduction of capecitabine in the combination arm, while 37% required reduction of capecitabine in the capecitabine arm. Sixty-four percent of cycles were administered at full dose of ixabepilone and 70% at full dose of capecitabine in the combination arm, while 64% of cycles were at full dose in the capecitabine alone arm.

Prior Therapy

Nearly all patients in both arms had received prior therapy for breast cancer in the adjuvant/neo-adjuvant setting, the metastatic setting, or both. Ninety-four percent of patients in the combination arm, and 93% in the capecitabine arm received two or more chemotherapy regimens. Ninety-seven percent of patients in both arms met requirements either for minimal anthracycline dose or progression or relapse following anthracycline therapy. Doxorubicin was the most commonly used anthracycline, with 58% of patients total receiving doxorubicin therapy. Most of the remaining patients received epirubicin, with a small number of patients (28 total in both arms, 4%) receiving another anthracycline. Specific anthracyclines used were balanced across both arms. Similarly, all but eight patients in the combination arm and fourteen patients in the capecitabine arm met criteria for prior taxane use. In the combination arm docetaxel and paclitaxel were used evenly (180 vs. 184 patients (48% vs. 49%) respectively), while in the capecitabine arm, docetaxel was used somewhat more frequently (192 vs. 169 patients for docetaxel vs. paclitaxel respectively (51% vs. 45%). A very small (<1%) minority of patients in each arm received both drugs.

Reviewer's Comments: The population studied is one which has extensive disease and has received extensive chemotherapy with active agents. The arms were well balanced with regards to extent and location of disease, and prior chemotherapeutic regimens. There is a slight imbalance in the use of docetaxel vs. paclitaxel in the capecitabine arm, but this is not expected to influence the outcome or the measurement of the activity of ixabepilone. Protocol violations were evenly balanced across both arms. Somewhat more patients in the capecitabine arm had moderate to severe hepatic dysfunction (16 patients in the combination arm, 26 patients in the capecitabine arm). Given the toxicities observed with hepatic dysfunction during combination therapy, this imbalance favors the combination arm. Overall the population is representative of patients with extensive disease seen in clinical practice, and was balanced in both arms

Progression Free Survival

A planned interim analysis was performed after 369 events in the first 450 patients randomized. The O'Brien-Fleming boundary for the p-value for the interim analysis was 0.0083 and the final p-value was set at 0.0473. The DMC did not recommend stopping the trial after the interim analysis.

The primary endpoint of the study was PFS as determined by the IRRC. Data for PFS are presented in reviewer Table 8 below

Table 8 Progression Free Survival-ITT Population (IRRC Determination)

Treatment	Median Time (Months)	Lower 95%	Upper 95%	Median Time (Weeks)	Lower 95%	Upper 95%
Capecitabine	4.1725	3.8111	4.4025	18.143	16.571	19.143
Ixabepilone + Capecitabine	5.848	5.3552	6.9651	25.429	23.286	30.286

These values were determined using the EFF_RAD dataset and agree with those reported by the sponsor. The data were analyzed using JMP 6.0. In this analysis, patients were grouped by randomization arm, regardless of treatment. Patients who received no study drug were censored on the first day of enrollment. The reviewer determination agrees with that performed by the sponsor. When patients with eligibility violations are excluded from the analysis, the median survival for the Capecitabine arm does not change, but the median survival for the Combination arm increases to 27 weeks.

An analysis by the statistical reviewer confirms these results. When patients who received subsequent therapy are censored at the time of such therapy, the hazard ratio is 0.70 (95% CI, 0.59-0.83)

A similar analysis was performed using patients as treated (Table 9). Patients in this analysis were also censored on the day of enrollment if no study medication was administered. This analysis performed by the reviewer is listed below. In this analysis, 10 patients randomized to

capecitabine and 5 patients randomized to combination are not included. One patient randomized to combination but treated with capecitabine only is included in the capecitabine arm.

Table 9-PFS-As treated population (IRRC Determination)

Treatment	Median Time (Months)	Lower 95%	Upper 95%	Median Time (Weeks)	Lower 95%	Upper 95%
Capecitabine	4.1725	3.8111	4.4025	18.143	16.571	19.143
Ixabepilone + Capecitabine	5.9795	5.4538	6.9979	26	23.714	30.429

Censored patients

Patients censored for any reason were evaluated. A total of 48 patients in the capecitabine arm and 65 patients in the combination arm were censored. Most patients were censored on the date of the last tumor evaluation without documentation of death or evidence of progressive disease. Five patients in the capecitabine arm were censored on the enrollment date for protocol violations or withdrawal prior to the first scheduled assessment. Two patients in the combination arm were censored at enrollment for protocol violations. Four patients total had incorrect dates of last evaluation entered in the database, although these only differed by at most 4 days. Three patients in the combination arm and five patients in the capecitabine arm were censored on the date of the last radiological evaluation with that evaluation being reported as "Unable to evaluate (UE)". In these cases all of the scans were listed as UE. An additional three patients in the combination arm and ten in the capecitabine arm who had unevaluable scans had death as their event, without clear knowledge of prior radiologic progression. Censoring these 21 patients at the time of randomization yields a median survival (months) estimate of 4.17 (95% CI, 3.88, 4.50) for capecitabine and 5.81 (95% CI, 5.36, 6.93) for combination therapy, with a stratified log-rank p value of .0008 and HR of 0.76 (95% CI, 0.65, 0.98). This does not differ significantly from the ITT population results.

An analysis of the ITT population was performed using the investigator assessment of disease progression and the dataset EFFICACY.xpt. The results are presented in Reviewer Table 10 below:

Table 10: PFS by Investigator assessment, ITT Population

Treatment	Median Time (Months)	Lower 95%	Upper 95%	Median Time (Weeks)	Lower 95%	Upper 95%
Capecitabine	3.8111	2.8583	4.1725	16.571	12.429	18.143
Ixabepilone + Capecitabine	5.2567	4.271	5.5852	22.857	18.571	24.286

A similar analysis was performed of the as treated population. (Table 11 below)

Table 11: PFS by Investigator assessment, as treated population

Treatment	Median Time (Months)	Lower 95%	Upper 95%	Median Time (Weeks)	Lower 95%	Upper 95%
Capecitabine	3.7782	2.8583	4.1725	16.429	12.429	18.143
Ixabepilone + Capecitabine	5.2895	4.3039	5.5852	23	18.714	24.286

Both of these analyses were performed by the reviewer and agree with that performed by the sponsor and presented in the study report. Fewer patients were censored in the Investigator assessment of disease progression. Thirty patients (two at randomization) in the combination arm and 21 patients (five at randomization) in the capecitabine arm were censored in total. The remainder of the censored patients were censored at the time of the last tumor assessment. There was complete agreement between the IRRC assessment and the investigator assessment in 385 cases (51.2%). This degree of concordance is similar to that observed in other trials. In most cases the discrepancy is due to earlier adjudication of radiographic progression by the IRRC compared to the investigators. There does not appear to be a specific bias favoring one arm in this regard.

The results of these analyses are concordant. The investigators demonstrated a shorter median time to survival in both the capecitabine and combination arms, suggesting that if there was a bias, it was equally shared between both arms. There is a slightly smaller benefit with ixabepilone when assessed by the investigators, but the advantage of combination therapy for the PFS endpoint as determined by the investigators is still statistically significant. The difference in the number of patients censored is unlikely to be significant, and is similar between arms. Together, these data support the conclusion that addition of ixabepilone to standard capecitabine chemotherapy leads to a benefit in PFS, the primary endpoint of the study.

Subgroup analyses performed by the reviewer using the RAD_EFF data show that the prolongation in PFS is consistent for the two major races—Asian and white—enrolled in this study. Enrollment of subjects with other racial identification was insufficient to make conclusions about possible differences in efficacy. For patients age 65 and older, there was no statistically significant difference in PFS, however the study was not powered to detect a difference specifically in this population. Based on these two analyses, it does not appear that there is a major subgroup that is driving the prolongation of PFS.

Data Integrity

Seventy-five records were examined to determine concordance between radiographic progression dates as reported by [redacted] in the document "Independent Radiology Reports" and as recorded in the database RAD_EFF used to perform the PFS analysis reported above. In all cases, the dates reported were in concordance, either with the date of radiographic progression as determined by CT scan or by Oncology Review as reported [redacted]. A sampling of censored patients also revealed that the dates of censoring coincided with the last recorded radiographic assessment as reported by [redacted].

Secondary Endpoints

Overall Survival (OS)

The study is powered to detect a difference in overall survival after 631 total deaths. An unplanned interim analysis was requested by the FDA and performed prior to this number, and no difference in OS was detected at $p<0.0001$. The final analysis of OS will be performed after 631 deaths have occurred. The number of events in the interim analysis was not specified.

Objective Response Rate (ORR)

ORR was evaluated both by the investigators and by the IRRC. The reviewer's analysis of data from the IRRC is presented in table 12 below.

Table 12. Response by IRRC

Capecitabine (n=377)	#	% (ITT)	% (Evaluable)	Combination (n=375)	#	% (ITT)	% (Evaluable)
CR	0	0	0	CR	1	0.3	0.3
PR	54	14.3	16.3	PR	129	34.4	37.6
SD	175	46.4	52.9	SD	155	41.3	45.2
PD	102	27.1	30.8	PD	58	15.5	16.9
Unevaluable	46	12.2	na	Unevaluable	32	8.5	NA

These data agree with that presented by the sponsor. The objective response rate for the ITT population is 34.7% for the combination arm and 14.3% for the capecitabine arm. Patients were unevaluable primarily because only a screening exam was performed. Other reasons included inability to assess target lesions and complete lack of IRRC data as described in Table N. One patient in the combination arm was in fact treated with capecitabine only.

Investigator assessment of response revealed a higher rate of response as described in Reviewer Table 13 below

Table 13. Investigator assessment of response.

Capecitabine	#	% (ITT)	% (Evaluable)	Combination	#	% (ITT)	% (Evaluable)
CR	3	0.8	0.9	CR	12	3.2	3.5
PR	82	21.8	24.3	PR	146	38.9	42.3
SD	144	38.2	42.6	SD	136	36.3	39.4
PD	109	28.9	32.2	PD	51	13.6	14.8
Unevaluable	39	10.3	NA	Unevaluable	30	8.0	NA

The ORR with reviewer assessment was 22.5% for Capecitabine and 41.9% for the combination, somewhat higher than that determined by the IRRC. The number of unevaluable patients was similar in both assessments.

The ORR as determined by the IRRC and Investigator are similar. Since the Investigators were not necessarily blinded as to treatment, there is the obvious possibility of bias, but both arms saw a similar increase in response rate compared to the IRRC analysis. The one patient in the combination arm treated only with capecitabine achieved a partial response. This does not significantly change the results of the ITT analysis.

Time to Response and Response Duration

Time to response and duration were the last two objective clinical parameters defined as secondary outcomes prior to study initiation. Based on the sponsor's data, there was no significant difference in either of these two parameters. Time to response was 11.7 weeks in the combination arm and 12 weeks in the capecitabine alone arm. Similarly, the duration of response did not differ significantly between the two arms. The median duration of response in the capecitabine arm was 5.6 months and in the combination arm it was 6.4 months, but the 95% confidence intervals overlapped with the point estimates in both cases. An analysis of all patients for time in response, attributing a response time of one day to those who had progressive disease at the first assessment, showed a benefit to therapy with ixabepilone with a hazard ratio of 0.79 (95% CI: 0.68, 0.92). This result is to be considered exploratory.

Time to response and duration of response did not demonstrate a benefit for ixabepilone in this trial, although duration of response showed a trend to benefit with ixabepilone. No conclusions about response duration with ixabepilone therapy can be drawn from the data presented. The sponsor's analysis was not reproduced by the reviewer.

Patient Reported Outcomes

The FBSI was used to assess symptoms during therapy. An analysis plan for analyzing data collected with the FBSI was prospectively generated. The comparability of the baseline scores between treatment groups was assessed using a Wilcoxon rank sum test. Changes in the FBSI scores while on treatment versus baseline were examined using longitudinal analysis and descriptive statistics. The primary analysis to compare treatment arms will be the Wei-Lachin test for stochastic ordering.

There are significant difficulties with interpreting the results of these analyses, despite the clearly defined plan. The major problem is the unblended nature of the trial. Patients receiving combination therapy clearly knew that they were administered study drug. This makes any interpretation of differences in subjective responses, as measured by the FBSI or any similar device, difficult. There was a significant drop out rate for respondents, particularly at the first follow up visit after discontinuation of study drug. At baseline, 89.6% of patients in the combination arm and 87.8% in the capecitabine arm completed the FBSI questionnaire. By week 6, only 65.7% and 64.7% of eligible patients in the combination and capecitabine arm completed the questionnaire. Thus, over one-third of eligible patients in either arm did not complete the questionnaire. It is impossible to know if these dropouts would be evenly balanced in their responses. The response rates continued to drop throughout the study.

There was a statistically significant change in FBSI scores from baseline by week 24 favoring the capecitabine group. The absolute change did not reach 2.5 points, the prespecified threshold for a clinically relevant difference. Sensitivity analyses performed by the sponsor led to similar results. The sponsor has several plausible explanations for the relative performance of the two therapies in this regard. There was poor compliance with follow-up questionnaires, suggesting that the FBSI measured a significant number and severity of symptoms due to chemotherapy, since patients in the combination remained on therapy longer on average. A sensitivity analysis performed by the sponsor to take into account the faster rate of PD and death in the capecitabine arm showed no statistically significant difference in symptom scores at week 24.

Reviewer's Comment: No conclusions can be reached from the PRO data. The pre-specified design did not take into account the possibility of loss of respondents due to an inferior therapy. The absolute improvement in symptom scores in the capecitabine group did not reach a clinically meaningful level. There was poor compliance following the baseline evaluation. While the sponsors explanations for the differences are plausible, the post-hoc sensitivity analysis is somewhat questionable. While it is possible that patients on combination therapy do not have as much symptom improvement as those on capecitabine only, this cannot be certain and should not be credited to capecitabine or blamed on the combination.

6.2 Indication - Monotherapy

Proposed Indication 2. Ixabepilone as monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capecitabine.

6.2.1 Methods

The principal trial supporting the above indication is CA163081 (A Phase 2 Trial of Novel Epothilone BMS-247550 in Patients with Advanced Breast Cancer Who Are Resistant to an Anthracycline, a Taxane, and Capecitabine). Supporting studies are CA163009 (A Phase 2 Study of the Epothilone B Analog BMS-247550 in Patients with Taxane-resistant Metastatic Breast Cancer) and CA163010 (A Phase 2 Study of the Epothilone B Analog BMS-247550 in Patients with Metastatic Breast Cancer Previously Treated with an Anthracycline). All three studies are single-arm, open-label, multicenter trials.

6.2.2 General Discussion of Endpoints

Endpoints for the principal trial CA163081 were discussed at End-of-Phase 2 meeting. The Sponsor proposed Objective Response Rate (ORR) as determined by investigators as the primary

efficacy endpoint and ORR as determined by IRRC, duration of response, time to response, progression-free survival (PFS) and overall survival (OS) as secondary endpoints. Duration of response and time of response endpoints were based on IRRC assessments. The Agency suggested ORR as determined by IRRC as the primary endpoint and ORR as determined by investigators as a secondary endpoint. The Sponsor accepted this suggestion. Tumor response was assessed according to RECIST criteria by both IRRC and the investigators.

Objective response rate that is relatively durable provides evidence of antitumor activity and for that reason is commonly used in single-arm trials. PFS and OS provide supportive evidence, but are not as useful as in randomized trials in which these efficacy parameters can be compared between treatment arms.
Because the target population MBC patients were not candidates for therapy with anthracyclines, taxanes or capecitabine, there was no realistic comparator to perform a randomized trial of ixabepilone.

The primary efficacy endpoints in clinical studies CA163009 and CA163010 were also tumor response rates. However, tumor response was assessed according to modified WHO criteria and the sponsor's medical team made these assessments based on the tumor measurements collected on CRFs using criteria defined in the protocols.

The Agency was willing to consider ORR in the trials in this setting because of the refractory populations and because of the availability of data from the randomized trials in related patient populations.

6.2.3 Study Design

CA163081

Clinical study CA163081 was a multinational (sites in the U.S., Canada, Latin America, and Europe), multicenter (36 study sites), single-arm, Phase 2 study of the efficacy and safety of ixabepilone in patients with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane and capecitabine. An external independent radiology review committee (IRRC) reviewed the tumor scans and assessed response. Tumor response was also assessed by the investigator. The protocol underwent a Special Protocol Assessment by the Agency.

Study Period: The study initiation date was February 24, 2004. The first subject was enrolled on February 24, 2004; the last subject was enrolled on May 6, 2005. Database lock occurred on December 21, 2005. The study report date was May 4, 2006. The 120-Day Safety and Efficacy Update database lock was on December 15, 2006 and the update report was dated July 13, 2007.

6.2.3.1 Objectives:

- Primary: To assess the tumor response rate of ixabepilone in patients with advanced breast cancer who are resistant to an anthracycline, a taxane and capecitabine.
- Secondary: To assess time to response, time to progression, duration of response, and survival. Evaluation of safety of ixabepilone in the study population.

6.2.3.2 Study Population: Main eligibility criteria were

- Women aged 18 years or older with a histologic or cytologic diagnosis of adenocarcinoma originating in the breast that was metastatic or locally advanced and not curable by local measures (by surgery or radiation),
- Had received at least 1 and not more than 3 chemotherapy regimens for metastatic disease,
- Had prior therapy with an anthracycline (in neo/adjuvant or metastatic setting or both), a taxane (in neo/adjuvant or metastatic setting or both), and capecitabine (in locally advanced/metastatic setting),
- Resistant to all 3 of these chemotherapy regimens, defined as progression within 8 weeks in the metastatic setting or recurrence within 6 months of neo/adjuvant anthracycline or taxane, or had received a cumulative dose of 240 mg/m^2 of doxorubicin or 360 mg/m^2 of epirubicin,
- Have at least one radiographically measurable target lesion,
- Must have been treated with trastuzumab and progressed, if HER2 is over-expressed or amplified.

6.2.3.3 Treatment:

- Ixabepilone administered as monotherapy at 40 mg/m^2 IV over 3 hours every 21 days for a maximum of 18 cycles or until evidence of progressive disease (PD) and/or patient met discontinuation criteria.
- All patients will be pre-medicated with an oral H1 blocker and an oral H2 blocker. If the patient experiences a hypersensitivity reaction other premedication regimens (consisting of IV dexamethasone, IV cimetidine and IV diphenhydramine) are described.
- Dose modifications for ixabepilone are: -1 is 32 mg/m^2, -2 is 25 mg/m^2 . If patients require dose reductions below dose -2, ixabepilone must be discontinued unless the patient is experiencing a response.
- Criteria for dose reduction are: Grade 4 neutropenia lasting $\geq$ 7 days, febrile neutropenia, Grade 4 thrombocytopenia, Grade 3 thrombocytopenia with bleeding, Grade 3 or 4 stomatitis/vomiting/diarrhea despite maximal medical intervention, Grade 2 neuropathy lasting $\geq$ 7 days.
- Criteria for ixabepilone discontinuation: Grade 3 or 4 neuropathy lasting < 7 days. Other criteria are standard.

6.2.3.4 Statistical Methods: The study used a modified Gehan two-stage design. The first stage required at least 1 responder (as assessed by the investigator) among the first 29 patients accrued. Approximately 125 patients were expected to be accrued in order to obtain a minimum of 100 response-evaluable patients.

The protocol describes two populations that will be analyzed: 1) all treated subjects, i.e. those who took at least one dose of study drug (this population the Sponsor calls the intent-to-treat population), and 2) response-evaluable Patients, i.e. all patients with measurable disease, who

received any treatment and who met the eligibility criteria related to prior chemotherapy. Results in both subject populations will be used to assess efficacy endpoints.

Efficacy measures:

- The primary efficacy endpoint was Tumor response rate (ORR) by RECIST criteria as assessed by IRRC (total number of patients whose best response is CR or PR, divided by the number of response-evaluable patients (for the response-evaluable patients), or divided by the number of all treated patients (for the all treated population). For this analysis, the Clopper Pearson 95% CI was computed. As a secondary analysis, ORR was computed on all treated patients using the total number of treated patients as the denominator. The ORR based on the investigator's assessment of response was also computed.
- Secondary:
    - Duration of response (CR or PR). Duration of response will be measured from the time of measurement criteria are first met for CR or PR until the first date of documented PD or death. Patients who neither relapse nor die will be censored on their last tumor assessment.
    - Time to response is defined as the time from the first dose of study therapy until measurement criteria are first met for CR or PR.
    - Time to progression is defined as the time from the first day of treatment until the date PD or death is first recorded. Patients who die without a reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress will be censored at the day of their last tumor assessment.
    - Survival will be defined as the time from the first day of therapy to the date of death. If the patient is lost to follow-up, survival will be censored on the last date the patient was known to be alive.

Safety: AEs, SAEs and laboratory abnormalities were summarized by severity.

6.2.3.5 Protocol Amendments:
Amendment 1
Date: February 12, 2004 (there were no patients enrolled in this study at the time of this amendment).
Inclusion/exclusion criteria are clarified regarding prior trastuzumab and hormonal therapy. Candidates for such therapy are excluded.
Primary efficacy endpoint tumor response will be assessed by an Independent Radiology Review Committee (IRRC) rather than by the Sponsor.

6.2.3.6 IRRC Charter
Final Charter date was April 1, 2004. Final Charter Amendment #1 was on February 1, 2006.

The charter describes the objectives of independent review, image handling, tumor assessment schedule, radiologist reading sessions, radiographic assessments of disease sites, image review, lesion measurement, oncologic review of lesions, response determination, intra-reader and inter-

reader variability testing, data management, quality assurance and deliverables to the Sponsor and to the FDA.

The following are of interest in review of this NDA:

- Measurable lesions: in one dimension, longest diameter of 20 mm with non-spiral CT or 10 mm with spiral CT.
- Non-target lesions: bone lesions assessed by bone scan, inflammatory breast disease and non-measurable skin lesions, measurable lesions > 10, groups of small numerous lesions, pleural or pericardial effusion and ascites.
- Lesion measurement will be performed by using electronic calipers. Lesion diameters will be reported in mm.
- Responses of target and non-target lesions are defined. Confirmed responses are defined.
- Inter-reader variability testing will consist of 20% of CA163081 study cases. These reads will be considered secondary reads. Discrepancies will be defined as one-step or two-step discrepancies (a CR or PR by one reader and PD in the same patient by a second reader, or a CR by one reader and SD in the same patient by another reader).
- Intra-reader variability will be assessed using a set of 10% of CA163081 study cases, randomly selected for re-evaluation at least 3 months after the initial read.
- Quality control procedures are described.
- An Internal Audit by the QA Department reviews 100% of source documents prior to release, and 10% of the entire database prior to release.

Inter-reader variability testing: There were 2 one-step discrepancies among 24 patients (SD vs. PR in one; PD vs. SD in another). There were no two-step discrepancies.

Intra-reader variability testing: There were 4 one-step discrepancies among 13 patients (all four were PD vs. SD). There were no two-step discrepancies.

[redacted] conclusion: The frequency of one-step discrepancies was in line with past experience.

6.2.4 Efficacy Findings

6.2.4.1 Study Population:

Disposition of Patients: Of the 128 enrolled patients, 126 were treated with study drug. Two patients were still on treatment at the time of the December 21, 2005 database lock. By the time of the 120-Day Safety Update in December, 2006, all patients were off treatment. The most common reason for discontinuing participation in the study was PD (74% of patients). The second most common reason was study drug toxicity (about 12% of patients).

Among the 8 patients who discontinued because of investigator's request, 7 discontinued for reasons consistent with PD or maximal benefit achieved and one, because of progressive pain. Of the 3 patients who requested to be discontinued, one wanted to move back home, one did not want further treatment, and one because of Grade 3 thoracic pain during the last cycle.

6.2.4.2 Population Data Sets:
The study protocol defines the two population datasets, as shown below:

- All enrolled patients – 128.
- All treated patients – 126 who received any ixabepilone dose.
- All response-evaluable patients – 113 patients with measurable disease, as determined by IRRC, who received any ixabepilone dose and who met eligibility criteria.
    - Eleven (11) patients did not have measurable disease, according to IRRC. Of these, nine "had no scans except at screening" *(Reviewer's note: IRRC selected different target lesions than did the investigators, hence there were no follow-up scans).* Two patients were on study for < 2 cycles and thus did not get the first tumor assessment, which was scheduled after 2 cycles of therapy.
    - "Two patients did not meet prior chemotherapy resistance criteria." *(Reviewer's note: These patients were assessed and diagnosed with PD 8 weeks and 5 days from the last dose of taxane chemotherapy, instead of 8 weeks as required by the protocol).*

6.2.4.3 Demography and Patient Characteristics:
Baseline demographics are presented in Table 14, Sponsor's Table S.8.3. These data are shown as presented by the Sponsor. The dataset was not reviewed by the reviewer. All 126 treated patients were women, 79% were White, the median age was 51 years, the age range was 30 to 78 years, about 86% were less than 65 years of age, about 86% were post-menopausal, and the Karnofsky PS was 80% to 100% in 96%.

Table 14. Patient characteristics

Table 8.3: Pretreatment Patient Characteristics

	Number of Patients (%)	
	Response Evaluable N = 113	Treated N = 126
Gender		
FEMALE	113 (100.0)	126 (100.0)
Race		
WHITE	89 (78.8)	99 (78.6)
BLACK/AFRICAN AMERICAN	5 (4.4)	6 (4.8)
ASIAN	1 (0.9)	2 (1.6)
OTHER	11 (9.7)	12 (9.5)
NOT REPORTED	7 (6.2)	7 (5.6)
Age (years)		
N	113	126
Median	51.0	51.0
Min - Max	30.0 - 78.0	30.0 - 78.0
< 65	98 (86.7)	108 (85.7)
>=65	15 (13.3)	18 (14.3)
Karnofsky Performance Status		
100	30 (26.5)	33 (26.2)
90	49 (43.4)	55 (43.7)
80	29 (25.7)	33 (26.2)
70	5 (4.4)	5 (4.0)
Menopausal Status		
PRE-MENOPAUSAL	12 (10.6)	13 (10.3)
PERI-MENOPAUSAL	2 (1.8)	2 (1.6)
POST-MENOPAUSAL	97 (85.8)	109 (86.5)
NOT REPORTED	2 (1.8)	2 (1.6)

Source: Supplemental Table S.8.3

6.2.4.4 Medical History:
These data are shown as presented by the Sponsor. The dataset was not reviewed by the reviewer.
Receptor Status: About 77% of response-evaluable patients had HER2-negative cancer and 6% had HER2-positive (HER2 status was not determined in 17%). All patients with HER2-positive tumors had progressed after or during treatment with trastuzumab. About 47% of the response-evaluable patients were ER-positive and 48%, ER-negative. About 39% were PR-positive and 55%, PR-negative. About 37% were triple-negative.

6.2.4.5 Prior Chemotherapy: These data are shown as presented by the Sponsor. The dataset was not reviewed by the reviewer.
All patients were previously treated with an anthracycline, a taxane, and capecitabine. About 88% had received at least 2 prior chemotherapy regimens and 49%, 3 prior chemotherapy regimens. All but two treated patients (98%) met the criteria for taxane resistance (see above, under population data sets). About 38% of patients were anthracycline-resistant and 62% had reached the minimum required cumulative dose of either doxorubicin or epirubicin. All 100% of patients met the criteria for capecitabine resistance. In addition, many patients had received prior treatment with other chemotherapies in the metastatic setting, including vinorelbine (25%) and gemcitabine (13%) (Table 15, Sponsor's Table S.8.15).

Table 15. Prior chemotherapy

CA163081

Table S.8.15:
Prior Chemotherapy Drugs - Treated Subjects

	Number of Subjects (%)	
	Response Evaluable N = 113	Treated N = 126
Number of subjects with prior neo-adjuvant/adjuvant chemotherapy (a)	85 (75.2)	95 (75.4)
Prior neo-adjuvant/adjuvant chemotherapy drugs (generic name)		
BLEOMYCIN	1 (0.9)	1 (0.8)
CAPECITABINE	1 (0.9)	1 (0.8)
CISPLATIN	2 (1.8)	2 (1.6)
CYCLOPHOSPHAMIDE	81 (71.7)	90 (71.4)
DOCETAXEL	18 (15.9)	21 (16.7)
DOXORUBICIN	54 (47.8)	59 (46.8)
EPIRUBICIN	28 (24.8)	32 (25.4)
FLUOROURACIL	51 (45.1)	58 (46.0)
HYDROXYUREA	1 (0.9)	1 (0.8)
METHOTREXATE	8 (7.1)	10 (7.9)
MITOMYCIN	1 (0.9)	1 (0.8)
MITOXANTRONE	3 (2.7)	3 (2.4)
PACLITAXEL	15 (13.3)	15 (11.9)
VINBLASTINE	1 (0.9)	1 (0.8)
VINCRISTINE	1 (0.9)	1 (0.8)
VINORELBINE	2 (1.8)	2 (1.6)

6.2.4.6 Other Prior Anticancer Therapy: These data are shown as presented by the Sponsor. The dataset was not reviewed by the reviewer. Seventy-nine (79%) of treated patients had prior RT and 63% had prior hormonal/immuno/biologic therapy. These data are not surprising, since breast-sparing surgery combined with local RT is the current mode of initial breast cancer treatment.

6.2.4.7 Extent of Disease:

The extent of disease as reported by the investigators (in All Treated Patients) and as identified by the IRRC (in All Treated Patients and in Evaluable Patients) are shown Table 16 (data from Sponsor's Tables 8.4.3.1 and 8.4.3.2A).

Table 16. Tumor Assessments at Baseline by Investigators and by IRRC

	IRRC Response-evaluable Patients, N = 113	**IRRC All Treated Patients N = 126**	**Investigator All Treated Patients N = 126**
No. of subjects with at least one lesion	**113 (100%)**	**126 (100%)**	**126 (100%)**
Number of disease sites			
1	**10 (8.8%)**	**12 (9.5%)**	**27 (21.4%)**
2	**29 (25.7%)**	**33 (26.2%)**	**45 (35.7%)**
3	**37 (32.7%)**	**44 (34.9%)**	**34 (27.0%)**
4	**18 (15.9%)**	**18 (14.3%)**	**12 (9.5%)**
≥ 5	**19 (16.8%)**	**19 (15.1%)**	**8 (6.3%)**

	IRRC Response-evaluable Patients, N = 113	IRRC All Treated Patients N = 126	Investigator All Treated Patients N = 126
Disease Sites: Patients may have lesions at > 1 site			
Ascites	10 (8.8%)	10 (8.8%)	0
Bone	41 (36.3%)	44 (34.9%)	45 (35.7%)
Breast	26 (23.0%)	26 (20.6%)	13 (10.3%)
CNS	1 (0.9%)	1 (0.8%)	0
Chest Wall	5 (4.4%)	7 (5.6%)	19 (15.1%)
Effusion	22 (19.5%)	25 (19.8%)	0
Lymph Node	72 (63.7%)	81 (64.3%)	45 (35.7%)
Other	8 (7.1%)	9 (7.1%)	10 (7.9%)
Peritoneum	4 (3.5%)	4 (3.2%)	0
Pleura	13 (11.5%)	14 (11.1%)	23 (18.3%)
Skin, Soft Tissue	15 (13.3%)	18 (14.3%)	15 + 8=23 (18.3%)
Visceral, Liver	79 (69.9%)	82 (65.1%)	69 (54.8%)
Visceral, Lung	45 (39.8%)	51 (40.5%)	48 (38.1%)
Visceral, Other	13 (11.5%)	13 (10.3%)	6 (4.8%)
Visceral disease in liver and/or lung			97 (77.0%)
Liver + lung + skin/soft tissue + bone			69 (54.8%)
Lung + skin/soft tissue + bone			28 (22.2%)
Skin/soft tissue + bone			27 (21.4%)

Reviewer's Notes:

- *As the Sponsor states, patients had extensive disease at baseline, as shown by the number of sites, the frequent involvement of visceral sites and the broad range of metastatic sites. All 126 treated patients had target disease at baseline, according to investigators, but not according to IRRC (see below).*
- *There are some notable discrepancies between investigators' assessments and IRRC assessments:*
    - *IRRC diagnosed greater percentages of patients with 3 or more disease sites in the all treated population than the investigators (64.3% vs. 42.8%).*
    - *IRRC diagnosed ascites, effusions, one CNS metastasis, and peritoneal disease, while the investigators did not.*
    - *IRRC diagnosed more patients with liver, lymph node and other metastases than the investigators.*
    - *IRRC diagnosed fewer patients with pleural and skin/soft tissue metastases than did the investigators, as per IRRC Charter.*
    - *The discrepancy between the numbers of patients with breast lesions and with chest wall lesions is probably not significant, since when both categories of lesions are totaled, the numbers match.*

6.2.4.7 Target Lesions:

As assessed by the IRRC, 115 (91%) of patients had at least 1 target lesion. The majority (74%) of response-evaluable patients had 2 or more target lesions, including 42% with ≥ 5 target lesions. One-third (33%) of response-evaluable patients had at least one target lesion > 50 mm and 43% of response-evaluable patients had a sum of longest diameter > 100 mm.

Target lesions identified by IRRC are shown in Table 17 (Sponsor's Table 8.4.3.2B). The most common sites of target lesions are in the liver, lymph nodes, and lungs.

Table 17. Target Lesions at Baseline

Table 8.4.3.2B: Summary of IRRC Tumor Assessments at Baseline (Target Lesions)

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	Number of Patients (%)	
	Response Evaluable N = 113	Treated N = 126
Presence of Target Lesions		
Patients with at least one target lesion	113 (100.0)	115 (91.3)
Number of Target Lesions		
1	29 (25.7)	29 (23.0)
2	22 (19.5)	22 (17.5)
3	12 (10.6)	12 (9.5)
4	3 (2.7)	5 (4.0)
>= 5	47 (41.6)	47 (37.3)
Longest Diameter of Largest Target Lesion in mm		
10 to < 30	43 (38.1)	43 (34.1)
30 to < 50	33 (29.2)	34 (27.0)
50 to < 100	32 (28.3)	32 (25.4)
>= 100	5 (4.4)	6 (4.8)
Sum of Longest Diameter of Target Lesions in mm		
< 50	38 (33.6)	38 (30.2)
50 to < 100	26 (23.0)	27 (21.4)
>= 100	49 (43.4)	50 (39.7)
Site of target lesion (a)		
Bone	1 (0.9)	1 (0.8)
Breast	5 (4.4)	5 (4.0)
CNS	1 (0.9)	1 (0.8)
Chest Wall	2 (1.8)	3 (2.4)
Lymph Node	52 (46.0)	54 (42.9)
Other	2 (1.8)	2 (1.6)
Peritoneum	1 (0.9)	1 (0.8)
Pleura	4 (3.5)	5 (4.0)
Skin/Soft Tissue	4 (3.5)	4 (3.2)
Visceral, Liver	66 (58.4)	66 (52.4)
Visceral, Lung	27 (23.9)	28 (22.2)
Visceral, Other	4 (3.5)	4 (3.2)
Procedures for Evaluating Target Lesions		
CT/MRI + - Ultrasound/Sonogram + - X-Ray + - Photo + - bone scan	113 (100.0)	115 (91.3)

(a) Patients may have target lesions at more than one site

Source: Supplemental Table 8.8.6

6.2.4.8 Study Therapy: Ixabepilone was infused at 40 mg/m² over 3 hours every 21 days, as per protocol, in about 80% of treatment cycles. Ixabepilone was administered at reduced doses of 32mg/m² (dose level -1) in 16% of cycles and 25 mg/m² (dose level -2) in 4% of cycles.

6.2.4.9 Concomitant Medications:

- All patients (99.7% of cycles) received pre-medication for HSR (H1-blocker + H2-blocker in 78% of cycles and H1-blocker + H2-blocker + steroids in 20% of cycles).
- Other concomitant medications were anti-emetics and anti-nauseants (48%), antacids (42%), systemic corticosteroids (41%), anti-bacterials (40%), psycholeptics (37%), anti-epileptics (28%), antispasmodics (28%), treatments for bone disease (27%), psychoanaleptics (26%) and laxatives (25%).
- G-CSF or GM-CSF was used in 17%, and erythropoietins in 14%. *Reviewer's Note: The relatively frequent use of G-CSF and GM-CSF correlates with the relatively frequent Grade 4 neutropenia.*

6.2.4.10 Protocol Deviations:

- A total of 56 patients had one or more protocol deviations. The deviations were classified as eligibility and on-study deviations.
- Among eligibility deviations were non-measurable disease (PET scan instead of CT or MRI was used for assessment), baseline hepatic, renal or hematologic function, Grade 4 cardiac failure, failed taxane resistance criteria (last dose 8 weeks and 5 days instead of protocol-specified 8 weeks). Four of these patients were excluded from response-evaluable population.
- On-study deviations included no pre-medication for HSR, treatment after PD diagnosed, no dose reduction for neuropathy or neutropenia, started on new cycle before recovery from grade 2 neuropathy or grade 3 neutropenia, a new anticancer agent co-administered in one patient (Megace that was given for anorexia but is classified as an anticancer agent).

6.2.4.11 Efficacy Results:

Primary efficacy endpoint: ORR as assessed by IRRC

The objective response rate (ORR), as assessed by IRRC, was 12% (14/113 or 12.4% of response-evaluable patients and 15/126 or 11.9% of all treated patients), as shown in Table 18. All of the responders had a PR; there were no CRs.

In the initial Sponsor's CSR, there were 13 patients with PR among evaluable patients (ORR=11.5%, CI 6.3, 18.9) and 14 patients with PR among all treated patients (ORR=11.9%, CI, 6.8, 18.9). The response of one patient was changed from SD to PR by the time of 120-day safety update. (*Reviewer's Note: This patient [ID number CA163081-78-79] was diagnosed as having an unconfirmed PR after 2 cycles and confirmed PR after 4 cycles by the investigator. The IRRC assessment was SD during the first 16 cycles, and PR after 18 cycles).*

Table 18. Primary Efficacy Endpoint – Objective Response Rate As Assessed by IRRC

Tumor Response	**Evaluable Patients N = 113**	**All Treated Patients N = 126**
CR	0	0
PR	14 (12.4%) (95% CI, 6.9 – 19.9)	15 (11.9%) (95% CI, 6.8 – 18.9)

The Reviewer corroborated the tumor response data submitted by the IRRC by examining subject listings and percent changes in the sum of the longest diameter of target lesions over the treatment period (Appendix 10.10). Examination of these records reveals certain complexities in the use of ORR as an efficacy endpoint. For example,

- The results are easier to interpret when the sum of the longest diameter (LD) relatively large, e.g. > 100 mm. Then a decrease of 30% clearly meets the criteria of PR. It is less easy to interpret ≥ 30% decreases of an initial lesion of 20 mm or less (e.g. 13, 14 mm).
- IRRC presents evidence for changes in target lesions and diagnose the response, then notes the response in ono-target lesions, notes if any new lesions had arisen, and presents the integrated response. Of note,
    - PRs diagnosed in target lesions were never accompanied by PRs in non-target lesions, but rather by SDs (all 14 cases in Appendix 10.10).
    - Most of the PRs in target lesions continued to be accompanied by SDs in non-target lesions. In two cases (patient IDs -4-53 and -80-126), non-target lesions changed from SD to PD while the target lesions remained PR. At this time, the patient was diagnosed with PD.
    - There was one case of CR in target lesions, but because non-target lesion remained SD, the integrated response was PR. When a new lesion arose, the integrated response changed to PD (patient ID -48-40).
    - There were two CRs in non-target lesions; in one the target lesions remained SD (patient ID -31-51) and the integrated diagnosis was SD; while in the other the target lesions showed PD (patient ID -18-102) and the integrated response was PD.
    - The rules for decision-making were: PR (in target lesions) + SD (in non-target) = PR (integrated response); SD (in target lesions) + SD (in non-target) = SD (integrated response); SD (in target lesions) + PD (in non-target) = PD (integrated response. However, judgment was required with some of the unusual cases described above.

Secondary Efficacy Endpoints: Duration of Response and Time to Response

Duration of Response and Time to Response are based on IRRC data (from Sponsor's Table 10C in the updated Study Addendum 02) and are shown in Reviewer's Table 19 below. Reviewer's Note: In the initial submission the range of time to response among 14 responders was 5.0 to 19.0 weeks. The addition of the last responder after 54.4 weeks (18 cycles of therapy) extended this range. According to the investigator, this patient had a PR after 6 weeks of therapy (2 cycles). The Reviewer finds the response after 54.4 weeks contrary to the experience of all other responders, and favors the investigator's assessment.

Table 19. Secondary Efficacy Endpoints: Duration of Response and Time to Response

Endpoint	Response-evaluable Patients N = 113	All Treated Patients N = 126
Duration of Response Median, months (95% CI)	N = 14 6.0 months (5.0 – 7.6)	N = 15 6.3 months (5.0 – 7.6)
Time to Response Median, weeks (95% CI)	N = 14 6.1 weeks (5.0 – 54.4)	N = 15 6.1 weeks (5.0 – 54.4)

Secondary Efficacy Endpoints: PFS and Survival

Both PFS and survival, shown in Table 20, are exploratory endpoints in a single arm trial. Kaplan-Meier plots are shown below, even though they are of limited interest.

Table 20. Secondary Efficacy Endpoints: PFS and Survival

Endpoint	Response-evaluable Patients N = 113	All Treated Patients N = 126
PFS Median, months (95% CI)	3.5 months (2.8 – 4.4)	3.2 (2.8 – 4.3)
Survival Median, months (95% CI)	8.9 months (7.2 – 11.2)	9.0 months (7.3 – 11.2)

Kaplan-Meier plots of PFS and of overall survival for all treated patients are shown below in Figures 2 and 3 (from Sponsor's Figures 10.2A and 10.2C in Clinical Study Report Addendum 02).

Figure 2.

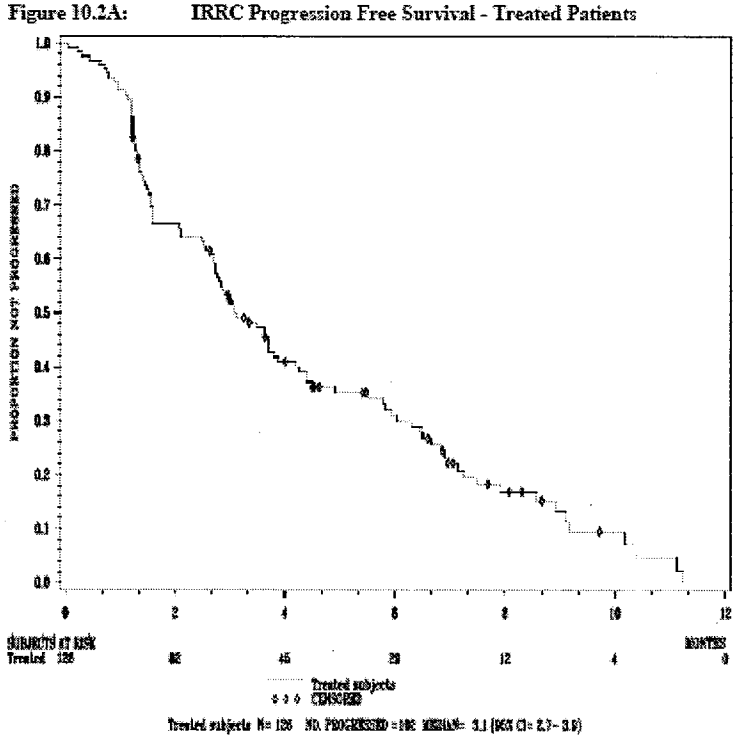

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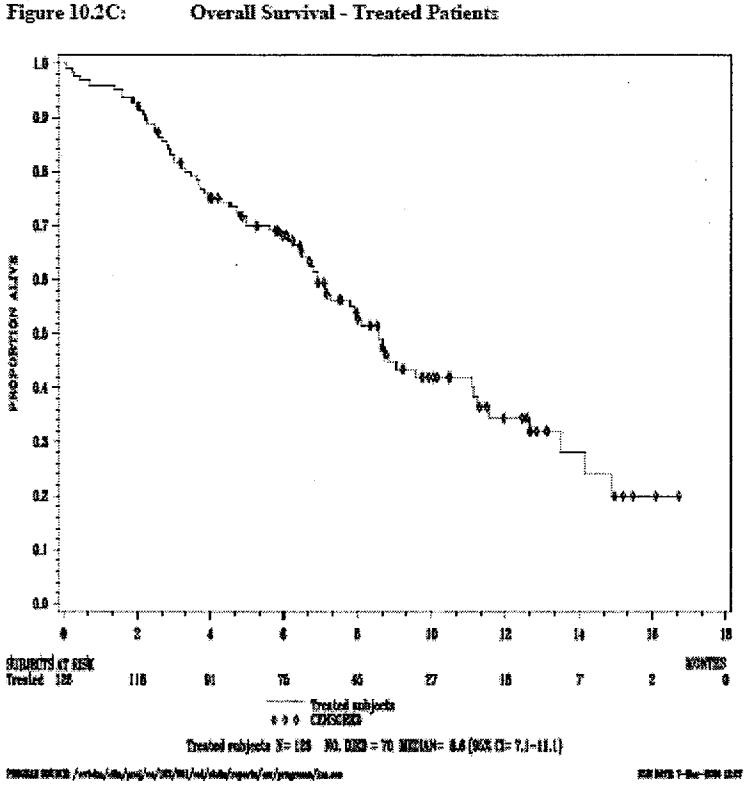
Figure 3.



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Secondary efficacy endpoint, ORR as assessed by Investigator: According to investigators, there were 22 patients with PR and one with CR, with the ORR of 18.3% (Table 21, data from Sponsor's Table 10B).

Table 21. Secondary Efficacy Endpoint – Objective Response Rate As Assessed by Investigators

Tumor Response	**All Treated Patients N = 126**
CR	1
PR	22
Total	23 (18.3%) (95% CI, 11.9 – 26.1)

Reviewer's Note: There were substantial differences in assessments between IRRC and investigators. The most important are in the numbers of patients experiencing responses. Investigators assessed one patient with CR and 22 patients with PRs. Of the 22 patients with PRs, 11 were also assessed as having PRs by IRRC (50% agreement). These differences are discussed below.

Exploratory Analysis: Characteristics of Responders

The Sponsor makes the following comments on the quality of responses:

- One responder had complete regression of all target lesions (5 target lesions in the liver totaling 60 mm). Because of persistence of ascites and a bone lesion, she was not considered a CR.
- Seven of the responders had > 50% decrease in target disease.
- All of the responders had liver metastases, seven had lung metastases. Twelve had had 5 or more sites of disease.
- All had extensive prior therapy and were resistant to prior treatment. All had 2 or more prior chemotherapy regimens for the metastatic disease.
- Eight of the responders had prior gemcitabine or vinorelbine treatment in addition to an anthracycline, a taxane, and capecitabine.
- Responses occurred across all patient subsets, including ER- and ER+ patients, HER2- and HER+ patients, and ER-/PR-/HER2- (triple negative) patients.

IRRC-assessed responses by pre-specified subsets of response-evaluable patients is shown in Table 22 (Sponsor's Table 10.1.1.2).

Table 22. IRRC Objective Response by Pre-specified Subsets – Response-Evaluable Patients

Table 10.1.1.2: IRRC Objective Response by Subsets - Response-Evaluable Patients

	Number of Patients (%) N = 113
Age	
< 65	12/98 (12)
>= 65	1/15 (7)
Race	
White	10/89 (11)
Black	0/5 (0)
Asian	1/1 (100)
Other	2/18 (11)
Presence of visceral metastases in liver and/or lung	
Yes	13/99 (13)
No	0/14 (0)
Performance Status at baseline	
>=70-<=90	4/34 (12)
>80-<=100	9/79 (11)
Number of disease sites	
<=2 sites	5/39 (13)
>2 sites	8/74 (11)
Time from cancer diagnosis to start of Ixabepilone	
<2 years	3/26 (12)
>=2 years	10/87 (11)
Number of prior chemotherapy regimens for metastatic cancer	
<2	0/14 (0)
>=2	13/99 (13)
ER receptor status	
Positive	5/54 (9)
Negative	8/53 (15)
Not reported	0/6 (0)
HER2 Status	
Positive	1/7 (14)
Negative	11/87 (13)
Not reported	1/19 (5)
ER-,PR-,HER2-	
Yes	5/42 (12)
No	8/71 (11)

Source: Supplemental Tables S.8.17 and S.10.7; Table 10.1.1.1C.

Reviewer's Comments:
Subset analysis failed to reveal a characteristic patient group with either a substantially greater ORR or a substantially lower ORR. All subgroups appear to have had similar rates of response, with possible exceptions of patients without visceral metastases and patients with fewer than 2 chemotherapy regimens for metastatic disease. These conclusions are tentative, because of the small number of responders in a relatively small trial.

Stable disease (SD) was the best IRRC-assessed response in 50% of patients with a median duration of 4.5 months, as compared to a median duration of PR of 6.0 months. "Disease Control Rate" (SD + PR) was assessed in about 61% of patients.

Exploratory Analysis: Differences between IRRC and Investigator Assessments

Table 23 (Sponsor's Table 10.1.3) shows agreements of assessments in all response categories by IRRC and investigators. The sponsor claims that there was a 71% agreement on best tumor response. However, some important failures of agreement are evident.

- *IRRC did not diagnose an investigator-diagnosed CR, and IRRC diagnosed only 50% (11/22) of investigator-diagnosed PRs.*
- *There was agreement by the investigators on only 11/15 (73%) IRRC-diagnosed PRs.*

Table 23. Agreement between IRRC and Investigator Best Tumor Response - All Treated Patients

Table 10.1.3: Agreement Between IRRC and Investigator Best Tumor Response - Treated Patients

	Number (%) of Patients, N = 126				
	Investigator Best Tumor Response				
IRRC Best Tumor Response	CR	PR	SD	PD	Unable to determine
PR	0	11 (9)	4 (3)	0	0
SD	1 (1)	9 (7)	43 (34)	8 (6)	1 (1)
PD	0	2 (2)	7 (6)	28 (22)	2 (2)
Unable to determine	0	0	1 (1)	1 (1)	8 (6)
Patients whose IRRC and Investigator best tumor response agree				90 (71)	

Source: Supplemental Table S.10.3A

The Sponsor addresses the discrepancies of investigators' and IRRC assessments by citing published analyses of this phenomenon[1,2], and by providing summaries of 10 cases in which PRs by investigators were not assessed as such by IRRC.

Broadly, the reasons can be grouped as follows:

- Exclusion of physical examination measurements from IRRC assessment (skin, lymph nodes),
- Unevaluable assessments due to incomplete radiology at all time points,
- IRRC selection of baseline lesions from scans not performed at regular intervals,
- Inter-observer variability in measurements (e.g. multiple small target lesions),
- Differences in the selection of target lesions, and the weight given to target and non-target lesions (e.g. Patient ID 31-51 had SD of target lesions and CR of non-target lesions as assessed by IRRC; in the converse situation of, the patient would be had a CR not an SD)
- Differences in the timing and identification of new tumor lesions.

In general, this reviewer is impressed by the variation in both target and non-target lesions selected by the investigators and IRRC. Reviewer's Table 24 shows differences in target lesions selected by IRRC and by investigators in the 11 patients assessed as PR by both IRRC and investigators (**in bold type**), in the 4 patients who were assessed as PRs by IRRC and as SD by investigators (***in bold type italicized***), and in the 12 patients, who were assessed as PRs by

investigators and as 10 SDs and 2 PDs by IRRC (unbolded type) (data from listings 10.10, 10.11, 10.12, 10.13 and Sponsor's Tables 10.1.2A, B, C).

Table 24. Baseline Target Lesions Selected by IRRC and by Investigators and Percent Decreases of Target Lesions in Patients with PRs

Patient ID	IRRC Target Lesions	%↓	Investigator Target Lesions	%↓
1-54	*(1) lymph node*	*55%*	*(2) lymph nodes (L axilla, subcarinal)*	*7%*
4-97	*(4) lung, (1) lymph node (mediastinal)*	*32%*	*(3) lung*	*16%*
5-50	*(4) liver, (1) lymph node (subcarinal)*	*62%*	*(2) liver, (1) pelvis*	*30%*
9-30	**(2) lymph nodes (R axilla)**	**57%**	**(1) lymph node (R axilla)**	**92%**
18-48	**(1) liver**	**38%**	**(1) liver**	**36%**
20-16	**(1) liver**	**56%**	**(1) liver**	**36%**
34-24	**(1) lymph node (mediastinal)**	**68%**	**(1) lung (R basal)**	**56%**
35-92	*(5) liver*	*52%*	*(5) liver*	*49%*
47-66	**(5) lymph nodes (R para-tracheal, L mediastinal, R & L para-aortic)**	**46%**	**(3) mediastinum (pre-vascular, pre-tracheal, subcarinal), (2) lymph nodes (retroperitoneal, latero-aortic)**	**69%**
48-40	**(5) liver**	**100%**	**(5) liver**	**46%**
61-115	**(2) lung, (5) lymph nodes, (2) liver**	**46%**	**(3) lymph nodes**	**65%**
75-123	**(3) lung**	**41%**	**(2) lung**	**50%**
78-79	**(1) lung, (1) pleura**		**(2) lung**	**47%**
80-120	**(1) lymph node, (2) lung, (1) pleura**	**38%**	**(1) lung**	**48%**
80-126	**(2) lung, (3) lymph nodes**	**38%**	**(2) lung**	**54%**
4-73	(5) liver	34%*	(4) liver	51%
18-9	(2) lymph node (R cervical, L axilla)	25%	(1) chest wall mass	73%
18-38	(1) liver), (1) R breast	5%	(2) chest wall masses (parasternal, parietal)	36%
18-112	(1) lung, (2) liver	14%	(2) liver	63%
22-6	(1) liver	↑14%	(1) pelvis, (1) pleura (chest), (1) liver	70%
22-12	(3) lymph node	30%**	(6) lymph nodes, (2) lung	47%
35-47	(2) liver	61%***	(2) mediastinum, (2) liver	63%
35-128	(1) R breast	9%	(1) R breast	45%
48-21	(1) R lung	10%	(1) R lung	50%
48-77	(1) liver	29%	(1) liver, (2) lymph nodes	47%
49-63	None [non-measurable disease, hence non-evaluable]	0%	(1) chest wall mass [decreased from 78 mm to 15 mm], (1) lymph node	81%
80-83	(1) sternal mass, (1) R lung, (2) lymph nodes	16%	(1) lung	33%

***IRRC: unconfirmed response of 25%, 34% and 14% decreases in diameter in successive assessments.**
**** IRRC: decreases of 17%, 24%, 26%, and 30% after 2, 4, 6, and 8 cycles.**
*****IRRC: decreases of 26%, 53% and 61% after 2, 4, and 6 cycles.**

The above differences become important in view of persistence of SD in non-target lesions, while IRRC-selected target lesions showed responses (see above under Primary Efficacy Endpoint).

Table 25 shows Sponsor's Comments on investigator-assessed PRs that were assessed as SD or PD by IRRC:

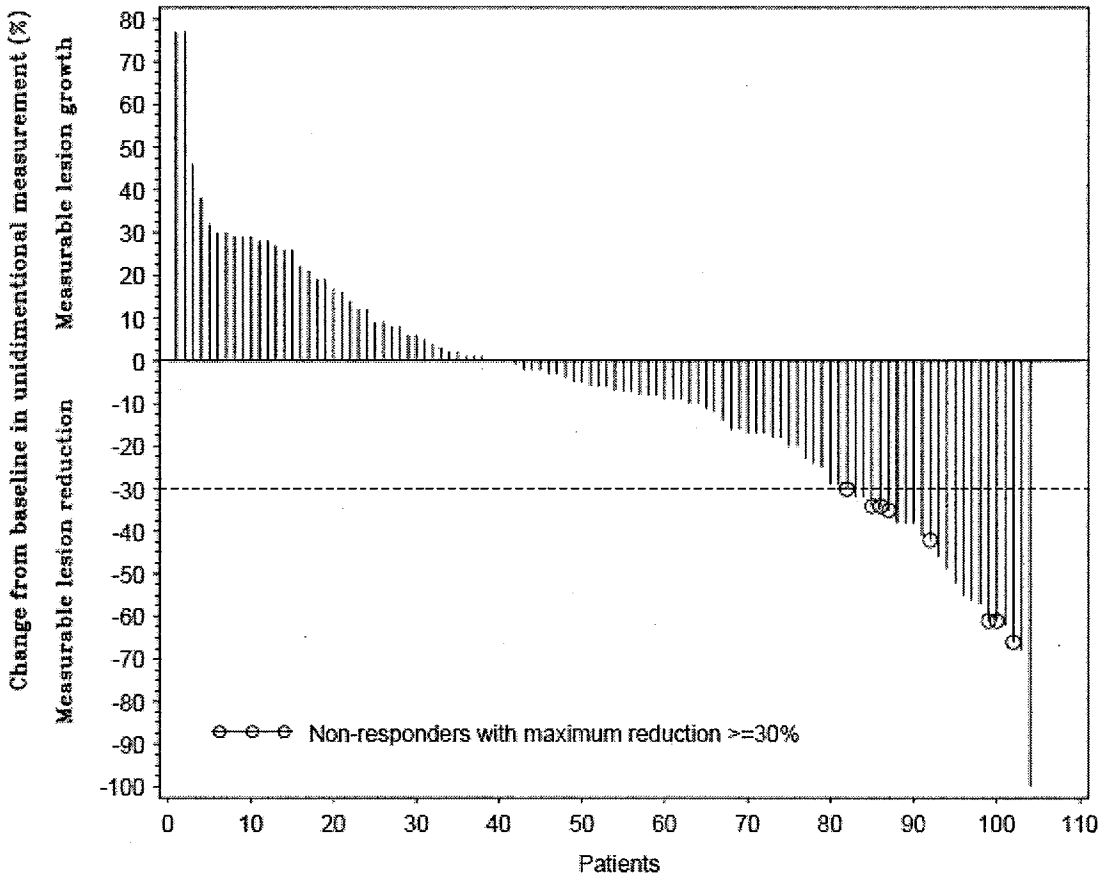
Table 25.

Patient ID #	Sponsor's comments
4-73	Investigator assessed PR at cycle 4; IRRC, at cycle 6. Both assessed PD at cycle 7.
18-9	IRRC selected a cervical lymph node as target; regular neck CTs were not obtained.
18-38	Infiltrating chest wall lesion was selected as target lesion by investigator, but not by IRRC.
18-112	Different target lesions selected. New tumor lesion not identified by investigator.
22-6	No comment.
22-12	Investigator followed multiple superficial lymph nodes by physical examination; IRRC charter does not classify such as measurable disease.
35-47	As tumor was shrinking, the investigator diagnosed PR at cycle 2, while IRRC documented a 26% decrease at cycle 2 and an unconfirmed PR at cycle 4.
35-128	A baseline bone scan was not provided to IRRC, who diagnosed PD at cycle 2. Investigator diagnosed PR on the basis of bone scan changes from baseline to end of cycle 2.
48-21	Small multiple target lesions (about 10 mm in diameter) are highly subject to inter-observer variability.
48-77	No comment.
49-63	Investigator selected a large chest wall lesion and a lymph node. IRRC classified these as non-target.
80-83	Different target lesions selected. New tumor lesion not identified by investigator.

The Sponsor performed an analysis of the maximum reduction of target lesions. This is shown in Figure 4 (Sponsor's Figure 10.1.1.5). The graph shows a continuum from clear increases in target lesion diameters to a relatively large number of target lesions that are stable, and clear decreases in target lesions. There is an evident clustering of non-responders around the 30% measurable disease reduction level (the border between PR and SD). The Sponsor points out that there were 8 partial responders according to this graph, who were not confirmed as such by IRRC.

Figure 4.

Figure 10.1.1.5: Maximum Reduction of Target Lesions (IRRC) - All Patients with at Least One Target Lesion and On-Study Tumor Measurements



Reviewer's Comments on PRs as diagnosed by IRRC and investigators:

- *Some of the differences in response assessments are clearly related to differences in target lesions chosen by IRRC and by investigators. In particular, lesions that are assessed by physical examination will be better evaluated by investigators than by IRRC (patients 18-9, 18-38, 22-12, 49-63 were probably PRs).*
- *Depending on classification of lesions as target or non-target, different response diagnoses will emerge, as noted above (see above in Primary Efficacy Endpoint).*
- *Missing baseline scans (i.e. not provided to IRRC) will result in new disease being diagnosed instead of known disease improving (patient 35-128).*
- *Some discrepancies in assessments by IRRC and investigators remain hard to reconcile. The discrepancy between PR and SD is only one-step, and one-step discrepancies appear to be common when intra-reader and inter-reader reproducibility of readings is tested (see 6.2.3.6 [redacted] testing).*

- *The exact number of PRs is uncertain. There were probably more than 15, as assessed by IRRC, and as many as 23 as assessed by investigators.*

Reviewer's Comments:

- *Ixabepilone therapy clearly demonstrates activity in this population. In patients with PRs target lesions decrease progressively although at different rates. At the 1st assessment period (after 2 cycles of treatment) 10/15 patients (67%) had target lesion decreases to meet the PR criteria, at the 2nd assessment period, an additional 3 patients met the PR criteria (87%, 13/15), and by the 3rd assessment all 100% of patients had met response criteria.(An additional PR was diagnosed by IRRC after being classified as SD for 54.4 weeks; the same patient was diagnosed as PR by the investigator at the first assessment following 6 weeks of therapy).*
- *Some of the 20 SD patients were treated for up to 12 cycles but continued to have SD or developed PD.*
- *Patients who met PR criteria on only one assessment were classified as "unconfirmed PR" and were not listed as having PR (6 patients).*
- *Patients with PD at 1st assessment or patients who develop PD after SD are unlikely to respond to continued therapy. Most of the patients who were assessed as having PD at the 1st assessment (25 patients after 2 cycles of therapy; 4 patients after one cycle) discontinued ixabepilone therapy, as per protocol. However, some patients were continued on study drug for up to ten cycles. None of them had a PR. Neither did any of the patients, who had SD and later developed PD. Some of these patients were continued on study drug for as many as 12 cycles.*
- *Some patients showed shrinkages of target lesions sufficient to meet PR criteria, and were diagnosed as PRs as long as non-target lesions remained at least SD. When patients developed new lesions, the integrated response was changed to PD (patients 4-53, 9-30, 35-47, and 52-85). They were classified as having SD.*

6.2.4.6 Supportive Study CA163009: A Phase 2 Study of Epothilone B Analog BMS-247550 in Patients with Taxane-resistant Metastatic Breast Cancer.

6.2.4.6.1 Study Design:
This was a single-arm, multicenter (11 study centers in the U.S., Spain, France, and Italy), open-label study that was carried out between May 22, 2001 (first subject enrolled) and April 21, 2004 (last subject completed follow-up). At the beginning of the study ixabepilone was administered at a dose of 50 mg/m² infused over 1 hour. After the enrollment of 8 patients, the infusion time was increased from 1 hour to 3 hours because of neurotoxicity observed with this regimen in a Phase 1 study (CA163001) and a Phase 2 study (CA163010). After the first 9 patients were enrolled and treated, the dose was reduced to 40 mg/m² because of grade 4 myelosuppression and mucositis. *(Clarification: There were 8 patients who were treated with 50 mg/m² ixabepilone infused IV over 1 hour, and 9 patients who were treated with the same dose infused over 3 hours).* The primary objective of the study was revised to assess the clinical activity of

ixabepilone, as measured by tumor response rate, in patients treated with 40 mg/m^2 every 3 weeks regimen.

6.2.4.6.2 Objectives:
Primary: To assess the clinical activity of ixabepilone by tumor response rate in taxane-resistant metastatic breast cancer.
Secondary: To evaluate safety, response duration, time to progression and survival in this population.

6.2.4.6.3 Study Population:
Main eligibility criteria were

- Women with histological or cytological diagnosis of Stage IV or distal metastatic breast cancer,
- Metastatic lesions were bi-dimensionally measurable,
- Taxanes as most recent therapy with progression on therapy or within 4 months of the last dose, with or without a response.

Treatment was monotherapy with ixabepilone for a maximum of 18 cycles, unless there was evidence of PD and/or the patient met discontinuation criteria. Patients who discontinued treatment were followed for 3 months or until death. Patients who developed any study drug-related toxicity were followed every 4 weeks until resolution, stabilization, return to baseline or were deemed irreversible.

6.2.4.6.4 Criteria for evaluation:
Efficacy population included all patients with the correct diagnosis who were treated with 40 mg/m^2 of ixabepilone every 21 days and received at least one dose of ixabepilone (49 patients; the 17 patients who received 50 mg/m^2 ixabepilone every 21 days are excluded from efficacy analysis).

Response was assessed by the BMS medical team according to modified WHO criteria. The investigators collected all measurements of lesions from CRFs and forwarded them to BMS head office. Overall tumor response was based on the integration of the evaluation of target, non-target, and new lesions. All measurable lesions, up to 5 lesions per organ and 10 lesions total were identified as target lesions. The target lesions were representative of all involved organs. In addition, target lesions were selected based on their size and suitability for accurate repeat assessment. At baseline, a sum of the products of diameters for all target lesions was calculated and considered the baseline sum. Measurable lesions in excess of 10 and non-measurable lesions were assessed at the same time as target lesions. In subsequent assessment non-target lesions were recorded as "stable or decreased", "absent", or "unequivocal progression". Unequivocal progression of non-target lesions implied that the patient had PD. Definitions of Tumor Response are shown in Table 26 below:

Table 26.

6.3.5.2 *Definition of Tumor Response*

The following definitions were used to assess response:

- Complete Response (CR): Disappearance of all clinical and radiological evidence of target lesions and non-target lesions with no new lesions confirmed on at least two consecutive observations at least four weeks apart
- Partial Response (PR): 50% or greater decrease in the overall sum of the products of diameters of all target lesions in reference to the baseline sum, persistence of 1 or more non-target lesions with no new lesions confirmed on at least two consecutive observations at least four weeks apart
- Stable Disease (SD): Failure to observe CR or PR as described above, in the absence of any progressive or new lesions, confirmed on at least two consecutive observations at least four weeks apart
- Progressive Disease (PD): A 25% or greater increase in the overall sum of the products of diameters of all target lesions in reference to the smallest sum recorded at or following baseline or unequivocal progression of existing non target lesions overall or presence of new lesion

The above definition of Partial Response appear to this Reviewer more stringent than by RECIST criteria for the following reasons: 1) bi-dimensional measurement of lesions, 2) a 50% decrease in the sum of target lesions rather than a 30% decrease in uni-dimensional measurements, 3) PD of non-target lesions in the presence of PR or SD of non-target lesions results in overall diagnosis of PD rather than SD in RECIST criteria. On the other hand, the value of the study is diminished by the absence of an independent assessment of tumor response. All assessments were performed by the Sponsor's medical team using tumor measurements that were collected by investigators on CRFs.

Safety population included all patients who received at least one dose of ixabepilone.

6.2.4.6.5 Subject disposition is shown in Reviewer's Table 27 (Sponsor's Table 8.1 in CA163009 Study Report.)