# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-065**

# STATISTICAL REVIEW(S)

**Addendum to Statistical Review and Evaluation of NDA22065**

**NDA/Serial Number:** 22,065/N000
**Drug Name:** Ixabepilone (MBS-247550)
**Indication:** Metastatic or Local Advanced Breast Cancer
**Statistical Reviewer:** Xiaoping (Janet) Jiang, Ph.D.

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This is an addendum to my Statistical Review and Evaluation of NDA22,065 /N000 (Ixabepilone) that was filed into DFS on 10/05/2007.

**Description of correction:**

**Where: the cover of Review**

**Error:**

Submission Date: April 16, 2006
PDUFA Date: October 16, 2006

**Correction:**

Submission Date: April 16, 2007
PDUFA Date: October 16, 2007

Xiaoping (Janet) Jiang, Ph.D.
Mathematical Statistician
Date: 10/11/2007

Cc:
HFD-710/ Xiaoping (Janet) Jiang, Ph.D.
HFD-710/ Raji Sridhara, Ph.D.

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/s/

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Xiaoping Jiang
10/11/2007 11:22:42 AM
BIOMETRICS

Rajeshwari Sridhara
10/11/2007 11:54:50 AM
BIOMETRICS

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# Statistical Review and Evaluation

CLINICAL STUDIES

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|---|---|
| **NDA/Serial Number:** | 22-065 / N000 |
| **Drug Name:** | Ixabepilone (MBS-247550) |
| **Indication(s):** | Metastatic or Local Advanced Breast Cancer |
| **Applicant:** | Bristol-Myers Squibb Company |
| **Date(s):** | Submission Date: April 16, 2006<br>PDUFA Date: October 16, 2006 |
| **Review Priority:** | Priority. |
| **Biometrics Division:** | Division of Biometrics V |
| **Statistical Reviewer:** | Xiaoping (Janet) Jiang, Ph.D. |
| **Concurring Reviewers:** | Division Deputy Director: Rajeshwari Sridhara, Ph.D.<br>Division Director: Aloka Chakravarty, Ph.D. |
| **Medical Division:** | Division of Drug Oncology Product (HFD-150) |
| **Clinical Team:** | Reviewers: E. Kaminiskas M.D.<br>R. Lechleider M.D.<br>Division Deputy Director: Ramzi Dagher, M.D. |
| **Project Manager:** | Sharon Thomas |

**Keywords:** Superiority, log-rank test.

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# 1 EXECUTIVE SUMMARY

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion, based on the materials submitted for this NDA, the results from the study CA163046 support the sponsor's claim that ixabepilone and capecitabine administered as combination therapy demonstrated statistically significant improvements in progression free survival (PFS) over capecitabine alone for the patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant. Based on independent radiology review committee (IRRC) assessment, the estimated median PFS is 5.65 months for combination treatment of Ixabepilone and capecitabine versus 4.10 months for capecitabine treatment alone (stratified log-rank p-value<0.0001). As of database lock (01-Dec-2006), 483 patients had died. The sponsor has reported that at the unscheduled interim analysis of OS with at least 483 deaths, no statistical difference was observed. Whether Ixabepilone shows survival benefit as a combination therapy for the patients will depend on the survival results when data are mature. The final analysis of OS will be conducted when 631 patients have died as specified in the protocol.

The sponsor claimed the effectiveness of ixabepilone as monotherapy was supported by the results of the single-arm study CA163081 and based on the object response rate (ORR) per the IRRRC assessment. No statistical comparison was conducted in study CA163081 and therefore no statistical inference will be drawn from the study. The sponsor claimed that ixabepilone administered as a single agent demonstrated clinical activity in patients with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. Per sponsor, the observed IRRC ORR was 11.9% in 126 treated patients and the estimated median duration of response was 6.3 months. FDA's estimated median duration of response is 5.3 months. Whether its effectiveness is adequate for approval of ixabepilone as monotherapy for the proposed indication will be determined by clinical judgment.

## 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA submission, efficacy data of ixabepilone were collected by the sponsor from two studies CA163046 and CA163081 to support two proposed indications separately. The results of study CA163046 are used to support the first indication "

The results of study CA163081 support the second indication

Study CA163046 was a multicenter, open-label, randomized Phase 3 trial of ixabepilone (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. In study

CA163046, patients were randomized in a 1:1 ratio to receive ixabepilone plus capecitabine (arm A) or capecitabine alone (arm B). The patients in arm A received Ixabepilone 40 mg/m2 administered as a 3-hour intravenous (IV) infusion on Day 1 of each cycle only (21-day cycle), plus oral capecitabine 1000 mg/m2 twice a day (BID) x 14 days and patients in arm B received Capecitabine 1250 mg/m2 BID x 14 days. Randomization was stratified according to the presence of visceral metastases in liver and/or lung (yes/no), minimum of either doxorubicin 240 mg/m2 or epirubicin 360 mg/m2 and relapsed > 6 months in the adjuvant setting (yes/no), prior chemotherapy for metastatic disease (yes/no) and investigator site. Progression free survival (also referred to as time to progression in the protocol), tumor response (using RECIST criteria), and duration of response, were evaluated for all randomized subjects. The primary analyses of the primary endpoint PFS were based on assessments of a blinded independent radiology review committee (IRRC) for all randomized patients. The first patient was randomized to Study CA163046 on September 4, 2003 and the last patient was randomized on January 12, 2006. At the time of data cut-off (30 Nov 2006), a total of 752 patients were randomized into this study of which 737 patients received study drug. IRRC completed reads for 747 subjects (10 of which never received study drug).

The results of study CA163081 are used to support the indication for using Ixabepilone as monotherapy. Study CA163081 was a multinational, multicenter, single-arm 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 determined by the investigator. The first patient was enrolled on February 24, 2004 and the last patient was enrolled on May 06, 2005. A total of 128 patients were enrolled in study CA163081, 126 patients were treated and 113 out of 126 patients were response-evaluable. In study CA163081, Ixabepilone was administered as a 3 hour infusion on Day 1 of a 21-day course at a starting dose of 40 mg/m2. The primary objective of this study was to assess the tumor response rate of Ixabepilone in subjects with advanced breast cancer who are resistant to an anthracycline, a taxane, and capecitabine. In study CA163081, patients were evaluated for tumor response by CT scan every two cycles (six weeks). Primary analysis of best overall tumor response, response rate, duration of response, progression free survival (also referred to as time to progression in the protocol), and time to response were based on the assessments of the IRRC.

## 1.3 STATISTICAL ISSUES AND FINDINGS

A total of 752 patients were randomized at the ratio 1:1 to study CA163046 at the data cutoff date. Of those, 375 patients were randomized to the combination of Ixabepilone + capecitabine and 377 patients to capecitabine alone. The primary efficacy endpoint was PFS, defined as the time (in months) from randomization to the date of progression (per IRRC review). An interim analysis was planned on the first 450 subjects randomized when approximately 369 events (progressions or deaths) have occurred. A Data Monitoring Committee (DMC) was in charge of reviewing the results of the efficacy interim analysis.

**Statistical Issues:**

There are two statistical issues in the results of the primary analysis of PFS in Study CA163046 and one in the result of duration of response in study CA163081.

- Per the statistical analysis plan (SAP), PFS was defined per subject as the time (in months) from randomization to the date of progression (as defined by the IRRC review). Subjects who die without a reported prior progression would be considered to have progressed on their date of death (as found in the BMS clinical database). Subjects who did not progress or die would be censored on the date of their last tumor assessment (as determined from the IRRC data). During the review process, this reviewer found out that there were 157 patients (82 in Ixabepilone + Capecitabine arm and 75 in Capecitabine arm) who received subsequent therapy. Because it is difficult to ascertain if the cause of change of therapy could be due to progression, PFS for a patient who received subsequent therapy before regression or death should be censored at the date of last assessment prior to the earliest start date of any subsequent therapy. FDA sent out a statistical request to ask the sponsor to confirm if the PFS was censored at the date of last assessment prior to the earliest start date of any subsequent therapy for the patient who received subsequent therapy in the primary analysis of PFS and provided the PFS analysis by using the above appropriate censoring scheme. In the response to the FDA statistical request, the sponsor confirmed that in their PFS primary analysis, subjects who had progressive disease or died without a reported prior progression were considered to have progressed on their date of progression or the date of death regardless of the patients having subsequent therapy prior to the date of progression or death. The result of revised PFS analysis is consistent to the result of primary analysis of PFS.

- In study CA163046, there was an inability to evaluate tumors by the IRRC for 14 patients (5 in combination of Ixabepilone + Capecitabine arm and 9 in Capecitabine arm). In the sponsor's primary analysis of PFS, these 14 patients were censored on the date of death or the date of last assessment if the patient were alive. Based on the medical reviewer's adjudication, this reviewer performed a FDA analysis by censoring the PFS on the date of the randomization for these 14 patients and censoring the PFS at the date of last assessment prior to the earliest start date of any subsequent therapy for patients who received subsequent therapy. The results of the FDA's PFS analysis are consistent with the sponsor's PFS primary analysis results and are shown in the following Table A.

- In study CA163081, there is a patient who was dead without an IRRC progression date. In the sponsor's result of duration of response, the duration of response for this patient was calculated as the duration from the first date of response to the date of death in the sponsor's result of the duration of response analysis. Per the medical reviewer, this patient was not assessed after the 4th cycle and died a year later. In study CA163081, patients were evaluated for tumor response by CT scan every two cycles (six weeks). Since this patient missed more than one assessment not using the date, this reviewer performed an analysis of duration of response by censoring the duration of response for this patient at the date of the last assessment. The sponsor's and FDA's results of duration of response are shown in the following Table B.

**Findings**

- The following Table A shows the sponsor's and FDA's PFS results per IRRC assessment in study CA163046. The results show that there was statistically significant difference between ixabepilone plus capecitabine administered as combination therapy and capecitabine alone in favor of ixabepilone plus capecitabine with respect to PFS. The FDA PFS analysis result is consistent to the sponsor's PFS result.

**Table A. Sponsor's and FDA's Results of Progression Free Survival in Study CA163046 (ITT population)**

| Treatment | Number of PFS Events (%) | Median PFS (months, 95% CI) | P-value* (stratified log-rank) | Hazard Ratio** (Ixabepilone + Capecitabine / Capecitabine) (95% CI ) |
|---|---|---|---|---|
| ***Sponsor's Results*** | | | | |
| **Ixabepilone + Capecitabine (N=375)** | 310 (82.7) | 5.85 (5.45, 6.97) | 0.0003 | 0.75 (0.64-0.87) |
| **Capecitabine (N=377)** | 329 (87.3) | 4.17 (3.81, 4.50) | | |
| ***FDA's Results*** | | | | |
| **Ixabepilone + Capecitabine (N=375)** | 242 (64.5) | 5.65 (4.76, 6.70) | <0.0001 | 0.69 (0.58, 0.83) |
| **Capecitabine (N=377)** | 256 (67.9) | 4.10 (3.12, 4.27) | | |

** Stratified log-rank test. ** Cox Proportional model without co-variates. A hazard ratio of greater than 1 indicates that Ixabepilone+ Capecitabine is associated with higher risk of progression or death compared to Capecitabine.*

- The following Table B shows the sponsor's and FDA's results of objective response rate and duration of response per IRRC assessment in study CA163081.

**Table B. Sponsor's and FDA's Results of Objective Response Rate in Study CA163081 (Treated Patients)**

| | Number of Patients (%) |
|---|---|
| | N=126 |
| **IRRC Best Response** | |
| **PR** | 15 |
| **SD** | 62 |
| **PD** | 39 |
| **Unable to determine** | 10 |
| **IRRC Objective Response Rate, %** | 11.9 |
| **95% CI, %** | 6.8,18.9 |
| **Duration of Response (*Sponsor's Result*)** | |
| **Median (Months)** | 6.3 |
| **95%CI** | 5.0,7.5 |
| **Duration of Response (*FDA's Result*)** | |
| **Median (Months)** | 5.3 |
| **95%CI** | 4.4, 6.3 |

# 2 INTRODUCTION

## 2.1 OVERVIEW

[redacted]

Study CA163046 was a randomized, multicenter, global, open-label, Phase 3 study comparing progression-free survival with ixabepilone plus capecitabine to capecitabine alone in patients with taxane-resistant and anthracycline-pretreated or resistant metastatic or locally advanced breast cancer. This study was conducted in 160 study sites in 22 countries. A total of 752 patients were randomized into this study of which 375 patients in ixabepilone plus capecitabine group and 377 patients in capecitabine group.

Study CA163081 was a multinational, multicenter, single-arm 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 determined by the investigator. A total of 128 patients were enrolled in Study CA163081. Among them, 126 patients were treated and 113 patients were response-evaluable.

**Reviewer Comments**:

[1] There has been 6 protocol amendments for study CA163046 entitled *"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"*. The purpose of amendment 1 was to improve the consistency and clarity of the protocol. Following are key changes addressed in the amendment 1:

- defining measurable lesions when being objectively measured by MRI, ultrasound, or physical examination as ≥ 20 mm in at least one diameter;
- ensuring that the radiographic requirements for bone lesions being followed as sites of non-measurable disease are assessed by methods other than a bone scan (e.g., MRI, CT);
- defining the criteria for complete response for target lesions as the disappearance of all clinical and radiographical evidence of target lesions;
- modifying the inclusion criteria to ensure that at least one target lesion is radiographical measurable at baseline;
- clarifies that a data monitoring committee will be charged with reviewing the safety data as well as the efficacy data from the interim analysis and;
- as with BMS-247550, dose modifications are not required for capecitabine for alopecia, Grade 2 and 3 fatigue/asthenia, and Grade 2 and transient Grade 3 arthralgias/myalgias.

The amendment 02, 03 and 05 were site specific to protocol CA163046. The amendment 04 was to eliminate the requirement for at least one prior metastatic regimen. And the purpose of amendment 06 was to update section 6.5 of the protocol 'Prohibited and Restricted Therapies During Study Conduct', to address the potential for drug interactions with strong inhibitors of CYP3A4 as outlined in Version 6 of the Ixabepilone Investigator Brochure dated 11- Mar-2005, as well as add an exclusion criterion relating to the ongoing use of these drugs.

## 2.2 DATA SOURCES

Data used for review are from the electronic submission received in April 16, 2007. The network path is "\\Cdsesub1\evsprod\NDA022065\0000" in the electronic document room (EDR).

# 3 STATISTICAL EVALUATION

This review focuses on study CA163046 and study CA163081 with more focus on randomized study CA163046. Section 3.1 includes efficacy evaluation for the study CA163046 and study CA163081.

## 3.1 EVALUATION OF EFFICACY

This section provides the description and results of study CA163046 and study CA163081 based on the sponsor's study reports. Any difference between the sponsor's study reports and the protocols are also discussed in this section.

### 3.1.1 STUDY OBJECTIVES

The primary objective of study CA163046 was to compare the time to progression for ixabepilone plus capecitabine versus capecitabine alone in patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant.

The secondary objectives of this study were as follows:

- To compare overall survival (OS) with ixabepilone plus capecitabine vs. capecitabine alone in this patient population.
- To compare the objective response rate (ORR) with ixabepilone plus capecitabine vs. capecitabine alone in this patient population.
- To estimate time to response and response duration with ixabepilone plus capecitabine vs. capecitabine alone in this patient population.
- To compare the safety of ixabepilone plus capecitabine vs. capecitabine alone in this patient population.
- To compare the impact of ixabepilone plus capecitabine vs. capecitabine alone on patients' symptoms using the Functional Assessment of Cancer Therapy-Breast (FACT-B) symptom index (FBSI)

The primary objective of study CA163081 was to assess the tumor response rate of ixabepilone (BMS-247550) in patients with metastatic or locally advanced breast cancer who are resistant to an anthracycline, a taxane and capecitabine. The secondary objective included time to progression, time to response, response duration and survival of patients in the study population treated with ixabepilone

### 3.1.2 STUDY DESIGN

Study CA163046 was designed as a large, randomized, multicenter, global, open-label study in patients with taxane-resistant and anthracycline-pretreated or resistant metastatic or locally advanced breast cancer. A total of 750 patients were planned to be randomized 1:1 to the following groups, using a 21-day cycle:

- Ixabepilone 40 mg/m2 administered as a 3-hour intravenous (IV) infusion on Day 1 of each cycle only, plus oral capecitabine 1000 mg/m2 twice a day (BID) x 14 days
- Capecitabine 1250 mg/m2 BID x 14 days

The randomization were stratified according to the presence of visceral metastases in liver and/or lung (yes/no), minimum of either doxorubicin 240 mg/m2 or epirubicin 360 mg/m2 and relapsed > 6 months in the adjuvant setting (yes/no), prior chemotherapy for metastatic disease (yes/no), and investigator site. There have been six amendments to the protocol CA163046. The factor 'prior chemotherapy for metastatic disease (yes/no)' was added as a stratification factor after fourth amendment (dated on Feb 3 rd, 2005). Primary analyses of efficacy endpoints were based on assessments of an Independent Radiology Review Committee (IRRC), using modified Response Evaluation Criteria in Solid Tumors (RECIST). The IRRC, who was blinded to treatment group, investigator selection of target and non-target lesions, and investigator response assessments, received baseline and subsequent radiological images directly from investigators. Per the IRRC charter, specific clinical information was provided to the IRRC by Bristol-Myers Squibb (BMS). None of the data provided included information that could directly or indirectly divulge treatment assignment. The overall IRRC response for each cycle was based on the integration of the IRRC radiologist's and oncologist's assessments. Patients in both groups were assessed symmetrically every 6 weeks while on treatment until investigators documented progressive disease (PD). Patients who discontinued treatment for reasons other than documented progression were assessed every 6 weeks until 24 weeks from randomization, and then every 3 months until investigators documented PD. After progression, patients were followed every 3 months until death. An independent Data Monitoring Committee (DMC) monitored efficacy and safety throughout the study.

Study CA163081 was designed as a multicenter, single arm study to evaluate the clinical activity and tolerability of ixabepilone administered intravenously (IV) once every 3 weeks in patients with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. The primary endpoint was objective response rate by on IRRC assessment. The study was planned to enroll a minimum of 100 response evaluable patients with advanced breast cancer who were resistant to an anthracycline, a taxane, and capecitabine. Ixabepilone would be administered as a 3 hour infusion on Day 1 of a 21-day course at a starting dose of 40 mg/m2. A modified Gehan two-stage design would be used to test whether the objective response rate was of clinical interest. In the first stage, 29 response-evaluable subjects would be accrued. If no responses are observed, the study would be closed to accrual with the conclusion that the true response rate was unlikely to be greater than or equal to 10%. Otherwise, if there was at least one response, 71 additional response-evaluable subjects would be accrued in the second stage. Patients were evaluated for tumor response by CT scan every two cycles (six weeks).

Please refer to FDA clinical reviews for more detail of inclusion and exclusion criterion for study CA163046 and study CA163081.

**Reviewer Comments**:

[1] The fourth amendment of study CA163046, dealt with the following topics, as stated in the amendment: The amendment extended the disease free interval requirement from 6 to 12 months following adjuvant therapy with Taxane in order to make the protocol compliant with a more commonly accepted definition of Taxane resistance. Per the sponsor, a general practice in the follow-up of women with breast cancer who have completed prior therapy included clinic visits approximately every 3 months at which time additional workup to evaluate the extent of disease may be scheduled for a later time. This amendment extended the interval from the last taxane dose to disease progression in the metastatic setting from 3 to 4 months. The amendment also eliminated the requirement for at least one prior metastatic regimen. As a result of protocol amendment 04, the factor 'prior chemotherapy for metastatic disease (yes/no)' was added as an additional stratified factor in randomization to ensure balance in randomization. Subjects randomized before activation of amendment # 4 were categorized as having received prior chemotherapy for metastatic disease. It is not clear how many patients were on study prior to this amendment. Per SAP, because of the addition of a new stratification factor, all planned efficacy analyses for PFS, overall survival and response rate, were changed the analyses with 3 stratification factors: the presence of visceral metastases in liver and/or lung (yes/no), minimum of either doxorubicin 240 mg/m2 or epirubicin 360 mg/m2 and relapsed > 6 months in the adjuvant setting (yes/no), and prior chemotherapy for metastatic disease (yes/no).

### 3.1.3 EFFICACY ENDPOINTS

#### 3.1.3.1 Primary Efficacy Endpoint

Per protocol, the primary endpoint in study CA163046 was progression free survival (PFS). PFS was defined as the time (in months) from randomization to the date of progression (as determined by the IRRC). Subjects who die without a reported prior progression would be considered to have progressed on their date of death (as found in the BMS clinical database). Subjects who did not progress or die would be censored on the date of their last tumor assessment (as determined from the IRRC data). Subjects who did not receive any study treatment or who have no on-study IRRC assessment (and have no death reported in the BMS clinical database) would be censored on the day they were randomized. Per SAP, if the study was not stopped based on the outcome of the interim analysis, the final analysis of PFS would be conducted when approximately 615 events (progressions or deaths) had occurred or 4 months after the last subject had been randomized, whichever came last.

In study CA163081, the primary efficacy endpoint was objective response rate (ORR), defined as the number of patients with a best response of complete response (CR) or partial response (PR), as assessed by the IRRC, divided by the total number of response-evaluable patients.

**Reviewer Comments**:

[1] The submitted results of the final PFS analysis in study CA163046 were based on data that included 639 PFS events (progression or deaths) determined by IRRC in a total of 752 enrolled patients.

[2] In this NDA submission, there were 128 patients enrolled and 126 patients were treated in study CA163081.

### 3.1.3.2 Secondary Efficacy Endpoints

In study CA163046, the secondary efficacy endpoints were overall survival (OS), objective response rate (ORR), time to response, duration of response (DR), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) symptom index (FBSI). The definitions of the selected secondary endpoints are as follows.

- **Overall survival (OS),** defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time would be censored at the last date the patient is known to be alive. Patients lacking data beyond randomization would have their survival times censored on the date of randomization.

- **Objective response rate (ORR)** in each arm, defined as the number of patients in that arm whose best response is PR or CR (as defined by the IRRC), divided by the total number of randomized subjects in that treatment arm (for all randomized population).

- **Duration of overall response,** measured from the time (in months) measurement criteria are first met for PR or CR, whichever is recorded first, until the date of documented progressive disease or death. The duration of overall response would be computed based upon the best overall response, date of first response, date of progression, and date of last tumor assessment, as determined by the IRRC. Subjects who neither relapse nor die would be censored on the date of their last tumor assessment.

Analyses of overall survival and ORR would be based on all randomized subjects. Duration of response and time to response would be estimated on all randomized subjects who were assessed as having a complete or partial response (as determined by the IRRC). In addition, the primary analysis of response rate will be the Cochran-Mantel-Haenszel (CMH) test, with an associated odds ratio estimate and 95% confidence interval, stratified by presence of visceral metastases in liver and/or lung (yes, no), minimum of either doxorubicin 240 mg/m2 or epirubicin 360 mg/m2 and relapse > 6 months in adjuvant setting (yes, no) and prior chemotherapy for metastatic disease (yes, no) to compare the response rates between the two arms.

In study CA163081, the secondary efficacy endpoints were progression free survival, time to response, duration of response and survival.

### 3.1.4 SAMPLE SIZE CONSIDERATIONS

In study CA163046, the number of events and power for this study were calculated assuming an exponential progression free survival distribution in each arm. The alpha level for PFS was adjusted for a planned interim analysis using the O'Brien-Fleming spending function (see Section 6 of the DMC charter and Section 7.5.2.4 of the analysis plan). The final analysis required at least 615 events (progressions or deaths); this was the number of events needed for a two-sided, log-rank test at an experiment wise $\alpha = 0.05$ level to have 90% power to show a statistically significant difference assuming the true hazard ratio was 0.77 (i.e., when the median PFS in the combination arm was 30% greater than the median PFS of 3 months in the control arm). A total of 750 subjects were planned to be randomized. It was estimated that the study would take approximately 28 months to accrue and the final PFS analysis would be performed 4 months following the last subject accrued or when approximately 615 events (progressions or deaths) had occurred, whichever comes last. Per SAP, if the study completes to full accrual, the analysis of survival would only be performed when approximately 631 subjects had died (84% of total sample size). This analysis was expected to occur 47 months after the first subject is randomized. The sample size would provide 80% power to show a statistically significant difference between treatment arms in overall survival assuming the true hazard ratio was .80 (i.e., when the median survival in the combination arm was 25% greater than the median survival of 10 months in the control arm). With a sample size of 750 subjects, there would be at least 95% power to detect a significant difference in response rate of 32% in the combination arm compared with a response rate of 20% in the Capecitabine alone arm. The sponsor had no plan to adjust the $\alpha$ for the interim analysis on response rate since the decision on whether to stop the study at the interim analysis was based upon the results of PFS. In the event that the study was stopped early with 450 subjects, it was estimated that there would be at least 80% power to detect a difference in response rate of 32% versus 20% at $\alpha = 0.05$.

In study CA163081, a modified Gehan two-stage design would be used. In the first stage, 29 response evaluable subjects would be accrued. If no responses are observed, the study would be closed to accrual with the conclusion that the true response rate was unlikely to be greater than or equal to 10%. Otherwise, if there was at least one response, 71 additional response evaluable subjects would be accrued in the second stage. Per SAP, there was 5% or less chance of stopping the study after the first stage if the true response rate was at least 10%. With a total accrual of 100 response-evaluable subjects, the maximum width of the exact two-sided 95% confidence interval would be 14.9% when the response rate was in the expected 5%-15% range. Assuming that some subjects were not evaluable for response, a total of approximately 125 subjects were expected to be accrued, in order to obtain a minimum of 100 response evaluable subjects.

### 3.1.5 INTERIM ANALYSIS

Per SAP, an interim analysis was planned on the first 450 subjects randomized when approximately 369 events (progressions or deaths) occurred in study CA163046. A Data Monitoring Committee (DMC) was charged with reviewing the results of the efficacy interim analysis. Based on the guidelines stated in the DMC charter, at the interim, the nominal significance level for PFS would be adjusted using the O'Brien-Fleming stopping boundary to

reject the null hypothesis controlling at one-sided type I error rate alpha of 1%. This criterion rules out a 2 week difference in PFS between the two arms (assuming a 3 month median control) which is considered to be clinically meaningful. In addition to PFS, week 12 progression free rate, best response, response rate, duration of response, time to response and month 6 stable disease rate will be analyzed at the time of the interim analysis but should have no bearing on the decision of the conduct of the trial since these are not primary endpoints. The analysis of overall survival would not be performed at the time of the interim analyses. If the enrollment is stopped at the interim, the survival analysis would be performed at the time approximately 631 (84% of the accrued) patients had died.

There were no plans to stop the study at the interim due to better survival of the combination arm compared to the single arm, so the nominal significance level to reject the null hypothesis of equal survival would be taken at 0.0001. Per SAP, in case of any unscheduled look after the interim, the nominal significance level to reject the null hypothesis of equal survival would be taken at 0.0001. For unscheduled efficacy look prior to the interim analysis, the null hypothesis of equal hazard rate for survival can not be rejected with such a small data set and hence no formal statistical testing will be performed. There would also be an option for the DMC members to recommend stopping the study at the interim due to lack of benefit in survival for the combination arm compared to the Capecitabine arm. The O'Brien-Fleming boundary to reject the alternative hypothesis of non-equal survival time will be generated by a beta-spending function that spends the type-2 error. The overall one-sided type-2 error spent would be 2.5%. In case of an unscheduled look after the interim analysis, the boundary to reject the alternative hypothesis of non-equal survival would be adjusted using the O'Brien-Fleming stopping rule.

No interim analysis was planned for study CA163081.

**Reviewer's Comments:**

[1] In study CA163046, an interim analysis was performed when 344 PFS events per IRRC were observed in the first 450 randomized patients. The alpha spent at the interim look was 0.0009 (1-sided) based on 344 PFS events at that time. The two-sided nominal significant level for the final analysis would be 0.0483.

### 3.1.6 STATISTICAL METHODOLOGIES

#### 3.1.6.1 Sponsor's Protocol/Statistical Analysis Plan

Per sponsor's protocol, the primary analysis for study CA163046 would be a comparison of PFS between the two treatment arms using a log-rank test, stratified by presence of visceral metastases in liver and/or lung (yes, no), minimum of either doxorubicin 240 mg/m2 or epirubicin 360 mg/m2 and relapse > 6 months in adjuvant setting (yes, no) and prior chemotherapy for metastatic disease (yes, no) as assigned at the time of randomization (Table 10.10). The strata were coded as follows:

• Presence of visceral metastases in liver and/or lung: (1="yes", 2="no")

• Minimum of either doxorubicin 240 mg/m2 or epirubicin 360 mg/m2 and relapse > 6 months in adjuvant setting: (1="yes", 2="no")
• Prior chemotherapy for metastatic disease (1="yes", 2="no")

An interim analysis was planned on the first 450 subjects randomized when approximately 369 events (progressions or deaths) had occurred. The alpha level would be adjusted using an O'Brien Fleming spending function to reject the null hypothesis of equality of PFS, controlling at type I error rate two sided alpha of 5%. PFS for each treatment arm would be estimated using the Kaplan-Meier product-limit method. Kaplan-Meier curves by treatment arm (as randomized) would be produce.

Per the protocol of study CA163046, progression free survival (also referred to as time to progression in the protocol), tumor response (using RECIST criteria), and duration of response, would be evaluated for all randomized subjects. An external independent radiologic review committee (IRRC) would be charged with reviewing the tumor assessments of all subjects. Progression-free survival (referred to as time to progression in the study protocol) was defined as the time, in months, from randomization to the IRRC date of progression. Patients who died without a reported prior progression based on RECIST were considered to have progressed on their date of death, as reported in the BMS clinical database. Patients who did not progress by RECIST or die were censored on the date of their last IRRC tumor assessment. Patients who did not receive any study treatment or had no on-study IRRC assessment (and had no death reported in the BMS clinical database) were censored on the date of randomization. All analyses would be performed using the treatment arm as randomized (intent to treat), with the exception of dosing and safety, for which the treatment arm as treated will be used.

Per SAP of study CA163081, exact two-sided 95% Clopper-Pearson confidence intervals for the objective response rates would be computed on the response evaluable subject dataset. The objective response rate on all treated subjects (along with its Clopper-Pearson 95% confidence interval) would also be presented as a secondary analysis using the total number of treated subjects as the denominator for computing the response rate. The duration of overall response would be estimated using the Kaplan-Meier product limit method.

### 3.1.7 SPONSOR'S RESULTS AND STATISTICAL REVIEWER'S COMMENTS/FINDINGS

This section summarizes the sponsor's major efficacy results from study CA163046 and CA163081 and provides the statistical reviewer's comments and findings. Per the pre-specified statistical analysis plan for study CA163046, the final PFS analysis would require at least 615 PFS events (progressions or deaths); however, the actual number of occurred PFS events was 639 per IRRC assessment.

#### 3.1.7.1 Disposition of Patients

The following Table 1 is the sponsor's summary of patient disposition in study CA163046. As seen in this table, as of the date (December 01, 2006) of the database lock, nearly all randomized patients were off treatment. Disease progression/relapse was the most common reason for

discontinuation in each group. More patients in the ixabepilone plus capecitabine group than in the capecitabine group discontinued all study treatment due to study drug toxicity;

**Table 1: Sponsor's Summary of Patient Disposition (ITT Population)**

| Number of Patients | Ixabepilone + Capecitabine | Capecitabine |
|---|---|---|
| **All randomized** | 375 (100.0) | 377 (100.0) |
| **Never treated** | 5 (1.3) | 10 (2.7) |
| **Treated** | 370 (98.7) | 367 (97.3) |
| still on Treatment | 6 (1.6) | 12 (3.3) |
| off treatment | 364 (98.4) | 355 (96.7) |
| **Reason off Treatment** | | |
| Adverse events related to study Drug | 2 (7) | 4 (1.1) |
| Completed treatment | 6 (3) | 3 (3) |
| Death | 12 (3.2) | 8 (2.2) |
| Deterioration w/o progression | 15 (4.1) | 27 (7.4) |
| Disease progression/relapse | 221 (59.7) | 267 (72.8) |
| Investigator request | 15 (4.1) | 9 (2.5) |
| Lost to follow-up | 1 (0.3) | 0 (0) |
| Other | 3 (0.8) | 1 (0.3) |
| Study drug toxicity | 68 (18.4) | 24 (6.5) |
| Patient request | 21 (5.7) | 12 (3.3) |

*[Source: Sponsor's Study Report CA163046 Table 8.1 ]*

## Reviewer's Comment:

[1] Table 1 has been verified.

### 3.1.7.2 Demographic and Baseline Characteristics

Table 2 shows the demographic and baseline characteristics for the 752 patients in study CA163046. As indicated in the following table, most randomized patients were white, were < 65 years of age and had a KPS score of ≥ 90. Per the sponsor, all treated patients were women; one man was randomized to the capecitabine group in error but never treated.

**Table 2: Sponsor's Summary of Demographic and Selected Baseline Characteristics in Study CA163046 (ITT Population)**

| | Ixabepilone + Capecitabine (N = 375) | Capecitabine (N = 377) |
|---|---|---|
| **Race [n (%)]** | | |
| White | 275 (68.5) | 247 (65.5) |
| Black | 11 (2.9) | 11 (2.9) |
| Asian | 83 (22.1) | 87 (23.1) |
| American Indian/Alaska native | 1 (0.3) | 0 |
| Other | 23 (6.1) | 32 (8.5) |
| **Age (years)** | | |
| Median (range) | 53.0 (25.0 – 76.0) | 52.0 (25.0 – 79.0) |
| < 65 [n (%)] | 336 (89.6) | 322 (85.4) |
| ≥ 65 [n (%)] | 39 (10.4) | 54 (14.3) |
| **Karnofsky performance status [n (%)]** | | |
| 100 | 108 (28.8) | 105 ( 27..9) |
| 90 | 145(38.7) | 132(35.0) |
| 80 | 86 (22.9) | 102 (27.1) |
| 70 | 33 (8.8) | 34 (9.0) |
| <70 | 0 | 1 (0.8) |
| Not report | 3 (0.8) | 3 (0.8) |
| **Menopausal status [n (%)]** | | |
| Pre-menopausal | 54 (14.4) | 51 (13.5) |
| Peri-menopausal | 19 (5.1) | 23 (6.1) |
| Post-menopausal | 288 (76.8) | 289 (76.7) |
| Not reported | 14 (3.7) | 14 (3.7) |

*[Source: Sponsor's Study Report CA163046 Table 8.3]*

**Reviewer Comments:**

[1] As seen in Table 2, demographic and baseline characteristics appeared balanced between the two treatment groups in study CA163046.

### 3.1.7.3 Progression Free Survival (Primary Endpoint)

Per sponsor's statistical analysis plan (SAP) of study CA163046, the primary endpoint progression free survival (PFS) was defined as the time (in months) from randomization to the date of progression (as defined by the IRRC review). Subjects who die without a reported prior progression would be considered to have progressed on their date of death (as found in the BMS clinical database). Subjects who did not progress or die would be censored on the date of their last tumor assessment (as determined from the IRRC data). Subjects who did not receive any study treatment or who have no on-study IRRC assessment (and have no death reported in the BMS clinical database) would be censored on the day they were randomized.

**Table 3: Sponsor's Results of primary Analyses of Progression Free Survival per IRRC (All Randomized Patients)**

| | Ixabepilone + Capecitabine | Capecitabine | P-value* | Hazard Ratio ([Ixabepilone+ Capecitabine]/ Capecitabine) |
|---|---|---|---|---|
| | N=375 | N=377 | | |
| **Number of Events (Progression or death), n (%)** | 310 (83%) | 329 (87%) | | |
| Median Progression Free Survival (months) | 5.85 | 4.17 | 0.0003* | 0.75 |
| 95% Confidence Interval | (5.45, 6.97) | (3.81, 4.50) | | (0.64, 0.87) |

** Stratified log-rank test*
*[Source: Sponsor's Study Report CA163046 Table 10.A]*

**Reviewer Comments:**

[1] Per the SAP of study CA163046, PFS was defined per subject as the time (in months) from randomization to the date of progression (as defined by the IRRC review). Subjects who die without a reported prior progression would be considered to have progressed on their date of death (as found in the BMS clinical database). Subjects who did not progress or die would be censored on the date of their last tumor assessment (as determined from the IRRC data). During the review process, this reviewer found out that there were 157 patients (82 in Ixabepilone + Capecitabine arm and 75 in Capecitabine arm) who received subsequent therapy. Because it is difficult to ascertain if the cause of changes of therapy could be due to progression, PFS for a patient who received subsequent therapy before regression or death should be censored at the date of last assessment prior to the earliest start date of any subsequent therapy. FDA sent out a statistical request to ask the sponsor to confirm if the PFS was censored at the date of last assessment prior to the earliest start date of any subsequent therapy for the patient who received subsequent therapy in the primary analysis of PFS and provided the PFS analysis by using the above appropriate censoring scheme. In the response to the FDA statistical request, the sponsor confirmed that in their PFS primary analysis, subjects who had progressive disease or died without a reported prior progression were considered to have progressed on their date of progression or the date of death regardless of the patients having subsequent therapy prior to the date of progression or death. The provided result of revised PFS analysis is consistent to the result of primary analysis of PFS.

[2] In the NDA submission, the sponsor provided a sensitivity analysis of PFS by censoring at the start date of the earliest subsequent therapy, rather than their last tumor assessment (provided they received the subsequent therapy prior to the

last tumor assessment) for patients who received subsequent therapy in study CA163046. The PFS result of the sponsor's sensitivity analysis is consistent to the primary analysis result.

[3] Per sponsor, the alpha spent at the interim look was 0.0009 (1-sided) based on 344 PFS events at that time. The sponsor did not provide details of interim PFS analysis. The nominal significance level for the final analysis was 0.0483, adjusted using the 2-sided alpha of 5% to reject the null hypothesis of equality in PFS, as specified in the protocol.

[4] In study CA163046, there was an inability to evaluate tumors by the IRRC for 14 patients (5 in combination of Ixabepilone + Capecitabine arm and 9 in Capecitabine arm). In the sponsor's primary analysis of PFS, these 14 patients were censored on the date of death or the date of last assessment if the patient were alive. Based on the medical reviewer's adjudication, this reviewer performed a FDA analysis by censoring the PFS on the date of the randomization for these 14 patients and censoring the PFS at the date of last assessment prior to the earliest start date of any subsequent therapy for patients who received subsequent therapy. The FDA's PFS results and Kaplan-Meier curves are shown in the following Table 4 and Figure 1. The results of the FDA's PFS analysis are consistent with the sponsor's PFS primary analysis results.

**Table 4: FDA's Results of Progression Free Survival per IRRC in Study CA163046**

| | **Ixabepilone + Capecitabine N=375** | **Capecitabine N=377** | **P-value*** | **Hazard Ratio** ([Ixabepilone+ Capecitabine]/ Capecitabine)** |
|---|---|---|---|---|
| **Number of Events (Progression or death), n (%)** | 242 (64.5%) | 256 (67.9%) | | |
| **Median PFS (months)** | 5.65 | 4.10 | <0.0001 | 0.69 |
| **95% CI** | (4.76, 6.70) | (3.12, 4.27) | | (0.58, 0.83) |

** Stratified log-rank test. ** Cox Proportional model without co-variates. A hazard ratio of greater than 1 indicates that Ixabepilone+ Capecitabine is associated with higher risk of progression or death compared to Capecitabine.*

**Figure 1: Reviewer's Kaplan-Meier Curves of Progression Free Survival per IRRC**

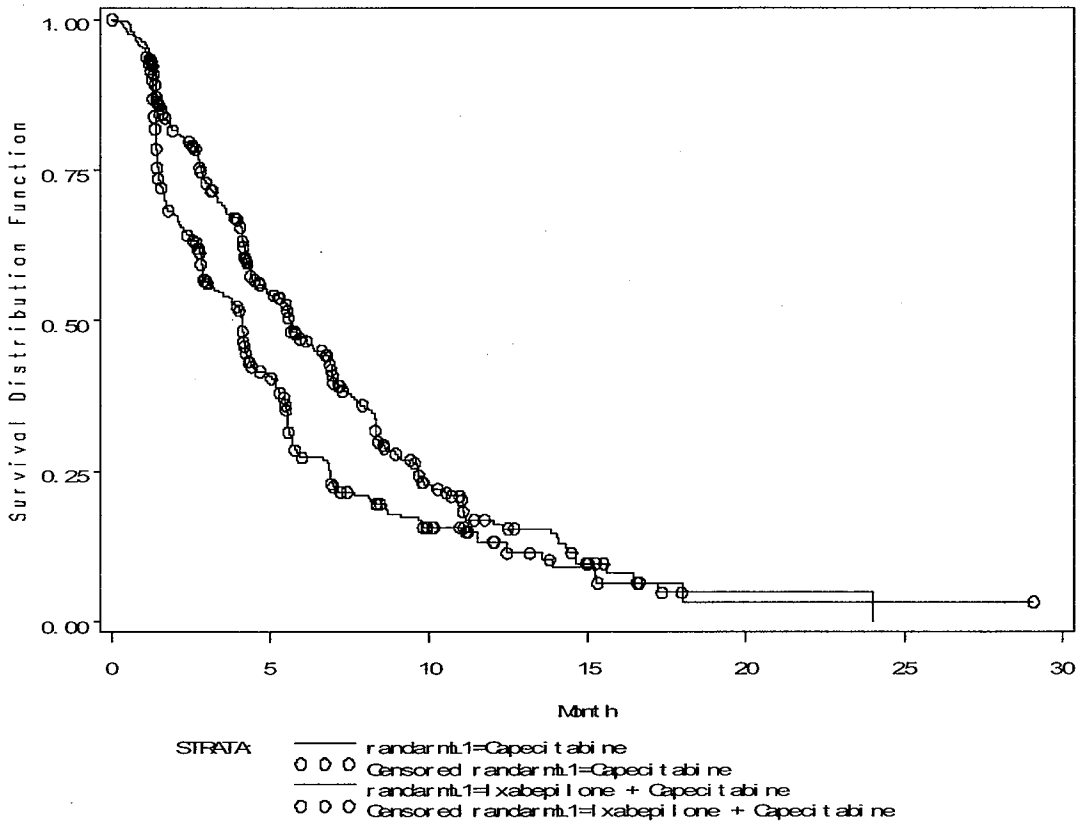



**Table 5: Sponsor's Result of Objective Response Rate in Study CA163081 (Treated Patients)**

| | Number of Patients (%) |
|---|---|
| | N=126 |
| **IRRC Best Response** | |
| **PR** | 15 |
| **SD** | 62 |
| **PD** | 39 |
| **Unable to determine** | 10 |
| **IRRC Objective Response Rate, %** | 11.9 |
| **95% CI, %** | 6.8,18.9 |

*[Source: Sponsor's Study Report CA163081 and the sponsor's Response to FDA Clinical Review Team Query dated 25-June-2007]*

**Reviewer Comments:**

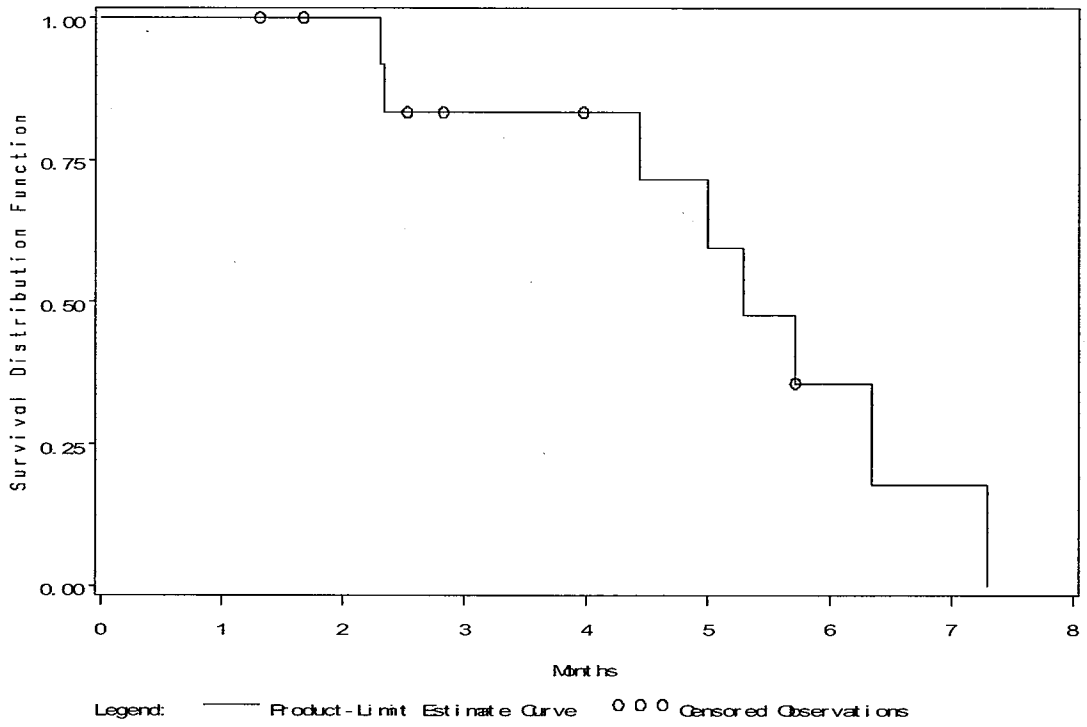
[1] In the submission of NDA, the number of responders was 14. The sponsor updated the number of responders from 14 to 15 in their Response to FDA Clinical Review Team Query dated 25-June-2007.

[2] In study CA163081, there is a patient who was dead without an IRRC progression date. In the sponsor's result of duration of response, the duration of response for this patient was calculated as the duration from the first date of response to the date of death in the updated result of the duration of response analysis. Per the medical reviewer, this patient was not assessed after the 4th cycle and died a year later. In study CA163081, patients were evaluated for tumor response by CT scan every two cycles (six weeks). Since this patient missed more than one assessment not using the date, this reviewer performed an analysis of duration of response by censoring this patient at the date of the last assessment. The FDA's results of duration of response are shown in the following Table 6 and Figure 2.

**Table 6: Sponsor's and FDA's Results of Duration of Response in Study CA163081**

| | |
|---|---|
| ***Sponsor's Result*** | |
| **Median (Months)** | 6.3 |
| **95%CI** | 5.0,7.5 |
| ***FDA's Result*** | |
| **Median (Months)** | 5.3 |
| **95%CI** | 4.4, 6.3 |

**Figure 2: Reviewer's Kaplan-Meier Curve of Duration of Response in Study CA163081**

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### 3.1.7.4 Secondary Endpoints

In study CA163046, secondary efficacy endpoints were overall survival (OS), objective response rate (ORR), time to response, duration of response (DR), and the Functional Assessment of Cancer Therapy-Breast (FACT-B) symptom index (FBSI). The following Table summarizes the sponsor's results of the selected secondary endpoints based on IRRC assessments.

**Table 7: Sponsor's Results of selected Secondary Endpoints in Study CA163046 (ITT Population)**

| | Capecitabine | Ixabepilone+ Capecitabine |
|---|---|---|
| **ORR** | 54 (14.3%) | 130 (34.7%) |
| Complete Response | 0 | 1 |
| Partial Response | 54 | 129 |
| Progressive Disease | 102 | 58 |
| Stable Disease | 175 | 155 |
| Unable To Determine | 46 | 32 |
| Total | 377 | 375 |
| P-value* | <0.0001 | |
| **Duration of Response** | | |
| Median Duration (Months) | 5.5 | 6.4 |
| 95%CI | (4.2,7.4) | (5.6,7.1) |

**CMH test stratified with 3 randomized factors.*
*[Source: Sponsor's study report for study CA163046.]*

## Reviewer's Comment:

[1] This reviewer verified the results in Table 4.

[2] The results of RR in Table 4 show statistical difference in RR in favor of the ixabepilone in combination with capecitabine compared to capecitabine monotherapy. However, the sponsor did not pre-specify the order of secondary endpoints which would be tested in [redacted] after the results of the primary endpoint show statistical persuasive evidence. By the time of this analysis, the data for overall survival were not matured.

[3] Overall survival is an important secondary endpoint in study CA163046. Per sponsor, the DMC had performed an unscheduled interim OS analysis. Having analyzed the overall survival data (using monitoring boundary $p<0.0001$), DMC concluded that the interim OS data did not suggest an overall survival benefit for the addition of ixabepilone, but rather an absence of detriment with regard to overall survival. DMC recommended continuation of the trial for follow-up of survival to the pre-specified 631 deaths.

### 3.2 EVALUATION OF SAFETY

Please refer to the FDA clinical review for safety evaluation of ixabepilone.

# 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section will be focused on the reviewer's results of the exploratory subgroup analyses of the primary endpoint, progression free survival (PFS) in study CA163046.

## 4.1 GENDER, RACE, AGE AND REGION

The following table shows this reviewer's summary of subgroup analyses in study CA163046. These subgroups included subsets of patients with different category of age, race, Karnofsky Performance Status and receptor status (such as PR status, ER status and HER2). Since all patients (except 1 patient) were women, there is no need to perform subgroup analysis by gender. In addition, the subgroup results appeared consistent with the results of overall ITT population.

**Table 8: Summary of Subgroup Analyses of Progression Free Survival in Study CA163046 (FDA's Analysis)**

| Subgroup | Number of Patients | | Hazard Ratio (Ixabepilone + Capecitabine / Capecitabine) (95% CI) |
|---|---|---|---|
| | Capecitabine | Ixabepilone + Capecitabine | |
| Age >= 65 | 54 | 39 | 0.91 (0.58, 1.40) |
| Age <65 | 322 | 336 | 0.73 (0.62,0.87) |
| White | 247 | 257 | 0.73 (0.61, 0.89) |

**Reviewer's Comment:**

[1] The results of primary endpoint, progress free survival in subgroups of patients with age great than or equal to 65, age less than 65, female patients, male patients, white patients are consistent with the results of overall ITT population.

[2] The results of subgroup analyses should be considered as exploratory/supportive.

## 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

The results of this reviewer's exploratory subgroup analyses by Karnofsky Performance Status, receiving previous chemotherapy and receptor status (such as PR status, ER status and HER2) are summarized in the following table.

**Table 9: Summary of Subgroup Analyses of Progression Free Survival in Study CA163046 (FDA's Analysis)**

| Subgroup | Number of Patients | | Hazard Ratio (Ixabepilone + Capecitabine / Capecitabine) (95% CI) |
|---|---|---|---|
| | Capecitabine | Ixabepilone + Capecitabine | |
| Prior chemotherapy (Yes) | 344 | 348 | 0.77 (0.65, 0.90) |
| Karnofsky Performance Status (70-80) | 136 | 119 | 0.68 (0.52,0.89) |
| Karnofsky Performance Status (90-100) | 237 | 253 | 0.79 (0.65, 0.96) |
| ER+ | 178 | 173 | 0.81 (0.64, 1.02) |
| ER- | 161 | 164 | 0.70 (0.56, 0.88) |
| HER2 negative | 238 | 220 | 0.76 (0.60, 1.01) |
| HER2 positive | 53 | 59 | 0.69 (0.47, 1.02) |
| PR- | 179 | 187 | 0.73 (0.59, 0.91) |
| PR+ | 145 | 136 | 0.78 (0.60, 0.88) |
| ER+, PR+ | 126 | 126 | 0.81 (0.61, 1.07) |
| ER-, PR- | 140 | 146 | 0.69 (0.54, 0.88) |
| ER-PR-HER2- (Yes) | 96 | 91 | 0.68 (0.50, 0.92) |
| ER-PR-HER2- (No) | 281 | 284 | 0.74 (0.62, 0.88) |
| Disease sites <=2 | 132 | 124 | 0.67 (0.51,0.88) |
| Disease sites >2 | 243 | 247 | 0.79 (0.65, 0.96) |

**Reviewer's Comment:**

[1] The results of primary endpoint, progress free survival in subgroups by Karnofsky Performance Status, number of disease sites, prior chemotherapy status and receptor status for ER, PR, and HER2 are consistent with the results of overall ITT population.

[2] The results of subgroup analyses should be considered as exploratory/supportive.

# 5 SUMMARY AND CONCLUSIONS

## 5.1 SPONSOR'S EFFICACY CONCLUSIONS

The study CA163046 was a multicenter, open-label, randomized; Phase 3 trial of Ixabepilone (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. The primary efficacy endpoint was progression free survival, defined as the time (in months) from randomization to the date of progression (as defined by the IRRC review). The sponsor reported that based on independent radiology review committee (IRRC) assessment, median PFS were 5.85 month for combination treatment of ixabepilone and capecitabine versus 4.17 months for capecitabine treatment alone (stratified log-rank p-value=0.0003). The sponsor used the results of CA163046 to claim that ixabepilone and capecitabine administered as combination therapy demonstrated statistically significant and clinically meaningful superiority in PFS compared with capecitabine alone, as determined by an IRRC blinded to investigator assessments and patients' treatment group.

Study CA163081 was a multinational, multicenter, single-arm 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. The sponsor claimed the effectiveness of ixabepilone as monotherapy was supported by the results of study CA163081 and based on the object response rate (ORR) per the IRRRC assessment. The sponsor claimed that ixabepilone administered as a single agent demonstrated clinical activity in patients with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. Per sponsor, The IRRC ORR was 11.9% in 126 treated patients and the median duration of response was 6.3 months.

## 5.2 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion, the results from the study CA163046 support the sponsor's claim that ixabepilone and capecitabine administered as combination therapy demonstrated statistically significant improvements in progression free survival (PFS) over capecitabine alone for the patients with advanced breast cancer previously treated with or resistant to an anthracycline and who are taxane resistant. Based on independent radiology review committee (IRRC) assessment, the results of FDA PFS analysis show that the estimated median PFS are 5.65 months for combination treatment of ixabepilone and capecitabine versus 4.10 months for capecitabine treatment alone (stratified log-rank p-value<0.0001). As of database lock (01-Dec-2006), 483 patients had died. The sponsor has reported that at the unscheduled interim analysis of OS with at least 483 deaths, no statistical difference was observed. The final analysis of OS will be conducted when 631 patients have died as specified in the protocol. Whether ixabepilone shows

survival benefit as a combination therapy for the patients will depend on the survival results when data are mature.

The sponsor claimed the effectiveness of ixabepilone as monotherapy was supported by the results of single-arm study CA163081. No statistical comparison was conducted in study CA163081 and therefore no statistical inference will be drawn from the study. The sponsor claimed that ixabepilone administered as a single agent demonstrated clinical activity in patients with metastatic or locally advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. Per sponsor, the observed IRRC ORR was 11.9% in 126 treated patients and the estimated median duration of response was 6.3 months. FDA's estimated median duration of response is 5.3 months. Whether its effectiveness is adequate for approval of ixabepilone as monotherapy for the proposed indication will be determined by clinical judgment.

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