CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203971Orig1s000

STATISTICAL REVIEW(S)

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
ADDENDUM #1

NDA/BLA #:	NDA 203971
Drug Name:	Xofigo® (Radium-223)
Indication(s):	Symptomatic castration-resistant prostate cancer (CRPC) patients with bone metastases and no evidence of visceral metastatic disease
Applicant:	Bayer Healthcare Pharmaceuticals Inc.
Date(s):	Date of Application: December 14, 2012 PDUFA due date: August 14, 2013 Review finish date: April 2, 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Hui Zhang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Paul G. Kluetz, M.D. William F. Pierce, Pharm.D. Virginia E. Mather, M.D.
Project Manager:	Elleni Alebachew

Keywords:
Double-blind, intent-to-treat, interim analysis, log-rank test, Cox regression

This is a correction to a typographical error in the earlier Statistical Review and Evaluation (April 2, 2013) in the first paragraph of Section 3.2.4.2 ***Time to First Symptomatic Skeletal Event***. The correct hazard ratio, confidence interval, p-value, and median in the analysis of time to first SSE reported by the applicant are:

HR: 0.610 (Instead of 0.600 as reported earlier)
95% CI: 0.461 – 0.807 (Instead of 0.456 – 0.788 as reported earlier)
p-value: 0.00046 (Instead of 0.0002 as reported earlier)
Median: 8.4 months for placebo (Instead of 8.1 months for placebo as reported earlier)

The same correction should also be applied to Dr. Shenghui Tang's Team Leader's Memo (April 2, 2013).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUI ZHANG
04/04/2013

SHENGHUI TANG
04/04/2013

RAJESHWARI SRIDHARA
04/04/2013

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

NDA/BLA #:	NDA 203971
Drug Name:	Xofigo® (Radium-223)
Indication(s):	Symptomatic castration-resistant prostate cancer (CRPC) patients with bone metastases and no evidence of visceral metastatic disease
Applicant:	Bayer Healthcare Pharmaceuticals Inc.
Date(s):	Date of Application: December 14, 2012 PDUFA due date: August 14, 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Hui Zhang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Paul G. Kluetz, M.D. William F. Pierce, Pharm.D. Virginia E. Mather, M.D.
Project Manager:	Elleni Alebachew

Keywords:

Double-blind, intent-to-treat, interim analysis, log-rank test, Cox regression

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This is an original New Drug Application (NDA) seeking the approval of Radium-223 dichloride, an alpha-emitting nuclide, for the treatment of symptomatic castration-resistant prostate cancer (CRPC) patients with bone metastases and no evidence of visceral metastatic disease.

The application is primarily based on a pivotal phase 3 study BC1-06 (ALSYMOCA) which was a randomized, double-blind, multinational, placebo-controlled study to evaluate the efficacy and safety of Radium-223 dichloride plus best standard of care (BSoC) compared to matching placebo plus BSoC in patients with symptomatic CRPC with bone metastases and no evidence of visceral metastatic disease. The primary efficacy endpoint for this pivotal study was overall survival (OS). The pre-specified interim OS analysis presented in this submission was conducted with data from the 14 October 2010 cut-off date (314 death events). An updated descriptive OS analysis included data collected up to a second data cut-off date (15 July 2011) in a cumulative database.

The pre-specified interim analysis with 314 OS events (49% of OS events required for the planned final analysis) demonstrated a statistically significant OS improvement with a hazard ratio (HR) of 0.695 (95% CI: 0.552, 0.875; p=0.00185) for the experimental group (n=541) versus the placebo control group (n=268). The median OS was 14.0 months in the Radium-223 group versus 11.2 months in the placebo group. Based on these significant results which crossed the pre-specified significance boundary for efficacy, the independent data monitoring committee (IDMC) recommended that the trial be unblinded and that patients who were randomized to placebo be offered treatment with Radium-223.

An updated analysis of OS without crossovers was performed with 528 deaths (82.5% of the planned number of deaths for the final analysis, the data cut-off date of July 15, 2011). Results from the updated OS analysis confirmed the interim analysis results (HR=0.695; 95% CI: 0.581, 0.832; p=0.00007). The median OS was 14.9 months in the Radium-223 group versus 11.3 months in the placebo group.

Furthermore, subgroup analyses showed consistent results in favor of Radium-223 dichloride treatment. No major statistical issues were identified in efficacy analyses.

The final decision on the benefit-risk evaluation of Radium-223 treatment is deferred to the clinical review team.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

Prostate cancer is the most common cancer in men worldwide and one of the leading causes of cancer mortality. It is estimated that in 2013 in the United States, about 238,590 new cases of prostate cancer will be diagnosed, and about 29,720 men will die of prostate cancer. The most common site of metastases in patients with CRPC is bone, and bone metastases pose a serious threat to a patient's survival and quality of life.

Docetaxel was approved in 2004 as an anti-androgen front-line therapy for patients with CRPC and has been shown to prolong survival compared with mitoxantrone. Cabazitaxel with prednisone was approved in 2010 as a second-line therapy for patients with metastatic CRPC who had progressed after docetaxel. Abiraterone acetate (ZYTIGA), a CYP17 inhibitor, was approved for use with prednisone for the treatment of patients with metastatic CRPC following docetaxel. MDV3100 (XTANDI) was approved in 2012 for the treatment of metastatic CRPC patients who have previously received docetaxel.

Radium-223 dichloride injection is the first alpha emitting pharmaceutical with targeted anti-tumor effects on bone metastases. Alpha-pharmaceuticals have a more localized action (a range of 2-10 cell diameters) and a higher energy compared to beta-emitting radiopharmaceuticals.

In the current NDA submission, the indication proposed by the applicant is for the treatment of CRPC patients with bone metastases. This indication was supported by a single pivotal trial, BC1-06 (ALSYMOCA), under Investigational New Drug (IND) 67,521.

2.1.2 Clinical Studies

Study BC1-06 (ALSYMOCA) compared the efficacy and safety of Radium-223 dichloride plus BSoC with placebo plus BSoC. The BSoC was the routine standard of care at each center, for example, local external beam radiation therapy (EBRT), corticosteroids, antiandrogens, estrogens (e.g., stilboestrol), estramustine or ketoconazole.

Study BC1-06 (ALSYMOCA) was titled “A double-blind, randomized, multiple dose, Phase III, multicenter study of Radium-223 in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases”. At the time of the data cut-off for the interim OS analysis (October 14, 2010), a total of 809 subjects from 128 centers worldwide were enrolled and randomized into the study. The first subject was randomized on June 12, 2008. At the time of the data cut-off for the updated OS analysis (July 15, 2011), 921 subjects from 136 centers worldwide were enrolled and randomized into the study. The last subject was randomized on February 1, 2011.

With Study BC1-06, the sponsor also submitted 3 phase 1 studies and 3 phase 2 studies. This reviewer will focus on Study BC1-06 outlined in Table 1 for a full statistical review and evaluation.

Table 1: Overview of Pivotal Study BC1-06

Study Design	Treatment Period	Follow-up Period	Treatment arms (number of subjects)	Enrollment period
Phase 3, randomized (2:1), double-blinded, placebo-controlled study of Radium-223 in the treatment of patients with symptomatic hormone refractory prostate cancer with skeletal metastases	Subjects received 6 administrations of study drug every 4 weeks.	From 4 weeks after last administration of study drug until 3 years from first administration. Subjects are evaluated every 2 months until 1 year after first administration, and thereafter every 4 months until 3 years from first administration. Date of death collected for all subjects until the last subject has been in accordance with routine investigator.	Radium-223 (n=541) Placebo (n=268)	First randomization date: June 12, 2008 Last randomization date: February 1, 2011 On October 14, 2010, 128 centers worldwide had randomized at least one subject Most subjects are from Europe 10 U.S. subjects

Throughout this review, subjects who were randomized to receive Radium-223 dichloride plus BSoC are referred as "Radium-223 group" in the text and as "Radium-223" in the tables/figures, whereas subjects who were randomized to receive placebo plus BSoC are referred as "placebo group" in the text and as "placebo" in the tables/figures.

2.1.3 Study BC1-06 Protocol Amendments

On December 20, 2007, Algeta submitted the IND 67,521 to the Food and Drug Administration (FDA). It was transferred to Bayer HealthCare Pharmaceuticals Inc on May 27, 2011. On behalf of Algeta, (b) (4) made all Statistical Analysis Plan (SAP) changes for the pivotal phase 3 study BC1-06.

The original BC1-06 protocol was dated December 14, 2007. Table 2 shows the protocol amendments and SAP amendments regarding statistical issues that were more relevant to this NDA statistical review.

- In the Protocol Amendment #2 (dated July 9, 2008), the study increased sample size from 450 patients to 750 patients to account for the introduction of prior docetaxel use (yes/no) as a stratification factor during randomization. The required number of OS events was increased from 286 to 490. In addition, an unblinded interim efficacy analysis of OS was added in this amendment. SAP draft version 0.3 (dated December 8, 2008) reflected these changes.
- In the Protocol Amendment #3 (dated July 10, 2009), the study changed the sample size re-estimation time from approximately 350 patients to 500-600 patients enrolled. The applicant stated that the rationale for this change was to ensure that the sample size re-estimation is based on a larger of survival data. SAP v1.0 (dated July 10, 2009) incorporated changes from Protocol Amendment #3, and was sent to the FDA on July 10, 2009 [IND 67,521 SN 038].
- In the Protocol Amendment #4 (dated June 23, 2010), the study increased power from 80% to 90%. This resulted in an increase in the required number of OS events from 490 to 640 and an increase in the sample size from 750 patients to 900 patients. The applicant stated that the rationale for this change was to reduce the likelihood of false negative results and get a more precise estimate of the primary efficacy endpoint. SAP v1.1 incorporated changes from this amendment and was sent to the FDA on July 7, 2010 [IND 67,521 SN 093].
- In the Protocol Amendment #5 (dated January 20, 2011), the study identified 5 main secondary endpoints according to their clinical importance: Time to total ALP progression, total-ALP response, time to occurrence of first SSE, total-ALP normalization and time to PSA progression. Three of these main secondary endpoints were previously included in the protocol as secondary endpoints: time to total ALP progression, total-ALP response, and time to PSA progression. Two main secondary endpoints were added in this Amendment: time to occurrence of first SSE and total-ALP normalization. SAP v2.1 (dated February 4, 2011) incorporated changes from this amendment, and was sent to the FDA on February 28, 2011 [IND 67,521 SN 158].
- Interim Analysis Addendum to the SAP v2.2 contains the proper signatures. No other changes were made to Interim Analysis Addendum to the SAP v2.2 compared to Interim Analysis Addendum to the SAP v2.1.

Reviewer's comments:
The amendments related to SAP were acceptable since they were based on blinded OS data.

On June 3, 2011, based on the interim OS analysis results, IDMC determined that primary efficacy endpoint had been reached and recommended to close the study. Patients on the placebo group can cross over to radium-223 group.

Table 2: BC1-06 Study: Timeline of Protocol Versions Impacted SAP

Protocol Version (Date)	SAP Version (Date)	Changes Impacting SAP	Rationale	Note
Version 1 (Dec 14, 2007)		None	NA	
Amend. # 1 (23 May 2008)		None	NA	
Amend. # 2 (Jul 9, 2008)	SAP v0.3 (Dec 8, 2008)	• Sample size increased from 450 to 750 patients • Plans for unblinded interim analysis of OS	• Addition of prior docetaxel use as stratification factor • Stopping early for efficacy or futility	Jun 12, 2008: First patient randomized
Amend. # 3 (Jul 10, 2009)	SAP v1.0 (Jul 10, 2009)	• Timing change for sample size re-estimation from 350 to 500-600	• Sample size re-estimation based on a larger volume of blinded survival data	Apr 30, 2010: Sample size re-estimation
Amend. # 4 (Jun 23, 2010)	SAP v1.1 (Jun 23, 2010)	• Power increased from 80% to 90% (sample size increased from 750 to 900)	• Reduce the likelihood of type II error	
Amend. # 5 (Jan 20, 2010)	SAP v2.1 (Feb 4, 2011)	• Identify 5 main secondary efficacy endpoints: addition of time to SSE and total-ALP normalization		Feb 1, 2011: Last patients randomized
Amend. # 6 (Jun 24, 2011)		NA	NA	Jun 3, 2011: IA data provided to IDMC

2.2 Data Sources

Materials reviewed for this application include the submitted clinical study reports, raw and derived datasets, original and amended protocols, statistical analysis plans, documents of regulatory communications, and the applicant's presentation slides.

Electronic submission including the clinical study reports, analysis datasets, and SDTM tabulations for the interim analysis (IA) based on the cut-off date October 14, 2010 is located in \\CDSESUB1\EVSPROD\NDA203971\0000\M5\DATASETS\A58799\ANALYSIS\LEGACY\DATASETS.

Electronic submission including the clinical study reports, analysis datasets, and SDTM tabulations for the updated analysis (UA) based on the cut-off date July 15, 2011 are located in \\CDSESUB1\EVSPROD\NDA203971\0000\M5\DATASETS\A58800\ANALYSIS\LEGACY\DATASETS.

3 STATISTICAL EVALUATION

This statistical evaluation is based on data from the pivotal study BC1-06.

3.1 Data and Analysis Quality

The OS time and censoring status were derived and saved in an analysis dataset "SURV". Variables were clearly formatted and labeled. From raw tabulation, the primary endpoint OS was reproducible based on the programming algorithm defined by the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study BC1-06 was a phase 3, randomized, double-blind, placebo-controlled study of Radium-223 in the treatment of patients with symptomatic CRPC with bone metastases and no evidence of visceral metastatic disease. The primary endpoint was OS, supported by key secondary endpoints including: (1) time to total-ALP progression, (2) total-ALP response at Week 12, (3) time to occurrence of first SSE, (4) total-ALP normalization, and (5) time to PSA progression.

As of the study cut-off date of the interim OS analysis (October 14, 2010), a total of 809 subjects from 128 centers worldwide were enrolled and randomized into the study from June 12, 2008. These subjects were randomized at a 2:1 ratio to receive 6 intravenous (IV) administrations of Radium-223 (50 kBq/kg b.w.) separated by 4-week intervals plus BSoC or matching placebo

plus BSoC, stratified by total ALP (< 220 U/L versus ≥ 220 U/L), current use of bisphosphonates (yes versus no), and any prior use of docetaxel (yes versus no). Subjects were followed from 4 weeks after last administration of study drug until 3 years from first administration. Subjects were evaluated every 2 months from first administration to 1 year from first administration and every 4 months from first administration to 3 years from first administration.

3.2.1.1 Sample Size Determination

The sample size estimation for study BC1-06 was based on the OS data from the phase 2 study BC1-02. In the study BC1-02, the hazard was low during the first months in both treatment groups. The hazard increased after 5-6 months in the Radium-223 group and after 3-4 months in the placebo group, respectively. Furthermore, the hazard rate was expected to be higher for patients with prior use of docetaxel. Per the SAP, a Cox proportional hazards regression stratified by whether the patient had prior docetaxel treatment was used to calculate the sample size.

The sample size estimation was based on the following assumptions:

- Two-sided Type I error: 5%;
- Power: 90%;
- Treatment allocation ratio: 2:1 (Radium-223 : placebo);
- 50% of patients have had prior docetaxel treatment;
- Common hazard during the first 4 months: 1.4%;
- Hazard in the Radium-223 group after 4 months – no prior docetaxel treatment: 3.6%;
- Hazard in the placebo group after 4 months – no prior docetaxel treatment: 4.5%;
- Hazard in the Radium-223 group after 4 months – prior docetaxel treatment: 5.8%;
- Hazard in the placebo group after 4 months – prior docetaxel treatment: 8.0%;
- Estimated number of events: 640;
- Accrual time: 30 months;
- Maximum follow-up time: 36 months;
- Time of primary analysis: 46 months after study start;
- Uniform patient accrual.

Under these assumptions, the applicant proposed accruing 900 patients to the BC1-06 trial. Final analysis would be performed when 640 death events occurred. The sample size estimation was performed using simulations in R. A planned interim analysis would be conducted when 320 deaths (50% of required deaths for final analysis) were observed. The nominal significance level for the interim analysis with 320 deaths was 0.0031 (two-sided) using the Lan-DeMets alpha-spending approach with O-Brien-Fleming spending function.

Sample Size Re-estimation

A sample size re-estimation was planned when approximately 500-600 patients had been entered into the ITT population. The intent of the sample size re-estimation was to make sure that the

required number of deaths was observed during the study period so that 80% power for the primary efficacy analysis would be maintained.

The sample size re-estimation evaluated the OS curve for all patients in the study at that time using the method described by Bolland et al [1]. Bolland et al [1] stated that no adjustment to the Type I error was required since the effect on Type I error of such a sample size re-estimation procedure was negligible. If the re-evaluation suggested an increase in sample size, the study would achieve this increase by extending accrual time, extending the follow-up period, and/or delaying the time of analysis after the last patient was enrolled.

The sample size re-estimation was conducted by a blinded statistician at (b) (4) on April 30, 2010. The conclusion of the pre-planned sample size re-estimation was that the study accruing rate was sufficient to maintain 80% power for the primary efficacy analysis in the required timeline.

Reviewer's comments:

The sample size re-estimation was based on pooled data without unblinding treatment allocation. No adjustment for the Type I error was required.

3.2.1.2 Analysis Population

The intent-to-treat (ITT) population was the primary efficacy analysis population, which was defined as all randomized patients. Patients will be included in all ITT analyses according to the treatment to which they were randomized.

3.2.1.3 Efficacy Endpoints

3.2.1.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint was OS, which was defined as the time in months from the date of randomization to the date of death from any cause. Survival time for patients who were still alive at the time of the analysis or who were lost to follow-up was censored at the last available date on which the patient was known to be alive or at the data cut-off date, whichever had come first.

3.2.1.3.2 Secondary Efficacy Endpoints

Analyses of the secondary efficacy endpoints were conducted sequentially and only if the results for OS were significant.

Secondary efficacy endpoints included:

(1) Time to total ALP progression
Total ALP progression was defined as:

- in subjects with no total ALP decline from baseline as: ≥ 25% increase from the baseline value, at least 12 weeks from baseline
- in subjects with an initial total ALP decline from baseline as: ≥ 25% increase above the nadir value, which was confirmed by a second value obtained ≥ 3 weeks later

(2) Total ALP response defined as:
Confirmed total ALP response: ≥ 30% reduction of the blood level, compared to the baseline value, confirmed by a second total ALP value approximately ≥ 4 weeks later

(3) Time to occurrence of first SSE.
An SSE was the use of EBRT to relieve skeletal symptoms or the occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumor related orthopedic surgical intervention

(4) Total ALP normalization defined as:
The return of total ALP value to within normal range at 12 weeks in 2 consecutive measurements (at least 2 weeks apart) after start of treatment in subjects who have their total ALP above ULN at baseline

(5) Time to PSA progression
PSA progression was defined as:
- in subjects with no PSA decline from baseline as: ≥ 25% increase from the baseline value and an increase in absolute value of ≥ 2 ng/mL, at least 12 weeks from baseline
- in subjects with an initial PSA decline from baseline as: ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir value, which was confirmed by a second value obtained ≥ 3 weeks later

A gatekeeping procedure was used to control the overall type I error rate. These five secondary endpoints were ordered hierarchically. Each endpoint was tested at a 0.05 significance level. No claims could be based on a secondary endpoint which had a rank lower than the secondary endpoint which was the first in the hierarchical sequence that did not reach a significant result.

3.2.1.3.3 Other Efficacy Endpoints

Other exploratory secondary efficacy endpoints included:
- Time to occurrence of first use of EBRT to relieve skeletal symptoms (included for SSE)
- Time to occurrence of first use of radio-isotopes to relieve skeletal symptoms
- Time to occurrence of first new symptomatic pathological bone fractures (vertebral and non-vertebral) (included for SSE)
- Time to occurrence of first tumor related orthopedic surgical intervention (included for SSE)
- Time to occurrence of first spinal cord compression (included for SSE)
- Time to occurrence of first start of any other anti-cancer treatment
- Time to occurrence of first deterioration of ECOG PS by at least 2 points from baseline [includes death (score of 5), by definition]
- Changes in PSA
- Changes in total ALP

3.2.2 Statistical Methodologies

Overall survival was compared between the two treatment groups in the ITT population using a stratified log-rank test with three binary stratification factors at randomization: total ALP (< 220 U/L versus ≥ 220 U/L), current use of bisphosphonates (yes versus no), and any prior use of docetaxel (yes versus no). The hazard ratio and corresponding 95% confidence interval were estimated using the Cox proportional hazards model stratified by the same stratification factors. Kaplan-Meier method was used to estimate median survival times and corresponding 95% confidence intervals. Kaplan-Meier survival curves were used to compare survival in the treatment groups.

The following sensitivity analyses were conducted by the applicant and this reviewer to evaluate the robustness of the primary analysis: a stratified log-rank test using Interactive Voice Response System (IVRS) randomization stratification factors. In addition, this reviewer conducted the following sensitivity analyses: an unstratified log-rank test, a stratified analysis adjusted for baseline PSA, a stratified analysis adjusted for baseline Gleason score, a stratified analysis adjusted for TNM staging, and a stratified analysis adjusted for time from initiation of hormone therapy to castration resistance.

Furthermore, the main secondary endpoints such as time to occurrence of first SSE, time to total-ALP progression and time to PSA progression were compared between the two treatment groups by stratified log-rank test. The hazard ratio and the corresponding 95% confidence interval were estimated using the Cox proportional hazards model. The other two main secondary endpoints, total-ALP response and total ALP normalization, were analyzed using Cochran-Mantel-Haenszel (CMH) tests controlling for the 3 binary stratification factors. The type I error rate for these five main secondary endpoints was controlled using a gatekeeping procedure (see more details in Section 3.2.1.3.2).

No type I error adjustments were planned for the exploratory efficacy endpoints.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In the interim OS analysis with the cut-off date of October 14, 2010, a total of 809 subjects were randomized in study BC1-06 between June 12, 2008 and October 14, 2010, with 541 patients in the Radium-223 group and 268 in the placebo group. A total of 128 investigative sites were involved. The majority of patients (85%) were enrolled in Europe, and 3% of patients were enrolled in North America (1.2% in the U.S. and 2.2% in Canada).

Patient Disposition

Efficacy analyses were based on these 809 patients (the ITT population). Thirty-three patients in the Radium-223 group and 14 patients in the placebo group did not receive any study treatment. These patients were either withdrawn from the treatment before the first injection but still in

study or withdrawn from the study before the first injection or had not received their first injection yet, as they had just been randomized into the study at the data cut-off date. One subject was randomized to placebo group but received Radium-223 only at Week 0. This subject was summarized as randomized in the placebo group in the ITT population.

Table 3 shows the patient disposition at the clinical data cut-off date of October 14, 2010 for the OS interim analysis. The proportion of subjects who withdrew from the study were 38.8% in the Radium-223 group and 51.5% in the placebo group. The most common reason for study discontinuation was death (22.6% in the Radium-223 group and 31.7% in the placebo group).

Table 3: BC1-06 Study: Subject Disposition, ITT Population, Interim Analysis

Disposition	**Radium-223 N (%)**	**Placebo N (%)**	**Overall N (%)**
Enrolled	541	268	809
Randomized (ITT population)	541 (100)	268 (100)	809 (100)
Included in the PP population [a]	404 (74.7)	173 (64.6)	577 (71.3)
Included in the safety population [b]	509 (94.1) [b]	253 (94.4) [b]	762 (94.2)
Treated [c]	508 (93.9) [b]	254 (94.8) [b]	762 (94.2)
Withdrawn early from the study	210 (38.8)	138 (51.5)	348 (43.0)
AE	23 (4.3)	19 (7.1)	42 (5.2)
Subject request	25 (4.6)	14 (5.2)	39 (4.8)
Investigator request	11 (2.0)	5 (1.9)	16 (2.0)
Death	122 (22.6)	85 (31.7)	207 (25.6)
Lost to follow-up	0 (0)	0 (0)	0 (0)
Other	4 (0.7)	2 (0.7)	6 (0.7)
Disease progression	25 (4.6)	13 (4.9)	38 (4.7)
Withdrawn from study relative to first injection			
Before first injection	10 (1.8)	5 (1.9)	15 (1.9)
Within 1 week	1 (0.2)	0 (0)	1 (0.1)
1 - < 4 weeks	5 (0.9)	2 (0.7)	7 (0.9)
4 - < 8 weeks	12 (2.2)	12 (4.5)	24 (3.0)
8 - < 12 weeks	14 (2.6)	16 (6.0)	30 (3.7)
12 - < 16 weeks	21 (3.9)	24 (9.0)	45 (5.6)
16 - < 20 weeks	24 (4.4)	13 (4.9)	37 (4.6)
20 - < 24 weeks	22 (4.1)	9 (3.4)	31 (3.8)
24- < 52 weeks	74 (13.7)	38 (14.2)	112 (13.8)
≥ 52 weeks	27 (5.0)	19 (7.1)	46 (5.7)
Entered 3-year follow-up period [d]	221 (40.9)	90 (33.6)	311 (38.4)

[a] The PP population was defined as all subjects in the ITT population who received at least 3 treatment cycles and did not have any major protocol violation or deviation.
[b] Subject BC1-06-026-014 was randomized to placebo but received Radium-223 at Week 0. Hence, this subject is summarized as randomized in the placebo group for the ITT population and in the Radium-223 group for the Safety population, and is excluded from the PP population. In this summary this subject is counted as having received Radium-223 in the Safety population row only.
[c] The subjects not being treated were either withdrawn from the treatment before 1st injection or withdrawn from the study before 1st injection or had not received their first injection yet, as they had just been randomized into the study at the data cut-off date.
[d] No subject had completed the 3-year follow-up period at the time of data cut-off.
Note: Cut-off date October 14, 2010.
PP = per-protocol
[*Source: A58799 Study Report Text Table 4*]

Demographic, Baseline Characteristics and Disease Characteristics

Patient demographics, baseline characteristics, and disease characteristics are shown in Tables 4-6.

Table 4: BC1-06 Study: Demographics (ITT Population, at the Time of Interim OS Analysis)

Characteristic	Radium-223 N=541	Placebo N=268	Overall N=809
Age (years)			
n	541	268	809
Mean (SD)	70.2 (8.08)	70.7 (7.81)	70.4 (7.99)
Median	71.0	70.5	71.0
Min – Max	49.0 – 90.0	44.0 – 94.0	44.0 – 94.0
Age category (years), n (%)			
n	541	268	809
< 65	139 (25.7)	65 (24.3)	204 (25.2)
65 – 75	252 (46.6)	125 (46.6)	377 (46.6)
> 75	150 (27.7)	78 (29.1)	228 (28.2)
Race, n (%)			
n	541	268	809
Caucasian	507 (93.7)	252 (94.0)	759 (93.8)
Hispanic	0 (0)	1 (0.4)	1 (0.1)
Black	10 (1.8)	3 (1.1)	13 (1.6)
Asian	19 (3.5)	12 (4.5)	31 (3.8)
Other	5 (0.9)	0 (0)	5 (0.6)
Height (cm)			
n	516	255	771
Mean (SD)	173.9 (7.40)	173.2 (8.46)	173.6 (7.77)
Median	174.0	174.0	174.0
Min – Max	151.0 – 195.0	124.0 – 193.0	124.0 – 195.0

Weight (kg) at screening			
n	537	266	803
Mean (SD)	82.9 (14.78)	82.5 (14.87)	82.7 (14.80)
Median	82.0	81.9	82.0
Min – Max	40.0 – 139.0	47.0 – 130.0	40.0 – 139.0

Note: Cut-off date October 14, 2010.
[*Source: A58799 Study Report Text Table 6*]

Table 5: BC1-06 Study: Baseline Characteristics (ITT Population, at the Time of Interim OS Analysis)

Characteristic	**Radium-223 N=541**	**Placebo N=268**	**Overall N=809**
Total ALP, n (%)	541	268	809
< 220U/L	305 (56.4)	147 (54.9)	452 (55.9)
≥ 220 U/L	236 (43.6)	121 (45.1)	357 (44.1)
Current use of bisphosphonates, n (%)	541	268	809
Yes	220 (40.7)	111 (41.4)	331 (40.9)
No	321 (59.3)	157 (58.6)	478 (59.1)
Any prior use of docetaxel, n (%)	541	268	809
Yes	314 (58.0)	156 (58.2)	470 (58.1)
No	227 (42.0)	112 (41.8)	339 (41.9)
ECOG PS grade [a], n (%)	539	267	806
0	137 (25.4)	62 (23.2)	199 (24.7)
1	330 (61.2)	167 (62.5)	497 (61.7)
2	71 (13.2)	37 (13.9)	108 (13.4)
3	1 (0.2)	1 (0.4)	2 (0.2)
Missing	2	1	3
WHO Ladder for cancer pain, n (%)	541	268	809
0	12 (2.2)	2 (0.7)	14 (1.7)
1	235 (43.4)	124 (46.3)	359 (44.4)
2	132 (24.4)	72 (26.9)	204 (25.2)
3	162 (29.9)	70 (26.1)	232 (28.7)
EBRT within 12 weeks of Screening, n (%)	541	268	809
Yes	91 (16.8)	42 (15.7)	133 (16.4)
No	450 (83.2)	226 (84.3)	676 (83.6)
Albumin (g/L) [b]			

n	539	268	807
Mean (SD)	39.4 (4.62)	39.5 (4.72)	39.5 (4.65)
Median	40.0	40.0	40.0
Min – Max	24.0 – 53.0	23.0 – 50.0	23.0 – 53.0
Hemoglobin (g/dL) [b]			
n	541	268	809
Mean (SD)	12.09 (1.460)	12.06 (1.493)	12.08 (1.470)
Median	12.20	12.10	12.20
Min – Max	8.5 – 15.7	8.5 – 16.4	8.5 – 16.4
LDH (U/L) [b]			
n	535	267	802
Mean (SD)	394.0 (277.20)	445.2 (420.80)	411.0 (332.59)
Median	317.0	328.0	321.0
Min – Max	76.0 – 2171.0	132.0 – 3856.0	76.0 – 3856.0
PSA (µg/L) [b]			
n	490	250	740
Mean (SD)	437.1 (832.77)	524.4 (1215.05)	466.63 (978.80)
Median	159.1	195.2	166.0
Min – Max	3.8 – 6026.0	1.5 – 14500.0	1.5 – 14500.0
Total ALP (U/L) [b]			
n	541	268	809
Mean (SD)	369.3 (460.32)	382.2 (477.48)	373.6 (465.82)
Median	213.0	224.0	218.0
Min – Max	32.0 – 4661.0	29.0 – 3225.0	29.0 – 4661.0

[a] Baseline was defined as the value recorded at Screening.
[b] Baseline was defined as the value recorded at Week 0. If this value was missing, then the value recorded at Screening was used.
Note: Cut-off date October 14, 2010.
Max = maximum; Min = minimum; SD = standard deviation;
ALP = alkaline phosphatase; EBRT = external beam radiation therapy;
ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase;
PS = performance status; PSA = prostate specific antigen; WHO = World Health Organisation.
[*Source: A58799 Study Report Text Table 6*]

Table 6: BC1-06 Study: Diagnosis and Previous Treatments of Prostate Cancer and Bone Metastases (ITT Population, at the Time of Interim OS Analysis)

Subject status	**Radium-223**	**Placebo N=268**	**Overall N=809**
Time since diagnosis of PC (months), n	481	235	716
Mean (SD)	69.54 (46.65)	61.78 (47.38)	66.99 (47.00)
Median	59.03	51.13	56.67
Min - Max	7.6-312.5	1.2-347.2	1.2-347.2

Time since diagnosis of BM (months), n	467	224	691
Mean (SD)	30.25 (26.96)	30.23 (27.22)	30.24 (27.03)
Median	24.57	23.27	24.17
Min - Max	0.0-254.2	0.2-183.2	0.0-254.2
Time between diagnosis of PC and BM (years) C, n, n (%)	434	203	637
<0	35 (8.1)	30 (14.8)	65 (10.2)
0-1	147 (33.9)	84 (41.4)	231 (36.3)
1-5	137 (31.6)	49 (24.1)	186(29.2)
>5	115 (26.5)	40 (19.7)	155 (24.3)
Missing, n	107	65	172
Extent of Disease (EOD) Grading, n , n(%)	541	267	808
EOD 1 (<6 metastases)	88 (16.3)	33 (12.3)	121 (15.0)
EOD 2 (6-20 metastases)	235 (43.5)	129 (48.1)	364 (45.0)
EOD 3 (>20 lesions but not a Superscan)	169 (31.3)	80 (29.9)	249 (30.8)
EOD 4 (Superscan)	48 (8.9)	26 (9.7)	74 (9.2)
Missing, n	1	0	1
Received any previous treatment for PC, n (%)	534 (98.7)	264 (98.5)	798 (98.6)
Radical prostatectomy	103 (19.0)	26 (9.7)	129 (15.9)
External radiotherapy to the prostate	191 (35.3)	75 (28.0)	266 (32.9)
Brachytherapy	14 (2.6)	8 (3.0)	22 (2.7)
Orchiectomy bilateral	82 (15.2)	44 (16.4)	126 (15.6)
LHRH agonists	184 (34.0)	81 (30.2)	265 (32.8)
Antiandrogens	469 (86.7)	229 (85.4)	698 (86.3)
Cytotoxic chemotherapy	319(59.0)	157 (58.6)	476 (58.8)
Bisphosphonates	98 (18.1)	47 (17.5)	145 (17.9)
Systemic radiotherapy	21 (3.9)	8 (3.0)	29 (3.6)
External radiotherapy to bone	274 (50.6)	129 (48.1)	403 (49.8)
Other	140 (25.9)	70 (26.1)	210 (26.0)

BM = bone metastases; LHRH = luteinizing hormone-releasing hormone; PC =prostate cancer; SD = standard deviation.

[*Source: A58799 Study Report Text Table 7*]

Reviewer's comments:

1. Patient demographics appear to be balanced between the two treatment groups, as shown in Table 4. The median age was 71 (range 44 – 94). Ninety-four percent of patients were Caucasian, 4% were Asian, 2% were black, and less than 1% was other. Patients were enrolled predominantly from Europe (85%), with 4% of patients enrolled in North America.
2. Baseline characteristics appear to be balanced between the two groups except baseline PSA.
3. A sensitivity analysis for OS adjusting for imbalance in baseline PSA at Screening was performed by this reviewer to evaluate the robustness of the primary OS analysis (see Section 3.2.4.1 for more details).

Protocol Deviations

A total of 232 (28.7%) patients had at least one major protocol violation or deviation. Of these 232 patients, 64 patients had at least one major violation of the inclusion/exclusion criterion (7.6% ,41/541 in the Radium-223 group; 8.6%, 23/268 in the placebo group), 186 patients had at

least one major protocol deviation (20.3%, 110/541 in the Radium-223 group; 28.4%, 76/268 in the placebo group). The most common major protocol deviations were for subjects receiving less than 3 doses of study treatment (20.3%, 110/541 in the Radium-223 group; 27.6%, 74/268 in the placebo group). Protocol violation or deviations by treatment group are listed in Table 7 below:

Table 7: BC1-06 Study: Summary of Major Protocol Violations and Deviations, ITT Population

Number of subjects	Radium-223 N=541	Placebo N=268	Overall N=809
With at least one major protocol violation or deviation	137 (25.3%)	95 (35.4%)	232 (28.7%)
With at least one major protocol violation	41 (7.6%)	23 (8.6%)	64 (7.9%)
Violated inclusion criterion 1	8 (1.5%)	2 (0.7%)	10 (1.2%)
Violated inclusion criterion 2a	14 (2.6%)	7 (2.6%)	21 (2.6%)
Violated inclusion criterion 2b	2 (0.4%)	2 (0.7%)	4 (0.5%)
Violated inclusion criterion 2c	17 (3.1%)	7 (2.6%)	24 (3.0%)
Violated exclusion criterion 1	0 (0)	0 (0)	0 (0)
Violated exclusion criterion 3	0 (0)	3 (1.1%)	3 (0.4%)
Violated exclusion criterion 8	1 (0.2%)	0 (0)	1 (0.1%)
Violated exclusion criterion 9	6 (1.1%)	3 (1.1%)	9 (1.1%)
Violated exclusion criterion 10	3 (0.6%)	0 (0)	3 (0.4%)
With at least one major protocol deviation	110 (20.3%)	76 (28.4%)	186 (23.0%)
Lack of multiple skeletal metastases (≥2 hot spots)	0 (0)	1 (0.4%)	1 (0.1%)
Prohibited medication/treatment	0 (0)	0 (0)	0 (0)
Received less than 3 doses of study treatment	110 (20.3%)	74 (27.6%)	184 (22.7%)
Received incorrect study treatment at Week 0	0 (0)	1 (0.4%)	1 (0.1%)

Inclusion criterion 1: Histologically or cytologically confirmed adenocarcinoma of the prostate.
Inclusion criterion 2: Known hormone refractory disease defined as:
a) Castrate serum testosterone level: ≤ 50 ng/dL (1.7 nmol/L)
b) Bilateral orchiectomy or maintenance on androgen ablation therapy with LHRH agonist or polyestradiol phosphate throughout the study
c) Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference value, each measurement at least 1 week apart
Exclusion criterion 1:Treatment with an investigational drug within previous 4 weeks, or planned during treatment period
Exclusion criterion 3: Treatment with cytotoxic chemotherapy within previous 4 weeks, or planned during the treatment period, or failure to recover from AEs due to cytotoxic chemotherapy administered > 4 weeks ago (however ongoing neuropathy is permitted)

Exclusion criterion 8: Other malignancy treated within the last 5 years (except non-melanoma skin cancer or low-grade superficial bladder cancer)
Exclusion criterion 9: History of visceral metastasis, or visceral metastases as assessed by abdominal/pelvic CT or chest X-ray within previous 8 weeks
Exclusion criterion 10: Malignant lymphadenopathy exceeding 3 cm in short-axis diameter
Note: Cutoff October 14, 2010.
[*Source: A58799 Study Report Table 14/1.5*]

Reviewer's comments:

1. The major protocol violations of inclusion/exclusion criteria were comparable between the two treatment groups.
2. The most common major protocol deviation was receiving less than 3 doses of study treatment. The rate of subjects receiving less than 3 doses of study treatment in placebo group was slightly higher than that in Radium-223 group (20.3%, 110/541 in the Radium-223 group; 27.6%, 74/268 in the placebo group). This may be caused by that more patients in the placebo group were discontinued for disease progression or death prior to receiving their 3rd treatment dose compared to patients in the Radium-223 group.

Stratification assignment was performed using an integrated voice response system (IVRS). It is noted that there were 83 subjects (10.3%) with inconsistent stratification factor data between IVRS and actual stratification factors (Table 8). No significant imbalance was seen between the two treatment groups.

Table 8: BC1-06 Study: Discrepancies between IVRS Randomization Stratification Factors and Actual Randomization Stratification Factors (ITT Population, at the Time of Interim OS Analysis)

	Radium-223 N=541	**Placebo N=268**	**Overall N=809**
Total number of subjects with discrepancies	60 (11.1)	23 (8.6)	83 (10.3)
For each stratification factor			
Total ALP	13 (2.4)	9 (3.4)	22 (2.7)
Current use of bisphosphonates	44 (8.0)	13 (4.9)	57 (7.0)
Prior use of docetaxel	5 (0.9)	2 (0.7)	7 (0.9)

[*Source: eCTD sequence no.*0008, *Table FDA60.1.6*]

Reviewer's comments:
The primary analysis of OS used actual randomization stratification factors. Given the discrepancies between IVRS randomization stratification factors and actual randomization stratification factors, a sensitivity analysis of OS was performed using IVRS randomization stratification factors. The sensitivity analyses results were consistent with the primary analysis results, supporting that the primary OS analysis is robust. (See Section 3.2.4.1 for more details.)

3.2.4 Results and Conclusions

3.2.4.1 Primary endpoint Overall Survival

Primary Findings Based on Interim Analysis

The interim analysis of OS was based on the data with cut-off date October 14, 2010. The ITT population included 809 patients with 314 death events: 191 in the Radium-223 group and 123 in the placebo group. On this cut-off date, 49% of the total number of deaths for the final OS analysis had occurred.

The stratified log-rank test demonstrated a statistically significant difference in OS favoring the Radium-223 group (p=0.00185). The hazard ratio for Radium-223 relative to placebo was 0.695 (95% CI: 0.552, 0.875) (Table 9). The median overall survival was 14.0 months for patients in Radium-223 group and 11.2 months for patients in placebo group.

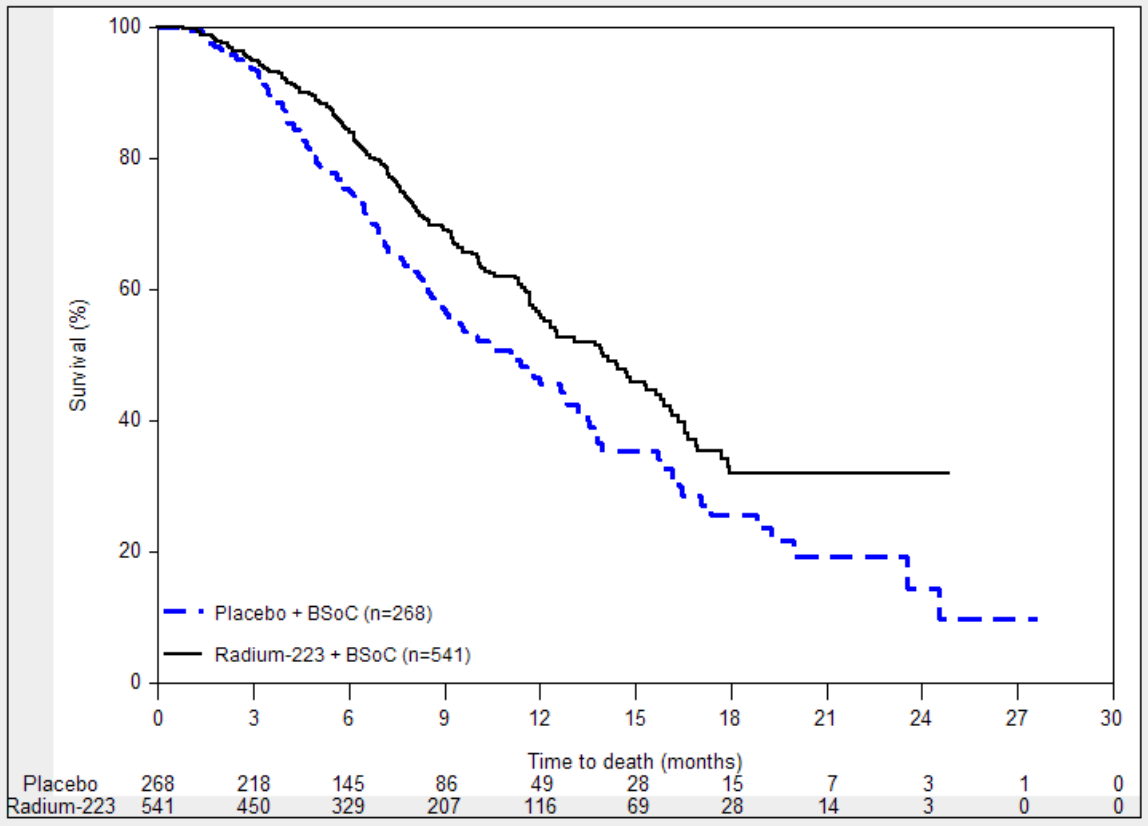
Table 9: Study BC1-06: Interim Overall Survival Results, ITT Population

	Radium-223 (N=541)	**Placebo (N=268)**
Subjects randomized	541	268
Death	191 (35.3%)	123 (45.9%)
Censored	350 (64.7%)	145 (54.1%)
Overall survival (months) [a] Median (95% CI)	14.0 (12.1, 15.8)	11.2 (9.0, 13.2)
p value [b]	0.00185	
Hazard ratio (95% CI) [c]	0.695 (0.552, 0.875)	

[a] Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.
[b] p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.
[c] Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Radium-223.
Note: Cut-off date October 14, 2010.
[*Adapted from A58799 Study Report Text Table 11*]

Kaplan-Meier survival curves are illustrated in Figure 1. The Kaplan-Meier estimate of median OS was 14.0 months (95% CI: 12.1, 15.8) for patients in the Radium-223 group and 11.2 months (95% CI: 9.0, 13.2) for patients in the placebo group.

Figure 1: Study BC1-06: Kaplan-Meier Overall Survival Curves, ITT Population, Interim Analysis



Note: Cut-off date October 14, 2010.
[*Adapted from A58799 Study Report Figure Text Figure 3*]

Reviewer's comments:

Per the O'Brien-Fleming boundary, the significance level for the interim OS analysis with 314 deaths was a two-sided alpha of 0.0027. The p-value from the interim OS analysis was 0.00185, which indicates a statistically significant improvement of OS for the Radium-223 treatment.

Findings Based on Updated Analysis

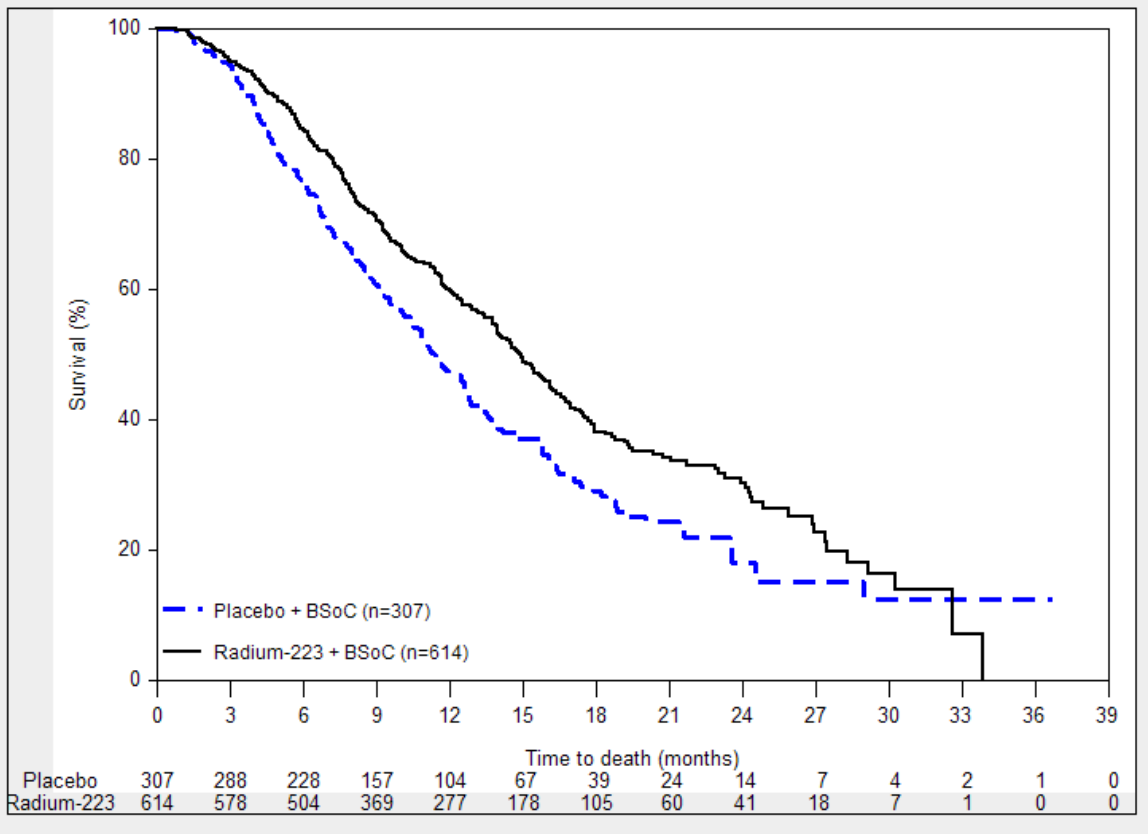
An updated overall survival analysis was conducted when 528 deaths were observed (82% of the planned number of deaths for final analysis). Results of the updated analysis are shown in Table 10. The estimated hazard ratio was 0.695 (95% CI: 0.581, 0.832). The median survival was 14.9 months in the Radium-223 group and 11.3 months in the placebo group. Kaplan-Meier survival curves are displayed in Figure 2.

Table 10. Study BC1-06: Updated Overall Survival Results, ITT Population

	Radium-223 (N=614)	Placebo (N=307)
Subjects randomized	614	307
Death	333 (54.2%)	195 (63.5%)
Censored	281 (45.8%)	112 (36.5%)
Overall survival (months) [a]	14.9	11.3
Median (95% CI)	(13.9, 16.1)	(10.4, 12.8)
p value [b]	0.00007	
Hazard ratio (95% CI) [c]	0.695 (0.581, 0.832)	

[a] Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.
[b] p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.
[c] Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Radium-223.
Note: Cut-off date July 15, 2011.
[*Adapted from A58800 Study Report Text Table 8*]

Figure 2: Study BC1-06: Kaplan-Meier Overall Survival Curves, ITT Population, Updated Analysis



Note: Cut-off date July 15, 2011.
[*Adapted from A58800 Study Report Text Figure 3*]

Reviewer's comments:

There were no crossovers in the updated OS analysis. The updated OS analysis was consistent with the interim analysis on the primary findings.

Sensitivity Analyses for Overall Survival

Several sensitivity analyses for OS were performed by this reviewer to evaluate the robustness of the OS benefit of Radium-223 treatment. The results are shown in Table 11.

Table 11: Study BC1-06: Sensitivity Analyses of Overall Survival (ITT Population, at the Time of Interim OS Analysis)

Sensitivity Analysis Description	HR (95% CI) [a]	p-value
1. Unstratified analysis	0.690 (0.550, 0.865)	0.0013 [b]
2. Stratified analysis based on IVRS randomization stratification factors	0.663 (0.528, 0.834)	0.0004 [b]
3. Stratified analysis adjusted for baseline PSA	0.713 (0.563, 0.903)	0.0049 [c]
4. Stratified analysis adjusted for baseline Gleason score [d]	0.694 (0.551, 0.874)	0.0019 [c]
5. Stratified analysis adjusted for TNM staging [e]	0.689 (0.546, 0.868)	0.0016 [c]
6. Stratified analysis adjusted for time from initiation of hormone therapy to castration resistance [f]	0.667 (0.554, 0.803)	<0.0001 [c]

[a] Hazard ratio is from a Cox proportional hazards model. Hazard ratio < 1 favors Radium-223dichloride.
[b] p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.
[c] p-value is from a Cox proportional hazards model stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.
[d] Gleason score is categorized as Missing, <=7 or >7.
[e] M stage is categorized as M0, M1, or Unknown (Mx or missing).
[f] This analysis used updated analysis data with cut-off date July 15, 2011.

Reviewer's comments:

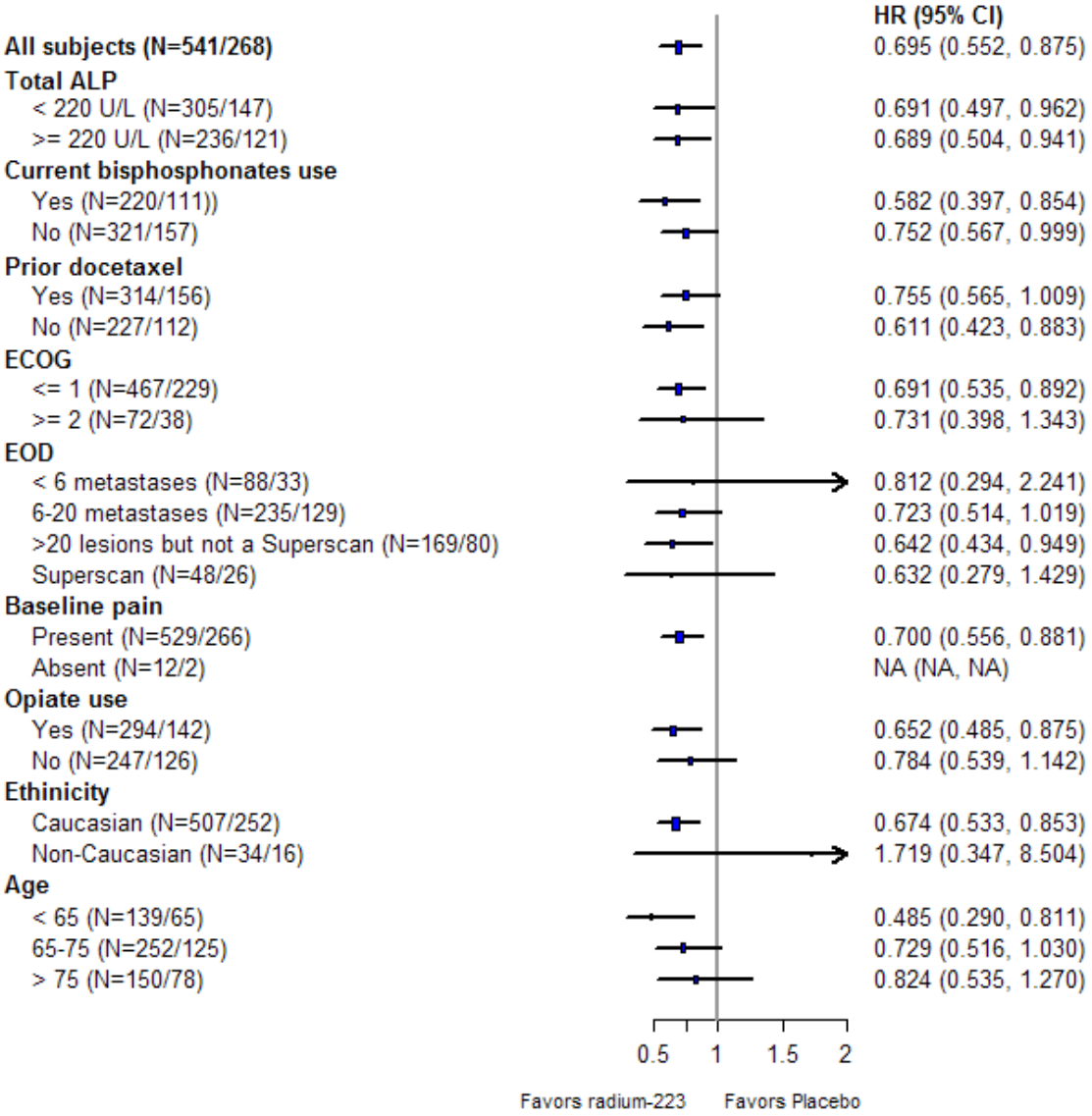
The sensitivity analyses results were consistent with the primary analysis results.

Subgroup Analyses for Overall Survival

The effect of Radium-223 on OS was examined in subgroups that make up important prognostic factors. Results of the subgroup analyses conducted by the applicant and this reviewer are

displayed in Figure 3. The treatment effect of Radium-223 on OS was consistently favorable in most subgroups except in the non-Caucasian subgroup. The estimated hazard ratio for non-Caucasian subgroup crossed the no-treatment-effect reference of HR=1.0, potentially due to very small sample size (34 Radium-223 patients and 16 placebo patients).

Figure 3: Study BC1-06: Subgroup Analyses for OS, ITT Population (ITT Population, at the Time of Interim OS Analysis)



Reviewer's comments:

Patients who are younger than 65 appear to benefit more from Radium-223 treatment compared to patients who are age 65 or older.

3.2.4.2 Key Secondary Endpoints

Time to First Symptomatic Skeletal Event

A summary of subjects who experienced an SSE during the study is presented in Table 12. The majority of SSE consisted of external beam radiotherapy. Time to first SSE was statistically significantly longer for patients in the Radium-223 group compared to those in the placebo group (HR=0.600, 95% CI: 0.456 – 0.788, p=0.0002). The median time to first SSE was 13.5 months for Radium-223 versus 8.1 months for placebo.

Table 12: Study BC1-06: Analysis of Time to First SSE (ITT Population, at the Time of Interim OS Analysis)

	Radium-223 (N=541)	**Placebo (N=268)**
Subjects randomized	541	268
Experienced	132 (24.4%)	82 (30.6%)
Censored	409 (75.6%)	186 (69.4%)
Time to first SSE (months) [a] Median (95% CI)	13.5 (12.2, 19.6)	8.4 (7.2, NE)
p value [b]	0.00046	
Hazard ratio (95% CI) [c]	0.610 (0.461, 0.807)	

[a] Time to first SSE is calculated as months from date of randomization to date of occurrence of first SSE. Subjects who died without reporting an SSE were no longer at risk for SSE.
[b] p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior used of docetaxel.
[c] Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior used of docetaxel. Hazard ratio < 1 favors Radium-223.
Note: Cut-off date October 14, 2010.
[*Adapted from A58799 Study Report Text Table 17*]

Reviewer's comments:

1. In the analysis of time to first SSE performed by the applicant, subjects who were dead without experiencing SSEs were censored at the last disease assessment date. This introduces informative censoring.
2. This reviewer conducted a sensitivity analysis for time to first SSE. In this sensitivity analysis, death was considered as an event. The median time to first SSE was 8.2 months in the Radium-223 group versus 6.1 months in the placebo group (HR=0.657; 95% CI: 0.538, 0.803; p<0.0001). The magnitude of difference in medians is only 2.1 months between treatment groups. While the results show a statistically significant difference, it is unclear if this is clinically meaningful.

Other key secondary endpoints

The results of other key secondary endpoints are summarized as below:

- Treatment with Radium-223 decreased the hazard of total ALP progression by 84% compared with placebo (HR = 0.162; 95% CI: 0.120 – 0.220; p < 0.00001).
- The proportion of subjects who achieved a confirmed total ALP response (≥ 30% reduction in total ALP blood levels at Week 12) was higher in the Radium-223 group compared to that in the placebo group (46.2% versus 2.5%; p < 0.001).
- The proportion of subjects who achieved a total ALP normalization was higher in the Radium-223 group compared to that in the placebo group (32.9% versus 0.9%; p < 0.001).
- Treatment with Radium-223 decreased the hazard of PSA progression by 32.9% compared with placebo (HR = 0.671; 95% CI: 0.546 – 0.826; p = 0.00015).

Reviewer's comments:

The sensitivity analyses results were consistent with the primary analysis results. Per the SAP, a gatekeeping procedure was used to control the overall type I error rate. These five secondary endpoints were ordered hierarchically (time to total-ALP progression, total-ALP response at Week 12, time to occurrence of first SSE, total-ALP normalization, and time to PSA progression). Each endpoint was tested at a 0.0027 significance level.

3.2.4.3 Conclusions for Efficacy

The pivotal trial BC1-06 met the study objective by showing a hazard ratio of 0.695 (95% CI: 0.552 – 0.875, p-value = 0.00185) for the Radium-223 group versus the placebo group in overall survival at the interim OS analysis with 49% information (314 deaths). The median survival time was 14.0 months in the Radium-223 group compare to 11.2 months in the placebo group. The finding was confirmed by the updated overall survival analysis with 528 deaths (82.5% of the planned number of deaths for final analysis), with a hazard ratio of 0.695 (95% CI: 0.581 – 0.832, p-value =0.00007). Furthermore, subgroup analyses showed consistent results in favor of Radium-223 treatment. No major statistical issues were identified in efficacy analyses.

3.3 Evaluation of Safety

Please refer to clinical evaluations of this application for detailed safety evaluation and interpretation.

3.4 Benefit-Risk Assessment

Please refer to clinical evaluation of this application for a benefit-risk evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Race, and Geographic Region

Table 13 shows the summary of overall survival subgroup analyses for study BC1-06 by age, race, and geographic region.

Table 13: Hazard Ratios for OS by Age, Race, and Geographic Region (ITT Population, at the Time of Interim OS Analysis)

Variable	Group	Radium-223 #deaths/n	Placebo #deaths/n	Hazard Ratio	(95%CI)	
Age	<65	36/139	31/65	0.485	(0.290,	0.811)
	65-75	89/252	56/125	0.729	(0.516,	1.030)
	>75	66/150	36/78	0.824	(0.535,	1.270)
Race	Caucasian	180/507	120/252	0.674	(0.533,	0.853)
	Non- Caucasian	11/34	3/16	1.719	(0.347	8.504)
Region	Europe	169/458	115/229	0.663	(0.521,	0.844)
	North America	3/21	1/7	0.816	(0.050,	13.241)

Reviewer's comments:

The subgroup analyses showed that the effect of Radium-223 on OS was consistent across the subgroups except for non-Caucasian subjects. However, the HR for non-Caucasian subjects was not robust due to a small sample size (n=50). In addition, results of the subgroup analysis for patients from North America should be interpreted with caution due to the small sample size (n=28). Please also note that only 10 U.S. (1.2%) subjects were enrolled in Study BC1-06.

4.2 Other Special/Subgroup Populations

The applicant performed subgroup analyses for overall survival by the following prognostic factors: baseline total ALP, baseline current bisphosphonates use, baseline prior docetaxel use, baseline ECOG, baseline EOD, baseline pain, and opiate use. Results of these subgroup analyses for OS are displayed in Section 3.2.4.1 Figure 3.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified in this application.

5.2 Collective Evidence

In the BC1-06 trial, patients treated with Radium-223 had a significant survival benefit compared with patients treated with placebo. Patients in the Radium-223 group had a 3.8 months survival advantage over patients in the placebo group. The hazard ratio of 0.695 (95% CI: 0.552 – 0.875) indicates that patients in the Radium-223 group had a lower risk of death compared to patients in the placebo group.

5.3 Conclusions and Recommendations

This NDA submission is to support administration of Radium-223 for the treatment of symptomatic CRPC patients with bone metastases and no evidence of visceral metastatic disease. In this NDA submission, study BC1-06 is the only randomized pivotal study conducted to establish efficacy. The primary efficacy endpoint of this study was OS. The statistical analysis results from the BC1-06 trial support the applicant's efficacy claims on OS. Data from the BC1-06 trial indicates that there is a significant survival benefit in patients treated with Radium-223 compared to those treated with placebo. The final decision on the benefit-risk evaluation of Radium-223 in treatment of the proposed indication is deferred to the clinical review team.

5.4 Labeling Recommendations

The results of the interim and updated OS analyses will be included in the label.

6 REFERENCES

1. Bolland K, Sooriyarachchi M R, Whitehead J. Sample size review in a head injury trial with ordered categorical responses. *Stat Med* 1998; **17**: 2835-2847

7 APPENDIX: LIST OF ABBREVIATION

Abbreviation	Definition
ALP	Alkaline Phosphatase
BSoC	Best Standard of Care
b.w.	Body Weight
CI	Confidence Interval
CRPC	Castration-Resistant Prostate Cancer
CSR	Clinical Study Report
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
EOD	Extent of Disease
FDA	Food and Drug Administration
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug (application)
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
kBq	kilo Becquerel
kg	kilogram
LHRH	Luteinizing Hormone-Releasing Hormone
LDH	Lactate Dehydrogenase
Max	Maximum
Min	Minimum
NDA	New Drug Application
NE	Not Estimable
OS	Overall Survival
PP	Per-protocol
PS	Performance Status
PSA	Prostate Specific Antigen
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SSE	Symptomatic Skeletal Event
WHO	World Health Organization

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUI ZHANG
04/02/2013

SHENGHUI TANG
04/02/2013

RAJESHWARI SRIDHARA
04/02/2013

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-TEAM LEADER'S MEMO

NDA/BLA Serial Number:	NDA 203971
Drug Name:	Xofigo® (Radium-223)
Indication(s):	Symptomatic castration-resistant prostate cancer (CRPC) patients with bone metastases and no evidence of visceral metastatic disease
Applicant:	Bayer Healthcare Pharmaceuticals Inc.
Date(s):	Date of Application: December 14, 2012 PDUFA due date: August 14, 2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Primary Reviewer:	Hui Zhang, Ph.D.
Secondary Reviewer:	Shenghui Tang, Ph.D., Team Leader
Concurring Reviewer:	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Oncology Drug Products (HFD-150)
Clinical Team:	Paul G. Kluetz, M.D. William F. Pierce, Pharm.D. Virginia E. Mather, M.D.
Project Manager:	Elleni Alebachew

Keywords:
Double-blind, intent-to-treat, interim analysis, log-rank test, Cox regression

This is an original New Drug Application (NDA) seeking the approval of Radium-223 dichloride, an alpha-emitting nuclide, for the treatment of symptomatic castration-resistant prostate cancer (CRPC) patients with bone metastases and no evidence of visceral metastatic disease. The application is primarily based on a pivotal phase 3 study BC1-06 (ALSYMOCA) which was a randomized, double-blind, multinational, placebo-controlled study to evaluate the efficacy and safety of Radium-223 dichloride plus best standard of care (BSoC) compared to matching placebo plus BSoC in patients with symptomatic CRPC with bone metastases and no evidence of visceral metastatic disease. The primary efficacy endpoint for this pivotal study was overall survival (OS).

The pre-specified interim analysis with 314 OS events (49% of OS events required for the planned final analysis) demonstrated a statistically significant OS improvement with a hazard ratio (HR) of 0.695 (95% CI: 0.552, 0.875; p=0.00185) for the experimental group (n=541) versus the placebo control group (n=268). The median OS was 14.0 months in the Radium-223 group versus 11.2 months in the placebo group. An updated analysis of OS without crossovers was performed with 528 deaths (82.5% of the planned number of deaths for the final analysis). Results from the updated OS analysis confirmed the interim analysis results (HR=0.695; 95% CI: 0.581, 0.832; p < 0.0001). The median OS was 14.9 months in the Radium-223 group versus 11.3 months in the placebo group. Furthermore, subgroup analyses showed consistent results in favor of Radium-223 dichloride treatment. No major statistical issues were identified in efficacy analyses. For further details regarding the design, data analyses, and results of this phase 3 study, please refer to the statistical review by Dr. Hui Zhang (April 2, 2013).

The applicant claimed that Radium-223 dichloride had benefit in time to first symptomatic skeletal event (SSE). In the applicant's analysis, time to first SSE was statistically significantly longer for patients in the Radium-223 group compared to those in the placebo group (HR=0.600, 95% CI: 0.456 – 0.788, p=0.0002). The median time to first SSE was 13.5 months for Radium-223 versus 8.1 months for placebo. However, in this analysis, subjects who were dead without experiencing SSEs were censored at the last disease assessment date. This introduced informative censoring and biased the results. Dr. Hui Zhang conducted a sensitivity analysis for time to first SSE. In this sensitivity analysis, death was considered as an event. The median time to first SSE was 8.2 months in the Radium-223 group versus 6.1 months in the placebo group (HR=0.657; 95% CI: 0.538, 0.803; p<0.0001). The magnitude of difference in medians is only 2.1 months between treatment groups. While the results show a statistically significant difference, it is unclear if this is clinically meaningful.

This team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Hui Zhang) of this application. The inference regarding favorable benefit-risk profile for the use of Radium-223 dichloride for the treatment of symptomatic castration-resistant prostate cancer (CRPC) patients with bone metastases and no evidence of visceral metastatic disease is deferred to the clinical review team.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHENGHUI TANG
04/02/2013

RAJESHWARI SRIDHARA
04/02/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203971 **Applicant: Bayer Healthcare** **Stamp Date: 12/14/2012**

Drug Name: Xofigo **NDA/BLA Type: Priority**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Efficacy data based on a single pivotal Phase 3 study.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			1. Only men were enrolled in the pivotal study. 2. Subgroup analyses of OS by Race was performed.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Hui Zhang	2/11/2013
Reviewing Statistician	Date
Shenghui Tang	2/11/2013
Supervisor/Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUI ZHANG
02/11/2013

SHENGHUI TANG
02/11/2013