

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203415Orig1s000

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

CLINICAL STUDIES-TEAM LEADER'S MEMO

NDA/BLA Serial Number: NDA 203415

Drug Name: Xtandi (enzalutamide)

Indication(s): Metastatic castration-resistant prostate cancer in patients who have previously received docetaxel

Applicant: Medivation, Inc.

Date(s): Date of Application: May 21, 2012

Review Priority: Priority

Biometrics Division: Division of Biometrics 5 (HFD-711)

Primary Reviewer: Stella W. Karuri, Ph. D.

Secondary Reviewer: Shenghui Tang, Ph.D., Team Leader

Concurring Reviewer: Rajeshwari Sridhara, Ph.D., Division Director

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Keywords:

double-blind, hazard ratio, interim analysis, Kaplan-Meier product limit estimator, logrank test, multi-center, proportional hazard model, stratification

This application requests approval of MDV3100 (Xtandi, enzalutamide) as a treatment of castration resistant prostate cancer in patients who have received prior docetaxel (b) (4). The pivotal trial related to this application is the CRPC2 trial, which is also referred to as the AFFIRM trial. This is a multinational, double blind, randomized, phase III clinical.

The pivotal trial met its study objective by showing a hazard ratio of 0.63 (95% confidence interval: 0.53-0.75, $p < 0.0001$) for the MDV3100 arm (n=800) versus the placebo control arm (n=399) in overall survival, at the interim analysis when 520 deaths (80% of the planned number of deaths for the final analysis) were observed. The median survival time was 18.4 months in the MDV3100 arm compared to 13.6 months in the placebo control arm. The findings were confirmed in an updated overall survival analysis with 576 deaths (87% of the planned number of deaths for the final analysis). Furthermore, subgroup analyses showed consistent results in favor of the MDV3100 arm. 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. Stella W. Karuri (August 15, 2012).

In general, this team leader concurs with the recommendations and conclusions of the statistical reviewer (Dr. Stella W. Karuri) of this application. The final decision on the benefit-risk evaluation of MDV3100 is deferred to the clinical team. In the section 5.4 (Labeling Recommendations) of Dr. Karuri's review, Dr. Karuri recommended that the results of the updated OS analysis be included in the labeling. The updated OS analysis was not pre-specified and only had 56 more deaths (7% information) compared with the pre-specified interim OS analysis with 520 deaths. Therefore, this team leader believes that the results of the pre-specified interim OS analysis with 520 deaths should be included in the labeling.

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/s/

SHENGHUI TANG
08/20/2012

RAJESHWARI SRIDHARA
08/20/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203415

Applicant: Medivation, Inc.,

Stamp Date:

Drug Name: MDV3100

NDA Type: NME

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			ISE was not submitted based on Agency's recommendation.
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. Age and race are reported as baseline patient Characteristics, 93% patients were white and 3.4% patients were black. 3. Subgroup analyses of OS by age were 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	X			

File name: 5_Statistics Filing Checklist for a New NDA202379

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

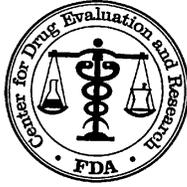
Stella Karuri	May 31, 2012
Reviewing Statistician	Date
Shenghui Tang	May 31, 2012
Supervisor/Team Leader	Date

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/s/

STELLA W KARURI
06/18/2012

SHENGHUI TANG
06/18/2012



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Applicant: Medivation, Inc.

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Statistical Reviewer: Stella W. Karuri, Ph. D.

Concurring Reviewers: Shenghui Tang, Ph.D., Team Leader
Rajeshwari Sridhara, Ph.D., Division Director

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1 EXECUTIVE SUMMARY

This application requests approval of MDV3100 (Xtandi, enzalutamide), an androgen receptor signaling inhibitor, as a treatment of castration resistant prostate cancer in patients who have received prior docetaxel (b)(4). The pivotal trial related to this application is the CRPC2 trial, which is also referred to as the AFFIRM trial. This is a multinational, double blind, randomized, phase III clinical.

The primary endpoint in the CRPC2 trial was overall survival (OS). Based on significant findings during interim analysis, the data monitoring committee (DMC) recommended that the trial be stopped. All analyses presented in the applicant's submission used the interim analysis date, the date of the 520th death (b)(6) as the data cut-off date. On this date, 80% of the total number of deaths required for the final OS analysis had occurred.

The estimated median survival of 18.4 months for patients treated with MDV3100 is higher than the estimated 13.6 months median survival for patients treated with the placebo. The p-value which is less than 0.0001 indicates significantly different survival in the two treatment arms. The hazard ratio estimate of 0.63 (95% CI: 0.53 – 0.75) indicates a 37% reduction in risk of death for patients treated with MDV3100.

The robustness of the OS was examined in the review process with a number of sensitivity analyses. An updated analysis of OS was also performed with the data cut-off date set to the database lock date of December 16, 2011. Results from the updated analysis confirm the interim analysis results and indicate a survival benefit in patients treated with MDV3100. Subgroup analyses were also consistent with the primary analysis and point to survival benefit for patients treated with MDV3100.

No major statistical issues were identified in the efficacy analyses. The final decision on the benefit-risk evaluation of MDV3100 is deferred to the clinical team.

2 INTRODUCTION

2.1 Overview

Prostate cancer is a leading cause of cancer mortality in men world wide. In 2011, it was estimated that approximately 34,000 men in the US would die from prostate cancer, making it the second most common cause of cancer death in men. Prostate cancer tumors eventually lose their early sensitivity to hormonal therapies despite castrate levels of testosterone in the blood. Patients who have castration-resistant progression ultimately succumb to the disease. Clinical studies have shown that androgen receptors in progressing tumors remain functional; tumor cells should therefore respond to treatment strategies directed at the androgen receptor signaling (ARS) pathway.

Docetaxel with Prednisone was approved in 2004 as an anti-androgen front-line therapy for patients with castration-resistant prostate cancer. In the pivotal trial, docetaxel with prednisone demonstrated a 2.4 month survival benefit over mitoxantrone with prednisone. In 2011, abiraterone acetate, an oral inhibitor of androgen biosynthesis, was approved for treatment of metastatic castration-resistant prostate cancer in patients who have previously been treated with docetaxel. Approval was based on a 3.9 month benefit of abiraterone acetate over placebo.

MDV3100 is an oral androgen receptor signaling inhibitor designed to block multiple steps in the ARS pathway, while being devoid of receptor agonist activity. It inhibits binding of androgen to the androgen receptor in multiple steps in the ARS pathway, thereby disrupting the mechanism of tumor cell growth. This in turn decreases the growth of cancer cells and can induce cancer cell death and tumor regression.

Studies in the clinical development program for MDV3100 include:

- 1) CRPC2 (AFFIRM) – A controlled phase III study for efficacy, safety and pharmacokinetic (PK) involving 1199 patients, randomized into the trial between September 22, 2009 and November 15, 2010,
- 2) CRPC-MDA-1 – A supportive open-label dose escalation study for safety and efficacy involving 140 patients,
- 3) 9875-CL-0111 – A phase I study with 6 healthy volunteer for PK,
- 4) MDV3100-5 – A phase I study in 60 healthy volunteers for PK.

The study selected for full statistical review is the CRPC2 trial, which is the controlled study supporting this application.

2.1.1 CRPC2 Trial Protocol Amendments

The original protocol dated May 21, 2009, was titled: “A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Patients with Progressive Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy”. It was first amended on July 30, 2009 where the daily MDV3100 dose was

lowered from 240 to 160 mg. No patients had been randomized into the trial by this date. The second amendment dated April 1, 2010 added a health-related quality of assessment to be collected at baseline. This was the European Quality-of-Life 5 domain scale (EQ5-D) questionnaire. A total of 250 patients had been randomized into the trial by this date. The third and final amendment was dated April 19, 2011. A total of 1199 patients had been randomized into the trial by this date. The amendment included the following changes:

- 1) A reduction in the target hazard ratio of MDV3100 to placebo from 0.8 to 0.76. This resulted in a reduction in the number of target events for final analysis from 786 to 650 deaths.
- 2) An interim stage was included in the design with interim analysis to be performed with 520 (80%) events.
- 3) The secondary endpoint of progression free survival (PFS) was changed to radiographic progression free survival (rPFS), defined by both bone and soft tissue scans.
- 4) The secondary endpoint of time to radiographic progression (TTrP) as was removed.

Following significant findings at the interim analyses which showed a survival benefit of patients on the MDV3100 arm compared to the placebo, a decision was made to submit a New Drug Application (NDA) based on this study population.

Table 1: Overview of Pivotal Study CRPC2

Study design	Treatment Period	Follow-up Period	Number of Subjects per Arm	Enrollment period Geographic region: n
A randomized, double-blind, placebo-controlled phase III study in patients with progressive castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy	Treatment continued until progression and the initiation of another systemic antineoplastic therapy	<ul style="list-style-type: none"> • Safety followup 30 days after last dose • Long term follow up every 12 weeks 	MDV3100 arm (n=800) Placebo arm (n=399)	September 22, 2009 to November 15, 2010 Europe: 684 North America: 395 Australia: 93 South America: 22 South Africa: 6

2.2 Data Sources

Datasets supporting the clinical study reports are provided in SDTM and ADaM format. Analysis datasets and SDTM tabulations are located in the network via the path:

<\\Cdsesub1\evsprod\NDA203415\0000>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data on the primary efficacy endpoint of OS is in the file ADTTE. Data on secondary endpoints is also in this file. This reviewer verified that OS computations can be reproduced from the NDA source datasets.

3.2 Evaluation of Efficacy

Evaluation of efficacy was performed on the the Intention-to-treat (ITT) population in the CRPC2 trial. The ITT population was defined as all randomized patients. Subjects were analyzed in the treatment group to which they were assigned.

3.2.1 Study Design and Endpoints

The CRPC2 trial was a randomized double blinded, placebo controlled, phase III trial of MDV3100 in patients with castration resistant prostate cancer who had prior doxetacel therapy. The study was a multinational study involving 156 sites in North America, Europe, Latin America and the rest of the world. The primary objective of the trial was to determine the benefit of MDV3100 as compared to placebo as assessed by OS. Key secondary efficacy endpoints in order of analysis were:

- Time to Prostate-Specific Antigen (PSA) progression,
- Duration of radiographic Progression Free Survival (rPFS),
- Time to first skeletal-related events (SRE).

Planned enrollment was 1170 patients randomized at a 2:1 ratio to orally receive 160 mg of MDV3100 daily versus placebo. Randomization was stratified by two factors:

1. The Eastern Cooperative Oncology Group (ECOG) performance score, grouped into 0 -1 versus 2.
2. The mean Brief Pain Inventory Short Form score Question #3 (BPI-SF Q3), grouped into <4 versus ≥ 4 .

Sample size determination

The CRPC2 trial was powered to evaluate treatment efficacy on OS. The trial was sized to detect a hazard ratio of 0.76, which equates to a median OS of 12 months on the placebo arm versus 15.7 months on the MDV3100 arm. To detect the proposed hazard ratio using the logrank test with a two-sided 0.05 significance level, the applicant proposed accruing 1170 patients to the CRPC2 trial. Final analysis would be performed when 650 deaths occurred. This number of events would provide 90% power. A planned interim analysis was to be performed when 520 deaths (80%) deaths occurred. The interim alpha ($\alpha_{interim} = 0.0244$) was determined by a Lan-DeMets alpha-spending function.

Efficacy endpoints

The primary endpoint was OS. This was defined as time from randomization to death from any cause. There were several secondary endpoints. Analysis of the secondary endpoints was to be performed sequentially and only if the results for OS were significant. The key secondary endpoints in order of analysis were:

- (i) Time to PSA progression – Progression defined by: (a) A 25% PSA increase and (b) An absolute increase of ≥ 2 ng/mL. This increase was a change from nadir for patients with PSA decline at Week 13 or a change in the documented baseline.
- (ii) Radiographic progression free survival (rPFS) – Radiographic disease progression defined by RECIST 1.1 for soft tissue disease, or the appearance of two or more new bone lesions on bone scan.
- (iii) Time to skeletal related event (SRE) – A SRE event defined as radiation therapy, bone surgery, pathologic bone fracture, spinal cord compression or change of antineoplastic therapy to treat bone pain.

Reviewer's notes:

The primary endpoint of OS is appropriate endpoint for the indication; at the initiation of the study, there was no treatment for castration resistant prostate cancer in patients who had been treated with docetaxel.

Other secondary endpoints include:

- Quality of life (QOL) – This was assessed by Functional Assessment of Cancer Therapy – Prostate (FACT-P). A response was defined as a 10-point improvement in their global FACT-P score compared to baseline.
- European Quality of Life Five-Domain Scale (EQ-5D) – This was summarized descriptively by treatment group and study visit.
- Pain palliation – The proportion of patients with pain palliation was assessed for patient with stable and sufficient pain burden at study entry and was measure by BPI-SF Q3 score.
- PSA response – Response was defined as $\geq 50\%$ and $\geq 90\%$ reduction in PSA from baseline to lowest post baseline result.
- Best overall soft tissue radiographic response (BORR) – Response was assessed by investigator using RECIST v1.1 for patients with measurable soft tissue disease at screening.
- Circulating tumor cell count – Measured from blood samples in a subset of patients in specific sites.

Efficacy Analysis Population.

The ITT population was the primary analysis population for all efficacy analyses, as well as for analyses of disposition, demographic, and baseline diseases characteristics.

3.2.2 Statistical Methodologies

A stratified logrank test was used to analyze OS as well as the secondary time to event endpoints. The stratification factors used were ECOG status and Mean BPI-SF Q3. Randomization was performed centrally on day 1, and used the Interactive Voice Response System (IVRS) and the Interactive Web Response System (IWRS). Kaplan-Meier estimates of survival probabilities were used to obtain median survival times and their 95% confidence intervals. Kaplan-Meier Survival Curves were used to compare survival in the treatment arms and to assess the appropriateness of the proportional hazard model. The hazard ratio as well as its 95% CI from the stratified proportional hazard model was estimated for time to event endpoints.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The 1199 patients accrued were randomized 2:1, 899 patients to the MDV3100 arm and 399 patients to the placebo arm. A total of 156 investigative sites from 15 countries in North America, Europe, Australia, South America and South Africa were involved. Table 2 gives the ITT population's patient disposition. Treatment was continued until disease progression was confirmed and the patient was scheduled to initiate another systematic antineoplastic therapy. Patients were free to withdraw consent to participate in the study at any time for any reason and were subsequently discontinued from treatment. By the data cutoff date of [REDACTED]^{(b) (6)}, 28.9% of the patients randomized to the MDV3100 arm remained on treatment compared to 4.8% of the patients randomized to the placebo arm. A total of 737 patients had treatment discontinued due to progressive disease. Approximately 29% on the MDV3100 arm and 40% on the placebo arm discontinued treatment due to clinical progression. Patients who discontinued treatment were followed for radiographic progression, skeletal-related events, additional treatments for prostate cancer, and survival. Loss to follow up was relatively low; one patient in each arm was lost to follow up.

Table 2: Patient Disposition of ITT Population

	MDV3100	Placebo
ITT - Randomized and started treatment	800 (100%)	399 (100%)
Treatment discontinued (data cut-off)	569 (71.1%)	380 (95.2%)
Reason for discontinuation of treatment		
Adverse event	61 (7.6%)	39 (9.8%)
Other	26 (3.3%)	18 (4.5%)
Progressive disease	441 (55.1%)	296 (74.2%)
Radiographic progression	246 (30.8%)	180 (45.1%)
Clinical progression	231 (28.9%)	159 (39.8%)
skeleteal related event	81 (10.1%)	39 (9.8%)
Protocol violation	1 (0.1%)	1 (0.3%)
Withdrawal by subject	23 (2.9%)	20 (5.0%)

[Source: Clinical Study Report CRPC2 Table 10.1-3]

Patient demographics, baseline characteristics and disease characteristics are shown in Table 3-4. Patient characteristics were balanced in the two treatment arms. Majority of the patients were white (93%). The proportion of African American patients in the study was 4%.

Reviewer's notes:

Racial minorities were under-represented in this study. African Americans make up only 3.9% of the ITT population. The incidence of prostate cancer in African Americans is 232 cases per 100,000, which is higher than the rate in whites which is 146 per 100,000.

Table 3: Demographic and Baseline Characteristics

	MDV3100 (n=800)	Placebo (n=399)	Total
Age (years)			
Mean (SD)	68.8 (8.0)	68.6 (8.4)	68.7 (8.1)
Age group (years)			
<65	232 (29.0%)	130 (32.6%)	362 (30.2%)
65 to 74	369 (46.1%)	165 (41.4%)	534 (44.5%)
≥ 75	199 (24.9%)	104 (26.1%)	303 (25.3%)
Ethnicity			
Hispanic or Latino	32 (4.0%)	23 (5.8%)	55 (4.6%)
Not Hispanic or Latino	768 (96.0%)	376 (94.2%)	1144 (95.4%)
Race			
American Indian or Alaska Native	1 (0.1%)	1 (0.3%)	2 (0.2%)
Asian	5 (0.6%)	8 (2.0%)	13 (1.1%)
Black or African American	27 (3.4%)	20 (5.0%)	47 (3.9%)
Native Hawaiian/Pacific Islander	1 (0.1%)	0 (0.0%)	1 (<0.1%)
White	745 (93.1%)	366 (91.7%)	1111 (92.7%)
Other	21 (2.6%)	4 (1.0%)	25 (2.1%)
Geographic Region			
USA	181 (22.6%)	107 (26.8%)	288 (24.0%)
Rest of the world	619 (77.4%)	292 (73.2%)	911 (76.0%)
Baseline PSA (ng/mL) Mean (SD)	415.6 (930.76)	389.4 (1105.72)	406.9 (992.02)
Baseline Alkaline Phosphates (U/L) Mean (SD)	233.1 (380.87)	236.6 (420.65)	234.3 (394.38)
Concomitant Use of Glucocorticoids	383 (47.9%)	182 (45.6%)	565 (47.1%)

[Source: Clinical Study Report CRPC2 Table 11.2.1-1]

Table 4: Baseline Disease Characteristics Of ITT Population

	MDV3100 (n=800)	Placebo (n=399)	Total
PSA (ng/mL) Mean (SD)	415.6 (930.76)	389.4 (1105.72)	406.9 (992.02)
Alkaline Phosphates (U/L) Mean (SD)	233.1 (380.87)	236.6 (420.65)	234.3 (394.38)
Mean Total Dosage (mg/m ²) (SD)	664.5 (348.15)	667.0 (332.51)	665.3 (343.04)
ECOG Status			
0	298 (37.3%)	156 (39.1%)	454 (37.9%)
1	432 (54.0%)	211 (52.9%)	643 (53.6%)
2	70 (8.8%)	32 (8.0%)	102 (8.5%)
Mean BPI-Q3 Score			
<4	574 (71.8%)	284 (71.2%)	858 (71.6%)
≥ 4	226 (28.3%)	115 (28.8%)	341 (28.4%)
Gleason score at Diagnosis			
≤7	360 (49.6%)	175 (47.6%)	535 (48.9%)
>8	366 (50.4%)	193 (48.4%)	559 (51.1%)
Number of Prior Chemotherapy Regimens			
1	579 (72.4%)	296 (74.2%)	875 (73.0%)
≥2	221 (27.6%)	103 (25.8%)	324 (27.0%)
Number of Bone Metastases			
≤20	498 (62.3%)	248 (62.2%)	746 (62.2%)
>20	302 (37.8%)	151 (37.8%)	453 (37.8%)
Type of progression at study entry			
PSA progression only	326 (41.0%)	164 (41.2%)	490 (41.0%)
Radiographic progression	470 (59.0%)	234 (58.8%)	704 (59.0%)
Bone only	205 (25.6%)	117 (29.3%)	322 (26.9%)
Soft tissue only	127 (15.9%)	59 (14.8%)	186 (15.5%)
Bone and soft tissue	138 (17.3%)	58 (14.5%)	196 (16.4%)
Disease localization at screening			
Bone only	225 (28.1%)	123 (30.8%)	348 (29.0%)
Soft tissue only	62 (7.8%)	34 (8.5%)	96 (8.0%)
Both bone and soft tissue	505 (63.1%)	241 (60.4%)	746 (62.2%)
None	8 (1.0%)	1 (0.3%)	9 (0.8%)
Distribution of disease at screening			
Bone	730 (92.2%)	364 (91.5%)	1094 (91.9%)
Lymph node	442 (55.8%)	219 (55.0%)	661 (55.5%)
Visceral liver	92 (11.6%)	34 (8.5%)	126 (10.6%)
Visceral lung	122 (15.4%)	59 (14.8%)	181 (15.2%)
Other soft tissue	147 (18.6%)	70 (17.6%)	217 (18.2%)
Missing	8	1	9

[Source: Clinical Study Report CRPC2 Table 11.2.1-1]

Efficacy analysis used stratification from the case report form (CRF). The discordance in stratification factors between CRF and IVRS/IWRS as shown in Table 5 was relatively low and occurred in 50 (4.2%) patients.

Table 5: Discrepancy between stratification from Case Report Form (CRF) and IVRS/IWRS in the ITT population

	MDV3100 (n=800)	Placebo (n=399)
Total number of patients with discrepancy	29 (3.6%)	21 (5.3%)
For each stratification factor		
ECOG Status	11 (1.4%)	2 (0.5%)
BPI-SF Q3	18 (2.3%)	19 (4.8%)

Protocol Deviation

A total of 167 patients had at least one major protocol deviation. As shown in Table 6, deviations were roughly balanced on the two arms. The most frequent reason for protocol deviation was unmet eligibility or exclusion criteria. The second most frequent reason for protocol deviation was the use of an excluded concomitant medication. Out of the 78 patients that received excluded concomitant medication, 7 patients on the MDV3100 arm and 3 patients on the placebo arm had chemotherapy.

Table 6: Protocol deviations in ITT population

	MDV3100 (n=800)	Placebo (n=399)
Number with at least 1 deviation	117 (14.6%)	50 (12.5%)
Eligibility criteria not met	60 (7.5%)	30 (7.5%)
Developed criteria for removal from study and did not discontinue the study	4 (0.5%)	0 (0%)
Received excluded concomitant medication	56 (7.0%)	22 (5.5%)
Received wrong treatment/dose	1 (0.1%)	0 (0.0%)

[Source: Clinical Study Report CRPC2 Table 10.2-1]

Reviewer's notes:

The following sensitivity analyses were conducted for OS:

- 1) An analysis that excludes patients whose treatment was discontinued based on clinical progression,
- 2) An analysis using stratification from IVRS/IWRS stratification,
- 3) An analysis excluding patients with major protocol deviation.

3.2.4 Results and Conclusions

The applicant's cut-off-date [REDACTED] ^{(b) (6)} was the date of the 520th death. On this date, 80% of the total number of deaths for the final OS analysis had occurred. On this date, there were 308 deaths on the MDV3100 arm and 212 deaths on the placebo. A total of 11 patients had unknown survival status, 6 were on the MDV3100 and 5 were on the placebo. These were treated as censored events in the OS analysis.

Table 7a gives stratified and unstratified results of OS from the interim analysis. The results from the Kaplan-Meier estimates indicate that patients on the MDV3100 arm have a higher median survival of 18.4 months compared to the placebo arm's median survival of 13.6 months. Median follow up times were 14.4 months for both treatment arms. The p-value for logrank test has a value less than 0.0001 which indicates that survival in the two arms is significantly different. The hazard ratio estimate of 0.63 (95% CI: 0.53 – 0.75) indicates a survival advantage in patients treated with MDV3100.

Kaplan-Meier survival curves are shown in Figure 1a. The separation of the survival curves occur by the 5th months after randomization, with survival on the MDV3100 arm being higher than the placebo. The difference in the survival probabilities over time indicates that the proportional hazard assumption was not invalidated.

In the updated analysis, there were 576 deaths, 87% of the total number of deaths required for the final OS analysis. Results in the updated analysis are given in Table 7b and Figure 1b. These support the interim analysis results. Median survival for patients on the MDV3100 arm was estimated at 17.8 months, 4.5 months longer than the median survival for patients on the Placebo arm. The p-value (<0.0001) indicates significantly different survival in the two treatment arms. The estimated stratified hazard ratio of 0.62 (95% CI: 0.52 – 0.73) indicates a survival advantage in patients treated with MDV3100 compared to patients treated with the placebo.

Table 7: Efficacy Results for OS: (a) Interim Analysis Using 80% Planned Deaths, (b) Updated Analysis Including 87% Deaths at Data-Lock Date

(a)

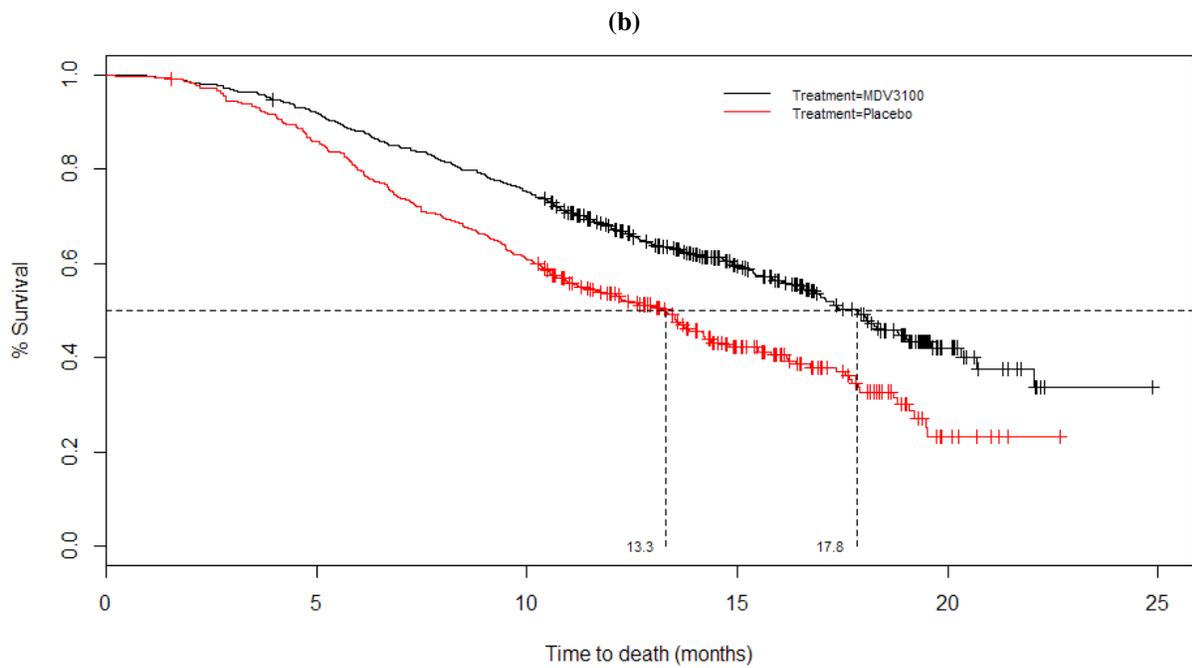
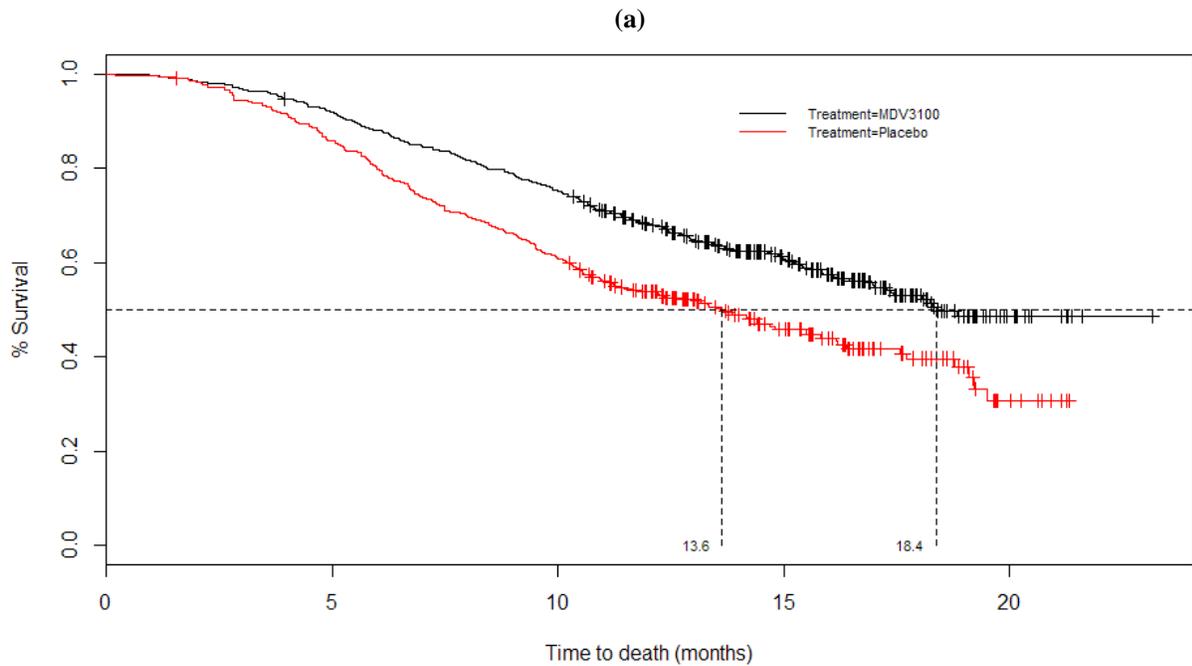
	MDV3100 (n=800)	Placebo (n=399)
Deaths (%)	308 (39%)	212 (53%)
Median survival in months (95% CI)	18.4 (17.3, NM)	13.6 (11.3, 15.8)
p-value (logrank)		
Stratified		< 0.0001
Unstratified		< 0.0001
Hazard ratio (95% CI)		
Stratified		0.63 (0.53, 0.75)
Unstratified		0.63 (0.53, 0.75)

[Source: Clinical Study Report CRPC2 Table 11.4.1.2-1]

(b)

	MDV3100 (n=800)	Placebo (n=399)
Deaths (%)	344 (43%)	232 (58%)
Median survival in months (95% CI)	17.8 (16.7, 18.8)	13.3 (11.2, 14.1)
p-value (logrank)		
Stratified		< 0.0001
Unstratified		< 0.0001
Hazard ratio (95% CI)		
Stratified		0.62 (0.52, 0.73)
Unstratified		0.62 (0.53, 0.75)

Figure 1: Kaplan-Meier Survival Curves¹: (a) Interim Analysis Using 80% Planned Deaths, (b) Updated Analysis Including 87% Deaths at Data-Lock Date



¹ Vertical Bars Indicate Censored Values.

Reviewer's notes:

The updated OS analysis was conducted as per the Agency's request in order to confirm OS estimates. By the data-lock date of December 16, 2011 there were no patients that had crossed-over to the MDV3100 arm. No cross-over data was submitted with this NDA.

Sensitivity Analyses

The applicant performed an unstratified analysis for sensitivity. The results are shown in Table 7a. The p-value from the logrank test has value less than 0.0001. The hazard ratio value of 0.63 (95% CI: 0.53 – 0.75) is consistent with the stratified analysis.

This reviewer performed three other sensitivity analyses for OS to validate the applicant's findings. These were:

1. A stratified analysis using stratification from the IVRS/IWRS system. The applicant's efficacy results used stratification from the CRF. The discordance information from the stratification methods is given in Table 5.
2. A stratified analysis excluding patients with major protocol deviation.
3. A stratified analysis excluding patients whose treatment was discontinued due to clinical progression.

Table 8 gives the estimated hazard ratio, its 95% confidence interval, and the p-value from the logrank test for each analysis. The results from the sensitivity analysis are consistent with the primary analysis and indicate a significant survival advantage in patients on the MDV3100 arm.

Table 8: Hazard ratio estimates from sensitivity analyses of OS

		HR(95%CI) ¹	p-value ²
1	Stratified test with stratification from IVRS/IWRS	0.61 (0.52, 0.73)	<0.0001
2	Excluding 167 patients with major protocol deviation	0.67 (0.55, 0.81)	<0.0001
3	Excluding 85 patients ³ with clinical progression	0.59 (0.49, 0.70)	<0.0001

¹ The hazard ratio estimates are from the Cox proportional hazard model.

² The p values are from the log-rank test.

³ Patients identified by clinical team

Subgroup Analyses of OS

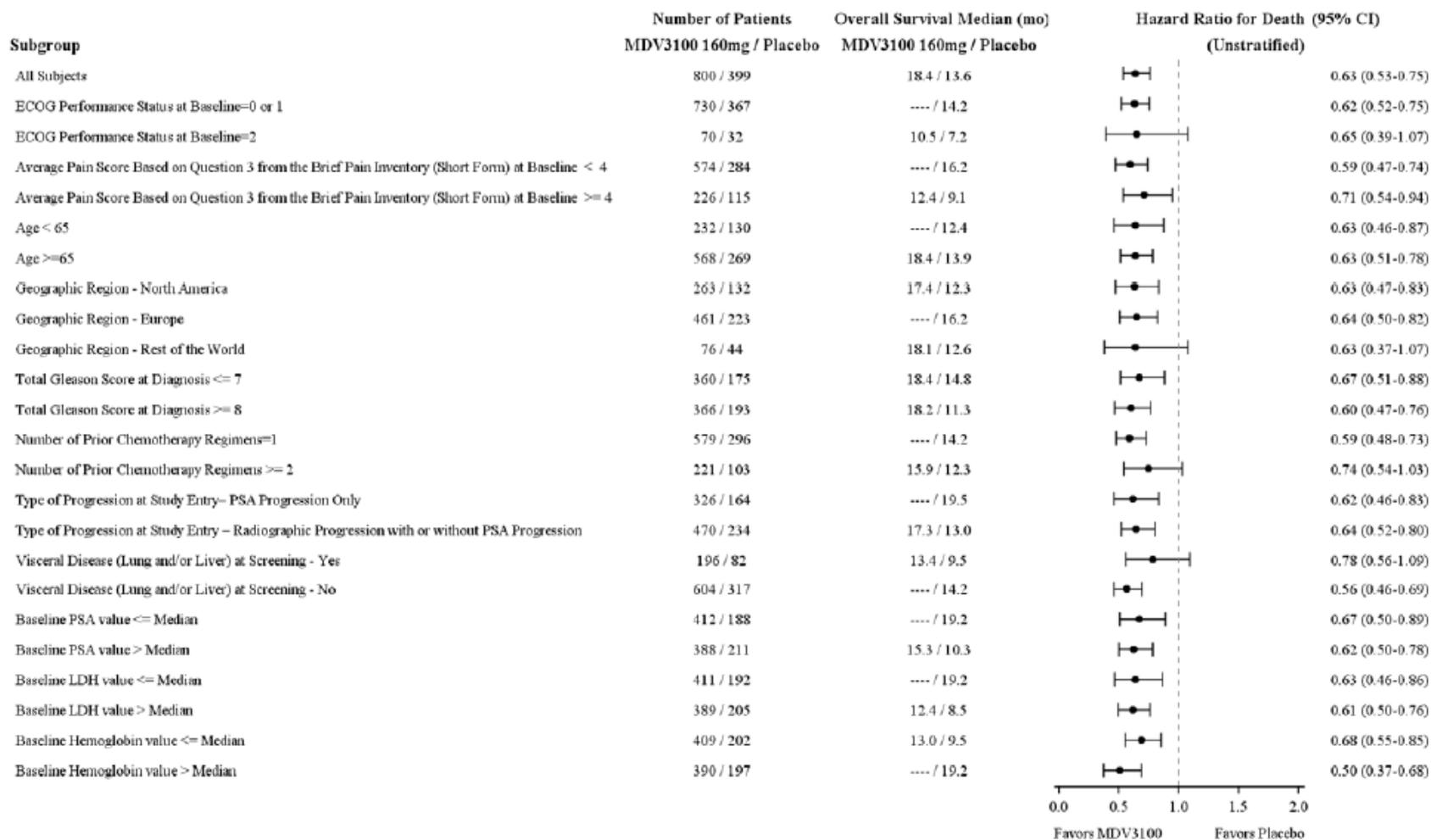
The effect of MDV3100 on OS was examined in subgroups that make up important prognostic factors. Figure 2 summarizes the results from the following subgroups:

- ECOG status at study entry (0 or 1 vs. 2);
- Average pain score based on Question 3 from the Brief Pain Inventory – Short Form at study entry (< 4 vs. \geq 4);
- Age (< 65 vs. \geq 65);
- Geographic region (North America vs. Europe vs. rest of the world);
- Gleason Score at diagnosis (\leq 7 vs. \geq 8);
- Number of prior chemotherapy regimens (1 vs. \geq 2);
- Type of progression at study entry (PSA progression only vs. radiographic progression with or without PSA progression);
- Visceral disease at study entry (yes vs. no);
- Baseline PSA value (\leq median vs. > median);
- Baseline lactate dehydrogenase value (\leq median vs. > median); and
- Baseline hemoglobin value (\leq median vs. > median).

The hazard ratio estimates in all the subgroups have value less than one which indicates a survival advantage on the MDV3100 arm. In most subgroups, the 95% confidence intervals do not cross one. The few exceptions occur when frequency counts are low, for instance with ECOG status of 2. This can be attributed to more sampling variability due to low patient numbers.

Figure 2: Subgroup Analyses for OS

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[Source: Clinical Study Report CRPC2 Figure 11.4.2.8-1]

Secondary Endpoints

Finding from key secondary endpoints were validated and are given in Table 9.

Table 9: Results from Key Secondary Efficacy Endpoint

Secondary endpoint	MDV3100 median (95% CI)	Placebo median (95% CI)	Hazard Ratio	p-value
Time to PSA progression (months)	8.3 (5.8, 8.3)	3 (2.9, 3.7)	0.248	<0.0001
rPFS (months – Protocol defined progression date)	8.3 (8.2, 9.4)	2.9 (2.8, 3.4)	0.404	<0.0001
<i>rPFS (Using visit date and modified censoring)</i>	<i>8.3 (8.2, 9.0)</i>	<i>2.8 (2.8, 3.2)</i>	<i>0.406</i>	<i><0.0001</i>
Time to skeletal related events (SRE) (months)	16.7 (14.6, 19.1)	13.3 (9.9, NM)	0.689	<0.0001

The best overall radiographic response (BORR) was also validated. BORR was determined by RECIST v1.1 and only evaluated in patients who had measurable soft tissue disease at screening. There were a total of 654 patients in this analysis, 446 on the MDV3100 arm and 208 on the placebo arm. Confirmation of response was not required. The estimated BORR (complete + partial response) on the MDV3100 arm was 28.9% (95% CI: 24.8 – 33.4%). The BORR on the placebo arm was 3.8% (95% CI: 1.7 – 7.4%).

Reviewer's comments

An Information Request was sent to the applicant by the FDA on July 20, 2012 regarding censoring and progression determination for rPFS. The applicant responded on August 7th, 2012 with more analyses using amended censoring and progression dates for rPFS. This reviewer verified the new analysis on rPFS using the amended dataset ADRPFS. Table 10 gives the results for the revised rPFS analyses.

Key secondary endpoints will not be included in the label due to validity concerns and clinical interpretation.

Table 10: Reassessed Duration of Radiographic Progression-Free Survival in Response to Information Request

	MDV3100 (n=800)	Placebo (n=399)
rPFS events	326 (40.8%)	129 (32.3%)
Radiographic Progression	277 (34.6%)	83 (20.8%)
Death without documented radiographic progression	49 (6.1%)	46 (11.5%)
Censored	474 (59.3%)	270 (67.7%)
Median rPFS duration in months (95% CI)	11.0 (10.6, 11.1)	5.6(5.5, 5.8)
Stratified hazard ratio (95% CI)	0.424 (0.342, 0.526)	
P-value (log-rank)	<0.0001	

[Source: Response to Clinical and Statistical IR, August 6, 2012]

3.3 Evaluation of Safety

Please refer to clinical evaluations of this application for safety results and conclusions.

3.4 Benefit-Risk Assessment

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 11 gives OS hazard ratios and 95% confidence interval for the subgroups of race, age and geographic region. With the exception of black patients, the subgroup analyses are consistent with those of the ITT population. The estimated hazard ratio for black patients is not robust due to the low frequency counts (n=47).

Table 11: Hazard ratios for OS by Age, Race and Region

Variable	Group	MDV3100 #deaths/n	Placebo #deaths/n	Hazard Ratio	(95%CI)
Age	<65	86/232	66/130	0.63	(0.46, 0.87)
	>=65	222/568	146/269	0.63	(0.51, 0.78)
Race	Black	13/27	9/20	1	(0.43, 2.35)
	White	283/745	199/366	0.61	(0.50, 0.73)
Country	non-USA	231/619	145/292	0.66	(0.54, 0.81)
	USA	77/181	67/107	0.58	(0.42, 0.80)

4.2 Other Special/Subgroup Populations

Other subgroups analyzed by the applicant include: ECOG status, mean BPI-SF Q3, geographic, Gleason score at diagnosis, number of prior chemotherapy regimens, type of progression at study entry, visceral disease at study entry, baseline PSA, baseline lactate dehydrogenase, and baseline hemoglobin. More details are given in Section 3.2.2. Hazard ratios, frequency counts and subgroup median survival estimates are given in Figure 2.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The CRPC2 trial is a well controlled study of MDV3100. No major statistical issues were identified.

5.2 Collective Evidence

In the CRPC2 trial, patients treated with MDV3100 had a significant survival benefit compared to patients treated with placebo. Patients on the MDV3100 arm had a 4.8 months survival advantage over patients on the placebo arm. The hazard ratio of 0.63 (95% CI: 0.53 – 0.75) indicates that patients on the MDV3100 arm had a lower risk of death compared to patient on the placebo arm.

5.3 Conclusions and Recommendations

The statistical analysis of the results from the CRPC2 trial support the applicant's efficacy claims on OS. Data from the CRPC2 trial indicates that there is a significant survival benefit in patients treated with MDV3100 compared to those treated with the placebo. This benefit is also observed in subgroups that make up important prognostic factors. The final decision on the benefit-risk

evaluation of MDV3100 in treatment of the proposed indication is deferred to the clinical review team.

5.4 Labeling Recommendations

The results of the updated OS analysis will be included in the labeling. Key secondary endpoints will not be included in the label due to validity concerns and clinical interpretation.

6. Appendix A: List of Abbreviations

Abbreviation	Definition
ARS	androgen receptor signaling
BPI-SF Q3	Brief Pain Inventory, Short Form, Question 3
CI	Confidence Interval
CRF	Case Report Form
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	European Quality of Life 5-Domain Scale
FACT-P	Functional Assessment of Cancer Therapy-Prostate
ITT	Intent-to-Treat
(IVRS)	Interactive Voice Response System
IWRS	Interactive Web Response System
OS	Overall Survival
QOL	Quality of life
PK	pharmacokinetic
PSA	Prostate-Specific Antigen
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
rPFS	Radiographic Progression Free Survival
SD	Standard Deviation
SRE	Skeletal Related Event
TTrP	Time to Radiographic Progression

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/s/

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08/15/2012

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