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TITLE: Development of Pain Endpoint Models for Use in Prostate Cancer
Clinical Trials and Drug Approval

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14. ABSTRACT OBJECTIVE: The objective of this work is to establish standard methods for measuring pain palliation and pain progression in prostate cancer clinical trials that are feasible, methodologically rigorous, and meet regulatory requirements for drug approval and labeling. The primary aim of this award is to conduct an observational longitudinal study in men with castrate-resistant metastatic prostate cancer receiving docetaxel-based chemotherapy, in order to establish key design elements of a pain endpoint model which can be used in pivotal trials. SUMMARY: At the close of the first year, we report the following progress: (1) we anticipate the study designed to address Aim 1 to open at UNC and MSKCC in January / February 2013, and the study will open at the additional sites in Q2 2013; (2) the work outlined for Aim 2 will be conducted, as scheduled, in Months 16-36; and (3) the manuscript resulting from work described in Aim 3 is under review by a major scientific journal.					
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INTRODUCTION

Pain is common in men with metastatic prostate cancer and can substantially impair functioning and quality of life. Regulatory standards for the design of symptom endpoints have evolved substantially over the past decade (culminating in an FDA Guidance document issued on this topic in December 2009), and approaches used previously to assess cancer-related pain and analgesic use are no longer considered sufficiently methodologically rigorous. The objective of this work is to establish standard methods for measuring pain palliation and pain progression in prostate cancer clinical trials that are feasible, methodologically rigorous, and meet regulatory requirements for drug approval and labeling. The primary aim of this award is to conduct an observational longitudinal study in men with castrate-resistant metastatic prostate cancer receiving docetaxel-based chemotherapy, in order to establish key design elements of a pain endpoint model which can be used in pivotal trials. The second aim is to analyze data from a feasibility study of pain assessment nested within an industry-sponsored phase II treatment trial conducted in the Prostate Cancer Clinical Trials Consortium. The third aim is to conduct literature reviews and moderate a consensus meeting, with input from investigators in the Prostate Cancer Clinical Trials Consortium, FDA Office of Oncology Drug Products, FDA Study Endpoint and Label Development Team, and FDA Division of Anesthesia, Analgesia and Rheumatology Products, in order to establish discrete guidelines and produce a publication delineating key methodological components of pain studies in prostate cancer.

BODY

In this section, we report the progress made towards the completion of each Aim.

Aim 1 To conduct an observational longitudinal study in men with castrate-resistant metastatic prostate cancer receiving docetaxel-based chemotherapy, in order to establish key design elements of a pain endpoint model which can be used in pivotal trials.

MSKCC was initially the coordinating site for this study. Since Dr. Basch now has his primary appointment at University of North Carolina (UNC) we will be moving the study so that UNC is the coordinating center, for both study data and contracts. This has added 4 months to time which we anticipated starting enrollment. The study is scheduled to open at UNC and MSKCC in Jan/Feb 2013, and at additional sites in Q2 2013.

The table below lists the first three Tasks of Aim 1 as outlined in the Statement of Work (PC100563 Basch 7-20-2011) and the current status is noted:

Table 1. Current Status of Tasks Outline in Scope of Work

<u>Task 1. Develop study protocol and obtain IRB approval (Months 1 – 6)</u> IN PROGRESS
1a. Submit Letter of Intent to Prostate Cancer Clinical Trials Consortium (Month 3) Completed
1b. Elicit input on study design from collaborators (Months 1 – 2) Completed
1c. Draft study protocol, including all case report forms (CRFs) (Months 1 – 3) Completed
1d. Submit protocol to departmental review committees at MSKCC (Month 3) Completed
1e. Obtain IRB approval at MSKCC (the study's coordinating center) (Months 4 – 6) Completed – 6/5/2012
1f. Submit for HRPO review (Month 6) Completed – 9/17/2012
New: Submit for IRB approval at UNC (study's new coordinating center) In progress (Anticipated Nov/Dec 2012)
New: Submit UNC protocol for HRPO approval (Anticipated Dec 2012/ Jan 2013)
New: Revise MSKCC protocol to indicate UNC is coordinating center; submit IRB amendment and re-submit to HRPO. (Anticipated Dec 2012/ Jan 2013)
1g. Submit for IRB review at participating sites (Johns Hopkins and Oregon Health & Sciences University) (Month 8) Participating sites will submit to IRB once we receive HRPO approval for UNC.
<u>Task 2. Prepare for data collection and analysis (Months 1 – 6)</u> IN PROGRESS
2a. Develop IVRS platform (Months 1 – 3) Completed
2b. Develop study databases on secure, password-protected server (Months 3 – 6) In Progress
2c. Draft statistical analysis plan and elicit feedback from collaborators (Months 1 – 6) In Progress
<u>Task 3. Implement study protocol (Months 9 – 33)</u> IN PROGRESS
3a. Conduct site orientations (Month 9) Training of MSKCC staff has begun
3b. Recruit and enroll patients (Months 9 – 20) We anticipate patient enrollment to begin Jan./Feb. 2013 at UNC and MSKCC.
3c. Track accrual/follow-up, conduct weekly telephone meetings with site data managers, and conduct monthly telephone meetings with site PIs (Months 9 – 33)

Aim 2 To analyze data from a feasibility study of pain assessment nested within an industry-sponsored phase II treatment trial conducted in the Prostate Cancer Clinical Trials Consortium.

This aim is scheduled to be addressed in Months 16-36.

Aim 3 To conduct literature reviews and moderate a consensus meeting, with input from investigators in the Prostate Cancer Clinical Trials Consortium, FDA Office of Oncology Drug Products, FDA Study Endpoint and Label Development Team, and FDA Division of Anesthesia, Analgesia and Rheumatology Products, in order to establish discrete guidelines and produce a publication delineating key methodological components of pain studies in prostate cancer.

The following manuscript has been prepared as a result of a series of meetings with FDA and is currently under review at Journal of Clinical Oncology: “Pain palliation measurement in cancer clinical trials: the FDA perspective”

KEY RESEARCH ACCOMPLISHMENTS

Aim 1. The protocol and appendices are completed. The original MSKCC protocol was approved by HRPO on 9/17/2012. The revised protocol, indicating UNC as the coordinating center, is currently under review at UNC. This work addresses:

Milestone 1. Completed study protocol, MSKCC IRB approved (Month 6)

Aim 3. The following manuscript has been prepared as a result of a series of meetings with FDA and is currently under review at Journal of Clinical Oncology: “Pain palliation measurement in cancer clinical trials: the FDA perspective”. This work addresses:

Milestone 2. Manuscript delineating guidelines and key methodological component of pain studies in prostate cancer. Lead author: Basch (Month 21)

REPORTABLE OUTCOMES

Aim 1 – Research is in progress

Aim 3 – Manuscript is under review

CONCLUSIONS

We are accomplishing the tasks and milestones for this study. At the close of the first year, we report the following progress: (1) we anticipate the study designed to address

Aim 1 to open at UNC and MSKCC in January / February 2013, and the study will open at the additional sites in Q2 2013; (2) the work outlined for Aim 2 will be conducted, as scheduled, in Months 16-36; and (3) the manuscript resulting from work described in Aim 3 is under review by a major scientific journal.

REFERENCES

None

APPENDICES

None