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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: We report the following progress: (1) the study designed to address Aim 1 is accruing patients at all four sites; (2) a manuscript resulting from the work described in Aim 2 has been published in the journal *European Urology,* titled: "Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort" and (3) the manuscript resulting from work described in Aim 3 has been published by the journal *Cancer*, titled: "Pain Palliation Measurement in Cancer Clinical Trials: The US Food and Drug Administration Perspective." Both manuscripts have been attached to annual report submitted to Department of Defenses in November 2015.

15. SUBJECT TERMS

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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.

KEYWORDS

Pain, metastatic castrate resistant prostate cancer, clinical trials, FDA, study endpoints

OVERALL PROJECT SUMMARY

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.

- The award was originally grant to Memorial Sloan Kettering Cancer Center
- Initial award period 30 SEPT 2011-29 SEPT 2014
- In 2011, Dr. Ethan Basch moved from Memorial Sloan Kettering Cancer Center to University of North Carolina at Chapel Hill
- The award was relinquished by MSKCC to UNC in 2011, but administrative delays prevented Pain Registry study from opening until 2013 (aim 1)
- The second award period was 30 SEPT 2011-29 SEPT 2015
- In AUG 2015 we have requested a 30 months no cost extension, as we are currently in progress of obtaining HRPO approval to re-open the study at MSKCC
- The current award period is 30 SEPT 2011-31 MARCH 2018

The table below lists Tasks of Aim 1 as outlined in the Statement of Work (PC100563 Basch 7-20-2011, revised 8-3-2015)

Summary of events:

SITE	Date of Initial IRB Approval	Date of Initial HRPO Approval	Date of First Enrollment	Projected Date of Closure to Accrual	Projected Date of Closure to Participant Follow-up	Data Analysis End Date	Projected Study End Date
UNC	29 JAN 2013	15 AUG 2013	23 JAN 2014	30 SEPT 2016	30 SEPT 2017	31 MAR 2018	31 MAR 2018
OHSU	10 MAY 2013	27 AUG 2013	22 APR 2014	29 FEB 2016	28 FEB 2017	NA	28FEB 2017
JHU	9 MAY 2013	29 AUG 2013	28 MAY 2014	29 FEB 2016	28 FEB 2017	NA	28 FEB 2017
UW	6 NOV 2013	14 MAR 2014	12 SEPT 2014	29 FEB 2016	28 FEB 2017	NA	28 FEB 2017
MSKCC	15 JUL 2015	Pending	Estimated OCT 2015	30 SEPT 2016	30 SEPT 2017	NA	SEPT 2017

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

Task 1. Develop study protocol and obtain IRB approval (Months 1 – 6)
IN PROGRESS

1a. Submit Letter of Intent to Prostate Cancer Clinical Trials Consortium (Month 23)
Completed – AUG 2013

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 UNC (Month 14)
Completed – NOV 2012

1e. Obtain IRB approval at UNC (Months 19)
Note: Revise protocol to indicate UNC is now coordinating center. Submit for IRB approval at UNC (Month 20). Administrative delays prevented the opening of the study at UNC Chapel Hill until JAN 2013
Completed – JAN 29 2013

1f. Submit for IRB and HRPO review at participating sites:

SITE	Date of Initial IRB Approval
OHSU	29 JAN 2013
JHU	10 MAY 2013
UW	9 MAY 2013
MSKCC	6 NOV 2013

1g: Complete the transition of the award from MSKCC (original lead site) to UNC (SEPT 2013, Month 24)
Completed – 9/30/2013

1h. Submit each site for HRPO review: pending HRPO approval for newly added site MSKCC

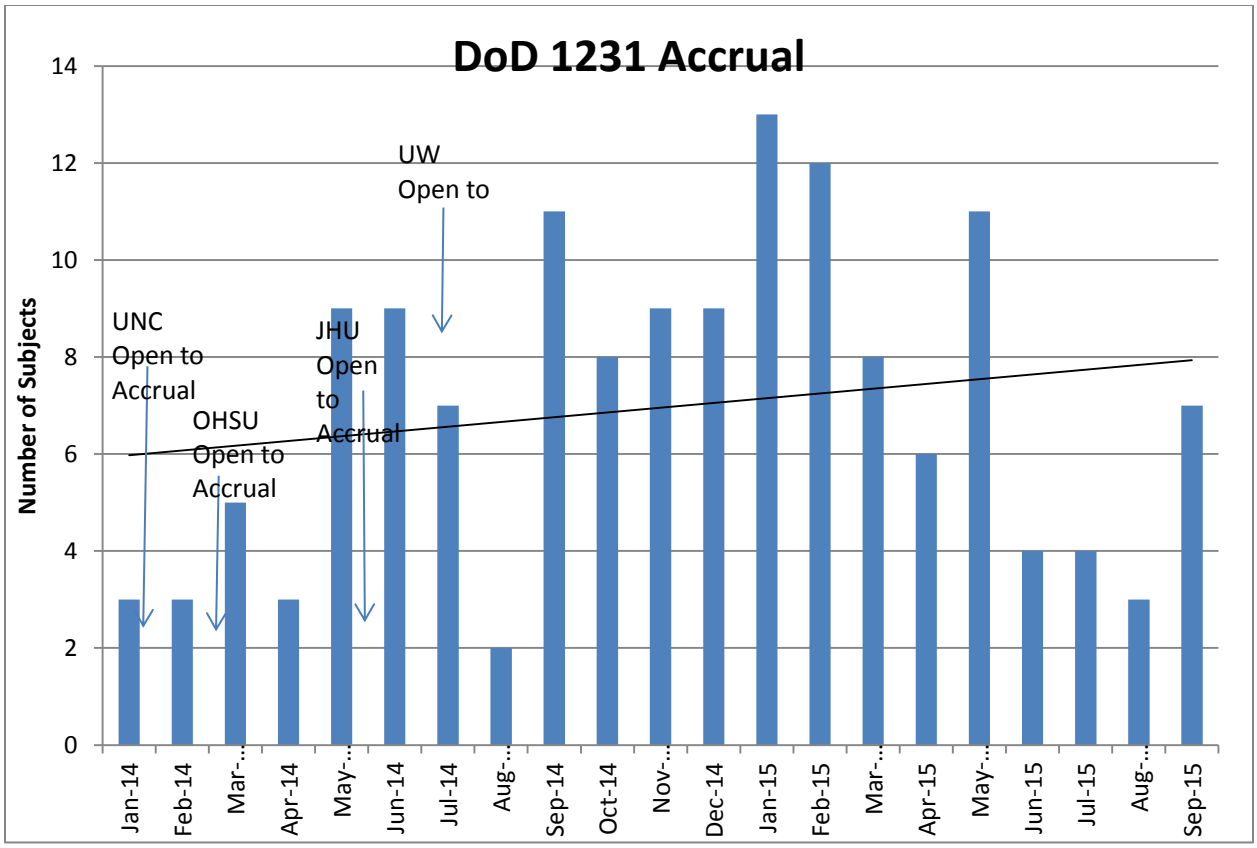
SITE	Initial HRPO Approval Date
UNC	15 AUG 2013
OHSU	27 AUG 2013
JHU	29 AUG 2013
UW	14 MAR 2014
MSKCC	Pending

Task 2. Prepare for data collection and analysis (Months 1 – 6)
IN PROGRESS

2a. Develop IVRS platform (Months 1 – 3) **Completed**
2b. Develop study databases on secure, password-protected server (Months 3 – 6) **Completed**
2c. Draft statistical analysis plan and elicit feedback from collaborators (Months 1 – 6) **In Progress**
Task 3. Implement study protocol (Months 23-60) **IN PROGRESS**
3a. Conduct site orientations (Month 25-48) **Completed**
3b. Recruit and enroll patients (Months 23-61) **In Progress**
3c. Track accrual/follow-up, conduct weekly telephone meetings with site data managers, and conduct monthly telephone meetings with site PIs (Months 23-75) **In Progress**
Task 4. Analyze study data (Months 23 – 72) 4a. Import data from IVRS to secure study database (Months 23 – 78) **In Progress** 4b. Collect CRFs completed by clinic staff on monthly basis (Months 23 – 73) **In Progress** 4c. Enter CRF data into secure study database (Months 23 – 78) **In Progress** 4d. Perform data quality audits on monthly basis (Months 23 – 78) **In Progress** 4e. Analyze data, per SAP, and prepare tables and figures (Months 47 – 78) 4f. Prepare manuscripts and abstracts with input from collaborators (Months 47 – 78)

The current accrual for each site is as follows:

SITE	Number of Patients Screened and Approached	Number of Patients Enrolled	Consent Rate %
UNC	35	35	100%
OHSU	43	39	90%
JHU	68	53	77%
UW	22	21	95%
MSK	Should start accrual soon		
TOTAL	**168**	**147**	**87%**



As note in the most recent SOW, submitted to Department of Defense on August 2015 we are resetting the total patient accrual from 400 to 225. The accrual has been slower than originally hoped, but follow up and compliance have been higher than anticipated resulting in richer follow-up data and better overview of outcome. Based on data from the Prostate Cancer Clinical Trials Consortium (PCCTC) showing past accrual rates to prostate cancer trials of patients with planned eligibility criteria at the study sites, as well as pain prevalence survey data from the PCCTC, accrual of the planned sample size is feasible given the timeline. Specifically, during the 12 month accrual period, to enroll 225 patients, an average of 2 to 3 patients per week will need to be accrued which are well within the range of past recruitment rates and current site estimates of feasibility. A follow-up formal feasibility assessment will be conducted by the PCCTC once the protocol is complete

Through the careful work of the project manager (Diana Mehedint) and multi-site coordinator (Diane Joyal) we have strong relationships with the research staff at each of the studies sites. The activities of the study are progressing well and there are open lines of communication with the sites to ensure data quality. The renewal of subcontracts and the renewal of IRB approvals (continuing review) is proceeding well at each site.

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.

Data analysis from pain assessment nested in a phase II clinical trial of cabozantinib has been analyzed. The manuscript, published by the journal *European Urology*, has been attached to the annual report submitted to Department of Defenses in November 2015.

Basch E, Autio KA, Smith MR, et al: Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort. Eur Urol. 2015 Feb;67(2):310-8. doi: 10.1016/j.eururo.2014.02.013. PMID: 24631409

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.

A meeting with the relevant stakeholders was held. A manuscript was written with FDA collaboration. This manuscript, published by the journal *Cancer,* has been attached to the annual report submitted to Department of Defenses in November 2015.

Basch E, Trentacosti AM, Burke LB, Kwitkowski V, Kane RC, Autio KA, Papadopoulos E, STansbury JP, Kluetz PG, Smith H, Justice R, Pazdur R. Pain Palliation Measurement in Cancer Clinical Trials: The US Food and Drug Administration Perspective. Cancer, 2014 Mar 1;120(5):761-7. doi: 10.1002/cncr.28470

KEY RESEARCH ACCOMPLISHMENTS

Aim 1. The study is open and accruing patients at four sites.

Aim 2. A study was designed and conducted with an industry sponsor phase II trial. Results were analyzed and manuscript was published in *European Urology* (Basch, Euro Urol 2015) In addition, patient understanding and acceptance of the worst pain NRS was established in this population (Bennett et al, ASCO and ISPOR, 2013). The manuscript and abstracts are included in the Appendix.

Aim 3. A meeting with the relevant stakeholders was held and a manuscript was written with FDA collaboration. This manuscript was been published by the journal *Cancer.* (Basch, Cancer 2014), has been attached to the annual report submitted to Department of Defenses in November 2015.

The findings of Aim 2 and Aim 3 are described below in REPORTABLE OUTCOMES

CONCLUSIONS

Opening the observational longitudinal study (Aim 1) required surmounting multiple challenges in the first year of the award. At this time, the study is now open and accruing patients at each of the four study sites (n=50). We have strong working relationships with each of the sites which will facilitate management of the study and ensure data quality. We anticipate substantial accrual to the study in the next annual period. Aims 2 and 3 of this project are now complete, with each resulting in a peer-reviewed manuscript published in high impact journals.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS

Basch E, Autio KA, Smith MR, et al: Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort. Eur Urol. 2015 Feb;67(2):310-8. doi: 10.1016/j.eururo.2014.02.013. PMID: 24631409

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Bennett AV**,** Eremenco S, Heon N, Scheffold C, Schimmoller F, Weitzman AL, Basch E. Mode equivalence of Interactive Voice Response (IVR) and paper versions of the Brief Pain Inventory (BPI) "worst pain" item in metastatic resistant prostate cancer (MCPRC) evaluated conceptually using qualitative methods. International Society for Pharmacoeconomics and Outcomes Research. 16th Annual European Congress, Dublin, Ireland, November 2-6, 2013.

Bennett AV, Atkinson TM, Heon N, O'Keefe B, Scheffold C, Schimoller F, Basch E. Qualitative assessment of the Brief Pain Inventory (BPI) "pain at its worst in the last 24 hours" item to support assessment of pain as a clinical trial endpoint in metastatic castrate resistant prostate cancer (mCRPC) per FDA labeling standards. Abstract. American Society of Clinical Oncology. Chicago IL, June 1-5, 2013.

INVENTIONS, PATENTS AND LICENSES

None

REPORTABLE OUTCOMES

Aim 1 – Research is in progress

Aim 2 – Research findings include:

1. Collection of pain data via automated telephone system is feasible in a clinical trial including symptomatic men with advanced metastatic CRPC that is heavily pretreated.
2. Tabulation of total analgesic dose is feasible and can be combined with pain intensity data in clinical trial response and definition.
3. Content validity of a patient pain diary was established
4. Patient understanding and acceptance of the worst pain NRS was established in this population (Bennett et al, ASCO and ISPOR, 2013)
5. Related end points including sleep quality and general activity were significantly associated with pain response.
6. Results of the phase 2 pain analysis: Cabozantinib demonstrated clinically meaningful pain palliation, reduced or eliminated patients' narcotic use, and improved patient functioning, thus meriting prospective validation in phase 3 studies. (Basch, Euro Urol, 2015)
7. Results from this phase II pain assessment served as rationale for design of phase 3 trial with primary pain endpoints.

Aim 3 – Key findings of this paper (Basch, Cancer 2014) include articulations of current FDA thinking about the design end points in cancer trails. This includes:

1. Methodological criteria for selective pain measurements
2. Approaches for analgesic tabulation
3. Approach to demonstrating durability of pain response
4. Role of pain end points in drug approval and labeling
5. Issues related to pain measurements in open and unblinded trials

OTHER ACHIEVEMENTS

None at this time

REFERENCES

Basch E, Autio KA, Smith MR, et al: Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort. Eur Urol. 2015 Feb;67(2):310-8. doi: 10.1016/j.eururo.2014.02.013. PMID: 24631409

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Bennett AV, Atkinson TM, Heon N, O'Keefe B, Scheffold C, Schimoller F, Basch E. Qualitative assessment of the Brief Pain Inventory (BPI) "pain at its worst in the last 24 hours" item to support assessment of pain as a clinical trial endpoint in metastatic castrate resistant prostate cancer (mCRPC) per FDA labeling standards. Abstract. American Society of Clinical Oncology. Chicago IL, June 1-5, 2013.

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APPENDICES

The following manuscripts and abstracts have been attached to the annual report submitted to Department of Defense in November 2015. Please see enclosed PDF at the bottom of this page.

Basch E, Autio KA, Smith MR, et al: Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort. Eur Urol. 2015 Feb;67(2):310-8. doi: 10.1016/j.eururo.2014.02.013. PMID: 24631409

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Appendix for DOD Annual Report 2015