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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 <i>European Urology</i> , 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 <i>Cancer</i> , titled: "Pain Palliation Measurement in Cancer Clinical Trials: The US Food and Drug Administration Perspective." Both manuscripts are attached to this report.					
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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.

University of North Carolina at Chapel Hill is now the coordinating center for the study data and contracts. In the prior year (2013), administrative logistical delays related to institutional move, from Memorial Sloan Kettering Cancer Center, led to substantial delays in opening the study. The study is now open and actively accruing patients at all four sites: University of North Carolina, John Hopkins University, Oregon Health and Sciences University, and University of Washington.

The table below lists the first three Tasks of Aim 1 as outlined in the Statement of Work (PC100563 Basch 7-20-2011, revised 4-20-2013) 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 (Months 14 – 16) Completed – 6/5/2012
1f. Submit for HRPO review (Month 19-21) Completed – 9/17/2012
New: Revise protocol to indicate UNC is now coordinating center. Submit for IRB approval at UNC (Month 20) Completed – 01/29/2013
New: Submit UNC protocol and site documents for HRPO approval Completed – 08/15/2013
1g. Submit for IRB review at participating sites (Johns Hopkins, Oregon Health & Sciences University, University of Washington) (Month 8) Johns Hopkins Approved 05/09/2013 Oregon Health & Sciences University Approved 05/10/2013 University of Washington Approved 11/06/2013
New: Submit Johns Hopkins, Oregon Health & Sciences University, and University of Washington protocol and site documents for HRPO approval Johns Hopkins Approved 8/29/2013 Oregon Health & Sciences University Approved 08/27/2013 University of Washington Approved 03/14/2014
<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) Completed
2c. Draft statistical analysis plan and elicit feedback from collaborators (Months 1 – 6) In Progress
<u>Task 3. Implement study protocol (Months 21-45)</u> IN PROGRESS
3a. Conduct site orientations (Month 21) Completed
3b. Recruit and enroll patients (Months 21-32) In Progress

3c. Track accrual/follow-up, conduct weekly telephone meetings with site data managers, and conduct monthly telephone meetings with site PIs (Months 21-45) In Progress
Task 4. Analyze study data (Months 21 – 48)
4a. Import data from IVRS to secure study database (Months 21 – 45) In Progress
4b. Collect CRFs completed by clinic staff on monthly basis (Months 21 – 45) In Progress
4c. Enter CRF data into secure study database (Months 21 – 45) In Progress
4d. Perform data quality audits on monthly basis (Months 21 – 45) In Progress
4e. Analyze data, per SAP, and prepare tables and figures (Months 45 – 48)
4f. Prepare manuscripts and abstracts with input from collaborators (Months 45 – 48)

The current accrual for each site is as follows:

SITE	CURRENTLY ON-STUDY	DISCONTINUED (primarily due to hospice or death)	TOTAL ACCRUAL
UNC	11	7	18
JHU	14	3	17
OHSU	12	2	14
UW	1	0	1
TOTAL	38	12	50

Three of the four sites are progressing well towards the total accrual goal (UNC, JHU, and OHSU). The fourth site, UW, was the last to begin accrual. The sites had initially been encouraged not to enroll patients who are participating on other clinical trials. In order to increase the rate of accrual, sites will now be enrolling patients who are on other study protocols as long as those protocols do not include survey assessments. We anticipate the enrollment at JHU, OHSU, and UW will progress more rapidly in the coming months because of this.

Through the careful work of the project manager, Diana Mehedint, 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, which is included in the Appendix, has been published by the journal *European Urology*.

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*. [Epub ahead of print: Feb 20, 2014] doi: 10.1016/j.eururo.2014.02.013

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, which is included in the Appendix, has been published by the journal *Cancer*:

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 all 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* 2014) 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). It is included in the Appendix.

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*. [Epub ahead of print: Feb 20, 2014] doi: 10.1016/j.eururo.2014.02.013. PMID: 24631409

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

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, 2014)
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 trials. 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*. [Epub ahead of print: Feb 20, 2014] 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 are included in the Appendix:

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*. [Epub ahead of print: Feb 20, 2014] doi: 10.1016/j.eururo.2014.02.013. PMID: 24631409

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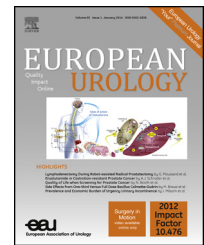
Bennett AV, Atkinson TM, Heon N, O'Keefe B, Scheffold C, Schimmoller F, Basch E. Qualitative assessment of the Brief Pain Inventory (BPI) "pain at its worst in the last 24 hours" item to support assessment of pain as a clinical trial endpoint in metastatic castrate resistant prostate cancer (mCRPC) per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

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.

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European Association of Urology



Prostate Cancer

Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort

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Abstract

Background: Pain negatively affects quality of life for cancer patients. Preliminary data in metastatic castration-resistant prostate cancer (mCRPC) suggested a benefit of the oral tyrosine kinase inhibitor cabozantinib to pain palliation.

Objective: Prospective evaluation of cabozantinib's benefits on pain and narcotic use in mCRPC.

Design, setting, and participants: This was a nonrandomized expansion (NRE) cohort ($n = 144$) of a phase 2 randomized discontinuation trial in docetaxel-refractory mCRPC patients. Pain and interference of symptoms with sleep and general activity were electronically self-reported daily for 7-d intervals at baseline and regularly scheduled throughout the study. Mean per-patient scores were calculated for each interval. Narcotic use was recorded daily during the same intervals.

Intervention: Open-label cabozantinib (100 mg or 40 mg).

Outcome measurements and statistical analysis: The following stringent response definition was used: clinically meaningful pain reduction ($\geq 30\%$ improvement in mean scores from baseline) confirmed at a later interval without concomitant increases in narcotics. Only patients with moderate or severe baseline pain were analyzed.

Results and limitations: Sixty-five patients with moderate or severe baseline pain were evaluable. Of these, 27 (42%) experienced pain palliation according to the stringent

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response definition. Thirty-seven patients (57%) had clinically meaningful pain relief at two consecutive intervals, reported ≥ 6 wk apart in the majority. Forty-four patients (68%) had palliation at one or more intervals; 36 (55%) decreased narcotic use during one or more intervals. Clinically meaningful pain reduction was associated with significant ($p \leq 0.001$) improvements in sleep quality and general activity. A limitation of this study was its open-label design.

Conclusions: Cabozantinib demonstrated clinically meaningful pain palliation, reduced or eliminated patients' narcotic use, and improved patient functioning, thus meriting prospective validation in phase 3 studies.

Patient summary: We evaluated the potential of cabozantinib to improve symptoms in patients with metastatic prostate cancer that no longer responds to standard therapies. We saw a promising reduction in pain and reduced need for narcotic painkillers. Larger, well-controlled trials are necessary to confirm these findings.

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1. Introduction

Most patients with advanced castration-resistant prostate cancer (CRPC) develop bone metastases frequently associated with debilitating pain that is, itself, associated with shorter survival [1]. For those with severe pain, symptoms are rarely eliminated despite optimal management with narcotic analgesics [2], which carry numerous side effects, thus reducing overall functioning even further. Anticancer treatments are needed in this disease that effectively control pain and enable reduction of narcotics.

The receptor tyrosine kinase MET and the vascular endothelial growth factor (VEGF) signaling pathway are implicated in development and progression of CRPC [3]. MET expression appears to be greater in bone metastases than primary tumors and lymph node metastases [4]; the VEGF pathway promotes bone lesion development and activates MET in advanced prostate cancer [3]. Cabozantinib is an orally bioavailable tyrosine kinase inhibitor of MET and VEGF receptor 2 that has demonstrated clinical activity in multiple types of solid tumors [5,6]. In a recent phase 2 randomized discontinuation trial (RDT) that enrolled 171 patients with metastatic CRPC (mCRPC), single-agent cabozantinib demonstrated increased progression-free survival compared with placebo, along with reductions in soft-tissue lesions, bone metastasis burden, and bone-turnover markers; common toxicities seen at the 100-mg dose in this population included fatigue, hand-foot syndrome, and diarrhea, which were typically manageable with either a dose reduction, treatment interruption, or supportive measures [7]. Randomization was halted early due to the clinical activity observed [7]. In a prospective, nonrandomized expansion (NRE) cohort of the phase 2 study, cabozantinib resulted in improvements on bone scans as well as reductions in bone biomarkers, soft-tissue disease, and circulating tumor cells [8,9].

Separately, a retrospective survey of participating investigators found widespread perceptions of pain benefits in the RDT. To explore this further, a formal prospective evaluation of pain using a rigorous measurement approach in accordance with relevant US Food and Drug Administration (FDA) guidance on patient-reported outcomes (PROs) [10,11] that met contemporary standards for pain assessment was needed [12,13]. Evaluating pain is no different from the development of other biomarkers, requiring

analytically valid measurements and demonstrated clinical validity in appropriately designed and powered prospective trials. Studies of approved anticancer therapies in mCRPC have demonstrated modest pain palliation [14–16], but have not consistently evaluated PROs in line with current FDA guidance and contemporary methodology [13,17–21]. Supplemental Table 1 provides an overview of these requirements.

Since pain palliation is a stand-alone primary end point for which therapies have been approved in this disease, we explored whether the pain benefit observed in the RDT was sufficient to warrant the design of a phase 3 registration trial in mCRPC with a dedicated pain end point. To this end, we applied contemporary pain assessment methodology to the NRE cohort [13,22], exploring changes in pain, interference of symptoms with patients' daily living, and narcotic analgesia use.

2. Patients and methods

The patients described in this report were from the NRE cohort of the fully enrolled, phase 2 RDT XL184-203 [7]. Patients with progressive mCRPC (according to standard, objective criteria [23,24]) during treatment with a taxane- or abiraterone-containing regimen (or within 6 mo following the last dose), evidence of bone metastasis on bone scans, and previous docetaxel treatment were sequentially enrolled to two starting doses of open-label cabozantinib, first 100 mg then 40 mg daily, as part of a dose-ranging evaluation. Patients taking prednisone ≤ 10 mg/d were eligible for enrollment. The study design is described in detail elsewhere [22] and in the Supplement.

The study was approved by all local institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. The trial is registered at ClinicalTrials.gov (identifier: NCT00940225).

Once daily, patients were to self-report pain and interference of symptoms with daily living, using an automated, telephone, interactive voice-response system (IVRS), over 7-d intervals at screening (within 14 d before the first dose), at week 3, week 6, and every 6 wk thereafter, using select items from the Brief Pain Inventory short form (BPI-SF) and MD Anderson Symptom Assessment Inventory (MDASI) questionnaires [25,26]. Pain assessments were halted at patient request or if patients discontinued study treatment other than for progression. During each interval, patients reported their worst pain in the prior 24 h (item 3 on the BPI-SF) and the interference of cancer symptoms with sleep and general activity over the same period (items 4 and 14, respectively, on the MDASI). All three items use a 0–10 numeric rating scale, with higher scores representing greater pain intensity or symptom interference.

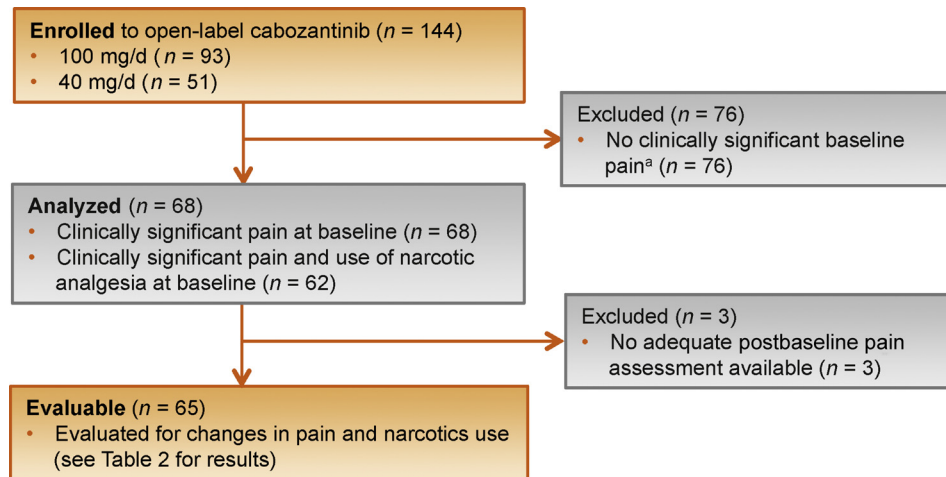


Fig. 1 – Flowchart of patient enrollment and pain analyses in the nonrandomized expansion metastatic castration-resistant prostate cancer cohort.

^a Mean score of the “worst pain reported over 24 h” item of the Brief Pain Inventory Short Form questionnaire over the 7-d baseline reporting interval (scores for at least 4 d had to be reported) was <4.

Patients reported daily analgesic medication use via a paper diary during the same assessment intervals in which pain scores were measured. Prior to each interval, clinical research nurses prepopulated the diary of each participant with the names and dosages of the narcotic medications prescribed, so that patients merely had to indicate the number of doses taken by the end of each 24-h period. This approach closely follows current regulatory recommendations [13]. For each interval, patients’ mean narcotics use was calculated by multiplying the daily dose unit by the number of units taken, averaged by the number of days with available data. Changes in narcotic use were qualified as decreased (including discontinued), stable, or increased, based on the average daily narcotics use relative to the baseline interval. Narcotics use was considered stable if the average daily dose of a given narcotic was identical. Equianalgesia calculations [27] were required to quantify narcotic use if patients changed narcotic type or if dosages were changed in patients concomitantly receiving different narcotic types. In cases where equianalgesia calculations were required, narcotics use was considered stable if the calculated equivalents were within 5% of the baseline dose.

Mean scores for pain, disturbed sleep, and interference with general activity were calculated over each 7-d interval. For an interval to be considered evaluable for analysis of a specific measure (including analgesic use), reporting on ≥ 4 d out of 7 was required. Only patients with a baseline, mean worst pain score ≥ 4 , corresponding to moderate or severe pain using a verbal analog scale [28], and one or more evaluable follow-up assessments were included in the analyses. A decrease in the mean worst pain score $\geq 30\%$ from baseline was prospectively defined as clinically meaningful improvement based on standard definitions [20,21]. The pain response definition used for the main analysis was the currently recommended [10,13,24], more conservative measure, requiring a clinically meaningful improvement that is confirmed at a later time point without a concurrent increase in narcotics use. There was no prespecified decision rule as to the proportion of patients experiencing a response to inform the decision to further study cabozantinib for a pain relief indication.

A decrease in the mean sleep disturbance or mean symptom interference scores (determined over the same 7-d interval as the mean worst pain score) from baseline corresponded to an improvement in sleep or functioning, respectively. Differences in measures of symptom interference between patients with and without clinically meaningful pain palliation were assessed by the Mann-Whitney test.

3. Results

A total of 144 mCRPC patients were enrolled to the NRE cohort at 13 sites in the United States and one in the United Kingdom between February 2011 and April 2012. Patients were enrolled sequentially to two starting doses of open-label cabozantinib: first 100 mg daily ($n = 93$) then 40 mg daily ($n = 51$). Main results, including details on dose reductions, are presented in detail elsewhere [22].

A total of 68 patients (47%) who reported moderate or severe pain at baseline constituted the population for this analysis, of whom 62 also reported baseline narcotic analgesia use (Fig. 1). The median baseline pain score was 5.9 (range: 4.0–7.9; lower and upper quartiles: 4.7 and 6.7, respectively). Additional baseline characteristics for the analysis population are listed in Table 1. Of note, in addition to prior docetaxel, patients were heavily pretreated with

Table 1 – Characteristics of patients with baseline pain score ≥ 4 ($n = 68$)

Age, yr, median (lower quartile, upper quartile)	64 (57, 70)
ECOG performance status, no. (%) ^a	
0	17 (25)
1	50 (74)
Bone disease, no. (%)	68 (100)
At least two prior regimens for mCRPC, no. (%)	52 (76)
Prior treatment, no. (%)	
Docetaxel	68 (100)
Abiraterone	34 (50)
Cabazitaxel	16 (24)
Enzalutamide	2 (3)
Radionuclide	7 (10)
Use of bone-targeted therapy ^b , no. (%)	44 (65)

ECOG = Eastern Cooperative Oncology Group; mCRPC = metastatic castration-resistant prostate cancer.

^a One patient was enrolled with an ECOG performance status of 2.

^b Zoledronic acid or denosumab at baseline (includes one patient who discontinued zoledronic acid within 60 d prior to first dose of cabozantinib).

Table 2 – Effects of cabozantinib on mean worst pain and narcotic use

	Cabozantinib cohort		
	100 mg	40 mg	Combined
Pain ≥ 4 at baseline ^a , no.	39	26	65
Pain reduction $\geq 30\%$ at any time point, no. (%) [95% CI]	25 (64) [47–79]	19 (73) [52–88]	44 (68) [55–79]
Pain reduction $\geq 30\%$ at two or more consecutive assessments ^b , no. (%) [95% CI]	22 (56) [40–72]	15 (58) [37–77]	37 (57) [44–69]
Pain reduction $\geq 30\%$ at two or more consecutive assessments ^b with no concomitant increase in narcotics ^c , no. (%) [95% CI]	15 (38) [23–55]	12 (46) [27–67]	27 (42) [29–54]
Median best change in pain, % reduction	46	49	46
Decreased narcotics at any time point ^d , no. (%) [95% CI]	22 (56) [40–72]	14 (54) [33–73]	36 (55) [43–68]
Decreased narcotics at two or more consecutive assessments ^e , no. (%) [95% CI]	21 (54) [37–70]	13 (50) [30–70]	34 (52) [40–65]

Data are shown for the 65 patients with pain score ≥ 4 at baseline who had at least one adequate postbaseline pain assessment. Equianalgesia calculations were used to determine changes in narcotic use for patients who modified narcotic types throughout the assessments.

^a Patients with at least one adequate postbaseline pain assessment, denominator for percent calculations.

^b Includes eight patients whose consecutive assessments were at week 3 and week 6; for the remaining patients, the two consecutive assessments were at least 6 wk apart.

^c Includes patients who did not take any narcotics at baseline and did not add any narcotics, as well as patients who stayed on the same dose of narcotics at baseline and the two consecutive assessments.

^d Includes patients who discontinued narcotics at any time point (100 mg [$n = 12$]; 40 mg [$n = 1$]).

^e Includes patients who discontinued narcotics at two consecutive time points (100 mg [$n = 9$]; 40 mg [$n = 1$]).

other medications for mCRPC, including abiraterone (50% of patients), cabazitaxel (24%), and enzalutamide (3%). Overall, 76% of patients had received two or more prior regimens (including docetaxel) for mCRPC. Patients readily complied with the IVRS reporting: In the analysis population, a total of 292 IVRS reporting intervals were administered (through week 18) prior to treatment discontinuation, and 93% of these intervals were evaluable (ie, patients reported pain on ≥ 4 d out of 7 for the respective interval).

Pain and narcotic use were evaluable for 65 of the 68 patients and are summarized in Table 2, categorized by dose group (100 mg, $n = 39$; 40 mg, $n = 26$). Overall, 27 of the 65 patients (42%) reported a clinically meaningful improvement ($\geq 30\%$ decrease) in the mean worst pain score at two consecutive assessments without a concomitant increase in narcotic use (Table 2), representing a conservative definition of durable pain palliation according to Prostate Cancer Working Group 2 (PCWG2) criteria and other current guidance [10,13,24]. Additional analyses showed that 44 patients (68%) had one or more postbaseline assessments with a clinically meaningful improvement (Fig. 2A); median change in pain score was a 46% reduction that was confirmed at a subsequent assessment in 37 patients (57%) (Table 2).

Of those with evaluable data at week 6 ($n = 61$) and week 12 ($n = 49$), 57% and 53%, respectively, reported a clinically meaningful decrease in the mean worst pain score (Fig. 2B and 2C). The median change in mean worst pain score was below baseline for each time point (Fig. 3): -22% (week 3), -38% (week 6), -31% (week 12), and -36% (week 18). In the majority of patients (76–84%, depending on the specific time point) with concomitant narcotics reporting, clinically meaningful reductions in pain were not associated with increased narcotics use (Fig. 2A–2C; Table 2). Pain palliation effects were similar in the 40-mg and 100-mg cohorts (Fig. 2A–2C; Table 2).

Thirty-six of the 65 evaluable patients (55%) reported a decrease in narcotic use during one or more postbaseline intervals, including 13 (20%) who discontinued narcotics during that period. Proportions of patients who decreased narcotics at any time point were comparable between both dose groups (Table 2). Overall, 34 patients (52%) decreased narcotics at two or more consecutive assessments. At each time point, the majority of patients reported either decreased or stable narcotics (Fig. 4).

The relationships between clinically meaningful pain palliation and both sleep disturbance and general activity were assessed at matching time intervals. At each of these time points, patients with pain palliation were significantly more likely to experience improvements in sleep quality and interference with general activity than patients without pain palliation. Figure 5A illustrates that improvements in disturbed sleep differed significantly between those who experienced a $\geq 30\%$ reduction in pain and those who did not, with median changes of -53% versus 1% at week 3, -47% versus -4% at week 6, -41% versus 5% at week 12, and -56% versus -9% at week 18 ($p < 0.0001$ for each time interval). As shown in Figure 5B, improvements in functioning differed significantly between those who experienced a $\geq 30\%$ reduction in pain and those who did not, with median changes of -32% versus 0% at week 3 ($p = 0.0006$), -43% versus -3% at week 6 ($p < 0.0001$), -42% versus 8% at week 12 ($p < 0.0001$), and -32% versus 14% at week 18 ($p = 0.001$).

4. Discussion

By rigorous contemporary assessment standards, cabozantinib demonstrated pain palliation in heavily pretreated men with symptomatic mCRPC in this phase 2 NRE cohort. Overall, 42% of evaluable patients reported clinically meaningful improvement in worst pain confirmed at a

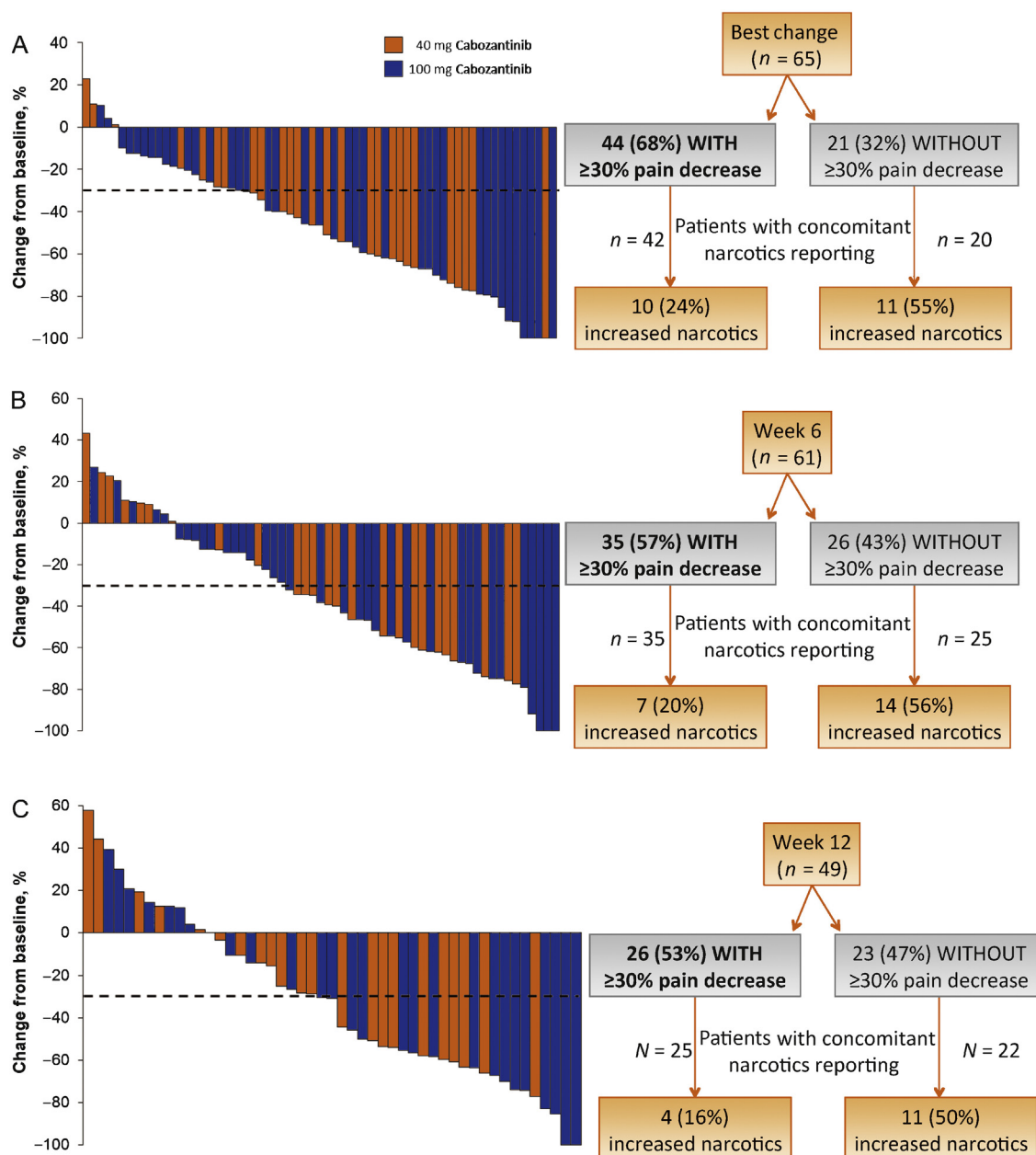


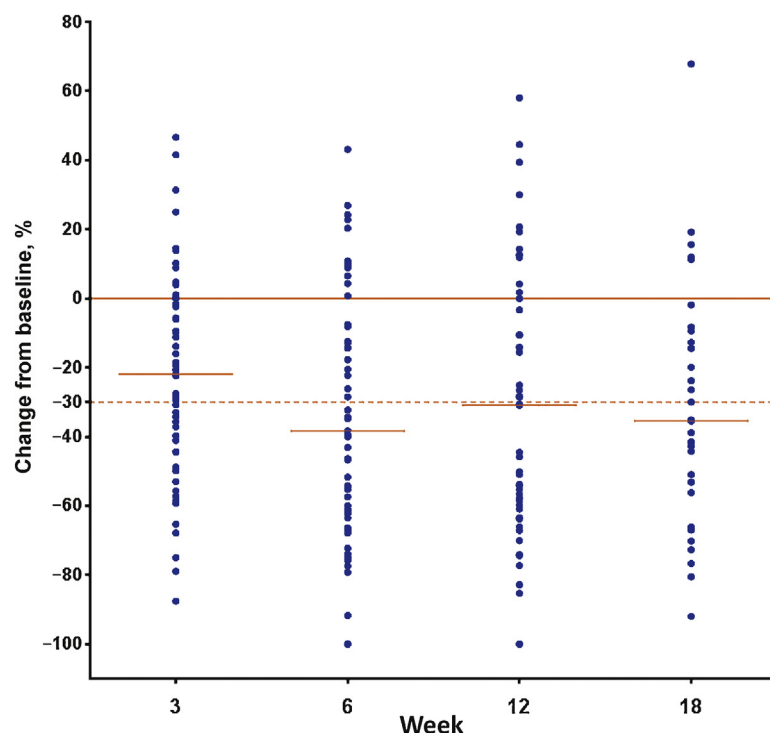
Fig. 2 – Change from baseline in mean worst pain and associated narcotics changes. Starting doses of cabozantinib were 100 mg and 40 mg. (A) Best change. Data are shown for the 65 patients with pain score ≥ 4 at baseline who had a least one adequate postbaseline pain assessment. The dashed line denotes a 30% improvement in mean worst pain score. (B) Data are shown for the 61 patients with pain score ≥ 4 at baseline and adequate pain reporting at week 6. (C) Data are shown for the 49 patients with pain score ≥ 4 at baseline and adequate pain reporting at week 12.

second assessment without concomitant increases in narcotics use, a conservative definition of pain palliation in cancer trials [10,13,24]. More than two-thirds of patients experienced one or more assessment intervals with clinically meaningful pain improvement, enabling 20% of patients to discontinue narcotic usage. The global impact of pain palliation on overall patient well-being was shown by parallel improvements in sleep and daily function.

Preclinical models of prostate cancer indicate that cabozantinib targets prostate cancer cells as well as cells of the bone microenvironment (including osteoblasts and osteoclasts), inhibiting tumor growth and tumor-induced

bone changes [29,30]. The impact of cabozantinib on pain due to bone metastases may be related to its effects on both cancer cells and the surrounding bone microenvironment.

Pain palliation appeared as early as week 3, when 39% of patients with evaluable data reported clinically meaningful pain reduction, and increased to 57% at week 6. Overall, 57% of evaluable patients reported improvement at two consecutive assessment intervals. Pain outcomes were similar for the 40-mg and 100-mg starting-dose groups. Of note, cabozantinib dose-reduction rates were similar to those in the overall NRE cohort, in which 84% of patients enrolled to the 100-mg cohort had one or more dose



	Week 3	Week 6	Week 12	Week 18
Patients evaluable, no.	61	61	49	31
Median change in pain score, %	-22	-38	-31	-36
Pain reduction $\geq 30\%$, no. (%)	24 (39)	35 (57)	26 (53)	18 (58)

Fig. 3 – Changes in mean worst pain over time. Data are shown for patients with pain score ≥ 4 at baseline with ≥ 4 of 7 d reported during each postbaseline interval. The dashed line denotes a 30% improvement in mean worst pain.

reductions [22]. The outcomes for the 100-mg and 40-mg cohorts are not directly comparable, because the study was not randomized and due to the relatively small patient number per cohort. Moreover, due to protocol-specified

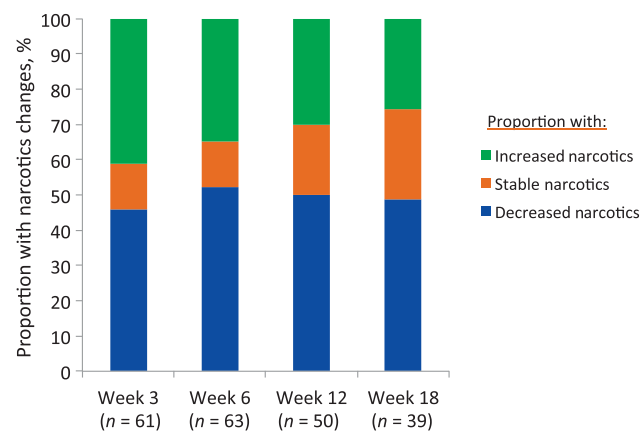


Fig. 4 – Proportion of patients with narcotics changes over time. The proportion of patients with changes in narcotic use is shown for patients with pain score ≥ 4 at baseline and available diary data at each time point.

dose modifications in the overall NRE population, the median average daily dose in the 100-mg cohort was actually 55 mg/d, minimizing the difference in actual dose administered between cohorts; based on these results, 60 mg/d was selected as the starting dose for subsequent phase 3 trials [22].

For historical comparison, in a recent phase 3 trial in docetaxel-refractory mCRPC patients, 7.7% of mitoxantrone-treated patients showed a pain response; mitoxantrone remains the only chemotherapeutic agent with a pain palliation FDA-labeling claim in mCRPC. That trial used a different pain scale than our study, but similarly used repeated pain assessments over 7 d self-reported by IVRS, and incorporated analgesic use and the requirement for a confirmatory response at a second time point [16].

At baseline, $>90\%$ of our patients with moderate or severe pain received narcotic analgesics, which is not surprising given their pain levels and the fact that all patients were managed by oncologists specializing in caring for prostate cancer patients. This rate is higher than reported in large, community-based cohort studies, which have suggested underuse of narcotics in cancer patients [31]. This high prevalence of narcotic use provides valuable

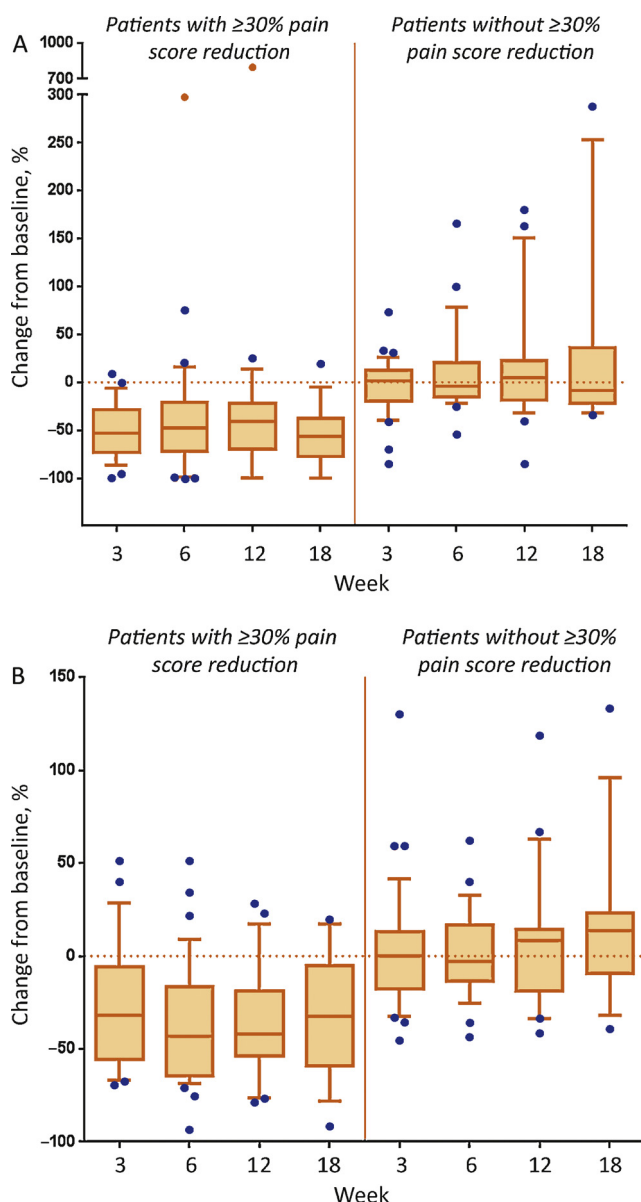


Fig. 5 – Relationship of pain with sleep disturbance and functioning over time. (A) Percent change from baseline in disturbed sleep score in patients with or without clinically meaningful pain score reduction. (B) Percent change from baseline in symptom interference score (interference with general activity) in patients with or without clinically meaningful pain score reduction.

insight into the palliative benefit of cabozantinib, since $>50\%$ of evaluable patients were able to decrease these medications. The ability to reduce narcotics may have the additional benefit of alleviating the side effects associated with these agents; ongoing trials of cabozantinib are formally evaluating this topic.

The prevalence of moderate or severe baseline pain was similar to that reported in recent phase 3 studies among mCRPC patients who experienced disease progression despite prior docetaxel therapy (28–46%) [14,16,32]. Like other PROs in clinical trials, methods for evaluating pain have evolved over time, and previous studies generally used

less rigorous methods for assessing pain and analgesic usage. Our study used a rigorous contemporary methodology to critically evaluate pain.

Key elements of contemporary pain studies in oncology include the use of validated PRO measures for a particular population, repeated measurements to obtain an average score, meaningful intervals that can also assess the durability of response, and incorporation of analgesic use into responder definitions [13]. Our study fulfilled these criteria. The BPI instrument, in particular the worst pain item assessing the prior 24 h, has well-established psychometric properties that meet FDA guidelines for PRO end point measures [10,11,33]. The repeated daily assessments over 7-d intervals used to determine an average score are preferred over single scores, which may be more susceptible to random day-to-day variation. A priori definition of a clinically meaningful difference for all evaluated PRO measures is another important principle. In the case of patient-reported pain, a $\geq 30\%$ change from baseline is widely accepted as such a meaningful difference [20]. While the data from this NRE cohort suggest a promising palliative response with cabozantinib, direct comparisons with other agents cannot be made, due to differences in study design, patient populations, and sample sizes of relevant published clinical trials.

A key to conducting successful pain palliation trials is close coordination between the treating team and their patients. Notable here is that compliance with PRO reporting was high, with 93% of relevant assessment intervals (through week 18) completed adequately. This may be attributable partially to the IVRS system and automated, real-time assessments (with reminders) that are convenient to use for patients and investigators. Adequate compliance is essential for trials reporting PRO measures, since noncompliance could be reflective of worsening symptomatology.

This open-label, nonrandomized, phase 2 design is not definitive, due to possible bias in PRO reporting associated with unblinded assessments. The study design precluded any meaningful analysis of associations between pain control and markers of disease progression. The degree of palliation observed resulted in the decision to design a prospective, phase 3, double-blind, randomized trial of cabozantinib with a primary end point of pain palliation. Lack of an analgesic optimization phase prior to study entry, which could potentially have altered results, is a limitation of the current study. However, patients received narcotics with much greater frequency than in community-based samples among populations with similar pain severity [31], suggesting that some of the obstacles to analgesic use (eg, physician failure to recognize pain and patient concerns for addiction) were being well-managed in this patient cohort.

Taken together, the results reported here, which are based on contemporary methods and regulatory guidance for PRO assessment, found pain palliation rates were well in excess of those seen in control arms of registration trials in mCRPC, many of which used prednisone in the control arm, rather than placebo. Prednisone is an active agent in this context, with reported pain palliation at stable or reduced

analgesic consumption reported in 12–29% of patients [14,15]. Since the pain palliation signal and the reductions in narcotic use observed with cabozantinib substantially exceed these previously reported levels, an effect beyond placebo is likely and justifies the design and conduct of a dedicated pain palliation phase 3 trial towards a formal indication [16,34].

5. Conclusions

Pain palliation remains a critical unmet need in treating patients with mCRPC. According to PCWG2 recommendations, relief or elimination of disease-related symptoms is a clinical benefit of prostate cancer therapy [22], with pain palliation being a clinical benefit that is an approvable end point in its own right [13]. Our results illustrate that contemporary pain palliation trials [11], while challenging to conduct, are feasible and can generate valuable information about symptoms as directly reported by patients. This phase 2 NRE cohort implemented key elements desired from a modern pain trial and thus provided justification for, as well as informed the study design of, the blinded, randomized, phase 3 COMET-2 trial; ClinicalTrials.gov identifier NCT01522443). That trial will further assess the promising pain response observed with cabozantinib as the primary end point, as well as evaluate whether pain improvement is reflective of disease regression or stabilization. In that trial, which includes mitoxantrone plus prednisone as an active control, a similar conservative definition of pain palliation at two consecutive time points with no increase in narcotics is the primary efficacy outcome. The present analysis, analogous to a phase 2 signal-seeking study, was an essential step in the clinical qualification process prior to conducting a randomized, controlled, phase 3 trial. This step-wise approach reflects the rigorous methodology that is needed to ultimately validate and potentially qualify a biomarker (ie, pain palliation). For future trials evaluating therapies for advanced cancer, investigators are encouraged to implement patient-reported measures to fully elucidate the potential clinically meaningful benefits of novel antitumor agents.

Author contributions: Ethan Basch had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Basch, Autio, MR Smith, Bennett, Weitzman, Scheffold, Sweeney, Sartor, Vogelzang, Corn, Schimmoller, Scher.

Drafting of the manuscript: Basch, Autio, Bennett, Scher.

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Statistical analysis: Basch, Bennett, Schimmoller.

Obtaining funding: Weitzman.

Administrative, technical, or material support: Scheffold, Schimmoller.

Supervision: Basch, Weitzman.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2014.02.013>.

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Pain Palliation Measurement in Cancer Clinical Trials

The US Food and Drug Administration Perspective

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BACKGROUND: Pain palliation resulting from antitumor therapy provides direct evidence of treatment benefit when combined with evidence of antitumor activity. The US Food and Drug Administration (FDA) previously issued guidance regarding the use of patient-reported outcome (PRO) measures to support labeling claims. The purpose of this article is to identify common challenges and key design strategies when measuring pain palliation in antitumor therapy clinical trials that are consistent with PRO Guidance principles. **METHODS:** Antitumor clinical protocols submitted to the FDA between 1995 and 2012 that included pain palliation as a primary or secondary endpoint were reviewed. Challenges in critical trial design components were identified. Design strategies consistent with PRO Guidance principles are proposed. **RESULTS:** The challenges identified were measurement of pain intensity and analgesic use, enrollment eligibility criteria, data collection methods, responder definitions, missing data, and blinding. Strategies included the use of well-defined, reliable, PRO assessments of pain intensity and analgesics; ensuring that enrollment criteria define patients with clinically significant pain attributable to cancer on an optimal analgesic regimen; defining responders using both pain and analgesic use criteria; incorporating an analysis of tumor response to support evidence of pain response; and minimizing missing data and inadvertent unblinding. **CONCLUSIONS:** Improvement in cancer-related pain resulting from antitumor therapy is an important treatment benefit that can support drug approval and labeling claims when adequately measured if study results demonstrate statistically and clinically significant findings. Sponsors are encouraged to discuss pain palliation assessment methods with the FDA early in and throughout product development. *Cancer* 2014;120:761-7. © 2013 American Cancer Society.

KEYWORDS: pain, patient-reported outcome, clinical trial, cancer, analgesic, narcotic, guidance, FDA, Food and Drug Administration.

INTRODUCTION

Pain Assessment in Clinical Research

Pain related to cancer can be debilitating for patients. The importance of creating tools that will provide direct evidence of how cancer patients feel, particularly within the context of a clinical trial evaluation, has been discussed previously.¹⁻³ These discussions highlight the importance of using patient-reported outcome (PRO) measures to evaluate clinically relevant changes in pain intensity.

The US Food and Drug Administration (FDA) also recognizes the value that PRO measures offer to stakeholders in drug development. In December 2009, the agency published the *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* ("PRO Guidance").⁴ The guidance provides recommendations for developing and implementing PRO measures in clinical trials and defines a PRO as any report of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Accordingly, PRO instruments are appropriate for measuring symptom efficacy outcomes (eg, pain intensity) in clinical

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trials. Measures that use clinician interpretation of patient symptoms, such as a clinician-reported pain assessment, may not adequately represent the patients' perspective of their symptoms. Such measures are not recommended for evaluating treatment benefit.

US Regulatory Considerations

PRO measures used in product labeling must provide adequate evidence to satisfy established FDA regulations. Specifically, the approval of medical products must be based on "substantial evidence" of effectiveness, and assessments that are used to establish this evidence must be "well-defined and reliable."⁵ The development and reliability of PRO measurements must also be informed by the intended context of use, with due consideration for disease condition, target population, treatment intervention, and overall study design, including methods of data analysis.

PRO measures have been used as efficacy endpoints to support labeling claims for numerous medical products approved by the FDA in recent years.⁶⁻⁸ In all likelihood, the value of PRO metrics in making anticancer drugs available to patients will become increasingly important in future clinical trials.

In recent years, the FDA has worked to clarify its expectations regarding the adequacy of symptom measurement to support drug approval or labeling claims.^{9,10} The PRO Guidance outlines general principles for developing scientifically sound measures in clinical trials; however, unique challenges exist that are related to the development of measures for specific diseases and in specific populations, such as pain palliation in patients with cancer. Many of the challenges that must be confronted in measuring pain intensity in oncology trials have been highlighted by expert panelists at a recent workshop sponsored by Friends of Cancer Research and the Brookings Institution.¹¹ As with any outcome assessment, the approach to collecting and analyzing PRO measures should be detailed a priori in a protocol and in the statistical analysis plan if the outcome of interest is intended for labeling.

The approval of cancer drugs is supported by direct evidence of clinical benefit (eg, improvement in survival, physical functioning, or tumor-related symptoms) or an improvement in an established surrogate for clinical benefit. Tumor-related endpoints, such as objective response rate (the percentage of patients with a reduction in tumor size of a predefined amount and for a minimum time period) may not predict or correlate with clinical benefit. Evidence that a cancer drug not only treats the tumor but also improves cancer-related symptoms (ie, pain) may be sufficient to support regular approval.¹²

MATERIALS AND METHODS

Identifying Key Study Design Challenges in Oncology Pain Assessment

The following sources were reviewed: 1) clinical protocols that included pain palliation as a primary or secondary endpoint that were submitted to the Office of Hematology and Oncology Products of the FDA's Office of New Drugs in the Center for Drug Evaluation and Research between 1995 and 2012; 2) the FDA's PRO Guidance⁴; 3) the FDA's 2010 draft *Guidance for Industry: Qualification Process for Drug Development Tools*¹³; and 4) oncology pain panel discussions in which the FDA participated (including the 2011 and 2012 Brookings Institution/Friends of Cancer Research "Conference on Clinical Cancer Research" meetings). Key study design challenges and possible strategies for overcoming these challenges that are consistent with the PRO Guidance when assessing pain palliation in oncology were identified.

RESULTS

Measurement and Analysis Approaches Consistent With PRO Guidance

Six discrete study design challenges were extracted from the protocols (Table 1), and are discussed below.

Measurement of pain intensity and analgesic use

Pain may be assessed using a variety of measures in clinical trials. Most often, the concept of pain intensity is assessed; however, decisions about how to best capture pain as a clinical trial endpoint need to be made with the specific patient population and trial design in mind.

Pain assessment is best derived from patient self-report based on PRO Guidance principles. Similar to all clinical trial outcome assessments, pain assessments must be demonstrated to be valid, reliable, and sensitive to changes over time in the target population. Evidence that the PRO measure is appropriate, interpretable, and significant for the target population, based on qualitative research (eg, patient interviews or focus groups), is necessary to demonstrate that the measure adequately represents the concept of interest (ie, content validity).¹⁴ If the PRO measure will be used in multinational trials, it is important to confirm that the instrument is culturally adapted and adequately translated for all study populations in which it is intended to be used.

A measure of pain intensity that is increasingly used and is consistent with PRO Guidance principles is a single item that asks patients to self-report their worst pain or average pain intensity over the prior 24-hour period using a numerical rating scale (NRS) ranging from 0 to 10, with 0

TABLE 1. Study Design Challenges and Corresponding Strategies Consistent With PRO Guidance

Study Design Challenges	Strategies Consistent With PRO Guidance
Measurement of pain intensity and analgesic use	• Pain intensity and analgesic use are assessed via PRO measures. • PRO measures are developed and implemented using methods described by the US FDA.
Enrollment eligibility determination	• Study enrollment criteria include patients with clinically significant pain attributed to cancer at baseline. • Patients with clinically significant levels of pain are receiving optimized treatment for baseline pain with analgesics.
Data collection methods	• Assessments of pain intensity and analgesic use at prespecified time points are used. • The timing and frequency of pain assessments are appropriate to the target population, product, and indication. • Electronic administration of patient-reported measures allows for time-/date-stamping of responses, real-time monitoring of compliance, and automated reminders.
Responder definitions	• The definition of a pain palliation responder considers both changes in pain scores and analgesic use. • Evidence to support a clinically significant improvement in the pain intensity score for the target population is used to justify the responder definition. • A time point for the primary pain palliation analysis is selected based on characteristics of the target population and projected efficacy of the product. • Confirmation and durability of response, as measured by consecutive time points with sustained pain response, is included in the responder definition. • Continuous distribution of response displays are used to describe the full spectrum of pain responses at the time point(s) of interest. • A prespecified method is used to tabulate total analgesic use for each patient at each time point of interest. • A systematic method is used to determine whether overall analgesic use has increased, decreased, or remained stable at each time point of interest. • Antitumor responses are measured. • Additional patient-reported measures are considered, such as impact of pain on activities of daily living and other disease-specific symptoms.
Missing data	• Plans to minimize and handle missing data are included in the protocol.
Blinding	• Efforts are made to retain blinding whenever possible. • If blinding is challenging or not feasible, methods may be used to attempt to limit the impact of bias on the interpretability of results such as requiring a large effect size.

Abbreviations: PRO, patient-reported outcome; US FDA, US Food and Drug Administration.

representing “no pain,” and 10 representing “pain as bad as you can imagine” (11-point NRS item).¹⁵⁻¹⁹

In this article, we focus on products indicated for the treatment of cancer (rather than analgesic drugs, which treat pain in general). Therefore, in addition to adequately measuring pain, it is equally important to adequately track analgesic use to ensure that the pain palliation observed is not the result of an increase in analgesic use but rather the effect of the antitumor treatment being studied. A content-valid analgesic log that is understandable to patients and can be completed by them using a similar schedule and recall period as that used for the evaluation of pain intensity (eg, within the past 24 hours) should be used. Patient-reported data can be supplemented with a medication log that is completed or verified by staff at visits.

Enrollment eligibility criteria

To significantly assess pain palliation in a given clinical trial, the eligible population should include patients experiencing pain that is attributable to cancer at baseline. This may mean that not all patients with a certain tumor type are eligible for enrollment. In addition, ideally, an optimized analgesic regimen should be confirmed before baseline pain scoring for trial entry.

In determining eligibility criteria, it is advantageous to have previously identified a minimum baseline pain intensity score is that is “clinically meaningful” to the target population²⁰⁻²² and which, when reduced by treatment, is perceived by patients to represent a significant improvement.²³⁻²⁶ The protocols reviewed commonly enrolled patients with relatively stable baseline pain who had baseline weekly average “worst pain in past 24 hours” scores of ≥ 3 or ≥ 4 on an 11-point NRS. However, because the threshold of pain intensity used for a patient eligibility criterion is specific to the study design and objectives, higher or lower pain intensity score averages may be appropriate.

A systematic approach to determining whether overall analgesic use is stable, increased, or decreased at follow-up compared with baseline is desirable. An approach used is to provide each patient with their own individual analgesic regimen that typically includes a chronic long-acting narcotic analgesic and a short-acting rescue narcotic analgesic. Using this approach, although different patients in a study population may use different narcotic agents from each other, any given patient should ideally continue using the same long-acting narcotic drug and the same rescue drug product throughout the trial (ie, not switch to different narcotic agents).

In the clinical trials reviewed, a 7-day run-in period (before randomization and treatment) is commonly included to assess baseline pain intensity and analgesic use. Using this approach, randomization is then predicated on the requirement that each patient report on at least a pre-specified minimum number of days (eg, ≥ 4 of 7 days). The average of these daily scores is tabulated to determine a baseline mean pain score value for analysis, an approach intended to minimize reliance on a single day's experience. The run-in period may need to be repeated for patients who require an adjustment in their analgesic dose, such as those with poorly controlled pain (eg, mean scores exceed a predetermined maximum level) before randomization.

Mode of data collection

The choice of data collection mode for pain intensity or analgesic use include paper, Internet Web site, hand-held device, interactive voice response system, or one administered by the interviewer.²⁷⁻³⁰ There are several favorable characteristics associated with the electronic administration of patient-reported measures, including the capacity for time-stamping/date-stamping of responses, real-time monitoring of compliance, and automated reminders. In keeping with PRO Guidance principles, measurement properties of PRO instruments are specific to the mode of administration.³¹

To optimally represent patients' experiences at a given time point of interest during a trial, pain and analgesic assessments have been measured over several consecutive days (eg, daily over a 7-day period). Averages during the period of reporting are calculated. Patient reports are ideally obtained during the same predetermined time period each day. A minimum number of completed daily reports at each reporting time point has been required in protocols for a patient to be considered evaluable (eg, ≥ 4 of 7 days). If fewer than the minimum number of reports are available at the planned time point for assessment, this would constitute missing data and would be recorded as a nonresponse or failure of pain control.

The frequency and timing of pain intensity and analgesic use assessments are generally determined by characteristics of the target patient population, the expected onset of treatment effect, and indication. Whenever possible, the timing of pain assessments is coordinated with scheduled follow-up clinic visits or treatments (eg, daily during the week before a visit). Pain intensity and analgesic use assessments are continued throughout study participation to evaluate the duration of response. When patients withdraw from a study, pain intensity and analgesic use assessments are conducted (and assessments may be continued for longer if a time-to-event analysis is planned).

Responder definitions

The definition of a pain palliation responder is generally based on 3 related components: 1) reduction in pain intensity; 2) stability or reduction in analgesic use; and 3) durability of the improvement. Pain intensity and analgesic use are assessed at baseline and at each preselected follow-up time point to calculate the percentage of patients in each arm meeting the responder definition.

Selection of primary follow-up time point and assurance of response durability

Although pain and analgesic measurements are usually obtained at multiple time points during a trial, the protocol should specify and justify the selection of the time point(s) when the primary analysis will be conducted (ie, the time when efficacy is observed). This time interval may be related to the anticipated duration of the antitumor activity of the treatment and is sufficient in duration to be clinically significant. Thus, in addition to an initial time point at which the response criteria are first fulfilled, the definition of a responder generally includes at least 1 additional assessment time point to confirm that response and provide evidence of its durability.

Pain intensity component

In keeping with PRO Guidance principles, the definition of a pain intensity response should represent a clinically significant improvement in pain for the target population.²³⁻²⁶ Ideally, this definition is justified before commencing with pivotal studies, usually through dedicated research in the target population to establish definitions of significant response. In analgesic trials, a 30% decrease from the baseline pain intensity score on a single-question NRS has been reported as being clinically significant to patients, although to the best of our knowledge such evaluations in cancer-specific populations are limited.^{23,24} It is important to consider that the percentage change from baseline in pain intensity that might be considered a clinically significant response will vary according to the absolute pain scores at baseline. For example, a 50% reduction in mean change from baseline may be considered relatively modest in terms of absolute magnitude if the mean baseline scores are low.

Analgesic use component

As noted above, analgesic use, both narcotic and nonnarcotic, has been captured using an analgesic patient log that can be supplemented with staff verification or a staff medication log. One method used involves fixing the dose of all but a single rescue analgesic for each patient to limit the number of medications to tabulate. This approach can help to simplify the analysis regarding whether narcotic

		ANALGESIC USE		
		Decrease	Stable	Increase
PAIN	Decrease	Responder	Responder	Non-responder
	Stable	Non-responder	Non-responder	Non-responder
	Increase	Non-responder	Non-responder	Non-responder

Figure 1. Potential approach to defining responders in cancer pain palliation evaluations based on changes in pain intensity and narcotic analgesic use over time is shown.

analgesic use is stable, increased, or decreased at follow-up compared with baseline.

Overall pain palliation responder definition

Figure 1 shows a model for defining pain palliation responders and nonresponders to treatment. Pain palliation for an anticancer product is based on improvement in pain intensity attributed to antitumor treatment over time. An evaluation of change in analgesic use is used to ensure that the observed pain palliation was not due to increased analgesic use. In this model, patients are only considered responders if they experience a clinically significant decrease in pain intensity compared with baseline at the primary analysis time point, and overall analgesic use is either decreased or stable compared with baseline. If pain remains stable from baseline and analgesic use is decreased from baseline, patients are not considered to be responders because the observed treatment effect does not define a clear benefit in pain reduction for the patient (eg, the patient's measured pain is not improved). Patients whose pain is increased or stable are considered to be nonresponders. The primary pain palliation analysis should report the percentage of patients in each study arm meeting responder criteria. Evaluation of pain progression as a clinical trial endpoint is beyond the scope of this discussion.

Cumulative distribution of response

Although the definition of a primary pain responder is based on a preselected percent improvement in the pain score from baseline, it is desirable to understand the full spectrum of pain response in each treatment arm through the display of the cumulative distribution of scores.³² At a given time point, a cumulative distribution curve can show the percentage of patients in each arm along the range of possible

improvements and decrements of scores as defined by the outcome variable. For example, changes in pain scores from baseline to the time of the primary analysis can be displayed. A variable can also be defined that integrates analgesic use into the score. Generally, there should be agreement between responder analyses and changes in mean scores.

Support of pain endpoint with other measures

A measurable benefit in a given population in terms of both pain response and cancer-related (antitumor) outcomes provides assurance that changes in pain are related to antitumor effects rather than an action that is independent of antitumor activity. Pain-reducing treatments that act in the absence of an observed antitumor effect in the study population would be assessed as analgesics as opposed to cancer treatments. Supporting evidence of an antitumor effect is particularly useful in trials in which blinding is difficult or not feasible. Evidence of improvements in patient-reported sequelae of significant pain (eg, activities of daily living and sleep) and improvements in other disease-specific symptoms may also provide supporting evidence of treatment benefit.^{33,34}

Handling of missing data

Missing data can lead to uninterpretable study results. Careful consideration of study design characteristics and methods of data analysis is critical in eliminating unnecessary missing data in clinical studies.³⁵ An approach using the last observation carried forward alone is generally not adequate for overcoming problems with missing data when assessing pain palliation. Patients for whom there are insufficient data available at an assessment time must be considered nonresponders and it is inappropriate to simply exclude them from the analysis. In recent trials, methods to minimize missing data have included education and reminders to participants and staff. The use of electronic or telephone monitoring to capture PRO measures may offer the additional benefit of automatic reminders and minimization of missing data in real time. A methodology for handling and minimizing missing data should be included in a protocol's design and implementation. Every effort should be made to collect complete information from all study participants.

Blinding

Patients or investigators who know which treatment is received may overestimate or underestimate benefit. In unblinded studies, it may not be clear whether the observed results of patient-reported assessments are attributable to treatment effect or to biased reporting. In blinded controlled trials, inadvertent unblinding, in which the assigned

treatment group is deduced by the investigator and/or patient, can raise similar questions of interpretability. Inadvertent unblinding may particularly occur in oncology trials, in which readily apparent toxicities are associated with treatments (eg, rash). Efforts should be made in controlled trials that include PROs to retain blinding whenever possible. Research is needed in this area to assess the extent of the impact of unblinding on PROs.

DISCUSSION

This article describes some of the challenges faced by drug developers when designing pain palliation clinical trials in the oncology setting, as well as strategies used in recent applications that are consistent with PRO Guidance principles. Measuring treatment benefit via PRO measures merits attention to guidance principles that are intended to generate a better understanding of how patients feel and function as related to their disease and treatment. Drug approval and labeling claims can be based on improvements in how patients feel or function if the outcomes, endpoint model, and analysis plan are clearly described a priori in the protocol with adequate statistical power, and if study results demonstrate statistically and clinically convincing findings.

Sponsors are encouraged to discuss the development and planned measurement of PROs with the FDA early and throughout product development. If a PRO measure is planned for use in a pivotal trial and information concerning the measure's properties in the target population are already known, then discussion at the end of phase 2 may be appropriate. However, if there is limited information regarding the use of the measure in the target population, then an earlier discussion with the FDA should be planned to allow time for instrument development and/or evaluation before phase 3.

Methods described in this article are provided as examples and are not regarded as the exclusive means of assessing pain palliation in oncology clinical trials. Approaches may evolve over time as the science of pain assessment in clinical trials advances. This article focuses exclusively on pain palliation. Pain progression is a related endpoint that has been used in past applications, but has distinct methodological and logistic challenges that are beyond the scope of this work.

In conclusion, as a measure of treatment benefit, pain palliation can serve as the basis for drug approval and labeling claims.^{7,8} As the population of cancer patients and survivors grows, it is increasingly important to be able to adequately measure patients' symptom experiences and functioning in clinical trials. The rigorous development

and inclusion of patient-reported assessments in clinical research can enhance our understanding of treatment benefit and lead to improved therapies.

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CONFLICT OF INTEREST DISCLOSURES

Subsequent to the completion of this work and his Guest Worker position at the US Food and Drug Administration, Dr. Basch has provided uncompensated input regarding analysis and publication of patient-reported outcome assessments for Exelixis and Janssen, and served as the uncompensated study chair for a prostate cancer pain trial by Exelixis. Dr. Basch's research is supported by grants from the National Cancer Institute and the Department of Defense (grant W81XWH-11-1-0639). This work does not represent the views or opinions of the Department of Defense.

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ABSTRACT 1

Mode equivalence of Interactive Voice Response (IVR) and paper versions of the Brief Pain Inventory (BPI) “worst pain” item in metastatic resistant prostate cancer (MCRPC) evaluated conceptually using qualitative methods

Bennett AV, Eremenco S, Heon N, Scheffold C, Schimmoller F, Weitzman AL, Basch E.

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OBJECTIVES: The BPI “pain at its worst in the last 24 hours” item is often administered as a primary or key secondary endpoint in clinical trials using an IVR daily diary. However, evidence of equivalence between the validated paper version and IVR has not been published. This study evaluated conceptual equivalence between IVR and paper version of this item using qualitative methods.

METHODS: Twenty-six patients with mCRPC in a non-randomized expansion cohort (N=144) of phase 2 study XL184-203 were interviewed to confirm their comprehension of the BPI “worst pain” item administered using an IVR simulation by the interviewer and presented on paper. Patient interpretation of the item’s meaning in both modes was elicited and compared to identify similarities between the modes. Patients were also interviewed regarding the usability of IVR during the trial.

RESULTS: Patients (median age = 68; range 44-81) had ECOG performance status of 0 (38%) and 1 (62%). Nearly all patients answered the IVR version of the question as intended – by considering the past 24 hours (72%; 18% did not specify); including non-cancer related pain (96%); and reporting pain experienced with analgesia (100%). Patients did not interpret the paper version of the pain question differently from the IVR version; 4 patients spontaneously stated that the paper version was the same as the IVR version they had used. All patients reported that the IVR was easy to use to answer the diary.

CONCLUSIONS: This study provides important qualitative support of conceptual equivalence between an IVR and paper version of the BPI “worst pain” item. These results confirm that this item is well understood by patients, and that they interpret the question similarly whether administered via IVR or on paper. The results also show good usability and acceptability of IVR administration of this important item in clinical trials.

ABSTRACT 2

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

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BACKGROUND: Pain is common in men with mCRPC and can substantially impair function and quality of life. For assessment of pain as a clinical trial endpoint, substantial validation work has been conducted on the BPI “pain at its worst in the last 24 hours” item, but additional qualitative study of patient understanding of this item is necessary to fully meet FDA labeling standards.

METHODS: Twenty-six patients with mCRPC in a non-randomized expansion cohort (N=144) of phase II study XL184-203 were interviewed to confirm their comprehension of the BPI “pain at its worst in the last 24 hours” item, and elicit their interpretation of points on the 0-10 response scale to establish levels of intra-patient pain rating consistency. Patient descriptions were evaluated and further compared with previously identified associations between pain severity and pain interference ratings.

RESULTS: Patients (median age = 68; range 44-81) had ECOG performance status of 0 (38%) and 1 (62%). Nearly all patients answered the question as intended – by considering the past 24 hours (72%; 18% did not specify); including non-cancer related pain (96%); and reporting pain experienced with analgesia (100%). Patients described pain of “2” as relatively mild, noticeable, and not limiting; pain of “5” as moderate and limiting activity; and pain of “8” as severe and more or less incapacitating. Interpretation of the response scale was highly consistent both among patients and in comparison to levels of pain severity and interference identified in previous large statistical analyses.

CONCLUSIONS: This study provides important qualitative support for the use of the BPI “pain at its worst in the last 24 hours” item to assess pain per FDA labeling standards in men with mCRPC. Consistent with prior qualitative work, these results confirm this item is well understood by patients. The interpretation of the response scale is remarkably consistent among patients, as well as with results from large statistical analyses, demonstrating the reliability of this item to assess patient-reported pain in cancer trials.