Prevalence of Pain and Analgesic Use in Men With Metastatic Prostate Cancer Using a Patient-Reported Outcome Measure

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Abstract

Purpose: Contemporary tumor-directed therapies for metastatic castration-resistant prostate cancer (mCRPC) are approved to prolong life, but their effects on symptoms such as pain are less well understood as a result of the lack of analytically valid assessments of pain prevalence and severity, clinically meaningful definitions of therapeutic benefit, and methodologic standards of trial conduct. This study establishes pain characteristics in the mCRPC population using a PRO measure.

Materials and Methods: Patients with prostate cancer participated in an anonymous survey at five US comprehensive cancer centers in the Prostate Cancer Clinical Trials Consortium that incorporated the Brief Pain Inventory (BPI), analgesic use, and interference with daily activities. Prevalence and severity of cancer-related pain and analgesic use were tabulated according to castration-resistant status and exposure to docetaxel chemotherapy.

Results: Four hundred sixty-one patients with prostate cancer participated, of whom 147 had mCRPC involving bone (61% [89 of 147] docetaxel exposed, 39% [58 of 147] docetaxel naive). Pain of any level was more common among docetaxel-exposed versus docetaxel-naive patients with mCRPC (70% [62 of 89] v 38% [22 of 58], respectively; $P < .001$). BPI score ≥ 4 was reported by 38% (34 of 89) of docetaxel-pretreated and 24% (14 of 58) of docetaxel-naive patients with mCRPC; 40% of these patients with pain intensity ≥ 4 reported no current narcotic analgesic.

Conclusion: Pain prevalence and severity were higher in patients with prior docetaxel exposure. Analgesics were underutilized. These results provide a method for estimating accruals along the disease continuum, and for enabling design of trials appropriately powered to assess pain.

Introduction

Pain is one of the most feared complications of cancer, as it can produce debilitating symptoms that significantly impair function and quality of life.¹ Patients with pain at baseline have shorter survival times than those without baseline pain.^{2,3} Agents that control, relieve, or eliminate pain represent a direct clinical benefit that can lead to regulatory approvals. Historically, only one tumor-directed systemic therapy, mitoxantrone plus prednisone, and two bone-directed radiopharmaceuticals have held formal pain relief indications in prostate cancer, and these were achieved more than 15 years ago.⁴⁻⁷ All other agents have been approved for the delay or prevention of skeletal-related events, which in most trials occur infrequently, or prolongation of life. Indeed, the four tumor-directed, one radiopharmaceutical, and one immunologic agent approved for metastatic castration-resistant prostate cancer (mCRPC) in the past decade have all been approved on the basis of prolonging survival,^{8-12,12a} and although some of these trials reported on pain relief, none were conducted in a manner that would enable formal labeling for this indication.

There are multiple reasons for this, but the underlying theme is that the assessment of pain had not been approached in the same systematic manner as molecular or other biomarkers. To establish the presence of pain, pain severity, and pain relief, consideration must be given to the specific patient population, using instruments with defined psychometric properties. The assessment of pain in particular is optimally reported directly by the patient as a patient-reported outcome (PRO). Barriers to patients under-reporting their own pain do exist (eg, as a result of concern about adverse effects of narcotics and/or misconceptions about addiction)¹³; however, the literature suggests that clinicians often under-report patients' pain intensity in comparison to the patients' own report of their pain. Therefore, an unfiltered representation of the patient's experience, as measured using a PRO, is preferred.^{14,15}

Some of the challenges that have contributed to the absence of US drug labeling for pain palliation in cancer therapies include ill-defined patient cohorts, strict eligibility requirements, unclear measurement properties of selected instruments, questions about what score changes constitute a clinically meaningful benefit, missing data and inadequate patient compliance

with reporting, expense, and limited a priori specification of PRO analytic plans in protocols without allocation of statistical power for PRO end points.¹⁶⁻¹⁸ Failure to engage regulatory agencies in the planning stages of trial development and limited involvement of PRO experts in trial design have also impeded the systematic development and validation of PRO end point models.¹⁵

The field, however, has evolved. In 2009, the US Food and Drug Administration (FDA) released a Guidance for Industry on the development and incorporation of PRO measures that addressed product approval and labeling.¹⁷ The following year, the FDA put forth a guidance on biomarker qualification that included a pathway for qualifying PRO measures for use in the regulatory context.¹⁹ The approach to using PRO measures emulates that for other molecular biomarkers, and statistical power to detect meaningful therapeutic differences must be preserved if the agent intends to seek a pain palliation claim.

Recently, ruxolitinib, a JAK2 inhibitor, received FDA approval in intermediate-risk and high-risk myelofibrosis using novel clinical trial end points: a reduction in spleen size and a 50% or greater improvement in total symptom score that included pain based on patient reporting.²⁰⁻²² The combination of a biologic end point and an end point with direct patient-reported benefit represents a milestone in contemporary drug development in oncology and establishes the feasibility of a regulatory strategy based on demonstrating symptom benefits. The approval of ruxolitinib also underlines the importance of evaluating the patients' symptom responses early in the drug development process and of careful attention to trial methodology.

Similar principles are directly applicable to the study of pain in prostate cancer. mCRPC has a distinct predilection for bone, which can result in skeletal complications such as fracture, bone pain, and epidural disease. The prevalence of baseline pain attributed to mCRPC, as reported in regulatory phase III therapeutic trials over the past decade, has ranged from 2% to 46% (Figure 1).^{9-12,12a,23-27} The measurements of pain and the definitions used varied widely, limiting the ability to draw comparisons between studies. This is partly because the development of pain as a biomarker in mCRPC was immature. In the process of clinical validation of a biomarker, it is essential to first determine the prevalence, severity, and duration of symptoms of interest in the target population. In the aforementioned trials, consistently 90% of patients had good performance status, defined as Eastern Cooperative Oncology Group scores of 0 to 1, suggestive of a highly selected population.^{9,10,23,24} The patients with worse performance status, who were not selected for trial participation, may also have had higher pain prevalence and pain severity. Currently, the prevalence and severity of pain in unselected outpatients with metastatic prostate cancer, stratified by chemotherapy exposure, is not well established. Once this information is determined, investigators can not only establish if an unmet need exists, but can predict rates of accrual and create an effective trial design.

Materials and Methods

Questionnaire

An anonymous patient survey was developed that included the Brief Pain Inventory (BPI) and questions about diagnosis, treatment, analgesic use, and demographic information (Data Supplement). The BPI, a validated pain instrument commonly used in oncology, measures pain with a 0 to 10 numeric rating scale ("11-point NRS") in which 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine."²⁸ The survey included versions of the BPI using recall periods of both 24 hours and 7 days.²⁹ It also measured pain-related interference with work, sleep, or enjoyment of life using an 11-point NRS. Patients were also asked to rate their worst pain during the previous 24 hours using a verbal analog scale. Before the survey, 20 patient interviews were conducted to refine and ensure comprehension of the questions about diagnosis, treatment, and analgesic use. The final survey included 44 questions in English and took approximately 15 minutes to complete.

Research Approval and Sample Size

The survey was approved by the Prostate Cancer Clinical Trials Consortium and the institutional review boards of participating institutions, which granted waivers for anonymous administration of the survey. The five participating institutions were Memorial Sloan-Kettering Cancer Center, Duke University Cancer Institute, Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, M.D. Anderson Cancer Center, and Oregon Health & Science University Knight Cancer Institute.

Patient Recruitment

Patients were approached by research study assistants in outpatient prostate cancer clinics at each institution. After verification that each patient was diagnosed with prostate cancer and had not previously completed the survey, the patient was invited to complete a numbered survey.

Data Analysis

All data entry was performed at Memorial Sloan-Kettering Cancer Center. Audits were conducted on 20% of surveys to ensure accuracy of data transcription. The prevalence of cancer-related pain among subgroups with disease metastatic to bone, classified by castration-resistant state, and prior or current docetaxel use was tabulated. "Worst" pain scores (as compared with "average" or "least") were reported.²⁹

The difference in pain prevalence among patients who were docetaxel exposed versus those who were docetaxel naive was evaluated by Fisher's exact test. The equality of distribution of scores for worst pain in the past 7 days and in the past 24 hours was estimated for these two groups via Wilcoxon rank sum test.

The 11-point NRS for the BPI was mapped to five verbal descriptors (none, mild, moderate, severe, disabling). Kendall's tau correlation coefficient was calculated to assess the performance of three mapping approaches between the 11-point scale and the verbal descriptor scale.

Figure 1. Baseline pain observed for varying clinical states of prostate cancer in this and other trials. Registration trials have reported varying results in metastatic castration-resistant prostate cancer using different instruments of pain assessment,^{c-e} highlighting the need for an analytically validated biomarker in this disease. Results from this study, using the worst pain item from the Brief Pain Inventory, with two recall periods (24 hours and 7 days) are provided for comparison. ALSYMPCA, A Phase III Study of Radium-223 Dichloride in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases; PSA, prostate-specific antigen; SWOG, Southwest Oncology Group. ^aBrief Pain Inventory, worst pain item ≥ 4 , in past 24 hours; ^bBrief Pain Inventory, worst pain item ≥ 4 , in past 7 days; ^cMcGill Pain Questionnaire, Present Pain Intensity score ≥ 2 on 1 to 5 scale²⁵; ^dClinician-reported bone pain grade ≥ 2 on 1 to 4 scale in Common Terminology Criteria for Adverse Events; ^eWHO ladder cancer pain index ≥ 2 (pain required for trial eligibility).^{12a} Adapted from Scher & Heller, *Urology* 55:323-327, 2000.

Results

Study Population

Between August and December 2008, 507 men with different prostate cancer disease states, who were being followed in outpatient clinics of participating centers, were invited to complete the survey. Six percent (31 of 507) declined, and 3% (15 of 507) did not return the survey, thus 461 men participated. As seen in Table 1, 250 respondents (54%) reported metastatic disease.

Appendix Figure A1 (online only) provides the algorithm used to derive the subset of castration-resistant patients with bone metastases who experienced pain. Among 250 patients with prostate cancer metastatic to any site, 178 (71%) reported bone metastases, of whom 147 (83%) had castration-resistant disease. Of these 147 patients, 89 (61%) noted past or current use of docetaxel, and 58 (39%) were docetaxel naive.

Comparing Docetaxel-Exposed and Docetaxel-Naïve Patients

Overall, of the 89 docetaxel-exposed patients, 59 (66%) reported a "worst pain intensity" score ≥ 1 in the previous 7 days; of these, 34 (58%) reported pain ≥ 4 (a cutoff score frequently used to determine eligibility for pain palliation analyses). Thus, 38% (34 of 89) of men with mCRPC and previous or current use of docetaxel experienced pain ≥ 4 in the past 7 days, and would hence be eligible for a dedicated pain palliation trial on

the basis of this eligibility criterion. If pain over the past 24 hours were to determine eligibility, 55 of 89 (62%) docetaxel-exposed men with CRPC metastatic to bone reported pain ≥ 1 , of whom 26 (47%) reported pain ≥ 4 . Thus, 29% (26 of 89) of docetaxel-exposed patients with mCRPC had pain ≥ 4 in the past 24 hours.

Fifty-eight respondents with bone metastases and castration-resistant disease were docetaxel naive. Twenty-two (38%) of these reported any pain in the past 7 days, of whom 14 (64%) reported pain ≥ 4 . Thus, 24% (14 of 58) of docetaxel-naïve patients had pain ≥ 4 in the past 7 days. When focusing on pain in the past 24 hours, 19 of 58 (33%) reported any pain, of whom seven (37%) reported pain ≥ 4 . Thus, 12% (seven of 58) of docetaxel-naïve patients had pain ≥ 4 in the past 24 hours. The proportion of patients with CRPC with bone metastases who reported any pain in the past 7 days was significantly larger in the group with prior docetaxel use compared with those who were docetaxel naive (66% v 38%; $P < .001$). Thirty-one respondents with bone metastases had castration-sensitive disease. In this group, 12 (39%) reported any pain in the past 7 days (eight with BPI ≥ 4), and eight (26%) reported any pain in the past 24 hours (five with BPI ≥ 4).

The cumulative distribution of pain scores over the past 7 days for docetaxel-exposed versus docetaxel-naïve patients with CRPC metastatic to bone did not differ ($P = .60$) and showed a relatively uniform distribution across different pain score lev-

Table 1. Patient Characteristics

Characteristic	Total Patients (N = 461)		Patients With mCRPC (n = 147)	
	No.	%	No.	%
Age, years				
Mean	68		67	
SD	9.6		9.3	
39-49	10	2	3	2
50-59	73	16	29	20
60-69	180	39	53	36
≥ 70 *	196	43	62	42
Not reported	2	2	0	0
Cancer location				
Localized	211	46	0	0
Metastases (any site)	250	54	147	100
Bone metastases	178	39	147	100
Castration resistant	147	32	147	100
Non-castration resistant	31	7	0	0
Treatment history				
Androgen deprivation therapy				
Past or current	354	77	147	100
Never	107	23	0	0
Antiandrogen				
Past or current	256	56	124	84
Never	205	44	23	16
Docetaxel				
Past or current	120	26	89	61
Never	341	74	58	39
Clinical trial				
Past or current	162	35	90	61
Never	299	65	57	39
Study site/clinic				
Memorial Sloan-Kettering	170	37	49	33
Duke	70	15	33	24
Johns Hopkins University	50	11	14	10
M.D. Anderson	35	8	14	10
Oregon Health & Science	136	29	37	25
Education level				
Some high school or less	21	5	2	1
High school graduate or GED	55	12	16	11
Vocational college or some college	79	17	24	16
College degree	120	26	47	32
Professional or graduate degree	185	40	57	38
Not reported	1	1	1	1
Computer at home	392	85	130	88
E-mail user	349	76	121	82

Abbreviations: GED, general equivalency diploma; SD standard deviation.

* Patients age ≥ 90 (n = 6) included in mean (SD) as age 90; exact age of patients ≥ 90 not recorded in order to protect patient privacy.

els (Appendix Figure A2, online only). The distribution of pain scores over the past 24 hours between these groups also did not differ ($P = .87$; Table 2). This implies that although a larger proportion of docetaxel-exposed than docetaxel-naïve men experience pain (66% v 38%), among those with pain, the distributions are similar.

Interference Scores

Interference with work, sleep, or enjoyment of life as a result of pain was measured. For docetaxel-exposed patients with CRPC metastatic to bone who experienced pain in the past 7 days, 53 of 59 (90%) noted interference of any level with at least one of these activities that was attributable to pain, and 14 of 59 (24%) experienced “severe” interference (defined as score ≥ 7 on a 0-10 NRS). For docetaxel-naïve patients with CRPC metastatic to bone with pain in the past 7 days, 21 of 22 (95%) noted interference, and 7 of 22 (32%) experienced “severe” interference.

Analgesic Use

Analgesic use was tabulated for the subset of patients with CRPC metastatic to bone who ever experienced pain attributed to prostate cancer (n = 84). Among these patients, 42 (50%) were using a narcotic analgesic, with 30 (36%) taking a rescue (short-acting) narcotic only and 12 (14%) taking a long-acting narcotic either alone or with a rescue agent. Twenty (24%) used non-narcotics only, whereas 22 (26%) reported no analgesic use. Appendix Table A1 (online only) reports analgesic use by level of pain experienced by patients over the past 7 days. Among the 48 patients with mCRPC with pain levels ≥ 4, 10 (21%) reported no analgesic whatsoever, nine (19%) reported only the use of a nonsteroidal anti-inflammatory drug or neuroleptic (no opioid), and 29 (60%) were receiving short-acting and/or long-acting narcotics.

Mapping Pain Intensity on a 0 to 10 NRS to a Verbal Descriptor Scale

As seen in Appendix Table A2 (online only), pain intensity scores were mapped via different response options approaches: a 0-10 NRS compared with a five-option verbal descriptor scale (none, mild, moderate, severe, disabling). The highest correlation was found for a mapping of mild pain to an NRS score range of 1 to 4; moderate pain to 5-6; severe pain to 7-8; and disabling pain to 9-10 (Kendall's tau = 0.757; $P < .001$), although correlations were similar for other mapping approaches in which thresholds were shifted by one point on the NRS.

Discussion

Pain is commonly present, commonly undertreated, and often severe in men with metastatic prostate cancer. Although metastatic disease is incurable, drug development and clinical trials have focused more on establishing longevity and less on the direct improvement in patients' symptoms or health-related quality of life as the yardstick for success and regulatory approval.

Table 2. Distribution of Self-Reported Pain Level Among Men With Prostate Cancer Metastatic to Bone Who Had Ever Experienced Prostate Cancer–Related Pain

Pain Level	n	Mean*	SD	Median	IQR	Range
Worst pain in past 7 days (n = 96)						
Castration-resistant disease	84	4.4	2.5	4	2-7	0-10
Prior or current docetaxel	62	4.4	2.6	4	2-7	0-10
No prior or current docetaxel	22	4.6	2.2	5	2-7	2-8
Non-castration-resistant disease	12	4.8	2.8	4.5	2.5-7	1-10
Worst pain in past 24 hours among patients with any pain in past 7 days (n = 93)†						
Castration-resistant disease	77	3.9	2.7	3	2-7	0-10
Prior or current docetaxel	58‡	4.0	2.8	3	2-7	0-10
No prior or current docetaxel	19§	3.8	2.5	3	2-7	1-8
Non-castration-resistant disease	11	3.6	3.0	3	0-7	0-7

Abbreviation: IQR, interquartile range.

* For worst pain in past 7 days and worst pain in past 24 hours, the distribution of scores do not differ between patients with castration-resistant and non-castration-resistant disease or between patients with and without prior docetaxel (range of *P* values: 0.60-0.87).

† This excluded three patients who reported zero pain for the past 7 days.

‡ Missing data for one patient.

§ Missing data for three patients.

|| Three patients reported no pain in the previous 24 hours.

als.^{30,31} By contrast, the first priority for a patient with debilitating symptoms is the relief of those symptoms,³² valuing symptom control and quality of life in the short term over extension of survival.^{33,34} Treatments directed specifically at the tumor may serve both therapeutic objectives, based on the assumption that effectively treating cancer will have secondary benefit in symptom palliation. Cancer-related pain must also be distinguished from noncancer pain such as arthralgias or neuropathy, as the former may be amenable to palliation with tumor-directed therapy, and the latter is generally not.

Clinical trials in mCRPC over the past decade have not assessed pain palliation in a manner that could support a label for this purpose, due in part to the complexities of PRO measures and shortcomings in trial design and biomarker development. Older trials of mitoxantrone and beta-emitting radiopharmaceuticals in mCRPC that led to regulatory approval on the basis of pain palliation would face substantial challenges today, in part because the limitations of PRO measures then in use were not as well appreciated, and because regulatory science has evolved. For instance, the Canadian randomized trial of mitoxantrone plus prednisone versus prednisone for palliative response was not blinded and used the McGill-Melzack Pain Questionnaire, in which response options, content, and construct validity are less clear.^{4,35} Cancer and Leukemia Group B trial 9182 evaluated the same combination for survival, also in an unblinded fashion, with underpowered secondary analyses assessing pain with another instrument (Symptom Distress Scale)⁵; 35% to 40% of patients were not receiving analgesics at baseline, and 35% did not complete follow-up quality-of-life assessments. Registration trials for beta-emitting radiopharmaceuticals were limited by mixed patient populations and mixed symptom assessment tools as well.⁶

Analyses in the current study were based on the worst pain item from the BPI, which is one of the most widely used vali-

dated pain measures in oncology.^{28,29,36} “Worst pain” in the past 24 hours has established analytic validation as a PRO, and the BPI instrument has well-defined psychometric properties such as high internal consistency and test-retest reliability.²⁹ Our results establish that an unmet need for pain palliation exists in mCRPC, that an analytically validated biomarker is in place, and that accrual to a dedicated pain trial for use in product approval and labeling appears feasible.

Regulatory authorities have emphasized the distinction between pre- and postchemotherapy populations in pivotal trials, and the results directly speak to the prevalence of pain in docetaxel-naïve versus docetaxel-exposed patients with mCRPC. Notably, the prevalence of pain was considerably higher in patients with prior or current docetaxel use than in docetaxel-naïve patients. Figure 1 illustrates these results in the context of other key regulatory trials that reported baseline pain, albeit with other instruments and methodologic limitations. Our finding that 29% of docetaxel-exposed patients had a BPI ≥ 4 in the past 24 hours is lower than what was reported in regulatory trials of cabazitaxel and abiraterone (45% to 46%), and similar to that reported for enzalutamide (28%).^{9,10,37} This survey was conducted before regulatory approval of abiraterone acetate for use in docetaxel-exposed patients, thus the distinction between patients pre- and postchemotherapy is relatively straightforward and may simply be a surrogate for more advanced disease. To enrich study samples to include patients who are more likely to have pain, patients with prior docetaxel use may be selected. The lower prevalence of pain in docetaxel-naïve patients does not preclude including such patients in pain trials, but fewer may be affected; future research is required to determine whether the time to onset of pain, for those who are pain-free, is comparably delayed versus a “time to pain progression” analysis.

This study used a cross-sectional design and thus did not assess for pain scores over time. Another limitation of this study

is that the anonymous approach did not allow for chart verification with clinician reports. This design was implemented to ensure wider representation and inclusion of patients who might have been reluctant to complete a survey otherwise. A multicenter longitudinal cohort study of patients with mCRPC is underway and is designed to address these limitations, capturing changes in pain scores over time in both asymptomatic and symptomatic patients, as well as other disease-related assessments (ClinicalTrials.gov Identifier: NCT01617174).

A striking finding of this study is the apparent underuse of analgesics, including narcotic analgesics, among the men with pain, consistent with other recent reports.³⁸ Forty percent of patients with mCRPC with a worst BPI pain score ≥ 4 (ie, “moderate pain”)³⁹ in the past 7 days reported no narcotic analgesic use. Among those with BPI scores ≥ 7 (ie, “severe” pain), only 27% (six of 22) reported use of a long-acting narcotic and 18% (four of 22) reported no analgesic whatsoever.

Of methodological interest in this study is the mapping of a measure of worst pain on the BPI NRS to a verbal descriptor scale with a high level of correlation. Regulatory agencies and methodologists have focused on numeric 0 to 10 scales,⁴⁰ but verbal descriptions may be equally valid biomarkers. It is also of interest that measures of interference with work, sleep, and enjoyment of life paralleled patients’ reports of pain intensity. Measurement of functional impairment provides additional evidence of clinical benefit in the regulatory context.

There is growing interest in developing standard methods for enhancing the patient centeredness of clinical research and for incorporating measurement of PROs.⁴¹ This study substantiates the importance and feasibility of pain as a PRO biomarker in metastatic prostate cancer clinical trials that will enhance our understanding of the impact of disease and potential treatment benefits.

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Authors’ Disclosures of Potential Conflicts of Interest

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Appendix

Table A1. Distribution of Pain Level (worst pain reported for the past 7 days) by Analgesic Use, for Men With Symptomatic Castration-Resistant Prostate Cancer Metastatic to Bone

Worst Pain in Past 7 Days	Long-Acting Narcotic	Rescue Narcotic Only	NSAIDs or Neuroleptic Agents	No Analgesic Use Reported	Total
0	0	0	0	3	3
1-3	3	10	11	9	33
4-6	3	11	6	6	26
7-8	4	9	3	3	19
9-10	2	0	0	1	3
Total	12	30	20	22	84

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

Table A2. Correlation of Mapping “Worst Pain in 24 Hours” Item With 0-10 Scale Onto a 0-4 Scale

Categorization of 0-10 Scale	Kendall's Tau Correlation	P
0, 1-4, 5-7, 8-9, 10	0.748	< .001
0, 1-4, 5-6, 7-8, 9-10	0.757	< .001
0, 1-3, 4-6, 7-8, 9-10	0.744	< .001

NOTE. In a measure validation study of the Brief Pain Inventory, optimal cutpoints formed three distinct levels of pain severity on a 0-10 numerical rating scale such that 1-4 = mild; 5-6 = moderate; 7-10 = severe.³⁹

Figure A1. Diagram of patient characteristics, focusing on pain among men with metastatic castration-resistant prostate cancer (mCRPC) with bone metastases. This depicts the prevalence and quantification of pain, using the “worst pain” item from the Brief Pain Inventory in the subgroup of patients with mCRPC separated by docetaxel exposure.

Figure A2. Cumulative distribution of "worst pain in past 7 days" reported by men with pain attributable to metastatic castration-resistant prostate cancer involving bone.