US Food and Drug Administration Pooled Analysis to Assess the Impact of Bone-Only Metastatic Breast Cancer on Clinical Trial Outcomes and Radiographic Assessments

Suparna B. Wedam, Julia A. Beaver, Laleh Amiri-Kordestani, Erik Bloomquist, Shenghui Tang, Kirsten B. Goldberg, Rajeshwari Sridhara, Amma Ibrahim, Geoffrey Kim, Paul Kluetz, Amy McKee, and Richard Pazdur

Author affiliations and support information (if applicable) appear at the end of this article.

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S.B.W., J.A.B., L.A.-K., and E.B. contributed equally to this work and are co-first authors.

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Corresponding author: Suparna B. Wedam, MD, CDER, Food and Drug Administration, Building 22, Room 2112, 10903 New Hampshire Ave, Silver Spring, MD 20993-0004; e-mail: suparna.wedam@fda.hhs.gov.

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ABSTRACT

Purpose

The outcome and proportion of patients with bone-only (BO) metastatic breast cancer (MBC) has not been well described. We sought to describe the differential outcomes of patients with BO MBC in clinical trials and explore whether there was a discrepancy in radiographic reads between investigator and blinded independent central review.

Methods

We pooled and analyzed data on 10,521 patients from 13 prospective trials submitted for MBC treatment in initial or supplemental New Drug or Biologics License Applications from 2005. Three subsets were evaluated: BO, bone with other metastases (BWO), and no bone metastases (NBM). Early discordance rate and late discordance rate were calculated from 3,733 and 2,813 patients subject to a blinded independent central review, respectively.

Results

Bone metastases were identified in 49% (range: 42% to 73%) of patients across trials. BO disease was present in 12.5% (range: 4% to 26%), dependent on subtype. Investigator-assessed progression-free survival (PFS) and overall survival (OS) for the pooled trials demonstrated improved outcomes for the BO subgroup compared with other subgroups (BO *v* BWO PFS hazard ratio [HR], 0.64; 95% CI, 0.591 to 0.696; BO *v* NBM PFS HR, 0.70; 95% CI, 0.65 to 0.76; BO *v* BWO OS HR, 0.56; 95% CI, 0.50 to 0.61; BO *v* NBM OS HR, 0.68; 95% CI, 0.61 to 0.76). The BO subgroup has a higher early discordance rate and lower late discordance rate than the BWO and NBM subgroups.

Conclusion

To our knowledge, this review is the largest analysis to date of the BO subgroup of MBC and suggests this subgroup may have a distinct natural history. There also seems to be a difference in how the local investigators assessed progression events in the BO subgroup when compared with the other two groups.

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INTRODUCTION

Bone metastases are common in metastatic breast cancer (MBC)¹ and can be a major cause for morbidity.^{2,3} However, bone-only (BO) MBC is not as common⁴ and consequently is often combined with non-BO disease in clinical trials or occasionally is considered a stratification variable. Previous studies have reported that BO MBC has a different natural history and a better prognosis than non-BO disease, occurring more commonly in hormone receptor (HR)-positive MBC.⁵⁻⁷ These studies, however, have only been with limited sample sizes. We sought to conduct

a more comprehensive approach for studying BO MBC.

Imaging of bone metastases is difficult and especially challenging in breast cancer, where both osteolytic and osteoblastic lesions may be present.⁸ This is particularly problematic when the only site of disease is bone with no other lesions to reliably follow and can result in patients without measurable disease being excluded from clinical trials. Various imaging modalities exist for the detection of bone metastases in MBC, yet most breast cancer guidelines and consensus recommendations do not specify which test should be preferentially used. Thus, clinical trials and clinical practice differ widely regarding the

imaging modality that is used. Assessing response to therapy in patients with BO MBC also poses a unique challenge, because increased sclerosis noted on certain imaging modalities (computed tomography scan, bone scan) or a flare on bone scan associated with treatment response may be mistaken as progression. In addition, no reliable criteria exist for evaluating responses in bone metastases. Response Evaluation Criteria in Solid Tumors (RECIST),⁹ the most widely used criteria for clinical trials, is inadequate for the assessment of bone metastases.

The US Food and Drug Administration (FDA) comprehensively reviews efficacy and safety for new or supplemental drug applications. Efficacy end points such as overall response rate and progression-free survival (PFS) require radiologic tumor assessments. Therefore, the FDA must be assured of the imaging modality and criteria for assessments used before making regulatory decisions on the basis of such efficacy end points. Difficulty in assessing bone metastases can result in discrepancies between investigator and blinded independent central review (BICR) assessment and potentially affect characterization of drug effect. To our knowledge, discrepancies between investigator and BICR assessment in BO disease have not been comprehensively investigated across several trials. Therefore, to further evaluate the BO subset, we conducted an analysis of trials submitted to the FDA since 2005 for MBC.

METHODS

Selection Criteria

We searched the FDA electronic database for MBC trials submitted as initial or supplemental New Drug or Biologics License Applications since 2005 (when electronic data sets were first submitted for review). Trials chosen were limited to randomized, active-controlled trials that had electronic data set submission.

Baseline lesion data were systematically analyzed from each trial (including both target and nontarget lesions). Each patient was then categorized into one of three groups on the basis of site of disease at entry onto the clinical trial: only bone lesions at baseline (BO), bone plus other lesions at baseline (BWO), or no bone metastases at baseline (NBM).

Outcome measures evaluated included: PFS by investigators, PFS by a BICR (where available), and overall survival (OS) data. When available, updates to the PFS or OS data were used for the analyses. Additional data were also collected on various subgroups, including postmenopausal status, HR status (estrogen and/or progesterone receptor), human epidermal growth factor receptor 2 (HER2) status, age, line of metastatic therapy (first line or beyond first line), and whether the patient was randomly assigned to the treatment or control arm.

Statistical Methods

The proportion of the three bone subgroups (BO, BWO, and NBM) in each trial was described with respect to breast cancer subtype (ie, HR positive, HER2 positive, triple negative) and other subgroups. In addition, the outcome measures across all trials were assessed using a frailty-based Cox proportional hazard survival model.¹⁰ Under this approach, each trial in the full analysis is allowed to vary with a γ -distributed frailty parameter, but relative measures such as the hazard ratio (HR) are still able to be estimated. This approach allowed for a comparison between the BO subgroup and the other two subgroups across the trials. To handle inherent differences in each study, a frailty parameter was introduced to allow for a random effect across trials.

The regression analyses only adjusted whether a patient was randomly assigned to the treatment arm in any particular trial. Additional covariates were also tested but did not remain part of the final results

presented. This was done primarily because most of the additional covariates except for age (ie, menopausal status, estrogen receptor status, HER2 status) were inclusion/exclusion criteria and were therefore confounded by frailty parameter used to allow for differences between studies.

Discordance between PFS assessed by local investigators and PFS assessed by BICR was assessed. Using previously described methods,¹¹ we estimated the early discordance rate (EDR) and late discordance rate (LDR) on 6,305 patients (nine trials) subject to a BICR. The EDR represents the proportion that the investigator calls a progression event earlier than the BICR as a proportion of the total number of investigator progression events. An event can be called earlier in two ways. One, the investigator can call an event as progression and the BICR says no progression. Or two, both the investigator and the BICR can determine progression, but the investigator's time is sooner than the BICR. Similarly, the LDR represents the proportion of times the investigator calls progression later than the BICR, in the subset of patients where the local investigator and BICR do not agree (agreement means the investigator and BICR agree on the timing and whether a progression event had occurred). We refer the reader to Amit et al¹¹ for the mathematical definitions of EDR and LDR. Overall discordance was also assessed and is defined as the percentage of patients for whom the local investigator and BICR disagreed divided by the total number of patients subject to a BICR. The overall discordance and the LDR differ in terms of the denominator used.

Whenever the EDR and LDR rates were estimated, we reported the effective sample size (ESS), which represents the denominator used in the EDR or LDR calculation. The statistical analyses were done in SAS (Version 9.3; SAS Institute, Cary, NC). The figures were made in the R software package.

RESULTS

Thirteen trials were selected for pooled analysis, including 10,521 patients using 10 experimental agents over 13 trials (Table 1). The 10 experimental agents included: two chemotherapeutic agents, one biologic in combination with chemotherapy, four agents for HR-positive disease, and three HER2-targeted agents. Although the eligibility of BO disease was not formally addressed in all of the selected trials, there were patients with BO disease enrolled in all 13 trials, as listed in Table 1. Seven out of the 13 trials required measurable disease, with four of these trials specifically allowing BO disease if it met certain requirements (ie, predominantly lytic component or confirmed on specific imaging modality). The other three trials requiring measurable disease made no mention regarding BO disease eligibility. Six out of the 13 trials allowed patients with measurable and/or nonmeasurable disease.

Bone metastases were identified in 49% (range: 42% to 73%) of patients across trials. BO disease was present in 12.5% (range: 4% to 26%), of patients, varying by subtype and menopausal status, as listed in Table 2. Patients with HER2-positive disease and triple-negative disease had low levels of BO disease (HER2-positive, 5.9%; triple-negative breast cancer, 4.0%), whereas patients with HR-positive disease had BO disease approximately 15% of the time.

Time-to-Event Analyses

The definition for PFS was the same in all 12 trials: PFS was defined as the time from random assignment to the time of the first documented disease progression or death, whichever occurred first. PFS (as assessed by the investigator) for the pooled trials demonstrated an HR of 0.64 (95% CI, 0.591 to 0.696) for the BO

Table 1. Summary of Metastatic Breast Cancer Trials Included in the Pooled Analysis and Bone Subset Demographics

Study Name	Agent	Population (line)	Treatment Arm	Control Arm	BWO No. (%)	NBM No. (%)	BO No. (%)
BO17708 (NCT00333775)	Bevacizumab	HER2 negative (1)	Bevacizumab plus docetaxel	Docetaxel	390 (53.0)	308 (41.9)	39 (5.2)
RIBBON1 (NCT00262067)	Bevacizumab	HER2 negative (1)	Bevacizumab plus chemotherapy*	Chemotherapy	635 (51.3)	493 (39.9)	109 (8.8)
PALOMA-1 (NCT00721409)	Palbociclib	HR positive (1)	Palbociclib plus letrozole	Letrozole	93 (56.4)	43 (26.1)	29 (17.6)
PALOMA-2 (NCT01740427)	Palbociclib	HR positive (2)	Palbociclib plus fulvestrant	Fulvestrant	276 (52.9)	134 (25.7)	111 (21.3)
PALOMA-3 (NCT01942135)	Palbociclib	HR positive (1)	Palbociclib plus letrozole	Letrozole	331 (49.7)	185 (27.8)	150 (22.5)
BOLERO-2 (NCT00863655)	Everolimus	HR positive (2)	Everolimus plus exemestane	Exemestane	398 (54.9)	171 (23.6)	155 (21.4)
EMBRACE (NCT00388726)	Eribulin	All (3)	Eribulin	Physician's choice	432 (56.7)	298 (39.1)	32 (4.2)
CONFIRM (NCT00099437)	Fulvestrant	HR positive (2)	Fulvestrant 500 mg	Fulvestrant 250 mg	255 (34.6)	287 (39.9)	194 (26.3)
CA163-048 (NCT00082433)	Ixabepilone	All (3)	Ixabepilone plus capecitabine	Capecitabine	468 (38.3)	651 (53.3)	102 (8.4)
EGF30008 (NCT00073528)	Lapatinib	HR positive (1)	Lapatinib plus letrozole	Letrozole	579 (45.0)	533 (41.5)	174 (13.5)
CLEOPATRA (NCT00567190)	Pertuzumab	HER2 positive (1)	Pertuzumab plus docetaxel plus trastuzumab	Docetaxel plus trastuzumab	324 (40.1)	446 (55.2)	38 (4.7)
MONALEESA-2 (NCT01958021)	Ribociclib	HR positive (1)	Ribociclib plus letrozole	Letrozole	345 (51.7)	192 (28.7)	131 (19.6)
EMILIA (NCT00829166)	(ado) trastuzumab emtansine	HER2 positive (2)	(ado) trastuzumab emtansine	Lapatinib plus capecitabine	368 (37.1)	575 (58.0)	48 (4.8)
Total					4,894 (46.5)	4,316 (41.0)	1,311 (12.5)

Abbreviations: BO, bone-only metastases; BOLERO, Breast Cancer Trials of Oral Everolimus; BWO, bone with other sites of metastases; CLEOPATRA, Clinical Evaluation of Pertuzumab and Trastuzumab; CONFIRM, Comparison of Faslodex in Recurrent or Metastatic Breast Cancer; EMBRACE, Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer; EMILIA, trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MONALEESA, Mammary Oncology Assessment of LEE011's Efficacy and Safety; NBM, no bone metastases; PALOMA, Palbociclib; Ongoing Trials in the management of Breast Cancer; RIBBON, Regimens in Bevacizumab in Breast Oncology. *Investigator's choice of capecitabine, taxane therapy (nanoparticle albumin-bound paclitaxel or docetaxel), or anthracycline based therapy (doxorubicin or epirubicin combinations).

Table 2. Bone-Only Demographics by Subtype

Subtype	BWO	NBM	BO
HR positive/HER2 negative			
First line	2,035 (52.0)	1,309 (33.5)	567 (14.5)
≥ Second line	1,126 (54.6)	618 (30.0)	318 (15.4)
HR positive/HER2 positive	380 (33.2)	713 (62.3)	51 (4.5)
HR negative/HER2 positive	520 (45.4)	540 (47.2)	85 (7.4)
TNBC	298 (33.2)	565 (62.9)	36 (4.0)
Postmenopausal	3,875 (47.1)	3,223 (39.2)	1,128 (13.7)
Premenopausal	774 (43.1)	871 (48.5)	150 (8.3)
≥ 65 years	1,373 (47.6)	1,141 (39.6)	370 (12.8)
< 65 years	3,521 (46.1)	3,175 (41.6)	941 (12.3)

NOTE. Data presented as No. (%). Menopausal status was missing for 500 women. Subtype information was missing for 1,360 women.

Abbreviations: BO, bone-only metastases; BWO, bone with other sites of metastases; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NBM, no bone metastases; TNBC, triple-negative breast cancer.

subgroup when compared with the BWO subgroup, an HR of 0.70 (95% CI, 0.65 to 0.76) for the BO subgroup compared with the NBM subgroup, and an HR of 0.67 (95% CI, 0.62 to 0.73) for the BO subgroup compared with the NBM and BWO subgroups combined. The HR for the NBM subgroup was 0.90 (95% CI, 0.86 to 0.95) when compared with the BWO subgroup. There was no interaction seen between BO disease status and treatment group in the Cox proportional hazard model.

For OS pooled across trials, a similar trend was observed. The BO subgroup demonstrated an HR of 0.56 (95% CI, 0.50 to 0.61) when compared with the BWO subgroup, an HR of 0.68 (95% CI, 0.61 to 0.76) when compared with the NBM subgroup, and an HR of 0.61 (95% CI, 0.55 to 0.67) when compared with the BWO and

NBM subgroups combined. The NBM had an HR of 0.80 (95% CI, 0.76 to 0.86) when compared with the BWO subgroup. Similar to PFS, there was no interaction seen between BO disease status and being in the treatment group.

In addition to pooling results across all trials, we also considered results within three treatment settings: first-line HR-positive, HER2-negative (all therapies); second-line HR-positive, HER2-negative (all therapies); and third-line chemotherapy. In each treatment setting, patients were pooled across treatment groups and data were presented by BO, BWO, and NBM status. Kaplan-Meier results of the PFS and OS data are shown in Figures 1 to 3.

As seen in Figures 1 to 3, the PFS results had consistent ordering across all disease settings. The BO group had a favorable PFS effect, followed by the NBM and BWO subgroups. In the OS setting, the BO group fared better than the two other groups in the first-line and third-line setting (Figs 1 and 3). In the second-line setting, however, the BO subgroup had mixed results when compared with the NBM subgroup (Fig 2). Still, the BO subgroup had a favorable treatment effect compared with the BWO subgroup.

Discrepancy Between Local and Central Review

EDR and LDR rates for PFS were estimated from patients for whom PFS was assessed by a local investigator and BICR. From the total population of 10,521 patients, this included 6,305 patients from nine of the trials listed in Table 1. Of these 6,305 patients, 2,987 were in the BWO group, 2,509 were in the NBM group, and 809 were in the BO group. The ESS for the EDR calculation consisted of 3,733 patients (35.5% of all patients), and the ESS for the LDR calculation consisted of 2,813 patients (26.7% of all patients). The BO group had 373 total patients available for

Fig 1. Kaplan-Meier estimates of progression-free survival (PFS), and overall survival (OS) in pooled patients (n = 3,911) with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer treated with first-line therapy (including hormonal therapy or chemotherapy) by bone metastases subtype: bone only (n = 567), no bone metastases (n = 1,309), and bone with other metastases (n = 2,035).

Fig 2. Kaplan-Meier estimates of progression-free survival (PFS), and overall survival (OS) in pooled patients (n = 1,172) with hormone-receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer treated with second-line therapy (including hormonal therapy or chemotherapy) by bone metastases subtype: bone only (n = 249), no bone metastases (n = 291), and bone with other metastases (n = 632).

the EDR rate and 323 total patients available for the LDR rate. [Table 3](#) lists the EDR and LDR rates for the various subgroups by breast cancer subtype and targeted agent. The EDR and LDR rate across trials is depicted in [Table 4](#). The table demonstrates

that across all studies, the BO subgroup has a higher EDR than the BWO and NBM subgroups. Also, the BO subgroup has a smaller LDR rate than the other two groups in eight of the nine studies

Fig 3. Kaplan-Meier estimates of progression-free survival (PFS), and overall survival (OS) in pooled patients (n = 1,983) treated with third-line chemotherapy by bone metastases subtype: bone only (n = 134), no bone metastases (n = 900), and bone with other metastases (n = 949).

Table 3. EDR/LDR Rates

Study	BWO	NBM	BO
All studies			
EDR, % (ESS)	45.3 (1,880)	37.9 (1,480)	63.2 (373)
LDR, % (ESS)	40.0 (1,419)	47.6 (1,071)	26.9 (323)
HR-positive agents			
EDR, % (ESS)	48.3 (642)	43.4 (304)	61.6 (190)
LDR, % (ESS)	37.6 (497)	41.9 (227)	30.4 (168)
HER2-positive agents			
EDR, % (ESS)	48.0 (868)	38.3 (934)	66.9 (160)
LDR, % (ESS)	38.8 (676)	48.4 (694)	20.7 (135)
Chemotherapy agents			
EDR, % (ESS)	34.5 (370)	29.3 (242)	52.2 (23)
LDR, % (ESS)	48.0 (246)	52.7 (150)	40.0 (20)

NOTE. The ESS represents the denominator used to calculate each individual rate.

Abbreviations: BO, bone-only metastases; BWO, bone with other sites of metastases; EDR, early discrepancy rate; ESS, effective sample size; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LDR, late discrepancy rate; NBM, no bone metastases.

We tested whether the EDR and LDR rates for the BO subgroup differed statistically from the EDR and LDR rates of the BWO and NBM subgroups using Fisher's exact test. The results were not conclusive, however, and the BO subgroup did not consistently differ statistically from the other two groups.

We examined the overall level of discordance (proportion of cases where BICR and local investigator did not agree) across the three subgroups. Using all data, the BO subgroup had the lowest level of discordance (39.9%), followed by the NBM subgroup (42.6%) and the BWO subgroup (47.5%). In each study, however, this ordering only occurred six out of nine times.

DISCUSSION

This pooled analysis reports a description of frequency and outcomes of patients with BO, NBM, and BWO MBC in clinical trials. Although the strengths of this analysis rest in the large sample size of the pooled trials, allowing for a more representative natural history and frequency analysis in the clinical trial population, the outcome analyses presented here are considered exploratory and nonrandomized. The pooled trials include various classes of therapeutic agents, multiple lines of therapies, and different breast cancer subtypes, making it difficult to draw definite conclusions from this heterogeneous population. In addition, it should be noted that the PFS and OS data presented here may be more favorable than those seen in the general population, because it is known that patients included in clinical trials differ from patients in routine clinical practice. However, it seems that bone metastases are common in patients with MBC, and patients with BO disease are not as common, with variability by breast cancer subtype. In general, PFS for patients in the BO subset was better than the other subgroups. It is not surprising that BO MBC carries a potentially improved prognosis, given that organ function would not be affected. However, it is possible that the BO subset may respond differently to different types of therapies, given the natural history. Trials looking at sequencing of therapy and potential de-escalation of therapy are merited.

Although the EDR and LDR rates differ in absolute magnitude across the trials, the ordering of the EDR and LDR rates for each individual study is the same, with the lone exception being study 8

(Table 4). In particular, the EDR rates for the BO group are consistently larger than the EDR rates for the BWO and NBM subgroups. Likewise, the LDR rates for the BO subgroup are consistently smaller than the LDR rates for the BWO and NBM subgroups. Thus, when the local investigator and the BICR disagree, the local investigator will tend to call BO disease progression earlier than the independent review committee. It is important to note that the EDR and LDR rates only use individuals about whom there is disagreement, and that the BO subgroup has the lowest rate of overall disagreement (see Results). As such, we hesitate to conclude that the BO subgroup is being called early. Instead, we only can conclude that in those individuals where there is disagreement, the local investigator tends to call the event earlier. Ultimately, there seems to be an inherent difference in how the BO subgroup and the other two subgroups are assessed using RECIST.

EDR and LDR estimates are often performed in trials to assess bias.¹¹ We hypothesize that one reason for this discrepancy is likely the difficulty in imaging and assessing bone metastases. In addition, bone metastases are common in HR-positive breast cancer that is treated with hormonal agents. A flare phenomenon¹² can occur in images in patients treated with such agents, complicating tumor progression assessments. When eligible, patients with BO disease are enrolled in clinical trials available for MBC; however, tumor assessments for these patients are not standardized. Although challenging, measurement of disease progression for those with bone metastases is not insurmountable, and lessons can be learned from efforts in the metastatic prostate cancer setting.¹³ Only one of the trials included in the pooled analysis prospectively defined the BO subgroup and incorporated that subgroup as a stratification factor in the statistical analysis plan. Given the results presented here, it may be appropriate, particularly in clinical trials examining HR status–targeted agents, to prospectively define this population and stratify based on the BO subgroup, because of potential differences in the interpretation of imaging.

Further investigations into the implications of treatment on the BO subgroup are needed. These investigations could explore whether additional biomarkers may be incorporated to better account for treatment effect. Patient-reported outcomes are another

Table 4. EDR/LDR Rates Across Studies

Study	EDR (%)			LDR (%)		
	BO	BWO	NBM	BO	BWO	NBM
1	55.0	40.0	27.1	38.2	47.3	58.7
2	52.2	34.5	29.3	40.0	48.0	52.7
3	58.8	50.9	55.7	25.0	34.5	28.9
4	73.1	60.4	54.2	16.3	24.2	26.0
5	38.9	26.7	28.1	30.0	62.5	63.0
6	77.1	57.2	56.3	21.3	28.6	26.5
7	56.5	40.9	30.7	38.1	48.7	58.6
8	57.1	37.9	41.9	42.9	40.5*	48.0
9	66.7	52.4	32.0	33.3	40.0	61.9

NOTE. The table lists the EDR and LDR rates for the BO, BWO, and NBM subgroups across studies. In each study, the BO subgroup had a higher EDR rate than the BWO and NBM subgroups. In eight of the nine studies, the BO subgroup had a lower LDR rate than the BWO and NBM subgroups. The order of these studies is de-identified and does not correspond to Table 1 or text.

Abbreviations: BO, bone-only metastases; BWO, bone with other sites of metastases; EDR, early discrepancy rate; LDR, late discrepancy rate; NBM, no bone metastases.

*Lone observation that did not fit the pattern.

potential avenue to explore in the BO subgroup, because bone pain is a cardinal disease symptom that patients with bone metastases experience. Further efforts are warranted to describe the appropriate imaging modalities and end points to better describe response to therapy and standardize bone radiographic evaluation for breast cancer clinical trials and clinical practice.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Suparna B. Wedam, Julia A. Beaver, Laleh Amiri-Kordestani, Shenghui Tang, Rajeshwari Sridhara, Geoffrey Kim, Richard Pazdur

Administrative support: Kirsten B. Goldberg

Collection and assembly of data: Suparna B. Wedam, Julia A. Beaver, Laleh Amiri-Kordestani, Erik Bloomquist, Shenghui Tang, Rajeshwari Sridhara, Richard Pazdur

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Affiliations

All authors: Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD.

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Suparna B. Wedam

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Julia A. Beaver

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Laleh Amiri-Kordestani

No relationship to disclose

Erik Bloomquist

No relationship to disclose

Shenghui Tang

No relationship to disclose

Kirsten B. Goldberg

No relationship to disclose

Rajeshwari Sridhara

No relationship to disclose

Amna Ibrahim

No relationship to disclose

Geoffrey Kim

Employment: AstraZeneca/MedImmune

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Paul Kluetz

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