JOURNAL OF CLINICAL ONCOLOGY

Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer

Susan Halabi, William Kevin Kelly, Hua Ma, Haojin Zhou, Nicole C. Solomon, Karim Fizazi, Catherine M. Tangen, Mark Rosenthal, Daniel P. Petrylak, Maha Hussain, Nicholas J. Vogelzang, Ian M. Thompson, Kim N. Chi, Johann de Bono, Andrew J. Armstrong, Mario A. Eisenberger, Abderrahim Fandi, Shaoyi Li, John C. Araujo, Christopher J. Logothetis, David I. Quinn, Michael J. Morris, Celestia S. Higano, Ian F. Tannock, and Eric J. Small

Listen to the podcast by Dr Agarwal at www.jco.org/podcasts

ABSTRACT

Purpose

Reports have suggested that metastatic site is an important predictor of overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC), but these were based on a limited number of patients. We investigate the impact of site of metastases on OS of a substantial sample of men with mCRPC who received docetaxel chemotherapy in nine phase III trials.

Patients and Methods

Individual patient data from 8,820 men with mCRPC enrolled onto nine phase III trials were combined. Site of metastases was categorized as lymph node (LN) only, bone with or without LN (with no visceral metastases), any lung metastases (but no liver), and any liver metastases.

Results

Most patients had bone with or without LN metastases (72.8%), followed by visceral disease (20.8%) and LN-only disease (6.4%). Men with liver metastases had the worst median OS (13.5 months). Although men with lung metastases had better median OS (19.4 months) compared with men with liver metastases, they had significantly worse median survival duration than men with nonvisceral bone metastases (21.3 months). Men with LN-only disease had a median OS of 31.6 months. The pooled hazard ratios for death in men with lung metastases compared with men with bone with or without LN metastases and in men with any liver metastases compared with men with lung metastases were 1.14 (95% CI, 1.04 to 1.25; $P = .007$) and 1.52 (95% CI, 1.35 to 1.73; $P < .0001$), respectively.

Conclusion

Specific sites of metastases in men with mCRPC are associated with differential OS, with successive increased lethality for lung and liver metastases compared with bone and nonvisceral involvement. These data may help in treatment decisions, the design of future clinical trials, and understanding the variation in biology of different sites of metastases in men with mCRPC.

J Clin Oncol 34:1652-1659. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Several studies have identified the presence of visceral disease as an important adverse prognostic factor of overall survival (OS) in men with metastatic castration-resistant prostate cancer (mCRPC).[1-9] More recent analyses have demonstrated that the presence of liver metastases seems to be an important adverse predictor of OS in men with mCRPC.[4-9] However, because liver and lung metastases have traditionally been relatively rare events in patients with mCRPC, these observations are based on analyses of relatively small numbers of patients with visceral metastases; thus, estimated hazard ratios (HRs) may be unstable. A more accurate characterization of the impact of site of metastases on OS has the potential to influence therapeutic approaches, trial stratification, and patient counseling.

Therefore, a meta-analysis of phase III trials of men with mCRPC was undertaken, with the expectation that such an approach would lead

to a greater precision in detecting the impact of the site of metastases on OS. We hypothesized that patients with lung metastases would have a shorter median OS time than patients with bone metastases and that patients with liver metastases would, in turn, have a shorter median OS time than patients with mCRPC and lung metastases (with or without bone involvement). Because docetaxel was used as a standard of care in the majority of trials available for analysis and because in clinical practice chemotherapy was used preferentially in otherwise fit patients with visceral metastases, we elected to include only trials that included docetaxel.

PATIENTS AND METHODS

Trial Inclusion Criteria

We performed a systematic search of published literature from January 2004 to July 2015 and identified candidate studies using PubMed and ClinicalTrials.gov that included all phase III trials of docetaxel versus docetaxel plus an experimental agent that were reported between 1999 and 2015.[10-19] To be included in this meta-analysis, a trial had to satisfy the following inclusion criteria: there was institutional review board approval; the study was a phase III trial in which men had received docetaxel (in studies with a non–docetaxel-containing arm [SWOG 9916 and TAX 327] men not receiving docetaxel were excluded from the analysis); patients had chemotherapy-naïve mCRPC; OS was the primary end point; and all patients provided written informed consent.

Data

We requested the following individual patient data from each identified trial: date of random assignment, date of last observation or follow-up, date of death, OS status at the date of last observation, cause of death, treatment assignment, date of birth (or age in years), date of initial diagnosis, date of metastatic diagnosis, hemoglobin, prostate-specific antigen (PSA), performance status, alkaline phosphatase, creatinine, testosterone, Gleason score, prior radiation therapy, prior hormone therapy, hormonal therapy agents, luteinizing hormone–releasing hormone agonists, site of metastases at baseline, and stratification factors. Site(s) of metastases at baseline was obtained from the case report forms; imaging was not centrally reviewed. In all trials, patients underwent staging with standard imaging tests (eg, bone scan, computed tomography scans), as indicated by the individual trial's eligibility and baseline test requirements.[9-18] Data were submitted to the first author at the Department of Biostatistics and Bioinformatics at Duke University, and the analysis was approved by the Duke Institutional Review Board.

Classification of Site of Metastases

Patients were classified according to the site of their metastatic disease in one of the following two mutually exclusive groups: non-visceral and visceral disease (Table 1). Visceral disease was broadly defined as soft tissue metastases other than lymph node (LN) metastases and included metastatic disease to lung, liver, adrenal glands, brain, and other sites (unspecified). Visceral disease patients were, in turn, placed in one of the following three categories: any patient with liver metastases was categorized as having liver metastases even if they had other metastatic sites; patients with lung metastases were denoted as having lung metastases, unless they also had liver metastases; and all other patients with visceral disease were categorized as having non-hepatic, nonpulmonary visceral metastases (such as adrenal, kidney, and others). In the nonvisceral disease group, patients were classified as either having LN-only disease or bone metastases with or without nodal involvement.

Statistical Analysis

The primary end point was OS, defined as the interval between date of random assignment and date of death from any cause. The primary goals of this analysis were to estimate the pooled HR and to test the following two hypotheses: that patients with lung metastases would have a shorter median OS time than patients with bone metastasis, and that patients with liver metastases would, in turn, have a shorter median OS time than patients with mCRPC and lung metastases (with or without bone involvement). In addition, secondary analysis was performed to estimate the OS distribution by the site of metastases categorized as LN only, bone with or without LN involvement, and visceral disease. Furthermore, analyses were performed to estimate the pooled HR for death in patients with LN-only metastases versus patients with bone metastases with or without nodal involvement and in patients with liver metastases versus those with bone disease.

The statistical analysis followed the standard meta-analytic procedure using a two-stage approach.[20,21] In the first stage, each clinical trial was analyzed separately to obtain trial-specific estimates of the previously mentioned HRs. The trial-specific estimates were then combined in a weighted form to obtain an overall estimate of the HRs and their estimated variances.[21] It is noted that Whitehead and Whitehead required that the effect size be normally distributed, which is not the case for the log HR estimators.[20] However, estimators of the coefficients in the Cox regression model, which are the logarithms of the HR estimators, have asymptotic normal distributions. Therefore, we derived our results in two steps. We first computed weighted average coefficients, 95% CIs, and the Q and I^2 statistics for the coefficients. Next, we took the exponential of the coefficients and were able to compute the 95% CIs. We used the variance formula for the log-normal distribution to compute the variance of the summary HRs.

We used the Q and I^2 statistics to test for between-study heterogeneity. The Q statistic was used to test for the homogeneity of the HRs across the nine studies, whereas the I^2 statistic described the proportion of

Table 1. Classification of Site of Metastases by Mutually Exclusive Categories

Site of Metastases	Presence of LN Metastases	Presence of Bone Metastases	Presence of Visceral Metastases	Category
LN only	Yes	No	No	LN
Bone only	No	Yes	No	Bone
Bone with LN involvement	Yes	Yes	No	Bone
Lung	No/Yes	No	Yes	Lung
Lung	No/Yes	Yes	Yes	Lung
Liver	No/Yes	No	Yes	Liver
Liver with any visceral disease	No/Yes	No	Yes	Liver
Liver	No/Yes	Yes	Yes	Liver
Liver with any visceral disease	No/Yes	Yes	Yes	Liver

Abbreviation: LN, lymph node.

the total variation in the study estimates that was a result of heterogeneity. In the event that the Q (and I^2) statistic was significant (ie, $P < .05$), the random effect approach became the primary analysis.

An intent-to-treat analysis was applied within each clinical trial, with the analysis population based on all randomly assigned patients. In addition, the proportional hazards model was used within each trial to estimate the HR adjusting for the following baseline prognostic variables that were common in the nine trials: age, performance status, and PSA. Furthermore, the Kaplan-Meier product-limit approach was used to estimate the OS distribution by the metastatic site.

Because we were testing two hypotheses, the Bonferroni correction was used to adjust for the type I error rate. $P < .025$ was considered statistically significant, and all P values were based on two-sided tests. We summarized the results by means of forest plots, and individual and pooled HR estimates were presented with 95% CIs.

RESULTS

Trials Identified

Figure 1 presents the PRISMA diagram of how the trials were identified and screened. Ten trials met the inclusion criteria. These were SWOG 9916,[10] TAX 327,[11] Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT),[12] Cancer and Leukemia Group B (CALGB) 90401,[13] Endothelin A Use (ENTHUSE) 33,[14] SWOG 0421,[15] VENICE,[16] READY,[17] MAINSAIL,[18] and SYNERGY.[19] Of these 10 trials, nine sponsors were willing to share the data; the tenth sponsor became financially insolvent and was unable to provide the trial data.[12]

Table 2 lists the trials that were included in this meta-analysis. A total of 8,820 men with mCRPC who were treated with docetaxel or a docetaxel-containing regimen were enrolled from October 1999 to November 2012. The median age was 68 years, the majority

of men were white, and 94% of them had a performance status of 0 or 1 (Table 2). The median hemoglobin, PSA, and alkaline phosphatase levels were 12.9 g/dL, 97 ng/mL, and 138 U/L, respectively. The median follow-up time among surviving patients was 21.8 months (range, 0 to 91.2 months), with a total of 5,470 deaths.

Distribution of Metastatic Site

Most patients were in the bone metastases group (n = 6,356; 72.8%); 42.9% of the entire cohort had bone disease only, and 29.8% had bone disease with LN involvement. Visceral disease was present in 1,815 men (20.8%), and 565 men (6.4%) had LN-only disease. Among patients with visceral disease, 791 (9.1%) had lung metastases and 752 (8.6%) had liver metastases (173 patients had both liver and lung disease and were grouped in the liver group). A small proportion of patients (3%) had adrenal, brain, kidney, or other unspecified visceral metastases (in the absence of liver metastases) and were excluded from the hypothesis testing because of the small sample size. The frequency of the site of metastases was comparable across studies, perhaps reflecting similar inclusion criteria (Appendix Fig A1A, online only). In addition, 19 patients with no metastases and 65 patients with missing site of metastases were excluded from the analysis. The final number of patients included in the meta-analysis was 8,736.

Table 3 lists the baseline characteristics of patients by site of metastases. There were some differences in baseline variables by the site of metastases (Table 2). Not surprisingly, men who were in the LN-only group had the lowest median PSA and median alkaline phosphatase values and had higher median hemoglobin levels compared with the other groups. By comparison, patients with liver metastases had the highest median alkaline phosphatase and
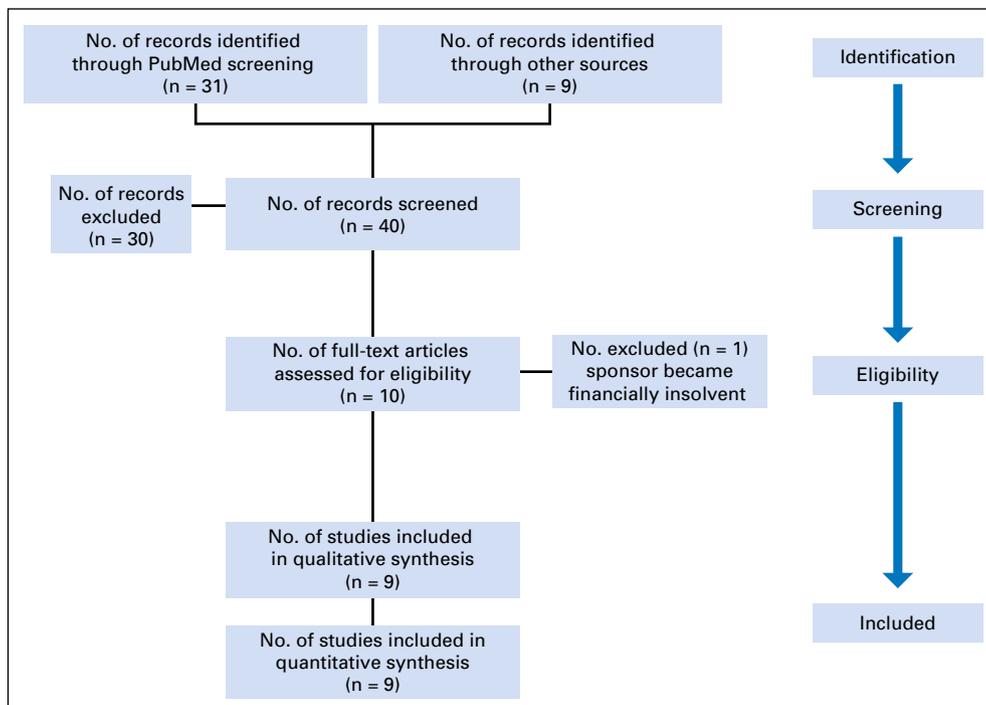

Fig 1. PRISMA diagram.

Trial	Total Sample Size (No. of patients)	Calendar Year of Recruitment	Study Population	Treatment Arms (No. of patients)
			Table 2. Summary of Trials Included in the Meta-Analysis	
SWOG 9916[10]	674	October 1999 to January 2003	Pathologically confirmed adenocarcinoma of the prostate and progressive metastatic disease (stage D1 or D2) despite androgen ablative therapy and cessation of antiandrogen treatment	Docetaxel + estramustine (338) Mitoxantrone + prednisone (336)
TAX 327[11]	1,006	March 2000 to June 2002	Men with metastatic hormone-refractory prostate cancer	Docetaxel + prednisone (669) Mitoxantrone + prednisone (337)
CALGB 90401[13]	1,050	May 2005 to December 2007	Chemotherapy-naive progressive metastatic castration-resistant prostate cancer with ECOG performance status ≤ 2 and adequate bone marrow, hepatic, and renal function	Docetaxel + prednisone + bevacizumab (524) Docetaxel + prednisone (526)
SWOG 0421[15]	994	August 2006 to May 2010	Pathologically confirmed prostate adenocarcinoma with bone metastases on a bone scan, unresponsive or refractory to hormone treatment; Zubrod performance status ≤ 3	Atrasentan + docetaxel (498) Placebo + docetaxel (496)
VENICE[16]	1,224	August 17, 2007, to February 11, 2010	Histologically or cytologically confirmed prostate cancer and evidence of metastatic disease that had progressed on hormonal therapy or after surgical castration	Docetaxel + prednisone + aflibercept (612) Docetaxel + placebo (612)
ENTHUSE[14]	1,052	January 24, 2008, to May 10, 2011	Men with histologically or cytologically confirmed prostate adenocarcinoma, surgically castrated or continuously medically castrated	Docetaxel + zibotentan (524) Docetaxel + placebo (528)
READY[17]	1,522	October 30, 2008, to April 11, 2011	Histologically confirmed metastatic prostate cancer that had progressed despite castrate concentrations of serum testosterone	Docetaxel + dasatinib (762) Docetaxel + placebo (760)
MAINSAIL[18]	1,059	November 2009 to November 2011	Confirmed metastatic adenocarcinoma of prostate that is refractory to hormonal therapy	Docetaxel + prednisone + lenalidomide (533) Docetaxel + prednisone + placebo (526)
SYNERGY[19]	1,022	August 2010 to April 2014	Histologically confirmed metastatic prostate cancer that had progressed despite castrate concentrations of serum testosterone	Docetaxel + prednisone + custirsen (510) Docetaxel + prednisone (512)

Abbreviations: CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; ENTHUSE, Endothelin A Use.

the lowest median hemoglobin levels. Men in the bone with nodal disease group had the highest median PSA level.

Impact of Metastatic Site

The median OS duration by the site of metastases across the trials is presented in Appendix Figure A1B. In general, median OS in the metastatic site subgroups was roughly comparable across trials, with the exception of MAINSAIL, which tested the addition of lenalidomide to standard docetaxel therapy. Of studies that allowed enrollment of LN-only patients, this study had both the lowest number of LN-only men and also a discrepantly low median OS in this group of patients.

We sought to test the hypothesis that patients with lung metastases would have a shorter median OS time than patients with bone metastasis. Figure 2A presents the Kaplan-Meier survival curves by the site of metastases. The median OS time was 21.3 months (95% CI, 20.8 to 21.9 months) in men with bone metastasis compared with 19.4 months (95% CI, 17.8 to 20.7 months) in men with lung metastases (Fig 2A).

The median OS times by trial and pooled across all trials are presented in a forest plot (Fig 2B). Overall, there was marginal variability in the observed median OS time for men with bone metastases with or without nodal involvement and for men with lung metastases across trials. The median OS times in men with bone metastases with or without LN and in those with lung metastases ranged from 17 to 23 months and 15 to 22 months, respectively. The HRs for most of the trials were greater than 1, indicating that men with lung metastases had shorter survival duration than men with bone involvement, with the exception of the VENICE and MAINSAIL trials. The pooled multivariable HR of 1.14 (95% CI, 1.04 to 1.25) demonstrates that overall men with lung metastases have a statistically significant increased risk of death compared with men with bone metastases ($P = .007$).

We also tested our second hypothesis that men with mCRPC and liver metastases would have a shorter median OS time than men with lung metastases. The median OS time was 19.4 months (95% CI, 17.8 to 20.7 months) in men with lung metastases compared with 13.5 months (95% CI, 12.7 to 14.4 months; Fig 2A) in men with liver metastases. Minimal variability was observed in median OS times by liver metastases across the nine trials, ranging from 9 to 14 months (Fig 2C). The pooled multivariable HR for men with liver metastases was 1.52 (95% CI, 1.35 to 1.73; $P < .0001$).

Table 3. Baseline Patients Characteristics by Site of Metastases

Characteristic	LN Only (n = 565)	Bone With or Without LN (n = 6,356)	Lung (n = 791)	Liver (n = 752)	Total (n = 8,736)
Median age, years (25th-75th percentile)	69 (63-75)	68 (63-74)	69 (64-75)	69 (62-74)	68 (63-74)
White, %	77	74	77	74	74
PS* 0-1, %	96	95	94	91	94
Median PSA, ng/mL (25th-75th percentile)	58 (23-146)	89 (32-261)	77 (25-218)	93 (34-294)	86 (31-250)
Median alkaline phosphatase, U/L (25th-75th percentile)	78 (64-101)	150 (91-308)	124 (81-242)	172 (92-342)	138 (86-287)
Median hemoglobin, g/dL (25th-75th percentile)	13.6 (12.4-14.9)	12.9 (11.7-14.0)	13 (11.8-14.3)	12.5 (11.3-13.7)	12.9 (11.7-14.1)

Abbreviation: LN, lymph node; PS, performance status; PSA, prostate-specific antigen.
*PS is Zubrod PS for Southwest Oncology Group 0421 trial, WHO PS for Endothelin A Use (ENTHUSE) study, Karnofsky PS for TAX 327, and Eastern Cooperative Oncology Group PS for all other studies.

Additional secondary analyses were conducted to estimate the median OS in other categories for metastatic sites. Men with LN-only disease had an observed median OS of 31.6 months (95% CI, 27.9 to 35.5 months), and men with any visceral disease had the lowest median OS time of 16.3 months (95% CI, 15.6 to 17.3 months; Appendix Fig A2, online only). In addition, we estimated the pooled HR for death in men with LN-only disease compared with men with bone with or without nodal involvement. The HR was 0.61 (95% CI, 0.54 to 0.69; Appendix Fig A3A, online only). Furthermore, the pooled HR for death was 1.82 (95% CI, 1.67 to 2.0; Appendix Fig A3B) in men with liver metastases compared with men with bone with or without nodal involvement.

DISCUSSION

In this analysis of almost 9,000 patients, we confirm that the baseline presence of visceral disease is a negative prognostic factor of OS in men with mCRPC who were subsequently treated with docetaxel. This large sample size allowed us to estimate the prevalence of disease site with reasonably high precision, and to test for differences in outcomes among men with different metastatic sites. Overall, almost 20.8% of men with mCRPC had visceral disease, 8.6% of patients had liver metastases, and 9.1% of patients had lung metastases (without liver involvement). The OS of men treated with docetaxel who had liver metastases was substantially worse than the OS of men with lung metastases. The median OS time for 752 men with liver metastases was 13.5 months compared with 19.4 months for 791 men with lung metastases (P < .0001). With the exception of the VENICE trial, within this group of patients with liver metastases, the OS seems to be homogenous, with median OS ranging from 9 to 14 months. These results are expected and confirm prior published reports that patients with liver metastases represent a poor-risk group.[3-9] Although the presence of liver metastases may simply reflect a lead time bias that selects for patients with temporally more advanced disease, the present data set does not allow testing of this hypothesis.[22]

In addition, we found differences in survival duration in men with bone plus nodal disease compared with men with lung metastases. Patients with lung metastases (with or without bone disease) had shorter survival duration than patients with bone disease with or without nodal involvement (P = .007). Not

surprisingly, men with LN-only disease had a longer survival duration than men with bone involvement.

Our results suggest that prognostic subgroups should be considered for novel therapies and in the design of future clinical trials for men with mCRPC. Furthermore, these results should help guide clinical decision making for men with mCRPC. The data included in this analysis are derived from well-designed and well-conducted phase III trials involving the use of docetaxel for patients with mCRPC[10,11,13-19] closed to accrual between June 2002 (TAX 327)[11] and November 2012 (SYNERGY).[19] It is intriguing to note that the variability in OS for each metastatic site subset across the trials is not large, suggesting that the differences observed in median OS from trial to trial could be explained by the relative proportion of the metastatic subsets enrolled in each particular trial.

The heterogeneity of men with mCRPC enrolled onto trials and the substantially different outcomes among these subgroups highlight the importance of reporting OS by disease location. These data suggest that the distribution of patients across the following categories should be routinely reported: LN-only disease, bone with or without LN involvement with no visceral metastases, any lung metastases (but no liver), and any liver metastases. Although the Prostate Cancer Clinical Trials Working Group[23] recommends the reporting of end points by site of metastases, this has been only recently implemented in several recent phase III trials.[24-26]

There are several limitations of this meta-analysis as a result of its retrospective nature. First, data from more recent trials were excluded, and the analysis could not include all known prognostic factors across the trials. This highlights the difficulty in performing this type of analysis as a result of the lack of harmonization in data collected across phase III studies. In addition, neither imaging nor imaging reports were centrally reviewed, and as such, we cannot distinguish between nodular lung metastases and lymphangitic spread, nor can we assess the impact of the metastatic burden or the number of metastases. Furthermore, most of the trials included in this analysis were conducted before the approval and broad use of abiraterone acetate or enzalutamide, which are now generally used before the use of chemotherapy. Nevertheless, the sample size and number of deaths in the pooled analysis were substantial, providing excellent statistical power. Therefore, this analysis is likely to have high validity. Finally, this analysis only applies to men with mCRPC who are treated with docetaxel, but because docetaxel is used

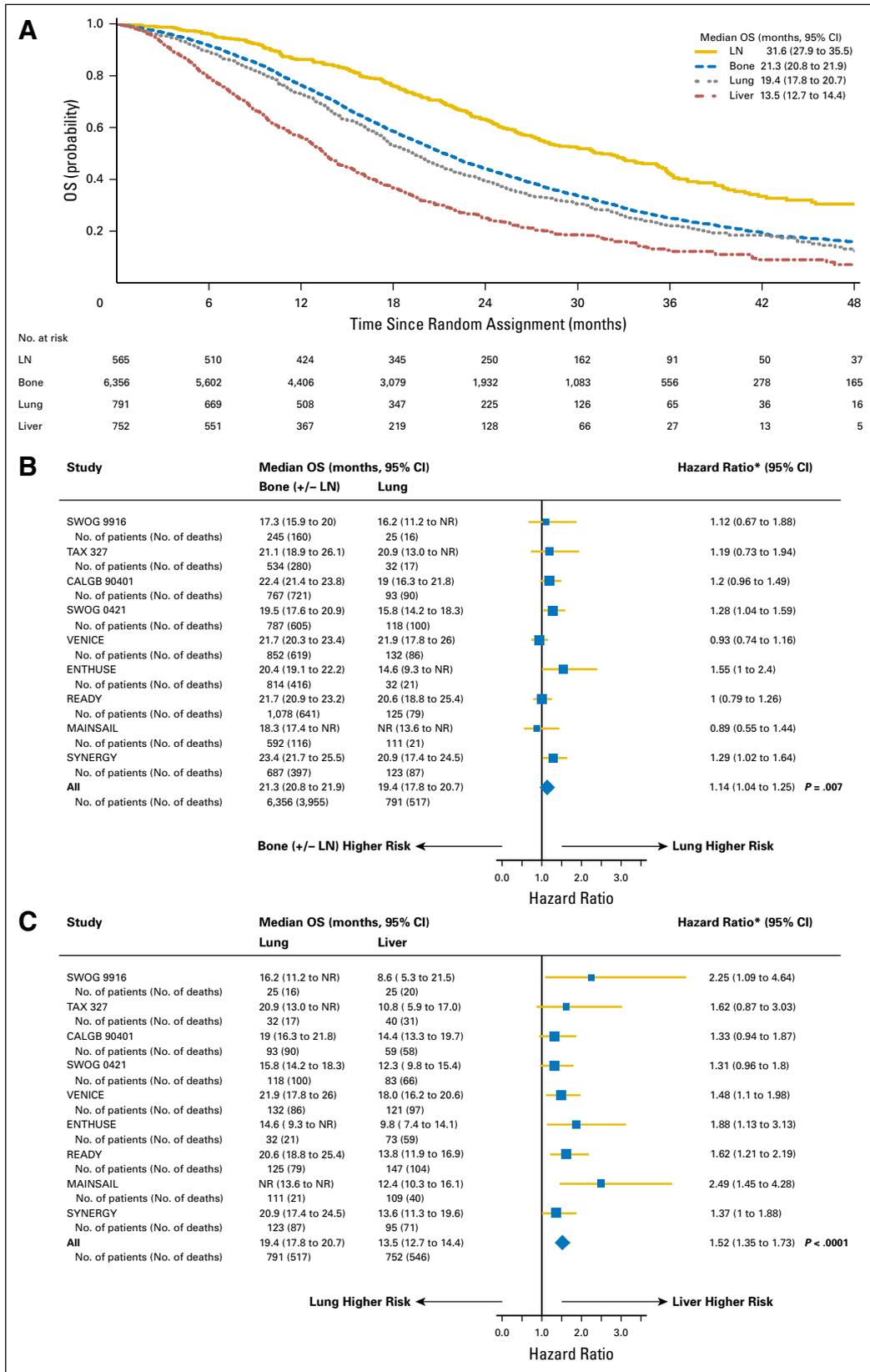## Site of Visceral Metastases Predicts Overall Survival

Fig 2. (A) Kaplan-Meier overall survival (OS) curves by site of metastases. (B) Forest plot comparing men with lung metastases to men with bone metastases with or without nodal involvement (reference group = bone with or without nodal involvement; Q = 8.42, df = 8, P = .393; I^2 = 0.05). (*) Adjusted on age, performance status, and prostate-specific antigen (with the exception of the summary hazard ratio). (C) Forest plot with hazard ratios comparing men with liver metastases to men with lung metastases (reference group = lung; Q = 7.93, df = 8, P = .441; I^2 = 0.00). (*) Adjusted on age, performance status, and prostate-specific antigen (with the exception of the summary hazard ratio). CALGB, Cancer and Leukemia Group B; ENTHUSE, Endothelin A Use; LN, lymph node; NR, not reached.

commonly in patients with mCRPC with visceral metastases, this analysis also has practical utility.

In summary, men with mCRPC treated with docetaxel who have liver metastases had worse OS duration than men with lung metastases. Men with lung metastases, in turn, had worse OS than men with bone with or without LN metastases. This meta-analysis provides evidence-based rationale for the recommendations of the Prostate Cancer Clinical Trials Working Group and for prospectively stratifying for type of visceral metastases in future phase III trials.[23,27] Our understanding of what drives the development of different metastatic patterns of this disease is limited and underscores the need to biopsy patients with recurrences to identify underlying mechanisms and develop novel treatment approaches for men with mCRPC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: Susan Halabi, William Kevin Kelly, Eric J. Small
Financial support: Susan Halabi
Provision of study materials or patients: Susan Halabi, William Kevin Kelly, Karim Fizazi, Daniel P. Petrylak, Kim N. Chi, Johann de Bono, Mario A. Eisenberger, Abderrahim Fandi, John C. Araujo, David I. Quinn, Michael J. Morris, Celestia S. Higano, Ian F. Tannock, Eric J. Small
Collection and assembly of data: Susan Halabi, William Kevin Kelly, Karim Fizazi, Catherine M. Tangen, Mark Rosenthal, Daniel P. Petrylak, Ian M. Thompson, Kim N. Chi, Johann de Bono, Andrew J. Armstrong, Mario A. Eisenberger, Abderrahim Fandi, John C. Araujo, David I. Quinn, Michael J. Morris, Celestia S. Higano, Ian F. Tannock
Data analysis and interpretation: Susan Halabi, William Kevin Kelly, Hua Ma, Haojin Zhou, Nicole C. Solomon, Karim Fizazi, Daniel P. Petrylak, Maha Hussain, Nicholas J. Vogelzang, Ian M. Thompson, Kim N. Chi, Johann de Bono, Andrew J. Armstrong, Mario A. Eisenberger, Shaoyi Li, Christopher J. Logothetis, David I. Quinn, Michael J. Morris, Celestia S. Higano, Ian F. Tannock, Eric J. Small
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Halabi S, Small EJ, Kantoff PW, et al: Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 21:1232-1237, 2003

2. Armstrong AJ, Garrett-Mayer ES, Yang YC, et al: A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: A TAX327 study analysis. Clin Cancer Res 13:6396-6403, 2007

3. Kelly WK, Halabi S, Carducci MA, et al: Liver metastases predict for shorter overall survival in metastatic castration-resistant prostate cancer. J Clin Oncol 30, 2012 (suppl; abstr 4655)

4. Halabi S, Lin CY, Small EJ, et al: Prognostic model predicting metastatic castration-resistant prostate cancer survival in men treated with second-line chemotherapy. J Natl Cancer Inst 105:1729-1737, 2013

5. Halabi S, Lin CY, Kelly WK, et al: Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 32:671-677, 2014

6. Templeton AJ, Pezaro C, Omlin A, et al: Simple prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil-to-lymphocyte ratio. Cancer 120:3346-3352, 2014

7. Pond GR, Sonpavde G, de Wit R, et al: The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. Eur Urol 65:3-6, 2014

8. Loriot Y, Fizazi K, de Bono JS, et al: Outcomes in patients with liver or lung metastatic castration-resistant prostate cancer (mCRPC) treated with the androgen receptor inhibitor enzalutamide: Results from the phase III AFFIRM trial. J Clin Oncol 31, 2013 (suppl; abstr 5065)

9. Chi KN, Kheoh TS, Ryan CJ, et al: A prognostic model for predicting overall survival (OS) in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) treated with abiraterone acetate (AA) after docetaxel. J Clin Oncol 31, 2013 (suppl; abstr 5015)

10. Petrylak DP, Tangen CM, Hussain MHA, et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 351:1513-1520, 2004

11. Tannock IF, de Wit R, Berry WR, et al; TAX 327 Investigators: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-1512, 2004

12. Scher HI, Jia X, Chi K, et al: Randomized, open-label phase III trial of docetaxel plus high-dose calcitriol versus docetaxel plus prednisone for patients with castration-resistant prostate cancer. J Clin Oncol 29:2191-2198, 2011

13. Kelly WK, Halabi S, Carducci M, et al: Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. J Clin Oncol 30:1534-1540, 2012

14. Fizazi K, Higano CS, Nelson JB, et al: Phase III, randomized, placebo-controlled study of docetaxel in combination with zibotentan in patients with metastatic castration-resistant prostate cancer. J Clin Oncol 31:1740-1747, 2013 [erratum: J Clin Oncol 32:3461, 2013]

15. Quinn DI, Tangen CM, Hussain M, et al: Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): A randomised phase 3 trial. Lancet Oncol 14:893-900, 2013

16. Tannock IF, Fizazi K, Ivanov S, et al; VENICE Investigators: Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): A phase 3, double-blind randomised trial. Lancet Oncol 14:760-768, 2013

17. Araujo JC, Trudel GC, Saad F, et al: Docetaxel and dasatinib or placebo in men with metastatic castration-resistant prostate cancer (READY): A randomised, double-blind phase 3 trial. Lancet Oncol 14:1307-1316, 2013

18. Petrylak DP, Vogelzang NJ, Budnik N, et al: Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 16:417-425, 2015

19. Chi KN, Higano CS, Blumenstein BA, et al: Phase III SYNERGY trial: Docetaxel +/- custirsen and overall survival in patients (pts) cancer with metastatic castration-resistant prostate cancer (mCRPC) and poor prognosis. J Clin Oncol 33, 2015 (suppl; abstr 5009)

20. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 7:177-188, 1986

21. Whitehead A, Whitehead J: A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 10:1665-1677, 1991

22. Pezaro CJ, Omlin A, Lorente D, et al: Visceral disease in castration-resistant prostate cancer. Eur Urol 65:270-273, 2014

23. Scher HI, Halabi S, Tannock I, et al; Prostate Cancer Clinical Trials Working Group: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159, 2008

24. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators: Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 368:138-148, 2013

25. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators: Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 371:424-433, 2014

26. Fizazi K, Jones R, Oudard S, et al: Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. J Clin Oncol 33:723-731, 2015

27. Scher HI, Morris MJ, Stadler W, et al: Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group (PCWG3). J Clin Oncol , (in press)

Affiliations

Susan Halabi, Hua Ma, Nicole C. Solomon, and Andrew J. Armstrong, Duke University, Durham, NC; William Kevin Kelly, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA; Haojin Zhou, Merck, Beijing, China; Karim Fizazi, Institut Gustave Roussy, University of Paris Sud, Villejuif, France; Catherine M. Tangen, Southwest Oncology Group Statistical Center; Mark Rosenthal, Royal Melbourne Hospital, Melbourne, Victoria, Australia; Daniel P. Petrylak, Yale Cancer Center, New Haven, CT; Maha Hussain, University of Michigan, Ann Arbor, MI; Nicholas J. Vogelzang, US Oncology, Las Vegas, NV; Ian M. Thompson, University of Texas at San Antonio, San Antonio; John C. Araujo and Christopher J. Logothetis, The University of Texas MD Anderson Cancer Center, Houston, TX; Kim N. Chi, British Columbia Cancer Agency–Vancouver Cancer Centre, Vancouver, British Columbia; Ian F. Tannock, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada; Johann de Bono, Institute for Cancer Research, Royal Marsden Hospital, Sutton, Surrey, United Kingdom; Mario A. Eisenberger, Johns Hopkins University–School of Medicine, Oncology Center, Baltimore, MD; Abderrahim Fandi and Shaoyi Li, Celgene Corporation, Summit, NJ; David I. Quinn, University of Southern California Norris Cancer Center, Los Angeles; Eric J. Small, University of California San Francisco, San Francisco, CA; Celestia S. Higano, University of Washington, Seattle, WA; and Michael J. Morris, Memorial Sloan-Kettering Cancer Center New York, NY.

■ ■ ■

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men with Castration-Resistant Prostate Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Susan Halabi
Consulting or Advisory Role: Bayer, Genentech
Travel, Accommodations, Expenses: Bayer, Genentech

William Kevin Kelly
Consulting or Advisory Role: sanofi-aventis
Research Funding: sanofi-aventis (Inst), Novartis (Inst)
Other Relationship: sanofi-aventis

Hua Ma
No relationship to disclose

Haojin Zhou
Employment: Merck
Travel, Accommodations, Expenses: Merck

Nicole C. Solomon
No relationship to disclose

Karim Fizazi
Honoraria: sanofi-aventis, Janssen, Medivation/Astellas
Consulting or Advisory Role: sanofi-aventis, Janssen, Astellas Pharma, Orion Genomics, Bayer, AstraZeneca

Catherine M. Tangen
No relationship to disclose

Mark Rosenthal
No relationship to disclose

Daniel P. Petrylak
Honoraria: Bayer, Bellicum Pharmaceuticals, Dendreon, sanofi-aventis, Johnson & Johnson, Exelixis, Ferring, Millennium Pharmaceuticals, Medivation, Pfizer
Consulting or Advisory Role: Bayer, Bellicum Pharmaceuticals, Dendreon, sanofi-aventis, Johnson & Johnson, Exelixis, Ferring, Millennium Pharmaceuticals, Medivation, Pfizer, Tyme, Merck Serono, Merck, Genentech, AstraZeneca
Research Funding: Oncogenex, Progenics, Johnson & Johnson, Millennium Pharmaceuticals, Celgene, Dendreon, sanofi-aventis, Eli Lilly, Pfizer, AstraZeneca, Genentech, Merck
Travel, Accommodations, Expenses: Bayer, Bellicum Pharmaceuticals, Dendreon, sanofi-aventis, Exelixis, Ferring, Medivation, Pfizer, Oncogenex, Progenics, Johnson & Johnson, Millennium Pharmaceuticals, Celgene

Maha Hussain
Consulting or Advisory Role: Essa, AstraZeneca
Research Funding: Genentech (Inst), Medivation (Inst), Pfizer (Inst), Bayer (Inst)
Patents, Royalties, Other Intellectual Property: Title: Systems and Methods for Tissue Imaging, 3676 Our File: Serial Number: UM-14437/US-1/PRO 60/923,385 UM-14437/US-2/ORD 12/101,753US 8,185,186 (US patent number) Systems and methods for tissue imaging (issued patent) EP 08745653.9 (EP application number) Systems and methods for tissue imaging (pending) CA 2683805 (Canadian application number) Systems and methods for tissue imaging (pending) US 13/362,500 (US application number) Systems and Methods for Tissue Imaging (continuation application of US 8,185,186). Title: Method of Treating Cancer Docket No: Serial Number: 224990/10-016P2/311733 61/481/671 Application Filed on: 5/2/2011. TITLE: Dual Inhibition of MET and VEGF for the treatment of castration resistant prostate cancer and osteoblastic bone metastases. Applicant/Proprietor Exelixis, Inc. Application No/Patent No. 11764665.4-1464 Application No/Patent No. 11764656.2-1464 Application Filed on: 26/9/2011

Nicholas J. Vogelzang
Employment: US Oncology
Stock or Other Ownership: Caris Life Sciences
Honoraria: DAVA Oncology, MannKind, UpToDate, AbbVie, Bavarian Nordic, Endocyte
Consulting or Advisory Role: Janssen Biotech, Amgen, AVEO, BIND Biosciences, LSK Biopharma–Apatinib, Cerulean Pharma, Pfizer
Speakers' Bureau: Medivation, Dendreon, Bayer, Caris MPI, Millennium Pharmaceuticals, sanofi-aventis, GlaxoSmithKline, Pfizer, Genentech
Research Funding: PAREXEL International (Inst), Progenics (Inst), Exelixis (Inst), US Oncology (Inst), Viamet Pharmaceuticals (Inst), Endocyte (Inst), GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: Genentech, Celgene, US Oncology, Dendreon, Novartis, Pfizer, Bayer/Onyx, Exelixis

Ian M. Thompson
Consulting or Advisory Role: Exosome Diagnostics, Magforce
Patents, Royalties, Other Intellectual Property: I have been involved in the establishment of a new company, NanoTX Therapeutics, to commercialize a novel therapy for glioblastoma for our cancer center. I am on the Board of Directors, and it has intellectual property developed by our cancer center. I have several patents with colleagues involving novel biomarkers for cancer and two devices for sexual dysfunction and urinary incontinence. No revenues at this time and our university IP office is working with industry to determine if these can be commercialized.

Kim N. Chi
Honoraria: sanofi-aventis, Janssen Pharmaceuticals, Astellas Pharma
Consulting or Advisory Role: ESSA, Astellas Pharma, Janssen Pharmaceuticals, sanofi-aventis, Eli Lilly/ImClone, Amgen, Bayer, Takeda
Research Funding: Janssen Pharmaceuticals (Inst), Astellas Pharma (Inst), Amgen (Inst), Bayer (Inst), Novartis (Inst), sanofi-aventis (Inst), Exelixis (Inst), Tokai Pharmaceuticals (Inst), Oncogenex (Inst), TEVA Pharmaceuticals (Inst)

Johann de Bono
Honoraria: AstraZeneca, sanofi-aventis, Astellas Pharma, Pfizer, Genentech
Consulting or Advisory Role: AstraZeneca, sanofi-aventis, Genentech, Astellas Pharma
Research Funding: AstraZeneca (Inst), Genentech (Inst), sanofi-aventis (Inst)
Patents, Royalties, Other Intellectual Property: Abiraterone Rewards to Inventors (Inst), PARP inhibitors and DNA repair defects (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Astellas Pharma, GlaxoSmithKline, Orion Pharma, sanofi-aventis, Genmab, Taiho Pharmaceutical, Qiagen, Vertex
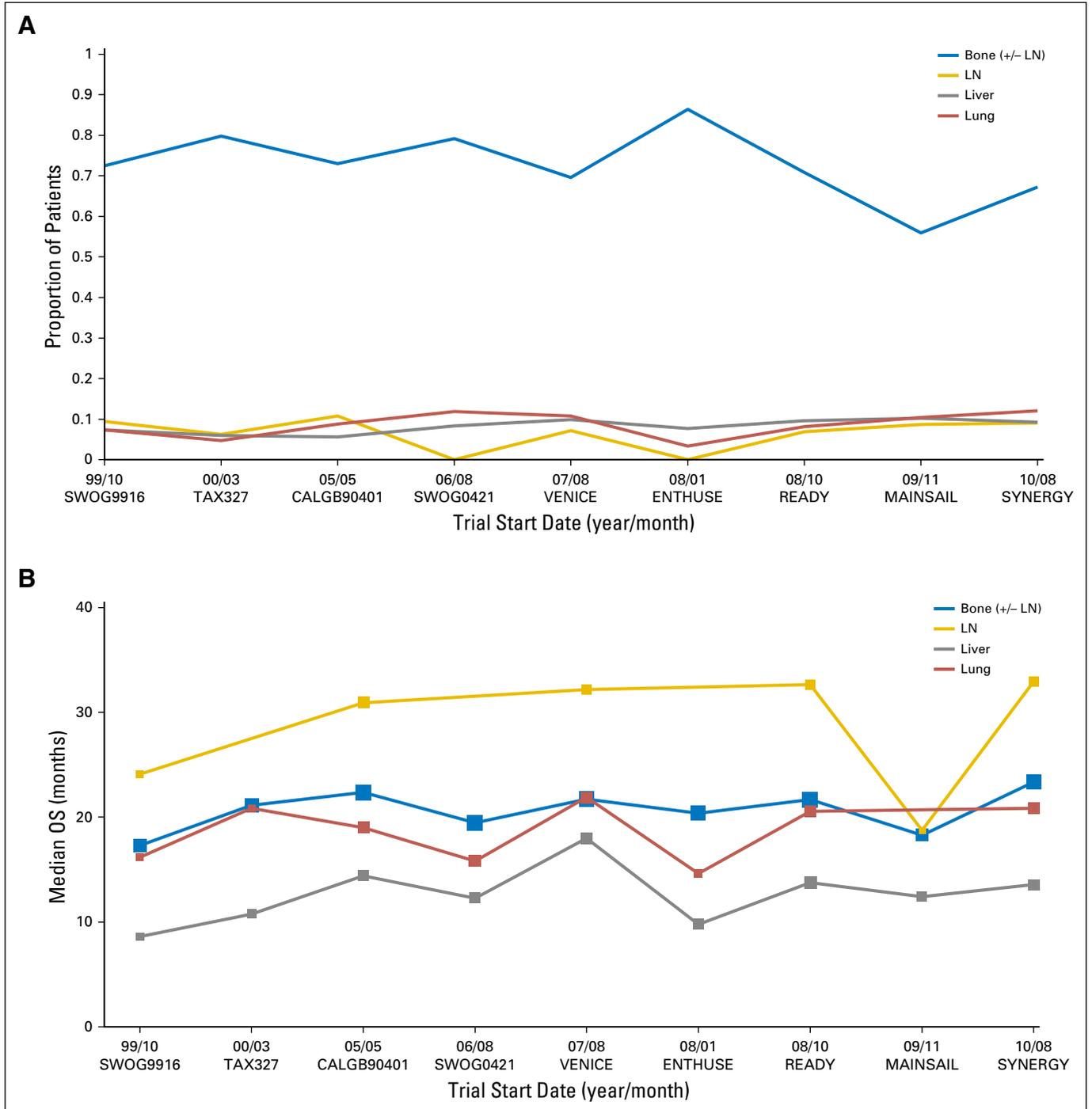
Appendix

Fig A1. (A) Proportion of patients by site of metastases by trial start date across the different trials. (B) Median overall survival (OS) by site of metastases and by trial start date across the different trials. CALGB, Cancer and Leukemia Group B; ENTHUSE, Endothelin A Use; LN, lymph node.
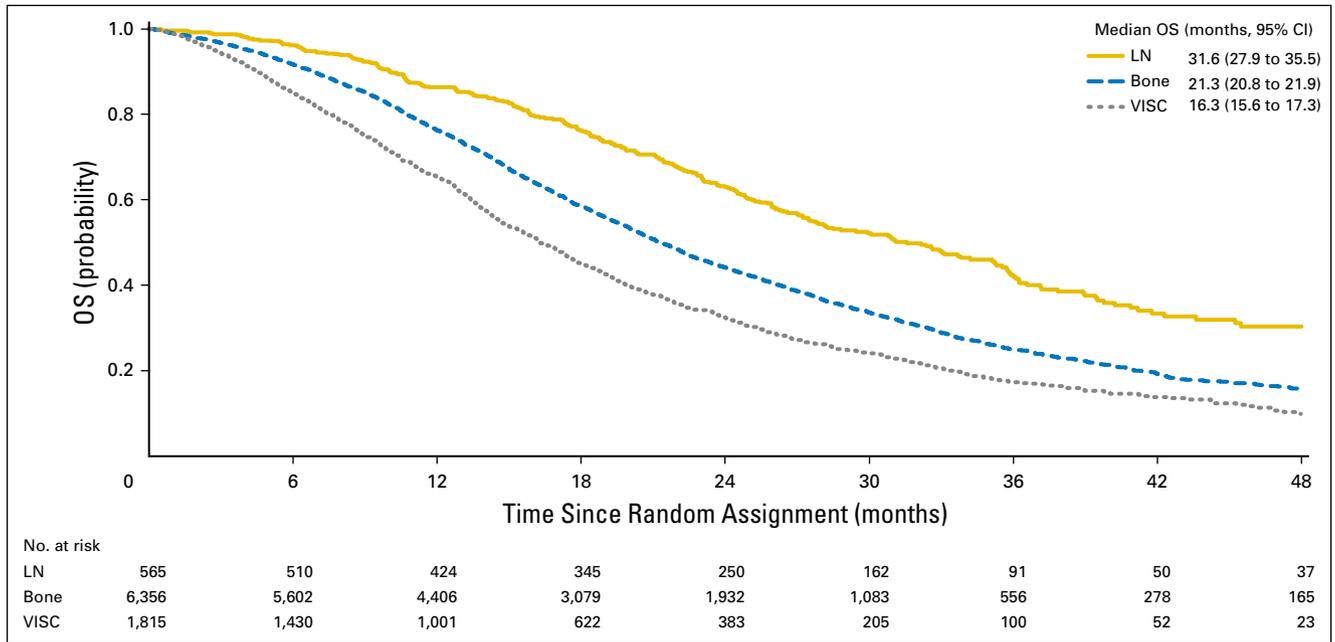
Fig A2. Kaplan-Meier overall survival (OS) curves by the site of metastases. LN, lymph node; VISC, visceral.
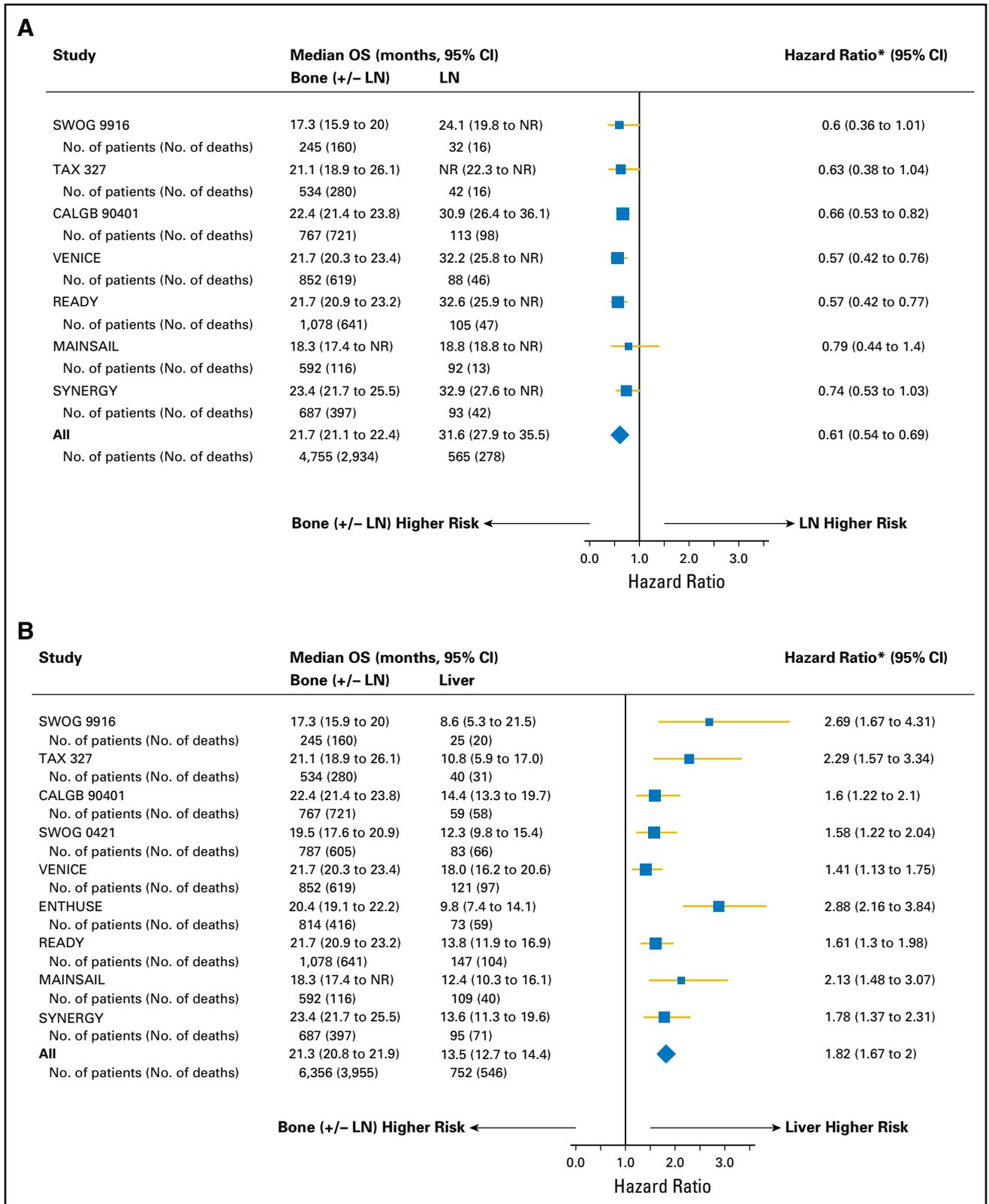
Fig A3. (A) Forest plot with hazard ratios comparing men with lymph node (LN)-only metastases to men with bone metastases with or without nodal involvement (reference group = bone with or without nodal involvement; Q = 1.829, df = 6, P = .935, I^2 = 0.00). (*) Adjusted on age, performance status, and prostate-specific antigen (with the exception of the summary hazard ratio). The SWOG 0421 and Endothelin A Use (ENTHUSE) trials did not have patients with LN metastases and were excluded from this comparison. (B) Forest plot with hazard ratios comparing men with liver metastases to men with bone metastases with or without nodal involvement (reference group = bone with or without nodal involvement; Q = 8.064, df = 8, P = .427, I^2 = 0.00). (*) Adjusted on age, performance status, and prostate-specific antigen (with the exception of the summary hazard ratio). CALGB, Cancer and Leukemia Group B; NR, not reached; OS, overall survival.