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Authors

Lara, Primo N

Mayerson, Edward

Gertz, Erik

et al.

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Bone biomarkers and subsequent survival in men with hormone sensitive prostate cancer: results from the SWOG S1216 phase III trial of androgen deprivation therapy with or without orteronel

Primo N. Lara Jr.,
University of California Davis Comprehensive Cancer Center, Sacramento, CA

Edward Mayerson,
SWOG Statistical Center, Seattle, WA

Erik Gertz,
US Department of Agriculture, Western Human Nutrition Research Center, University of California Davis, Davis, CA

Catherine Tangen,
SWOG Statistical Center, Seattle, WA

Amir Goldkorn,
USC Norris Comprehensive Cancer Center, Los Angeles, CA

Marta van Loan,
US Department of Agriculture, Western Human Nutrition Research Center, University of California Davis, Davis, CA

Maha Hussain,
Northwestern University, Chicago, IL

Shilpa Gupta,
Cleveland Clinic, Cleveland, OH

Jingsong Zhang,
Moffit Cancer Institute, Tampa Bay, FL

Mamta Parikh,
University of California Davis Comprehensive Cancer Center, Sacramento, CA

Przemyslaw Twardowski,
St. John's Cancer Institute, Providence Health, Santa Monica, CA

David I. Quinn,

Address for editorial correspondence: Primo N. Lara, Jr., M.D., Professor of Medicine and Executive Associate Dean, University of California School of Medicine, Director, University of California Davis Comprehensive Cancer Center, 4501 X Street, Sacramento, CA 95817, Tel: 916-734-3771; Fax: 916 734 7946, pnlara@ucdavis.edu. Address for other inquiries: Southwest Oncology Group Chair's Office, Group Chair's Office, OHSU Knight Cancer Institute, Marquam II, 2611 SW 3rd Avenue MQ280, Portland, OR 97201, Tel. 503.505.4198, arlauskp@ohsu.edu.

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USC Norris Comprehensive Cancer Center, Los Angeles, CA

Michael LeBlanc,
SWOG Statistical Center, Seattle, WA

Nicholas J. Vogelzang,
Comprehensive Cancer Centers of Nevada, Las Vegas, NV

Ian Thompson,
Christus Santa Rosa Health System, San Antonio, TX Health, San Antonio, TX

Neeraj Agarwal
Huntsman Cancer Institute, Salt Lake City, UT

Abstract

Background: Bone biomarkers are strongly prognostic for overall survival (OS) in men with castration resistant prostate cancer but not fully established for hormone sensitive prostate cancer (HSPC). Bone biomarkers in HSPC were prospectively evaluated as part of a phase III study of androgen deprivation therapy +/− the CYP17 inhibitor orteronel.

Methods: Bone resorption [C-telopeptide (CTx) and Pyridinoline (PYD)] and bone formation markers [C-terminal collagen propeptide (CICP) and bone alkaline phosphatase (BAP)] were assessed from patient sera. Patients were randomly divided into training (n=316) and validation (n=633) sets. Recursive partitioning and Cox proportional hazard models were employed.

Results: Of 1,279 men, 949 had evaluable baseline bone biomarkers. Optimal cutoffs were identified to define elevated levels of each of the four biomarkers (all $p<0.05$) that were associated with worse OS. After adjusting for clinical risk factors in the validation set, elevated bone biomarkers were statistically significantly associated with an increased risk of death (hazard ratios ranging from 1.37 – 1.92). Recursive partitioning algorithms applied to the training set identified three risk groups (low, intermediate, and poor) with differential OS outcomes (median OS: 8.2, 5.1, and 2.1 years, respectively) based on combinations of bone biomarkers. These results were confirmed in the validation set.

Conclusions: In men with HSPC initiating androgen deprivation therapy, bone biomarkers are strongly and independently prognostic for OS. Bone biomarker levels alone or in combination with clinical covariates identify unique subsets of men with differential OS outcomes. These results validate the clinical value of bone biomarker assessment in the HSPC state, extending bone biomarker utility beyond the castration resistant state.

Statement of Translational Relevance

Bone biomarkers in men with hormone sensitive prostate cancer (HSPC) were evaluated as part of S1216, a phase III study of androgen deprivation therapy with or without the CYP17 inhibitor orteronel, a trial that established new overall survival (OS) benchmarks in HSPC. The results of this prospective study showed that bone metabolism biomarkers have statistically significant associations with OS in these men. Elevated levels of each of four baseline bone biomarkers measured in this trial were strongly and statistically significantly (all $p<0.05$) prognostic for worse survival, adjusted for traditional risk factors. Recursive partitioning algorithms identified three risk groups (low, intermediate, and poor risk) with markedly different OS outcomes (median

OS: 8.2, 5.1, and 2.1 years, respectively) based on bone biomarker combinations and findings were confirmed in the validation set. These results validate the clinical value of bone biomarker assessment beyond castration resistance and into the hormone sensitive state of prostate cancer and have implications for clinical care and future research.

Background

Bone homeostasis - a finely balanced interplay between bone formation mediated by osteoblasts and bone resorption mediated by osteoclasts - is commonly perturbed in men with advanced prostate cancer.[1] These men often present with skeletal metastasis, a common source of morbidity such as bone pain and fracture. For those with radiographically evident bone metastases, there is a predominance of osteoblastic activity which manifests as sclerotic bony disease. In addition, as a component of frontline therapy, men with metastatic hormone sensitive prostate cancer (HSPC) are typically treated with androgen deprivation therapy (ADT) which disrupts bone turnover and subsequently contributes to the development of osteopenia and osteoporosis.[2]

Circulating markers of bone turnover can be readily measured in patient serum using commercially available, validated assays.[3] We have previously shown that elevated levels of blood-based biomarkers of bone turnover are independently prognostic for survival in men with castration resistant prostate cancer (CRPC).[4 5] We also showed that in subset of men with CRPC, highly elevated markers predict for better survival with bone targeted therapy.

We sought to extend our observations in CRPC to the HSPC context by evaluating the prognostic and predictive value of bone turnover biomarkers in men with advanced or metastatic HSPC who are initiating ADT as part of a large phase III clinical trial. We also sought to identify unique subsets of patients with differential survival outcomes as defined by clinical variables and bone turnover biomarkers.

Methods

SWOG S1216 was a phase 3, randomized, open-label, multicenter trial in men with metastatic HSPC. The primary results of S1216 have been previously reported.[6] Patients were enrolled from 248 academic and community centers throughout the United States. The NCI Central Institutional Review Board approved the study. The study was conducted in accordance with the International Conference on Harmonization of Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. Signed written consent was obtained from all participants. Eligible patients were required to have histologically confirmed adenocarcinoma of the prostate and metastatic disease as evidenced by soft tissue and/or bony metastases. Eligible patients had a Zubrod performance status of 0–2 (although performance status 3 was allowed if from bone pain only) and a prostate-specific antigen (PSA) level of ≥ 2.0 ng/mL. Extent of disease was defined as “minimal” if involving vertebrae and/or pelvic bones and/or lymph nodes, or as “extensive” if greater than minimal involvement; this criterion has been employed in all SWOG trials in HSPC since 1989. No other prior systemic therapy for metastatic prostate cancer was allowed, with the exception

of up to 30 days of ADT for metastatic disease prior to randomization, and at least six months must have elapsed since completion of prior neoadjuvant and/or adjuvant ADT. Patients were randomly assigned in a 1:1 ratio to receive orteronel (300 mg) orally twice daily or bicalutamide (50 mg) administered orally once daily, in addition to continuous ADT. Although S1216 did not meet the primary endpoint of improved overall survival with ADT plus orteronel compared to ADT plus bicalutamide, there was statistically significant improvement in progression-free survival (PFS) and PSA response seen in the orteronel plus ADT compared to bicalutamide plus ADT. New benchmarks for overall survival in HSPC were established by this trial, with median overall survival of 81.1 months in the orteronel arm and 70.2 months in the control arm.

Markers for bone formation (C-terminal collagen propeptide [CICP] and bone alkaline phosphatase [BAP]) and bone resorption (C-telopeptide [CTx] and pyridinoline [PYD]) were assessed in baseline sera who from men participating in SWOG S1216. Participation in this translational study was not required for S1216, but participants must have been offered the opportunity to participate. CICP was evaluated using a sandwich enzyme-linked immunosorbent assay (Quidel Corp, San Diego, CA) on a microtiter plate coated with monoclonal anti-C1CP antibody. Bone-specific alkaline phosphatase (BAP) activity was assessed using the Microvue BAP enzyme-linked immunosorbent assay (Quidel Corp) employing a monoclonal anti-BAP antibody coated on a microtiter plate. C-telopeptide (CTx) was measured by a competitive enzyme-linked immunosorbent assay (Wampoles Laboratories, Princeton, NJ). Pyridinoline (PYD) was assessed using a competitive enzyme immunoassay (Quidel Corp). Bone biomarker results were rounded to the largest whole number (BAP, CICP) or tenth (CTx, PYD).

Patients were randomly split into training (1/3; n=316) and validation (2/3; n=633) sets for model development and evaluation. Utilizing the training dataset, survival tree algorithms developed by Leblanc and Crowley were used to identify split points in each individual bone marker using survival data.[7] The ideal univariate split point within each biomarker was defined as the value at which the log-rank test statistic for survival between the groups was maximized, allowing for the distinction within each bone biomarker when risk becomes elevated. Separately, survival tree algorithms were used to identify linear combinations of biomarker splits that maximized differences in survival in the training set to create categorical risk groups within the population. This approach assesses potential interactions among the four bone biomarkers. Splits were identified through recursive testing that maximized the log-rank statistic between groups, resulting in multiple possible splits within individual bone markers. All recursive partitioning required a minimum of 10% of patients in each group to reduce the influence of extreme outliers on splits, and a tree pruning algorithm was applied to only select groups with close to statistically significant splits (nominal p-value < 0.1) in the recursive partitioning algorithm. There was no adjustment for other risk factors at this point in the analysis.

After determining split points for elevated bone markers, the split points were applied to the validation set, and the elevation of each individual bone marker and the combination of markers were individually evaluated as a potential prognostic factor for overall survival using Cox proportional hazards models. These models adjusted for treatment arm, disease

extent, Zubrod performance status, African American (Y/N), Gleason Score, age (divided by 5), the natural logarithm of PSA at S1216 randomization, and presence of visceral metastases. An additional interaction term between bone marker elevation and treatment arm was evaluated using a score chi-square test; in the event of a statistically significant interaction ($p< 0.1$), implying that the bone marker was a predictive factor, two separate models would be developed for each of the treatment arms.

All p-values reported are two-sided with a p-value ≤ 0.05 considered statistically significant. An additional Bonferroni correction for n=5 models (4 individual bone marker tests and one linear combination of markers) was calculated and applied to bone marker significance tests, allowing readers to draw conclusions based on the multiple comparisons (see footnote in Table 3). All split points were identified utilizing programs developed in the R programming language, and all confirmatory analyses were performed using SAS 9.3.

Results

Of 1,313 patients enrolled in S1216, 1,279 were eligible and followed for survival. Of these 1,279 eligible patients, baseline blood serum samples were drawn from 995 patients. Forty-six patients were excluded from this analysis due to missing one or more bone biomarkers at baseline; the resulting 949 patients with all four bone markers (BAP, CICP, CTx, PYD) having a measured result constituted the analysis population. Patient characteristics are summarized in Table 1. Median age was 67 years (IQR 61–73). Median prostate specific antigen (PSA) level was 30 ng/dL (IQR 10–109). Gleason score greater than 7 was seen in 60% of participants. Most men (97%) had a Zubrod performance status of 0 or 1. Only 13% of patients had visceral metastatic disease while 713 (75%) had bone metastases at study entry.

Baseline bone biomarker distributions are summarized in Table 2. The median for each bone biomarker value observed were: CTx 0.4 ng/mL; PYD 1.6 nmol/L; CICP 125 ng/mL; BAP 3 u/L. Biomarker values at dichotomized cut-points that maximized survival differences were: CTx 0.6 ng/mL; PYD 2.0 nmol/L; CICP 245 ng/mL; BAP 37 u/L. Interestingly, for three bone markers, the split was somewhere close to the 85^{th} percentile, while the split point for maximal survival difference in PYD was found to be closer to the median (see Supplementary Table S1).

Allowing for possible linear combinations of the four bone markers, four groups of patients with differential survival outcomes were identified based on splits in CTx and CICP. Splits in the other two bone markers, BAP and PYD, were not identified as providing a statistically significant contribution to explaining differences in overall survival after accounting for CTx and CICP values. Additional assessment of combination bone biomarker groups during the training process led to the consolidation of the four risk groups into three risk groups, as two of the groups with intermediate survival outcomes identified showed no statistically significant difference in survival (Log-Rank test statistic = 0.65, df=1, p=0.4). The three risk groups were categorized as low, intermediate, and poor risk, each with differential survival outcomes (lower half of Table 3). Applying those risk group algorithms in the validation set, low risk patients had a median survival time of 8.2 years (95% CI: 6.9, NR). Intermediate

risk patients had a median survival time of 5.1 years (95% CI: 4.0, 6.3). Poor risk patients had a median survival time of 2.1 years (95% CI: 1.5, 3.4), mirroring survival estimates for men with advanced castration resistant disease (Figure 1).

Within the population of patients with bone markers available at baseline in the validation set, elevated levels of each of the four biomarkers were statistically significantly associated with an increased risk of death after adjusting for other risk factors (Table 3; Supplementary Figure S1). Elevated CICP had a hazard ratio of 1.92 ($p<0.001$; 95% CI 1.40, 2.64): men with low CICP had median OS of 7.6 years versus 2.4 years for those with high CICP. Elevated BAP had a hazard ratio of 1.43 ($p=0.040$; 95% CI 1.02, 2.01): men with low BAP had median OS of 6.8 years versus 3.3 years for those with high BAP. Elevated CTx had a hazard ratio of 1.37 ($p=0.010$; 95% CI 1.07, 1.77): men with low CTx had median OS of 7.7 years versus 4.0 years for those with high CTx. Elevated PYD had a hazard ratio of 1.77 ($p<0.001$; 95% CI 1.39, 2.25): men with low PYD had median OS of 8.2 years versus 3.4 years for those with high PYD. There was no evidence of an interaction between elevation of individual bone markers and treatment ($p> 0.4$ for all markers). The combination bone marker groups (2 indicators for 3 groups) were also statistically significantly associated with an increased risk of death over the course of follow-up on S1216 (2 df test, $p<0.001$), with elevated groups having a higher risk of death over those with lower bone marker values. No treatment interaction was found with the risk groups ($p=0.4$). Supplementary Figure S2 shows the bone marker combination tree for all patients in the training set, while Supplementary Figure S3 shows the survival curves for the bone marker combination groups for those patients in the training set.

Discussion

The results of this prospectively designed study demonstrate the strong association between biomarkers of bone turnover and overall survival in men with advanced or metastatic hormone sensitive prostate cancer. Clinically annotated serum specimens collected from nearly a thousand men with prostate cancer enrolled in the SWOG S1216 phase III trial allowed for a robust evaluation of the association between marker levels and patient outcome. Elevated levels of each of the four bone biomarkers – using cut-points derived from a training set and subsequently tested in a validation set – showed statistically significant association with worse survival outcomes, independent of traditional clinical risk factors. Importantly, using regression tree analysis, unique subsets of men with differential survival outcomes (i.e., low, intermediate, and poor risk) were identified employing combinations of bone markers. These results have potentially important clinical implications.

Prior work in this context had focused on men with advanced castration resistant prostate cancer (CRPC), a cohort of patients who have had prolonged exposure to androgen deprivation therapy and whose tumor cells have developed mechanisms of resistance. Most of the biomarker work in prostate cancer such as circulating tumor cells or prostate specific membrane antigen (PSMA) expression has been performed in men with castration resistant disease.[8 9] Even our prior work defining the value of bone turnover markers in prostate cancer was limited to the CRPC setting. In a study of men with CRPC enrolled

in SWOG S0421 – a phase III trial of docetaxel/prednisone with or without the endothelin antagonist atrasentan – we reported that high levels of baseline circulating markers of bone metabolism were not only prognostic for survival, but were predictive of a survival benefit from atrasentan in a subset of men with the highest bone marker levels. [4 10] Similar to the present study, we also performed a classification and regression tree analysis as part of the S0421 study wherein bone biomarkers were evaluated in conjunction with baseline clinical covariates. In that work, we identified five prognostic subgroups of CRPC patients with differential survival outcomes.[11] Thus, the findings reported in the present work extend the clinical utility of circulating markers of bone metabolism from the CRPC state to the hormone sensitive state.

Additionally, bone turnover biomarkers are poised for pragmatic clinical use: they can be conveniently obtained through phlebotomy and measured using commercially available assays. Clinicians and researchers are therefore able to obtain such specimens and be able to interpret those results – in conjunction with the results presented here – to guide patient counselling and future research. For example, future early phase clinical trials can employ this information to identify high risk groups to screen for new drugs by identifying those with worse prognosis in order to increase pace of trial.[12] Additionally, bone biomarkers could someday be a component of a biologically-informed multi-dimensional model that comprises complex molecular and clinical data to yield prognostic and predictive utility.

This study has several limitations. First, only four bone biomarkers were evaluated – two each to represent bone resorption and formation. Conceivably, other related or newer bone biomarkers (e.g., those involved in RANK ligand signaling) – either circulating in blood or tissue-based – could have contributed even more convincing associations with patient outcome. Second, the bone biomarkers in this study only showed strong prognostic value but not predictive (or prescriptive) value. As reported here, high bone biomarker levels were not predictive of a survival benefit from the investigational agent orteronel. Future studies of therapeutic agents specifically targeted against bony metastatic disease could provide an additional platform on which to assess the predictive value of bone metabolism biomarkers. Third, the association of elevated baseline bone biomarkers with subsequent development of skeletal related events (such as bone pain or fracture) was not a focus of the present analysis. Finally, the dynamics of bone biomarkers in blood could potentially be influenced by any number of external factors, including the timing of androgen deprivation therapy initiation, calcium/vitamin D supplementation, or the use of anti-resorptive therapies such as bisphosphonates. It must be noted that the role of anti-resorptive therapy in hormone sensitive prostate cancer is limited and presently remains an area of controversy.[13] In fact, in the S1216 study, only 5% of patients were receiving any type of anti-resorptive therapy at the time of study entry. Their small numbers did not influence the results reported here. Nevertheless, it is notable that a prior phase 3 trial found no improvement in the rate of skeletal related events with early use of zoledronic acid in men with metastatic hormone sensitive prostate cancer,[14] even though it is acknowledged that such therapy may have some influence on bone biomarker dynamics.

In summary, the subsequent survival of men with newly diagnosed metastatic hormone sensitive prostate cancer following the initiation of androgen deprivation therapy is strongly

and statistically significantly associated with baseline serum levels of bone metabolism biomarkers. These results can be employed by clinicians in counselling patients and by researchers in the design and conduct of future trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Whitburn J, Edwards CM. Metabolism in the Tumour-Bone Microenvironment. Curr Osteoporos Rep. 2021 Oct;19(5):494–499. [PubMed: 34319488]
2. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, Penson DF, Rosario DJ, Tombal B, Smith MR. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67(5):825–36. [PubMed: 25097095]
3. Smith MR. Markers of bone metabolism in prostate cancer. Cancer Treat Rev. 2006;32 Suppl 1:23–6. [PubMed: 16680835]
4. Lara PN Jr, Ely B, Quinn DI, Mack PC, Tangen C, Gertz E, Twardowski PW, Goldkorn A, Hussain M, Vogelzang NJ, Thompson IM, Van Loan MD. Serum biomarkers of bone metabolism in castration-resistant prostate cancer patients with skeletal metastases: results from SWOG 0421. J Natl Cancer Inst. 2014;106(4): dju013 [PubMed: 24565955]
5. Lara PN Jr, Stadler WM, Longmate J, et al. A randomized phase II trial of the matrix metalloproteinase inhibitor BMS-275291 in hormone-refractory prostate cancer patients with bone metastases. Clinical Cancer Research 2006;12:1556–63. [PubMed: 16533781]
6. Agarwal N, Tangen CM, Hussain MA, et al. Orteronel for metastatic hormone sensitive prostate cancer: A multicenter, randomized, open-label phase III trial (SWOG-1216). Journal of Clinical Oncology (in press)
7. Leblanc M, Crowley J. Survival Trees by Goodness of Split. Journal of the American Statistical Association 1993. 88:422, 457–467.
8. Pantel K, Hille C, Scher HI. Circulating Tumor Cells in Prostate Cancer: From Discovery to Clinical Utility. Clin Chem. 2019;65(1):87–99. [PubMed: 30602476]
9. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, Tagawa ST, Nordquist LT, Vaishampayan N, El-Haddad G, Park CH, Beer TM, Armour A, Pérez-Contreras WJ, DeSilvio M, Kpamegan E, Gericke G, Messmann RA, Morris MJ, Krause BJ; VISION Investigators. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2021;385(12):1091–1103. [PubMed: 34161051]
10. Quinn DI, Tangen CM, Hussain M, Lara PN Jr, Goldkorn A, Moinpour CM, Garzotto MG, Mack PC, Carducci MA, Monk JP, Twardowski PW, Van Veldhuizen PJ, Agarwal N, Higano CS, Vogelzang NJ, Thompson IM Jr. Docetaxel and atrasentan versus docetaxel and placebo for men with advanced castration-resistant prostate cancer (SWOG S0421): a randomised phase 3 trial. Lancet Oncol. 2013;14(9):893–900. [PubMed: 23871417]
11. Lara PN Jr, Plets M, Tangen C, Gertz E, Vogelzang NJ, Hussain M, Twardowski PW, Garzotto MG, Monk JP, Carducci M, Goldkorn A, Mack PC, Thompson I, Van Loan M, Quinn DI. Bone turnover biomarkers identify unique prognostic risk groups in men with castration resistant prostate cancer and skeletal metastases: Results from SWOG S0421. Cancer Treat Res Commun. 2018;16:18–23. [PubMed: 31298998]

12. Saad F, Lipton A. Bone-marker levels in patients with prostate cancer: potential correlations with outcomes. Curr Opin Support Palliat Care. 2010 Sep;4(3):127–34. [PubMed: 20489645]
13. Todenhöfer T, Stenzl A, Hofbauer LC, Rachner TD. Targeting bone metabolism in patients with advanced prostate cancer: current options and controversies. Int J Endocrinol. 2015; Epub 2015 Jan 31.
14. Smith MR, Halabi S, Ryan CJ, et al. Randomized controlled trial of early zoledronic acid in men with castration-sensitive prostate cancer and bone metastases: results of CALGB 90202. J Clin Oncol 2014;32(11):1143–50. [PubMed: 24590644]

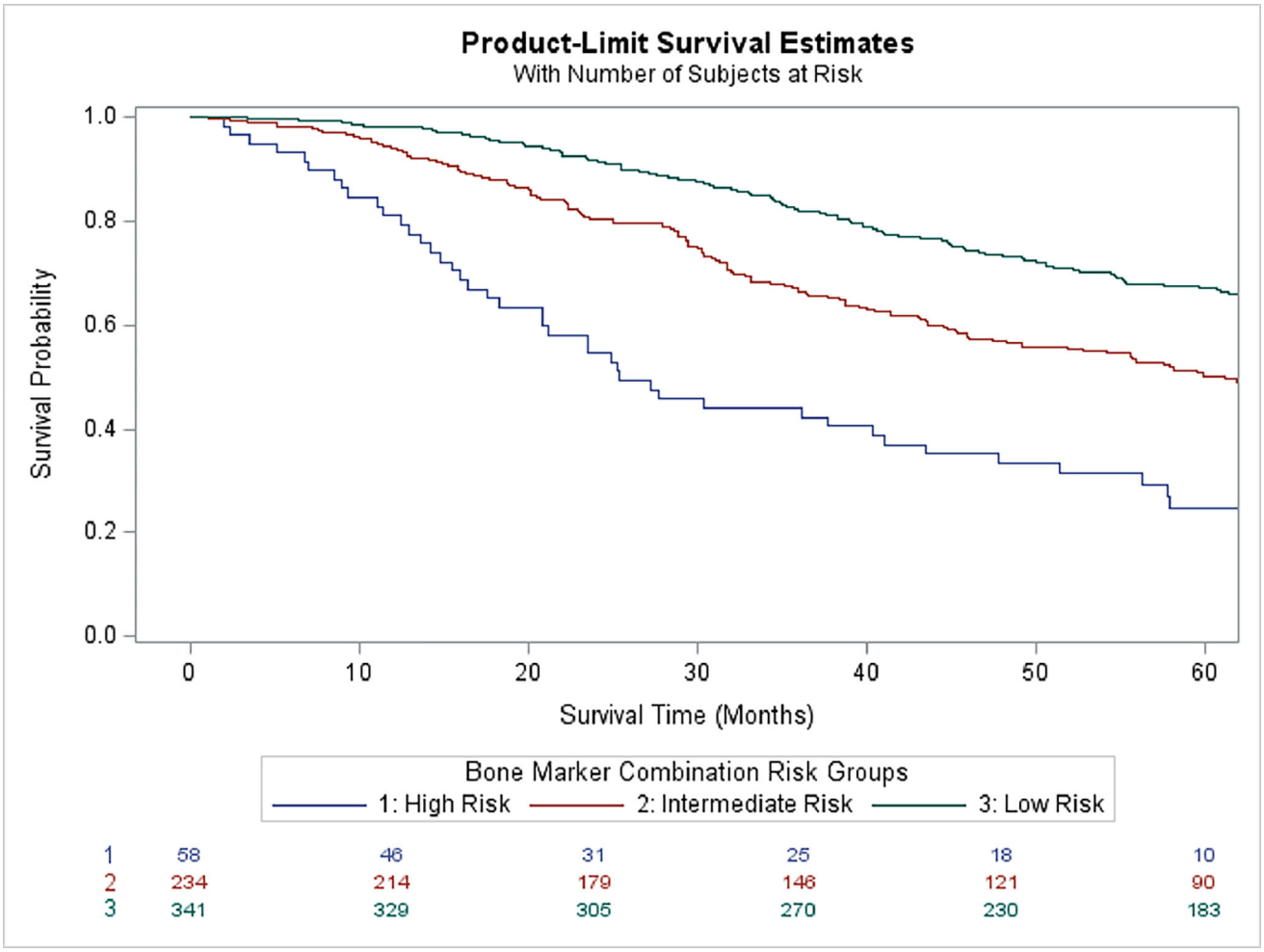

Figure 1:
Kaplan-Meier Curves for Bone Marker Combination (Validation Set)

Table 1:

Baseline characteristics of patients included in the pooled arms bone marker analyses

	S1216 Primary Analysis Population	**All Patients with Baseline Bone Markers**
	N=1279	N=949
Pct. Patients on TAK-700 Treatment Arm	50%	50%
Minimal Severity of disease*	51%	50%
Zubrod performance status 0–1	96%	97%
PSA at study entry – Median (IQR 25, 75)	30 (10, 109)	28 (9, 100)
Gleason Score		
<= 6	6.7%	7.0%
7	26%	26%
>= 8	59%	60%
missing	8.2%	7.5%
Visceral Metastases**	14%	13%
Age at study entry, years – Median (IQR 25,75)	67 (61, 73)	68 (62, 73)
Race		
Black	11%	9.4%
White	84%	86%
Asian	1.8%	1.9%
Native-American	0.2%	0.2%
Pacific Islander	0.1%	0%
Multiple	0.2%	0.1%
Other race, unknown	2.9%	2.6%

*Minimal disease is defined as involvement of vertebrae and/or pelvic bones and/or lymph nodes, while extensive disease is defined as that with greater than minimal involvement.

**In the 949 patients included in this analysis, 2.4% had liver metastases while 11.4% had visceral metastases at other sites IQR = interquartile range

Table 2:

Baseline Serum Bone Marker Concentrations

		All Patients with Baseline Bone Markers (n=949)
BAP (U/L)	Median (25 %tile, 75 %tile)	3 (1, 22)
CICP (ng/mL)	Median (25 %tile, 75 %tile)	125 (93, 178)
CTx (ng/mL)	Median (25 %tile, 75 %tile)	0.4 (0.3, 0.7)
PYD (nmol/L)	Median (25 %tile, 75 %tile)	1.6 (1.2, 2.2)

Table 3:

Hazard Ratio Estimates for Elevated Bone Markers – Validation Set (N=633)

Bone Marker	Median Survival by Group – Years (95% CI)	Hazard Ratio for Elevated Markers* (95% CI)	Bone Marker p-value*^
BAP (U/L)	Hi: 3.3 (2.4, 4.0) Lo: 6.8 (5.7, NR)	1.43 (1.02, 2.01)	0.040
CICP (ng/mL)	Hi: 2.4 (1.9, 3.4) Low: 7.6 (6.4, NR)	1.92 (1.40, 2.64)	<0.001†
CTx (ng/mL)	Hi: 4.0 (3.2, 5.0) Low: 7.7 (6.6, NR)	1.37 (1.07, 1.77)	0.014
PYD (nmol/L)	Hi: 3.4 (3.0, 4.3) Low: 8.2 (6.8, NR)	1.77 (1.39, 2.25)	<0.001†
Bone Marker Combination			<0.001†
Low Risk CTx < 0.6 & CICP < 161	8.2 (6.9, NR)	1 (reference)	
Intermediate Risk CTx < 0.6 & CICP >= 161 Or CTx >= 0.6 & CICP < 286	5.1 (4.0, 6.3)	1.41 (1.10, 1.83)	
High Risk CTx >= 0.6 & CICP > 286	2.1 (1.5, 3.4)	2.15 (1.45, 3.18)	

*Adjusted for treatment arm, extent of disease, Zubrod PS, PSA at randomization, Gleason Score, age, African-American (Y/N), and visceral mets status (Y/N).

^p-values from Wald Chi-Square test for Type 3 analysis of effects, testing global hypothesis (i.e., do the risk groups have different survival distributions?)

†indicates statistical significance when adjusting for multiple comparisons using Bonferroni correction (n=5 tests; p<0.01)

NOTE: NR indicates survival estimate was not reached