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ORIGINAL ARTICLE

Correlation analyses of radiographic progression-free survival with clinical and health-related quality of life outcomes in metastatic castration-resistant prostate cancer: Analysis of the phase 3 VISION trial

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Abstract

Background: [^{177}Lu]Lu–PSMA-617 (^{177}Lu-PSMA-617) plus protocol-permitted standard of care (SOC) prolonged overall survival (OS) and radiographic progression-free survival (rPFS) versus SOC in patients with prostate-specific membrane antigen (PSMA)–positive metastatic castration-resistant prostate

This trial was registered at ClinicalTrials.gov (NCT03511664) and EudraCT (2018-000459-41).

cancer (mCRPC) in the phase 3 VISION study, in addition to beneficial effects on symptomatic skeletal events (SSEs) and health-related quality of life (HRQOL).

Methods: Post hoc analyses used the full analysis set from the VISION study (N = 831) overall and by randomized treatment arm (^{177}Lu-PSMA-617 plus SOC, n = 551; SOC, n = 280). Correlations were determined between OS and rPFS and between rPFS or OS and time to SSE or to worsening HRQOL (Functional Assessment of Cancer Therapy–Prostate [FACT-P] and 5-level EQ-5D [EQ-5D-5L]). Correlation analyses used an iterative multiple imputation copula-based approach (correlation coefficients [rho] of <0.3 were defined as weak, ≥0.3 and <0.5 as mild, ≥0.5 and <0.7 as moderate, and ≥0.7 as strong).

Results: In the overall population, rPFS correlated strongly with OS (rho, ≥0.7). Correlations between rPFS or OS and time to SSE without death were weak or mild. Time to worsening in the FACT-P total score and emotional and physical well-being domains correlated mildly or moderately with rPFS and moderately with OS. Correlation coefficients for time-to-worsening EQ-5D-5L scores were mild to moderate for both rPFS and OS. Correlation coefficients were similar between treatment arms.

Conclusions: In this analysis of the VISION study, rPFS correlated strongly with OS but not with time to SSE or worsening HRQOL. These findings require further investigation.

KEYWORDS
^{177}Lu-PSMA-617, health-related quality of life (HRQOL), metastatic castration-resistant prostate cancer (mCRPC), radiographic progression-free survival (rPFS)

INTRODUCTION

Metastatic castration-resistant prostate cancer (mCRPC) is incurable and fatal.[1,2] It is a complex disease where progression can often occur in the absence of measurable lesions, and there are few generally accepted biomarkers or intermediate end points to act as response criteria.[3,4]

The US Food and Drug Administration and the European Medicines Agency have previously called for additional, clinically meaningful criteria that might be used to support regulatory evaluation of new prostate cancer treatments.[5–7] Consequently, the Prostate Cancer Working Group (PCWG) issued consensus-based recommendations to standardize outcomes in mCRPC trials, which included radiographic progression-free survival (rPFS).[3,8,9] In the third PCWG iteration (PCWG3), rPFS was defined as "the time interval from random assignment to the date when the first site of disease is found to progress (using a manifestation-specific definition of progression), or death, whichever occurs first."[9] This definition does not include symptomatic skeletal events (SSEs),[10] although PCWG3 recognizes their clinical relevance when they are symptomatic and clinically significant.[9]

The clinical usefulness of rPFS has been demonstrated in multiple clinical trials of androgen receptor pathway inhibitors (ARPIs) in chemotherapy-naive men with mCRPC. The first such trial, COU-AA-302,[11] revealed a strong correlation between rPFS and overall survival (OS) (Spearman correlation coefficient, 0.72),[12] which was recognized by regulators as clinically meaningful.[3,13] The association between OS and rPFS was subsequently validated in the PREVAIL study[14] and in other analyses.[15,16]

[^{177}Lu]Lu–PSMA-617 (^{177}Lu-PSMA-617) is recommended in clinical guidelines for patients with prostate-specific membrane antigen (PSMA)–positive mCRPC who have progressed after at least one previous ARPI and one or two previous taxanes.[17–20] In the large, prospective, randomized phase 3 VISION clinical trial in this population, ^{177}Lu-PSMA-617 plus protocol-permitted standard of care (SOC) prolonged OS and PCWG3-defined rPFS versus SOC alone (which included ARPIs).[21] Treatment with ^{177}Lu-PSMA-617 plus SOC was also associated with a longer time to worsening of health-related quality of life (HRQOL) and to first SSE compared with SOC alone.[18,21,22] In the ongoing phase 3 PSMAfore trial (NCT04689828), ^{177}Lu-PSMA-617 prolonged rPFS versus a change in ARPI in taxane-naive patients with mCRPC.[23]

To date, the strength of the correlation between rPFS and OS in patients with mCRPC receiving ^{177}Lu-PSMA-617 plus SOC is unexplored. Additionally, associations between clinical end points (i.e., rPFS and OS) and time to first SSE or worsening HRQOL and pain warrant further investigation.[24] We analyzed the strengths of these associations in the VISION population overall and by treatment arm.

MATERIALS AND METHODS

Objectives of the post hoc analysis

This was an exploratory post hoc analysis of the randomized phase 3 VISION study of ^{177}Lu-PSMA-617 in patients with mCRPC (ClinicalTrials.gov: NCT03511664; EudraCT: 2018-000459-41).[21] The aim was to determine the strength of correlation between the two VISION alternate primary end points, rPFS and OS, in the whole study population and by randomized treatment arm. Because SSEs are excluded from PCWG3-defined rPFS,[9] we also investigated the correlations between each of the primary end points and time to first confirmed SSE. Additionally, we investigated associations between the primary end points and time to worsening in measures of HRQOL and pain.

In the VISION study, adults with progressive PSMA-positive mCRPC (N = 831) were randomized to receive ^{177}Lu-PSMA-617 7.4 GBq every 6 weeks for up to six cycles plus protocol-permitted SOC (n = 551) or SOC alone (n = 280), as previously described.[21] Protocol-permitted SOC included hormonal treatments (including abiraterone and enzalutamide), bisphosphonates, radiation therapy, denosumab, or glucocorticoids at any dose. Full eligibility criteria plus patient disposition and baseline characteristics have been published previously.[21]

OS was assessed in all randomized patients on an intent-to-treat (ITT) basis with the full analysis set (FAS; N = 831). All other analyses used the progression-free survival full analysis set (PFS-FAS) on an ITT basis. The PFS-FAS (n = 581) included all patients randomized on or after March 5, 2019, of whom 385 were randomized to receive ^{177}Lu-PSMA-617 plus SOC and 196 were randomized to receive SOC.

End points were predefined in the VISION protocol. OS was the time from randomization to the date of death from any cause. rPFS was defined as the time (in months) from the date of randomization to the date of radiographic disease progression based on central review assessment per the PCWG3 criteria or death from any cause (whichever occurred first).[9] In the ^{177}Lu-PSMA-617 arm, rPFS events occurred in 254/385 patients (66.0%) (171 radiographic progressions and 83 deaths [PFS-FAS]). In the SOC arm, rPFS events occurred in 93/196 patients (47.4%) (59 radiographic progressions and 34 deaths [PFS-FAS]).

Time to SSE was predefined as the time from randomization to the first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain, or death from any cause (whichever occurred first). In the ^{177}Lu-PSMA-617 arm there were 256 of 385 first SSEs (66.5%) (60 SSEs and 196 deaths [PFS-FAS]), and in the SOC arm there were 137 of 196 first SSEs (69.9%) (34 SSEs and 103 deaths [PFS-FAS]). For this post hoc investigation, SSE data were also analyzed excluding deaths.

Prostate cancer–specific and generic HRQOL were assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) and 5-level EQ-5D (EQ-5D-5L) instruments, respectively. The level and impact of pain was assessed with the Brief Pain Inventory–Short Form (BPI-SF) questionnaire. For each measure, time to worsening was predefined according to changes from baseline in instrument scores as defined in Table 1.

TABLE 1 Definitions of time to worsening in HRQOL measures.

HRQOL measure	Time-to-worsening definition
FACT-P	
Total score	≥10-point decrease from baseline
Emotional well-being	≥3-point decrease from baseline
Functional well-being	≥3-point decrease from baseline
Prostate cancer subscale	≥3-point decrease from baseline
Pain-related subscale	≥2-point decrease from baseline
Physical well-being	≥3-point decrease from baseline
Social/family well-being	≥3-point decrease from baseline
EQ-5D-5L utility score	Earliest occurrence of "no change" or "any decrease" relative to baseline
BPI-SF	
Severity	≥30% and ≥2-point change from baseline
Interference	≥30% and ≥2-point change from baseline

Abbreviations: BPI-SF, Brief Pain Inventory–Short Form; EQ-5D-5L, 5-level EQ-5D; FACT-P, Functional Assessment of Cancer Therapy–Prostate; HRQOL, health-related quality of life.

The VISION trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Independent ethics review boards approved the trial protocol at each trial site. An independent committee monitored safety throughout the trial. All patients participating in the VISION trial provided written informed consent.

Censoring and correlation analyses

Censoring was performed as follows. For OS, patients not known to have died were censored at the date of last contact. For rPFS as defined in PCWG3 (including death),[9] patients without disease progression were censored at the date of their last evaluable scan. Those without evaluable scans were censored at the date of randomization, and patients with two or more consecutive missed scans immediately before disease progression or death were censored at the date of their last evaluable scan before the first of the two consecutive missing scans.

For this post hoc analysis, early censored time-to-event data for OS and rPFS were imputed. Dropouts and missed/inadequate assessments were the major causes of censoring for OS and rPFS, respectively. For OS, a nonparametric imputation method with time-dependent covariates[25] was used to adjust for informative censoring caused by dropouts. For rPFS, interval imputation[26] was used to generate an intermediate time point between an expected visit and the

known time of death or progression for patients who would otherwise be censored because of a missed or inadequate clinical assessment.

For SSEs, events were recorded up to 30 days after the time of the first treatment change (Table S1). If no SSE was recorded, OS data were used instead. Observed SSE data included death in the event definition; imputed SSE data omitted death from the event definition. Early censored SSE data were not imputed because the early censoring rates were too high and too few events were recorded in both arms.

Only unadjusted data were used for HRQOL and pain measures, without any imputation of early censored data. HRQOL and pain data did not include death or disease progression. Information on the approach to missing data and questionnaire completion rates for FACT-P, EQ-5D-5L, and BPI-SF time-to-worsening end points has been previously published.[22]

Correlation analyses

Correlation analyses of patient-level data were done via an iterative multiple imputation copula-based approach.[27] Correlation analyses were performed for the overall VISION study population and for each treatment arm. Data are reported as correlation coefficients (rho) and 95% confidence intervals (CIs). CIs were obtained via bootstrapping. All analyses were post hoc, noninferential, and exploratory. The strength of correlations between individual end points and outcomes was predefined according to cutoff values for correlation coefficients. Correlations were considered weak for rho <0.3, mild for rho ≥0.3 and <0.5, moderate for rho ≥0.5 and <0.7, and strong for rho ≥0.7.

Sensitivity analyses

The robustness of each correlation was determined via two Spearman rank methods (restricted and highest rank) in addition to iterative multiple imputation.[28] For the restricted rho estimate, the correlation was calculated with only the probability limits defined by the available data. For the highest rank correlation method, the correlation included the potential for events to occur beyond the defined follow-up times. Both the restricted and highest rank methods are adaptations of the Spearman rank method to make them applicable to time-to-event data.

RESULTS

Correlation of rPFS with OS

In the overall VISION population, rPFS was strongly correlated with OS (rho, ≥0.7) with the PCWG3 definition of rPFS (Figure 1).[9] The strength of the correlation was similar for the observed and imputed data, although the association was numerically stronger in the observed data (Figure 1). In the ^{177}Lu-PSMA-617 and SOC arms, rPFS and OS were also strongly correlated, with no clear differences in the strength of the correlation between the arms and overlapping 95% CIs (Figure 2).

Correlations of rPFS or OS with SSE with or without death

rPFS correlated moderately (rho, ≥0.5 and <0.7) with time to SSE when death was included in the SSE definition but only weakly (rho, <0.3) when death events were censored (Figure 1). OS correlated strongly with time to SSE with but not without death (rho, 0.8 and 0.3, respectively; Figure 3). In the ^{177}Lu-PSMA-617 and SOC arms, there were no clear differences in the strength of the correlation between the arms (Figures 2 and 4).

Correlations between rPFS or OS and time to worsening in HRQOL and pain measures

The correlation of rPFS with time to worsening in the FACT-P total score was mild (rho, ≥0.3 and <0.5) or moderate (rho, ≥0.5 and <0.7) in the overall population (Figure 1). For OS, the correlation with time to worsening in the FACT-P total score was moderate (rho, ≥0.5 and <0.7; Figure 3). Correlation coefficients were similar for observed and imputed data (Figures 1 and 3). For the FACT-P, the strongest correlations of both rPFS and OS were with time to worsening in emotional and physical well-being, and the weakest correlation was for the pain-related subscale. In the ^{177}Lu-PSMA-617 and SOC arms, there were no clear differences in the strength of correlation between the arms (Figures 2 and 4).

Correlations with time to worsening in the EQ-5D-5L utility score were mild for both rPFS and OS (rho, ≥0.3 and <0.5; Figures 1 and 3). Correlation coefficients for time to worsening in the BPI-SF were mild for rPFS (rho, ≥0.3 and <0.5) and moderate (rho, ≥0.5 and <0.7) for OS in the overall population. In the ^{177}Lu-PSMA-617 and SOC arms, there were no clear differences in the strength of the correlation between the arms.

Sensitivity analysis

Via the restricted and highest rank correlation methods, correlation strengths were similar to those observed with iterative multiple imputation in all cases (Tables S2–5). Numerically, restricted rank correlation coefficients were often lower than those for the other two methods but the differences were not consistent.

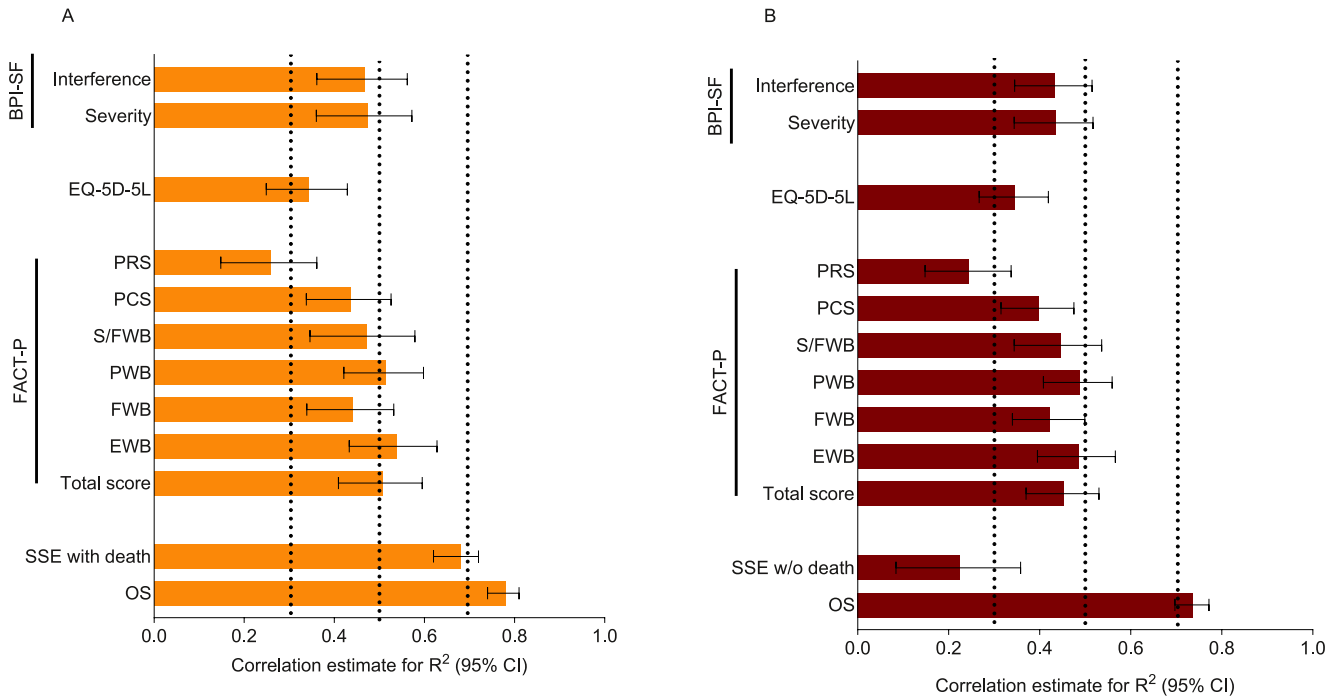

FIGURE 1 Correlations of rPFS with OS, SSE, and HRQOL in the overall population with observed data (A) and imputed data (B). Dotted vertical lines represent the cutoff points for the strength of correlation (rho): <0.3, weak; ≥0.3 and <0.5, mild; ≥0.5 and <0.7, moderate; and ≥0.7, strong. BPI-SF indicates Brief Pain Inventory–Short Form; CI, confidence interval; EQ-5D-5L, 5-level EQ-5D; EWB, emotional well-being; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FWB, functional well-being; HRQOL, health-related quality of life; OS, overall survival; PCS, prostate cancer subscale; PRS, pain-related subscale; PWB, physical well-being; rPFS, radiographic progression-free survival; S/FWB, social/family well-being; SSE, symptomatic skeletal event; w/o, without.

DISCUSSION

The results of this post hoc analysis of the VISION study demonstrated a strong correlation between rPFS as defined in PCWG3[9] and OS in patients with mCRPC receiving PSMA-targeted radioligand therapy. The strength of the correlation in the VISION study was independent of the randomized treatment arm.

This is the first investigation of correlations between rPFS and OS in patients receiving radioligand therapy plus SOC including ARPIs. A strong correlation between rPFS and OS in mCRPC has previously been demonstrated in the prechemotherapy setting in the COU-AA-302 and PREVAIL trials of abiraterone and enzalutamide.[12,14] Our results demonstrate similar correlation coefficients to those found in these other studies. The strong correlation between rPFS and OS in the VISION study was found among a population of patients with highly pretreated mCRPC, whose cancers are likely to have a high degree of molecular heterogeneity.

The iterative multiple imputation method used in the present analysis of the VISION data was similar to that used in other analyses of data from the COU-AA-302 and PREVAIL trials.[12,14] This method can be considered equivalent to but more efficient than the standard copula methods used previously.[29] The similarity of the findings between the iterative multiple imputation method of correlation analysis and the sensitivity analyses via the Spearman restricted and highest rank approaches indicates that these results are robust. The observation of numerically lower rho values when using the restricted methods most likely arises from the reliance on actual event time, whereas other methods include assumptions for events occurring beyond the observed follow-up times.

The correlation results were similar with observed and imputed data. Imputation was used to account for missing data for two main reasons. First, there was a high dropout rate in the control arm of the VISION trial soon after the start of the study (21% in the control arm vs. 6% in the treatment arm).[21] Second, high rates of early censoring were evident in the rPFS data (48% in the control arm and 16% in the investigational arm),[21] with many patients recorded as either having died or progressed before the end of follow-up. On becoming aware of this, the study sponsor undertook to resolve the matter by updating the study site training materials to clarify the eligibility criteria, mandating involvement of multidisciplinary teams in the provision of care, and emphasizing the importance of retaining patients in the control arm. These interventions were implemented on March 5, 2019.

The observed SSE data included a high proportion of deaths, which led to overestimation of the strength of the correlation between the primary end points and time to first SSE. Death was therefore omitted from the definition of SSE in the imputed data set, which revealed weak correlations of time to SSE with rPFS and OS. Further analysis of specific SSEs was not possible because of the low numbers of patients (Table S1).

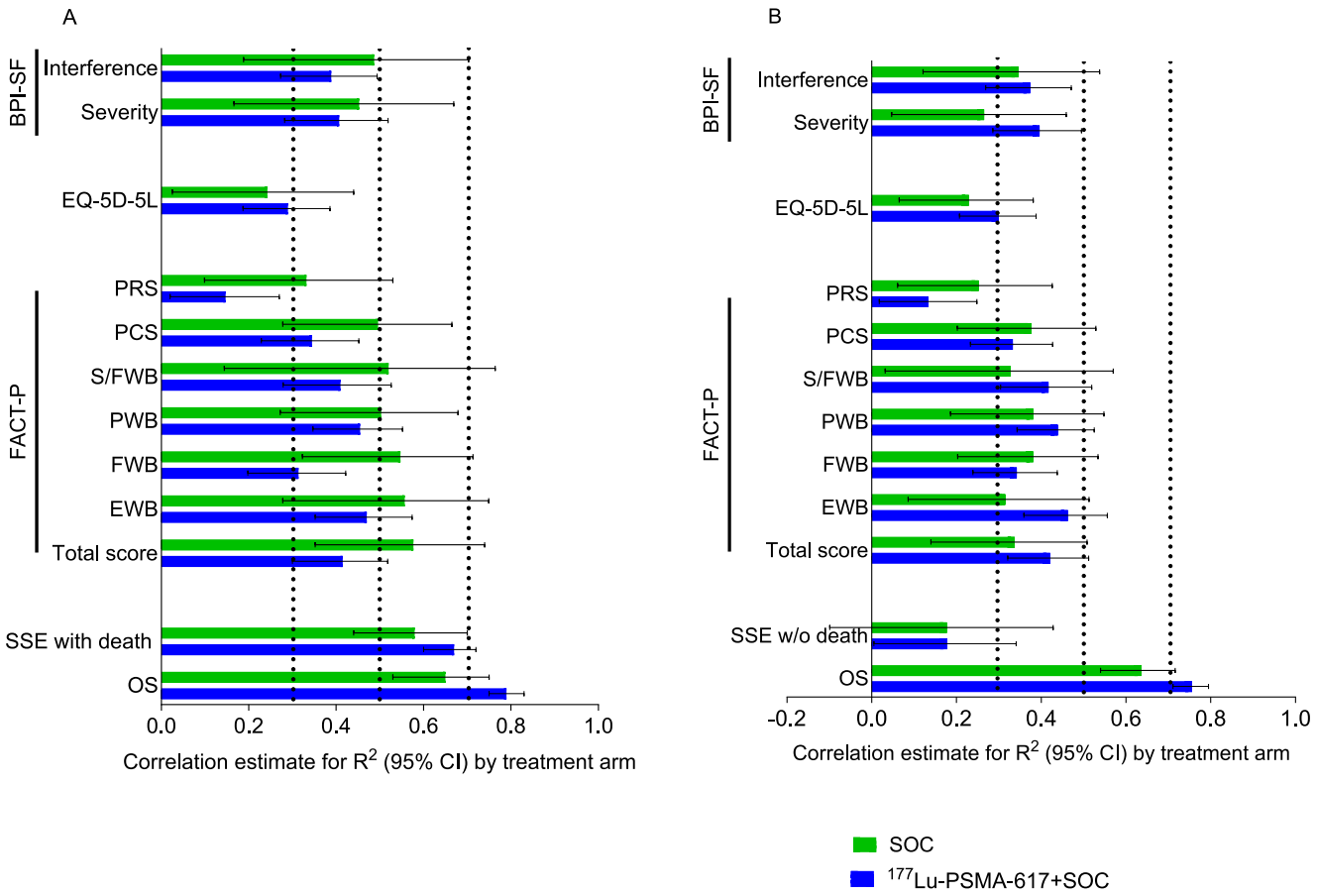

FIGURE 2 Correlations of rPFS with OS, SSE, and HRQOL by study arm with observed data (A) and imputed data (B). Dotted vertical lines represent the cutoff points for the strength of correlation (rho): <0.3, weak; ≥0.3 and <0.5, mild; ≥0.5 and <0.7, moderate; and ≥0.7, strong. BPI-SF indicates Brief Pain Inventory–Short Form; CI, confidence interval; EQ-5D-5L, 5-level EQ-5D; EWB, emotional well-being; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FWB, functional well-being; HRQOL, health-related quality of life; ^{177}Lu-PSMA-617, [^{177}Lu]Lu-PSMA-617; OS, overall survival; PCS, prostate cancer subscale; PRS, pain-related subscale; PWB, physical well-being; rPFS, radiographic progression-free survival; S/FWB, social/family well-being; SOC, standard of care; SSE, symptomatic skeletal event; w/o, without.

The moderate to weak correlations between rPFS and worsening HRQOL/pain outcomes could be explained by several factors. First, the extensively pretreated patients with mCRPC in the VISION trial were often in poor health with comorbidities and concomitant treatments, which may have contributed to the HRQOL in addition to disease progression. Second, self-assessment questionnaires reflect patients' own perception of their HRQOL with no external or internal standard, and patients' expectations and tolerance may adapt and change over time.[30,31] Third, the use of time-to-worsening end points may not capture potential HRQOL improvement in patients with complete or partial responses but aim instead to capture delay in the inevitable decline of HRQOL in patients with advanced mCRPC. Finally, although questionnaire completion rates were similar between the ^{177}Lu-PSMA-617 and control arms among patients remaining in the study, the dropout rate was higher in the control arm.[22] This was mitigated by analyzing HRQOL and pain outcomes in the set of patients enrolled after enhanced study site education measures were implemented to reduce the dropout rate in the control arm.[21,22] The present findings on HRQOL and pain are therefore exploratory, and require replication in future studies.

This post hoc analysis had several inevitable limitations. Most notably, the high degree of missing data leading to censoring and necessitating data imputation is a weakness of the analysis. Dropouts and missed assessments may have resulted in the underestimation of the strength of the association in these analyses. Also, the definition of rPFS used in the VISION study included death (per the PCWG3 criteria[9]), which may have obscured effects due solely to radiographic disease progression. In particular, the results for SSEs should be interpreted with caution because of heavy censoring. Additionally, low patient numbers meant we were unable to investigate the contributions of patient-specific clinical details that may influence outcomes, such as previous or concomitant treatments, changes in opioid use, occurrence of spinal compression, and Eastern Cooperative Oncology Group performance status.[16] The contributions of these factors to outcomes deserve to be explored further. Likewise, including other measures of treatment outcome, for example, an objective response in evaluable patients and its components, would be of interest subject to adequate sample sizes.

Prospectively planned studies designed to address the prognostic value of clinical features in the context of unequivocal clinical

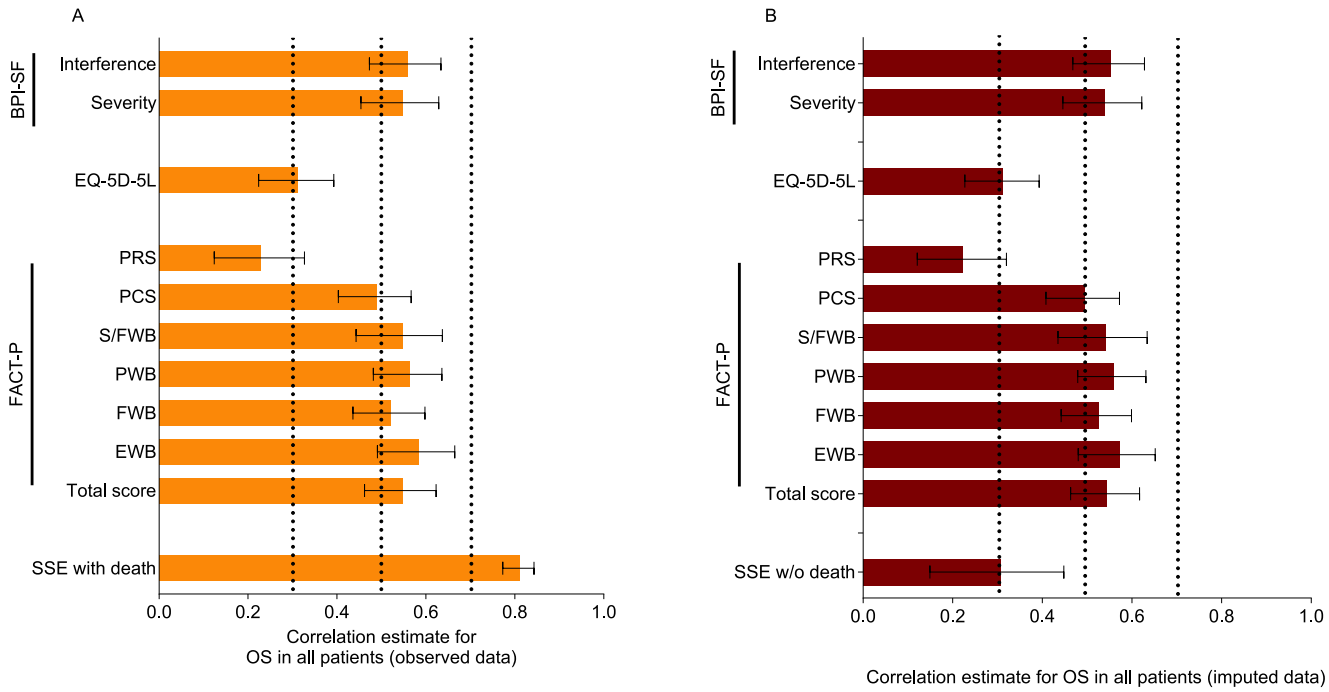

FIGURE 3 Correlations of OS with SSE and HRQOL in the overall population with observed data (A) and imputed data (B). Dotted vertical lines represent the cutoff points for the strength of correlation (rho): <0.3, weak; ≥0.3 and <0.5, mild; ≥0.5 and <0.7, moderate; and ≥0.7, strong. BPI-SF indicates Brief Pain Inventory–Short Form; EQ-5D-5L, 5-level EQ-5D; EWB, emotional well-being; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FWB, functional well-being; HRQOL, health-related quality of life; OS, overall survival; PCS, prostate cancer subscale; PRS, pain-related subscale; PWB, physical well-being; rPFS, radiographic progression-free survival; S/FWB, social/family well-being; SSE, symptomatic skeletal event; w/o, without.

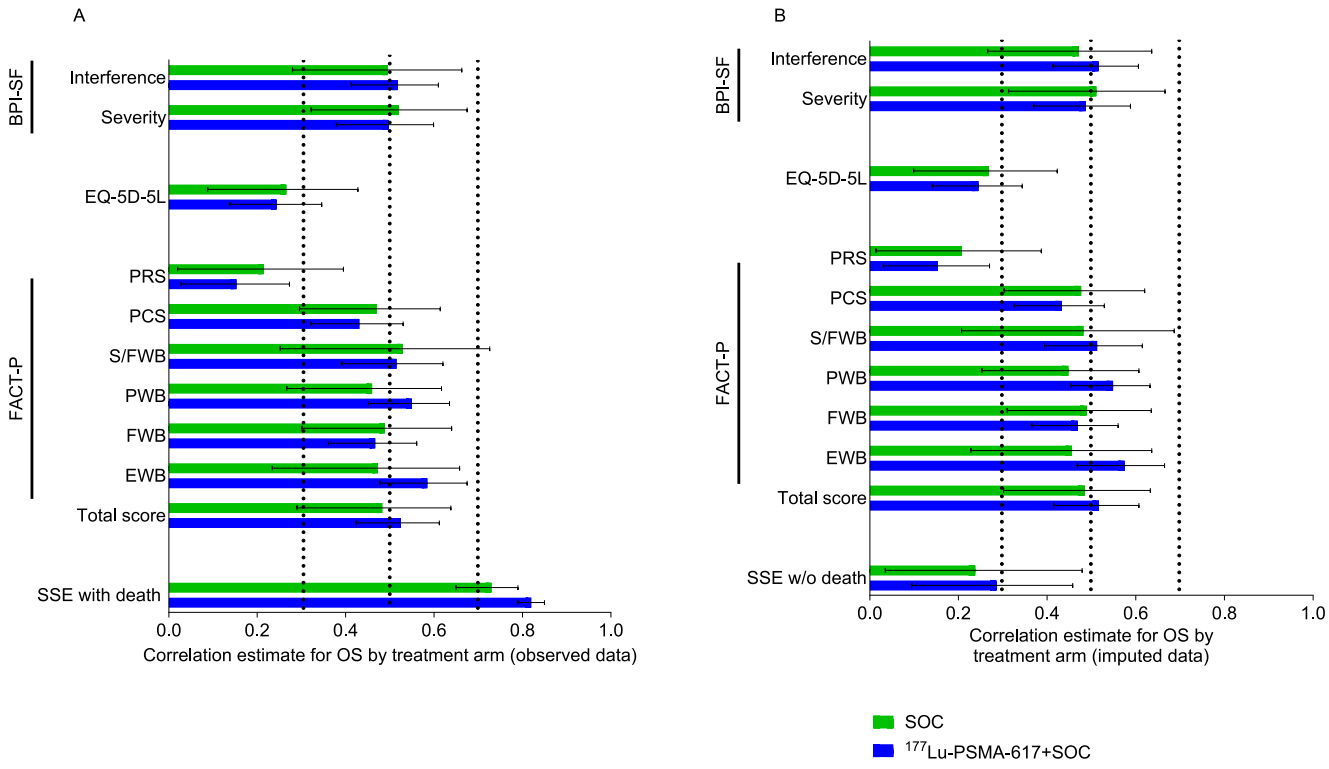

FIGURE 4 Correlations of OS with SSE and HRQOL by study arm with observed data (A) and imputed data (B). Dotted vertical lines represent the cutoff points for the strength of correlation (rho): <0.3, weak; ≥0.3 and <0.5, mild; ≥0.5 and <0.7, moderate; and ≥0.7, strong. BPI-SF indicates Brief Pain Inventory–Short Form; EQ-5D-5L, 5-level EQ-5D; EWB, emotional well-being; FACT-P, Functional Assessment of Cancer Therapy–Prostate; FWB, functional well-being; HRQOL, health-related quality of life; ^{177}Lu-PSMA-617, [^{177}Lu]Lu-PSMA-617; OS, overall survival; PCS, prostate cancer subscale; PRS, pain-related subscale; PWB, physical well-being; rPFS, radiographic progression-free survival; S/FWB, social/family well-being; SOC, standard of care; SSE, symptomatic skeletal event; w/o, without.

progression[16] are needed. Future analyses of the results from trials such as PSMAfore[18] and PSMAddition,[32] as well as other PSMA-targeted radioligands in phase 3 development,[33] will help to further our understanding of how rPFS and other end points can aid clinical decision-making and facilitate drug development for the long-term management of patients with prostate cancer. For example, PSMAfore[18] and PSMAddition[32] are determining the efficacy and safety of ^{177}Lu-PSMA-617 in less heavily treated patients than those in the VISION trial. Also, as noted above, the generally accepted PCWG3 definition of rPFS includes death, which may obscure the effects of radiographic progression per se. Understanding the correlation between rPFS without death and OS in prospectively planned trials will be informative in this regard.

In conclusion, this analysis of the VISION study demonstrated that rPFS was strongly correlated with OS in patients with mCRPC receiving PSMA-targeted radioligand therapy. Correlations between rPFS or OS and time to SSE were weak or mild if deaths were not included in the latter outcome. Both rPFS and OS were mildly or moderately correlated with FACT-P scores, except for the pain-related subscale, and measures of pain with the BPI-SF questionnaire. Effects were observed regardless of randomized treatment. Further study is needed in suitably powered trials to investigate the value of rPFS in predicting long-term outcomes in patients receiving PSMA-targeted radioligand therapy treatment.

AUTHOR CONTRIBUTIONS

Michael J. Morris: Conceptualization, investigation, and writing–review and editing. **Johann de Bono**: Conceptualization, writing–review and editing, and investigation. **James Nagarajah**: Conceptualization, investigation, and writing–review and editing. **Oliver Sartor**: Conceptualization, investigation, and writing–review and editing. **Xiao X. Wei**: Conceptualization, investigation, and writing–review and editing. **Luke T. Nordquist**: Conceptualization, investigation, and writing–review and editing. **Vadim S. Koshkin**: Conceptualization, investigation, and writing–review and editing. **Kim N. Chi**: Conceptualization, investigation, and writing–review and editing. **Bernd J. Krause**: Conceptualization, investigation, and writing–review and editing. **Ken Herrmann**: Conceptualization, investigation, and writing–review and editing. **Kambiz Rahbar**: Conceptualization, investigation, and writing–review and editing. **Adrian Vickers**: Conceptualization, investigation, writing–review and editing, and formal analysis. **Osvaldo Mirante**: Conceptualization, investigation, writing–review and editing, and formal analysis. **Ray Ghouse**: Conceptualization, investigation, writing–review and editing, and formal analysis. **Karim Fizazi**: Conceptualization, investigation, and writing–review and editing. **Scott T. Tagawa**: Writing–review and editing, conceptualization, and investigation.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Novartis is committed to sharing access to anonymized patient-level data and clinical study reports from eligible studies with qualified external researchers. The data that support the findings of this study are available at https://www.clinicalstudydatarequest.com/ upon reasonable request. All data provided are anonymized to respect the privacy of patients who have participated in the trials in line with applicable laws and regulations.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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