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Impact of clinical versus radiographic progression on clinical outcomes in metastatic castration-resistant prostate cancer

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ABSTRACT

Objectives Unequivocal clinical progression (UCP)—a worsening of clinical status with or without radiographic progression (RAD)—represents a distinct mode of disease progression in metastatic prostate cancer. We evaluated the prevalence, risk factors and the impact of UCP on survival outcomes.

Methods A post-hoc analysis of the COU-AA-302, a randomised phase 3 study of abiraterone plus prednisone (AAP) versus prednisone was performed. Baseline characteristics were summarised. Cox proportional-hazards model and Kaplan-Meier method were used for survival and time to event analyses, respectively. Iterative multiple imputation method was used for correlation between clinicoradiographic progression-free survival (crPFS) and overall survival (OS).

Results Of 736 patients with disease progression, 280 (38%) had UCP-only and 124 (17%) had UCP plus RAD. Prognostic index model high-risk group was associated with increased likelihood of UCP (p<0.0001). Median OS was 25.7 months in UCP-only and 33.0 months for RAD-only (HR 1.39; 95% CI 1.16 to 1.66; p=0.0003). UCP adversely impacted OS in both treatment groups. Lowest OS was seen in patients with prostate specific antigen (PSA)-non-response plus UCP-only progression (median OS 22.6 months (95% CI 20.7 to 24.4)). Including UCP events lowered estimates of treatment benefit—median crPFS was 13.3 months (95% CI 11.1 to 13.8) versus median rPFS of 16.5 months (95% CI 13.8 to 16.8) in AAP group. Finally, crPFS showed high correlation with OS (r=0.67; 95% CI 0.63 to 0.71).

Conclusions UCP is a common and clinically relevant phenomenon in patients with metastaticcastration-resistant prostate cancer (mCRPC) treated with AAP or prednisone. UCP is prognostic and associated with inferior OS and post-progression survival. A combination of PSA-non-response and UCP identifies patients with poorest survival. When included in PFS analysis, UCP diminishes estimates of treatment benefit. Continued study of UCP in mCRPC is warranted.

Key questions

What is already known about this subject?

- Unequivocal clinical progression (UCP)—a worsening of clinical status with or without radiographic progression (RAD)—is the frequently observed mode of metastatic prostate cancer progression in clinical practice.
- UCP is, in part, a function of limitations of currently used imaging modalities.
- Physicians change treatment due to UCP, but there's lack of consistency in management due to varying definitions of UCP and knowledge about impact on outcomes.

What does this study add?

- UCP is more common than previously estimated, occurring in 37% of patients in the COU-AA-302 study.
- Risk of UCP is higher in patients with aggressive disease biology as captured by prognostic index model risk group.
- UCP has substantial adverse impact on overall survival and post-treatment survival; and including UCP events shortens estimates of treatment benefit (progression-free survival).

How might this impact on clinical practice?

- UCP can be clinically used by itself and in combination with prostate specific antigen-non-response (a marker of treatment insensitivity) to identify patients with poorest prognosis and proactively tailor treatment approach including early genomic testing to find targetable alterations.

INTRODUCTION

Assessing treatment outcomes in prostate cancer clinical trials is complicated by the fact that the majority of patients with metastatic prostate cancer have bone-only or bone-predominant disease.[1] To detect and monitor these lesions, 99mTc-methylene diphosphonate radionuclide bone scintigraphy remains the most widely used radiographic modality. The validated regulatory time to event endpoint of radiographic disease progression in the Prostate Cancer Working Group (PCWG) consensus guideline includes an assessment of disease progression using bone scintigraphy.[2] However, bone scintigraphy provides an imperfect

assessment of disease burden and treatment response[3 4] and in virtually all contemporary metastatic castration-resistant prostate cancer (mCRPC) trials, a subset of patients experienced clinical deterioration in the form of new pain, worsening performance status and so on *without* meeting PCWG criteria for radiographic progression. The type of disease progression—serologic alone, radiographic or clinical—has been shown to impact the choice of subsequent therapy in clinical practice.[5] The clinicopathological factors associated with such clinical progression and the relationship between the occurrence of clinical progression and overall survival has not been well studied.

COU-AA-302 was a phase 3, randomised, double-blind, multinational registration clinical trial in which asymptomatic or mildly symptomatic patients with progressive chemotherapy-naïve mCRPC were randomised to receive abiraterone acetate 1000 mg daily plus prednisone 5 mg two times per day (AAP group) or placebo plus prednisone 5 mg two times per day (prednisone group). The results showed the superiority of AAP over prednisone in both co-primary endpoints of radiographic progression free survival (rPFS) and overall survival (OS) despite the availability and use of effective agents after discontinuation of protocol therapy.[6 7] The trial results led to the expansion of the indication of AAP to include all patients with progressing mCPRC independent an individual's taxane exposure history.[8] A subsequent analysis showed a high degree of correlation between rPFS and OS (Spearman's correlation coefficient, 0.72).[9] Demonstration of similarly high correlation between rPFS and OS in COU-AA-302 and other prospective randomised controlled trials formed the basis for acceptance of rPFS as a surrogate endpoint for clinical trials in mCRPC.[2 9–11]

An important feature of the COU-AA-302 trial was that the discontinuation of study therapy was not required at serological or radiographic progression. As a result, many patients continued protocol therapy beyond radiographic progression or until they experienced unequivocal clinical progression (UCP), an indication that, based on physician judgement, they were 'no longer clinically benefitting' from the treatment.[2] UCP was prespecified in the protocol by any one of the following: the occurrence of cancer pain requiring chronic opiate analgesia, a decline in Eastern Cooperative Oncology Group (ECOG) performance status to 3 or greater, or an immediate need to initiate cytotoxic chemotherapy, radiation therapy or surgical intervention for disease-related events. We evaluated the relationship between UCP and radiographic progression, the characteristics of patients experiencing UCP and the association of UCP with survival outcomes. Because patients with non-radiographic progression are excluded from rPFS analyses, we also evaluated if a composite clinicoradiographic PFS endpoint would improve on the correlation between rPFS and OS in mCRPC.

METHODS

A post-hoc retrospective analysis was performed using the data from COU-AA-302 trial. Patients discontinuing the trial therapy due to disease progression were categorised into three cohorts based on the event that resulted in treatment discontinuation—UCP-only, radiographic progression (RAD)-only and UCP plus RAD. Baseline clinicopathological factors including Gleason grade, AJCC TNM stage, prostate specific antigen (PSA) level at initial diagnosis and time from initial diagnosis to initiation of protocol therapy and the prognostic index model (PIM)-risk groups were evaluated for association with UCP. PIM was created using patient-level data from COU-AA-302 trial and has been associated with overall survival in this setting.[12] The model incorporates four baseline variables: Brief Pain Inventory score, lactate dehydrogenase level, alkaline phosphatase level and presence of ≥10 bone metastases. Because higher PIM scores correlate with a higher bone metastatic tumour burden and clinically-symptomatic disease at presentation, we hypothesised that PIM poor-risk patients would be more likely to have UCP than PIM good or intermediate-risk patients. Descriptive analyses were performed for baseline demographics and clinicopathological characteristics including the PIM-risk group.

OS was defined as the time from randomisation to death from any cause; rPFS as time from randomisation to radiographic disease progression or death; and the duration of subsequent survival (DSS) as the time from study therapy discontinuation to death. Notably, after the interim OS analysis, the study's independent data monitoring committee allowed patients in the prednisone group to cross-over to treatment with AAP on disease progression. DSS was calculated from the time of discontinuation of the first therapy in such cases. The relationship between treatment sensitivity (using PSA response; defined as >=50% PSA reduction from baseline per PCWG2) and mode of disease progression was explored with the hypothesis that a combination of PSA-non-response and UCP-only progression would predict the worst survival outcomes. Median overall survival with 95% CIs was estimated using the Kaplan-Meier method. The Cox proportional-hazards model was used to estimate the HR and its associated 95% CI.

In COU-AA-302 study, a proportion of patients discontinued protocol-specified assessments for radiographic progression after occurance of UCP and were censored from the rPFS analyses. A composite endpoint of clinicoradiographic PFS (crPFS), defined as the time from randomisation to discontinuation of therapy due to UCP, RAD progression or both or death, was created to capture the disease progression outcomes of these patients. We performed an exploratory analysis of crPFS and OS for the study population and individual treatment groups using an iterative multiple imputation method, where the censored times are iteratively augmented. This method is similar to Spearman's rank correlation, but incorporates

Table 1 Summary of treatments and modes of disease progression

	Abiraterone plus prednisone (n=546)	Placebo plus prednisone (n=542)
Patients treated, n (%)	542 (100)	540 (100)
Treatment discontinued	500 (92)	540 (100)
Treatment ongoing	42 (8)	0 (0)
Reasons for discontinuation, n (%)	366 (68)	370 (69)
UCP-only	138 (26)	142 (26)
RAD-only	160 (30)	172 (32)
RAD plus UCP	68 (13)	56 (10)
Adverse event	50 (9)	33 (6)
Other	42 (8)	30 (6)
Withdrawal of consent	41 (8)	56 (10)
Lost to follow-up	1 (0.2)	0

All values are n (%).
RAD, radiographic progression; UCP, unequivocal clinical progression.

the censoring information which is better suited to assess the relationship between two 'time-to-event' variables.[13]

RESULTS

The final analysis of COU-AA-302 was conducted at 96% of planned deaths, with a median follow-up of 49.2 months. Study treatment was discontinued by 500 (92%) patients in the AAP group and 540 (100%) in the prednisone group. Of the 736 patients who discontinued treatment for a protocol-defined progression measure, 280 (38%) discontinued for UCP-only, 332 (45%) for RAD-only and 124 (17%) for UCP plus RAD. These proportions were balanced between the two treatment groups (table 1).

The most common UCP events were the need to initiate chemotherapy (50% in AAP group vs 53% in prednisone group) and need to initiate radiation therapy (36% in AAP group vs 27% in prednisone group). As previously published, 522 of 532 (99%) patients in the AAP group, and 506 of 522 (97%) patients in the prednisone group had no or minimal pain at study entry.[6] However, increased cancer pain requiring chronic opiate therapy was the cause for treatment discontinuation in 45 of 366 (12.3%) patients in the AAP group and 51 of 370 (13.8%) patients in the prednisone group.

Predictors of unequivocal clinical progression

The clinicopathological characteristics were comparable in the UCP-only, RAD-only and UCP plus RAD cohorts (online supplemental table 1). Notably, 126 of 280 (45.0%) patients in UCP-only, 195 of 332 (58.7%) in RAD-only and 71 of 124 (57.3%) in UCP plus RAD had visceral metastatic disease. PIM-risk group was associated with a higher risk of UCP in our analysis. Patients in poor-risk group had higher rate of UCP-only progression compared with the other two risk groups (46% vs 21% in good-risk and 30% in intermediate-risk; p<0.0001).

Unequivocal clinical progression as a negative prognostic marker for survival

UCP was associated with inferior survival outcomes independent of the treatment arm. In the study population, median OS was 25.7 months in UCP-only cohort and 26.9 months in UCP plus RAD cohort, compared with 33.0 months for RAD-only cohort, translating into a 39% higher likelihood of death in UCP-only cohort (HR 1.39; 95% CI 1.16 to 1.66; p=0.0003) and a 36% higher likelihood of death in the UCP plus RAD cohort (HR 1.36; 95% CI 1.08 to 1.71; p=0.0079) (figure 1).

The deleterious effect of UCP was also seen in each of the treatment groups. In the AAP group, the median OS was 27.7 months in UCP-only cohort (HR 1.36; 95% CI 1.04 to 1.76; p=0.0224) and 26.9 months in UCP plus RAD cohort (HR 1.53; 95% CI 1.11 to 2.11; p=0.0091), compared with 34.9 months in RAD-only cohort. In the prednisone group, the median OS was 23.4 months in UCP-only cohort (HR 1.44; 95% CI 1.13 to 1.84; p=0.003) and 27.0 months in UCP plus RAD cohort (HR 1.23; 95% CI 0.88 to 1.71; p=0.219), compared with 30.3 months in RAD-only cohort (figure 2).

In the study population, the median DSS was 15.8 months for UCP-only cohort compared with 19.0 months for RAD-only cohort (HR 1.27; 95% CI 1.06 to 1.51; p=0.0092), translating into a 27% higher risk of death after treatment discontinuation for patients with UCP-only progression. Median DSS was 13.4 months in the UCP plus RAD cohort, translating into a 31% higher risk of death after treatment discontinuation compared with RAD-only cohort (HR 1.31; 95% CI 1.04 to 1.65; p=0.02). Similarly, UCP-only progression appeared to have an adverse impact on DSS in both treatment groups, but these differences did not reach statistical significance.

Taken together, these results suggest that UCP is associated with an inferior overall and post-treatment survival regardless of therapy.

Unequivocal clinical progression events lower the estimates of treatment benefit

Consistent with our hypothesis, incorporation of UCP events diminished the magnitude of PFS in both treatment arms. In the AAP group, the median crPFS was 13.3 months (95% CI 11.1 to 13.8) and median rPFS was 16.5 months (95% CI 13.8 to 16.8). In the prednisone group, the median crPFS was 6.0 months (95% CI 5.5 to 8.2) and median rPFS was 8.3 months (95% CI 8.0 to 9.7). However, AAP treatment was associated with an improvement in both crPFS (HR 0.55, 95% CI 0.48 to 0.64, p<0.0001) and rPFS (HR 0.56, 95% CI 0.49 to 0.65, p<0.0001) compared with prednisone suggesting that occurrence of UCP does not selectively diminish benefit from either of these therapies.

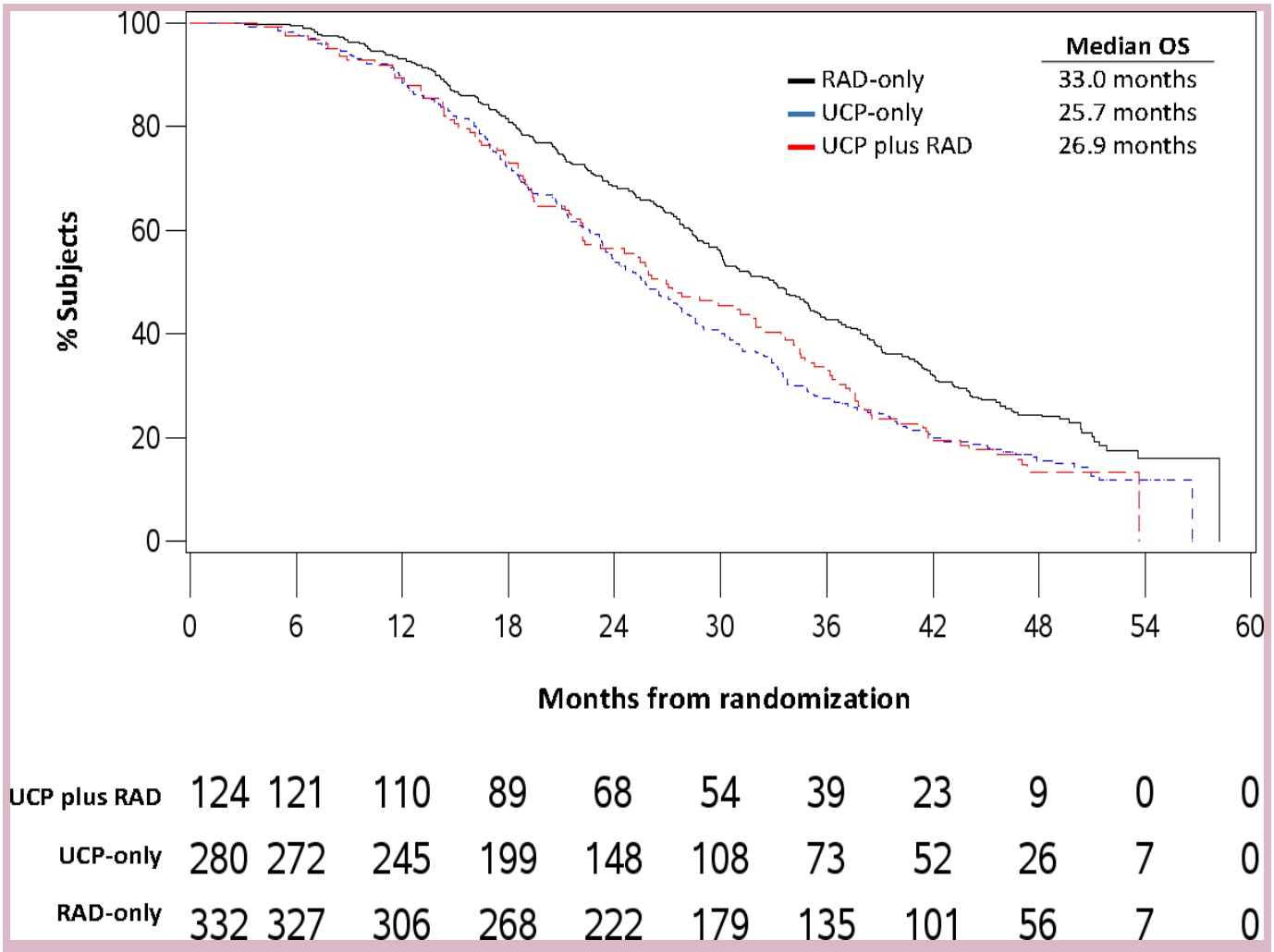

Figure 1 Kaplan-Meier plots of overall survival by the type of disease progression in the study population. OS,overall survival; RAD, radiographic progression;UCP, unequivocal clinical progression.

Clinicoradiographic progression-free survival and overall survival

In the study population, we found a high but similar correlation between crPFS and OS (r=0.67; 95% CI 0.63 to 0.71) and between rPFS and OS (r=0.63; 95% CI 0.58 to 0.67). This finding is consistent with comparable HRs seen in the crPFS and rPFS analyses above.

Treatment insensitivity and unequivocal clinical progression

In the study population, patients with a combination of PSA-non-response and UCP-only progression had inferior survival (median OS 22.6 months (95% CI 20.7 to 24.4)) than those with PSA-non-response and RAD-only progression (median OS 27.7 months (95% CI 24.2 to 30.1)), PSA response and UCP-only progression (median OS 33.2 months (95% CI 28.5 to 36.3)) and PSA response and RAD-only progression (median OS 40.2 months (95% CI 36.6 to 45.6)) (online supplemental figure 1).

DISCUSSION

In this post-hoc analysis of a large phase 3 trial, we showed that unequivocal clinical progression is a common event in men receiving abiraterone or prednisone therapy for mCRPC, and that a high-risk PIM score that reflects a higher mortality risk and disease burden is associated with a higher likelihood that treatment will be discontinued because of an UCP event. We found that inclusion of UCP as a progression measure lowers the estimates of benefit from treatment, and that the survival benefit from an effective treatment for patients who have UCP is less than for those who only show radiographic progression, particularly when combined with PSA-non-response as a marker of treatment insensitivity.

A substantial proportion (38%) of patients in COU-AA-302 trial discontinued treatment for non-radiographic progression including approximately 12% of patients who had no or minimal pain at study entry who eventually discontinued treatment due to cancer-related pain requiring chronic opiate analgesia. The overall rate of UCP is higher than reported in a sensitivity analysis of phase 3 trial of enzalutamide versus placebo in first-line mCRPC (PREVAIL), where 6.9% patients in enzalutamide group and 20.9% in the placebo group discontinued treatment due to clinical progression.[10] These

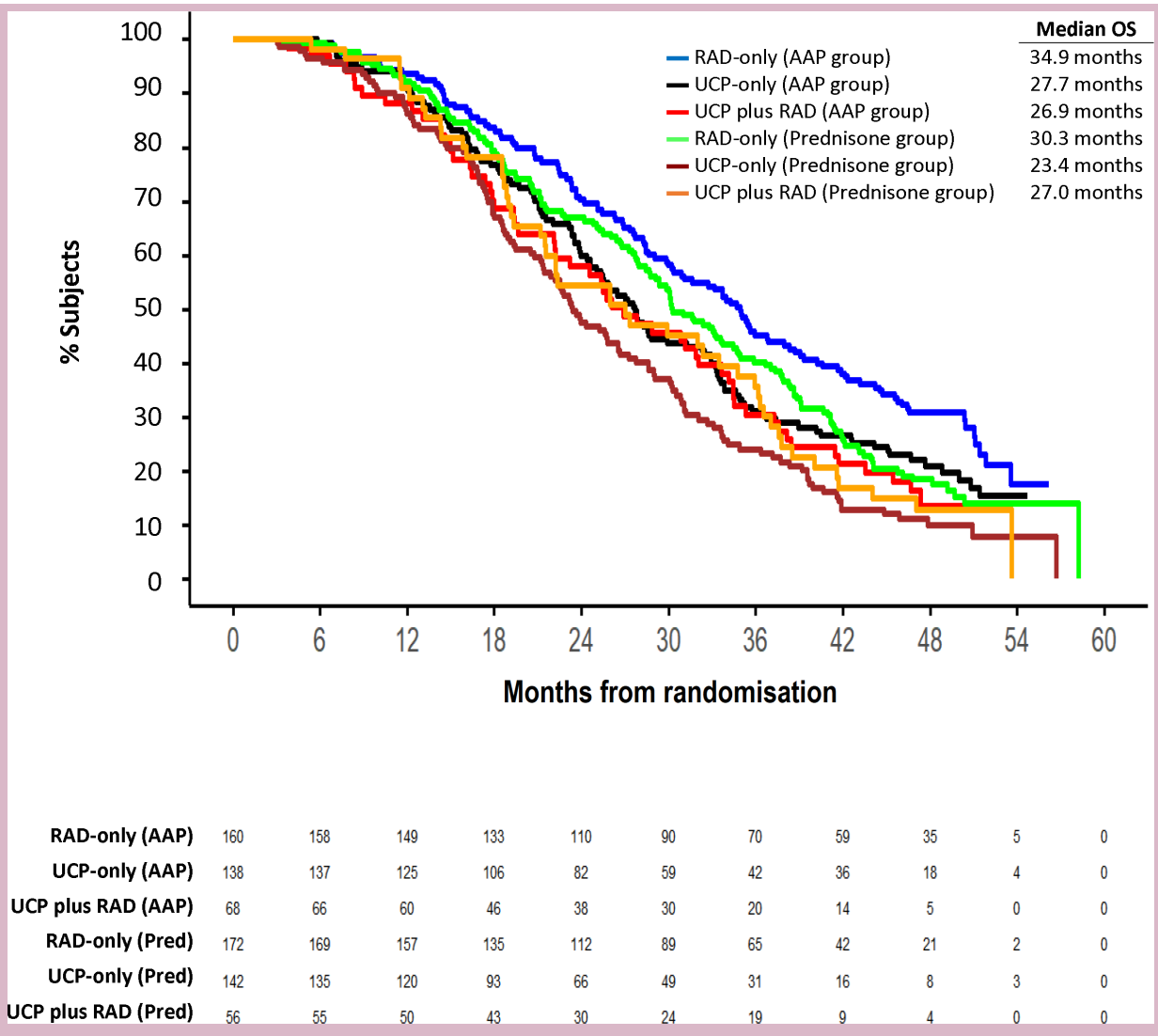

Figure 2 Kaplan-Meier plots of overall survival by the type of disease progression in each of the treatment groups. AAP,abiraterone acetate and prednisone; OS, overallsurvival; Pred, prednisone; RAD, radiographicprogression; UCP, unequivocal clinical progression.

differences could be explained by inclusion of patients who experienced RAD progression and then continued treatment until UCP progression in the COU-AA-302 trial; and the stricter definition of UCP in the PREVAIL trial, where UCP was as a combination of a skeletal-related event AND either initiation of cytotoxic chemotherapy or initiation of an investigational agent for treatment of prostate cancer.

UCP occurred at a similar frequency in both treatment groups suggesting that it is independent of the antiandrogen therapies used in the COU-AA-302 trial. PIM-risk group was associated with an increased likelihood of UCP. Because PIM comprises of several clinical parameters that are associated with a higher tumour burden, this correlation between an increased risk of UCP in men with poor-risk disease is hypothesis-generating.

In our analysis, patients who experienced UCP-only progression uniformly had a shorter overall survival as well as the time from study therapy discontinuation to death compared with patients with RAD-only progression strongly suggesting that this mode of disease progression has important prognostic implications. Furthermore, when clinical progression events were incorporated into PFS analysis, it diminished the PFS benefit in both AAP and placebo groups. Our findings could help refine estimates of treatment benefits with AAP therapy in routine clinical practice. Despite this, AAP treatment demonstrated improvement in outcomes compared with prednisone. A similar effect was observed in the sensitivity analyses of rPFS in the PREVAIL trial of enzalutamide.

We found that a composite end point of crPFS failed to demonstrate a higher correlation with OS compared with rPFS. This may be due to lack of sufficient sample size in the post-hoc analysis as a whole, or because clinicians decided to continue treatment beyond UCP due to lack of subsequent effective treatment options, thus increasing the proportion of patients in the UCP plus RAD group at the cost of UCP-only group. Notably, the correlation

between rPFS and OS also appears to be lower in our study than previously reported,[9] possibly due to our use of data from the final cut-off (2014) and differences in method of statistical analysis.

It is possible that inclusion of clinical progression events in PFS analysis may not build on the work that has gone into establishing rPFS as a surrogate endpoint in prostate cancer.[11 14] However, crPFS can serve an as a clinically meaningful endpoint within the framework of the 'no longer clinically benefitting' (NLCB) time-to-event measure introduced in PCWG3 that promotes assessment of clinical need for changing the treatment rather than strictly at the first evidence of radiographic progression.[2] Thus, our study provides support for development of a unified definition of UCP and incorporation of crPFS in mCRPC clinical trials.

The finding that a combination of PSA-non-response and UCP are correlated with the worst survival outcomes could have important consequences as well. The use of these two easily evaluable treatment response variables can identify the group of patients at the highest risk of poor outcomes in routine clinical practice.

Our study shares some of the limitations of exploratory subgroup analyses.[15] Further, the definition of UCP used in COU-AA-302 trial could have arguably adversely impacted survival by allowing patients to continue on treatment until significant worsening of clinical status. At the time that COU-AA-302 was designed, there were few effective treatment options for mCRPC and this definition of UCP, while somewhat subjective and clinician judgement-dependent, was clinically appropriate. In contemporary clinical practice with availability of several therapies in post-abiraterone setting, the construct of NLCB that allows for continuation of therapy until the clinical status remains stable (rather than UCP which requires treatment until clinical deterioration) may be better suited to assist clinicians with the decision to switch therapies. The relatively narrow definition of UCP also has the potential to miss a subset of patients with other clinical findings of progression (eg, worsening quality of life scores). Importantly, while abiraterone is now widely used for men with metastatic hormone-sensitive prostate cancer (mHSPC), because of differences in clinical characteristics of mHSPC and mCRPC patients, it is unknown if our results can be applied to patients treated with abiraterone acetate plus prednisone for mHSPC. Additionally, generalisation of findings to patients receiving non-androgen receptor (AR) targeted therapies such as docetaxel or radium-223 may be limited.

CONCLUSIONS

UCP is a clinically-significant phenomenon that occurred independently of radiographic progression in a high proportion of patients with chemotherapy-naïve mCRPC in COU-AA-302 trial. Risk of UCP was highest in patients with poor baseline PIM-risk group, suggesting a correlation of UCP with adverse biology. UCP is prognostic, with occurrence associated with inferior OS and DSS, independent of treatment group. Further, a combination of PSA-non-response, a marker of treatment insensitivity, and UCP can be used to identify patients with poorest survival. Incorporating clinical progression events in PFS analysis resulted in decreased magnitude of benefit, further underscoring the prognostic significance of UCP. While crPFS failed to show a better correlation with OS than rPFS, our findings support further development of crPFS within the framework of NLCB as proposed in PCWG3. Future clinical trials should report the outcomes for patients with UCP to help validate our findings and inform subsequent treatment strategies in this group of patients.

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