

ORIGINAL ARTICLE

Circulating tumour cell increase as a biomarker of disease progression in metastatic castration-resistant prostate cancer patients with low baseline CTC counts

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Background: The development of treatment response and surrogate biomarkers for advanced prostate cancer care is an unmet clinical need. Patients with baseline circulating tumour cell (BLCTCs) counts <5/7.5 mL represent a good prognosis subgroup but are non-evaluable for response assessment (decrease in CTCs). The aim of the study is to determine the value of any increase in CTCs (CTC progression) as an indicator of progression in prostate cancer patients with low pre-treatment CTCs (<5).

Patients and methods: We carried out a post hoc analysis of patients with BLCTCs < 5 treated in the COU-AA-301 (abiraterone or placebo + prednisone) and IMMC-38 (chemotherapy) trials. The association of CTC progression (increase in CTCs at 4, 8 or 12 weeks) with overall survival (OS) was evaluated in multi-variable Cox regression models. Performance of survival models with and without CTC progression was evaluated by calculating ROC curve area under the curves (AUCs) and weighted c-indices.

Results: Overall, 511 patients with CTCs < 5 (421 in COU-AA-301 and 90 in IMMC-38) were selected; 212 (41.7%) had CTC progression at 4, 8 or 12 weeks after treatment initiation. CTC progression was associated with significantly worse OS [27.1 versus 15.1 m; hazard ratio (HR) 3.4 (95% confidence interval [CI] 2.5–4.5; $P < 0.001$)], independent of baseline CTCs and established clinical variables. Adding CTC progression to the OS model significantly improved ROC AUC (0.77 versus 0.66; $P < 0.001$). Models including CTC progression had superior ROC AUC (0.77 versus 0.69; $P < 0.001$) and weighted c-index [0.750 versus 0.705; delta c-index: 0.045 (95% CI 0.019–0.071)] values than those including CTC conversion (increase to CTCs ≥ 5). In COU-AA-301, the impact of CTC progression was independent of treatment arm.

Conclusions: Increasing CTCs during the first 12 weeks of treatment are independently associated with worse OS from advanced prostate cancer in patients with baseline CTCs < 5 treated with abiraterone or chemotherapy and improve models with established prognostic variables. These findings must be prospectively validated.

Key words: castration-resistant prostate cancer, treatment outcome, progression, circulating tumour cells, abiraterone, chemotherapy

Introduction

Advanced prostate cancer is a major cause of cancer morbidity and mortality. In the past decade, several drug development

breakthroughs have greatly increased the therapeutic armamentarium, improving outcomes from this lethal disease [1]. Despite this, resistance eventually occurs and the prognosis remains, in fit

patients, approximately 34 and 58 months, respectively, for metastatic castration-resistant and metastatic non-castrate disease [1].

Determining response to treatment continues to represent one of the greatest challenges in advanced prostate cancer care. Prostate Cancer Working Group (PCWG) 3 guidelines, which summarize recommendations for outcome assessment of patients treated within clinical trials, have incorporated circulating tumour cell (CTC) enumeration as an end point in clinical trials [2]. Outside clinical trials, however, treatment response assessment continues to rely on prostate-specific antigen (PSA), bone scintigraphy (BS) and computed tomography, which have important limitations. Neither PSA nor bone scans allow early evaluation of disease progression. For instance, PCWG3 recommend that rising PSA values before 12 weeks not be considered progression [2]; similarly, progression by bone scintigraphy cannot be determined before at least 12–16 weeks of treatment due to the potential for spurious, ‘flare reactions’ [2, 3]. Furthermore, neither BS nor PSA response are established surrogates of survival [4].

A significant number of patients have exclusively bone disease for much of their disease course, which is not amenable to evaluation by RECIST [5]. Furthermore, currently available biomarkers for advanced prostate cancer treatment response assessment are not consistently utilized in daily clinical practice, with many physicians continuing to rely on highly subjective ‘clinical progression’ to discontinue treatment [6]. Delays in identifying progressive disease lead to overtreatment with ineffective agents, and arguably to more patients experiencing clinical deterioration on progression.

The enumeration of circulating tumour cell counts (CTCs) has emerged as a powerful biomarker for the assessment of prognosis and response to treatment. A baseline CTC count $\geq 5/7.5$ ml has been consistently associated with worse outcome across large, randomized clinical trials [7–9]. Furthermore, the assessment of a composite biomarker [CTCs and lactate dehydrogenase (LDH)] after 12 weeks of treatment has been shown to be a surrogate of survival at the individual-patient level [9].

A number of studies have also evaluated the value of CTC enumeration as a response biomarker, that is, the association of changes in CTCs during treatment with outcome. In patients with unfavourable (≥ 5 CTCs/7.5 ml) counts, a decline in CTCs has been associated with improved outcomes and response to treatment in patients treated with both chemotherapy and hormone therapy [10]. Furthermore, CTC enumeration has proven to be a more powerful biomarker than PSA [11]. PCWG3 recommendations now include CTC enumeration for the assessment of patients in clinical trials.

Patients with favourable (<5 CTCs/7.5 mL) baseline counts represent a subgroup of patients with a significantly better prognosis. These patients, especially those with undetectable CTCs at baseline, are not evaluable for response. Monitoring CTC counts in these patients can enable the detection of ‘CTC progression’, which has been evaluated as either a ‘conversion’ to unfavourable CTC counts [12, 13] or as any increase in CTC numbers.

We have previously reported the association of 30% CTC falls with improved outcome in patients with unfavourable (≥ 5 CTCs/7.5 ml) baseline CTCs [10]. In the present study, we aimed

to analyse the value of CTC increases in patients with low (<5 CTCs/7.5 ml) baseline CTCs participating in the prospective COU-AA-301 and IMMC-38 trials.

Methods

Study population and procedures

We report an unplanned post hoc analysis of the COU-AA-301 and IMMC-38 trials, both of which have been published previously [12, 14]. The phase III COU-AA-301 trial compared abiraterone and prednisone with placebo with prednisone in metastatic castration-resistant prostate cancer (mCRPC) patients previously treated with chemotherapy. IMMC-38 was a prospective, open-label study in patients with mCRPC undergoing treatment with chemotherapy (70% of patients receiving docetaxel) as first, second or third line [12]. CTCs were collected at baseline, cycle 2 day 1 (weeks 4–5), cycle 3 day 1 (weeks 8–9) and cycle 4 day 1 (weeks 12–13) in COU-AA-301. In IMMC-38, CTCs were evaluated at weeks 2–5 (median: 4 weeks), weeks 6–8 (median: 7 weeks) and weeks 9–12 (median: 11.9 weeks). CTCs were determined with the CellSearchTM (Menarini Silicon Biosystems) assay. Haemoglobin (Hb), alkaline phosphatase (ALP), albumin and LDH concentrations were obtained at baseline and at each study visit. Eastern Cooperative Oncology Group (ECOG)-PS was obtained at baseline. PSA values were obtained every 4 weeks in IMMC-38 and every 12 weeks in COU-AA-301. Both studies were approved by local institutional boards. All patients provided written informed consent.

Statistical analysis

Kaplan–Meier analysis was used to estimate overall survival. CTC progression was defined as any increase in CTC count relative to baseline at either 4, 8 or 12 weeks after treatment initiation. Uni- and multi-variable Cox proportional hazards models were used to explore the association of baseline CTC counts, CTC progression and CTC conversion (defined as increase in CTCs from <5 to ≥ 5), with survival. Baseline LDH, ALP, PSA and CTCs, included as continuous variables, were \log_{10} -transformed due to their positively skewed distribution. In order to include patients with no detectable CTCs in the baseline count in the survival analyses, which required \log_{10} transformation, 0.1 was added to all the baseline CTC counts. Logistic regression models were used to compare differences in PSA response and treatment arm by CTC progression and CTC conversion status.

Cox-regression models constructed including a ‘Baseline’ model (which included established clinical prognostic biomarkers: ECOG-PS, LDH, PSA, Hb, ALP and albumin); a ‘Baseline CTC model’ (adding baseline CTC counts to the ‘baseline model’) and a ‘CTC progression Model’ (adding CTC progression to the ‘baseline CTC model’). A test of proportionality based on the Schoenfeld residuals was applied to evaluate the proportional hazards assumption (supplementary Figure S2, available at *Annals of Oncology* online). The value of baseline CTCs and of CTC progression was assessed by calculating Uno’s inverse-probability weighted c-index and time-dependent incident dynamic ROC area under the curve (AUC) values (with a 22-month survival end point, which represents the median survival of the dataset) of each of the models, according to the method proposed by Blanche et al. [15]. Bootstrapping was used to calculate the 95% confidence interval (CI) and the difference (delta) between c-indices of each of the models [16]. Analyses were carried out with SPSS v23 (SPSS Inc, IBM Corporation, Armonk, New York, US) and the R statistics package v3.4.0 (R Foundation).

Table 1. Baseline patient characteristics

	All patients	COU-301 Subset	IMMC-38 Subset
N	511	421	90
BLCTC			
0	259 (50.7%)	212 (50.4%)	47 (52.2%)
1–2	175 (34.3%)	146 (33.7%)	29 (32.2%)
3–4	77 (15.2%)	63 (16%)	14 (15.6%)
LDH (IU/L)	197.5 (167–233)	196 (167–230.8)	203 (167.8–247.3)
PSA (ng/mL)	71.6 (23.5–211.6)	69.6 (23–214.4)	79 (26.1–214.3)
Hb (g/dL)	12.5 (11.4–13.4)	12.4 (11.3–13.1)	13.2 (12.1–13.8)
ALP (IU/L)	87 (68–130)	86 (67–127.8)	96 (76–142)
Albumin (g/dL)	4.1 (3.8–4.3)	4.1 (3.9–4.4)	3.9 (3.6–4.3)
ECOG-PS			
0–1	485 (95.3%)	401 (95.2%)	84 (93.3%)
2	24 (4.7%)	20 (4.8%)	4 (4.4%)
Abiraterone	—	289 (68.6%)	—
Placebo	—	132 (31.4%)	—

BLCTC, baseline circulating tumour cell; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; Hb, haemoglobin; ALP, alkaline phosphatase; ECOG, Eastern Cooperative Oncology Group.

Results

Patient characteristics

Overall, a total of 511 patients participating in the COU-AA-301 ($n = 421$; 82.4%) and IMMC-38 ($n = 90$; 17.6%) clinical trials met the selection criteria with baseline CTC counts < 5 cells/7.5 ml and were included in the analysis. [Supplementary Figure S1](#), available at *Annals of Oncology* online represents the Consort Diagram with details of patients excluded from the analysis. An analysis of patients with baseline CTC counts ≥ 5 cells/7.5 ml has been published previously [10]. No major differences in baseline patient characteristics were observed between IMMC-38 and COU-AA-301 participants (Table 1). Median follow-up was 17.4 months (range: 3.2–27.1 months); 217 patients (43.6%) had died at the time of analysis, 190 (45.3%) in COU-AA-301 and 27 (30%) in IMMC-38. Median overall survival was 21.98 (95% CI 20.7–23.3) months; there were no significant differences in survival between patients in the COU-AA-301 and IMMC-38 trials (22.0 and 21.4 months, respectively; $P = 0.146$).

Baseline CTC count and survival

Median baseline CTC count was 0 cells/7.5 ml (0 cells/7.5 ml in both COU-AA-301 and IMMC-38). 259 patients (50.7%) had 0 CTCs at baseline; 212 (50.4%) in COU-301 and 47 (52.2%) in IMMC-38. Baseline CTC count, as a \log_{10} -transformed continuous variable, was associated with survival in these patients overall [hazard ratio (HR) 1.65; 95% CI 1.32–2.05; $P < 0.001$], and when analysing patients from COU-AA-301 (HR 1.57; 95% CI: 1.25–1.96; $P < 0.001$) and IMMC-38 (1.98; 95% CI 1.09–3.61; $P = 0.026$) separately. There was a significant linear trend in survival when comparing patients with 0 (median 27.1 months; 95% CI NR–NR), 1–2 (median 21.6 months; 95% CI 19.7–23.5)

and 3–4 (median 15.1 months; 95% CI 12.4–17.8) baseline CTCs (P -value for linear trend = 0.001) (Figure 1).

CTC progression is associated with adverse outcome

Overall, 213 (41.7%) patients experienced CTC progression in the first 12 weeks of treatment; 184 (43.7%) in COU-AA-301 and 29 (32.2%) in IMMC-38; 117 (25.8%), 103 (23.8%) and 124 (24.4%) patients experienced CTC progression at 4, 8 and 12 weeks, respectively. Patients experiencing CTC progression at 4 weeks [23.8 versus 14.8 months; HR 2.8 (95% CI 2.1–3.7); $P < 0.001$], 8 weeks [24.1 versus 14.7 months; HR 3.0 (95% CI 2.2–4); $P < 0.001$] and 12 weeks [27.1 versus 13.6 months; HR 3.9 (95% CI 2.9–5.2); $P < 0.001$] had significantly reduced survival compared with those not experiencing CTC progression. At any of the time-points, the association of CTC progression with reduced survival was independent of other known prognostic baseline characteristics. The impact of CTC progression was similar for both COU-AA-301 and IMMC-38 cohorts (Figure 2; [supplementary Table S1](#), available at *Annals of Oncology* online). Similarly, the impact of CTC progression in multi-variable analysis (Table 2) was similar among patients with undetectable [baseline CTC (BLCTC) = 0: HR 2.9 (95% CI 1.8–4.7); $P < 0.001$] and detectable [BLCTC ≥ 1 : HR 3.5 (95% CI 2.4–5.1); $P < 0.001$] counts (interaction test: $P = 0.734$).

To evaluate the added value of incorporating CTC Progression for predicting survival, we constructed a survival model incorporating baseline CTC counts and other prognostic clinical variables and determined the survival models' receiver operating characteristic (ROC) curve AUC and c-index. The ROC curve AUC for the baseline model was 0.66 (95% CI 0.59–0.74). A non-significant increase to an AUC of 0.67 (95% CI 0.59–0.75) was observed when adding baseline CTC counts to this baseline CTC model ($P = 0.63$). Adding CTC

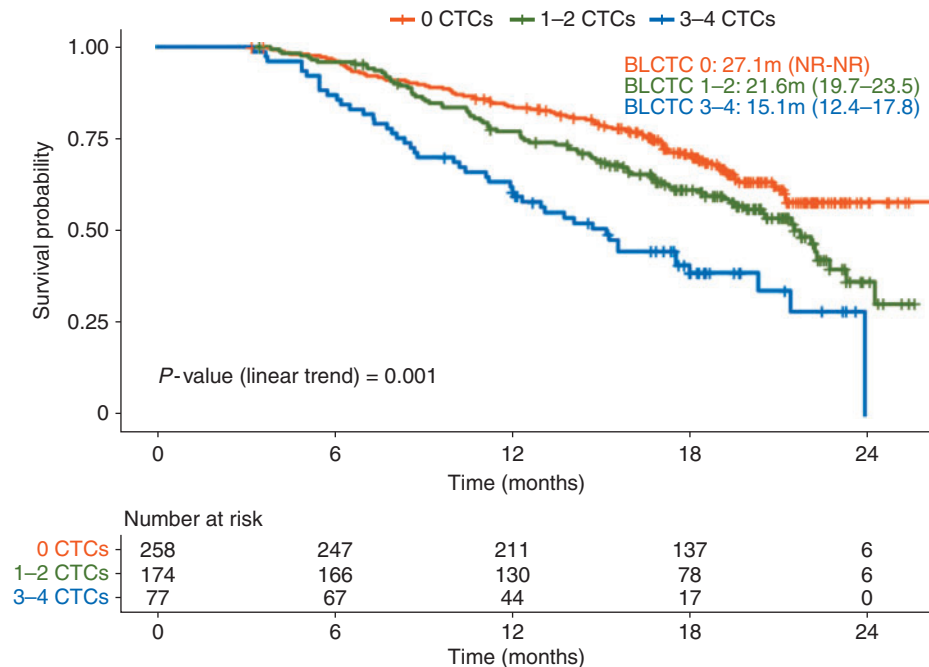


Figure 1. Kaplan–Meier survival curves in patients with 0, 1–2 or 3–4 circulating tumour cells at baseline (BLCTC).

progression to the model substantially increased the ROC AUC value (AUC 0.77; 95% CI 0.70–0.84) when compared with the baseline CTC model ($P < 0.001$) (Figure 3). The weighted c-index of the baseline model (0.682; SE: 0.023) increased to 0.694 (SE: 0.026) after including baseline CTCs. Inclusion of CTC progression in the model increased the weighted c-index to 0.748 (SE: 0.019) (delta c-index = 0.056; 95% CI 0.025–0.087).

Overall, furthermore, 500 patients (98.2%) had data on PSA response. PSA response, defined as a 50% decline from baseline, was observed in 118 (28.2%) patients from COU-AA-301 and 42 (51.9%) patients from IMMC-38. Patients with CTC progression had a significantly lower rate of PSA response than those without CTC progression [11.4% versus 47.1%; odds ratio (OR) 0.14 (95% CI 0.09–0.23), $P < 0.001$]; similar associations were observed in the COU-AA-301 [OR 0.14 (95% CI 0.08–0.24); $P < 0.001$] and IMMC-38 [OR 0.17 (95% CI 0.06–0.48); $P = 0.001$] patient subsets (supplementary Table S2, available at *Annals of Oncology* online).

Comparing CTC progression and CTC conversion

Overall, 90 patients (17.7%) experienced a conversion to unfavourable (≥ 5 CTCs/7.5 mL) counts during the first 12-weeks of treatment; 76 (18.1%) in the COU-AA-301 and 14 (15.6%) in the IMMC-38 trials. A CTC conversion was associated with a worse outcome (23.8 vs 10 months; HR: 3.78 [95%CI: 2.82–5.06]; $p < 0.001$) in both uni- and multi-variable Cox-regression models (supplementary Table S3, available at *Annals of Oncology* online), as well as a reduced PSA response rate (OR 0.08 [95%CI: 0.03–0.2]; $p < 0.001$); only 4 (4.4%) patients with a CTC conversion experienced a PSA response (supplementary Table S2, available at *Annals of Oncology* online).

The weighted c-index of the model including CTC progression was significantly higher than that of the model including CTC conversion (0.750 vs 0.705; delta c-index: 0.045 [95%CI: 0.019–0.071]). The ROC curve AUC index was also significantly higher for CTC progression than for CTC conversions (0.77 vs 0.69; 95% CI: 0.61–0.76; $p < 0.001$) (supplementary Figure S3, available at *Annals of Oncology* online).

CTC progression in COU-AA-301: Interaction with treatment arm

Overall, 419 patients participating in the COU-AA-301 trial were included in this analysis, 288 (68.7%) receiving abiraterone + prednisone and 131 (31.3%) placebo + prednisone. There was no significant difference in survival between these cohorts (HR 0.86; 95% CI 0.63–1.17; $P = 0.330$). CTC progression was more frequent in the placebo (68 patients, 51.9%) arm than in the abiraterone (115 patients, 39.9%) arm (OR 0.6; $P = 0.022$). The survival decrease in patients experiencing CTC progression was similar in the abiraterone (24.1 versus 15.1 months; HR 3.76; $P < 0.001$) and placebo arms (NR versus 13.8 months; HR 3.23; $P < 0.001$). The interaction test between treatment arm and CTC progression was not significant ($P = 0.952$), indicating that the impact of CTC progression on survival was similar for patients in both trial arms.

Discussion

Improvements in the development of predictive biomarkers for advanced prostate cancer care including AR splice variants and AR genomic aberrations for novel hormonal agents; DNA repair aberrations for PARP inhibitors and PTEN loss for agents targeting the PI3K/AKT pathway are anticipated in the future [17]. The

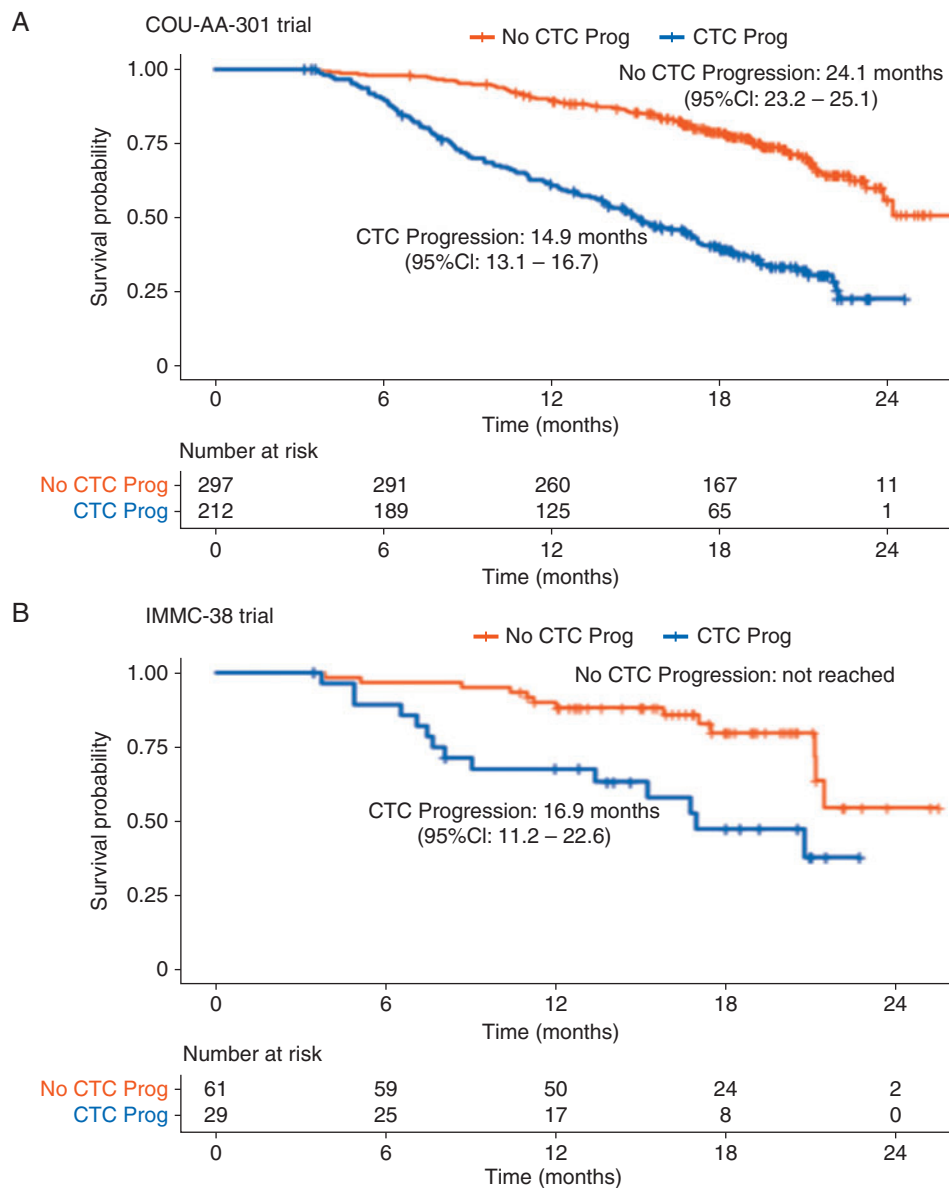


Figure 2. Kaplan–Meier survival curves in patients with and without circulating tumour cells (CTC) progression at 4, 8, or 12 weeks in the COU-AA-301 (abiraterone or placebo + prednisone) subset (A) and IMMC-38 (chemotherapy) subset (B).

development of response biomarkers to rapidly identify resistant disease and guide early treatment switches remains, however, an unmet clinical need. The value of circulating tumour cells as a prognostic indicator for advanced prostate cancer care has been well described [8, 9, 13]. Because of regulatory concerns about assay performance when CTCs are low, patients have been categorized into unfavourable (CTCs $\geq 5/7.5$ ml) and favourable CTC count groups, which have distinct prognoses. The value of CTCs as an indicator of clinical activity has also been reported: post-treatment CTC declines, either as a fold-decline, 30% decline or conversion to favourable counts have all been associated with improved survival in the subgroup of patients with unfavourable baseline CTC counts [7, 10, 12]. PCWG3 now recommends the use of CTCs as an end point for activity in patients with unfavourable counts at baseline in the setting of clinical trials [2]. This approach, however, captures only approximately

50% of patients (with unfavourable baseline counts) as assessable and classifies those with favourable baseline counts as non-assessable for response.

The role of increasing CTC counts as an indicator of disease progression has been less well studied. We present what is, to our knowledge, the largest dataset analysing the role of increasing CTCs as a biomarker of progression analysing exclusively patients with low (<5) baseline CTC counts at baseline, treated with AR targeting agents (COU-AA-301) and chemotherapy (IMMC-38) in each of the prospective clinical trials. In our study, CTC progression (defined as any increase in CTC counts) and ‘CTC conversions’ (defined as an increase to at least 5 CTCs/7.5 ml) during the first 12 weeks of treatment are associated with a worse outcome in patients treated with either abiraterone or chemotherapy. Furthermore, CTC progression increased the power of the survival model that included key clinical variables and baseline

Table 2. Association of CTC progression and survival (multivariable cox-regression model – CTC progression model)

	HR	95% CI	p-value
CTC progression ^a	3.33	2.50–4.44	<0.001
Baseline CTC count ^b	1.48	1.19–1.85	<0.001
Baseline PSA ^b	0.98	0.79–1.21	0.85
Baseline ALP ^b	1.56	0.95–2.58	0.08
Baseline LDH ^b	15.33	6.04–38.95	<0.001
Baseline albumin	0.65	0.44–0.95	0.03
Baseline haemoglobin	0.94	0.84–1.04	0.24
ECOG performance status	3.01	1.84–4.92	<0.001

^aCTC progression at 4, 8 or 12 weeks.

^bBaseline CTC count, PSA, ALP and LDH were log-transformed.

CTC, circulating tumour cell; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group.

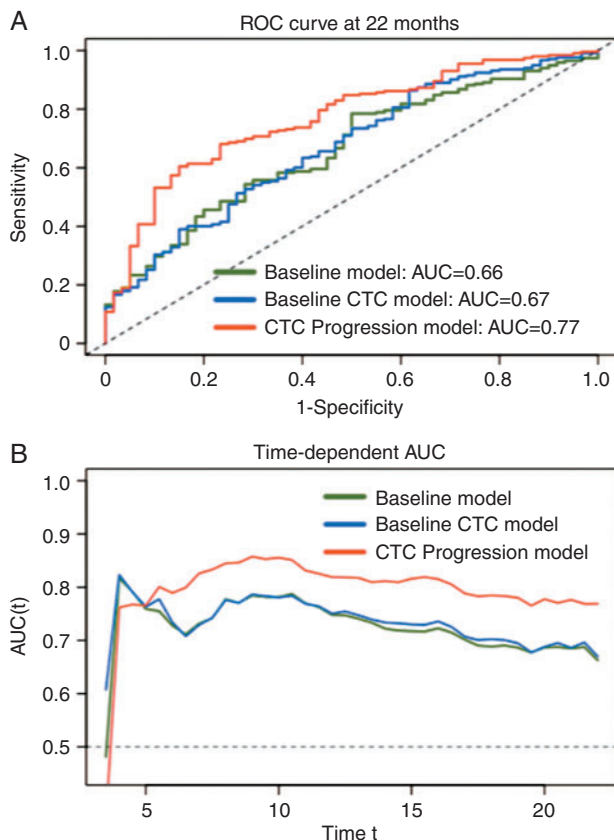


Figure 3. Area under the curves (AUC) of the baseline, baseline circulating tumour cell (CTC) and CTC progression survival models.

CTCs. We show that CTC progression is superior to CTC conversion as a biomarker of poor overall survival with superior model performance as defined by ROC AUC values and *c*-indices. This is in line with our previous conclusions in patients with unfavourable CTC counts, where failure to effectively reduce CTCs ('stable' CTC counts) had a similar adverse impact to primary

'progressing' CTC counts [10]. Recently, Heller et al. [18] presented a pooled analysis of five randomized mCRPC trials, where both a CTC conversion (≥ 5 CTCs to < 5 CTCs) and a CTC0 end point (> 1 CTCs to 0 CTCs) had a higher discriminatory value (*c*-index) than commonly used PSA end points. CTC0 end points were able to evaluate a significantly higher number of patients than CTC conversion end points. In patients with treatment naive mCRPC (ELM-PC-4 trial), however, as many as 33% and 61% of patients were non-assessable for CTC0 (due to baseline 0 CTC) and CTC conversion (due to baseline < 5 CTCs), respectively [18]. An approach incorporating CTC increase end points for patients with low baseline CTC counts could therefore render all patients assessable for CTC efficacy end points.

A number of limitations to our study should, however, be acknowledged: (i) its unplanned, post hoc nature (ii) not all patients enrolled in COU-AA-301 had CTCs (CTCs were collected in 858 of 1195 [71.8%] patients), which could have led to a selection bias; (iii) the unavailability of CTC counts beyond 12 weeks in COU-AA-301, with our results therefore not being applicable to CTC counts beyond that time-point; (iv) the fact that patients treated in COU-AA-301 were over fourfold more numerous than those in IMMC-38 and (v) LDH kinetics were not incorporated into the analyses.

In conclusion, these data indicate that CTC progression in the first 12 weeks of chemotherapy or endocrine therapy can identify patients with low baseline CTC counts (< 5) not benefiting from treatment. These data have significant clinical and health economic implications and could guide the response assessment of patients during the first 12 weeks of treatment, identifying early disease progression, and could be used as efficacy biomarkers in clinical trials. Prospective phase III trials are now needed to validate these findings, and confirm the clinical utility of CTCs [9].

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Disclosure

DD, DB, GS, PF, MC, IF, SM, and JSdB are employees of the Institute of Cancer Research, which has a commercial interest in abiraterone. All remaining authors have declared no conflicts of interest.

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