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Brief Correspondence

External Validation of a Prognostic Model Predicting Overall Survival in Metastatic Castrate-resistant Prostate Cancer Patients Treated with Abiraterone

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Abstract

A prognostic model was derived from the population of the COU-AA-301 phase 3 trial for metastatic castrate-resistant prostate cancer patients treated with abiraterone after docetaxel, and it stratifies patients into three risk groups based on clinical parameters. We validated this model in an independent cohort of patients treated with abiraterone after docetaxel outside a clinical trial (group A; $n = 94$) and explored its utility in patients treated with abiraterone in the prechemotherapy setting (group B; $n = 64$). For group A, median overall survival (mOS) was significantly different across the three prognostic groups (good: $n = 39$, mOS: 21.8 mo; intermediate: $n = 44$, mOS: 10.6 mo; poor: $n = 7$, mOS: 6.8 mo; $p < 0.001$; area under the curve [AUC]: 0.71). Analysis of group B confirmed the ability of the model to prognosticate for survival in the prechemotherapy setting: (good: $n = 44$, mOS: 45.6 mo; intermediate or poor: $n = 20$, mOS: 34.5 mo; $p = 0.042$; AUC: 0.61). These results serve to validate the prognostic model in an independent population treated with abiraterone after docetaxel and support clinical implementation of the score. Calibration of the model was poorer in patients receiving abiraterone prechemotherapy. Prospective evaluation of this model in clinical trials is needed.

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Prostate cancer, the most common male cancer, accounts for >70 000 deaths in Europe each year [1]. Over the past decade, several new therapeutic agents were shown to provide a survival benefit for men with metastatic castrate-resistant prostate cancer (mCRPC) including abiraterone [2], enzalutamide [3], radium-223 [4], and cabazitaxel [5]. Along with docetaxel, the prior established standard of care, the judicious use of these newer agents has the potential to extend survival of mCRPC patients to several years, although the precise sequencing of these therapies to achieve such a benefit needs to be elucidated.

Abiraterone, a CYP-17 inhibitor that inhibits testicular and extragonadal androgen synthesis, has been shown to increase survival in mCRPC patients who have received

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Table 1 – Baseline characteristics of metastatic castrate-resistant prostate cancer patients receiving either abiraterone after docetaxel outside a clinical trial (group A) or abiraterone before docetaxel (group B)

	Group A	Group B
Total no. of patients	94	64
Age, yr, median (range)	69.5 (44.7–85.1)	70.2 (48.2–85.5)
Baseline PSA, median (range)	235 (2.32–11)	75 (5.34–9)
Gleason score, median (range)	8 (2–10)	8 (6–10)
Performance status, *n* (%)		
0	16 (17)	38 (59)
1	61 (66)	26 (41)
2	16 (17)	0 (0)
Presence of visceral disease, *n* (%)	14 (15)	7 (11)
Duration of abiraterone therapy, d, median (range)	144 (34–979)	466 (27–2443)
Risk group, *n* (%)		
Good	39 (43)	44 (69)
Intermediate	44 (49)	19 (30)
Poor	7 (8)	1 (0)

PSA = prostate-specific antigen.

prior chemotherapy [2], as well as to improve radiographic progression-free survival in chemotherapy-naive patients [6]. Although validated prognostic models predicting survival in mCRPC patients undergoing first-line [7] and second-line chemotherapy [8] exist, contemporary survival figures suggest these prognostic nomograms require updating and revalidation [9].

Chi and colleagues recently presented a prognostic model predicting overall survival in mCRPC patients receiving abiraterone after chemotherapy that they derived using data from the COU-AA-301 phase 3 randomised controlled trial [10]. The model relies on six baseline clinical parameters: (1) Eastern Cooperative Oncology Group performance status of 2, (2) presence of liver metastases, (3) time from start of initial luteinising hormone-releasing hormone agonist therapy to abiraterone treatment ≤36 mo, (4) low albumin, (5) high alkaline phosphatase, and (6) high lactate dehydrogenase. It then stratifies patients into three risk groups (good [0–1], intermediate [2,3], and poor [4–6]) depending on the number of adverse parameters present at the start of abiraterone therapy. The aim of this study was to validate this model externally in an independent cohort of post-chemotherapy mCRPC patients who were treated outside the setting of a clinical trial, as well as to explore the prognostic use of the model in the prechemotherapy population.

Electronic patient records of consecutive mCRPC patients who received abiraterone at our institution between January 2006 and June 2013 were reviewed. All patients had provided consent for data collection in protocols approved by the institutional review board. Patients were stratified according to previous treatment with docetaxel, and clinical information at the start of abiraterone therapy was collected. Patients who received abiraterone after docetaxel within a phase 1, 2, or 3 clinical trial were excluded to ensure the cohort was representative of routine clinical practice and independent of those included in the derivation of the prognostic model [10]. For the time-to-next-event analysis within the predocetaxel cohort, an event was defined as the receipt of chemotherapy or death (whichever occurred earlier).

Survival estimates were performed with the Kaplan-Meier method. The log-rank test and Cox proportional hazards model were used to detect differences in survival between groups. The performance of the prognostic score was evaluated with receiver operating characteristic curves and the associated c-index (area under the curve [AUC]) based on an outcome of death at the point of median survival of each of the patient cohorts and at fixed time points (6, 12, 18, 24, 36, and 48 mo). Statistical analysis was performed using SPSS v.20 (IBM Corp., Armonk, NY, USA).

Overall, 158 patients were eligible for this analysis (postdocetaxel nontrial cohort [group A], $n = 94$; predocetaxel cohort [group B], $n = 64$). Table 1 shows the baseline characteristics of both cohorts. Median duration of abiraterone therapy in groups A and B was 144 and 466 d, respectively, with median overall survival of 13.3 mo (group A) and 40.4 mo (group B). Most patients in both groups were either good or intermediate risk, as classified by the prognostic model. Supplemental Table 1 shows the uni- and multivariate prediction of survival by the six variables used in the model in groups A and B.

Application of the risk stratifications to group A confirmed the ability of the model to prognosticate for overall survival (hazard ratios [HR] [good: reference]: intermediate, HR: 2.73 [95% confidence interval [CI], 1.61–4.64], poor, HR: 3.79 [95% CI, 1.52–9.45]; Fig. 1). The AUC of the prognostic score in this cohort was 0.71 (95% CI, 0.60–0.80).

In an exploratory analysis, we applied the risk score to patients receiving abiraterone prechemotherapy. Because only one patient in this cohort was classified as poor risk, comparisons were made between good- and intermediate- or poor-risk patients. Median overall survival was significantly longer in the good-risk population compared with intermediate/poor-risk men (45.5 mo vs 34.5 mo; $p = 0.042$; HR: 1.79 [95% CI, 1.02–3.17]; Fig. 2a), and median time to

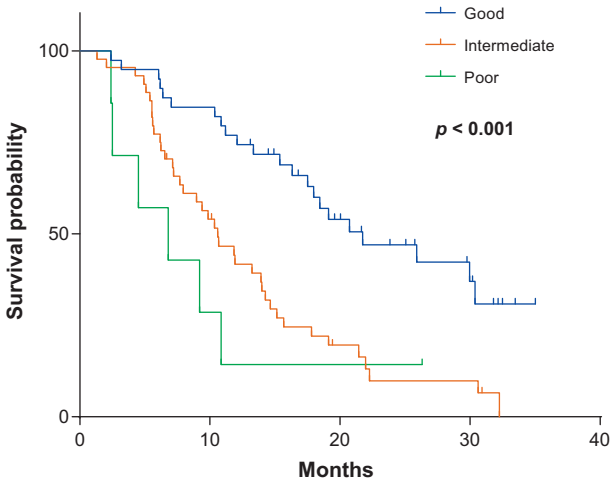

Fig. 1 – Kaplan-Meier curve showing overall survival of metastatic castrate-resistant prostate cancer patients receiving abiraterone after docetaxel outside a clinical trial, stratified by prognostic risk group.