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The development of risk groups in men with metastatic castration-resistant prostate cancer based on risk factors for PSA decline and survival

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ARTICLE INFO

Article history:
Received 12 August 2009
Received in revised form 6 November 2009
Accepted 12 November 2009
Available online 11 December 2009

Keywords:
Castration-resistant
Prostate cancer
Risk groups
Hormone-refractory
Survival
PSA response
Predictive factor
Prognostic factor
Metastatic

ABSTRACT

Aims of the study: There are no known predictive factors of response in men receiving chemotherapy for metastatic castration-resistant prostate cancer (mCRPC). We investigated pre-treatment factors that predicted a ⩾30% PSA decline (30% PSAD) within 3 months of starting chemotherapy, and assessed performance of a risk group classification in predicting PSA declines and overall survival (OS) in men with mCRPC.

Methods: In TAX327, 1006 men with mCRPC were randomized to receive docetaxel (D) in two schedules, or mitoxantrone (M), each with prednisone: 989 provided data on PSA decline within 3 months. Predictive factors for a 30% PSAD were identified using multivariable regression in D-treated men ($n = 656$) and validated in M-treated men ($n = 333$).

Results: Four independent risk factors predicted 30% PSAD: pain, visceral metastases, anaemia and bone scan progression. Risk groups (good: 0–1 factors, intermediate: 2 factors and poor: 3–4 factors) were developed with median OS of 25.7, 18.7 and 12.8 months ($p < 0.0001$); 30% PSAD in 78%, 66% and 58% of men ($p < 0.001$); and measurable disease response in 19%, 9% and 5% of men ($p = 0.018$), respectively. In the validation cohort, similar predictive ability was noted for 30% PSAD, tumour response and OS. PCWG2 subtypes were also predictive but resulted in unequal grouping. C-indices were 0.59 and 0.62 for 30% PSAD and OS in the validation dataset, respectively.

Conclusions: Risk groups have been identified and validated that predict PSAD and OS in men with mCRPC and may facilitate evaluation of new systemic regimens warranting definitive testing in comparison with docetaxel and prednisone. Prospective validation of this classification system is needed.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.11.007

1. Introduction

Metastatic castration-resistant prostate cancer (mCRPC) remains a common and often fatal disease in Europe and the United States in 2009.[1,2] Docetaxel and prednisone were reported in 2004 to improve survival, response and quality-of-life in men with mCRPC, but since then no approved agents have further improved outcomes over docetaxel in phase III studies.[3,4]

Barriers to the identification of active agents in clinical trials of men with mCRPC include the lack of strong surrogates of survival and the potential length of time necessary to reach survival-based end-points.[5–7] The identification of potentially effective agents in phase II trials is confounded by the presence of prognostic factors that may lead to selection bias and to apparently favourable results that are not confirmed in definitive phase III clinical trials. Validated prognostic nomograms have identified risk factors for survival that have been used to stratify men with mCRPC in clinical trials.[8–10] However, these risk factors have not been fully utilised to restrict eligibility in conducting clinical trials or to identify risk groups of men with CRPC who may benefit from more aggressive intervention.[11,12] In addition, no known factors reliably predict the PSA declines in men with mCRPC and this may identify groups at higher risk for rapid disease progression.

A $\geqslant$30% decline in serum PSA in the 3 months (30% PSAD) following chemotherapy initiation has been identified as a valid surrogate of overall survival (OS) in men with mCRPC based on retrospective analyses from two pivotal phase III trials of docetaxel-based regimens.[7,13] Guidelines developed by the Prostate Cancer Working Group 2 (PCWG2) have since recommended the use of progression rather than response end-points to inform upon selection of active agents in phase II trials.[14] However, neither PSA or pain response nor progression-based end-points have been validated prospectively as surrogates of OS, and recent retrospective studies have shown quite modest surrogacy for current measures of progression-free survival (PFS) and PSA declines.[7,13,15–17] While recent definitions of PFS or changes in biomarkers such as circulating tumour cell count may improve upon surrogacy, a $\geqslant$30% PSAD and pain improvements following chemotherapy initiation are amongst the strongest predictors of OS, and can generally be ascertained within the first four cycles of chemotherapy.[14,17,18] We thus hypothesise that survival-based risk factors will also predict for PSA and tumour response outcomes and that these risk factors will facilitate communication with patients about expected responses to docetaxel chemotherapy and aid in selection of agents for definitive testing that surpass these expected outcomes in early phase studies.

2. Patients and methods

TAX327 was a randomized phase III study involving 1006 men with progressive metastatic CRPC, conducted from March 2000 to June 2002.[3] Eligible men had histologically documented metastatic PC despite castrate serum testosterone levels ($\leqslant$50 ng/dl), with disease progression defined clinically, radiographically or by PSA criteria. No prior chemotherapy other than estramustine was allowed, and men were required to have stable pain scores at entry. An Institutional Review Board approved the study at each participating institution.

Participants were randomised to one of three arms: three-weekly docetaxel (q3w, 75 mg/m^2), weekly docetaxel (q1w, 30 mg/m^2 5 weeks of 6) or q3w mitoxantrone (12 mg/m^2), all with prednisone 5 mg twice daily, with treatment planned for 30 weeks in the absence of progression. The present analysis is based on updated survival as of 7th November 2006, at which time 800 deaths had occurred.

2.1. Analysis of response-based outcomes

The primary objective of this analysis was the development of a predictive model for the attainment of a $\geqslant$30% decline in PSA within 3 months of treatment initiation (PSAD), without requirement for confirmation and irrespective of baseline PSA. Percent decline was taken as the nadir value during the 3-month interval as compared to baseline. Secondary end-points included a $\geqslant$50% confirmed PSA decline, PSA normalisation, pain response, tumour response and overall survival.[19] PSA normalisation required a PSA $\leqslant$4 ng/ml on protocol treatment amongst men with baseline PSA $\geqslant$20 ng/ml.[7] PSA was measured at each cycle.

Baseline pain was measured at each cycle using the Present Pain Intensity (PPI) score and an analgesic score (AS) was calculated from an analgesic diary where a standard dose of narcotic medication (e.g. 10 mg oral morphine) scored 4 points: a PPI of $\geqslant$2 and/or an AS of $\geqslant$10 were used as indicative of significant pain.[20] Pain response was defined as a $\geqslant$2 point-reduction from the baseline PPI without an increase in the AS or a >50% reduction in the AS without an increase in the PPI. Tumour response was evaluated every 2 months according to World Health Organisation (WHO) criteria.[3,4]

2.2. Model development

We first sought to identify independent factors that were predictive of 30% PSAD. We split the dataset into development and validation cohorts. Given the superiority of docetaxel to mitoxantrone and the larger sample size of docetaxel-treated men, we included men randomised to docetaxel (n = 656) in the development cohort. The validation cohort included men randomised to mitoxantrone/prednisone (n = 333). Baseline variables considered included the presence of visceral metastases, significant pain, alkaline phosphatase, investigator-determined mode of progression, haemoglobin, number of hot spots on bone scan, number of metastatic sites, PSA, PSA doubling time, time since diagnosis, tumour grade, prior therapies and Karnofsky performance status.[8–10] Multivariable logistic regression was performed, retaining variables that remained statistically significant (level of $p < 0.10$) after adjustment, and lacking co-linearity with other known prognostic factors. For each patient, a predictive score was computed from the estimated regression coefficients based on the fitted model and used to classify patients in risk groups. A concordance index was estimated as a measure of predictive ability in each cohort. Secondary outcomes were then assessed across risk groups. Differences in the proportion of men who achieved these outcomes across risk groups were

evaluated by χ^2 or log-rank analysis. Hochberg's method was used to control for the type I error in analysing the secondary outcomes.[21] Furthermore, the Kaplan–Meier method was used to estimate survival distributions and the log-rank statistic was utilised to compare survival times across risk groups.

3. Results

Amongst 1006 men randomised in theTAX327study, 989 men received protocol-directed therapy and had baseline and at least one follow-up PSA value within 3 months of treatment initiation, and were included in the development or validation cohorts. Baseline demographic and clinical variables did not differ between the development and validation cohorts (Table 1).

As compared to men who did not achieve a 30% PSAD, men who achieved a 30% PSAD had a significantly lower prevalence of visceral metastases (20% versus 28%), significantly less baseline pain (42% versus 54%), higher mean haemoglobin, fewer bone scan lesions and a lower alkaline phosphatase, and differed according to how progression was defined prior to receiving chemotherapy (Table 2). Responders were also significantly less likely to have received prior estramustine (15% versus 26%). Men who achieved a 30% PSAD were more likely to have progressed at entry by PSA criteria only (18% versus 13%) and were less likely to have progressed by bone scan criteria (67% versus 77%).

3.1. *Development cohort*

Baseline factors were then evaluated by multivariable logistic regression for their ability to predict 30% PSAD. Important factors were the presence of significant baseline pain (OR 0.65 95% confidence interval (CI): 0.46–0.92), visceral metastases (OR 0.64 95% CI: 0.43–0.95), anaemia (OR 0.77 95% CI: 0.54–1.09), progression by new bone scan lesions at baseline (OR 0.61 95% CI: 0.41–0.89) and prior estramustine therapy (OR 0.51 (0.34–0.77). Given that estramustine is no longer widely used and is of limited prognostic value for overall survival

Table 1 – Baseline characteristics of TAX327 men according to assigned group, including the development cohort (all docetaxel and prednisone treated subjects) and the validation cohort (all mitoxantrone and prednisone treated subjects). IQR = interquartile range (25th and 75th percentiles).

Baseline characteristics	Development cohort (docetaxel) $N = 656$	Validation cohort (mitoxantrone) $N = 333$
Demographics		
Age, mean (years)	67	67
Race: white (%)	93.5	92.5
Black (%)	2.4	3
Hispanic (%)	2.3	2.7
Asian (%)	0.6	0.9
Other (%)	1.2	0.9
Baseline clinical characteristics		
Visceral metastases (%)	23	22
High grade disease (%)*	39	36
Significant pain (%)	46	46
>2 Metastatic sites (%)	13	11
Multiple hot spots on bone scan (%)	82	84
Poor performance status (KPS $\leqslant$ 70) (%)[a]	12	14
Rising PSA only (%)	15	15
Bone scan progression (%)	70	69
Measurable disease progression (%)	29	28
Mean time since diagnosis (months)	53	53
Laboratory variables		
PSA, mean (ng/dl)	459	399
median (ng/dl) and IQR	110 (41, 325)	123 (50, 411)
PSADT, mean (d)[b]	81	75
median (d) and IQR	58 (37, 90)	54 (35, 84)
Mean haemoglobin and IQR (g/dl)	12.6 (11.7, 13.5)	12.6 (11.6, 13.7)
Presence of anaemia (Hgb < 13.0) (%)	43	43
Mean alkaline phosphatase (IU/d)	442	424
Median (IU/dl) and IQR	206 (111, 461)	200 (106, 449)
Prior therapies		
Radical prostatectomy (%)	64	62
Radiation (%)	48	51
Estramustine (%)	19	21
Number of prior hormonal therapies (% $\geqslant$3)	13	15

a $n = 655$ with available information on performance status.
b $n = 449$ with evaluable PSADT.
* WHO grade 3–4 or Gleason sum 8–10.

Table 2 – Baseline characteristics of TAX327 men according to attainment of a ⩾30% PSA decline from baseline (n = 656 docetaxel-treated patients).

Baseline characteristics	No. ⩾30% PSA decline (95% confidence interval) n = 214	⩾30% PSA decline (95% confidence interval) n = 442	p-Value
Demographics			
Age, mean (years)	68	68	0.15
Race: (%) Caucasian	95	92	0.06
Baseline clinical characteristics			
Visceral metastases (%)	28	20	0.03
High grade disease (%)*	41	39	0.49
Significant pain (%)	54	42	0.003
>2 Metastatic sites (%)	16	12	0.09
Multiple hot spots on bone scan (%)	86	79	0.03
Poor performance status (KPS⩽70) (%)[a]	14	11	0.32
Rising PSA only (%)	13	18	0.07
Bone scan progression (%)	77	67	0.007
Measurable disease progression (%)	32	27	0.22
Time since diagnosis (months)	49 (43–55)	55 (51–59)	0.07
Laboratory variables			
PSA, mean (ng/dl)	350 (260–441)	527 (264–791)	0.36
Median (ng/dl)	129 (102–161)	107 (90–124)	
PSADT, mean (d)[b]	91 (66–116)	76 (68–83)	0.14
median (d)	56 (52–61)	56 (52–64)	
Mean haemoglobin (g/dl)	12.4 (12.2–12.6)	12.7 (12.6–12.8)	0.004
Presence of anaemia (Hgb < 13.0) (%)	64	54	0.016
Mean alkaline phosphatase (IU/d)	521 (394–648)	404 (349–459)	0.05
Median	245 (218–282)	182 (172–200)	
Prior therapies			
Radical Prostatectomy (%)	62	64	0.60
Radiation (%)	50	49	0.85
Estramustine (%)	26	15	<0.001
Number of prior hormonal therapies (% ⩾3)	15	13	0.40

*n = 603 with tumour grade available.
†n = 652 with pain scores available.
a n = 655 with available information on performance status.
b n = 449 with evaluable PSADT.
* WHO grade 3–4 or Gleason sum 8–10.

(data not shown), this variable was not included in the final classification (Table 3).[8]

A prognostic score was derived from the estimated regression coefficients. The score was 1.591 (intercept) minus a sum of the following coefficients: 0.323 (if patient had anaemia), 0.410 (pain at baseline present), 0.514 (progression by bone scan) and 0.632 (presence of visceral disease). Median score was 0.68 (range: –0.11, 1.59). There was a linear relationship between predicted score and the probability of achieving a 30% PSAD. To make this model useful and applicable in the clinic, patients were classified into three relatively equal sized groups based on their predictive score. Patients with a score greater than 0.86 had an observed 30% PSAD of 78% (good risk). This corresponded to having either 0 or 1 risk factor present. Patients who had score between 0.40 and 0.86 had 2 risk factors present and an observed 30% PSAD of 66% (intermediate risk). Patients with scores less than or equal to 0.40 had 3–4 risk factors present and an observed 30% PSAD of 58% (poor risk).

Table 3 – Multivariable odds of obtaining a ⩾30% PSA Decline within 3 months of initiating chemotherapy, amongst men treated with docetaxel and prednisone (development cohort). See text for the definition of pain.

Baseline factors	OR (95% confidence interval)	p-value
Visceral metastases, yes/no	0.63 (0.43–0.93)	0.021
Significant pain, yes/no	0.66 (0.47–0.93)	0.028
Presence of anaemia (Hgb < 13.0 g/dL), yes/no	0.72 (0.51–1.02)	0.069
Bone scan progression, yes/no	0.60 (0.41–0.88)	0.009

Table 4 – Prostate cancer-specific outcomes according to risk groups in the development cohort (docetaxel-treated men). Good risk: 0–1 risk factors; intermediate risk: 2 risk factors; poor risk: 3–4 risk factors.

Outcome (95% confidence interval)	Risk groups			
	Good risk $n = 215$	Intermediate risk $n = 238$	Poor risk $n = 199$	p_{χ^2}
⩾30% 3-month PSA decline (%)	78 (72–83)	66 (59–72)	58 (51–65)	<0.0001
Confirmed ⩾50% PSA decline (%)	58 (50–66)	46 (39–53)	40 (33–48)	0.003*
PSA normalisation (%)[a]	23 (17–30)	17 (12–23)	8 (5–14)	0.001*
Pain response (%)[†]	39 (17–64)	33 (24–43)	34 (27–41)	0.88
Measurable disease response (WHO) (%)[°]	19 (12–31)	9 (4–16)	5 (1–11)	0.018*
Median overall survival (months)	25.7 (23.3–28.6)	18.7 (17.3–19.7)	12.8 (11.5–14.6)	<0.0001*
One year survival rate (%)	87 (81–91)	73 (67–78)	55 (48–62)	<0.0001*

[a] PSA normalisation is defined as a PSA decline to 0–4 ng/ml at any time on protocol-directed therapy, amongst those men with a baseline PSA of at least 20 ng/ml.

† In those with significant baseline pain ($n = 298$). Pain response defined as a 2 point-reduction in the Present Pain Inventory (PPI) score without an increase in the analgesia score (AS) or a ⩾50% decrease in the AS without an increase in the PPI.

° In those with baseline bidimensional measurable disease ($n = 233$).

* p-value statistically significant based on the Hochberg method controlling for the type I error rate for secondary end-points (does not apply to primary end-point, PSAD).

3.2. *Association of prognostic score with other clinical end-points*

Across risk group, we found statistically significant differences for 30% PSAD, PSA response, overall survival and tumour response after adjusting for multiple comparisons (Table 4). Objective responses were observed in 19%, 9% and 5% of men in these groups ($p = 0.018$). Median survival times were 25.7, 18.7 and 12.8 months for good, intermediate and poor risk groups, respectively ($p < 0.0001$ for trend). Kaplan–Meier estimates for OS according to risk group classification (good, intermediate and poor) are shown in Fig. 1.

We evaluated outcomes amongst docetaxel-treated men according to Prostate Cancer Working Group 2 (PCWG2) clinical subtypes.[14] Three of the five subtypes were identified in TAX327 and included: (1) lymph node-only disease ($n = 30$), (2) metastatic disease to bone with or without nodal disease but no visceral disease ($n = 470$) and (3) visceral metastatic disease ($n = 150$). The two remaining subtypes (locally progressive disease and rising PSA only CRPC) were not eligible for TAX327. PCWG2 subtypes were equally distributed by the treatment arm ($p = 0.94$, data not shown). The proportion of men achieving a 30% PSAD was 79%, 61%, and 51% for node-only, bone metastatic and visceral metastatic subtypes, respectively ($p < 0.0001$). With the exception of pain response and PSA normalisation, secondary outcomes were statistically significant across risk groups controlling for the type I error rate for multiple comparisons. Median survival times for these clinical subtypes were 35.0 (95% CI: 22.4–41.5), 19.5 (95% CI: 18.4–21.6) and 14.5 (95% CI: 12.2–16.9) months, respectively (log-rank $p < 0.0001$). Significant differences across subtypes were noted for the rates of a ⩾50% confirmed PSA decline and measurable disease response (Table 5). Kaplan–Meier plots for OS according to PCWG2 subtypes are presented in Fig. 2. Most men with mCRPC were categorised in the intermediate PCWG2 category in the TAX327 study.

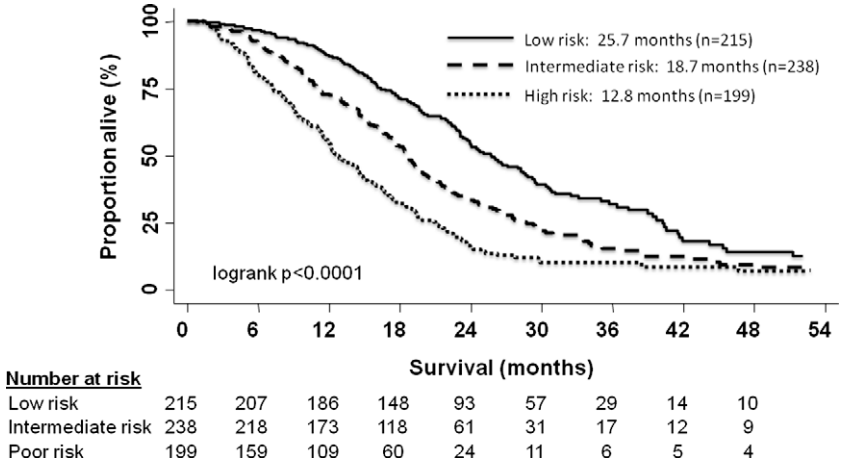

Fig. 1 – Kaplan–Meier estimates of overall survival according to risk group classification. Median survival figures are represented in the legend.

Table 5 – Prostate cancer-specific outcomes according to Prostate Cancer Working Group 2 (PCWG2) disease subtypes amongst those men treated with docetaxel and prednisone (either schedule).

Outcome (95% confidence interval)	PCWG2 subtypes			
	1 Nodal disease only ($n = 30$)	2 Bone metastases ± nodal disease ($n = 470$)	3 Visceral metastases ($n = 150$)	p_{χ^2}
⩾30% 3 month PSA decline (%)	90 (73–98)	68 (64–72)	60 (52–68)	0.004
Confirmed 50% PSA decline (%)	74 (52–90)	49 (44–54)	40 (31–49)	0.007*
PSA normalisation (%)	26 (10–48)	17 (14–21)	11 (6–18)	0.13
Pain response (%)†	29 (4–71)	36 (29–42)	27 (17–39)	0.41
Measurable disease response (WHO) (%)°	28 (12–49)	11 (6–17)	6 (3–13)	0.007*
Median overall survival (months)	35.0 (22.4–41.5)	19.5 (18.4–21.6)	14.5 (12.2–16.9)	<0.0001*
One year survival rate (%)	54 (39–69)	75 (71–79)	59 (50–67)	<0.0001*

a PSA normalisation defined as a PSA decline to 0–4 ng/ml at any time on protocol-directed therapy, amongst those men with a baseline PSA of at least 20 ng/ml.

† In those with significant baseline pain ($n = 298$). Pain response defined as a 2 point-reduction in the Present Pain Inventory (PPI) score without an increase in the analgesia score (AS) or a ⩾50% decrease in the AS without an increase in the PPI.

° In those with baseline bidimensional measurable disease ($n = 233$).

* p-Value statistically significant based on the Hochberg method controlling for the type I error rate for secondary end-points (does not apply to primary end-point, PSAD).

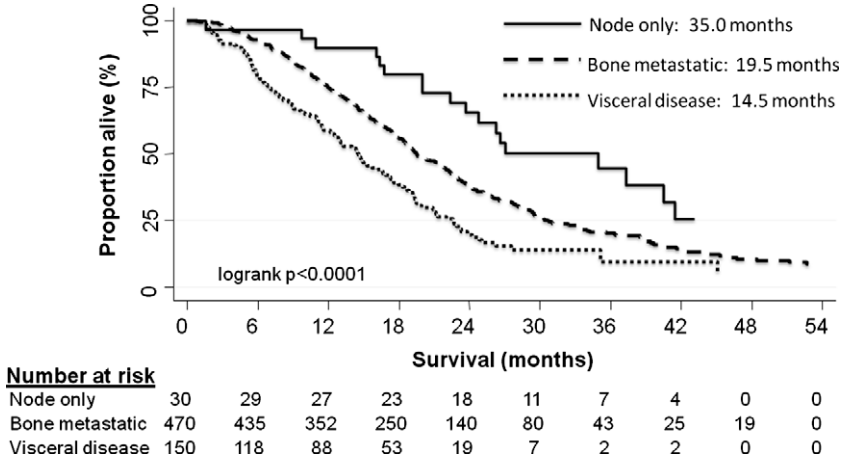

Fig. 2 – Kaplan–Meier estimates of overall survival according to PCWG2 clinical subtype classification. Median survival figures are represented in the legend.

3.3. *Validation set*

In the validation cohort (Table 6) of men treated with mitoxantrone and prednisone, the observed rates of 30% PSAD were 54%, 40%, and 40% for good, intermediate and poor risk categories, respectively ($p = 0.06$). The proportion of men with a 30% PSAD was 76%, 49%, 40%, 43% and 21% for 0, 1, 2, 3 and 4 risk factors ($p = 0.011$). Median survival times for good, intermediate and poor risk groups were 22.5, 16.0 and 11.8 months, respectively ($p < 0.0001$). There was a statistically significant trend ($p = 0.001$) for confirmed ⩾50% PSA response, radiological response ($p = 0.014$) and 1 year survival ($p < 0.0001$) across risk categories. The concordance index (c-index) was 0.62 for OS and 0.59 for 30% PSAD, indicating modest predictive accuracy in this cohort of MP-treated subjects. However, with the exception of pain, secondary response-based and survival outcomes were significantly different across risk groups after adjusting for the multiple comparisons (Table 6), with non-overlapping 95% CIs for overall survival estimates.

3.4. *Association of risk groups with docetaxel survival benefit*

We next examined the relationship between OS in men who received q3w docetaxel and prednisone compared to mitoxantrone and prednisone according to risk group categorisation for the entire data set. Amongst 330 men with good risk disease, the median survival times were 26.0 and 22.5 months (HR 0.76, 95% CI: 0.56–1.03, $p = 0.076$); in the 350 men with intermediate risk disease, median survival was 19.1 and 16.0 months (HR 0.71, 95% CI: 0.53–0.94, $p = 0.019$); in the poor risk group of 303 men, median survival was 13.4 and 11.8 months, respectively (HR 0.86, 95% CI: 0.64–1.15, $p = 0.31$). There were no significant differ-

Table 6 – Prostate cancer-specific outcomes according to risk groups in the validation cohort (mitoxantrone treated men). Good risk: 0–1 risk factors; intermediate risk: 2 risk factors; poor risk: 3–4 risk factors.

Outcome (95% confidence interval)	Risk groups (number of risk factors)			
	Good risk $n = 115$	Intermediate risk $n = 112$	Poor risk $n = 104$	p_{χ^2}
⩾30% 3-month PSA decline (%)	53.9 (44.4–63.2)	40.2 (31.0–50.0)	40.4 (30.9–50.5)	0.06
Confirmed ⩾50% PSA decline (%)	44.6 (34.7–54.8)	30.7 (21.9–40.7)	20.4 (12.8–30.0)	0.001*
PSA normalisation (%)[a]	14.9 (8.6–23.3)	5.0 (1.6–11.1)	4.3 (1.2–10.6)	0.01*
Pain response (%)†	20.0 (2.5–55.6)	22.8 (12.7–35.8)	22.4 (14.0–32.7)	0.98
Measurable disease response (WHO) (%)°	15.6 (6.5–29.5)	2.6 (0.0–13.5)	2.0 (0.0–10.4)	0.014*
Median overall survival (months)	22.5 (20.5–25.8)	16.0 (13.3–17.8)	11.8 (10.3–13.2)	<0.0001*
One year survival rate (%)	79 (71–86)	67 (57–76)	48 (38–58)	<0.0001*

a PSA normalisation defined as a PSA decline to 0–4 ng/ml at any time on protocol-directed therapy, amongst those men with a baseline PSA of at least 20 ng/ml.

† In those with significant baseline pain ($n = 298$). Pain response defined as a 2 point-reduction in the Present Pain Inventory (PPI) score without an increase in the analgesia score (AS) or a ⩾50% decrease in the AS without an increase in the PPI.

° In those with baseline bidimensional measurable disease ($n = 233$).

* p-Value statistically significant based on the Hochberg method controlling for the type I error rate for secondary end-points (does not apply to primary end-point, PSAD).

ences in hazard ratios across risk groups (p-interaction >0.60), indicating that every 3 weeks DP was associated with a similar relative survival advantage across risk groups.

4. Discussion

We identified four pre-treatment risk factors that predict for PSA declines and survival in men with metastatic CRPC, including the presence of anaemia, development of new bone metastatic lesions, significant pain (measured as a score of ⩾2 on a 5-point scale or as consumption of a narcotic equivalent dose of 10 mg morphine sulphate) and the presence of visceral metastases. The major contributions of the current analysis include the identification of these independent predictors of post-chemotherapy PSA declines, tumour response and survival and the establishment of a simple risk group classification in men with metastatic CRPC. We and others have shown previously that a ⩾30% 3-month PSA decline is independently prognostic, predictive and a moderate surrogate for overall survival.[7,8,13] Our proposed risk group classification provides a modest but distinct separation of the expected proportion of men who achieve a post-chemotherapy PSA decline and good separation of OS, similar to current nomograms.[8–10] The risk classification was internally validated within the large TAX327 trial, is easy to use without a major loss of predictive ability compared to current nomograms, and is able to predict several response-based outcomes (PSA decline, objective tumour response) and overall survival unlike current survival-based nomograms. However, the prognostic ability of this classification remains modest, and thus this classification should not be used to guide therapy nor to judge the survival benefit of docetaxel chemotherapy, given that all risk groups seemed to derive at least some benefit. Further prospective validation of these risk categories, or those including novel prognostic factors, using a variety of intermediate outcomes (PFS, tumour and PSA response, survival) is worthy of further study.

This classification accounts for some but not all the heterogeneity seen in the outcomes of men with metastatic CRPC that participate in clinical studies evaluating chemotherapy.[8] Our data also provide historical outcome-based controls which may be used to evaluate chemotherapy regimens for activity and selection for more definitive testing. For example, a phase II trial of docetaxel plus a targeted agent reporting a 70% rate of 30% PSAD and a 21 months overall survival may seem promising, but if all men in this trial met favourable risk group criteria, the expected outcome would be 78% and median expected survival would be 25.7 months with docetaxel/prednisone alone. The risk groups are clinically relevant in the care of men with metastatic CRPC, in that they provide predictive estimates of the expected rates of PSA decline, tumour response, pain response and survival according to a simple risk factor scoring system, in which the overall predictive ability is comparable to more complex nomograms.[8–10] These factors also identify a subgroup of good risk men with a more prolonged natural history who may benefit from potentially less toxic therapies designed to delay or prevent symptomatic progression. While docetaxel-based chemotherapy provides a 3–4 months survival advantage in this good risk population, alternative strategies such as novel hormonal, immunological or targeted molecular therapies could be reasonably studied in this population.

This paper has several limitations. One limitation is lack of information about progression-free survival (PFS). In TAX327, data were collected on progression according to protocol-defined criteria, but due to censoring at the time of progression (PSA, tumour or pain), reliable rates of PFS are not available, particularly as defined by PCWG2 criteria.[14] Future analyses should investigate the relationship between baseline factors and measures of PFS, including PSA, pain and radiological progression as well as composite clinical definitions (e.g. decreased performance status, weight loss).[22,23] A second limitation is the modest predictive accuracy of this model in predicting PSA decline in the validation set. Additional biological factors related to tumour or host are likely important in determining outcomes, including but not limited to tumour-

derived fusion proteins or other biomarkers such as gene expression signatures, serum LDH and circulating factors such as vascular endothelial growth factor and tumour cells.[9,18,18,24–26] Future prospective studies should evaluate these factors in docetaxel-treated men with mCRPC. However, the modest concordance index for 30% PSAD in mitoxantrone treated patients may also be related to the overall low rate of PSA declines in this cohort. In addition, we noted a slightly higher c-index for overall survival as compared to PSA declines.[27] This may be due to the confounding element of PSA flare or the timing of PSA measurements, or that overall survival is generally a more robust end-point. Despite this, the predictive accuracy for overall survival remains fair to moderate in each cohort, with non-overlapping CIs that provide a clear separation of outcomes according to risk group classification. These factors may help in the interpretation of early phase trial results in CRPC, particularly for survival, response and time-to-event end-points, and illustrate the need for randomised phase 2 and 3 trials in this disease to account for these heterogeneous outcomes and confounding prognostic factors.

This risk group classification for men with CRPC may allow for improved discrimination of active systemic agents in early stages of development by permitting adjustment for known patient-related confounders. In addition, a novel combination strategy could be designed primarily for men with intermediate to poor risk CRPC, for whom current survival-based outcomes with docetaxel and prednisone alone are insufficient. The current data provides benchmarks for PSA and tumour response rates and survival outcomes in this setting that should be improved upon. In developing these risk groups, we assigned equal weight to each predictive risk factor for the development of risk groups, based on similar odds ratios for 30% PSAD (Table 3). Given the heterogeneity of PC outcomes, applicability of this approach should be further validated in large independent, prospectively phase III trials. However, the strong statistical significance of response and survival-based outcomes across risk categories despite adjustment for multiple comparisons testify to the robustness of these factors. These risk groups are not intended to identify men who would not benefit from docetaxel, given that all risk subgroups seem to derive a similar relative survival benefit with docetaxel-based therapy. We found that PCWG2 disease states were also prognostic of response and survival in men with mCRPC, but had a major disadvantage of classifying men into unequal risk groups' size compared to the current proposed classification.[14] Finally, we found a consistent hazard ratio for the OS benefit conferred by docetaxel/prednisone across all risk groups, indicating that benefits of this regimen are not limited to patients with pain or poor prognostic features.

In conclusion, we identified predictors of PSAD in men with metastatic CRPC. The risk groups that emerged from this analysis were also predictors of tumour response and overall survival, and illustrate the importance of these factors in patient management.

Conflict of interest statement

The following authors (abbreviations used) have received research support from Sanofi Aventis: A.J.A., M.E., S.H., I.T., R.W. The following authors have served on the speaker's bureau for Sanofi Aventis: A.J.A. The following authors have served as consultants to Sanofi Aventis: A.J.A., M.E., I.T., R.W. The TAX327 international randomised trial was conducted and sponsored by sanofi-aventis. The current analysis is based on the updated clinical trial database. Sanofi-aventis did not participate in the analysis or interpretation of this current study. Drugs used in this study include docetaxel, mitoxantrone, and prednisone. Docetaxel was provided by sanofi-aventis.

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