

Prediction of Survival following First-Line Chemotherapy in Men with Castration-Resistant Metastatic Prostate Cancer

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Abstract

Purpose: We sought to evaluate predictors of overall survival following progression after systemic chemotherapy in men with metastatic castration-resistant prostate cancer.

Experimental Design: For our study population, we used the TAX327 multicenter randomized phase III trial comparing administration of docetaxel and prednisone every 3 weeks, weekly administration of docetaxel and prednisone, and administration of mitoxantrone and prednisone every 3 weeks. Progression was defined as the earliest of prostate-specific antigen (PSA), tumor, or pain progression. We analyzed predictors of postprogression survival according to both prechemotherapy and postchemotherapy variables with adjustment for potential confounders.

Results: Among 1,006 men, 640 had evaluable information on protocol-defined progression leading to further therapy. Median postprogression survival was 14.5 months. In the multivariable analysis, several pretreatment factors were associated with postprogression survival: pain, performance status, alkaline phosphatase, number of sites of metastatic disease, liver metastases, hemoglobin, PSA, and time since diagnosis. In addition, we found that the number of progression factors (PSA, pain, and tumor size), the duration of first-line chemotherapy, and whether progression occurred during chemotherapy independently predicted postprogression survival. We found evidence for the benefit of continuation of chemotherapy beyond progression only for men who had isolated worsening of pain. A nomogram was constructed and internally validated with a concordance index of 0.70.

Conclusions: An internally validated model to predict postchemotherapy survival was developed. Evaluation of men in the postdocetaxel setting should consider the type of progression, duration of therapy, and known pretreatment prognostic factors. Definitions of progression in castration-resistant prostate cancer that include pain should also consider composite measures of tumor or PSA progression. External validation is planned. *Clin Cancer Res*; 16(1); 203–11. ©2010 AACR.

In 2009, prostate cancer remains a highly fatal malignancy among American men, accounting for nearly 75 deaths per day (1). Following the development of castration resistance and progressive metastatic disease, few therapies

are known to prolong survival, with docetaxel-based chemotherapy providing a modest 2- to 3-month survival advantage over older strictly palliative chemotherapy regimens (2). After the failure of docetaxel, no agents to date have been shown to have a survival advantage over best supportive care. However, with the development of multiple novel agents in current development in this second-line setting, there is a renewed interest in understanding and characterizing the prognostic factors for survival (3–5). These factors should describe the natural history of prostate cancer after first-line chemotherapy and facilitate the interpretation of clinical trials in this setting, as well as improve communication with patients about prognosis.

Several prognostic nomograms exist for men with metastatic castration-resistant prostate cancer (CRPC) who are undergoing systemic chemotherapy (6–8). However, the survival after cessation of chemotherapy or progression on chemotherapy is poorly characterized and limited to case series and a few unpublished randomized studies (9, 10). In addition, prognostic factors for survival after first-line chemotherapy have not, to date, been evaluated in multivariable analysis. Given the need for more information in this chemorefractory disease state,

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Translational Relevance

This article describes the prognostic factors relevant to men who have progressed or completed standard docetaxel chemotherapy for castration-resistant metastatic prostate cancer (CRPC). Given the explosion of novel agents that are currently in development in this disease state, the predictive model and nomogram generated by this large prospectively followed cohort of trial subjects may help guide clinical trial development (sample size estimates, end points) and, importantly, may also improve the information delivered to these men with CRPC about prognosis. The prognostic factors identified in this study include both known prechemotherapy factors and type of progression and duration of chemotherapy. These factors may assist in formulating rational definitions for progression for men with CRPC.

we sought to characterize postprogression survival among men treated with modern chemotherapy regimens. In this study, we developed a multivariate model and a nomogram, using both prechemotherapy and postchemotherapy variables, to predict overall survival (OS) after first-line chemotherapy. We also sought to better characterize the prognostic relevance of type of progression [prostate-specific antigen (PSA), pain, or radiologic] while on chemotherapy or after cessation of chemotherapy, and the relationship of progression type with postchemotherapy survival.

Materials and Methods

Eligibility for TAX327 trial. TAX327 was a randomized, nonblinded, multinational phase III study involving 1,006 men with progressive metastatic CRPC. Full details of the eligibility and baseline characteristics for this trial are provided in the original report (2). Briefly, men were eligible if they had documented metastatic prostatic adenocarcinoma in the face of castrate levels of serum testosterone (<50 ng/mL), and if they had evidence of progression as defined by clinically or radiographically measurable disease or by PSA criteria. Baseline information collected on each individual included serum PSA, age, performance status, pain and analgesic score, hemoglobin, alkaline phosphatase, prior Gleason sum or tumor grade, presence of visceral metastases, location and number of metastases, prior therapies, and how progression was defined, in addition to other clinical variables. An approved and signed Institutional Review Board informed consent form was obtained for all participants at each participating institution.

Analysis plan. In this trial, men were randomly assigned to either administration of docetaxel and prednisone (DP) every 3 wk ($n = 335$), weekly administration of DP ($n =$

334), or administration of mitoxantrone and prednisone (MP) every 3 wk ($n = 337$). Treatment continued until toxicity or progression or death, with up to 30 wk of chemotherapy allowed [10 cycles of DP/MP every 3 wk or 5 cycles of weekly DP (6-wk cycles with a 1-wk break included)]. Given the uncertainties around defining progression in this disease state, treatment was allowed to be continued beyond protocol-defined progression if, in the judgment of the treating physician, further benefit to the patient was possible with continuation of therapy. Other treatments beyond progression were recorded. Patients were followed until death.

In this trial, postchemotherapy progression was defined in one of three ways. PSA progression was defined as an increase in serum PSA from the nadir value of either at least 25% for men without PSA response ($\geq 50\%$ confirmed PSA decline from baseline) or at least a 50% increase from nadir for all others. Tumor progression was defined according to WHO criteria, which is a $>25\%$ increase in the sum of the product of the two largest perpendicular diameters of one measurable lesion or the appearance of a new lesion (11). Pain progression was defined according to the present pain inventory score or an analgesic score (12). An increase in the present pain inventory score of at least one point from the nadir, an increase from baseline of at least 25% in the analgesic score, or a requirement for palliative radiotherapy indicates pain progression. The primary end point in our analyses is the time from postchemotherapy progression until death, where postchemotherapy progression may occur any time after initiation of chemotherapy. Consequently, progression may occur while a patient is on chemotherapy treatment or some time after discontinuation.

Eligibility for current analysis. The present analysis is based on updated survival as of November 7, 2006, at which time 800 deaths had occurred. To be eligible for this analysis, men with CRPC had to be treated with first-line chemotherapy according to protocol and develop disease progression either after completion of the planned 30 wk of therapy or while on therapy (see Fig. 1 for consort diagram). In addition, patients had to have nonmissing data on pain, performance status, duration of therapy, and metastatic sites. The time from the first progression event (pain, tumor, or PSA) to death was recorded for each subject. The initial treatment received after protocol-defined progression was recorded for each subject, including palliative therapies, study chemotherapy, alternative systemic therapy, surgery, or radiotherapy. Prechemotherapy factors that were considered in the multivariate analysis of postchemotherapy survival included age, tumor grade (Gleason sum or radiologic), presence of significant pain, visceral or liver metastases, the number of metastatic sites, Karnofsky Performance Status, type of progression before receiving chemotherapy, PSA, PSA doubling time, alkaline phosphatase, prior estramustine, hemoglobin, the number of hotspots on bone scan, and the time from diagnosis of prostate cancer to chemotherapy initiation. Posttreatment factors that were considered in the multivariable modeling

included the duration of first-line chemotherapy administration, type of progression on chemotherapy (PSA, pain, radiologic), whether progression occurred while receiving chemotherapy or after chemotherapy, and achievement of a $\geq 30\%$ or $\geq 50\%$ confirmed PSA decline within the first 3 mo after chemotherapy. We also looked at the relationship of continuation of protocol-directed chemotherapy beyond progression with postprogression survival.

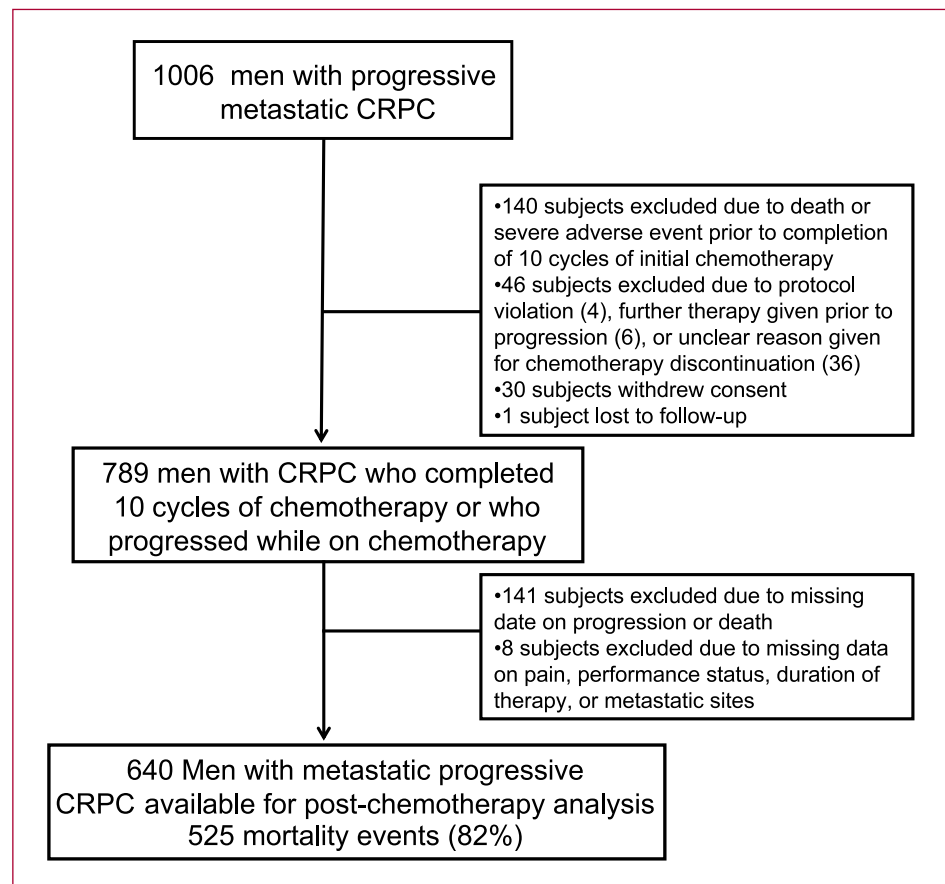
Statistical analysis. Cox proportional hazards modeling with backward manual selection of statistically significant variables was conducted ($P < 0.10$). Kaplan-Meier curves were generated and graphically displayed. The proportional hazards assumption was assessed for each covariate using graphical displays. Specifically, $-\ln\{-\ln(\text{survival})\}$ curves for each category of the covariate of interest versus $\ln(\text{time})$ were created and were assessed to determine if the curves were relatively parallel. Continuous variables were discretized to assess the assumption, and no variables were found to be in violation of proportional hazards. For multiple regression models, Schoenfeld residuals were calculated to perform a global test of proportionality with α set at 0.01 given the large sample size. A concordance index (c-index) was estimated for the final model. Internal bootstrap validation and bias-corrected 95% confidence intervals (95% CI) for hazard ratios (HR) in the final model were calculated using 200 resamples. For the analysis of

postprogression survival and continuation of chemotherapy, a 3-mo landmark analysis was done including only patients surviving 3 mo beyond progression in the analysis. A nomogram was developed based on the final model and a bootstrap-corrected c-index was calculated as a measure of internal validity of this final model (13). In this analysis, a c-index of 0.50 represents random prediction, whereas a c-index of 1.0 represents a perfectly discriminating model. All analyses were done using Stata version 9.2 or R 2.9.0 (The R Foundation for Statistical Computing, 2009).

Results

Of the 1,006 men randomized in the TAX327 trial, 789 men completed 10 cycles of protocol-assigned chemotherapy or progressed before completion of the assigned chemotherapy regimen. Figure 1 shows the consort diagram for inclusion of subjects for this analysis. One hundred and forty men died before completion of chemotherapy ($n = 17$) or suffered chemotherapy-related toxicity ($n = 123$) that prevented further chemotherapy administration; these men were excluded from the analysis. Seventy-seven subjects were excluded from analysis because of the lack of a clear rationale for chemotherapy cessation (36), withdrawal of consent (30), further

Fig. 1. Consort diagram showing patients included or excluded from the primary analysis of postchemotherapy survival.



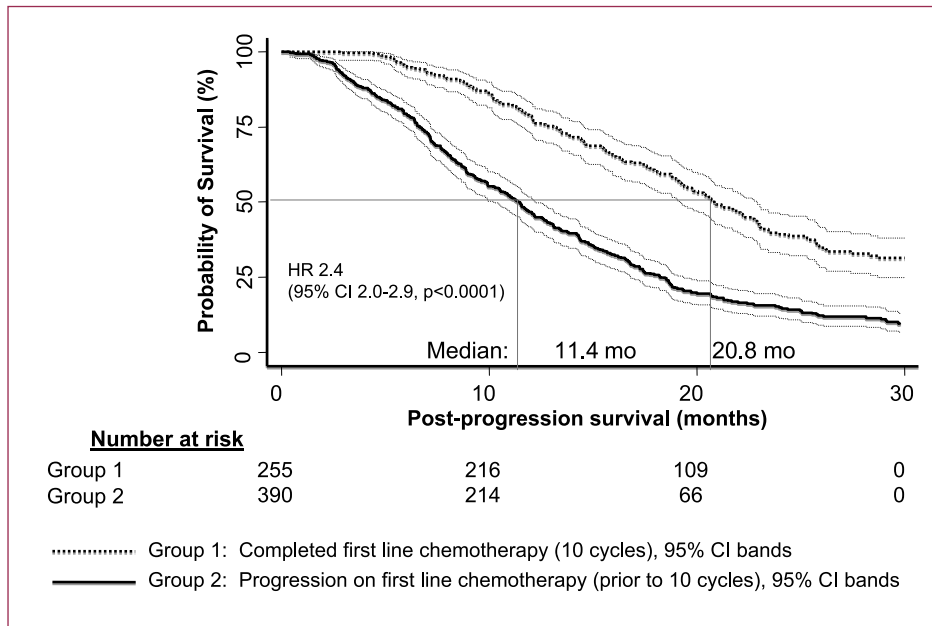


Fig. 2. Kaplan-Meier estimates of overall postprogression survival among chemotherapy-treated subjects according to whether progression occurred after completion of the prescribed course of chemotherapy (30 wk, group 1), or while receiving first-line chemotherapy (group 2).

nonprotocol therapy administered before progression (6), major protocol violations (4), or loss to follow up (1). Of these 789 men, 141 were further excluded due to missing date of death or progression; 8 men were excluded due to missing covariates (typically pain or performance status). This left 640 men available for analysis, including 525 mortality events (82% complete). Men included in this analysis did differ substantially from men excluded from analysis as might be expected, shown in Supplementary Table S1. However, the intent of this study was to develop predictors of survival for men who progressed on or after completion of chemotherapy that may be clinically relevant to the postchemotherapy setting. The factors contributing to early cessation of chemotherapy are primarily those commonly seen in the clinic, and thus, the included subjects can be considered representative of our target population.

The median survival of men who progressed on or after first-line chemotherapy was 14.5 months (95% CI, 13.4-25.8). Postprogression survival was strongly associated with whether progression occurred while receiving first-line chemotherapy compared with progression after the completion of the prescribed 30 weeks (Fig. 2). Men who progressed during first-line chemotherapy had a median survival in this setting of 11.4 months (95% CI, 10.2-12.2), whereas men who progressed after the completion of chemotherapy had a median survival of 20.9 months (95% CI, 19.2-22.9). This difference was highly significant (HR, 2.4; $P < 0.0001$). The median postprogression survival following progression on DP chemotherapy every 3 weeks was 16.8 months (95% CI, 15.3-19.2), 14.0 months (95% CI, 11.7-16.2) for weekly DP, and 15.6 months (95% CI, 14.3-17.4) for MP every 3 weeks. Among men who completed DP chemotherapy every 3 weeks, the median survival was 22.9 months (95% CI, 19.3-25.9) com-

pared with 12.0 months (95% CI, 9.3-14.8) for men who progressed while on docetaxel chemotherapy (HR, 2.6; $P < 0.0001$). Among the 232 men who completed MP chemotherapy every 3 weeks, median survival was 19.5 months (95% CI, 15.9-22.2) compared with 11.5 months (95% CI, 10.0-12.6) for the men who progressed while on mitoxantrone chemotherapy (HR, 2.04; $P < 0.0001$).

We next looked at univariate and multivariate predictors of postprogression survival using backward stepwise regression. Only significant variables ($P < 0.10$) were kept in the final model after adjustment. Further model reduction was done based on lack of effect on overall concordance of the model, for reasons of parsimony. In multivariate analysis (Table 1), we found that several prechemotherapy factors remained highly associated with postprogression survival: significant baseline pain ($P = 0.005$), Karnofsky Performance Status (≤ 70 versus > 80 ; $P = 0.063$), alkaline phosphatase (categorical or continuous; $P = 0.012$ - 0.033), number of sites of metastatic disease (> 2 versus ≤ 2 discrete sites; $P = 0.001$), liver metastases ($P = 0.89$), hemoglobin (categorical or continuous; $P = 0.012$), and time since diagnosis ($P = 0.004$). We also found that several postchemotherapy factors were highly associated with postprogression survival in multivariate analysis: number of progression factors [1, 2 ($P = 0.073$), or 3 ($P < 0.0001$), including PSA, pain, or radiologic progression], whether progression occurred during first-line chemotherapy administration ($P = 0.001$), and the number of cycles of chemotherapy ($P = 0.022$). For example, for a one-cycle (3 weeks) increase in chemotherapy administration time, the HR for postprogression survival was 0.94 ($P = 0.007$). Analogously, for a four-cycle increase in chemotherapy administration, the HR is 0.81. The estimated

HRs for the prechemotherapy and postchemotherapy factors related to postprogression survival and the bootstrap-corrected 95% CIs for these estimates are shown in Table 1. All variables not included in Table 1 were dropped from the final model due to lack of significance or lack of predictive ability beyond the final model. Treatment group was not significantly associated with postchemotherapy survival after adjustment for other prognostic variables ($P = 0.22$ for DP every 3 weeks) and was thus not included in the final model.

We found that the number of progression factors at the time of progression was highly associated with postprogression survival. These factors included PSA (PSAWG1 criteria), radiologic (WHO criteria), and pain progression (TAX327 definition) and were categorized at the time of initial disease progression as one, two, or all three factors. Postprogression survival was associated with the number of progression factors and type of progression, as shown in Table 2 and Fig. 3. For example, men who have PSA-only progression (the most common type of progression) on the first-line chemotherapy have a median postprogression survival of 15.5 months (95% CI, 12.8-16.8; $n = 170$), similar to that seen for pain-only (median, 17.0 months; 95% CI, 13.8-19.1; $n = 157$) and radiologic-only (median, 15.8 months; 95% CI, 13.0-18.8; $n = 137$) progression. Men who had only one progression factor at the time of progression lived a median of 15.9 months after chemotherapy (95% CI, 14.5-17.2). Similarly, men who progressed by two factors had a shorter median survival (median, 13.2 months; 95% CI, 10.9-15.1; $n = 128$). Men who progressed according to all three criteria had a median survival of 8.0 months ($n = 53$; 95% CI, 5.8-11.9 months). The difference in postprogression survival according to the number of progression criteria was highly significant ($P < 0.0001$; Fig. 3).

We next examined whether continuation of protocol-directed chemotherapy beyond progression was associated with a survival benefit. Men who progressed on first-line chemotherapy were allowed to continue this therapy, at the discretion of the treating physician, and differed significantly from men who did not continue chemotherapy in several ways. Continuation of chemotherapy beyond progression ($n = 330$) was associated with lack of prior confirmed $\geq 50\%$ PSA decline or tumor response, shorter time-to-progression (PSA, pain, or radiologic), and progression by only one criteria (Supplementary Table S1) compared with the use of alternative therapies at the time of progression ($n = 315$). The types of nonprotocol therapy beyond progression included alternative chemotherapy ($n = 128$, 40.1%), hormonal therapies ($n = 27$, 8.6%), surgery ($n = 14$, 4.4%), palliative radiation ($n = 57$, 18.1%), radiopharmaceuticals ($n = 8$, 2.5%), bisphosphonates ($n = 19$, 6.0%), systemic steroids ($n = 17$, 5.4%), unknown therapy ($n = 43$, 13.7%), and PC-SPEs ($n = 2$, 0.6%). In unadjusted and adjusted analyses, continuation of protocol chemotherapy beyond progression was associated with improved postprogression survival, regardless of treatment group (Table 2). This observed benefit was primarily limited to men who had isolated pain progression compared with other definitions of progression (HR 0.57, $P = 0.01$; Supplementary Fig. S1). Continuation of chemotherapy beyond progression remained significantly associated with improved survival in men with isolated pain progression using a landmark analysis including only men surviving >3 months beyond progression (HR, 0.61; $P = 0.03$). The benefit of continuation of protocol-directed therapy beyond progression was independent of treatment arm (docetaxel on either schedule or mitoxantrone; data not shown). Although continuation of chemotherapy beyond progression

Table 1. Multivariable model for overall postprogression survival used for nomogram construction

Prognostic factor	HR	Bootstrap-corrected 95% CI	P
Prechemotherapy variables			
Liver metastases	1.48	0.94-2.30	0.089
Significant pain	1.31	1.08-1.56	0.005
>2 metastatic sites	1.71	1.23-2.25	0.001
Poor performance status (KPS ≤ 70)	1.39	0.97-1.92	0.063
Time since diagnosis, y	0.95	0.93-0.99	0.004
Presence of anemia (Hgb < 13.0)	1.30	1.05-1.58	0.012
Alkaline phosphatase, IU/dl (<200 vs 200-1,000)	1.26	1.02-1.55	0.033
Alkaline phosphatase, IU/dl (<200 vs $>1,000$)	1.55	1.11-2.21	0.012
Postchemotherapy initiation variables			
Duration of first-line chemotherapy (mo)	0.95	0.91-0.99	0.022
No. of progression factors (2 vs 1)	1.26	0.95-1.60	0.073
No. of progression factors (3 vs 1)	2.64	1.86-3.75	<0.0001
Progression on chemotherapy (yes/no)	1.72	1.24-2.32	0.001

NOTE: Bootstrap corrected c-index is 0.7049. $n = 640$.

Abbreviations: KPS, Karnofsky Performance Status; Hgb, hemoglobin.

Table 2. Postprogression survival is shown according to the definition of progression in TAX327

Type of progression	n	Postprogression survival (95% CI)	HR for benefit associated with continuation of chemotherapy	P
PSA only progression	170	15.5 (12.8-16.8)	1.04	0.82
Pain only progression	157	17.0 (13.8-19.1)	0.57	0.01
Radiologic only progression	137	15.8 (13.0-18.8)	1.08	0.68
Progression by any 1 criteria	464	15.9 (14.5-17.2)	0.86	0.18
PSA and radiologic progression	63	14.4 (12.2-18.5)	2.01	0.05
Pain and radiologic progression	32	10.9 (5.9-18.2)	0.62	0.38
PSA and pain progression	33	9.8 (7.9-15.1)	0.52	0.11
Progression by any two criteria	128	13.2 (10.9-15.1)	0.87	0.55
Progression by all three criteria	53	8.0 (5.8-11.9)	N/a	N/a
All patients (unadjusted)	645	14.6 (13.4-15.8)	0.76	0.002
All patients (adjusted)	645		0.80	0.033

NOTE: The HR and P value (adjusted for other prognostic clinical variables in nomogram) is shown for postprogression survival comparing men who had protocol-directed chemotherapy beyond progression vs men who received other therapies after progression.

Abbreviation: N/a, not applicable.

remained associated with postprogression survival in multivariable analysis ($P = 0.033$), this factor was not included in the final multivariate model, as the overall c-index was not significantly improved by its incorporation (no improvement in c-index, see below).

Finally, we developed a postprogression nomogram (Fig. 4) for the prediction of OS after first-line chemotherapy using the final multivariable model shown in Table 1. This nomogram and model was validated internally using bootstrap methods and 200 resamples, and found to have a c-index of 0.711 (bootstrap-corrected c-index of 0.705). The bootstrap-calculated 95% CIs for each variable includ-

ed are shown in Table 1. Calibration of this nomogram for comparing observed versus predicted outcomes of 6-, 12-, and 24-month postprogression survival was excellent (Supplementary Fig. S2).

Discussion

In this study, we have developed a comprehensive nomogram for the prediction of postprogression survival in men with metastatic CRPC who have progressed on or after completion of first-line chemotherapy. This nomogram

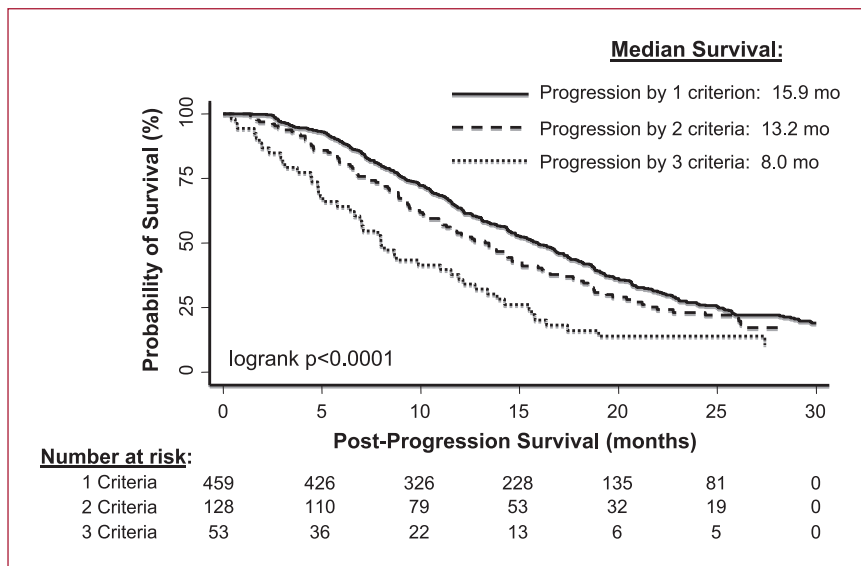


Fig. 3. Kaplan-Meier estimates of overall postprogression survival according to number of progression factors at progression on or after chemotherapy.

incorporates seven prechemotherapy factors and three postchemotherapy factors that are generally clinically available at the time of progression after first-line chemotherapy and can be used to estimate median, 6-, 12-, and 24-month survival in this postchemotherapy setting. We found several novel postchemotherapy factors that were highly predictive of survival, including the number of cycles of first-line chemotherapy (duration of therapy), number of progression factors (1, 2, or 3 of pain, PSA, or radiographic progression), and whether progression occurs while receiving chemotherapy or after completion of a prescribed course of chemotherapy. The nomogram had moderate predictive ability, comparable with prechemotherapy nomograms that are widely used for bedside prognostication and clinical trial stratification (6–8). This model was internally validated with good calibration for the survival end points evaluated. In addition, we found that several well-known prognostic factors (visceral disease, pain, performance status, anemia, alkaline phosphatase, number of sites of metastatic disease, and time from diagnosis to chemotherapy) remain highly associated with

postprogression survival. Of note, original treatment assignment was not associated with postprogression survival, and as previously published, cross-over from docetaxel to mitoxantrone or from mitoxantrone to docetaxel was not associated with a survival difference; thus, these treatment factors were not included in the current postprogression model (14).

Progression-free survival (PFS) has recently been shown to be predictive of OS in men with metastatic CRPC undergoing hormonal and chemotherapies (15, 16). However, the association between PFS (PSA or radiologic) and OS is relatively weak, underscoring the limitations of current definitions of PFS in this disease state, and the multiple confounding factors that may influence survival without directly affecting PFS (17). In fact, several recent studies have shown improvements in OS without a corresponding increase in PFS (18, 19); likewise, multiple studies have shown improvements in PFS without translating into improvement in survival (20, 21). In the current study, we have shown that various measures of clinical progression and the number of progression criteria met

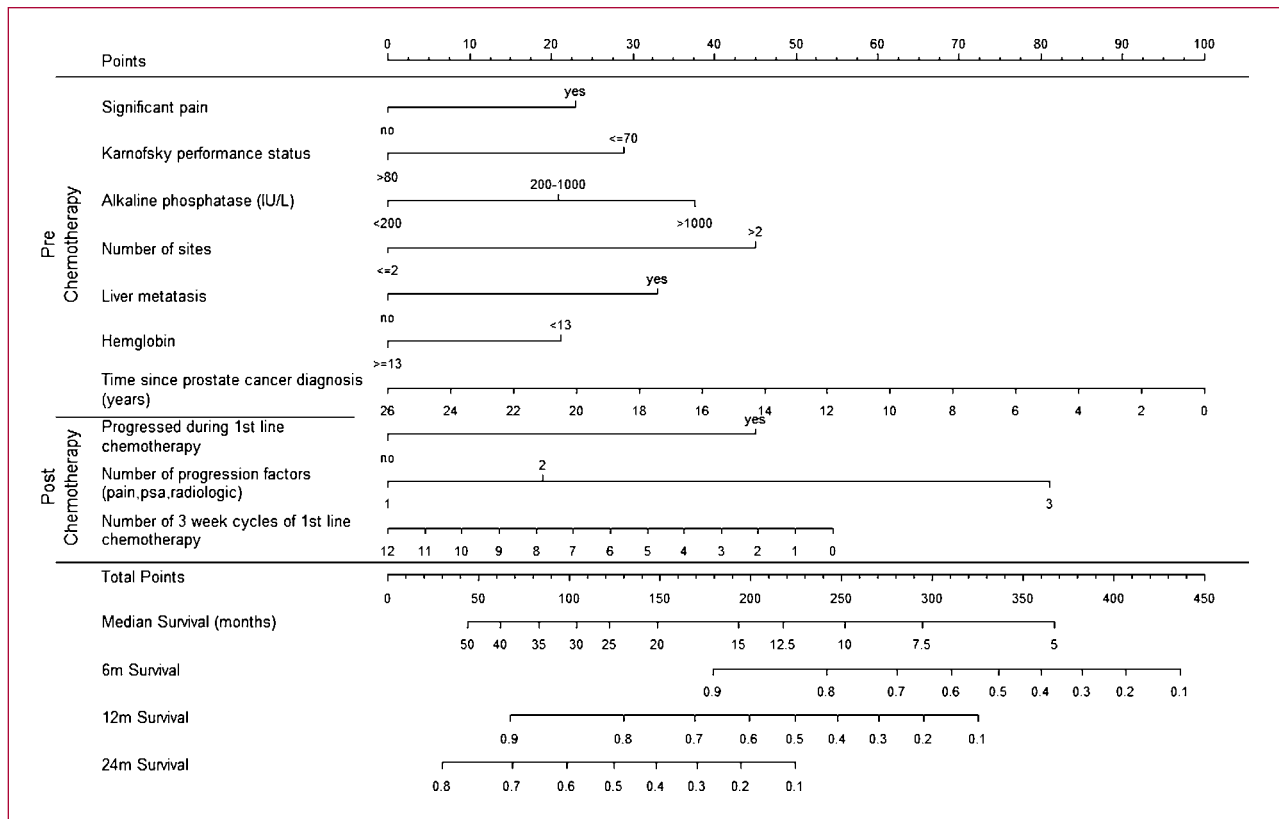


Fig. 4. Nomogram depicting estimates of postprogression survival, including estimates of 6-, 12-, and 24-month OS according to prechemotherapy and postchemotherapy factors. Note: a present pain inventory of ≥ 2 and/or an analgesic score of ≥ 10 were defined in the original protocol as indicative of the presence of significant pain. Instructions for Physician: Locate the “Significant Pain” axis. Draw a straight line downward to the Points Axis to determine how many points toward survival the patient receives for the presence or absence of significant pain. Repeat this process for each predictor variable and sum the points for each predictor. Locate this sum on the Total Points Axis. Draw a straight line downward from the Total Points Axis to identify the predicted median survival, and the predicted 6-, 12-, and 24-month predicted OS probabilities. Instructions to Patient: “Mr. X, if we had 100 men exactly like you, we would expect (nomogram prediction \times 100) to be alive in 6, 12, and 24 mo, respectively, and we expect 50 of those men to be alive after (median survival prediction) months.”

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while on chemotherapy or after completion of a prescribed course of chemotherapy are predictive of OS in men with CRPC. In addition, for men with isolated pain progression, continuation of chemotherapy beyond progression was associated with improved OS compared with chemotherapy cessation, indicating that if pain scales are to be used to define progression in men with CRPC, studies should additionally incorporate other measures of progressive disease before withdrawal of a patient from therapy. For example, men with CRPC are known to have transient worsening of PSA levels or pain reporting after the initiation of chemotherapy that are not adversely prognostic (22, 23). In these men with PSA or pain flares, early cessation of chemotherapy is clearly not indicated and may be detrimental. In addition, nonmalignant causes of pain progression should be evaluated before cessation of a potentially beneficial therapy. For composite definitions of progression (PSA, pain, or radiologic tumor growth), no benefit was observed for the continuation of chemotherapy, indicating that these definitions are likely to be more predictive of survival than single criteria definitions.

This study has several limitations. The TAX327 trial was a first-line chemotherapy study and was not designed specifically to study the postchemotherapy disease state. However, this study was updated over time to provide information on mortality events such that a high number of these events (>80%) are now captured. By following men prospectively from the date of first progression to death, we have more fully characterized the natural history of this disease state, rather than starting from an arbitrary time point of trial randomization. Some progression dates may be erroneously assigned due to issues of PSA, bone scan, or pain flares during chemotherapy. This phenomenon reflected the current practice and standard definitions of progression at the time that this trial was conducted. In addition, unrecognized differences in therapies given beyond progression may also be important in determining prognosis. Although protocol therapy beyond progression was a significant factor in this analysis, it did not substantially add to the predictive value of the nomogram and was not included. Future analyses should consider potentially beneficial second-line therapies that may have a greater effect on survival. In addition, future analyses using more recent progression criteria such as requiring confirmatory scans will be needed to assess the effect of these changes on predictors of postprogression survival (24, 25). Treatment beyond progression was left to the discretion of the treating physician, and included continuation of protocol therapy, alternative chemotherapy or trial regi-

mens, hormonal therapies, radiation, steroids, bisphosphonates, and surgery. Thus, the survival estimates are a reflection of the real-time practical treatment of these men in the postchemotherapy setting at the time that this trial was completed in the past 5 years. Given that no therapies have been shown to improve survival for men with CRPC after docetaxel, our results remain generalizable. In addition, the majority of men received first-line docetaxel-based chemotherapy, which remains the current standard-of-care for men with metastatic CRPC worldwide. Thus, we feel that these results are generalizable to men with CRPC who have progressed on or after front-line chemotherapy.

Finally, this nomogram derived from theTAX327 database contains some factors that were also included within our original published prognostic nomogram of survival from time of chemotherapy initiation (6). The fact that these factors remain significant in multiple models of different time periods and across different published data sets testifies to their prognostic import and generalizability (7, 8). Our analysis of the second-line CRPC setting revealed clinically important and novel postprogression factors that are not available at the initiation of chemotherapy and that are independently prognostic for survival after first-line chemotherapy.

In conclusion, we have identified several well-known and several novel predictors of survival in the postchemotherapy setting and developed a clinically applicable and internally validated nomogram that may be useful for prognostication as well as for stratification in and interpretation of clinical trials and sample size planning. External validation in a prospective clinical trial in the postdocetaxel setting is required and planned.

Disclosure of Potential Conflicts of Interest

A.J. Armstrong: consultant, honoraria, and commercial research grant, Sanofi Aventis. R. de Wit, I. Tannock, and M. Eisenberger: consultants and research support, Sanofi Aventis. E. Garrett-Mayer has no conflicts of interest.

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