Review – Prostate Cancer

Time-to-event Outcomes in Men with Nonmetastatic Castrate-resistant Prostate Cancer—A Systematic Literature Review and Pooling of Individual Participant Data

Markus Aly, Mahmoud Hashim, Bart Heeg, Johan Liwing, Amy Leval, Maneesha Mehra, Joe Lawson, Sabine D. Brookman-May, Olof Akre

Article info

Article history:
Accepted March 14, 2018

Associate Editor:
Christian Gratzke

Keywords:
Nonmetastatic castration-resistant prostate cancer
Time to event
Treatment
Disease burden

Abstract

Context: Until recently, there has been a lack of evidence-based treatment alternatives in men with nonmetastatic castrate-resistant prostate cancer (NM-CRPC). However, new evidence-based treatment alternatives are emerging.

Objective: We aimed to describe time-to-event outcomes in NM-CRPC patients based on evidence from both prospective and retrospective studies. Second, we aimed to describe predictors of these outcomes in the same patient population.

Evidence acquisition: A systematic review was conducted to identify clinical studies (both prospective and retrospective) in NM-CRPC patients. All published Kaplan-Meier curves were digitized, and individual participant data were extracted using a published and validated R code. The following outcomes were considered: overall survival (OS), bone metastasis-free survival (BMFS), time to bone metastasis (TTBM), metastasis-free survival, time to metastasis, time to progression (TPP), progression-free survival, and time to prostate-specific antigen (PSA) progression. Second, we described all predictor/outcome relationships.

Evidence synthesis: Median survival times, in months, for OS, BMFS, TTBM, and TPP in placebo arms of randomized clinical trials are 45.3 (95% confidence interval [CI]: 43.5–46.8), 31.5 (95% CI: 28–33.4), 28.8 (95% CI: 25.2–31.6), and 22.2 (95% CI: 19.3–24.8), respectively. In general, reported outcomes in retrospective studies seemed to be longer than those reported in clinical trials. Baseline PSA nadir levels, PSA doubling time, PSA velocity, and alkaline phosphatase velocity are reliable predictors of time-to-event outcomes in NM-CRPC patients, whereas Gleason score is not.

Conclusions: NM-CRPC is a long-standing condition where effective treatments to slow down disease progression historically have been lacking. Compared with prospective studies, retrospective studies have had limited ability to correctly identify NM-CRPC patients and estimate time to different outcomes in NM-CRPC patients.

Patient summary: For patients with nonmetastatic castration-resistant prostate cancer (NM-CRPC), currently no effective treatments resulting in longer survival compared with watchful waiting are available. On average, without additional treatment, half of these patients survive <.45 mo after NM-CRPC diagnosis.

1 These authors contributed equally to this work.

* Corresponding author. Ingress-health, Health Economics and Real World Evidence, Hofplein 20, Rotterdam 3032 AC, The Netherlands. Tel.: +31 103 330 877.

E-mail address: mahmoud.hashim@ingress-health.com (M. Hashim).

https://doi.org/10.1016/j.euf.2018.03.010

Eur Urol Focus (2018), https://doi.org/10.1016/j.euf.2018.03.010
1. Introduction

Nearly all patients with early-stage prostate cancer progress over time with androgen deprivation therapy (ADT) to castration-resistant prostate cancer (CRPC) [1]—a disease state defined by rising serum prostate-specific antigen (PSA) levels, despite a serum testosterone level of <50 ng/dl. If the imaging studies remain negative for distant metastatic lesions, this disease state is known as nonmetastatic CRPC (NM-CRPC) [2].

Emerging data suggest a clinical benefit of active treatment in NM-CRPC patients. A few phase 3 randomized clinical trials (RCTs) have been conducted in men in this stage of the disease [3–6]. These trials have investigated bone-targeted agents, such as denosumab, which has been shown to delay bone metastasis development, with no significant survival benefits. However, the limited median time to metastasis in the control arm underlines the need for effective treatment in this patient population. Newer antiandrogens such as apalutamide, enzalutamide, and orteronel that have been investigated or approved for metastatic CRPC are now being investigated in men without metastases [7–11]. Data from such trials have not been examined systematically and/or pooled together. Thus, we sought to describe time-to-event outcomes in NM-CRPC patients based on evidence from both prospective and retrospective studies. Second, we aimed to assess predictors of these outcomes in the same patient population.

2. Evidence acquisition

2.1. Systematic literature review

We conducted a systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of individual participant data (PRISMA-IPD) statement [12]. In October 2017, we searched one bibliographic database, Medline, to identify published clinical trials (both prospective and retrospective) in NM-CRPC. Men included in the trials were of high-risk character for recurrence or progression, which was defined in terms of high PSA as well as high PSA doubling time (PSA-DT) in most studies. The search was restricted to English-language publications carried out in humans and with no limitation on publication date. We used the following search syntax: “(castration resistant prostate cancer) OR (hormone refractory prostate cancer) OR (androgen independent prostate cancer) OR (endocrine resistant prostate cancer)) AND (‘non-metastatic’[All Fields] OR “non metastatic”[All Fields] OR “nonmetastatic”[All Fields]) AND ((randomized controlled trial[ptyp] OR controlled clinical trial[ptyp]) OR randomized controlled trial OR placebo OR “drug therapy”[Subheading] OR randomly OR trial OR groups OR prospective OR observational OR retrospective OR cohort OR chart OR database OR claims OR registry)) AND English[lang]”.

Two investigators independently reviewed the titles, abstracts, and full-text of retrieved articles sequentially using the predefined eligibility criteria. A third investigator resolved any disagreement. At the full-text stage, references in publications were also reviewed to identify further relevant trials. Upon agreement on the final list of included trials, one investigator extracted data from the included trials into a predefined Microsoft Excel template. Subsequently, another investigator validated the extracted data by re-extracting them. The following data items were extracted: trial identification items, for example, PMID, first author, year, study design; interventions and target population; basic patient and disease characteristics; and a matrix of reported time-to-event end points (yes/no) and/or whether predictors of these end points were investigated and reported (yes/no). One investigator (M.D.) assessed the quality of included studies using the Cochrane Collaboration’s relevant tools.

2.2. Outcomes and Individual participant data extraction

Key time-to-event outcomes that may be reported in NM-CRPC studies were considered for assessment, including overall survival (OS), bone metastasis-free survival (BMFS), time to bone metastasis (TTBM), metastasis-free survival (MFS), time to metastasis (TTM), time to progression (TTP), progression-free survival (PFS), and time to PSA progression (TTPP). OS was defined as the time from randomization to death. TTBM was defined as the time to first positive bone scan/radiograph and BMFS as the time to first positive bone scan/radiograph or death. TTM was defined as the time to radiographic evidence of metastatic disease and MFS as the time to radiographic evidence of metastatic disease or death. All definitions of TTP, PFS, and TTPP were considered.

During the data collection process, an index of all Kaplan-Meier (KM) curves was prepared per study and per outcome. First, all KM curves were digitized by one investigator using Engauge Digitizer (version 9.2). Another investigator validated extracted KM curve coordinates by overlying extracted curve coordinates with the originally published image. Time unit (x-axis) of all curves was converted into months. Then, individual participant data using a published and validated R code were extracted [13]. Finally, the individual participant data were used to reconstruct KMs and then compare with the published curve.

2.3. Primary analysis

Our primary aim was to pool individual participant data from KM curves of placebo arms of RCTs. Before pooling individual participant data from several KM curves, we compared patient population (inclusion/exclusion criteria), treatments given to these patients (placebo, active treatment), and end point definitions. When possible, we carried out other exploratory pooling scenarios where we included either all data from active arms of RCTs where interventions had a similar mechanism of action (eg, bone-targeted agents or antiandrogens) or pooled data from prospective and retrospective studies.

2.4. Additional analysis

Additionally, studies that reported associations/relationships between one of the patients’ baseline characteristics
(predictors) and time-to-event outcomes were selected in the study selection process. A qualitative summary of these associations/relationships was compiled per predictor per outcome.

3. Evidence synthesis

Out of the 121 reports screened, we included 20 reports in our review. Supplementary Figure 1 shows the study selection process. For pooling time-to-event outcomes (descriptive and quantitative analysis), we included 17 reports, and for descriptive analysis of outcome predictors in NM-CRPC patients, we included 12 reports. Study and population characteristics for these studies, 20 in total, are summarized in Table 1. The quality assessment of individual studies is presented in the Supplementary material.

3.1. Pooled time-to-event outcomes in NM-CRPC

Figure 1 shows pooled KM curves for different time-to-event outcomes in placebo arms of RCTs. Individual studies and corresponding digitized KM curves per outcome are presented in the Supplementary material.

For the primary analysis, only RCTs investigating bone-targeted agents had placebo arms [3–6]. In these placebo arms, patients received different treatments. All patients in the zoledronic acid trial, who received ADT before enrollment, continued treatment throughout the study, and further treatment with secondary hormonal therapy or chemotherapy was at the discretion of the treating physician [3]. Likewise, in the zibotentan trial, patients in both intervention and placebo arms were permitted additional prostate cancer therapies in conjunction with study treatment [6]. In the denosumab trial, patients enrolled in the placebo arm had a chance to receive denosumab for at least 24 mo after primary analysis cut-off date [4]. Similarly, in the atrasentan trial, patients with confirmed disease progression at the primary analysis cut-off date were eligible for enrollment in an open-label extension study in which participants received atrasentan [5]. In summary, the placebo groups are heterogeneous with respect to treatments [4,5].

Table 1 shows baseline characteristics of the study populations in these trials. Patients’ age and time since initial diagnosis were comparable in all RCTs investigating bone-targeted agents [3–6], but the study populations were more heterogeneous with respect to race, baseline PSA, and Gleason score. The median PSA values were higher in the zoledronic acid trials, and more patients in the atrasentan trial had Gleason score >7 compared with those in zoledronic acid and denosumab trial.

Since our aim was a description of prognosis in NM-CRPC, KM curves were pooled for the placebo groups per end point despite some differences in the definition of permitted treatments, baseline characteristics, and prognosis. Overall four OS KM curves (n = 1980) [3–6], three BMFS KM curves (n = 1248) [3,4,14], and three TTBM KM curves (n = 1248) were pooled together [3,4,14]. Additionally, we retrieved KM curve for TTP (atrasentan trial, n = 470) [5] and PFS/MFS (zibotentan trial, n = 589) [6]. The definition of the PFS outcome in the zibotentan trial was similar to the definition of MFS: “time from randomization to documented progression of metastatic disease or death in the absence of progression” [10]. Figure 1 shows these five KM curves: OS, BMFS, TTBM, TTP, and PFS/MFS. In summary, median survival times, in months, for OS, BMFS, TTBM, PFS/MFS, and TTP in placebo arms of RCTs are 45.3 (95% confidence interval [CI]: 43.5–46.8), 31.5 (95% CI: 28–33.4), 28.8 (95% CI: 25.2–31.6), 17.8 (95% CI: 14.8–22.1), and 22.2 (95% CI: 19.3–24.8), respectively.

None of the studied bone-targeted agents was associated with prolonged OS, and we explored various other pooling scenarios (Supplementary material). We pooled OS KM curves from intervention arms of the RCTs investigating bone-targeted agents (three KM curves, n = 1775) [4–6], and from both placebo and intervention arms of the RCTs investigating bone-targeted agents (seven KM curves, n = 3755) [3–6], and found only marginal differences in median survival compared with the pooled placebo groups. Median pooled OS rates from intervention-arm-only studies and the entire study populations were 46.6 (95% CI: 43.9–49.6) and 45.7 (95% CI: 44.2–47.2) mo, respectively.

No further pooling scenarios were performed using OS KM curves reported in retrospective studies. In these studies, more heterogeneity was observed in the included patient populations [1,15,16]. The starting time point for the reported OS KM curve by Banefelt et al [1] was the initiation of continuous ADT rather than CRPC diagnosis. In the second study by Metwalli and colleagues [16], men with a PSA nadir of >4 ng/ml were excluded from their CRPC study population. Additionally, 21.8% of patients had metastasis already. In the third study by D’Amico et al [15], the study sample included patients treated with radical prostatectomy or radiation therapy, followed by salvage hormonal therapy for increasing PSA with no evidence of metastasis. In that study, it was not clear how castration-resistant patients were identified. Survival in these retrospective studies might be affected by selection bias, and therefore, the true survival length might be either over [1,15] or underestimated [16]. Median OS was 78.8 mo in the study by Banefelt and colleagues [1] and was not reached in the other two studies [15,16]. In summary, the observed differences in these retrospective trials made the pooling of data from RCTs impossible.

With regard to BMFS, we pooled KM curves from all included studies apart from that by Metwalli et al [16] (eight KM curves, n = 2150) [1,3,4,14,17], which was excluded due to high risk of selection bias.

Concerning TTBM, we pooled KM curves from all studies excluding those by Banefelt et al [1] and McNeel et al [18] (five KM curves, n = 2422) [3,4,14,19]. As described above, Banefelt and colleagues [1] did not use CRPC diagnosis as a starting point, and McNeel and colleagues [18] reported a small prospective vaccine study (n = 16). The pooled median TTBM was 33.0 mo (95% CI: 29.7–34.0).

With regard to MFS, digitized KM curves from single-arm studies investigating a new androgen therap-
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Interventions</th>
<th>Age, median (range)</th>
<th>Race (%)</th>
<th>Timesince initial diagnosis(yr), median (range)</th>
<th>Prior initial/local treatment (%)</th>
<th>PSA (ng/ml), % or median (range)</th>
<th>Gleason score, % or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al (2005) [3]</td>
<td>Randomized controlled trial, analysis of placebo arm</td>
<td>201</td>
<td>Placebo arm of zoledronic acid trial</td>
<td>73 (7) (^a)</td>
<td>White (87%); black (8%); other (5%)</td>
<td>6.1 (1.0–25.9)</td>
<td>Prostatectomy (34%)</td>
<td>13.8 (5.6–35.6) (^b)</td>
<td>Gleason &gt;7 (29%)</td>
</tr>
<tr>
<td>Nelson et al (2008) [5]; Smith et al (2011) [14]</td>
<td>Randomized controlled trial</td>
<td>941</td>
<td>Atrasentan, placebo</td>
<td>Intervention arm: 75 (47–92)</td>
<td>White (89.9%); black (5.8%); other (4.2%)</td>
<td>Intervention arm: 7.1 (0.9–22.9)</td>
<td>NA</td>
<td>Intervention arm: 11.1 (1.2–732.9)</td>
<td>Intervention arm: 7.0 (2.0–10.0)</td>
</tr>
<tr>
<td>Smith et al (2012) [4]; Smith et al (2013) [29]</td>
<td>Randomized controlled trial</td>
<td>1432</td>
<td>Denosumab, placebo</td>
<td>Intervention arm: 74 (67–80) (^b)</td>
<td>White (85%); black (6%); Hispanic (4%); other (5%)</td>
<td>Intervention arm: 6.10 (3.5–9.1)</td>
<td>Control arm: 6.10 (3.6–9.5)</td>
<td>Prostatectomy and/or radiation</td>
<td>Intervention arm: 44%</td>
</tr>
<tr>
<td>Miller et al (2013)[6]</td>
<td>Randomized controlled trial</td>
<td>1421</td>
<td>Zbotenant, placebo</td>
<td>Intervention arm: 73 (44–93)</td>
<td>White (70.4%); black (1.8%); Asian (24.4%); other (3.2%)</td>
<td>NA</td>
<td>Intervention arm: prostatectomy (15.2%); radiotherapy (36.6%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>McNeel et al (2014) [18]</td>
<td>Randomized controlled trial</td>
<td>17</td>
<td>pTVC-HP vaccine</td>
<td>Intervention arm: 76.1 (47–89)</td>
<td>All Caucasian</td>
<td>NA</td>
<td>Intervention arm: prostatectomy (62.5%); radiotherapy (12.5%)</td>
<td>Intervention arm: 16.7 (3.06–54.4)</td>
<td>Intervention arm: Gleason ≥7 (75%)</td>
</tr>
<tr>
<td>Chu et al (2015) [21]</td>
<td>Randomized controlled trial</td>
<td>127</td>
<td>Bicalutamide with or without dutasteride</td>
<td>Intervention arm: 78 (63–89)</td>
<td>White (81%); African American (16%)</td>
<td>Intervention arm: 10.2 (1.3–22.7)</td>
<td>Prostatectomy plus radiotherapy</td>
<td>Intervention arm: &lt;10 ng/ml (82%)</td>
<td>Intervention arm: Gleason ≥7 (33%)</td>
</tr>
<tr>
<td>Penson et al (2016) [11]</td>
<td>Randomized controlled trial</td>
<td>139</td>
<td>Enzalutamide, bicalutamide</td>
<td>Intervention arm: 72 (46–92)</td>
<td>White (80.8%); African American (14.6%)</td>
<td>NA</td>
<td>NA</td>
<td>Intervention arm: 11.0 (0.0–1499.7)</td>
<td>Intervention arm: Gleason &lt;7 (50.5%)</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Study design</td>
<td>No. of patients</td>
<td>Interventions</td>
<td>Age, median (range)</td>
<td>Race (%)</td>
<td>Timesince initial diagnosis(yr), median (range)</td>
<td>Prior initial/local treatment (%)</td>
<td>PSA (ng/ml), % or median (range)</td>
<td>Gleason score, % or median (range)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------------------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>----------</td>
<td>-------------------------------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Small et al (2007)</td>
<td>Single-arm trial</td>
<td>58</td>
<td>Gefitinib</td>
<td>73 (54–88)</td>
<td>Black (16), Caucasian (78), Hispanic (7)</td>
<td>NA</td>
<td>Radiotherapy (43%); radical prostatectomy (21%)</td>
<td>23 (5–187)</td>
<td>NA</td>
</tr>
<tr>
<td>Ogita et al (2012)</td>
<td>Single-arm trial</td>
<td>15</td>
<td>Bevacizumab</td>
<td>70 (51–87)</td>
<td>White (60%); African American (40%)</td>
<td>NA</td>
<td>Prostatectomy (20%); radiotherapy (93%); c cryotherapy (7%)</td>
<td>27 (2.6–104)</td>
<td>Gleason &gt;7 (47%)</td>
</tr>
<tr>
<td>Hussain et al (2014)</td>
<td>Single-arm trial</td>
<td>39</td>
<td>Orteronel</td>
<td>71 (53–81)</td>
<td>White (90%); black or African American (10%)</td>
<td>NA</td>
<td>Prostatectomy (67%)</td>
<td>12.1 (2.6–67.8)</td>
<td>Gleason &gt;7 (51%)</td>
</tr>
<tr>
<td>Smith et al (2016)</td>
<td>Single-arm trial</td>
<td>51</td>
<td>Apalutamide</td>
<td>71 (51–88)</td>
<td>NA</td>
<td>10 (1.67–19.8)</td>
<td>NA</td>
<td>10.7 (0.5–201.7)</td>
<td>Gleason &lt;7 (57%)</td>
</tr>
<tr>
<td>Lodde et al (2010)</td>
<td>Prospective observational study</td>
<td>38</td>
<td>Bicalutamide 150 mg</td>
<td>69.8 (56–85)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Prostatectomy (76.3%); radiotherapy (5.2%)</td>
<td>1.5 (0.18–33)</td>
</tr>
<tr>
<td>D’Amico et al (2005)</td>
<td>Retrospective</td>
<td>919</td>
<td>Salvage hormonal therapy</td>
<td>63.9 (43.3–78.2)</td>
<td>NA</td>
<td>NA</td>
<td>PSA &gt;4 ng/ml (44.5%)</td>
<td>NA</td>
<td>Gleason &lt;6 (57%)</td>
</tr>
<tr>
<td>Banerjee et al (2014)</td>
<td>Retrospective</td>
<td>446</td>
<td>Antiandrogen therapy</td>
<td>78.1 (6.5)</td>
<td>NA</td>
<td>2.7 (3.2)</td>
<td>Prostatectomy (14%); radiotherapy (0.7%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Moreira et al (2016)</td>
<td>Retrospective</td>
<td>458</td>
<td>Antiandrogen therapy</td>
<td>75 (67–81)</td>
<td>Black (31%)</td>
<td>NA</td>
<td>60% received radical prostatectomy and/or radiation</td>
<td>4.3 (2.9–9.2)</td>
<td>Gleason 2–6 (17%); Gleason 7 (25%); Gleason 8–10 (25%)</td>
</tr>
<tr>
<td>Haneyok et al (2018)</td>
<td>Retrospective</td>
<td>232</td>
<td>NA</td>
<td>75 (67–81)</td>
<td>Nonblack (67%), black (33%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Metwalli et al (2014)</td>
<td>Retrospective</td>
<td>165</td>
<td>Antiandrogen therapy</td>
<td>67.2 (8.1)</td>
<td>African American (27.9%); Caucasian and other (70.9%)</td>
<td>0.23 (0–5.5)</td>
<td>NA</td>
<td>16.5 (3.1–414.2)</td>
<td>Gleason sum &lt;7 (58.2%); Gleason sum &gt;8 (29.1%)</td>
</tr>
</tbody>
</table>

NA = not available; PSA = prostate-specific antigen; SD = standard deviation.

* Median (SD).
* Median (interquartile range).
* Mean (range).
* Mean (SD).
of 40.4 mo (95% CI: 33.9–52.4) reported by Moreira and colleagues (a retrospective study) [19].

3.2. Predictors of time-to-event outcomes in NM-CRPC

Table 2 shows a summary of our findings regarding the relation between various predictors (age, race, primary localized treatment, Gleason score, baseline PSA levels, PDA-DT, PSA velocity, alkaline phosphatase velocity, testosterone levels, etc.) and time-to-event outcomes (OS, BMFS/TTBM, TTM/MFS, and TTP/PFS).

In summary, higher baseline PSA levels, shorter PDA-DT, and higher PSA velocity were associated with worse outcomes [1.3,14–17,19,20–22]. Moreover, a higher alkaline phosphatase velocity was associated with both TTM and OS [16]. There is also increasing evidence that higher testosterone levels at baseline are associated with decreased disease progression risk [21]. Age was associated with TTBM and BMFS but not with other time-to-event outcomes [14,19,21,23]. Race may be associated with disease progression risk, but it is not associated with other time-to-event outcomes [19,21,23]. There was no clear association between initial local treatment or Gleason score and time-to-event outcomes [3,14,15,19,20,21,23]. Other potential baseline predictors, such as the method of castration, body mass index, Karnofsky performance status, lactate dehydrogenase, hemoglobin, alkaline phosphatase serum levels, time from ADT to CRPC (years), time from CRPC diagnosis, regional lymph node metastases at diagnosis, and estimated glomerular filtration rate expression, were not associated with any of the outcomes [3,14,19,24].

3.3. Discussion

In the pooled analysis of the placebo arms of studies testing bone-targeted agents, we estimated that median times for different time-to-event outcomes are 45.3 OS months (95% CI: 43.5–46.8), 31.5 BMFS months (95% CI: 28–33.4), 28.8 TTBM months (95% CI: 25.2–31.6), and 22.2 TTP months (95% CI: 19.3–24.8). Although there was some heterogeneity of baseline characteristics and prognosis in the pooled study arms, these are the only available estimates for time-to-event outcomes in NM-CRPC.

Median survival times in retrospective studies were not comparable with those reported in RCTs. Median OS in the RCTs investigating bone-targeted agent, both intervention and placebo arms, was 45.7 mo (95% CI: 44.2–47.2) compared with 78.8 mo (95% CI 67.6–NR) in the retrospective study by Banefelt and colleagues [1]. Similarly, and despite longer follow-up duration, median BMFS and TTBM were not reached in reports by Metwalli et al [16] and Banefelt et al [1], respectively. These differences made pooling of data from retrospective studies with data from RCTs inappropriate. This might be explained by the possible differences in the identification of NM-CRPC patients in RCTs and retrospective studies. For example, the starting time point for the reported KM curve by Banefelt and colleagues [1] was the initiation of continuous ADT rather than CRPC diagnosis. In another
**Table 2 – Predictors of time-to-event outcomes in NM-CRPC.**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OS</th>
<th>BMFS/TTBM</th>
<th>MFS/TTM</th>
<th>TTP/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>1-yr age increase was not associated with OS in both uni- (RR = 1.01; 95% CI: 0.99, 1.03) and multivariate (RR = 1.01; 95% CI: 0.98, 1.03) analyses [14]</td>
<td>1-yr age increase was associated with BMFS in both uni- (RR = 0.96; 95% CI: 0.94, 0.98) and multivariate (RR = 0.97; 95% CI: 0.94, 0.99) analyses [14]</td>
<td>1-yr age increase did not predict soft tissue metastasis, visceral and lymph node metastasis [23], or any metastasis [19]</td>
<td>1-yr age increase was associated with disease progression risk: HR = 0.92 (95% CI: 0.89, 0.96) [21]</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>NA</td>
<td>NA</td>
<td>Race did not predict soft tissue metastasis, visceral and lymph node metastasis [23], or any metastasis [19]</td>
<td>The nonwhite race was associated with decreased disease progression risk (HR = 0.41; 95% CI: 0.18, 0.92) [21]</td>
</tr>
<tr>
<td><strong>Primary localized treatment (prostatectomy or radiotherapy)</strong></td>
<td>Prior prostatectomy was not associated with OS [3,14]</td>
<td>Prior prostatectomy was not associated with BMFS and TTBM [3,14]</td>
<td>Patients who had received primary localized treatment had a higher risk of metastasis in both uni- (HR = 1.31; 95% CI: 1.02, 1.69) and multivariate (HR = 1.38; 95% CI: 1.04, 1.82) analyses [19]</td>
<td>Prior radiotherapy predicted better treatment effect size: absolute difference in 3-yr survival was 19% in total population compared with 33% in patients with prior radiation [20]</td>
</tr>
<tr>
<td><strong>Gleason score</strong></td>
<td>Gleason score was not associated with OS [3,14]</td>
<td>Gleason score was not associated with BMFS/TTBM [3,14]</td>
<td>Gleason score 8–10 was associated with metastasis (HR = 1.61; 95% CI: 1.06, 2.43) [19]</td>
<td>Gleason score was not associated with increased risk of PSA progression [21]</td>
</tr>
<tr>
<td><strong>Baseline PSA levels</strong></td>
<td>Baseline PSA ≥10 ng/ml was associated with OS in both uni- (HR = 3.10; 95% CI: 1.47, 6.34) and multivariate (HR = 2.99; 95% CI: 1.38, 6.46) analyses [3]</td>
<td>Baseline PSA ≥10 ng/ml was associated with TTBM in both uni- (HR = 2.96; 95% CI: 1.53, 5.38) and multivariate (HR = 3.56; 95% CI: 1.88, 6.74) analyses [3]</td>
<td>Higher PSA levels (log PSA) at CRPC diagnosis was independently associated with shorter TTM (HR = 1.6; 95% CI: 1.44, 1.87) [19]</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Post-CRPC PSA nadir (ng/ml)</strong></td>
<td>Post-CRPC PSA nadir (ng/ml) was associated with OS (OR = 1.72; 95% CI: 1.14, 2.57) [16]</td>
<td>Post-CRPC PSA nadir (ng/ml) was associated with TTBM and BMFS in both uni- (HR = 2.36; 95% CI: 1.72, 3.23) and multivariate (HR = 2.43; 95% CI: 1.75, 3.37) analyses [14]</td>
<td>Post-ADT PSA nadir (ng/ml) association with TTBM did not achieve statistical significance (OR = 1.42; 95% CI: 0.93, 2.18) [16]</td>
<td>Post-ADT PSA nadir (ng/ml) association with TTBM did not achieve statistical significance (OR = 1.42; 95% CI: 0.93, 2.18) [16]</td>
</tr>
</tbody>
</table>

Please cite this article in press as: Aly, M. et al. Time-to-event Outcomes in Men with Nonmetastatic Castrate-resistant Prostate Cancer – A Systematic Literature Review and Pooling of Individual Participant Data. Eur Urol Focus (2018), https://doi.org/10.1016/j.euf.2018.03.010
### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OS</th>
<th>BMFS/TTBM</th>
<th>MFS/TTM</th>
<th>TTP/PFS</th>
</tr>
</thead>
</table>
| Baseline PSA levels < 20 ng/dl       | Predicted better treatment effect size: absolute difference in 3-yr survival was 19% in total population compared with 51% in patients who had baseline PSA levels < 20 ng/dl [20]  
| PSA-DT                               | PSA-DT > 10 mo had worse OS: OR = 3.98 (95% CI: 1.58, 10.01) [16]  
| PSA velocity                         | PSA velocity (log [ng/ml]/yr) was associated with OS: HR = 1.39 (95% CI: 1.15, 1.69) [3]  
| Alkaline phosphatase velocity        | Alkaline phosphatase velocity > 6.3 U/l/yr was associated with OS (OR = 5.11; 95% CI: 2.24, 11.67) [16]  
| Testosterone levels                  | Higher testosterone levels were associated with decreased disease progression risk (HR = 0.18; 95% CI: 0.06, 0.33) [21]  
| Other potential baseline predictors  | Other potential baseline predictors were not associated with OS [3,14,19,24]  

ADT = androgen deprivation therapy; BMFS = bone metastasis-free survival; CI = confidence interval; CRPC = castrate-resistant prostate cancer; EGFR = estimated glomerular filtration rate; HR = hazard ratio; MFS = metastasis-free survival; NA = not available; NM-CRPC = nonmetastatic castrate-resistant prostate cancer; OR = odds ratio; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; PSA-DT = PSA doubling time; RR = risk ratio; TTBM = time to bone metastasis; TTM = time to metastasis; TTP = time to progression.

* Vaccine trial.

1. In that study, patients who had a PSA nadir of >4 ng/ml were excluded.

2. Method of castration, body mass index, Karnofsky performance status, lactate dehydrogenase, hemoglobin, alkaline phosphatase serum levels, time from ADT to CRPC (years), time from CRPC diagnosis, regional lymph node metastases at diagnosis, and EGFR expression.
study by Metwalli and colleagues [16], there was a high risk of selection bias due to the exclusion of men with a PSA nadir of >4 ng/ml and the inclusion of patients with metastasis. In other studies, it was not clear how NM-CRPC patients were identified [15,19]. On the contrary, in an RCT, randomization is the starting point. This may not coincide with the first sign of CRPC, and RCTs may, for this reason, underestimate the time to the event.

As an additional objective, we aimed to describe predictors of these outcomes in the same patient population. Based on the extracted data, baseline PSA nadir levels, PSA-DT, PSA velocity, and alkaline phosphatase velocity were predictors of time-to-event outcomes in NM-CRPC patients. These predictors may be used to define high-risk inclusion criteria for future NM-CRPC randomized clinical trials. This has been used to identify patients in three phase 3 trials involving NM-CRPC patients [7,8,25]. In both PROSPER and ARAMIS trials, only patients with PSA-DT ≤10 mo and PSA level >10 ng/ml were included [8,25]. In SPARTAN trial, only patients with PSA-DT ≤10 mo were included. It is unclear whether these findings would also apply to patients developing resistance after having been treated upfront with abiraterone [26].

At NM-CRPC diagnosis, Gleason score was not clearly associated with time-to-event outcomes. Gleason score was not associated with OS, BMFS, TTBM, and TTPP [3,14,21]. Only in one study, Gleason score 8–10 was associated with metastasis [19]. Few previous studies have reported the prognostic value of Gleason score at this stage of disease. It seems plausible that the prognostic information in Gleason is lost at the time when the tumor has progressed to the point where it is escaping the castration effect. However, Nakabayash and colleague [27] reported that, among men with mainly metastatic disease, a higher biopsy Gleason score was predictive of shorter OS.

Studies considered and analyzed in this review have not incorporated and analyzed molecular and genetic markers as potential prognostic factors, which represents a general limitation of recent studies. Future studies need to incorporate these in order to define and stratify patients and to analyze their potential prognostic and predictive abilities.

Interpretation of reported PFS in the zibotentan trial is challenging [6]. The definition used for PFS was different from the one used by Penson and colleagues [11]; PFS was defined as the time from randomization to documentation of progressive metastatic disease or death in the absence of progression. By contrast, Penson and colleagues [11] included PSA progression in the definition. Therefore, reported PFS outcome may also be considered an information source for MFS in NM-CRPC population. It was expected that median survival times for PFS and MFS are longer than those for TTP and BMFS, respectively. Nevertheless, median PFS/MFS time in the zibotentan trial, median 17.8 mo (95% CI: 14.8–22.1), was shorter than reported TTP time, median 22.2 mo (95% CI: 19.3–24.8), and BMFS time, median 31.5 mo (95% CI: 28–33.4), in other bone-targeted agents. Based on an ad hoc analysis reported by trial investigators, this may be attributed to the high frequency of included asymptomatic metastasis in men thought to have the nonmetastatic disease [28]. Characterization of patients as being M0 or M1 is dependent on the radiological method used to screen the patient at the time of diagnosis or progression of the disease. Even if most studies included in this review have been conducted prior to the prostate-specific membrane antigen positron emission tomography (PSMA-PET) era and have used computed tomography imaging for clinical staging, some studies may also have allowed the use of more sensitive methods such as magnetic resonance imaging or PSMA-PET, which could have classified some patients as M1 rather than M0 in these studies. This would likely improve OS and time to progression as an effect of the Will Rogers phenomenon for the true M0 patients. A potential impact of imaging methods might also be caused by different methods used for the screening of bone metastasis in local departments, which has to be taken into account when generalizing these study results to our clinical situation.

This work has some limitations. First, our literature review was based on one bibliographic database. Second, there are limitations concerning the method used to extract individual participant data from KM curves [13]. The quality of the reported images, data about censoring, and the process of digitizing KM curves are variable. Having individual participant data would provide more robust estimates. However, we implemented strategies that could minimize such risks.

4. Conclusions

Based on data from previous trials, we have pooled estimates of the time to different adverse events among men with NM-CRPC. With a median OS of <4 yr, there is a need for effective treatment options in this patient population to slow down the progression of the disease. Additionally, based on analysis of both prospective and retrospective studies, retrospective studies seem to be limited regarding the proper identification of the NM-CRPC patients and reported outcomes in these studies seem to underestimate the actual disease burden in this patient population. Furthermore, relevant knowledge is built about potential clinically relevant prognostic markers, which could subsequently be applied as risk criteria for inclusion and patient stratification in clinical trials. Finally, before implementing these markers for decision making in clinical routine, validation of their prognostic and predictive values in clinical trials and the clinical routine is needed to confirm their independent impact.

**Author contributions:** Markus Aly and Mahmoud Hashim had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** All authors.

**Acquisition of data:** Hashim, Heeg, Liwing.

**Analysis and interpretation of data:** All authors.

**Drafting of the manuscript:** Aly, Hashim, Heeg, Liwing.
Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Hashim, Heeg.

Obtaining funding: Heeg, Liwing, Lawson.

Administrative, technical, or material support: Liwing.

Supervision: Akre.

Other: None.

Financial disclosure: Mahmoud Hashim certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Markus Aly and Olof Akre have no conflicts of interest to report. Mahmoud Hashim is an employee at Ingress-health. Bart Heeg is managing partner at Ingress-health and has received funding from Amgen, AstraZeneca, Janssen, Merck, Takeda, Teva, and UCB. Johan Liwing is an employee of Janssen–Cilag, Sweden, and owns stock in Johnson & Johnson. Amy Leval is an employee of Janssen–Cilag, Sweden, and owns stock in Johnson & Johnson. Maneesha Mehra is an employee of Janssen Global Services and owns stock in Johnson & Johnson. Joe Lawson is an employee of Janssen Research & Development and has stock options with Johnson & Johnson. Sabine Brookman-May is an employee of Janssen Research & Development and owns stock in Johnson & Johnson.

Funding/Support and role of the sponsor: This project was funded through grants from the public-private-world evidence collaboration between Karolinska Institutet and Janssen Pharmaceuticals (contract: 5-63/2015).

Acknowledgments: The authors wish to thank Fanni Soikkeli and Monica Duran. Both of them, as junior research students at Ingress-health (Rotterdam, the Netherlands), supported Mahmoud Hashim and Bart Heeg with data acquisition and analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.euf.2018.03.010.

References


