EUROPEAN UROLOGY FOCUS XXX (2018) XXX–XXX

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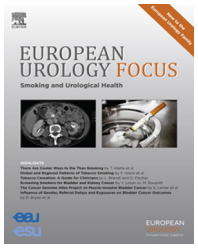

Review – Prostate Cancer

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

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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 (TTP), 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 TTP 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.

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

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

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 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

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(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 enrolment, 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 documentation of progressive 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 MFS KM curves from single-arm studies investigating a new antiandrogen therapy (two KM curves, n = 90) were pooled [9,10]. The resulting median was 34 mo (34–NR) compared with median MFS

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Table 1 – Included studies characteristics.

Author (year)	Study design	No. of patients	Interventions	Age, median (range)	Race (%)	Timesince initial diagnosis(yr), median (range)	Prior initial/local treatment (%)	PSA (ng/ml), % or median (range)	Gleason score, % or median (range)
Smith et al (2005) [3]	Randomized controlled trial, analysis of placebo arm	201	Placebo arm of zoledronic acid trial	73 (7) [a]	White (87%); black (8%); other (5%)	6.1 (1.0–25.9)	Prostatectomy (34%)	13.8 (5.6–35.6) [b]	Gleason >7 (29%)
Nelson et al (2008) [5]; Smith et al (2011) [14]	Randomized controlled trial	941	Atrasentan, placebo	Intervention arm: 75 (47–92)	Intervention arm: white (89.9%); black (5.8%); other (4.2%).	Intervention arm: 7.1 (0.9–22.9)	NA	Intervention arm: 13.1 (1.2–732.9)	Intervention arm: 7.0 (2.0–10.0)
				Control arm: 74 (48–93)	Control arm: white (94.3%); black (4.9%); other (0.8%)	Control arm: 6.9 (0.9–23.4)		Control arm: 13.2 (2.1–79)	Control arm: 7.0 (2.0–10.0)
Madan et al (2008) [20]	Randomized controlled trial	42	Poxvirus-based PSA vaccine, nilutamide	Intervention arm: 69 (51–87)	NA	Intervention arm: 0.91	NA	Intervention arm: 8.74 (1.61–292.8)	Intervention arm: 7 (3–9)
				Control arm: 69 (51–87)		Control arm: 0.65		Control arm: 16.51 (0.74–62.19)	Control arm: 7.2 (4–10)
Smith et al (2012) [4]; Smith et al (2013) [29]	Randomized controlled trial	1432	Denosumab, placebo	Intervention arm: 74 (67–80) [b]	Intervention arm: white (85%); black (6%); Hispanic (4%); other (5%)	Intervention arm: 6.10 (3.5–9.1) Control arm: 6.10 (3.6–9.5)	Prostatectomy and/or radiation Intervention arm: 44%	12.2 (4.7–27.5)	Intervention arm: Gleason <7 (56%) Control arm: Gleason <7 (60%)
				Control arm: 74 (67.5–80) [b]	Control arm: white (84%); black (5%); Hispanic (5%); other (6%)		Control arm: 46%		
Miller et al (2013)[6]	Randomized controlled trial	1421	Zibotentan, placebo	Intervention arm: 73 (44–93)	Intervention arm: white (70.4%); black (1.8%); Asian (24.4%); other (3.2%),	NA	Intervention arm: prostatectomy (15.2%); radiotherapy (36.6%)	NA	NA
				Control arm: 73 (44–93)	Control arm: white (70.4%); black (2.9%); Asian (23.5%); other (3.2%)		Control arm: prostatectomy (15.1%); radiotherapy (38.1%)		
McNeel et al (2014) [18]	Randomized controlled trial	17	pTVG-HP vaccine	Intervention arm: 76.1 (47–89)	All Caucasian	NA	Intervention arm: prostatectomy (62.5%); radiotherapy (12.5%)	Intervention arm: 16.7 (3.06–54.4)	Intervention arm: Gleason ≥7 (75%)
				Control arm: 67.7 (60–76)			Control arm: prostatectomy (66.66%); radiotherapy (22.22%)	Control arm: 9.1 (2.3–25.4)	Control arm: Gleason ≥7 (88.89%)
Chu et al (2015) [21]	Randomized controlled trial	127	Bicalutamide with or without dutasteride	Intervention arm: 78 (63–89)	Intervention arm: white (81%); African American (16%)	Intervention arm: 10.2 (1.3–22.7)	Prostatectomy plus radiotherapy Intervention arm: 55%	Intervention arm: <10 ng/ml (82%)	Intervention arm: Gleason <7 (33%)
				Control arm: 79 (54–89)	Control arm: white (78%); African American (17%)	Control arm: 8.2 (1.1–24.4)	Control arm: 63%	Control arm: <10 ng/ml (88%)	Control arm: Gleason <7 (43%)
Penson et al (2016)[11]	Randomized controlled trial	139	Enzalutamide, bicalutamide	Intervention arm: 72 (46–92)	Intervention arm: white (80.8%); African American (14.6%)	NA	NA	Intervention arm: 11.0 (0.0–1499.7)	Intervention arm: Gleason <7 (50.5%)

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Table 1 (*Continued*)

Author (year)	Study design	No. of patients	Interventions	Age, median (range)	Race (%)	Timesince initial diagnosis(yr), median (range)	Prior initial/local treatment (%)	PSA (ng/ml), % or median (range)	Gleason score, % or median (range)
				Control arm: 74 (50–91)	Control arm: white (85.4%); African American (12.1%)			Control arm: 13.2 (0.2–2849.7)	Control arm: Gleason <7 (49%)
Small et al (2007) [24]	Single-arm trial	58	Gefitinib	73 (54–88) [c]	Black (16), Caucasian (78), Hispanic (7)	NA	Radiotherapy (43%), radical prostatectomy (21%)	23 (5–187)	NA
Ogita et al (2012) [30]	Single-arm trial	15	Bevacizumab	70 (51–87)	White (60%); African American (40%)	NA	Prostatectomy (20%); radiotherapy (93%); cryotherapy (7%)	27 (2.6–104)	Gleason >7 (47%)
Hussain et al (2014)[9]	Single-arm trial	39	Orteronel	71 (53–81)	White (90%); black or African American (10%)	NA	Prostatectomy (67%)	12.1 (2.6–67.8)	Gleason >7 (51%)
Smith et al (2016)[10]	Single-arm trial	51	Apalutamide	71 (51–88)	NA	10 (1.67–19.8)	NA	10.7 (0.5–201.7)	Gleason <7 (57%)
Lodde et al (2010) [17]	Prospective observational study	38	Bicalutamide 150 mg	69.8 (56–85)	NA	NA	Prostatectomy (76.3%); radiotherapy (5.2%)	1.5 (0.18–33)	Gleason <6 (23.7%), Gleason 7 (39.5%), Gleason 8–10 (36.8%)
D'Amico et al (2005) [15]	Retrospective	919	Salvage hormonal therapy	63.9 (43.3–78.2)	NA	NA	NA	PSA >4 ng/ml (44.5%)	Gleason <6 (57%)
Banefelt et al (2014) [1]	Retrospective	446	Antiandrogen therapy	78.1 (6.5) [d]	NA	2.7 (3.2) [d]	Prostatectomy (1.4%); radiotherapy (0.7%)	NA	NA
Moreira et al (2016) [19]	Retrospective	458	Antiandrogen therapy	75 (67–81) [b]	Black (31%)	NA	60% received radical prostatectomy and/or radiation	4.3 (2.9–9.2) [b]	Gleason 2–6 (17%), Gleason 7 (25%), Gleason 8–10 (25%)
Hanyok et al (2016) [23]	Retrospective	232	NA	75 (67–81) [b]	Nonblack (67%), black (33%)	NA	NA	NA	NA
Metwalli et al (2014) [16]	Retrospective	165	Antiandrogen therapy	67.2 (8.1) [d]	African American (27.9%); Caucasian and other (70.9%)	0.23 (0–5.5)	NA	16.5 (3.1–414.2)	Gleason sum ≤7 (58.2%), Gleason sum ≥8 (29.1%)

NA = not available; PSA = prostate-specific antigen; SD = standard deviation.
[a] Median (SD).
[b] Median (interquartile range).
[c] Mean (range).
[d] Mean (SD).

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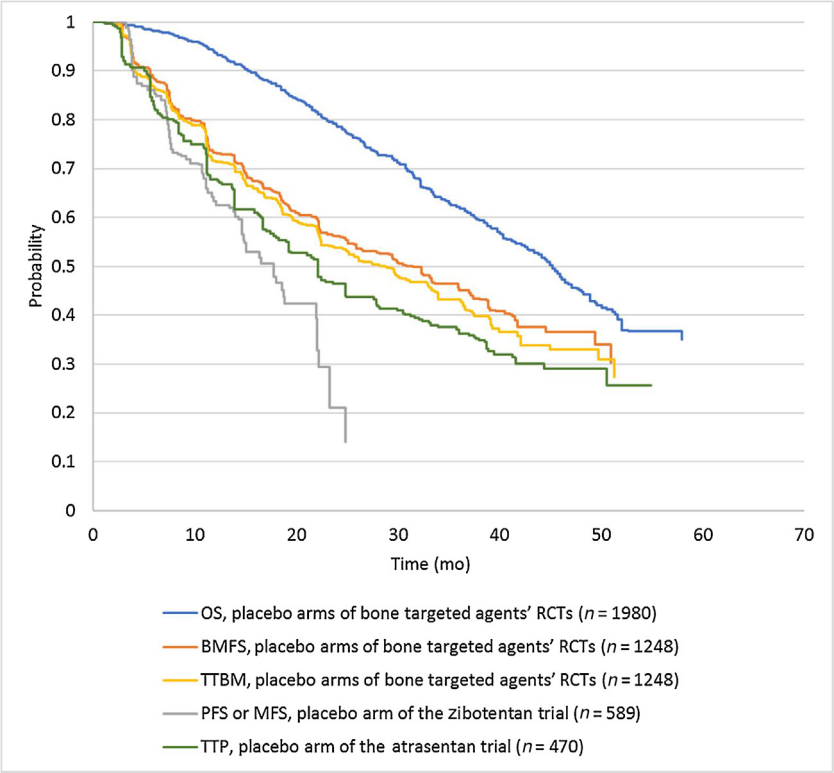

Fig. 1 – Time-to-event outcomes in placebo arms of RCTs. BMFS = bone metastasis-free survival; MFS = metastasis-free survival; OS = overall survival; PFS = progression-free survival; RCT = randomized clinical trial; TTBM = time to bone metastasis; TTP = time to progression.

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 PSA-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

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Table 2 – Predictors of time-to-event outcomes in NM-CRPC.

Predictor	OS	BMFS/TTBM	MFS/TTM	TTP/PFS
Age	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]	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]	1-yr age increase did not predict soft tissue metastasis, visceral and lymph node metastasis [23], or any metastasis [19]	1-yr age increase was associated with disease progression risk: HR = 0.92 (95% CI: 0.89, 0.96) [21]
Race	NA	NA	Race did not predict soft tissue metastasis, visceral and lymph node metastasis [23], or any metastasis [19]	The nonwhite race was associated with decreased disease progression risk (HR = 0.41; 95% CI: 0.18, 0.92) [21]
Primary localized treatment (prostatectomy or radiotherapy)	Prior prostatectomy was not associated with OS [3,14]	Prior prostatectomy was not associated with BMFS and TTBM [3,14]	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]	
	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] [a]			
Gleason score	Gleason score was not associated with OS [3,14]	Gleason score was not associated with BMFS/TTBM [3,14]	Gleason score 8–10 was associated with metastasis (HR = 1.61; 95% CI 1.06, 2.43) [19]	Gleason score was not associated with increased risk of PSA progression [21]
	Lower initial Gleason score predicted better treatment effect size: absolute difference in 3-yr survival was 19% in total population compared with 33% in patients who had Gleason score ≤7 [20] [a]			
Baseline PSA levels	Baseline PSA ≥10 ng/ml was associated with OS in both uni- (HR = 3.10; 95% CI: 1.47, 6.54) and multivariate (HR = 2.99; 95% CI: 1.38, 6.46) analyses [3]	Baseline PSA ≥10 ng/ml was associated with TTBM in both uni- (HR = 2.96; 95% CI: 1.63, 5.38) and multivariate (HR = 3.56; 95% CI: 1.88, 6.74) analyses [3]	Higher PSA levels (log PSA) at CRPC diagnosis was independently associated with shorter TTM (HR = 1.6; 95% CI: 1.44, 1.87) [19]	NA
	Baseline PSA ≥13.1 ng/ml was associated with OS 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]	Baseline PSA ≥13.1 ng/ml was associated with both TTBM and BMFS in both uni- (HR = 2.02; 95% CI: 1.46, 2.80 and HR = 2.02; 95% CI: 1.48, 2.76, respectively) and multivariate (HR = 2.11; 95% CI: 1.49, 2.97 and HR = 2.08; 95% CI: 1.51, 2.89, respectively) analyses [14]		
	Post-CRPC PSA nadir (ng/ml) was associated with OS (OR = 1.72; 95% CI: 1.14, 2.57) [16]	Post-ADT PSA nadir (ng/ml) association with TTBM did not achieve statistical significance (OR = 1.42; 95% CI: 0.93, 2.18) [16] [b]		

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Table 2 (*Continued*)

Predictor	OS	BMFS/TTBM	MFS/TTM	TTP/PFS
	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] [a]	Patients who achieved PSA response had longer median BMFS (52.5 median months) compared with those who did not (15.7 median months)		
PSA-DT	PSA-DT ≥10 mo had worse OS: OR = 3.98 (95% CI: 1.58, 10.01) [16] [b]	Patients with PSA-DT ≤6 mo had an increased risk of BMFS (HR = 2.01; 95% CI: 1.19, 3.41) [1]	Metastasis was associated with PSA-DT ≤6 mo: HR = 1.42 (95% CI: 1.02, 1.98) [19]	NA
		Patients with PSA-DT ≥10 mo had worse BMFS (OR = 12.1; 95% CI: 3.59, 40.54) [16]		
PSA velocity	PSA velocity (log [ng/ml]/yr) was associated with OS: HR = 1.39 (95% CI: 1.15, 1.69) [3] PSA velocity >1.5 ng/ml was associated with higher prostate cancer-specific mortality in both uni- (HR = 81; 95% CI: 11, 598) and multivariate (HR = 239; 95% CI: 10, 5549) analyses [15]	PSA velocity (log [ng/ml]/yr) was associated with BMFS: HR = 1.48 (95% CI: 1.25–1.74) [3]	NA	NA
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] [b]		Alkaline phosphatase velocity ≥6.3 U/l/yr was associated with TTM (OR = 2.70; 95% CI: 1.25, 5.80) [16] [b]	
Testosterone levels				Higher testosterone levels were associated with decreased disease progression risk (HR = 0.18; 95% CI: 0.06, 0.53) [21]
Other potential baseline predictors [c]	Other potential baseline predictors were not associated with OS [3,14,19,24]	Other potential baseline predictors were not associated with TTBM/BMFS [3,14,19,24]	NA	NA

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.

[a] Vaccine trial.

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

[c] 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.

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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 >2 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 real-world evidence collaboration between Karolinska Institutet and Janssen Pharmaceuticals (contract: 5-63/2015).

Acknowledgments: The authors would like 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

[1] Banefelt J, Liede A, Mesterton J, et al. Survival and clinical metastases among prostate cancer patients treated with androgen deprivation therapy in Sweden. Cancer Epidemiol 2014;38:442–7.
[2] Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65:467–79.
[3] Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 2005;23:2918–25.
[4] Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. Lancet 2012;379:39–46.
[5] Nelson JB, Love W, Chin JL, et al. Phase 3, randomized, controlled trial of atrasentan in patients with nonmetastatic, hormone-refractory prostate cancer. Cancer 2008;113:2478–87.
[6] Miller K, Moul JW, Gleave M, et al. Phase III, randomized, placebo-controlled study of once-daily oral zibotentan (ZD4054) in patients with non-metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis 2013;16:187–92.
[7] Aragon Pharmaceuticals, Inc. A study of apalutamide (ARN-509) in men with non-metastatic castration-resistant prostate cancer (SPARTAN). clinicaltrials.gov/ct2/show/NCT01946204.
[8] Medivation, Inc. Safety and efficacy study of enzalutamide in patients with nonmetastatic castration-resistant prostate cancer (PROSPER). clinicaltrials.gov/ct2/show/NCT02003924.
[9] Hussain M, Corn PG, Michaelson MD, et al. Phase II study of single-agent orteronel (TAK-700) in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen. Clin Cancer Res 2014;20:4218–27.
[10] Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G. Phase 2 study of the safety and antitumor activity of apalutamide (ARN-509), a potent androgen receptor antagonist, in the high-risk nonmetastatic castration-resistant prostate cancer cohort. Eur Urol 2016;70:963–70.
[11] Penson DF, Armstrong AJ, Concepcion R, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE trial. J Clin Oncol 2016;34:2098–106.
[12] Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD statement. JAMA 2015;313:1657–65.
[13] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
[14] Smith MR, Cook R, Lee KA, Nelson JB. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer 2011;117:2077–85.
[15] D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Surrogate end point for prostate cancer specific mortality in patients with nonmetastatic hormone refractory prostate cancer. J Urol 2005;173:1572–6.
[16] Metwalli AR, Rosner IL, Cullen J, et al. Elevated alkaline phosphatase velocity strongly predicts overall survival and the risk of bone metastases in castrate-resistant prostate cancer. Urol Oncol 2014;32:761–8.
[17] Lodde M, Lacombe L, Fradet Y. Salvage therapy with bicalutamide 150 mg in nonmetastatic castration-resistant prostate cancer. Urology 2010;76:1189–93.
[18] McNeel DG, Becker JT, Eickhoff JC, et al. Real-time immune monitoring to guide plasmid DNA vaccination schedule targeting prostatic acid phosphatase in patients with castration-resistant prostate cancer. Clin Cancer Res 2014;20:3692–704.
[19] Moreira DM, Howard LE, Sourbeer KN, et al. Predictors of time to metastasis in castration-resistant prostate cancer. Urology 2016;96:171–6.
[20] Madan RA, Gulley JL, Schlom J, et al. Analysis of overall survival in patients with nonmetastatic castration-resistant prostate cancer treated with vaccine, nilutamide, and combination therapy. Clin Cancer Res 2008;14:4526–31.
[21] Chu FM, Sartor O, Gomella L, et al. A randomised, double-blind study comparing the addition of bicalutamide with or without dutasteride to GnRH analogue therapy in men with non-metastatic castrate-resistant prostate cancer. Eur J Cancer 2015;51:1555–69.
[22] Hernandez RK, Cetin K, Pirolli M, et al. Estimating high-risk castration resistant prostate cancer (CRPC) using electronic health records. Can J Urol 2015;22:7858–64.
[23] Hanyok BT, Howard LE, Amling CL, et al. Is computed tomography a necessary part of a metastatic evaluation for castration-resistant

prostate cancer? Results from the Shared Equal Access Regional Cancer Hospital Database. Cancer 2016;122:222–9.

[24] Small EJ, Fontana J, Tannir N, DiPaola RS, Wilding G, Rubin M. A phase II trial of gefitinib in patients with non-metastatic hormone-refractory prostate cancer. BJU Int 2007;100:765–9.

[25] Bayer. Efficacy and safety study of BAY1841788 (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer (ARAMIS). clinicaltrials.gov/ct2/show/NCT02200614.

[26] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51.

[27] Nakabayashi M, Hayes J, Taplin ME, et al. Clinical predictors of survival in men with castration-resistant prostate cancer: evidence that Gleason score 6 cancer can evolve to lethal disease. Cancer 2013;119:2990–8.

[28] Yu EY, Miller K, Nelson J, et al. Detection of previously unidentified metastatic disease as a leading cause of screening failure in a phase III trial of zibotentan versus placebo in patients with nonmetastatic, castration resistant prostate cancer. J Urol 2012;188:103–9.

[29] Smith MR, Saad F, Oudard S, et al. Denosumab and bone metastasis-free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 2013;31:3800–6.

[30] Ogita S, Tejwani S, Heilbrun L, et al. Pilot phase II trial of bevacizumab monotherapy in nonmetastatic castrate-resistant prostate cancer. ISRN Oncol 2012;2012:242850.

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