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Randomised phase II/III study of docetaxel with or without risedronate in patients with metastatic Castration Resistant Prostate Cancer (CRPC), the Netherlands Prostate Study (NePro)

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Abstract ***Background:*** This multicentre, randomised, open label, phase II/III study aimed to investigate the potential benefit of adding risedronate (R) to docetaxel (D) in patients with metastatic Castration Resistant Prostate Cancer (CRPC).

Patients and methods: CRPC patients with bone metastasis were randomly assigned to receive D 75 mg/m^2 every 3 weeks and prednisone as first line chemotherapy, with or without R 30 mg oral once daily. The primary end-point was time to progression (TTP). A composite end-point of objective progression by RECIST criteria, PSA progression, or pain progression, whichever occurred first, was applied. The study had 80% power to detect an improvement of 30% in median TTP in the DR group (two-sided $\alpha = 0.05$).

Results: Five hundred and ninety-two men (301 D versus 291 DR) were randomised. TTP was 7.4 [D] versus 6.5 [DR] months ($p = 0.75$). PSA and pain response rates were similar, 66.3%

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[D] versus 65.9% [DR] and 27.9% [D] versus 31.2% [DR], respectively. Median overall survival (OS) was 18.4 [D] versus 19.2 [DR] months ($p = 0.33$). There were no differences in toxicity.

Conclusion: The addition of the third generation bisphosphonate, risedronate, in the setting of effective first line docetaxel based chemotherapy did not increase efficacy, as indicated by the lack of improvement in TTP, OS, PSA- and pain response.

1. Introduction

Approximately 80% of patients with advanced Castration Resistant Prostate Cancer (CRPC) develop bone metastases that often lead to severe bone pain, hypercalcaemia and skeletal-related events (SREs).[1,2] Despite the osteoblastic appearance of prostate cancer bone metastases, there is increasing evidence that most metastases are characterised by excessive activity of both osteoblasts and osteoclasts.[3–6]

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption. In CRPC zoledronic acid has shown to delay the onset and the incidence of SREs.[2,7] Zoledronic acid was approved and quickly became established as the standard of care in the United States in 2002. In several European countries the introduction of zoledronic acid took a slower pace since the delay of SREs was considered a weak primary end-point to justify expensive medication. In 2004, the treatment paradigm of metastatic CRPC changed after two landmark trials,[8,9] demonstrated for the first time a survival benefit in patients with metastatic CRPC utilising docetaxel based chemotherapy, setting a new standard of care for patients with CRPC. With the results of these studies the question arose in Europe what the role of bisphosphonates was relative to the initiation of effective chemotherapy.

An emerging body of preclinical evidence indicate that bisphosphonates also exhibit direct anti-tumour activity.[10–12] *In vitro* data have shown that bisphosphonates directly inhibit breast and prostate carcinoma cell invasion.[13,14]

However, clinical data of bisphosphonates, on anti-tumour efficacy are limited, and provide conflicting evidence. Risedronate is an oral third generation pyridinyl bisphosphonate, which reduces bone turnover and reduces osteoclast-mediated resorption.[15]

Data from animal models have shown that risedronate and docetaxel act synergistically to decrease tumour burden of established bone metastases from breast cancer cells.[16]

Since both *in vivo* and *in vitro* studies have shown synergistic action of zoledronate and taxanes,[17–19] there is a rationale to conduct this study to evaluate the efficacy and safety profile of adding risedronate to docetaxel in patients with CRPC with bone metastases.

2. Materials and methods

2.1. Patients

This randomised, open label, phase II/III trial was undertaken at 45 centres in the Netherlands and one in Norway. Patients had histologically proven prostate cancer with progression during prior castration and castration levels of testosterone. Progressive disease was defined as PSA progression documented by at least two consecutive increases relative to a reference value measured at least a week apart. The initial protocol included all patients with metastatic CRPC, but during the early phase of the trial, the eligibility criteria were modified so that only patients with bone metastases were to be included. Patients without bone metastases at randomisation were excluded from the efficacy analysis. Eligible patients were $\geqslant 18$ years, with an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$, and adequate haematological, hepatic and renal function. Patients with disease related pain at entry must have been on a stable analgesic regimen $\geqslant 1$ week prior to registration. Prior antiandrogen withdrawal followed by progression had to have taken place at least 4 weeks prior to randomisation (6 weeks for bicalutamide). LHRH analogues were continued, unless patients were surgically castrated. Any prior or concomitant use of bisphosphonates was excluded. Patients who had received radiotherapy within 4 weeks before enrolment, CNS involvement, or other serious illness (including secondary cancer) were excluded.

The study was conducted according to the Declaration of Helsinki and in compliance with Good Clinical Practice and local ethical and legal requirements. Written informed consent was obtained from all participants.

2.2. Study design

Patients were randomly assigned to receive docetaxel 75 mg/m^2 intravenously, every 3 weeks and prednisone 5 mg bid, with or without risedronate 30 mg oral od. Chemotherapy was continued until progression, unacceptable toxicity, or withdrawal of consent for a maximum of 10 cycles. In the DR group, R and prednisone was continued until progression. At the time of progression, further treatment was at the discretion of the

investigator. Upon progression patients in the D alone arm were offered R. Treatment delays of up to two weeks and up to two dose reductions were allowed.

2.3. Follow-up and outcomes

Pre-treatment evaluations included a medical history, ECOG performance status, physical examination, laboratory screening, serum PSA and testosterone concentration, chest X-ray or CT scan, abdominal CT scan and a bone scan. Pain and analgesic consumption was assessed at baseline, every three weeks, at end of study and then every month until pain progression or further anti-tumour therapy. Pain was assessed with Present Pain Intensity (PPI) scale from the McGill–Melzack questionnaire.[20] Physical examinations and blood tests, including PSA, were repeated before each infusion of docetaxel and at the end of treatment, and then every month during 6 months and every 2 months thereafter until PSA progression or further anti-tumour therapy.

Bone scans were performed before study entry, after week 30, to confirm a response, and at study discontinuation. In patients with measurable disease, CT scans were repeated at intervals of 9 weeks, when clinical progression was suspected, and at end of chemotherapy. All assessments were repeated to confirm a response at least 4 weeks later.

The primary end-point of the phase II part was the rate of objective (PSA) responses to treatment. Per an attained phase III design, at least 26 responses out of 69 evaluable patients must have been observed in the experimental arm, to continue the study as a randomised phase III study. In the phase III part the primary end-point was TTP. A composite end-point of objective progression by Response Evaluation Criteria in Solid Tumours (RECIST)[21] criteria, PSA progression, or pain progression, whichever occurred first, was applied. PSA progression was defined as an increase of $\geqslant 25\%$ over nadir PSA concentration provided that the increase in the absolute PSA value was $\geqslant 5$ ng/ml for men without PSA response, or $\geqslant 50\%$ over nadir for PSA responders. Pain progression was defined as an increase in median PPI score of $\geqslant 1$ point from the nadir, increase in analgesics class compared to nadir, or requirement for palliative radiotherapy.

Secondary end-points included PSA response, duration of PSA response and pain response. PSA response was defined by $\geqslant 50\%$ decline in serum PSA concentration compared to baseline in patients with a baseline value of $\geqslant 20$ μg/L, confirmed at least 4 weeks later. Pain response was defined as $\geqslant 2$ point reduction from baseline median PPI score, without increase in analgesic class, or a decrease in analgesic class without an increase in PPI score, maintained for 2 consecutive evaluations at least three weeks apart. Other secondary end-points were toxicity, response by RECIST and overall survival (OS). Toxicity was assessed before each treatment cycle and graded according to the National Cancer Institute Common Terminology Criteria for adverse events (version 2).

On the basis of emerging guidelines recommending the delivery of 12 weeks of treatment before adjustment of therapy for metastatic CRPC,[22] an amendment was made to the trial protocol after 115 patients had been enrolled to ensure that PSA increase only did not qualify for progression within the first four cycles of treatment.

2.4. Statistical analysis

This study consisted of a phase II and a phase III part. In the randomised phase II part, Simon's two-stage minimax design was used,[23] where the experimental treatment would be declared of insufficient activity if 25 or fewer PSA responses would be observed out of 69 evaluable patients in the experimental arm with 90% power at $\alpha = 0.1$. If this criterion was met, the study was extended into phase III, with TTP as the primary end-point.

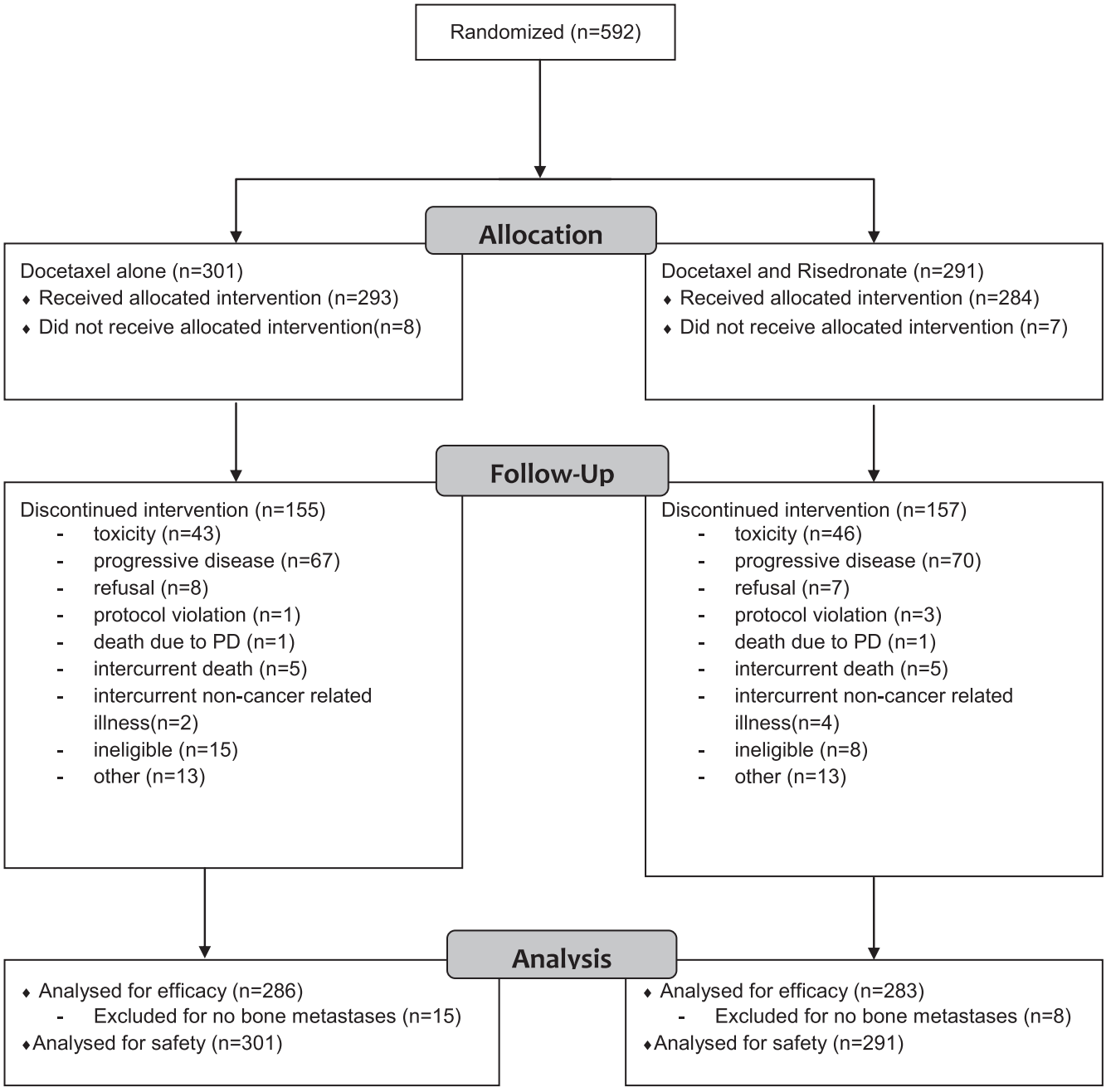
A sample size of 589 patients was required (456 events), to detect an improvement of 30% in median TTP in the DR group relative to the D group (HR = 0.77) with 80% power, with a two-sided signifi-

Table 1
Baseline characteristics.

Characteristic	Docetaxel ($N = 301$)	Docetaxel and risedronate ($N = 291$)
Age (years)		
Median [range]	69 [46–84]	68 [46–89]
WHO PS		
0 or 1	88%	89%
2	6%	5%
NA	6%	7%
PSA (ng/ml)		
Median [range]	168 [2–8046]	206 [8–11,443]
Disease location		
Bone	95%	97%
Node	42%	45%
Visceral	16%	18%
Measurable disease		
Measurable	58%	58%
Non-measurable	42%	42%
Alkaline phosphatase (U/L)		
Median [range]	195 [40–8130]	201 [45–6045]
Albumin (g/L)		
Median [range]	40 [25–50]	40 [20–50]
Baseline PPI		
0–1	76%	76%
$\geqslant 2$	24%	24%
Class of analgetics		
Non-narcotic analgetics (I + II)	62%	68%
Mild opiates (III)	8%	9%
Opiates (IV + V)	23%	18%
NA	7%	5%

PS, performance score; NA, not applicable; PSA, prostate specific antigen; PPI, present pain intensity score.

Table 2
Consort diagram.



cance level of 0.05, assuming a median TTP of 6 months in the D group. Patients were randomised between two groups (1:1 ratio), stratifying according to measurable versus non-measurable disease and median PPI at baseline ($\geqslant 2$ versus <2). TTP, OS and duration of response were analysed using the Kaplan–Meier method, with log rank comparison. Response rates were calculated as percentage of evaluable patients along with binomial confidence intervals. TTP was calculated from the date of randomisation to the date of RECIST, PSA, or pain progression, whichever occurred first. Patients without progression at death or last follow-up were censored. TTP was also calculated for the composite end-points separately, censoring patients for a particular type if they experienced another type first.

Safety analyses included all randomised men. Hazard ratios (HR) and 95% confidence intervals (95% CIs) were calculated with a Cox proportional hazards model. A separate analysis for TTP was performed excluding the group of patients with disease progression only

based on PSA increase during the first four cycles of treatment. SAS software (version 9.2) and R (version 2.14.0) were used for all analyses.

3. Results

3.1. Patients and treatment

From January 2004 to April 2010, 592 patients were enrolled and randomly assigned to one of the study arms (301 D and 291 DR). Patient demographics and baseline characteristics were well balanced between the two groups (Table 1). There were 23 patients without bone metastases enrolled before the amendment to require evidence of bone metastases. Exposure to docetaxel was similar between the two groups, with a median of nine cycles. Most discontinuations were because of end of protocol treatment (277 of 592; 47%) and were balanced between the two groups (Table 2). The median follow-up was 42 months.

3.2. Efficacy

At data cut off 1st July 2011 about 86% of the patients in both groups had investigator determined progressive disease (Table 3). Upon progression 97 patients in the D alone arm were treated with R. Median TTP (a composite end-point) was 7.4 versus 6.5 months (HR 1.04; 95% CI 087–1.24) for D and DR, respectively (Fig. 1). Furthermore, there were no differences in time to progression (TTP) by the separate end-points of pain progression, PSA progression and time to objective progression according to RECIST criteria (Fig. 2). The adjusted analysis excluding the 2 patients (both in the D group) with disease progression only based on PSA increase during the first four cycles of treatment, showed a median TTP of 7.5 versus 6.5 months for the D and DR group respectively. The Kaplan–Meier analysis showed no difference in OS. Median OS was 18.4 months for D and 19.2 months for DR (HR = 1.09; $p = 0.33$; Fig. 3). The objective response according to RECIST, pain response and/or PSA response were similar in both groups (Table 4). Eighteen patients (9 D versus 9 DR) required palliative radiotherapy within 3 months after last chemotherapy.

Table 3
Time to progression of eligible patients (excluding patients without bone metastases).

	Docetaxel ($N = 286$)	Docetaxel and risedronate ($N = 283$)
Total no. of patients with progression	248 (87%)	242 (86%)
During docetaxel	91 (37%)	106 (44%)
Within 3 months after docetaxel	67 (27%)	73 (30%)
Between 3 and 6 months after docetaxel	54 (22%)	29 (12%)
Later than 6 months after docetaxel	33 (13%)	31 (13%)
Progression, but date end of chemotherapy missing	3 (1%)	3 (1%)

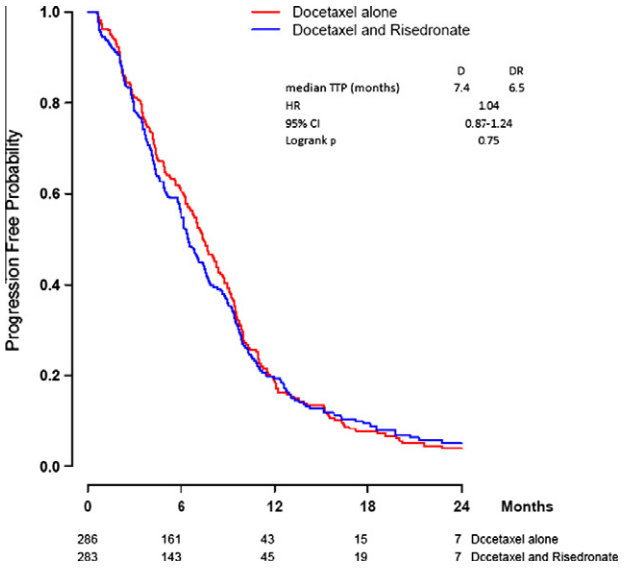


Fig. 1. Time to progression. D, docetaxel; DR, docetaxel and risedronate; TTP, time to progression; HR, hazard ratio; CI, confidence interval.

3.3. Toxicity

No significant differences were observed between the D and DR arm in the incidence grade 3/4 toxicity. The most frequent non-haematological grade 3 or higher adverse events were neurotoxicity, diarrhoea and nausea (Table 5). The information on the frequency of grade 3–4 haematological toxicity is limited since weekly blood counts were not mandatory. Neutropenic fever was observed in 5% versus 8% of the patients in the D and DR group respectively. No cases of osteonecrosis of the jaw were observed. Of the 436 deaths, 215 and 221 deaths occurred in the D group and DR group, respectively. Twelve patients (6 DR and 6 D) died within 30 days after the last cycle of docetaxel treatment. The most frequent cause of death was related to disease progression. There were 2 treatment related deaths (all in the D group) 1 due to neutropenic sepsis and 1 patient died from sepsis during docetaxel treatment but was not neutropenic. During the follow-up phase similar number of patients in the D and DR group received second line antineoplastic therapy (33% D versus 36% DR).

4. Discussion

When bisphosphonates, such as zoledronic acid, were introduced in Europe in the early 2000s, to delay SREs

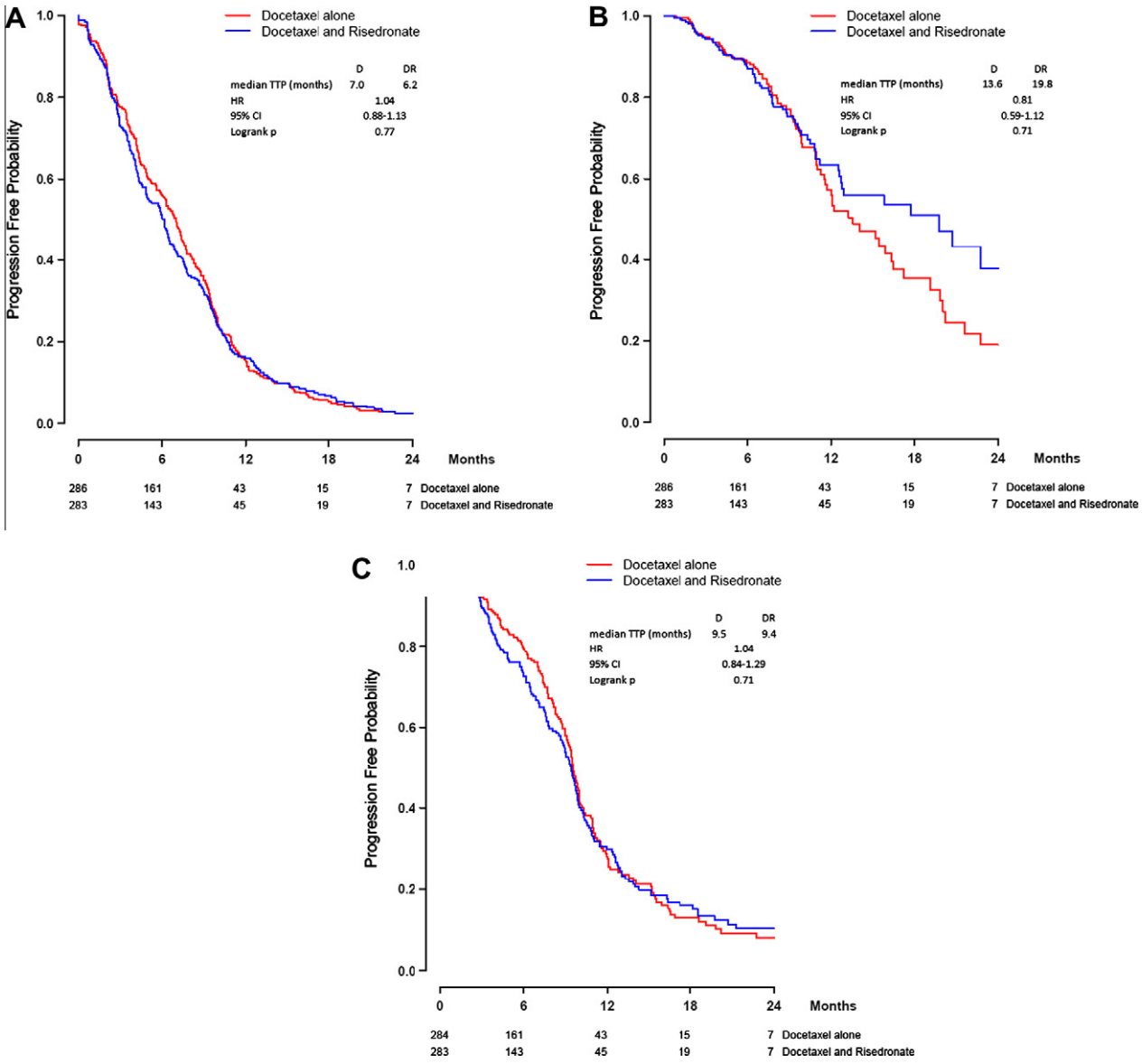


Fig. 2. Kaplan–Meier curves for separate progression end-points. (A) Pain progression; (B) progression according to RECIST; (C) PSA progression. D, docetaxel; DR, docetaxel and risedronate; TTP, time to progression; HR, Hazard ratio; CI, confidence interval.

in the setting of CRPC, the results became available of the phase III docetaxel studies that showed survival benefit.[8,9] In Europe many patients did not yet routinely receive zoledronic acid until they had reached a mCRPC status. The obvious question therefore was whether bisphosphonates would provide an additional benefit at the time of initiation of effective docetaxel chemotherapy.

There are clinical and preclinical data suggesting that bisphosphonates have osteoclast-independent effects that can be associated with an anti-tumour effect.

Data from animal models have shown that risedronate and docetaxel act synergistically to protect bone and decrease tumour burden of established bone metastases from breast cancer cells.[16] The current study is the first prospective study evaluating the effectiveness of the third generation bisphosphonate risedronate in combination with docetaxel in CRPC. Our results demonstrate that the addition of risedronate to docetaxel, although well tolerated, has no impact on disease progression and OS. We found neither reduction in pain scores with the addition of risedronate to docetaxel in our study. The median OS in this study is comparable to previous studies with docetaxel based chemotherapy.

We found a higher incidence of neutropenic fever in our study compared to previous studies.[8,9] This might be attributable to differences in patient populations. As a result of the established OS benefit and the previously reported low incidence of neutropenic fever, in recent years there may have been a shifting threshold in treating more frail patients with more advanced disease with an associated higher risk of neutropenic complications.

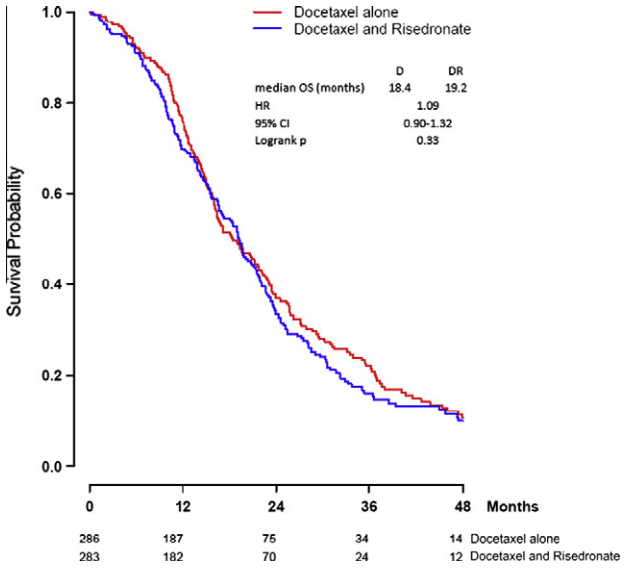


Fig. 3. Overall survival. D, docetaxel; DR, docetaxel and risedronate; OS, overall survival; HR, Hazard ratio; CI, confidence interval.

Table 4
Response rate and duration of response.

	D	DR	Hazard ratio (95% CI)
Tumour assessment			
Response rate[a]	20.8%	25.1%	
Duration of response (months)	9.4	9.5	1.05 (0.70–1.57)
PSA assessment			
Response rate[a]	66.3%	65.9%	
Duration of response (months)	8.0	8.1	0.94 (0.73–1.20)
Pain assessment			
Response rate[a]	27.9%	31.2%	
Duration of response (months)	5.5	3.4	1.27 (0.84–1.92)

D, docetaxel; DR, docetaxel and risedronate; CI, confidence interval.
[a] Determined only for subjects with at baseline measurable disease, PSA $\geqslant$20 ng/ml, or median PPI >2 on McGill–Melzack scale, respectively.

Table 5
Adverse events. D, docetaxel; DR, docetaxel and risedronate.

	D ($N = 301$)		DR ($N = 291$)	
	All grades	Grade $\geqslant$3	All grades	Grade $\geqslant$3
Any adverse event	289 (96%)	163 (54%)	284 (98%)	161 (55%)
Febrile neutropenia		15 (5%)		23 (8%)
Diarrhoea	86 (29%)	9 (3%)	96 (33%)	6 (2%)
Neurotoxicity	139 (46%)	11 (4%)	149 (51%)	10 (3%)
Nausea	101 (34%)	3 (1%)	112 (38%)	3 (1%)
Hypocalcaemia	0 (0%)	0 (0%)	3 (1%)	1 (0.3%)

The addition of risedronate to docetaxel did not increase toxic effects associated with standard docetaxel and could be safely administered.

Four parameters should be considered when selecting a bisphosphonate: efficacy, compliance, adherence and safety. The choice of risedronate in our study was for an oral rather than an intravenous route of administration. Risedronate is the most potent oral nitrogen containing bisphosphonate available and there is strong pre-clinical evidence of a possible efficacy of the drug in skeletal metastases.[15,24] Patient's adherence to drug intake was monitored at each study visit by directly interviewing patients if they had been taking their prescribed medication, both by the treating physicians and at the time of collecting the patient diaries by the oncology nurses.

A potential confounder of this trial was its open-label design. Pain scores, analgesic use and quality of life are difficult to objectively measure and may be confounded by the absence of blinding and could have potentially introduced observer and patient biases. However, since the study is entirely negative we do not believe that the results have been subjected by bias, as we found neither differences in palliative outcome measures, nor an improvement in TTP and OS by adding risedronate to docetaxel.

In patients with hormone-sensitive prostate cancer and bone metastases, sodium clodronate, an oral first generation bisphosphonate, may improve OS when given in addition to standard hormone therapy.[25] Thus far this is the only trial that has shown such benefit in patients with prostate cancer. The effects of zoledronic acid are currently being evaluated in patients with metastatic hormone-sensitive prostate cancer who are receiving androgen deprivation therapy in the Cancer and Leukaemia Group B (CALGB) 90202 trial. Results from this trial may provide further insights into the potential benefits of bisphosphonates in the setting of hormone-sensitive disease.[26]

Our study though, demonstrates that the addition of the third generation risedronate to docetaxel in patients with CRPC with bone metastases, although well tolerated, has no effect on TTP, PSA- and pain response and OS. Therefore, the addition of this bisphosphonate to docetaxel based chemotherapy cannot be recommended.

Conflict of interest statement

This work was supported by Sanofi-Aventis, Gouda, The Netherlands. Ronald de Wit has consultant/advisory relationships with Sanofi-Aventis and has received honoraria and research funding from Sanofi-Aventis. He has no employment or leadership position, stock ownership, research funding, expert testimony or other remuneration disclosures. The other authors have no conflict of interest.

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