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Randomised phase II study of siltuximab (CNTO 328), an anti-IL-6 monoclonal antibody, in combination with mitoxantrone/prednisone versus mitoxantrone/prednisone alone in metastatic castration-resistant prostate cancer

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ABSTRACT

Purpose: This open-label phase II trial assessed mitoxantrone/prednisone (M/P) with and without siltuximab (CNTO 328), an anti-interleukin-6 chimeric monoclonal antibody, for patients with metastatic castration-resistant prostate cancer who received prior docetaxel-based chemotherapy.

Methods: Part 1 assessed the safety of biweekly siltuximab 6 mg/kg plus M 12 mg/m^2 every 3 weeks and P. Part 2 assessed efficacy and safety of siltuximab plus M/P versus M/P alone. The primary end-point was progression-free survival (PFS). Progression was defined as progressive disease per Response Evaluation Criteria in Solid Tumours (RECIST), or $\geqslant$3 new skeletal lesions with clinical deterioration or without deterioration confirmed by repeated bone scan. Rising prostate-specific antigen was not considered progression.

Results: Siltuximab plus M/P was well tolerated in Part 1 (n = 9). In Part 2, 48 and 49 patients received siltuximab plus M/P or M/P alone, respectively. Enrolment was prematurely terminated by the Independent Data Monitoring Committee since an apparent imbalance in patient baseline characteristics (favoring the M/P only arm) made it unlikely that the study could achieve its primary efficacy end-point. Median PFS was 97 days with siltuximab combination and 228 days with M/P alone (hazard ratio, 1.72; P = 0.043). Use of a novel non-validated PFS definition may have contributed to this result. Abnormal laboratory

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assessments were more frequent with the combination. Infection and febrile neutropenia rates were similar between groups. Greater C-reactive protein suppression was achieved during siltuximab combination treatment compared with M/P alone ($P = 0.0003$).
Conclusion: While siltuximab plus M/P appeared well tolerated, improvement in outcomes was not demonstrated.

1. Introduction

Prostate cancer is the most common cancer diagnosed and a leading cause of cancer death among men in the United States and the European Union.[1,2] Current treatments include surgery, radiation, anti-androgen therapies and chemotherapy. While anti-androgen therapy may temporarily control prostate tumours, they inevitably develop into castration-resistant prostate cancer (CRPC).[3] Mitoxantrone combined with prednisone has been a reference cytotoxic treatment for metastatic CRPC despite the absence of survival improvement. Results from two phase III trials changed this treatment paradigm[4,5]; docetaxel combined with prednisone is now considered the first-line treatment of choice for metastatic CRPC. Future treatment strategies for CRPC may involve a combination of cytotoxic agents and targeted therapies with complementary mechanisms of action and non-overlapping toxicities.

Overproduction of interleukin-6 (IL-6) may contribute to the pathogenesis of solid tumours, including prostate cancer.[6,7] Elevated IL-6 in patients with prostate cancer is strongly associated with disease stage, presence of metastases, and poor prognosis.[8–10] Moreover, IL-6 may act as a growth factor and protect cancer cells from certain chemotherapeutic agents, including doxorubicin, etoposide and cisplatin.[11,12]

Siltuximab (CNTO 328) is an anti-IL-6 chimeric monoclonal antibody that has been shown to markedly reduce expression of IL-6 and has demonstrated inhibition of androgen resistance and androgen-independent prostate tumour growth in xenograft models.[13] In a phase 1 study of siltuximab as monotherapy prior to radical prostatectomy, analysis of gene expression patterns indicated inhibition of the IL-6- and androgen-signalling pathways.[14] In a mouse model of prostate cancer, siltuximab enhanced the antitumour activity of cytotoxic agents, including mitoxantrone. This phase II study was conducted to evaluate the safety and efficacy of siltuximab plus mitoxantrone/prednisone compared with mitoxantrone/prednisone alone in patients with metastatic CRPC. This trial was registered at www.clinicaltrials.gov as #NCT00385827.

2. Patients and methods

2.1. Eligibility criteria

Enrolled patients were men aged 18 years or older with histologically or cytologically confirmed prostate adenocarcinoma; radiologically documented metastatic disease; at least 6 weeks of treatment with one prior docetaxel-based chemotherapy for metastatic CRPC; and disease progression during or within 6 months of cessation of prior docetaxel-based chemotherapy, determined by serum prostate-specific antigen (PSA; PSA $\geqslant$5.0 ng/mL at screening) or radiologic evidence (bone scan). Additional eligibility criteria included orchiectomy or testosterone <50 ng/dL by pharmacologic/chemical castration, at least 4 weeks from prior anticancer therapy, no prior siltuximab or mitoxantrone treatment for CRPC, an Eastern Cooperative Oncology Group Performance Status $\leqslant$2, and normal organ function including left ventricular ejection fraction. Patients with known central nervous system metastases, prior recent malignancy (excluding prostate cancer), serious concurrent illness or uncontrolled medical condition, bisphosphonate therapy initiated less than 6 weeks prior to first study dose, or therapy with more than 1 line of systemic chemotherapy for metastatic CRPC were excluded.

All patients provided written informed consent prior to study participation. Institutional review boards approved the protocol and informed consent documents. The study complied with the International Conference on Harmonisation guidelines on good clinical practise, the principles of the Declaration of Helsinki and other applicable national and local laws and regulations.

2.2. Study design

This open-label, multicentre, phase II study comprised two parts. Part 1 assessed the safety of siltuximab 6 mg/kg intravenously every 2 weeks combined with mitoxantrone 12 mg/m^2 every 3 weeks. During Part 2, the efficacy and safety of siltuximab plus mitoxantrone was compared with mitoxantrone alone. All patients in both study parts received oral prednisone 5 mg twice daily continuously, starting from the first administration of mitoxantrone. The maximum treatment duration was 10 cycles for mitoxantrone, based on cumulative dose.

Patients were required to meet protocol-specified criteria prior to each scheduled dose of study medication, including appropriate haematology and blood chemistry laboratory parameters. If these criteria were not met, study drug was delayed for up to 14 days to allow for recovery from toxicities; if not resolved within 14 days, study drug was discontinued. Protocol-specified dose reductions were permitted for mitoxantrone, but not siltuximab.

2.3. Study end-points

The primary end-point was progression-free survival (PFS). Secondary end-points included safety, time to clinical deterioration, overall survival (OS), PSA response and

pharmacodynamic biomarker responses (e.g. C-reactive protein [CRP]).

2.4. Study evaluations

All patients underwent screening within 4 weeks of study drug administration, including physical examination, serum PSA, electrocardiogram, laboratory assessments and radiologic assessments. Assessments during Part 1 were conducted on the same schedule as that for the combination group in Part 2. Serum PSA was evaluated every 3 weeks, until disease progression was documented radiographically. Radiographic assessments were performed 12 weeks from treatment initiation, every 9 weeks thereafter until the end of treatment, then once every 3 months until disease progression was documented radiographically. Laboratory assessments were performed more frequently in the combination arm (every 1–2 weeks) than in the mitoxantrone/prednisone-alone arm (every 3 weeks). Pharmacodynamic samples were collected every other cycle (Cycle 1, 3, 5, etc.) prior to mitoxantrone administration (Part 2 only).

2.5. Statistical analyses

Approximately 143 patients were to be enrolled, including nine patients in Part 1 and 134 in Part 2, and randomised 1:1 to siltuximab plus mitoxantrone/prednisone and mitoxantrone/prednisone alone. If the safety profile of the combination was acceptable during Part 1 and supported by the Independent Data Monitoring Committee (IDMC), the study proceeded to Part 2. No interim analysis was planned; however, the IDMC reviewed safety data periodically during Part 2 and could make recommendations regarding the study conduct, as appropriate. The primary analysis for Part 2 was to be conducted when 112 PFS events had occurred and all ongoing patients had been treated for at least 6 months. Assuming a 70% improvement in median PFS of the combination arm over the control arm, the study had at least 80% power to achieve statistical significance at a two-sided level of 0.05, under exponential distribution for PFS.

PFS was defined as the time from treatment initiation (Part 1) or randomisation (Part 2) until first documentation of disease progression or death due to any cause, whichever was earlier. The primary PFS analysis included all randomised patients. Per protocol, this study used a novel definition of progression, which was determined as: progressive disease as per Response Evaluation Criteria in Solid Tumours (RECIST) for the evaluation of soft tissue or the presence of bone lesions ($\geqslant$3 new lesions with confirmation with second bone scan or clinical deterioration [composite of pain requiring palliative intervention, skeletal-related events, or other disease-related events requiring intervention]). Rising PSA was not considered evidence of progression. An *ad hoc* analysis of PFS using a conventional definition of progression (based on bone scan not requiring confirmation or in combination with clinical deterioration, clinical deterioration alone, or initiation of subsequent anticancer therapy) was also performed. Time to clinical deterioration was defined as the time from treatment initiation/randomisation until the first documented clinical deterioration or death due to any cause, whichever was earlier. PSA response was defined as a 50% or greater reduction in PSA below the screening value, confirmed by a second PSA value at least 3 weeks later. Time-to-event parameters were estimated using Kaplan–Meier methodology. The log-rank test was used for between-group comparisons.

Adverse events (AEs) were monitored throughout the study and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, Version 3.0. Patients assigned to siltuximab plus mitoxantrone/prednisone were assessed for AEs more frequently (every 2 weeks) than patients receiving mitoxantrone/prednisone alone (every 3 weeks) due to differences in the drug administration schedule. All patients who received at least one dose of study drug were evaluable for safety.

3. Results

3.1. Study conduct

The study was conducted in 31 sites from October 2006 to February 2008. Nine patients were treated in Part 1, and 97 patients were treated in Part 2. Study treatment was suspended for a planned safety review, and enrolment was prematurely stopped by the IDMC after their review showed an imbalance in the patient characteristics (favoring the mitoxantrone/prednisone arm) that made it very unlikely, in their view, that the study could achieve its primary efficacy end-point. The IDMC review did not disclose any safety concerns associated with siltuximab plus mitoxantrone/prednisone. Most patients did not resume CNTO 328 dosing after the IDMC review.

3.2. Patient population

In Part 2, 49 and 48 patients were assigned to mitoxantrone/prednisone and siltuximab plus mitoxantrone/prednisone, respectively (Fig. 1). Patient characteristics are summarised in Table 1. All patients discontinued siltuximab prior to completion of the maximum 1 year of treatment. Mitoxantrone discontinuations included 8 (88.9%) patients in Part 1, 31 (66.0%) in Part 2 for the mitoxantrone/prednisone arm, and 38 (82.6%) in Part 2 for the siltuximab plus mitoxantrone/prednisone arm. The most common reason why patients discontinued treatment with siltuximab or mitoxantrone was disease progression (Table 2).

3.3. Efficacy

Median PFS was 228 days with mitoxantrone/prednisone alone and 97 days with siltuximab plus mitoxantrone/prednisone (hazard ratio [HR] = 1.72, $P = 0.043$; Table 3, Fig. 2A). Median time to clinical deterioration was also longer with the mitoxantrone/prednisone arm compared with siltuximab plus mitoxantrone/prednisone, but the difference was not statistically significant (Table 3). Median OS was 394 days with mitoxantrone/prednisone and 311 days with siltuximab plus mitoxantrone/prednisone (HR = 1.45, $P = 0.226$; Fig. 2B). In Part 2, 12 of 46 patients (26.1%) in the mitoxantrone/prednisone arm and 7 of 45 patients (15.6%) in the combination arm experienced a PSA response.

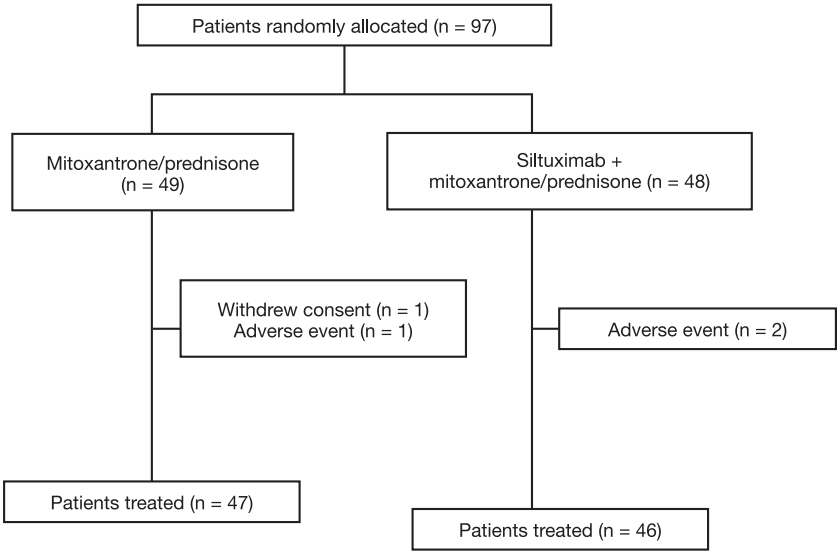


Fig. 1 – Patient disposition during Part 2 of the study.

Table 1 – Patient demographic and baseline clinical characteristics.

Characteristic	Part 1	Part 2		Total (*N* = 106)
	Siltuximab + mitoxantrone/ prednisone (*n* = 9)	Mitoxantrone/ prednisone (*n* = 49)	Siltuximab + mitoxantrone/ prednisone (*n* = 48)	
Median age (range), y	68 (57–84)	69 (51–79)	67 (49–87)	67.5 (49–87)
Race, *n* (%)				
Caucasian	8 (88.9)	45 (91.8)	46 (95.8)	99 (93.4)
Black	1 (11.1)	3 (6.1)	2 (4.2)	6 (5.7)
Other	0	1 (2.0)	0	1 (0.9)
ECOG Performance Status, *n* (%)				
0–1	9 (100)	42 (85.7)	44 (91.7)	95 (89.6)
2	0	7 (14.3)	4 (8.3)	11 (10.4)
Median total Gleason score (range)	8 (5–9)	8 (6–10)	8 (4–10)	8 (4–10)
Median PSA (range), ng/mL	96.2 (32.5–2220)	241.8 (9.1–2496)	125.6 (9.3–4896.5)	158.5 (9.1–4896.5)
Disease progression type, *n* (%)				
PSA progression	5 (55.6)	19 (38.8)	18 (37.5)	42 (39.6)
Radiologic progression	2 (22.2)	5 (10.2)	5 (10.4)	12 (11.3)
Both	2 (22.2)	25 (51.0)	25 (52.1)	52 (49.1)
Median baseline value (range)				
Haemoglobin, g/dL	11.1 (10–15.7)	11.5 (9.6–14.6)	11.9 (9–16)	
LDH, IU/L	245 (134–1851)	308 (121–897)	285 (144–3154)	
Alkaline phosphatase, IU/L	137 (57–343)	139 (55–1638)	197 (40–973)	
CRP, mg/dL	10.1 (1.8–77.2)	11.2 (1.4–147)	13.1 (0.2–363)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LDH, lactate dehydrogenase; CRP, C-reactive protein.

3.4. *Safety*

Median duration of exposure to siltuximab was 92 days (range, 1–225 days) in Part 1 and 58 days (range, 1–225 days) in Part 2. The shorter duration of siltuximab exposure during Part 2 was mainly due to the suspension of siltuximab treatment. Median duration of exposure to mitoxantrone in Part 1 was 78 days (range, 1–189 days) and in Part 2 was 90 days (range, 22–200 days) in the mitoxantrone/prednisone arm and 81.5 days (range, 1–246 days) in the siltuximab combination arm.

Table 2 – Reasons for disease progression.

Patients, *n*	Part 1	Part 2		Total (*N* = 106)
	Siltuximab + mitoxantrone/ prednisone (*n* = 9)	Mitoxantrone/ prednisone (*n* = 49)	Siltuximab + mitoxantrone/ prednisone (*n* = 48)	
Bone scan with ⩾3 new skeletal lesions + clinical deterioration[a]	1	6	6	13
Bone scan with ⩾3 new skeletal lesions without clinical deterioration[a]	0	0	2	2
Radiologic progressive disease	4	15	17	36

[a] Clinical deterioration was defined as the composite of pain requiring palliative intervention, skeletal-related events, or other disease-related events requiring intervention.

Table 3 – Summary of efficacy end-points: randomised patients in Part 2.

Efficacy parameter, median (95% CI), d	Mitoxantrone/ prednisone (*n* = 49)	Siltuximab + mitoxantrone/ prednisone (*n* = 48)	HR (95% CI)	*P*-value
Progression-free survival				
Primary analysis[a]	228 (155–303)	97 (84–179)	1.72 (1.01–2.93)	0.043
Ad hoc analysis[b]	128 (82–190)	87 (80–130)	1.33 (0.85–2.10)	0.215
Time to clinical deterioration	298 (128–342)	183 (142–274)	1.23 (0.69–2.21)	0.482
Overall survival	394 (311–438)	311 (226–NE)	1.45 (0.79–2.68)	0.226

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable.

[a] Progression was defined as the following: soft tissue, as per Response Evaluation Criteria in Solid Tumours (RECIST); bone, ⩾3 new lesions with confirmation with second bone scan or clinical deterioration.

[b] Definition of progression was based on bone scan not requiring a confirmation or in combination with clinical deterioration, clinical deterioration alone or initiation of subsequent anticancer therapy.

The combination group had higher percentages of patients with any AE, grade ⩾3 AEs and discontinuation of mitoxantrone due to AEs (Table 4). In Part 1, 2 (22.2%) patients experienced more than 2 siltuximab dose delays. In Part 2, the number of patients with dose delays was similar in both treatment arms. However, more patients in the combination arm had mitoxantrone dose reductions compared with the mitoxantrone/prednisone-alone arm, even though both groups received the same median dose intensity of mitoxantrone (11.8 mg/m^2/cycle). AEs leading to discontinuation were mostly haematologic and not associated with clinically relevant outcomes such as infection or febrile neutropenia.

More deaths occurred with siltuximab plus mitoxantrone/prednisone (*n* = 9) than with mitoxantrone/prednisone alone (*n* = 4); however, all but three deaths in the combination arm were due to disease progression. One patient with grade 4 neutropenia received siltuximab, then developed pneumonia and septic shock and died of cardiac failure within 30 days of the last siltuximab dose. Other AE-related deaths were due to cerebral haemorrhage and general physical health deterioration; both were beyond 30 days of the last siltuximab dose.

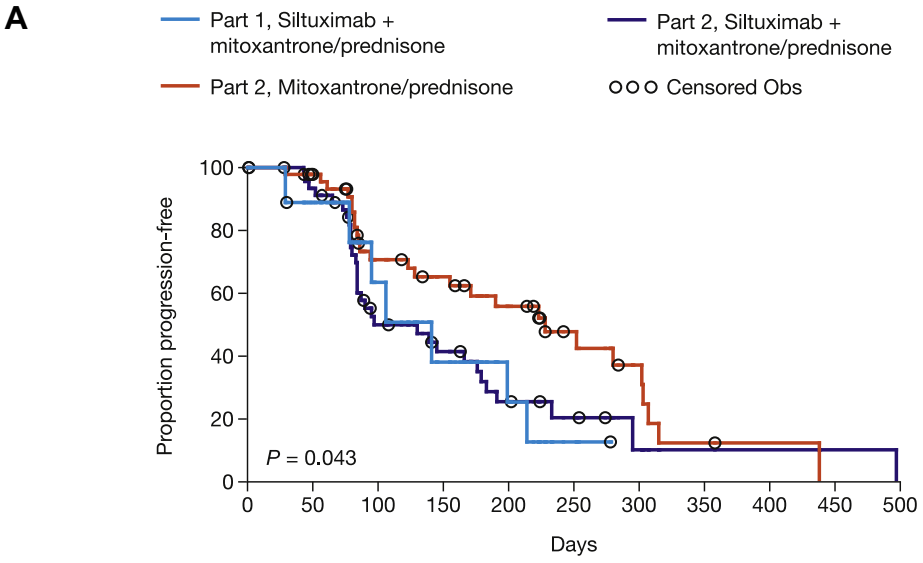
Part 1 demonstrated acceptable safety of siltuximab plus mitoxantrone/prednisone (Table 5), allowing for continuation with Part 2. In Part 2, grade ⩾3 AEs occurred more frequently with siltuximab plus mitoxantrone/prednisone than with mitoxantrone/prednisone alone (Table 5). Between-group differences were most apparent for haematologic AEs, likely reflecting the different schedule of laboratory events for the two study arms. Despite higher rates of neutropenia and leukopaenia with combination treatment, rates of infection (4.3% for combination versus 6.4% with mitoxantrone/prednisone alone) and febrile neutropenia (2.2% versus 0%, respectively) were similar between treatment groups.

3.5. *Pharmacodynamic biomarker studies*

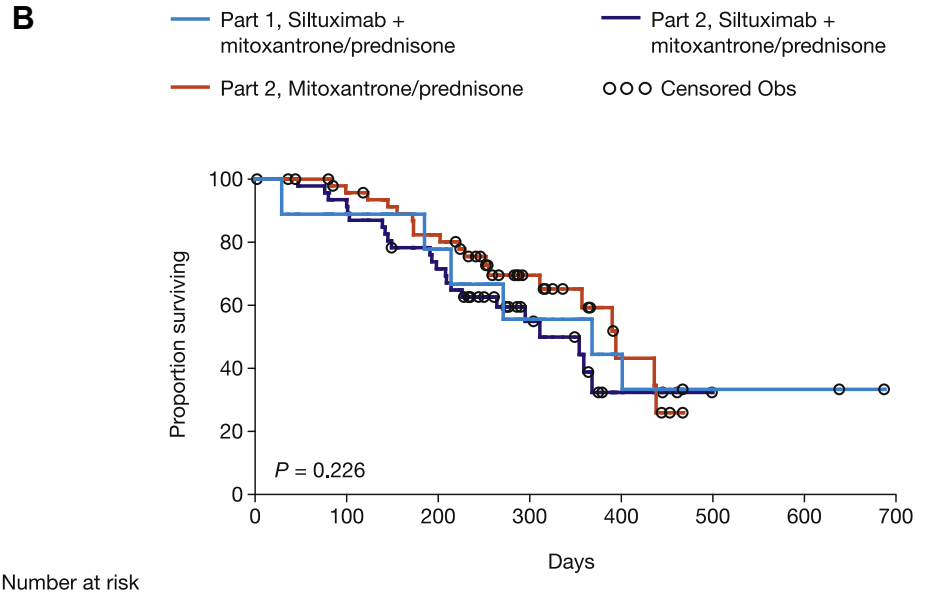
In Parts 1 and 2, CRP levels decreased after siltuximab administration and remained below baseline at all time points. Greater CRP suppression was observed during treatment with siltuximab plus mitoxantrone/prednisone than with mitoxantrone/prednisone alone (*P* = 0.0003; Fig. 3).

4. Discussion

Despite evidence of an additive effect in a preclinical study, the combination of siltuximab and mitoxantrone/prednisone did not demonstrate improvement in clinical outcomes over mitoxantrone/prednisone alone in metastatic CRPC. There are several possible explanations. First, the PFS observed with mitoxantrone/prednisone alone markedly exceeded historical



Number at risk						
Part 1, Siltuximab + mitoxantrone/ prednisone	9	6	3	1	0	0
Part 2, Mitoxantrone/ prednisone	49	28	18	8	1	0
Part 2, Siltuximab + mitoxantrone/ prednisone	48	22	10	3	1	1



Number at risk								
Part 1, Siltuximab + mitoxantrone/ prednisone	9	8	8	5	5	3	2	1
Part 2, Mitoxantrone/ prednisone	49	45	37	20	9	1	0	0
Part 2, Siltuximab + mitoxantrone/ prednisone	48	43	35	19	6	2	0	0

Fig. 2 – Kaplan–Meier estimates of (A) progression-free survival and (B) overall survival.

expectations,[15–21] likely because of the novel and invalidated definition of progression used. This definition of progression led to premature censoring in an unacceptably high proportion of patients due to unrecorded clinical progression (e.g. asymptomatic new bone metastases or rising PSA), which was biased towards the control arm (i.e. 23 patients in the control arm

Table 4 – Treatment-emergent adverse events by dose group: treated patients in Part 1 and 2.

Patients, *n* (%)	Part 1	Part 2	
	Siltuximab + mitoxantrone/ prednisone (*n* = 9)	Mitoxantrone/ prednisone (*n* = 47)	Siltuximab + mitoxantrone/ prednisone (*n* = 46)
Any AE	9 (100)	45 (95.7)	46 (100)
Any grade ⩾3 AE	9 (100)	20 (42.6)	35 (76.1)
Any serious AE	5 (55.6)	18 (38.3)	18 (39.1)
Any serious grade ⩾3 AE	5 (55.6)	14 (29.8)	16 (34.8)
Permanently discontinued siltuximab due to AE	3 (33.3)	N/A	12 (26.1)
Permanently discontinued mitoxantrone due to AE	3 (33.3)	7 (14.9)[b]	15 (32.6)[b]
Dose delay of siltuximab	2 (22.2)	N/A	11 (23.9)
Dose delay or reduction of mitoxantrone	2 (22.2)	13 (27.7)	12 (26.1)
Died due to AE[a]	3 (33.3)	4 (8.5)	9 (19.6)
Died due to PD	2	4	6

Abbreviations: AE, adverse event; N/A, not applicable; PD, progressive disease.

[a] Deaths include AEs due to progressive disease.

[b] One patient in the mitoxantrone/prednisone arm and three patients in the siltuximab plus mitoxantrone/prednisone arm had disease progression but were reported to have been discontinued from the study agent due to an AE.

Table 5 – Treatment-emergent grade ⩾ 3 adverse events occurring in ⩾ 2 patients in any treatment group.

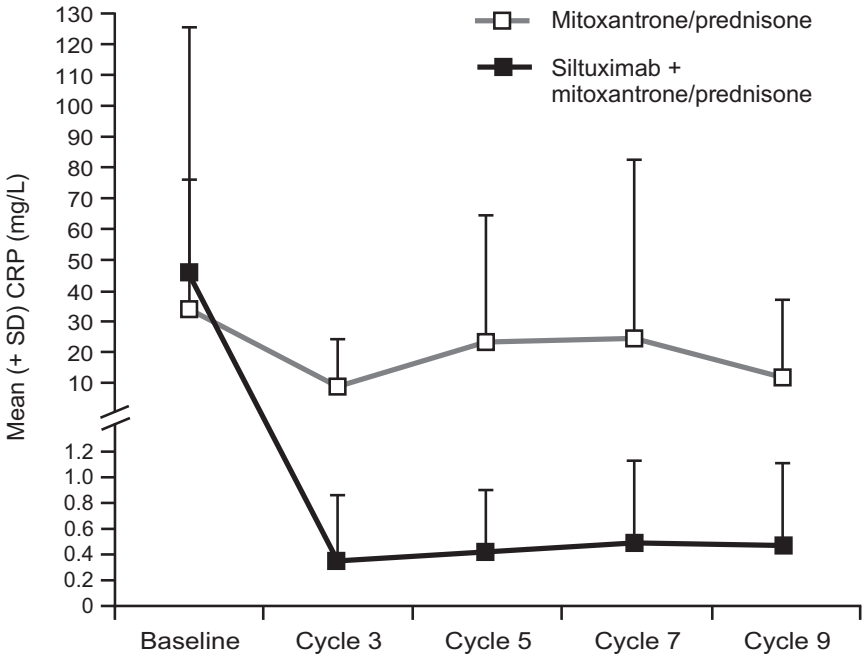
Adverse event, n (%)	Part 1	Part 2	
	Siltuximab + mitoxantrone/ prednisone (*n* = 9)	Mitoxantrone/ prednisone (*n* = 47)	Siltuximab + mitoxantrone/ prednisone (*n* = 46)
Haematologic			
Neutropenia	9 (100)	5 (10.6)	24 (52.2)[a]
Leukopaenia	6 (66.7)	0	6 (13.0)
Lymphopenia	0	2 (4.3)	1 (2.2)
Anaemia	0	1 (2.1)	3 (6.5)
Thrombocytopenia	0	1 (2.1)	3 (6.5)
Non-haematologic			
Hypotension	2 (22.2)	0	0
Fatigue	1 (11.1)	1 (2.1)	3 (6.5)
Asthaenia	1 (11.1)	0	2 (4.3)
Back pain	0	3 (6.4)	2 (4.3)
Bone pain	0	2 (4.3)	2 (4.3)
Pulmonary embolism	0	3 (6.4)	0
Urinary tract infection	0	2 (4.3)	0
Spinal cord compression	0	0	2 (4.3)

[a] Differences between groups in Part 2 were likely due to more frequent laboratory assessments in the combination arm than in the mitoxantrone/prednisone-only arm.

versus 16 patients in the test arm). Also, the IDMC cited imbalances in patient characteristics in their decision to prematurely terminate enrolment. Because a high rate of censoring could have biased the study results, an *ad hoc* analysis of PFS was performed using a more conventional definition of progression and showed no significant between-group difference (siltuximab and mitoxantrone/prednisone PFS = 87 days versus mitoxantrone/prednisone PFS = 128 days, $P = 0.215$; Table 3).

In addition, dosing and dose schedule of siltuximab may have biased the study towards a null result. Siltuximab dosing was not maintained, owing to the suspension of study accrual during the IDMC review. Although the suspension was short-lived, most patients never resumed siltuximab dosing. Moreover, the dose schedule of siltuximab (6 mg/kg every 2 weeks) may have contributed to the lack of improved efficacy, as this dose would not be expected to provide continuous pharmacodynamic effect.[22]

Siltuximab plus mitoxantrone/prednisone appeared to be tolerable, despite a higher frequency of AEs and treatment discontinuations compared with mitoxantrone/prednisone alone. Mitoxantrone dosing was asymmetric, since more patients discontinued the combination. This mainly reflects the increased frequency of discontinuation for AEs with the combination, mostly haematologic, although a corresponding



Mitoxantrone/prednisone (SD)	33.92 (42.03)	8.79 (15.19)	23.25 (41.13)	24.43 (58.09)	11.76 (25.03)
Siltuximab + mitoxantrone/prednisone (SD)	45.89 (79.62)	0.35 (0.51)	0.42 (0.49)	0.49 (0.65)	0.47 (0.65)

Fig. 3 – Summary of CRP (mg/L) levels at baseline and post-treatment. *Abbreviations:* CRP, C-reactive protein; SD, standard deviation.

increase in clinically significant AEs (e.g. infection or bleeding complications) was not seen. Ascertainment bias may have played a role in these treatment decisions and the higher incidence of observed AEs, since patients receiving siltuximab plus mitoxantrone/prednisone routinely had additional mid-cycle blood counts and more frequent AE evaluations due to the asymmetric dosing schedule. In particular, while more frequent cytopenias were reported, the incidence of infection was not increased in the combination arm.

The study design of clinical trials in metastatic CRPC is a continuing problem that needs to be addressed. For example, PFS as an appropriate end-point in CRPC trials is questionable.[23,24] Historically, assessment of PFS has been difficult, and it is unclear whether PFS is a valid surrogate for survival in this population. The Prostate Cancer Clinical Trials Working Group noted that conventional PFS analyses may lead to difficulties in interpretation,[25] and recently recommended an interval-censored approach in which all PFS assessments are performed at the same time points. Improved intermediate end-points that robustly associate with OS are urgently needed to accelerate anticancer drug development for advanced prostate cancer, particularly given the recent trials showing a survival benefit.[26–28] Studies evaluating circulating tumour cells (CTC) as an approvable primary end-point for registration studies are ongoing, based on clinical data demonstrating that CTC counts are independently prognostic in this disease, with post-treatment falls associating with improved OS.[29]

In conclusion, despite preclinical evidence of an additive effect, siltuximab plus mitoxantrone/prednisone did not demonstrate improvement in clinical outcomes over mitoxantrone/prednisone alone in patients with metastatic CRPC. While the combination appeared tolerable, no further clinical evaluation of this regimen in CRPC is planned. Because of the multiple biases in study design and execution that may have contributed to the results, the study is best viewed as inconclusive. Improved patient selection and stratification biomarkers, as well as robust intermediate end-points, are urgently needed to decrease the risk of early termination of randomised trials in patients with CRPC.

Role of the funding source

As authors of the manuscript, employees of the study sponsor participated with the external authors in the study conception and design; collection, analysis, and interpretation of data; writing and editing of the manuscript and the decision to submit the manuscript for publication.

Conflict of interest statement

K. Fizazi has served as a non-compensated consultant/advisor for Centocor, Inc. J.S. De Bono has served as a consultant/advisor and received honoraria from Johnson & Johnson. A. Heidenreich has served as a consultant/advisor for Amgen, Novartis, and Sanofi-Aventis. Ming Qi, R. Bande-

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