Pre-clinical and clinical evaluation of estramustine, docetaxel and thalidomide combination in androgen–independent prostate cancer

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OBJECTIVE

To evaluate the combination of docetaxel plus estramustine (which prolongs survival in patients with androgen-independent prostate cancer, AIPC), and thalidomide (that also adds to docetaxel activity), both pre-clinically and clinically in AIPC.

PATIENTS, MATERIALS AND METHODS

In the pre-clinical evaluation we injected PC3 cells subcutaneously into severely combined immunodeficient mice and started treatment after the tumour volume reached 50 mm³. We also evaluated the combination using luciferase-labelled PC3M-luc-C6 cells in nude mice. We enrolled 20 patients with metastatic progressive AIPC into a phase II clinical trial to evaluate this combination. Docetaxel (30 mg/m²) was administered every week, for 3 of 4 weeks. The dose of thalidomide was 200 mg/day and estramustine was given three times a day at 1, 2, 3, 8, 9, 10, 15, 16 and 17 days.

RESULTS

In the mice, thalidomide with docetaxel plus estramustine reduced tumour volume by 88% at 17 days vs the control treatment (p = 0.001). The combination of docetaxel, estramustine and thalidomide nearly eradicated the signal from the luciferase-expressing PC3M cells in the metastasis model. Clinically, the progression-free time was 7.2 months with this combination; 18 of 20 patients had a decline of half or more in prostate-specific antigen level and two of 10 patients with soft-tissue lesions had a partial response on computed tomography. There were 24 grade 3 and two grade 4 complications associated with this combination. There was a statistically significant association between overall survival and the CYP1B1*3 genotype (P = 0.013).

CONCLUSION

Docetaxel-based chemotherapy is now regarded as a standard regimen for metastatic AIPC. The combination of estramustine, docetaxel and thalidomide is an advantageous treatment in pre-clinical models of prostate cancer and is a safe, tolerable and active regimen in patients with AIPC.

KEYWORDS
cancer, oncology, taxanes, drug development, clinical, phase II, xenografts, PC3 cells, pharmacogenetics, cytochrome P450, CYP1B1

INTRODUCTION

Although mortality due to metastatic prostate cancer has declined recently, this disease remains one of the leading causes of cancer death in men in the USA, with an estimated 27 350 deaths projected in 2006 [1]. Prostate cancer is extremely difficult to treat, with very few antineoplastic agents with meaningful activity after the development of androgen-independent prostate cancer (AIPC, which is also referred to as hormone-refractory disease). However, treatment options for AIPC have increased considerably over the last decade, aided by the use of serum PSA as a biomarker for tumour burden [2,3].

In the present study we evaluated the effectiveness of combined therapy with estramustine, docetaxel and thalidomide in AIPC. Estramustine, a combination of oestradiol and nonnitrogen mustard, was the first agent approved for the treatment of AIPC. Activity was reported when estramustine was combined with other chemotherapeutic agents such as etoposide, vinblastine or paclitaxel [4–6]. Docetaxel is a semi-synthetic taxane analogue isolated from the European yew (Taxus baccata), which has confirmed activity as a single agent in the treatment of metastatic prostate cancer [7,8]. Kreis et al. [9] were the first to describe synergistic activity between estramustine and docetaxel in human prostate cancer cell lines. As a result of this observation, several studies were reported using this combination. Petrylak et al. [10] performed a phase I trial of estramustine at a fixed dose of 280 mg given three times daily on days 1–5, and with escalating doses of docetaxel from 40 mg/m² to 80 mg/m² given on day 2; the treatment was repeated every 21 days. Patients were stratified into extensively pre-treated and minimally pre-treated groups; 70% of the latter and half the former group had a decrease in PSA level by half or more. A Southwestern Oncology Group/Intergroup trial accrued 770 patients, of whom 674 were eligible and randomized to receive...
Thalidomide was marketed in Europe as a non-barbiturate sedative, but was subsequently withdrawn 30 years ago because of its teratogenic effects [14]. In recent years it was shown that thalidomide inhibits angiogenesis in pre-clinical models [15–17]. Following these pre-clinical observations, we conducted a phase II clinical trial of this agent in patients with AIPC. Using 200 mg/day of thalidomide, 18% of patients (50 for the low-dose arm) had a PSA decline of half or more [18]. Subsequently, we evaluated the combination of thalidomide plus docetaxel in pre-clinical models for prostate cancer (Fig. 1 shows the PC3 xenograft [14] evaluation of docetaxel plus thalidomide) [19,20]. After showing clear additive activity of this combination in the laboratory, we then conducted a randomized trial in 75 chemotherapy-naïve patients with AIPC, comparing docetaxel with docetaxel plus thalidomide [21]; the percentage of patients with a decline of half or more in PSA level was higher after treatment with the combination (53% vs 37%). There was also a survival advantage in the combination group (median 14.7 vs 28.9 months, P = 0.041) [22]. Thus, thalidomide has emerged as an angiogenesis inhibitor with confirmed clinical efficacy in AIPC [20,23–26].

Docetaxel plus estramustine prolongs survival in patients with AIPC, yet the median survival was <1.5 years. Thalidomide also enhances docetaxel activity in prostate cancer [22]. Thus, we evaluated the combination of estramustine, docetaxel and thalidomide both pre-clinically and then clinically in this disease. This combination is attractive due to differences in the mechanisms of action of these agents, and the lack of significant bone-marrow toxicity with either estramustine or thalidomide. The primary objective of the study in mice was to determine whether the combination of estramustine, docetaxel and thalidomide was active in pre-clinical models of prostate cancer. The primary objective of the human trial was to determine whether this combination resulted in a sufficiently high proportion of patients with a PSA response to warrant further investigation in metastatic prostate cancer.

**PATIENTS, MATERIALS AND METHODS**

For the human prostate cancer xenograft model in mice, all experiments were done in accordance with institutional guidelines for animal welfare. PC3 cells, an AIPC (5 × 10⁶) (ATCC, Manassas, VA, USA) were injected s.c. into 5–6-week-old male severely combined immunodeficient mice. For the thalidomide (Celgene, Inc., Summit, NJ, USA) and docetaxel (Aventis Pharmaceutical, Bridgewater, NJ, USA) study, mice were randomized into four groups of five each) after the tumour volume reached 50 mm³. For the thalidomide, docetaxel and estramustine (Pharmacia, Kalamazoo, MI, USA) study, mice were randomized into four groups of 10 each) when the tumour volume reached 200–300 mm³. The mice received the vehicle (0.5% carboxymethylcellulose), thalidomide (100 mg/kg) or thalidomide plus estramustine (4 mg/kg) for 5 days by i.p. injection. Docetaxel (10 mg/kg) was administered as an i.v. bolus on day 2 and the treatment lasted for 17 days.

For the clinical trial, all patients had a histopathological diagnosis of adenocarcinoma of the prostate; they were required to have metastatic, progressive AIPC either while receiving a GnRH agonist or after surgical castration. Progressive disease (PD) was defined by persistently increasing PSA levels, the development of new metastatic lesions on a bone scan, or progression of soft-tissue disease (either by the size of the lesion or development of new areas of malignant disease). Patients not treated by surgical castration were required to have a serum testosterone level of ≥50 ng/mL and continue their GnRH agonist. Patients receiving an antiandrogen agent were required to discontinue the receptor antagonist and have an increasing PSA level. Patients who had received previous chemotherapy were excluded. An Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 was required. Patients were required to have normal organ and bone marrow function, defined as follows: absolute neutrophil count ≥1500/mL; platelets ≥100 000/mL; haemoglobin ≥7.5 g/dL (no transfusions within the previous 2 weeks), aspartate aminotransferase and alanine transaminase ≥2.5 times the institutional upper limit of normal; creatinine ≥1.5 mg/dL. Patients were excluded if they had known CNS metastases, anti-retroviral therapy for HIV, New York Heart Association class II–IV congestive heart failure.

**FIG. 1. Thalidomide, docetaxel and the combined treatment of thalidomide/docetaxel inhibited PC3 xenograft tumour growth.**
failure, a history of myocardial infarction within the past 6 months or uncontrolled angina pectoris. Patients were also excluded if they had another active malignancy within the past 2 years, except for non-melanoma skin cancer or superficial bladder carcinoma, had grade 2 peripheral neuropathy, and had a history of transient ischaemic attacks or cerebrovascular accident within the past 2 years. These studies were approved by the National Cancer Institute Institutional Review Board and all patients provided written informed consent before enrolment.

The treatment of the patients comprised docetaxel (30 mg/m\(^2\) i.v. over 30 min) every week for three consecutive weeks (day 1, 8, 15), followed by a 1-week rest period (28-day cycle). Thalidomide (200 mg) was given orally each day at bedtime. Estramustine was given three times a day on three consecutive days of the first 3 weeks of each 4-week cycle (days 1, 2, 3, 8, 9, 10, 15, 16 and 17). On the first of the 3 days of each week, each dose was 420 mg and on the subsequent 2 days it was 280 mg. All patients received 4 mg of oral dexamethasone, 12 h before, 1 h before and 12 h after docetaxel treatment. Low-molecular weight heparin (enoxaparin) was administered to patients at 1 mg/kg/day (rounded to the nearest 20 mg increment) because of the high incidence of thromboembolic events noted with the combination of docetaxel plus thalidomide.

All patients had CT of the chest, abdomen and pelvis, and whole-body bone scans within 4 weeks before enrolment. Patients were seen every 4 weeks and evaluated serologically at that time. The PSA level was measured every 4 weeks. Radiographic assessments of disease, including CT and bone scan, were done every 8 weeks for the first 2 months, then every 3 months unless clinically indicated. Patients with stable disease or objective responses continued to receive treatment.

The National Cancer Institute Common Toxicity Criteria (version 2.0) was used to grade treatment-related toxicity. Response and progression were evaluated by the Response Evaluation Criteria in Solid Tumors Committee system [28]. Measurable disease was defined as lesions that were ≥20 mm in largest dimension on CT, MRI or X-ray, or ≥10 mm on spiral CT. A complete response (CR) was defined as the disappearance of all target lesions; a partial response (PR) was defined as a ≥30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. PD was defined as a ≥20% increase in the sum of the LD of target lesions taking as reference the smallest sum LD. Stable disease was defined as neither sufficient shrinkage for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum LD since the treatment started. The time to progression was defined as the interval between the date of the start of treatment and the date of disease progression.

Biochemical response criteria were applied as outlined by the PSA consensus criteria reported by Bubley et al. [29]. PSA values indicating response or progression required confirmation by a second value 4 weeks later. If there was disease progression, two documented PSA level were required in the absence of new or expanding lesions on radiographic studies. For patients with a decrease of half or more in PSA level, progression by PSA criteria was defined as a 50% increase in PSA over the nadir, confirmed by a second reading. For patients who had no decline by at least half in PSA level, progression by PSA criteria was defined as a 25% increase over nadir confirmed by a second reading. For patients who had no decrease in PSA, a 25% increase over baseline was defined as progression if confirmed by a second reading.

Docetaxel was withheld if there was dose-limiting toxicity, defined as grade 4 haematological toxicity or grade 3 non-haematological toxicity. Patients had an absolute neutrophil count of ≥1500 cells/mm\(^3\), a platelet count of ≥75000 cells/mm\(^3\), a haemoglobin level of ≥7.5 g/dL and resolution of any non-haematological toxicity to-grade 1 or baseline before initiating another treatment cycle of docetaxel. For grade 3 constipation or fatigue, treatment was resumed with a 25% dose reduction after resolution of toxicity to ≤ grade 2. The occurrence of dose-limiting toxicity or a delay of ≥2 weeks in initiating a new treatment cycle for the recovery of docetaxel-induced toxicity would result in a docetaxel dose reduction of 25%. For thalidomide, the patients with any grade 3 or 4 non-haematological toxicity felt to be caused by thalidomide had their thalidomide withheld. Thalidomide was resumed with a dose reduction of ≥50 mg when toxicity returned to the patient’s baseline or was ≤ grade 1. Patients who developed ≥ grade 2 peripheral neuropathy had their thalidomide dose withheld until toxicity resolved to ≤ grade 1, at which point thalidomide was restarted at half the dose. The dose of estramustine was reduced to a third for the patients who had persistent nausea unresponsive to anti-emetic therapy. As this trial allowed patients to receive treatment indefinitely, patients might have the doses of any or all drugs temporarily withheld, and potentially resume treatment as long as they do not fulfil the off-study criteria.

For the genotype analysis, genomic DNA was extracted from buffy-coat cells using the QiA blood extraction kit (Qiagen, Valencia, CA, USA). For analysis of CYP1B1 genotypes, a 50-µL reaction was prepared for PCR amplification using the following PCR primer combination: 5′-GGTATCCGTGTTGCAAGACTCG-3′ and 5′-TGGACAGCACATCAAGAGGCT-3′. The reaction consisted of 1× PCR buffer, 2 mm of each of the four dNTPs, 1.5 mm magnesium chloride, and 1 unit of platinum Taq DNA polymerase (Invitrogen, Carlsbad, CA, USA). PCR conditions were as follows: 94°C for 5 min, followed by 40 cycles of 94°C for 30 s, 68°C for 30 s, and 72°C for 30 s, with a final 7-min cycle at 72°C. Direct nucleotide sequencing PCR was conducted using the Big Dye Terminator Cycle Sequencing Ready Reaction Kit V3.1 (Applied Biosystems, Foster City, CA, USA) using the following sequencing primers: 5′-TGCTGTCATATCCTCCTAGCC-3′ and 3′-GGTACGGCAAGTAGGGAAGCT-5′. Sequences were generated on an ABI Prism 310 Genetic Analyser. All genotypes are referred to by the nomenclature set forth by the Human Cytochrome P450 Nomenclature Committee (http://www.imm.ki.se/CYPalleles/cyp1b1.htm).

Tumour sizes in control and treated groups at 17 weeks in the pre-clinical experiments were compared using an exact Wilcoxon rank-sum test; all P values are two-tailed and were adjusted for multiple comparisons, within each of two experiments, using the Hochberg method [30].

The clinical trial was designed using a two-stage MinMax design [31] intending to exclude a 65% proportion of patients with a PSA response (p0 = 0.65) and targeting an 80% proportion of patients with a PSA response (p1 = 0.80) (using α = 0.10 and
β = 0.10 as allowable errors). The probability of progression-free survival and survival as a function of time was estimated using the Kaplan–Meier method, and the statistical significance of the difference between survival curves reported as a two-tailed P value, determined by an exact log-rank test.

RESULTS

In the human prostate cancer xenograft model, when the initial tumour volume was ≈50 mm$^3$ and treatment was started, thalidomide significantly inhibited PC3 xenograft growth, with tumours a mean of 46% smaller than those of vehicle controls at day 17 ($P = 0.032$ after adjustment, Fig. 1). Docetaxel treatment caused a delay in initial tumour growth, followed by tumour shrinkage at day 9. When tumour volumes at day 17 in mice treated with docetaxel were compared to those at the same time in the control mice, docetaxel treatment resulted in a 93% reduction ($P = 0.024$). The combination of thalidomide and docetaxel induced tumour shrinkage sooner than docetaxel alone, and decreased tumour volume slightly further, resulting in tumours that were a mean of 97% smaller than those of the controls on day 17 ($P = 0.032$).

Treatment with thalidomide at a later stage of tumour growth (initial tumour volume ≈250 mm$^3$) inhibited tumour growth by 23% at day 17 versus controls (Fig. 2). Treatment with docetaxel plus estramustine reduced the tumour volume by 77% at day 17 versus vehicle-treated controls ($P = 0.003$). The combination of all three agents resulted in a somewhat greater reduction in tumour volume (88%) than in controls ($P = 0.001$).

In the human prostate cancer metastasis model, treatments were initiated when bioluminescent signals indicated metastases (signal $= 10^7$). The metastases in control-treated mice continued to grow, as shown by the increasing signal with time (Fig. 3A). Treatment with docetaxel alone or docetaxel and estramustine (Fig. 3B) failed to inhibit the growth of metastases, as did thalidomide or estramustine as a single-agent (data not shown). However, the combination of docetaxel and thalidomide reduced the intensity of the signal by 62.5%, whereas the combination of all three agents nearly eradicated the signal, with a reduction of 99.8% (Fig. 3C).

In the clinical trial, 20 men (median age 70 years, range 52–77) with AIPC were enrolled; Table 1 shows the demographic factors. Sixteen patients were Caucasian; the ECOG performance status was either 1 or 2 for all patients. The median Gleason score was 8 and the median baseline PSA was 138 ng/mL. All patients were either maintained on medical castration (16) or had had a bilateral orchidectomy (four). None of the patients had received previous chemotherapy, but 16 had received an antiandrogen (bicalutamide, nilutamide or flutamide) and an additional five had received a secondary hormonal manipulation (e.g. ketoconazole, megace, oestrogen). Three men had received a bisphosphonate before enrolment, to prevent bone metastasis.
The mean (SD, range) number of treatment cycles (monthly) was 7.8 (4.7, 2–20); two men were still receiving therapy at +25 and +17 months. The median potential follow-up was 19.5 months; 16 of the patients remain alive. The median progression-free survival was 7.2 months, and the 6- and 12-month progression-free probabilities were 69% and 28%; Fig. 4 shows the Kaplan–Meier curve for progression-free survival. Of the 20 patients, 18 (90%) had a decline of half or more in PSA level with estramustine, docetaxel and thalidomide (Table 1). Most of these declines were rapid and sustained. Only two men did not have a halving of PSA level; one of them had a PSA decline of 30% and the other had a rapid increase in PSA level and was removed from active treatment after three cycles. Ten of the 20 patients had soft-tissue lesions shown by CT; of these 10, two had a PR. Eighteen patients had bone scan evidence of metastatic disease; two of them had improvements in their bone scans while on therapy, concurrent with declines in PSA level. Of the 20 patients, 17 required dose reductions of at least one of the three agents. There were 24 grade 3 complications and two grade 4 adverse events among 13 of the 20 patients (65%) enrolled (Table 2). There were minor adverse events (grade 1 and 2) consistent with the anticancer agents (all three agents) in most patients (e.g. nail changes, nausea, sedation, constipation, alopecia). In general, the combined regimen of all three agents was well tolerated only after dose reduction of one or more of the agents. Although most patients required dose reduction, we identified no pattern of adverse events/toxicity that appeared to result from synergy among these three agents. All 20 patients were available for the genetic analysis of CYP1B1. The observed genotype frequencies were in Hardy–Weinberg equilibrium (P > 0.371), and similar to a those in a previously published study in the Caucasian population [32]. There was a statistically significant association between overall survival and the CYP1B1*3 genotype (P = 0.013). Patients homozygous for the CYP1B1*3 genotype had a significantly lower median overall survival (15.7 months; Fig. 5A) and 18-month probability of survival (50%)
than the group of patients homozygous or heterozygous for the CYP1B1*1 allele (93% 18-month probability). Genotypes were grouped based on previous observations in patients treated with docetaxel alone (data not shown). Although the association between the CYP1B1*4 allele and overall survival was not statistically significant (P = 0.18), notably all patients heterozygous for the CYP1B1*4 allele are currently surviving (Fig. 5B).

DISCUSSION

Systemic chemotherapy has an important emerging role in the management of hormone-refractory disease since the introduction of docetaxel-based treatment for AIPC that have a clear survival benefit in randomized clinical studies [2]. The phase III trial of docetaxel plus prednisone showed a significant improvement in overall survival, PSA response rate, pain-relief response rate, and quality of life compared with mitoxantrone and prednisone [13]. While single-agent docetaxel has shown PSA declines and measurable disease responses, favourable response rates were also reported for docetaxel used in combination with estramustine [10,33,34]. A recent phase III trial showed that docetaxel/estramustine significantly improved overall survival, progression-free survival and PSA response rate vs mitoxantrone plus prednisone [11]. As such, docetaxel-based chemotherapy is now regarded as the standard regimen for metastatic AIPC, with considerable optimism that treatment can be further improved by combinations with anti-angiogenic or pathway-targeted agents. In the present study, we showed that all three agents combined provided an advantageous treatment in pre-clinical models of prostate cancer, and was an active regimen for patients with AIPC. The rate of a decline in PSA by half-weight heparin (enoxaparin) was initiated in all patients. Despite efforts with prophylactic anticoagulation, two patients had a grade 3 thromboembolic event noted with the combination of docetaxel plus thalidomide [35], and with estramustine-related vascular events, prophylaxis with low-molecular weight heparin (enoxaparin) was initiated in all patients. Despite efforts with prophylactic anticoagulation, two patients had a grade 3 or 4 toxicity related to a thrombotic event.

Although the overall toxicity profile was manageable and limited to grade 1 or 2 toxicity, the current regimen is safe and tolerable only after dose reduction of one or more agents. Because of the high incidence of thromboembolic events noted with the combination of docetaxel plus thalidomide [35], and with estramustine-related vascular events, prophylaxis with low-molecular weight heparin (enoxaparin) was initiated in all patients. Despite efforts with prophylactic anticoagulation, two patients had a grade 3 or 4 toxicity related to a thrombotic event. In addition, there was no pattern of complications that would result from synergy of the combined treatment.

Despite significant pre-clinical data showing synergy of estramustine with other tubulin-
targeting agents, estramustine therapy is rarely used, due to its toxicity profile and lack of randomized data that show it to be better than adding prednisone to docetaxel. Although the TAX 327 and Southwest Oncology Group 9916 trial each reported survival data in the combination arm (docetaxel/prednisone and docetaxel/estramustine, respectively) of =18 months, many of the patients in the latter trial received only 80% of the every-3-week dose received by the patients in TAX 327 [11,13]. Thus, it is possible that estramustine might have compensated for the lower dose of docetaxel. While we do not think that a randomized trial is warranted to address this issue, there might still be a role for estramustine in the treatment of AIPC, given the paucity of active agents for treating this disease.

Combined therapy with all three agents presents a potentially active new treatment for metastatic AIPC. Adding thalidomide to estramustine and docetaxel requires subsequent confirmation, due to the sample size and intent of the present study. While the present study was not designed to have sufficient patients to evaluate survival as a primary endpoint, future follow-up studies, including larger randomized trials, are needed to better evaluate the efficacy of this regimen in men with AIPC. Nevertheless, the present results suggest that additional studies of docetaxel-based regimens combined with inhibitors of tumour angiogenesis are warranted in these patients.

One interesting observation from the present study was the pharmacogenetic correlation with CYP1B1. In vitro models show a potential link between CYP1B1 metabolism and docetaxel [36]. As the CYP1B1*3 and CYP1B1*4 alleles have been shown to be associated with CYP1B1 activity and expression [37,38], a possible link between the efficacy of docetaxel treatment and CYP1B1 polymorphisms might exist. Indeed, several approved and investigational agents are currently being evaluated as novel docetaxel-based combined therapy for AIPC. A phase II trial by Picus et al. [39,40] evaluated combined docetaxel and estramustine with bevaczumab, a monoclonal antibody that targets vascular endothelial growth factor. Patients received docetaxel (70 mg/m² every 21 days), estramustine (280 mg on days 1–5), and bevaczumab (15 mg/kg) over a 21-day cycle. Preliminary analysis showed that 65% of patients had a PSA response and that 53% had a PR in their measurable disease. Although the regimen was fairly well tolerated, there was an increase in thrombotic events. Based on these findings, a forthcoming randomized phase III trial is being planned to evaluate the combination of docetaxel plus prednisone with or without bevaczumab. The substitution of prednisone for estramustine was made to improve the toxicity profile. In addition, as both the docetaxel/thalidomide and the docetaxel/bevaczumab combinations have significant activity in prostate cancer, presumably through targeting different angiogenic factors, we are currently conducting a phase II trial of a four-drug combination consisting of docetaxel, prednisone, thalidomide and bevaczumab in men with chemotherapy-naive, progressive AIPC. Furthermore, docetaxel has also been studied in combination with other agents with novel mechanisms of action, including the endothelin-A receptor antagonist atrasentan [41,42] and the antiproliferative, pro-apoptotic agent calcitriol [43,44].

The improved survival with docetaxel-based chemotherapy has made this regimen (docetaxel plus prednisone) the standard front-line treatment option for patients with AIPC. While several phase II trials have shown promising results with docetaxel combined with either targeted therapy or angiogenesis inhibitors, conducting randomized phase III trials becomes essential to validate these findings. The future management of patients with AIPC will involve building on the success of docetaxel to further improve outcomes for these patients. With novel docetaxel-based combinations on the horizon, current and ongoing clinical trials will focus on seeking effective new treatment strategies for PD and formalising treatment recommendations for metastatic AIPC.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: AIPC, androgen-independent prostate cancer; CR, complete response; PR, partial response; LD, longest diameter; PD, progressive disease; ECOG, Eastern Cooperative Oncology Group.