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Phase II Study on the Addition of ASA404 (Vadimezan; 5,6-Dimethylxanthenone-4-Acetic Acid) to Docetaxel in CRMPC

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Abstract

Purpose: This randomized phase II study evaluated ASA404 (vadimezan; 5,6-dimethylxanthenone-4-acetic acid) in combination with docetaxel in castration-refractory metastatic prostate cancer (CRMPC).

Experimental Design: Seventy-four patients with histopathologically confirmed CRMPC previously untreated with chemotherapy were randomized to receive either ≤10 cycles of docetaxel 75 mg/m^2 alone (D; n = 39) or docetaxel plus ASA404 1,200 mg/m^2 (A-D; n = 35). Study endpoints included prostate-specific antigen response, tumor response, median time to tumor progression, median survival, and toxicity.

Results: The overall pattern of adverse events was similar in the two groups; however, there was a higher incidence of cardiac adverse events and neutropenia in the A-D group. Coadministration of ASA404 with docetaxel did not affect total systemic exposure of either drug. A higher prostate-specific antigen response rate was reported with A-D versus D (59.4% versus 36.8%), together with a larger median percentage reduction in prostate-specific antigen (84.0% versus 61.9%) and a shorter median time to prostate-specific antigen nadir (105 versus 119 d). Tumor response rate was 23.1% with A-D and 9.1% with D. Time to tumor progression and median survival were similar in the groups (time to tumor progression, 8.7 mo for A-D and 8.4 mo for D; survival, 17.0 mo for A-D and 17.2 mo for D). Hazard ratios for time to tumor progression and survival were 0.81 and 0.80, respectively, favoring A-D; 2-year survival was 33.3% with A-D and 22.8% with D.

Conclusion: The study met some endpoints (prostate-specific antigen response, tumor response) but not others (i.e., time to tumor progression). The results indicate that the combination of ASA404 with docetaxel has acceptable toxicity, lacks adverse pharmacokinetic interaction, and, overall, has activity in CRMPC. *Clin Cancer Res; 16(10); 2906–14. ©2010 AACR.*

Advanced prostate cancer is treated with androgen deprivation therapy but usually becomes unresponsive to this treatment over time and progresses to a castration-refractory state. Cytotoxic chemotherapy had provided scant survival advantage in this setting (1) until the safety and efficacy of docetaxel were established in a randomized clinical trial involving >1,000 men with castration-refractory metastatic prostate cancer (CRMPC; ref. 2). In this phase III trial, docetaxel, given every 3 weeks in combination with prednisone, provided a survival advantage of ~2.5 months over mitoxantrone plus prednisone. Nevertheless, responses with docetaxel are often of short duration, and there remains a high unmet clinical need for effective and well-tolerated therapies for patients with CRMPC. This has led to investigations of regimens in which other agents are used in combination with docetaxel.

The small molecule tumor-vascular disrupting agent ASA404 (vadimezan; 5,6-dimethylxanthenone-4-acetic acid) has shown therapeutic potential in combination with taxanes (3, 4). Tumor-vascular disrupting agents target established tumor vasculature, which is required by the tumor to survive and grow (5). This action is distinct from that of antiangiogenic agents, which predominantly target neovascularization (6). ASA404 induces apoptosis of tumor vascular endothelial cells, cytokine production, and tumor vascular collapse (6–8), effects that culminate in necrosis of the central tumor region *in vivo* (9–13).

In animal models, ASA404 has been shown to act synergistically with chemotherapy (3, 14, 15), with taxanes

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Translational Relevance

This article reports the results of a randomized phase II clinical trial to evaluate the efficacy, safety, and pharmacokinetics of the tumor-vascular disrupting agent, ASA404, in combination with docetaxel in patients with castration-refractory metastatic prostate cancer (CRMPC). ASA404 is a novel targeted anticancer therapy that is also being evaluated in non–small cell lung cancer, with two large phase III trials ongoing. Results of this study indicate that the combination of ASA404 and docetaxel has acceptable toxicity and may improve efficacy over docetaxel alone in CRMPC. This is an important study because it reports evidence of activity with addition of a novel therapy to existing regimens in CRMPC, in which there is significant unmet need. In addition, this study provides information relevant to the ongoing phase III study with ASA404 added to docetaxel in second-line non–small cell lung carcinoma.

providing the most striking therapeutic gain. Scheduling studies indicated that activity was optimized when ASA404 was administered shortly after chemotherapy (16).

Following encouraging phase I results (16–18), CRMPC was chosen as one of three indications [alongside advanced non–small cell lung carcinoma (NSCLC) and platinum-sensitive ovarian cancer] for initial randomized phase II trials investigating ASA404 as an anticancer agent in a combination setting. Results from the phase II study in NSCLC suggest a survival benefit when ASA404 1,200 mg/m^2 is added to paclitaxel-based chemotherapy (median survival, 14.0 mo with ASA404 plus carboplatin and paclitaxel versus 8.8 mo with carboplatin and paclitaxel alone; ref. 19). The phase II study described here was conducted to determine the safety, pharmacokinetics, and efficacy of ASA404 1,200 mg/m^2 in combination with docetaxel in patients with CRMPC.

Patients and Methods

Patient population. Men of ≥18 years of age with histopathologically confirmed, metastatic, progressive, castration-refractory adenocarcinoma of the prostate with no previous chemotherapy treatment were eligible for inclusion. Progressive disease (with ongoing androgen-deprivation therapy) required at least one of the following variables to be documented: progressive disease according to Response Evaluation Criteria In Solid Tumors (RECIST; ref. 20) within 30 days, ≥1 new lesion on bone scan within 30 days and prostate-specific antigen concentration ≥5 ng/mL, or nonprogressive (RECIST) disease or bone scan with rising prostate-specific antigen concentration from a baseline >5 ng/mL. Other requirements included Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, life expectancy ≥3 months, serum testosterone ≤50 ng/mL if chemically castrated, and adequate hematologic, renal, and hepatic functions.

Main exclusion criteria were decreasing prostate-specific antigen concentration after antiandrogen withdrawal; central nervous system metastases; clinically significant cardiac arrhythmia or heart-rate corrected QT interval prolongation; severe or uncontrolled systemic disease; and use of medication known to affect systemic serotonin levels or corrected QT interval ≤2 weeks before ASA404 administration or treatment with agents having known potential for interaction with docetaxel.

Patients were recruited from 19 centers in the United States and Australia. The study was conducted according to the Declaration of Helsinki. Ethics committee approval and informed patient consent were obtained.

Study design. This open-label, randomized, parallel group phase II study evaluated the addition of ASA404 1200 mg/m^2 to standard therapy with docetaxel 75 mg/m^2. All patients could receive prednisone 5 mg twice daily as concomitant therapy for palliation of symptoms from bone metastases. Patients were randomized 1:1 to receive ASA404 plus docetaxel (A-D group) or docetaxel alone (D group). Randomization was done centrally using sealed envelopes. The first six patients randomized to the A-D group were recruited under early stopping rules to monitor safety before the study progressed further. On the basis that ≤1 dose limiting toxicity, clearly attributed to ASA404, was observed in the first six patients, enrolment continued until ~33 eligible patients were recruited into each of the A-D and D groups.

On day 1 of each cycle, patients received docetaxel as a 1-hour i.v. infusion, then, if allocated, ASA404 as a 20-minute i.v. infusion. Treatment was given every 21 days for up to 10 cycles or until patient withdrawal, whichever was earlier. The docetaxel dose was permitted to be reduced to 60 mg/m^2 in patients who experienced unacceptable toxicity; the ASA404 dose was permitted to be delayed if docetaxel treatment was delayed but could not be altered.

Patients attended a screening visit ≤4 weeks before treatment, a study visit every week (patients undergoing pharmacokinetics assessment) or every 3 weeks (all other patients), and a follow-up visit 4 weeks after study completion/withdrawal. Tumors were measured every 6 weeks until disease progression. Upon disease progression, suitable patients randomized to the D group could switch to ASA404 monotherapy at a dose of 1,200 mg/m^2 weekly for up to six cycles. Survival was assessed every 3 months.

Assessments. The first 12 patients in the A-D group had extensive pharmacokinetics assessments; subsequent patients in this group had sparse pharmacokinetics assessments. Plasma samples were frozen and shipped through specialized courier to a nominated central laboratory for analysis. Levels of ASA404 and of docetaxel were measured using high performance liquid chromatography with tandem mass spectrometric detection. In patients undergoing extensive pharmacokinetics assessments, blood samples were collected at cycle 1 before the start of the

docetaxel and ASA404 infusions, at the end of the infusions, then at regular intervals up to 48 hours after the end of the infusions (30 min, 1.5 h, 3 h 40 min, 4.5 h, 7.5 h, 9.5 h, 23.5 h, and 47.5 h). In patients undergoing sparse pharmacokinetics assessments, samples were collected at cycle 1 at the end of the docetaxel and ASA404 infusions, 6 hours after the start of the docetaxel infusion, and 4 hours after the start of the ASA404 infusion.

Total serum prostate-specific antigen concentration was measured at screening (≤2 wk before the start of treatment), at each cycle before the start of docetaxel infusion, before the start of ASA404 infusion (if allocated), and at the safety follow-up visit.

Tumors were measured using computed tomography or magnetic resonance imaging and bone scan. Tumor response was evaluated using RECIST and categorized as complete, partial, stable disease, or progressive disease. Response was confirmed by examination ≥4 weeks after the first assessment. An independent outcome committee carried out a blinded radiological review of all tumor assessments.

Safety assessments included a symptom-directed clinical examination before each cycle, on days 8 and 15 after drug administration (only patients undergoing pharmacokinetics assessment), and at the safety follow-up visit. Laboratory analyses (hematology and biochemistry) were conducted at these same time points. A urine sample was collected for urinalysis at screening and before the start of drug administration at cycles 1, 3, 5, 7, and 9, and at the safety follow-up visit.

Standard 12-lead electrocardiograms (ECG) were obtained in both groups at screening and at final assessment. In the A-D group at cycle 1, triplicate ECGs were acquired during the 30 minutes before docetaxel administration and immediately before ASA404 administration. Further ECGs were acquired 10 minutes, 20 minutes, and 1, 2, and 4 hours after the start of ASA404 administration. At cycles 2 to 10, ECGs were acquired immediately before docetaxel administration and immediately before and 1 hour after the start of ASA404 administration. In the D group, ECGs were acquired at withdrawal or at the safety follow-up visit. If a patient developed a corrected QT interval prolongation (Bazett's correction) >60 ms compared with baseline, further ECGs were acquired, and the patient was monitored until the corrected QT interval returned to within 30 ms of baseline on two consecutive ECGs.

In patients receiving ASA404, ophthalmic tests were done before treatment and 2 weeks after the last ASA404 dose. These included best corrected visual acuity, ophthalmologic examination, contrast sensitivity, color vision/color contrast sensitivity, and central visual field.

Patients from the D group who crossed-over to receive ASA404 monotherapy on progression underwent safety monitoring, including ECG and ophthalmic assessments at each treatment visit, and pharmacokinetics samples were collected after the 1st cycle.

Statistical methodology and analysis. Study populations were defined prospectively. Efficacy analyses were done on all eligible patients (those who met the inclusion criteria and received ≥1 dose of study medication). Safety analyses were done on all patients who received ≥1 dose of study medication.

Primary safety outcomes were treatment-emergent adverse events, laboratory abnormalities, effect on corrected QT interval, and ophthalmic toxicity. A treatment-emergent adverse event was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product (including abnormal laboratory findings or worsening of pre-existing conditions), whether or not considered related to the study drug.

Adverse events were coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 or as mild, moderate, or severe if NCI-CTCAE were not applicable. Relationships of adverse events to treatment were assessed as definite, probable, possible, or unrelated.

Plasma concentrations of ASA404 and docetaxel were summarized at each time point for each group. A regression line was fitted to the last three nonzero points on a log-linear plot to evaluate the elimination phase and standard pharmacokinetics variables.

There were several efficacy endpoints: objective response rate, time to tumor progression, survival, prostate-specific antigen response rate (21), and time to prostate-specific antigen progression. Time to tumor progression and survival were defined as time from treatment initiation to first objective documentation of progression or death, respectively. In the absence of progression (time to tumor progression endpoint) or death (survival endpoint), data were censored at the last disease assessment date and survival follow-up date, respectively. Prostate-specific antigen response was defined as a 50% reduction from baseline, confirmed by measurement of prostate-specific antigen concentration ≥4 weeks later. For patients with prostate-specific antigen decline of ≥50%, prostate-specific antigen progression was defined as a >50% increase from the nadir (absolute increase, ≥5 ng/mL). For patients with prostate-specific antigen decline of <50%, prostate-specific antigen progression was defined as a 25% increase from the nadir or baseline, whichever was lower (absolute increase, ≥5 ng/mL). Kaplan-Meier curves were fitted for time to tumor progression and survival and were used to estimate median values.

At least 33 patients were planned to be evaluated in each treatment group; this would allow detection of 100% improvement in median time to tumor progression between the groups at a 5% significance level and 80% power.

Results

Patients. A total of 74 patients were randomized (A-D, $n = 35$; D, $n = 39$). Three patients withdrew from the study, leaving 71 patients who received study medication and

were included in the safety analysis (A-D, $n = 33$; D, $n = 38$). The two groups were well balanced for pretreatment characteristics (Table 1). There were no differences of note in terms of cancer-related history, medical history, physical examination, previous/concomitant medication, or median prostate-specific antigen at screening. Most patients had an ECOG performance status of 0 to 1.

One patient was not included in the eligible population because he did not meet the inclusion criteria, having had previous chemotherapy treatment for prostate cancer (eligible population, $n = 32$ for A-D and $n = 38$ for D). Eleven eligible patients (A-D, $n = 6$; D, $n = 5$) were not assigned a RECIST response by independent assessment.

Twenty-eight patients reached cycle 10 of treatment (A-D, $n = 13$; D, $n = 15$), with one patient in the D group inadvertently missing cycle 2. The main reason for discontinuation was progressive disease (A-D, $n = 10$; D, $n = 6$). Four patients crossed-over from the D group to receive ASA404 monotherapy; three received six cycles of ASA404 monotherapy and completed the study; one patient withdrew because of progressive disease after receiving four cycles of ASA404.

Treatment status. Twenty-seven patients completed 10 cycles of treatment (A-D, $n = 13$; D, $n = 14$). The median number of cycles was seven in the A-D group and eight in the D group, with 210 and 259 cycles given in total, respectively. The mean total doses of docetaxel were similar in the two groups (A-D, 907 mg; D, 1026 mg). Dose reductions of docetaxel were mainly as a result of neutropenia; 10 (30.3%) patients in the A-D group and five (13.2%) in the D group required a docetaxel dose reduction in ≥1 cycle. More treatment cycles were delayed by ≥3 days in the D group [14 (5.4%) versus 9 (4.3%) cycles in the A-D group].

Pharmacokinetics. Mean pharmacokinetics variables are shown in Table 2. Analysis of samples taken from patients in the D group who crossed-over to receive ASA404 monotherapy ($n = 4$) indicated that pharmacokinetics variables for ASA404 were consistent with those reported previously from phase I studies (16).

Coadministration of ASA404 with docetaxel did not seem to affect the systemic exposure of docetaxel, which was similar to published data (21), nor the systemic exposure and disposition of total ASA404. Systemic exposure to free ASA404 seemed reduced, and clearance was markedly increased, whereas volumes of distribution for free ASA404 were similar for the combination treatment and ASA404 alone.

Safety. Safety profiles for the two groups are shown in Tables 3 and 4. The proportions of patients with adverse events, treatment-related adverse events, serious adverse events, and deaths or study discontinuations because of adverse events were similar in the two groups.

Most adverse events were consistent with known adverse reactions to docetaxel chemotherapy (22, 23). The most frequently occurring adverse events attributed to ASA404 were infusion site reaction, nausea, diarrhea, and fatigue. In the A-D group, six (18.2%) patients reported ASA404-related serious adverse events and six patients (18.2%) reported docetaxel-related serious adverse events. In the D group, eight (21.1%) patients reported docetaxel-related serious adverse events. The most frequently occurring serious adverse event was febrile neutropenia (A-D group, 12.1%; D group, 7.9%). There were three fatal adverse events, one of which, neutropenic sepsis in the A-D group, was considered to be related to docetaxel. The other two fatal adverse events (myocardial infarction in the A-D group and cerebrovascular accident in the D group) were

Table 1. Baseline characteristics of randomized patients (safety population)

	A-D ($n = 33$)	D ($n = 38$)
Median age, y (range)	68.0 (49-87)	67.0 (48-84)
Race, *n* (%) Caucasian	29 (88)	36 (95)
*Cancer-related medical history, *n* (%)		
Arthralgia	6 (18)	6 (16)
Back pain	11 (33)	7 (18)
Metastases to bone	7 (21)	13 (34)
Hematuria	4 (12)	6 (16)
Nocturia	4 (12)	10 (26)
†ECOG performance status, *n* (%)		
0	12 (38)	16 (42)
1	20 (63)	19 (50)
2	0	3 (8)
Median PSA at screening, ng/mL (range)	73.3 (8-19,000)	78.7 (4-1,229)

Abbreviation: PSA, prostate-specific antigen.
*Most commonly reported.
†Eligible population.

Table 2. Summary of the mean pharmacokinetic variables

Variable	Dose of ASA404*			
	Administered alone (n = 4)		Administered in combination with docetaxel (n = 12)	
	Total	Free	Total	Free
$AUC_{0\text{-}t}$, ng × h/mL	631,000	5,370	641,000	1,410
C_{max}, ng/mL	209,000	2,830	243,000	1,600

	Dose of docetaxel†		
	Administered in combination with ASA404		Docetaxel historical PK variables‡
	Total (n = 12)	Free (n = 9)	
$AUC_{0\text{-}t}$, ng × h/mL	1,950	51.6	3,450
C_{max}, ng/mL	2,000	68.1	2,780

Abbreviation: AUC, area under the curve; PK, pharmacokinetics.

*Determined for total and free ASA404 following single i.v. doses of ASA404 when administered at 1,200 mg/m^2 alone and in combination with docetaxel (75 mg/m^2).

†Determined for total and free docetaxel following single i.v. doses of docetaxel when administered at 75 mg/m^2 alone and in combination with ASA404 (1,200 mg/m^2).

‡Taken from Taxotere Summary of Product Characteristics, pharmacokinetic variables for docetaxel 100 mg/m^2, and dose adjusted to 75 mg/m^2.

not considered related to docetaxel or ASA404 by investigator assessment.

The incidence of cardiac adverse events of any grade was higher in the A-D group than in the D group (27.3% versus 10.5%). Cardiac serious adverse events were reported in four patients in the A-D group (infarction, acute infarction, ischemia, and supraventricular tachycardia). Three of these led to withdrawal, one of which was fatal. None was definitely attributable to treatment with ASA404, and there was no apparent temporal relationship between onset of cardiac serious adverse event and administration of ASA404. One patient in the D group reported a cardiac serious adverse event (atrial fibrillation/flutter).

Table 3. Summary of treatment-emergent adverse events (safety population)

	A-D (n = 33), n (%)	D (n = 38), n (%)
≥1 Adverse event	33 (100.0)	37 (97.4)
Related to A	28 (84.8)	—
Related to D	33 (100.0)	35 (92.1)
Grade 1*/mild†	2 (6.1)	5 (13.2)
Grade 2*/moderate†	6 (18.2)	6 (15.8)
Grade 3*/severe†	18 (54.5)	22 (57.9)
Grade 4*,†	7 (21.2)	4 (10.5)
Adverse event leading to death	2 (6.1)	1 (2.6)
Adverse event leading to withdrawal	10 (30.3)	11 (28.9)
≥1 Serious adverse event	14 (42.4)	13 (34.2)
Related to A	6 (18.2)	—
Related to D	6 (18.2)	8 (21.1)

*NCI-CTCAE grading.

†Worst severity grade.

Other adverse events leading to withdrawal included nervous system disorders (A-D, n = 4; D, n = 6), gastrointestinal disorders (A-D, n = 1; D, n = 2), general disorders and administrative site conditions (A-D, n = 1; D, n = 2), febrile neutropenia (A-D, n = 2), infection/sepsis (A-D, n = 2), skin and s.c. disorders (D, n = 2), hypersensitivity (A-D, n = 1), neoplasm progression (D, n = 1), confusional state (D, n = 1), and interstitial lung disease (D, n = 1).

Grade 3/4 hematologic toxicities based on laboratory values were similar in the two groups. Neutrophil count shifted from grade 0 to 3 in 28.1% of the A-D group and 41.7% of the D group and from grade 0 to 4 in 56.3% of the A-D group and 36.1% of the D group. The pattern was similar for changes in WBC count.

There was a general reduction in corrected QT relative to study baseline with time and treatment in the A-D group (at least until cycle 6) and intracycle increases in corrected QT after administration of docetaxel and ASA404. The intracycle increases were transient and of relatively small magnitude (mean, 4.6 ms). ECG morphologic analysis showed a relatively high frequency of ST-depression associated with combination treatment, which appeared

in cycle 1 in ~14% of patients and increased in incidence to almost 20% of patients at cycles 2 and 3. A similar pattern (but with a smaller magnitude of effect) was seen after dosing in cycles 4 and 5; from cycle 6 onwards, the incidence of ST-depression was much lower.

No patient had significant deterioration in ophthalmic variables after ASA404 treatment. Two patients had visual acuity changes of ≥15 letters (three lines), but they did not have an associated reduction in contrast sensitivity.

Efficacy. Prostate-specific antigen response data were available from 70 eligible patients as shown in Fig. 1. The prostate-specific antigen response rate was 22.6% [95% confidence interval (95% CI), -0.4 to 45.4] higher in the A-D group than in the D group (59.4% versus 36.8%). The presence of a prostate-specific antigen response was usually (with one exception) associated with partial remission or stable disease, but a large proportion of patients with stable disease did not have a prostate-specific antigen response.

There was a general downward trend in prostate-specific antigen concentration in both groups. Among patients with a postbaseline reduction in prostate-specific antigen concentration, those in the A-D group had a larger median percentage reduction than those in the D group (84.0% versus 61.9%, respectively). The median time to prostate-specific antigen concentration nadir among patients with a reduction in prostate-specific antigen concentration from baseline was slightly shorter in the A-D group (105 versus 119 d in the D group).

RECIST response outcomes by independent assessment gave a best overall response of partial remission, with a higher confirmed response rate in the A-D group than the D group (23.1% versus 9.1%; 14.0% difference; 95% CI, -4.9% to 32.9%). A slightly higher proportion of patients in the D group had stable disease (66.7% versus 57.7% in the A-D group; 9% difference; 95% CI, -33.9% to 15.9%). Investigator assessment showed similar results.

Median time to tumor progression (independent assessment) was similar in the two groups (8.7 mo for A-D versus 8.4 mo for D).The hazard ratio for time to tumor progression was 0.81 (95% CI, 0.39-1.70; $P = 0.58$; Fig. 2), favoring the A-D group.

At the end of the 2-year survival follow-up, median survival was similar in the two groups (17.0 mo for A-D versus 17.2 mo for D). The hazard ratio for survival was 0.80 (95% CI, 0.46-1.39; $P = 0.42$; Fig. 2), favoring the A-D group. Two-year survival rates were 33.3% (95% CI, 15.8-50.9) in the A-D group and 22.8% (95% CI, 8.3-37.3) in the D group.

Discussion

Adequate vasculature is a prerequisite for solid tumors to grow and metastasize. Agents that target tumor neovascularization have become established treatments for various tumors, including colon, lung, and renal cell cancer. Antiangiogenic agents such as the antivascular endothelial growth factor monoclonal antibody, bevacizumab, and the angiogenesis inhibitor/immunomodulator thalidomide have shown promise for the treatment of CRMPC in phase II studies when combined with docetaxel (24, 25). The tumor-vascular disrupting agent ASA404 targets existing tumor vasculature and therefore offers a distinct approach from that of antiangiogenesis. Furthermore, ASA404 has shown a synergistic effect with docetaxel in animal tumor models (13).

This randomized phase II study evaluated the pharmacokinetics, safety, and efficacy of ASA404 when added to standard docetaxel therapy in patients with CRMPC.

Table 4. Most frequently occurring grade 3 and 4 toxicities (safety population)

Nonhematologic toxicities	**A-D (*n* = 33), *n* (%)**		**D (*n* = 38), *n* (%)**	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Gastrointestinal disorders	4 (12.1)	0 (0.0)	4 (10.5)	0 (0.0)
General disorders and administration site conditions	4 (12.1)	0 (0.0)	4 (10.5)	0 (0.0)
Nervous system disorders	3 (9.1)	1 (3.0)	4 (10.5)	0 (0.0)
Cardiac disorders	4 (12.1)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	3 (9.1)	1 (3.0)	4 (10.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (9.1)	0 (0.0)	4 (10.5)	0 (0.0)
Skin and s.c. tissue disorders	2 (6.1)	0 (0.0)	6 (15.8)	0 (0.0)
Hematologic toxicities	**A-D (*n* = 32), *n* (%)**		**D (*n* = 36), *n* (%)**	
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**
Neutrophils	9 (28.1)	18 (56.3)	15 (41.7)	13 (36.1)
Hemoglobin	2 (6.3)	0 (0.0)	2 (5.6)	0 (0.0)
Platelets	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukocytes	15 (46.9)	8 (25.0)	22 (61.1)	4 (11.1)

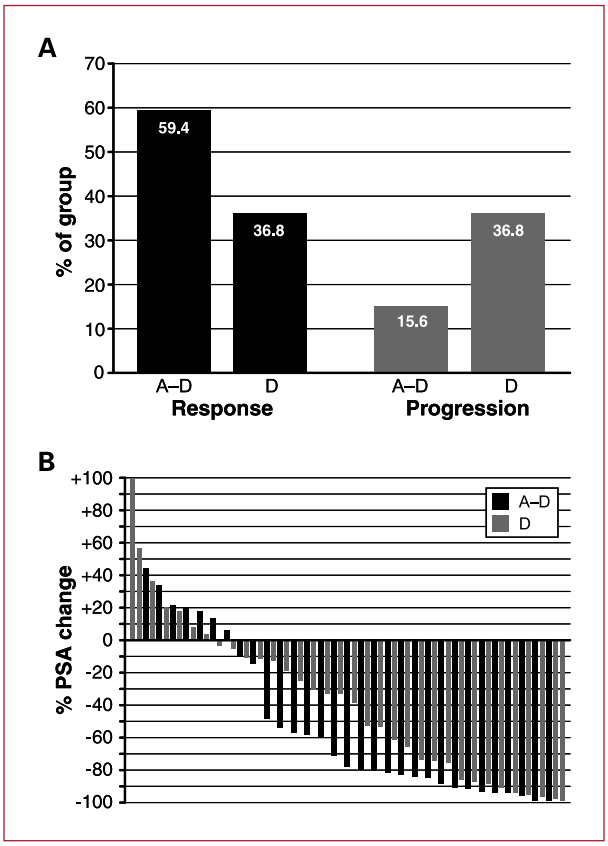

Fig. 1. Effect of addition of ASA404 to docetaxel on prostate-specific antigen levels. A, proportion of patients with prostate-specific antigen response or prostate-specific antigen progression. Response defined as confirmed ≥50% decrease in prostate-specific antigen versus baseline; progression defined as confirmed ≥25% increase in prostate-specific antigen versus nadir or baseline (A-D, *n* = 32; D, *n* = 38). B, maximum percentage reduction in prostate-specific antigen for each individual patient (A-D, *n* = 31; D, *n* = 34). PSA, prostate-specific antigen.

The study showed no evidence of pharmacokinetic interaction between ASA404 and docetaxel. Coadministration did not seem to have an impact on the systemic exposure of docetaxel nor on the systemic exposure and disposition of total ASA404.

The overall pattern of adverse events was similar in the two groups. More dose reductions due to adverse events were needed in the A-D group, whereas more dose delays of ≥3 days occurred in the D group. Although there was a higher incidence of grade 4 neutropenia and leukopenia in the A-D group, there were no other clinically relevant differences in hematology findings.

The incidence of cardiac adverse events was higher in the A-D group, and three patients in this group were withdrawn because of cardiac adverse events. Nonetheless, a causal relationship to ASA404 was not clearly established. It is worth noting that cardiac toxicity was not prevalent in two phase II trials of ASA404 in combination with paclitaxel and carboplatin in NSCLC (19, 26). In phase I studies on ASA404, the predominant cardiac adverse event seen at high doses (≥2000 mg/m^2) was corrected QT interval prolongation (17, 18). In this study, ECG data revealed a reduction in corrected QT with treatment and time, at least until cycle 6 (after which, the decrease stabilized). There were also small transient increases in the corrected QT interval after each administration of ASA404, but these were well within the acceptable regulatory threshold. An increased incidence of ischemic ST changes was observed with time; however, in the absence of ECGs at corresponding time points in the D group, these effects cannot be associated unequivocally with ASA404. Overall, the clinical relevance of these observations is unclear, and the cardiac safety profile of ASA404 should continue to be monitored in future studies.

Intensive assessments showed no clear evidence of clinically significant ophthalmic toxicity associated with ASA404. This suggests that ASA404 can be combined with docetaxel without the potential for the ophthalmic adverse events seen at high monotherapy doses (16–18)

Endpoints in the study included prostate-specific antigen response, tumor response, time to tumor progression, and overall survival. The study met some of these endpoints (prostate-specific antigen and tumor response) but not others (i.e., time to tumor progression). A higher proportion of patients in the A-D group were prostate-specific antigen responders and prostate-specific antigen response was associated with tumor response; tumor response rates were higher in the A-D group. Although

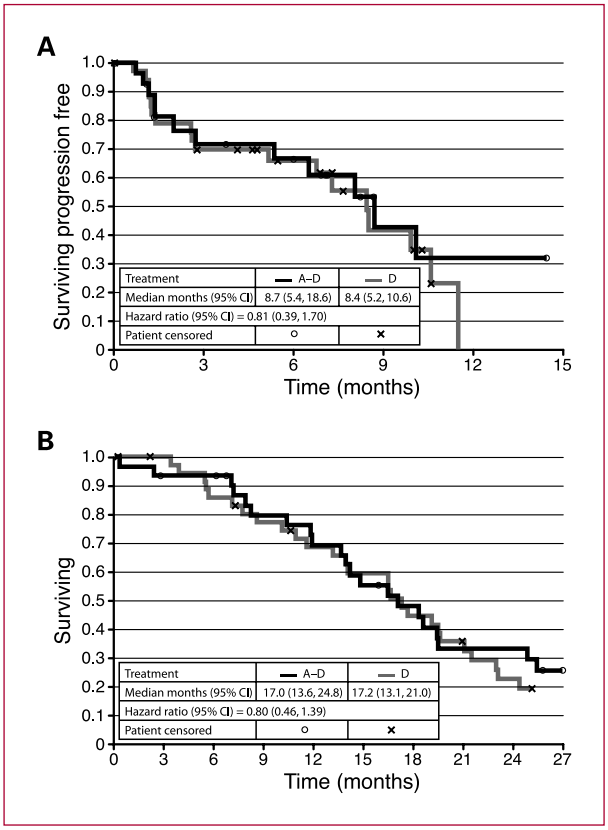

Fig. 2. Kaplan-Meier estimates for the eligible population (A-D, *n* = 32; D, *n* = 38). A, time to tumor progression. B, overall survival.

median values for time to tumor progression and overall survival were similar in the two groups, there was a tendency toward treatment benefit with A-D. Two-year survival findings suggested a greater proportion of longer-term survivors among patients receiving A-D.

Prostate-specific antigen and tumor response rates favoring the A-D arm suggest clinical activity for this combination, and it is possible that the lack of difference between the two arms with respect to median time to tumor progression and survival could be due to insufficient sample size. Other possible factors that could have contributed to the lack of observed survival benefit, such as a higher incidence of adverse event–related mortality or study discontinuations in the A-D arm, were not evident in this study. One can also postulate that a higher dose of ASA404 could have a greater therapeutic index, as was found to be the case in NSCLC, in which a dose of 1,800 mg/m^2 rather than 1,200mg/m^2 is being tested in phase III studies with ASA404.

The molecular mechanism responsible for the enhanced antitumor effect of the combination of ASA404 with docetaxel in preclinical models remains to be elucidated. It has been speculated that a tumor-vascular disrupting agent can increase the concentration of the chemotherapy agent by entrapping it within the tumor. The sequence of administration of the tumor-vascular disrupting agent is therefore important, and optimal preclinical results have been observed when ASA404 was administered after the chemotherapeutic agent (3, 4).

In conclusion, this study indicates that the combination of the tumor-vascular disrupting agents ASA404 and docetaxel has acceptable toxicity, lacks adverse pharmacokinetics interactions, and has activity in CRMPC. Combining ASA404 with docetaxel provides a feasible regimen for further study. A phase III trial of ASA404 plus docetaxel as second-line therapy for advanced NSCLC [ATTRACT-2 (Antivascular Targeted Therapy: Researching ASA404 in Cancer Treatment-2)] is ongoing.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Yagoda A, Petrylak D. Cytotoxic chemotherapy for advanced hormone-resistant prostate cancer. Cancer 1993;71:1098–109.
2. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
3. Siim BG, Lee AE, Shalal-Zwain S, Pruijn FB, McKeage MJ, Wilson WR. Marked potentiation of the antitumour activity of chemotherapeutic drugs by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA). Cancer Chemother Pharmacol 2003;51:43–52.
4. McKeage MJ. The potential of DMXAA (ASA404) in combination with docetaxel in advanced prostate cancer. Expert Opin Investig Drugs 2008;17:23–9.
5. Hahnfeldt P, Panigrahy D, Folkman J, Hlatky L. Tumor development under angiogenic signaling: a dynamical theory of tumor growth, treatment response, and postvascular dormancy. Cancer Res 1999;59:4770–5.
6. Baguley BC. Antivascular therapy of cancer: DMXAA. Lancet Oncol 2003;4:141–8.
7. Ching LM, Cao Z, Zwain S, Jameson MB, Baguley BC. Induction of endothelial cell apoptosis by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid. Br J Cancer 2002;86:1937–42.
8. Tozer GM, Kanthou C, Baguley BC. Disrupting tumour blood vessels. Nat Rev Cancer 2005;5:423–35.
9. Ching LM, Goldsmith D, Joseph WR, Körner H, Sedgwick JD, Baguley BC. Induction of intratumoral tumor necrosis factor (TNF) synthesis and hemorrhagic necrosis by 5,6-dimethylxanthenone-4-acetic acid (DMXAA) in TNF knockout mice. Cancer Res 1999;59:3304–7.
10. Ching LM, Zwain S, Baguley BC. Relationship between tumour endothelial cell apoptosis and tumour blood flow shutdown following treatment with the antivascular agent DMXAA in mice. Br J Cancer 2004;90:906–10.
11. Joseph WR, Cao Z, Mountjoy KG, Marshall ES, Baguley BC, Ching LM. Stimulation of tumors to synthesize tumor necrosis factor-α *in situ* using 5,6-dimethylxanthenone-4-acetic acid: a novel approach to cancer therapy. Cancer Res 1999;59:633–8.
12. Laws AL, Matthew AM, Double JA, Bibby MC. Preclinical *in vitro* and *in vivo* activity of 5,6-dimethylxanthenone-4-acetic acid. Br J Cancer 1995;71:1204–9.
13. Zwi LJ, Baguley BC, Gavin JB, Wilson WR. Correlation between immune and vascular activities of xanthenone acetic acid antitumor agents. Oncol Res 1994;6:79–85.
14. McKeage MJ, Kelland LR. 5,6-Dimethylxanthenone-4-acetic acid (DMXAA); clinical potential in combination with taxane-based chemotherapy. Am J Cancer 2006;5:155–62.
15. Pruijn FB, van Daalen M, Holford NH, Wilson WR. Mechanisms of enhancement of the antitumour activity of melphalan by the tumour-blood-flow inhibitor 5,6-dimethylxanthenone-4-acetic acid. Cancer Chemother Pharmacol 1997;39:541–6.
16. Jameson MB, Thompson PI, Baguley BC, et al. Clinical aspects of a phase I trial of 5,6-dimethylxanthenone-4-acetic acid (DMXAA), a novel antivascular agent. Br J Cancer 2003;88:1844–50.
17. McKeage MJ, Fong P, Jeffery M, et al. 5,6-Dimethylxanthenone-4-acetic acid in the treatment of refractory tumors: a phase I safety study of a vascular disrupting agent. Clin Cancer Res 2006;12:1776–84.

18. Rustin GJ, Bradley C, Galbraith S, et al. 5,6-Dimethylxanthenone-4-acetic acid (DMXAA), a novel antivascular agent: phase I clinical and pharmacokinetic study. Br J Cancer 2003;88:1160–7.
19. McKeage MJ, Von Pawel J, Reck M, et al. Randomised phase II study of ASA404 combined with carboplatin and paclitaxel in previously untreated advanced non-small cell lung cancer. Br J Cancer 2008;16:2006–12.
20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
21. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999;17:3461–7.
22. Extra JM, Rousseau F, Bruno R, Clavel M, Le Bail N, Marty M. Phase I and pharmacokinetic study of taxotere (RP 56976; NSC 628503) given as a short intravenous infusion. Cancer Res 1993;53:1037–42.
23. Eisenhauer EA, Vermorken JB. The taxoids: comparative clinical pharmacology and therapeutic potential. Drugs 1998;55:5–30.
24. Dahut WL, Gulley JL, Arlen PM, et al. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. J Clin Oncol 2004;22:2532–9.
25. Picus J, Halabi S, Rini B, et al. The use of bevacizumab with docetaxel and estramustine in hormone refractory prostate cancer: initial results of CALGB 90006. Proc Am Soc Clin Oncol 2003;22:1578.
26. McKeage MJ, Reck M, Jameson MB, et al. Phase II study of ASA404 (vadimezan, 5,6-dimethylxanthenone-4-acetic acid/DMXAA) 1800 mg/m^2 combined with carboplatin and paclitaxel in previously untreated advanced non-small cell lung cancer. Lung Cancer 2009;65:192–7.