Phase I Study of Samarium-153 Lexidronam With Docetaxel in Castration-Resistant Metastatic Prostate Cancer

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose

Early studies of patients with castration-resistant metastatic prostate cancer (CRMPC) suggest that chemotherapy administered with a dose of a bone-seeking radiopharmaceutical is superior to chemotherapy alone. To build on this strategy and fully integrate a repetitively dosed bone-seeking radiopharmaceutical into a contemporary chemotherapy regimen, we conducted a phase I study of docetaxel and samarium-153 (^{153}Sm) lexidronam.

Patients and Methods

Men with progressive CRMPC were eligible. Cohorts of three to six patients were defined by dose escalations as follows: docetaxel 65, 70, 75, 75, 75 mg/m² and ^{153}Sm ethylenediaminetetramethylenephosphonate (EDTMP) 0.5, 0.5, 0.5, 0.75, 1 mCi/kg. Each cycle lasted a minimum of 6 (cohorts 1 through 5) or 9 (cohort 6) weeks. Docetaxel was administered on days 1 and 22 (and day 43 for cohort 6), and ^{153}Sm -EDTMP was administered on day -1 to 1 of each cycle. Patients with acceptable hematologic toxicities were eligible to receive additional cycles until progression.

Results

Twenty-eight men were treated in six cohorts. Maximum-tolerated dose was not reached, because full doses of both agents were well tolerated, even using an every-6-week dosing schedule of ^{153}Sm -EDTMP. Patients received an average of 5.6 docetaxel doses (range, one to 13 doses) and 2.9 ^{153}Sm -EDTMP doses (range, one to six doses). Fifteen patients demonstrated a more than 50% decline in prostate-specific antigen. Treatment significantly reduced indices of bone deposition and resorption.

Conclusion

Docetaxel and ^{153}Sm -EDTMP can be combined safely at full doses over repeated cycles. Responses were seen in the small group of patients with taxane-resistant disease tested. The optimal phase II doses for patients with taxane-naïve disease may differ from those optimal for patients with taxane-resistant disease.

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INTRODUCTION

Bone metastases are the primary source of morbidity and mortality in patients with prostate cancer, comprise the reservoir of treatment-resistant disease, and are the most frequent site of disease relapse. Existing treatments for castration-resistant metastatic prostate cancer (CRMPC) are limited. The only life-prolonging therapy after castration resistance is docetaxel, which confers a brief survival advantage of 2 to 3 months^{1,2} and is the standard of care for patients with CRMPC.

A method of targeting the bone microenvironment, as well as irradiating tumor localized to bone, is through the use of bone-seeking radiopharmaceu-

tics. These agents are currently approved only for the palliation of bone pain. However, such drugs have demonstrated systemic benefits beyond palliation. For example, a randomized phase II study using sequential ketoconazole plus doxorubicin and a dose of strontium-89 resulted in prolonging survival from 16.8 to 27.7 months relative to chemotherapy alone.³

Clinicians have approached repetitive dosing of bone-seeking radiopharmaceuticals and combinations with chemotherapy with caution, given concerns about marrow toxicity, in particular in regard to long-term thrombocytopenia. However, samarium-153 ethylenediaminetetramethylenephosphonate (^{153}Sm -EDTMP) has a lower mean

energy beta emission than strontium-89 ($0.23 \nu 0.59$ MeV) and a shorter half-life ($1.9 \nu 50.5$ days), thus allowing for a lesser marrow exposure to radiation. It can be safely given repetitively as a single agent at both US Food and Drug Administration–approved and two-fold higher doses.^{4,5}

We sought to leverage the potential advantages of bone-seeking radiopharmaceuticals and taxane-based chemotherapy by exploring a repetitively dosed regimen of docetaxel coadministered with ^{153}Sm -EDTMP.

PATIENTS AND METHODS

Study Design

Patients were assigned to six different cohorts based on increasing doses first of docetaxel and then of ^{153}Sm -EDTMP. As demonstrated in Figure 1, for cohorts 1 through 5, one cycle consisted of docetaxel and ^{153}Sm -EDTMP followed by docetaxel alone 3 to 4 weeks later, followed by a 3- to 5-week observation period. Patients in cohort 6 received a third docetaxel administration 3 to 4 weeks after the second dose during each cycle. Cycle 1 toxicity was used to define dose-limiting toxicity (DLT); however, all cycle toxicities were recorded. Patients could receive additional cycles of treatment if requirements for toxicity recovery were met. The protocol was approved by the Memorial Sloan-Kettering Cancer Center institutional review board. All patients furnished written informed consent.

Patients

Men with histologically confirmed prostatic adenocarcinoma were eligible if they had at least three bone metastases and progressive CRMPD deter-

mined by imaging or by prostate-specific antigen (PSA). For the latter, a minimum of three increasing PSA values of at least 25% from a baseline of 4 ng/mL obtained ≥ 1 week apart or two measurements ≥ 2 weeks apart were required. For the former, new bone lesions by bone scintigraphy or progressive soft tissue disease by Response Evaluation Criteria in Solid Tumors (RECIST) were necessary.⁶ Patients were required to maintain testosterone levels of less than 50 ng/mL, fail antiandrogen withdrawal if on an antiandrogen as initial therapy, and have a Karnofsky performance score more than 60. One prior treatment with a bone-seeking radiopharmaceutical was permitted, as was concomitant use of bisphosphonates.

Patients were required to have a WBC count of at least $3,000/\mu\text{L}$, absolute neutrophil count of at least $1,500/\mu\text{L}$, platelet count of at least $100,000/\mu\text{L}$, and hemoglobin of ≥ 10 g/dL. Erythropoietin and RBC transfusion support were allowable to maintain eligibility. Bilirubin levels of less than the upper limit of normal were stipulated. ALT and AST levels had to be no greater than $1.5\times$ the upper limit of normal and serum creatinine less than 2.0 mg/dL.

Patients were excluded for symptomatic lymphadenopathy, more than three liver or lung metastases, long-bone fractures or spinal cord compression, and prior exposure to more than one course of external-beam radiation therapy for bone lesions.

Treatment

The starting dose of docetaxel was $65 \text{ mg}/\text{m}^2$, well within therapeutic range,^{1,2} whereas the starting dose of ^{153}Sm -EDTMP was $0.5 \text{ mCi}/\text{kg}$, half the US Food and Drug Administration–approved dose for pain palliation. Docetaxel dose was escalated to $75 \text{ mg}/\text{m}^2$, after which ^{153}Sm -EDTMP was escalated to $1.0 \text{ mCi}/\text{kg}$, as shown in Table 1. Because no significant toxicity was seen in cohort 5 cycle 1 using full doses of both drugs with ^{153}Sm -EDTMP dosed every 6 weeks, we chose to explore the regimen with an eye toward chronic therapy. In the interest of safety, we extended the dosing interval for the ^{153}Sm -EDTMP from every 6 weeks to every 9 weeks in cohort 6. All patients received 5 mg prednisone twice daily during the study and dexamethasone 4 mg twice daily the day before, of, and after docetaxel administration.

On day 1 of each cycle, ^{153}Sm -EDTMP was given intravenously at least 6 hours before administration of docetaxel to allow for renal clearance. On day 22, patients received a second dose of docetaxel in the absence of grade 3 or worse neutropenia, anemia, thrombocytopenia, or nonhematologic toxicity. A delay of 1 week was allowed for count recovery before the second docetaxel administration. For cohort 6, patients received a third dose of docetaxel on day 43, based on these same parameters. Additional cycles of treatment were permitted if patients did not have grade ≥ 3 nonhematologic toxicities, had grade 0 to 1 neutropenia, and had a platelet count of at least $100,000/\mu\text{L}$. A delay of 2 weeks was permitted between cycles to allow for recovery.

Hematologic measurements were taken at day 1 and every 7 days thereafter. Granulocyte colony-stimulating factor (G-CSF) was given for grade 4 neutropenia that did not resolve after day 15 after docetaxel administration to

Fig 1. (A, B) Treatment schedule. ^{153}Sm , samarium-153.

Table 1. Dose Escalation by Study Cohorts

Cohort	No. of Patients	Docetaxel Every 3 Weeks (mg/m^2)	^{153}Sm -EDTMP Every 6 Weeks Unless Noted (mCi/kg)
1	3	65	0.5
2	7*	70	0.5
3	3	75	0.5
4	3	75	0.75
5	6†	75	1.0
6	6†	75	1.0‡

Abbreviation: ^{153}Sm -EDTMP, samarium-153 ethylenediaminetetramethylphosphonate.

*Cohort expanded to further assess safety by principal investigator preference, not for a protocol-mandated expansion as a result of toxicity.

†Cohorts 5 and 6 were six patients by design.

‡Cohort 6 received ^{153}Sm -EDTMP every 9 weeks.

allow patients to stay on schedule. Grade 3 to 4 neutropenia for more than 7 days despite growth factor support or grade 3 thrombocytopenia triggered a 25% dose reduction of docetaxel and ^{153}Sm -EDTMP in subsequent treatment cycles. Dose reductions were imposed for both drugs in the event of other serious hematologic or nonhematologic toxicities. Patients were taken off the study if they required more than two dose reductions, experienced grade 3 or 4 nonhematologic toxicities, or had grade 2 events that failed to resolve within 2 weeks.

Study End Points

Safety. The primary end point of the study was safety, as measured by National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0. DLT was defined as any neutropenic fever, a grade ≥ 3 nonhematologic toxicity, grade 3 neutropenia that lasted for more than 29 days without G-CSF support, grade 4 neutropenia that lasted for ≥ 7 days despite growth factor support, grade 3 to 4 anemia or thrombocytopenia that lasted 5 or more days, or failure of count recovery to allow for docetaxel treatment alone or to allow for recycling. Maximum-tolerated dose (MTD) was defined as the dose preceding that of a cohort for which two or more DLTs occurred.

Antitumor effects. Antitumor responses were recorded per PSA Working Group 2 criteria for phase II studies of CRMPC.⁷ Soft tissue lesions were assessed according to RECIST criteria. PSA was assessed at every docetaxel administration. Computed tomography of the chest, abdomen, and pelvis and bone scintigraphy were obtained every two cycles (except for the final cohort, when they were obtained every 12 weeks to maintain consistency with previous cohorts).

Bone marker analyses. Indices of bone deposition (bone-specific alkaline phosphatase, osteocalcin) and bone resorption (serum and urine N-telopeptide) were assessed at every docetaxel administration.

Statistical Methods

The dose-escalation scheme of the protocol was such that if the true risk of toxicity were 0.10, 0.20, 0.30, 0.40, 0.50, or 0.60, then the probability of escalation would be 0.91, 0.71, 0.49, 0.31, 0.17, or 0.08, respectively.

To test whether bone markers changed significantly, the data were log-transformed, the marker concentrations were plotted against time, and an area under curve (AUC) of each marker was computed using the trapezoidal method.⁸ The following measure was used:

$$\Delta_i = \sum_j (AUC_{ij} - AUC_{ij0}) \quad (1)$$

where i indicates index of bone marker ($i = 1 \dots 8$) and j indicates index of patient ($j = 1 \dots 27$). Concentration versus time plots were used to examine the AUC of bone markers and PSA, to determine whether the AUC changed significantly over time, and to compare the change in AUC of bone markers to the change in AUC of PSA. Spearman ρ was used to estimate the association between the AUCs of each bone marker and PSA.

RESULTS

Patients

Twenty-eight patients with a median age of 69 years were enrolled onto the study (Table 1). The demographics of these patients are detailed in Table 2. The patients generally had been extensively pretreated; the median number of prior hormonal therapies was three, and 12 (43%) of 28 patients had received prior taxane therapy, of whom four patients (25%) were classified as having outright taxane-refractory disease (having experienced definitive disease progression biochemically or radiographically or both) before study registration. Although eligibility criteria limited the number of sites of prior radiation therapy, 75% of the patients had received some form of external radiation in the past. Nine patients received prior radiation

Table 2. Patient Characteristics at Baseline

Characteristic	Totals, All Cohorts (N = 28)
Age, years	
Median	69
Range	41-89
Extent of disease	
Bone only disease	22
Both measurable and bone disease	6
Prior treatment	
Taxane naïve	16
Taxane exposed but not refractory	8
Weekly taxane	3*
No. of cycles	
Median	5
Range	4-6
No. of doses	
Median	16
Range	15-18
Q3W docetaxel	4
No. of doses	
Median	6
Range	3-8
Docetaxel schedule not documented	1
Docetaxel refractory	4
Weekly docetaxel	1
No. of cycles	7
No. of doses	21
Q3W docetaxel	3
No. of doses	
Median	12
Range	7-17
No. of prior hormonal regimens	
Median	3
Range	1-5
Prior radiation therapy	21
Primary radiotherapy	17
Radiotherapy to metastatic sites	9†
Spine	7
Pelvis	3
Both primary and metastatic sites	5
Scores	
Baseline ECOG	
Median	1
Range	0-1
Gleason, n = 27	
Median	8
Range	6-9
Baseline PSA, ng/mL	
Median	262
Range	< 0.05-1199.41

Abbreviations: Q3W, every 3 weeks; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

*Two patients received docetaxel and one patient received paclitaxel.

†One patient has radiation therapy to two different metastatic sites.

tion to a metastatic site, whereas 17 patients underwent primary radiation therapy.

Treatment

Eighty-two cycles of treatment were delivered during the trial, for a total of 82 ^{153}Sm -EDTMP treatments and 156 docetaxel treatments.

Each patient received a median of three cycles (range, one to six cycles). Taxane-naïve patients received a median of six doses of docetaxel ($n = 16$, range one to 12 doses), whereas patients with taxane-exposed (but not refractory) disease received a median of five doses ($n = 8$; range, two to 13 doses), and patients with taxane-refractory disease only received a median of 3.5 doses ($n = 4$; range, one to eight doses). No patients met the criteria for a dose reduction.

Total cumulative doses of docetaxel and samarium did not seem to be wholly contingent on prior taxane exposure. The median cumulative dose of docetaxel received per patient in each cohort was 390, 490, 600, 225, 450, and 300 mg/m². In terms of doses, the median number of doses of docetaxel administered to each patient was six, seven, eight, three, six, and four in each respective cohort. Note that cohort 3 received the greatest amount of docetaxel—600 mg/m² or eight doses. Cohort 4, in which the median cumulative dose of docetaxel seemed to drop off, represents the first cohort in which the ¹⁵³Sm-EDTMP dose was escalated (to 0.75 mCi/kg). Conversely, the median total cumulative dose of ¹⁵³Sm-EDTMP was 2, 2, 2, 1.5, 3.5, and 2 mCi/kg per patient per cohort. Note that the highest cumulative exposure to ¹⁵³Sm-EDTMP was in cohort 5, when using full doses of ¹⁵³Sm-EDTMP given in a dose-dense fashion every 6 weeks. The most common reason for discontinuing treatment was disease progression (nine patients). Eight patients discontinued treatment because of hematologic toxicities. The remainder of patients came off for concurrent illness and other issues, as detailed in Appendix Table A1 (online only).

Safety

The greatest risk of toxicity was hematologic, as shown in Table 3.

Neutropenia

Neutropenia after treatment occurred across all cohorts and always recovered in time for re-treatment. One patient each in cohorts 5 and 6 experienced an uncomplicated neutropenic fever and recovered without sequelae. Twelve patients required G-CSF support for neutropenia.

Thrombocytopenia

Thrombocytopenia was not a DLT for any patient. Median cycle 1 nadir was 118,000/ μ L (range, 51,000 to 183,000/ μ L), and median all-cycle nadir was 80,000/ μ L (range, 7,000 to 172,000/ μ L). Six patients, representing cohorts 1, 2, 5, and 6, came off study for all-cycle thrombocytopenia. The median days to platelet recovery ($\geq 100,000$ / μ L) was 9 for all-cycle thrombocytopenia, with three patients (two from cohort 2 and one from cohort 5) having prolonged thrombocytopenia (159 to 238 days) that failed to recover after three, three, and four cycles. Patterns of platelet declines for cohorts 2 and 5 (which used the highest doses in the most dose-dense fashion of all cohorts) are compared in Figures 2A and 2B. As can be seen, curves are quite similar, underscoring that dose is only one factor among many (such as previous treatment and burden of disease) that may determine platelet toxicities.

Nonhematologic Toxicity

Cycle 1 adverse events are reported in Table 3. Of reported grade 3 or worse nonhematologic toxicities in cycle 1, fatigue (4%), febrile neutropenia (7%), and hyperglycemia (7%) were likely related to docetaxel treatment. Two patients discontinued treatment because of grade 1 edema at their request, although the protocol did not demand

Table 3. Cycle 1 Adverse Events (N = 28*)

Adverse Event†	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Blood/bone marrow								
Lymphopenia	0	0	0	0	13	46	0	0
Hemoglobin	28	100	7	28	1	4	0	0
Leukocytes	10	36	22	79	19	68	5	18
Neutrophils	9	32	21	75	21	75	12	43
Platelets	25	89	2	7	0	0	0	0
Constitutional, fatigue	10	36	1	4	2	7	0	0
Coagulation, INR	2	7	2	7	1	4	0	0
Infection, febrile neutropenia	0	0	0	0	2	7	0	0
Metabolic/laboratory								
Albumin, low	8	29	0	0	0	0	0	0
Alkaline phosphatase	13	46	6	21	5	18	0	0
AST	8	29	0	0	0	0	0	0
Creatinine	5	18	2	7	0	0	0	0
Glucose, high	25	89	11	39	2	7	0	0
Neurology								
Cerebrovascular ischemia	0	0	0	0	0	0	1	4
Syncope	0	0	0	0	1	4	0	0
Visual changes	0	0	0	0	1	4	0	0
Pain, various sites	4	14	4	14	0	0	0	0

Abbreviation: INR, international normalized ratio.

*Twenty-eight patients receiving 28 cycles of therapy, which included 57 doses of docetaxel and 28 doses of samarium-153 ethylenediaminetetramethylenephosphonate. Percentages are based on 28 patients.

†Events $\leq$ grade 2 are reported if they occurred in $\geq 25\%$ of patients, unless grade 3 to 4 toxicity was noted. All grade 3 to 4 events are included.

Fig 2. (A, B) Post-treatment changes in platelets (PLT) for patients in cohorts 2 and 5. Both show a decline in platelet counts. A clear relationship between the severity or duration of thrombocytopenia and either the dose of docetaxel or the dose of samarium-153 (^{153}Sm) ethylenediaminetetramethylenephosphonate is not seen.

it. All-cycle adverse events are reported in Appendix Table A2 (online only).

Antitumor Effects

Figure 3 demonstrates the PSA waterfall curves for all assessable patients, broken down by taxane exposure and cohort. Two patients were removed from study for protocol violations and are assessable for toxicity only. Fifteen (58%) of 26 assessable patients achieved more than 50% PSA decline on study, including eight (57%) of the chemotherapy-naïve patients, five (62.5%) of the previously taxane-treated patients, and two (50%) of the patients with taxane-refractory disease. One partial response was seen by RECIST criteria among six patients who had measurable disease.

Bone Markers

Urine and serum *n*-telopeptides changed significantly as a result of treatment, as did osteocalcin (as shown in Appendix Tables A3 and A4, online only). These three markers were correlated with PSA decline (correlation coefficients of 0.5 [95% CI, 0.120 to 0.754; $P = .009$] and 0.43 [95% CI, 0.056 to 0.726; $P = .022$]). Bone-specific alkaline phosphatase, however, did not achieve such significance, nor was it correlated with PSA.

DISCUSSION

This study demonstrates that historic concerns about repetitive dosing of bone-seeking radiopharmaceuticals with chemotherapy are disproportionate to the actual toxicity of treatment. We demonstrated that ^{153}Sm -EDTMP can be coadministered with docetaxel at life-prolonging doses repetitively. MTD was not reached, and thrombocytopenia was not the primary cause of treatment discontinuation. Further, thrombocytopenia was not associated with any particular cohort, which speaks to the fact that factors other than dose can determine hematologic toxicity, including disease burden, prior marrow insults from prior treatment, and degree of marrow infiltration by tumor.

The study raises a number of provocative issues, both for the clinical investigator and community practitioner. For the clinical investigator, the primary question is what is the appropriate phase II dose? To address this issue, much must be read into cohorts involving small numbers of patients representing mixed tumor burdens, taxane exposures, and treatment histories, as is true with any phase I study. Even with these caveats, though, it is instructive to dissect what factors limited treatment. Historically, patients with

Fig 3. Waterfall graphs of prostate-specific antigen (PSA) response by cohort. (A) All patients; (B) patients with taxane-naïve disease; (C) taxane pretreated patients; (D) patients with taxane-refractory disease.

taxane-naïve CRMPC tolerate a median of 9.5 doses of docetaxel and prednisone.² By contrast, the average number of treatments that each patient received in this study was 2.9 treatments of ^{153}Sm -EDTMP and 5.6 doses of docetaxel.

Two factors seemed to limit treatment and total cumulative exposures to either drug. The first seemed to be prior taxane exposure, as disease progression was the leading cause of treatment termination (nine patients), whereas hematologic toxicity limited treatment in eight patients, six of whom had thrombocytopenia. The second may have been the dose of ^{153}Sm -EDTMP. Patients in cohort 3, who received 75 mg/m² of docetaxel and 0.5 mCi/kg of ^{153}Sm -EDTMP, seemed to tolerate the highest median cumulative exposure to docetaxel, amounting to eight doses per patient. However, when the dose of ^{153}Sm -EDTMP was escalated to more than 0.5 mCi/kg in cohorts 4 to 6, patients received lower cumulative doses of docetaxel. It should be noted that these later cohorts also did not have a disproportionate number of patients with taxane-refractory disease (indeed, eliminating them from the analysis does not change the finding).

For a phase II study of patients with taxane-naïve disease, the optimal dose and schedule would seem to be that of cohort 3, as it seemed to be associated with the highest cumulative docetaxel exposure per patient, and maximizing docetaxel is of prime importance to such patients, as it is the only drug known to prolong life. Conversely, for patients with taxane-refractory disease, the priority is to maximize the ^{153}Sm -EDTMP rather than the docetaxel. Whether chemotherapy sensitizes patients to the delivered radiation, the ^{153}Sm -EDTMP resensitizes patients to chemotherapy, or some other interaction is at work is not clear, but it does seem that the combination of the two can induce responses in selected patients with taxane-refractory disease. In Cohort 5, patients received the highest cumulative dose ^{153}Sm -

EDTMP as well as full doses of docetaxel, suggesting that full doses of both drugs using an every-6-weeks cycle length is optimal for a phase II study of patients with taxane-refractory disease.

Both of these preliminary findings are surprising. We had presumed that the optimal phase II dose would be that of cohort 6, as we guessed that the every-9-weeks dosing of ^{153}Sm -EDTMP would be gentler and allow for more chronic treatment. On the basis of this assumption, we designated cohort 6 as the expansion cohort, which is presently being explored. However, it does seem that the regimen of cohort 6 does not optimize exposure to either docetaxel or ^{153}Sm -EDTMP. We are therefore reconsidering which cohorts to further explore on the basis of the taxane sensitivity of the patients.

For the community practitioner, the data from this study have profound implications for the use of bone-seeking radiopharmaceuticals. First, they challenge the conception that ^{153}Sm -EDTMP should be used only to palliate pain in patients with the most advanced disease, who have experienced treatment failure with prior chemotherapy and are near the end of life. ^{153}Sm -EDTMP can and should be considered as a palliative measure in patients who are chemotherapy-naïve or otherwise early in the natural history of the disease, both alone and in combination with chemotherapy. Such early applications of ^{153}Sm -EDTMP are safe, and patients who are suffering from diffuse bone pain should not be denied this valuable tool as a result of largely archaic concerns that ^{153}Sm -EDTMP causes prolonged and profound cytopenias that preclude either chemotherapy or other systemic treatments. This study demonstrates that such events are rare, and when cytopenias do limit therapy, they generally occur after several doses are administered with chemotherapy.

Our correlative data suggest that this regimen does mitigate the deleterious effects that disease has on bone metabolism. In particular,

indicators of resorption significantly were reduced with treatment, and such reductions were significantly associated with PSA declines. Baseline markers of bone resorption and formation are prognostic for disease extent and survival in prostate cancer, as are post-treatment changes.⁹⁻¹¹ It should be noted, however, that 15 study participants were already receiving zoledronic acid during this regimen, and only two patients actually started taking zoledronic during the course of treatment.

In summary, the combination of docetaxel and ¹⁵³Sm-EDTMP seems to be safe and can be given with docetaxel at doses and schedules shown to prolong life. Phase II studies specifically examining the taxane-refractory and taxane-naïve populations are planned.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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