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ORIGINAL REPORT

Double-Blinded Randomized Study of High-Dose Calcitriol Plus Docetaxel Compared With Placebo Plus Docetaxel in Androgen-Independent Prostate Cancer: A Report From the ASCENT Investigators

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Oregon Health & Science University (OHSU) and Tomasz M. Beer have a significant financial interest in Novacea Inc, a company that may have a commercial interest in the results of this research and technology. This potential conflict was reviewed and a management plan approved by the OHSU conflict of interest in research committee and the integrity program oversight council was implemented.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
To compare the safety and activity of DN-101, a new high-dose oral formulation of calcitriol designed for cancer therapy, and docetaxel with placebo and docetaxel.

Patients and Methods
Patients with progressive metastatic androgen-independent prostate cancer and adequate organ function received weekly docetaxel 36 mg/m^2 intravenously for 3 weeks of a 4-week cycle combined with either 45 μg DN-101 or placebo taken orally 1 day before docetaxel. The primary end point was prostate-specific antigen (PSA) response within 6 months of enrollment, defined as a 50% reduction confirmed at least 4 weeks later.

Results
Two hundred fifty patients were randomly assigned. Baseline characteristics were similar in both arms. Within 6 months, PSA responses were seen in 58% in DN-101 patients and 49% in placebo patients ($P = .16$). Overall, PSA response rates were 63% (DN-101) and 52% (placebo), $P = .07$. Patients in the DN-101 group had a hazard ratio for death of 0.67 ($P = .04$) in a multivariate analysis that included baseline hemoglobin and performance status. Median survival has not been reached for the DN-101 arm and is estimated to be 24.5 months using the hazard ratio, compared with 16.4 months for placebo. Grade 3/4 adverse events occurred in 58% of DN-101 patients and in 70% of placebo-treated patients ($P = .07$). Most common grade 3/4 toxicities for DN-101 versus placebo were neutropenia (10% *v* 8%), fatigue (8% *v* 16%), infection (8% *v* 13%), and hyperglycemia (6% *v* 12%).

Conclusion
This study suggests that DN-101 treatment was associated with improved survival, but this will require confirmation because survival was not a primary end point. The addition of weekly DN-101 did not increase the toxicity of weekly docetaxel.

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INTRODUCTION

Calcitriol (1,25-dihydroxycholecalciferol, 1,25$(OH)_2$-D_3) is the natural ligand for the vitamin D receptor (VDR). This compound, as well as synthetic VDR ligands, has been extensively examined using in vitro and in vivo models of adenocarcinoma of the prostate[1-7] and many other neoplasms. These studies have indicated significant antitumor activity through inhibition of proliferation, induction of apoptosis, and reduction in tumor invasiveness and angiogenesis. The antineoplastic activity of VDR ligands is synergistic or additive with the activity of several classes of agents including cytotoxic chemotherapy drugs, such as paclitaxel,[8] docetaxel,[9] platinum compounds,[10] and mitoxantrone.[11] The antineoplastic activity of calcitriol occurs at concentrations of calcitriol that substantially exceed the physiologic range, and are achievable with intermittent, but not continuous dosing of calcitriol in humans.[12-18]

Docetaxel-containing chemotherapy was recently shown to prolong survival and has become the standard of care in metastatic androgen-independent prostate cancer (AIPC).[19,20] Calcitriol was first combined with docetaxel in a phase

II trial reported by investigators at Oregon Health & Science University (Portland, OR).[21] Prostate-specific antigen (PSA) decline of 50% or greater was seen in 81% of patients.

In order to overcome the limitations of previous calcitriol formulations (nonlinear, variable pharmacokinetics and the very large number of capsules required at one time), Novacea Inc (South San Francisco, CA) developed DN-101, a high concentration formulation of calcitriol specifically designed for use in cancer treatment.[22]

AIPC Study of Calcitriol Enhancing Taxotere (ASCENT) is a double-blind randomized phase II study to further evaluate the efficacy and safety of DN-101 (high-dose calcitriol) plus weekly docetaxel compared with placebo plus weekly docetaxel in AIPC.

PATIENTS AND METHODS

Eligibility

Men with histopathologically or cytologically proven metastatic adenocarcinoma of the prostate with evidence of progression (the development of new metastatic lesions or rising PSA[23]) despite standard hormonal management (orchiectomy, gonadotropin-releasing hormone agonist or antagonist including withdrawal of antiandrogens, if applicable; 6 weeks for bicalutamide, 4 weeks for flutamide or nilutamide) were eligible. Other eligibility criteria were: serum PSA $\geq$ 5.0 ng/mL, serum testosterone level $\leq$ 50 ng/dL, Eastern Cooperative Oncology Group performance status $\leq$ 2, life expectancy $\geq$ 3 months, age $\geq$ 18 years, patient agreement to use adequate contraception, and patient ability to give informed consent.

Patients were excluded if they had an active malignancy within 5 years (except nonmelanoma skin cancer), significant active medical illness that would preclude protocol treatment, a history of hypercalcemia or vitamin D toxicity, or hospitalization for treatment of angina, myocardial infarction, or congestive heart failure in the previous 12 months. Patients were also excluded for kidney stones (calcium salt) within 5 years, hypersensitivity to calcitriol or drugs formulated with polysorbate-80, grade 2 or higher peripheral neuropathy, neutrophil count less than 1,500/mm^3, platelet count lower than 100,000/mm^3, serum creatinine more than upper limit of normal (ULN), serum calcium more than ULN (for patients with an albumin lower than 3.0, a corrected calcium = serum calcium + [0.8][3.5 − serum albumin] was used), conjugated bilirubin more than ULN, alkaline phosphatase more than 4 $\times$ ULN (patients with known bone involvement and a normal conjugated bilirubin, ALT, and AST were not excluded), ALT or AST more than 2.0 $\times$ ULN when alkaline phosphatase is less than 2.5 $\times$ ULN, ALT or AST more than 1.5 $\times$ ULN when alkaline phosphatase is more than 2.5 $\times$ ULN.

In addition, patients were excluded for prior investigational therapy or use of calcitriol within 30 days, prior chemotherapy for prostate cancer except for adjuvant therapy more than 12 months before enrollment, prior chemotherapy with docetaxel, treatment with radiotherapy within 4 weeks or treatment with other radiopharmaceuticals within 8 weeks. The study was approved by institutional review boards at all participating institutions.

Study End Points and Statistical Design

The primary objective of this study was to evaluate the proportion of patients achieving PSA response ($\geq$ 50% PSA reduction, confirmed at least 4 weeks later) in the two treatment arms. Secondary objectives included overall survival, PSA,[23] tumor, and clinical progression-free survival, tumor response rate in measurable disease, skeletal morbidity-free survival, as well as safety and tolerability of the study treatment. Progression by serum PSA was defined by consensus criteria.[23] Tumor progression was defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[24] Skeletal morbidity-free survival was defined as the time from random assignment to a skeletal-related event or death from any cause. Skeletal-related events were defined as pathologic bone fracture, spinal cord compression, surgery to the bone, or radiation to the bone. Clinical progression was defined as either tumor progression, occurrence of a skeletal-related event, or death from any cause.

The primary analysis for efficacy was on the intention to treat population and toxicity was evaluated in the as-treated population. These two populations were identical.

A sample size of at least 116 patients per treatment group was expected to provide 85% power to detect a 20% absolute increase in the PSA response rate (from 45% to 65%) with a two-sided significance level of .045 based on a two-group comparison using an uncorrected χ^2 test. The significance level of .045 was selected to account for the alpha of .005 allocated to a planned interim analysis of PSA response rate. The power for the secondary end points was lower than 80% and there was no plan for correction for multiple comparisons.

The initial analysis plan underwent two modifications. The first modification was made before any analysis and called for a change in the primary end point from PSA response overall to PSA response achieved within 6 months of enrollment and for elimination of a planned interim analysis of the primary end point. The second modification to the analysis plan was made after the analysis of the primary end point and an interim analysis of secondary end points and prior to the prespecified final analysis of survival. This modification specified that the final analysis of survival was to be performed using multivariate Cox regression including the known prognostic factors of baseline hemoglobin and performance status as covariates. The modified analysis plan also included a sensitivity analysis of survival data with unadjusted log-rank test.

Pretreatment Evaluation

A complete physical examination, history of skeletal-related events, and concomitant medications were reviewed. A radionuclide bone scan, computed tomography scan of the abdomen and pelvis, and radiographs of the lateral, thoracic, and lumbar spine were obtained. Pretreatment laboratory evaluations included a hematology profile, serum chemistry profile, serum lactate dehydrogenase, serum PSA, and a urinalysis.

Random Assignment

An unstratified random assignment, blocked by center was used to assign patients to the DN-101 or placebo groups.

DN-101 (45 μg) or placebo was administered orally on day 1 followed by docetaxel 36 mg/m^2 intravenously on day 2 along with dexamethasone (4 mg orally 12 hours before, 1 hour before, and 12 hours after docetaxel administration). This regimen was administered weekly for 3 consecutive weeks of a 4-week cycle. For each patient, the first dose of docetaxel (week 1, cycle 1 only) was attenuated (27 mg/m^2) to collect additional safety data for the combination of DN-101 with docetaxel.

Treatment on ASCENT continued until disease progression (either by PSA measurements or tumor assessments by imaging), unacceptable toxicity, or patient request. Patients enrolled in ASCENT who reached a confirmed PSA $\leq$ 4.0 ng/mL and met criteria for PSA response had the option to continue their treatment in the form of intermittent chemotherapy as previously described.[25] Briefly, treatment was suspended until PSA rose by 50% and was at least 2 ng/mL or there was other evidence of progression, at which time study treatment was resumed. Patients continued regular monitoring during this intermittent therapy phase. For patients on intermittent treatment, progression during active treatment was required for withdrawal from study treatment.

Concomitant Medications

Primary hormonal therapy with gonadotropin-releasing hormone agonists or antagonists was maintained during the study. Magnesium-containing antacids, bile-resin binders, calcium supplements, ketoconazole and related compounds, estrogen-containing compounds and any other hormonal or chemotherapeutic agents, radiopharmaceutical or external-beam radiation for prostate cancer were not allowed during study treatment. The use of bisphosphonates was not restricted.

On Study Evaluations

Physical examination, assessment of adverse events including skeletal-related events, concomitant medications, urinalysis, and serum PSA were completed every 4 weeks. In addition, body weight, hematology profile, chemistry profile, and urinalysis (cycles 1 and 2 only) were evaluated weekly on treatment visits. A radionuclide bone scan was obtained at the time of PSA

progression and as clinically indicated. In patients with measurable disease at baseline, computed tomography (CT) scans of the abdomen and pelvis were obtained every 8 weeks and at the time of PSA progression. In patients with no measurable disease at baseline, CT scans of the abdomen and pelvis were obtained at the time of PSA progression and as clinically indicated. Radiographs of the lateral thoracic and lumbar spine were obtained at the time of PSA progression and as clinically indicated to assess for skeletal-related events.

RESULTS

Patients

Two hundred fifty patients were randomly assigned at 48 sites between September 2002 and January 2004. At the time of this data analysis the median duration of follow-up was 18.3 months, 229 patients (92%) have completed study treatment and 122 patients (49%) have died. All randomly assigned patients were treated and all patients are included in the analyses presented here.

The baseline characteristics of patients are summarized in Table 1. Briefly, the two groups were well matched with respect to age, performance status, extent of disease, serum PSA, and serum lactate dehydrogenase. There were no statistically significant differences between the two groups in any of these categories.

Table 1. Patient Characteristics

Characteristic	Placebo + Docetaxel	DN-101 + Docetaxel
Randomly assigned, No.	125	125
Age, years		
Median	70	68
Range	47-92	45-87
Race, %		
White	84	80
African American	10	13
Other	6	7
ECOG performance status, %		
0	47	54
1	47	43
2	6	3
Site of metastatic disease, %		
Bone	85	90
Any measurable disease	47	38
Lymph node*	44	35
Liver*	5	8
PSA, ng/mL		
Median	91	123
Range	5-6,288	4-4,453
Hemoglobin, g/dL		
Median	12.5	12.5
Range	8.1-15.5	8.0-15.2
LDH, U/L		
Median	231	211
Range	82-1,688†	93-3,759‡
Alkaline phosphatase, U/L		
Median	130	211
Range	34-2,025§	36-3,739¶
Participated in intermittent chemotherapy	20	25

Abbreviations: DN-101, high-dose oral formulation of calcitriol; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.
*Several patients had measurable disease in more than one site.
†n = 111.
‡n = 115
§n = 120.
¶n = 124.

Response to Therapy

PSA decline (> 50% confirmed 4 weeks later) within 6 months of enrollment, the primary end point, was reached in 49% of placebo-treated patients and 58% of DN-101-treated patients ($P = .16$). At any time while on study, this end point was achieved in 52% of placebo-treated patients and 63% of DN-101-treated patients ($P = .07$). Median time to PSA response was 5.3 months in placebo-treated patients and 2.9 months in DN-101-treated patients ($P = .06$). Median duration of PSA progression-free survival was 7.6 months for placebo-treated patients and 7.9 months for DN-101-treated patients ($P = .7$).

Measurable disease meeting RECIST criteria was present in 59 of placebo-treated patients (47%) and 48 of DN-101 treated patients (38%). Tumor response in this group of patients was seen in 14 (24%) and 14 (29%) of placebo and DN-101-treated patients, respectively ($P = .51$). Median duration of tumor progression-free survival and median duration of clinical progression-free survival could not be reliably assessed due to the lack of regularly scheduled tumor imaging for those patients (57%) who entered the study without measurable tumor lesions meeting RECIST criteria as target lesions and because many of the patients with measurable disease were removed from the study due to increases in PSA without evidence for objective disease progression.

Skeletal Morbidity-Free Survival

Duration of skeletal morbidity-free survival is shown in Figure 1. The median duration of skeletal morbidity-free survival trended in favor of DN-101 (13.4 months) over placebo (11.9 months; hazard ratio [HR], 0.78; 95% CI, 0.57 to 1.074; $P = .13$). Forty-five patients in the placebo group and 38 patients in the DN-101 group experienced a skeletal-related event. The types of skeletal-related events observed in the placebo and DN-101 groups were: bone fracture (11 and 14), spinal cord compression (6 and 6), surgery to the bone (0 and 1), and radiation to the bone (29 and 18). The use of zoledronic acid was

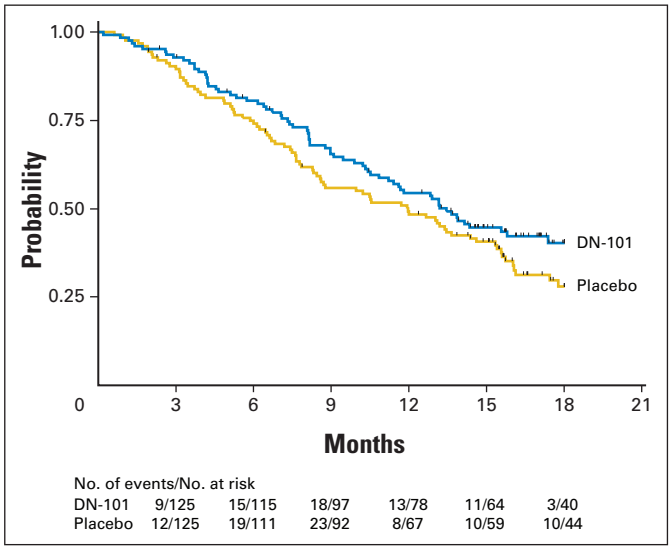

Fig 1. Kaplan-Meier curves of skeletal morbidity-free survival. DN-101, a new high-dose oral formulation of calcitriol.

neither required nor prohibited in ASCENT (Table 2). Eighty-five subjects (40 placebo treated; 45 DN-101 treated) received zoledronic acid while on study. Among patients who received zoledronic acid, the skeletal-related event incidence rate in the DN-101 and placebo group was 29% and 40%, respectively. For the 165 subjects who did not receive zoledronic acid, the skeletal-related event incidence rate in the DN-101 and placebo groups was 31% and 34%, respectively.

Overall Survival

The secondary end point of overall survival is shown in Figure 2. After adjustment for baseline characteristics of hemoglobin and Eastern Cooperative Oncology Group performance status, overall survival showed a promising improvement in the DN-101 group over the placebo group with a HR of 0.67 (95% CI, 0.45 to 0.97; $P = .04$). While the median survival in the placebo was 16.4 months, it has not been reached in the DN-101 group, but is estimated to be 24.5 months using the adjusted HR. Likewise, in a sensitivity analysis, the unadjusted HR similarly favored DN-101 (HR, 0.70; 95% CI 0.48 to 1.028; $P = .07$).

Toxicity

All adverse events are reported regardless of perceived relationship to treatment. Overall, no increase in toxicity was seen with the addition of DN-101 to docetaxel. There were reductions in the frequency of several classes of adverse events observed in the DN-101-treated group. The incidence of any grade 3 or 4 adverse events was 70% in placebo treated patients and 58% in DN-101 treated patients ($P = .065$). Adverse effects leading to discontinuation of therapy were seen in 28% of placebo-treated patients and 22% of DN-101-treated patients. Serious adverse events, generally those requiring hospitalization, were observed in 41% of placebo-treated patients and 27% of DN-101-treated patients ($P = .023$).

Table 2. Toxicity

	%			
	Placebo + Docetaxel (n = 125)		DN-101 + Docetaxel (n = 125)	
Toxicity	Grade 3/4	All	Grade 3/4	All
Hematologic				
Leukopenia	4	7	4	9
Neutropenia	8	14	10	14
Neutropenic fever	0	0	0	0
Anemia	6	33	4	30
Thrombocytopenia	0	3	0	4
Nonhematologic				
Fatigue	16	81	8	71
Infection	13	55	8	45
Nausea	3	52	4	46
Diarrhea	5	50	5	48
Dysgeusia	1	41	0	40
Alopecia	0	41	0	45
Anorexia	2	38	2	30
Peripheral edema	2	37	1	31
Constipation	2	33	2	34
Nail disorder	1	32	0	33
Lacrimation	1	31	1	33
Insomnia	0	30	0	24
Hyperglycemia	12	26	6	20
Dyspnea	6	25	3	18
Back pain	4	24	4	22
Vomiting	5	23	2	23
Arthralgia	4	22	3	17
Cough	0	22	0	30
Epistaxis	0	22	1	26
Asthenia	2	18	5	20

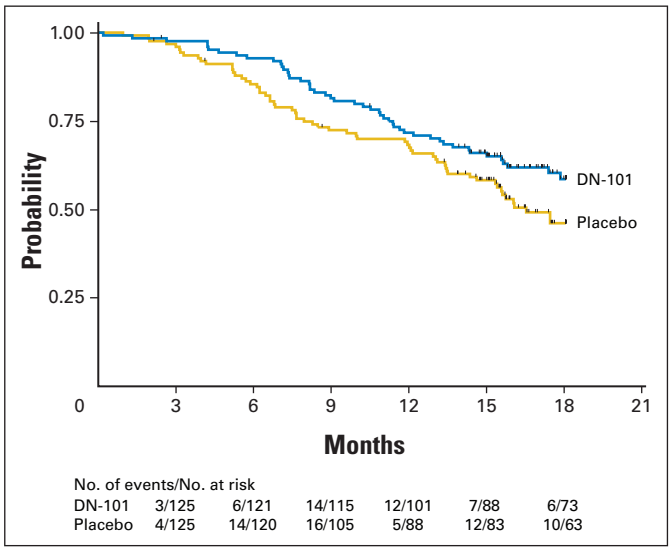

Fig 2. Kaplan-Meier curve of overall survival. DN-101, a new high-dose oral formulation of calcitriol.

Grade 3 or 4 hematologic toxicity was uncommon and no patients in either arm were diagnosed with neutropenic fever. Among the grade 3 or 4 nonhematologic toxicities, the most common were fatigue (16% placebo; 8% DN-101), infection (13% placebo; 8% DN-101), and hyperglycemia (12% placebo; 6% DN-101). Adverse event frequencies are summarized in Table 2.

Toxicities that might be expected with administration of supraphysiologic doses of calcitriol were uncommon with weekly administration of DN-101 except for mild hypercalcemia. There were no grade 3 or 4 creatinine elevations, hypercalcemia, or renal calculi. Six percent of placebo-treated patients and 7% of DN-101-treated patients had grade 1 to 2 creatinine elevation, 8% of placebo-treated patients and 33% of DN-101-treated patients had transient hypercalcemia. All the hypercalcemia episodes observed in the DN-101 arm were grade 1 and required no intervention, and did not result in dose reduction or delay in therapy. In the placebo arm, there was one episode of grade 3 hypercalcemia and all other episodes of hypercalcemia were grade 1 and were self-limited. No patients on placebo and one patient on DN-101 experienced symptomatic renal calculi.

Exploratory Analyses of Toxicity

The observed reduction in serious adverse events in the DN-101-treated group prompted exploratory analyses of safety. The observed reduction in serious adverse events in the DN-101 treated group does not appear to be due to a difference in the docetaxel exposure. The DN-101-treated group received a median cumulative dose of 1,044 mg (range, 64 to 3,586 mg) while the placebo-treated group received a median cumulative dose of 1,062 mg (range, 43 to 3,686 mg). When expressed as dose of docetaxel per body-surface area, the cumulative dose of docetaxel for DN-101-treated patients was 524.8 mg/m^2 and for placebo-treated patients was 506.7 mg/m^2. Likewise, the median length of time on study

treatment was 154 days for the DN-101-treated patients and 155 days for the placebo-treated patients. There were fewer gastrointestinal (2.4% *v* 9.6%; $P = .02$) and thromboembolic (1.6% *v* 7.2%; $P = .03$) serious adverse events in the DN-101 arm as compared with the placebo arm. All other categories of serious adverse events were balanced between the two groups.

DISCUSSION

ASCENT is the first placebo-controlled randomized study to test targeting the VDR for prostate cancer treatment. The addition of DN-101 to weekly docetaxel did not produce a statistically significant improvement in the PSA response rate. Overall the response rate was 63% in DN-101-treated patients and 52% for placebo-treated patients ($P = .07$). In contemplating the meaning of these PSA response data, it is worthwhile to consider the limitations of the PSA response as a predictor of a survival benefit that have come to light since ASCENT was designed. Southwest Oncology Group 9916 investigators showed that a 50% reduction in PSA did not satisfy the Prentice criteria for surrogacy.[26] TAX327 investigators reported that the PSA response rate explained approximately half of the observed survival differences.[19,27]

ASCENT results are consistent with these observations in so far as the apparent survival advantage seen with DN-101 is more impressive than the PSA response rates might lead one to expect. The addition of DN-101 to docetaxel was associated with a reduction in the risk of death by approximately one third. If confirmed in a phase III trial, this represents a large difference in this disease where randomized studies of 3-weekly docetaxel-based chemotherapy, using mitoxantrone and prednisone as control therapy, reported HRs for death of 0.8 and 0.76.[19,20]

The addition of weekly DN-101 to weekly docetaxel was not associated with any apparent increase in toxicity. This encouraging finding is consistent with the previously reported phase II results from Oregon Health & Science University.[21] The lack of toxicity attributable to DN-101 means that treatment assignment was in fact blinded to patients and caregivers and therefore increases our confidence in the observations made within ASCENT.

In an exploratory safety analysis, the number of serious gastrointestinal events was reduced in the DN-101 arm (2.4%) as compared with the placebo arm (9.6%; $P = .02$). Previous epidemiologic investigations have established that serum concentrations of vitamin D are inversely correlated with the proliferation of the colonic epithelium as determined by the crypt index in rectal biopsies of healthy human subjects.[28] Similar studies in animal models showed that higher levels of vitamin D metabolites are associated with reduced proliferation of gastrointestinal epithelial cells.[29] Therefore, one mechanism by which DN-101 might reduce the gastrointestinal toxicity of docetaxel would be to induce temporary cell cycle arrest in the rapidly proliferating cells of the gastrointestinal tract, rendering them less sensitive to the cytotoxic effects of docetaxel chemotherapy. This hypothesis should be tested prospectively in future studies of DN-101.

The trends favoring DN-101 over placebo with regard to skeletal morbidity-free survival are consistent with the hypothesis that more effective antineoplastic therapy may result in delay of skeletal-related events. It is also possible that the observed trends reflect direct effects of DN-101 on bone metastases. These hypotheses should also be tested prospectively in future studies.

In summary, the survival difference between the two groups, the other efficacy results, and the safety profile of DN-101 seen in ASCENT are compelling for further evaluation of this combination in AIPC. These results have led to the initiation of a phase III study (ASCENT-2) that compares the weekly DN-101 plus weekly docetaxel regimen described here to the standard 3-weekly regimen of docetaxel therapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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