CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Open-Label Study Evaluating DN-101 in Combination with Docetaxel in Androgen-Independent Prostate Cancer (AIPC) (ASCENT-2)
Sponsor:	Novacea, Inc. 601 Gateway Blvd., Suite 800 South San Francisco, CA 94080
IND No.:	64,141
EudraCT number	2006-001702-88
Protocol No.:	011-007
Study Chairs:	[redacted]
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Medical Monitor:	[redacted]
Study Contact (Germany):	[redacted]
Protocol Version/Date:	FINAL, 16 November 2005 Amendment 1, FINAL, 24 April 2006

CONFIDENTIALITY STATEMENT

1. PROTOCOL SYNOPSIS

NAME OF SPONSOR/COMPANY: Novacea, Inc. **TITLE OF STUDY:** A Phase 3, Randomized, Open-label Study Evaluating DN-101 in Combination with Docetaxel in Androgen-Independent Prostate Cancer (AIPC) (ASCENT-2)

NAME OF FINISHED PRODUCT:	**NAME OF ACTIVE INGREDIENT:**
DN-101	Calcitriol
STUDY PERIOD (YEARS):	**PHASE OF DEVELOPMENT:**
2-3 years	Phase 3

OBJECTIVES:

Effectiveness

The primary objective of this study is:

To evaluate the efficacy of weekly DN-101 in combination with weekly docetaxel (the ASCENT regimen) in the treatment of metastatic AIPC as measured by duration of survival.

The secondary objectives of this study are:

1) To determine the efficacy of ASCENT regimen as measured by thromboembolic event (TE) rate
2) To determine the efficacy of ASCENT regimen as measured by duration of skeletal-related event (SRE)-free survival

The effect of the ASCENT regimen on quality of life (QOL), pain, and PSA will be evaluated as exploratory analyses. QOL (FACT-P and related questions, including measurement of fatigue using the Brief Fatigue Inventory) and pain (the Brief Pain Inventory) will only be assessed at sites in North America.

Safety

To evaluate the safety and tolerability of the ASCENT regimen. In particular, the serious adverse event (SAE) rate and gastrointestinal (GI) event rate will be specified as safety endpoint analyses.

Note

The following sub-studies will be performed under separate protocols at selected sites in North America:

- Population pharmacokinetics (PK)
- Biomarkers

METHODOLOGY:

This Phase 3 study is a randomized, open-label, multicenter, international study. Subjects will be randomized 1:1 to one of two study treatment arms through a centralized procedure. The randomization will be stratified by geographic region and Eastern Cooperative Oncology Group (ECOG) performance status. The two study treatment arms are:

- Control Arm: Every three weeks docetaxel and twice daily prednisone (up to 30 weeks)
- ASCENT Arm: Once weekly DN-101 in combination with weekly docetaxel (up to 30 weeks)

The study will consist of two phases: the Study Treatment phase and the Follow-up phase. The Study Treatment phase is defined as the period in which the subject receives the study treatment (Control Arm or ASCENT Arm). The Follow-up phase is defined as the period after the subject has completed the Study Treatment phase until end of study. Subjects in the ASCENT Arm may continue to receive treatment with DN-101.

Safety and efficacy evaluations will be performed at specified time points throughout the study.

Blood samples for hematology, serum chemistry, serum testosterone, and prostate-specific antigen (PSA) levels will be obtained at baseline. Docetaxel-related laboratory assessments will be performed per standard of care as directed in the labeling. Laboratory assessments relating to treatment with DN-101 need to include serum chemistry panel (including serum calcium and serum creatinine) and will be performed at specified time points in the study. Clinically significant abnormal lab values will be reported as adverse events.

Number of Subjects (Planned and Analyzed)

Approximately 900 subjects are planned for enrollment into the study.

Diagnosis and Main Criteria for Inclusion

Adult subjects must have:

- Progressive castrate metastatic prostate cancer (detectable disease on an imaging study)
- No prior chemotherapy except for estramustine
- Histologically or cytologically proven adenocarcinoma of the prostate
- Adequate bone marrow, renal, and hepatic function

Subjects who have serum calcium above the ULN are ineligible.

ASCENT Arm: Dose and Mode of Administration

One capsule (45 µg) of DN-101 (study drug) will be taken orally (PO) on days 1, 8, and 15 of a 28-day cycle.

Docetaxel [36 mg/m^2 body surface area (BSA)] will be administered as a 30-minute intravenous (IV) infusion on days 2, 9, and 16 of each 28-day cycle. Dexamethasone (8 mg PO) will be given about 12 hours, 3 hours, and 1 hour prior to each docetaxel

infusion in each cycle.

Control Arm: Dose and Mode of Administration

Docetaxel (75 mg/m^2 BSA) will be administered as a 1-hour IV infusion on day 2 of a 21-day cycle. Dexamethasone (8 mg PO) will be given about 12 hours, 3 hours, and 1 hour prior to docetaxel infusion in each cycle. Prednisone 5 mg PO will be given bid starting on day 1 of cycle.

Duration of Treatment

Treatment with docetaxel (Control Arm and ASCENT Arm) will continue for up to 30 weeks, or until unacceptable docetaxel toxicity or clinical disease progression (as per Section 10.1). In cases of treatment delays, subjects should continue docetaxel treatment for a total of 10 doses in the Control Arm and a total of 23 doses in the ASCENT Arm. Treatment with DN-101 in the ASCENT Arm will continue until unacceptable DN-101 toxicity or initiation of products not approved for marketing (experimental agents) and is not limited to the Study Treatment phase. Treatment with prednisone in the Control Arm will continue until completion of Study Treatment phase.

Subjects in both arms will be followed for long-term survival to end of study. Subjects may withdraw from treatment at any time upon request.

CRITERIA FOR EVALUATION:

Survival

Survival is defined as the time between the date of randomization and the date of death, whatever the cause.

Thromboembolic Event (TE)

Thromboembolic events are defined as:

- Myocardial infarction
- Cerebrovascular accident (hemorrhagic and / or ischemic)
- Pulmonary embolism
- Deep venous thrombosis
- Arterial thrombosis

Skeletal-related Event (SRE)-free Survival

Skeletal-related events (SRE) are defined as:

- Pathologic bone fracture
- Spinal cord compression
- Surgery to the bone
- Radiation therapy to the bone

Duration of SRE-free survival is defined as the time between the date of randomization and the date on which the first SRE occurs or the date of death due to any cause, whichever occurs first.

Serious Adverse Event (SAE)

Serious adverse event is defined according to ICH criteria and will be recorded throughout the study (Section 11.2).

Gastrointestinal (GI) Event

Gastrointestinal events are defined as:

- anorexia
- diarrhea
- dysphagia
- esophagitis
- nausea
- pharyngitis
- stomatitis
- vomiting

STATISTICAL METHODS:

Sample Size

The planned sample size of approximately 900 subjects (450 per arm) and estimated total study duration (including follow-up) of approximately 2-3 years are based on the following assumptions:

- A 1:1 randomization to the two treatment arms
- Median survival of 18.9 months in Control Arm
- A minimum of 445 deaths are required for completion of the study
- A two-sided significance level of $\alpha = 0.05$ and a minimum statistical power of 0.85 to detect a hazard ratio of 0.75

The sample size and power calculation is based on log-rank test and performed using the software package EaST 3.0 (Cytel Software Corp, Cambridge, MA).

Analyses

The intent-to-treat (ITT) population will consist of all subjects who are randomized in the study, regardless of actual receipt of study treatment. Subjects will be included in the ITT analysis according to their randomized treatment arm assignment. The safety population will consist of all subjects who received at least one dose of study treatment. Subjects will be included in the safety analysis according to the treatment actually received.

Statistical analyses of primary and secondary efficacy endpoints will be carried out on the ITT population. The comparison of the treatment arms for the primary efficacy endpoint of survival and secondary efficacy endpoints will be conducted at a two-sided significance level of $\alpha = 0.05$. The final analysis will be conducted when a minimum of 445 total deaths have occurred. Statistical analyses of safety will be performed on the safety population.

Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will monitor safety and tolerability during the two study phases (Study Treatment phase and Follow-up phase). In addition, a planned safety review will be performed after approximately 50 subjects have been entered in the Follow-up phase. Details regarding DSMB membership, function, and rules will be described in the DSMB charter.

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3. ABBREVIATIONS

° C	degrees Centigrade
° F	degrees Fahrenheit
AE	adverse event
AIPC	androgen-independent prostate cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
API	active pharmaceutical ingredient
ASCENT	AIPC Study of Calcitriol Enhancing Taxotere
AST	aspartate aminotransferase
AUC	area under the concentration vs. time curve
bid	twice daily
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
BP	blood pressure
BSA	body surface area
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CRF	Case Report Form(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
DSMB	Data Safety Monitoring Board
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
FDA	(U.S.) Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
h	hour(s)
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITT	intent-to-treat (population)
IU	International Units
IV	intravenous
kg	kilogram(s)
LD	longest dimension
LDH	lactate dehydrogenase
LHRH	luteinizing hormone releasing hormone

mg	milligram(s)
min	minute(s)
mL	milliliter(s)
m^2	meters squared
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ng	nanogram
nM	nanomolar
NSAIDS	non-steroidal anti-inflammatory drugs
OHSU	Oregon Health & Sciences University
OTC	over-the-counter
PE	physical examination
PK	pharmacokinetics
PO	per os (oral)
PSA	prostate-specific antigen
PTH	parathyroid hormone
PTHrP	parathyroid hormone related protein
PVC	polyvinylchloride
QOL	quality of life
qw	each week
q3w	once every three weeks
q8w	once every eight weeks
RDA	recommended daily allowance
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SRE	skeletal-related event
Study drug	DN-101
Study treatment	DN-101 plus qw docetaxel, prednisone plus q3w docetaxel
TE	thromboembolic event
tid	thrice daily
TPGS	D-alpha-tocopheryl polyethylene glycol 1000 succinate
TPR	temperature / pulse / respiration
μg	microgram
ULN	upper limit of the normal range
VDR	vitamin D receptor
VDRE	vitamin D response element

4. INTRODUCTION

4.1 Background

4.1.1 Metastatic Androgen-Independent Prostate Cancer

Adenocarcinoma of the prostate is a major public health problem. In 2005 in the United States alone, an estimated 232,000 men will be diagnosed with this disease and approximately 30,000 will die of prostate cancer (American Cancer Society, Cancer Facts and Figures 2005). The clinical course of prostate cancer is best considered as a series of discreet clinical states (Scher and Heller, 2000). The most advanced of these clinical states occurs in men with progressive disease despite castrate levels of testosterone. This state, termed *clinical metastases castrate* was previously termed variously as metastatic androgen-independent prostate cancer (AIPC) or hormone refractory prostate cancer. It is in men with metastatic AIPC that most of the prostate cancer-specific mortality and much of the morbidity of this disease occurs.

In metastatic AIPC, bone metastases are the most frequent complication and are present in approximately 90% of patients (Scher et al., 2005). Metastases to bone in prostate cancer tend to follow the distribution of adult bone marrow in axial skeleton (Imbriaco et al., 1998). Although blastic on bone radiographs, histologically both lytic and blastic components are visible which can lead to erosion through vertebral bodies into the epidural space leading to pain and neurologic compromise. With disease progression, anemia, fatigue and complications related to the analgesics or medications required to control the pain further compromise quality of life. Therapies that diminish the signs and symptoms of skeletal morbidity would provide important clinical benefit to these patients (Weinfurt et al., 2005). Quadramet and bisphosphonate are already approved for this indication but have only modest effects on the progression of the underlying disease. The combination of lytic disease and epidural tumor can result in substantial morbidity due to pain. Prostate cancer can also produce metastatic deposits at other sites such as viscera but such metastases are much less common (12%) in metastatic AIPC than in other malignancies (Scher et al., 2005).

Patients with metastatic AIPC have a limited life expectancy and ultimately die of their cancers. Recently, models that allow prediction of life expectancy using baseline factors such as performance status, anemia and others have been developed based on long-term follow-up of large patient cohorts (Smaletz et al., 2002). Despite the improved survival provided by the availability of docetaxel-containing regimens, the median survival of patients with metastatic AIPC is approximately 1.5 years (Tannock et al., 2004; Petrylak et al., 2004).

Metastatic AIPC is uniformly fatal and survival beyond 4-5 years is uncommon.

4.1.2 Current Therapy for AIPC

In the 1970's, estramustine was approved for palliative treatment of patients with metastatic and/or progressive carcinoma of the prostate. This was followed in the mid-1990's, by the combination of mitoxantrone and prednisone for the palliation of symptoms related to progressive castrate metastatic disease based on a randomized comparative study vs. prednisone alone. More recently, zoledronic acid was approved for the treatment of patients

with documented bone metastases from solid tumors, in conjunction with standard hormone therapy. None of these approved agents has been shown in prospective randomized comparisons to prolong life.

In 2004, the combination of docetaxel and prednisone was approved in various regions for the treatment of metastatic AIPC based on the results of an international, multicenter, Phase 3 study in subjects with metastatic AIPC (Study TAX327; Tannock et al., 2004). In this study, docetaxel (75 mg/m^2) was administered by intravenous (IV) infusion once every 3 weeks (q3w) in combination with twice daily (bid) oral (PO) prednisone (5 mg) in one arm, docetaxel (30 mg/m^2 IV) was administered once every week (qw) in combination with daily PO prednisone in a second arm, and mitoxantrone (12 mg/m^2 IV q3w) was administered in combination with daily PO prednisone in the third control arm. For the primary endpoint of survival, the q3w docetaxel regimen resulted in a statistically significant increase in median survival [18.9 months, 95% confidence interval (CI), 17.0 - 21.2] compared to the mitoxantrone regimen (16.5 months, 95% CI, 14.4 - 18.6). This translated into a statistically significant decrease in the hazard ratio for death (0.76, 95% CI, 0.62 - 0.94) (p=0.009) for the q3w docetaxel regimen compared to the mitoxantrone regimen.

The activity of docetaxel in metastatic AIPC observed in the TAX327 study was supported by the results of another multicenter Phase 3 metastatic AIPC study (Study SWOG S9916) that compared docetaxel (60 mg/m^2 IV q3w) and estramustine [280 mg PO three times per day (tid) x 5 days] to mitoxantrone (12 mg/m^2 IV q3w) and prednisone (5 mg PO bid) in three week treatment cycles (Petrylak et al., 2004). Significant increases in median survival (17.5 vs. 15.6 months, p=0.02), hazard ratio (0.80, 95% CI, 0.67 - 0.97), median time to progression (6.3 vs. 3.2 months, p<0.001), and prostate-specific antigen (PSA) response defined as a 50% or greater decline in PSA (50% vs. 27%, p<0.001) were reported for docetaxel/estramustine compared to the mitoxantrone/prednisone

As docetaxel-based chemotherapy is not curative, virtually all patients eventually progress. At this point, there are no approved treatment standards for patients who progressed after chemotherapy and many are only offered supportive care. Further, although responses have been reported with mitoxantrone in patients who have progressed on docetaxel, and docetaxel after mitoxantrone, neither agent has been shown to prolong life as second line therapy. Based on these results a key focus of clinical research in prostate cancer is to identify new approaches to increase the efficacy of docetaxel in the first line setting, and to identify new therapies for patients who have progressed on docetaxel as second line treatment.

4.1.3 Mechanism of Action of Calcitriol and Preclinical Results

Calcitriol has potent regulatory effects on many cell types, including ones not directly related to calcium and phosphorous homeostasis. Its genomic actions are mediated through the cytosolic/nuclear vitamin D receptor (VDR), a member of the nuclear receptor superfamily of transcription factors. Vitamin D receptor is found in over 30 tissues, including intestine, kidney, bone, brain, stomach, heart, pancreas, skin, colon, ovary, breast, prostate and activated lymphocytes (Beer and Myrthue, 2004). The calcitriol-VDR complex, in combination with the retinoid-X or retinoid-A receptor, interacts with vitamin D response element (VDRE) DNA sequences in the promoter regions of a variety of genes, leading to

activation or suppression of gene transcription. Vitamin D response elements (VDREs) have been identified in a wide variety of genes, including those coding for proteins involved in bone and calcium metabolism, cell cycle regulation, and cell surface/extracellular matrix interactions, as well as genes that code for hormones, growth factors, and growth factor receptors (Beer and Myrthue, 2004). A number of co-activators and co-repressors have been identified, resulting in the diversity of actions of the calcitriol/VDR complex.

The primary recognized endocrine role of calcitriol is to act on the intestine, bone and kidney to increase serum calcium and phosphorous levels. In bone, calcitriol in concert with parathyroid hormone (PTH) stimulates bone resorption by mobilizing stem cells to become osteoclasts, which in turn mobilize calcium and phosphorous stored in the bone. In the kidney, calcitriol and PTH act together to regulate calcium and phosphorous levels although the precise mechanism of action of this synergistic effect is unclear.

At physiological levels (approximately 0.05 nM), calcitriol plays a key role in maintaining calcium homeostasis, primarily by regulating the absorption of calcium in the intestinal tract, excretion of calcium by the kidneys, and mobilization of calcium from bone. At higher levels (1-3 nM), calcitriol exhibits an effective anti-cancer activity in multiple *in vitro* and *in vivo* prostate tumor models. These anti-cancer effects of calcitriol result from various properties and interactions, as follows:

- Induction of differentiation
- Anti-proliferative activity
- Cell cycle arrest
- Induction of apoptosis
- Growth factor signaling
- Inhibition of tumor growth and metastasis *in vivo*
- Suppression of PTH related protein (PTHrP)

Several *in vitro* and *in vivo* nonclinical evaluations have demonstrated that calcitriol can be effective by itself or is synergistic with various chemotherapeutic agents, including taxanes, platinums, dexamethasone, doxorubicin, mitoxantrone, and gemcitabine, as well as non-steroidal anti-inflammatory drugs (NSAIDs) (Moreno et al., 2005). Building on these data, clinical efforts to evaluate the effect of calcitriol as anticancer therapy began with studies of daily dosing with marketed formulations such as Rocaltrol®. This approach allowed only modest escalation of the dose beyond physiological replacement before hypercalcemia and or hypercalciuria developed (Osborn et al., 1995; Gross et al., 1998).

Several studies subsequently established that significant dose escalation was feasible with intermittent dosing. Subcutaneous administration of calcitriol every other day produced peak blood concentrations of 0.7 nM (Smith et al., 1999). However, weekly PO administration produced peak serum concentrations ranging between 3.7 and 6 nM (Beer et al., 2001). In a Phase 1 study, administration of calcitriol in combination with zoledronate and dexamethasone at doses up to 30 μg daily times three each week produced plasma levels of greater than 2 nM. Subjects tolerated therapy well and no maximum tolerated dose (MTD) was defined (Morris et al., 2004). A separate Phase 2 study testing the regimen of 0.5 μg/kg

PO calcitriol weekly resulted in average peak calcitriol concentrations of 2 nM, with no Grade 3 or 4 toxicities (Beer et al., 2003). Calcitriol administered at doses of up to 38 µg for 3 days out of every 7 days combined with paclitaxel in a Phase 1 study also encountered no dose-limiting toxicities (DLT) and resulted in peak concentrations of 1.4 to 3.5 nM (Muindi et al. 2002). Thus, studies using intermittent dosing with commercially available formulations of calcitriol succeeded in substantially increasing plasma concentrations of the drug to supraphysiologic levels. However, these studies were limited by non-linear pharmacokinetics (PK) above doses of about 0.5 µg/kg (Beer et al., 2001; Muindi et al., 2002). The non-linear PK was suggestive of an absorption ceiling and precluded escalation of weekly calcitriol to dose-limiting toxicity.

The activity of intermittent, high dose calcitriol in combination with docetaxel was evaluated in the Phase 2 trial reported by Investigators at Oregon Health and Sciences University (OHSU) (Beer et al., 2003). Thirty-seven (37) chemotherapy-naïve metastatic AIPC subjects received oral calcitriol (0.5 µg/kg) on day 1 followed by docetaxel (36 mg/m^2) on day 2 weekly on a 6 out of 8 week schedule. PSA decline of 50% or greater was seen in 81% of subjects (95% CI, 68% - 94%). Activity in measurable disease and survival also suggested that the combination may be more active than docetaxel alone: confirmed partial responses were seen in 8 of 15 subjects with measurable disease (53%, 95% CI, 27%-79%) and median survival was 19.5 months (95% CI, 15.3 months to incalculable). In general, toxicities were similar to those expected with docetaxel. Hypercalcemia was seen in 3 subjects (2 subjects reported Grade 1 elevations and 1 patient reported a Grade 2 elevation after an overdose). Six (6) subjects developed transient Grade 1 creatinine elevations that resolved without intervention.

In order to overcome the limitations of previous calcitriol formulations (non-linear, variable PK, and the very large number of capsules required at one time), Novacea, Inc. developed DN-101 in high dose therapy for use in cancer treatment. DN-101 is a novel, oral, high concentration formulation (45 µg) of calcitriol in a gelatin capsule. The PK of DN-101 is linear up to 165 µg, the maximum dose studied, without absorption maximum. A 45 µg capsule results in average peak plasma levels (C_{max}) of 3.4 nM with average exposure (AUC) of 25 ng·h/mL.

4.2 Rationale for the Current Study

The current study seeks to build on the results of the ASCENT study (Study DN101-002), which evaluated the potential beneficial effects of DN-101 in combination with weekly administration of docetaxel for the treatment of metastatic AIPC. The ASCENT study was a randomized, double-blind, placebo-controlled, multicenter evaluation in which 250 subjects were treated with docetaxel (36 mg/m^2 IV weekly three of four weeks) plus either placebo or DN-101 (45 µg) (ASCENT regimen) given the day prior to each docetaxel dose. The primary endpoint of the ASCENT study was PSA response (defined as percent of subjects with > 50% PSA reduction, confirmed at least four weeks later) by six months. The study was powered (80%) to detect an increase in the frequency of PSA response (primary endpoint) from 45% in the docetaxel monotherapy arm, to 65% in the ASCENT regimen arm. Secondary endpoints included survival, tumor response in subjects with measurable

disease, skeletal morbidity-free survival, as well as safety and tolerability of the study treatment.

The results of the ASCENT study demonstrated a trend in favor of the ASCENT Arm in comparison to docetaxel as monotherapy in all efficacy endpoints (Beer et al., 2005). The PSA response was achieved by 58% of the subjects in ASCENT regimen arm compared to 49% in the docetaxel monotherapy arm. The estimated median survival for the ASCENT regimen arm was 24.5 months, in contrast to an observed 16.4 month median survival for subjects who received docetaxel as monotherapy (multivariate hazard ratio 0.67, p=0.035). Other secondary endpoints, such as duration of skeletal morbidity-free survival and tumor response rates, also favored the addition of DN-101 to docetaxel when compared to docetaxel alone.

Serious adverse events (SAEs) were reported in 27% of subjects in the ASCENT regimen arm compared to 41% in weekly docetaxel monotherapy arm (p = 0.023). In addition, Grade 3 or 4 adverse events (AEs) were reported in 58% of subjects in the ASCENT regimen arm and 70% of subjects in the docetaxel group (p = 0.065). Toxicities that might be expected with high-dose administration of calcitriol were uncommon. No Grade 3 or 4 creatinine elevation or hypercalcemia was observed. A single episode of nephrolithiasis was observed in one subject in the ASCENT regimen arm. Reversible low grade (Grade 1) hypercalcemia was observed in 33% of subjects who received DN-101, and only 8% of the subjects who received placebo. In only 8% of the DN-101 treated subjects was hypercalcemia considered clinically significant and reported as an AE by the Investigator. None of the subjects discontinued from therapy due to hypercalcemia.

In the current study, subjects will continue on DN-101 after docetaxel is discontinued. This approach seeks to maximize the anti-tumor and palliative effects of DN-101 and the potential beneficial effects of DN-101 on SREs and TE events. Discontinuation of docetaxel on disease progression is standard practice due to the toxicity of continued docetaxel in subjects without perceived benefit. DN-101 therapy has a favorable safety profile and, in the absence of significant toxicity, it is therefore reasonable to continue this agent beyond the disease progression. To date, results with DN-101 and with commercial formulations of calcitriol used in high-dose pulse administration have failed to demonstrate safety concerns for the use of high-dose calcitriol in combination with other anticancer and palliative drugs commonly used in subjects with metastatic AIPC. In the ASCENT study, subjects concomitantly used DN-101 with zoledronic acid and narcotic analgesics. Reports of high-dose calcitriol in combination with chemotherapy agents commonly used as second-line therapy for AIPC such as estramustine (Tiffany et al., 2005), carboplatin (Beer et al., 2004), and mitoxantrone (Dr. Christopher Ryan, OHSU, personal communication) have provided evidence that would indicate DN-101 can be given safely in combination with other agents for second-line therapy of metastatic AIPC.

4.3 Rationale for Selection of Dose (DN-101 45 µg PO)

The current study seeks to directly compare the efficacy of the ASCENT treatment regimen (weekly DN-101 at 45 µg PO and weekly docetaxel at 36 mg/m^2 IV) to the currently approved docetaxel regimen of 75 mg/m^2 IV administered once q3w plus prednisone (5 mg PO bid) as measured by survival as the primary study objective. As noted in Section 4.2, the

use of 45µg PO DN-101 in combination with weekly docetaxel was demonstrated to be safe and tolerable. In addition, analyses of the efficacy endpoints are highly suggestive of a clinical benefit.

In the Phase 1 dose-escalation study (Study No. I-001), conducted in subjects with advanced malignancies, the MTD for weekly administration of DN-101 was established as 45 µg. The DLT for DN-101 was transient, reversible, self-limited Grade 2 hypercalcemia observed in two subjects who had received nine weekly doses of 60 µg DN-101; no hypercalcemia or other DLTs were reported for the other four subjects treated with 60 µg DN-101 for up to seven weeks. Subsequent experience with DN-101, either as monotherapy or in combination with docetaxel, has shown that a weekly dosage of up to 180 µg DN-101 is well-tolerated. Therefore, weekly administration of 45 µg DN-101 and docetaxel dose combination has been selected to be investigated in the current study.

4.4 Rationale for the Selection of Endpoints

4.4.1 Primary Endpoint

Duration of Survival

Duration of survival has been selected as the primary efficacy endpoint for this study. An improvement in survival is universally accepted as the most clinically meaningful outcome measure for patients with AIPC. The ASCENT study results suggest that the ASCENT regimen may provide both a clinically significant and a statistically significant increase in survival.

4.4.2 Secondary Efficacy Endpoints

1) Thromboembolic Event (TE) Rate

The ASCENT study results, which showed a statistically significant reduction in the frequency of Grade 3/4 TEs (p=0.018) and serious TEs (p=0.031) in the ASCENT arm compared to placebo control arm (Table 1), suggest that the ASCENT regimen may provide a significant clinical benefit (decreased incidence of TEs) for AIPC subjects. A thromboembolic event (TE) is defined as one of the following: pulmonary embolism, deep venous thrombosis, myocardial infarction, cerebrovascular accident (hemorrhagic and/or ischemic), or arterial thrombosis.

Table 1. Summary of Thromboembolic Event (TE) Rate in ASCENT Study

AE Class	Placebo + Docetaxel N=125	DN-101 + Docetaxel (ASCENT Regimen) N=125	p-value
TE events	11 (8.8%)	3 (2.4%)	0.028
Grade 3 / 4 TE events	10 (8.0%)	2 (1.6%)	0.018
Serious TE events	9 (7.2%)	2 (1.6%)	0.031

An anti-thrombotic mechanism of action for calcitriol is supported by several known downstream molecular and biochemical actions of calcitriol. Calcitrol has been shown to alter monocyte production of two components of the extrinsic coagulation pathway, upregulation of thrombomodulin (an anticoagulant) and down regulation of tissue factor (a procoagulant) (Koyama et al., 1998; Koyama and Hirosawa, 1998). Also, in VDR deficient "knockout" mice, the animals have a congenital coagulopathy predisposing them to diffuse thrombosis (Aihara et al., 2004). The actions of calcitriol acting through VDR appear to produce a reduction in the activity of the extrinsic coagulation pathway and might be expected to reduce the incidence of hypercoagulation-related complications, a known morbidity of advanced cancer patients, in an at-risk patient population. This study will test the hypothesis that the addition of DN-101 to docetaxel therapy results in a reduced frequency of TEs.

2) Duration of Skeletal-related Event (SRE)-free Survival

Metastases to bone are a prominent feature of the spread of metastatic prostate cancer and result in considerable morbidity, including pain, pathologic fracture, and neurological compromise resulting from spinal cord compression. In the ASCENT study, the DN-101 treated subjects had a longer duration of skeletal morbidity-free survival than subjects who received docetaxel monotherapy (13.4 vs. 11.9 months), although the difference did not reach statistical significance (hazard ratio 0.78, p=0.13). Skeletal-related event (SRE) is defined as one of the following: pathologic bone fracture, spinal cord compression, surgery to bone or radiation therapy to bone. The endpoint of skeletal-related events is a significant measure of clinical benefit that led to the approval of mitoxantrone and prednisone, and zoledronic acid, for patients with progression AIPC. The reduction of SREs could provide an important additional clinical benefit to the AIPC patient population prone to this disabling morbidity.

Based on the results of the ASCENT study, the estimated median SRE-free survival for ASCENT regimen was 1.5 months longer than the control arm (13.4 vs. 11.9 months), therefore, the one-week difference in assessment of the two arms in the current study design should not have significantly impact to the statistical analysis of SRE-free survival data.

4.4.3 Safety Endpoints

1) Serious Adverse Events (SAEs) Rate

In an exploratory analysis of the safety events occurring in the ASCENT study, it was noted that there were fewer serious adverse events (SAEs) in the DN-101 treated subjects (27% in docetaxel plus DN-101-treated subjects vs. 41% in docetaxel plus placebo-treated subjects, p=0.023). The reduction of SAEs could provide an important additional clinical benefit to the AIPC patient population.

2) Gastrointestinal (GI) Event Rate

Docetaxel is known to cause AEs in the GI system of the majority of treated subjects. In the ASCENT study, the frequency of GI events was lower in the ASCENT regimen arm (86%) compared to the placebo arm (94%) (p=0.02; Table 2). The number of serious GI events was also reduced in the DN-101 arm (2.4%) as compared to the placebo arm (9.6%) (p=0.017).

Previous epidemiological 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 normal human subjects (Moan et al., 2005; Studzinski et al., 2005; Robsahm et al., 2004; Holt et al., 2002; Garland et al., 1989). Similar studies have also been performed in animal models again showing that higher levels of vitamin D metabolites are associated with reduced proliferation of epithelial cells in the GI system (Cantorna et al., 2000). Therefore, one mechanism by which DN-101 may prevent or reduce the GI toxicity of docetaxel is to induce temporary cell cycle arrest in the rapidly proliferating cells of the GI tract, rendering them less sensitive to the cytotoxic effects of docetaxel chemotherapy. This study will test the hypothesis that the addition of DN-101 to docetaxel therapy results in a reduced frequency of the most common GI events experienced by docetaxel treated subjects. Gastrointestinal (GI) event is defined as one of the following: anorexia, diarrhea, dysphagia, nausea, esophagitis, stomatitis, vomiting or pharyngitis.

Table 2. Summary of Gastrointestinal Event (GI) Rate in ASCENT Study

AE Class	Placebo + Docetaxel N=125	DN-101 + Docetaxel (ASCENT Regimen) N=125	p-value
GI events	118 (94.4%)	107 (85.6 %)	0.020
Grade 3 / 4 GI events	19 (15.2%)	16 (12.8%)	0.650
Serious GI events	12 (9.6%)	3 (2.4%)	0.017

4.4.4 Exploratory Endpoints

1) Quality of Life

While the primary endpoint of this study is survival, concern for the psychosocial needs of patients and quality of life (QOL) on cancer chemotherapy is also of great interest to patients, their families and their treating physicians. For this reason, an assessment of QOL will be

performed for subjects at sites in North America to allow an exploratory analysis comparing the QOL of subjects on the two treatment arms. The Functional Assessment of Cancer Therapy Scale (FACT) (Cella, et al., 1993) and more specifically a version developed for assessment of prostate cancer patients (FACT-P) will be used as the instrument along with additional related questions. Fatigue will be assessed using the Brief Fatigue Inventory questionnaire (Mendoza et al., 1999).

2) Pain

As described above, pain is a common symptom among men with metastatic AIPC. Until the advent of docetaxel, therapies for AIPC such as mitoxantrone and corticosteroids were prescribed for their ability to improve pain. Despite a more recent focus on survival, control of symptoms such as pain remains a goal of novel therapies in AIPC. For this reason, a self-assessment of pain using the Brief Pain Inventory (Cleeland and Ryan, 1994) will be performed by subjects enrolled at sites in North America.

5. OBJECTIVES

5.1 Effectiveness

The primary objective of this study is:

To evaluate the efficacy of weekly DN-101 in combination with weekly docetaxel (the ASCENT regimen) in the treatment of metastatic AIPC as measured by duration of survival.

The secondary objectives of this study are:

1) To determine the efficacy of ASCENT regimen as measured by thromboembolic event (TE) rate
2) To determine the efficacy of ASCENT regimen as measured by duration of skeletal-related event (SRE)-free survival

The effect of the ASCENT regimen on quality of life (QOL), pain, and PSA will be evaluated as exploratory analyses. QOL (FACT-P and related questions, including measurement of fatigue using the Brief Fatigue Inventory) and pain (the Brief Pain Inventory) will only be assessed at sites in North America.

5.2 Safety

To evaluate the safety and tolerability of the ASCENT regimen. In particular, the serious adverse event (SAE) rate and gastrointestinal (GI) event rate will be specified as safety endpoint analyses.

Note:

The following sub-studies will be performed under separate protocols at selected sites in North America:

- Population pharmacokinetics (PK)
- Biomarkers

6. INVESTIGATIONAL PLAN

6.1 Design Description

This Phase 3 study is a randomized, open-label, multicenter, international study. Subjects will be randomized 1:1 to one of two study treatment arms through a centralized procedure. The randomization will be stratified by geographic region and Eastern Cooperative Oncology Group (ECOG) performance status. The two study treatment arms are:

- Control Arm: Every three weeks docetaxel and twice daily prednisone (up 30 weeks)
- ASCENT Arm: Once weekly DN-101 in combination with weekly docetaxel (up to 30 weeks)

The study will consist of two phases: the Study Treatment phase and Follow-up phase. The Study Treatment phase is defined as the period in which a subject receives the study treatment (Control Arm or ASCENT Arm). The Follow-up phase is defined as the period after the subject completes the Study Treatment phase until end of study. Subjects in the ASCENT Arm may continue to receive treatment with DN-101. A schematic diagram of ASCENT-2 study is illustrated in Figure 1 in Section 6.2.

Safety and efficacy evaluations will be performed at specified time points throughout the study.

In both study arms, docetaxel therapy is continued until completion of the Study Treatment phase (up to 30 weeks of treatment). In the ASCENT Arm, treatment with DN-101 will continue until unacceptable DN-101 toxicity (per Section 8.1.1.8) or initiation of products not approved for marketing (experimental agents). In the Control Arm, prednisone therapy is administered for the duration of the Study Treatment phase or until unacceptable prednisone toxicity.

Subjects may withdraw from treatment at any time upon request.

6.2 Study Diagram

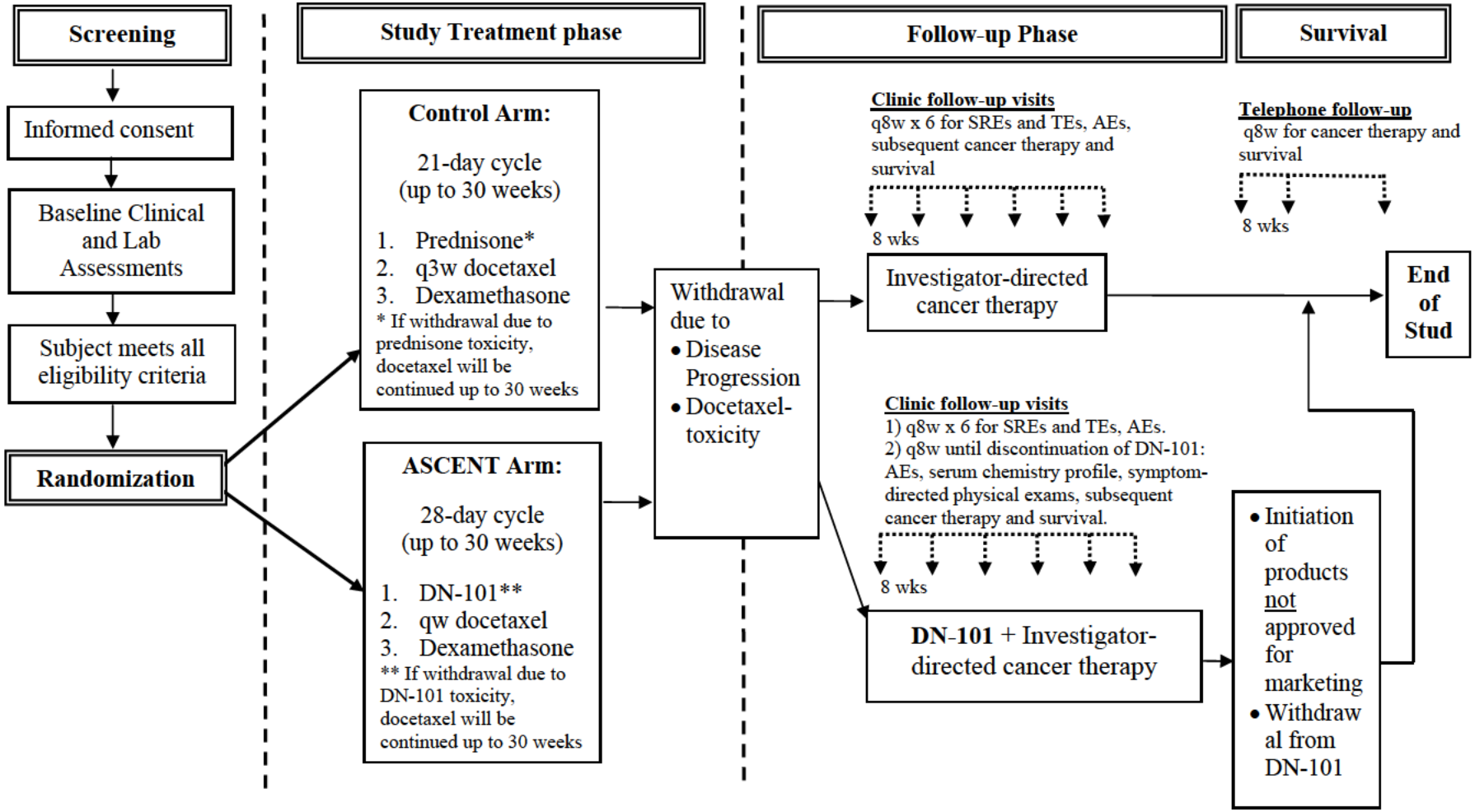
Schematic diagram of the ASCENT-2 study is shown in Figure 1.

6.3 Treatment Plan and Regimen

6.3.1 Diet

Subjects should take DN-101 on an empty stomach (at least one hour before or two hours after meals) and drink approximately 4 cups of liquids in addition to their usual intake on the day of DN-101 administration and for the next two consecutive days.

Figure 1. ASCENT-2 Study Diagram



6.3.2 Dosing

Table 3. Study Dosing Regimens

Control Arm: 21-day dosing cycle		
Drug	Dose	Administration
Prednisone	5 mg	PO bid daily starting on day 1
Docetaxel	75 mg/m^2 BSA	One-hour IV infusion on day 2
Dexamethasone	8 mg	PO about 12 hours, 3 hours and 1 hour prior to docetaxel infusion
ASCENT Arm: 28-day dosing cycle		
Drug	Dose	Administration
DN-101	45 μg	PO on an empty stomach (at least one hour before or two hours after meals) on days 1, 8 and 15
Docetaxel	36 mg/m^2 BSA	30-minute IV infusion on days 2, 9 and 16
Dexamethasone	8 mg	PO about 12 hours, 3 hours and 1 hour prior to docetaxel infusion

6.3.3 Duration

Treatment with docetaxel (Control Arm and ASCENT Arm) will continue for up to 30 weeks, or until unacceptable docetaxel toxicity or clinical disease progression (as per Section 10.1). In cases of treatment delays, subjects should continue docetaxel treatment for a total of 10 doses in the Control Arm and a total of 23 doses in the ASCENT Arm. Treatment with DN-101 in the ASCENT Arm will continue until unacceptable DN-101 toxicity or initiation of products not approved for marketing (experimental agents) and is not limited to the Study Treatment phase. Treatment with prednisone in the Control Arm will continue until completion of study treatment phase.

Subjects in both arms will be followed for long-term survival to the end of study. Subjects may withdraw from treatment at any time upon request.

6.3.4 Distribution

DN-101 will be supplied to sites by the Sponsor through a drug distribution center. Docetaxel, prednisone, and dexamethasone will be supplied by the clinical site pharmacy, unless special arrangements have been made with the Sponsor prior to study start.

6.4 Randomization, Stratification, and Blinding

The study is open-label in that study treatments will not be blinded. Procedures will be implemented to control possible study bias (see Section 12.5). Subjects will be randomly assigned to either the Control Arm or the ASCENT Arm in a 1:1 ratio using a central block

randomization procedure. The randomization will be stratified by geographic region (North America, Western Europe and/or Rest of World) and ECOG performance status (0 versus 1, 2). The total number of subjects with ECOG performance status of 0 at the time of randomization will be limited to a maximum of 450 subjects.

7. SUBJECT POPULATION

7.1 Number of Subjects and Subject Selection

Approximately 900 AIPC subjects (450 subjects in each arm) will be enrolled in this randomized, two-arm study.

7.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Signed informed consent prior to beginning protocol specific procedures. Subject must be capable of providing informed consent.
2) Histopathologically or cytologically proven adenocarcinoma of the prostate.
3) Metastatic prostate adenocarcinoma documented by computed tomography (CT), magnetic resonance imaging (MRI), or bone scan. A bone scan is required within 4 weeks prior to study randomization as baseline measurement.
4) Prior therapy by androgen ablation either by orchiectomy and/or luteinizing hormone releasing hormone (LHRH) agonists or antagonists.
5) Subjects who have received any of the following additional hormonal therapies remain eligible:
    - Anti-androgens
    - Monotherapy with estramustine (> 4 weeks must have elapsed since completion of prior estramustine therapy with full recovery from any side effects)
    - Prior therapy with corticosteroids and/or ketoconazole
    - Other hormonal agents for therapy of prostate cancer
6) If a subject has been treated or is currently receiving treatment with bisphosphonates, the subject is eligible for the study and the therapy can continue at investigator's discretion.
7) Maintaining castrate status: Subjects who have not undergone surgical orchiectomy should continue on medical therapies with a LHRH agonist or LHRH antagonist to maintain castrate levels of serum testosterone.

8) Documented progression while on androgen ablation therapy detected by rising PSA and/or imaging. Progression for study eligibility is defined as at least one of the following (Bubley et al, 1999):
   - PSA progression: An elevated PSA ($\geq$ 5 ng/mL) which has risen serially from baseline (#1) on two occasions each at least one week apart. If the confirmatory PSA (#3) is less than PSA value #2, then a subsequent test for rising PSA (#4) is required to be taken and must be greater than the 2nd measure (#2). A schematic illustration of eligibility definition based on PSA progression is shown in Figure A of Appendix 2.
   - Progression of target lesions: change in size of lymph nodes or parenchymal masses, bidimensional or unidimensional, on PE or x-rays (RECIST criteria, Appendix 3)
   - Progression of non-target lesions (except bone) (RECIST criteria, Appendix 3)
   - Bone scan progression: worsening bone scan as evidenced by the appearance of two or more new skeletal lesions that are not felt to be consistent with tumor flare. Subjects whose sole evidence of progression is on bone scan must also have a PSA > 5 ng/mL.
9) Prior radiation therapy to less than 25% of the bone marrow only (excluding whole pelvic irradiation) is allowed if at least four weeks have elapsed since completion of therapy.
10) Prior surgery is allowed if at least four weeks have elapsed since completion of the surgery.
11) Life expectancy $\geq$ 3 months.
12) Willingness to discontinue prohibited concomitant medications or diet supplements including calcium supplements, pharmacologic doses of vitamin D or derivatives, ketoconazole or related drugs, and systemic steroids (Section 8.3).
13) ECOG Performance Status $\leq$ 2.
14) Age $\geq$ 18 years.
15) Laboratory requirements:
   - <u>Hematology:</u>
     - absolute neutrophil counts (ANC) $\geq 1.5 \times 10^9$/L
     - hemoglobin $\geq$ 10 g/dL (Erythropoietin and darbopoetin use is allowed but red blood cell transfusion to upgrade the hemoglobin level is not allowed)
     - platelets $\geq 100 \times 10^9$/L
   - <u>Hepatic function:</u>
     - total bilirubin < the upper-normal limit (ULN)
     - alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 1.5 times the ULN
   - <u>Renal function:</u>
     - serum creatinine concentration $\leq$ 1.5 times the ULN

- serum calcium ≤ the ULN

- Testosterone:
  - testosterone < 50 ng/mL

16) Subjects who have received prior therapy with vaccines or other immunotherapy remain eligible for study participation.

7.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:

1) Prior cytotoxic chemotherapy, except monotherapy with estramustine.
2) Prior chemotherapy with docetaxel.
3) Prior isotope therapy (e.g., strontium-89, samarium-153, etc.).
4) Prior malignancy other than prostate cancer except the following: adequately treated basal cell or squamous cell skin cancer, or any other cancer from which the subject has been disease-free for > 5 years.
5) Known brain or leptomeningeal involvement. Subjects with stable treated epidural lesions are eligible for participation in the study.
6) History of cancer-related hypercalcemia, known hypercalcemia, or vitamin D toxicity.
7) Active uncontrolled infection.
8) Active symptomatic peptic ulcer disease, unstable diabetes mellitus or other contraindications for the use of corticosteroids.
9) Other serious illness or medical condition that in the opinion of the Investigator would be expected to interfere with the subject's ability to receive study treatment or to comply with study procedures.
10) Symptomatic peripheral neuropathy ≥ Grade 2 according to the NCI-CTCAE version 3.0.
11) Hypersensitivity to drugs formulated with polysorbate-80 (a component of the docetaxel formulation).
12) Hypersensitivity to calcitriol.
13) Prior investigational therapy within the 28 days prior to randomization.
14) Prior use of calcitriol (e.g. generic calcitriol, Rocaltrol®, Calcijex®, and DN-101) or paricalcitol (Zemplar®) within 28 days prior to randomization.

7.4 Criteria for Withdrawal of Subjects

7.4.1 Withdrawal of Subject from Study

Subjects should be withdrawn from the study for the following reasons:

- Withdrawal of consent
- Lost to follow-up, defined as at least three documented unsuccessful attempts to contact the subject by telephone and one unsuccessful attempt to contact the subject by letter
- Death

7.4.2 Withdrawal of Subjects from Study Treatment Phase

Subject should be withdrawn from Study Treatment phase upon:

1) The occurrence of an AE that in the judgment of the Investigator significantly outweighs the potential benefits of continuing study treatment:
   - If a subject develops a life-threatening and/or irreversible toxicity due to docetaxel (not manageable by symptomatic care, dose reduction, or delay in study treatment), treatment with docetaxel will be discontinued. In this case, subjects will be withdrawn from the Study Treatment phase.
     - **Subjects in the ASCENT Arm will continue on DN-101 and will be entered into the Follow-up phase.**
     - **Subjects in the Control Arm will be entered into the Follow-up phase.**
   - If a subject develops a life-threatening and/or irreversible toxicity attributed to DN-101 or prednisone (not manageable by symptomatic care or delay of either agent), treatment with DN-101 or prednisone will be discontinued.
     - **Subjects in both arms will continue on docetaxel up to 30 weeks before entering the Follow-up phase.**
2) Administration of any other anti-tumor chemotherapy, radiotherapy, or products not approved for marketing (experimental agents) during the study. Subjects should be withdrawn from study treatment and will enter the Follow-up phase.
3) Subject requests termination of protocol-specified docetaxel regimen. Subject will be entered into the Follow-up phase.
4) Subject requests termination of DN-101. Subject will be managed as those who withdrawal from study treatment due to DN-101 toxicity (Section 7.4.2, #1).
5) Disease progression (as defined in Section 10.1)

   In the event of disease progression, subjects should be withdrawn from treatment with docetaxel.
   - **Subjects in the ASCENT Arm will continue on DN-101 and will be entered into the Follow-up phase.**
   - **Subjects in the Control Arm will be entered into the Follow-up phase.**

8. STUDY DRUGS, LABORATORY MONITORING AND CONCOMITANT MEDICATIONS

8.1 Study Treatment

8.1.1 Study Drug: DN-101 (Calcitriol)

8.1.1.1 Drug Substance

Calcitriol is in the class of antirachitic agents. Calcitriol, the biologically active form of vitamin D, is the active pharmaceutical ingredient (API) in DN-101. Calcitriol is a white to almost white crystalline powder that has minimal solubility in aqueous solutions and high solubility in oil-based solutions. The molecular weight is 416.66; the molecular formula is $C_{27}H_{44}O_3$.

8.1.1.2 Formulation

DN-101 is supplied as a green opaque hard gelatin capsule containing 45 µg of calcitriol. The API is formulated in an oil-based solution; excipients include Miglyol 812N, vitamin E TPGS, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) to form the active drug product, DN-101. BHA and BHT are antioxidants. All excipients have been used in approved products. DN-101 is designed to rapidly disperse upon exposure to gastric fluids and to have improved bioavailability at higher doses than the currently marketed formulation.

8.1.1.3 Storage Conditions

DN-101 capsules should be protected from light and stored at controlled room temperature, 66° to 77° F (20° to 25° C).

8.1.1.4 Preparation

Study drug will be supplied as capsules (45 µg calcitriol per capsule). Each 40 cc plastic bottle contains 3 capsules.

8.1.1.5 Handling

No special precautions are required.

8.1.1.6 Adverse Effects

In monotherapy studies in subjects with malignancies, DN-101 has been well-tolerated. Low grade hypercalcemia (generally Grade 1) is the most commonly reported AE, reported by 22% of subjects. Two (2) of 6 subjects treated with 60 µg DN-101 weekly in the Phase 1 study (Study I-001) and 3 of 37 subjects with myelodysplasia treated with 45 µg DN-101 weekly (Study DN101-003) developed transient Grade 2 hypercalcemia. Other commonly reported AEs of low grade (Grade 1) included fatigue (22%), nausea (12%), increase in ALT (5%) and increase in serum creatinine (5%). One (1) subject with Grade 3 ALT increase was reported. Discontinuation of treatment due to DN-101 related toxicity has been rare.

In studies where DN-101 was used in combination with docetaxel, AEs have generally been consistent with those expected with docetaxel monotherapy with the exception of hypercalcemia. In the ASCENT study (DN101-002), 33% of the subjects in the DN-101 arm and 8% in the placebo arm reported Grade 1 elevations in blood calcium. In only 8% of the DN-101 treated subjects and 1% of the subjects in the placebo arm was hypercalcemia considered clinically significant and reported as an AE by the Investigator.

In rare cases, SAEs, including disseminated intravascular coagulation, interstitial pneumonitis and pulmonary embolism (one each), have been attributed to DN-101. At this time, the Sponsor cannot conclusively determine the causal relationship of these SAEs to DN-101 administration.

Although DN-101 has been well-tolerated to date, based on the preclinical toxicology studies, the Sponsor cannot rule out the possibility that DN-101 use might be associated with clinically significant hypercalcemia, renal dysfunction, nephrolithiasis or soft tissue calcification, particularly if overdosage were to occur. Digoxin toxicity may be potentiated in hypercalcemia, which is a risk in both DN-101 and thiazide diuretic usage. Please refer to the Investigator's Brochure for further information.

8.1.1.7 Excluded Medications

Excluded medications include:

- Bile acid binding resin drugs [such as cholestyramine (Questran®) and colestipol (Colestid®)], which may interfere with intestinal absorption of calcitriol
- Calcium supplements in excess of 500 mg [50% of the recommended daily allowance (RDA)], which may increase potential toxicity of hypercalcemia
- Pharmacological doses of vitamin D, its derivatives or analogues, including vitamin D supplements in excess of the RDA of 400 International Units (IU) or 10 μg
- Oral ketoconazole (Nizoral®) and related compounds such as metronidazole (Flagyl®), fluconazole (Diflucan®), itraconazole, voriconazole or posaconazole, which may prolong the half-life of calcitriol

8.1.1.8 Toxicity and Dose Modification

Toxicities will be assessed using the NCI-CTCAE version 3.0. Toxicities will be reported as descriptive findings.

Toxicities thought to be related to DN-101 and requiring dose delay of study drug will not affect docetaxel dosing, which should continue on schedule. Dose delay of DN-101 will be based on AEs and laboratory values from the previous cycle of study treatment. The dose of DN-101 cannot be reduced; however, DN-101 may be held until toxicities have resolved to an acceptable level after which DN-101 may be resumed with close monitoring and attention to hydration. Table 4 outlines the conditions and permitted length of time which DN-101 should be held. If toxicities do not resolve in the stated timeframe, then DN-101 should be discontinued. If DN-101 is discontinued, the subject may continue to receive docetaxel up to

30 weeks and will remain in the Study Treatment phase of the study.

Table 4: Dose Delays for DN-101-related Toxicity

Hypercalcemia	
Grade 2-4	Hold DN-101 until hypercalcemia is reduced to a Grade 1 or less.
Grade 2- 4 for greater than 2 weeks or a second episode of ≥ Grade 2	Discontinue DN-101
Creatinine elevation	
Grade 2-4	Hold DN-101 until return of creatinine to Grade 1 or less.
Grade 2-4 for greater than 2 weeks or a second episode of ≥ Grade 2	Discontinue DN-101
Symptomatic Nephrolithiasis	
1st episode	Hold DN-101 (for up to 2 weeks) until resolution.
Symptoms persist for greater than 2 weeks or a second episode of ≥ Grade 2	Discontinue DN-101
Other DN-101 related toxicity	
Grade 3-4	Hold DN-101 until resolution to Grade 1 or less
Grade 3-4 for greater than 2 weeks	Discontinue DN-101

Adverse event grades listed are defined by NCI-CTCAE v3.0.

8.1.2 Docetaxel (Taxotere®)

For storage, handling, and administration conditions refer to the prescribing information.

8.1.2.1 Adverse Effects

The dose for docetaxel therapy in the Control Arm is 75 mg/m^2 delivered q3w. At this dose, the most frequently reported side effects are alopecia, fatigue, Grade 3 or 4 neutropenia, diarrhea, nausea and vomiting. Additional information about toxicity is available in the Taxotere® package insert.

With weekly docetaxel at the study dose of 36 mg/m^2 in subjects with AIPC (ASCENT study), the most frequently reported AEs include alopecia, fatigue, nausea and vomiting, nail changes, and diarrhea.

8.1.2.2 Toxicity and Dose Modification

Toxicities will be assessed using the NCI-CTCAE version 3.0. Toxicities will be reported as descriptive findings. If possible, toxicities should be managed symptomatically and the appropriate treatment used to ameliorate signs and symptoms including antiemetics for nausea and vomiting, antidiarrheals for diarrhea, and antipyretics or antihistamines for drug fever. If toxicity requires a docetaxel dose to be held, the subject will be evaluated for

resolution of toxicity as soon as is clinically appropriate. Docetaxel will be discontinued if chemotherapy is withheld or interrupted for more than 4 weeks from the scheduled date of dosing, unless permission is obtained from the Medical Monitor.

Dose reductions should be adjusted according to Table 5 below.

Table 5: Dose Levels for Dose Reduction of Docetaxel

Dose Level	Docetaxel Every 3 Weeks (Control Arm)	Docetaxel Weekly (ASCENT Arm)
Protocol specified dose	75 mg/m^2	36 mg/m^2
1st dose reduction	60 mg/m^2	27 mg/m^2
2nd dose reduction	45 mg/m^2	20 mg/m^2
3rd dose reduction	Discontinue	Discontinue
Note: A reduced dose will not be re-escalated throughout the remainder of a subject's time on study. No more than 2 dose reductions are permitted. DN-101 dosing will be unaffected by docetaxel dose reductions, and should continue as scheduled. If a third dose reduction is needed, the subject will discontinue docetaxel but may continue receiving DN-101 (if in the ASCENT Arm) and be entered into the Follow-up phase.		

Hematological Toxicity

If the platelet count is < 100 x 10^9/L or ANC is < 1.5 x 10^9/L (< 1.0 x 10^9/L for ASCENT Arm) on the scheduled day of docetaxel treatment, the next dose of docetaxel will be held until both the platelet count and ANC are above these parameters.

The next dose of docetaxel will be reduced according to the schedule shown in Table 5 if:

1) More than one dose has to be delayed due to hematological toxicity, or
2) The subject experiences any of the following:
   - Grade 4 neutropenia (ANC < 0.5 x 10^9/L) for ≥ 7 days
   - Febrile neutropenia [defined as a temperature greater than 101ºF (38.3ºC) concurrent with ANC < 1.0 x 10^9/L]
   - Grade 4 infection during a docetaxel cycle, or
   - Grade 4 thrombocytopenia (platelets < 25 x 10^9/L) at any time during the study period.

Abnormal Liver Function

Subjects who develop abnormal liver function tests for any reason while on this study will have the following docetaxel dose delays or reductions described in Table 6.

Table 6: Dosing Adjustments for Abnormal Liver Function

Bilirubin		ALT or AST	Action
> ULN	or	> 5 x ULN	Delay ≤ 3 weeks. If recovered*, reduce docetaxel dose by one dose level. If not, discontinue docetaxel.
≤ ULN	and	2.0 – 5 x ULN	Reduce docetaxel dose by one level

*Bilirubin ≤ ULN *and* ALT ≤ 5 x ULN and AST ≤ 5 x ULN.

Hypersensitivity Reactions

Any hypersensitivity reaction should be recorded as an AE. Subjects with hypersensitivity reactions to docetaxel are at risk for recurrent reactions. These subjects must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored (Table 7).

Delayed Hypersensitivity Reactions: In case of late-occurring hypersensitivity symptoms (e.g., appearance within 1 week after treatment of a localized or generalized pruritus), symptomatic treatment may be given (e.g., PO antihistamine). Additional PO or parenteral premedication with antihistamines may also be given for the next cycle of treatment, depending on the intensity of the reaction observed. No dose reductions should be made.

Table 7: Treatment Guidelines for Acute Hypersensitivity Reactions to Docetaxel

ACUTE HYPERSENSITIVITY REACTIONS TO DOCETAXEL	
Severity of Symptoms	**Treatment Guidelines**
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	• consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor subject, then complete docetaxel infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure (BP) > 80 mmHg	• interrupt docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor subject until resolution of symptoms • resume docetaxel infusion after recovery of symptoms; depending on the investigator's assessment of the subject, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (e.g. infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the 1-hour infusion rate) • depending on the intensity of the reaction observed, additional PO or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1 hour infusion, (e.g. infuse at an 8-hour rate for 5 minutes, then at a 4-hour rate for 5 minutes, then at a 2-hour rate for 5 minutes, then finally, resume at the 1-hour infusion rate)
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80 mmHg, angioedema	• immediately discontinue docetaxel infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor subject until resolution of symptoms • the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed
Anaphylaxis (NCI Grade 4 reaction)	*TREAT ANAPHYLAXIS URGENTLY! NO FURTHER STUDY TREATMENT*

Edema/Fluid Retention

Edema should be managed at early stages; advanced fluid retention is much more difficult to treat. Weight gain that is not explained by other factors, with or without mild edema, should be managed by early institution of mild diuretic treatment. Suggested treatment includes the following (thiazide diuretics are not recommended due to their potential for inhibition of urinary calcium excretion):

- Furosemide 20 - 40 mg PO daily. Potassium supplementation may be given as needed.
- If the above treatment was ineffective after a trial of ≥ 2 weeks, treat with furosemide 20 - 40 mg PO daily plus metolazone 2.5 mg PO daily with potassium supplementation as needed.
- Further therapy should be at the discretion of the treating physician.

Hyperlacrimation

Excessive lacrimation seems to be the result of a chemical conjunctivitis and/or chemical inflammation (with edema) of the lacrimal duct epithelium (producing a reversible lacrimal duct stenosis). The excessive lacrimation (epiphora) seen in some subjects receiving docetaxel appears to be related to cumulative dose (median ~300 mg/m^2) and resolves after treatment cessation. The following approach for clinically significant hyperlacrimation is suggested:

- Frequent instillation of artificial tears.
- Prescribe a steroid ophthalmic solution (e.g. prednisolone acetate) 2 drops each eye bid for 3 days starting the day before docetaxel administration in subjects without a history of herpetic eye disease.
- Consider withholding docetaxel treatment for two weeks for Grade 3 hyperlacrimation then restart treatment without a dose reduction if it is thought to be in the subject's best interest.
- Ophthalmologic consultation for significant and/or recurrent hyperlacrimation.

Peripheral Neuropathy

The docetaxel dose should be reduced by one dose level for Grade 2 peripheral neuropathies unless present at baseline. Treatment should be discontinued for Grade 3 or 4 neuropathies.

Stomatitis

If Grade 1 or 2 stomatitis is present on a scheduled treatment day, treatment may be withheld until stomatitis has resolved at the discretion of the Investigator. For Grade 3 or 4 stomatitis, the dose of docetaxel should be reduced by one dose level for subsequent cycles.

Other Non-hematological Toxicities

For other Grade 3 or 4 non-hematological toxicities considered to be docetaxel-related, treatment should be withheld until the toxicity resolves to ≤ Grade 1 or pre-study baseline, then reinstituted (if medically appropriate) at one dose level reduction (no later escalation is allowed). If treatment is withheld for longer than four weeks beyond the scheduled date of dosing due to Grade 3 or 4 toxicity, the subject will discontinue docetaxel.

8.1.3 Dexamethasone

For storage, handling, administration conditions, and side effects, refer to the prescribing information.

8.1.3.1 Toxicity and Dose Modification

The dexamethasone dose may be reduced for any dexamethasone-related toxicity in the absence of docetaxel hypersensitivity reactions at the discretion of the treating physician.

8.1.4 Prednisone

For storage, handling, administration conditions, and side effects, refer to the prescribing information.

8.2 Laboratory Monitoring

Investigators administering study treatments should monitor the subject laboratory values as clinically indicated and/or according to standard of care directed by center specific requirements.

As directed by the prescribing information for docetaxel, subjects should be monitored for the following laboratories during the course of treatment:

- Frequent monitoring for blood counts
- Liver function tests (bilirubin, ALT, AST, and alkaline phosphatase) prior to each cycle of docetaxel

During the course of treatment with DN-101, subjects should be monitored with a serum chemistry panel which includes both serum calcium and serum creatinine on day 2 of each treatment cycle.

8.3 Supportive Care and Concomitant and Prohibited Medication

Good clinical practice with respect to oncology supportive care is expected, including antibiotics, antipruetics, antiemetics, etc.

The following ancillary treatments are specifically permitted:

- Granulocyte colony stimulating factor (G-CSF) (only in case of febrile neutropenia and/or infection, and only after dose reduction guidelines for docetaxel, dexamethasone or DN-101 are followed)
- Additional use of G-CSF, including prophylactic use for subject deemed high risk for development neutropenia, needs to be discussed with and approved by a Novacea Medical Monitor
- Anti-allergic measures
- Erythropoietin, darbopoetin, or transfusions for anemia
- Bisphosphonate therapy

Prohibited concomitant medications include:

- Calcium supplements in excess of 500 mg (50% of the RDA)
- Pharmacological doses of vitamin D or its derivatives, including vitamin D supplements in excess of the RDA of 400 IU or 10 μg
- Oral ketoconazole (Nizoral®) and related compounds such as metronidazole (Flagyl®), fluconazole (Diflucan®), itraconazole, voriconazole, posaconazole
- Systemic corticosteroids except dexamethasone and prednisone per protocol.
- Other investigational drugs

- Other anticancer treatments including prescribed compounds and/or over-the-counter (OTC) products for the treatment of prostate cancer are prohibited during the Study Treatment phase

8.4 Study Drug Accountability

The responsibility for drug accountability at the study site rests with the Investigator. The Investigator may assign some of the Investigator's duties for drug accountability at the study site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the Investigator/institution.

Records should be maintained for Sponsor-provided drug(s) receipt, inventory, use, reconciliation and return to the Sponsor or alternative disposition of unused product(s). This information is to be captured on the Drug Accountability Log to be provided by the Sponsor. Records should include dates, quantities, batch/serial numbers, and expiration dates (as required). Investigators should maintain records that adequately document that subjects were provided the doses specified by the protocol.

Any Sponsor-provided drug product(s) unused at the conclusion of the study will be either returned to the Sponsor/designee or disposed of in accordance with instructions that will be provided by the Sponsor.

9. STUDY PROCEDURES (SEE APPENDIX 1)

The study procedures to be conducted for each subject enrolled in the study are presented in Appendix 1 and detailed in the text that follows. Any deviation from protocol procedures must be noted in the source documents and Case Report Forms (CRFs).

9.1 Screening (day -14 to day -1)

Each subject must sign an informed consent form prior to the conduct of any protocol-specific screening procedures. Screening evaluations will be used to determine the eligibility of each candidate for study enrollment. Candidates who fail to meet eligibility criteria by screening evaluations may be re-screened only if there is reasonable expectation that the candidate will be eligible after repeat screen. All screen and re-screen failures will be recorded in a Subject Screening Log, including the reason for exclusion from the study.

9.1.1 Clinical Assessments

The interval between the clinical screening evaluations and randomization must not exceed 14 days.

Informed Consent must be obtained (up to 28 days prior to randomization) prior to any of the following protocol-specific procedures:

- Demographic data
- Medical history including:
    - Documented adenocarcinoma of the prostate with Gleason score, T stage and PSA at diagnosis
    - Date of initial diagnosis
    - Metastatic disease documented radiographically (see Section 9.1.3)
    - History of prior treatment (e.g. surgery, radiation, estramustine) for adenocarcinoma of the prostate
    - History (within past 12 months) of any SRE or TE
    - Pain assessment (within 7 days prior to randomization)
    - QOL assessment and related questions (within 7 days prior to randomization)
    - History of androgen deprivation (drug-induced or orchiectomy)
    - Documented progression of AIPC
- Complete Physical Exam including:
    - Vital signs: blood pressure (BP), temperature/pulse/respiration (TPR)
    - Height
    - Weight
    - Current ECOG Performance Status
- Concomitant medications including all medications administered within 7 days prior to randomization

9.1.2 Laboratory Assessments

Central Laboratory tests must be obtained within 7 days prior to randomization. These values will be used as baseline measurements. If labs are obtained prior to day -7, then they must be repeated.

- PSA
- Hematology - CBC: hemoglobin, white blood cell count, absolute neutrophil count, platelet count
- Serum chemistry: calcium, creatinine, total bilirubin, AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase
- Serum testosterone level

Local laboratory tests obtained within 7 days prior to randomization can be used to determine subject eligibility. Subjects may be randomized based on local laboratory test used for eligibility. However, for all subjects, blood must be drawn and sent to central laboratory prior to subject randomization.

9.1.3 Radiographic Assessment

- Radiographic demonstration of metastatic disease must be present by computerized axial tomography (CT), magnetic resonance imaging (MRI), or bone scan obtained prior to study randomization
- A baseline bone scan must be obtained within 4 weeks prior to study randomization.

9.2 Subject Randomization and Enrollment (day -3 to day 1)

Subjects who sign the informed consent and meet all selection criteria will be randomized at or within 3 days prior to study treatment.

In order to enroll a subject, the Investigator or site representative will provide the following information to the Sponsor or its designee: subject's initials (or subject code), date of birth, ethnicity, ECOG performance status, date of consent and confirmation that the subject meets all eligibility criteria.

Following collection of this information, subjects will be assigned a randomization number and will be assigned to a treatment arm. Subjects will be considered enrolled into the study after randomization.

9.3 Study Treatment Phase

9.3.1 Study Treatments

Study treatment regimens for the Control and ASCENT Arm are summarized in Table 8.

Table 8. Study Dosing Regimens

Control Arm: 21-day dosing cycle		
Drug	Dose	Administration
Prednisone	5 mg	PO bid daily starting day 1
Docetaxel	75 mg/m^2 BSA	One-hour IV infusion on day 2
Dexamethasone	8 mg	PO about 12 hours, 3 hours and 1 hour prior to docetaxel infusion
ASCENT Arm: 28-day dosing cycle		
Drug	Dose	Administration
DN-101	45 μg	PO on an empty stomach (at least one hour before or two hours after meals) on days 1, 8 and 15
Docetaxel	36 mg/m^2 BSA	30-minute IV infusion on days 2, 9 and 16
Dexamethasone	8 mg	PO about 12 hours, 3 hours and 1 hour prior to docetaxel infusion

9.3.2 Study Treatment Window

For cycles without a dose delay, dosing should occur within one day of protocol specified dosing times. For cycles with dose delays, the following rules apply:

Treatment window for Control Arm:

- For any delay of docetaxel dosing, the date of administration (restart) of docetaxel following the delay will be considered and recorded as the same cycle for which the docetaxel was delayed.
- Up to 30 weeks of docetaxel or 10 doses at 75 mg/m^2 BSA will be administered.

Treatment windows for ASCENT Arm:

- If DN-101 dosing is delayed, docetaxel dosing should continue on schedule. DN-101 should be resumed once DN-101 toxicity resolves per Section 8.1.1.8.
- DN-101 should not be administered less than 5 days from the previous dose.
- For any delay of docetaxel dosing, the date of administration (restart) of docetaxel following the delay will be considered and recorded as the same cycle for which the docetaxel was delayed.
- Up to 30 weeks of docetaxel or 23 doses at 36 mg/m^2 BSA will be administered.

In both treatment arms, dexamethasone (8 mg PO) will be given about 12 hours (evening before), 3 hours and 1 hour prior to each docetaxel infusion. If the pre-treatment dexamethasone is missed, it may be administered IV prior to the docetaxel infusion.

9.3.3 Clinical Assessments

The following will be performed and documented; assessments are to be performed on day 2 of each cycle prior to docetaxel therapy. Assessments may be performed up to 72 hours before day 2 treatment:

- Modified physical exam – including vital signs (BP, TPR) and weight
- Concomitant medications
- Adverse events
- Pain assessment questionnaire
- QOL assessment questionnaire and related questions
- SREs, TE, and GI events

9.3.4 Laboratory Assessments

Laboratory assessments relating to treatment with docetaxel should be performed per standard of care (Control Arm: day 2 of 21-day cycle; ASCENT Arm: days 2, 9, 16 of 28-day cycle) (see Section 8.2). Assessments may be performed up to 72 hours before docetaxel administration.

Laboratory assessments relating to treatment with DN-101 need to include serum chemistry panel (including serum calcium and serum creatinine) and will be performed on days 2 of each 28-day cycle. Assessments may be performed up to 72 hours before DN-101 administration.

Clinically significant abnormal values per standard of care laboratory procedures will be reported as AEs. Laboratory values will not be collected in the database.

9.3.5 PSA Assessments

PSA will be obtained as part of baseline central laboratory assessment. PSA value should be obtained and available prior to starting subsequent treatment cycle. PSA may be obtained up to 9 days prior to the beginning of each study treatment cycle.

PSA progression is defined as per protocol Section 10.1 (biochemical progression).

9.3.6 Bone Scan

Bone scans are performed as clinically indicated.

9.3.7 Withdrawal of Subjects from Study Treatment Phase

Subjects who meet any of the criteria as described in Section 7.4.2 should be withdrawn from the Study Treatment phase and be entered into the Follow-up phase.

9.4 Follow-up Phase

9.4.1 Treatment

After withdrawal from docetaxel, subjects will continue DN-101 (ASCENT Arm) until unacceptable toxicity or initiation of treatment with a product not approved for marketing. After withdrawal from docetaxel, subjects in Control Arm will be treated per the discretion of the investigator. The Follow-up phase regimens for the ASCENT and Control Arm subjects are summarized in Table 9.

Subjects will be considered lost to follow-up only after at least three documented unsuccessful attempts to contact the subject by telephone and one unsuccessful attempt to contact the subject by letter.

Table 9. Dosing Regimen in Follow-up Phase

Control Arm		
Drug	Dose	Administration
Prostate cancer therapy per investigator discretion	N/A	Other cancer therapy per investigator discretion
ASCENT Arm		
Drug	DN-101 Dose	Administration
DN-101 + Prostate cancer therapy per investigator discretion	45 μg	PO on an empty stomach (at least one hour before or two hours after meals) on days 1, 8 and 15 of a 28-day cycle Other cancer therapy per investigator discretion

9.4.2 Treatment Window

For subjects in the ASCENT Arm, DN-101 should be taken within one day of protocol specified dosing times.

9.4.3 Clinical Assessments

The following will be performed and documented; assessments are to be performed every 8 weeks (q8w) (±2 weeks) for a period of 48 weeks:

- Subjects on Control Arm or ASCENT Arm (whether on or off DN-101)
    - Clinic follow-up visits (q8w x 6) including
        - Concomitant medications
        - Adverse events
        - TE, SRE and GI events
        - Pain assessment questionnaire (first Follow-up visit only)

- QOL assessment questionnaire and related questions (first Follow-up visit only)
- Survival status, including date and cause of death if subject is deceased
- Subsequent cancer therapy

- Subjects on ASCENT Arm who are still taking DN-101

  Note: The following assessments are required for the entire duration that subject is taking DN-101.
  - Symptom-directed physical exam - including vital signs (BP, TPR) and weight
  - Laboratory assessments as per Section 9.4.4
  - Concomitant medications
  - Adverse events
  - Survival status, including date and cause of death if subject is deceased
  - Subsequent cancer therapy-chemotherapy, radiation etc.

- Survival:

  After completion of 48 weeks follow-up, telephone or clinic visit q 8 weeks (for subjects on Control Arm and for subjects on ASCENT Arm once DN-101 is discontinued):
  - Survival status, including date and cause of death if subject is deceased
  - Subsequent cancer therapy-chemotherapy, radiation etc. including subsequent calcitriol therapy

Other clinical assessments during administration of all protocol and non-protocol specified agents will occur per standard of care as determined by the investigator.

9.4.4 Laboratory Assessments

The following will be performed and documented. Assessments are to be performed q 8 weeks (±2 weeks):

- Laboratory assessment of serum chemistry including serum calcium and serum creatinine will be performed for subjects on ASCENT Arm until DN-101 is discontinued.
- Laboratory assessments for non-protocol treatments should be performed according to standard of care.

Other laboratory assessments during administration of all protocol and non-protocol specified agents will occur per standard of care as determined by the investigator. Clinically significant abnormal values per standard of care laboratory procedures will be reported as AEs. Laboratory values will not be collected in the database.

9.4.5 Cancer-related Treatments

At the discretion of the investigator, during the Follow-up phase, standard of care cancer-related treatments for AIPC other than non-marketed products (experimental agents) may be used. Subsequent cancer therapies must be documented. Subject assessments including subject visits, physical examination, and laboratory assessment will be conducted per standard of care.

9.5 Termination Evaluations

9.5.1 Termination from Study Treatment Phase

The reason for termination from Study Treatment phase will be collected.

9.5.2 Termination from Follow-up Phase

Subjects may withdraw from Follow-up phase upon request. Survival status should be noted.

9.5.3 Termination Due to Death

If a subject terminates from the study due to death, an attempt should be made to obtain the date and cause of death.

9.6 Declaration End of Clinical Study

The declaration end of the clinical study will be when the primary efficacy analysis occurs with respect to the requirement for notification of the Competent Authority as detailed in the Clinical Trials Directive 2001/20/EC.

10. STUDY ASSESSMENTS

Study assessments include disease progression, survival, TE, SRE, SAE, GI, QOL, and pain. Biomarkers and population PK will be collected under separate protocols.

10.1 Disease Progression

Subjects should be taken off treatment with docetaxel for clinical disease progression. Subject should receive 12 weeks of treatment before clinical disease progression assessments are determined, unless clinically indicated.

Clinical parameters of disease progression include:

1) Biochemical (PSA) progression. PSA progression is defined as a 25% increase over baseline or nadir, whichever is lower, and an increase in the absolute value of PSA level by an increment of 5 ng/mL that is confirmed by another PSA level at no less than a 4-week interval (Appendix 2, Figure B). S**ubjects must have received a minimum of 12 weeks of study treatment, before progression could be determined solely by rising PSA**. **In the case of disease progression determined solely by rising PSA, additional clinical assessments should be consistent with disease progression.**
2) Radiographic progression
   - Target or non-target lesions progression as defined by RECIST criteria (Appendix 3)
   - Bone scan progression: worsening bone scan as evidenced by the appearance of two or more new skeletal lesions that are not felt to be consistent with tumor flare. Subjects whose sole evidence of disease progression is bone scan progression must also have a PSA $\geq$ 5 ng/mL
3) Clinical disease progression as assessed by the Investigator
   - Example is worsening ECOG performance status thought to be due to disease progression

10.2 Survival

Survival is defined as the time between the date of randomization and the date of death, whatever the cause.

10.3 Thromboembolic Event (TE)

Thromboembolic events will be observed up to 48 weeks after termination of Study Treatment phase for all subjects. TE events are defined as:

- Myocardial infarction
- Cerebrovascular accident (hemorrhagic and / or ischemic)
- Pulmonary embolism
- Deep venous thrombosis
- Arterial thrombosis

10.4 Skeletal-related Event (SRE)-free Survival

Skeletal-related events (SRE) will be observed up to 48 weeks after termination of Study Treatment phase for all subjects. SRE events are defined as:

- Pathologic bone fracture: Bone fractures which occur spontaneously or which result from minor trauma. A new compression fracture is defined as a decrease in total vertebral height, or anterior vertebral height, or posterior height of ≥ 25% from baseline. A further reduction in the vertebral height by ≥ 25% during the study is classified as a new fracture. Each pathological fracture (vertebral and non-vertebral) is to be documented by X-ray and is to be counted separately.
- Spinal cord compression: Compression will be confirmed by MRI or CT scan. If spinal cord compression occurs in conjunction with a vertebral compression fracture, each will be counted as a separate SRE.
- Surgery to the bone: Procedures performed to set or stabilize pathologic fractures or areas of spinal cord compression, and surgical procedures performed to treat or prevent fracture or spinal cord compression.
- Radiation therapy to the bone: Radiation administered to bone to palliate painful lesions or to prevent or treat fractures or spinal cord compressions. Each part of radiation will be considered a separate event. Administration of a radioisotope such as Strontium will be included as radiation to bone.

Duration of skeletal-related event-free survival is defined as the time between the randomization date and the date on which the first SRE occurs or the date of death due to any cause, whichever occurs first.

10.5 Serious Adverse Event (SAE)

Serious adverse events, as defined in Section 11.2.1, will be collected throughout the study.

10.6 Gastrointestinal (GI) Event

Gastrointestinal events will be observed up to 48 weeks after termination of Study Treatment phase and are defined as:

- anorexia
- diarrhea
- dysphagia
- esophagitis
- nausea
- pharyngitis
- stomatitis
- vomiting

10.7 Quality of Life Assessment and Related Questions

The Functional Assessment of Cancer Therapy-Prostate (FACT-P, version 4) QOL assessment questionnaire and related questions, including measurement of fatigue using the Brief Fatigue Inventory, will be administered up to 8 weeks (± 2 weeks) after termination of the Study Treatment phase. The QOL questionnaires (FACT-P and the Brief Fatigue Inventory) and related questions will only be collected from centers in the North American region. The questionnaire will be self-administered.

10.8 Pain Questionnaires

The pain assessment questionnaire (the Brief Pain Inventory) will be administered up to 8 weeks (± 2 weeks) after termination of the Study Treatment phase. The questionnaire will only be collected from centers in the North American region. The questionnaire will be self-administered.

10.9 Population Pharmacokinetics (PK) Sub-study

A sub-study to determine the population PK of DN-101 will be conducted at selected study sites. A separate protocol and informed consent will be used for this sub-study.

10.10 Biomarker Sub-study

A sub-study to evaluate the effect of DN-101 on hypothesis-driven biomarkers will be conducted at selected study sites in North America. A separate protocol and informed consent will be used for this sub-study.

11. ADVERSE EVENT AND TOXICITY MANAGEMENT

11.1 Adverse Events

11.1.1 Definitions

An AE is any reaction, side effect, or other undesirable event that occurs in conjunction with the use of a drug, biological product, or diagnostic agent in humans, whether or not considered drug-related. In addition to new events, any increase in the severity of a pre-existing condition that occurs after the subject begins taking study medication is considered an adverse event. This includes any side effect, injury, toxicity, or sensitivity reaction.

Any condition or laboratory abnormality, physical finding with an onset date before the initial study drug administration is considered to be pre-existing in nature and part of the medical history. These pre-existing events should only be noted in the AE CRF if they worsen in severity or frequency after the start of study drug administration.

11.1.2 Recording Requirements

Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration and before the post-treatment assessment visit should be recorded as an AE on the CRF, regardless of the severity or relationship to study treatment. All AEs related to study drug must be followed to resolution or to stabilization if improvement is not expected.

11.1.3 Toxicity Criteria and Grading

Toxicities will be assessed using the NCI-CTCAE version 3.0. Toxicities will be reported as descriptive findings. Events or symptoms not included on the NCI-CTCAE scale will be assessed using the Grades described in Table 10:

Table 10: Toxicity Criteria

Grade	Description
1	mild AE
2	moderate AE
3	severe AE
4	life-threatening or disabling AE
5	death related to AE

For assigning study drug attribution of the adverse event, the following questions will be applied:

1. Does the Investigator suspect that the event may have been caused by docetaxel?
2. Does the Investigator suspect that the event may have been caused by study drug DN-101?
3. Does the Investigator suspect that the event may have been caused by prednisone?

The answer “yes” or “no” or “N/A” will be entered on the CRF for each question.

11.2 Serious Adverse Events

11.2.1 Definition

A **serious adverse event** (SAE) is defined as follows:

Any untoward medical occurrence that at any dose results in:

- Death;
- Inpatient hospitalization or prolongation of existing hospitalization (except scheduled hospitalization for non-acute, unrelated cause such as elective surgery);
- A life-threatening untoward medical event that does not result in hospitalization; examples include medical bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect; or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.2.2 Serious Adverse Event Reporting Requirements

All SAEs occurring during the Study Treatment phase, and for 48 weeks after termination of Study Treatment phase, or up to 30 days following the last dose of DN-101, whichever is the longest, will be reported on the AE CRF. All SAEs must be followed to resolution or to stabilization if improvement is not expected. These reporting requirements apply to all SAEs, regardless of relationship to study treatment, and whether they are unexpected (i.e., not described in nature or severity in the current Investigator's Brochure or package label) or expected/labeled.

All SAEs must be entered into the clinical database within 24 hours. Requested follow-up information such as specific source documents can be sent by email or fax to Sponsor or designee:

Fax: 1-650-228-1897

E-mail: ascent2safety@Novacea.com

For urgent, safety-related medical questions, the Sponsor Drug Safety Officer or designee may be reached by calling 1-650-228-1898.

Unexpected and drug-related SAEs will be reported to regulatory health authorities, ethics committees, and participating study centers according to applicable requirements. As survival (as measured by death) is the protocol specified outcome measure, individual cases of deaths will be monitored by Sponsor's Safety Committee.

12. STATISTICAL METHODS

12.1 Endpoints

12.1.1 Efficacy

The primary efficacy endpoint is duration of survival.

The secondary efficacy endpoints are:

- TE rate
- Duration of SRE-free survival

12.1.2 Safety

Safety endpoints are:

- SAE rate
- GI event rate

12.2 Definition

12.2.1 Baseline

Generally, for purposes of clinical management, baseline is defined as the last measurement for the endpoint of interest obtained within 28 days prior to initiation of study treatment.

12.2.2 Duration of Survival

The duration of survival is defined as the time between the date of randomization and the date of death, whatever the cause. Subjects who are alive will be censored at the time of their last contact date.

12.2.3 Thromboembolic Event (TE) Rate

Thromboembolic event rate is defined as the fraction of subjects with a TE.

12.2.4 Duration of Skeletal-related Event (SRE)-free Survival

Duration of skeletal-related event-free survival is defined as the time between the randomization date and the date on which the first SRE occurs or the date of death due to any cause, whichever occurs first. Subjects who are alive and have not reported an SRE event will be censored at the time of their last evaluation / contact.

12.2.5 Serious Adverse Event (SAE) Rate

Serious adverse event rate is defined as the fraction of subjects with an SAE. Serious adverse events are defined in Section 11.2.1.

12.2.6 Gastrointestinal (GI) Event Rate

Gastrointestinal event rate is defined as the fraction of subjects with a GI event.

12.3 Analysis Sets

The intent-to-treat (ITT) population will consist of all subjects who are randomized in the study, regardless of actual receipt of study treatment. Subjects will be included in the ITT analysis according to their randomized treatment arm assignment. The safety population will consist of all subjects who received at least one dose of study treatment. Subjects will be included in the safety analysis according to the treatment actually received.

Statistical analyses of primary and secondary efficacy endpoints will be carried out on the ITT population. The comparison of the treatment arms for the primary efficacy endpoint of survival and secondary efficacy endpoints will be conducted at a two-sided significance level of $\alpha = 0.05$.

The efficacy endpoints will be tested using the following hierarchical procedure:

Step 1. If the comparison of primary endpoint is found to be statistically significant at the 0.05 level, go to step 2, otherwise no further analysis will be performed.

Step 2. The TE event will be statistically compared between the two treatment groups at the 0.05 level. If the comparison of TE event is found to be statistically significant, go to step 3, otherwise no further analysis will be performed.

Step 3. The SRE-free survival will be statistically compared between the two treatment groups at the 0.05 level.

The final analysis will be conducted when a minimum of 445 total deaths have occurred. Statistical analyses of safety will be performed on the safety population.

Details of statistical analysis will be described in the Statistical Analysis Plan.

12.3.1 Efficacy Analysis

12.3.1.1 Duration of Survival

Duration of Survival will be summarized by treatment group using the Kaplan-Meier methods. The treatment groups will be compared using the Cox regression model adjusting for ECOG performance status and hemoglobin at baseline. This methodology is efficient (Anderson and Fleming, 1995; Anderson, 1989) as it takes into account the influence of known strong prognostic factors on survival in prostate cancer (Halabi et al. 2003; Scher et al. 1999). The stratified log-rank analysis will be provided as a supportive analysis to confirm robustness. The hazard ratio of the median survival and the 95% CI will be calculated to estimate the relative treatment effect. The Control Arm will serve as the reference treatment group in the calculation of the hazard ratios. The final analysis of survival data will be performed provided that at least 445 deaths have been observed overall. This is estimated to occur within 18 months after the recruitment of the last subject.

12.3.1.2 Thromboembolic Event (TE) Rate

Thromboembolic event rate will be summarized based on the crude proportion of subjects with one or more TEs at the time of the final analysis. The treatment groups will be

compared using Pearson χ^2 test, performed at 0.05 level. The primary analysis will include any TE event reported in the Study Treatment phase. The secondary analysis will include any TE event reported in the Study Treatment phase and the Follow-up phase.

12.3.1.3 Duration of Skeletal-related Event (SRE)-free Survival

Duration of skeletal-related event (SRE)-free survival will be summarized by treatment group using the Kaplan-Meier methods. The treatment groups will be compared using the Cox regression model adjusting for ECOG performance status and hemoglobin at baseline. The primary analysis will only include the SRE data in the Study Treatment phase. The secondary analysis will include any SRE event reported in the Study Treatment phase and the Follow-up phase.

12.3.2 Safety Analysis

Adverse events will be mapped to preferred terms and system organ class using the MedDRA dictionary. The incidence of subjects with an AE, study drug-related AEs, SAEs, and AEs resulting in study medication discontinuation will be summarized by treatment group according to preferred term and system organ class. Subjects will undergo a modified physical exam on day 2 of each 21-day or 28-day cycle. Abnormal events will be recorded as AEs when appropriate. Information regarding the occurrence of SREs, TEs, and GI events will be recorded on specific CRFs. Clinically significant laboratory abnormalities will be recorded as AEs.

Serious adverse event (SAE) rate will be summarized based on the crude proportion of subjects with one or more SAEs at the time of the final analysis. The treatment groups will be compared using Pearson χ^2 test, performed at 0.05 level.

Gastrointestinal (GI) event rate will be summarized based on the crude proportion of subjects with one or more GI events at the time of the final analysis. The treatment groups will be compared using Pearson χ^2 test, performed at 0.05 level.

12.3.3 Exploratory Analysis

The exploratory efficacy endpoints are:

- Quality of Life (QOL)
- Pain
- PSA

Analyses for exploratory endpoints will be detailed in the Statistical Analysis Plan.

12.3.4 Interim Analysis

Interim efficacy analysis is not currently planned. If for any unforeseen reasons, the DSMB committee recommends to perform an interim efficacy analysis, a detailed plan will be prepared before the interim efficacy analysis can be conducted. The level of significance for this analysis is set at the 0.0001 level.

12.3.5 Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will monitor safety and tolerability during the two study phases (Study Treatment phase and Follow-up phase). In addition, a planned safety review will be performed after approximately 50 subjects have been entered in the Follow-up phase. Details regarding DSMB membership, function, and rules are described in the DSMB charter.

12.4 Sample Size Considerations

The planned sample size of approximately 900 subjects (450 per arm) and estimated total study duration (including follow-up) of approximately 2-3 years are based on the following assumptions:

- A 1:1 randomization to the two treatment arms
- Median survival of 18.9 months in Control Arm, based on TAX327
- A minimum of 445 deaths are required for completion of the study
- A two-sided significance level of $\alpha = 0.05$ and a minimum statistical power of 0.85 to detect a hazard ratio of 0.75

The sample size and power calculation is based on log-rank test and performed using the software package EaST 3.0 (Cytel Software Corp, Cambridge, MA).

Based on the ASCENT study, assume the TE rate is 8.8% and 2.4% for placebo and ASCENT regimen arm, respectively, 450 subjects per treatment arm will provide a 98.8% power to detect this treatment difference at the two-sided significance level of 0.05.

Based on the ASCENT study, 450 subjects per treatment arm will provide at least 80% power to detect the hazard ratio for SRE-free survival of 0.78 with two-sided significance level of 0.05.

12.5 Control for Bias

The following study design components will facilitate the control for bias:

- Large (approximately 900 subjects)
- Multicenter
- Randomized

The randomization code will be controlled through a centralized procedure and will not be known to personnel directly involved with study conduct or analysis of results until the study database is closed. The randomization code will be held by an independent clinical contract research organization. No one individual will know the aggregate treatment assignment until study unblinding to treatment assignment is to occur.

The treatment assignment for any individual study subject will not be known to study and site personnel or the subject prior to subject randomization into the study.

13. RESPONSIBILITIES

13.1 Good Clinical Practice

The Investigator and Sponsor will ensure that this study is conducted in full compliance with "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, Edinburgh and clarified in Washington and Tokyo), International Conference on Harmonization (ICH) guidelines, the Code of Federal Regulations and/or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

13.2 Institutional Review Board (IRB) / Research Ethics Board (REB) / Independent Ethics Committee (IEC) Approval

The protocol and informed consent form for this study must be approved in writing by the appropriate IRB, REB or IEC in accordance with the laws and regulation of the country in which the research is conducted prior to any subject being registered in this study.

Obligations of Investigators: All adverse events occurring during the study, whether or not attributed to the investigational drug / biotherapy, observed by the investigator or reported by the subject, must be reported as specified in Section 11.2.2. The investigators responsibilities are listed in full in the investigator agreement.

13.3 Informed Consent

Written informed consent will be obtained from all subjects, or the legally authorized representative of the subject, participating in this study in accordance with the laws and regulation of the country in which the research is conducted. The original signed consent form shall be maintained in the subject's study file.

The principles of informed consent must be followed to be in compliance with health authorities' regulations for the conduct and monitoring of clinical investigations.

13.4 Confidentiality

The investigator must ensure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials or an identification code (i.e., not names) should be recorded on any form submitted to the Sponsor and IRB/REB/IEC.

The investigator agrees that all information contained in this protocol and information related to high dose administration of DN-101 including but not limited to the Investigator's Brochure, this protocol, CRFs, the study drug, and any other study information, remain the sole and exclusive property of the Sponsor. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study, regulatory authority or health authority inspectors, or as required by law) without prior written authorization from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

13.5 Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 separate categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendment, IRB/REB/IEC approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence, as per local guidelines and requirements.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include subject hospital/clinic records, physician's and nurse's notes, appointment books, original laboratory reports, X-rays, CT and bone scans, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

All clinical study documents must be retained by the investigator for at least 10 years or at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements or request by the Sponsor. The investigator must notify the Sponsor prior to destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

13.6 Case Report Forms and Record Maintenance

For each subject enrolled, all CRFs must be completed and signed off by the principal investigator or co-/sub-investigator within a reasonable time period after data collection has been completed. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

13.7 Drug Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. See Section 8.4 for specifics.

13.8 Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or designee, or regulatory and health authority inspectors.

13.9 Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

13.10 Study Report and Publications

It is expected that no individual site principal investigator or designee will publish, present, or communicate study results without coordination with the protocol chairman and the Sponsor. After conclusion of the study investigators in this study may not communicate orally, present, or publish in scientific journals or other scholarly media any results of this study without prior written approval from the Sponsor and the protocol chair. The Sponsor will have the right to review proposed presentations and publications. Investigators will submit to the Sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days prior to submission of the publication or presentation. The investigator will comply with any Sponsor or supporter request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

No such communication, presentation, or publication will include the Sponsor's confidential information (see Section 13.4).

13.11 Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator FDA Form 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the Investigator's Brochure; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

13.12 Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols, and promptly inform investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

13.13 Protocol Modifications

Changes in any portion of this protocol must be documented in the form of an amendment from the Sponsor and must be approved by the site's IRB/REB/IEC before the amendment may be implemented at that site. The IRB/REB/IEC chairperson may approve minor changes, or may designate one or more regulatory members to approve revisions.

A substantial amendment is one that must be notified to the Health Authorities for each participating country in addition to each IEC. Substantial amendments to the conduct of a clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments to the trial are regarded as substantial where they are likely to have a significant impact on:

- The safety or physical or mental integrity of the subjects
- The scientific value of the trial
- The conduct or management of the trial
- The quality or safety of any investigational medicinal product (IMP) used in the trial

13.14 Access to Information for Monitoring

In accordance with ICH-GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the data capture system for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study, to verify adherence to the protocol, and the completeness, consistency and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.15 Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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Appendix 1: Schedule of Assessments

Table 1: Study Procedures for CONTROL Arm

	Screening			Randomize	Study Treatment phase 21-day cycle (up to 30 weeks)			Follow-up phase	Long-term Survival
Day **ASSESSMENTS**	**-28 to -1**	**-14 to -1**	**-7 to -1**	**-3 to 1**	**1**	**2**	**3-21**	**q 8 weeks (± 2 wks) x 6 clinic visits**	**q 8 weeks (± 2 wks) via telephone**
Written Informed Consent	X								
Medical History		X							
Physical Exam		X				X[4]		X	
Vital Signs (incl. weight)		X				X			
Height		X							
ECOG Status		X							
Hematology			X[3]			X[5]			
Serum Chemistry			X[3]			X[5]			
PSA			X[3]			X[6]			
Serum Testosterone			X[3]						
Bone Scan	X								
Randomize Subject				X					
Docetaxel (75mg/m^2 BSA iv)						X			
Prednisone 5 mg PO bid					X	X	X		
Dexamethasone						X			
QOL, Fatigue, and Pain Assessment Questionnaire[1]			X			X		X[7]	
Concomitant Medications			X			X		X	
Adverse Events						X		X	
Thromboembolic Events		X				X		X[8]	
Gastrointestinal Events						X		X[8]	
Skeletal-related Events		X				X		X[8]	
Survival					X ----------				----------X
Further Cancer Therapy[2]								X----------	----------X

[1] To be performed at sites in North America.
[2] Follow-up for subsequent cancer treatment (chemotherapy, radiation etc. including subsequent calcitriol therapy)
[3] Screening labs are processed centrally (central labs)
[4] Modified physical exam including vital signs (BP and TPR) and weight
[5] Labs are performed per standard of care as noted in the labeling
[6] PSA to be performed within 9 days prior to the next docetaxel dosing.
[7] To be collected on the first follow-up visit only.
[8] To be collected for q8w x 6 (up to 48 weeks) after completion of Study Treatment phase.

Table 2: Study Procedures for ASCENT Arm

	Screen			Randomize	Study Treatment phase 28-day cycle (up to 30 weeks)						Follow-up phase (on DN-101)	Long-term Survival
Day **ASSESSMENTS**	**-28 to -1**	**-14 to -1**	**-7 to 1**	**-3 to 1**	**1**	**2**	**8**	**9**	**15**	**16**	**q 8 wks (±2 wks) clinic visits**	**q 8 weeks (±2 week) via telephone**
Written Informed Consent	X											
Medical History		X										
Physical Exam		X				X[4]					X[7]	
Vital Signs (incl weight)		X				X					X	
Height		X										
ECOG Status		X										
Hematology			X[3]			X[5]						
Serum Chemistry			X[3]			X[5]					X	
PSA			X[3]			X[6]						
Serum Testosterone			X[3]									
Bone Scan	X											
Randomize Subject				X								
DN-101					X		X		X		X[10]	
Docetaxel (36mg/m^2 BSA iv)						X		X		X		
Dexamethasone						X		X		X		
QOL, Fatigue, and Pain Assessment Questionnaire[1]			X			X					X[8]	
Concomitant Medications			X			X					X	
Adverse Events						X					X	
Thromboembolic Events		X				X					X[9]	
Gastrointestinal Events						X					X[9]	
Skeletal-related Events		X				X					X[9]	
Survival					X----------							----------X
Further Cancer Therapy[2]											X----------	----------X

[1] To be performed at sites in North America
[2] Follow-up for subsequent cancer treatment (chemotherapy, radiation etc. including subsequent calcitriol therapy)
[3] Screening labs are processed centrally (central labs)
[4] Modified physical exam including vital signs (BP and TPR) and weight
[5] Labs are performed per standard of care as noted in the labeling
[6] PSA to be performed within 9 days prior to the next docetaxel dosing
[7] Symptom-directed physical examination
[8] To be collected on the first follow-up visit only.
[9] To be collected for q8wks x 6 (up to 48 weeks) after completion of Study Treatment phase
[10] DN-101 administration on days 1, 8, and 15 of a 28-day cycle until unacceptable toxicity or initiation of products not approved for marketing.

Appendix 2: Eligibility and Response Reporting Guidelines for Clinical Trials in AIPC

Reference: Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, 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.

1. Eligibility

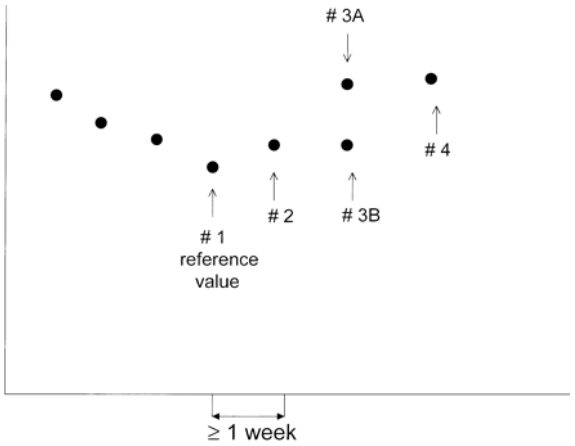

Figure A. For defining eligibility, the reference value (no. 1) is the last PSA level before a sequence of increases. The interval between the reference value and time point no. 2 must be a minimum of 1 week. If the PSA at time point no. 3 (value no. 3A) is greater than at time point no. 2, then the requirement for a sequence of three increases has been met. If the third value is not greater than value no. 2, but value no. 4 is, then increasing PSA has been confirmed, and the patient can be eligible. In all cases, value no. 3A or no. 4 must be greater than or equal to 5 ng/mL.

2. Reporting Guideline Based on PSA Progression

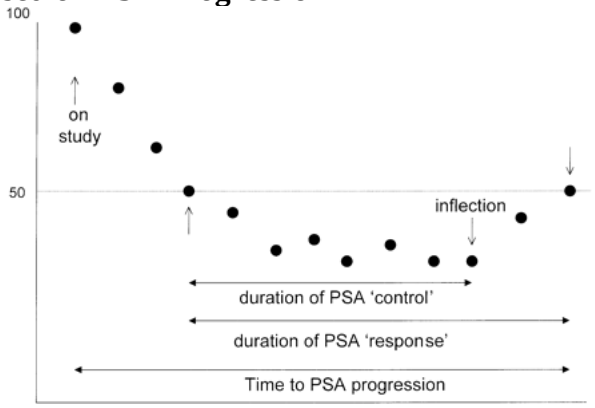

Figure B. The duration of both PSA-based reporting end points are measured from the first time point at which the PSA has declined by at least 50% (which must eventually be confirmed by a second value). The duration of PSA response is the time until PSA has increased back to 50% of the original on-study value. However, in many cases, it will be possible (in retrospect) to identify an inflection point, the point at which PSA began what became a continuous increase. Some investigators feel that this may be considered the point at which disease control could be assumed to be lost. Thus, the duration of PSA control may be also be reported. Others prefer the time to PSA progression, which is defined as the time at which therapy started and ends when the PSA increases by 50% above the nadir.

Appendix 3: RECIST Criteria

Reference:

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Gwyther SG, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92:205-16.

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan T. van Oosterom, Michaele C. Christian, Steve G. Gwyther

Anticancer cytotoxic agents go through a process by which their antitumor activity—on the basis of the amount of tumor shrinkage they could generate—has been investigated. In the late 1970s, the International Union Against Cancer and the World Health Organization introduced specific criteria for the codification of tumor response evaluation. In 1994, several organizations involved in clinical research combined forces to tackle the review of these criteria on the basis of the experience and knowledge acquired since then. After several years of intensive discussions, a new set of guidelines is ready that will supersede the former criteria. In parallel to this initiative, one of the participating groups developed a model by which response rates could be derived from unidimensional measurement of tumor lesions instead of the usual bidimensional approach. This new concept has been largely validated by the Response Evaluation Criteria in Solid Tumors Group and integrated into the present guidelines. This special article also provides some philosophic background to clarify the various purposes of response evaluation. It proposes a model by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment. Methods of assessing tumor lesions are better codified, briefly within the guidelines and in more detail in Appendix I. All other aspects of response evaluation have been discussed, reviewed, and amended whenever appropriate. [J Natl Cancer Inst 2000; 92:205–16]

A. Preamble

Early attempts to define the objective response of a tumor to an anticancer agent were made in the early 1960s *(1,2).* In the mid- to late 1970s, the definitions of objective tumor response were widely disseminated and adopted when it became apparent that a common language would be necessary to report the results of cancer treatment in a consistent manner.

The World Health Organization (WHO) definitions published in the 1979 *WHO Handbook (3)* and by Miller et al. *(4)* in 1981 have been the criteria most commonly used by investigators around the globe. However, some problems have developed with the use of WHO criteria: 1) The methods for integrating into response assessments the change in size of measurable and "evaluable" lesions as defined by WHO vary among research groups, 2) the minimum lesion size and number of lesions to be recorded also vary, 3) the definitions of progressive disease are related to change in a single lesion by some and to a change in the overall tumor load (sum of the measurements of all lesions) by others, and 4) the arrival of new technologies (computed tomography [CT] and magnetic resonance imaging [MRI]) has led to some confusion about how to integrate three-dimensional measures into response assessment.

These issues and others have led to a number of different modifications or clarifications to the WHO criteria, resulting in a situation where response criteria are no longer comparable among research organizations—the very circumstance that the WHO publication had set out to avoid. This situation led to an initiative undertaken by representatives of several research groups to review the response definitions in use and to create a revision of the WHO criteria that, as far as possible, addressed areas of conflict and inconsistency.

In so doing, a number of principles were identified:

1) Despite the fact that "novel" therapies are being developed that may work by mechanisms unlikely to cause tumor regression, there remains an important need to continue to describe objective change in tumor size in solid tumors for the foreseeable future. Thus, the four categories of complete response, partial response, stable disease, and progressive disease, as originally categorized in the *WHO Handbook (3),* should be retained in any new revision.
2) Because of the need to retain some ability to compare favorable results of future therapies with those currently available, it was agreed that no major discrepancy in the meaning and the concept of partial response should exist between the old and the new guidelines, although measurement criteria would be different.
3) In some institutions, the technology now exists to determine

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See "Note" following "References."

changes in tumor volume or changes in tumor metabolism that may herald shrinkage. However, these techniques are not yet widely available, and many have not been validated. Furthermore, it was recognized that the utility of response criteria to date had not been related to precision of measurement. The definition of a partial response, in particular, is an arbitrary convention—there is no inherent meaning for an individual patient of a 50% decrease in overall tumor load. It was not thought that increased precision of measurement of tumor volume was an important goal for its own sake. Rather, standardization and simplification of methodology were desirable. Nevertheless, the guidelines proposed in this document are not meant to discourage the development of new tools that may provide more reliable surrogate end points than objective tumor response for predicting a potential therapeutic benefit for cancer patients.

4) Concerns regarding the ease with which a patient may be considered mistakenly to have disease progression by the current WHO criteria (primarily because of measurement error) have already led some groups such as the Southwest Oncology Group to adopt criteria that require a greater increase in size of the tumor to consider a patient to have progressive disease *(5).* These concerns have led to a similar change within these revised WHO criteria (*see* Appendix II).
5) These criteria have not addressed several other areas of recent concern, but it is anticipated that this process will continue and the following will be considered in the future:
   - Measures of antitumor activity, other than tumor shrinkage, that may appropriately allow investigation of cytostatic agents in phase II trials;
   - Definitions of serum marker response and recommended methodology for their validation; and
   - Specific tumors or anatomic sites presenting unique complexities.

B. Background

These guidelines are the result of a large, international collaboration. In 1994, the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group set up a task force (*see* Appendix III) with the main objective of reviewing the existing sets of criteria used to evaluate response to treatment in solid tumors. After 3 years of regular meetings and exchange of ideas within the task force, a draft revised version of the WHO criteria was produced and widely circulated (*see* Appendix IV). Comments received (response rate, 95%) were compiled and discussed within the task force before a second version of the document integrating relevant comments was issued. This second version of the document was again circulated to external reviewers who were also invited to participate in a consensus meeting (on behalf of the organization that they represented) to discuss and finalize unresolved problems (October 1998). The list of participants to this consensus meeting is shown in Appendix IV and included representatives from academia, industry, and regulatory authorities. Following the recommendations discussed during the consensus meeting, a third version of the document was produced, presented publicly to the scientific community (American Society for Clinical Oncology, 1999), and submitted to the *Journal of the National Cancer Institute* in June 1999 for official publication.

Data from collaborative studies, including more than 4000 patients assessed for tumor response, support the simplification of response evaluation through the use of unidimensional measurements and the sum of the longest diameters instead of the conventional method using two measurements and the sum of the products. The results of the different retrospective analyses (comparing both approaches) performed by use of these different databases are described in Appendix V. This new approach, which has been implemented in the following guidelines, is based on the model proposed by James et al. *(6).*

C. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines

1. Introduction

The introduction explores the definitions, assumptions, and purposes of tumor response criteria. Below, guidelines that are offered may lead to more uniform reporting of outcomes of clinical trials. Note that, although single investigational agents are discussed, the principles are the same for drug combinations, noninvestigational agents, or approaches that do not involve drugs.

Tumor response associated with the administration of anticancer agents can be evaluated for at least three important purposes that are conceptually distinct:

- Tumor response as a prospective end point in early clinical trials. In this situation, objective tumor response is employed to determine whether the agent/regimen demonstrates sufficiently encouraging results to warrant further testing. These trials are typically phase II trials of investigational agents/regimens (*see* section 1.2), and it is for use in this precise context that these guidelines have been developed.
- Tumor response as a prospective end point in more definitive clinical trials designed to provide an estimate of benefit for a specific cohort of patients. These trials are often randomized comparative trials or single-arm comparisons of combinations of agents with historical control subjects. In this setting, objective tumor response is used as a surrogate end point for other measures of clinical benefit, including time to event (death or disease progression) and symptom control (*see* section 1.3).
- Tumor response as a guide for the clinician and patient or study subject in decisions about continuation of current therapy. This purpose is applicable both to clinical trials and to routine practice (*see* section 1.1), but use in the context of decisions regarding continuation of therapy is not the primary focus of this document.

However, in day-to-day usage, the distinction among these uses of the term "tumor response" can easily be missed, unless an effort is made to be explicit. When these differences are ignored, inappropriate methodology may be used and incorrect conclusions may result.

1.1. Response Outcomes in Daily Clinical Practice of Oncology

The evaluation of tumor response in the daily clinical practice of oncology may not be performed according to predefined criteria. It may, rather, be based on a subjective medical judgment that results from clinical and laboratory data that are used to assess the treatment benefit for the patient. The defined criteria

developed further in this document are not necessarily applicable or complete in such a context. It might be appropriate to make a distinction between "clinical improvement" and "objective tumor response" in routine patient management outside the context of a clinical trial.

1.2. Response Outcomes in Uncontrolled Trials as a Guide to Further Testing of a New Therapy

"Observed response rate" is often employed in single-arm studies as a "screen" for new anticancer agents that warrant further testing. Related outcomes, such as response duration or proportion of patients with complete responses, are sometimes employed in a similar fashion. The utilization of a response rate in this way is not encumbered by an implied assumption about the therapeutic benefit of such responses but rather implies some degree of biologic antitumor activity of the investigated agent.

For certain types of agents (i.e., cytotoxic drugs and hormones), experience has demonstrated that objective antitumor responses observed at a rate higher than would have been expected to occur spontaneously can be useful in selecting anticancer agents for further study. Some agents selected in this way have eventually proven to be clinically useful. Furthermore, criteria for "screening" new agents in this way can be modified by accumulated experience and eventually validated in terms of the efficiency by which agents so screened are shown to be of clinical value by later, more definitive, trials.

In most circumstances, however, a new agent achieving a response rate determined *a priori* to be sufficiently interesting to warrant further testing may not prove to be an effective treatment for the studied disease in subsequent randomized phase III trials. Random variables and selection biases, both known and unknown, can have an overwhelming effect in small, uncontrolled trials. These trials are an efficient and economic step for initial evaluation of the activity of a new agent or combination in a given disease setting. However, many such trials are performed, and the proportion that will provide false-positive results is necessarily substantial. In many circumstances, it would be appropriate to perform a second small confirmatory trial before initiating large resource-intensive phase III trials.

Sometimes, several new therapeutic approaches are studied in a randomized phase II trial. The purpose of randomization in this setting, as in phase III studies, is to minimize the impact of random imbalances in prognostic variables. However, randomized phase II studies are, by definition, not intended to provide an adequately powered comparison between arms (regimens). Rather, the goal is simply to identify one or more arms for further testing, and the sample size is chosen so to provide reasonable confidence that a truly inferior arm is not likely to be selected. Therefore, reporting the results of such randomized phase II trials should not imply statistical comparisons between treatment arms.

1.3. Response Outcomes in Clinical Trials as a Surrogate for Palliative Effect

1.3.1. Use in nonrandomized clinical trials. The only circumstance in which objective responses in a nonrandomized trial can permit a tentative assumption of a palliative effect (i.e., beyond a purely clinical measure of benefit) is when there is an actual or implied comparison with historical series of similar patients. This assumption is strongest when the prospectively determined statistical analysis plan provides for matching of relevant prognostic variables between case subjects and a defined series of control subjects. Otherwise, there must be, at the very least, prospectively determined statistical criteria that provide a very strong justification for assumptions about the response rate that would have been expected in the appropriate "control" population (untreated or treated with conventional therapy, as fits the clinical setting). However, even under these circumstances, a high rate of observed objective response does not constitute proof or confirmation of clinical therapeutic benefit. Because of unavoidable and nonquantifiable biases inherent in nonrandomized trials, proof of benefit still requires eventual confirmation in a prospectively randomized, controlled trial of adequate size. The appropriate end points of therapeutic benefit for such a trial are survival, progression-free survival, or symptom control (including quality of life).

1.3.2. Use in randomized trials. Even in the context of prospectively randomized phase III comparative trials, "observed response rate" should not be the sole, or major, end point. The trial should be large enough that differences in response rate can be validated by association with more definitive end points reflecting therapeutic benefit, such as survival, progression-free survival, reduction in symptoms, or improvement (or maintenance) of quality of life.

2. Measurability of Tumor Lesions at Baseline

2.1. Definitions

At baseline, tumor lesions will be categorized as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as $\geqslant$20 mm with conventional techniques or as $\geqslant$10 mm with spiral CT scan [*see* section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

(*Note:* Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.)

2.2. Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

2.2.1. Clinical examination. Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography—including a ruler to estimate the size of the lesion—is recommended.

2.2.2. Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. More details concerning the use of this method of assessment for objective tumor response evaluation are provided in Appendix I.

2.2.3. CT and MRI. CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis, while head and neck tumors and those of the extremities usually require specific protocols. More details concerning the use of these methods of assessment for objective tumor response evaluation are provided in Appendix I.

2.2.4. Ultrasound. When the primary end point of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions that are clinically not easily accessible. It may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. Justifications for not using ultrasound to measure tumor lesions for objective response evaluation are provided in Appendix I.

2.2.5. Endoscopy and laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully or widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may be available only in some centers. Therefore, utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete histopathologic response when biopsy specimens are obtained.

2.2.6. Tumor markers. Tumor markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all tumor lesions have disappeared. Specific additional criteria for standardized usage of prostate-specific antigen and CA (cancer antigen) 125 response in support of clinical trials are being validated.

2.2.7. Cytology and histology. Cytologic and histologic techniques can be used to differentiate between partial response and complete response in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). New techniques to better establish objective tumor response will be integrated into these criteria when they are fully validated to be used in the context of tumor response evaluation.

3. Tumor Response Evaluation

3.1. Baseline Evaluation

3.1.1. Assessment of overall tumor burden and measurable disease. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion (as defined in section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

3.1.2. Baseline documentation of "target" and "nontarget" lesions. All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

3.2. Response Criteria

3.2.1. Evaluation of target lesions. This section provides the definitions of the criteria used to determine objective tumor response for target lesions. The criteria have been adapted from the original *WHO Handbook (3)*, taking into account the measurement of the longest diameter only for all target lesions: complete response—the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

3.2.2. Evaluation of nontarget lesions. This section provides the definitions of the criteria used to determine the objective tumor response for nontarget lesions: complete response—the disappearance of all nontarget lesions and normalization of tumor marker level; incomplete response/stable disease—the persistence of one or more nontarget lesion(s) and/or the maintenance of tumor marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions *(1)*.

(*Note:* Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the

treating physician should prevail and the progression status should be confirmed later by the review panel [or study chair]).

3.2.3. Evaluation of best overall response. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (*see* section 3.3.1). Table 1 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

(*Notes:*

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective disease progression, even after discontinuation of treatment.
- Conditions that may define early progression, early death, and inevaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine-needle aspiration/biopsy) before confirming the complete response status.)

3.2.4. Frequency of tumor re-evaluation. Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up of every other cycle (i.e., 6–8 weeks) seems a reasonable norm. Smaller or greater time intervals than these could be justified in specific regimens or circumstances.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the phase II trial has, as a goal, the response rate or the time to an event (disease progression/death). If time to an event is the main end point of the study, then routine re-evaluation is warranted of those patients who went off the study for reasons other than the expected event at frequencies to be determined by the protocol. Intervals between evaluations twice as long as on study are often used, but no strict rule can be made.

Table 1. Overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions*

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. *See* text for more details.

3.3. Confirmatory Measurement/Duration of Response

3.3.1. Confirmation. The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomized trials where response is the primary end point. In this setting, to be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6–8 weeks) that is defined in the study protocol (*see* section 3.3.3).

(*Note:* Repeat studies to confirm changes in tumor size may not always be feasible or may not be part of the standard practice in protocols where progression-free survival and overall survival are the key end points. In such cases, patients will not have "confirmed response." This distinction should be made clear when reporting the outcome of such studies.)

3.3.2. Duration of overall response. The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for complete response until the first date that recurrent disease is objectively documented.

3.3.3. Duration of stable disease. Stable disease is measured from the start of the treatment until the criteria for disease progression is met (taking as reference the smallest measurements recorded since the treatment started). The clinical relevance of the duration of stable disease varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of stable disease. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

(*Note:* The duration of response or stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency that should take into account many parameters, including disease types and stages, treatment periodicity, and standard practice. However, these limitations to the precision of the measured end point should be taken into account if comparisons among trials are to be made.)

3.4. Progression-Free Survival/Time to Progression

This document focuses primarily on the use of objective response end points. In some circumstances (e.g., brain tumors or investigation of noncytoreductive anticancer agents), response evaluation may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases, progression-free survival/time to progression can be considered valuable alternatives to provide an initial estimate of biologic effect of new agents that may work by a noncytotoxic mecha-

nism. It is clear though that, in an uncontrolled trial proposing to utilize progession-free survival/time to progression, it will be necessary to document with care the basis for estimating what magnitude of progression-free survival/time to progression would be expected in the absence of a treatment effect. It is also recommended that the analysis be quite conservative in recognition of the likelihood of confounding biases, e.g., with regard to selection and ascertainment. Uncontrolled trials using progression-free survival or time to progression as a primary end point should be considered on a case-by-case basis, and the methodology to be applied should be thoroughly described in the protocol.

4. Response Review

For trials where the response rate is the primary end point, it is strongly recommended that all responses be reviewed by an expert or experts independent of the study at the study's completion. Simultaneous review of the patients' files and radiologic images is the best approach.

(*Note:* When a review of the radiologic images is to take place, it is also recommended that images be free of marks that might obscure the lesions or bias the evaluation of the reviewer[s]).

5. Reporting of Results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (*Note:* By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4–9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4–9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

6. Response Evaluation in Randomized Phase III Trials

Response evaluation in phase III trials may be an indicator of the relative antitumor activity of the treatments evaluated but may usually not solely predict the real therapeutic benefit for the population studied. If objective response is selected as a primary end point for a phase III study (only in circumstances where a direct relationship between objective tumor response and a real therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applicable to phase II trials (RECIST guidelines) should be used.

On the other hand, some of the guidelines presented in this special article might not be required in trials, such as phase III trials, in which objective response is *not* the primary end point. For example, in such trials, it might not be necessary to measure as many as 10 target lesions or to confirm response with a follow-up assessment after 4 weeks or more. Protocols should be written clearly with respect to planned response evaluation and whether confirmation is required so as to avoid *post-hoc* decisions affecting patient evaluability.

Appendix I. Specifications for Radiologic Imaging

These notes are recommendations for use in clinical studies and, as such, these protocols for computed tomography (CT) and magnetic resonance imaging (MRI) scanning may differ from those employed in clinical practice at various institutions. The use of standardized protocols allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

Specific Notes

- For chest x-ray, not only should the film be performed in full inspiration in the posteroanterior projection, but also the film to tube distance should remain constant between examinations. However, patients in trials with advanced disease may not be well enough to fulfill these criteria, and such situations should be reported together with the measurements.

Lesions bordering the thoracic wall are not suitable for measurements by chest x-ray, since a slight change in position of the patients can cause considerable differences in the plane in which the lesion is projected and may appear to cause a change that is actually an artifact. These lesions should be followed by a CT or an MRI. Similarly, lesions bordering or involving the mediastinum should be documented on CT or MRI.

- CT scans of the thorax, abdomen, and pelvis should be contiguous throughout the anatomic region of interest. As a rule of thumb, the minimum size of the lesion should be no less than double the slice thickness. Lesions smaller than this are subject to substantial "partial volume" effects (i.e., size is underestimated because of the distance of the cut from the longest diameter; such a lesion may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size [Fig. 1]). This minimum lesion size for a given slice thickness at baseline ensures that any lesion appearing smaller on subsequent examinations will truly be decreasing in size. The longest diameter of each target lesion should be selected in the axial plane only.

The type of CT scanner is important regarding the slice thickness and minimum-sized lesion. For spiral (helical) CT scanners, the minimum size of any given lesion at baseline may be 10 mm, provided the images are reconstructed contiguously at 5-mm intervals. For conventional CT scanners, the minimum-sized lesion should be 20 mm by use of a contiguous slice thickness of 10 mm.

The fundamental difference between spiral and conventional CT is that conventional CT acquires the information only for the particular slice thickness scanned, which is then expressed as a two-dimensional representation of that thickness or volume as a gray scale image. The next slice thickness needs to be scanned before it can be imaged and so on. Spiral CT acquires the data for the whole volume imaged, typically the whole of the thorax or upper abdomen in a single breath hold of about 20–30 seconds. To view the images, a suitable reconstruction algorithm is selected, by the machine, so the data are appropriately imaged. As suggested above, for spiral CT, 5-mm reconstructions can be made, thereby allowing a minimum-sized lesion of 10 mm.

Spiral CT is now the standard in most hospitals involved in cancer

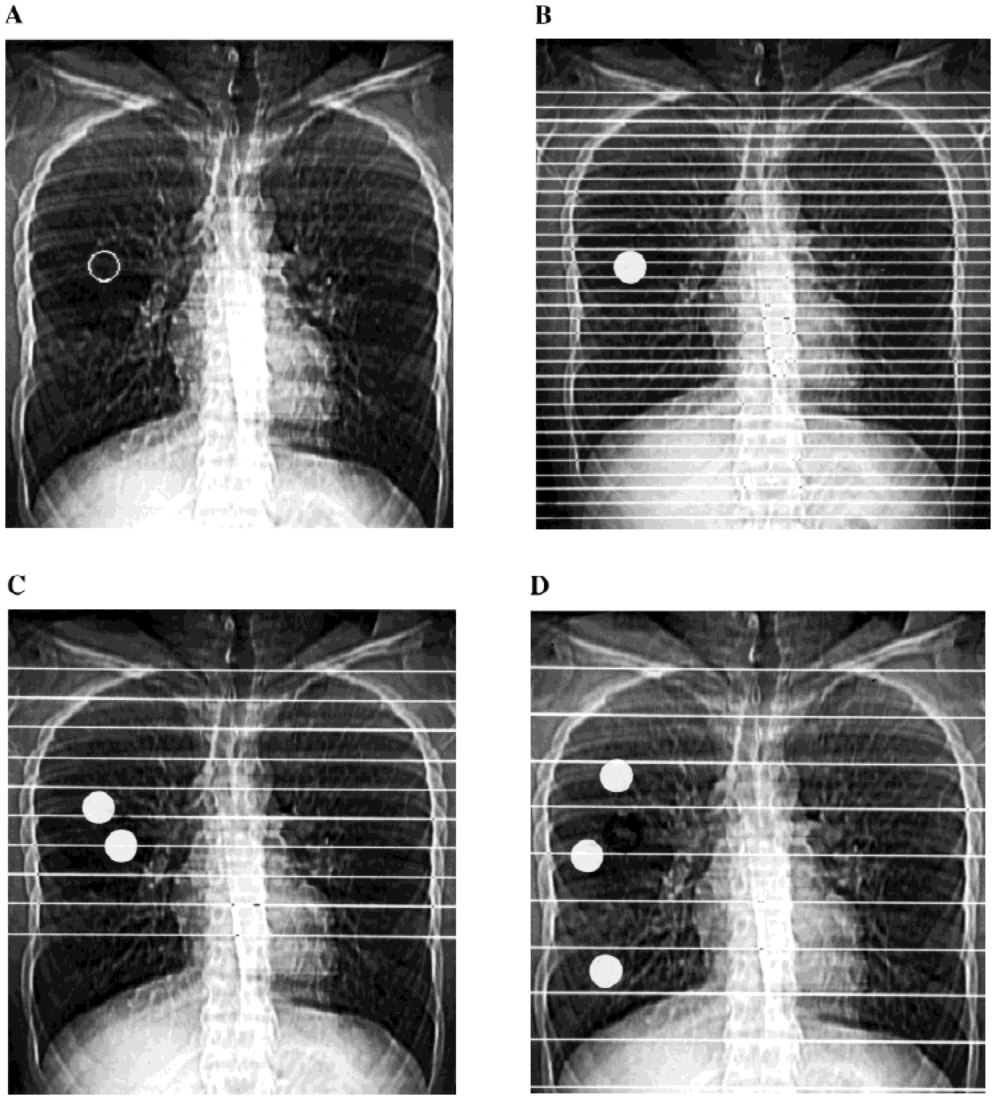

Fig 1. A) Computed tomography (CT) "scannogram" of the thorax with a simulated 20-mm lesion in the right mid-zone. **B)** CT "scannogram" of the thorax with contiguous slices of 10-mm thickness. Each volume within the slice thickness is scanned, and the average attenuation coefficient (i.e., density of multiple small cubes [voxels]) is represented spatially in two dimensions (pixels) as a cross-sectional image on a gray scale. It is important to note each line on the figure is a spatial representation of the average density for the structures that pass through that slice thickness, and the line does not represent a thin "cut" through it at that level. Therefore, a lesion of at least 20 mm will appear about its true diameter on at least one image because sufficient volume of the lesion is present so as not to average it down substantially. **C)** CT scannogram performed at 15-mm intervals. Depending on how much of the tumor is within the slice thickness, the average density may be substantially underestimated, as in the upper of the two lesions, or it may approximate the true tumor diameter, lower lesion. This is an oversimplification of the process but illustrates the point without going into the physics of CT reconstruction. **D)** CT scannogram performed at 24-mm intervals and of 10-mm thickness. The lesion may be imaged through its diameter, it may be partially imaged, or it may not be imaged at all. This is the equivalent of imaging a very small lesion and trying to determine whether its true diameter has changed from one examination to the next.

management in the United States, Europe, and Japan, so the above comments related to spiral CT are pertinent. However, some institutions involved in clinical trials will have conventional CT, but the number of these scanners will decline as they are replaced by spiral CT.

Other body parts, where CT scans are of different slice thickness (such as the neck, which is typically 5-mm thickness), or in the young pediatric population, where the slice thickness may be different, the minimum-sized lesion allowable for measurability of the lesion may be different. However, it should be double the slice thickness. The slice thickness and the minimum-sized lesion should be specified in the study protocol.

In patients in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel against other soft-tissue masses. This procedure is almost universally undertaken on a routine basis.

Intravenous contrast agents should also be given, unless contraindicated for medical reasons such as allergy. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. Although, in clinical practice, its use may add little, in the context of a clinical study where objective response rate based on measurable disease is the end point, unless an intravenous contrast agent is given, a substantial number of otherwise measurable lesions will not be measurable. The use of intravenous contrast agents may sometimes seem unnecessary to monitor the evolution of specific disease sites (e.g., in patients in whom the disease is apparently restricted to the periphery of the lungs). However, the aim of a clinical

study is to ensure that lesions are truly resolving, and there is no evidence of new disease at other sites scanned (e.g., small metastases in the liver) that may be more easily demonstrated with the use of intravenous contrast agent that should, therefore, also be considered in this context.

The method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient.

All images from each examination should be included and not "selected" images of the apparent lesion. This distinction is intended to ensure that, if a review is undertaken, the reviewer can satisfy himself/herself that no other abnormalities coexist. All window settings should be included, particularly in the thorax, where the lung and soft-tissue windows should be considered.

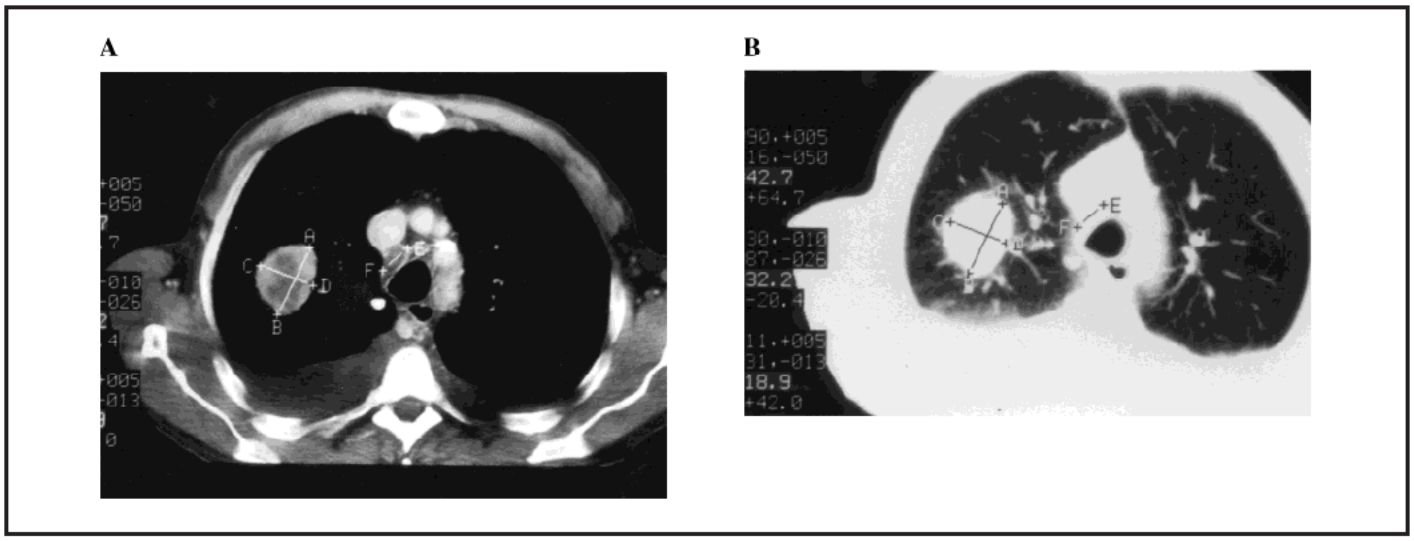

Fig 2. A) Computed tomography (CT) scan of the thorax at the level of the carina on "soft-tissue" windows. Two lesions have been measured with calipers. The intraparenchymal lesion has been measured bidimensionally, using the greatest diameter and the greatest perpendicular distance. Unidimensional measurements require only the greatest diameter to be measured. The anterior–carinal lymph node has been measured using unidimensional criteria. **B)** The same image as above imaged on "lung" windows, with the calipers remaining as they were for the soft-tissue measurements. The size of the lung lesion appears different. The anterior–carinal lymph node cannot be measured on these windows. The same windows should be used on subsequent examinations to measure any lesions. Some favor soft-tissue windows, so paratracheal, anterior, and subcarinal lesions may be followed on the same settings as intraparenchymal lesions.

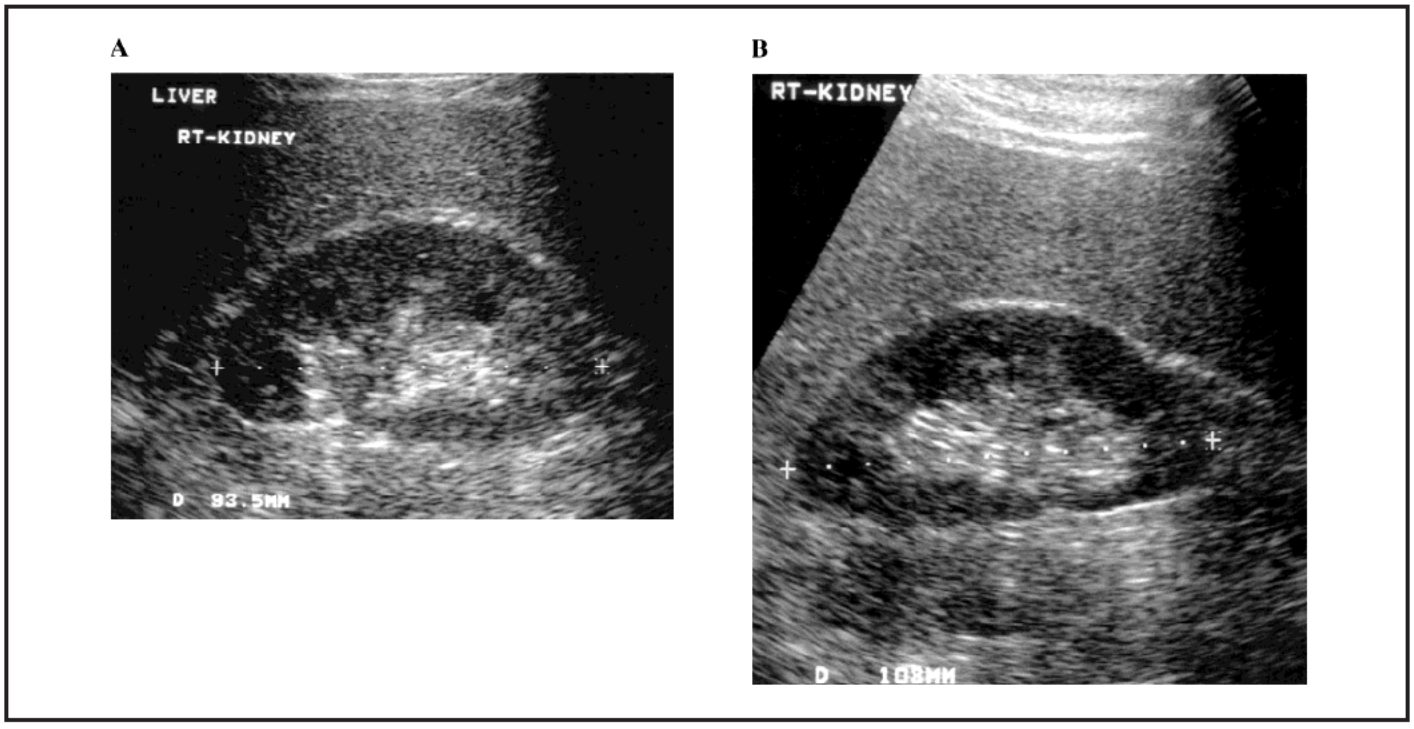

Fig 3. A) Ultrasound scan of a normal structure, the right kidney, which has been measured as 93 mm with the use of callipers. **B)** Ultrasound scan of the same kidney taken a few minutes later when it measures 108 mm. It appears to have increased in size by 16%. The difference is due to foreshortening of the kidney in panel A. The lack of anatomic landmarks makes accurate measurement in the same plane on subsequent examinations difficult. One has to hope that the measurements given on the hard copy film are a true and accurate reflection of events.

Lesions should be measured on the same window setting on each examination. It is not acceptable to measure a lesion on lung windows on one examination and on soft-tissue settings on the next (Fig. 2). In the lung, it does not really matter whether lung or soft-tissue windows are used for intraparenchymal lesions, provided a thorough assessment of nodal and parenchymal disease has been undertaken and the target lesions are measured as appropriate by use of the same window settings for repeated examinations throughout the study.

- Use of MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomic planes. It is, therefore, important that, when MRI is used, lesions must be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. Some of the factors involved include the magnet strength (high-field magnets require shorter scan times, typically 2–5 minutes), the coil design, and patient cooperation. Wherever possible, the same scanner should be used. For instance, the images provided by a 1.5-Tesla scanner will differ from those provided by a 0.5-Tesla scanner. Although comparisons can be made between images from different scanners, such comparisons are not ideal. Moreover, many patients with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence—on the order of 2–5 minutes—is limited. Any movement during the scan time leads to motion artifacts and degradation of image quality, so that the examination will probably be useless. For these reasons, CT is, at this point in time, the imaging modality of choice.
- Ultrasound examinations should not be used in clinical trials to measure tumor regression or progression of lesions that are not superficial because the examination is necessarily subjective. Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events (Fig. 3). Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

The same imaging modality must be used throughout the study to measure disease. Different imaging techniques have differing sensitivities, so any given lesion may have different dimensions at any given time if measured with different modalities. It is, therefore, not acceptable to interchange different modalities throughout a trial and use these measurements. It must be the same technique throughout.

It is desirable to try to standardize the imaging modalities without adding undue constraints so that patients are not unnecessarily excluded from clinical trials.

Appendix II. Relationship Between Change in Diameter, Product, and Volume

Appendix II, Table 2. Relationship between change in diameter, product, and volume*

	Diameter, $2r$	Product, $(2r)^2$	Volume, $4/3\pi r^3$
Response	Decrease	Decrease	Decrease
	30%	50%	65%
	50%	75%	87%
Disease progression	Increase	Increase	Increase
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

*Shaded areas represent the response evaluation criteria in solid tumors (diameter) and World Health Organization (product) criteria for change in tumor size to meet response and disease progression definitions.

Appendix III. Response Evaluation Criteria in Solid Tumors (RECIST) Working Group and Special Acknowledgments

RECIST Working Group

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Retrospective Analyses

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Appendix IV. Participants in the October 1998 Workshop to Develop the Final Response Evaluation Criteria in Solid Tumors (RECIST) Document and Further Acknowledgments

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Appendix V. Retrospective Comparison of Response/Disease Progression Rates Obtained With the World Health Organization (WHO)/Southwest Oncology Group Criteria and the New Response Evaluation Criteria in Solid Tumors (RECIST) Criteria

To evaluate the hypothesis by which unidimensional measurement of tumor lesions may substitute for the usual bidimensional approach, a number of retrospective analyses have been undertaken. The results of these analysis are given below in this section.

1. Comparison of Response and Disease Progression Rates by Use of WHO (or Modified WHO) or RECIST Methods

1.1. Trials Evaluated

No specific selection criteria were employed except that trial data had to include serial (repeated) records of tumor measurements. Several groups evaluated their own data on one or more such studies (National Institute of Canada Clinical Trials Group, Kingston, ON; U.S. National Cancer Institute, Bethesda, MD; and Rhone-Poulenc Rorer Pharmaceuticals Inc., Paris, France) or made data available for evaluation to the U.S. National Cancer Institute (Southwest Oncology Group and Bristol-Myers Squibb, Wallingford, CT)

1.2. Response Criteria Evaluated

Not all databases were assessed for all response outcomes. At the outset of this process, the most interest was in the assessment of complete plus partial response rate comparisons by both the WHO and new RECIST criteria. Once these data suggested no impact of using the new criteria on the response rate, several more databases were analyzed for the impact of the use of the new criteria not only on complete response plus partial response but also on stable disease and progressive disease rates (*see* Appendix V, Table 4) and on time to disease progression (*see* Appendix V, Table 5).

1.3. Methods of Comparison

For each patient in each study, baseline sums were calculated (sum of products of the two longest diameters in perpendicular dimensions for WHO and sum of longest diameters for RECIST). After each assessment, when new tumor measures were available, the sums were recalculated. Patients were assigned complete response, partial response, stable disease, and progressive disease as their "best" response on the basis of achieving the measurement criteria as indicated in Appendix V, Table 3. For both WHO and RECIST, a minimum interval of 4 weeks was required to consider complete response and partial response confirmed. Each patient could, therefore, be assigned a best response according to each of the two criteria. The overall response and disease progression rates could be calculated for the population studied for each trial or dataset examined.

(*Note:* For WHO progressive disease, as is the convention in most groups, an increase in sums of products was required, not an increase in only one lesion.)

1.4. Results

2. Evaluation of Time to Disease Progression

Time to disease progression was evaluated, comparing WHO criteria with RECIST in a dataset provided by the Southwest Oncology Group

Appendix V, Table 3. Definition of best response according to WHO or RECIST criteria*

Best response	WHO change in sum of products	RECIST change in sums longest diameters
CR	Disappearance; confirmed at 4 wks†	Disappearance; confirmed at 4 wks†
PR	50% decrease; confirmed at 4 wks†	30% decrease; confirmed at 4 wks†
SD	Neither PR nor PD criteria met	Neither PR nor PD criteria met
PD	25% increase; no CR, PR, or SD documented before increased disease	20% increase; no CR, PR, or SD documented before increased disease

*WHO = World Health Organization; RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response, PR = partial response, SD = stable disease, and PD = progressive disease.

†For the Bristol-Myers Squibb (Wallingford, CT) dataset, only unconfirmed CR and PR have been used to compare best response measured in one dimension (RECIST criteria) versus best response measured in two dimensions (WHO criteria). The computer flag identifying confirmed response in this dataset could not be used in the comparison for technical reasons.

Appendix V, Table 4. Comparison of RECIST (unidimensional) and WHO (bidimensional) criteria in the same patients recruited in 14 different trials*

Tumor site/type	Criteria	No. of patients evaluated	Best response				RR	PD rate
			CR	PR	SD	PD		
Breast†	WHO	48	4	22			54%	
	RECIST	48	4	22			54%	
Breast‡	WHO	172	4	36			23%	
	RECIST	172	4	40			26%	
Brain†	WHO	31	12	10			71%	
	RECIST	31	12	10			71%	
Melanoma†	WHO	190	9	37			24%	
	RECIST	190	9	34			23%	
Breast§	WHO	531	50	102			29%	
	RECIST	531	50	108			30%	
Colon§	WHO	1096	12	137			14%	
	RECIST	1096	12	133			13%	
Lung§	WHO	1197	60	317			32%	
	RECIST	1197	60	318			32%	
Ovary§	WHO	554	24	108			24%	
	RECIST	554	24	105			23%	
Lung†	WHO	24	0	4	16	4	17%	17%
	RECIST	24	0	4	19	1	17%	4%
Colon†	WHO	31	1	6	15	9	23%	29%
	RECIST	31	1	5	16	9	21%	29%
Sarcoma†	WHO	28	1	4	13	10	18%	36%
	RECIST	28	1	5	17	5	21%	18%
Ovary†	WHO	45	0	7	19	19	16%	42%
	RECIST	45	0	6	21	18	13%	40%
Breast‖	WHO	306	18	114	117	57	43%	19%
	RECIST	306	18	108	124	56	41%	18%
Breast‖	WHO	360	10	73	135	142	23%	39%
	RECIST	361	10	70	139	142	22%	39%
Total (all studies where tumor response was evaluated)	WHO	4613	205	977			25.6%	
	RECIST	4614	205	968			25.4%	
Total (all studies where PD as well as CR + PR were evaluated)	WHO	794			315	241		30.3%
	RECIST	795			336	231		29%

*WHO = World Health Organization *(3);* RECIST = Response Evaluation Criteria in Solid Tumors; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; and RR = response rate.

†Data from the National Cancer Institute of Canada Clinical Trials Group phase II and III trials.

‡Data from the National Cancer Institute, United States phase III trial.

§Data from Bristol-Myers Squibb (Wallingford, CT) phase II and III trials.

‖Data from Rhone-Poulenc Rorer Pharmaceuticals Inc., (Paris, France) phase III trials (*note* one patient in this database had unidimensional measured lesions only and could not be evaluated with the WHO criteria).

Appendix V, Table 5. Proportions of patients with disease progression by different assessment methods*

	No. of patients	%
Total No. of progressors	234	100
Progress by appearance of new lesions†	118	50
Progress by increase in pre-existing measurable disease	116	50
Same date of disease progression by WHO and RECIST criteria	215	91.9
Different date of disease progression	19	8.1
Earlier PD with WHO criterion	17	7.3
Earlier PD with unidimensional criterion	2	0.9

*PD = progressive disease; WHO = World Health Organizaiton; and RECIST = Response Evaluation Criteria in Solid Tumors.

†Also includes a few patients with PD because of marked increase of nonmeasurable disease.

Appendix V, Table 6. Magnitude of time to disease progression disagreements when differences existed*

	No. of patients	% (of 234, *see* above)
No. of progressors with differing progression dates	19	8.1
8–9 wks' difference	3	1.3
12 wks' difference	1	0.4
24–31 wks' difference†	2	0.9
Difference uncertain due to censoring of either WHO or RECIST progression time‡	13	5.6

*WHO = World Health Organization; RECIST = Response Evaluation Criteria in Solid Tumors.

†For one patient, progression by RECIST (one-dimension) criteria preceded that by WHO criteria by 24 weeks due primarily to one-dimensional growth. For a second patient, with a colon tumor that increased in cross-section by 25%, then regressed completely, and then recurred, progression by WHO criteria preceded that by RECIST criteria by 31 weeks.

‡As indicated in Appendix V, Table 6, 13 of the 19 patients had uncertain disease progression time differences when comparing RECIST and WHO criteria. In these patients, the RECIST progression criteria were not met by the time that disease progression by Southwest Oncology Group (SWOG) criteria *(5)* had occurred (50% increase or a 10 cm^2 increase in tumor cross-section). Notably, six of these patients had the same disease progression dates determined by use of WHO (25% bidimensional increase) and SWOG (50% bidimensional increase) criteria. Since 20% unidimensional increase (RECIST) is equivalent to approximately 44% bidimensional increase, it is likely, although not certain, that disease progression by RECIST unidimensional criteria would have occurred soon after disease progression by SWOG and WHO criteria. For three patients, the difference between the WHO and SWOG 50% bidimensional increase was 10–12 weeks. Again, it is likely, although it cannot be proven, that RECIST criteria would have been met soon after. The remaining four of the 13 patients where difference between WHO and RECIST progression times are uncertain were categorized as progressive disease following SWOG's criteria *(5)* because of an increase of the tumor surface of greater than or equal to 10 cm^2. For these patients, the magnitude of the difference is entirely uncertain.

(SWOG). Since SWOG criteria *(5)* for disease progression is a 50% increase in the sum of the products, or new disease, or an absolute increase of 10 cm^2 in the sum of the products, this dataset provided the means of assessing the impact of time to disease progression differences between a 25% increase in the sum of the products and a 20% increase in the sum of the longest diameters (equivalent to approximately a 44% increase in the product sum).

2.1. Dataset Evaluated

The dataset includes 234 patients with progressive disease as defined by the SWOG *(5)*. All patients had baseline measurable disease followed by the same technique(s) until disease progression. The tumor types included were melanoma and colorectal, lung, and breast cancers.

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NOTE

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Appendix 4. Amendment 1 - Summary of Changes to Protocol

Revisions have been made to Protocol No. 011-007, dated November 16, 2005 in response to comments received from the FDA dated February 23, 2006, and feedback from the study investigators. In addition, other minor changes have been incorporated into the protocol to remove inconsistencies in the original protocol.

In brief the following revisions have been made:

- The Medical Monitor information has been changed to reflect a new Medical Monitor for the study Craig Berman, MD., and the Study Contact information for Germany has been added.
- Study Treatment has been limited to up to 30 weeks which resulted in revisions to the Study Treatment windows, withdrawal criteria and conduct of study procedures.
- Deletion of the Post-Study Treatment Phase. Extensive changes were made to the Follow-up phase of the study as a result of the deletion of the Post-Study Treatment phase
- Deletion of the continuation of prednisone therapy following the completion or discontinuation of docetaxel treatment
- Cerebrovascular accident, both hemorrhagic and ischemic events will now be collected as thromboembolic events.
- The addition of a baseline bone scan within 4 weeks prior to randomization.
- Clarification of inclusion criteria #3, #4, #6, #7, #9, #15 and the addition of inclusion criteria #16 to allow enrollment of subjects who have received therapy with vaccines or other immunotherapies.
- Exclusion # 10 has been revised to exclude subjects with Grade 2 peripheral neuropathy.
- Revisions have been made to the criteria for withdrawal of subjects to reflect the deletion of the Post-Study Treatment phase and the limit to Study Treatment duration.
- Table 4 has been revised to clarify the dose delays to be followed for subjects experiencing hypercalcemia and /or symptomatic nephrolithiasis.
- Table # 7 was moved to the end of section 8.1.2.2.
- Dexamethasone dose restrictions have been modified.
- Metastatic disease must be documented radiographically. A bone scan is required to have been completed within 4 weeks prior to enrollment for each subject.
- An allowance for local laboratories to be used for eligibility purposes and confirmation that central laboratories must be collected for baseline purposes
- The requirements for disease progression have been modified
- The addition of a serum chemistry panel and symptom-directed physical exam q8 weeks in the Follow-up phase for subjects in ASCENT Arm

- PSA can be collected up to 9 days prior to each docetaxel administration
- Thromboembolic and skeletal-related events will be observed up to 48 weeks after termination of the Study Treatment phase for all subjects
- The QOL and related questions, the Brief Fatigue Inventory, and the Pain questionnaires will be administered up to 8 weeks (± 2 weeks) after termination from the Study Treatment phase.
- Revision to SAE reporting requirements as a result of the deletion of the Post-Study Treatment phase.
- Clarification that the study endpoints will be tested using a hierarchical procedure
- Clarification that the log-rank analysis will be provided as supportive analysis to confirm robustness.
- Clarification that the sample size and power calculation is based on log-rank test.

The revisions to the protocol are discussed in detail below:

Study Treatment Duration

To standardize the Study Treatment duration, subjects in both arms of the study will now receive a maximum of 30 weeks of Study Treatment; previously there was no limit to the number of treatment cycles that a subject could receive.

- Control Arm: Every three weeks docetaxel and twice daily prednisone (up 30 weeks)
- ASCENT Arm: Once weekly DN-101 in combination with weekly docetaxel (up to 30 weeks)

Treatment with docetaxel (Control Arm and ASCENT Arm) will continue for up to 30 weeks, or until unacceptable docetaxel toxicity or clinical disease progression (as per Section 10.1). In cases of treatment delays, subjects should continue docetaxel treatment for a total of 10 doses in the Control Arm and a total of 23 doses in the ASCENT Arm. Treatment with DN-101 in the ASCENT Arm will continue until unacceptable DN-101 toxicity or initiation of products not approved for marketing (experimental agents) and is not limited to the Study Treatment phase. Treatment with prednisone in the Control Arm will continue until completion of study treatment phase.

Subjects in both arms will be followed for long-term survival to the end of study. Subjects may withdraw from treatment at any time upon request.

These changes are also reflected in the following sections of the protocol: Study Synopsis, Sections 6.1, 6.3.3, and 8.1.1.8.

Post-Study Treatment Phase

The Post-Study Treatment Phase of the protocol was deleted from the study. Subjects in the Control Arm will no longer receive study directed treatment. There are now only 2 phases to the study; the Study Treatment phase and the Follow-up phase.

Following completion of the Study Treatment phase subjects will enter the Follow-up phase. In the Follow-up phase subjects in the Control Arm will no longer receive study directed treatment with prednisone. Subjects in the ASCENT Arm will continue to receive treatment with DN-101 as noted above.

Control Arm: Investigator directed Prostate Cancer Therapy

ASCENT Arm: Once weekly dosing with DN-101 for 3 out of every 4 weeks.

These changes are also reflected in the following sections of the protocol: Study Synopsis, Section 6, and Section 9.3.7.

Section 4.2 Rationale for the Current Study

The following sentence was deleted from the text as a result of the discontinuation of study directed treatment of subjects in the Control arm with prednisone.

However, corticosteroids are commonly used as palliative therapy even in progressing patients.

Section 4.4.2 Secondary Efficacy Endpoints

The subset of thromboembolic events: cerebrovascular infarction was revised and further defined as cerebrovascular accident (hemorrhagic and/or ischemic). This change is reflected in the Study Synopsis, and Section 10.3.

Section 6.2 Study Diagram

Study diagram (Figure 1) was revised extensively to reflect changes in the protocol.

Section 7.2 Inclusion Criteria

Inclusion Criterion #3 was revised to include the requirement of a bone scan within 4 weeks prior to study randomization as a baseline measurement and now reads as follows:

- Metastatic prostate adenocarcinoma documented by computed tomography (CT), magnetic resonance imaging (MRI), or bone scan. A bone scan is required within 4 weeks prior to study randomization as baseline measurement.

Inclusion Criterion #4 was revised to move the requirement that LHRH agonists or antagonists treatment must be continued and now reads as follows:

- Prior therapy by androgen ablation either by orchiectomy and/or luteinizing hormone releasing hormone (LHRH) agonists or antagonists.

Inclusion Criterion # 6 was revised as follows to clarify that subjects currently receiving treatment with bisphosphonates are eligible for the study and now reads as follows:

- If a subject has been treated or is currently receiving treatment with bisphosphonates, the subject is eligible for the study and the therapy can continue at investigator's discretion.

Inclusion Criterion #7 was revised as follows to clarify the medical therapies that subjects should continue to receive to maintain castrate levels of testosterone and now reads as follows:

- Maintaining castrate status: Subjects who have not undergone surgical orchiectomy should continue on medical therapies with a LHRH agonist or LHRH antagonist to maintain castrate levels of serum testosterone.

Inclusion Criterion # 9 was reworded to clarify that subjects must have received less than 25% radiation therapy to bone marrow and now reads as follows:

- Prior radiation therapy to less than 25% of the bone marrow only (excluding whole pelvic irradiation) is allowed if at least four weeks have elapsed since completion of therapy.

Inclusion Criterion # 15, bullet # 1: the use of darbopoetin was added to the medications allowable for upgrade of hemoglobin levels and now reads as follows:

- hemoglobin $\geq$ 10 g/dL (Erythropoietin and darbopoetin use is allowed but red blood cell transfusion to upgrade the hemoglobin level is not allowed)
- This change is also reflected in Section 8

Inclusion Criterion # 16 was added to allow for the enrollment of subjects who have received therapy with vaccines or other immunotherapies. This new criterion reads as follows:

- Subjects who have received prior therapy with vaccines or other immunotherapy remain eligible for study participation.

Section 7.3 Exclusion Criteria

Exclusion Criterion # 10 was revised to exclude subjects with Grade 2 peripheral neuropathy and now reads as follows:

- Symptomatic peripheral neuropathy $\geq$ Grade 2 according to the NCI-CTCAE version 3.0.

Section 7.4.1 Withdrawal of Subject from Study

- Subjects will not be withdrawn from the study due to lack of adherence to the protocol. This change is reflected in the addition of the requirement for subjects to only be withdrawn from the Study Treatment phase due to lack of adherence to the protocol, see Section 7.4.2 # 6..

Section 7.4.2 Withdrawal of Subjects from Study Treatment Phase

Previously subjects were withdrawn from Study Treatment Phase and entered into either the Post-Study Treatment phase or the Follow-up phase. The deletion of the Post-Study Treatment phase necessitated the revision of Section 7.4 to redefine the circumstances under which subjects should be withdrawn from the Study Treatment phase and entered into the Follow-up phase.

Section 7.4.2., #1

If a subject develops a life-threatening and/or irreversible toxicity due to docetaxel (not manageable by symptomatic care, dose reduction, or delay in study treatment), treatment with docetaxel will be discontinued. In this case, subjects will be withdrawn from the Study Treatment phase.

- Subjects in the ASCENT Arm will continue on DN-101 and will be entered into the Follow-up phase.
- Subjects in the Control Arm will be entered in the Follow-up phase.

If a subject develops a life-threatening and/or irreversible toxicity attributed to DN-101 or prednisone (not manageable by symptomatic care or delay of either agent), treatment with DN-101 or prednisone will be discontinued.

- In this case, subjects in both arms will continue on docetaxel up to 30 weeks before entering the Follow-up phase.

If a subject requests withdrawal from DN-101 they will be managed in the same manner as those subjects withdrawn from study treatment due to DN-101 toxicity.

- Subject requests termination from DN-101. Subject will be managed in the same manner as those who withdraw from study treatment due to DN-101 toxicity (Section 7.4.2. #1)

Section 7.4.2, #5

In the case of disease progression (as defined in Section 10.1)

- In the event of disease progression, subjects should be withdrawn from treatment with docetaxel.
- Subjects in the ASCENT Arm will continue on DN-101 and will be entered into the Follow-up phase.
- Subjects in the Control Arm will be entered into the Follow-up phase.

Section 8.1.1.8 Toxicity and Dose Modification Table 4

Table #4 was amended to add clarification for the dose delays for DN-101 related toxicity. The table was expanded to better describe specific AEs that are known to be related to hypercalcaemia (i.e. hypercalcaemia, elevated creatinine and symptomatic nephrolithiasis)

and other AEs that the investigator determines to have a reasonable possibility of being related to DN-101. The table now reads as follows:

Table 4: Dose Delays for DN-101-related Toxicity

Hypercalcemia	
Grade 2-4	Hold DN-101 until hypercalcemia is reduced to a Grade 1 or less.
Grade 2- 4 for greater than 2 weeks or a second episode of ≥ Grade 2	Discontinue DN-101
Creatinine elevation	
Grade 2-4	Hold DN-101 until return of creatinine to Grade 1 or less.
Grade 2-4 for greater than 2 weeks or a second episode of ≥ Grade 2	Discontinue DN-101
Symptomatic Nephrolithiasis	
1st episode	Hold DN-101 (for up to 2 weeks) until resolution.
Symptoms persist for greater than 2 weeks or a second episode of ≥ Grade 2	Discontinue DN-101
Other DN-101 related toxicity	
Grade 3-4	Hold DN-101 until resolution to Grade 1 or less
Grade 3-4 for greater than 2 weeks	Discontinue DN-101

Adverse event grades listed are defined by NCI-CTCAE v3.0.

Section 8.1.2.2 Toxicity and Dose Modifications (Docetaxel)

The text in Table 5 Note was revised to reflect the deletion of Post-Study Treatment. The revised text is as follows:

- If a third dose reduction is needed, the subject will disconitnu docetaxel but may continue receiving DN-101 (if in ASCENT Arm) and be entered into the Follow-up phase.

The paragraph discussing Delayed Hypersensitivity was moved to before Table 7 rather than after. No other changes were made to this section.

Section 8.1.3.1 Toxicity and Dose Modification (Dexamethasone)

A revision was made to allow for the reduction of dexamethasone dose for dexamethasone-related toxicity without restriction. Previously a dose reduction was permitted to a minimum of 2 doses of 8 mg of dexamethasone. This section now reads as follows:

- The dexamethasone dose may be reduced for any dexamethasone-related toxicity in the absence of docetaxel hypersensitivity reactions at the discretion of the treating physician.

Section 8.3 Supportive Care and Concomitant and Prohibited Medication

One additional ancillary treatment use was permitted:

- Additional use of G-CSF, including prophylactic use for subject deemed high risk for development neutropenia, needs to be discussed with and approved by a Novacea Medical Monitor

Section 9.1.1 Clinical Assessments

Clarification was added in the medical history inclusions to define that the documentation of metastatic disease should be radiographic documentation. The revision is as follows:

- Metastatic disease documented radiographically (see Section 9.1.3)

Section 9.1.2 Laboratory Assessments

Local laboratory tests are now permitted to determine subject eligibility in circumstances where there are time constraints to obtaining the results from the central laboratory. Central laboratory test must still be obtained for baseline measurements. The revision is as follows:

- Local laboratory tests obtained within 7 days prior to randomization can be used to determine subject eligibility. Subjects may be randomized based on local laboratory test used for eligibility. However, for all subjects, blood must be drawn and sent to central laboratory prior to subject randomization.

These changes are also reflected in Appendix 1.

Section 9.1.3 Radiographic Assessment

Section 9.1.3 was added to further define the radiographic assessment requirements and reads as follows:

- Radiographic demonstration of metastatic disease must be present by computerized axial tomography (CT), magnetic resonance imaging (MRI), or bone scan obtained prior to study randomization
- A baseline bone scan must be obtained within 4 weeks prior to study randomization.

Section 9.3.2 Study Treatment Window

Section 9.3.2 has been revised to incorporate treatment windows for the Control and ASCENT Arms required by the limits put in place for docetaxel treatment. The revisions are as follows:

Treatment window for Control Arm:

- For any delay of docetaxel dosing, the date of administration (restart) of docetaxel following the delay will be considered and recorded as the same cycle for which the docetaxel was delayed.
- Up to 30 weeks of docetaxel or 10 doses at 75 mg/m^2 BSA will be administered.

Treatment windows for ASCENT Arm:

- If DN-101 dosing is delayed, docetaxel dosing should continue on schedule. DN-101 should be resumed once DN-101 toxicity resolves per Section 8.1.1.8.
- DN-101 should not be administered less than 5 days from the previous dose.
- For any delay of docetaxel dosing, the date of administration (restart) of docetaxel following the delay will be considered and recorded as the same cycle for which the docetaxel was delayed.
- Up to 30 weeks of docetaxel or 23 doses at 36 mg/m^2 BSA will be administered.

If the pre-treatment dexamethasone is missed, it may be administered IV prior to the docetaxel infusion. The sentence "A protocol deviation should be noted in the CRF" has been removed as this is no longer considered a protocol deviation.

Section 9.3.4 Laboratory Assessments

In Section 9.3.4.the window for laboratory assessments has been expanded from 48 hours to 72 hours before docetaxel administration. In addition, serum chemistry is required for subjects receiving DN-101 including serum calcium and serum creatinine. This section now reads as follows:

- Assessments may be performed up to 72 hours before docetaxel administration.
- Laboratory assessments relating to treatment with DN-101 need to include serum chemistry panel (including serum calcium and serum creatinine) and will be performed on days 2 of each 28-day cycle. Assessments may be performed up to 72 hours before DN-101 administration.

These changes are also reflected in the Study Synopsis and Appendix 1.

Section 9.3.5 PSA Assessments

Section 9.3.5.has been revised to allow for the PSA assessments to be obtained up to 9 days prior to the beginning of each study treatment cycle. The revision is as follows:

- PSA will be obtained as part of baseline central laboratory assessment. PSA may be obtained up to 9 days prior to the beginning of each study treatment cycle.

This change is also reflected in the Appendix 1.

Section 9.3.6 Bone Scan

- Bone scans are performed as clinically indicated.

Section 9.4 Follow-up Phase

Extensive changes were made to this section to incorporate the revisions required following the elimination of the Post-Study Treatment and the discontinuation of prednisone therapy in the Control Arm after the completion or discontinuation of docetaxel treatment.

During the Follow-up phase subjects in the Control Arm will no longer continue treatment with prednisone and will be treated with prostate cancer therapies at the discretion of the investigator. Subjects in the ASCENT Arm will continue treatment with DN-101 until unacceptable toxicity or initiation of treatment with a product not approved for marketing (experimental) and prostate cancer therapies at the discretion of the investigator. The Follow-up phase regimens for the ASCENT and Control Arms are summarized in Table 9.

Section 9.4.3 Clinical Assessments

All subjects will be assessed clinically every 8 weeks (± 2 weeks) for a period of 48 weeks.

- Subjects on Control Arm or ASCENT Arm (whether on or off DN-101)
    - Clinic follow-up visits (q8w x 6) including
        - Concomitant medications
        - Adverse events
        - TE, SRE and GI events
        - Pain assessment questionnaire (first Follow-up visit only)
        - QOL assessment questionnaire and related questions (first Follow-up visit only)
        - Survival status, including date and cause of death if subject is deceased
        - Subsequent cancer therapy

- Subjects on ASCENT Arm who are still taking DN-101

Note: The following assessments are required for the entire duration that subject is taking DN-101.

  - Symptom-directed physical exam - including vital signs (BP, TPR) and weight
  - Laboratory assessments as per Section 9.4.4
  - Concomitant medications
  - Adverse events
  - Survival status, including date and cause of death if subject is deceased
  - Subsequent cancer therapy-chemotherapy, radiation etc. including subsequent calcitriol therapy

- Survival:

After completion of 48 weeks follow-up, telephone or clinic visit q 8 weeks for subjects on Control Arm and for subjects on ASCENT Arm once DN-101 is discontinued:

  - Survival status, including date and cause of death if subject is deceased
  - Subsequent cancer therapy-chemotherapy, radiation etc. including subsequent calcitriol therapy

Other clinical assessments during administration of all protocol and non-protocol specified agents will occur per standard of care as determined by the investigator.

These changes are also reflected in Appendix 1.

Section 9.4.4 Laboratory Assessments

Laboratory assessments will only be required for subjects in the ASCENT Arm until DN-101 treatment is discontinued. This section now reads:

The following will be performed and documented. Assessments are to be performed q 8 weeks (±2 weeks):

- Laboratory assessment of serum chemistry including serum calcium and serum creatinine will be performed for subjects on ASCENT Arm until DN-101 is discontinued.
- Laboratory assessments for non-protocol treatments should be performed according to standard of care.

Other laboratory assessments during administration of all protocol and non-protocol specified agents will occur per standard of care as determined by the investigator. Clinically significant abnormal values per standard of care laboratory procedures will be reported as AEs. Laboratory values will not be collected in the database.

These changes are also reflected in Appendix 1.

Section 9.4.5 Cancer-related Treatments

This section has been revised to allow for the deletion of the Post-Study Treatment phase.

Section 9.5.1 Termination from Study Treatment Phase

The study treatment termination visit has been removed and only the reason for termination from Study Treatment phase will be collected. Pain, fatigue and QOL questionnaires will be completed at the first Follow-up visit only. The revision is as follows:

- The reason for termination from Study Treatment phase will be collected.

Appendix 1 has been updated and the Termination Visit has been removed from the schedule of events.

Section 9.5.2 Termination from Follow-up Phase

Subjects may withdraw from Follow-up phase upon request. Survival status should be noted.

Section 9.6 Declaration End of Clinical Study

Section 9.6 has been revised and end of study is defined as the time when the primary efficacy analysis occurs. The revision is as follows:

- The declaration end of the clinical study will be when the primary efficacy analysis occurs with respect to the requirement for notification of the Competent Authority as detailed in the Clinical Trials Directive 2001/20/EC.

Section 10.1 Disease Progression

Section 10.1 has been revised to further clarify the requirements for disease progression. Assessment for disease progression is no longer restricted to 12 week intervals following the initial 12 weeks of Study Treatment. Additionally clinical disease progression is permitted, see # 3. The revised text now reads:

Subjects should be taken off treatment with docetaxel for clinical disease progression. Subject should receive 12 weeks of treatment before clinical disease progression assessments are determined, unless clinically indicated.

Clinical parameters of disease progression include:

1) Biochemical (PSA) progression. PSA progression is defined as a 25% increase over baseline or nadir, whichever is lower, and an increase in the absolute value of PSA level by an increment of 5 ng/mL that is confirmed by another PSA level at no less than a 4-week interval (Appendix 2, Figure B). S**ubjects must have received a minimum of 12 weeks of study treatment, before progression could be determined solely by rising PSA**. **In the case of disease progression determined solely by rising PSA, additional clinical assessments should be consistent with disease progression.**
2) Radiographic progression
   - Target or non-target lesions progression as defined by RECIST criteria (Appendix 3)

- Bone scan progression: worsening bone scan as evidenced by the appearance of two or more new skeletal lesions that are not felt to be consistent with tumor flare. Subjects whose sole evidence of disease progression is bone scan progression must also have a PSA ≥ 5 ng/mL

3) Clinical disease progression as assessed by the Investigator
   - Example is worsening ECOG performance status thought to be due to disease progression

Section 10.3 Thromboembolic Event (TE)

Due to the deletion of the Post Study Treatment phase the observation period for TEs has been redefined. Thromboembolic events will be observed for up to 48 weeks after termination of Study Treatment phase for all subjects.

Section 10.4 Skeletal-related Event (SRE)-free Survival

Due to the deletion of the Post Study Treatment phase the observation period for SREs has been redefined. Skeletal-related events will be observed up to 48 weeks after termination of Study Treatment phase for all subjects.

Section 10.6 Gastrointestinal Event (GI)

Due to the deletion of the Post-Study Treatment phase the observation period for GIs has been redefined. Gastrointestinal events will be observed up to 48 weeks after termination of Study Treatment phase for all subjects.

Section 10.7 Quality of Life Assessment and Related Questions

The final QOL assessment and related questions will be performed at the first Follow-up visit after termination of Study Treatment Phase. The revised text as the following:

The Functional Assessment of Cancer Therapy-Prostate (FACT-P, version 4) QOL assessment questionnaire and related questions, including measurement of fatigue using the Brief Fatigue Inventory, will be administered up to 8 weeks (± 2 weeks) after termination of the Study Treatment phase.

Section 10.8 Pain Questionnaires

The final pain assessment will be performed at the first Follow-up visit after termination of Study Treatment Phase. The revised text is as follows:

The pain assessment questionnaire (the Brief Pain Inventory) will be administered up to 8 weeks (± 2 weeks) after termination of the Study Treatment phase.

Section 11.2.2 Serious Adverse Event Reporting Requirements

As a result of the deletion of the Post-Study Treatment phase the reporting requirements for SAEs has been revised to note that all SAEs occurring during the Study Treatment phase and for 48 weeks after termination of Study Treatment phase, or up to 30 days following the last dose of DN-101, whichever is the longest, will be reported on the AE CRF.

Individual cases of deaths will be monitored by Sponsor's Safety Committee, and not by an independent study monitor.

Section 12.2.2. Duration of Survival

Clarification was added that subjects who are alive at the time of primary analysis will be censored at the time of their last contact date.

Section 12.2.4 Duration of Skeletal-related Event (SRE)-free Survival

Clarification was added that subjects who are alive and have not reported an SRE event will be censored at the time of their last evaluation.

Section 12.3 Analysis Sets

Language was added to clarify how the efficacy endpoints would be tested using the following hierarchical procedure:

The efficacy endpoints will be tested using the following hierarchical procedure:

Step 1. If the comparison of primary endpoint is found to be statistically significant at the 0.05 level, go to step 2, otherwise no further analysis will be performed.

Step 2. The TE event will be statistically compared between the two treatment groups at the 0.05 level. If the comparison of TE event is found to be statistically significant, go to step 3, otherwise no further analysis will be performed.

Step 3. The SRE-free survival will be statistically compared between the two treatment groups at the 0.05 level.

Section 12.3.1.1 Duration of Survival

Language was added and the revised text as follows:

- This methodology is efficient (Anderson and Fleming, 1995; Anderson, 1989) as it takes into account the influence of known strong prognostic factors on survival in prostate cancer (Halabi et al. 2003; Scher et al. 1999). The stratified log-rank analysis will be provided as a supportive analysis to confirm robustness.

Section 12.3.1.2 Thromboembolic Event (TE) Rate

Language was added to note that the secondary analysis will include any TE event reported in the Study Treatment phase and the Follow-up phase.

Section 12.3.1.3 Duration of Skeletal-related Event (SRE)-free Survival

Language was added to note that the secondary analysis will include any SRE event reported in the Study Treatment phase and the Follow-up phase.

Section 12.3.2 Safety Analysis

The statements "The primary analysis will only include data in the Study Treatment Phase" at the end of the paragraphs on the SAE rate and GI event rate have been removed.

Section 12.4 Sample Size Considerations

Language was added to clarify that the sample size and power calculation is based on log-rank test in Section 12.4 and Study Synopsis. The revised text is as follows:

- The sample size and power calculation is based on log-rank test and performed using the software package EaST 3.0 (Cytel Software Corp, Cambridge, MA).

References

Two additional references were added:

Halabi S, Small EJ, Kantoff PW, Kattan MW, Kaplan EB, Dawson NA, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol. 2003 21:1232-1237.

Scher,H.I.; Kelly,W.M.K.; Zhang,Z.F.; Ouyang,P.; Sun,M.; Schwartz,M.; Ding,C.; Wang,W.; Horak,I.D.; Kremer,A.B. Post-therapy serum prostate-specific antigen level and survival in patients with androgen-independent prostate cancer. J. Natl. Caner Inst 1999; 91:244-251.

Appendix 1. Schedule of Assessments

Extensive changes were made to Appendix 1 to incorporate the revisions required following the changes in study design and study assessments as described previously in this section.

General

Minor grammatical and language changes have been made throughout the protocol to provide further consistency required by the changes in study design.