Genta Incorporated
Two Connell Drive
Berkeley Heights, NJ 07922 USA
Phone: (908) 286-9800
Fax: (908) 464-9353

GENASENSE™
(oblimersen sodium) Injection

FDA Advisory Committee Briefing Document

NDA 21-649

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or specialized term	Explanation
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT])
Apr	April
AST	aspartate aminotransferase (serum glutamic oxaloacetic transaminase [SGOT])
Aug	August
bcl-2	messenger ribonucleic acid (mRNA) name for *BCL2*
BCL2	B-cell leukemia/lymphoma 2 gene
Bcl-2	B-cell lymphoma break point 2; a protein that suppresses apoptosis and is upregulated in many types of tumors
BCT	biochemotherapy
BUN	blood urea nitrogen
CI	confidence interval
Cl	clearance
Cl_r	renal clearance
C_{ss}	concentration at steady state
CT	computed tomography
CVD	cisplatin, vincristine, and DTIC
DNA	deoxyribonucleic acid
DTIC	dacarbazine
ECOG	Eastern Cooperative Oncology Group
excl	excluding
FDA	Food and Drug Administration
ICU	Intensive Care Unit
IL	interleukin
IV	intravenous

Abbreviation or specialized term	Explanation
Jan	January
LD	longest diameters
LDH	lactate dehydrogenase
Mar	March
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
N-1	the 17-mer metabolite of G3139
N-2	the 16-mer metabolite of G3139
NDA	New Drug Application
NJ	New Jersey
PET	positron emission tomography
RECIST	Response Evaluation Criteria in Solid Tumors
SD	standard deviation
$t_{1/2}$	half-life

4. SUMMARY

Advanced malignant melanoma is one of the most chemoresistant types of human cancers. Virtually no recent progress has been made in the treatment of patients with this disease. In the past 30 years, the Food and Drug Administration (FDA) has approved only 2 agents, dacarbazine (DTIC) and interleukin-2 (IL-2), which were approved on the basis of overall response and durable response, respectively. Neither agent has ever been shown to affect survival. The most recent randomized study of DTIC yielded an overall response rate (complete response plus partial response) of 7%. Nonetheless, no other drug or any combination of drugs has ever shown a survival benefit when compared with DTIC alone, and it remains a regulatory standard of care.

Melanoma is characterized by overexpression of Bcl-2, a protein that prevents or substantially retards the onset of programmed cell death (apoptosis) induced by cytotoxic chemotherapy. Genasense blocks production of Bcl-2, and its use with chemotherapy is being tested as a means of improving current levels of therapeutic efficacy. The utility of the approach in any disease may depend upon the intensity of the apoptotic stimulus (ie, the inherent effectiveness of chemotherapy) with which it is paired.

In a New Drug Application (NDA) filed in 2003, the Sponsor presented data for the largest randomized clinical study ever conducted in patients with advanced malignant melanoma. In the study, 771 patients were randomly assigned to receive DTIC alone or DTIC in combination with Genasense. When compared with DTIC alone, the Genasense/DTIC combination has yielded:

- A trend toward improvement in overall survival by log-rank analysis (P = 0.18)
- A statistically significant increase in the overall response rate (11.7% vs 6.8%; P = 0.019), along with an increase in the "durable response" rate (3.4% vs 1.3%; P = 0.057), with responses seen in M1a, M1b, and M1c disease
- An increase in the number of complete responses (1.3% vs 0.5%)
- A statistically significant increase in time to disease progression (hazard ratio = 0.73; P = 0.0003)
- An acceptable safety profile for use as an outpatient treatment in all age groups studied
- A favorable benefit:risk comparison

The aggregate of these data shows an internally consistent benefit for patients across all efficacy endpoints and subgroups. The Sponsor believes that the Genasense/DTIC combination represents an important step in the development of more effective treatments for patients with advanced melanoma.

5. INTRODUCTION

NDA 21-649 was submitted to the FDA for the use of GENASENSE™ (oblimersen sodium) Injection in combination with DTIC for the treatment of patients with advanced melanoma who have not received prior chemotherapy.

This document provides a summary of the key nonclinical and clinical findings related to the efficacy and safety of Genasense in humans.

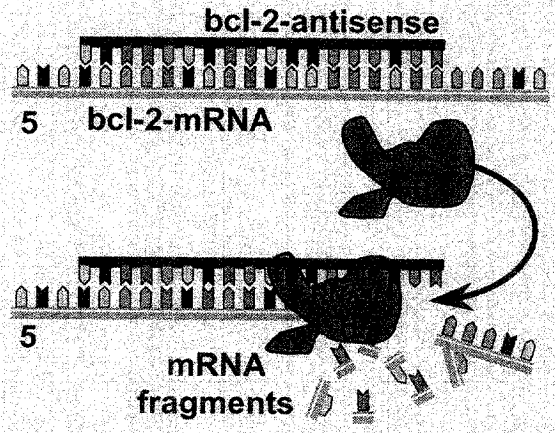
6. BACKGROUND

6.1 Pharmacology

Genasense (oblimersen sodium, Bcl-2 antisense oligonucleotide, G3139) belongs to a class of drugs known as antisense. Antisense represents a pharmacologic mechanism for selectively reducing production of a specific protein. In making an antisense drug, a series of nucleotides are engineered in a sequence that is complementary to the normal ("sense") strand of messenger ribonucleic acid (mRNA), the precursor to final translation of the protein. When the antisense drug binds to its complementary sequence of mRNA, the mRNA is enzymatically cleaved, which prevents translation of the protein.

Genasense is a synthetic, 18-base, single-stranded phosphorothioate oligonucleotide and has a molecular weight of 6058.3 daltons. The phosphorothioate modification substitutes a sulfur atom in place of a nonbridging oxygen atom on the phosphate group along the backbone of the molecule, which is comprised of alternating phosphorothioate and 2-deoxyribose sugar groups. This modification yields greater stability and a longer half-life to the molecule. Genasense selectively targets the first 6 codons (ie, 18 bases) of the mRNA open reading frame that encodes a protein known as Bcl-2. As shown in Figure 1, formation of the mRNA/antisense duplex recruits an enzyme (RNase H) that breaks apart the mRNA strand and releases the antisense strand, allowing the drug to bind and cleave additional Bcl-2 mRNA molecules. Cleavage of the Bcl-2 mRNA eliminates the ability of the molecule to generate Bcl-2 protein.

Figure 1: Binding of antisense to mRNA recruits RNase H, which fragments mRNA and prevents production of Bcl-2 protein



6.2 Clinical Background and Treatment of Advanced Malignant Melanoma

Melanoma is predominantly a disease of adults.(1) The tumor arises from melanocytes that are most commonly in the skin, although the disease can also arise from sites in the mucosa or internal organs.(1)

Melanoma is an increasingly common disease worldwide, with an annual increase in incidence of approximately 3% to 7%.(2) This increase is evident in the United States, Japan, and Australia, among other countries,(3,4,5) and may be partly attributed to the earlier detection of melanoma.(3) It is estimated that 54,200 persons were newly discovered to have melanoma and 7,600 individuals died as a result of melanoma in the United States in 2003.(1)

A variety of clinical factors have been reported to predict survival in advanced-stage melanoma. Positive factors include female gender, no impairment of performance status, and young age.(6,7) Patients with metastases confined to the skin, subcutaneous tissue, lymph nodes, and lung appear more likely to respond to any type of therapy and have superior survival relative to patients with metastases to other sites.(6) Factors associated with short survival include high lactate dehydrogenase (LDH; > 500 IU/mL) and metastases to brain or liver.(6)

No curative treatment exists for advanced malignant melanoma, and approved treatment options (ie, DTIC and IL-2) are extremely limited.

DTIC: DTIC, the only cytotoxic agent approved by the FDA for malignant melanoma, received marketing approval in 1975 on the basis of response rate only. This drug is considered to be the most active single agent for the management of advanced malignant melanoma and historically induces objective tumor responses in 10% to 20% of patients.(8,9,10) These response rates were reported prior to the publication of the Response Evaluation Criteria in Solid Tumors (RECIST).(11) Nearly all of these responses are partial, although complete responses have been observed.(10,12,13) In a more recent study that utilized RECIST measurement criteria, an overall response rate (complete response plus partial response) of only 7% has been reported with single-agent DTIC, which is probably a more accurate reflection of its activity alone.(10)

The toxicity of DTIC has been well established. Commonly reported side effects include severe nausea and vomiting, myelosuppression, loss of appetite, flu-like syndrome, injection site reactions, and fatigue. Hypersensitivity reactions have been reported and include anaphylaxis, breathlessness, erythematous and urticarial rashes, anxiety, and other manifestations. Hypotension, hepatic toxicity, hepatic vein thrombosis, and hepatocellular necrosis have occurred more rarely.

DTIC plus other chemotherapy: The addition of such agents as cisplatin, nitrosoureas, and vinca alkaloids has been reported to increase response rates in single-institution Phase II studies.(14) In particular, the "Dartmouth regimen" (ie, cisplatin, DTIC, carmustine, and tamoxifen) showed unexpectedly high objective response rates in early single-institution, nonrandomized studies.(15) However, subsequent Phase II/III studies have shown no statistically significant advantage over DTIC alone.(12,16)

In the definitive study of this combination chemotherapy, Eastern Cooperative Oncology Group (ECOG) investigators randomized 240 patients to receive either the Dartmouth regimen or single-agent dacarbazine at a dose of 1000 mg/m^2 every 3 weeks.(12)

At baseline, the median age was 52 years in patients who received the Dartmouth regimen. The median Karnofsky Performance Status Score was 90; 42% of these patients had disease involvement limited to the skin, lymph nodes, and lung.

Final results (non-RECIST) showed a nonsignificant difference in response rate for the Intent-to-Treat population: 16.8% among patients who received the Dartmouth regimen and 9.9% among those treated with single-agent DTIC. There were no complete responses in either treatment group. The median survival time was 7.7 months versus 6.3 months for the Dartmouth regimen and DTIC alone, respectively. (Time-to-progression was not reported.)

Considerably more toxicity was observed with the Dartmouth regimen than with DTIC alone. Significantly higher rates of Grade 3 and Grade 4 neutropenia, anemia, leukopenia in the absence of neutropenia, and thrombocytopenia occurred among patients treated with the combination regimen. Discontinuations due to toxicity occurred in 25 (21%) patients and 3 (2%) patients treated with the Dartmouth regimen and DTIC alone, respectively.

To date, no large randomized study has shown that the addition of any other cytotoxic or hormonal drug to DTIC has increased time to progression or survival.

Interleukin-2: An NDA for high-dose IL-2 was reviewed by the FDA in 1997 in an evaluation of 8 nonrandomized clinical studies in which 270 patients were enrolled.(17)

Patients were carefully screened prior to initiation of IL-2 therapy and were required to have an ECOG Performance Status of ≤ 1. Stress testing (echocardiography or other) and pulmonary function testing were routinely required in most of these studies, in addition to extensive laboratory testing.

The median age of patients treated was 42 years. More than 70% of patients had an ECOG Performance Status of 0. In 31% of patients, disease involvement was limited to the cutaneous/subcutaneous tissue and lymph nodes.

The overall response rate (not based on RECIST) was 16% (n = 43), including 6% (n = 17) of patients with a complete response. The majority of the 43 responding patients in these 8 studies combined had favorable disease characteristics (ie, disease limited to the lymph nodes, subcutaneous tissue, and/or lung; LDH status was not reported) at baseline. Only 3 of the 17 patients with complete response had an ECOG Performance Status > 0 at baseline. Multivariate analyses showed that Performance Status (specifically, a Performance Status of 0), female gender, and young age were significantly associated with response. Ten of the 17 patients who achieved a complete response had responses that lasted longer than 24 months, compared with 3 of the 26 patients who attained a partial response. After cessation of IL-2 therapy, 5 of the 17 complete responders and 10 of the 26 partial responders underwent surgical resection or received local radiation, and 5 of the responding patients remained free of disease for a prolonged period thereafter.

Toxicities from the high-dose IL-2 regimen were severe, and 6 (2.2%) patients died as a result of a treatment-related toxicity. Severe adverse reactions were primarily characterized by findings that resembled septic shock. Hypotension was the most commonly reported adverse event, affecting 64% of patients. Other commonly occurring events of particular concern included dyspnea, confusion, elevated bilirubin and transaminase levels, oliguria, and increased creatinine levels, thrombocytopenia, anemia, and rash. Grade 3 or 4 occurrences were often reported for hypotension (45% of patients), oliguria (39% of patients), and thrombocytopenia (17% of patients), as well as for vomiting and diarrhea. High-dose IL-2 treatment routinely requires ICU level monitoring.

IL-2 was approved on the basis of the small number of patients who achieved durable responses. In practice, use of high-dose IL-2 has generally been restricted to administration in young patients with good performance status by teams with considerable experience in managing the side effects of the drug. Administration of this agent is primarily reserved for the treatment of melanoma confined to the skin and subcutaneous tissue.

Biochemotherapy: Before multiagent chemotherapy was shown to be no more effective than DTIC alone, investigators from the MD Anderson Cancer Center reported improved response rates by adding IL-2 and interferon-alpha to the combination of cisplatin/vinblastine/DTIC (CVD) ("biochemotherapy" [BCT]).(18) Subsequently, drug doses and schedules in the regimen evolved to reduce toxicity, and the ECOG coordinated a US Intergroup study (E3695) that randomized patients with advanced melanoma to CVD or to BCT.(19) The study underwent an expansion of its planned sample size from 294 to 482 patients to

adjust the hazard ratio to more appropriately reflect anticipated survival benefit, but was terminated early after an interim analysis by a data safety monitoring board showed no evidence of possible benefit. At the time of its initial report at the 2003 American Society of Clinical Oncology annual meeting, this study of 416 patients was the largest study ever conducted in this patient population.

At baseline, two thirds of the patients had an ECOG Performance Status of 0. Compared with CVD chemotherapy, results of E3695 showed that BCT provided no significant difference in overall response rate, complete response rate (BCT = 1.4%; CVD = 3.0%), progression-free survival, or median survival (BCT = 8.4 months; CVD = 8.7 months). Life-threatening Grade IV toxicity was observed in 39% to 63% of patients, with a 1.5% treatment-related mortality reported.

In conclusion, available treatment options for patients with advanced melanoma, especially those ≥ 65 years of age and those with symptomatic disease, provide limited benefit and an unacceptable toxicity profile for most. Improved therapy for patients with advanced melanoma remains a major unmet need in medical oncology.

6.3 Rationale for the Development of Genasense

In the 1990s, an extensive body of literature accumulated that showed the importance of apoptosis—a series of biochemical reactions that lead to cell death. These data forced a reexamination of a central concept of human cancer. Whereas the disease was formerly thought to consist of cells that were rapidly dividing out of control, new research indicated that solid tumors were more generally characterized by an imbalance between the proportion of cells that lived or died. Moreover, it was recognized that even slight imbalances in the relative fraction of cancer cells that survived were sufficient to cause overgrowth of the tumor and death of the patient. Thus, considerable efforts were redirected towards identifying proteins that were critical regulators of cell survival.

The target of Genasense is a protein called Bcl-2, which was originally described in association with a B-cell lymphoma. Subsequently, Bcl-2 was shown to be a homolog of a normal protein (known as Ced-9) that had been linked to cell survival in *Caenorhabditis elegans*. Bcl-2 is now broadly described as a key "anti-apoptotic factor" (ie, a protein that can prevent or delay the onset of programmed cell death).

Bcl-2 is normally found within the membrane of the cell's mitochondria. Current data suggest that this protein negatively regulates either the size or voltage potential of a mitochondrial transmembrane pore. That is, high levels of Bcl-2 block the pore, and lower levels permit the pore to open.

Cancer chemotherapy, formerly thought to be directly lethal to cancer cells, is now believed to trigger a highly regulated program of cell suicide, or apoptosis. After exposure to a lethal dose of chemotherapy, a "death signal" is sent to the mitochondrion, which stimulates the release of cytochrome c from the mitochondrion into the cytoplasm. Cytochrome c then activates a cascade of enzymes (collectively known as caspases) that fragment proteins and break up DNA, which ultimately results in death of the cell.

By controlling the pore through which cytochrome C is released, Bcl-2 acts as a negative regulator of apoptosis — an anti-apoptotic factor — that can prevent or substantially retard the onset of programmed cell death. As such, increased expression of Bcl-2 effectively acts as a survival factor for cancer cells, allowing them to withstand the cytotoxic effects of chemotherapy. Thus, Bcl-2 appears to function as a fundamental (although not sole) cause of the inherent resistance of cancer cells to chemotherapy.

Antisense represents a general pharmacologic approach to selectively reduce production of a specific protein. The goal of Genasense therapy is to relieve the block in apoptosis associated with Bcl-2 and thereby maximize the effectiveness of coadministered cancer chemotherapy. Thus, Genasense can be viewed as a chemosensitizing agent that may enable conventional anticancer drugs to function more effectively.

Melanoma was one of the earliest targets for Genasense therapy, since more than 90% of tumors from patients with advanced disease have been reported to express Bcl-2.(20) In a Phase I-II study originally reported in *The Lancet*, 33 patients with advanced malignant melanoma were treated with Genasense plus DTIC,(21) and several noteworthy responses were reported.(Protocol GM103) One patient, who had not received prior cytotoxic therapy, had a biopsy-proven complete response to G3139 (6.5 to 7.7 mg/kg/day) and DTIC (800 to 1000 mg/m^2). This patient survived for 2.2 years after receiving the first dose of study medication. Two other patients, both of whom had received prior cytotoxic therapy, had partial responses after receiving maximum G3139 doses of 6.5 mg/kg/day. One of the 2 patients survived for 1.7 years after receiving the first dose of study medication, and the other survived for 2.7 years after receiving the first dose of study medication. Serial biopsies of superficial melanoma lesions from several patients showed that G3139 treatment was associated with a decrease in Bcl-2 protein. These findings suggested that the combination of G3139 at doses $\geq$ 6.5 mg/kg/day plus DTIC might prove useful for treatment of patients with malignant melanoma.

6.4 Nonclinical Data

6.4.1 Nonclinical Pharmacology

The nonclinical pharmacology of G3139 is primarily based on a review of the relevant published literature. G3139 was selected for development from among 40 phosphorothioate oligodeoxynucelotides in a screening process designed to detect downregulation of *bcl-2* mRNA expression. The nucleotide sequence of G3139 was designed to be antisense to the first 6 codons of the open reading frame downstream from the AUG start site of the *bcl-2* mRNA sequence.

The effects of G3139, alone and in combination with many cytotoxic drugs, have been assessed in a wide variety of cancer models.(22) The results have been broadly consistent: decreased expression of *bcl-2* mRNA and protein, reduced cellular viability, increased apoptosis, reduction of tumor size, prolongation of survival in tumor-bearing animals treated with G3139 plus chemotherapy, and synergistic cytotoxic activity with anticancer drugs.

6.4.2 Nonclinical Safety Evaluation

The nonclinical development program was designed and conducted by the Sponsor in accordance with recommendations given by the Division of Oncology Drug Products on 17 Aug 2001 as part of End-of-Phase-II discussions for Genasense. The FDA confirmed acceptance of the overall content of the nonclinical development program in pre-NDA dialogue on 08 Apr 2003.

Key nonclinical findings that pertain to the safety of G3139 include the following:

- The kidney is the major tissue of distribution for G3139.
- Plasma concentrations of G3139 and the N-1 and N-2 active metabolites (ie, metabolites of 17 and 16 bases in length, respectively, which result from sequential nuclease cleavage of the 18-base parent compound) are achieved rapidly, increase with increasing dose, and are relatively consistent across species.
- G3139 is not teratogenic or mutagenic.
- Induction or inhibition of P450 isozymes by G3139 is unlikely at clinically relevant G3139 concentrations.
- The toxicity of G3139 is dose related and consistent with the class toxicity profile for oligonucleotides when administered to rodents and monkeys. This profile is independent of nucleotide sequence, indicating that the toxicities of these compounds do not result from their targeted pharmacologic effects. This profile consists of increased coagulation time, complement activation, uptake of test article in kidney and liver resulting in tubular nephropathy and

Kupffer cell activation, and immune stimulation, including splenomegaly, lymphoid hyperplasia, and mononuclear cell infiltration in many tissues.

- The toxicologic effects suggest an adequate safety margin for the proposed human use of this drug product.

7. CLINICAL PHARMACOLOGY

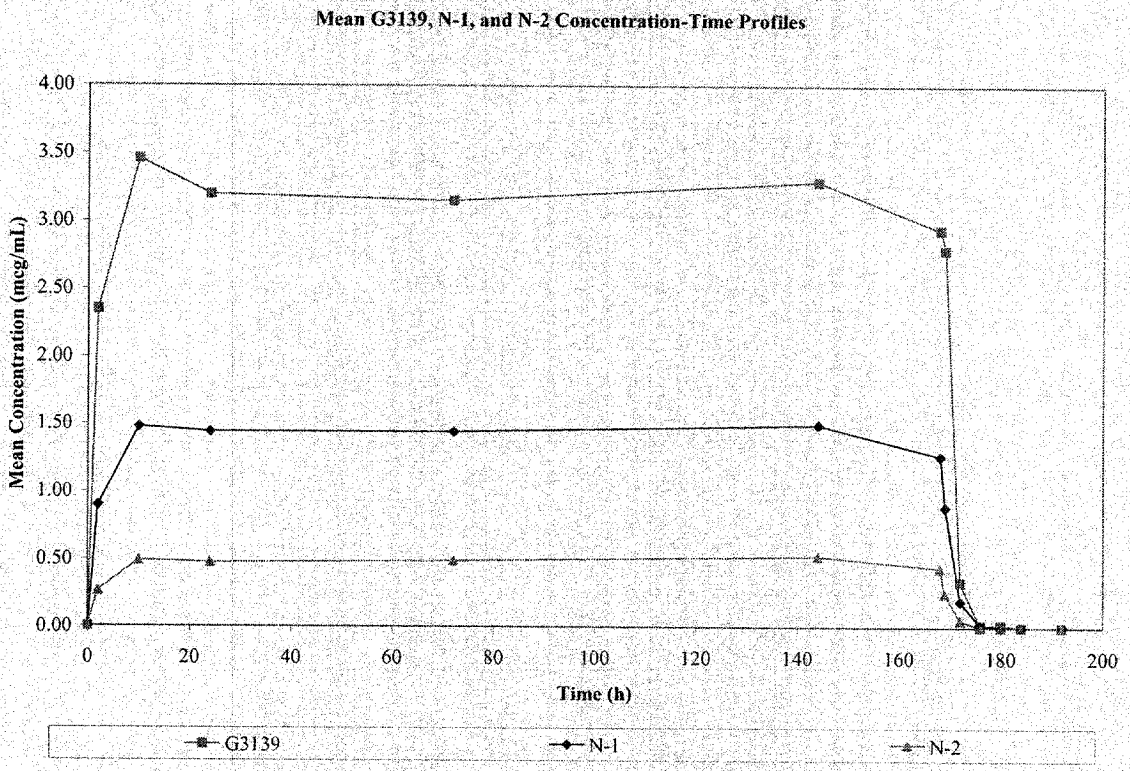
7.1 Pharmacokinetics

The clinical pharmacokinetics of G3139 and its metabolites, N-1 and N-2, were investigated in 2 primary studies:

- Protocol GPK101 was a Phase I study conducted to evaluate the pharmacokinetics and safety of G3139 given in combination with DTIC to 24 patients with advanced malignant melanoma. In the pharmacokinetic portion of this study, G3139 7 mg/kg/day was administered as a continuous intravenous (IV) infusion for 7 days and DTIC 1000 mg/m^2 was administered IV over a 60-minute period beginning 120 hours after the start of the G3139 infusion.
- Protocol GL208 was a Phase I/II study of G3139 in patients with advanced chronic lymphocytic leukemia. G3139 3 to 7 mg/kg/day was administered as a continuous 5-day IV infusion in Cycle 1. (Protocol GL208 was conducted in patients with chronic lymphocytic leukemia and is not further discussed in this document.)

The mean G3139, N-1, and N-2 pharmacokinetic parameters in Protocol GPK101 are shown in Figure 1.

Figure 1: Mean G3139, N-1, and N-2 plasma concentration-time profiles



The single dose level (7 mg/kg/day) administered in this study did not permit rigorous determination of dose proportionality or evaluation of changes in clearance (CL) and renal clearance (CL_r) with increasing doses of G3139. The exposure (mean C_{ss} ratio) of patients to the N-1 and N-2 metabolites was approximately 45% and 19%, respectively, of the exposure to G3139. Plasma concentrations for G3139 and the N-1 metabolite reached steady state in approximately 10 hours.

The mean half-life ($t_{1/2}$) for G3139 was 2.4 hours and was consistent with the attainment of steady state by approximately 10 hours. The mean $t_{1/2}$ of 2.3 hours for the N-1 metabolite was similar to that for G3139 (there were insufficient data to calculate a $t_{1/2}$ for N-2). The total clearance of G3139 for an average individual (70 kg) would be expected to be approximately 6.09 L/h. The mean renal clearance for G3139 was estimated to be 0.058 L/h in this study. The results for total and renal clearance suggested that renal clearance represented only a small portion of the total clearance for intact G3139. These results are consistent with literature reports for other phosphorothioate oligonucleotides.(23,24,25)

7.2 Metabolism

Although no formal human in vivo metabolism studies were conducted by the Sponsor for G3139, the plasma time course of the N-1 and N-2 metabolites of G3139 was determined in the primary pharmacokinetic study GPK101. The exposure (mean C_{ss} ratio) of patients to the N-1 and N-2 metabolites was approximately 45% and 19%, respectively, of the exposure to G3139 in this study. The mean half-life for the N-1 metabolite was similar to the half-life for G3139 (2.3 vs 2.4 h, respectively).

Published studies report that phosphorothioate oligonucleotides are rapidly metabolized in both plasma and tissues following administration in mice, rats, monkeys, and humans (25,26,27). These studies present evidence that the metabolism of phosphorothioate oligonucleotides results in sequential removal of nucleotide bases to form N-1, N-2, etc, metabolites in plasma and/or tissues.

7.3 Plasma Protein Binding

A Genta-sponsored study evaluated the extent of protein binding of G3139 in human plasma.(28) The ^{3}H-G3139 was incubated at 0.025 to 0.2 μg/mL in normolipidemic human plasma for up to 2 hours. The majority of the radioactivity was found in the lipoprotein-deficient fraction, which includes albumin. In this fraction, 85% of the radioactivity was protein bound.

Phosphorothioate oligonucleotides in general have been found to be highly bound to plasma proteins. Plasma protein binding ranges from 65% to 99% for various sequences of oligonucleotides in mouse, rat, dog, and human plasma.(25,27,29, 30,31,32) Phosphorothioate oligonucleotides have been primarily found to bind to albumin (low affinity, high capacity) and alpha-2 macroglobulin (low capacity, high affinity). The binding to bovine serum albumin has been shown to be salt- and pH-dependent, suggesting that it is likely to be a nonspecific electrostatic interaction.(33) Binding to alpha-1 acid glycoprotein has been found, in general, to be negligible.(25)

7.4 Special Populations

Based on the human biopharm pre-NDA discussion with the FDA on 23 Sep 2003, the Sponsor committed to conduct 2 studies in special populations. Protocols for the evaluation of Genasense in patients with renal and hepatic impairment were designed in concurrence with the FDA and were submitted to the Agency on 25 Nov 2003.

7.5 Dose Selection

Target Plasma Concentration: Given its high potency, extensive preclinical data have shown that G3139 concentrations below 1 μg/mL were sufficient to achieve maximal downregulation of intracellular Bcl-2 protein in vitro.(34) Such concentrations can easily be achieved with doses of about 2 mg/kg/day. Early clinical studies also suggested that G3139 plasma concentrations > 1 μg/mL downregulated Bcl-2 in both tumor cells and peripheral blood mononuclear cells. This concentration was then established as a minimum target.

Dosing Interval Relative to Chemotherapy: Limited in vivo data have shown that G3139 treatment in advance of, or coincident with, cytotoxic chemotherapy maximized the chemosensitizing effect.(35) Overlap of G3139 treatment with chemotherapy did not appear to increase chemosensitization compared with G3139 pretreatment alone. By contrast, regimens in which chemotherapy was administered first, followed by treatment with G3139, were demonstrably inferior and yielded efficacy results that were similar to the use of chemotherapy alone.

Route of Administration: Preclinical toxicology studies suggested that subcutaneous or continuous IV infusion schedules were better tolerated and maintained more stable steady-state plasma drug concentrations compared with bolus IV injections. Together with the short plasma half-life of G3139 and the relatively long half-life of intracellular Bcl-2, this information suggested that continuous IV infusion was an appropriate route of administration.

Daily Dose and Schedule: Phase I studies of G3139 broadly examined 2 dosing schedules using continuous IV infusion: daily for durations of 5 to 7 days; and daily for durations of 14 days (or longer). Both schedules were examined in combination with myelosuppressive chemotherapy.

With the 5- to 7-day schedules using G3139 in combination with DTIC chemotherapy, thrombocytopenia was found to be limiting at a daily G3139 dose of 12 mg/kg/day.(21,36) On 14(+)-day schedules, a somewhat different safety profile was observed. Dose-limiting reactions, including severe fatigue and reversible increases in hepatic enzymes (aspartate aminotransferase), occurred at a G3139 dose of 6.5 mg/kg/day, which was declared as the maximally tolerated dose on that schedule.(37)

A G3139 dose of 7 mg/kg/day for 5 days by continuous IV infusion, followed by DTIC on Day 5, was selected for extended evaluation for several reasons:

- This dose consistently yielded plasma drug concentrations that comfortably exceeded target concentrations for maximal Bcl-2 downregulation. Limited data also suggested that maximal downregulation of Bcl-2 was achieved within 5 days of drug exposure. Preliminary data suggested that, while

extended treatment might prolong the duration of Bcl-2 downregulation, it did not appear to yield a further decrease in the absolute percentage of downregulation (ie, Bcl-2 levels were maximally decreased by Day 5). Lastly, since the treatment goal was maximization of chemotherapy efficacy, it was believed desirable to limit the Bcl-2 downregulation to a duration when the apoptotic stimulus was maximal (ie, the time of chemotherapy treatment).

- Although the selected dose approximated the maximum tolerated dose on the extended-dosing schedule, it was less than the maximum tolerated dose on the shorter schedule (when used in combination with DTIC).

These observations suggested that the selected dose would provide an acceptable therapeutic index, especially for seriously ill patients who were expected to enroll in the randomized study.

8. EFFICACY RESULTS IN RANDOMIZED PHASE III STUDY

A Phase III study was conducted to compare the efficacy and safety of G3139 in combination with DTIC versus DTIC alone.

8.1 Design and Methods for Protocol GM301

8.1.1 Study Objectives

This study was conducted to compare the efficacy and safety of G3139 in combination with a conventional chemotherapeutic agent (DTIC) approved for use in metastatic malignant melanoma versus DTIC alone.

The primary endpoint was survival. Secondary endpoints included progression-free survival, response rate, duration of response, durable response rate, and performance status.

8.1.2 Study Design and Treatment Regimen

This study was conducted using a randomized, multicenter, open-label, parallel-group design. Prior to randomization, patients were stratified on the basis of known prognostic factors (ie, ECOG Performance Status, liver metastases, and lactate dehydrogenase level) to prevent uneven distribution in treatment groups.

All patients were treated in 21-day cycles. During each cycle, patients received either:

- DTIC 1000 mg/m^2 administered by IV infusion over 60 minutes on Day 1, or
- G3139 7 mg/kg/day administered by continuous IV infusion (delivered via computerized ambulatory infusion pump with central venous access) for 5 days and DTIC 1000 mg/m^2 administered by IV infusion over 60 minutes immediately upon completion of the G3139 infusion

Treatment continued for a maximum of 8 cycles, but was stopped if disease progression was documented or if the patient incurred intolerable drug-related side effects that did not respond to dose modification. Protocol therapy and related testing were to be completed in the outpatient setting, but inpatient treatment and testing were permitted at the discretion of the investigator.

All randomized patients (including those who never initiated protocol therapy, those who discontinued protocol therapy prematurely, and those who completed protocol therapy) were followed every 2 months after discontinuation of protocol therapy up to 2 years from the date of randomization to determine clinical status and to document duration of survival. Patients in the G3139 plus DTIC group who

completed 8 cycles of treatment and showed response or stable disease after 8 cycles could enroll in Protocol GM214, an open-label continuation study, if they met eligibility requirements for that study. No patient who received DTIC alone in Protocol GM301 was allowed to cross over and receive G3139 plus DTIC.

8.1.3 Entry Criteria

Key inclusion criteria included the following:

1. Histologically confirmed diagnosis of malignant melanoma
2. Progressive local disease that was not surgically espectable, or metastatic Stage IV disease
3. Measurable disease, defined as at least 1 malignant lesion that could be accurately and serially measured in at least 1 dimension and for which the greatest diameter was ≥ 20 mm as measured by contrast-enhanced or spiral computed tomography (CT) scan for visceral or nodal/soft tissue disease, or ≥ 10 mm as measured by caliper for superficial cutaneous metastases
4. ECOG Performance Status of 0, 1, or 2
5. Adequate organ function determined within 2 weeks prior to randomization

Key exclusion criteria included the following:

1. Prior cytotoxic chemotherapy, including regional perfusion
2. History of brain metastasis or leptomeningeal disease
3. Significant medical disease other than cancer
4. History of second cancer (except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient had been disease-free for 5 or more years)
5. Bone-only metastatic disease
6. Primary ocular or mucosal melanoma
7. Concomitant anticoagulant therapy (other than warfarin 1 mg/day for central line prophylaxis)

8.1.4 Efficacy Assessments

Efficacy assessment was based on tumor measurement by physical measurement; photographs of superficial target lesions; radiographs of target lesions; and assessment of nontarget lesions. Patients in the G3139 plus DTIC group and the DTIC group were assessed at the same 21-day intervals during the treatment phase and the same 2-month intervals during the follow-up phase.

Measurable Disease

Measurable disease was defined by the presence of at least 1 measurable lesion, as adapted from RECIST.(11) Specifically, measurable lesions were defined as lesions that could be accurately and serially measured in at least 1 dimension and for which the greatest diameter was ≥ 20 mm as measured by contrast-enhanced or spiral CT scan for visceral or nodal/soft tissue disease, or ≥ 10 mm as measured by caliper for superficial cutaneous metastases.

Nonmeasurable lesions were those that did not meet the definition of measurable lesions. All bone lesions, ascites, pleural/pericardial effusions, abdominal masses that were not confirmed and were followed by imaging techniques, and tumors treated by irradiation or by intratumor injection therapy (unless progression outside the treated area had occurred) were considered to be nonmeasurable.

A total of no more than 10 measurable lesions with the longest diameter were selected as target lesions. All lesions not identified as target lesions were considered nontarget lesions. The sum of the longest diameters (sum LD) was defined as the sum of the longest diameters of the target lesions.

Antitumor Response

For target lesions, complete response was defined as the disappearance of all target lesions, and partial response was defined as at least a 30% reduction in the sum LD of target lesions taking as a reference the baseline sum LD. For nontarget lesions, complete response was defined as the disappearance of all nontarget lesions.

If progression was suggested by increased size of 1 or more target lesions without evidence of clearly defined new metastases, then all target lesions were measured and progression was confirmed by determination of the sum LD. If progression was indicated by the well-defined development of new metastatic disease, repeat evaluation of all target lesions was not required, but could be performed at the investigator's discretion. Based on RECIST, progressive disease was defined as at least a 20% increase from the minimum in the sum LD of the target lesions, the appearance of 1 or more new lesions, or unequivocal progression of existing nontarget lesions.

Stable disease was defined as any measurement not meeting the criteria for either response or progressive disease.

Overall Response

Assessments of response of target and nontarget lesions and appearance of new lesions were used to determine overall response as shown in Table 1.(11)

Table 1: Determination of overall response

Presence of:			
Target lesions	**Nontarget lesions**	**New lesions**	**Overall response**
Complete response	Complete response	No	Complete response
Complete response	Stable disease	No	Partial response
Partial response	Stable disease	No	Partial response
Stable disease	Stable disease	No	Stable disease
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease

If it was difficult to distinguish residual disease from normal tissue, the residual lesion was to be biopsied, especially if the response was believed to be complete. In cases where biopsy was not appropriate, positron emission tomography (PET) scans were used to document absence of residual disease.

Confirmation of Objective Response

A patient was assigned a response of confirmed complete response or confirmed partial response if this response was confirmed by a repeat evaluation done no less than 3 weeks after response was first noted. The confirmatory evaluation after a 3-week interval reflects a modification from the 4-week interval specified by RECIST. The 3-week interval was chosen in order to coincide with the schedule of study visits specified by protocol.

Independent, Blinded Assessment of Response

RadPharm (Princeton, NJ) conducted a blinded assessment of response in responding patients. They independently reviewed the data of patients who were identified as having a response on the basis of lesion measurements. Study sites were instructed to remove all markings on x-rays, and no clinical information was provided to RadPharm.

8.1.5 Statistical Considerations

It was assumed that median survival time for patients treated with DTIC would be 6 months and median survival for patients treated with G3139 plus DTIC would be 8 months. Using the log-rank test, 750 patients (375 patients per treatment group) followed until 508 events (ie, deaths) occurred would provide a power of 90% to detect a significant difference between the 2 treatment groups in the survival distribution at a 2-sided significance level of 0.05.

The protocol was amended twice to increase the sample size from 270 to 450 (change of power from 80% to 90%; amended protocol approved by the FDA in Jan 2002) and from 450 to 750 (change in the assumption of hazard ratio from 1.50 to 1.33; amended protocol approved by the FDA in Jun 2002). The final statistical analysis plan was approved by the FDA prior to unblinding of the study. The increases in sample size were determined without performing any interim analyses, and the Sponsor remained blinded until unblinding of the study in September 2003.

The Intent-to-Treat Population was defined as all patients randomized. The Safety Population was defined as all Intent-to-Treat subjects who received any protocol therapy.

The following endpoints were analyzed:

- **Survival:** Survival was calculated as the number of days from randomization to the date of death.
- **Antitumor Response Rate:** For each patient, response was independently calculated based on the totals of the individual lesion measurements recorded on the case report form and included evaluation of nonmeasurable lesions, as well as the presence or absence of new lesions. The antitumor response rate was calculated as the percentage of patients with complete response or partial response for the Intent-to-Treat Population.
- **Duration of Response:** The duration of response was measured from the first date that criteria for complete response or partial response (whichever was recorded first) were met, until the first date that recurrent or progressive disease was objectively documented.
- **Durable Response:** A durable response was defined as a complete or partial response lasting ≥ 6 months from the date the response was first recorded. No anticancer therapy other than protocol therapy was to be administered during the 4 months after the response was initially determined.
- **Progression-Free Survival:** Progression-free survival was defined as the time from the date of randomization to the first date when criteria for progression

were met or when the patient died, whichever occurred first. Only deaths occurring within 60 days from the last lesion measurement were considered as events in the progression-free survival analyses. For patients who died more than 60 days after the last lesion measurement, the progression-free survival was censored at the date of the last lesion measurement.

8.2 Study Population

A total of 771 patients were randomized at 139 study sites in 9 countries (G3139 plus DTIC group, 386 patients; DTIC group, 385 patients). Subjects were enrolled during a 2.5-year period. The first patient was enrolled in July 2000, and the last patient was enrolled in February 2003. Notably, 251 (32.6%) patients were enrolled during the last 6 months of the study and 160 (20.8%) were enrolled during the last 3 months of the study. Overall, all 771 patients randomized comprised the Intent-to-Treat Population.

A total of 15 (3.9%) patients in the G3139 plus DTIC group and 25 (6.5%) patients in the DTIC group were randomized but did not initiate protocol therapy (see Table 2). The most frequently reported reason for discontinuing prior to initiation of protocol therapy differed between the 2 treatment groups and included patient ineligibility in the G3139 plus DTIC group and patient choice in the DTIC group.

Table 2: Disposition of patients not treated

Reason for discontinuation	G3139 plus DTIC (n = 15)	DTIC (n = 25)
Disease progression or relapse	3	4
Patient choice	4	15
Patient ineligible	5	3
Death	2	2
Other	1	1

A total of 731 (94.8%) patients initiated protocol therapy. Overall, most patients in each treatment group who initiated protocol therapy discontinued from the study early (ie, before completion of 8 cycles of protocol therapy). In both treatment groups, disease progression was the most frequently reported reason for discontinuation (239 [64.4%] patients in the G3139 plus DTIC group and 262 [72.8%] patients in the DTIC group).

Patients were evenly distributed in the 2 treatment groups with respect to age, gender, and race (see Table 3). The mean age in both groups was 59 years; females represented a little more than one third of the patients randomized to each group. More than 95% of patients in both treatment groups were white. Patients ≥ 65 years of age represented approximately 38% of those randomized in both treatment groups and approximately 15% were ≥ 75 years of age. Overall, this patient population was older than those historically included in other melanoma studies.(17)

Table 3: Demographic characteristics by treatment group: Intent-to-Treat Population

Demographic characteristic	G3139 plus DTIC (N = 386)	DTIC (N = 385)	Overall (N = 771)
Age, years			
n	386	385	771
Mean (SD)	58.6 (13.94)	58.7 (13.87)	58.7 (13.90)
Median	59.0	60.0	59.0
Minimum, maximum	17, 93	16, 89	16, 93
Age group, n (%)[a]			
< 65 years	239 (61.9)	241 (62.6)	480 (62.3)
≥ 65 years	147 (38.1)	144 (37.4)	291 (37.7)
≥ 75 years	47 (12.2)	54 (14.0)	101 (13.1)
Gender, n (%)[a]			
Female	150 (38.9)	132 (34.3)	282 (36.6)
Male	236 (61.1)	253 (65.7)	489 (63.4)
Race, n (%)[a,b]			
Caucasian/White	375 (97.2)	371 (96.4)	746 (96.8)
All other	10 (2.6)	12 (3.1)	22 (2.9)
Unknown[c]	1 (0.3)	2 (0.5)	3 (0.4)

SD = standard deviation
[a] Percentages were calculated by using N, the total number of patients in the group, as the denominator.
[b] Racial categories on the case report form included Caucasian/White, Hispanic, Asian, Black, and Other.
[c] Recording of race was not permitted at the study site.

The median time from initial diagnosis to randomization was similar in the 2 treatment groups: 29.5 months in the G3139 plus DTIC group and 26.4 months in the DTIC group (see Table 4).

Unlike other studies in which subjects with an ECOG Performance Status > 1 were excluded,(17) approximately 7% of subjects in both groups had an ECOG Performance Status of 2. In addition, 1 patient in the G3139 plus DTIC group and 2 patients in the DTIC group who had a performance status of 2 at the time of randomization had a deterioration in clinical status prior to initiation of protocol therapy with a resultant ECOG Performance Status of 3 at the time of first dosing.

The distribution of patients in the 2 treatment groups was similar based on classification according to American Joint Committee on Cancer (AJCC) criteria.(38) These criteria, which were published in 2002 after the protocol had been prepared and the study initiated, were not used as stratification factors. There was a small difference between treatment groups in the percentage of patients in the M1c category, with a greater percentage of patients in the DTIC group falling in this category. The potential impact of this observed difference on efficacy parameters was rigorously examined using the Cox Proportional Hazard model and logistic regression analysis and was determined to have no effect on any efficacy parameter measured.

Table 4: Melanoma history and disease characteristics at baseline by treatment group: Intent-to-Treat Population

Characteristic	G3139 plus DTIC (N = 386)	DTIC (N = 385)
Time from initial diagnosis to randomization, months		
n	386	384
Median	29.5	26.4
Metastasis[a], n (%)[b]		
Local regional disease only	34 (8.8)	22 (5.7)
Distant metastatic disease	352 (91.2)	363 (94.3)
AJCC LDH-disease site distribution, n (%)[b, c]		
Nonvisceral and nonelevated LDH (M1a)	61 (15.8)	50 (13.0)
Lung and nonelevated LDH (M1b)	93 (24.1)	75 (19.5)
Visceral other than lung, or elevated LDH (M1c)	226 (58.5)	257 (66.8)
Unknown	6 (1.6)	3 (0.8)
ECOG Performance Status, n (%)[d]		
0	207 (54.8)	220 (57.4)
1	146 (38.6)	132 (34.5)
2	24 (6.3)	29 (7.6)
3	1 (0.3)	2 (0.5)

AJCC = American Joint Committee on Cancer; LDH = lactate dehydrogenase; SD = standard deviation

[a] Referred to as "general metastasis" on the case report form. Patients with both local regional disease and distant metastatic disease counted in distant metastatic disease category.

[b] Percentages were calculated by using N, the total number of patients in the group, as the denominator.

[c] Based on the AJCC classification. A baseline LDH value was not available for 6 patients in the G3139 plus DTIC group and for 3 patients in the DTIC group.

[d] Percentages were calculated based on the number of patients with ECOG Performance Status data at baseline.

The percentage of patients who had received previous cancer treatment by type of treatment was similar in the 2 treatment groups (see Table 5). Most patients in each treatment group had received previous surgical intervention. Previous immunotherapy (primarily interferon-alpha) was also frequently reported in both treatment groups.

Table 5: Previous cancer treatment by treatment group: Intent-to-Treat Population

Characteristic	G3139 plus DTIC (N = 386)	DTIC (N = 385)	Overall (N = 771)
Prior surgery, n (%)[a, b]	369 (95.6)	372 (96.6)	741 (96.1)
Prior radiation therapy, n (%)[a]	73 (18.9)	65 (16.9)	138 (17.9)
Prior immunotherapy/cytokine therapy, n (%)[a]	156 (40.4)	142 (36.9)	298 (38.7)

[a] Percentages were calculated by using N, the total number of patients in the group, as the denominator.
[b] Includes diagnostic procedures

Patients were evenly distributed between treatment groups in each of the 6 randomization strata (see Table 6).

Table 6: Stratification information by treatment group: Intent-to-Treat Population

Stratum	ECOG score	Liver metastases	Disease distribution and LDH status	G3139 plus DTIC (N = 386) n (%)[a]	DTIC (N = 385) n (%)[a]	Overall (N = 771) n (%)[a]
1	0	Present	Not considered if liver metastasis was present	70 (18.1)	63 (16.4)	133 (17.3)
2	1 or 2	Present	Not considered if liver metastasis was present	58 (15.0)	73 (19.0)	131 (17.0)
3	0	Absent	Disease in visceral organ other than liver, or elevated LDH	113 (29.3)	120 (31.2)	233 (30.2)
4	1 or 2	Absent	Disease in visceral organ other than liver, or elevated LDH	82 (21.2)	78 (20.3)	160 (20.8)
5	0	Absent	Disease in skin, subcutaneous tissue, and/or lymph nodes without visceral metastases, and LDH not elevated	36 (9.3)	32 (8.3)	68 (8.8)
6	1 or 2	Absent	Disease in skin, subcutaneous tissue, and/or lymph nodes without visceral metastases, and LDH not elevated	25 (6.5)	18 (4.7)	43 (5.6)

[a] Percentages were calculated by using N, the total number of patients in the group, as the denominator. Due to missing information, 2 patients in the G3139 plus DTIC group and 1 patient in the DTIC group could not be categorized by randomization stratum.

In both groups, most patients initiated ≤ 2 cycles of protocol therapy (see Table 7). Since the first disease restaging was required at the conclusion of Cycle 2, many patients had demonstrable disease progression and were removed from the study at that time. At the time of the cutoff date for the NDA (01 Aug 2003), 11 subjects (including 10 in the G3139 plus DTIC group and 1 in the DTIC group) were in the treatment phase of the study.

Table 7: Number (%) of patients by maximum number of cycles initiated by treatment group: Intent-to-Treat Population

Maximum number of cycles initiated	G3139 plus DTIC (N = 386) n (%)[a]	DTIC (N = 385) n (%)[a]	Overall (N = 771) n (%)[a]
0 (not treated)	15 (3.9)	25 (6.5)	40 (5.2)
1	38 (9.8)	45 (11.7)	83 (10.8)
2	147 (38.1)	164 (42.6)	311 (40.3)
3	36 (9.3)	23 (6.0)	59 (7.7)
4	40 (10.4)	33 (8.6)	73 (9.5)
5	18 (4.7)	9 (2.3)	27 (3.5)
6	20 (5.2)[b]	24 (6.2)	44 (5.7)
7	13 (3.4)	5 (1.3)	18 (2.3)
≥ 8	59 (15.3)	57 (14.8)	116 (15.0)

[a] Percentages were calculated by using N, the total number of patients in the group, as the denominator.
[b] One patient had completed Cycle 6 but not yet initiated Cycle 7 as of the data cut-off date of 01 Aug 2003. This patient is reported in this table as initiating a maximum of 6 cycles at the time of the data cut-off date.

The relatively similar number of treatment cycles received by subjects in both treatment groups reflects the lack of important differences between the treatment groups in dose-limiting toxicities.

Both the mean and median normalized doses of DTIC were similar in the 2 treatment groups, confirming that the usual dosing with DTIC was maintained in patients who received G3139 (see Table 8).

Table 8: Descriptive statistics for cumulative (total) dose of study drug across all cycles: Safety Population

	G3139 plus DTIC (N = 371)		DTIC (N = 360)
Study drug (units)	**G3139 (mg/kg)**	**DTIC (mg/m^2)**	**mg/m^2**
n	371	365[a]	360
Mean (SD)	126.1 (85.30)	3417.9 (2191.40)	3371.9 (2300.82)
Median	76.9	2054.9	2008.1
25^{th} percentile	68	1944	1957
75^{th} percentile	177	4795	4862
Minimum, maximum	9, 608	873, 9000	901, 9845

SD = standard deviation

[a] A total of 6 patients initiated Cycle 1 but discontinued from the study prior to receiving the scheduled dose of DTIC.

8.3 Efficacy Results

8.3.1 Overall Survival

In accordance with the statistical analysis plan, unblinding was event driven. It was to occur after at least 508 events (ie, deaths) had been reported. Unblinding of the study was performed when 537 events had occurred. Two deaths occurred after 2 years of follow-up (Subjects 90201 and 92602, both in the G3139 plus DTIC group), and, as specified in the analysis plan, the survival times for these 2 patients were censored at 2 years (730 days). Therefore, a total of 535 events were included in the survival analysis.

Table 9 provides the results of the survival time analysis for the Intent-to-Treat Population. In the Intent-to-Treat Population, 68.9% (266 of 386) of patients in the G3139 plus DTIC group and 69.9% (269 of 385) of patients in the DTIC group had died by the time of analysis or at the end of the 2-year follow-up, whichever came first. The median survival time was 274 days in the G3139 plus DTIC group and 238 days in the DTIC group. The hazard ratio was 0.89. The difference between groups in survival distribution was not statistically significant (log-rank test, P = 0.18).

Table 9: Survival time analysis: Intent-to-Treat Population

Parameter	G3139 plus DTIC (N = 386)	DTIC (N = 385)	Hazard ratio[b]	Log-rank P value
Number (%)[a] of patients who died	266 (68.9)	269 (69.9)		
Median survival time (days)	274	238	0.89	0.18
95% confidence interval	232 –306	219 – 271	0.75-1.06	

Survival time was defined as the time from the date of randomization to the date of death.
[a] Percentages were calculated by using N, the total number of patients in the group, as the denominator.
[b] Hazard ratio and 95% confidence interval from the unadjusted Cox Proportional Hazards Model

Kaplan-Meier survival curves by treatment group for the Intent-to-Treat Population are shown in Figure 2. The curves are nearly superimposable for the first 6 months and then begin to separate before the median. The separation is most pronounced around the 75th percentile, at which time a greater than 3-month difference is apparent (G3139 plus DTIC group, 522 days; DTIC group, 421 days; see Figure 2 and Table 10). It is noteworthy that more than 20% (160) of the 771 patients randomized were enrolled during the last 3 months of recruitment.

Figure 2: Kaplan-Meier survival curves by treatment group: Intent-to-Treat Population (N = 771)

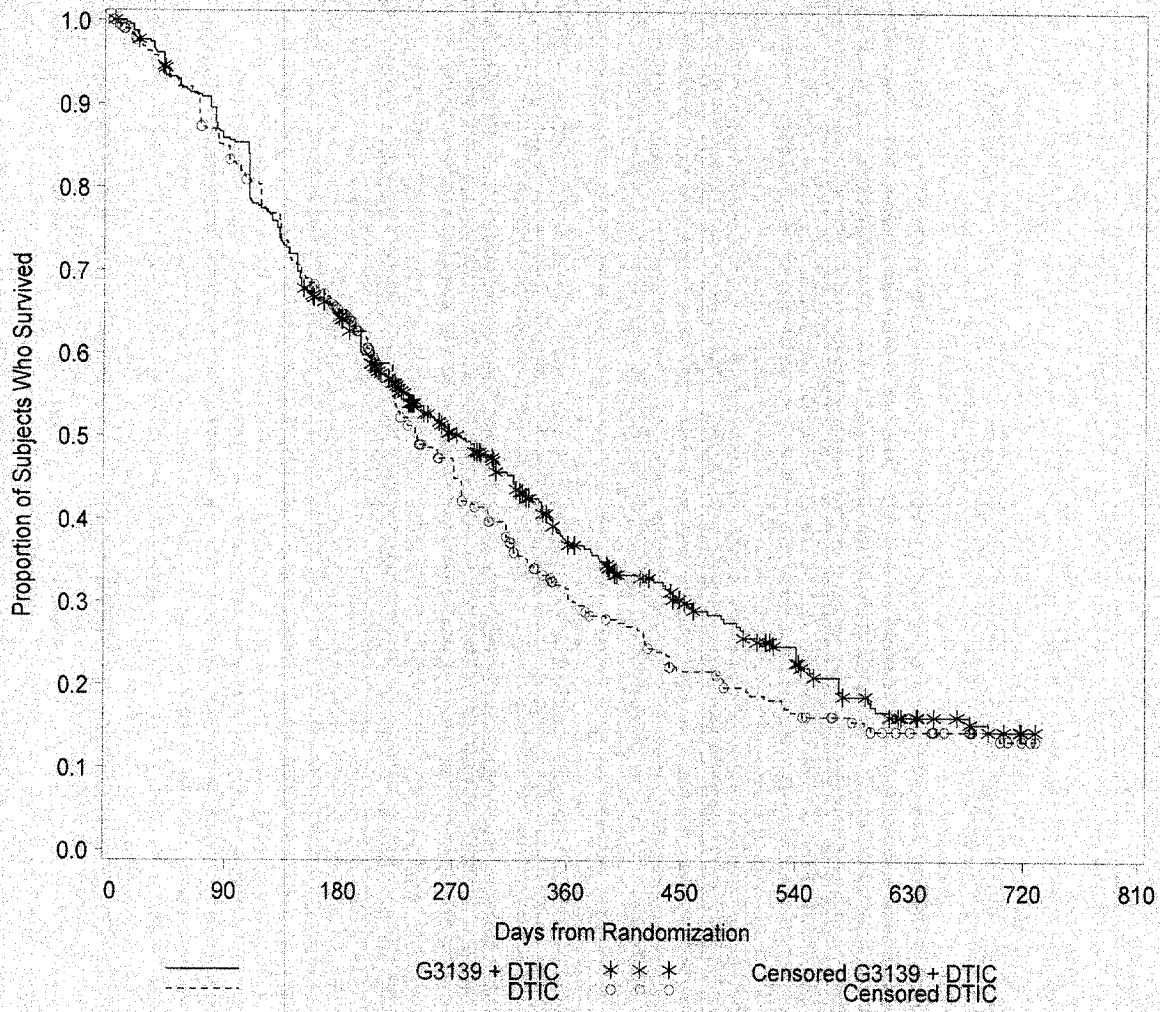


Table 10: Survival time (in days) by percentile: Intent-to-Treat Population

Percentile	G3139 plus DTIC	DTIC	Treatment difference (G3139 plus DTIC – DTIC)
25th	128	127	1
50th	274	238	36
75th	522	421	101

At the time of analysis, the median follow-up time was 7.1 months (212 days) in the Intent-to-Treat Population. The data for 236 (30.6%) patients included in the survival analysis were censored, including 189 (24.5%) patients who were in follow-up at the time of the data cut-off date (01 Aug 2003). Of the remaining 47 censored patients, 24 (3.1%) patients had reached their 2-year follow-up and 23 (3.0%) patients were lost to follow-up or withdrew consent.

8.3.2 Progression-Free Survival

As shown in Table 11 and Figure 3 for the Intent-to-Treat Population, progression-free survival time was statistically significantly longer in the G3139 plus DTIC group than in the DTIC group (median of 74 days versus 49 days), and the hazard ratio was 0.73 (log-rank test, P = 0.0003), representing a 27% reduction of risk of disease progression and a 37% improvement in progression-free survival.

Table 11: Progression-free survival analysis: Intent-to-Treat Population

Parameter	G3139 plus DTIC (N = 386)	DTIC (N = 385)	Hazard ratio[b]	Log-rank P value
Number (%)[a] of patients with disease progression or death	263 (68.1)	260 (67.5)		
Disease progression	257 (66.6)	255 (66.2)		
Death within 60 days of last lesion measurement	6 (1.6)	5 (1.3)		
Median progression-free survival, days	74	49	0.73	0.0003
95% confidence interval	62-91	48-55	0.62-0.87	

Time to progression was calculated from the date of randomization to the date progression was first documented or the patient died within 60 days of last lesion measurement.

[a] Percentages were calculated by using N, the total number of patients in the group, as the denominator.

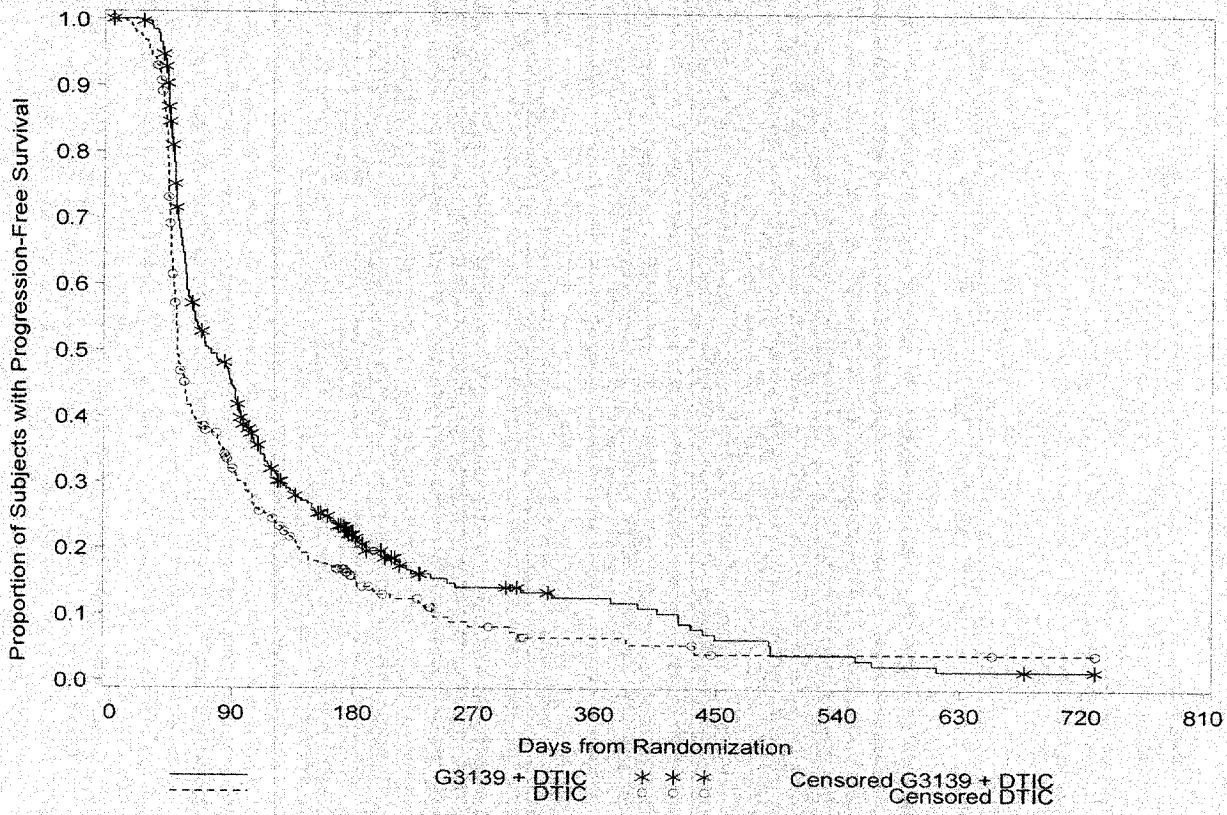
[b] Hazard ratio and 95% confidence interval from the unadjusted Cox Proportional Hazards Model

The differences between treatment groups increased with time. There was a 25-day difference at the median and a 40-day difference at the 75th percentile.

Table 12: Progression-free survival (in days) by percentile: Intent-to-Treat Population

Percentile	G3139 plus DTIC	DTIC	Treatment difference (G3139 plus DTIC – DTIC)
25th	48	42	6
50th	74	49	25
75th	158	118	40

Figure 3: Kaplan-Meier progression-free survival curves by treatment group: Intent-to-Treat Population (N = 771)



The data for 248 (32.2%) patients included in the Intent-to-Treat progression-free survival analysis were censored. Of these patients, 139 had no lesion measurements or had lesion measurements at baseline only, primarily due to rapid disease progression or death. Progression-free survival time for those patients was censored on Day 1. For the remaining 109 patients, progression-free survival time was censored at the last lesion assessment because the patient had either a response (complete or partial) or stable disease. Of these patients, 58 were in follow-up at the time of the analysis.

To examine the robustness of the results, several sensitivity analyses were performed. Results of all sensitivity analyses yielded findings supportive of the original results in progression-free survival: progression-free survival was statistically significantly longer in the G3139 plus DTIC group than in the DTIC group (median of 74 days versus 49 days; hazard ratio = 0.73; log-rank test, P = 0.0003).

Among the sensitivity analyses performed, time to progression between the 2 treatment groups was compared. The difference between progression-free survival and time to progression was limited to 11 patients who died within 60 days of their last lesion measurement. The results of the time-to-progression analysis were the same as the results of the analysis performed for progression-free survival and showed a significant difference between treatment groups in favor of the G3139 plus DTIC group (median, 74 days versus 49 days; hazard ratio = 0.73; log-rank test, P = 0.0003).

An additional sensitivity analysis was performed and included expansion of "progression" to include additional events, thereby reducing the percentage of censored data. Based on the investigator's evaluation, reasons for discontinuation of study treatment due to "progression or relapse," "intercurrent illness," "adverse drug toxicity," or "death" were considered "events" in this sensitivity analysis. Other sensitivity analyses were performed for various scenarios that might impact progression-free survival; the hazard ratio ranged from 0.73 to 0.78 for these sensitivity analyses (see Table 13). The results show consistent statistically significant improvement in favor of the G3139 plus DTIC group and support the robustness of the observation. Table 13 provides details for all sensitivity analyses performed for progression-free survival.

Table 13: Sensitivity analyses performed for time to progression and progression-free survival: Intent-to-Treat Population

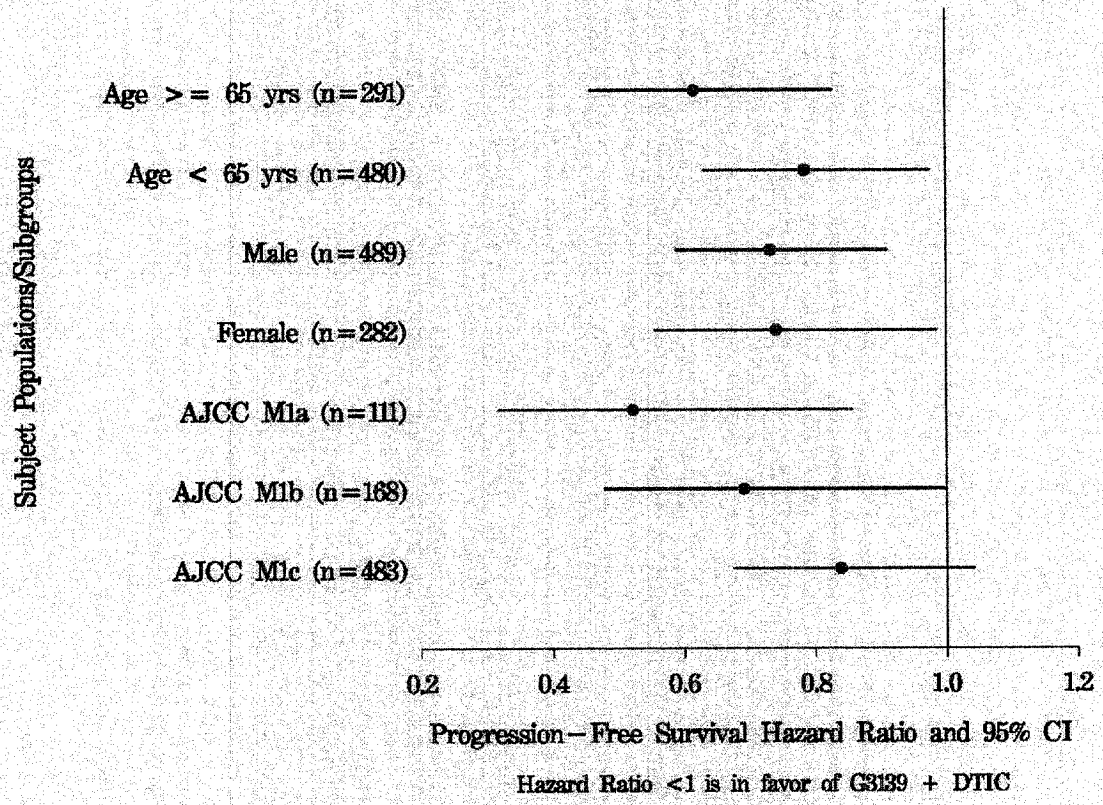
Method	Parameter	G3139 plus DTIC N = 386	DTIC N = 385	Hazard ratio[b]	Log-rank P value
Time to progression	Number (%)[a] of patients with events	257 (66.6)	255 (66.2)		
	Median progression-free survival, days	74	49	0.73	0.0003
	95% confidence interval	62-90	48-55	0.61-0.87	
Average of prior and postobservation measurements used for missing target lesion data	Number (%)[a] of patients with disease progression or death	263 (68.1)	260 (67.5)		
	Median progression-free survival, days	72	49	0.74	0.0004
	95% confidence interval	61-91	48-55	0.62-0.87	
Progression-free survival or discontinuation due to progressive disease, intercurrent illness, adverse drug toxicity, or death	Number (%)[a] of patients with events	343 (88.9)	332 (86.2)		
	Median progression-free survival, days	59	48	0.78	0.0008
	95% confidence interval	54-67	46-50	0.67-0.90	
Progression free survival censored at 60 days after last lesion measurement date	Number (%)[a] of patients with disease progression or death	263 (68.1)	260 (67.5)		
	Median progression-free survival, days	85	50	0.75	0.001
	95% confidence interval	64-93	48-56	0.64-0.90	
Earliest lesion measurement date used for a given cycle to determine date of disease progression or censoring date	Number (%)[a] of patients with disease progression or death	262 (67.9)	260 (67.5)		
	Median progression-free survival, days	69	48	0.73	0.0002
	95% confidence interval	58-89	45-50	0.61-0.86	

Method	Parameter	G3139 plus DTIC N = 386	DTIC N = 385	Hazard ratio[b]	Log-rank P value
Progression-free survival censored at end of treatment phase	Number (%)[a] of patients with disease progression or death	232 (60.1)	247 (64.2)		
	Median progression-free survival, days	69	49	0.73	0.0005
	95% confidence interval	59-87	48-55	0.61-0.87	
Nontarget lesion measurements used to determine progression of disease status when target lesion is absent or indicating stable disease or responding status	Number (%)[a] of patients with disease progression or death	289 (74.9)	287 (74.5)		
	Median progression-free survival, days	67	49	0.75	0.0006
	95% confidence interval	57-84	48-54	0.64-0.89	

[a] Percentages were calculated by using N, the total number of patients in the group, as the denominator.
[b] Hazard ratio and 95% confidence interval from unadjusted Cox Proportional Hazards Model

To evaluate the consistency of results for progression-free survival, the protocol specified that analyses would be performed on several subgroups of potential clinical relevance (eg, age, gender). Analyses of progression-free survival showed a consistent treatment effect across subgroups based on age, gender, and AJCC criteria (see Figure 4), demonstrating that the treatment effect was not driven by any specific subgroup(s): the effect was seen across the entire study population.

Figure 4: Plots of hazard ratios and 95% confidence intervals for progression-free survival: Intent-to-Treat Population



8.3.3 Antitumor Response Rate

A response was defined as either complete or partial regression of disease. Only response confirmed by a repeat measurement performed no less than 3 weeks after the response was first noted was called a confirmed response. Responses were calculated by determining computerized lesion measurements (using the information recorded on the case report form) based on RECIST, including confirmation measurements at least 3 weeks after the initial response and the presence of new lesions or unequivocal increase or decrease in existing nonmeasurable lesions.

The confirmed response rate was 11.7% in the G3139 plus DTIC group and 6.8% in the DTIC group (chi-square test, P = 0.019; see Table 14).

Table 14: Antitumor response rates during the treatment phase by treatment group: Intent-to-Treat Population

	G3139 plus DTIC (N = 386) n (%)	DTIC (N = 385) n (%)	P value
30% reduction at = 2 assessments (RECIST)			
Objective response	45 (11.7)	26 (6.8)	0.019
Complete	5[a] (1.3)	2 (0.5)	
Partial	40 (10.4)	24 (6.2)	
Stable disease	116 (30.1)	106 (27.5)	
Progressive disease	152 (39.4)	178 (46.2)	
Inevaluable[b]	73 (18.9)	75 (19.5)	
30% reduction at = 1 assessment			
Objective response	64 (16.6)	42 (10.9)	0.022

[a] Includes 2 complete responses subsequently documented by biopsy and/or PET scan in follow up
[b] Includes those patients for whom no tumor measurements were available after baseline due primarily to disease progression or death

Findings based on = 1 assessment also showed that a greater percentage of patients in the G3139 plus DTIC group than in the DTIC group achieved a complete response or a partial response: 64 (16.6%) patients in the G3139 plus DTIC group and 42 (10.9%) patients in the DTIC group (chi-square test, P = 0.022; see Table 14). It should be noted that the response rate was calculated based on the Intent-to-Treat Population and included all inevaluable patients, unlike analyses reported in other published studies.(12)

Stable disease was reported for 116 (30.1%) patients in the G3139 plus DTIC group versus 106 (27.5%) patients in the DTIC group as best response. The percentage of patients with complete response, partial response, or stable disease as the best response during treatment was 41.7% in the G3139 plus DTIC group and 34.3% in the DTIC group (chi-square test, P = 0.034).

Three patients in the G3139 plus DTIC group and 2 patients in the DTIC group had complete responses during the treatment period and did not require biopsy or PET scan confirmation. In the follow-up period, 2 complete responses determined by case report form data were further documented in the G3139 plus DTIC group:

Subject 30026 (response confirmed by biopsy) and Subject 91702 (response confirmed by PET scan).

- Subject 30026, a 61-year-old male, had subcutaneous and lymph node metastases at the time of entry in the study. This patient had complete remission of measurable disease with only a solitary skin lesion on the chest at the conclusion of Cycle 5 therapy, which was thought by the investigator to be nonmalignant. A subsequent biopsy confirmed that the lesion was benign, and the patient remains free of disease as of 31 Jan 2004. This patient remains in clinical remission 1 year following randomization.
- Subject 91702, a 55-year-old female, had extensive bilateral pelvic and inguinal lymph node and soft tissue metastases at study entry, which rendered her non-ambulatory, and demonstrated a dramatic reduction in all measurable lesions. A CT scan showed a small residua in a single site of previous pelvic node involvement, which was not amenable to biopsy, at the protocol conclusion visit. A PET scan conducted during the follow-up period showed absence of any viable signal, consistent with the clinical presentation of complete response. As of 31 Jan 2004, this patient remains in complete clinical remission approximately 3 years following randomization.

Neither of these 2 patients received any surgical, chemotherapeutic, or biologic intervention after completing treatment with G3139 plus DTIC.

Responses to treatment with G3139 plus DTIC were seen across subgroups based on age, gender, and AJCC criteria (see Table 15), demonstrating that the treatment effect was not driven by any specific subgroup(s): the effect was seen across the entire study population.

Table 15: Response rates by subgroup: Intent-to-Treat Population

		% of responding patients[a]	
		G3139 plus DTIC	DTIC
Age group	< 65 years (n = 480)	13.8	6.6
	≥ 65 years (n = 291)	8.2	6.9
Gender	Male (n = 489)	11.4	5.1
	Female (n = 282)	12.0	9.8
AJCC LDH – disease site distribution	M1a (n = 111)	21.3	12.0
	M1b (n = 168)	17.2	12.0
	M1c (n = 483)	7.1	4.3

AJCC = American Joint Committee on Cancer; LDH = lactate dehydrogenase

[a] Percentages were calculated by using the total number of patients in the subgroup as the denominator.

8.3.4 Duration of Antitumor Response

The duration of antitumor response was calculated from the date the response was first documented until disease progression or the date of the last lesion measurement.

Among the 71 responding subjects included in the analysis of duration of response at the data cutoff date (ie, 45 in the G3139 plus DTIC group and 26 in the DTIC group), the median duration of antitumor response was similar between the 2 treatment groups (126 days for the G3139 plus DTIC group and 128 days for the DTIC group; see Table 16). Duration of response at the 75th percentile differed in the 2 treatment groups by more than 3 months (238 days in the G3139 plus DTIC group versus 142 days in the DTIC group).

Table 16: Duration of antitumor response in responding patients by treatment group: Intent-to-Treat Population

Days	G3139 plus DTIC (N = 386)	DTIC (N = 385)
n[a]	45	26
Mean (SD)	175.7 (136.0)	153.5 (99.2)
Median	126	128
25th percentile	86	84
75th percentile	238	142
Minimum, maximum	41, 565	42, 390

SD = standard deviation

[a] Calculated only for those patients who responded (ie, those who had a complete response or a partial response) by RECIST criteria

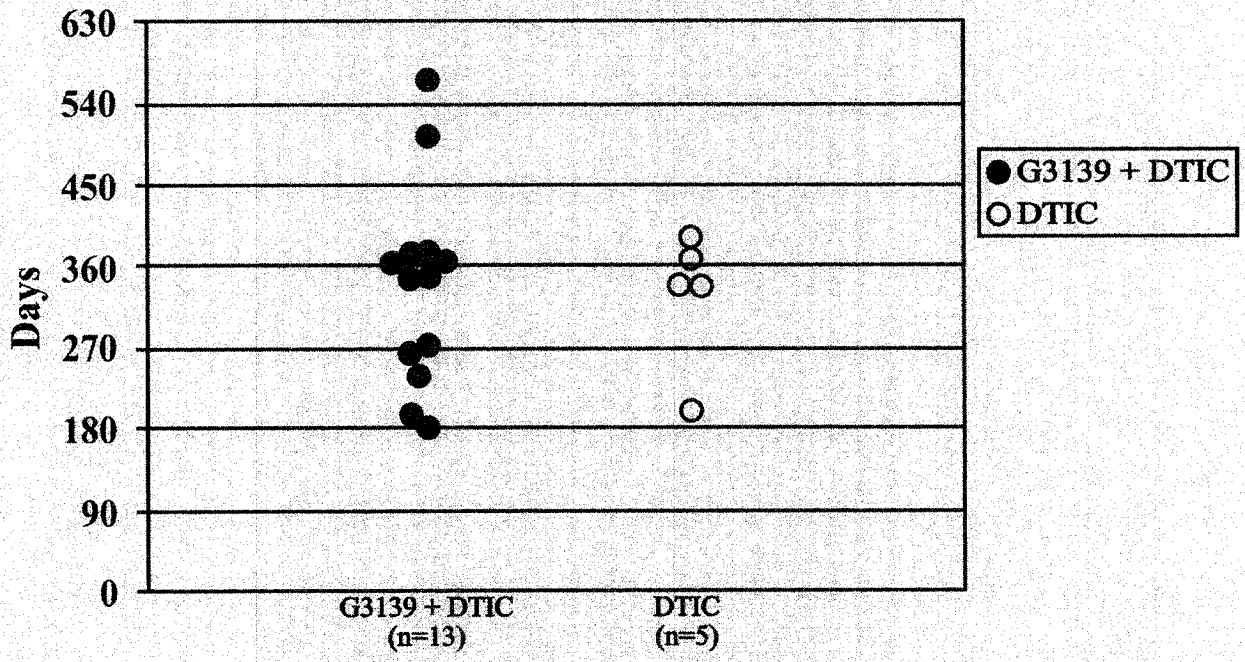
8.3.5 Durable Response Rate

Durable response was defined as a complete or partial response lasting ≥ 6 months from the date the response was first documented; no type of anticancer therapy was to be administered during the 4 months after the response was initially determined.

A total of 13 (3.4%) patients in the G3139 plus DTIC group and 5 (1.3%) patients in the DTIC group had a durable response (P = 0.057; see Figure 5).

Although not included as a durable responder, 1 patient with multiple liver metastases at baseline was randomized to receive G3139 plus DTIC in July 2001 and had a complete remission by the end of Cycle 8 treatment in January 2002. Despite continued complete regression of liver metastases, the subject required excison of new subcutaneous lesions in March 2002 and has been maintained in surgical remission without receiving further systemic treatment for melanoma as of 31 Jan 2004.

Figure 5: Durable responses: Intent-to-Treat Population



8.3.6 ECOG Performance Status

Shifts from baseline in ECOG Performance Status to a less favorable category were apparent in both treatment groups overall; there were no clinically meaningful differences between treatment groups.

8.4 Efficacy Conclusions

The proposed mechanism of Bcl-2 downregulation suggested that the addition of G3139 would enhance the activity of DTIC in patients with malignant melanoma. Although the primary efficacy endpoint of overall survival for the Intent-to-Treat Population was not statistically significant by the time of study unblinding, the results favored the G3139 plus DTIC group. All secondary endpoints significantly supported the response benefit achievable with G3139 plus DTIC. At the time of analysis, the median follow-up time was only 7.1 months.

Progression-free survival time was statistically significantly longer in the G3139 plus DTIC group than in the DTIC group (median of 74 days versus 49 days; hazard ratio = 0.73; log-rank test, P = 0.0003). The results of multiple sensitivity analyses of progression-free survival, including time to progression, which evaluated a variety of scenarios, consistently favored the G3139 plus DTIC group, indicating that this finding was robust. Analyses of progression-free survival in a number of prespecified subgroups (including those based on baseline LDH-disease distribution [ie, AJCC classification], age, gender) provided consistent results showing longer progression-free survival in the G3139 plus DTIC group.

The confirmed antitumor response rate for G3139 plus DTIC was 11.7% versus 6.8% for DTIC (odds ratio = 1.82; P = 0.019). This response rate for single-agent DTIC was consistent with that reported in a recent study that utilized RECIST measurement criteria, in which a response rate of 7% has been reported.(10) The low response rate probably more accurately reflects single-agent DTIC activity than reported in previous studies. The observed mean duration of response was greater in the G3139 plus DTIC group than in the DTIC group, and more patients in the G3139 plus DTIC group had a durable response (≥ 180 days) than in the DTIC group (13 and 5 patients, respectively).

Overall, the G3139 plus DTIC regimen provided a 27% reduction of risk of disease progression (ie, a 37% improvement in progression-free survival time) and an 82% improvement in response rate.

The robust and statistically significant benefit shown for progression-free survival and confirmed antitumor response rate in the Intent-to-Treat Population, as well as the consistency of efficacy results across endpoints and subgroups provides compelling evidence of the benefit of G3139 plus DTIC when compared to DTIC

alone. This treatment regimen is a promising alternative to existing therapies for patients with advanced melanoma.

9. SAFETY RESULTS

A total of 1052 patients were treated in 14 completed studies (including the single randomized study, Protocol GM301, as well as 13 nonrandomized studies) reported in the NDA, as follows:

- 692 patients received G3139 only or G3139 in combination with chemotherapy (371 [53.6%] of these patients were treated in the randomized, Phase III study in advanced malignant melanoma [Protocol GM301])
- 360 patients received a comparative agent (Protocol GM301, DTIC only)

These 14 completed studies were conducted in patients with advanced malignant melanoma, in patients with other solid tumors (breast cancer, prostate cancer, and other cancers), and in patients with various hematologic malignancies (chronic lymphocytic leukemia and lymphoma).

In addition, a total of 555 patients were treated in ongoing studies reported in the NDA, including:

- 307 patients who received G3139 only or G3139 in combination with chemotherapy
- 248 patients who received chemotherapy only

9.1 Randomized Phase III Study in Advanced Malignant Melanoma

9.1.1 Safety Assessments

Safety assessments included adverse events and changes in clinical laboratory findings, vital signs, and physical examination findings. Adverse events were categorized based on the Medical Dictionary for Regulatory Activities (MedDRA, Version 4.0). The severity of adverse events and laboratory changes was assessed according to the National Cancer Institute Common Toxicity Criteria (Version 2.0). A Data Safety Monitoring Board reviewed safety data periodically to alert the Sponsor to possible safety concerns for patients in the study.

Some differences between treatment groups in the incidence of adverse events were anticipated because of the 5-day continuous intravenous infusion required for G3139 therapy. In particular, patients in the G3139 plus DTIC group had more opportunities for observation due to the need for line placement and maintenance and were at increased risk of developing events associated with the central line.

Additionally, the investigator and study site personnel were aware of the treatment group to which a patient had been randomized and may have been more likely to report adverse events for the investigational treatment.

Treatment-emergent adverse events were defined as adverse events with an onset date on or after the start date of the first study drug infusion and within 30 days of the last study drug infusion. Events that were present at baseline and worsened during the treatment phase of the study also were considered treatment-emergent adverse events.

Treatment-related treatment-emergent adverse events included those treatment-emergent adverse events considered by the investigator to be probably or definitely related and possibly related, as well as events for which this information was not recorded. When assessing the relationship of an adverse event to study drug, the investigator could assign relationship to G3139 only, to DTIC only, or to both G3139 and DTIC separately for the specific event. In the event that relationship was assigned to G3139 as well as DTIC, then the event was counted as being related to the G3139/DTIC combination. Among patients in the G3139 plus DTIC group, an event was considered treatment related regardless of whether the investigator considered the event to be related to G3139 only, DTIC only, or the G3139/DTIC combination.

A serious adverse event was defined as any adverse event occurring at any dose that resulted in any of the following outcomes: death; a life-threatening adverse drug experience (defined as any adverse drug experience that placed the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred, ie, not including a reaction that, had it occurred in a more severe form, might have caused death); inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability (defined as a substantial disruption of a person's ability to conduct normal life functions)/incapacity; congenital anomaly/birth defect; or a significant medical event that may not have resulted in death, been considered life-threatening, or required hospitalization. An event also could be reported as a serious adverse drug experience when, based upon appropriate medical judgment, the event required medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.1.2 Overview of Treatment-Emergent Adverse Events

Most patients in both treatment groups had at least 1 treatment-emergent adverse event (see Table 17). This was not unexpected given the advanced disease in this patient population.

A total of 69 (18.6%) subjects in the G3139 plus DTIC group and 39 (10.8%) of subjects in the DTIC group discontinued protocol therapy due to at least 1

treatment-emergent adverse event. In the G3139 plus DTIC group, 42 (60.9%) of the 69 patients had adverse events clearly associated with or reported as disease progression that led to discontinuation. In the DTIC group, 30 (76.9%) of the 39 patients had adverse events clearly associated with or reported as disease progression that led to discontinuation. Additionally, 5 patients in the G3139 plus DTIC group had injection site infections or catheter-related thromboses that were not fatal and resulted in discontinuation. The remaining subjects in both groups had diverse adverse events that occurred in 1 or 2 patients each and resulted in discontinuation.

Notably, the percentage of patients who discontinued protocol therapy due to a treatment-related treatment-emergent adverse event was low in both groups: G3139 plus DTIC group, 6.2% and DTIC group, 2.2%.

The percentage of patients who had an adverse event with an outcome of death (regardless of relationship to treatment) was low and similar in both treatment groups: G3139 plus DTIC group, 8.6% and DTIC group, 9.2%.

Table 17: Overview of treatment-emergent adverse events by treatment group: Safety Population

	All treatment-emergent		Treatment-related treatment-emergent	
Treatment-emergent adverse event	**G3139 plus DTIC (N = 371) n (%)**	**DTIC (N = 360) n (%)**	**G3139 plus DTIC (N = 371) n (%)**	**DTIC (N = 360) n (%)**
Any	365 (98.4)	342 (95.0)	347 (93.5)	287 (79.7)
Grade 3 or 4	249 (67.1)	154 (42.8)	182 (49.1)	80 (22.2)
Serious	149 (40.2)	97 (26.9)	65 (17.5)	27 (7.5)
Leading to discontinuation	69 (18.6)	39 (10.8)	23 (6.2)	8 (2.2)
With outcome of death[a]	32 (8.6)	33 (9.2)	3 (0.8)	2 (0.6)
Death = 30 days from last dose of study drug	29 (7.8)	25 (6.9)	3 (0.8)	1 (0.3)

[a] Deaths occurring = 30 days and > 30 days from last dose of study drug are included.

It is noteworthy that patients in the G3139 plus DTIC group had more opportunities for observation and intervention due to the need for line placement

and maintenance during the 5-day Genasense infusion than did patients in the DTIC group who received a 60-minute infusion of DTIC in each 21-day cycle.

9.1.3 Treatment-Emergent Adverse Events

More treatment-emergent adverse events were seen with the combination of G3139 and DTIC than with DTIC alone. However, the types of events reported were similar in the 2 treatment groups (see Table 18). In large part, the events observed in both groups were consistent with the known side-effect profile of single-agent DTIC: myelosuppression, especially neutropenia and thrombocytopenia, as well as nausea and vomiting, and flu-like symptoms. Notably, neutropenia was associated with infection in only a small number of patients in each treatment group. In particular, 12 patients in the G3139 plus DTIC group and 5 patients in the DTIC group had a Grade 2, 3, or 4 infection in the presence of Grade 4 neutropenia. With respect to thrombocytopenia, there was a greater incidence of all grades of bleeding events in the G3139 plus DTIC group than in the DTIC group. However, this was primarily accounted for by more frequent Grade 1 or Grade 2 epistaxis and hematuria in the G3139 plus DTIC group than in the DTIC group.

The types of treatment-emergent adverse events considered related to study treatment were similar in the 2 treatment groups. The 2 treatment-emergent adverse events or types of events most clearly associated with G3139 were pyrexia and catheter-related events (ie, infection, thrombosis, and pump-related events); the latter were due to the requirement for an indwelling central catheter for the 5-day continuous IV administration of G3139.

Grade 3 and Grade 4 Treatment-Emergent Adverse Events

A total of 249 (67.1%) patients in the G3139 plus DTIC group and 154 (42.8%) patients in the DTIC group had at least 1 Grade 3 or Grade 4 treatment-emergent adverse event (see Table 17). As shown in Table 18, neutropenia and thrombocytopenia were the most frequently reported Grade 3 or Grade 4 treatment-emergent adverse events in both treatment groups. The percentages of patients with Grade 3 or Grade 4 neutropenia and Grade 3 or Grade 4 thrombocytopenia were greater in the G3139 plus DTIC group than in the DTIC group. Most serious infections that occurred in the G3139 plus DTIC group were not neutropenic in nature; injection site infections due to the central catheter were the most commonly reported type of serious infection in the G3139 plus DTIC group.

Despite the relatively greater incidence of Grade 3 or Grade 4 thrombocytopenia in the G3139 plus DTIC group, the incidence of Grade 3 or Grade 4 bleeding events was greater in the DTIC group than in the G3139 plus DTIC group,

reflecting more frequent and serious gastrointestinal bleeding events (ie, gastrointestinal hemorrhage, hematemesis, and melena).

In an attempt to more clearly delineate the toxicities related to G3139 administration, Grade 3 and Grade 4 events that occurred during the first 5-day infusion of G3139 prior to administration of DTIC were assessed. During this period, 34 (9.2%) subjects had at least 1 Grade 3 or Grade 4 treatment-emergent adverse event. The most frequently occurring Grade 3 or 4 event was pyrexia (10 [2.7%] patients). Other Grade 3 or Grade 4 events that occurred in > 1 patient in the G3139 plus DTIC group prior to DTIC dosing included headache (3 [0.8%] patients), thrombocytopenia (3 [0.8%] patients), anemia (2 [0.5%] patients), fatigue (2 [0.5%] patients), accidental overdose (2 [0.5%] patients), and night sweats (2 [0.5%] patients).

Serious Treatment-Emergent Adverse Events

A total of 149 (40.2%) patients in the G3139 plus DTIC group and 97 (26.9%) patients in the DTIC group had at least 1 serious treatment-emergent adverse event (see Table 17). As shown in Table 18, serious treatment-emergent adverse events that occurred in > 1% more subjects in the G3139 plus DTIC group than in the DTIC group included pyrexia, thrombocytopenia, nausea, vomiting, and neutropenia. Notably, pyrexia was the only serious adverse event that occurred in > 5% of patients in the G3139 plus DTIC group.

A detailed review of certain serious treatment-emergent adverse events was performed and events were categorized based on clinical findings. Review of these events usually confirmed the presence of multiple underlying factors related to metastatic melanoma that contributed to the occurrence and outcome of a majority of these events. Several of these serious treatment-emergent adverse events are briefly discussed:

- The incidence of serious treatment-emergent adverse events associated with bleeding was lower in the G3139 plus DTIC group (0.5%) than in the DTIC group (2.8%). This is noteworthy given the increased incidence of thrombocytopenia and all grades of bleeding events in the G3139 plus DTIC group compared with findings in the DTIC group.
- Most serious infections that occurred in the G3139 plus DTIC group were not neutropenic in nature; injection site infections due to the central catheter were the most commonly reported type of serious infection in the G3139 plus DTIC group.
- Catheter-related complications occurred at an incidence consistent with that reported in the literature,(39) and did not impede patients from receiving protocol therapy. A total of 8 (2.2%) patients in the G3139 plus DTIC group

had a serious thrombotic event related to central venous catheters and 15 (4.0%) patients had a serious injection site infection.

- Misprogramming of the infusion pump with resulting overdose occurred in 2 (0.5%) patients, both of whom received the entire Cycle 1 dose of G3139 in 5 hours instead of 5 days:
  - In 1 patient, adverse events reported in the 5-day period following the overdose of G3139 included Grade 1 tachycardia, hypomagnesemia, rash, and hematuria; Grade 2 vomiting, abdominal pain, fatigue, and pyrexia; and Grade 3 nausea and thrombocytopenia. All of these events resolved. This patient subsequently completed 4 cycles of protocol therapy and then discontinued from the study due to progressive disease.
  - In the remaining patient, adverse events reported in the 5-day period following the overdose of G3139 included Grade 1 hypokalemia, nausea, decreased blood magnesium, facial edema, tumor pain, and anemia; Grade 2 pyrexia, anemia, malaise, rigors, and nausea; and Grade 3 hypophosphatemia. All of these events except the tumor pain resolved (tumor pain continued). This patient subsequently completed 7 cycles of protocol therapy and had a confirmed partial response.

Table 18: Treatment-emergent adverse events that occurred in ≥ 20% of patients in either treatment group by preferred term: Safety Population

	All grades n (%)[b]		Grade 3 or 4[a] n (%)[b]		Serious[a] n (%)[b]	
Treatment-emergent adverse event	**G3139 plus DTIC (N = 371)**	**DTIC (N = 360)**	**G3139 plus DTIC (N = 371)**	**DTIC (N = 360)**	**G3139 plus DTIC (N = 371)**	**DTIC (N = 360)**
Nausea	231 (62.3)	169 (46.9)	26 (7.0)	9 (2.5)	14 (3.8)	5 (1.4)
Pyrexia	197 (53.1)	63 (17.5)	16 (4.3)	7 (1.9)	22 (5.9)	11 (3.1)
Fatigue	170 (45.8)	142 (39.4)	17 (4.6)	11 (3.1)	1 (0.3)	3 (0.8)
Vomiting	139 (37.5)	75 (20.8)	17 (4.6)	7 (1.9)	13 (3.5)	6 (1.7)
Anorexia	114 (30.7)	56 (15.6)	9 (2.4)	1 (0.3)	4 (1.1)	1 (0.3)
Thrombocytopenia	107 (28.8)	40 (11.1)	58 (15.6)	23 (6.4)	15 (4.0)	4 (1.1)
Constipation	103 (27.8)	93 (25.8)	8 (2.2)	3 (0.8)	5 (1.3)	1 (0.3)
Neutropenia	103 (27.8)	56 (15.6)	79 (21.3)	45 (12.5)	8 (2.2)	1 (0.3)
Diarrhea	100 (27.0)	63 (17.5)	6 (1.6)	3 (0.8)	1 (0.3)	2 (0.6)
Headache	97 (26.1)	47 (13.1)	10 (2.7)	1 (0.3)	3 (0.8)	0 (0.0)
Anemia	86 (23.2)	61 (16.9)	26 (7.0)	17 (4.7)	9 (2.4)	8 (2.2)
Rigors	76 (20.5)	16 (4.4)	3 (0.8)	0 (0.0)	2 (0.5)	0 (0.0)

n = the number of patients with at least 1 occurrence of the event in the specified category

[a] Shown only for those treatment-emergent adverse events that occurred in ≥ 20% of subjects in either treatment group

[b] Percentages were calculated using N, the total number of subjects in the group, as the denominator.

Discontinuations due to Treatment-Emergent Adverse Events

A total of 69 (18.6%) patients in the G3139 plus DTIC group and 39 (10.8%) patients in the DTIC group discontinued protocol therapy due to a treatment-emergent adverse event (see Table 17), including 15.6% of patients in the G3139 plus DTIC group and 9.2% of patients in the DTIC group who discontinued due to a Grade 3 or Grade 4 event. In both treatment groups, disease progression was the most frequently reported Grade 3 or Grade 4 treatment-emergent adverse event that resulted in discontinuation of protocol therapy (see Table 19).

Table 19: Grade 3 and Grade 4 adverse events resulting in discontinuation: Safety Population

Preferred term[a,b]	G3139 plus DTIC (N = 371) n (%)[c]	DTIC (N = 360) n (%)[c]
Disease progression	10 (2.7)	5 (1.4)
Neutropenia	5 (1.3)	1 (0.3)
Metastases to brain	4 (1.1)	2 (0.6)
Thrombocytopenia	4 (1.1)	0 (0.0)
Cardiorespiratory arrest	3 (0.8)	1 (0.3)
Injection site infection	3 (0.8)	0 (0.0)
Sepsis	2 (0.5)	2 (0.6)
Abdominal pain	2 (0.5)	1 (0.3)
Pneumonia	2 (0.5)	1 (0.3)
Pulmonary embolism	2 (0.5)	1 (0.3)
Cardiac arrest	2 (0.5)	0 (0.0)
Convulsions	2 (0.5)	0 (0.0)
Hyperglycemia	2 (0.5)	0 (0.0)
Hypotension	2 (0.5)	0 (0.0)
Leukopenia	2 (0.5)	0 (0.0)
Multiorgan failure	2 (0.5)	0 (0.0)
Muscle weakness	2 (0.5)	0 (0.0)
Renal failure	2 (0.5)	0 (0.0)
Deep venous thrombosis	1 (0.3)	2 (0.6)
General physical health deterioration	1 (0.3)	2 (0.6)
Pain	1 (0.3)	1 (0.3)
Pyrexia	1 (0.3)	1 (0.3)
Small intestinal obstruction	1 (0.3)	1 (0.3)

Table continued on next page

Preferred term[a,b]	G3139 plus DTIC (N = 371) n (%)[c]	DTIC (N = 360) n (%)[c]
Akathisia	1 (0.3)	0 (0.0)
Alanine aminotransferase increased	1 (0.3)	0 (0.0)
Anorexia	1 (0.3)	0 (0.0)
Ascites	1 (0.3)	0 (0.0)
Aspartate aminotransferase increased	1 (0.3)	0 (0.0)
Atrial fibrillation	1 (0.3)	0 (0.0)
Bacteremia	1 (0.3)	0 (0.0)
Cerebral hemorrhage	1 (0.3)	0 (0.0)
Depression	1 (0.3)	0 (0.0)
Difficulty in walking	1 (0.3)	0 (0.0)
Febrile neutropenia	1 (0.3)	0 (0.0)
Hepatic failure	1 (0.3)	0 (0.0)
Hypoglycaemia	1 (0.3)	0 (0.0)
Infection	1 (0.3)	0 (0.0)
Loss of consciousness	1 (0.3)	0 (0.0)
Metastases to spine	1 (0.3)	0 (0.0)
Musculoskeletal pain	1 (0.3)	0 (0.0)
Myalgia	1 (0.3)	0 (0.0)
Neutropenic sepsis	1 (0.3)	0 (0.0)
Edema lower limb	1 (0.3)	0 (0.0)
Edema	1 (0.3)	0 (0.0)
Pleuritic pain	1 (0.3)	0 (0.0)
Respiratory distress	1 (0.3)	0 (0.0)
Respiratory failure (excl neonatal)	1 (0.3)	0 (0.0)
Spinal cord compression	1 (0.3)	0 (0.0)
Subclavian vein thrombosis	1 (0.3)	0 (0.0)
Thrombosis	1 (0.3)	0 (0.0)
Dyspnea	0 (0.0)	3 (0.8)
Gastrointestinal hemorrhage	0 (0.0)	3 (0.8)
Fatigue	0 (0.0)	2 (0.6)
Hypoxia	0 (0.0)	2 (0.6)
Nausea	0 (0.0)	2 (0.6)
Weakness	0 (0.0)	2 (0.6)
Abdominal distension	0 (0.0)	1 (0.3)

Table continued on next page

Preferred term[a,b]	G3139 plus DTIC (N = 371) n (%)[c]	DTIC (N = 360) n (%)[c]
Cardiac failure congestive	0 (0.0)	1 (0.3)
Cardiac failure	0 (0.0)	1 (0.3)
Coma	0 (0.0)	1 (0.3)
Hemothorax	0 (0.0)	1 (0.3)
Intestinal perforation	0 (0.0)	1 (0.3)
Jaundice	0 (0.0)	1 (0.3)
Malaise	0 (0.0)	1 (0.3)
Metastases	0 (0.0)	1 (0.3)
Myocardial infarction	0 (0.0)	1 (0.3)
Obstructive airways disorder	0 (0.0)	1 (0.3)
Pain in limb	0 (0.0)	1 (0.3)
Pancytopenia	0 (0.0)	1 (0.3)
Paraparesis	0 (0.0)	1 (0.3)
Tachycardia	0 (0.0)	1 (0.3)
Tumor pain	0 (0.0)	1 (0.3)
Urinary retention	0 (0.0)	1 (0.3)
Vomiting	0 (0.0)	1 (0.3)

n = the number of patients with at least 1 occurrence of the event in the specified category
excl = excluding
[a] Preferred terms are presented in descending order of incidence based on findings in the G3139 plus DTIC group.
[b] If a patient had more than 1 occurrence of the same adverse event, the patient was counted in the category of greatest known intensity for that event.
[c] Percentages were calculated by using N, the total number of patients in the group, as the denominator.

Deaths

In the G3139 plus DTIC group, 29 (7.8%) of the 371 patients treated died during treatment or within 30 days of the last dose of protocol therapy (see Table 17). Death more than 30 days after the last dose of study drug was reported for an additional 229 patients (61.7%). The majority of these deaths were due to malignant melanoma.

In the DTIC group, 25 (6.9%) of the 360 patients treated died during treatment or within 30 days of the last dose of protocol therapy. Death more than 30 days after the last dose of study drug was reported for an additional 230 patients (63.9%). The majority of these deaths were due to malignant melanoma.

9.1.4 Other Safety Evaluations

Shifts in laboratory parameters to Grade 3 or Grade 4 generally were transient (Table 20). Hematology assessments showed an increase in the incidence of Grade 3 or Grade 4 neutropenia and thrombocytopenia when G3139 was added to DTIC. However, the majority of patients recovered fully. The addition of G3139 to DTIC had little impact on hepatic and renal function. Most changes were transient, with patients recovering to Grade 0 or Grade 1 by the end of the treatment phase of the study.

Table 20: Shifts in laboratory parameters: Safety Population

	G3139 plus DTIC % of patients			DTIC % of patients		
Laboratory parameter	**To Grade 3-4 post baseline**	**Recovery: Grade 3 or 4 to Grade 0 or 1**	**(Difference)**	**To Grade 3-4**	**Recovery Grade 3 or 4 to Grade 0 or 1**	**(Difference)**
Absolute neutrophil count	29.5	23.0	6.5	14.4	9.2	5.2
Platelet count	19.2	13.6	5.6	7.4	5.1	2.3
Hemoglobin	4.4	0.8	3.6	4.6	0.6	4.0
Alkaline phosphatase	2.2	0.3	1.9	2.0	0.0	2.0
AST	3.9	1.7	2.2	0.9	0.0	0.9
ALT	4.8	2.7	2.1	0.6	0.3	0.3
Bilirubin	1.1	0.3	0.8	0.3	0.0	0.3
Creatinine	0.6	0.0	0.6	0.0	0.0	0.0
BUN	0.3	0.0	0.3	0.0	0.0	0.0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen

9.2 Other Completed Studies

The remaining completed studies were nonrandomized studies conducted in patients with solid tumors and various hematologic malignancies. In these studies, G3139 was well tolerated when administered as monotherapy or when administered with chemotherapies as part of a combination treatment. The type and severity of adverse events among patients receiving combination therapy was determined by the specific chemotherapeutic agents used. No unexpected or new toxicity was identified.

9.3 120-Day Safety Update

The 120-Day Safety Update included data for the remaining 10 patients in Protocol GM301 who completed treatment with G3139 plus DTIC subsequent to the NDA cutoff date and data for an additional 118 patients treated with G3139 alone or in combination with chemotherapy in ongoing studies.

Review of these data demonstrates that safety findings are consistent with those reported in the NDA. No new or unique adverse event was observed.

9.4 Overall Safety Conclusions

The safety of G3139 has been evaluated in approximately 1000 patients who received G3139 only or G3139 in combination with chemotherapy in completed and ongoing clinical studies. A total of 692 patients received G3139 in completed studies, including 371 patients randomized to receive G3139 plus DTIC in the controlled completed study in advanced malignant melanoma (Protocol GM301). As of 30 Nov 2003, a total of 425 patients had received G3139 in ongoing studies.

Analyses of safety data for G3139 support the following conclusions:

- Adding G3139 to full-dose chemotherapy is practical and safe for use in the outpatient setting. Full doses of chemotherapy can be administered on time and without unexpected toxicity.
- The types of adverse events seen were usually those associated with chemotherapy, such as cytopenias, nausea, vomiting, etc. No new or unique adverse event was observed.
- Two distinct adverse events were apparent with the G3139 plus DTIC regimen — pyrexia and catheter-related events. In general, fever occurred most frequently during the first 3 days of the treatment cycle in the G3139 plus DTIC group. Since G3139 administration required an indwelling central catheter for continuous intravenous infusion, the incidence of complications

related to central venous catheters was within expected limits and did not impede patients from receiving full protocol therapy.

- The incidence of neutropenia and thrombocytopenia was increased when G3139 was added to DTIC. Mild neutropenia and thrombocytopenia have been demonstrated in single-agent studies with G3139 in a variety of tumors. However, these laboratory changes were, for the most part, transient, and the majority of patients recovered fully. Moreover, neutropenia was associated with infection in only a small number of patients, with serious infections in the G3139 plus DTIC group most frequently related to the indwelling catheter. Thrombocytopenia was not associated with an increase in Grade 3 or Grade 4 bleeding events in patients treated with G3139 plus DTIC.
- There was a low rate of discontinuation due to a treatment-related safety finding, and most events were tolerable and self-limiting in nature. The percentage of patients who died while on protocol therapy was similar and low in both treatment groups.
- Most of the very common adverse events can be effectively managed with specific concomitant medications, such as antipyretics, colony stimulating factors and antiemetics/antinauseants.
- On the whole, treatment with G3139 was well tolerated for use in the outpatient setting.

10. CONCLUSIONS

The role of Bcl-2 in the survival of cancer cells has been well documented. In particular, this protein prevents or substantially retards the onset of cell death, thus enabling cancer cells to withstand the cytotoxic effects of chemotherapy. Antisense represents a pharmacologic approach to selectively reduce the production of specific proteins. Genasense, a novel Bcl-2 antisense agent, may function as a chemosensitizing agent and thus enable conventional anticancer drugs to function more effectively.

More than 90% of patients with advanced melanoma have been reported to express Bcl-2.(20) Thus, Genasense was administered in combination with a conventional cytotoxic agent (DTIC) in a Phase I-II study in patients with Stage IV melanoma.(21) Promising results were achieved based on both response and survival.(21) Accordingly, a randomized Phase III study (Protocol GM301) was conducted to assess the efficacy of Genasense in combination with DTIC in this patient population. A 5-day continuous IV infusion of G3139 7 mg/kg/day plus DTIC 1000 mg/m^2 was compared with DTIC 1000 mg/m^2 alone. A total of 771 patients were randomized at 139 study sites in 9 countries, and patients were stratified prior to randomization based on documented prognostic factors. Notably, this study was the largest randomized, controlled study conducted to date in patients with malignant melanoma.

The primary endpoint of overall survival was not achieved in this study. However, the results of the primary analysis clearly favored the Genasense plus DTIC treatment. In addition, Genasense in combination with DTIC provided highly significant benefit based on progression-free survival, including time to progression, and confirmed response rate: a 27% reduction of risk of disease progression (ie, a 37% improvement in progression-free survival time) and an 82% improvement in response rate were documented. Results of multiple sensitivity analyses of progression-free survival, including time to progression, were robust and showed a consistent difference between treatment groups that favored the Genasense plus DTIC regimen. Progression-free survival time was significantly longer in the Genasense plus DTIC group than in the DTIC group for patients with lung and non-visceral disease, as well as for patients with liver metastases. Analyses of progression-free survival in a number of additional subgroups (age, gender, US and non-US study sites, prior immunotherapy, and time since initial diagnosis) yielded similarly favorable and significant results. Objective responses were documented among patients with metastatic melanoma of the skin, subcutaneous tissue, lung, and liver. More patients treated with Genasense plus DTIC than with DTIC alone had a durable response (13 and 5 patients, respectively).

Pyrexia and catheter-related events were associated with administration of Genasense. In addition, Genasense increased the incidence of adverse events commonly reported with administration of DTIC, particularly neutropenia and thrombocytopenia. Nevertheless, treatment with the conventional dose of DTIC was maintained throughout Genasense administration, most adverse events were tolerable and self-limiting in nature, and the rate of discontinuation due to a treatment-related safety finding was low (6.2%). Notably, the percentage of patients who received Genasense plus DTIC and had an adverse event with an outcome of death was low (8.6%) and similar to that reported for patients treated with DTIC alone (9.2%).

Given the pressing need for improved therapy for patients with advanced malignant melanoma, Genasense 7 mg/kg/day administered by continuous intravenous infusion for 5 days in combination with DTIC 1000 mg/m^2 is a promising alternative as a first-line treatment for this patient population.

- The strong internal consistency of efficacy results across endpoints and subgroups provides compelling evidence of the benefit of G3139 plus DTIC when compared to DTIC alone.
- The adverse events observed with the Genasense plus DTIC regimen are predictable and clearly manageable in a routine practice setting by a qualified oncologist.

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