VOLUME 26 · NUMBER 30 · OCTOBER 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Lenalidomide Monotherapy in Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma

*Peter H. Wiernik, Izidore S. Lossos, Joseph M. Tuscano, Glen Justice, Julie M. Vose, Craig E. Cole, Wendy Lam, Kyle McBride, Kenton Wride, Dennis Pietronigro, Kenichi Takeshita, Annette Ervin-Haynes, Jerome B. Zeldis, and Thomas M. Habermann*

From Our Lady of Mercy Cancer Center, New York Medical College, Bronx, NY; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; University of California, Davis Cancer Center, Sacramento; Pacific Coast Hematology/Oncology Medical Group, Fountain Valley, CA; University of Nebraska, Nebraska Medical Center, Omaha, NE; Gundersen Clinic, La Crosse, WI; BC Community Oncology Trialists, Burnaby, British Columbia, Canada; Instat Services, Chatham; Celgene Corporation, Summit, NJ; and Mayo Clinic, Rochester, MN.

Submitted November 16, 2007; accepted May 14, 2008; published online ahead of print at www.jco.org on July 7, 2008.

Supported by Celgene Corporation, Summit, NJ. Editorial/writing support from Excerpta Medica (funded by Celgene).

Presented in part as oral presentations at the 48th Annual Meeting of the American Society of Hematology, December 9-12, 2006, Orlando, FL, and the 3rd International Conference of Innovative Therapies for Lymphoid Malignancies, September 28, 2006, Palermo, Italy; and as poster presentations at the 48th Annual Meeting of the American Society of Hematology, December 9-12, 2006, Orlando, FL, the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL; and the Pan Pacific Lymphoma Conference, June 11-15, 2007, Maui, HI.

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

Clinical Trials repository link available on JCO.org.

Corresponding author: Thomas M. Habermann, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: habermann.thomas@mayo.edu.



0732-183X/08/2630-4952/$20.00

DOI: 10.1200/JCO.2007.15.3429

## ABSTRACT

### Purpose
The major cause of death in aggressive lymphoma is relapse or nonresponse to initial therapy. Lenalidomide has activity in a variety of hematologic malignancies, including non-Hodgkin's lymphoma (NHL). We report the results of a phase II, single-arm, multicenter trial evaluating the safety and efficacy of lenalidomide oral monotherapy in patients with relapsed or refractory aggressive NHL.

### Patients and Methods
Patients were treated with oral lenalidomide 25 mg once daily on days 1 to 21, every 28 days, for 52 weeks, until disease progression or intolerance. The primary end point was response; secondary end points included duration of response, progression-free survival (PFS), and safety.

### Results
Forty-nine patients with a median age of 65 years received lenalidomide in this study. The most common histology was diffuse large B-cell lymphoma (53%), and patients had received a median of four prior treatment regimens for NHL. An objective response rate of 35% was observed in 49 treated patients, including a 12% rate of complete response/unconfirmed complete response. Responses were observed in each aggressive histologic subtype tested (diffuse large B-cell, follicular center grade 3, mantle cell, and transformed lymphomas). Of patients with stable disease or partial response at first assessment, 25% improved with continued treatment. Estimated median duration of response was 6.2 months, and median PFS was 4.0 months. The most common grade 4 adverse events were neutropenia (8.2%) and thrombocytopenia (8.2%); the most common grade 3 adverse events were neutropenia (24.5%), leukopenia (14.3%), and thrombocytopenia (12.2%).

### Conclusion
Oral lenalidomide monotherapy is active in relapsed or refractory aggressive NHL, with manageable side effects.

*J Clin Oncol 26:4952-4957. © 2008 by American Society of Clinical Oncology*

## INTRODUCTION

The natural history of diffuse large B-cell lymphoma (DLBCL) has been improved with the advent of immunochemotherapy. However, a significant number of patients experience disease progression or relapse or die from disease after initial therapy.[1-3] At 5 years, the expected overall survival rate is 60%, and the event-free survival rate is 50%.[2,4] Currently, mantle-cell lymphoma (MCL), a rare type of non-Hodgkin's lymphoma (NHL), is incurable with standard chemotherapy.[5] Peripheral-blood stem cell transplantation has the potential to improve survival in patients with aggressive NHL, although patients might not respond to treatment or may develop disease progression.[6] New drug development will be critical in further altering the natural history of aggressive NHL.

Lenalidomide (Revlimid; Celgene Corporation, Summit, NJ), an analog of thalidomide, is a promising new therapeutic agent. It has been hypothesized that the mechanism of action of lenalidomide includes immunomodulatory and nonimmunomodulatory activity.[7] Lenalidomide monotherapy can enhance Th1-type cellular immunity and natural killer T-cell cytotoxicity activation markers in patients with advanced cancers.[7,8] Lenalidomide also has direct antiproliferative effects on hematopoietic tumors by inhibiting the Akt pathway and increasing the expression of the p21 tumor suppressor protein, leading to G1 cell cycle arrest.[9-11] In addition,

 

lenalidomide inhibits T regulatory cell function and has antiangiogenic effects on the tumor microenvironment.[12,13]

Lenalidomide does not seem to cause significant somnolence, constipation, and neuropathy, which are usually dose-limiting for thalidomide.[14] We report the results of a prospective phase II multicenter trial evaluating the safety and efficacy of oral lenalidomide monotherapy in relapsed or refractory aggressive NHL.

## PATIENTS AND METHODS

### *Patients*

Institutional review boards or ethics committees at each participating center approved the study protocol. All patients provided written informed consent. The study was designed and conducted in accordance with the general ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization Guidelines, and Title 21 of the United States Code of Federal Regulations.

Key inclusion criteria were age ≥ 18 years, biopsy-proven aggressive NHL (acceptable histologies: follicular center lymphoma grade 3, DLBCL, MCL, and transformed low-grade lymphoma) that has relapsed or is refractory to previous therapy (with at least one prior treatment, such as radiation, immunotherapy, chemotherapy, or radioimmunotherapy), ineligibility or unwillingness to undergo autologous stem-cell transplantation, measurable disease on cross-sectional imaging that is ≥ 2 cm in longest diameter, and Eastern Cooperative Oncology Group performance status score of ≤ 2. Exclusion criteria included the presence of the following laboratory abnormalities: absolute neutrophil count less than 1,500 cells/$\mu$L; platelets less than 100,000/$\mu$L; serum creatinine more than 2.5 mg/dL; and serum AST or ALT levels more than 5× the upper limit of normal. Patients with CNS lymphoma were not eligible for the trial unless the disease had been treated and the patient remained asymptomatic (for at least 6 months) with no active CNS lymphoma, as determined by lumbar puncture, computed tomography scan, or magnetic resonance imaging. In addition to the standard exclusion criteria (eg, pregnancy, lactation), patients were ineligible to participate in the trial if they had experienced a grade ≥ 3 prior allergic reaction or hypersensitivity to thalidomide or grade ≥ 3 rash or any desquamation (blistering) while taking thalidomide.

### *Study Design*

This single-arm, multicenter, open-label, phase II study was designed to evaluate the safety and efficacy of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL. The primary end point was response rate. Secondary end points were duration of response, progression-free survival (PFS), and safety.

Patients self-administered oral lenalidomide (25 mg once daily) on days 1 to 21 of every 28-day cycle. Patients continued therapy for 52 weeks as tolerated or until disease progression. Lenalidomide was supplied as 25-mg and 5-mg capsules for oral administration. Patients were instructed to take lenalidomide at the same time each day. They were given enough capsules for each 21-day cycle and were required to return the study drug bottle (including any unused drug) on the next visit. At each scheduled study visit, lenalidomide capsule reconciliation was performed to monitor treatment compliance.

A strict dose-modification schema was implemented in response to sustained (ie, lasting ≥ 7 days) grade 3 neutropenia, grade ≥ 3 neutropenia associated with fever, or grade 4 neutropenia; grade ≥ 3 thrombocytopenia; grade ≥ 3 desquamating rash or grade 4 nondesquamating rash; grade ≥ 3 erythema multiforme; grade ≥ 2 neuropathy; grade ≥ 2 sinus bradycardia or other cardiac arrhythmias; grade ≥ 2 allergic reaction or hypersensitivity; grade ≥ 1 constipation; grade ≥ 3 venous thrombosis or embolism; grade ≥ 3 nonhematologic drug-related toxicity; and grade ≥ 2 hyperthyroidism or hypothyroidism.

Patients were encouraged to receive tumor lysis prophylaxis (with allopurinol or equivalent) and to be well hydrated during the first 7 days of lenalidomide treatment in cycle 1 or as clinically indicated. To manage complications of the disease or treatment, other concomitant therapies (ie, antibiotics, analgesics, antihistamines, growth factors, and transfusions of RBCs, platelets, or fresh-frozen plasma) were administered at the discretion of the treating physician. The concomitant use of other anticancer therapies was not

**Table 1.** Patient Demographics and Baseline Disease Characteristics (N = 49)

| Characteristic | No. of Patients | % |
|---|---|---|
| Age, years | | |
| Median | 65 | |
| Range | 23-86 | |
| Male sex | 25 | 51.0 |
| Time from diagnosis, years | | |
| Median | 2.7 | |
| Range | 0.4-32 | |
| Time from last therapy, months | | |
| Median | 3.9 | |
| Range | 1-59 | |
| No. of prior treatment regimens | | |
| 1 | 4 | 8 |
| 2 | 8 | 16 |
| 3 | 12 | 24 |
| 4 | 13 | 27 |
| ≥ 5 | 12 | 24 |
| Type of prior treatment regimens* | | |
| Rituximab plus combination chemotherapy, at least once | 36 | 74 |
| Combination chemotherapy, at least once | 29 | 59 |
| Rituximab, at least once | 45 | 92 |
| Stem-cell transplantation | 14 | 29† |
| Refractory to last therapy | 24 | 56‡ |
| Rituximab refractory | 25 | 58§ |
| Refractory to last chemotherapy | 22 | 55‖ |
| Histology | | |
| Diffuse large B-cell lymphoma | 26 | 53.1 |
| Follicular center lymphoma, grade 3 | 5 | 10.2 |
| Mantle-cell lymphoma | 15 | 30.6 |
| Transformed low-grade lymphoma | 3 | 6.1 |
| International prognostic index | | |
| 0-1 | 8 | 16.3 |
| 2 | 22 | 44.9 |
| 3 | 13 | 26.5 |
| 4-5 | 6 | 12.2 |

*Rituximab (R) plus combination chemotherapy included the following: cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH); dexamethasone, cisplatin, and cytarabine (R-DHAP); etoposide, methylprednisolone, cytarabine, and cisplatin (R-ESHAP); ifosfamide, carboplatin, and etoposide (R-ICE); carmustine, etoposide, cytarabine, and melphalan (R-BEAM); cyclophosphamide, vincristine, and prednisolone (R-CVP); gemcitabine, dexamethasone, and cisplatin (R-GDP); fludarabine, mitoxantrone, and rituximab; rituximab, gemcitabine, and vinblastine; rituximab, cytarabine, and methotrexate; and rituximab, cytarabine, methotrexate, and leucovorin. Combination chemotherapy included: CHOP; EPOCH; DHAP; ESHAP; ICE; BEAM; Mini BEAM; CVP; GDP; Hyper CVAD (cyclophosphamide, doxorubicin, vincristine, dexamethasone, cytarabine, and methotrexate); cyclophosphamide, dexamethasone, doxorubicin, mesna, and vincristine; carboplatin, ifosfamide, mesna, etoposide, dexamethasone, liposomal doxorubicin, and vinorelbine; bleomycin, cyclophosphamide, etoposide, prednisone, leucovorin, methotrexate, and vincristine; and cyclophosphamide, mitoxantrone, prednisone, and vincristine.

†Forty-eight patients had information on stem-cell transplantation.

‡Forty-three patients had sufficient information to characterize as refractory to last therapy or not.

§Forty-three patients had sufficient information to characterize as refractory to rituximab or not.

‖Forty patients had sufficient information to characterize as refractory to last chemotherapy regimen or not.



 

**Table 2.** Adverse Events Reported in at Least 10% of Patients (N = 49)

| Adverse Event | No. of Patients | % |
|---|---|---|
| Neutropenia | 26 | 53.1 |
| Thrombocytopenia | 26 | 53.1 |
| Fatigue | 24 | 49.0 |
| Anemia NOS | 20 | 40.8 |
| Constipation | 15 | 30.6 |
| Leukopenia NOS | 14 | 28.6 |
| Rash NOS | 13 | 26.5 |
| Diarrhea NOS | 12 | 24.5 |
| Pyrexia | 11 | 22.4 |
| Cough | 9 | 18.4 |
| Nausea | 9 | 18.4 |
| Arthralgia | 7 | 14.3 |
| Dyspnea NOS | 7 | 14.3 |
| Anorexia | 6 | 12.2 |
| Hyperglycemia NOS | 6 | 12.2 |
| Neuropathy NOS | 6 | 12.2 |
| Edema peripheral | 6 | 12.2 |
| Abdominal pain NOS | 5 | 10.2 |
| Disease progression NOS | 5 | 10.2 |
| Dizziness | 5 | 10.2 |
| Infection NOS | 5 | 10.2 |
| Insomnia | 5 | 10.2 |
| Night sweats | 5 | 10.2 |

Abbreviation: NOS, not otherwise specified.

**Table 3.** All Grade 3 and 4 Adverse Events by Preferred Term (N = 49)

| Adverse Event | Grade 3 | | Grade 4 | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Neutropenia | 12 | 24.5 | 4 | 8.2 |
| Leukopenia | 7 | 14.3 | 0 | 0 |
| Thrombocytopenia | 6 | 12.2 | 4 | 8.2 |
| Fatigue | 3 | 6.1 | 0 | 0 |
| Anemia | 2 | 4.1 | 1 | 2.0 |
| Dyspnea NOS | 2 | 4.1 | 0 | 0 |
| Febrile neutropenia | 2 | 4.1 | 1 | 2.0 |
| Pain NOS | 2 | 4.1 | 0 | 0 |
| Pneumonia NOS | 2 | 4.1 | 0 | 0 |
| Acute myocardial infarction | 0 | 0 | 1 | 2.0 |
| Alanine aminotransferase increased | 1 | 2.0 | 0 | 0 |
| Aspartate aminotransferase increased | 1 | 2.0 | 0 | 0 |
| Autoimmune hemolytic anemia NOS | 1 | 2.0 | 0 | 0 |
| Blood bilirubin increased | 1 | 2.0 | 0 | 0 |
| Cardiac failure congestive | 1 | 2.0 | 0 | 0 |
| Cauda equina syndrome | 0 | 0 | 1 | 2.0 |
| Cellulitis | 1 | 2.0 | 0 | 0 |
| Chest pain | 1 | 2.0 | 0 | 0 |
| Convulsions NOS | 1 | 2.0 | 0 | 0 |
| Diarrhea NOS | 1 | 2.0 | 0 | 0 |
| Diplegia | 0 | 0 | 1 | 2.0 |
| Dysphagia | 1 | 2.0 | 0 | 0 |
| Hematuria | 1 | 2.0 | 0 | 0 |
| Hemolysis NOS | 1 | 2.0 | 0 | 0 |
| Hyponatremia | 1 | 2.0 | 0 | 0 |
| Jugular vein thrombosis | 1 | 2.0 | 0 | 0 |
| Lymphopenia | 1 | 2.0 | 1 | 2.0 |
| Malaise | 1 | 2.0 | 0 | 0 |
| Mental status changes | 1 | 2.0 | 0 | 0 |
| Nausea | 1 | 2.0 | 0 | 0 |
| Osteomyelitis NOS | 1 | 2.0 | 0 | 0 |
| Pain in foot | 1 | 2.0 | 0 | 0 |
| Pneumonitis NOS | 1 | 2.0 | 1 | 2.0 |
| Pulmonary embolism | 0 | 0 | 1 | 2.0 |
| Rash NOS | 1 | 2.0 | 1 | 2.0 |
| Sepsis NOS | 1 | 2.0 | 0 | 0 |
| Spinal hematoma | 1 | 2.0 | 0 | 0 |
| Sweating increased | 1 | 2.0 | 0 | 0 |
| Urinary frequency | 1 | 2.0 | 0 | 0 |

Abbreviation: NOS, not otherwise specified.

permitted, and previous anticancer therapies were discontinued for at least 28 days before initiating lenalidomide treatment.

### *Response and Safety Assessments*

Study visits were scheduled to occur every 28 days to coincide with the beginning of each new treatment cycle. Target and nontarget lesions were assessed at baseline and every 2 months using a chest x-ray, conventional or spiral computed tomography, and/or magnetic resonance imaging. Bone marrow biopsy was used to confirm a complete response (CR) in patients who had bone marrow involvement at baseline and who had achieved all other criteria for a CR. Response and progression were evaluated using the International Workshop Lymphoma Response Criteria.[15] All patients who discontinued the treatment phase for any reason were observed until disease progression or administration of another lymphoma treatment. Patients who did not achieve a response (CR, unconfirmed CR [CRu], or partial response [PR]) to their last treatment regimen or last chemotherapy regimen were classified as refractory to last therapy or refractory to last chemotherapy, respectively. Patients with no response or a response lasting less than 6 months after their most recent rituximab-containing regimen were classified as rituximab refractory.

Safety assessments included adverse events, blood pressure and pulse rate assessments, hematology and chemistry laboratory values, and serum thyroid function tests. In women of child-bearing potential, serum/urine beta-human chorionic gonadotropin levels were also evaluated to determine pregnancy status.

### *Statistical Analysis*

The primary end point was the objective response rate, defined as the proportion of patients assessable for response whose best response was PR, CRu, or CR. Secondary efficacy measures were duration of response, PFS, and safety. Duration of response was calculated as the time from at least a PR to progression of disease, including death owing to NHL. PFS was defined as the time from the start of lenalidomide therapy to the first observation of disease progression or death from any cause.

PFS was censored for patients who had not experienced disease progression or had not died at the time of last follow-up. The study had a two-stage design, with a target enrollment of approximately 40 patients. The study was to be halted if there were no responses among the first 20 patients treated with lenalidomide (calculated based on the 0.88 probability of observing at least one response among 20 patients, if the true response rate was $\geq$ 10%). If one or more of these 20 patients achieved response to lenalidomide, enrollment was to continue to reach the target range.

Univariate analyses using Fisher's exact test were conducted to investigate and characterize associations of variables with response. Data from all patients treated with at least one dose of lenalidomide were included in the safety analysis. Adverse events and their severity were classified using the National Cancer Institute Common Toxicity Criteria. Results reported are based on data available on January 31, 2007. At this time, as per protocol, all patients had either experienced disease progression or completed six cycles of therapy. PFS and duration of response are based on data available on October 31, 2007. As per protocol, at this time at least 80% of patients had discontinued treatment.

  

## RESULTS

From August 2005 to September 2006, 50 patients enrolled at eight centers in the United States. However, only 49 patients received lenalidomide, because one patient was documented to have pathologic evidence of Hodgkin's lymphoma and, therefore, received no treatment. The median age was 65 years (Table 1). The most common histology was DLBCL (53%). The median time from diagnosis to lenalidomide treatment was 2.7 years, and patients had received a median of four prior treatment regimens for NHL. The median time from last therapy was 3.9 months. Ninety-two percent of patients had received prior rituximab, and 58% were deemed to be rituximab refractory. Twenty-nine percent of the patients had undergone prior stem-cell transplantation.

### *Safety*

The most common adverse events were hematologic, fatigue, gastrointestinal, and rash (Table 2). The most common grade 4 adverse events were neutropenia (8.2%) and thrombocytopenia (8.2%); the most common grade 3 adverse events were neutropenia (24.5%), leukopenia (14.3%), and thrombocytopenia (12.2%; Table 3).

Eighteen patients (37%) had a total of 32 dose reductions (nine patients required one dose reduction to 20 mg, five patients required two dose reductions to 15 mg, three patients required three dose reductions to 10 mg, and one patient required four dose reductions to 5 mg). Adverse events most commonly causing dose reduction were neutropenia (n = 15), thrombocytopenia (n = 5), and fatigue (n = 2).

Hematologic events (neutropenia, thrombocytopenia, leukopenia, and anemia) were manageable with dose reductions and resulted in only two patients discontinuing lenalidomide treatment (both owing to thrombocytopenia). Other reasons for treatment discontinuation were cauda equina syndrome, rash, autoimmune hemolytic anemia, myocardial infarction, pneumonia, disease progression, and CNS lymphoma. Eight patients discontinued treatment because of adverse events.

### *Response*

The overall response rate (ORR) was 35% (n = 17; Table 4). Two patients achieved CR, four patients achieved CRu, 11 patients achieved PR, and 11 patients had stable disease (SD). Patients with MCL achieved an ORR of 53%; this included one patient with CR (7%), one patient with CRu (7%), and six patients with PR (40%).

Five of the 17 patients who responded to lenalidomide monotherapy were refractory to their last prior therapy. They received a median number of four prior therapies. Three of these patients were refractory to autologous stem-cell transplantation, combination cyclophosphamide plus vincristine plus prednisone, and tositumomab, and each achieved a CRu to lenalidomide; two patients were refractory to rituximab plus methylprednisolone and SGN40, and each responded to lenalidomide with a PR. Five of the 25 rituximab-refractory patients achieved a response to lenalidomide, whereas eight of 18 patients sensitive to their last rituximab-containing regimen had treatment response to lenalidomide. Four patients were rituximab naïve, and of these, two patients achieved CR, one patient achieved PR, and one patient had SD.

Median time to PR was 1.9 months (range, 1.2 to 3.7 months), and median time to CR/CRu was 4.3 months (range, 1.9 to 10.5 months). Three (21%) of the 14 patients who had SD at the first assessment (cycle 2) exhibited a response (one CRu and two PRs) with continued treatment. Likewise, four (31%) of 13 patients with an initial PR after cycle 2 eventually achieved a CR/CRu with continued lenalidomide treatment.

The estimated median duration of response was 6.2 months (range, 0 to 12.8 months), and median PFS was 4.0 months (range, 0 to 14.5 months; Fig 1).

## DISCUSSION

In this phase II study, lenalidomide produced an ORR of 35% in 49 patients with relapsed or refractory aggressive NHL. Responses were observed in each aggressive histologic subtype tested (DLBCL, follicular center lymphoma grade 3, MCL, and transformed low-grade lymphoma). The 53% ORR seen in patients with relapsed or refractory MCL treated with lenalidomide, along with a manageable toxicity profile, suggests that lenalidomide is a potential treatment option for these patients. Twenty-five percent of patients with SD or PR at first assessment had improved responses with continued treatment. With a median follow-up of 3.7 months, the estimates for median duration of response and PFS were 6.2 and 4.0 months, respectively. The adverse events were predominantly hematologic, manageable, and consistent with lenalidomide therapy in patients with other diseases.

The population evaluated in this study had advanced disease, were heavily pretreated, and had limited treatment options. Overall, 29% of patients had undergone prior stem-cell transplantation, and 58% were refractory to rituximab-containing regimens. All except one patient had received prior chemotherapy regimens. This patient had previously undergone renal transplantation and had received thalidomide monotherapy after developing DLBCL. Also, this patient had a

**Table 4.** Objective Response of Patients Receiving Lenalidomide Therapy by Histology Type (N = 49)

| Histology | No. of Patients | CR | CRu | PR | SD | PD | ORR (%) |
|---|---|---|---|---|---|---|---|
| Aggressive NHL | 49 | 2 | 4 | 11 | 11 | 21 | 35 |
| Diffuse large B-cell lymphoma | 26 | 1 | 2 | 2 | 7 | 14 | 19 |
| Follicular center lymphoma, grade 3 | 5 | 0 | 1 | 2 | 0 | 2 | 60 |
| Mantle-cell lymphoma | 15 | 1 | 1 | 6 | 2 | 5 | 53 |
| Transformed low-grade lymphoma | 3 | 0 | 0 | 1 | 2 | 0 | 33 |

Abbreviations: NHL, non-Hodgkin's lymphoma; CR, complete response; CRu, unconfirmed CR; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate.

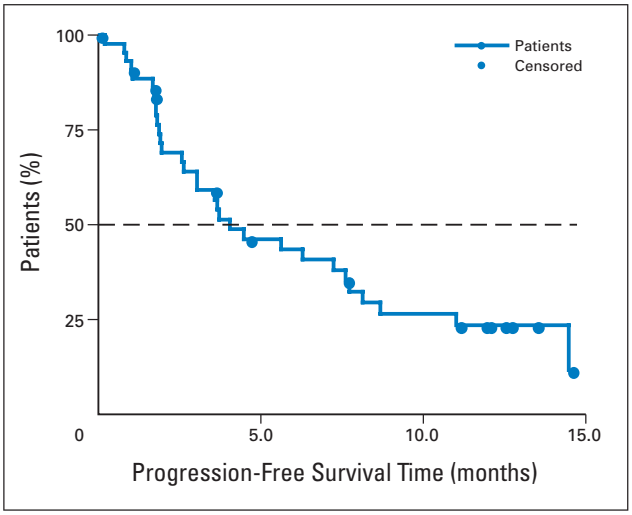


**Fig 1.** Kaplan-Meier plot of progression-free survival.

CR for 40 months after treatment with thalidomide and a CR with lenalidomide in the current trial, which continued at 7.6 months.

The responses to lenalidomide monotherapy compare favorably to that observed for other monotherapies evaluated in similar patient populations. Goy et al[16] reported an ORR of 32% with bortezomib monotherapy in patients with relapsed or refractory, indolent, and aggressive NHL. The ORR reported with gemcitabine monotherapy in rituximab-naïve patients was 20% (all PRs), and the median duration of response was 6 months.[17] Treatment with rituximab monotherapy in 54 patients with relapsed or refractory, aggressive, rituximab-naïve NHL yielded an ORR of 31% (33% in MCL and 37% in DLBCL) and a median time to progression of at least 105 days.[18] In the present study, three of four patients with rituximab-naïve disease had an objective response.

Lenalidomide, a known immunomodulatory drug, may control aggressive NHL by enhancing the immune system.[7,8,12,19-21] It was recently reported that when used in combination, lenalidomide and rituximab produce a robust response rate in relapsed or refractory MCL.[22] Other activities that might be relevant to the activity of lenalidomide in NHL, apart from its immunomodulatory activity, include its direct antiproliferative effect on the tumor and its pro-apoptotic effects via *p21*, as well as its inhibition of angiogenesis.[9-11,13]

Ongoing and future studies of lenalidomide in NHL include the use of lenalidomide as monotherapy and in combination with rituximab in indolent lymphoma and in combination with bortezomib in MCL.[23-25]

The results from this phase II study demonstrate the activity of oral lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL and warrant further investigation of lenalidomide therapy, alone or in combination, in the treatment of patients with aggressive NHL.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** Kenton Wride, Celgene Corp (C); Dennis Pietronigro, Celgene Corp (C); Kenichi Takeshita, Celgene Corp (C); Annette Ervin-Haynes, Celgene Corp (C); Jerome B. Zeldis, Celgene Corp (C) **Consultant or Advisory Role:** Peter H. Wiernik, Celgene Corp (U); Kyle McBride, Celgene Corp (C) **Stock Ownership:** Kenton Wride, Celgene Corp; Dennis Pietronigro, Celgene Corp; Kenichi Takeshita, Celgene Corp; Annette Ervin-Haynes, Celgene Corp; Jerome B. Zeldis, Celgene Corp **Honoraria:** Peter H. Wiernik, Celgene Corp; Joseph M. Tuscano, Celgene Corp **Research Funding:** Peter H. Wiernik, Celgene Corp; Julie M. Vose, Celgene Corp **Expert Testimony:** Jerome B. Zeldis, Celgene Corp (C) **Other Remuneration:** None

## AUTHOR CONTRIBUTIONS

**Conception and design:** Peter H. Wiernik, Dennis Pietronigro, Kenichi Takeshita, Annette Ervin-Haynes, Jerome B. Zeldis, Thomas M. Habermann
**Financial support:** Jerome B. Zeldis
**Administrative support:** Craig E. Cole, Dennis Pietronigro, Jerome B. Zeldis
**Provision of study materials or patients:** Peter H. Wiernik, Izidore S. Lossos, Joseph M. Tuscano, Glen Justice, Craig E. Cole, Wendy Lam, Dennis Pietronigro, Thomas M. Habermann
**Collection and assembly of data:** Peter H. Wiernik, Izidore S. Lossos, Glen Justice, Dennis Pietronigro, Annette Ervin-Haynes, Thomas M. Habermann
**Data analysis and interpretation:** Peter H. Wiernik, Izidore S. Lossos, Joseph M. Tuscano, Julie M. Vose, Kyle McBride, Kenton Wride, Dennis Pietronigro, Annette Ervin-Haynes, Jerome B. Zeldis, Thomas M. Habermann
**Manuscript writing:** Peter H. Wiernik, Izidore S. Lossos, Joseph M. Tuscano, Julie M. Vose, Dennis Pietronigro, Kenichi Takeshita, Annette Ervin-Haynes, Jerome B. Zeldis, Thomas M. Habermann
**Final approval of manuscript:** Peter H. Wiernik, Izidore S. Lossos, Joseph M. Tuscano, Glen Justice, Julie M. Vose, Craig E. Cole, Wendy Lam, Kyle McBride, Kenton Wride, Dennis Pietronigro, Kenichi Takeshita, Annette Ervin-Haynes, Jerome B. Zeldis, Thomas M. Habermann

## REFERENCES


**1.** Coiffier B, Lepage E, Briére J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med 346:235-242, 2002

**2.** Feugier P, Van Hoof A, Sebban C, et al: Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: A study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 23:4117-4126, 2005

**3.** Habermann TM, Weller EA, Morrison VA, et al: Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 24:3121-3127, 2006

**4.** Morrison VA, Weller EA, Habermann TM, et al: Maintenance rituximab (MR) compared to observation (OBS) after R-CHOP or CHOP in older patients (pts) with diffuse large B-cell lymphoma (DLBCL): An Intergroup E4494/C9793 update. J Clin Oncol 25:443s, 2007 (suppl; abstr 8011)

**5.** Witzig TE: Current treatment approaches for mantle-cell lymphoma. J Clin Oncol 23:6409-6414, 2005

**6.** Philip T, Armitage JO, Spitzer G, et al: High-dose therapy and autologous bone marrow transplantation after failure of conventional therapy in


  

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.