Randomized, Double-Blind, Active-Controlled Trial of Every-3-Week Darbepoetin Alfa for the Treatment of Chemotherapy-Induced Anemia

Jean-Luc Canon, Johan Vansteenkiste, György Bodoky, M. Victoria Mateos, Laurent Bastit, Irene Ferreira, Greg Rossi, Rafael G. Amado

For the Aranesp 20030231 Study Group

Background: In the United States, darbepoetin alfa (Aranesp) is often used to treat patients with chemotherapy-induced anemia using weekly or every-2-week administration schedules. In Europe, darbepoetin alfa is used either weekly or in every-3-week dosing. The every-3-week schedule can be synchronized with many chemotherapy regimens, resulting in fewer visits and reducing burden to patients, but the safety and efficacy of this regimen have not been clear. Methods: A randomized, double-blind, double-dummy, active-controlled phase 3 trial was performed in 110 European centers. Eligible patients (age ≥18 years) were anemic (hemoglobin level <11 g/dL), had a nonmyeloid malignancy, and were to receive at least 12 weeks of chemotherapy. Patients were randomly assigned 1:1 to darbepoetin alfa treatment every 3 weeks (500-μg dose) or weekly (2.25-μg/kg) for 15 weeks. We compared red blood cell transfusion incidence among the two arms from week 5 to the end of the treatment phase using a noninferiority study design. Noninferiority was determined if the upper limit of the 95% confidence interval (CI) for the difference in blood transfusions between groups, calculated using Kaplan–Meier methods, did not exceed 12.5%, a margin based on previous placebo-controlled studies. Results: A total of 705 patients were randomly assigned, and 672 remained in the study at week 5. Fewer patients in the every-3-week arm than in the weekly arm received blood transfusions from week 5 to the end of the treatment phase (unadjusted Kaplan–Meier estimates = 23% versus 30%, difference = −6.8%; 95% CI = −13.6 to 0.1). Percentages of patients achieving the target hemoglobin level (≥11 g/dL, consistent with evidence-based practice guidelines) were 84% (every 3 weeks) and 77% (weekly). The frequency of cardiovascular/thromboembolic adverse events was 8% in both groups, and safety was comparable. Conclusions: Patients with chemotherapy-induced anemia can safely and effectively be treated with 500 μg of darbepoetin alfa every 3 weeks. [J Natl Cancer Inst 2006;98:273–84]

Anemia is a frequent complication of malignant disease or chemotherapy and contributes to increased morbidity and reduced quality of life (1). Recombinant human erythropoietin (rHuEPO) has been shown to be effective in treating anemia in patients who undergo chemotherapy by increasing hemoglobin concentrations and reducing or eliminating the need for red blood cell (RBC) transfusions (2–8). In addition, patients have substantially less fatigue and better physical and functional well-being after treatment with erythropoietic therapy (5,8–13).

Darbepoetin alfa is an erythropoiesis-stimulating protein with a unique amino acid sequence, greater sialic acid content, longer half-life (74 hours in cancer patients), and greater biologic activity than rHuEPO (14,15). Because of differences in the pharmacokinetic properties of darbepoetin alfa and rHuEPO, darbepoetin alfa can be administered less frequently than rHuEPO without changes in efficacy and safety. Darbepoetin alfa was originally licensed for treatment of chemotherapy-induced anemia in many regions of the world, including the United States and Europe, based on a weekly 2.25-μg/kg dose (16,17). However, the number of studies showing that darbepoetin is safe and effective when used less frequently is increasing (2,15,18–23).

Administration of darbepoetin alfa every 3 weeks would coincide with many chemotherapy schedules and may be convenient to patients and their health care providers as well as improve health care resource use. A double-blind, placebo-controlled, dose-response study (2) evaluated several weight-based doses of every-3-week darbepoetin alfa (4.5, 6.75, 9, 12, 13, or 15 μg/kg). Darbepoetin alfa was shown to be effective at all every-3-week doses, with limited incremental benefit at doses greater than 6.75 μg/kg. A recent study of 81 anemic patients (15) provided further evidence of the effectiveness of darbepoetin alfa 6.75 μg/kg every 3 weeks for the treatment of chemotherapy-induced anemia. These data demonstrated the effectiveness of an every-3-week regimen of darbepoetin alfa irrespective of the timing of administration relative to concurrent chemotherapy. However, a study comparing the every-3-week regimen of darbepoetin alfa with the established weekly regimen has not yet been conducted.

Erythropoietic therapy has been shown to be effective and safe when administered as a fixed dose (7,9,13,20). Recently, a phase
2, randomized controlled trial of darbepoetin alfa (24) indicated that the efficacy profile was not affected if a fixed (versus weight-based) dose was used. This finding is consistent with the pharmacokinetico-pharmacodynamic modeling of darbepoetin alfa (25), based on data from previous studies, which suggested that patient body weight is not a primary determinant of efficacy for this molecule. The fixed-dose approach adds convenience for clinicians and is consistent with current patterns of practice (26).

This randomized, double-blind, double-dummy, active-controlled, phase 3 study compared the efficacy and safety of weekly and every-3-week regimens of darbepoetin alfa treatment. The primary hypothesis being tested was that cancer patients treated for chemotherapy-induced anemia with darbepoetin alfa using a fixed 500-μg dose every 3 weeks have an incidence of RBC transfusions that is comparable (defined as not inferior) to that of patients receiving the standard weekly (2.25 μg/kg) regimen of darbepoetin alfa. A description of the study may be found online (http://www.ClinicalTrials.gov, Identifier No. NCT00118638).

**Subjects and Methods**

**Study Population**

The independent ethics committee or central ethics committee for each of the 110 participating medical centers in 24 European countries approved the protocol. All patients gave oral and written informed consent before any study-specific procedures were initiated.

For entry into the study, patients were required to have a diagnosis of nonmyeloid malignancy and at least 12 additional weeks of planned cytotoxic chemotherapy (chemotherapy may have been ongoing at time of random assignment). Patients were eligible for the study if they were at least 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2, and had adequate renal (creatinine level less than twice the upper limit of normal) and hepatic (alanine aminotransferase and aspartate aminotransferase levels less than five times the upper limit of normal) function. Patients were required to have anemia (i.e., a hemoglobin level of <11 g/dL within 24 hours of random assignment) secondary to malignancy and chemotherapy treatment. Patients were excluded if they were iron deficient; had received more than two RBC transfusions within 4 weeks of random assignment or any RBC transfusions within 14 days of the first dose of investigational product (i.e., study day 1); had received rHuEPO therapy within 4 weeks of random assignment; or were pregnant, breast-feeding, or not using adequate birth control measures. Patients were also excluded if they had a history of seizure disorders, active cardiac disease, uncontrolled hypertension, active infection, or any chronic inflammatory or hematologic disorder that could cause anemia.

**Random Assignment**

This was a phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled study. After registration, patients were randomly assigned in a 1:1 ratio to receive blinded darbepoetin alfa subcutaneously, either at a fixed dose of 500 μg every 3 weeks or a weight-based dose of 2.25 μg/kg weekly. Random assignment was stratified by tumor type (lung or gynecologic versus others), screening hemoglobin concentration (<10.0 g/dL versus ≥10.0 g/dL), and European region (Western versus Central and Eastern) to ensure a balanced allocation of patients to darbepoetin alfa every-3-week and weekly groups within each stratum.

All patients were randomly assigned up to 3 days before study day 1. A blood sample was drawn within 24 hours of random assignment at a local laboratory to confirm hemoglobin concentration less than 11 g/dL, as well as to provide hemoglobin concentration data for stratification. The random allocation sequence was obtained using an interactive voice response system after the screening hemoglobin concentration result was entered.

**Treatment Schedule**

The study consisted of a screening period of up to 7 days before random assignment, followed by 15 weeks of blinded study treatment and a 2-week follow-up period after the last dose of study drug. A double-dummy design was used to ensure that patients in each treatment group received the same schedule of blinded injections. The every-3-week group received darbepoetin alfa dosing at weeks 1, 4, 7, 10, and 13 and a weekly blinded placebo injection. The weekly group received darbepoetin alfa dosing weekly from weeks 1 to 15 and blinded placebo administered every 3 weeks.

Darbepoetin alfa (Aranesp; Amgen Inc., Thousand Oaks, CA) was prepared in a phosphate buffer, pH 6.2, as a human serum albumin–free, polysorbate formulation. Patients received the study drugs from identical 500-μg vials that contained either a dose of darbepoetin alfa or a placebo. The delivered volumes of drug and placebo were identical.

At any time during the study, the dose of blinded study drug was withheld if a patient’s hemoglobin concentration was greater than 13 g/dL. After the patient’s hemoglobin concentration decreased to 12 g/dL or less, administration of the study drug was then reinstated at 60% of the previous dose at the next administration visit. Consistent with the package insert for darbepoetin alfa in the United States (16), patients were required to have a dose reduction if their hemoglobin concentration increased by 1 g/dL or greater over a 14-day period in the absence of RBC transfusion (during the previous 14 days); the dose of darbepoetin alfa was decreased to 60% of the previous dose. Further dose reductions proceeded in 40% dose decrements. A maximum of four dose reductions were permitted before the investigational product was to be discontinued.

To allow for regional- and center-based differences in transfusion policies, the protocol recommended, but did not mandate, transfusions for patients with hemoglobin concentrations of 8 g/dL or less. Transfusions were permissible for hemoglobin concentrations greater than 8 g/dL in symptomatic patients or as recommended by the physician.

LabCorp (Mechelen, Belgium) provided the central laboratory service for the analysis of hematology (except for hemoglobin), chemistry, and iron variables. Hemoglobin measurements on study were performed by local laboratories.

**Efficacy Evaluation**

The primary objective was to evaluate the efficacy of darbepoetin alfa administered as 500 μg every 3 weeks by showing that this dose and schedule are not inferior to darbepoetin alfa administered weekly as 2.25 μg/kg in the treatment of anemia.
in patients with nonmyeloid malignancies receiving cyclic chemotherapy. The primary endpoint of this noninferiority study was the incidence of RBC transfusions; therefore, information on the incidence and number of RBC transfusions was collected throughout the study. Data from previous randomized, placebo-controlled trials indicate that the effects of rHuEPO on the incidence of RBC transfusion are not apparent until the second month of treatment (5,9,27). Therefore, the proportion of patients receiving a transfusion was measured from week 5 to the end of the treatment phase, an endpoint that has been accepted by the regulatory agencies as sufficient for drug approval. However, because this study compared two active therapies, it was deemed appropriate to also evaluate the transfusion requirements over the entire course of therapy (week 1 to the end of the treatment phase) as well as the total number of RBC units transfused.

The effect of darbepoetin alfa treatment on hemoglobin concentration was an additional measure of efficacy. The therapeutic goals, with respect to hemoglobin levels, were the proportion of patients achieving a hemoglobin concentration of 11 g/dL or greater, and the proportion of patients subsequently maintaining hemoglobin levels in the 11–13 g/dL range. This target hemoglobin range is based on three well-recognized evidence-based practice guidelines for anemia management in cancer patients [National Comprehensive Cancer Network (28), American Society of Hematology (29)/American Society of Clinical Oncology (30), and European Organization for Research and Treatment of Cancer (31)], which recommend the attainment and subsequent maintenance of a target hemoglobin concentration between 11 and 13 g/dL to minimize transfusion requirements and maximize health-related quality of life benefits. In addition, the change in hemoglobin concentration was analyzed over time. Hemoglobin measurements made within 28 days of a RBC or whole blood transfusion were excluded from the analysis.

For this study, the primary health-related quality-of-life instrument was the Functional Assessment of Cancer Therapy (FACT)-Fatigue subscale, which has previously been validated in the oncology setting (32), along with additional quality of life questionnaires (FACT-General and all its subscales, EQ-5D Health State Index, Brief Symptom Inventory Anxiety and Depression scales, and the number of caregiver hours). A change in the FACT-Fatigue subscale score equal to or greater than three points during intervention has been described as a clinically meaningful change (33); hence, the proportion of patients achieving a change equal to or greater than three points in FACT-Fatigue was also assessed.

Safety Evaluation

A key objective of the study was to assess the overall safety of 500 μg of darbepoetin alfa given every 3 weeks and compare it with that of 2.25 μg/kg given weekly. The nature, frequency, severity, relationship to treatment, and outcome of all adverse events were measured. The safety of the fixed dosing regimen of darbepoetin alfa was evaluated by comparing the overall safety profile across weight and body mass index (BMI) groups of the standard weekly dose to the every-3-week dosing schedule. The safety profiles of the two treatment groups were evaluated with respect to changes in hemoglobin concentrations as follows: values greater than 13 g/dL at any time on study and increases of 2 g/dL or greater in a 28-day window or of 1 g/dL in a 14-day window.

Serum was collected before study drug administration, at week 10, and at the end of the treatment phase to screen for the presence of antibodies to darbepoetin alfa using a Biacore 3000 biosensor immunoassay (Biacore International, AB, Uppsala, Sweden). Any Biacore-positive sample (i.e., antibody concentration of ≥0.25 μg/mL) was routed for analysis using a bioassay to detect neutralizing antibodies and to characterize the antibody classes observed in the biosensor immunoassay. A central laboratory provided storage of samples for antibody testing. Anti-darbepoetin alfa antibody screening was done at MDS Pharma Services (St. Laurent, Quebec, Canada), and immunoassay characterization and bioassay were done at Amgen Inc. There was no data safety monitoring board for this study.

Statistical Analysis

The sample size of 705 randomly assigned patients provides 95% power to demonstrate noninferiority of the every-3-week regimen compared with the weekly regimen based on the primary endpoint of incidence of RBC transfusions from week 5 to the end of the treatment phase. A two-sided 95% confidence interval (CI) for the difference (every-3-week versus weekly regimen) in the proportion of patients experiencing at least one RBC transfusion from week 5 to the end of the treatment phase was calculated based on the unadjusted Kaplan–Meier estimates. Noninferiority of the every-3-week dosing schedule was declared if the upper limit of this confidence interval was less than or equal to 12.5%. The 12.5% cut point was based on an estimate of the 95% confidence interval for the difference in the rate of RBC transfusion between placebo and darbepoetin alfa groups obtained from two previous placebo-controlled, phase 3 studies (34), both of which used a starting dose of 2.25 μg/kg weekly. In a combined unadjusted analysis of the two trials, the difference between darbepoetin alfa treatment and placebo was 23%, with a lower 95% confidence interval of 16%. This effect size is consistent with the recent meta-analysis of randomized, placebo-controlled trials of erythropoietic agents in cancer patients (34). A noninferiority margin of 12.5% was selected to ensure that a substantial proportion of the treatment effect was maintained.

Analysis of the primary endpoint was based on the set of patients who were randomly assigned, received at least one dose of study medication, and were treated until at least day 29 (primary transfusion analysis set). Preplanned sensitivity analyses of the primary endpoint were performed using an alternate analysis set (per-protocol analysis set) and censoring mechanism (secondary censoring).

Statistical analyses were performed by the sponsor using SAS statistical software, version 8.2 (SAS Institute Inc., Cary, NC). Descriptive statistics included frequencies and means (with 95% confidence intervals or standard deviations [SDs]) for categorical and continuous variables, respectively. Changes in hemoglobin levels and FACT-Fatigue scores of each patient were analyzed using an analysis of covariance model including the stratification factors. Two analytical approaches—imputation (last-value-carried-forward) and available data—were used to account for missing hemoglobin data. Hemoglobin values within 28 days after a transfusion were considered to be missing; using the last-value-carried-forward imputation method, the pretransfusion hemoglobin value was used to impute all weekly hemoglobin values during the 28 days after a transfusion. Changes in hemoglobin were evaluated using both methods; achievement of target
hemoglobin was calculated using only the last-value-carried-forward method. Kaplan–Meier estimates for the proportion of patients achieving the target hemoglobin levels and for the proportion of patients achieving a clinically meaningful increase in FACT-Fatigue were adjusted for the baseline stratification factors of tumor type (lung or gynecologic versus others), screening hemoglobin concentration (<10.0 g/dL versus ≥10.0 g/dL), and European region (Western versus Central and Eastern). The adjusted Kaplan–Meier estimate is the weighted average of the Kaplan–Meier estimates obtained for each stratum. Primary analysis of transfusion-related endpoints was based on the unadjusted Kaplan–Meier estimates. In addition, transfusion results were examined using the adjusted Kaplan–Meier estimates, as well as an actuarial approach to estimate the crude proportion of patients receiving transfusions (crude estimates are not presented). Additional analyses of transfusion, hemoglobin, and safety endpoints were stratified by weight and BMI categories.

An exploratory piecewise mixed-effects model was developed to investigate the effect of dose reductions on hemoglobin levels (35). The mixed-effects model allows the hemoglobin slope to change before and after the first dose reduction, ensuring that these two lines intersect at the time of titration. As with other hemoglobin endpoints, the analysis was adjusted for study stratification factors, and hemoglobin measurements within 28 days of a RBC or whole blood transfusion were excluded from the analysis.

Safety was evaluated in all patients who received at least one dose of study drug, according to the treatment they actually received. Adverse events were grouped by primary system organ class and by preferred term within the primary system organ class according to the MedDRA dictionary. The frequency and percentage distributions of adverse events to the study drug were summarized.

**RESULTS**

**Study Population**

Of the 763 patients screened, 705 were randomly assigned. Enrollment was well distributed across study centers, with no center enrolling greater than 3% of patients. Patient disposition is outlined in Fig. 1. All 705 randomly assigned patients received darbepoetin alfa. Baseline demographics and clinical characteristics were similar in the two treatment groups (Table 1). A similar proportion of patients in each treatment group completed treatment: 75% in the 500 µg of darbepoetin alfa every-3-week group and 70% in the 2.25 µg/kg weekly group. Reasons for early discontinuation included death (31 patients [9%] in the every-3-week group and 39 [11%] in the weekly group), withdrawal of consent (17 [5%] in the every-3-week group and 28 [8%] in the weekly group), and adverse events (14 [4%] in each group). The distribution of patients across baseline stratification factors was balanced across both groups (data not shown).

**Darbepoetin Alfa Dose**

The mean numbers of darbepoetin alfa doses administered were 4.2 and 11.8 in the every-3-week and weekly groups,

![Fig. 1. CONSORT (Consolidated Standards for Reporting of Trials) diagram of patient disposition.](https://academic.oup.com/jnci/article-abstract/98/4/273/2521973)}
### Table 1. Demographic and laboratory characteristics at baseline *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Darbepoetin alfa 500 μg every 3 weeks</th>
<th>Darbepoetin alfa 2.25 μg/kg weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>353</td>
<td>352</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>167 (47)</td>
<td>155 (44)</td>
</tr>
<tr>
<td>Women</td>
<td>186 (53)</td>
<td>197 (56)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>58.7 (13.1)</td>
<td>59.3 (12.3)</td>
</tr>
<tr>
<td>Geographic region, No. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>205 (58)</td>
<td>206 (59)</td>
</tr>
<tr>
<td>Central and Eastern Europe</td>
<td>148 (42)</td>
<td>146 (41)</td>
</tr>
<tr>
<td>ECOG performance status, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>307 (87)</td>
<td>289 (82)</td>
</tr>
<tr>
<td>2</td>
<td>46 (13)</td>
<td>63 (18)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>9.76 (0.95)</td>
<td>9.78 (0.85)</td>
</tr>
<tr>
<td>Hemoglobin category, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 g/dL</td>
<td>175 (50)</td>
<td>176 (50)</td>
</tr>
<tr>
<td>≥10 g/dL</td>
<td>178 (50)</td>
<td>176 (50)</td>
</tr>
<tr>
<td>Serum eEPO, μU/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>108.2 (179.6)</td>
<td>127.3 (258.6)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>53.2 (31.9, 109.5)</td>
<td>59.0 (30.6, 111.5)</td>
</tr>
<tr>
<td>Ferritin, μL/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>539.9 (694.19)</td>
<td>576.5 (785.71)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>300.0 (111, 666)</td>
<td>298.0 (132, 754)</td>
</tr>
<tr>
<td>Transferrin saturation, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>30.1 (25.3)</td>
<td>30.3 (26.0)</td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>21.0 (12.0, 38.0)</td>
<td>21.0 (11.0, 40.5)</td>
</tr>
<tr>
<td>FACT-Fatigue score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.3 (11.6)</td>
<td>29.8 (11.6)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>69.3 (13.71)</td>
<td>67.8 (13.83)</td>
</tr>
<tr>
<td>Common tumor types, No. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>57 (16)</td>
<td>55 (16)</td>
</tr>
<tr>
<td>Large intestine/colon</td>
<td>65 (18)</td>
<td>51 (14)</td>
</tr>
<tr>
<td>Non–small-cell lung</td>
<td>34 (10)</td>
<td>32 (9)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>16 (5)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Other solid tumor</td>
<td>96 (27)</td>
<td>126 (36)</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>13 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>11 (3)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>26 (7)</td>
<td>17 (5)</td>
</tr>
<tr>
<td>Non–Hodgkin lymphoma</td>
<td>33 (9)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Disease stage at diagnosis, No. (%)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I, II, or III</td>
<td>188 (53)</td>
<td>186 (53)</td>
</tr>
<tr>
<td>IV</td>
<td>133 (38)</td>
<td>133 (38)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (6)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Unknown or missing</td>
<td>12 (3)</td>
<td>13 (4)</td>
</tr>
</tbody>
</table>

*ECOG, Eastern Cooperative Oncology Group; eEPO = endogenous erythropoietin concentration; FACT, Functional Assessment of Cancer Therapy.
†Western European countries included Austria, Belgium, Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and United Kingdom; and Central and Eastern European countries included Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovak Republic, and Ukraine.
‡Lung or gynecologic cancer category for randomization includes non–small-cell lung, small-cell lung, ovarian, endometrial, and cervical primary cancers.
§TNM classification.

Table 2. Dosing of Darbepoetin alfa

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Darbepoetin alfa 500 μg every 3 weeks (n = 353)</th>
<th>Darbepoetin alfa 2.25 μg/kg weekly (n = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of doses</td>
<td>4.2 (1.24)</td>
<td>11.8 (3.98)</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Duration of exposure, weeks*</td>
<td>12.8 (3.6)</td>
<td>12.3 (3.9)</td>
</tr>
<tr>
<td>Median</td>
<td>15.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Average planned weekly dose, μg/wk</td>
<td>Mean (SD)</td>
<td>166.7 (0)</td>
</tr>
<tr>
<td>Median</td>
<td>152.5 (31.1)</td>
<td></td>
</tr>
<tr>
<td>Average weekly dose, μg/wk†</td>
<td>Mean (SD)</td>
<td>125.2 (37.1)</td>
</tr>
<tr>
<td>Weight-adjusted average weekly dose delivered†, μg/kg/wk</td>
<td>Mean (SD)</td>
<td>1.87 (0.644)</td>
</tr>
<tr>
<td>Cumulative dose, μg</td>
<td>Mean (SD)</td>
<td>1608.2 (582.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1349.3 (661.4)</td>
</tr>
</tbody>
</table>

*Number of weeks between first and last dose adjusted by frequency. SD = standard deviation.
†Includes 0 doses, i.e., doses withheld or missed.

respectively (Table 2). The average planned weekly doses (i.e., at time of random assignment, before dose adjustment) were 166.7 μg (i.e., the 500-μg starting dose) and 152.5 (SD = 31.1) μg for the every-3-week and weekly groups, respectively. Because of dose modifications, the average weekly doses (including the weeks with withheld or missed doses) over the entire study were 1.87 (SD = 0.644) μg/kg for the every-3-week group and 1.59 (SD = 0.527) μg/kg for the weekly group (difference = 0.28 μg/kg, 95% CI = 0.17 to 0.39 μg/kg).

Dose modification in this study resulted predominantly from the dose reduction rule in patients with a hemoglobin rise of 1 g/dL or greater within any 14-day period (in the absence of a transfusion during the previous 14 days). Overall, a high proportion of patients had their dose reduced to 60% of the previous dose (adjusted Kaplan–Meier estimates = 74%, 95% CI = 69% to 75% and 80% and 75%, 95% CI = 70% to 80%, in the every-3-week and weekly groups, respectively) with a median time to first dose reduction of 43 days for the every-3-week group and 36 days for the weekly group (Table 3). Similar patterns were observed within each regimen when the active and placebo drug dosing changes were compared (data not shown).

### Efficacy Evaluations

**RBC transfusions.** The percentage of patients in the every-3-week group who had blood transfusions between week 5 and the end of the treatment phase was lower than that observed in the weekly group (unadjusted Kaplan–Meier estimates = 23% [95% CI = 19% to 28%] versus 30% [95% CI = 25% to 35%], difference = −6.8%; 95% CI = −13.6 to 0.1; Fig. 2, A). When the analyses were adjusted for stratification factors, results were consistent with the aforementioned unadjusted results. That is, fewer patients in the every-3-week arm than in the weekly arm received blood transfusions from week 5 to the end of the treatment phase (adjusted Kaplan–Meier estimates = 19% [95% CI = 15% to 23%] versus 28% [95% CI = 23% to 33%], difference = −6.7%, 95% CI = −13.2% to −0.2%).

The primary endpoint of RBC transfusions from week 5 to the end of the treatment phase was repeated using the per-protocol analysis set and the alternate (secondary) censoring approach, as described in “Subjects and Methods.” These sensitivity analyses

Downloaded from https://academic.oup.com/jnci/article-abstract/98/4/273/2521973 by guest on 10 October 2018
Table 3. Dose withholding and dose reductions on study in the absence of red blood cell transfusions∗

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Darbepoetin alfa 500 μg every 3 weeks (n = 353)</th>
<th>Darbepoetin alfa 2.25 μg/kg weekly (n = 352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with maximum hemoglobin ≥13.0 g/dL at any time during the study, No. (%)</td>
<td>76 (21.5)</td>
<td>84 (23.9)</td>
</tr>
<tr>
<td>Excess rise in hemoglobin, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2.0 g/dL in 28 days</td>
<td>118 (33.4)</td>
<td>118 (33.5)</td>
</tr>
<tr>
<td>≥1.5 g/dL in 21 days</td>
<td>207 (58.6)</td>
<td>206 (58.5)</td>
</tr>
<tr>
<td>≥1.0 g/dL in 14 days</td>
<td>232 (65.7)</td>
<td>222 (63.1)</td>
</tr>
<tr>
<td>Patients with at least one dose reduction due to rapid rate of rise in hemoglobin concentration Kaplan–Meier percent (95% CI)</td>
<td>74 (69 to 80)</td>
<td>75 (70 to 80)</td>
</tr>
<tr>
<td>Crude percent (95% CI)</td>
<td>66 (61 to 71)</td>
<td>69 (64 to 74)</td>
</tr>
<tr>
<td>Median time to first dose reduction due to rapid rate of rise in hemoglobin concentration (study day) (95% CI)</td>
<td>43 (43 to 61)</td>
<td>36 (35 to 49)</td>
</tr>
<tr>
<td>Hemoglobin concentration at time of first dose reduction due to rapid rate of rise in hemoglobin concentration (g/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>232</td>
<td>243</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>11.1 (11.0 to 11.3)</td>
<td>11.1 (10.9 to 11.2)</td>
</tr>
</tbody>
</table>

∗CI = confidence interval.

generated similar results, namely, that the upper limit of the 95% confidence interval for the difference in transfusion rates between groups was well below the prespecified noninferiority margin of 12.5% (Fig. 2, B).

The percentage of patients receiving RBC transfusions from week 1 to the end of the treatment phase yielded results consistent with the analysis of the primary endpoint. That is, patients in the every-3-week treatment arm had fewer blood transfusions than those in the weekly arm (unadjusted Kaplan–Meier estimates = 29% [95% CI = 24% to 34%] versus 36% [95% CI = 30% to 41%], difference = −6.9%, 95% CI = −14.0% to 0.2%).

In the analysis of transfusion rates by weight, no statistically significant differences were observed between any of the weight categories in the every-3-week schedule, suggesting that treatment effectiveness did not decrease with increasing body weight when fixed dosing was used (Fig. 3). Similar results were obtained for transfusion results by BMI categories (data not shown).

In the analysis evaluating the subset of patients who received transfusions, the numbers of RBC units transfused from study day 1 to the end of the treatment phase were similar among the two treatment groups (mean = 1.64 [SD = 3.87] and mean = 2.07 [SD = 4.52] [standard unit = 250 mL] for the every-3-week and weekly groups, respectively).

Change in hemoglobin and hemoglobin target. The hemoglobin profiles over time were similar for the two treatment groups. Hemoglobin concentrations increased from a mean baseline level of 9.8 g/dL to approximately 11 g/dL in the initial 7 weeks of therapy and then stabilized at this level (Fig. 4, A).

As previously noted, most patients experienced a dose reduction at least once during the study because of increases in hemoglobin concentration of 1 g/dL or greater in a 14-day period. The mean hemoglobin concentrations at the time of the first dose reduction were the same for the every-3-week and weekly groups (11.1 g/dL). The median time to the first dose reduction was similar in the two groups and corresponded to the time at which the hemoglobin concentration profiles for both groups stabilized. A piecewise mixed-effects model was developed to further investigate the effect of these dose reductions on hemoglobin levels. A linear increase in hemoglobin concentration of 0.34 g/dL per week up to the first dose reduction was observed with hemoglobin concentration stabilizing after the first dose reduction (subsequent increase of 0.028 g/dL per week), suggesting that a 40% dose reduction for either schedule effectively sustains hemoglobin levels in the setting of continuing chemotherapy administration.
Darbepoetin alfa 500 µg every 3 weeks
Darbepoetin alfa 2.25 µg/kg weekly

Fig. 3. Incidence of transfusions from week 5 to the end of the treatment phase by weight quintiles (kg) of patients in the two study arms. Unadjusted Kaplan–Meier estimates and 95% confidence intervals of RBC transfusion incidence from week 5 to the end of the treatment phase are shown (squares, 500 µg every 3 weeks; triangles, 2.25 µg/kg weekly). The total number of patients in each weight quintile is indicated below each plot. Quintile groups include the lower 3 weeks; between groups. This change was consistent, whether the analysis was based on available data or last-value-carried-forward (Fig. 5, A).

The target hemoglobin concentration was prespecified as 11 g/dL or greater. After adjustment for stratification variables, the Kaplan–Meier percentage of patients in the every-3-week and weekly groups achieving this target from week 1 to the end of the treatment phase was 84% (95% CI = 81% to 88%) and 77% (95% CI = 72% to 81%), respectively. The unadjusted Kaplan–Meier results were similar: 73% (95% CI = 68% to 78%) in the every-3-week group and 72% (95% CI = 67% to 77%) in the weekly group (Fig. 4, B). Median times to achievement of target hemoglobin levels were 36 and 43 days for patients in the every-3-week and weekly groups, respectively. The proportion of patients in the two study groups who reached the target hemoglobin concentration at the end of the treatment phase was similar (Fig. 5, B).

After achievement of target hemoglobin levels, patients’ mean hemoglobin concentration remained above 11 g/dL, consistent with evidence-based practice guidelines: 11.4 g/dL (95% CI = 11.4 to 11.6 g/dL) for the weekly group. The majority of patients subsequently maintained their hemoglobin levels in the target range of 11–13 g/dL.

**Patient self-reported assessment of fatigue.** Baseline FACT-Fatigue scores are shown in Table 1. Data from 295 (every 3 weeks) and 288 (weekly) patients who completed both the baseline and the end of the treatment phase FACT-Fatigue questionnaires were available for analysis. The mean changes in FACT-Fatigue subscale scores from baseline to the end of the treatment phase were similar for both treatment groups. More than half of the patients in each treatment group (adjusted Kaplan–Meier estimates = 57% and 58% in the every-3-week and weekly groups, respectively) had at least a three-point improvement in FACT-Fatigue subscale score from baseline by the end of the treatment phase (Kaplan–Meier difference between treatment groups = −0.9%, 95% CI = −9.7% to 7.8%). No statistically significant differences were observed between the two treatment groups for any other quality of life instruments.

**Safety**

In general, the incidence of adverse events was comparable in both groups (Table 4). Most adverse events were deemed by investigators to be unrelated to darbepoetin alfa treatment and were attributable to chemotherapy treatment or underlying malignancy. The most frequently reported adverse events were...
n needed dose. Causes of death were ascribed to disease progression, such as infections, or to cardiac and respiratory complications (Table 4). Results of stratified analysis of safety data by weight and BMI categories did not reveal differences for lighter versus heavier patients in either treatment group nor for men or women (data not shown).

As with all recombinant protein therapies, potential immunogenicity is an important safety concern. No anti–darbepoetin alfa antibodies were detected in this population of patients receiving darbepoeitin alfa.

### Discussion

Darbepoetin alfa is an erythropoietic agent with a prolonged serum half-life that has been shown to be safe and effective for the treatment of chemotherapy-induced anemia when administered using weekly or every-3-week dosing schedules (3,4,18–20). The primary objective of this randomized, double-blind, double-dummy, active-controlled, phase 3, noninferiority study was successfully achieved, demonstrating that a 500-μg darbepoeitin alfa treatment every 3 weeks was at least as effective as a weekly treatment of 2.25 μg/kg.

This is the first clinical trial, to our knowledge, to formally compare the effectiveness of the extended every-3-week dosing schedule of darbepoetin alfa with standard weekly dosing with respect to clinically important endpoints such as reduction in RBC transfusion requirements, improvement of fatigue, and achievement of a relevant target hemoglobin concentration. The noninferiority design, previously used in the study of erythropoiesis-stimulating agents (37–41), is endorsed by regulatory agencies to rigorously test whether a new therapeutic intervention is at least as effective as standard therapy (42). In this study, the noninferiority margin of 12.5% was based on transfusion incidence data from week 5 to the end of the treatment phase of two previous, placebo-controlled darbepoetin alfa 2.25 μg/kg
weekly studies (3,4) and ensured that a substantial fraction of the treatment effect could be observed. The results of all analyses met the prespecified criterion for noninferiority. Moreover, because the upper limit of the 95% confidence interval for the difference in RBC transfusions between every-3-week and weekly treatment groups was 0.1, substantially less than 12.5%, the same conclusion would have been reached if, hypothetically, a lower, more conservative noninferiority margin were used.

A series of sensitivity analyses were performed to confirm the robustness of the noninferiority conclusion. The results of the primary analysis were consistent across analysis sets (primary transfection versus per-protocol analysis sets), analysis methods (adjusted versus unadjusted, Kaplan–Meier proportions versus crude rates), and censoring mechanisms (primary versus secondary censoring), with a suggested decreased in incidence of transfusions in the every-3-week group compared with the weekly group. Analyses of transfusion endpoints and data analysis sets that were adjusted for stratification factors were statistically significantly favor of the every-3-week dosing schedule (data not shown).

The results of this study were consistent with results from the two previous randomized, double-blind, phase 3 studies of darbepoetin alfa 2.25 μg/kg weekly for 12 weeks (3,4), which showed statistically significant and clinically meaningful differences from placebo. If the treatment period is standardized to 12 weeks, the blood transfusion incidence from week 5 to the end of the treatment phase for the weekly arm of this study (unadjusted Kaplan–Meier estimate = 26% [95% CI = 21% to 31%]) corresponds to the transfusion rates associated with the active treatment arms of these two previous studies [27% (95% CI = 20% to 35%) (3) and 31% (95% CI = 24% to 38%) (4)] and to the rate observed in the 2.25 μg/kg control arm in another randomized, active-controlled, phase 3 trial (41).

An important difference in the design of this study, as compared with previously published studies evaluating the efficacy and safety of erythropoietic agents in oncology, was the use of strict dose adjustment rules. These rules, described in the package inserts for erythropoiesis-stimulating agents (16,43), stem from recommendations by the Oncology Drugs Advisory Committee of the Food and Drug Administration (44) in response to two placebo-controlled trials reporting adverse survival outcomes for the epoetin alfa (Eprex) and epoetin beta (NeoRecormon) groups (45,46). Consequently, greater than two-thirds of patients in both groups in the current study required dose reductions or withholding. Although previously reported analyses have shown an increased risk of cardiovascular or thromboembolic events associated with a 2 g/dL rise in hemoglobin in 28 days (47,48), data from this study did not indicate an increased risk among patients who exceeded a 1 g/dL increase in hemoglobin in 14 days (in the absence of an RBC transfusion). It is interesting to note, however, that similar rates of rise (i.e., increases in hemoglobin concentration of ≥1 g/dL in 14 days) have been observed in a substantial number of patients in the placebo groups of randomized, controlled trials of darbepoetin alfa for chemotherapy-induced anemia (3,4), reflecting the inherent variability of hemoglobin levels in patients receiving chemotherapy. These data suggest that further work is needed to determine the most appropriate recommendations for dose titration to prevent appropriately rapid rises in hemoglobin concentrations in cancer patients receiving chemotherapy.

The hemoglobin concentration profiles over time were similar for the two treatment groups and were characterized by an increase in hemoglobin concentration during the initial 7 weeks of therapy, followed by a slower rate of increase in hemoglobin levels that coincided with the median time to first dose reduction; incidentally, this occurred as the mean hemoglobin concentrations were greater than 11 g/dL. These hemoglobin profiles are consistent with the current National Comprehensive Cancer Network guidelines for cancer- and treatment-related anemia, which state that the goal of therapy should be to attain hemoglobin concentrations between 11 and 12 g/dL (28). Despite the strict dose adjustment rules in this study, the comparability of the two darbepoetin alfa regimens was supported by the high proportion of patients who achieved target hemoglobin levels and subsequently maintained these levels for the remainder of their treatment period. The response to darbepoetin alfa therapy before dose reduction suggests that the initial doses of darbepoetin alfa (2.25 μg/kg weekly and 500 μg every 3 weeks) were highly effective in stimulating erythropoiesis and correcting anemia. These data support the use of a reduced dose, after initial alleviation of anemia, to maintain hemoglobin concentrations throughout the remainder of chemotherapy treatment.

A fixed dose was selected for the every-3-week treatment arm of this study because unit dosing has been shown to be safe, effective, convenient (simplifying drug administration), and consistent with the pattern of usage of erythropoiesis-stimulating agents in clinical practice (7,22,24–26). Specifically, the 500-μg dose examined in this study approximates the approved every-3-week dose in Europe of 6.75 μg/kg (17) as well as an equivalent exposure to the standard weekly 2.25-μg/kg dose (16), for an average-weight patient of 74 kg. In this trial, the efficacy of a fixed dose of 500 μg every 3 weeks was compared with the approved weight–based starting dose. In both transfusion- and hemoglobin-related endpoints, no evidence of decreasing effect was observed with increasing weight or BMI, nor was there any evidence of inferior effectiveness for the fixed-dose group relative to the weight-based comparator at higher weight categories.

Determining the safety of the infrequent fixed dose of darbepoetin alfa was a key objective of this trial. There was no evidence of trends indicating a differential adverse event profile or adverse hemoglobin profile between groups or across weight or BMI categories. Importantly, the every-3-week regimen was not associated with an increased incidence of cardiovascular or thromboembolic adverse events when compared with the currently approved weekly starting dose. Furthermore, there was no evidence of differences in the rate of rise in hemoglobin concentration or maximum hemoglobin threshold concentration of 13 g/dL, nor was there any apparent delay in response to dose titration or dose withholding, indicating that a level of control similar to the weekly schedule is possible.

Although the noninferiority design is appropriate for the hypothesis tested in this study, it does not allow for a direct assessment of the treatment effect because there is no placebo group. An indirect assessment of the treatment effect was possible by comparing results from this trial with the results of the weekly 2.25 μg/kg arms of previous phase 3 trials of darbepoetin alfa (3,4). Analyses revealed results consistent with those obtained in the current study for the primary endpoint. Another limitation of the noninferiority design is the choice of population; in noninferiority studies, the intent-to-treat approach may not be conservative because protocol deviations tend to minimize differences between treatments. To assess the impact on our findings of analysis population, protocol deviations, and the pattern
of withdrawal, a series of prespecified sensitivity analyses were performed. These demonstrated the consistency of the findings regardless of the analysis set use, confirming the validity of the noninferiority conclusion. In addition, the strict dose adjustment rules applied in this study appeared to lessen the observed overall change in hemoglobin, as compared with historical data, thereby potentially limiting the conclusions to the use of darbepoetin alpha under these dose modification conditions. However, because these rules are consistent with the revised product labels for erythropoietic therapies in oncology (16,43), these findings are relevant to current usage of this agent. Moreover, these rules appeared to have no obvious impact on the transfusion requirements in this population when compared with the historic data (3,4).

Finally, the primary endpoint selected in this study excluded the first 4 weeks of therapy because noninferiority studies inherently rely on historic data, and this has been the standard transfusion endpoint used in placebo-controlled trials for erythropoietic product registration in oncology. Transfusion incidence from week 5 to the end of treatment phase may be a conservative endpoint in placebo-controlled trials; however, in active-controlled trials, the exclusion of the first 4 weeks of therapy may introduce bias, particularly in relation to unequal distribution of early withdrawal. To address this potential bias, a prespecified secondary endpoint evaluated transfusion incidence over the entire treatment phase. This key secondary endpoint yielded results consistent with the analysis of the primary endpoint.

This study represents the progress of randomized, controlled trials in the study of erythropoiesis-stimulating agents from more frequent to less frequent administration and from weight-based to fixed every-3-week dosing. Randomization was performed every 3 weeks using a fixed 500-μg dose, achieves clinical outcomes comparable to those with the current labeled starting dose of darbepoetin alfa (2.25 μg/kg weekly). There was no decrease in effectiveness observed for heavier patients, nor were there increased safety concerns apparent in patients with lower weights. Therefore, patients receiving chemotherapy who develop anemia can safely and effectively be treated with darbepoetin alfa every 3 weeks. The fixed every-3-week dosing allows for a convenient, infrequent schedule that permits the synchronization of anemia treatment with the administration of many common chemotherapy regimens. The ability to administer erythropoietic therapy on a schedule that synchronizes with chemotherapy administration can enhance patient convenience and lessen resource utilization. Although differences in practice patterns may exist between Europe and North America with respect to the rates of erythropoietic therapy use in oncology (49,50), there is no evidence to suggest that patients from these two regions would exhibit different anemia-related outcomes when given comparable regimens of darbepoetin alfa. The potential health economic benefit of reduced number of patient visits associated with anemia intervention administered on the same schedule as chemotherapy should be examined in prospective randomized, controlled trials.

**APPENDIX**

Members of the Aranesp 20030231 Study Group are: G. Stegar, Universitätsklinik für Innere Medizin I, Vienna, Austria; J. Vansteenkiste, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; A. Neubauer, Klinikum der Philipps-Universität Marburg, Marburg, Germany; M. Aapro, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany; G. Peschel, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany; B. Emmerich, Klinikum der Universität München, Munich, Germany; A. Tomova, District Dispensary for Oncological Diseases With Stationary Hemotherapy Department, Plovdiv, Bulgaria; V. Malec, Nenomica F. D. Roosevelta, Banska Bystrica, Slovakia; N. Frickhofen, Dr. Horst-Schmidt-Kliniken GmbH Klinik Innere Medizin III, Wiesbaden, Germany; J. J. Cruz, Hospital Clinico Universitario, Salamanca, Spain; D. Bron, Institutt Jules Bordet Hematology, Brussels, Belgium; S. Pyrhoenen, Turku University Central Hospital, Turku, Finland; W. Hilgers, Institut Sainte Catherine Hôpital de Jour, Avignon, France; L. Bosquède, CHR Citadelle Pneumologie, Liège, Belgium; M. Clemens, Krankenanstalt Mutterhaus der Barmherzigen Schwestern, Saarbrücken, Germany; M. R. Nowrousian, Universitätsklinikum Essen Westdeutsches Tumorzentrum, Essen, Germany; F. Nobile, Ospedali Riuniti A. O. Bianchi-Melacrin-Rovereto, Reggio Calabria, Italy; A. H. Honkoop, Isala Klinieken Lokatie Sophia Zorggroep, Rotterdam, The Netherlands; H. W. A. Berenschot, Albert Schweitzer Ziekenhuis, Dordrecht, The Netherlands; M. R. Schaafsma, Medisch Spectrum Twente, Enschede, The Netherlands; P. Gascón, Hospital Clinic i’Provincial, Barcelona, Spain; A. Gürpide, Clinica Universitaria De Navarra, Pamplona, Spain; E. Kubista, Universitätsklinikum für Frauenheilkunde, Vienna; Austria; G. V. Kornek, Universitätsklinik für Innere Medizin I, Vienna, Austria; K. Gattringer, A. Ø. Bezirkskrankenhaus Kufstein, Kufstein, Austria; J. Van Droogenbroeck, A. Z. St. Jan, Brugge, Belgium; P. Zachee, A. Z. Stuivenberg, Antwerpen, Belgium; M. Hansen, Rigshospitalet, Copenhagen, Denmark; C. Aul, St. Johannes Hospital, Duisburg, Germany; A. Hanauske, Allgemeines Krankenhaus St. Georg, Hamburg, Germany; S. Korsten, Vinzenz-Pallotti-Hospital, Bergisch Gladbach, Germany; G. Wiedemann, Oberschwanib Klinik GmbH, Ravensburg, Germany; P. Marchetti, Istituto Dermopatico Dell’immunologia, Rome, Italy; A. Lop, Ospedale Civile, Latisana, Italy; R. Hermann, Kantonsspital Basel, Basel, Switzerland; D. Rauch, Spital Thun-Simmental AG, Thun, Switzerland; M. Bargetzi, Kantonsspital Aarau, Aarau, Switzerland; D. W. Milligan, Birmingham Heartlands Hospital, Birmingham, United Kingdom; A. Ferrant, UCL St. Luc, Brussels, Belgium; K. Van Egen, A. Z. Groeningen, Kortrijk, Belgium; U. Jäger, Universitätsklinikum für Innere Medizin I, Vienna, Austria; E. Gunsilius, Universitätsklinikum für Innere Medizin, Innsbruck, Austria; M. Aapro, Clinique de Genolier,Genolier, Switzerland; M. Wilhelm, Klinikum Nürnberg-Nord, Nürnberg, Germany; W. Brugger, Klinikum der Stadt Villingen-Schwenningen, Villingen-Schwenningen, Germany; E. D. Kreuser, Krankenhaus der Barmherzigen Brüder, Regensburg, Germany; M. J. Eckhart, Praxisgemeinschaft, Erlangen, Germany; O. Brudler, Hämatologisch-Onkologische Praxis Augsburg, Augsburg, Germany; B. Anker-Jensen, Sonderborg Sygehus, Sonderborg, Denmark; A. Lozano, Hospital Ciudad De Jaen, Jaén, Spain; A. Alcala, Hospital Ciudad De Jaen, Jaén, Spain; M. V. Mateos, Hospital Clinico Universitario, Salamanca, Spain; J. Sierra, Hospital Santa Creu l’ Sant Pau, Barcelona, Spain; A. Lopez, Hospital Vall d’Hebron, Barcelona, Spain; J. Mäenpää, Tampere University Hospital, Tampere, Finland; L. Bastit, Centre Frederic Jolliot, Lyon, France; L. M. Dourthe, Clinique Claude Bernard, Metz, France; P. Laplaige, Clinique Saint Come Oncologie, Blois, France; D. Castera, Clinique Saint Pierre, Perpignan, France; E. Antoine, Clinique Hartmann, Neuilly Sur Seine, France; H. P. Elkedal, Haukelands Universitetssykehus, Bergen, Norway; S. Barroso, Hospital de José Joaquim Fernandes, Beja, Portugal; E. Sanches, Instituto Portugués de Oncologia de Francisco Gentil, Porto, Portugal; G. Birgégard, Akademiska Sjukhuset, Uppsala, Sweden; M. H. M. Kramer, Meander Medisch Centrum Location, Amersfoort, The Netherlands; M. R. Schiffner, Ziekenhuis Leyenburg, Ziekenhuis Leyenburg.
Den Haag, The Netherlands; M. Boogaerts, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; E. Juvenon, Helsinki University Central Hospital, Helsinki, Finland; B. Lauri, Sunderby Sjukhus, Luleå, Sweden; J. Thaler, Klinikum Kreuzschwestern Wels GmbH 4, Wels, Austria; P. Sorensen, Odense Universitetshospital, Odense, Denmark; M. Smakal, Ustav Onkologie a Pneumologie Na Plesi, Nova Ves Pod Plesi, Czech Republic; P. Koralewski, Wojewodzki Szpital Specjalistyczny, Krakow, Poland; P. Serwatowski, Specjalistyczny Szpital IM, Szczecin, Poland; E. Simova, Nemocnica Zilina, Zilina, Slovakia; M. Galova, Masarykuv Onkologicky Ustav Brno, Brno, Czech Republic; M. Kuta, Nemocnice Chomutov, Chomutov, Czech Republic; M. Wojtkiewicz, Białostocki Osrodek Onkologiczny, Białystok, Poland; M. Kalatejek, Nemocnica Poprad, Poprad, Slovakia; R. Barila, Nemocnica S. Kukura, Michalovie, Slovakia; S. Spaniak, Onkologicky Ustav Sv. Alzbety, Bratislava, Slovakia; T. Pintér, Petz Aládár Megyei Kórház, Gyor, Hungary; G. Bodoky, Szent László Kórház, Budapest, Hungary; J. Szántó, Debreceni Egyetem, Debrecen, Hungary; K. Leppik, Tartu University Hospitals, Tartu, Estonia; T. Jogi, North Estonia Regional Hospital, Tallinn, Estonia; A. Brize, Latvian Oncology Centre, Riga, Latvia; G. Parkalne, P. Stradina Clinical University Hospital, Riga, Latvia; M. Bittina, Daugavpils Oncology Hospital, Daugavpils, Latvia; E. Hotko, Uzhgorod National University at Regional Oncology Centre, Uzhgorod, Ukraine; E. Juozaityte, Kauno Medicinos Universiteto Klinikos, Kaunas, Lithuania; Z. Saladzinskas, Kauno Medicinos Universiteto, Kaunas, Lithuania; E. Aleknavicius, Vilniaus Universiteto Onkologijos Institutas, Vilnius, Lithuania; N. Ivanova, Mhat Pleven, Pleven, Bulgaria; M. Racheva, District Dispensary for Oncological Diseases With Stationary, Tarnovo, Bulgaria; T. Cieuleanu, Institutul Oncologic, Cluj Napoca, Romania; M. Dediu, Institutul Oncologic, Bucuresti, Romania; A. Colita, Institutul Clinic Fundeni, Bucuresti, Romania; P. Oliynychenko, City Oncology Hospital, Kyiv, Ukraine; I. Vynnychenko, Regional Oncology Centre, Sumy, Ukraine; Y. Shapryk, State Regional Oncological Diagnostical and Medical Centre, Liviv, Ukraine; M. Pylpenko, Grigoriev Institute by Medical Radiology Ams of Ukraine, Kharkiv, Ukraine; I. Bondarenko, Dnepropetrovsk State Medical Academy at City Clinical Hospital, Dnepropetrovsk, Ukraine; I. Galachuk, State Medical Academy at Regional Oncology Centre, Ternopil, Ukraine.

REFERENCES

NOTES

The research of Drs. Canon and Vansteenkiste is funded by Amgen, and Drs. Ferreira, Rossi, and Amado work for Amgen and hold stock in the company. Amgen Limited, Cambridge, U.K. sponsored and funded the study (Amgen Study No. 20030231).

The authors thank the investigators, study coordinators, and participants at each of the institutions for their contributions to this study. We thank Sarah Carter and Elaine Harrop, MSc, for coordinating study conduct and data collection, and Alexander Liede, PhD, for assistance in writing this manuscript.

Funding to pay the Open Access publication charges for this article was provided by Amgen Inc.

Manuscript received July 26, 2005; revised December 2, 2005; accepted December 27, 2005.