

**Aranesp<sup>®</sup> (darbepoetin alfa) Safety**

**Oncologic Drugs Advisory Committee**

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**Table of Contents**

1	EXECUTIVE SUMMARY .....	7
2	BACKGROUND .....	10
2.1	Epoetin Therapeutics .....	10
2.2	Epoetin alfa and Epoetin beta: Recent Analyses .....	10
2.3	Clinical Syndromes Associated with Increased EPO Levels .....	11
2.4	Framework for Safety Analyses.....	12
3	ARANESP PROPERTIES .....	14
3.1	Erythropoietic Protein Super-Family .....	14
3.2	Aranesp is a Distinct Molecular Entity .....	14
3.3	Aranesp Receptor Binding.....	14
3.4	Aranesp Signaling.....	15
3.5	EPO-R Expression and Tumor Biology Considerations.....	16
4	ARANESP PRECLINICAL OBSERVATIONS.....	18
4.1	Aranesp Pharmacokinetics and Pharmacodynamics.....	18
4.2	Genotoxicity and Mutagenesis .....	18
4.3	Human Tissue Binding.....	18
4.4	Thrombotic Events .....	18
4.5	Tumor Initiation and Tumor Progression .....	18
5	ARANESP CLINICAL EXPERIENCE .....	20
6	THROMBOTIC EVENTS.....	21
6.1	Literature Review.....	21
6.2	Background Epidemiology .....	22
6.3	Aranesp Clinical Trial Experience.....	24
6.4	Proactive Aranesp Labeling.....	25
7	PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL .....	27
7.1	Individual Double-blind, Placebo-controlled Trials .....	28
7.1.1	Study 980297 .....	28
7.1.2	Study 20000161 .....	32
7.2	Pooled Randomized, Double-blind, Placebo-controlled Trials.....	37
7.2.1	Study 980291 .....	38
7.2.2	Study 990114 .....	39
7.2.3	Pooled Analyses.....	39
7.3	Relationship Between Hemoglobin Metrics and Survival.....	41
7.4	Tumor Types .....	44
7.5	Summary of Aranesp Clinical Trial Findings .....	46
8	OVERALL BENEFIT/RISK ASSESSMENT .....	47
9	ONGOING STUDIES AND PHARMACOVIGILANCE PROGRAM .....	48

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9.1	Pharmacovigilance Program Analyses.....	51
9.2	Amgen Study 20010145: Study in Small-cell Lung Cancer .....	52
9.3	Study FR-2003-3005: Study in Diffuse Large B-cell Lymphoma .....	52
9.4	Study SE-2002-9001: Study in Head-and-Neck Cancer .....	53
9.5	Study DE-2001-0033: Study in Neoadjuvant Breast Cancer .....	53
9.6	Study DE-2002-0015: Study in Adjuvant Breast Cancer .....	54
10	SUMMARY.....	55
11	REFERENCES .....	58

**List of Tables**

Table 1. Thrombotic Event Risk Pooled Trials ..... 24  
Table 2. Relationship Between Thrombotic Event History and Treatment ..... 25  
Table 3. Study 980297: Baseline Demographics ..... 29  
Table 4. Study 20000161: Baseline Demographics ..... 33  
Table 5. Study 980291 (Schedule 1): Baseline Demographics ..... 38  
Table 6. Study 980291 (Schedule 2): Baseline Demographics ..... 38  
Table 7. Study 990114: Baseline Demographics ..... 39  
Table 8. Treatment Endpoint Summaries by Study..... 40  
Table 9. Pooled Analysis: Cox Regression Models for ..... 42  
Table 10. Aranesp Pharmacovigilance Program Trials: Power and Sensitivity Calculations..... 50  
Table 11. Amgen Trials and Investigator-sponsored Trials: Pharmacovigilance Program Patient-years ..... 52

**List of Figures**

Figure 1. Patients and Patient-years of Aranesp Therapy Over Time ..... 20  
Figure 2. Age- and Sex-adjusted Relative Incidence of Venous Thrombotic Events Among Cancer Chemotherapy Patients Compared With the General Population in the General Practice Research Database..... 23  
Figure 3. Study 980297: Progression-free Survival (Non-small Cell Lung Cancer) ..... 30  
Figure 4. Study 980297: Progression-free Survival (Small-cell Lung Cancer) ..... 30  
Figure 5. Study 980297: Overall Survival (Non-small Cell Lung Cancer) ..... 31  
Figure 6. Study 980297: Overall Survival (Small-cell Lung Cancer) ..... 31  
Figure 7. Study 20000161: Progression-free Survival (Aggressive Non-Hodgkin's Lymphoma) ..... 34  
Figure 8. Study 20000161: Progression-free Survival (Indolent Non-Hodgkin's Lymphoma) ..... 34  
Figure 9. Study 20000161: Progression-free Survival (Multiple Myeloma) ..... 35  
Figure 10. Study 20000161: Progression-free Survival (Chronic Lymphocytic Leukemia) ..... 35  
Figure 11. Study 20000161: Overall Survival (Aggressive Non-Hodgkin's Lymphoma) ..... 36  
Figure 12. Study 20000161: Overall Survival (Indolent Non-Hodgkin's Lymphoma) ..... 36  
Figure 13. Study 20000161: Overall Survival (Multiple Myeloma)..... 37  
Figure 14. Study 20000161: Overall Survival (Chronic Lymphocytic Leukemia) ..... 37  
Figure 15. Pooled Data Set: Progression-free Survival ..... 41  
Figure 16. Pooled Data Set: Overall Survival..... 41  
Figure 17. Pooled Analysis: Progression-free Survival for Patients with Baseline Hemoglobin ..... 43  
Figure 18. Pooled Analysis: Overall Survival for Patients by Baseline Hemoglobin ..... 44  
Figure 19. Progression-free Survival Hazard Ratios Associated With Aranesp Versus Placebo Therapy ..... 45  
Figure 20. Overall Survival Hazard Ratios Associated With Aranesp Versus Placebo Therapy..... 45

**List of Abbreviations and Glossary**

<b>Abbreviation or Term</b>	<b>Definition/Explanation</b>
βc	β common chain
CHOP	chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMF	chemotherapy with cyclophosphamide, methotrexate, and fluorouracil
DA	darbepoetin alfa
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGF-R	epidermal growth factor receptor
EPO	(endogenous) erythropoietin
epoetin	Epoetin alfa and/or Epoetin beta
EPO-R	erythropoietin receptor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GPRD	General Practice Research Database
HER2	human epidermal growth receptor 2
hgb	hemoglobin
HR	hazard ratio
IL	interleukin
JAK-STAT	Janus kinase/signal transducer and activator of transcription
Kd	dissociation constant
kDa	kilodalton

continued

**List of Abbreviations and Glossary (continued)**

<b>Abbreviation or Term</b>	<b>Definition/Explanation</b>
Max	maximum
Min	minimum
NCCN	National Comprehensive Cancer Network
NE	not estimable
NHDS	National Hospital Discharge Survey
NHL	non-Hodgkin's lymphoma
NSCLC	non-small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee
PL	placebo
PY	patient-years
R-CHOP	chemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone
RFS	relapse-free survival
RR	relative risk
SCLC	small-cell lung cancer
VEGF	vascular endothelial growth factor

## 1 EXECUTIVE SUMMARY

Aranesp® (darbepoetin alfa) is a unique erythropoietic molecule that differs from other erythropoietic-stimulating proteins with regard to amino acid sequence, glycosylation, receptor affinity, and pharmacokinetic/pharmacodynamic profile. It is considered distinct from other erythropoietic molecules from scientific, clinical, legal, and regulatory perspectives. Aranesp is licensed for the treatment of anemia in patients with chronic renal failure and patients with non-myeloid malignancies receiving chemotherapy. Aranesp reduces fatigue and the need for transfusions and improves quality of life for patients with grievous illnesses. Aranesp has a favorable benefit/risk profile for the treatment of chemotherapy-induced anemia when used in accord with approved product labeling and published guidelines. Amgen fully supports hemoglobin targets and dosing adjustment regimens recommended in the approved package insert and in the National Comprehensive Cancer Network (NCCN) guidelines. Through December 2003, more than 427,000 patients have received Aranesp therapy, representing more than 268,000 patient-years of experience.

As the company that was first to clone erythropoietin (EPO) and was the original developer of Epoetin alfa and the creator, developer, and marketer of darbepoetin alfa, Amgen's central mission is to improve patients' lives while sustaining patient safety. No signal suggesting tumor progression or survival impairment has been observed in preclinical or clinical studies with Aranesp. In this document, we show that no findings from preclinical genotoxicity, mutagenicity, or chronic toxicity studies suggest that this agent initiates tumors or promotes tumor proliferation. In addition, we provide updated experience from long-term follow-up in Aranesp oncology clinical trials (Hedenus et al, 2003; Vansteenkiste et al, 2002) that indicates no tumor-promoting or detrimental effect on survival in patients with cancer.

Theoretical concerns regarding the potential for tumor progression by erythropoietic-stimulating proteins have been present since the original Epoetin alfa approval in 1988 for chemotherapy-induced anemia, and were represented in the initial product labeling. Erythropoietin receptors (EPO-R) have been reported to be present on a variety of normal non-hematopoietic cells and tumor cells, and the functional significance of these receptors remains the subject of ongoing investigation. The clinical relevance of EPO-R expression on different tumor types remains uncertain. Epoetins do not cause increased proliferation of most tumor cell lines in vitro, even at supra-pharmacologic doses. More importantly, no evidence exists that treatment with erythropoietic-stimulating proteins,

including Aranesp, increases tumor progression or decreases survival in tumor xenograft models. Epoetin receptors are not amplified or overexpressed in tumor cells, unlike other receptors that are clearly associated with tumor growth, including epidermal growth factor receptor (EGF-R) and human epidermal growth receptor 2 (HER2).

The 2 controlled trials published by Leyland-Jones et al (INT-76; Leyland-Jones, 2003) and Henke and colleagues (ENHANCE; Henke et al, 2003) were performed with Epoetin alfa (Eprex®) and Epoetin beta (NeoRecormon®), and resulted in safety observations that have led to the current review. These studies had significant design and conduct challenges that limit interpretation of their findings (Blumberg and Heal, 2004; Freidlin and Korn, 2004; Haddad and Posner, 2004; Kaanders and van der Kogel, 2004; Leyland-Jones and Mahmud, 2004). Reduced survival or increased tumor progression have not been observed in association with Aranesp therapy.

These studies have raised many unanswered questions: Is any erythropoietic-stimulating protein (at approved doses for approved indications) associated with a deleterious effect on survival in patients with cancer? Are there, in fact, safety profile differences between the different erythropoietic-stimulating proteins? If impaired survival is attributable to any erythropoietic therapies, what are the relative contributions of thrombotic events, tumor progression, and other adverse events; and are these events related to pretreatment hemoglobin or target hemoglobin concentration, hemoglobin rate of rise, dosing frequency, maximum concentration of or exposure to the erythropoietic agent, associated chemoradiotherapy regimens, cancer type or stage, or specific type of erythropoietic agent administered?

Amgen has been proactive in addressing safety concerns through product labeling, responsible clinical trial design, and active pharmacovigilance. Summarized in this document are analyses of more than 1100 patients receiving Aranesp therapy from 4 randomized, double-blind, placebo-controlled trials. These analyses reveal a stable rate of thrombotic events as expressed in the product label and reveal no evidence for increased tumor progression or reduced survival among patients receiving Aranesp.

Amgen has initiated the Aranesp Pharmacovigilance Program that includes a large, randomized, controlled study in patients with small-cell lung cancer receiving placebo or Aranesp in which survival is the primary outcome measure. An early interim analysis has been incorporated into this study to strengthen patient safety monitoring. In addition, Amgen is collaborating with oncologists conducting large investigator-sponsored trials evaluating survival outcomes in multiple oncology patient populations,

including patients with lymphoma, patients with head-and-neck malignancies receiving radiotherapy, and 2 studies in patients with breast cancer.

Amgen believes that full disclosure and publication of trial details is warranted for the INT-76 trial and the ENHANCE trial in order that a more complete understanding of the results of these trials can be achieved. Amgen believes that erythropoietic treatment of non-anemic patients or treatment regimens with higher-than-approved target hemoglobin concentrations should be performed only in the setting of well-designed and well-executed clinical trials with careful safety monitoring and sufficient patient numbers to permit meaningful safety assessments.

Amgen respects the prudence of the FDA and the Oncologic Drugs Advisory Committee (ODAC) in looking across erythropoietic therapies. At present, no evidence suggests that Aranesp is associated with impaired survival in patients with cancer. Amgen believes that the current Aranesp prescribing information accurately reflects the experience with this product and is committed to ongoing studies that will provide additional insights. Product-specific risk assessment should be evidence-based and driven, in large part, by product-specific observations.

Amgen is pleased to be able to share observations with the FDA and ODAC from both preclinical and clinical Aranesp experience and welcomes the opportunity to engage the committee to frame hypotheses for future investigation.

## 2 BACKGROUND

### 2.1 Epoetin Therapeutics

Amgen was the first to clone Epoetin alfa and is the sponsor of the Epoetin alfa Biologics License Application. In the United States, Epoetin alfa is marketed under the trade names EPOGEN® and PROCREDIT®. Amgen clinically develops, markets, and distributes Epogen, which is indicated for the treatment of anemia associated with chronic renal failure, including patients who are receiving dialysis. Ortho Biotech Products, L.P., a subsidiary of Johnson & Johnson, is responsible for the clinical development, marketing, and distribution of Procrit in the United States under license from Amgen. Amgen manufactures both Procrit and Epogen. Procrit is approved for a number of indications, including the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of chemotherapy. Amgen also created and developed Aranesp® (darbepoetin alfa), which is approved in many parts of the world for patients with non-myeloid malignancies who have chemotherapy-induced anemia, and for patients with anemia of chronic renal disease.

Epogen/Procrit is distinct from EPREX®, which is another Epoetin alfa manufactured by Johnson & Johnson and marketed in Europe, Australia, and Canada by Johnson & Johnson subsidiaries. Eprex is indicated for patients with the anemia of chronic renal disease and chemotherapy-induced anemia in patients with non-myeloid malignancies. Eprex is the medication that was employed in the INT-76 (BEST) trial described by Leyland-Jones (2003). Epoetin beta (NeoRecormon®) is manufactured by Roche and marketed outside the United States. NeoRecormon is the medication that was employed in the ENHANCE trial in head-and-neck cancer described by Henke et al (2003).

### 2.2 Epoetin alfa and Epoetin beta: Recent Analyses

The recent INT-76 and ENHANCE studies have been extensively discussed (Blumberg and Heal, 2004; Freidlin and Korn, 2004; Haddad and Posner, 2004; Kaanders and van der Kogel, 2004; Leyland-Jones and Mahmud, 2004), and Amgen will defer to the sponsors responsible for those studies to represent their experience. These studies employed treatment regimens that were outside the currently-approved labeling and guidelines. The results from these studies are not in keeping with previous epoetin oncology studies that have examined survival outcomes, and such findings have not been observed with Aranesp therapy.

Bohlius and colleagues from the Cochrane Hematological Malignancies Group (Bohlius et al, 2003) presented a comprehensive meta-analysis of randomized, controlled oncology trials examining the effects of epoetin therapy on tumor response and survival. The studies chosen were required to meet the following criteria: malignancy diagnosed by histologic or cytologic criteria; anemia or risk for anemia from chemotherapy, radiotherapy, or underlying malignancy; therapy with Epoetin alfa or Epoetin beta versus placebo or no additional therapy; red blood cell transfusions as necessary in both epoetin and placebo groups; conventional-dose cancer therapy in both epoetin and placebo groups; randomization with or without blinding; and a minimum of 10 patients per study group. Outcomes included overall survival and tumor response.

The Cochrane Group's search yielded 27 published studies with 3284 patients. The meta-analysis reveals no effect with regard to tumor response (relative risk [RR] = 1.4 [95% CI: 1.1, 1.7], 7 evaluable studies, n = 1150) and a trend toward favorable epoetin effect with regard to overall survival (hazard ratio [HR] = 0.80 [95% CI: 0.65, 1.00], 8 evaluable trials, n = 1624). The authors conclude that more clinical trials are needed to test the hypothesis that erythropoietic therapies may improve overall survival.

### **2.3 Clinical Syndromes Associated with Increased EPO Levels**

Clinical syndromes of altered human EPO physiology may provide insights into the potential role of erythropoietic-stimulating proteins in tumor initiation. Primary congenital disorders associated with increased EPO production, or mutations in the EPO-R leading to EPO hypersensitivity, are associated with erythrocytosis in humans. Prchal and Sokol (1996) have written a comprehensive review of primary familial and congenital polycythemia, including EPO overexpression and EPO-R mutations, in approximately 100 individuals in several families. In these families, no increased cancer incidence or leukemic transformation has been observed. A more recent publication further explored the genotype and phenotype of individuals with Chuvash polycythemia (Prchal, 2003). These patients have high EPO levels and polycythemia as a result of altered regulation of the HIF-1 $\alpha$  protein. Affected individuals develop peripheral vein varicosities, hypertension, an increased incidence of strokes, and increased serum levels of vascular endothelial growth factor (VEGF). These patients do not have an increased incidence of cancer, suggesting that increased EPO concentrations alone are not causally associated with tumors (Pastore et al, 2003).

## 2.4 Framework for Safety Analyses

In approaching the safety signals that have emerged from the INT-76 and ENHANCE trials, 3 distinct safety outcomes are under review: survival, tumor progression, and thrombotic events. Most observers agree that additional preclinical studies with cells in culture or with animals may be of interest but are unlikely to be conclusive in clarifying the clinical impact of erythropoietic-stimulating protein therapies in oncology patients. Discussions with investigators and regulatory authorities have been useful in framing oncology study design elements required to evaluate survival and tumor progression outcomes. These elements include a patient population with uniform tumor type, randomization of patients to erythropoietic-stimulating protein therapy versus control therapy, prospective design, stratification of important prognostic features for the type of tumor being studied, and sufficient size to permit detection of small differences in safety signals.

**Key Points:**

- Amgen originally cloned and developed Epoetin alfa (Procrit, Epogen) and created and developed darbepoetin alfa (Aranesp®).
- A recent meta-analysis of oncology trials has shown no signal for decreased tumor responses or reduced survival.
- The clinical trials that have raised concerns over tumor progression and survival have been performed with Epoetin alfa and Epoetin beta. Such findings have not been observed with Aranesp and, thus, do not constitute a class effect.
- Well-designed, prospective, randomized, controlled clinical trials with oncology patient populations that have the same tumor type, and stratification by prognostic factors, are required to evaluate tumor progression and survival signals.

### **3 ARANESP PROPERTIES**

#### **3.1 Erythropoietic Protein Super-Family**

The nucleotide and amino acid sequence of human EPO was first determined in 1983 (Lin et al, 1985), and several epoetin molecules subsequently were developed and approved for clinical use (Epoetin alfa, Epoetin beta, and Epoetin omega). These epoetins have in common the same amino acid sequence and similar, if not identical, physicochemical properties, EPO-R affinities, half-lives, and pharmacologic effects. Although manufacturing differences can substantially alter product quality and immunogenicity, the fundamental biologic and physicochemical properties of each epoetin molecule are dictated in large part by the common amino acid sequence.

#### **3.2 Aranesp is a Distinct Molecular Entity**

Aranesp represents a significant advance in the development of erythropoietic-stimulating protein therapy. Amgen engineered more than 450 epoetin glycosylation analogs containing altered amino acid sequences, and each of the molecules was evaluated for structural stability, biologic activity, and half-life. Five amino acid changes were combined into 1 distinct molecule to enable the addition of 2 new carbohydrate chains at unique sites on the protein backbone. The resulting molecule is distinct from epoetin with regard to physical size, proportion of molecular weight as carbohydrate, number of sialic acid moieties, and amino acid sequence. It has a longer terminal half-life (25.3 hours vs 8.5 observed with Epoetin alfa [Macdougall et al, 1999]), an approximately 5-fold reduction in EPO-R affinity, and a higher concentration is required to activate multiple in vitro assays (12-fold increase required for half-maximal activity in assays of hematopoietic cell growth [Amgen, data on file]). Therefore, Aranesp is considered a distinct molecular entity from scientific (Egrie et al, 2003; Elliott et al, 2003), clinical (Macdougall et al, 1999), legal, and regulatory perspectives.

#### **3.3 Aranesp Receptor Binding**

A higher Aranesp concentration is required to achieve maximal intracellular signaling in hematopoietic cells compared with epoetins. Similarly, the threshold concentration for activation of erythropoiesis in vitro is higher for Aranesp than for epoetins. The reduction in in vitro activity is likely because the EPO-R:epoetin-binding interface involves positive charges on epoetins and negative charges on the receptor (Syed et al, 1998; Elliott et al, 1997). This finding is consistent with the observation that sialic acid (a negatively charged sugar) reduces the on-rate of Aranesp binding to EPO-R through electrostatic charge shield effects (Darling et al, 2002). The lower receptor-binding affinity is

associated with significant biologic activity in part due to the longer Aranesp half-life in vivo (Egrie et al, 2003).

### 3.4 Aranesp Signaling

Aranesp works through interaction with EPO-R to promote proliferation, survival, and differentiation of hematopoietic cells in a manner consistent with the activity of endogenous EPO. It is not known whether Aranesp binding to EPO-R in other tissues results in different intracellular signaling from that observed with epoetins.

EPO-R proteins involved in hematopoiesis exist on the cell surface (Livnah et al, 1999; Remy et al, 1999) and activation occurs when 1 erythropoietic-stimulating protein binds 2 EPO-R molecules (Syed et al, 1998; Youssoufian et al, 1993). EPO-R signaling in hematopoietic cells predominately occurs through phosphorylation of JAK2, and subsequent activation of STAT5, PI3 kinase, and MAP kinase pathways. These and possibly other pathways are believed to produce the downstream effects of cellular proliferation, survival (anti-apoptosis), and differentiation although the criticality and redundancy of these and other intracellular pathways are still the subject of research. Although some of these pathways appear to be active in non-hematopoietic and tumor cell lines, other pathways have been identified as well, and it is unclear if these pathways lead to the proliferative effects or survival effects observed in hematopoietic cells.

Other components in addition to EPO-R may contribute to signaling in different non-hematopoietic cell types. The GM-CSF/IL-3/IL-5 receptor  $\beta$ -common chain ( $\beta$ c) has been found to associate with EPO-R (Jubinsky et al, 1997) and erythropoietic-stimulating proteins induce modification of the  $\beta$ c (Chin et al, 1997), which, in turn, promotes modification of EPO-R (Blake et al, 2002). Data suggest that EPO-R may also interact with the receptor for another regulatory molecule, stem cell factor (Wu et al, 1997; Wu et al, 1995). These interactions suggest functional "cross talk" between receptors and receptor complexes that contain EPO-R, and accessory receptors may affect epoetin downstream signaling differently in different cell types.

The relationships among receptor affinity, receptor number, tissue specificity, potential accessory molecules, receptor cross-talk, and signal transduction are not fully understood, particularly in the context of non-hematopoietic cell types. The downstream consequences of signaling by EPO through EPO-R in non-hematopoietic cells in vivo likely further alters the relationship between these variables and biologic response. It is inappropriate to assume that different erythropoietic-stimulating proteins

with different amino acid sequences and different receptor affinities have similar biologic effects on all cell types.

### **3.5 EPO-R Expression and Tumor Biology Considerations**

Based on EPO-R detection on tumors and the biologic functions of EPO, concerns have been raised regarding a potential role for erythropoietic-stimulating proteins in tumor progression. The role of erythropoietic-stimulating proteins and EPO-R in hematopoietic cell differentiation and survival is well defined. Erythropoietic-stimulating proteins, including darbepoetin alfa, work through interaction with EPO-R to normally promote the differentiation, proliferation, and survival of hematopoietic cells. EPO-R appears to be expressed on a wide range of normal non-hematopoietic tissues and malignancies, although its role in these tissues is less understood. In most cases where EPO-R has been detected on malignant tissue, EPO-R has been found on the tissue of origin as well. Although EPO-R can be detected by multiple methods, expression may not correspond with function.

In tumors, expression of known oncogenic growth factor receptors, such as EGF-R and HER2, can be increased as much as a 100-fold over normal cells. EGF-R and HER2 receptor overexpression is clearly associated with clinical outcomes. In contrast, tumor cell lines do not appear to have increased numbers of EPO-R on their surface. Where EPO-R affinity has been measured, major differences in receptor affinity on hematopoietic, non-hematopoietic, and tumor cell lines are not apparent.

The effect of epoetin in tumor cell line proliferation has been investigated in cell culture studies. In 5 published studies, with > 50 tumor cell lines, epoetin did not increase tumor cell proliferation even at supra-pharmacologic doses (Westphal et al, 2002; Rosti et al, 1993; Berdel et al, 1992; Mundt et al, 1992; Berdel et al, 1991). In the 3 studies in which epoetin appears to have increased tumor cell proliferation in vitro, epoetin exposure was associated with only a marginal proliferative signal (Acs et al, 2001; Takeshita et al, 2000; Westenfelder and Baranowski, 2000). Amgen is not aware that such studies have been performed with Aranesp.

In summary, the evidence that EPO-R and erythropoietic-stimulating proteins play a significant role in tumor progression is weak, and there is no evidence that Aranesp has a role in tumor initiation or progression.

**Key Points:**

- Aranesp is considered a distinct molecular entity from scientific, clinical, legal, and regulatory perspectives.
- There is no evidence that Aranesp promotes tumor progression in preclinical studies.
- EPO-R detection on non-hematopoietic cells and tumor cells does not correlate well with EPO-R function.
- The observation that EPO-R is detected on tumor cell lines and tissues does not mean that erythropoietic-stimulating proteins are drivers for tumor progression.
- EPO-R is expressed at similar levels and affinity in malignant tissues and in normal non-hematopoietic tissue of origin.
- EPO-R is not an established oncogene like HER2 or EGF-R.

## **4 ARANESP PRECLINICAL OBSERVATIONS**

### **4.1 Aranesp Pharmacokinetics and Pharmacodynamics**

The pharmacokinetic and pharmacodynamic properties of Aranesp and epoetin have been determined in a range of animal species. The data consistently indicate that Aranesp is cleared more slowly (generally 3-fold) than epoetin, has a similar volume of distribution (slightly larger than plasma volume), and has a longer terminal half-life (approximately 3-fold longer) (Egrie et al, 2003).

### **4.2 Genotoxicity and Mutagenesis**

Aranesp is not mutagenic or genotoxic. It produces negative results in the bacterial reverse mutation assay, the Chinese hamster ovary cell gene mutation assay, and the mouse bone marrow micronucleus assay.

### **4.3 Human Tissue Binding**

In a tissue-binding study performed with Aranesp and a panel of 23 normal human tissues, bone marrow was the only tissue that demonstrated Aranesp binding. These findings suggest that other tissues do not express EPO-R at sufficient density or affinity to result in detectable Aranesp binding.

### **4.4 Thrombotic Events**

Preclinical studies with rats, dogs, and monkeys have been performed to evaluate the relationship between thrombus formation and exposure to epoetin and Aranesp. Studies performed with rats and dogs treated with Aranesp for up to 6 months and a single-dose study in monkeys examined toxicities related to hemoglobin rate of rise and sustained high hematocrit. Animals were treated with supra-pharmacologic doses (up to 100 µg/kg [rats] or 50 µg/kg [dogs]) of Aranesp 3 times per week). These treatment schedules resulted in rates of hemoglobin rise that were at least 2.5 times greater than the rate recommended in the approved prescribing information for patients. This rapid rate of hemoglobin rise was not associated with mortality or other adverse events. As expected, thrombotic events were noted when hemoglobin levels were sustained above physiologic levels.

### **4.5 Tumor Initiation and Tumor Progression**

Several toxicology studies have been conducted in rats and dogs with supra-pharmacologic doses of Aranesp, all of which included extensive histologic investigations. Examination of numerous tissue types, including those commonly associated with spontaneous or inducible cancers, revealed no evidence of abnormal

mitogenic or tumorigenic responses. With the exception of tissue changes normally associated with the pharmacologic effect of Aranesp (ie, Kupffer cell hyperplasia associated with removal of degenerated erythrocytes), no evidence of hyperplasia, proliferation, abnormal tissue architecture, or increased tissue mitotic indices were observed. The long-term toxicology studies (up to 6 months) in which normal animals were exposed to very high levels of Aranesp provide preclinical evidence that chronic exposure to Aranesp is not associated with tumorigenesis.

Two studies have evaluated the impact of Aranesp in rodent tumor xenograft models (Kirkpatrick et al, 2003; Ning and Knox, 2004). Ning and Knox administered 30 µg/kg Aranesp every 1 or 2 weeks after induction of anemia by total body irradiation in tumor-bearing mice. Aranesp effectively corrected anemia, increased tumor oxygenation, and increased the radiosensitivity of established squamous cell carcinoma and fibrosarcoma to fractionated radiotherapy. The authors also reported a significant radiosensitivity increase in Aranesp-treated animals before anemia correction was evident and these beneficial effects of Aranesp occurred in a dose-dependent manner. In non-anemic rats bearing R3230 mammary carcinoma xenografts, administration of Aranesp at 3 µg/kg subcutaneously 3 times per week for 18 days significantly increased oxygen tension in the tumor but did not alter tumor growth or increase tumor response to radiation therapy (Kirkpatrick et al, 2003). This tumor cell line is known to express EPO-R as assessed by Western blotting (Arcasoy et al, 2002) and Aranesp exposure did not lead to increased tumor growth.

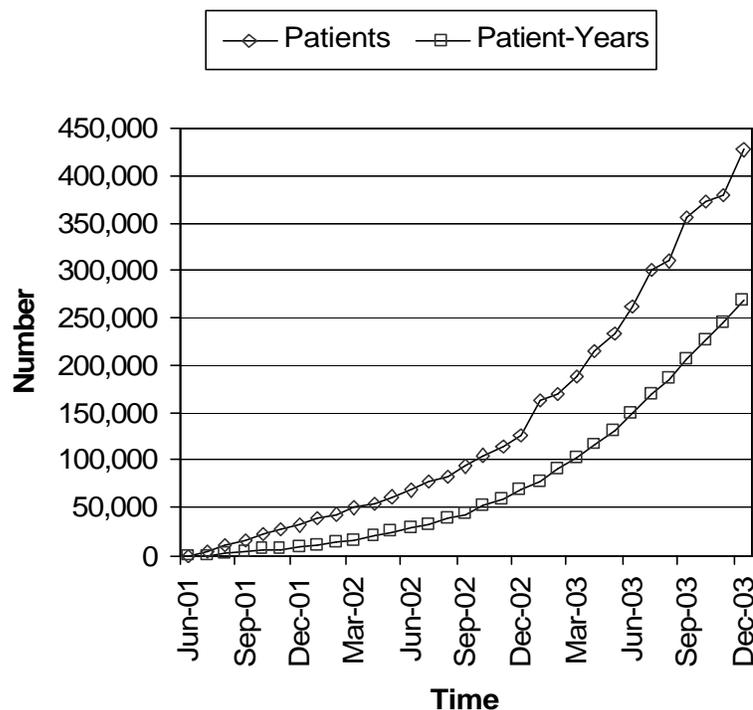
**Key Points:**

- There is no evidence from preclinical studies that Aranesp initiates tumors or promotes more rapid growth of pre-existing tumors.
- In some animal studies, Aranesp appears to increase the beneficial effects of radiotherapy.

## 5 ARANESP CLINICAL EXPERIENCE

Through December 2003, more than 427,000 patients have received Aranesp therapy, representing more than 268,000 patient-years of experience (Figure 1). Oncology patients represent a substantial proportion of this experience, and constitute 133,000 patients and 65,000 patient-years. The Aranesp clinical trial database for Amgen-sponsored trials through December 2003 includes more than 20,000 patients and represents more than 9700 patient-years of experience.

**Figure 1. Patients and Patient-years of Aranesp Therapy Over Time**



Amgen, data on file.

The efficacy of Aranesp at the licensed dose (2.25 µg/kg weekly) and the commonly used dosing regimen in the United States [200 µg every other week] has been well established (Hedenus et al, 2003; Schwartzberg et al, 2003; Vadhan Raj et al, 2003; Vansteenkiste et al, 2002). Significant reductions in transfusion requirements, and improvements in patients reporting fatigue have been demonstrated with both dosing regimens. In general, more than 70% of anemic cancer patients achieve the target hemoglobin range of 11 to 12 g/dL specified by the NCCN anemia guidelines (NCCN, 2003). In these clinical trials, subsequent maintenance of hemoglobin at approximately 12 g/dL on average was observed (Schwartzberg et al 2003; Amgen, data on file).

## 6 THROMBOTIC EVENTS

An association between Aranesp therapy and thrombotic events was described in the original licensing application and proactively represented in product labeling. More recently, Amgen has performed a comprehensive review of the medical literature regarding thrombotic events in malignancy, and performed multiple epidemiologic analyses to evaluate the background incidence rates of thrombotic events in patients with cancer. An analysis also has been updated regarding thrombotic event rates and risk factors from pooled Aranesp oncology trials, which includes studies performed before and after product approval.

### 6.1 Literature Review

Patients with cancer are at a higher risk for thrombotic events than individuals without cancer (Lee and Levine, 2003). The incidence of thrombotic events in patients with cancer in modern prospective studies has ranged from 13.1/1000 patient-years (PY) (Joung and Robinson, 2002) to 109/1000 PY (Otten et al, 2004), and thrombotic events contribute substantially to cancer patients' morbidity and mortality (Ambrus et al, 1975).

The etiology of thrombotic events in oncology patients is thought to be multifactorial (Kwaan et al, 2003; Caine et al, 2002). Hypercoagulable states, direct injury to the vascular endothelium, and inflammation may all predispose patients with cancer to thrombotic events (Falanga and Donati, 2001; Kakkar et al, 1995; Bevilacqua et al, 1986). Cancer type and stage (Lee and Levine, 2003; Levitan et al, 1999), indwelling catheters, surgery, and chemotherapy all contribute to the increased risk of developing thrombotic events observed in cancer patients (Otten et al, 2004; Verso and Agnelli, 2003; Heit et al, 2002; Lee and Levine, 1999; Pritchard et al, 1996; Clahsen et al, 1994; Levine et al, 1988).

A systematic review of the published literature from January 1990 to July 2003 was performed, selecting publications pertaining to epoetin or Aranesp in cancer anemia published in any of 5 languages (English, French, German, Italian, or Spanish). All randomized, controlled trials and prospective interventions were identified and examined for thrombotic events risk factors and the calculation of thrombotic event incidence rates. Studies that only appeared to report "drug-related" events or appeared to selectively report safety events were not included in statistical analyses. The review identified 63 studies that were included in the final study set for analysis. All studies included

patients treated with epoetin, Aranesp, or iron treatment with extractable (or logically imputable) numbers of safety events.

In this review, 70% of patients had solid tumors, 28% had hematologic cancer, and the remaining patients had unknown/mixed tumors. In studies reporting deep vein thrombosis as an outcome, the overall mean incidence of deep vein thrombosis was 37/1000 PY and the incidence among patients receiving epoetin was 46/1000 PY. The mean incidence of pulmonary embolism was 23/1000 PY, and patients receiving epoetin treatment had a mean incidence of 30/1000 PY. Few factors appeared to have significant impact on the incidence rate, but data for this evaluation were limited.

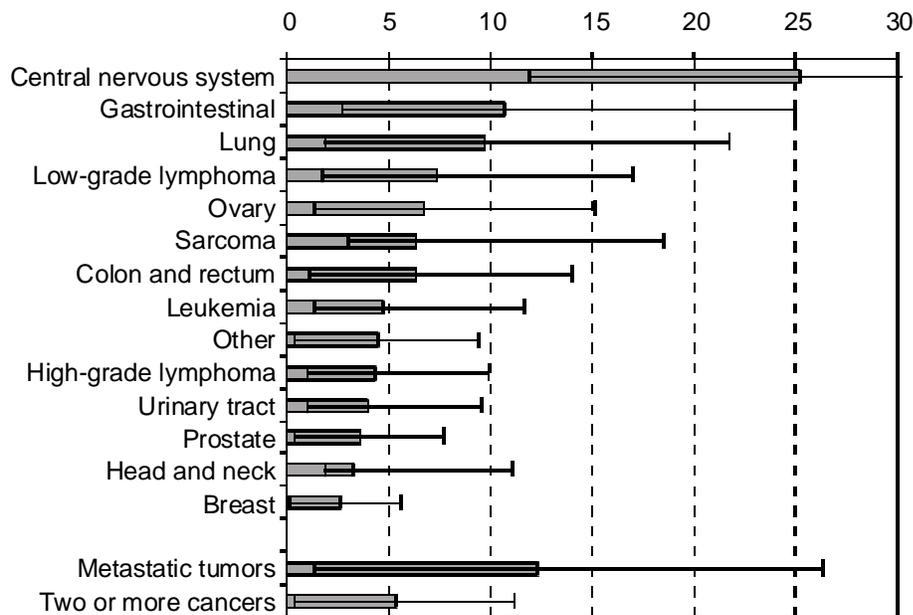
## 6.2 Background Epidemiology

Because of the limited information in the published literature, Amgen investigated the incidence of thrombotic events in several primary data analyses. The incidence in the general population was estimated using data from the National Hospital Discharge Survey (NHDS) and the United Kingdom General Practice Research Database (GPRD). Thrombotic event incidence in patients with cancer who were receiving chemotherapy was investigated using data from the GPRD and 2 large, nationwide claims-based databases: the UnitedHealth/Ingenix database, and the Medstat Marketscan database. The Medstat database offered the opportunity to investigate the incidence of thrombotic events among cancer chemotherapy patients with anemia.

The incidence rates of thrombotic events estimated in the NHDS United States population and GPRD United Kingdom population, when standardized to the age distribution of the Ingenix study population, were similar: 2.5/1000 PY for the NHDS (based on the 2001 United States population) and 2.7/1000 PY for the GPRD (based on approximately 35,000,000 PY). The incidence of thrombotic events among the cancer chemotherapy populations was substantially increased, ranging from 13.7/1000 PY in GPRD (based on approximately 108,000 PY) to 34.5 in Medstat (based on approximately 7000 PY) and 59.2 in Ingenix (based on approximately 4000 PY).

In the GPRD analysis, the rate of thrombotic events varied greatly by type of cancer (Figure 2). Patients with cancer of the central nervous system and those with metastatic disease had the highest rate of thrombotic events and patients with breast and head-and-neck cancers had the lowest rate. Similar trends were seen in the Medstat and Ingenix databases, although with more variability due to the smaller number of thrombotic events.

**Figure 2. Age- and Sex-adjusted Relative Incidence of Venous Thrombotic Events Among Cancer Chemotherapy Patients Compared With the General Population in the General Practice Research Database**



Low-grade lymphoma includes non-Hodgkin's lymphoma and cutaneous T-cell lymphoma, and high-grade lymphoma includes Hodgkin's disease, mantle cell, and non-cutaneous T-cell lymphoma. Metastatic tumors include patients who had metastases of their primary cancer. 95% confidence interval are shown in error bars.

The Medstat database allows for assessment of subsets of oncology patients receiving chemotherapy. Patient subsets include those with and without anemia, and the anemic patient subset can be further analyzed based on exposure to erythropoietic-stimulating protein. The cutoff for this database is 1999 and, therefore, all erythropoietic-stimulating protein treatment represents Epoetin alfa (Procrit) exposure. When stratifying the Medstat data by anemia, we found that anemic cancer chemotherapy patients had a substantially higher incidence of thrombotic events compared with patients without reports of anemia. The crude incidence rate among those with anemia was 120/1000 PY (based upon 831 PY) while the crude rate among those without anemia was 69/1000 PY (based upon 6013 PY), giving a crude relative hazard of 1.67 (95% CI: 1.34, 2.07). After adjusting for age, sex, cancer type, and comorbidities, the incidence of thrombotic events in the anemic group remained significantly increased compared with those patients without anemia (HR = 1.35; 95% CI: 1.08, 1.68). The higher risk for thrombotic events in anemic patients may reflect the independent association of both anemia and thrombotic risk with underlying disease severity.

The incidence rate in anemic patients after erythropoietic-stimulating protein exposure (176/1000 PY) also was greater than the incidence rate in anemic patients before or without erythropoietic-stimulating protein exposure (101/1000 PY). After adjusting for age, sex, cancer type, and comorbidities, a similar multivariate comparison of the incidence before or after erythropoietic-stimulating protein exposure continued to suggest a higher rate in the erythropoietic-stimulating protein group, but was not statistically significant (HR = 1.40, 95% CI: 0.90, 2.16).

### 6.3 Aranesp Clinical Trial Experience

Thrombotic event risk was evaluated using data from 11 studies, including all clinical development Aranesp oncology chemotherapy studies with a final (locked) database as of November 2003. These studies included placebo and non-placebo controls. All patients who received at least 1 dose of study drug are included. A total of 2251 patients were evaluated (1807 Aranesp and 444 placebo). Overall, 6% (111/1807) of Aranesp and 3% (15/444) of placebo patients reported thrombotic events.

Patients in the Aranesp group had a higher risk of any thrombotic event compared with patients in the placebo group ( $p = 0.02$  by log-rank test). Univariate analysis revealed 3 factors (Aranesp treatment, prior thrombotic event, and poor Eastern Cooperative Oncology Group [ECOG] performance status) with an unadjusted log-rank  $p$ -value  $< 0.05$ . Sex, age, prior cardiovascular events, race, obesity, baseline hemoglobin, dose schedule, baseline platelet counts, platinum chemotherapy, and baseline serum EPO concentration were not statistically associated with thrombotic event risk.

A Cox regression analysis was performed with the 3 significant risk factors (treatment, thrombotic event history, and ECOG performance status) identified by univariate log-rank tests. In this multivariate analysis, each effect remained significant predictors of thrombotic events (Table 1).

**Table 1. Thrombotic Event Risk Pooled Trials**

	Hazard Ratio	95% CI	p-value
History of thrombotic events	2.70	1.64, 4.45	< 0.001
Treatment (Aranesp vs Placebo)	1.97	1.15, 3.39	0.014
ECOG Performance Status (2 or 3 vs 0 or 1)	1.64	1.04, 2.59	0.033

No interactions among these variables were statistically significant at the 0.05 level, although the number of patients with a history of thrombotic events was low (Table 2).

**Table 2. Relationship Between Thrombotic Event History and Treatment**

Percentage of Patients with On-study Thrombotic Event	Aranesp % (n)	Placebo % (n)
No history of thrombotic event	6% (97/1703)	3% (11/412)
History of thrombotic event	13% (14/104)	13% (4/32)

The effects of time-varying hemoglobin changes were examined by Cox analyses, adjusted by the significant risk factors (treatment, thrombotic event history, and ECOG performance status). No association was found between thrombotic event risk and hemoglobin thresholds of 11, 12, 13, and 14 g/dL. The hazard ratio (p-values) were 1.11 (0.626), 1.34 (0.182), 1.09 (0.747), and 1.19 (0.635), respectively. No association was observed between thrombotic event risk and increasing hemoglobin. The hazard ratio associated with a 1-g/dL hemoglobin increase in any 14 days was 1.04; 95% CI: 0.66, 1.62; p = 0.878). While the hazard ratio associated with a 2-g/dL hemoglobin increase in 28 days was 1.5, it was not statistically significant (95% CI: 0.97, 2.24; p = 0.07).

#### **6.4 Proactive Aranesp Labeling**

Amgen proactively addressed thrombotic events at the time of the original Biologic License Supplement for the Aranesp oncology indication, which is reflected in the warning section of the product labeling. A comprehensive review of thrombotic events described in the medical literature and an examination of multiple population databases and the Aranesp clinical trials confirms the thrombotic event rates are similar to those represented in the product label. Therefore, the low risk of thrombotic events associated with Aranesp therapy is appropriately reflected in current product label language and the rate of thrombotic events has remained stable over time.

**Key Points:**

- Patients with cancer have a higher background incidence of thrombotic events than the general public.
- Risk factors for thrombotic events include the underlying type of malignancy, stage of disease, prior thrombotic events, performance status, and anemia.
- Clinical trials and epidemiologic studies show that thrombotic events are associated with currently available erythropoietic-stimulating therapy.
- Thrombotic events are appropriately addressed in the Aranesp product label.

## 7 PROGRESSION-FREE SURVIVAL AND OVERALL SURVIVAL

Subsequent to the reports describing findings from the INT-76 and ENHANCE studies, Amgen initiated a review of completed oncology clinical trials to determine whether similar survival observations were associated with Aranesp therapy. Studies primarily designed for the purpose of assessing tumor outcomes and survival in oncology patients should include the following design elements: randomized, controlled, homogenous tumor population; stratification for predictors of tumor response; collection of appropriate endpoint data; and adequate duration of follow-up. Many of the Aranesp trials were not appropriate for this kind of analysis, reflecting their focus on treatment of anemia, with short-term endpoints related to hemoglobin level and number of transfusions. All randomized, double-blind, placebo-controlled trials were selected and evaluated both as individual studies and as a pooled dataset. The analysis includes 2 trials (Studies 980297 and 20000161) conducted in patients with lung cancer and lymphoid malignancies, respectively, in which patients were followed after the treatment interval to evaluate prospectively defined progression-free survival and overall survival endpoints (Hedenus et al, 2003; Vansteenkiste et al, 2002). The same endpoints were analyzed using data from these 2 clinical trials combined with the data from 2 smaller, dose-finding, placebo-controlled studies (Studies 980291 and 990114) enrolling patients with mixed tumor types and lymphoid malignancies, respectively (Kotasek et al, 2003; Hedenus et al, 2002). Although the latter two 16-week, dose-finding studies did not contain a long-term follow-up phase, they were included in the pooled analysis because the safety signals observed in the INT-76 and ENHANCE trials were observed during the initial months in those studies, and these trials allowed comparative observation of survival over a similar time frame.

As noted, the 4 double-blind, placebo-controlled studies were designed to study the benefits of anemia therapy in the setting of chemotherapy-induced anemia, and therefore contain specific on-study design features (endpoints, patient population, sample size, treatment duration, and stratification factors) that differ from those included in classic cancer therapeutic studies. The duration of Aranesp therapy in all trials was at least 12 weeks, similar to the average duration of anemia treatment for patients receiving chemotherapy of 12 to 16 weeks. Although these studies are heterogeneous for some important factors used to assess the benefits of oncology therapeutics, including tumor histology, disease stage, chemotherapy treatment, method and timing of tumor assessment, and duration of follow-up, they did have uniform design elements

(including double-blind, placebo-controlled groups), inclusion criteria, trial endpoints, and trial methodologies. These studies constitute an appropriate data set to evaluate progression-free survival and overall survival outcomes. The sample size of the pooled analysis ( $n = 1129$ ) allows detection of relatively small differences in overall mortality risk. The hazard ratio for mortality was 0.97 with a 95% confidence interval of 0.79 to 1.18.

In addition, we considered the possibility that the safety observations from the INT-76 trial and ENHANCE trial may have been related to design features unique to those studies, such as the inclusion of patients with high baseline hemoglobin levels, the effect of rapid hemoglobin increases and the inclusion of selected tumor types. Parallel analyses of Aranesp trials were limited by the fact that Amgen trials restricted baseline hemoglobin, hemoglobin rate of rise, and maximum hemoglobin concentrations.

## **7.1 Individual Double-blind, Placebo-controlled Trials**

### **7.1.1 Study 980297**

Study 980297 was a multicenter, double-blind, placebo-controlled study designed to evaluate the effects of Aranesp at a dose of 2.25  $\mu\text{g}/\text{kg}$  once weekly on anemia endpoints in patients with both non-small cell lung cancer and small-cell lung cancer receiving platinum-containing chemotherapy (Vansteenkiste et al, 2002). A total of 314 anemic patients (hemoglobin concentration  $\leq 11$  g/dL) were randomly assigned to receive Aranesp or placebo administered weekly as a subcutaneous injection for 12 weeks, followed by a 4-week observation period. Baseline demographics and disease characteristics were similar between treatment groups (Table 3). Subsequent to the end of the study period, patients entered a long-term, open-label follow-up for tumor progression and survival status. The median follow-up in this study is 16 months.

**Table 3. Study 980297: Baseline Demographics**

	Placebo N = 159	Aranesp N = 155
Sex (n/%)		
Men	117 (74)	110 (71)
Women	42 (26)	45 (29)
Age (yr)		
Median	61	62
Min - Max	36 - 79	39 - 80
Small-cell lung cancer (n/%)	45 (28)	47 (30)
Limited disease <sup>a</sup>	19 (12)	16 (10)
Extensive disease <sup>b</sup>	26 (16)	31 (20)
Non-small cell lung cancer (n/%)	114 (72)	108 (70)
Stage I	2 (1)	2 (1)
Stage II	2 (1)	2 (1)
Stage III	48 (30)	29 (19)
Stage IV	62 (39)	75 (48)
Performance status		
0	23 (14)	22 (14)
1	99 (62)	108 (70)
2	37 (23)	24 (15)
>2	0	1 (1)

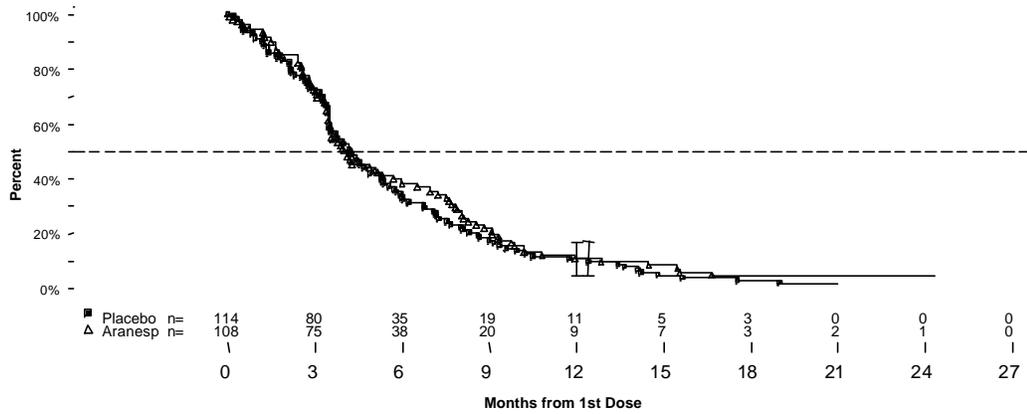
<sup>a</sup> Limited disease refers to disease within the thoracic cavity

<sup>b</sup> Extensive disease refers to disease extending beyond the thoracic cavity

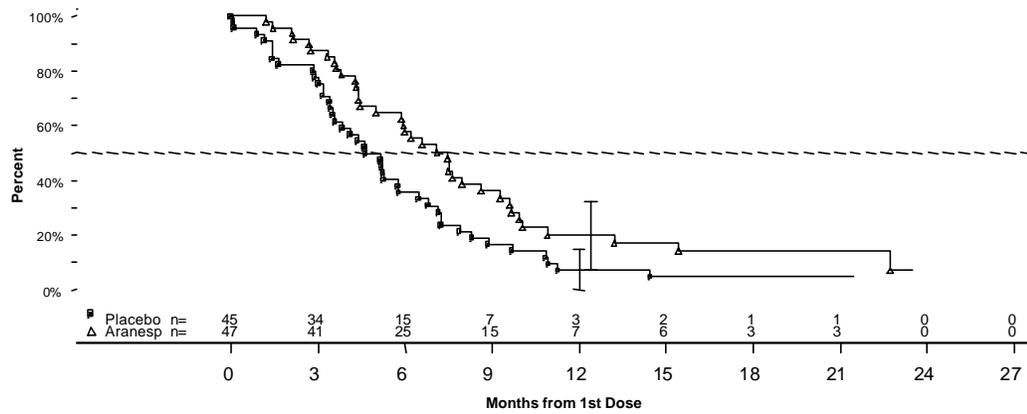
Min = minimum; Max = maximum

Three hundred and fourteen patients were treated (155 receiving Aranesp and 159 receiving placebo). Overall survival and progression-free survival for the non-small cell lung cancer and small-cell lung cancer histologies is shown in Figure 3 to Figure 6. No statistically significant differences between groups were seen at the 0.05 level when examining the individual tumor histologies or the overall groups.

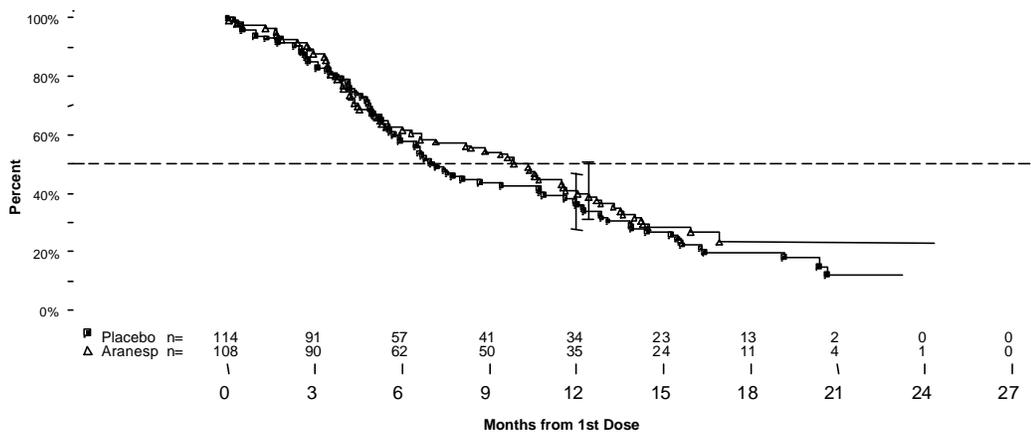
**Figure 3. Study 980297: Progression-free Survival  
 (Non-small Cell Lung Cancer)**



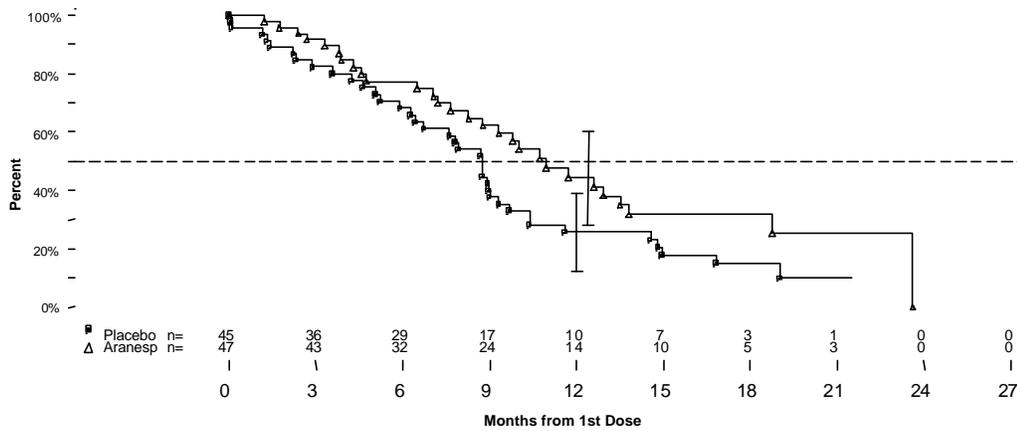
**Figure 4. Study 980297: Progression-free Survival  
 (Small-cell Lung Cancer)**



**Figure 5. Study 980297: Overall Survival  
 (Non-small Cell Lung Cancer)**



**Figure 6. Study 980297: Overall Survival  
 (Small-cell Lung Cancer)**



### 7.1.2 Study 20000161

In Study 20000161 (Hedenus et al, 2003), a randomized, double-blind, placebo-controlled study, 344 anemic patients (hemoglobin concentration  $\leq 11$  g/dL) with lymphoid malignancies and chemotherapy-induced anemia received Aranesp 2.25  $\mu\text{g}/\text{kg}$  once weekly or placebo as a subcutaneous injection for 12 weeks followed by a 4-week observation period. No restrictions on prior chemotherapy were included in this study, and patients were allowed to enter the study at any point during their course of therapy. Baseline demographics and disease characteristics in general were similar between treatment groups; however, in some tumor subsets, such as chronic lymphocytic leukemia, some imbalances were seen, such as more patients with indolent lymphoma being randomly assigned to placebo and more patients with a higher stage of disease being randomly assigned to treatment with Aranesp (Table 4). Subsequent to the end of the study period, patients entered a long-term, open-label follow-up for tumor progression and survival status. The median follow-up is 27 months.

**Table 4. Study 20000161: Baseline Demographics**

	Placebo N = 169	Aranesp N = 175
Sex (n/%)		
Men	78 (46)	87(50)
Women	91 (54)	88 (50)
Age (yr)		
Median	67	68
Min - Max	18 -87	20 - 86
Hodgkin's disease (n/%)	9 (5)	12 (7)
Non-Hodgkin's lymphoma (n/%)	45 (27)	39 (22)
Indolent	29 (64)	20 (51)
Aggressive	16 (36)	17 (44)
Multiple myeloma <sup>a</sup> (n/%)	83 (49)	90 (51)
Stage I	5 (3)	15 (9)
Stage II	23 (14)	21 (12)
Stage IIIA	50 (30)	52 (30)
Stage IIIB	5 (3)	2 (1)
Chronic lymphocytic leukemia <sup>b</sup> (n/%)	26 (15)	29 (17)
Stage A	7 (4)	5 (3)
Stage B	7 (4)	6 (3)
Stage C	11 (7)	17 (10)
Waldenstrom's macroglobulinaemia (n/%)	6 (4)	5 (3)

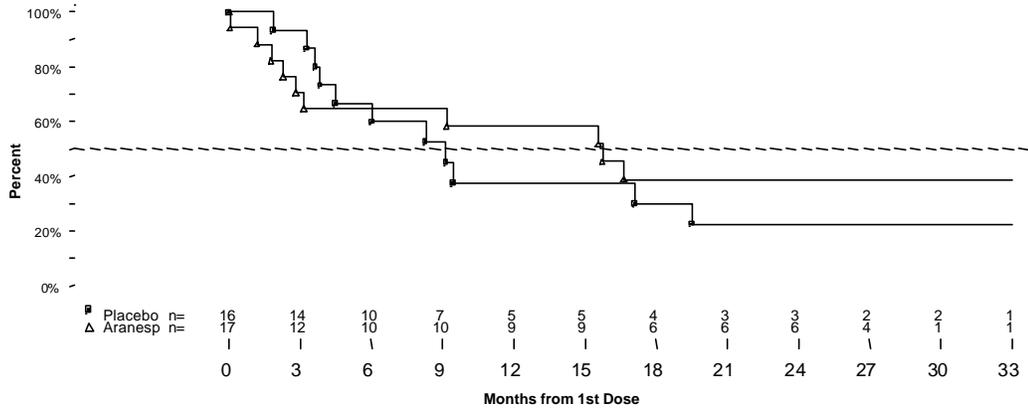
<sup>a</sup> Durie and Salmon staging system of multiple myeloma

<sup>b</sup> International Workshop on chronic lymphocytic leukemia

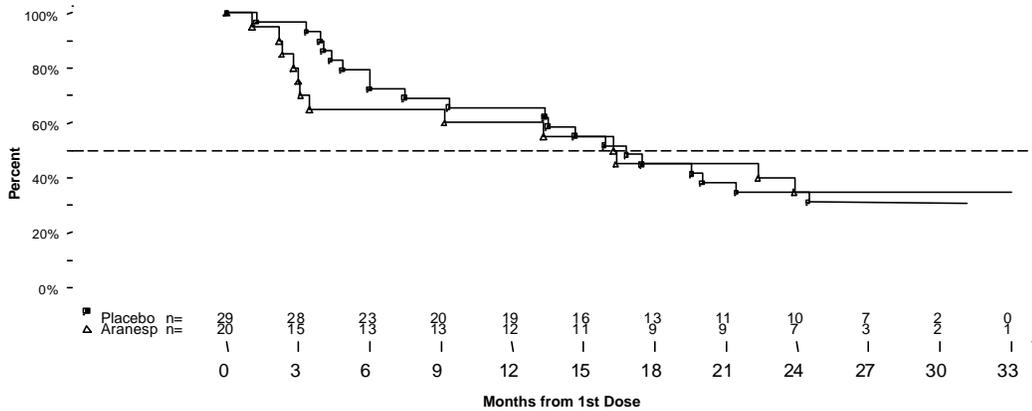
Min = minimum; Max = maximum

Figure 7 to Figure 14 show overall survival and progression-free survival for specific disease types. In all histologies, the results were similar for the Aranesp-treated patients and placebo patients.

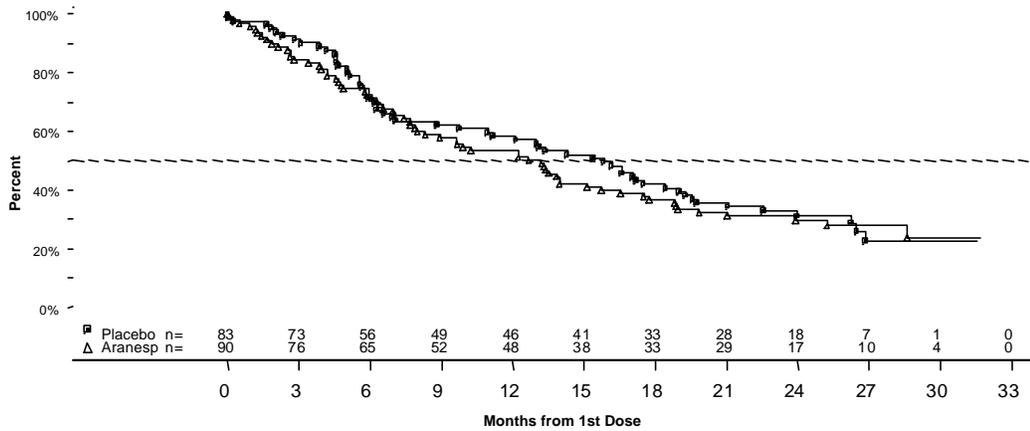
**Figure 7. Study 20000161: Progression-free Survival  
 (Aggressive Non-Hodgkin's Lymphoma)**



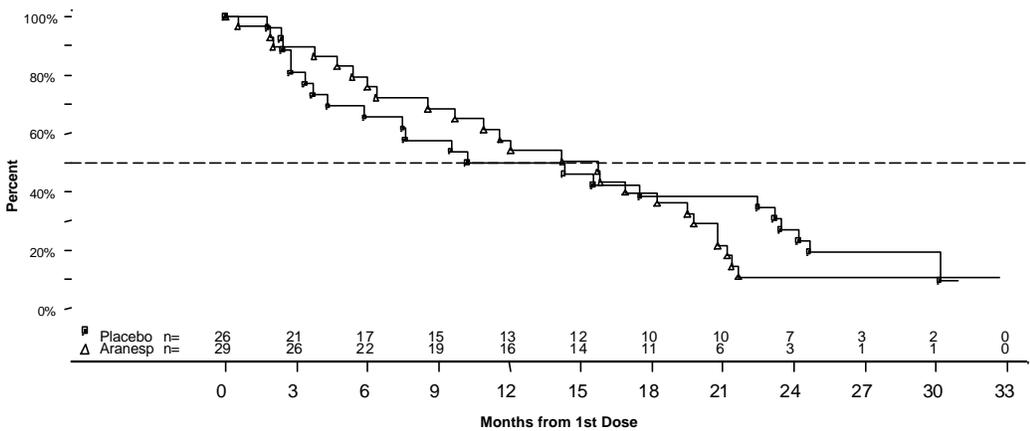
**Figure 8. Study 20000161: Progression-free Survival  
 (Indolent Non-Hodgkin's Lymphoma)**



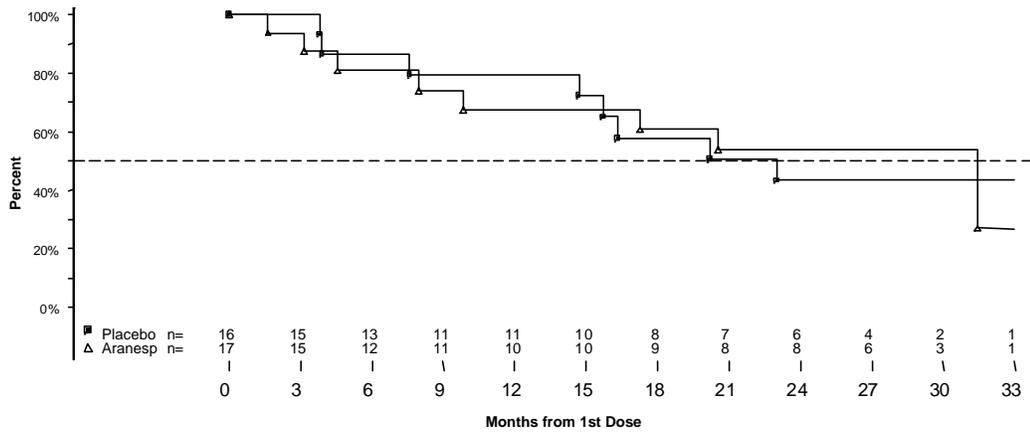
**Figure 9. Study 20000161: Progression-free Survival  
 (Multiple Myeloma)**



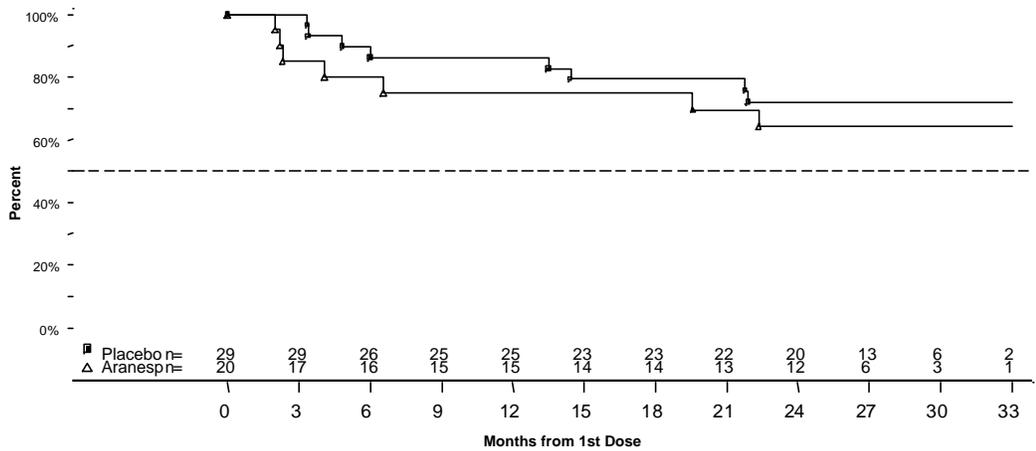
**Figure 10. Study 20000161: Progression-free Survival  
 (Chronic Lymphocytic Leukemia)**



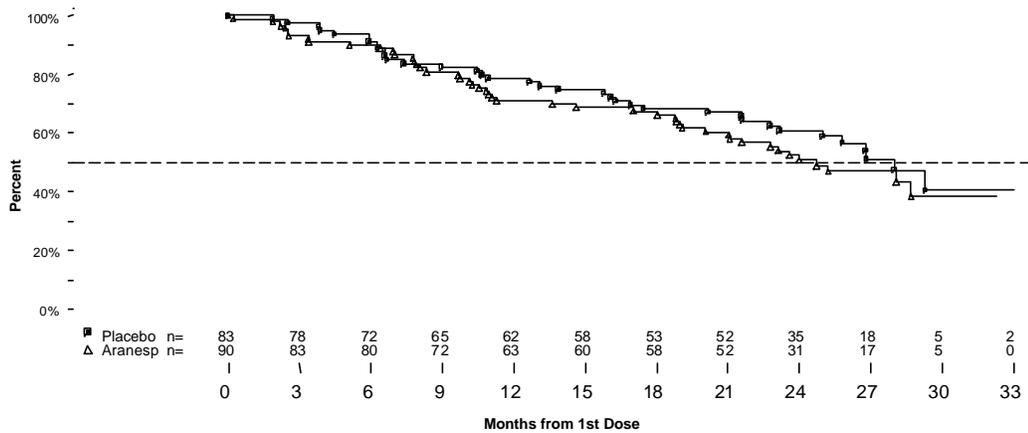
**Figure 11. Study 20000161: Overall Survival  
 (Aggressive Non-Hodgkin's Lymphoma)**



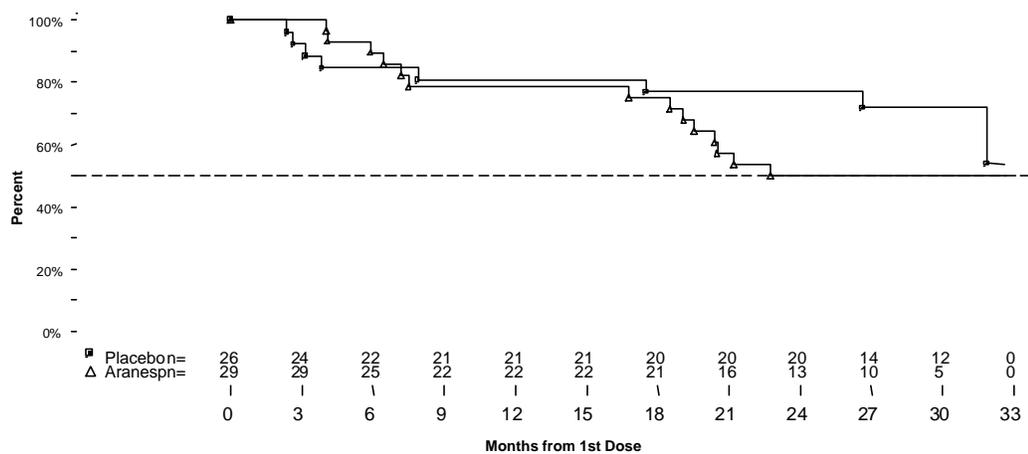
**Figure 12. Study 20000161: Overall Survival  
 (Indolent Non-Hodgkin's Lymphoma)**



**Figure 13. Study 20000161: Overall Survival  
 (Multiple Myeloma)**



**Figure 14. Study 20000161: Overall Survival  
 (Chronic Lymphocytic Leukemia)**



**7.2 Pooled Randomized, Double-blind, Placebo-controlled Trials**

As the safety signals observed in the INT-76 trial were observed during the first 4 months on study, evaluation of survival and disease progression endpoints within the first 16 weeks of exposure to erythropoietic therapies is appropriate. In addition to the two phase 3 studies already discussed, data from 2 other placebo-controlled studies in anemic cancer patients who were receiving concurrent chemotherapy are available and can be included in a pooled analysis of survival and disease progression. The controlled portion of the randomized, controlled trials included a follow-up of 16 weeks.

**7.2.1 Study 980291**

Study 980291 (Kotasek et al, 2003) was a dose-finding, double-blind, placebo-controlled study that evaluated the safety and efficacy of Aranesp administered once every 3 weeks (Schedule 1) or once every 4 weeks (Schedule 2) in patients with mixed solid tumors and chemotherapy-induced anemia (hemoglobin concentration = 11 g/dL). Four hundred five patients were randomly assigned on a 1:4 ratio to Aranesp or placebo. Baseline demographics are shown in Table 5 and Table 6.

**Table 5. Study 980291 (Schedule 1):  
 Baseline Demographics**

	Placebo N = 51	Aranesp N = 198
Sex (n/%)		
Men	16 (31)	56 (28)
Women	35 (69)	142 (72)
Age (yr)		
Median	56	58
Min - Max	22 - 77	29 - 84

Min = minimum; Max = maximum

**Table 6. Study 980291 (Schedule 2):  
 Baseline Demographics**

	Placebo N = 31	Aranesp N = 125
Sex (n/%)		
Men	7 (23)	44 (35)
Women	24 (77)	81 (65)
Age (yr)		
Median	58	63
Min - Max	34 - 74	33 - 83

Min = minimum; Max = maximum

Patients who completed the blinded treatment phase and continued to receive chemotherapy were given the option to receive open-label Aranesp for an additional 12 weeks. As patients receiving placebo during the blinded treatment phase were allowed to receive Aranesp during the open-label phase, for the analysis of progression-free and overall survival, patients were censored at the time they received their first dose of Aranesp treatment in the open-label phase. No long-term information was collected for patients in this study.

**7.2.2 Study 990114**

Study 990114 (Hedenus et al, 2002) was a randomized, double-blind, placebo-controlled study in which 66 patients with lymphoid malignancies and chemotherapy-induced anemia (hemoglobin concentration  $\leq 11$  g/dL) were randomly assigned to receive Aranesp at 1 of 3 dose levels or placebo for 12 weeks, followed by a 4-week observation period. Baseline demographics and disease characteristics were similar between treatment groups (Table 7). No long-term information was collected for patients in this study.

**Table 7. Study 990114: Baseline Demographics**

	Placebo N = 11	Aranesp N = 55
Sex (n/%)		
Men	2 (18)	35(64)
Women	9 (82)	20 (36)
Age (yr)		
Median	63	68
Min -Max	25 -80	20 - 84
Disease type (n/%)		
Hodgkin's disease	3 (27)	8 (15)
Non-Hodgkin's lymphoma	3 (27)	11 (20)
Chronic lymphocytic leukemia	2 (18)	10 (18)
Waldenstrom's macroglobulinaemia	0	11 (20)
Multiple myeloma	3 (27)	15 (27)
ECOG Performance status (n/%)		
0	5 (45)	16 (29)
1	6 (55)	32 (58)
2	0	7 (13)

Min = minimum; Max = maximum

**7.2.3 Pooled Analyses**

The pooled analyses of 1129 patients in the 4 double-blind, placebo-controlled studies are consistent with the observations within each individual phase 3 study (Table 8). The progression-free survival and overall survival were similar between the treatment and the no-treatment groups. The estimated hazard ratios related to Aranesp use were 0.93 (95% CI: 0.79, 1.09) and 0.97 (0.79, 1.18), for progression-free and overall survival, respectively (Figure 15 and Figure 16). In particular, there was no difference between groups over the first 16 weeks of treatment.

**Table 8. Treatment Endpoint Summaries by Study**

		Overall Survival		Progression-free Survival	
		Hazard Ratio: Aranesp to Placebo	95% CI	Hazard Ratio: Aranesp to Placebo	95% CI
Study 980297	NSCLC	0.85	0.62, 1.17	0.91	0.69, 1.21
	SCLC	0.62	0.38, 1.01	0.59	0.38, 0.93
	All Histologies	0.77	0.59, 1.01	0.79	0.62, 1.00
Study 2000016 <sup>1</sup>	Aggressive NHL	0.95	0.36, 2.53	0.80	0.34, 1.89
	Indolent NHL	1.41	0.51, 3.90	1.04	0.52, 2.09
	Multiple Myeloma	1.22	0.79, 1.89	1.08	0.76, 1.54
	CLL	1.84	0.76, 4.43	1.18	0.66, 2.12
	All Histologies	1.36	0.98, 1.90	1.06	0.82, 1.38
Study 980291 <sup>a</sup>	All Histologies	0.50	0.17, 1.46	0.72	0.39, 1.32
Study 980291 <sup>b</sup>	All Histologies	NE		1.07	0.49, 2.35
Study 990114	All Histologies	NE		NE	
Pooled Analysis	All Histologies	0.97	0.79, 1.18	0.93	0.79, 1.09

CLL = chronic lymphocytic leukemia; NE = not estimable because of too few events; NHL = non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; SCLC = small-cell lung cancer

<sup>a</sup> Schedule 1

<sup>b</sup> Schedule 2

Figure 15. Pooled Data Set: Progression-free Survival

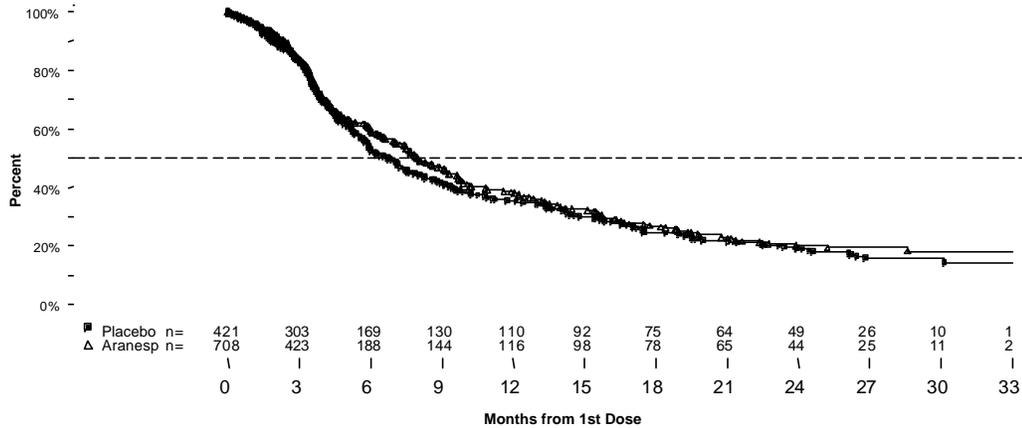
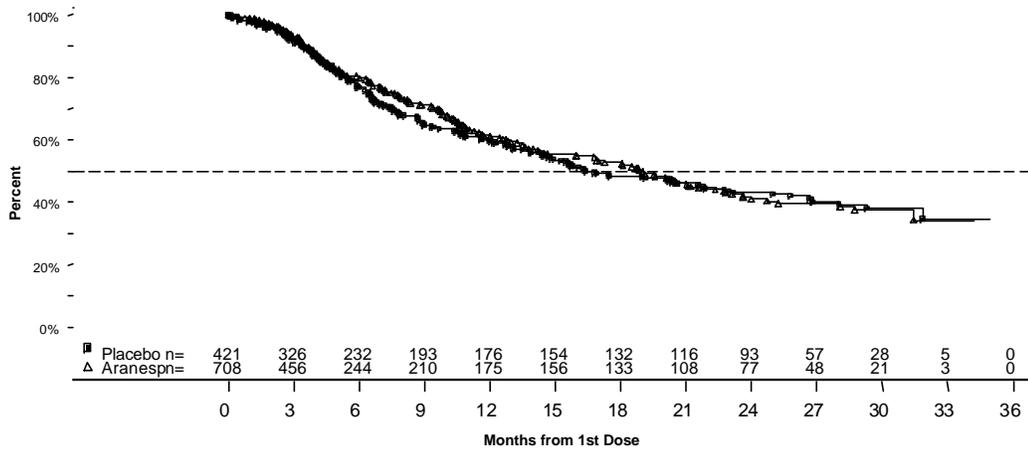


Figure 16. Pooled Data Set: Overall Survival



### 7.3 Relationship Between Hemoglobin Metrics and Survival

Individual, double-blind, placebo-controlled studies in chemotherapy-induced anemia and the pooled analysis revealed no suggestion of an adverse effect of Aranesp on progression-free or overall survival. Given the lack of any previous suggestion of survival issues despite the substantial patient-year experience with erythropoietic-stimulating proteins in both clinical research and oncology-practice settings, Amgen considered that the signals observed in the INT-76 and ENHANCE trials could have been related to unique design features of those studies. Therefore, we investigated our clinical trial database, using the pooled clinical trial database previously described (Section 7.2), for factors included in the design of the INT-76 and ENHANCE trials,

namely high baseline hemoglobin levels, rapid hemoglobin increases (as a result of higher-than-recommended doses, and the use of non-myelosuppressive radiation therapy in the case of the ENHANCE trial), as well as the inclusion of selected tumor types that could theoretically represent malignancies susceptible to proliferation through EPO-R engagement. Cox regression models stratified by study protocol were used to examine the relationship between treatment and baseline hemoglobin. In addition, time-dependent hemoglobin-related covariates, patients reaching hemoglobin thresholds, and rates of hemoglobin increase with time on study were used to examine the potential effect of changes in hemoglobin concentrations and their relationship to progression-free survival and overall survival. In these analyses, to exclude an effect of hemoglobin increases due to transfusions for patients receiving a transfusion, hemoglobin measurements on the day of a transfusion and for the next 28 days after a transfusion were excluded.

An association was observed between both improved survival and progression-free survival and a on-study increase in hemoglobin concentration of = 1 g/dL in 14 days. Similar associations were seen with achieving an on-study hemoglobin concentration of = 13 g/dL (Table 9).

**Table 9. Pooled Analysis: Cox Regression Models for Progression-free Survival and Overall Survival**

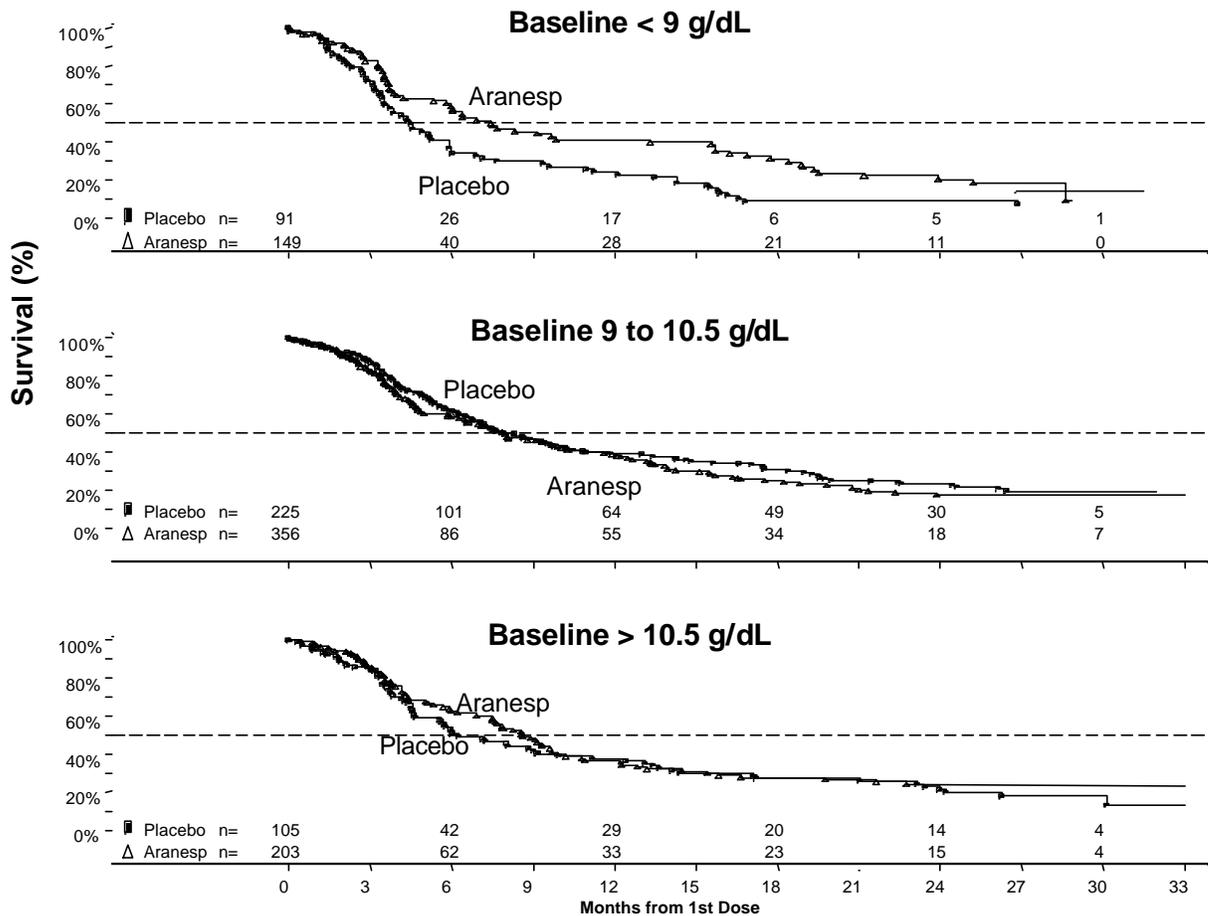
Model <sup>a</sup>	Endpoint	p-value	Hazard ratio	95% CI
= 1 g/dL hgb increase in 14 days	Survival	< 0.001	0.43	0.34, 0.56
= 1 g/dL hgb increase in 14 days	Progression-free Survival	< 0.001	0.51	0.42, 0.62
Achieved hgb of = 13 g/dL	Survival	0.001	0.56	0.40, 0.79
Achieved hgb of = 13 g/dL	Progression-free Survival	0.001	0.66	0.51, 0.84

<sup>a</sup> Models stratified by study; adjusted for Aranesp versus placebo and baseline hemoglobin value  
 CI = confidence interval; hgb = hemoglobin

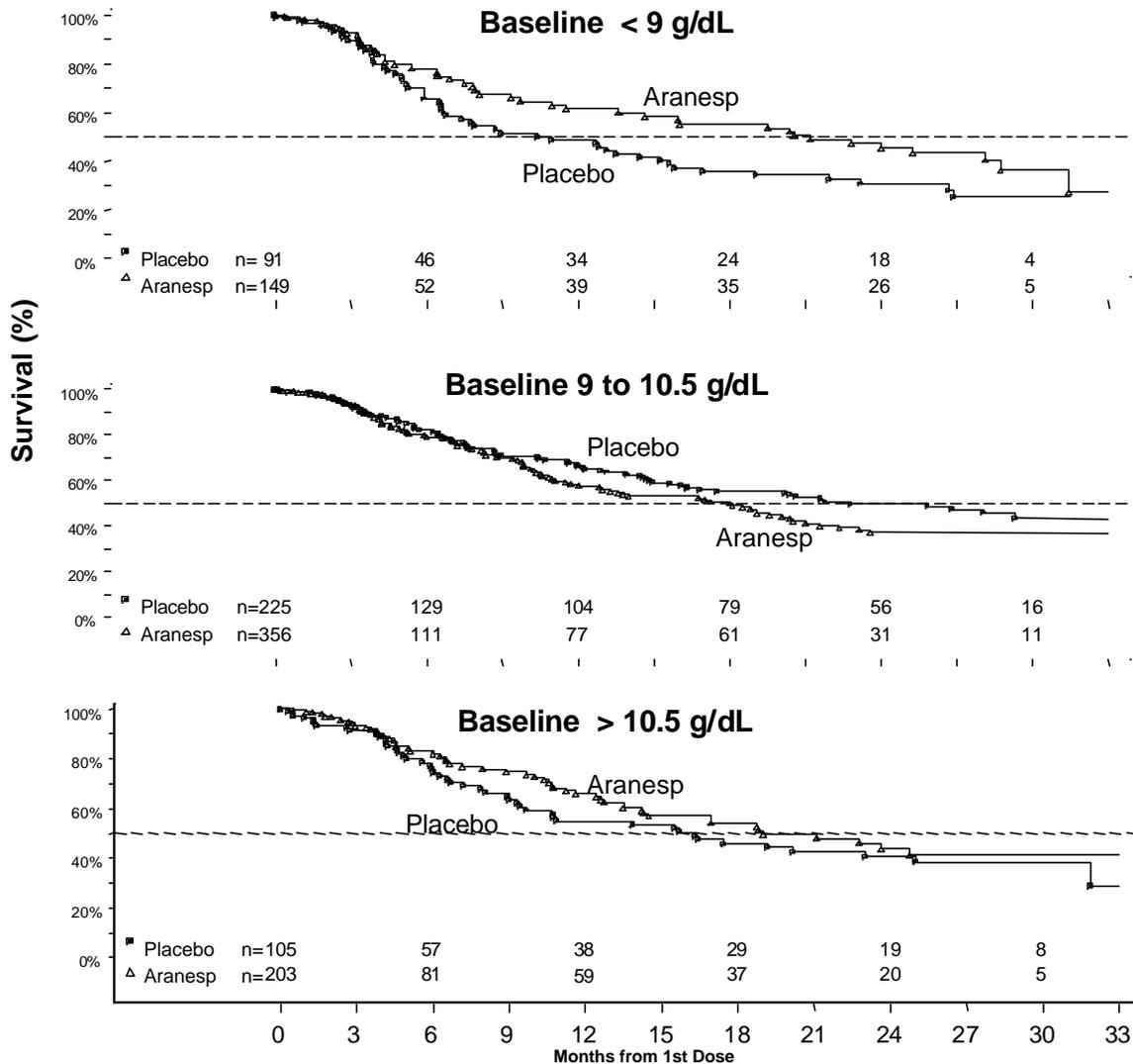
Comparisons of progression-free and overall survival between patients receiving Aranesp and placebo are shown by baseline hemoglobin categories in Figure 17 and Figure 18. These analyses suggest a benefit of Aranesp administration relative to placebo in terms of progression-free survival and overall survival for patients with severe anemia (baseline hemoglobin concentration < 9 g/dL), with a relative risk (95% CI) of 0.62 (0.45, 0.86) and 0.69 (0.46, 1.02), respectively. No significant differences between

Aranesp and placebo were observed for the other baseline hemoglobin categories for either endpoint.

**Figure 17. Pooled Analysis: Progression-free Survival for Patients with Baseline Hemoglobin**



**Figure 18. Pooled Analysis: Overall Survival for Patients by Baseline Hemoglobin**



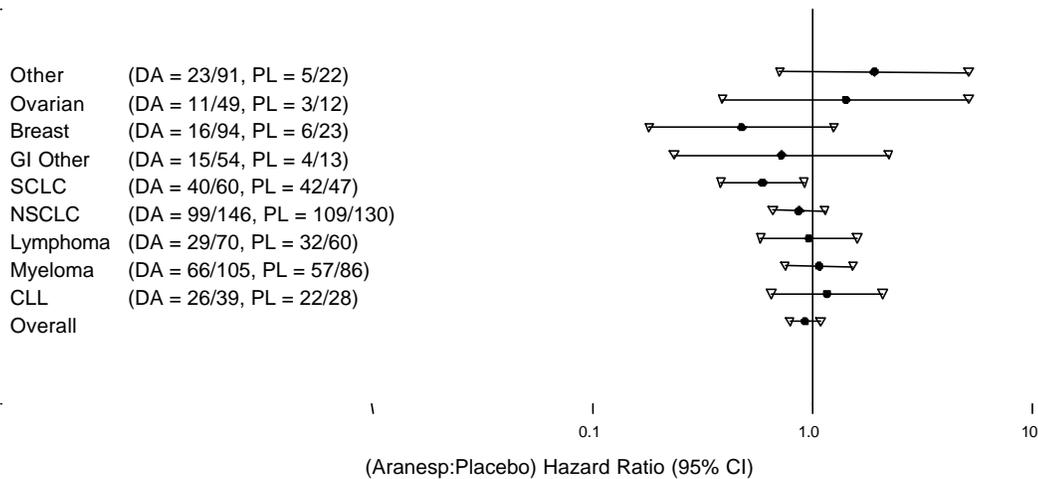
These observations do not support the concept that the adverse outcomes observed by Leyland-Jones (2003) and Henke et al (2003) were the results of a high hemoglobin (baseline or target) and hemoglobin rate of rise. However, firm conclusions regarding the effects of epoetin pharmacodynamics on progression and survival cannot be drawn from these results, as very high targets and rates of hemoglobin increases could not be studied given the original design of the Aranesp trials. Responsiveness to erythropoietic therapy may be a marker of general health rather than a reason for improved outcomes.

#### 7.4 Tumor Types

To explore whether particular tumor types may be more susceptible to tumor stimulation by Aranesp, we examined progression-free survival and overall survival by histology.

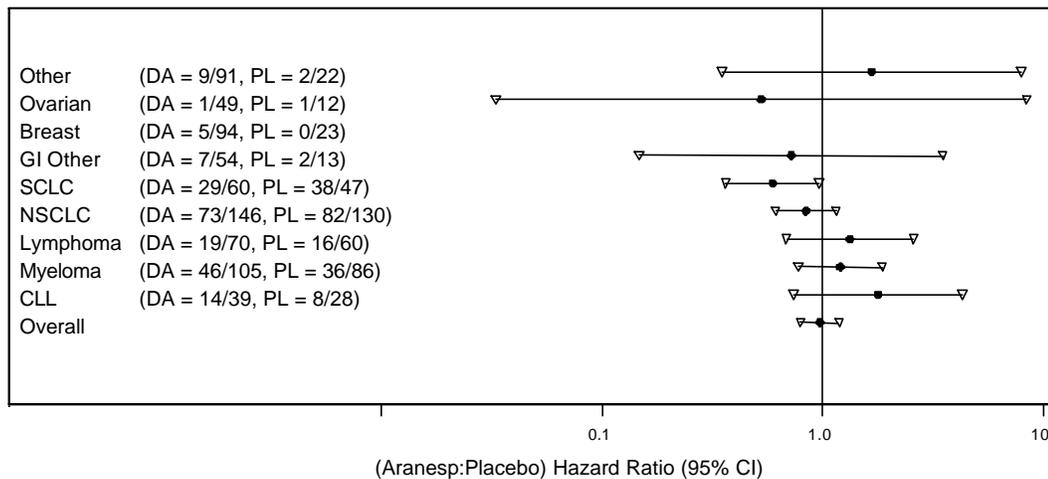
We did not observe a significant risk for overall survival or progression-free survival in any malignancy type analyzed (Figure 19 and Figure 20). For breast cancer, the tumor type studied in the INT-76 trial, no statistically significant increase in mortality was observed. The ENHANCE trial included patients with head-and-neck cancer. In the pooled analysis, only 1 patient had head-and-neck cancer and was classified as “GI Other”.

**Figure 19. Progression-free Survival Hazard Ratios Associated With Aranesp Versus Placebo Therapy**



CLL = chronic lymphocytic leukemia; DA = darbepoetin alfa; GI = gastrointestinal; NSCLC = non-small cell lung cancer; PL = placebo; SCLC = small-cell lung cancer

**Figure 20. Overall Survival Hazard Ratios Associated With Aranesp Versus Placebo Therapy**



CLL = chronic lymphocytic leukemia; DA = darbepoetin alfa; GI = gastrointestinal; NSCLC = non-small cell lung cancer; PL = placebo; SCLC = small-cell lung cancer

## 7.5 Summary of Aranesp Clinical Trial Findings

In summary, findings from analyses of the Aranesp clinical trial database indicate that, when prescribed in accord with the approved dosing regimens, Aranesp treatment is not associated with an increased risk of tumor progression and mortality in patients with chemotherapy-induced anemia in multiple different types of cancer.

### Key Points:

- Data from Aranesp oncology clinical trials do not reveal a significant effect on tumor progression or survival after short-term treatment (12 weeks) or in long-term follow-up (up to 2 years).
- Achieving a hemoglobin level of 13 g/dL is associated with improved survival in cancer patients.
- The clinical trials that have raised concerns over tumor progression and survival have been performed with Epoetin alfa and Epoetin beta. Such findings have not been observed with Aranesp and, thus, do not constitute a class effect.

## 8 OVERALL BENEFIT/RISK ASSESSMENT

Aranesp therapy improves chemotherapy-induced anemia and fatigue, reduces the need for transfusions, and enhances the quality of life for oncology patients afflicted with a variety of malignancies. Significant reductions in transfusion requirements are associated with Aranesp therapy (Hedenus et al, 2003; Vansteenkiste et al, 2002). The reduction of transfusions has many benefits, including reductions in the risk of transfusion reactions and transmission of infectious diseases. Patients treated with Aranesp also experience significant improvement in fatigue (Hedenus et al, 2003; Vansteenkiste et al, 2002).

Although safety observations have been reported from both Aranesp clinical trials and Aranesp practice experience, these events are uncommon and have been proactively communicated in the package insert. When prescribed in accord with approved product labeling and guidelines, Aranesp substantially improves the lives of patients with grievous illnesses. No evidence from either preclinical or clinical analyses suggests that Aranesp promotes tumor progression or reduces survival. The benefit/risk profile for Aranesp remains very favorable.

## 9 ONGOING STUDIES AND PHARMACOVIGILANCE PROGRAM

As discussed, Aranesp has had no detrimental effect on disease progression or overall survival in completed oncology placebo-controlled trials evaluating anemia outcomes. In order to more rigorously evaluate relevant cancer endpoints such as tumor response, time to tumor progression, and survival, oncology studies are typically randomized, controlled trials in patient populations with a uniform tumor type, stage, and treatment history. Treatment groups are balanced for important outcome predictors for specific malignancies. In addition, they contain prospective inclusion of survival as an endpoint; and adequate sample size, follow-up, and power to detect a clinically meaningful effect (Nottage and Siu, 2002). Amgen has initiated one large oncology trial and is supporting investigators conducting additional trials as part of the ongoing Aranesp Pharmacovigilance Program.

Amgen believes that most studies designed to investigate anemia outcomes do not provide definitive information on tumor progression or survival endpoints. Amgen further does not believe that it is helpful to append survival outcomes to short chemotherapy-induced anemia studies that, although designed rigorously for hematologic and patient-reported outcome endpoints, do not contain essential design elements to allow conclusive assessment of cancer outcomes.

To more formally and prospectively address disease progression and survival endpoints in patients who are receiving Aranesp therapy, the Aranesp Pharmacovigilance Program includes 5 randomized, prospective clinical trials designed to evaluate specific cancer endpoints in a variety of malignancies (Table 10). These clinical trials include both investigator-sponsored studies (FR-2003-3005, DE-2001-0033, DE-2002-0015, and SE-2002-9001) and an Amgen-sponsored study (20010145). The investigator-sponsored trials are open-label, randomized studies of Aranesp versus observation, and Amgen is collaborating with the investigators to support optimum study design, study conduct, and safety monitoring. As described below (Section 9.2), the Amgen-sponsored study (20010145) is randomized, double-blind, and placebo-controlled. Endpoints include event-free survival, relapse, overall survival, and locoregional control in patients receiving combination chemotherapy for extensive small-cell lung cancer.

The pharmacovigilance program includes large trials in patients with breast cancer and head-and-neck cancer (DE-2001-0033, DE-2002-0015, and SE-2002-9001), the 2 tumor types included in the INT-76 and ENHANCE trials (Table 10). As Aranesp has received marketing approval for the treatment of chemotherapy-induced anemia in all non-myeloid malignancies, studies also were included in patients with small-cell lung cancer (20010145) and non-Hodgkin's lymphoma (FR-2003-3005).

**Table 10. Aranesp Pharmacovigilance Program Trials:  
 Power and Sensitivity Calculations**

Study ID	Tumor Type	Design	Accrual January 2004	Progression Sensitivity 80% Power		Survival Sensitivity 80% Power	
				%	Hazard Ratio	%	Hazard Ratio
FR-2003-3005	Non-Hodgkin's lymphoma	R-CHOP 14 or R-CHOP 21 ± Aranesp	12/600	EFS 55% ± 11% at 3 years	1.45	65% ± 11% at 3 years	1.53
DE-2001-0033	Breast	Sequential or dose-intensified chemotherapy ± Aranesp	300/720	RFS 70% ± 10% at 5 years	1.53	80% ± 10% at 5 years	1.70
DE-2002-0015	Breast	Adjuvant chemotherapy ± Aranesp	10/1000	EFS 60% ± 9% at 5 years	1.35	75% ± 7% at 5 years	1.48
SE-2002-9001	Head and neck	Radiotherapy ± Aranesp	226/600	Local Control 50% ± 11% at 5 years	1.42	60% ± 11% at 5 years	1.49
20010145	Small cell lung	Cisplatin / Carboplatin/VP16 ± Aranesp	170/600	EFS 25% ± 9% at 6 months	1.32	50% ± 10% at 6 months	1.42

± indicates detectable difference; EFS = event-free survival; RFS = relapse-free survival

These investigator-sponsored studies are being conducted in conjunction with data safety monitoring boards and interim safety analyses to ensure careful monitoring. One trial being conducted in patients with head-and-neck cancer receiving curative radiotherapy includes patients with hemoglobin concentrations up to 14.5 g/dL and has a hemoglobin target of 15.5 g/dL (SE-2002-9001). This trial has been the subject of a recent interim safety analysis, and the monitoring committee has recommended continuation of the trial as planned. All studies directly sponsored by Amgen are conducted in accord with the approved product labeling for both dosing and hemoglobin targets.

Three of the European trials (20010145, DE-2001-0033 and DE-2002-0015) use a target hemoglobin value of 14 g/dL, which corresponds to approved label upper limit for dosing in the European Aranesp Summary of Product Characteristics. Although this number differs from that outlined in the United States package insert (13 g/dL), it was also the target selected for pivotal trials 980297 and 20000161, studies that revealed no increase in tumor progression or survival in conjunction with Aranesp therapy.

### **9.1 Pharmacovigilance Program Analyses**

A summary of the power and sensitivity of the Aranesp Pharmacovigilance Program is provided in Table 10. Individually, these trials have 80% power to rule out an increase in risk of 32% to 53% for disease progression and of 42% to 70% for survival with Aranesp, which include the magnitude of the risk observed in the ENHANCE and INT-76 studies. In combination with clinical experience derived from Amgen-sponsored trials containing long-term follow-up, the total patient exposure in the Aranesp Pharmacovigilance Program is 4176 patients, representing 1266 patient-years through March 2004 and increasing to 8503 patient-years in 2008 (Table 11). When pooled in a meta-analysis, they collectively represent the opportunity to detect a considerably smaller safety signal across a broader range of tumors.

**Table 11. Amgen Trials and Investigator-sponsored Trials:  
 Pharmacovigilance Program Patient-years**

Study ID	N	Cumulative and projected patient-years of follow-up <sup>a</sup>				
		Q1 2004	Q1 2005	Q1 2006	Q1 2007	Q1 2008
980297	312	360	368	372	374	374
20000161	344	638	791	920	1015	1145
20010145	600	88	263	473	613	700
FR-2003-3005	600	0	59	243	529	899
DE-2001-0033	720	67	354	852	1480	2074
DE-2002-0015	1000	0	99	409	894	1527
SE-2002-9001	600	113	405	857	1344	1784
Total	4176	1266	2339	4126	6249	8503

<sup>a</sup> Assumes exponential survival, uniform accrual, and all patients followed until death

**9.2 Amgen Study 20010145: Study in Small-cell Lung Cancer**

Study 20010145 is a randomized, double-blind, placebo-controlled study to evaluate the effects on survival of increasing or maintaining hemoglobin with Aranesp in patients receiving chemotherapy for previously untreated, extensive-stage small-cell lung cancer. Approximately 600 patients will be followed until death or until all patients have completed their end-of-study treatment visit and 496 deaths have occurred.

The co-primary endpoints for this study are change in hemoglobin from baseline to the end of the chemotherapy treatment period and survival time. In addition, the safety of Aranesp will be further evaluated based on the incidence and severity of adverse events, changes in laboratory results, changes in vital signs, and the incidence of concomitant medication use. This study includes a data monitoring committee.

**9.3 Study FR-2003-3005: Study in Diffuse Large B-cell Lymphoma**

The FR-2003-3005 study is an open-label, randomized, multicenter, phase 3 investigator-sponsored trial being run by Groupe d'Etude des Lymphomes de l'Adulte (Randomized Study of Intensified CHOP plus Rituximab Given Every 14 days [R-CHOP 14] versus CHOP plus Rituximab Given Every 21 Days [R-CHOP 21] and Randomized Study of Frontline/Prophylactic Darbepoetin alfa Treatment versus Usual Symptomatic Treatment of Anemia in Untreated Patients with Diffuse Large Cell Lymphoma). It is anticipated that 600 patients will be enrolled. The study evaluates the efficacy of rituximab plus CHOP chemotherapy given every 14 days (R-CHOP 14) compared with the standard R-CHOP 21 regimen, with and without Aranesp in previously untreated

patients aged 66 to 80 years with diffuse large B-cell lymphoma. The primary endpoint is event-free survival. Aranesp will be administered weekly for patients with hemoglobin concentrations < 13 g/dL. An interim analysis for safety and for the primary efficacy endpoint is planned after 2 years.

#### **9.4 Study SE-2002-9001: Study in Head-and-Neck Cancer**

This study is an open-label, randomized, multicenter, phase 3 investigator-sponsored trial to evaluate the effects of Aranesp in patients with head-and-neck cancer receiving primary curative radiotherapy (Study of the Importance of Novel Erythropoiesis Stimulating Protein [Aranesp] for the Effect of Radiotherapy in Patients with Primary Squamous Cell Carcinoma of the Head and Neck). It is anticipated that 600 patients will be accrued. The clinical hypothesis is that the addition of Aranesp to standard curative radiotherapy treatment of head-and-neck cancer will increase the locoregional disease control rate. The study is being performed by the Danish Head and Neck Cancer Study Group.

The primary endpoint of this study is loco-regional control (T+N localization). Secondary endpoints include local control (T-localization), overall survival, disease-specific survival, and hemoglobin concentrations during radiotherapy, and acute toxicity. A formal interim analysis will be performed after the observation of 150 locoregional failures.

#### **9.5 Study DE-2001-0033: Study in Neoadjuvant Breast Cancer**

This study is an open-label, randomized, multicenter, phase 3 trial to evaluate the effects of preoperative chemotherapy using a sequential dose-dense and dose-intensified regimen of epirubicin, paclitaxel, and CMF compared with preoperative sequential administration of epirubicin and cyclophosphamide followed by paclitaxel in patients with breast cancer (Randomized, Preoperative Epirubicin Paclitaxel Aranesp Study Comparing Sequential versus Dose Intensified Chemotherapy in Breast Cancer Patients and Randomized to Darbepoetin alfa versus Usual Anemia Therapy). The study is being conducted by the German Gynecological Oncology Study group. Seven hundred twenty patients are planned to be accrued to this study.

The primary endpoint of this study is the effect of dose-dense, dose-intense preoperative chemotherapy on relapse-free survival. Secondary endpoints are the effects of preoperative dose-dense, dose-intense preoperative chemotherapy on clinical and pathological remission rates and the effects of Aranesp on remission rate and quality of life. An interim analysis at 3 years is planned for safety and for the primary endpoint. This study includes a data monitoring committee.

### 9.6 Study DE-2002-0015: Study in Adjuvant Breast Cancer

This study is an open-label, randomized, multicenter, phase 3 trial to evaluate the effects of adjuvant chemotherapy with and without Aranesp on event-free survival rates in patients with breast cancer who have > 3 positive lymph nodes (Adjuvant Therapy of Breast Cancer: Relevance of Erythropoiesis-stimulating Factors for Survival in High-risk Breast Cancer). One thousand patients will be accrued to this study. Patients will receive local radiotherapy at the completion of chemotherapy. The study is being conducted by the West German Study Group.

The primary endpoint is event-free survival, defined as relapse (local or distant), deaths from any cause, or second primaries. The secondary endpoints are overall survival, local relapse rate, toxicity, cognitive function, and severity of patient-reported anemia symptoms. This study includes a data monitoring committee.

#### Key Points:

- Chemotherapy-induced anemia studies often have design elements that preclude meaningful assessment of survival and tumor-progression outcomes.
- Amgen has proactively developed a robust Aranesp Pharmacovigilance Program that includes epidemiologic studies, appropriately well-designed oncology clinical trials, and careful safety data monitoring.
- With over 8500 patient-years of follow-up, the Aranesp Pharmacovigilance Program will have significant sensitivity to detect potential signals regarding survival and tumor progression in multiple oncology populations.

## 10 SUMMARY

Aranesp is a unique erythropoietic molecule that is distinct from other erythropoietic-stimulating proteins in terms of amino acid sequence, glycosylation, receptor affinity, and pharmacokinetic/pharmacodynamic profile. Aranesp is licensed for the treatment of anemia in patients with non-myeloid malignancies receiving chemotherapy. Aranesp reduces fatigue and the need for transfusions, and improves quality of life for patients with grievous illnesses. Aranesp has a favorable benefit/risk profile for the treatment of chemotherapy-induced anemia when used in accord with approved product labeling and published guidelines. Through December 2003, more than 427,000 patients have received Aranesp therapy, representing more than 268,000 patient-years of experience.

The clinical trials that have raised concerns over tumor progression and survival were performed with Eprex and NeoRecormon. No such findings have been observed with Aranesp and, thus, do not suggest a class effect. The unique attributes of Aranesp may be relevant to the differences in the safety profile observed with these different erythropoietic-stimulating proteins.

EPO-R are expressed on hematopoietic tissues, other non-hematopoietic normal tissues and on a variety of tumors of different tissue origins. However, the presence of EPO-R, as measured by mRNA, protein, or receptor binding, does not always correlate with functional EPO-R on cells. These receptors are typically of lower affinity than those expressed in hematopoietic tissues and are of uncertain clinical relevance for cancer patients. Observations of in vitro proliferation of tumor cells with epoetins are mixed and are of uncertain relevance. No such in vitro studies have been reported with Aranesp. Aranesp therapy in tumor-bearing animals have shown benefit in conjunction with radiotherapy.

No reports suggest that EPO-R is amplified or constitutively activated in human tumors of non-hematopoietic origin. No animal models, or clinical syndromes, have been found in which prolonged exposure to EPO increases the incidence of tumors. No evidence suggests that EPO-R undergoes oncogenic transformation in solid tumors.

Amgen has proactively addressed safety observations. The Aranesp label already represents the low potential for oncology patients to experience thrombotic events in conjunction with erythropoietic-stimulating proteins. Analysis of more than 1100 patients receiving Aranesp in randomized, blinded, placebo-controlled trials reveal no evidence for increased tumor progression or reduced survival. Furthermore, Amgen is sponsoring

a large randomized, placebo-controlled trial in patients with small-cell lung cancer and is collaborating with investigators conducting 4 large randomized, controlled trials in patients with lymphoma and breast cancer receiving chemotherapy, and in patients with head-and-neck cancer receiving radiotherapy. These studies should permit further definition of Aranesp benefit/risk in cancer patients with a range of malignancies. In addition, in response to the INT-76 and ENHANCE trial results, Amgen has proactively contacted all worldwide investigators using Aranesp in investigator-sponsored oncology trials to review protocols and dosing regimens, in order to confirm rigor in trial design and conduct and to strengthen support for patient safety.

Amgen believes that erythropoietic treatment of non-anemic patients, or treatment regimens with higher-than-approved target hemoglobin values, should be evaluated in the setting of well-designed and executed clinical trials sufficiently powered to permit safety assessments. The results of such trials should be fully publicly disclosed. Amgen respects the prudence of the FDA and ODAC in weighing observations from all erythropoietic therapies but also believes that product assessments should be evidence-based and driven, in large part, by product specific observations.

**Key Points:**

- Amgen originally cloned and developed Epoetin alfa (Procrit, Epogen) and created and developed darbepoetin alfa (Aranesp).
- Aranesp is considered a distinct molecular entity from scientific, clinical, legal, and regulatory perspectives.
- Aranesp has a favorable benefit/risk profile for the treatment of chemotherapy-induced anemia when used in accord with approved product labeling and published guidelines. Aranesp reduces both fatigue and the need for transfusions and improves quality of life for patients with grievous illnesses.
- Cancer patients have an increased risk of thrombotic events; risk factors include the underlying type of malignancy, stage of disease, prior thrombotic events, performance status, anemia, and exposure to erythropoietic-stimulating proteins. Thrombotic events are appropriately represented in the Aranesp prescribing information.
- The clinical trials that have raised concerns over tumor progression and survival have been performed with Epoetin alfa and Epoetin beta. Such findings have not been observed with Aranesp and, thus, do not constitute a class effect.
- There is no preclinical or clinical evidence that Aranesp promotes cancer cell proliferation, tumor progression, or reduced oncology patient survival.
- With more than 8500 patient years of follow-up, the Aranesp Pharmacovigilance Program will have significant power and sensitivity to detect potential signals regarding survival and tumor progression in multiple oncology populations.

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