

**Appendix 1:** Additional background information on ESAs and the risk of increased tumor promotion, decreased survival, and increased thrombovascular events.

Table of contents

<b>Risks of tumor promotion, decreased survival, and increased thrombovascular events in patients with cancer receiving ESAs .....</b>	<b>25</b>
<b>ODAC 2004 Recommendations.....</b>	<b>29</b>
<b>Assessment of trials presented by Amgen and Ortho Biotech at ODAC 2004 .....</b>	<b>29</b>
<b>Events occurring between May 2004 and May 2007 ODAC.....</b>	<b>29</b>
<b>ODAC 2007 Recommendations.....</b>	<b>31</b>

**Risks of tumor promotion, decreased survival, and increased thrombovascular events in patients with cancer receiving ESAs**

Since the 1993 approval of epoetin alfa in patients with cancer, FDA has monitored new data addressing the risks and benefits of ESAs in oncology patients and sought advice regarding relevance of new clinical trial results of ESAs at Oncologic Drug Advisory Committee (ODAC) meetings in May 2004 and May 2007. Currently, eight studies provide evidence for shorter survival and poorer tumor outcomes when ESAs were used to achieve and maintain hemoglobin levels of 12 g/dL or higher, or in trials enrolling patients with cancer not receiving chemotherapy. In addition, numerous studies in both the oncology and non-oncology indications have observed increased risks of thrombovascular events (TVEs) which include myocardial infarction, cerebrovascular accident, angina, cardiac arrest, pulmonary embolism, and deep venous thrombosis. Increased TVEs in the oncology indication have been observed both with recommended and unapproved dosing strategies.

The hypothetical risk of tumor promotion through erythropoietin receptors either expressed on tumor cells or on tumor vasculature endothelial cells was identified during the review of initial studies supporting approval of epoetin alfa. At the current time, a direct relationship between the presence of erythropoietin receptors on tumor cells and tumor cell proliferation in response to exogenous erythropoietin has not been established.

The initial trials supporting US approval of epoetin alfa were not designed to adequately evaluate or exclude evidence of tumor promotion due to a heterogeneous patient population and the small size of the studies. Therefore Amgen agreed to conduct a post marketing randomized, double-blind, placebo-controlled study (N93-004) to investigate epoetin alfa's effect on tumor response rates in newly diagnosed, limited or extensive stage SCLC. All patients received etoposide and cisplatin chemotherapy, appropriate radiation, and epoetin alfa or placebo for the duration of chemotherapy. The trial was designed as a non-inferiority study to exclude a 15% reduction in overall response rate (ORR) after 3 chemotherapy cycles. Survival (OS) was a secondary endpoint. The trial was terminated early after enrolling 224 of a planned 400 patients between July 1993 and July 2001 due to slow accrual and study results were submitted to FDA in October 2002.

The study met its non-inferiority endpoint, ruling out a potential decrease in response rate of more than 6% in the ESA-treated arm compared to controls. For overall survival, the epoetin alfa vs. placebo hazard ratio was 1.17 (95% CI (0.89, 1.55)). The finding of a non-inferior response rate in Study N93-004 should be viewed cautiously since 17% of patients had missing tumor response data and the duration of response was not confirmed by repeat evaluation at least 4 weeks after the first assessment.<sup>1</sup>

In July 2002, the results of a Phase 3, double-blind, placebo-controlled study, Study 980297, in 314 anemic patients (Hgb  $\leq$  11 g/dL) with previously untreated SCLC and NSCLC supported a new indication for darbepoetin alfa for treatment of anemia in cancer patients receiving at least 12 weeks of platinum-containing chemotherapy. The study enrolled patients between September 1999 and November 2000. Hemoglobin was allowed to reach 15.0 g/dL (for men) or 14.0 g/dL (for women) before dosing of darbepoetin alfa was withheld. The data from this study was submitted to FDA and revealed no evidence of adverse effects on PFS or OS (Table 1 and Table 2). However, the sample size may have precluded the detection of small, yet clinically meaningful, differences.

<b>ITT Analysis</b>	<b>Hazard Ratio (ESA vs Control)</b>	<b>95% CI</b>	<b>p-value</b>
Overall	0.80	(0.61, 1.05)	0.09
SCLC	0.68	(0.41, 1.11)	0.12
NSCLC	0.86	(0.62, 1.18)	0.35

Table 1: Overall Survival, Study 980297

<b>ITT Analysis</b>	<b>Hazard Ratio (ESA vs Control)</b>	<b>95% CI</b>	<b>p-value</b>
Overall	0.80	(0.63, 1.03)	0.09
SCLC	0.58	(0.36, 0.93)	0.02
NSCLC	0.92	(0.68, 1.23)	0.56

Table 2: Progression-free survival, Study 980297

As stated above, in October 2002, data from Study N93-004 was submitted to FDA. During review of the N93-004 results, the results of two large, randomized studies (BEST and ENHANCE) were published. The Breast Cancer Erythropoetin Survival Trial (BEST) and Evaluation of NeoRecormon on outcome in Head And Neck Cancer in Europe (ENHANCE) trials reported decreased 12 month survival rates (BEST) and lower loco-regional control rates and decreased survival (ENHANCE) in patients randomized to receive ESA.<sup>3,4</sup> The results of BEST and ENHANCE are further discussed below.

The BEST trial enrolled 939 patients receiving first-line treatment for metastatic breast cancer who were randomized to receive either epoetin alfa or placebo for 12 months. Randomization was stratified by metastatic site, but not chemotherapy regimen. The trial's primary objective was to demonstrate superior 12-month survival rates in patients receiving ESAs. Secondary endpoints included ORR and time-to-progression (TTP). The

trial was terminated based on the recommendations of the data monitoring committee due to demonstration of a significant decrease in 12 month survival rates in epoetin alfa-treated patients (70% vs 76%; p=0.0117). The committee also noted increased mortality rates and shorter TTP at 4 months in ESA treated patients with no significant difference in ORR. Conclusions regarding effects on tumor progression are limited because more than 25% of patients enrolled had incomplete assessment of tumor sites at baseline and/or during treatment.<sup>2 3</sup>

The ENHANCE study enrolled 351 patients receiving definitive radiotherapy for initial treatment of advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Patients were randomized to receive either epoetin beta or placebo during radiotherapy; randomization was stratified by resection status. The primary objective was to demonstrate superior loco-regional progression-free survival (LR PFS) with ESAs; secondary endpoints included OS and loco-regional control. The trial demonstrated a significantly shorter LR PFS (HR 1.62; 95% CI 1.22, 2.14; p = 0.0008) and shorter OS (HR 1.39; 95% CI 1.05, 1.84; p = 0.02) in epoetin beta-treated patients compared to those receiving placebo after adjusted for treatment stratum and tumor stage.<sup>4</sup>

The results of the BEST and ENHANCE trials led FDA to seek advice regarding appropriate actions from the ODAC in May 2004. In addition to the BEST and ENHANCE trials, FDA also presented preliminary information (in the form of abstracts or communications) on other trials investigating the benefits of ESAs in patients with cancer, which suggested harmful effects. These included the CAN<sup>1</sup>-20 trial conducted in patients with NSCLC,<sup>5</sup> for which an unplanned analysis showed a trend towards increased mortality in ESA arm, and the Radiation Therapy Oncology Group (RTOG) 9903 trial in patients with head and neck cancer which was terminated following an unplanned analysis revealing a non-significant trend to lower loco-regional control rates and increased mortality in the ESA arm. In both trials, the unplanned analyses were triggered by the publications of the BEST and ENHANCE trials.<sup>4</sup> FDA also presented available data from randomized controlled trials that terminated early because of evidence of increased rates of TVEs.<sup>6</sup> These trials were EPO-CAN-15 (small cell lung cancer), PR00-03-006 (gastric and rectal cancer), GOG 191 (cervical cancer), and Rosenzweig (breast cancer) trial. Results from these four randomized trials, which assessed the benefits of ESA in patients with homogeneous cancers and homogeneous cancer treatment, were obtained from published reports. All four trials were terminated prematurely for evidence of an unacceptable increase in the risk of thrombotic and cardiovascular events in the ESA arm. Additional information on these trials can be found in FDA's May 2004 ODAC briefing document.<sup>6</sup>

Studies presented by Amgen and Ortho Biotech at the 2004 ODAC are summarized by Figure 1.

---

<sup>1</sup> Trials containing "CAN" in the title were conducted by academic investigators or groups with partial support from Ortho Biotech.

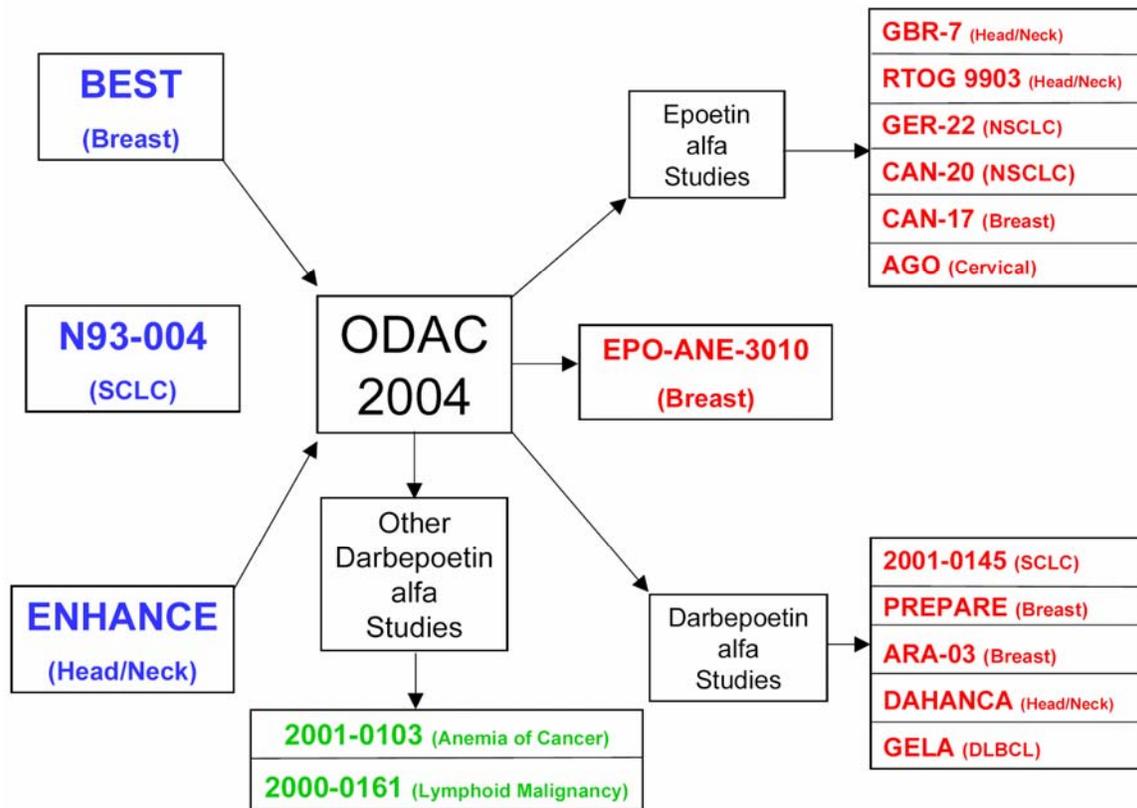


Figure 1: Overview of important oncology trials conducted with ESAs.

BEST denotes Breast Cancer Erythropoietin Survival Trial; ENHANCE, Evaluation of NeoRecormon on outcome in Head And Neck Cancer in Europe; RTOG, Radiation Therapy Oncology Group; AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; DAHANCA, Danish Head and Neck Cancer; GELA, Groupe d'Etude des Lymphomes de l'Adulte; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; and DLBCL, diffuse large B cell lymphoma

- The studies on the left side of Figure 1 (BEST, N93-004, and ENHANCE) were studies with results known prior to the May 2004 ODAC. The BEST and ENHANCE studies were primary contributing factors for the FDA to convene the May 2004 ODAC.
- The studies on the right side of Figure 1 (GBR-7, RTOG 9903, GER-22, CAN-20, CAN-17, AGO, EPO-ANE-3010, 2001-0145, PREPARE, ARA-03, DAHANCA, and GELA) were proposed by Amgen, Inc. and Ortho Biotech at the May 2004 ODAC to further assess safety concerns.
- All of these studies were ongoing as of the May 2004 ODAC except for EPO-ANE-3010. Therefore FDA did not have the opportunity to comment on the protocols nor to ensure that each study contained the study design elements (below) that were recommended by the ODAC 2004.
- The studies in the bottom of the figure (2001-0103 and 2000-0161) are other studies of interest with primary data submitted to FDA after the May 2004 ODAC.

### **ODAC 2004 Recommendations**

The 2004 ODAC recommended the conduct of additional double-blind, placebo-controlled trials, with primary endpoints of survival and adequate power to detect potential effects on survival. The committee further recommended that such trials be restricted to homogeneous tumor subtypes and stages, contain standardized treatment approaches with prospectively defined, systematic assessments of tumor progression to detect effects on tumor promotion, and include a systematic and prospective schedule of assessments for TVEs. Due to lack of well-characterized assays for erythropoietin receptors, tumor biopsy to assess for the presence of these receptors was deemed optional.

### **Assessment of trials presented by Amgen and Ortho Biotech at ODAC 2004**

Only two of the twelve trials (EPO-ANE-3010 and 2001-0145) on the right side of Figure 4 have nearly met all of the ODAC 2004 study design recommendations for adequately assessment of safety concerns of ESAs in patients with cancer. Study design flaws in the other ten trials (GBR-7, RTOG 9903, GER-22, CAN-20, CAN-17, AGO, PREPARE, ARA-03, DAHANCA, GELA) included lack of blinding, infrequent and insensitive baseline or surveillance tumor measurement assessments, lack of systematic assessment for detection and collecting the incidence of TVEs, and lack of placebo comparisons. All studies except EPO-ANE-3010 used off-label dosing regimens that permitted or attempted to achieve hemoglobin values of >12 g/dL.

### **Events occurring between May 2004 and May 2007 ODAC**

After the May 2004 ODAC, changes to the prescribing information were made and a “Dear Health Care Professional” letter was issued in June 2004 to include information from the BEST and ENHANCE trials. Negotiations regarding the trial design of study EPO-ANE-3010 occurred between May and December 2004, and this study began patient accrual in March 2006. The originally proposed study planned to enroll 2000 patients with metastatic breast cancer receiving first-line chemotherapy (corresponding to a HR 1.15), but was later reduced to a target enrollment of 1000 patients by the Sponsor (corresponding to a HR 1.25). EPO-ANE-3010 has had difficulty with patient accrual, and as of 12/11/07, has accrued only 236 patients. Other studies on the right side of Figure 1 were already accruing patients, and their results and primary data sets were expected to be presented to FDA in a timely fashion after ODAC 2004.

In December 2006, FDA was notified of the interim results of the DAHANCA study in 522 patients with head and neck cancer, where patients in both arms received definitive RT and were randomized to Aranesp vs transfusion support. Demonstration of superior loco-regional control rate was the primary endpoint; OS and disease specific survival were secondary endpoints. The study was terminated early after a planned interim analysis in October 2006 showed no evidence of potential benefit in the Aranesp arm. Based on summary results provided by DAHANCA, locoregional control was worse in the Aranesp arm (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02), and there was a trend to shorter survival in the Aranesp arm (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08). FDA is still awaiting primary data submission for this trial, and has not had the opportunity to perform an independent analysis of the results of the trial.

In January 2007, FDA was notified of summary results of the 2001-0103 (anemia of cancer) study, which enrolled 989 patients with a variety of non-myeloid malignancies who were not on chemotherapy or myelosuppressive RT. Patients were randomized to Aranesp vs placebo. The trial was intended to support expansion of product labeling for darbepoetin alfa to include treatment of anemia in cancer patients not receiving chemotherapy. The primary endpoint was a reduction in proportion of patients receiving RBC transfusions. Survival was assessed as a secondary endpoint in a safety analysis. Because of the heterogenous population enrolled, the effect of ESAs on tumor promotion could not be assessed. Analysis of the primary data submitted to FDA in March 2007 demonstrated a shorter OS (HR 1.30; [95% CI: 1.07, 1.57], p=0.008) in the Aranesp arm. The trial did not meet its primary endpoint of demonstrating a statistically significant reduction in proportion of patients receiving RBC transfusions in the darbepoetin alfa arm.

In February 2007, the results of the CAN-20 trial were electronically published in the Journal of Clinical Oncology.<sup>5</sup> The CAN-20 trial enrolled 70 patients with Stage III-IV or recurrent NSCLC who were on palliative care and not receiving chemotherapy or radiotherapy. Improvement in quality of life (QOL), the primary endpoint, was assessed by the Functional Assessment of Cancer Therapy-Anemia score. The trial was terminated early by the trial's steering committee due to increased TVEs seen in other trials and increased mortality reported in the BEST and ENHANCE trials. An unplanned analysis suggested increased mortality in ESA arm. Final analysis on this trial by the investigators showed a shorter survival in the ESA arm (HR 1.84; [95% CI, 1.01, 3.35], p= 0.04). Significant improvement in QOL in the ESA-treated arm was not demonstrated. FDA is still awaiting primary data submission for this trial, and has not had the opportunity to perform an independent analysis of the results of the trial.

In April 2007, updated primary data was submitted to FDA on results of the 2000-0161 (lymphoid malignancy) study, which enrolled 344 patients with multiple myeloma, non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia, Hodgkin's disease, and chronic lymphocytic leukemia. Tumor subtype and extent of prior chemotherapy were stratification variables. The primary endpoint was the proportion of subjects achieving a hemoglobin response of  $\geq 2.0$  g/dL. Because of the heterogeneity regarding underlying cancer type and treatment, an accurate assessment of tumor promotion could not be made. The results of this trial were presented by Amgen at ODAC 2004, and the results at that time did not show a difference in survival. However, based on FDA review of updated primary data in April 2007, this trial showed shorter OS (HR 1.37 [95% CI 1.02, 1.83], p=0.037) in the Aranesp arm.

The adverse results of these four trials (DAHANCA, 2001-0103, CAN-20, and 2000-0161), in addition to previously known results from the BEST and ENHANCE trials, led FDA to re-convene ODAC in May 2007 to reassess the risk to benefit ratio of ESAs and to seek advice regarding further regulatory actions. Prior to convening ODAC in May 2007, FDA had issued a black box warning for both epoetin alpha and darbepoetin alpha in March 2007. The black box emphasized the adverse results in BEST, ENHANCE,

DAHANCA, 2001-0103 trials and recommended to “Use the lowest dose of ESAs that will gradually increase the Hgb concentration to the lowest level sufficient to avoid the need for blood transfusion” and stated that ESA dosing should be discontinued for hemoglobin levels above 12 g/dL. Additional changes made to the prescribing information were the inclusion of recent adverse findings in trials in patients with chronic renal failure (CHOIR study)<sup>7</sup> or undergoing major orthopedic surgery (SPINE study)<sup>8</sup> and clarification of dosing instructions.

### **ODAC 2007 Recommendations**

The 2007 ODAC recommended that marketing authorization of ESAs be contingent upon further restrictions in product labeling and the conduct of additional clinical trials. In addition, labeling should state that ESAs are not indicated for use in the specific tumor types investigated in the trials that demonstrated adverse safety signals. The committee did not specify which tumor types should have restricted use.

Additionally, the ODAC recommended that product labeling should define a hemoglobin level for initiation of ESAs in asymptomatic patients, and that the hemoglobin level at which dosing is to be suspended should remain at 12 g/dL. Product labeling should recommend ESA discontinuation following the completion of a chemotherapy regimen and re-evaluation of the need for administration of ESAs based on the degree of anemia observed with subsequent chemotherapy regimen(s).

---

<sup>1</sup> Grote T, Yeilding AL, Castillo R et al. Efficacy and Safety Analysis of Epoetin Alfa in Patients With Small-Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Clin Oncology* 2005; 22: 9377-9386.

<sup>2</sup> Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving firstline chemotherapy: a survival study. *J Clin Oncol* 2005; 23: 5960-72.

<sup>3</sup> Leyland-Jones B. Breast cancer trial with erythropoietin terminated unexpectedly. *Lancet Oncol* 2003; 4: 459-60.

<sup>4</sup> Henke M, Laszig R, Rube C et al. Erythropoietin to treat head and neck cancer patients with anemia undergoing radiotherapy: randomized, double-blind, placebo-controlled trial. *Lancet* 2003; 362: 1255-1260.

<sup>5</sup> Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in Non-Small Cell Lung Cancer with disease related anemia. *J Clin Oncology* 2007; 25: 1027-1032.

<sup>6</sup> Luksenburg H, Weir A, Wager R. Safety Concerns Associated With Aranesp (Darbepoetin Alfa) Amgen, Inc. and Procrit (Epoetin Alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated With Cancer Chemotherapy. FDA Briefing

---

Document for May 4, 2004 ODAC meeting.

[http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2\\_04.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2_04.pdf)

<sup>7</sup> Singh AK, Szczech L, Tang KL, et al. Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. N Engl J Med 2006; 355: 2085-2098.

<sup>8</sup> Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy. FDA Briefing Document for May 10, 2007 ODAC meeting.

<http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf>