SOUTH SHORE HEMATOLOGY-ONCOLOGY ASSOCIATES, P.C.

Ivan K. Rothman, M.D.
Leonard Kessler, M.D.
Carl D. Atkins, M.D.
Ronald A. Primis, M.D.
Richard M. Lee, M.D.

242 Merrick Road, Suite 301
Rockville Centre, New York 11570
Telephone: (516) 536-1455
Fax: (516) 536-1598

February 19, 2008

Nicole Vesely
Center for Drug Evaluation and Research
HFD-21
Food and Drug Administration
5630 Fishers Lane, Room 1093
Rockville, MD 20857

Dear Ms. Vesely,

I would like to respectfully submit the following comments to ODAC for their consideration regarding the meeting on March 13, 2008 on the use of erythropoiesis stimulating agents (ESAs) for the treatment of anemia in patients with cancer.

The evaluation of the risks associated with the use of ESAs for the treatment of anemia in patients with cancer has been clouded by faulty statistical reasoning. Although the randomized controlled trial has rightly come to be considered the gold standard in evaluating medical therapies, the impact of the design and implementation of trials on the ability of randomization to eliminate bias has been underestimated. In the case of the effect of ESAs on survival in patients with cancer, the design and implementation of all five trials that have suggested a negative impact of ESAs on survival seriously limit their ability to yield survival estimates that are free of bias. The fact that the Bohlius meta-analysis[1] has failed to show a consistent negative survival effect of ESAs should also inform the interpretation of individual trials. In addition, there has been unnecessary confusion about the hemoglobin level at which ESAs should be started.

Bias caused by imbalances in the ENHANCE trial.

In the ENHANCE trial,[2] there was a baseline imbalance in the treatment and control groups in the number of patients who were smokers. When the authors analyzed their data adjusted for smoking status and several other factors using a multivariable analysis, the p value for the difference in outcome was 0.13, indicating that the difference could have been due to baseline differences rather than to treatment effect. It is a basic tenet of randomized trials that the ability of randomization to control for bias is directly proportional to the size of the trial. In other words, the fact that patients are allocated randomly does not guarantee that the baseline risks will be evenly balanced. It only guarantees that, on average, with a large enough trial, the risks will probably balance out. The more patients randomly allocated, the more likely the risks will be balanced. It is therefore always essential to analyze known risk factors at baseline for differences between allocated groups. When any differences are noted, an adjusted analysis should be

[1] Bohlius J, Wilson J, Seidenfield J, et al. Erythropoietin or Darbopoetin for patients with cancer [review]. Cochrane Database Syst Rev 2007; 2:CD003407.

[2] Henke M, Laszig R, Rübe, C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003; 362: 1255-60.

performed to see whether those differences alone might account for the observed results, regardless of any treatment effect.[3] The authors of ENHANCE appropriately carried out such an analysis, but incorrectly interpreted the result, ignoring the insignificant p value. It is the p value of the adjusted result that is important, not the p value of the unadjusted result. The unadjusted result does not account for the baseline imbalances introduced by the small size of the trial. The insignificant p value associated with the adjusted analysis indicates that the survival difference noted on the unadjusted analysis cannot reliably be attributed to treatment with ESA.

Bias caused by early withdrawals in the BEST trial.

The BEST study is completely invalidated by the fact that 221 out of 939 patients were "withdrawn from the double blind phase prematurely" (Fig. 2 of the article).[4] The most common reason given for withdrawal was "disease related." The survival outcomes of the withdrawn patients and the patients who completed the double-blind phase were entirely different. There was no difference in survival according to ESA treatment in the withdrawn patients; the survival difference was limited to the patients who remained in the double-blind phase. It is therefore possible that the investigators noted the sicker patients with progression of disease getting more anemic and withdrew them from the double-blind phase of the study. The ESA may have prevented anemia, masking progression in some patients, thus preventing withdrawal, making the ESA-treated patients potentially more prone to early progression and death compared to the patients who remained in the control population. With 23% of patients removed from the double-blind phase of the trial, the comparison of treatments is no longer double-blind and is potentially confounded by investigator bias introduced by treatment effect of ESA. The difference in survival outcome between patients withdrawn and those who remained in the double-blind phase of the study is the signal that bias has been introduced The fact that progression-free survival in ESA-treated and control populations did not differ should also raise concern that the survival difference observed is spurious. It should also be remembered that most of these patients were not anemic at baseline, so this trial did not address the issue of the treatment of cancer patients with anemia.

Ascertainment bias and inadequate baseline data in the EPO-CAN-20 trial.

The EPO-CAN-20 trial was halted early by its data safety monitoring board (DSMB) because of the finding of excess deaths in patients treated with ESAs with a p value of 0.03 (the p value after final analysis was 0.04).[5] However, for an unplanned analysis such as this, more stringent criteria are usually used because multiple testing of data will, by chance, increase the likelihood of finding a small p value (there is a one-in-twenty chance of finding a p value of 0.05 each time one looks at a data set that has no treatment effect). The DSMB decided to halt the trial because of recent trials suggesting there may be safety concerns with ESAs. Reporting a positive result as soon as one finds it leads to ascertainment bias, which makes positive results seem more common than they truly are. The Forest plot in the Bohlius meta-analysis shows this trial to be an outlier, which is what one would expect from ascertainment bias. Because the EPO-CAN-20 trial

---

[3] Rothman KJ. The assessment and control of confounding. In: Modern Epidemiology. 1st ed. Chapter 9. The Role of Statistics in Epidemiologic Analysis. (Boston: Little, Brown) 1986, 125-129.

[4] 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 first-line chemotherapy: A survival study. J Clin Oncol 2005;23:5960-72.

[5] 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 Oncol 2007;25:1027-32.

was not designed as a survival trial, but was looking for hemoglobin targets, baseline data relevant to survival were not routinely obtained. Therefore, at the time the trial was stopped, with only 70 patients randomized, baseline data was available for only 58 patients. Of the ESA-treated patients, 42% with baseline information had performance status 0 or 1, whereas 54% of control patients had performance status 0 or 1. With such a small number of patients randomized, fewer patients with complete baseline data, documented imbalances in performance status, and the possibility of ascertainment bias, the relevance of the survival difference (with p= 0.04) is questionable. There is insufficient data to determine whether the difference observed was due to treatment with ESAs or confounding due to the small sample size with inadequate balancing of baseline prognostic variables.

Inadequate data and absence of blinding in DAHANCA trial.

The DAHANCA trial has been published only in abstract form.[6] There were 522 patients randomized with an unspecified number of strata (four stratification parameters), unspecified randomization protocol and no mention of blinding. There was no difference in overall survival between patients treated with ESAs and control patients. Although the authors state that "the patients were evenly distributed according to the stratification parameters" they do not mention other baseline prognostic categories. Of course, if the study was properly conducted, the patients would have to be evenly distributed according to stratification parameters; otherwise the stratification would have not been accomplished. It is more important to know whether factors not stratified were evenly distributed. Moreover, the only difference the authors noted was an increase in locoregional progression. This is a subjective endpoint which could be affected by the lack of blinding. There is insufficient data in this report on which to base a decision regarding the risks associated with the use of ESAs in patients with cancer. Notably, the patients were not anemic and were treated to hemoglobins up to 15.5. This trial cannot, therefore, inform a decision on the treatment of anemic cancer patients.

Bias caused by small sample sizes from overstratification of the AMGEN-103 trial.

The AMGEN-103 trial had obvious imbalances in randomization as can be seen by the differences in male/female ratio in the treatment and control groups.[7] This was most likely due to an inappropriately large number of treatment strata for hemoglobin levels. This has the same effect as decreasing the sample size: each stratum is functionally the same as an individual randomized trail within the larger trial. This lead to an imbalance in disease stage, especially in myeloma and lymphoma patients, where the greatest differences in survival were seen. Only an adjusted survival analysis of this data has any statistical validity, as discussed above in regard to the ENHANCE trail. Making a decision about the adverse effects of ESAs based on the raw data from this trial, without an analysis of baseline differences and multivariable adjustment is wholly inappropriate. It is also noteworthy that patients who were to receive chemotherapy or radiotherapy were excluded from this trial, because they were judged have an unacceptably high

---

[6] Overgaard J, Hoff C, Hansen S, et al. Randomized 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 (HNSCC) – the Danish Head and Neck Cancer Group DAHANCA 10 randomized trial. Eur J Cancer Suppl 2007; 5:7.

[7] Food and Drug Administration Oncologic Drugs Advisory Committee Briefing Document. Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy. Washington ,DC. US Food and Drug Administration; 2007. http://www.fda.gov/ohms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf.

risk of requiring a transfusion without ESA treatment. Such patients are currently denied coverage for ESA treatment for their anemia because FDA has erroneously concluded that they are at increased risk of death and have no demonstrable benefit from treatment with ESAs.

Does starting ESA treatment at hemoglobin levels greater than 10 g/dL result in fewer transfusion?

The ASH/ASCO guideline found "insufficient evidence" that starting ESAs at hemoglobin levels greater than 10 g/dL resulted in fewer transfusions.[8] The authors ignore common sense and the type II error (finding no effect from a study when a true effect exists due to an inadequate sample size).[9] It is known that it usually takes 2 to 6 weeks for ESAs to effect a hemoglobin response.[10] It is obvious, then, that if a patient's hemoglobin is decreasing, if one waits until the hemoglobin is too low, the patient will require a transfusion before an ESA will take effect. A number of studies have shown that the lower the starting hemoglobin level, the more often patients require transfusions.[11] The lack of statistical significance of these studies should not obscure that obvious trend. There can be no doubt that with sufficient resources a large enough trial would clearly demonstrate that starting ESA treatment at a higher hemoglobin level will result in fewer transfusions. Failure to prove an association does not mean that one does not exist. The hemoglobin level at which ESA treatment should begin should take into account the patient's symptoms and comorbidity and the expected rate of decrease in hemoglobin and expected response time to ESA. This is common sense based on available data.

As a clinician, I have seen the adverse effect of over-interpretation of the data from these trials. Since the black box warning placed on the ESA labels by FDA and the resulting National Coverage Decision by the Centers for Medicare and Medicaid Services, the ability to treat anemic cancer patients with ESAs at clinically appropriate schedules has been curtailed and my patients have suffered as a result. My patients are more symptomatic and more of them require transfusions. A recent patient, because of inadequate ESA dosing, became so anemic she required admission to the hospital for transfusion, which was complicated by pulmonary edema, necessitating a week-long stay. This is only one example, but I use it to illustrate that decisions that seem conservative may have adverse consequences. A recent US Oncology practice survey confirms that community cancer patients across the nation are more symptomatic from anemia and are requiring more transfusions since the change in FDA labeling and the National Coverage Decision.

In summary, ODAC must consider that the safety signals presented by the above trials are false alarms. It is certainly reasonable to alert clinicians to the presence of these trails and advise them that they may want to discuss the implications of them with patients with cancer and

---

[8] Rizzo JD, Somerfield MR, Hagerly KL, et al. Use of epoetin and darbopoetin in patients with cancer: 2007 American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update. Blood 2007; 111:25-41.

[9] Freiman JA, Chalmers TC, Smith H, Jr., and Kuebler RR. The importance of beta, the type II error, and sample size in the design and interpretation of the randomized controlled trial: survey of two sets of "negative" trials. Chapter 19. In Medical Uses of Statistics. 2nd ed. Ed. John C. Bailar III and Frederick Mosteller. (Boston: NEJM Books) 1992:357-73.

[10] Aranesp® FDA-approved package insert.

[11] Ludwig H, Crawford J, Österborg A, et al. Patient-level integrated analysis of data from 6 randomized, double-blind, placebo-controlled trials of darbepoetin alfa (DA) in patients (pts) with chemotherapy-induced anemia (CIA). Eur J Cancer Suppl 2007; 5:142.

anemia before prescribing ESAs, but to do so in the context of the absence of evidence for an adverse survival effect on meta-analysis. It is also reasonable that FDA request that future trials using ESAs be designed to adequately measure survival endpoints by including appropriate baseline information, accruing large enough sample sizes, and avoiding stratification, relying rather on adjusted analyses to determine whether treatment with ESAs affects survival in anemic patients with cancer.

Respectfully,

Carl D. Atkins, MD
carl.atkins@usoncology.com

Curriculum Vitae

Carl D. Atkins, MD

South Shore Hematology-Oncology Associates, P.C.
242 Merrick Road, Suite 301
Rockville Centre, NY 11570-5254
516-536-1455 (W)
Fax: 516-536-1598

e-mail: carl.atkins@usoncology.com

[redacted]

Education

Sarah Lawrence College

Bronxville, NY

1971 - 1973

Massachusetts Institute of Technology

Cambridge, MA

1973 - 1975

Bachelor of Science (Biology)

(Phi Beta Kappa)

Tufts University School of Medicine

Boston, MA

1975 - 1979

Doctor of Medicine

Medical Licensure

New York State, August 22, 1980

Postgraduate Training

Residency in Internal Medicine

Montefiore Hospital and Medical Center

Bronx, NY

1979 - 1982

Fellowship in Medical Oncology
Memorial Sloan-Kettering Cancer Center
New York, NY
1982 - 1984

Accreditations

Internal Medicine
American Board of Internal Medicine
September 15, 1982

Medical Oncology
American Board of Internal Medicine
November 19, 1985

Professional experience

Full-time community-based group practice
South Shore Hematology-Oncology Associates, P.C.
Rockville Centre, NY
1984 - present

Attending Physician
South Nassau Communities Hospital
Oceanside, NY
1984 - present

Attending Physician
Mercy Medical Center
Rockville Centre, NY
1984 - present

Additional professional activities

President of the Medical Staff
South Nassau Communities Hospital
June 2006 – present

Vice President of the Medical Staff
South Nassau Communities Hospital
June 2004 – June 2006

Chairman, Medical Staff Performance Improvement Committee
South Nassau Communities Hospital
June 2004 – June 2006

Secretary of the Medical Staff
South Nassau Communities Hospital
June 2002 – June 2004

Member-at-large
Medical Board
South Nassau Communities Hospital
June 2000 – June 2002

Cancer Liaison to the Commission on Cancer
South Nassau Communities Hospital
September 1995 – January 2004

Managing Physician
Cancer Registry
South Nassau Communities Hospital
July 1995 – January 2004

Chairman
Medical Records Committee
South Nassau Communities Hospital
September 1991 – September 2002

Member
Advisory Committee of the Health Information Technology Program
Molloy College
1998 - 2000

Member

Massachusetts Institute of Technology

Committee on the Use of Humans as Experimental Subjects

1974 - 1975

Professional memberships

American Society of Clinical Oncology

American Medical Association

Nassau County Medical Society

Scientific Publications

1. Atkins CD. Exemestane or tamoxifen? Lancet 2007;369:1600 [letter]
2. Atkins CD. Potential hazards of mammography. J Clin Oncol 2007;25:604 [letter].
3. Atkins CD. Re: Survival effects of postmastectomy adjuvant radiation therapy using biologically equivalent doses: a clinical perspective. J Natl Cancer Inst 2006;98:1021 [letter].
4. Atkins CD. Overestimation of the prognostic significance of SUV measurement by positron emission tomography for non-small-cell lung cancer. J Clin Oncol 2005;23:6799-80 [letter].
5. Atkins CD. Re: Influence of the new AJCC breast cancer staging system on sentinel lymph node positivity and false-negative rates. J Natl Cancer Inst 2004;96:1639 [letter].
6. Atkins CD. Androgen supression plus radiation therapy for prostate cancer. JAMA 2004;292:2084 [letter].
7. Atkins CD. Dose-dense chemotherapy as adjuvant treatment for breast cancer. J Clin Oncol 2004; 22:749 [letter].
8. Atkins CD. Intraperitoneal chemotherapy for stage III ovarian cancer. J Clin Oncol 2003;21:957 [letter].
9. Atkins CD. Re: A Randomized, Placebo-Controlled Trial of Zolendroic Acid in Patients with Hormone-Refractory Metastatic Prostate Carcinoma. J Natl Cancer Inst 2003;95:332 [letter].
10. Atkins CD. Adjuvant chemoradiotherapy for gastric cancer. N Engl J Med 2002;346:210 [letter].
11. Atkins CD. Doxorubicn and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide for metastatic breast cancer. J Clin Oncol 2001;19:3441-3442 [letter].
12. Atkins CD. Re: Efforts aimed at risk communication flourish. J Natl Cancer Inst 2001;93:398 [letter].

13. Atkins CD. Tamoxifen and risk of endometrial cancer. Lancet 2001;357:65 [letter].
14. Atkins CD. Breast cancer survival advantage with radiotherapy. Lancet 2000;356:1269 [letter].
15. Atkins CD. Re: Randomized Intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst 2000;92:1446. [letter]
16. Atkins CD. Hepatic arterial infusion of chemotherapy for metastatic colorectal cancer. N Engl J Med 2000;342:1524-1525 [letter]
17. Atkins CD. Long term outcome of invasive breast cancer. Lancet 2000;355:1551-1552. [letter]
18. Atkins CD. Postoperative radiotherapy in high-risk postmenopausal breast cancer. Lancet 1999;354:865. [letter]
19. Atkins CD. Re: Colorectal cancer screening: sifting through the evidence. J Natl Cancer Inst 1999;91:1507. [letter]
20. Atkins CD. Autopsy rates and diagnosis. JAMA 1999;281:2181-2182. [letter]
21. Atkins CD. Clodronate in metastatic breast cancer. N Engl J Med 1998;339:1941. [letter]
22. Atkins CD. Adjuvant chemotherapy with CEF versus CMF for node-positive breast cancer. J Clin Oncol 1998;16:3916-3917. [letter]
23. Atkins CD. Dissection of regional lymph nodes in cutaneous melanoma. Lancet 1998;351:1884-1885. [letter]
24. Atkins CD. Prophylactic platelet transfusions in acute myeloid leukemia. N Engl J Med 1998;338:1468-1469. [letter]
25. Atkins CD. Ethics of off-label treatment. J Clin Oncol 1998;16:1637. [letter]
26. Atkins CD. Re: Tamoxifen and chemotherapy for lymph node-negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 1998;90:468. [letter]
27. Atkins CD. Locating and appraising systematic reviews. Ann Intern Med 1998;128: 323. [letter]
28. Atkins CD. Re: Comment on oncologists judge themselves the best judges of cancer treatments. J Natl Cancer Inst 1998;90:162-163. [letter]
29. Atkins CD. Re: Relationship between the size and margin status of ductal carcinoma *in situ* of the breast and residual disease. J Natl Cancer Inst 1998;90:160-161. [letter]
30. Atkins CD. Role of medical editors. Lancet 1997;350:1484. [letter]
31. Atkins CD. Postmenopausal hormone therapy and mortality. N Engl J Med 1997;337:1390-1391. [letter]
32. Atkins CD. Translating statistics for use in the clinic. J Gen Intern Med 1997;12:626-628.

33. Atkins CD, Warshaw M. Sentinel-node biopsy in breast cancer. Lancet 1997;350:808. [letter]
34. Atkins CD. Warfarin: less may be better. Ann Intern Med 1997;127:332. [letter]
35. Atkins CD. A clinician's view of statistics. J Gen Intern Med 1997;12:500-504.
36. Atkins CD. Bone mass and the risk of breast cancer. N Engl J Med 1997;337:199. [letter]
37. Atkins CD. Estrogen replacement therapy: new options, continuing concerns. JAMA 1997;277:1515. [letter]
38. Atkins CD. Acyclovir plus steroids for herpes zoster. Ann Intern Med 1997;126:831. [letter]
39. Atkins CD. Guidelines for the use of carcinoembryonic antigen in colorectal cancer. J Clin Oncol 1997;15:863-864. [letter]
40. Atkins CD. High-dose chemotherapy in multiple myeloma. N Engl J Med 1996;335:1844. [letter]
41. Atkins CD. Post-discharge deep-vein thrombosis after orthopedic surgery. Lancet 1996;348:1179. [letter]
42. Atkins CD. Re: Second cancers after adjuvant tamoxifen therapy for breast cancer J Natl Cancer Inst 1996;88:1496-7. [letter]
43. Atkins CD. Macronutrients and risk of breast cancer. Lancet 1996;348:137-138. [letter]
44. Atkins CD. Autologous bone marrow transplantation in relapsed non-Hodgkin's lymphoma. N Engl J Med 1996;334:990. [letter]
45. Atkins CD. Inflammatory bowel disease associated with levamisole and fluorouracil chemotherapy for colon cancer. J Natl Cancer Inst 1996;88:303. [letter]
46. Atkins CD. Reporting randomized controlled trials. JAMA 1995;274:1342. [letter]
47. Atkins CD. Effect of flutamide withdrawal on response assessment of estramustine and etoposide for prostate cancer. J Clin Oncol 1995;13:797. [letter]
48. Atkins CD. Estrogen replacement therapy in breast cancer survivors. JAMA 1995;273:619. [letter]
49. Atkins CD. Post-remission chemotherapy for acute myeloid leukemia. N Engl J Med 1995;332:334. [letter]
50. Atkins CD. Tamoxifen versus medroxyprogesterone acetate for metastatic breast cancer. J Clin Oncol 1994;12:2515. [letter]
51. Atkins CD. Preventive health services. N Engl J Med 1994;331:1157. [letter]

52. Atkins CD. Adjuvant therapy for breast cancer. N Engl J Med 1994;331:744. [letter]
53. Atkins CD. Re: Validation of the Gail et al. model for predicting individual breast cancer risk. J Natl Cancer Inst 1994;86:1350. [letter]
54. Atkins CD. Interferon alfa-2a for chronic myeloid leukemia. N Engl J Med 1994;331:401. [letter]
55. Atkins CD. A predictive model for non-Hodgkin's lymphoma. N Engl J Med 1994;330:574. [letter]
56. Warrell RP, Jr., Danieu L, Coonley CJ, Atkins CD: Salvage chemotherapy of advanced lymphoma with investigational drugs: mitoguazone, gallium nitrate, and etoposide. Cancer Treat Rep 1987;71:47-51.
57. Atkins CD, Coonley CJ, Kempin SJ, Straus DJ, Warrell RP, Jr. Effective salvage of relapsed lymphoma with investigational chemotherapy: gallium nitrate, VP-16-213, and methyl glyoxal bis (guanylhydrazone) (MGBG). Proc Am Soc Clin Oncol 1984;3:244. [abstract]
58. Li FP and Atkins CD. Non-Hodgkin lymphoma: etiology and epidemiology, in Crowther DG, ed., Advances in Medical Oncology, Research and Education, volume 7, Leukemia and Non-Hodgkin Lymphoma, New York: Pergamon Press, 1979:79-88.

Other Publications

1. Atkins, Carl D., ed. Shakespeare's Sonnets: With Three Hundred Years of Commentary, Madison, NJ: Fairleigh Dickinson University Press, 2007.
2. Atkins, Carl D. The Importance of Compositorial Error and Variation to the Emendation of Shakespeare's Texts: A Bibliographic Analysis of Benson's 1640 Text of Shakespeare's *Sonnets*. Studies in Philology 2007;104 (3):306-39.
3. Atkins, Carl D. The Application of Bibliographic Principles to the Editing of Punctuation in Shakespeare's *Sonnets*. Studies in Philology 2003;100 (4):493-513.

C3 COLORECTAL CANCER COALITION

Research ■ Policy ■ Awareness

February 27, 2008

Oncology Drug Advisory Committee
Food and Drug Administration
Via email to Nicole Vesely, Pharm.D. nicole.vesely@fda.hhs.gov

These comments are submitted on behalf of C3: Colorectal Cancer Coalition (C3), a non-profit, nonpartisan advocacy organization that is committed to the fight against colon and rectal cancer. We appreciate the opportunity to comment on the Food and Drug Administration (FDA) Oncology Drug Advisory Committee (ODAC) consideration of Erythropoiesis Stimulating Agents (ESAs) for non-renal disease applications.

C3 pushes for research to improve screening, diagnosis, and treatment of colorectal cancer; for policy decisions that make the most effective colorectal cancer prevention and treatment available to all; and for increased awareness that colorectal cancer is preventable, treatable, and beatable. C3 believes in fully disclosing sources of financial support, per our disclosure policy which can be viewed at www.FightColorectalCancer.org/funding.htm. In 2006 and 2007, C3 received funding from Amgen in the form of a charitable donation. Since the May 2007 Oncology Drug Advisory Committee (ODAC) meeting, C3 has met with Amgen and Johnson & Johnson (J&J) to increase our understanding of these issues and express our concerns. J&J held a meeting on February 19, 2008 in Washington, DC, and paid the travel expenses of a C3 Board member so that she could attend the meeting.

Neither these companies nor any of our other corporate supporters have influenced our comments on this issue.

As oncology patient advocates we are used to looking at complex risk/benefit situations, but in this case, there are an inordinate number of frustrating and concerning issues:

- There is a systemic inability to find and pull together all of the relevant data – who has it, who owns it, who can see it?
- The possibility exists that a supportive care drug could actually cause a patient's cancer to grow faster, and increase mortality.
- There is mistrust of the manufacturers and the oncology professional associations due to their large financial conflicts of interest.
- Leadership is unclear. Whose job is it to look out for the patient? Who can and will take charge of this situation and bring it to a quick resolution?
- There is a perceived lack of progress. ESAs have been on the market for many years, billions of dollars have been spent by insurers, millions of patients have been treated, and yet we still have many of the same unanswered questions we had at the 2004 ODAC.

After reviewing the publicly-available information, we have more questions than answers. These can be grouped into three areas:

1. What is the plan for answering the question of whether ESAs have a tumor-promoting effect?
2. What is the plan for answering the question of whether ESAs provide patient benefit when dosed according to the FDA label?
3. What is the appropriate clinical use of ESAs pending the answers to these questions?

We also hope that lessons learned from the past will be applied to future trials. A search of clinicaltrials.gov shows that 382 trials have been or are being conducted looking at epoetin alfa or darbepoetin alfa. Approximately 115 trials can be identified as occurring in oncology. These 115 trials intended to enroll over 30,000 patients, although an unknown number of trials were terminated early due to poor accrual. Our understanding is that most of these trials were conducted at higher doses than are currently acceptable, which limits the applicability of data to situations involving a lower dose. In discussions with the manufacturers, we learned that FDA has not had easy access to data generated overseas or data generated by independent investigators. We have also learned that a comprehensive list of all ESA trials does not seem to exist. We urge FDA to work closely with the manufacturers to ensure that future trial designs and locations result in accessible, meaningful data.

1. What is the plan for answering the question of whether ESAs have a tumor-promoting effect?

The possibility that ESAs may have a tumor-promoting effect is frightening. We urge FDA and the manufacturers to focus not only on the possible presence of erythropoietin receptors (EpoR) on cancer cells, but also areas such as:

- Cancer cell proliferation or growth due to EpoR signaling;
- Cancer cell resistance to chemotherapy due to EpoR signaling; and
- Tumor microenvironment changes due to promotion of angiogenesis.

Is there a plan in place to review all existing information and the areas where new research is going forward? Who is responsible for execution of the plan? Where will the results be published? The December 2007 National Cancer Institute meeting provided a platform for such a discussion; however, the results of the meeting have not yet been made public, and we are not aware of follow-up plans. In order to generate confidence in the quality of research being done, meetings such as this should be open to the public and provide timely communication of progress. We feel strongly that the ESA issue needs to be laid out clearly, in a public way.

2. What is the plan for answering the question of whether ESAs provide patient benefit when dosed according to the FDA label?

In a meeting with Amgen, we were told that a phase III trial was being designed to answer the question of whether ESAs provide patient benefit when dosed according to the current label (November 2007 version). As described to us, the trial will enroll

6000+ lung, breast and colorectal cancer patients over eight years in an international setting.

We have many questions and concerns about this trial:

- Will trial sites be overseas, in the US or both?
  - If overseas, what changes will be made to ensure that the data will be easily accessible to FDA?
  - The risks associated with blood transfusion vary widely throughout the world; how will that risk be leveled across all trial sites?
- Will the trial accrue?
  - Will patients and physicians be willing to participate?
  - Supportive care trials are historically difficult to accrue; for example, the current EPO-ANE-3010 trial is accruing slowly. What changes are being made to ensure that this trial will actually accrue on schedule?
- Will the results be meaningful?
  - Can results in three disease sites (breast, colorectal and lung) be extrapolated to the 200+ forms of cancer?

There is an old quote that says, *"Insanity is doing the same thing over and over, and expecting different results."* We are concerned that this phase III trial proposal is 'the same thing', and that after eight years of waiting, we will end up where we are today, without a definitive answer to our questions. Again, we feel strongly that the clinical research plan must be laid out clearly and publicly.

3. What is the appropriate clinical use of ESAs pending the answers to these questions?

The goal of every clinical intervention is increasing patient benefit while decreasing patient risk. J&J presented an overview of their RiskMAP program. As described, the program minimizes the risk of thrombovascular events by reducing exposure of patients to ESAs, especially patients with high risk of thrombovascular events. A key component of the program is the patient medication guide, which will help patients and physicians have a full discussion of the risks and benefits of ESA use.

We feel that this is a good start; however, we are not sure that patients and doctors will actually interact as planned. Many ODAC appointees are practicing oncologists, and have colleagues who practice in academic and community settings. Do you feel that community oncologists will have the time to spend reviewing this information with patients – people who are already ill and dealing with side effects of treatment?

In addition, we wonder if FDA could provide additional guidance about use in specific disease sites where risk is elevated above an acceptable level, or about concomitant medications which increase risk of thrombovascular events, such as bevacizumab.

Finally, we urge FDA and the manufacturers to consider capturing data from the ongoing use of ESAs through a patient registry.

One Alternative: Patient Registry

We feel that development of a patient registry to evaluate use of ESAs when patients are dosed according to the current FDA label could provide great value. There is precedent for such a registry:

- FDA implemented a patient registry and informed consent process for drugs such as thalidomide and natalizumab through the Special Restricted Distribution Program.

- CMS has used patient registries to evaluate use of devices such as the implantable cardioverter defibrillator and diagnostic use of PET scans for a variety of cancers.

We understand that designing such a registry would be complex, and that multiple barriers would need to be overcome. At the same time, we feel that a registry such as this could provide more robust data across all tumor types, perhaps even in a more timely way.

We greatly appreciate the opportunity to comment on the critical issues in front of ODAC and FDA, and look forward to listening to your discussion on March 13. Thank you very much for your consideration of our comments.

Sincerely,

Carlea Bauman, President
C3: Colorectal Cancer Coalition

BREAST CANCER ACTION

Via Facsimile 301-827-6776
Via e-mail nicole.vesely@fda.hhs.gov

February 27, 2008

Nicole Vesely
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: ESAs Administered to Cancer Patients

Dear Ms. Vesely:

Please provide a copy of this letter to the members of the ODAC who will be meeting on March 13 to discuss the cumulative data on the risk of erythropoeisis-stimulating agents (ESAs) when administered to cancer patients.

Breast Cancer Action (BCA), a national education and advocacy organization with over 19,000 members, believes that drugs used to ameliorate the side-effects of cancer chemotherapy must be both safe and effective. Based on emerging data concerning the use of ESAs in the cancer context, it appears that these drugs are neither safe nor effective. They should be removed from the market until such time as both efficacy and safety are demonstrated to the FDA.

In light of the safety data already reviewed by the FDA that prompted boxed warnings for ESAs in November 2007, and the additional safety information that has emerged since, BCA believes that removal from the cancer market of these drugs is the only available option that will adequately protect the health of breast cancer patients.

When the FDA issued Boxed Warning and Warnings sections on the labeling for Epogen/Procrit and Aranesp in late 2007, it did so based on the results of six studies showing decreased survival and/or tumor progression in patients with cancer receiving an ESA. The evidence that existed at that time showed that the

use of ESAs in patients with advanced breast cancer resulted in shortened survival and shortened time to progression of disease, and that these outcomes could not be excluded at dosages currently recommended for these drugs.

Shortly after these warnings were issued, information became available from the PREPARE trial showing higher rates of death and/or tumor progression in patients with primary breast cancer who received an ESA.

On February 26, 2008, a meta-analysis published in *JAMA* demonstrated that administration of ESAs to cancer patients is associated with increased risks of venous thromboembolism(VTE) and mortality. Since there seem to be more safety data emerging almost daily on ESAs in the cancer setting, leaving these drugs on the market now imperils the health of cancer patients.

The safety concerns about the use of ESAs in the breast cancer setting could not be clearer. Compounding BCA's safety concerns is the fact that ESA use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being in the cancer setting. Efficacy of these drugs in the cancer setting is as much at issue as safety.

While the manufacturers of ESAs will likely contend that there are some cancers for which safety concerns are not evident, absence of evidence is not evidence of absence. Furthermore, restricting marketing of these drugs to certain cancers will leave many breast cancer patients at risk of dangerous off-label use. As a practical matter, the public's health requires removal of ESAs from the cancer market at this time.

BCA believes that in all settings, including the supportive care setting, the efficacy and safety of drugs for cancer patients should be well established. ESAs have long been on the market in the absence of this type of evidence, and the emerging data on the dangers of these drugs in the cancer setting demands their removal from the market.

Respectfully submitted,

Barbara A. Brenner

Barbara A. Brenner
Executive Director

Written Comments to the Food and Drug Administration's Oncologic Drugs Advisory Committee (ODAC) on Erythropoiesis-Stimulating Agents (ESAs) and Bone Marrow Failure

Christin L. Engelhardt
Director of Patient Advocacy and Professional Programs

Submitted in advance of the March 13, 2008 ODAC meeting

Thank you for the opportunity to submit written comments in addition to the brief oral statement we will present at the upcoming ODAC meeting on March 13.

The Aplastic Anemia & MDS International Foundation (AA&MDSIF) is a non-profit organization that represents thousands of patients with rare bone marrow failure disease: aplastic anemia, paroxysmal nocturnal hemoglobinuria (PNH), and myelodysplastic syndromes (MDS). Governed by a volunteer board of directors (lay individuals personally affected by bone marrow failure and not tied to any manufacturer or marketer of erythropoietin-stimulating agents [ESAs]), the Foundation also has a volunteer Medical Advisory Board comprised of prominent experts in the field and chaired by Richard Stone, MD of the Dana Farber Cancer Center at Harvard University.

Before proceeding further, I want to note that I personally have no financial interest in any pharmaceutical company, including ESA manufacturers or marketers, other than what may be in a retirement mutual fund. No company will sponsor our presence on March 13, and since 1994, the Foundation, with an annual budget of more than $1 million, has received support from Amgen for some of our educational projects but less than a total of $35,000 over the years. The last contribution from Amgen was for our scientific symposium at the National Institutes of Health in 2005. We have received no funding from Johnson&Johnson or Ortho Biotech. The AA&MDSIF has no financial incentives to support or to oppose any work on the part of the Food and Drug Administration (FDA) or Centers for Medicare and Medicaid Services (CMS); our only incentives are the interests of patients.

The AA&MDSIF is closely following developments related to ESAs, which promote red blood cell growth, because many patients with bone marrow failure diseases like MDS use ESAs off-label. Medicare has covered this off-label use for MDS because the practice is supported by research cited in an approved compendium, namely the USP-DI. (The National Coverage Determination issued by CMS in late July 2007 did not cover the use of ESAs in MDS patients, so ESAs continue to be covered for MDS patients, albeit sometimes subject to local coverage determinations where implemented.) The findings in the USP-DI are not surprising, considering that ESAs are

approved to address anemia in certain patient populations and that the most common signs and symptoms associated with MDS are related to anemia.

We recognize that ESAs are not appropriate for all patients and not all patients with bone marrow failure respond to ESAs. Still, ESAs, which can reduce or eliminate the need for blood transfusions in patients with bone marrow failure, are a crucial part of treatment options for this patient population, and many patients with bone marrow failure are thought to benefit from ESAs.

There are no alternatives to ESAs other than blood transfusions, yet blood transfusions are not a solution for this patient population. (There are now three medications approved by the FDA to treat MDS, but treatment options for MDS are clearly limited, and most non-growth-factor medications for MDS work only 20-30% of the time and carry significant side effects.[1,2] Moreover, patients who take non-growth-factor medications may need ESAs in conjunction with those drugs.) In addition to the issue of blood-supply shortages, MDS patients typically need irradiated platelets. Irradiated platelets can be difficult to obtain, and this need both complicates the process and increases the expense. Further, bone marrow failure patients who get transfusions typically have a chronic need for them (something not seen in cancer and chemotherapy patients). This chronic need for transfusions puts MDS patients at great risk for iron overload which is difficult alone for these patients but is especially problematic with the 2007 revised FDA warning on Exjade, a medication used to treat iron overload. This warning is relevant to MDS patients, so treating physicians would have to devise carefully a treatment regimen for MDS patients.

If the Foundation believed that there was evidence that these growth factors were generally inappropriate for MDS patients, the Foundation would actively and promptly inform our patients of the change in the scientific consensus. However, we have not yet seen—from either the FDA or CMS, as outlined in our letter of June 13, 2007 to CMS—the rationale necessary to refute this consensus.

The Foundation does appreciate that the FDA must always address any new data that affect the safety of patients who take medication. Given the recent studies that have shown significant and life-threatening events in certain patients who have taken these growth factors, we understand why the FDA has acted over the past year or so, although we cannot comment on the studies in cancer or kidney patients. That is outside of our realm. We must note, however, that to date none of the studies cited as a concern appear to have included any patients with bone marrow failure (such as MDS) but only patients who had end-stage solid cancers and/or renal disease. Moreover, in most of the studies cited by the FDA, the patients' hemoglobin levels typically were kept above 12 g/dl while bone marrow failure patients rarely reach a hemoglobin level that high, even with the addition of growth factors.

Thus findings from these studies cannot be said to apply to patients with MDS. Further, as we have said before, the adverse events discovered in these studies—an increased risk of thrombotic events and stimulation of tumor growth—are not likely to be relevant

to patients with bone marrow failure: this diagnosis does not involve tumors or vascular disease that can increase one's risk for blood clots and strokes. Both of these potential problems are likely to involve non-erythopoietic effects of the growth factor erythropoietin (Epo) on endothelial cells or on tumors, where there are Epo receptors, although expressed at a low level. Moreover, many patients with bone marrow failure have low platelet counts, a condition which tends to decrease the chance of clotting. In fact, there have been some studies of ESAs in bone marrow failure patients that do not demonstrate a negative impact. Studies assessing the long term use of Epo (with or without granulocyte colony-stimulating factors) in MDS patients compared to either randomized controls[3] or historical controls[4,5] have shown no negative impact on survival or on evolution to acute myelogenous leukemia (AML) with such treatment.

In addition, the 2006 Jadersten et al study indicates improved survival in low-risk MDS patients with low transfusion need who have been treated with these agents. An even more recent article[6] provides more evidence for improved survival in low-risk MDS patients. We are still unaware of any data that would contraindicate the use of ESAs in responsive BMF individuals. The risk-benefit analysis of ESAs in MDS patients strongly favors their beneficial effect of minimizing blood transfusions in this highly compromised population, as a greater number of blood transfusions and resultant higher iron overload burden correlates with diminished survival in MDS patients.

In addition, clinical practice guidelines published by American Society of Clinical Oncology and the National Comprehensive Cancer Network continue to support certain uses of ESAs for treatment of myelodysplasia in select patients. Further, the consensus from experts in hematology, based on their vast clinical experience, is that the MDS patients do not generally share the same risks as patients who were part of the ESA studies on adverse events and have not experienced the same adverse events. Physicians of course still must monitor hemoglobin levels in bone marrow failure patients receiving ESAs, especially those with renal and/or heart disease, to ascertain that their levels do not rise above 12 g/dl. More studies on ESAs in bone marrow failure patients would help to better understand the drug and its impact on this unique patient group, but in the meantime, while the warning from the FDA must be assessed for each individual patient with bone marrow failure, patients with bone marrow failure should have access to ESAs when clinically indicated.

While the Foundation believes that there is evidence that ESAs are appropriate in patients who respond to them or who are undergoing a reasonable trial of twelve weeks, the AA&MDSIF and its Medical Advisory Board (MAB) do have unanswered questions about the benefits and risks of ESAs at higher hemoglobin levels, such as 11. There are also many questions about which patients are likely to benefit from ESAs and which patients are likely to be put at unnecessary risk from the administration of an ESA. It is also not known what role, if any, an ESA may play in the possible progression of MDS to leukemia. The answers to these questions are essential to our patients and their treating physicians, and recent reports of adverse incidents in other patient populations make the answers even more important. The Foundation thus wrote to Amgen, Johnson&Johnson, and Ortho Biotech in early December 2007 and called on them to

seek FDA approval, through a supplement to a New Drug Application, to market their ESAs for appropriate marrow failure syndromes, including MDS. If the current data are insufficient to make this application, we asked the companies to sponsor the requisite trials to examine rigorously the optimal dose of each product and to establish a sufficient level of safety to allow labeling for MDS. The companies have responded to us, and we are hopeful that any needed trials will soon be undertaken.

The Foundation has also had discussions with another patient organization as well as relevant professional societies about convening a working group, comprised of experts in the use of ESAs with MDS patients, to design a clinical trial that would answer these questions. While the working group is just in its formative stages, a conference call is planned for the first week of March. The Foundation has also approached both FDA and CMS about obtaining their input into the design of the clinical trial; it is our goal to bring together all of those with the ethics and the expertise to design a study that serves MDS patients well.

We appreciate your consideration of these comments—and of patients with bone marrow failure—as you look at all the data on the use of ESAs, especially in MDS patients. If the Foundation or any members of our Medical Advisory Board can provide ODAC members with any additional information, please do not hesitate to contact us.

1 Golshayan A, Jin T, Maciejewski J, Fu AZ, Bershadsky B, Kattan MW, Kalaycio ME, Sekeres MA. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes. Br J of Haematology 137: 125-132, 2007.
2 Sekeres MA, Fu AZ, Maciejewski JP, Golshayan A, Kalaycio ME, Kattan MW. A decision analysis to determine the appropriate treatment for low-risk myelodysplastic syndromes. Cancer. 109(6):1125-1132.
3 Miller KB, Kim HT, Greenberg P, van der Jagt R, Bennett JM, Tallman MS, Paietta E, Dewald G, Houston JG, Thomas M, Rowe J. Leukemia Committee, Eastern Cooperative Oncology Group, Brookline MA,; Leukemia Committee, Canadian Leukemia Study Group, Ottawa ON, Phase III Prospective Randomized Trial of EPO with or without G-CSF Versus Supportive Therapy Alone in the Treatment of Myelodysplastic Syndromes (MDS): Results of the ECOG- CLSG Trial (E1996), Proc Am Soc Hematology meeting, Blood 104 (No. 11): 24a, 2004.
4 Jadersten M, Montgomery SM, Dybedal I, Porwit-MacDonald A, Hellstrom-Lindberg E. Long-term outcome of treatment of anemia in MDS with erythropoietin and G-CSF, Blood 106 (No. 3): 803-11, 2005.
5 Jadersten M, Malcovati L, Dybedal I, Della Porta MG, Invernizzi R, Montgomery SM, Pascutto C, Porwit-MacDonald A, Cazzola M, Hellstrom-Lindberg E. Treatment with Epo and GCSF improves survival in MDS patients with low transfusion need. Proc Am Soc Hematology meeting, Blood 108 (No. 11): 158a, 2006.
6 Golshayan A, Jin T, Maciejewski J, Fu AZ, Bershadsky B, Kattan MW, Kalaycio ME, Sekeres MA. Efficacy of growth factors compared to other therapies for low-risk myelodysplastic syndromes, Br J of Haematology 137: 125-132, 2007.

"Experts in Hematology/Oncology from ASH, ASCO, NCCN, and the EORTC in Europe have come together to give us guidelines on the use of ESAs. Upon reviewing the considerable body of data available on ESA and CIA, they have all concluded that ESA's are important to use when the hemoglobin falls below 10g% **and** to consider using ESA's sooner if the hemoglobin falls toward 10g%. This latter point underscores the fact that, for example, all hemoglobin levels of say 11.3g% are not created equal. The patient who just started curative chemotherapy for his cancer with a hemoglobin of 13.3 first cycle, + who is now 11.3 second cycle is likely be transfused by fourth cycle if no intervention is undertaken with ESA. To wait until this patient falls further to an arbitrary value of 10g% actually exposes him to two risks: the risks of ESA (DVT, VTE) and blood transfusion.....the worst of both worlds. I would encourage the FDA, therefore, not to make the issue of starting and stopping hemoglobin values black and white, but rather gray so that clinicians and their patients can review the risks of ESAs and transfusions in the context of any co morbidity, and then decide on the best therapy for their anemia in the overall context of their cancer, their treatment, and their declining hemoglobin." DHHenry, for March 13, 2008 ODAC committe meeting.

David Henry, MD
Pennsylvania Hospital
Phila, PA

Robert A. Moss, M.D., F.A.C.P.
Hematology and Medical Oncology

Board Certified in
Hematology
Medical Oncology
Internal Medicine

11100 Warner Ave.
Suite 200
Fountain Valley, CA
92708
Ph: 714-641-1128
Fax: 714-540-7610

February 26, 2008

Nicole Vesely
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: March 12 Oncologic Drugs Advisory Committee discussion on ESAs

Dear Ms. Vesely,

I am writing to you as both a community oncologist in solo practice and as the President of the Medical Oncology Association of Southern California (MOASC). These comments are meant for inclusion in the Advisory Committee Meeting. I expect there will be considerable discussion about the safety and efficacy of Erythropoietin Stimulating Agents at this meeting and I will keep my comments as brief and on point as possible.

My main focus is the role of ESAs in actual everyday patient care from the perspective of community as opposed to academic or university based oncologists and hematologists. I will support this with results of clinical trials which we in the community rely on.

ESAs have been an important part of the practice of Oncology and Hematology for a number of years now. As a result of CMS rules changes and other controversies we in MOASC have had numerous discussions about our own personal experiences using these agents. Almost all of us have expressed the opinion that the two marketed drugs, Aranesp and Procrit, are essentially equal in efficacy and safety, though dosing and scheduling are different. The preference among most community oncologists is based on reimbursement which varies. Most of the clinical trials have used one agent or the other with different methodologies making direct comparisons impossible. The single large head to head trial indicated equivalence with no statistically significant difference in efficacy or safety. My point being that it is reasonable to "lump" both agents together in any general discussion of safety and efficacy.

All my colleagues seem to agree that ESAs are invaluable in treating older patients and only slightly less so younger patients receiving certain drugs as well as more aggressive

chemotherapy regimens. Cisplatin and doxorubicin are notorious for causing anemia as you well know and we've often seen it unpredictably with other drugs. I can tell you from personal experience that older patients in general and debilitated younger ones don't tolerate anemia very well. They end up in the hospital more often, appear respond less well to neutropenic sepsis and tolerate chemotherapy less well overall. This is as expected. What we don't know with certainty is whether people get more anemic because they are sicker from the chemo or whether the anemia is a major contributor to having complications.

But I can tell you from practice that we see fewer serious complications in patients treated with ESAs where the Hgb stabilizes or increases. Those patients just seem to do better. If the indication of chemotherapy induced anemia is eliminated oncologists will feel betrayed because we will be practicing medicine in which we cause moderate and severe debility in our patients without an important tool to mitigate those side effects. This would be most discouraging and is unwarranted based on the available evidence.

When patients develop symptomatic or severe anemia, in the absence of effective drug treatment they require transfusions. In addition to a degree of fear and trepidation (many people still worry about acquiring viral infections no matter what you tell them) there is the waste of manpower and downtime.
While the patient waits we write out orders and call the infusion center for a day when they have room. My local hospital closed its infusion center last year because of poor reimbursement. Many more will surely follow. The patient has to go in and have their blood drawn and sent to the blood bank for type and cross match which takes at least ninety minutes, often much longer. They must sit in the transfusion room with a group of strangers all receiving something intravenously: chemo, antibiotics or transfusions. Since it is only appropriate to slowly transfuse patients in these circumstances each unit takes at least three hours. Two units mean an entire day is lost with a trained nurse there the whole time. Patients hate the experience and often complain, but prefer it to dragging themselves around without the blood. The transfused units only last three weeks, so they are back at it in the infusion room before long. In many important ways blood transfusions are one of the miracles of twentieth century medical science. In other ways they are medieval.

My colleagues on the board at MOASC recently discussed whether we were ordering more transfusion under the new CMS guidelines and everyone agreed we were. We also agreed that the current guidelines are not workable and not based on science. You get only four weeks to get the Hgb to rise one gram yet some studies indicate it may take six weeks and on week five you only get to increase the dose by 25% a dose escalation below that used in the major trials. I don't mind starting treatment at Hgb levels below 10, but it should be remembered that Hgb varies from day to day due to hydration and from the variability in even the best instruments. Results often vary by as much as half a gram just on retesting. So if a patient gets dehydrated their Hgb may rise enough that we have to stop the ESA, the opposite of what would represent quality medicine. Furthermore, while it's reasonable to start below 10grams% we often have little leeway. The Hgb drops to say 9.7, an ESA is started and the Hgb is suddenly above

10 and we have to stop treatment. It makes no sense. It would be just as safe and more efficacious to continue therapy until the Hgb reaches 12grams% as an upper cutoff.

Although I know the FDA has not accepted the Quality of Life testing performed in a number of the ESA trials, the results at least are consistent and indicate better QOL at Hgb 12 than 10. Even if there is no validated difference having the allowance up to 12 is of great practical use in not stopping right away only to see the Hgb quickly fall as the patient simply drinks more water, then start again, etc. It can be very difficult just managing something as essentially simple as ESAs under the present guidelines. The combined ASCO/ASH 2007 guidelines support an upper limit of 12 and should be adopted.

Furthermore the safety data, I believe, is very convincing that Hgbs up to 12 are safe. A meta analysis of all Aranesp and Procrit trials where the upper limit of Hgb was at 12 showed no statistically increased rate of thromboembolism. I've been informed that this data will be presented to the Committee. The only studies showing an increase in thromboembolism set the desired Hgb levels above 12 presumably to maximize oxygen delivery to the tumor to increase the effects of ionizing radiation. Achieving Hgb levels in this range is not the goal of treating chemotherapy induced anemia and might be expected to increase thrombosis just on the basis of increased red blood cell mass alone, though other mechanisms involving ESA receptors have been proposed, but remain unproven. The point is that at Hgb levels at or below 12 there is good evidence that thrombosis and other side effects are not increased as demonstrated in the large meta analysis cited above. I do not believe this has been published, but will be presented in detail by others.

In summary, as a community oncologist and representing MOASC I would strongly urge the Committee to recommend to the FDA to reaffirm the use of ESAs consistent with the package insert and according to the recommendations of ASCO and ASH.

Sincerely yours,

Robert A. Moss, M.D., F.A.C.P.
President, Medical Oncology Association of Southern California

Maryann Napoli, Center for Medical Consumers, New York City
March 13, 2008 Oncologic Drugs Advisory Committee meeting

As a consumer advocate who attended the ODAC meeting about erythropoiesis-stimulating agents (ESAs) last May, I came away wondering why these drugs remain on the market. They cause some patients to die sooner. They have many other risks that are severe and well documented, and any quality-of-life benefit has yet to be proven. The FDA approved the first ESA because it reduced the percentage of patients transfused. But the agency has since acknowledged that the infectious disease risks of a blood transfusion are far lower now than they were in 1993.

No doubt there are many cancer patients who see these drugs as an instant cure for chemotherapy-induced fatigue or as the means of allowing chemotherapy to continue. The former indication was fostered by Johnson & Johnson's fraudulent ad campaign for Procrit, which continued for seven years in the mainstream TV and print media. I urge ODAC to discuss the misconceptions imparted by these ads and to consider recommending that the FDA require J&J to run a corrective ad campaign.

The ability of a cancer patient to make a truly informed decision with the help of her oncologist is seriously compromised by J&J's and Amgen's reprehensible practice of offering rebates—that is, kickbacks—to oncologists. Patients are always encouraged to discuss their treatment decisions with their doctors. Yet it's hard for them to believe oncologists' recommendations are unbiased when they are "reaping millions" from the prescription of anemia drugs, as The N.Y. Times reported last May. [1] Companies that give kickbacks and other financial incentives intended to manipulate oncologists into using the most expensive drugs are poisoning the doctor/patient relationship.

Where can people turn for unbiased information? It should be the FDA, but it's not clear to me that black box warnings are the way to go. The changes in the product labeling in 2004 did not change clinical practice.[2] And what do we know about the effects of black box warnings on the ones who need them the most—the cancer patients? The cancer patient should be given scientifically accurate, written information about ESA well *before* she needs it. The time to weigh the risks and benefits is not when she's awaiting her next chemo treatment and just learned that her hemoglobin is too low for the next round.

Patients cannot make truly informed decisions unless they are given *quantitative* information to help them decide whether ESA is appropriate. They need to know, for example, the chances of...1) needing a transfusion; 2) suffering harm by foregoing a transfusion, 3) experiencing a serious adverse effect from the transfusion itself, and 4) having a severe adverse effect from the ESA. Patients need to know, for example, the *magnitude* of each of these four risks. Telling them that ESA will reduce their risk of having a blood transfusion is simply too vague. It gives them no way to compare this purported benefit with the other risks of taking ESA. If the FDA will not remove these drugs from the market, it must find the best ways to get clearly written, accurate quantitative ESA information to cancer patients.

[1] Berenson A, Pollack A. "Doctors Reap Millions for Anemia Drugs." N.Y. Times, May 9, 2007

[2] Blau AC. "Erythropoietin in Cancer: Presumption of Innocence?" *Stem Cells* 2007; 25;2094-2097; originally published online Apr 26, 2007.

February 27, 2008

U.S. Food & Drug Administration
5630 Fishers Lane, Room 1093
Rockville, MD 20857

Attn: Nicole Vesely

Meeting of the Oncology Drug Advisory Committee, March 13, 2008

Dear Ms. Vesely:

As indicated in the *Federal Register* for January 25, 2008 (Volume 73, Number 17), pages 4580-4581, I am providing comments for the consideration of the Office of Oncology Drugs and the Oncology Drug Advisory Committee related to consideration of the cumulative data, including recent study results, on the risk of erythropoesis-stimulating agents (ESAs) when administered to patients with cancer at the upcoming meeting on March 13, 2008. I would like to focus my comments on patients with lung cancer and emphasize the following important points:

1. **About 90% of the chemotherapy regimens used to treat lung cancer patients in the U.S. are platinum-based which produce anemia more commonly and more severely than most other standard chemotherapy regimens used in other tumor types[1,2].** In fact, 90% of patients develop Hgb < 12.0 within the first 4 cycles of platinum-based chemotherapy and, in the absence of ESAs, 30-40% of patients receive one or more blood transfusions during treatment[1,2].

2. **In addition to the well-documented adverse effects of chemotherapy-induced anemia (CIA) on patient energy levels, activity tolerance and quality of life, in lung cancer patients CIA significantly exacerbates the disease-related symptoms of dyspnea, cough, and respiratory distress not often found in other non-pulmonary malignancies[2,3].**

3. **Over 2200 lung cancer patients have been treated in 8 separate randomized clinical trials with chemotherapy +/- ESAs; <u>none</u> have demonstrated an adverse survival outcome associated with ESAs and, in fact, two have shown a statistically significant or borderline significant positive survival effect favoring the use of ESAs[4].** A recent updated report of a very small randomized trial (70 patients) suggesting a possible adverse survival outcome with ESAs has several major flaws including (a) use of the ESA to a Hgb as high as 14 g/dL before withholding study drug (above recommended guidelines), (b) majority of patients entered with anemia unrelated to chemotherapy administration, and (c) imbalances in the proportion of patients with ECOG performance status 0-1 versus 2 and in baseline FACT-L scores, both of which predict survival in NSCLC, favoring the placebo arm of the study [5]. Most importantly, this study was closed early by an unplanned safety analysis because of a perceived higher incidence of thrombotic events; in fact, 90% of patients in both arms of the study died of progressive lung cancer rather than other "safety" issues.

4. **There is a growing interest in the use of pre-operative (neoadjuvant) chemotherapy in patients with localized or locally advanced non-small cell lung cancer. Without the use of ESAs, the frequency and severity of CIA in this setting will be significantly increased.**

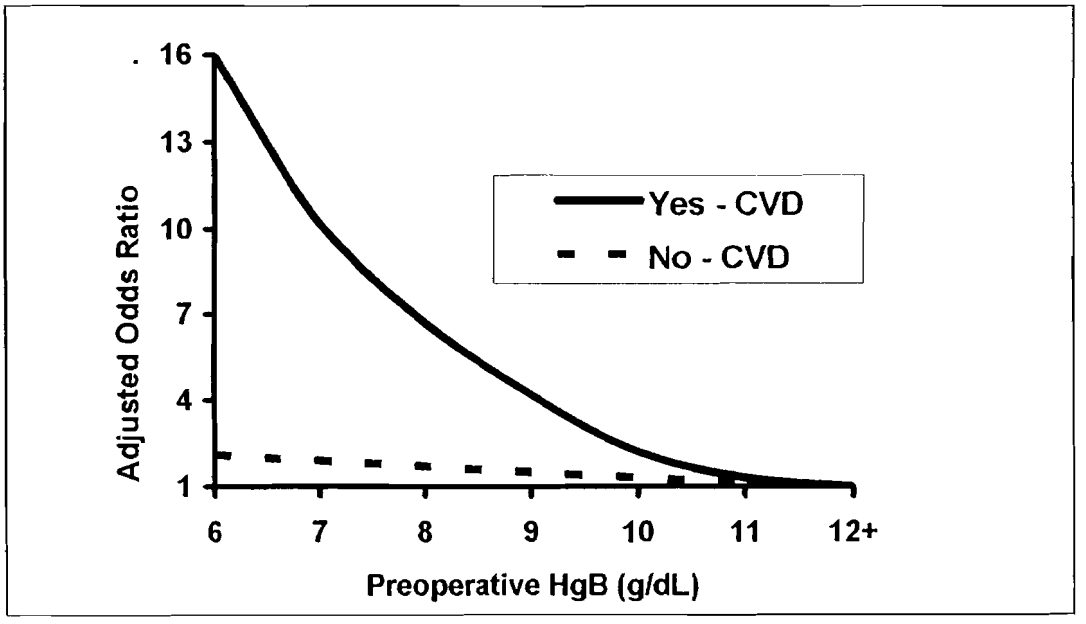
Unfortunately, preoperative anemia is known to significantly increase surgical morbidity and mortality. In an analysis of 1958 patients[6], 147 patients (7.5%) died or had a serious morbid event within the 30-day post-operative period. Although severe preoperative anemia was uncommon (only 11% of patients had a hemoglobin less than 10 g/dL), the relationship between preoperative anemia (Hgb < 12 g/dL) and morbidity/mortality was remarkably linear (as summarized in table 1, below).

Table1. Unadjusted relation between preoperative hemoglobin, mortality, and morbidity/mortality.

Pre-Op Hgb	No. Pts. (n = 1958)	No. Pts. (%) Dead (n = 63)	Unadjusted Relative Risk	No. Pts. (%) Morb/Mortality (n = 123)	Unadjusted Relative Risk
> 12.0	1411	18 (1.3%)	1.0 (reference)	56 (4.0%)	1.0 (reference)
11.0 – 11.9	212	5 (2.4%)	1.9	14 (6.6%)	1.7
10.0 – 10.9	109	5 (4.6%)	3.6	14 (12.8%)	3.2
9.0 – 9.9	75	6 (8.0%)	6.3	8 (10.7%)	2.7
8.0 – 8.9	39	5 (12.8%)	10.1	10 (25.6%)	6.5
7.0 – 7.9	49	6 (12.2%)	9.6	15 (30.6%)	7.7
6.0 – 6.9	27	5 (18.5%)	14.5	7 (25.9%)	6.5
< 6.0	36	12 (33.3%)	26.1	23 (63.9%)	16.1

Furthermore, logistic regression analysis of multiple variables revealed that the risk of death or morbid event with decreasing hemoglobin increased even more dramatically in patients with cardiovascular disease, **a risk factor that occurs frequently in the smoking-lung cancer population**. The adjusted odds ratios for preoperative hemoglobin stratified by cardiovascular disease are displayed in Figure 1, below.

Figure 1: Adjusted odds ratio for mortality by cardiovascular disease and preop Hgb.



5. **In addition to the many well known general risks of allogeneic blood transfusions, accumulating data suggest that perioperative allogeneic blood transfusions increase tumor recurrence rates and decrease long-term survival in several types of cancer including especially NSCLC[7-11].** Several mechanisms have been postulated to be responsible for this long-term adverse effect of blood transfusions including immunomodulation, subclinical graft versus host disease, reactivation of latent viruses and tissue injury with resulting cytokine release and dysregulation of endothelial cell adhesion molecules[12-17]. **These data raise the possibility of a potential adverse effect of allogeneic blood transfusions on cancer progression and patient survival in the non-operative setting.**

Based on the above facts, I respectfully recommend to the FDA and to the ODAC no further restrictions in the use of ESAs, at least in the case of lung cancer patients. Certainly, additional studies on the effects of ESAs and **allogeneic blood transfusions** on patient outcomes would be helpful. For now, the science supports the usefulness and importance of ESAs in the management of patients with lung cancer treated with chemotherapy.

Sincerely,

Ronald B. Natale, MD

Sr. Research Advisor and National Director,

Lung Cancer Clinical Research Program

Aptium Oncology, Inc.

1) Okamoto H, Saijo N, Shinkai T, et al. Chemotherapy-induced anemia in patients with primary lung cancer. Ann Oncol 3:819-824, 1992.
2) Langer C, Barsevik A, Bruner D, et al: Correlation of quality of life (QOL) with survival, treatment response, and anemia in patients with advanced non-small cell lung cancer (NSCLC) treated with carboplatin and paclitaxel. Lung Cancer 18(Suppl):23, 1997.
3) Thatcher N. Management of chemotherapy-induced anemia in solid tumors. Semin Oncol 25:23-26, 1998.
4) Bohlius J, Wilson J, Seidenfeld J, et. Al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patinets. J Natl Cancer Institut 98:708-714, 2006.
5) 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 Oncol 25:1027-1032, 2007.
6) Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 348:1055-1060, 1996.
7) Hyman NH, Foster RS, Demeules JE, et al. Blood transfusions and survival after lung cancer resection. Am J Surg 149:502-507, 1985.
8) Pastorino U, Valente M, Cataldo I, et al. Perioperative blood transfusion and prognosis of resected stage Ia lung cancer. Eur J Cancer 22:1375-1378, 1986.
9) Keller SM, Groshen S, Martini M, and Kaiser LR> Blood transfusion and lung cancer recurrence. Cancer 62:606-610, 1988.
10) Moores DWO, Piantadosi S, and McKneally MF. Effect of perioperative blood transfusion on outcome in patients with surgically resected lung cancer. Ann Thor Surg 47:346-351, 1989.
11) Little AG, Wu HS, Ferguson MK, et al. Perioperative blood transfusion adversely affects prognosis of patients with stage I non-small cell lung cancer. Am J Surg 160:630-633, 1990.
12) Smith DM. Immunosuppressive effects of blood transfusions. Clin Lab Med 12:723-741, 1992.
13) Blumberg N, Heal JM. Effects of transfusion on immune function. Arch Pathol Lab Med 118:371-379, 1994.
14) Landers DF, Hill GE Wong KC and Fox IJ. Blood transfusion-induced immunomodualtion. Anesth Analges 82:187-204, 1996.
15) Moroff G, Luban NL. Prevention of transfusion-associated graft-versus-host disease. Transfusion 32:102-103, 1992.
16) Lang DJ, Ebert PA, Rodgers BM, et al. Reduction of postperfusion CMV infections following the use of leukocyte depleted blood. Transfusion 17:391-395, 1988.
17) Quigley RL. The effect of leukocytes on adhesion molecules: an explanation of blood transfusion enhancement of tumor growth. Arch Surg 131:438-441, 1996.

National Organization for Rare Disorders, Inc. (NORD)
Remarks Submitted before the
FDA Oncological Drugs Advisory Committee
Gaithersburg, Maryland
March 13, 2008

The National Organization for Rare Disorders (NORD) is a non-profit voluntary health organization representing an estimated 25 million Americans with over 6,000 rare "orphan" diseases. Under federal law (*Orphan Drug Act of 1983*), a rare disease is defined as a disorder or condition that affects fewer than 200,000 Americans. There are several hundred different forms of cancer, and only five or six of them affect more than 200,000 Americans at any one time. Thus, we address the ESA problem on behalf of the many Americans who are afflicted with rare forms of cancer.

Evidence indicating that ESAs prescribed for cancer patients may cause safety problems has been emerging for some time. In the past, FDA has requested labeling changes on these products, which some patient advocates feel are insufficient to adequately protect cancer patients from the risk of tumor progression that may occur as a result of taking an ESA. In spite of labeling changes that included a Black Box Warning in 2007, concerns about the safety of ESAs for cancer patients have continued to mount instead of diminish. These concerns derive from the publication of two more studies that report tumor progression and higher death rates among breast and cervical cancer patients receiving ESAs.

NORD does not believe that the current Black Box warning is enough protection for cancer chemotherapy patients. NORD does not understand why the FDA has labeled the ESAs for cancer chemotherapy patients up to hemoglobin of 12 when the label clearly states that ESAs are indicated primarily "...to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of two months."

Since hemoglobin level of 8 or 9 is the trigger at which most medical oncologists initiate a blood transfusion in a cancer patient, what is the data-supported value for a patient receiving an ESA if their hemoglobin is between 10 and 12? Some oncologists and some patients will say, and I quote, "It makes me feel better." If that is a fact, where is the data to support that claim?

NORD believes the current indication for cancer chemotherapy patients should be removed from the ESA label until convincing evidence that an ESA provides a clinical benefit for a patient with hemoglobin above 10 has been submitted to, reviewed by, and approved by the FDA.

The ESA safety concerns that worry so many of us in the patient advocacy community are compounded by the perverse economic incentives that Amgen and Johnson and Johnson make available to physicians who prescribe ESAs. Physicians purchase the ESAs directly from the company's sales representatives and administer them directly to their patients in their offices.

Because the drugs are purchased at a lower price than is routinely billed to the patient's insurance company, oncologists can earn a profit on every dose they administer. Because of this perverse practice, NORD believes that Amgen and Johnson and Johnson/Ortho Biotech should remove these incentives now and until they have proven that ESAs do not cause cancer patients to be at a higher risk of dying while taking ESAs.

People with any life-threatening disease must put their life in the hands of their doctor, and "trust" is the most important aspect of that relationship. To some extent this trust has been broken when drug companies offer incentives to doctors to prescribe drugs that have unknown and possibly life threatening risks associated with them.

Additionally, patients need to be better informed about the current risk/benefit relationship before they receive an ESA. Changes to drug labels are rarely seen by patients. Even when a patient reads the label, it is very difficult to understand because drug labels are written in medical language that is not understandable to ordinary people. When a doctor administers a drug like an ESA, the patient usually doesn't even see the label. Moreover, doctors may read labeling in the *Physician's Desk Reference* (PDR) when a new drug reaches the market, but they usually don't re-read labeling every time they prescribe the same drug.

Patients rarely get educational materials for treatments injected or infused in hospitals, outpatient clinics, and doctor's offices. They trust that their physician would not prescribe an unsafe or ineffective drug to them, and they rely on oral instructions about side effects. We suggest that FDA mandate a patient education booklet to be given to patients getting ESAs so at the very least they can take it home and refer to it later in this time of great uncertainty about the safety of ESAs.

When patients are not able to protect themselves it is up to the FDA to protect them and make the scientific decisions that will protect them from unwarranted risk. The latest evidence indicating that ESAs can make tumors grow is very serious, and patients have a right to know. It is incumbent on FDA to ensure that patients and physicians are informed about these safety problems whenever they use ESAs and for the FDA to remove this indication from the label until more is known about its safety for cancer patients.

I leave you with one final question:

If the ODAC were meeting today to consider Aranesp for the very **first** marketing approval, would you approve it knowing what you know right now - that this drug might cause tumors to grow or cause cancer patients to die sooner? It's a speculative question but I am certain that you would not recommend approval of this drug.

NORD urges members of the FDA's Oncologic Drugs Advisory Committee to remove the marketing indication for cancer chemotherapy patients on ESAs until more and better safety data about the ESAs is provided to the FDA and the public.

Thank you.

INTERNATIONAL MYELOMA FOUNDATION
12650 Riverside Drive, Suite 206
North Hollywood, CA 91607-3421
Tel 818.487.7455
Fax 818.487.7454
TheIMF@myeloma.org
www.myeloma.org

February 25, 2008

U.S. Food & Drug Administration
5630 Fishers Lane, Room 1093
Rockville, MD 20857

Attn: Nicole Vesely

Meeting of the Oncology Drug Advisory Committee, March 13, 2008

Dear Ms. Vesely:

As indicated in the *Federal Register* for January 25, 2008 (Volume 73, Number 17), pages 4580-4581, we herewith provide comments for the consideration of the Office of Oncology Drugs and the Oncology Drug Advisory Committee related to consideration of the cumulative data, including recent study results, on the risks of erythropoeisis-stimulating agents (ESAs) when administered to patients with cancer and scheduled for March 13, 2008.

The International Myeloma Foundation (IMF) is not for profit 501(c)(3) organization that seeks to represent the interests of myeloma patients in the USA and around the world.

As you will see from the attached materials, the International Myeloma Working Group, under the auspices of the IMF, is currently working on development of guidelines specific to the use of ESAs in patients with myeloma. However, the first draft of these guidelines will not be available in time for this FDA meeting.

What the IMF can advise the FDA at the present time is that leading myeloma specialists around the world are extremely concerned that ESAs should continue to be available for the treatment of patients with myeloma. Management of myeloma has evolved rapidly in the past two years. New drugs have become available for treatment of this disease, and new data on the use of these drugs are presented at nearly every major cancer meeting.

None of the currently available data on the use of ESAs in myeloma have been generated since the abovementioned advances have taken place. It is now extremely unusual for any myeloma patient to receive ESAs in conjunction with traditional chemotherapy, and myeloma patients are living longer, which may impact the effects of historical myeloma on their renal function.

The Foundation respectfully recommends to the FDA and to the ODAC that, at least in the case of myeloma, what we are going to need to resolve some of the issues under consideration is more data, and not precipitate action that eliminates the ability of knowledgeable experts to make sound and well-considered recommendations with the full involvement of their patients and their families.

Despite the considerable steps that have been achieved in the past few years, myeloma is still a disease with no cure. As quantity of life has increased, our focus must now take account of ensuring quality of that extended life. ESAs may still have a significant role to play in this. We need data to confirm or deny this possibility that is specific to myeloma.

Sincerely

Susie Novis

Susie Novis
President, IMF

INFORMATION AND STATEMENT OF OPINION

FOR THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

March 12-13, 2008

Effectiveness and Safety of Erythropoiesis-Stimulating Agents in the Management of Patients with Myeloma

Submitted by the

INTERNATIONAL MYELOMA FOUNDATION

February 26, 2008

Global Headquarters

12650 Riverside Drive, Suite 206, North Hollywood, CA 91607

Tel: 818 487 7455 or 800 452 CURE *E-mail:* TheIMF@myeloma.org *Web:* www.myeloma.org

CONTENTS LIST

EXECUTIVE SUMMARY

- ***There is strong belief among international experts that erythropoeisis-stimulating agents (ESAs) continue to be an important treatment option for patients with myeloma.***

- The Foundation is aware of only one large, randomized, double-blind, controlled trial that compares the use of any ESA to either placebo or to any other ESA in the exclusive management of well-defined myeloma patients.

- The Foundation is aware of only one Phase III trial (Amgen study #20030232) comparing the use of darbepoetin alfa 300 mg q3w to placebo q3w for the treatment of anemia in subjects with non-myeloid malignancy receiving multicycle chemotherapy. We assume this study enrolled some patients with myeloma. (Total enrollment was 386 patients; 193 received active drug.) We are not aware of: (a) the number of myeloma patients who received either placebo or active drug on study; (b) the concomitant chemotherapy of these patients; (c) the disease stage or clinical history of myeloma patients in this trial.

- The Foundation is aware of the data presented by Glaspy at the American Association of Cancer Research annual meeting in 2007 (based on Amgen study #20010103) suggesting a significant risk associated with use of darbepoetin in treatment of myeloma.[9,10]

- Prospective data on the clinical benefit and risks of ESAs in the treatment of myeloma are limited. Clinical experience of use of ESAs in the treatment of myeloma appears to be largely restricted to routine clinical practice, based on physician expertise and experience.

- In November 2007 the US Food & Drug Administration announced significant revisions to all ESA product labels based on information presented at the ODAC meeting held May 10, 2007. These labeling changes appear to be in line with the limited available information about the appropriate use of ESAs in management of myeloma.

- In January 2008, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) issued updated clinical practice guidelines on the use of ESAs in patients with cancer.[11] These guidelines appear to be in line with the limited available information about the appropriate use of ESAs in management of myeloma.

- The International Myeloma Working Group,[12-14] under the auspices of the International Myeloma Foundation, is currently developing myeloma-specific practice guidelines on the role of ESAs in management of myeloma. An initial draft of these guidelines will be available soon, but was not available in time to submit to this meeting of ODAC.

- The Foundation concurs with ASCO and ASH in noting the following: [11]

  > "It is important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result."

- Some 55 percent of all patients with advanced myeloma may have end-stage renal disease (ESRD).[3] Given the recognized value of ESAs in the management of ESRD, the potential value of ESAs in management of patients with myeloma is still clear.

- The Foundation recognizes a need for additional research specific to the role of ESAs in the management of myeloma, and criteria to exclude use of ESAs in myeloma patients at greatest risk for adverse consequences of ESA treatment.

- Until such data are available, the Foundation believes that there is no good clinical option other than to rely on currently available guidelines for the treatment of anemia and ESRD in patients with myeloma. ESAs are a significant clinical option for management of anemia and ESRD. Lack of availability of such products would severely affect the treatment of myeloma.

GENERAL BACKGROUND

The International Myeloma Foundation is a not for profit, 501(c)(3) organization that seeks to represent the interests of myeloma patients in the USA and around the world. On behalf of the tens of thousands of patients and other members whom the Foundation represents, we would like to offer what we hope is constructive input to ongoing discussions regarding the clinical value and continuing use of erythropoiesis-stimulating agents (ESAs) in management of cancer patients with chemotherapy-induced anemias and anemias not directly associated with chemotherapy.

Many available data regarding the use of ESAs in the management of cancer-related anemias seem to be open to interpretation that depends on viewpoint. This situation is regrettable, since it has left patients and their family members in situations where they are unclear what may be in the best interests of any individual patient.

The incidence of myeloma has been gradually increasing. According to the most recent projections available from the American Cancer Society, nearly 20,000 new myeloma patients will be diagnosed in the USA in 2008.[1] The 2008 projections are open to some controversy, but there are certainly well over 50,000 Americans living with this disorder, and many more around the world. Myeloma is therefore an uncommon disorder that meets classical definitions for an "orphan disease." However, it is perhaps inappropriate to describe it as "rare" today. It is in fact the most common form of hematologic malignancy after non-Hodgkin's disease,[1] and over the past decade we have made huge strides in our ability to treat this disease since the initial recognition that thalidomide could profoundly impact disease progression, even in patients with very late stage disease.

Myeloma is strongly associated with loss of kidney function and ultimately with end-stage renal disease (ESRD). According to Mittelman,[2] approximately 25 percent of myeloma patients are diagnosed with ESRD, and as many as 55 percent of patients with advanced forms of myeloma may have ESRD. This connection between myeloma and renal disorder is clearly critical to

patient management, and it is not surprising that (since the early 1990s) clinicians have explored the potential of ESAs to manage anemia and renal disorders in myeloma patients, as opposed to the more traditional use of transfusions. Regrettably, however, there has only been one Phase III randomized, double-blind, well-controlled study exploring the role of ESAs specifically in the management of myeloma patients – including either placebo-controlled studies or ESA comparative studies.

It needs to be further noted that there have been dramatic changes in the management of myeloma in the past two years. Lenalidomide (Revlimid®/Celgene) has demonstrated exceptional effectiveness and safety in the treatment of myeloma in combination with low-dose dexamethasone, and even more recently bortezomib (Velcade®/Millennium) has demonstrated a high degree of effectiveness in the first-line treatment of myeloma.[3-6] In general, specialists are no longer treating myeloma with traditional chemotherapies. Myeloma has become a disease in which the value of targeted therapy has been tried and proven. No large clinical trial of any ESA has been carried out under circumstances in which these targeted agents had been adopted as first-line therapy for management of myeloma, and we have no data whatsoever to suggest whether ESAs can or will prove more or less beneficial for myeloma patients in such a clinical environment.

If there is a single, critical key learning for the Foundation in carrying out this analysis of the currently available data, it is that we desperately need additional studies to clarify the role of ESAs in management of myeloma patients specifically. Such studies probably need to include a very careful stratification of patients by stage, by treatment history, and by treatment regimen at the time of treatment with ESAs. In the case of myeloma patients with ESRD, for whom ongoing chemotherapy may not be appropriate, a range of other questions about the value of ESAs may be appropriate.

CURRENTLY AVAILABLE DATA

The Foundation is currently aware of a single large, double-blind, randomized, placebo-controlled trials of any ESA in the management of patients exclusively with myeloma. The protocol for this study is outlined in NCT00270101 in the clinicaltrials.gov database and a synopsis of the results of the trial is accessible on Veritas Medicine.[7,8]

Between February 1994 and September 1996 Johnson & Johnson Pharmaceutical Research & Development carried out a Phase III, randomized, double-blind, placebo-controlled trial on the impact of epoetin alfa in subjects with myeloma at 31 different centers in 12 countries. Primary outcomes of this study were the proportion of patients requiring transfusion and the number of units transfused relative to whether or not patients had received transfusions before being enrolled in the study. The full synopsis of the trial is provided below:

Synopsis of Results of NCT00270101

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE	(FOR NATIONAL AUTHORITY USE
The R.W. Johnson Pharmaceutical Research Institute	REFERRING TO PART OF THE DOSSIER	ONLY)
NAME OF FINISHED PRODUCT:	Volume:	
EPREX®, ERYPO® (Epoetin Alfa)	Page:	
NAME OF ACTIVE INGREDIENT(S):		
Recombinant human erythropoietin		

Protocol No.: CR005911 **Title of Study**: A Placebo-Controlled Study On The Effect of Epoetin Alfa in Subjects with Multiple Myeloma Followed by an Open-Label Extension

Investigators: 31 investigators

Study Center(s): 31 study centers in 12 countries

Publication (Reference): Dammacco F. XIVth Meeting of the International Society of Haematology Oral Session 10. 1997;O-046:49; Dammacco F. Eur J Cancer 1997;33(Suppl.8):394. Dammacco F, Castoldi G, Roedjer S. Blood 1997;90(Suppl.1):358a

Studied Period (years): February 17, 1994 - October 10, 1996 **Phase of development**: 3

RISKS OF ERYTHROPOIESIS-STIMULATING AGENTS WHEN ADMINISTERED TO PATIENTS WITH CANCER

Objectives: To compare the ability of epoetin alfa and placebo in preventing transfusions or anemia in subjects with multiple myeloma, and to investigate quality-of-life benefits associated with the use of epoetin alfa.

Methodology: This trial was a multicenter, double-blind, placebo-controlled study conducted in 12 countries, followed by an open-label extension. To enroll subjects thought to be at high risk for the development of transfusion-dependent anemia, enrollment was restricted to subjects who had a low baseline hemoglobin value and who had received chemotherapy starting at least six months previously. Subjects were stratified into two groups depending on whether or not they received at least one blood transfusion within the previous three months. If, after four weeks of therapy, a subject's hemoglobin level had increased by less than 1 g/dL above baseline, the initial dose (150 IU/kg t.i.w.) was to be adjusted to 300 IU/kg t.i.w. Treatment was to continue for 12 weeks. All subjects who completed this 12-week double-blind portion of the study were eligible to receive epoetin alfa for an additional 12 weeks in an open-label extension to the study.

Number of Subjects (planned and analyzed): 134 planned; 145 analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects, 40 to 80 years old, with documented multiple myeloma, with a performance score (ECOG) of 0, 1, 2, or 3 (i.e., not completely disabled) and a life expectancy of at least three months, and with a baseline hemoglobin ≤11 g/dL and baseline reticulocyte count ≤100,000/μL. At least six months were to have elapsed since the beginning of chemotherapy.

Test Product, Dose and Mode of Administration, Batch No.: Epoetin alfa (EPREX® or ERYPO®) at 150 IU/kg, s.c. t.i.w.; Batch Nos. 3H517T, 3M516T, 4B518T, 4C207T, 4D226T, 4E216T, 5A202T, 5H221T, 5K230T, 5L206T, 5M511T, 6B227T, and 6D226T.

Duration of Treatment: 12 weeks for the double-blind phase, and 12 weeks for the open-label extension.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo, s.c. t.i.w.; Batch Nos. 5F001T, 903401, and 923301.

Criteria for Evaluation:

Efficacy: Efficacy evaluations were based on comparisons between treatment groups of transfusion requirements (proportion of subjects transfused and number of units transfused) during the study stratified by baseline transfusion status, on the number of subjects whose hemoglobin level reached at least 12 g/dL (correctors) or had an increase in hemoglobin of at least 2 g/dL (responders), and on changes in quality-of-life parameters. Safety: Safety evaluations included assessments of the incidence and severity of adverse events, clinical laboratory tests, vital sign measurements, and physical examinations. Serum and urine M-protein levels were compared for changes in underlying disease.

Statistical Methods: The proportion of subjects transfused during Months 2 or 3 was the main focus of the analysis. The Cochran-Mantel-Haenszel test was used to compare the proportion of subjects transfused stratified by prestudy transfusion dependence. Secondary efficacy variables included additional transfusion variables, changes in hemoglobin and hematocrit levels, reticulocyte counts, and serum erythropoietin levels, proportions of correctors and responders, quality-of-life assessments, performance score, and the physician's global assessment.

Results and Conclusions

EFFICACY: The efficacy of epoetin alfa in treating subjects with multiple myeloma has been demonstrated in that the proportion of subjects transfused was significantly smaller in the epoetin alfa-treated group than in the placebo-treated group ($p=0.028$ for the efficacy population and $p=0.006$ for the intent-to-treat population, stratifying by prestudy transfusion dependence).

Proportion of Subjects Transfused During Months 2 or 3 of Double-Blind Phase, by Prestudy Transfusion Dependence (Efficacy Population) (Protocol CR005911)

Transfused prestudy	Transfused in months 2 or 3	Placebo (N = 66)	150 IU/kg epoetin alfa (N = 66)	p-value*
		N (%)	N (%)	
Yes	Yes	12 (52.2)	16 (72.7)	0.028
	No	11 (47.8)	6 (27.3)	
No	Yes	4 (9.3)	10 (22.7)	
	No	39 (90.7)	34 (77.3)	

*Cochran-Mantel-Haenszel test comparing the proportions of subjects transfused stratified by prestudy transfusion dependence

The effect of epoetin alfa was also clearly demonstrated by significantly greater increases in hemoglobin and hematocrit ($p<0.001$) and in reticulocyte counts ($p=0.025$) from baseline to last value compared with placebo, and by significantly more correctors (hemoglobin ≥12 g/dL reached) and responders (≥2 g/dL hemoglobin change from baseline) unrelated to transfusions ($p<0.001$). No significant differences were observed with regard to Week 12 change in quality-of-life scores. However, many more of the quality-of-life subscales showed significant improvement within the epoetin alfa-treated group than within the placebo-treated group. Significant improvements in change of performance scores based on investigator assessment were observed in the epoetin alfa-treated group compared with the placebo-treated group ($p=0.038$). Increases in hemoglobin levels and improvements in quality of life were generally observed among subjects who switched from placebo during the double-blind phase to epoetin alfa during the open-label phase, while maintenance of both hemoglobin levels and quality of life was observed among subjects who remained on epoetin alfa.

SAFETY: Overall, epoetin alfa was safe and well tolerated. Treatment-emergent adverse events were similar among treatment groups. Fever, leucopenia, and pain were the most frequently reported adverse events. Similar proportions of subjects (2.9% epoetin alfa-treated and 3.9% placebo-treated) discontinued treatment due to one or more adverse events. More placebo-treated subjects than epoetin alfa-treated subjects died (seven vs. one, respectively) and more placebo-treated subjects than epoetin alfa-treated subjects discontinued treatment due to disease progression (six vs. none, respectively) despite similar multiple myeloma disease staging at baseline and at the end of the study. Thus, epoetin alfa had no negative effect on disease progression. Serious adverse events were in general similarly distributed both across body systems and between treatment groups. There were no noteworthy differences between treatment groups in clinical laboratory test results, vital sign measurements, or other physical findings. As expected, mean iron stores decreased in epoetin alfa-treated subjects compared with placebo, reflective of the utilization of iron stores during enhanced erythropoiesis.

CONCLUSION: Epoetin alfa was safe and well tolerated in a multiple myeloma subject population, and there were no negative effects on disease progression. The efficacy of epoetin alfa was clearly demonstrated by lesser transfusion requirements and greater increases in erythropoietin parameters (hemoglobin levels, hematocrit levels, and reticulocyte counts) when compared with placebo.

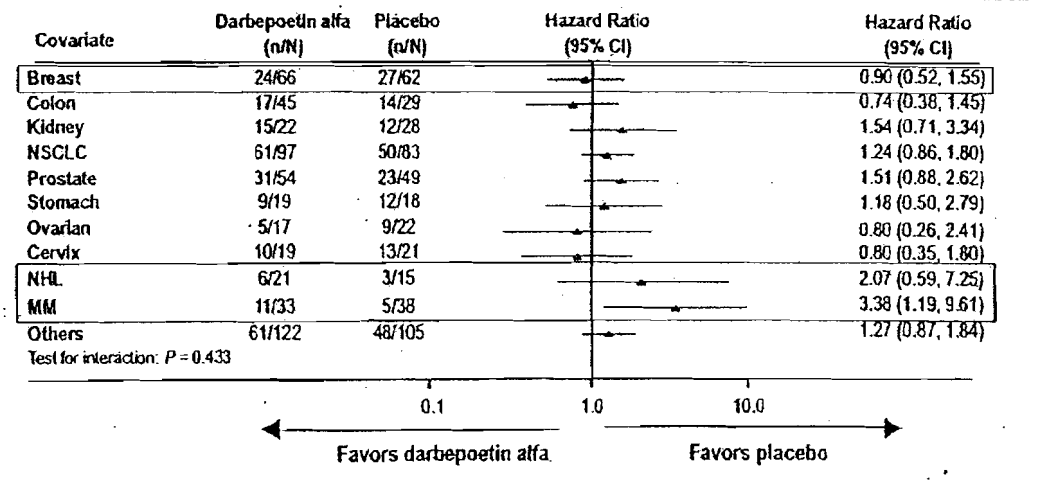
There is no explicit mention of thrombotic or other associated adverse reactions in the study synopsis. It is also stated quite clearly that "more placebo-treated patients died (seven vs one, respectively)." A review of the actual study data might be informative, but there is no reason at this time to question these data as presented.

A variety of other studies (including some multicenter, randomized, controlled phase III studies) has focused on the use of ESAs in the management of hematologic malignancies generally, and has certainly included patients with myeloma. However, we are not aware of any detailed breakdown or meta-analysis of information about myeloma patients in these trials (to date). Nor are we aware that critical data bout these patients (stage, current and prior chemotherapeutic agents, whether transplanted, etc.) were collected in the course of these trials.

Without data of this type, it is all but impossible to be able to make any meaningful analysis of the clinical value of ESAs in the long-term management of myeloma itself or in the management of renal disorders associated with myeloma.

The Foundation *is* fully aware of data presented by Glaspy at a plenary session of the annual meeting of the American Association for Cancer Research[9] (see figure).

Overall Survival During Treatment and Follow-up Period by Tumor Type



- The test for interaction was not significant

Glaspy's data, extracted from a multicenter, randomized, Phase III clinical trial designed to study the ability of darbepoetin to reduce the need for blood transfusions in patients with active cancer not undergoing chemotherapy, raise many questions. However, they include just 71 myeloma patients, of whom 16 died. This is only 7.2% of the 985 patients on whom data is provided and 3.4% of the 466 deaths. We would want to be very clear about the precise history and prior management of these patients before being able to state with any degree of certainty that the apparent difference in death rate were due to the use of the ESA as opposed to some other cause.

It should be noted that in a press release associated with the presentation of these data,[10] Dr. Glaspy himself was quoted as follows:

> "The findings will pose a particular puzzle to cancer researchers, as the exact mechanisms behind the observed decrease in patient survival is [*sic*] not clear," Glaspy said. "Likewise, we'll need to resolve these data in light of evidence that darbepoetin offers benefits for patients with certain types of cancer when used within chemotherapy. There are no obvious reasons for this discrepancy."

Dr. Glaspy — a respected authority on the use of ESAs in cancer — did not state at that time that he saw any reason to consider removal of darbepoetin or any other ESA from the US marketplace.

All other available data on the role of ESAs in the management of myeloma appear to come from small, non-randomized, single institution trials. While such trials may offer some guidance as to the impact of ESAs in myeloma, they are inherently not designed to offer neutral, controlled data about the relative value of any therapy in the management of any disease.

GUIDELINES

At present there are no available guidelines that address the appropriate and inappropriate uses of ESAs in the management of myeloma. However, such guidelines are in development, as will be discussed below.

The ASCO/ASH Guidelines on the Use of ESAs in Patients with Cancer

In January 2008, Rizzo et al. published updated guidelines on the use of ESAs in patients with cancer under the auspices of a joint committee of the American Society of Clinical Oncology and the American Society of Hematology.[11]

These guidelines took careful account of revised labeling of ESAs issued by the US Food & Drug Administration in November 2007, and made careful recommendations regarding the appropriate use of ESAs in management of patients with chemotherapy-induced anemia as well as in the management of anemia of patients not receiving chemotherapy. Either situation could occur in a patient with myeloma.

In the case of anemia in cancer patients not receiving concurrent chemotherapy, the updated guidelines make the following, strong statement and recommendation:

> "Analyses of primary data from study 20010103 (as yet unpublished) ***[the Glaspy analysis referenced earlier]*** submitted to the US Food and Drug Administration in March 2007, support a stronger recommendation against the use of ESAs to treat anemia associated with malignancy, or the anemia of cancer, among patients with solid or nonmyeloid hematologic malignancies who are not receiving concurrent chemotherapy."
>
> *Text in **bold italic** has been inserted by the authors for clarity.*

The updated guidelines also pointed out that this recommendation is consistent with the revisions to labeling for ESAs issued by the FDA. However, ESAs are still indicated for treatment of patients with end-stage renal disease, Thus there is an unanswered question here for the myeloma community. Are some or all ESAs useful in the treatment of myeloma patients with end-stage renal disease if they are not receiving chemotherapy?

In the case of patients with chemotherapy-induced anemia, the guidelines make two recommendations:

> "The use of [ESAs] is recommended as a treatment option for patients with chemotherapy-induced anemia and an Hb concentration that is approaching, or has fallen below, 10 g/dL, to increase Hb and decrease their transfusions."

and

> "For patients with declining Hb levels but less severe anemia ... the decision of whether to use [an ESA] immediately or to wait until the Hb levels fall closer to 10 g/dL should be determined by clinical circumstances ...."

The second of these recommendations is at the core of the clinical decision-making process. In the overall introduction to the guidelines, the guideline committee clearly state as follows:

> "It is important to emphasize that guidelines and technology assessments cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same result."

This is a statement that has the full support of the International Myeloma Foundation. Historical data clearly support the role of ESAs in the management of patients with anemia (see prior section); while we may need to augment these data to clarify the proper use of ESAs in myeloma, expert international medical and scientific leadership of the Foundation currently consider that the availability of ESAs is critical to best practices in the management of myeloma patients.

International Myeloma Working Group Guidelines

Given the currently available data, and the speed with which the data are evolving, the International Myeloma Foundation is not, at present, in a position to make any absolute recommendations to its members, or to specialists treating myeloma, regarding the use of ESAs in the management of this disorder. Analysis of the available data, and development of recommendations based on these data, are critical priorities for the International Myeloma Working Group — a transnational, ad hoc organization of over 90 myeloma specialists under the auspices of the International Myeloma Foundation. The International Myeloma Working Group intends to circulate a set of draft guidelines to its members in the near future as a basis for discussion. It is likely to be at least some months before a consensus statement is available.

For clarification only, there have been several previous successful efforts by the International Myeloma Working Group to develop and publish consensus guidelines related to the diagnosis and management of myeloma.[12-14]

STATEMENTS OF OPINION

The Foundation would like to make the following observations. We wish to be very clear that these are statements of opinion at this time, and cannot be substantiated with definitive data.

- There appears to be a general consensus among myeloma experts in many countries that the continued availability of ESAs for the treatment of myeloma is critical to the best possible management of patients.

- While there are clearly significant risks associated with the use of ESAs in management of some patients with chemotherapy-induced anemias, it seems equally clear that there are significant benefits associated with the use of these agents in other patients.

- Such variation in response to the use of ESAs is hardly surprising. Patients are not "average." Each patient is unique, and may have individual characteristics that predispose him or her to react well or poorly to any therapeutic agent. Such responses to drug therapy are not the exception. They are, in fact, the norm.

- Clinicians need help and guidance in determining how to assess the potential risks and benefits of the use of ESAs in individual patients. Absolute directions that limit use of these agents and that are not based on indisputable data will only foster the ongoing controversy.

- While the FDA may certainly determine that, for some subsets of patients, the data favor a strong recommendation to minimize use of ESAs, we are not yet convinced that the potential risks associated with the use of these agents necessarily outweigh their benefits for *all* groups of patients.

The Foundation encourages the FDA, and all parties to these discussions, to seek the greatest possible clarity regarding the available scientific and clinical data, and to issue guidance based

only on well-substantiated data. The best possible care and treatment of patients are the only determining factors that should be affecting decisions in this area.

For ESAs not to be easily available for treatment of those patients who clearly do benefit from their use would be every bit as disturbing as the inappropriate use of ESAs in those patients who clearly are harmed by such use.

REFERENCES

1. American Cancer Society. *Cancer Facts and Figures, 2008.* American Cancer Society, Atlanta, GA. 2008.
2. Mittelman M. The implications of anemia in multiple myeloma. *Clin Lymphoma* 2003;4:S23-S24.
3. Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: LBA8025
4. Palumbo A, Miguel JS, Sonneveld P, et al. Lenalidomide: a new therapy for multiple myeloma. *Cancer Treat Rev.* 2008 [January 28]; e-pub ahead of print.
5. San Miguel JF, Schlag R, Khuageva N, et al. MMY-3002: A Phase 3 Study Comparing Bortezomib-Melphalan-Prednisone (VMP) with Melphalan-Prednisone (MP) in Newly Diagnosed Multiple Myeloma. *Blood* (ASH Annual Meeting Abstracts), Nov 2007; 110: 76.
6. Cavo M, Patriarca F, Tacchetti P, et al. Bortezomib (Velcade®)-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (TD) in preparation for autologous stem-cell (SC) transplantation (ASCT) in newly diagnosed multiple myeloma (MM). *Blood* (ASH Annual Meeting Abstracts), Nov 2007; 110:73.
7. ClinicalTrials.gov. The effect of epoetin alfa on the anemia of patients with multiple myeloma (NCT00270101). Downloaded February 18, 2008 from www.clinicaltrials.gov/ct2/NCT00270101?term=myeloma+AND=epoetin&rank=3
8. Veritas Medicine. A placebo-controlled study on the effect of epoetin alfa in subjects with multiple myeloma followed by an open-label extension. Downloaded February 18, 2008 from http://download.veritasmedicine.com/PDF/CR005911_CSR.pdf.
9. Glaspy J. Plenary presentation at the annual meeting of the American Association for Cancer Research, 2007 [precise title unknown].
10. American Association for Cancer Research. Study produces conflicting findings on the use of anti-anemia drug. Media release issued April 16, 2007. Downloaded February 18, 2007 from http://www.aacr.org/home/public--media/public-policy--legislative-affairs/press-releases--articles.aspx?d=765

11. Rizzo JD, Somerfield MR, Hagerty KL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol.* 2008;26:132-149.
12. Greipp P, San Miguel J, Durie BG, et al. International staging system in multiple myeloma. *J Clin Oncol.* 2005;23:3412-3420.
13. Durie BGM, Harousseau J-L, San Miguel J, et al. International uniform response criteria for multiple myeloma. *Leukemia.* 2006;20:1467-1473.
14. Durie BGM. Use of bisphosphonates in multiple myeloma: IMWG response to Mayo Clinic Consensus Statement. *Mayo Clin Proc.* 2007;82:516-522.

Christina Gomes

From: [redacted]
Sent: Monday, February 18, 2008 5:53 AM
To: Brian Durie, MD; Katz, Mike [USA]
Cc: [redacted]
Subject: ESAs and myeloma AGAIN!
Importance: High

Are either of you aware of ANY large controlled clinical trial designed to assess the value of ESAs in myeloma patients specifically (either myeloma patients alone or myeloma patients as a predefined subset of a trial enrolling patients with non-myeloid hematologic malignancies)? I am not aware of any such trial in myeloma patients alone, but maybe there have been one or two trials in NMHMs that included a significant subset of myeloma patients.

Mike

E. Michael D. Scott
Principal and Executive VP
voxmedica
The Curtis Center, Suite 250-S
Independence Square West
Philadelphia, PA 19106, USA
Tel: 215 238 8500 ext 1300
Fax: 215 592 4287
E-mail: MScott@voxmedica.com

Christina Gomes

From: Mike Scott [mscott@voxmedica.com]
Sent: Monday, February 18, 2008 5:06 AM
To: SNovis@myeloma.org; Brian Durie, MD
Cc: Katz, Mike [USA]
Subject: ESAs and communications with Amgen -- PLEASE READ
Importance: High

Brian, Susie:

Per the voicemail that Brian left me last night regarding timing of decisions about involvement in the ODAC ESA process, I suggest as follows:

- We advise Amgen, in writing, by e-mail, **TODAY**, that the IMF does not intend to request time to make an "open microphone" presentation at the ODAC meeting. (Suggested e-mail copy is given below.)
- We further advise Amgen that the IMF **WILL** be submitting written comments to ODAC one or before February 27, 2008, and that Amgen and others will be copied on these comments.
- I shall develop a comprehensive draft of the proposed document for circulation to all concerned by end of day Wednesday this week (or earlier).

The implication of this is that I would appreciate seeing **ANYTHING** that Heinz Ludwig has developed as quickly as possible. I would also think it was wise if Heinz was asked to review my draft. Can one of you please contact him today ... or can you let him know that I will be contacting him. I will need to move on this ASAP.

Mike

E. Michael D. Scott
E-mail: MScott@voxmedica.com

PROPOSED E-MAIL TO AMGEN

Header: ESAs and their use in multiple myeloma/IMF comments to ODAC

Dear [insert name]:

After careful consideration, the International Myeloma Foundation has decided to submit detailed, written comments to the FDA regarding the use of ESAs in management of multiple myeloma. We do not intend to request time to present information at the "open microphone" portion of the ODAC meeting. The Foundation believes that by providing our comments to the committee in full, and in writing, we will better ensure that these comments are complete, and reflect a sound and unmisinterpretable representation of the IMF's position at this time.

You should be aware that the International Myeloma Working Group is currently working on an draft of guidelines for the use of ESAs in management of myeloma. However, this draft is not expected to be complete in time for submission to ODAC on or before February 27, and until such guidelines are complete and have been carefully reviewed by appropriate members of the International Myeloma Working Group, the IMF does not wish to take any position that specifically recommends or denies the use of ESAs in management of myeloma patients.

We shall, naturally, provide Amgen and Ortho Biotech with copies of our written comments to the FDA at the time of submission, so that all parties to this dicussion are appropriately informed. We would also appreciate receiving any unpublished information available to Amgen that clarifies the clinical benefits and risks of Epogen and Aranesp in treatment of multiple myeloma. Such data may be of assistance in the development of the International Myeloma Working Group's proposed guidelines.

Sincerely

Susie Novis

February 27, 2008

Oncology Drug Advisory Committee
Food and Drug Administration
Via email to Nicole Vesely, Pharm.D. nicole.vesely@fda.hhs.gov

Concerns Regarding ESAs administered to patients with cancer induced anemia

Introduction

The Ovarian Cancer National Alliance is an umbrella organization with 50 state and local groups representing grassroots activists, women's health advocates and health care professionals. According to the American Cancer Society, in 2008, 21,650 American women will be diagnosed with ovarian cancer, and 15,520 will lose their lives to this terrible disease. Ovarian cancer is the deadliest gynecologic cancer and the fifth leading cause of cancer death among women in America. Currently, more than half of the women diagnosed with ovarian cancer will die within five years. The Ovarian Cancer National Alliance submits this testimony regarding erythropoeisis-stimulating agents (ESAs) as a patient advocacy group with the aim of conquering ovarian cancer.

The Alliance works closely with Johnson & Johnson and Amgen, manufacturers of ESAs. We have received funding from both organizations in the past, and maintain working relationships in our mission to conquer cancer. We applaud the efforts of the companies to enhance the quality of life for cancer patients. Our relationships in no way influence the positions stated below.

Safety Signals

In recent months, studies have raised safety signals about the use of ESAs. Specifically, the incidence of thrombotic events as well as a shortened life span were seen in patients taking ESAs. Many of these studies involved off-label use of ESAs, targeting a hemoglobin level higher than recommended. Nonetheless, the Alliance remains unconvinced that a hemoglobin level of 12g/dL, as approved by the FDA, is a magic number, below which no harm will be done.

Data

Both the FDA and industry have given conflicting reports over who owns the data on ESAs, and who has the power to release these data. The Alliance has joined other organizations in calling for the release of data related to use of ESAs. Further, we continue to request that patient-friendly information be provided to all patients considering ESAs.

We are concerned about the process by which ESAs have been evaluated. This process should be science-based; instead, regulatory agencies have led the way. The FDA had a meeting in early 2007, after which CMS changed reimbursement policy. It was not until late 2007 that the NCI actually met to discuss ESAs. Evidence should guide practice and reimbursement, not the other way around.

Impact on Ovarian Cancer Patients

Anemia occurs more frequently in gynecological cancers than others. Because 70 percent to 90 percent of ovarian cancer patients have a recurrence and ovarian cancer patients may be on maintenance chemotherapy for years, ovarian cancer patients may be in a position to take more ESAs than other cancer patients. For them, and for all cancer patients, we must have sound medical and scientific advice so that patients and their health care providers can make informed decisions about treatment. Ovarian cancer has a high mortality; many patients remain on chemotherapy for years. These patients are at an increased risk of any negative effects of ESAs. A palliative care drug may be rendering the work of primary treatments useless.

The proposed studies on ESAs do not include ovarian cancer as a tumor type to be included. For this reason, it is imperative that any findings be translatable to all cancer types, and guide treatment practices for all types of cancer.

These safety signals are highly concerning. Since the aim of treatment is longer survival, any additional care should support that outcome while promoting a quality of life to the extent that palliative care is safe and feasible. Patient safety is of the utmost importance, and any FDA regulations must reflect scientifically-based evidence in furtherance of patient safety.

Stuart C. Spigel, M.D.
Charles E. McKay, M.D.
Eric L. Raefsky, M.D.
F. Anthony Greco, M.D.
John D. Hainsworth, M.D.
Anthony A. Meluch, M.D.
Dana S. Thompson, M.D.
Michel E. Kuzur, M.D.
Fernando T. Miranda, M.D.
Nancy W. Peacock, M.D.
Jeffrey F. Patton, M.D.
Howard A. Burris III, M.D.
John H. Barton Jr., M.D.
Mainuddin Ahmed, M.D.
Mitchell A. Toomey, M.D.
Victor G. Gian, M.D.
Adil I. Mohyuddin, M.D.
Dianna L. Shipley, M.D.
William H. Liggett Jr., M.D.
Rohit R. Patel, M.D.
Lester L. Porter III, M.D.
Natalie R. Dickson, M.D.
Denise A. Yardley, M.D.
Mark G. Mainwaring, M.D.
Kirk Barnes, M.D.
Habib Doss, M.D.
David R. Spigel, M.D.
James D. Peyton, M.D.
John D. Zubkus, M.D.
Laura F. McClure-Barnes, M.D.
R. Seth Cooper, M.D.
Alan G. Cohen, M.D.
W. Charles Penley, M.D.
Patrick B. Murphy, M.D.
Ruth E. Lamar, M.D.
Jia Bi, M.D.
Jamie K. Waselenko, M.D.
Ian W. Flinn, M.D.
Kent C. Shih, M.D.
Jeffrey R. Infante, M.D.
Jerry M. Foster, M.D.
Duyen T. Nguyen, D.O.
Daniel R. Couriel, M.D.

Health Psychologists
Amy Johnson, Ph.D.
Sherian Anderson, Ph.D.

Baptist Medical Building
Nashville, TN • (615) 329-0570

Centennial Medical Center
Nashville, TN • (615) 320-5090

Clarksville, TN • (931) 906-2004

Lebanon, TN • (615) 453-5623

Middle Tennessee Medical Center
Murfreesboro, TN • (615) 848-0488

Skyline Medical Center
Nashville, TN • (615) 860-1556

St. Thomas Hospital
Nashville, TN • (615) 385-3751

Summit Medical Center
Hermitage, TN • (615) 871-9996

Sumner Regional Medical Center
Gallatin, TN • (615) 451-5481

TN Oncology P.E.T. Services
Nashville, TN • (615) 320-7387

Tennessee P.E.T. Scan Center
Murfreesboro, TN • (615) 890-5858

Tullahoma, TN • (931) 393-3143

Tennessee Oncology

February 18, 2008

Mimi Phan
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Phan:

I am writing on behalf of the 53 physician oncologist group, Tennessee Oncology, but more importantly, on behalf of the patients for whom we care, regarding the upcoming ODAC meeting.

We have followed with great interest the recent publications suggesting a possible safety signal for the ESA class. Our evaluation shows that in every publication with a safety concern, ESAs were used in a method that is outside the norm for how these agents are used in the community oncology setting and outside of the FDA label. These studies either investigated the use of ESAs with a high hemoglobin target or investigated the use in patients with cancer not undergoing chemotherapy and near the end of life, neither of which is a standard practice in community oncology. The standard of care in the community is to follow accepted national clinical guidelines such as those published by ASCO and NCCN and supported by the FDA label.

Upon review of the significant literature, we are unable to find any suggestion of a safety signal when these agents are used while following these accepted clinical guidelines. There is actually a large literature, including pooled analysis that would strongly suggest that these agents are indeed safe when used according to widely accepted guidelines. In view of these data, it seems less than reasonable to extrapolate a safety signal seen in an experimental setting that does not apply to current clinical practice. We also note with great interest the conclusions form the NCI panel convened to evaluate the epo receptor in that they found no scientific evidence to suggest that the epo receptor is involved with promotion of tumor growth. There is clear evidence that elevated levels of hemoglobin can lead to poor patient outcomes and we feel that this alone explains the poor outcomes seen in these experimental studies that showed a safety signal. Our assessment suggests that any additional limitations of the FDA label would not be supported by the available scientific literature.

397 Wallace Road, Suite C-201 • Nashville, Tennessee 37211 • Phone (615) 333-2481 • Fax (615) 781-3923
Southern Hills Medical Center

As practicing oncologists, we have all experienced a significant improvement in the quality of life for our cancer patients since the advent of ESAs. Anyone who would deny that there is significant improvement in the quality of life of a patient who has an improvement in there baseline hemoglobin from 9 or 10 to 11 or 12 has certainly not cared for patients in the oncology setting. These agents make a significant impact on our patient's lives and we feel that limiting our patient's access to these quality of life improving agents would be tragic. As oncologists, we spend our entire careers making risk benefit decisions. Based upon our review of the literature and our greater than 10 years of experience, we feel the benefits greatly outweigh the risks to ESA use for the majority of our patients with anemia.

We ask that your final label be based upon the available scientific evidence and allow us to continue to follow our evidence based national treatment guidelines.

Respectfully,

Jeffrey F. Patton, M.D.
Chief Medical Officer
Tennessee Oncology

THE NEW JERSEY INSTITUTE FOR THE ADVANCEMENT OF BLOODLESS MEDICINE & SURGERY
AT ENGLEWOOD HOSPITAL AND MEDICAL CENTER
350 ENGLE STREET ENGLEWOOD, NJ 07631 TOLL FREE 1-888-766-2566

March 25, 2008

Nicole Vesely

Center for Drug Evaluation and Research

Food and Drug Administration

5630 Fishers Lane

Room 1093

Rockville, MD 20857

Fax number:301-827-6776

Dear Committee Members:

At the outset of this letter we would like to disclose that in the past, as well as in the distant past the first author of this letter, has served as a consultant, speaker and grant recipient from both OrthoBiotech and Amgen. But long before any perceived conflict arose, this physician was treating patients with Erythroid Stimulating Agents (ESA). It is this, our combined experience and observations, that the committee should consider, clouded or not.

We respectfully ask that the chair and members of the committee consider our plea on the basis of an account by practicing physicians whose sole intent is to provide good clinical care and improve outcome and quality of life of our patients.

Current review of ESA has been triggered by recent reports of increased mortality and recurrence of malignancy in patients treated with ESA for their underlying anemia as a result of cancer and those receiving chemotherapy. The intent in treating these patients with ESA is to reduce their exposure to allogeneic blood transfusion (ABT) and the known negative consequences associated with ABT. Although no head to head trials are available to review (both arms in all the reviewed trials received ABT), the group receiving high doses of ESA, and treated to a target hemoglobin (Hgb) greater than 12 gm/dL, accounted for more significant complications.

Not all patients in the ESA group responded negatively. Many patients had improved outcome as well as meeting primary objectives of the trials. Given the design of these studies, it is unknown whether the negative results apply to a sub population of chemotherapy treated cancer patients receiving ESA at doses titrated to achieve and maintain a Hgb level close to 12 gm/dL

Treatment of patients with high burden of disease, such as those with malignancy, requires aggressive measures and treatments with high complication rates and the significant burden of these complications. Chemotherapy infusions are a prime example. ESA have had a significant impact on ABT and improved wellness for many. While a subgroup of patients might do worse with these agents especially with higher doses, direct causality has not been established and a substantial number of previous studies support their safety and efficacy.

Additional restriction of their use will have significant intended and unintended consequences. "Collective punishment" may prove to be too harsh, as physicians will unavoidably resort to increase use of ABT. This change in practice will impact the current shortage of blood, will reduce the number of 'anemia free' days or weeks these patients may enjoy, increase the risk of alloimmunity in addition to side effects related to repeated ABT. Finally, additional restrictions will discourage the clinical trials that are needed, namely, adequately-powered, well designed trials designed to detect differences in survival and tumor progression in patients treated with ESA who avoid ABT.

Despite sparse level 1 evidence on improvement of quality of life, some data exists to support it, and reported observations by most of my colleagues suggest this is a real and important phenomenon.

The practice of medicine is a daily balance of benefit versus risk and weighing the burden of disease against the burden of therapy. ESA are not exempt from this daily exercise. Used cautiously, they can provide benefit while studies to indentify those at high risk for this therapy are performed.

As citizens, treating physicians and potential patients, we ask that the committee consider those who benefit from ESA with the same thoughtfulness and caution that is given to those who have had unfortunate side effects. It is a difficult task to protect some while not harming others and as such you have our sympathy and respect.

We hope we have spoken for those who have benefited and hope your decision will include this large patient population. We feel the current labeling for ESA adequately addresses the precautionary principle, and that more restrictive labeling will penalize patients who currently benefit from therapy with ESA while having a chilling effect on the design and implementation of new clinical trials.

Respectfully,

Aryeh Shander, M.D., FCCM, FCCP
Chief, Department of Anesthesiology,
Critical Care and Hyperbaric Medicine
Englewood Hospital and Medical Center

Clinical Professor of Anesthesiology,
Medicine and Surgery
Mount Sinai School of Medicine
Mount Sinai Hospital, New York

Irwin Gross, M.D.
Medical Director,
Transfusion Services
Eastern Maine Medical Center