Quick Minutes
Oncologic Drugs Advisory Committee Meeting
May 10, 2007

Summary Minutes of the Oncologic Drugs Advisory Committee
May 10, 2007:

The summary minutes for the May 10, 2007 meeting of the Oncologic Drugs Advisory Committee were approved on June 18, 2007.

I certify that I attended the May 10, 2007 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/
Johanna Clifford, M.Sc., RN

/s/
S. Gail Eckhardt, M.D., Acting ODAC Chair

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Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsors. The meeting was called to order by Gail Eckhardt, M.D. (Committee Chair); the conflict of interest statement was read into the record by Johanna Clifford (Executive Secretary). There were approximately 300 persons in attendance.

Issue:

The Committee met to discuss updated information on risks of erythropoeisis-stimulating agents (ARANESP, Amgen, Inc., Epogen, Amgen, Inc., and Procrit, Amgen, Inc.) for use in the treatment of anemia due to cancer chemotherapy.

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
James Doroshow, M. D., David Harrington., Ph.D., Pamela Haylock, RN (Consumer Representative), S. Gail Eckhardt,(Chair), Michael Link, M.D., Joanne Mortimer, M.D., Michael Perry, M.D., Ronald Richardson,M.D.

Industry Representative (non-voting):
Absent

Oncologic Drugs Advisory Committee Members Absent:
Ronald Bukowski, Maha Hussain, M.D., Alexandra Levine, M.D., Gary Lyman, M.D.

Oncologic Drugs Advisory Committee Consultants:
Kathy Albain, M.D., Carmen Allegra., M.D., Otis Brawley, M.D., James Krook, M.D., Athony Murgo., M.D.,Silvana Martino., D.O., Bruce Redman, D.O., David Stroncek, M.D. , Helen, Schiff (patient representative).

FDA Participants:
Richard Pazdur, M.D., Patricia Keegan, M.D., Vinni Junega. M.D. , Mark Rothman. Ph.D..

Open Public Hearing Speakers:
Robert Erwin, Marti Nelson Cancer Foundation
Samuel Silver, M.D., Ph.D., American Society of Hematology
Steven Gore, M.D. Johns Hopkins Oncology Center
Maryann Napoli, Center for Medical Consumers
M. Carolina Hinestrosa, M.A., MPH.
Lilla Romeo
John Theriault, Aplastic Anemia and MDS International Foundation
Loretta M., Metastatic Breast Cancer Network and South Jersey Breast Cancer Coalition
Roy Beverage, US Oncology

The agenda proceeded as follows:

Risks and Indications for RBCs Transfusions	**David Stroncek, MD** Chief, Laboratory Services Section

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Department of Transfusion Medicine, NIH

Sponsor Presentation	**Amgen, Inc.**
Introduction	Roger M. Perlmutter, M.D., Ph.D. Executive Vice President Research & Development, Amgen Inc.
Clinical Perspectives on ESAs	**Jeffrey Crawford, M.D.** George Barth Geller Professsor for Research in Cancer, Chief of Medical Oncology, Duke University
Benefit/Risk	**Roy Baynes, M.D., Ph.D.** Vice President, Global Development, Oncology Supportive Care
	Alex Zukiwski, M.D. Vice President, Head of Clinical Development Oncology, Johnson & Johnson Pharmaceutical Research and Development
Summary	**Roger Perlmutter, M.D., Ph.D.**
FDA Presentation	**Vinni Junega, M.D.** Medical Officer, DOBP, OODP, FDA

ODAC Discussion:

Background

New labeling claims for Epogen/Procrit and Aranesp for treatment of anemia in patients with cancer receiving chemotherapy was based on evidence of a reduction in the proportion of such patients requiring red blood cell (RBC) transfusions. The avoidance of RBC transfusions is considered a clinical benefit because patients are not exposed to infectious and other risks associated with RBC transfusions. However, since the first approval of an ESA for this indication in 1993, there has been substantial reduction in the infectious risks of RBC transfusions.

In addition, there has been accumulating evidence of increased mortality and poorer tumor outcomes in randomized controlled clinical trials. With one exception (Study 2001-0103), the goal of treatment in these studies was to achieve and maintain hemoglobin levels at or above 12 g/dL.

The graphic below provides a road map for trial results known prior to ODAC 2004 (BEST, N93-004, and ENHANCE), trials presented at ODAC 2004 (GBR-7, RTOG 9903, GER-22, CAN-20, CAN-17, AGO, EPO-ANE-3010, 2001-0145, PREPARE, ARA-03, DAHANCA, GELA), and other trials of interest (Anemia of Cancer, Lymphoid Ca, and Non-Myeloid).

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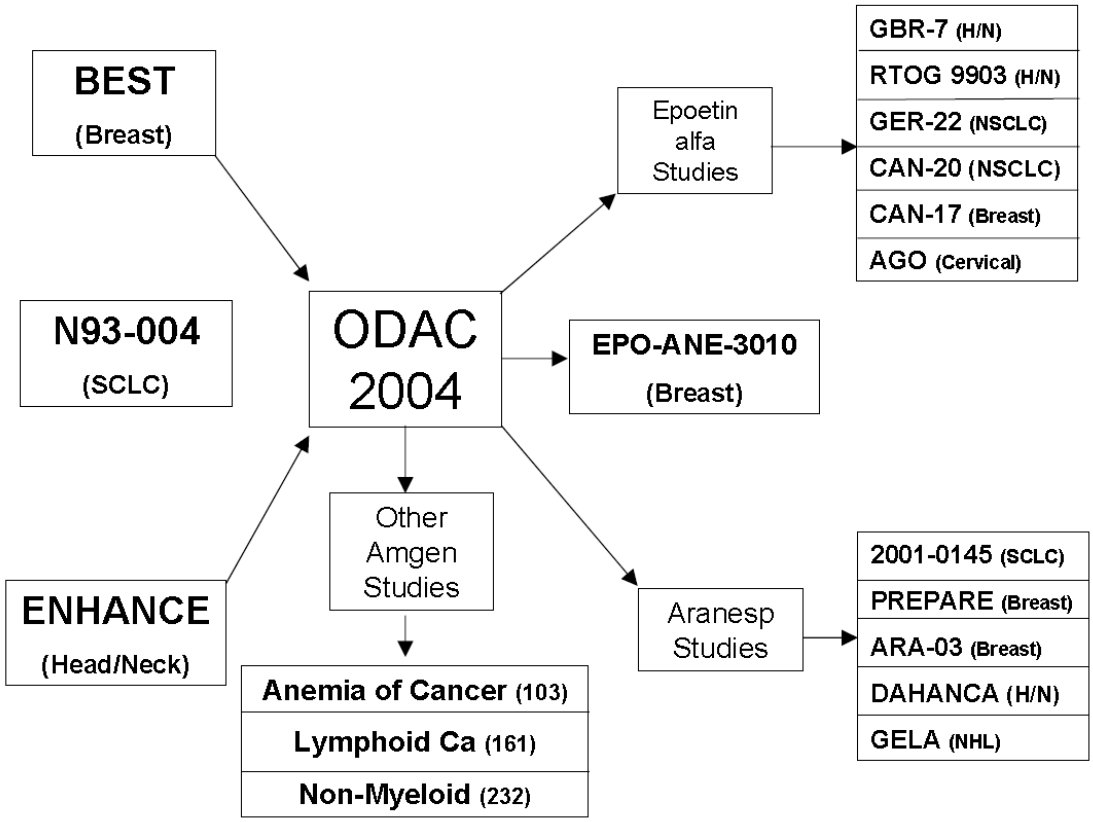

The following is a brief description of the relevant studies discussed during the FDA presentation (for further details, we refer you to our briefing document):

- **N93-004**: 224 SCLC pts; met its non-inferiority primary endpoint of ORR
- **BEST**: 939 Breast Ca pts; ↓ OS in ESA arm
- **ENHANCE**: 351 Head/Neck Ca pts; worse loco-regional PFS, worse loco-regional control, and ↓ OS in ESA arm
- **CAN-20**: 70 NSCLC pts; ↓ OS in ESA arm
- **EPO-ANE-3010**: 108 of a target 1000 Breast Ca pts accrued
- **2001-0145**: 596 SCLC pts; failed to demonstrate superior OS in ESA arm
- **DAHANCA**: 522 Head/Neck Ca pts; worse loco-regional in ESA arm
- **Anemia of Cancer**: 989 pts w/heterogeneous malignancies; ↓ OS in ESA arm
- **Lymphoid Ca**: 344 pts w/ heterogeneous lymphoid malignancies; ↓ OS in ESA arm

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QUESTIONS TO THE COMMITTEE

1. Continued Marketing Authorization for Oncology Indication

Since the first approval of an ESA for patients with cancer in 1993, both a reduction of the infectious risks of blood transfusion and the emergence of new data on safety concerns (tumor promotion and decreased survival) with ESAs have been noted. The FDA revised product labeling in March 2007 to include a Black Box Warning, a description of additional studies raising safety concerns, and a revision of the dosing directions (See Attachment). Should further marketing authorization be contingent upon: a) additional restriction in product labeling? and/or b) additional trials?

1a. ***Vote***: *Yes = 15* *No = 2*

1b. ***Vote***: *Yes = 17* *No = 0*

The committee felt that additional trials should be conducted to support the current marketing indications. The committee felt that an appropriate dose should be determined and that it was unclear as to whether the post marketing commitments were submitted to show these results. However, the committee did recognize the difficulty in accruing patients to these types of trials, suggesting a large simple trial in a homogenous disease population to determine the appropriate dose.

2. Tumor Types

Decreased survival signals were noted in trials enrolling patients with homogeneous tumor types including BEST (Breast), ENHANCE (Head/Neck Ca), and EPO-CAN-20 (NSCLC). Other trials showing decreased survival signals that were conducted in heterogeneous tumor types are 161 (Lymphoid Malignancy), and 103 (Anemia of Cancer). Decreased loco-regional control rates were observed in the DAHANCA (Head/Neck Ca) and ENHANCE (Head/Neck Ca) trials. Several of these trials employed a treatment strategy to achieve and maintain hemoglobin > 12 g/dL. The results of these clinical trials are provided in product labeling.

Should labeling specifically state that ESAs are not indicated for use in the specific tumor types studied in trials that showed adverse safety signals?

This restriction would apply until adequate trials and subsequent data are reviewed by FDA. Tumor types that may be included would be breast cancer, head and neck cancer, and NSCLC.

Vote: Yes = 12 No = 5

The committee was concerned that the BEST results did not show clear evidence that ESAs should be used in breast cancer patients and that ESAs should be restricted to non-metastatic diseases with supplemental indications for solid tumors and myeloid diseases. The committee discussed further the regulatory actions in applying specific restrictions to the label.

3. Indicated Population: Definition of Anemia (baseline hemoglobin level)

RBC transfusions are generally given if hemoglobin is < 8 g/dL unless symptomatic, and RBC transfusions are rarely given when hemoglobin > 10 g/dL.

Should product labeling define a hemoglobin level in asymptomatic patients at which ESAs should be initiated?

Vote: Yes = 15 No = 2

The committee felt that the labeling should define a Hb level and re-emphasized the need for a dose reduction study expressing concerns with the 12 g/dl limit.

4. Recommended Dosing: Hemoglobin Level Triggering Dose Modifications or Suspension of Dosing

The current product labeling states that the dose of ESA should be titrated for each patient to achieve and maintain the lowest hemoglobin level sufficient to avoid the need for transfusion and not to exceed 12 g/dL (See Attachment).

Should dosing be titrated to avoid transfusions, generally aiming at a lower hemoglobin level, e.g., 9 or 10 g/dL?

Vote: Yes = 6 No = 11

The committee noted that there is not enough data to define a Hb level at which to avoid transfusions as the data is not currently available to support such a definition, although felt that the QOL data suggested that there was a higher QOL life score when Hb was restored to a 10 or 11 than the placebo group.

5. Recommended Dosing: Duration of Use

Studies of ESAs supporting approval were generally limited to a 12-16 week course of chemotherapy. FDA is concerned that even when the ESAs are initiated for treatment of chemotherapy-induced anemia, the ESA may be continued when patients are treated with subsequent, less myelosuppressive chemotherapy, including regimens that are unlikely to result in clinically significant rates of anemia.

Should product labeling recommend discontinuation of the ESA following completion of a chemotherapy regimen and re-evaluation of the degree of anemia with subsequent chemotherapy regimen(s)?

Vote: Yes = 16 No= 1

The committee felt that ESAs should be limited, but did not commit to or define or conceptualize a timeframe for a recommended course.

6. Professional/Patient Education

ESAs are indicated for the treatment of anemia in patients where anemia is due to the effect of concomitantly administered chemotherapy. A study examining the treatment of the anemia of cancer, Study 103, showed decreased survival in patients receiving ESAs who were not receiving concomitant chemotherapy. FDA is concerned that adequate attention is not currently directed at the distinction between these two groups (anemia due to concomitant chemotherapy vs. anemia unrelated to concomitant chemotherapy).

Please discuss how this distinction can be communicated to patients and physicians.

The committee felt that the current marketing and advertisements of the product are misleading and suggested that the company should reach out to advocacy groups and physicians to define a campaign which provides accurate knowledge to patients about ESAs and clarify the public assumption. The committee further suggested that patient education materials be forwarded to the American Cancer Society and the American Society of Clinical Oncologists listing the signs and symptoms of cancer related anemia and that FDA post on its website the same listing of cancer related anemia.

7. Additional Oncology Trials

During the May 2004 ODAC meeting, the committee recommended the following key elements for trials intended to assess the effects of ESAs on tumor promotion, survival, and TVE rates.

- Double Blind, Placebo-Controlled Trials
- Preferred Primary Endpoint: Survival
- Adequately powered trials to detect survival differences
- Routine Assessment of Tumor Progression
- Homogenous Tumor Type
- Tumor biopsies to assess for EPO receptors was optional
- Studies conducted outside of the US would be generalizable to the US cancer population
- The assessment of TVEs should be a prospectively defined endpoint.
  - Case report forms should be designed to capture clinically symptomatic TVEs.
  - TVEs should be assessed at pre-specified intervals.

Additional safety data has emerged since ODAC 2004. Please discuss trials needed to investigate these safety issues and identify barriers to timely accrual of these trials.

The consensus of the committee was that a placebo controlled trial be conducted, although felt that this would be difficult given the number of previous failures of the no-treatment controlled trials. The committee felt that dose reduction trial would be important to define the exposure burden and dose response relationship.