# Trends-in-Medicine

**May 2004**
*By Lynne Peterson*


# Quick Pulse




**Trends-in-Medicine**
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
**772-334-7409 Fax 772-334-0856**
**www.trends-in-medicine.com**


## FDA Oncologic Drugs Advisory Committee (ODAC) Meeting on the Safety of Erythropoietin in Oncology

Gaithersburg, MD
May 4, 2004

The purpose of this ODAC panel was to help the FDA figure out how to structure the clinical trials the agency feels are necessary to prove whether *all* erythropoietins (EPOs) affect mortality (decrease survival) in cancer patients. Two European large, randomized studies, one of which was reported in *The Lancet*, questioned the safety of two erythropoietins sold in Europe – Roche's NeoRecormon (epoetin beta) and Johnson & Johnson's Eprex (epoetin alpha). The studies, which were in cancer patients on chemotherapy ± EPO, showed that EPO was associated with:

- Shorter overall survival (OS)
- Shorter progression-free survival (PFS)
- Increased incidence of thrombotic/cardiovascular events

These studies raised questions about whether EPO actually promotes tumor growth. In addition, concerns have been raised about whether EPO increases the risk of thrombotic events. In September 2003, three placebo-controlled European clinical trials in oncology patients, in which one arm received EPO to target a higher hemoglobin, were terminated because of unexpected rates of thrombotic events in the EPO arms.

Neither Eprex nor NeoRecormon is sold in the U.S. However, the FDA has repeatedly emphasized that it considers all the erythropoietins to be similar.

There was no buzz about this ODAC meeting or the safety of EPO at the American Association for Cancer Research (AACR) conference in late March 2004. However, panel members said that the issue has been (a) debated at their institutions and (b) a topic of discussion by patients.

### Industry Perspective

#### Roche

Roche defended the safety of its NeoRecormon. An official said the apparent progression-free survival (PFS) advantage of placebo over NeoRecormon in a European trial was "unexpected, so additional analyses were performed." He claimed the trial findings were flawed because:

- There were more smokers in the NeoRecormon arm.
- There was some indication of a lack of robustness of the data.

- Some of the findings were contradictory, raising questions about the results.
- A pooled analysis found no survival issue with NeoRecormon.
- The divergence in survival curves did not occur until after six months.

**Safety of Roche's NeoRecormon**

| Measurement | Placebo + radiotherapy | NeoRecormon + radiotherapy |
|---|---|---|
| **NeoRecormon Study MF-4449 in Head & Neck Cancer** | | |
| Smokers | 53% | 66% |
| Patients with thromboembolic events | 3.5% | 5.6% |
| CV deaths * | 5 patients | 10 patients |
| **Pooled Analysis of NeoRecormon Studies (n=1,409)** | | |
| Overall survival | Essentially the same | |
| Thromboembolic events | 4% | 6% |

* all but one >100 days

## JOHNSON & JOHNSON

J&J also defended the safety of its Eprex, which is sold in the U.S. as Procrit, though Procrit is made at a different facility than Eprex. A combined analysis of 10 randomized, placebo-controlled clinical trials of 1,976 patients was reviewed, and the company found no diminution in survival with Eprex. In a metastatic breast cancer trial (INT-76) of 939 women, the survival curves diverged relatively early and by Month 4 the separation was near maximal and remained parallel out to Month 12.

J&J official said there was an early survival disadvantage in the Eprex group, but he pointed out that the greater number of deaths due to disease progression in the Eprex arm was contradicted by TTP and CR/PR rates that were similar. He concluded, "There is a modestly increased risk of TVEs with Eprex…Our data indicate a favorable risk:benefit…with no signal of tumor proliferation in the setting of supportive anemia care…When used beyond anemia treatment, adverse outcomes have been seen, but there is no clear signal of tumor proliferation."

**Pooled Safety Analysis of J&J's Eprex**

| Measurement | Placebo | Eprex |
|---|---|---|
| Deaths | 24% | 30% (p=0.012) |
| Died within 4 months | 3% | 9% |
| **Investigator Findings** | | |
| Death attributed to disease progression | 13% | 28% |
| Death attributed to chemotherapy toxicity | 1% | 3% |
| Death attributed to thrombotic vascular events | 1% | 5% |
| **Blinded Chart Review** | | |
| Death attributed to disease progression | 10% | 21% |
| New lesions | 36% | 30% |

J&J is planning a non-inferiority/superiority trial to answer the FDA's questions. This is a 2,000 patient, double-blind, placebo-controlled, randomized trial in metastatic breast cancer patients taking first-line taxane and/or anthracycline chemotherapy. The design of the trial is: Eprex QW vs. placebo until TTP, chemotherapy is stopped, or the patient dies. The target hemoglobin is 12 g/dL, and Eprex will be stopped if hemoglobin exceeds 13 g/dL. The primary endpoint is progression-free survival (PFS). It has 80% power to find a 15% reduction in PFS (assuming non-inferiority). If non-inferiority is shown, then a superiority analysis will be done, with 80% power to show a 15% advantage to Eprex.

However, this trial has several challenges, and a company official asked the ODAC panel for its input. Those challenges include:

- Crossover of placebo patients
- Tissue acquisition for correlative studies of Eprex receptors
- Chemotherapy regimen
- Analysis of TVEs

## AMGEN

Amgen tried to distance itself from this issue, emphasizing at great length the differences between Aranesp and the other erythropoietins. An expert noted that the Aranesp label reflects an increased risk of thrombotic events, and a review of 11 Aranesp trials (of 1,305 patients using the MedStat Claims database) also found an increased risk of thrombotic events with Aranesp. A speaker concluded, "No effect on tumor progression or survival has been observed in Aranesp oncology clinical trials."

**Safety of Aranesp**

| Measurement | Placebo | Aranesp |
|---|---|---|
| PFS in lung cancer patients | 145 events | 131 events |
| OS in lung cancer patients | 119 deaths | 100 deaths |
| PFS in lymphoid malignancies | 113 events | 120 events |
| OS in lymphoid malignancies | 61 deaths | 80 deaths |
| PFS in 4 pooled trials (16 week data) | 1.02 hazard ratio with Aranesp | |
| OS in 4 pooled trials | 1.02 hazard ratio with Aranesp | |

## THE FDA PRESENTATION

The FDA concern is that the safety issues with J&J's Eprex and Roche's NeoRecormon may also apply to U.S.-licensed products – Amgen's Aranesp and J&J's Procrit. In the European trials that raised concerns about the safety of EPO, Eprex and NeoRecormon used a treatment strategy to achieve hemoglobin ≥12 g/dL, which is higher than recommended in the label information for U.S.-licensed products. U.S. clinical trials for EPO products were not designed to assess the impact on response rate, TTP/PFS or OS. The FDA reviewer said, "The FDA considers **all** of these products to be members of the same product class. These evolving safety issues are assumed to apply to all products unless adequate and well-controlled trials demonstrate otherwise."
Following are the figures the FDA cited from U.S. as well as European trials that raise concerns about EPO use in cancer patients.

**Erythropoietin Safety**

| Study | Drug | Placebo |
|---|---|---|
| **Aranesp (Study 980297)** | | |
| Median PFS | 5 months | 4 months |
| Median survival | 10 months | 8 months |
| Overall mortality | 14% | 12% |
| CV/thrombotic events | 5% | 3% |
| **Procrit (Study 93-004)** | | |
| Response rate | 72% | 67% |
| Median survival | 10.5 months | 10.4 months |
| Overall mortality | 92% | 88% |
| CV events | 22% | 23% |
| CV events not including "chest pain" | 14% | 9.5% |
| CV events (FDA registration studies) | 3% | 12% |
| **NeoRecormon (Henke et al in *The Lancet*)** | | |
| Cardiac death | 5.5% | 3% |
| Hypertensions and other CV symptoms | 11% | 5% |
| Locoregional tumor progression | Favored placebo | |
| Median overall survival | 605 days | 928 days |
| **Eprex (Best Trial)** | | |
| CV events | 2.3% | 0.4% |
| Disease progression at 4 months | 6% | 3% |
| Mortality at 4 months | 8.7% | 3.4% |
| Estimated 12-month survival | 70% | 76% |

**Erythropoietin Effect Based on Hematocrit Level**

| Study | Normal hematocrit | High hematocrit |
|---|---|---|
| Death | 30% | 24% |
| Non-fatal MI | 3.1% | 2.3% |

**Hematocrit Level by Cancer Type**

| Primary cancer | Target HgB (g/dL) | TVE | |
|---|---|---|---|
| SCLC (n=106) | 14-16 | 34% Eprex | 6% Placebo |
| Cervical cancer (n=113) | 13-14 | 16% Procrit | 5% Placebo |
| Gastric or rectal cancer (n=60) | 14-15 | 24% Procrit | 6% Placebo |

## THE FUTURE

J&J and Amgen have multiple trials ongoing – in the U.S. and in Europe – which could answer the questions about the effect of EPO on survival, but two panel members interviewed after the session doubted that there will be a clear-cut answer from these trials. They described the company presentations as "polished," but said they will shed little light on the issue. Rather, they suspected that the data from the ongoing trials will just continue the debate. A third panel member said he expects the trials to show that there is a negative effect to EPO, but he believes the benefits of EPO will still outweigh the risks in appropriate patients.

There was no discussion of Roche's new erythropoietin, CERA (continuous erythropoiesis receptor activator), which is in Phase III trials in the U.S. However, after the ODAC meeting a senior FDA official said the agency would expect a new EPO to answer the question about any survival decrement. However, this official indicated that – "out of fairness" – the determination probably would not be required pre-marketing and most likely could be determined in a post-marketing study. Thus, any conclusions that this FDA panel has negative implications for Roche's CERA would probably be wrong.

## FDA QUESTIONS TO THE ODAC PANEL

**QUESTION 1A:** *Are placebo controlled trials feasible?* J&J and Amgen have agreed to additional studies but have indicated that it may not be feasible to conduct placebo-controlled trials in the U.S. because of concerns regarding exposure of patients in the control arm to the potential risks of blood transfusions**. Is it reasonable to request that placebo-controlled trials be conducted to assess the risks of – or rule out – a negative effect of erythropoietin products on TTP and survival?**

**Chair summary: YES.** "My feeling is that we all feel it is not only reasonable but probably essential."

**QUESTION 1B:** *Can trials be done in the U.S.?* If there are countries where placebo-controlled trials are feasible, based on a difference in interpretation of the risk by the non-U.S.

medical community**, does the committee believe that results of such studies conducted outside the U.S. should be generalized to the U.S. cancer population?**

**Chair summary: YES.** It might be difficult, but the trials are accruing, and hopefully they will succeed. Trials should be done and should be done on both sides of the ocean – and hopefully with alacrity.

**QUESTION 1C:** *How should trials be designed?* What factors should be considered in the design of trials intended to assess the safety of erythropoietin products in cancer patients? Does the committee recommend more than one clinical trial?

**Chair summary:** "My feeling is that we first want a level of comfort at the indicated dose of the drug, that it is safe and effective. If there are questions, such as higher doses in head & neck cancer, then those are investigational doses that can be explored separately…Multiple trials are going on, and if there are concerns about specifics of the trials, we will go over them (the protocols with FDA staff) in our specific areas of expertise."

**QUESTION 2:** *Can EPO-R status be done?* Does the committee feel that EPO-R status data will be of value to the investigation of a possible connection between tumor stimulation and erythropoietin product use?

**Chair summary: NO.** The panel did not feel that EPO-R testing is feasible at this time. "It is difficult and may not be totally relevant. This is a nice idea, but it is not doable at this point in time."

**QUESTION 3:** Discuss the specific cardiovascular (CV) and thrombotic events that are clinically important and should be targeted for data collection in order to assess the relative risks of such events associated with erythropoietin use.

**Chair summary (paraphrased):** Patients in the clinical trials do not need to – and shouldn't – be screened for CV events prior to entry, but a careful history of each patient should be taken. Specific CV events do not need to be endpoints in the trials, but patients do need to be monitored for DVT, pulmonary embolism, MI, arterial thrombosis, and cerebrovascular accidents.

♦