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by D. Woods

SUMMARY

The FDA's Oncologic Drugs Advisory Committee recommended the Agency:

- Restrict the label even further for anemia drugs.
- Require additional safety trials for already approved products.
- Define a hemoglobin level in asymptomatic patients in which ESAs should be initiated.
- Restrict ESA use in certain tumors.
- Not require dose titration.

The FDA's Cardio-Renal Advisory Committee will meet in the fall to consider use of ESAs in renal patients.

Shortly after the panel meeting, and partly in reaction to it, CMS announced initiation of a National Coverage Decision that will reduce and limit reimbursement for these drugs in cancer patients.

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Advisory Committee Recommends New Studies, Tougher Labeling for Anemia Drugs

Silver Spring, MD
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The FDA's Oncologic Drugs Advisory Committee (ODAC), citing concerns about safety, voted 15-2 that the FDA should impose additional restrictions on use of erythropoiesis-stimulating agents (ESAs). The panel also voted unanimously that additional safety trials are needed. In March 2007, the FDA issued a warning after learning of some dangerous side effects with ESAs, including heart attacks and strokes, but the panel thought more needed to be done. Panel members expressed dismay at the dearth of valid data from any trials and expressed concern at the evidence that showed ESAs decrease survival and, in fact, may promote tumor growth. One medical oncologist asked if ESAs are "Miracle Gro for tumors."

ESAs – epoetin alfa (manufactured by Amgen, and marketed by Amgen as Epogen and by Johnson & Johnson as Procrit/Eprex) and darbepoetin alfa (Amgen's Aranesp) – are approved to treat anemia in patients with chronic kidney failure and in cancer patients whose anemia is caused by chemotherapy. Epogen and Procrit are also approved for patients scheduled for major surgery to reduce potential blood transfusions and for the treatment of anemia for certain HIV patients. These drugs are widely used off-label to treat patients with anemia of cancer not on chemotherapy and patients with chronic kidney disease not on dialysis. ODAC focused only on the use of ESAs for cancer patients receiving chemotherapy. The FDA's Cardio-Renal advisory committee will meet in early autumn on ESAs in patients with chronic renal failure.

Talking to reporters after the panel meeting, Dr. Richard Pazdur, director of the FDA's Office of Oncology Drug Products in the Center for Drug Evaluation and Research (CDER), said, "There will have to be more studies, study designs, to look at different targets, perhaps a placebo-controlled study. This is a major issue. There is considerable need for more data in the use of these products…Our concerns for safety have to be addressed."

Amgen and J&J tried to make the case that their ESAs are safe and effective, but the effort failed. One panel member called the companies' presentations "sleight of hand." Another asked, "The burning question is, does this actually kill people in the doses that you think are reasonable and appropriate? And I haven't seen anything that has an answer. I'd put a stop to all the trials that use higher doses than the recommended doses." Other panel members questioned the validity of Amgen's and J&J's study designs and results. The FDA staff told the panel that, of the few studies that were acceptable for analysis, it appeared that ESAs actually shorten outcome survival rates and increase tumor production.

The panel, while strongly insisting that more safety studies are needed, was uncertain as to what exactly should be studied.

- **Voted 12 to 5** that labeling should specifically state that ESAs are not indicated for use in specific tumor types, but left to a future meeting which types, which may include breast cancer, head and neck cancer, and non-small cell lung cancer (NSCLC).
- **Voted 15 to 2** that product labeling should define a hemoglobin (Hb) level in asymptomatic patients at which ESAs should be initiated, but did not specify the level.
- **Voted 12 to 5** against the idea that dosing should be titrated to avoid transfusions, generally aiming at a lower hemoglobin level, leaving that thorny question to future panels.
- **Voted 16 to 1** to recommend that labeling recommend discontinuation of the ESA following completion of a chemotherapy regimen.
- Agreed that there should be more patient/doctor education on adverse effects of ESAs.
- Generally agreed that a placebo-controlled ESA trial would be a good idea but difficult to implement.

Asked what the panel recommendations mean for other companies currently in clinical trials or planning trials, Dr. Pazdur said, "There have to be more studies, and the study designs look at different targets, perhaps against a placebo. This is a major issue, and there is considerable need for more data in the use of these products…It is important for us to carefully look at (safety) signals and not just ascribe (ESAs) to different diseases or populations…We're not talking about taking the drug off the market. What we're talking about is further discussion...to define the population." On May 18, 2007, just over a week after the panel, the FDA gave Roche an approvable letter for its anemia drug, Mircera (CERA). Roche indicated that it doesn't need to do any additional trials but that labeling cannot be finalized until after the fall Cardio-Renal panel on ESAs.

At the panel, Amgen and J&J presented a great amount of data from studies that the FDA staff said were faulty and unacceptable. Members of the panel often appeared frustrated when they would ask a question, only to have it deflected. For example, a panel member asked Amgen about a study that the company had called "extremely reassuring." However, after several more questions, the company admitted that the study, which was designed to show superiority, failed to do that.

Dr. Pazdur set the tone for the ODAC meeting, saying, "Studies to date have failed to demonstrate improved survival or improved tumor control (in cancer patients) with ESAs… The latest safety data…point to important risks that include increased cardiovascular (CV) events, decreased survival and increased tumor promotion…The use of ESAs in a risk:benefit analysis must be weighed against the decreasing risk of red cell transfusion…The FDA will look at trials conducted after the approval of ESAs. Many of these trials were conducted outside of the U.S., and we don't have access to the data for some of these trials for review. This situation is different from the usual pivotal studies presented here where the FDA has access to the trials' primary data, conducts its own analysis, and is able to directly verify."

CMS to Limit Coverage of ESAs

Just four days after the ODAC meeting, the Centers for Medicare and Medicaid Services (CMS), in a directly related move, announced that it was planning to limit coverage of ESAs for patients with cancer and related neoplastic conditions. CMS plans to issue a National Coverage Decision (NCD), proposing limits on dose and duration of therapy and setting a baseline. Public comments on the NCD will be accepted until June 13, 2007. Leslie Norwalk, acting CMS administrator, said, "We have carefully examined the evidence surrounding these labeling changes and have issued this proposed decision to protect our beneficiaries." The decision does not affect the use of ESAs in patients with kidney disease – for now – but CMS is watching that space, too.

The proposed ESA oncology limitations are:

- Hb immediately prior to initiation of dosing for the month should be <9 g/dL in patients without known cardiovascular disease and <10 g/dL in patients with documented symptomatic ischemic disease who cannot be treated with a blood transfusion.
- The maximum covered treatment duration would be 12 weeks per year.
- The maximum covered four-week treatment dose would be 126,000 units for Epogen and Procrit and 630 µg for Aranesp.
- Continued use of an ESA would not be considered reasonable and necessary if there is evidence of poor drug response (Hb rise of <1 g/dL) after four weeks of treatment.
- Continued administration of the drug would not be considered reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after two weeks of treatment.
- Continued administration of the drug would not be considered reasonable and necessary if there is a rapid rise in Hb >1 g/dL after two weeks of treatment.

CMS plans to allow payment for ESAs in certain cancers for which it believes the evidence supports use, including (but not limited to): sarcoma, neurologic, breast, cervical, colorectal, gastric, melanoma, head-and-neck (squamous cell), hepatic, lung, multiple myeloma, muscle (including cardiac), ovarian, pancreatic, prostate, retinal, and uterine cancer. However, CMS is proposing to stop covering ESA treatment for:

- Anemia in:
  - Myelodysplasia syndrome (MDS).

- Myeloid cancers.
- Cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, hemolysis, iron deficiency, bleeding, or bone marrow fibrosis.
- Treatment of myeloid cancers or erythroid cancers.
- Cancer not related to the cancer treatment.
- Radiotherapy.

➢ Prophylactic use to:
- Prevent chemotherapy-induced anemia.
- Reduce tumor hypoxia.

➢ Patients with:
- Erythropoietin-type resistance due to neutralizing antibodies.
- Treatment regimens including anti-angiogenic drugs such as Genentech's Avastin (bevacizumab).
- Treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor receptor (EGFR).
- Uncontrolled hypertension who have anemia due to cancer treatment.
- Thrombotic episodes related to malignancy.

INDUSTRY PERSPECTIVE

Amgen and J&J officials claimed that ESAs are safe and effective and that the benefits outweigh the risks when administered according to the label and to the indicated patient population. They also insisted that the risks are adequately addressed on the label. Amgen officials said that recent trials show a "reassuring pattern of overall survival."

Amgen officials said that the two studies which recently raised concerns about ESA safety (20010103 and DAHANCA-10) were conducted in off-label patient populations. An official said, "Those findings have been appropriately communicated and are incorporated in the product label for all ESAs in the form of a boxed warning. Thus, the current labeling…adequately reflects the identified potential risks...in these non-indicated populations."

Amgen and J&J officials said they made their own analysis of preclinical and clinical safety data, which supports the use of ESAs as indicated. They told the panel:

- Preclinical data are reassuring with regard to the effect of ESAs on tumor progression and overall survival.
- Clinical data continue to indicate that ESAs are associated with an increased risk of venous thromboembolism. This risk has been adequately quantified and is reflected in the product labels.
- Data, when used in the setting of chemotherapy-induced anemia (CIA), show a neutral effect on overall survival and tumor progression while demonstrating clear benefit in terms of reducing the need for blood transfusion.
- Four studies showed a significant adverse effect on overall survival with ESA use in cancer. All of these address experimental, unapproved indications.
- Only the 20010103 study and DAHANCA-10 are new studies since the 2004 ODAC meeting on ESAs. In the same interval, four other new studies have shown neutral effects on survival.
- In CIA, the data presented in 2004 concerning tumor progression and survival have become more extensive and robust. ESAs do not appear to increase these risks in patients within this approved indication.
- ESAs should not be used outside of the experimental setting to treat anemia associated only with active malignancy in patients who have exhausted other options, or as a strategy aimed at hyperoxic radiosensitization.
- Evidence supports the continued use of ESAs in CIA on label. Ongoing pharmacovigilance studies will further inform the risk:benefit assessment in the near future.

Dr. Roger Perlmutter, Amgen's executive vice president for R&D, asked the panel, "Why are we here? We're here to look at new data since the 2004 ODAC meeting. Since that time 36 randomized, controlled ESA studies in oncology have been completed, for a total of 55 studies. These studies – all of which looked at doses and populations beyond the approved labels – have raised additional concerns…Amgen has vigorously pursued pharmacovigilance studies…Those studies have gone forward, and 3,500 patients have been enrolled in these studies."

Dr. Perlmutter concluded:

- The benefits of ESAs in the indication – chemotherapy-induced anemia – are substantial and unambiguous.
- ESAs have no demonstrable effect on overall survival or tumor progression when used according to the FDA label.
- Recent updates provide prominent warning of important safety concerns, which are well known to the oncology community.
- Amgen and J&J are both committed to the continued assessment of the benefits and risks of ESA therapy.
- ESA risks in CIA are "well-characterized at the recommended dose and are supported by the totality of data. Data from studies spanning a range of Hb targets demonstrate no adverse effect of ESAs on overall survival or tumor progression…Amgen and J&J do not advocate targeting Hb >12 g/dL, and recent label updates provide prominent warning of risks associated with ESA use."

Responding to complaints that the FDA has not received data in a timely manner, Dr. Perlmutter insisted that Amgen has been forthcoming, "As soon as we received the data from the 103 study and 145 study, we made the datasets available to the FDA, provided Dear Health Care Provider letters, we posted

summary data on **www.clinicaltrials.gov**, and sent out our professional reps specifically to inform physicians about the new label changes – and that has been the only activity they've been engaged in. We've worked very hard to inform physicians about these risks as they've become known to us …Continuing data will be available within the next 12 months re: pharmacovigilance trials. One way to do this is to take patient-level data and make them available for independent evaluation. We'd like to get other sponsors with ESAs to participate. There are some open questions that could be addressed in future studies. I think one question is the use of ESAs in the anemia cancer setting and in different populations with anemia that is secondary to malignancy but not chemotherapy. Clearly, head and neck cancer is one area… And, lastly, (with respect to) risk management strategies for thrombotic vascular events (TVEs), it's plain there is an increased risk, and although there is no augmented risk specific to cancer patients, this is something we can look at."

Dr. Jeffrey Crawford of Duke Comprehensive Cancer Center made the case for the benefits of ESAs, saying that 90% of cancer patients develop anemia, and 40%-60% of anemic patients require a red blood cell (RBC) transfusion in the absence of an ESA. He said that transfusions have well-recognized dangers, including infections, volume overload, acute and delayed reactions, allo-immunization, iron overload, and suggestions of adverse cancer-related outcomes. Other considerations include demand on the national blood supply, which he claimed would intensify, and the use of transfusions to maintain Hb at a level necessary to minimize the signs and symptoms of anemia. He added that there is at least a 50% reduction in RBC transfusions when ESAs are used.

Dr. Roy Baynes, vice president of Amgen global clinical development for oncology, told the panel that the benefits of ESAs outweigh the risks. Looking at Amgen Study 145, he concluded:

- Aranesp maintained Hb and significantly reduced RBC transfusions.
- Superiority was not achieved but no difference in overall survival was observed.
- Increased thromboembolic events were observed with Aranesp, as expected in this population.

As for tumor progression, Dr. Baynes said that a review of all CIA studies with ESAs evaluating tumor progression and related endpoints showed 8 controlled CIA studies with ESAs have evaluated response to chemotherapy and tumor progression, and none reported significantly worse outcomes with an ESA. He concluded:

- ESAs are effective in reducing transfusions and avoiding symptoms and signs of anemia.
- Overall survival is neutral for ESAs in CIA – even at Hb targets above the labeled ceiling.
- ESAs do not promote tumor growth or progression in CIA.
- ESAs are associated with well-quantified and well-described increased risk of thromboembolism.

Looking at anemia of cancer, Dr. Baynes said that randomized clinical trial (RCT) data in broad anemia of cancer populations suggested a favorable risk:benefit profile. However, studies suggesting safety concerns were:

- The Wright study, or EPO-CAN-20 study, which was discussed in 2004.
- DA Study 103 (conducted in anemia of cancer patients) was a specific subset of anemia cancer patients. DA Study 103 looked at 989 patients with active cancer not receiving or planning to receive chemotherapy/radiotherapy. He said stratification was with the transfusion endpoint in mind.
- No one has seen the final data from the DAHANCA-10 study.

In terms of assessment of risk and in terms of overall survival, he said:

- No adverse effect has been observed with ESAs on overall survival.
- No adverse effect on tumor progression has been observed with ESAs (the preclinical data do not support a role for EPO).
- CV/thromboembolic events. In cancer patients, the risk is increased 4-10-fold and exacerbated by multiple modalities. TVEs are a well-established risk of ESA treatment.

Dr. Alex Zukiwski of Johnson & Johnson reiterated the companies' claims that Epogen/Procrit is safe and effective, has a favorable risk:benefit profile, with no discernable effect on tumor growth and overall survival. He said the TVE risk is known and reflected in the label and that no new noticeable adverse effects have been observed in the ongoing Phase IV commitment study.

FDA Perspective

Dr. Vinni Juneja of the FDA's Division of Biologic Oncology Products expressed the FDA's dissatisfaction with the amount and quality of data presented to the FDA on safety since 2004. He said that no trials have shown improved survival or tumor outcome with ESAs. In fact, the weight of the evidence shows that ESA use results in shortened survival outcome and increased risk. He cited these concerns:

- No completed or ongoing trial has addressed safety issues of ESAs in cancer patients without chemotherapy-associated anemia using currently approved dosing regimens in a generalizable tumor type.

- ESAs do not increase survival and may increase tumor growth.
- Post-approval studies: lower OS, decreased locoregional control, increased TVE risk.
- Efficacy of ESAs; lower RBC transfusions.
- Since 1993: decreased RBC transfusion infection risk vs. increased ESA risk.
- Reconsideration of risk:benefit ratio of ESAs.

Dr. Juneja said, "We asked the question: Have any ongoing trials at or since 2004 fully met the committee's recommendations? The answer unfortunately is no. Two trials have come close. They have met a number of ODAC 2004 recommendations, but neither has fully met all of the recommendations. Other trial designs have not met ODAC's recommendations. The two trials that have come close are Amgen's SCLC study and J&J's breast cancer study."

- The **Amgen SCLC study** results failed to demonstrate superior overall survival. Overall survival was 95%, with a hazard ratio of 0.93. There were increased TVEs in the Aranesp arm vs. placebo (12.3% vs. 7.4%).
- The **J&J Breast Cancer trial** involved 108 out of a planned 1,000 patients. Dr. Juneja said, "J&J updated that number (the day of the panel meeting). This was a non-inferiority trial on PFS (progression-free survival). It is the only cancer trial using ESAs that has routine thrombovascular event assessment. The design was presented at the previous ODAC…By reducing the size of the trial, it reduces the power. Also, accrual has been slow; the final protocol was submitted in December 2004, and enrollment began March 2006. As of March 2006, 108 out of a target 1,000 patients were accrued."

Dr. Juneja described the five studies with evidence of increased tumor production or decreased survival, with excessive target Hb: BEST, ENHANCE, DAHANCA, 161, and CAN-20. There was one study (103) with evidence of decreased survival with target Hb consistent with prior label (<13 g/dL). Out of 12 studies presented at ODAC 2004 as capable of addressing ESA tumor promotion risks, 10 are not adequately designed with respect to ODAC's 2004 recommendations. Primary data from five completed studies with no reported safety signals were not submitted to the FDA, and they finished accrual as long as six years ago.

Other points FDA staff made included:

- **The FDA considers all ESAs as members of the same product class, and the risks of ESAs apply to all products.**
- Studies supporting labeling expansion for Procrit and Aranesp "were not designed to assess for the impact of ESAs on survival or on tumor promotion."
- The five randomized clinical trials (BEST, ENHANCE, 20010103, 20000161, and EPO-CAN-20) demonstrated decreased survival times in cancer patients receiving ESAs compared with patients receiving transfusion. ENHANCE, BEST, and SE 2002-9001 DAHANCA showed poor tumor outcomes in ESA patients compared with transfusion patients. With the exception of one study of anemic cancer patients who were not receiving concurrent chemotherapy, the studies showed detrimental effects on survival/tumor outcomes. Contrary to what the companies said, the FDA staff said there are insufficient data to characterize effects of ESAs on survival or tumor promotion when ESAs are administered in accordance with recommended dosing in product label. The staff also said the increased risk of TVEs in patients receiving ESAs is "evident in multiple studies and across varied clinical settings." However, while an increase in the number of TVEs increases morbidity and likely increases mortality, their "detrimental effects on survival in patients receiving ESAs cannot be attributed solely to the higher rate of TVEs nor to the poor tumor outcomes."

Summary of post-ODAC 2004 trials with decreased survival or increased tumor production:

- **Anemia of cancer (variety of tumors):** Decreased overall survival (OS) with an ESA.
- **Lymphoid cancer (161 study):** Decreased overall survival with an ESA.
- **DAHANCA (head/neck cancer):** Decreased locoregional control with an ESA and a trend to decreased overall survival with an ESA.
- **EPO-CAN-20 (NSCLC):** Decreased OS with an ESA.

Nine completed or ongoing studies had no safety signals but had "significant design limitations," according to Dr. Juneja. Only one of the nine had primary data submitted to the FDA. One had primary data submitted, but the data was not analyzable. Seven of the nine provided summary results only.

Dr. Juneja referred to Amgen's meta-analyses, and listed the reasons why they are not acceptable when looking at safety signals. He said that only three of the 12 ongoing/proposed trials at ODAC 2004 are capable of addressing safety concerns of ESAs. Only one of the studies, EPO-ANE-3010, is "adequately" designed, though it has significant difficulties accruing patients. He said the collective evidence shows:

- 6 studies have demonstrated inferior overall survival, PFS, or locoregional control for the ESA-containing arm.
- No studies that the FDA has knowledge of has demonstrated superior overall survival or PFS for an ESA-containing arm.

PUBLIC HEARING

Four public speakers argued against ESAs and four argued for keeping ESA use status quo. Those generally speaking for continued use of ESAs as is were: a community oncologist who said that there is a 13-day wait for transfusions at his hospital, two people representing Myelodysplastic Syndromes (MDS) organizations who said that some in their particular patient population benefit greatly from ESAs, and a doctor who said that ESAs reduce transfusions and the need for blood. Speaking against ESAs and the companies that make them were three women with breast cancer and one consumer representative who said that company greed outweighs patient safety. One other speaker didn't really speak for or against ESAs, simply asking the panel for balance.

Balanced View

Robert Erwin of the Marti Nelson Cancer Foundation told the panel that he thinks the decreasing use of ESAs is reimbursement-driven. He asked the panel about meta-analyses data that suggest there are quality of life benefits.

Pro-ESAs

➢ **Dr. Samuel Silver, a hematologist/oncologist at the University of Michigan and chair of the reimbursement subcommittee of the American Society of Hematology (ASH)**, told the panel, "ESAs help decrease the need for transfusions and lessen the strain on the nation's blood supply." However, he added that ASH believes additional high quality trials are needed to assess the impact of ESAs.

He told the panel that ASH is updating its guidelines and will be willing to share information later this summer. He posed several questions – and offered ASH answers to those questions:

1. *Does the available data merit action for patients with hematologic deficiencies?* The recent black box warning cautions physicians that there is an increased risk of death …This warning was based on a study of patients with anemia of cancer who are not receiving active anti-cancer treatment.
2. *Should an appropriate period of time be considered under the umbrella of chemotherapy treatment?* ASH recommended that ESAs be used in chemotherapy-related anemia. ASH recommended that ESAs be continued for treatment of anemia for 90 days post-chemotherapy. If anemia persists, reevaluate.
3. *What about patients with low risk myelodysplasia?* In patients with anemia associated with low risk myeloma, multiple studies have demonstrated the effectiveness of ESAs to decrease the need for transfusions, and here the transfusions are more chronic.
4. *What are the treatment recommendations?* ESAs should be started in appropriate clinical settings at Hb ≤10 g/dL. That is not a trigger, but there may be extenuating circumstances when treating patients with comorbidities that could justify the use of ESAs before the Hb has decreased to 10. ESA should not be continued after eight weeks in the absence of response (a rise in Hb of 1 g/dL).

➢ **Dr. Steven Gore, an oncologist from Johns Hopkins was representing the Myelodysplastic Syndromes Foundation**. He disclosed that he signed an agreement with J&J to do a future trial of ESAs on MDS patients. He told the panel that ESAs are safe and effective for MDS patients, "While applauding the FDA's recent actions, we are concerned that MDS patients are becoming collateral damage. Current restrictions, we believe, are safe and effective. ESAs positively impact the quality of life…Anemia has a significant effect on MDS patients, including fatigue and lowered quality of life."

He pointed out that ESAs have been studied for more than 10 years, "Although it's quite clear the trials (have problems) and few have been randomized, there has been no evidence…to show an increased risk of thrombosis or death in this population." He also claimed there is some evidence to show ***increased*** survival in some MDS patients on ESAs.

Dr. Gore said that MDS patients can be selected for appropriateness of ESA therapy, and that patients who have the best chance of responding are those with a lower transfusion burden, "ESAs provide important palliation of anemia in a significant subset of MDS patients, who are burdened with chronic transfusions. MDS patients tolerate ESAs very well."

➢ **John Theriault of the Aplastic Anemia and MDS International Foundation**, said that his father, who was diagnosed with a bone marrow failure disease, has benefited from the careful administration of ESAs and wishes to continue doing so, "We are here because we are interested in the continued use of ESAs. Many of our members have benefited from ESAs. Medicare covers this off-label use because of practice supported by research. The most common sign/symptom of patients with MDS is anemia. Concern is warranted and appropriate, but these studies haven't included patients with bone marrow diseases such as MDS. In these studies, the patients' hemoglobin levels were typically kept above 12 g/dL. Findings from these studies can't be applied to patients with MDS. The adverse events are not likely to be relevant to patients with bone marrow diseases."

➢ **Dr. Roy Beverage, an oncologist and U.S. Oncology's medical director**, told the panel that he is concerned with the safety signal that the current studies have shown, and he supports a reexamination of the evidence supporting the use of the drugs, but he warned, "We shouldn't turn back the clock… We are all aware of the societal costs of ESAs and strongly support oncology guidelines for use of the products. We, as community oncologists, distinguish anemia of cancer and chemotherapy-induced anemia as two fundamentally different things…I believe that patients are well-versed in risk vs.

benefit…I think oncologists generally do the exact same thing with supportive drugs."

He also commented on the data presented to the panel earlier in the day: "In terms of a Hb cutoff of 7 to 8, remember the studies quoted were primarily in patients in the ICU and on the floor. As a medical oncologist, I'm treating patients who are your neighbors, friends, co-workers, who have kids…This is a fundamentally different population than those in the ICU (intensive care unit). There's no question that ESAs reduce the transfusion requirement, and I want to strongly emphasize that those of us who care for patients strongly believe the quality of life is improved when the drug is used appropriately. Resorting to transfusion in this cancer population is very problematic in today's world. There are the obvious safety issues, there is the taxing of the limited supply of blood that we have, and there is the taxing of the delivery system. I was at Fairfax Hospital (before the panel meeting), and the soonest we could schedule a transfusion is 13 days from now …In today's world, we have very good chemotherapy for a lot of things, but the associative toxicity is similarly greater. The need for supportive drugs is larger now…Medical oncologists would ask the committee to remember what it was like 20 years ago and not turn the clock back."

Anti-ESAs

➢ **Maryann Napoli of the Center for Medical Consumers** in New York said that ESAs have been oversold to the public by advertising campaigns, "Most of us first learned of the drugs while watching the Evening News. Those ubiquitous Procrit ads all have the same scenario…Who of us with cancer wouldn't ask our doctor for the drug? There is a drug that quickly cures chemo-induced fatigue…Why did the FDA allow those Procrit ads? The newly identified risk of anemia drugs and the circumstances in which they're likely to occur are simply too complicated for many TV and medical reporters. They'd have to explain the off-label use and how anemia can be caused by chemotherapy or the cancer itself… Given what we know about the increase in deaths, heart damage, and deep vein clots, the FDA should force J&J to run an ad campaign with the same demographics as the Evening News."

Napoli also was critical of "overzealous" physicians, "The huge expense and range of prices of these drugs are troubling. Then, there are the deep discounts offered to oncologists. It's likely these discounts fuel the inappropriate use of anemia drugs. These deep discounts achieve just what the drug companies wanted; they increase the use of the costliest drugs …Oncologists are running their own pharmacies. Consumers would naturally be suspicious of an herbalist selling his own herbal medicine or the vitamin doctor selling vitamins out of her own office. Things are far worse at the oncologist's office."

She urged the FDA to act, "Fifteen years after the drugs went on the market, we learn they can hasten death and cause severe injury. Why did it take so long to know this? The FDA should be given the power to require better safety studies in the pre-approval process and be able to exact a large penalty on any company that fails to comply with recommendations such as those made by the ODAC committee in 2004."

➢ **Carolina Hinestrosa, executive vice president of the National Breast Cancer Coalition** and a breast cancer survivor, said, "We want to make sure patients aren't harmed and don't get costly treatment they don't need. Consumers trust the system to offer interventions…Randomized trials are the gold standard…The (FDA warning) action (in March) was welcomed. It is a case in point of a system that allows the interests of stakeholders. Over the decades, we've witnessed a philosophy in cancer care where more is better. We've had toxic treatment after toxic treatment to achieve mildly better outcomes at best…It is not about selling more drugs or getting them approved faster or starting startup companies, it is about saving the lives of people. ESAs were first approved in cancer to meet a medical need – to lower the risk of transfusions. At that time, the FDA raised concerns about their potential to promote tumor growth…Now, we know that off-label use can promote death. It is up to the FDA to fix the problem; it must do its part to require high quality data…and assure the public that it is looking after their best interests…Do the risks outweigh the benefits? After 10 years, the risks of ESAs – at an approved dose – have not been characterized. It isn't acceptable that primary data haven't been submitted to the FDA and, in some cases, not even to the manufacturers. The May 2004 ODAC panel made specific requests. How come we have no answers?"

➢ **Lilla Romeo, who has recurring breast cancer**, said she would not be speaking at the panel if not for modern drugs, "Over the course of seven years of treatments with only one short chemo vacation, I've had many doses of Procrit and Aranesp. The news (of possible dangers) has caused me considerable worry, and I am not alone. The issue has raised fears in all of us who have used and continue to use these medications. I was told I'd have to use these drugs if my Hb count dropped below 10. I was assured that they were safe. I now know that that advice was questionable. Was I put at greater risk? Did the drugs cause tumor growth? How did they know that 10 was the magic number? Should I have been treated at 8? Like most lay people, I assumed all this had been established in clinical trials. I assumed survival had been studied in those trials…not that tumor aggression would have been dismissed before the drug (was marketed). I remain troubled about the lack of transparency…I understand now the financial incentives for the doctor and company to prescribe them at higher doses and off-label. Dosage ambiguity becomes a major risk to patients…We may be metastatic, but that's not a reason to experiment on us. In the case of EPOs, many people were distressed that Amgen delayed the results of the now well known Danish study. Was the delay due to the fear of seeing its stock price fall?…Many of us were saddened to see the ads from Procrit. Were they science-based or simply fantasy? As far as I know, there is no energy change in

patients on these drugs, yet we see grandparents in the commercials swinging children, living energetic lives…False hope is both insulting and cruel. Even critically ill patients deserve honesty along with hope…I understand the revenues of EPO drugs reached 10 billion last year, but wouldn't it be nice occasionally to hear drug companies helping people with safe, effective, and evidence-based medicine instead?"

➢ **Loretta M, a member of the Metastatic Breast Cancer Network in New York and founder of the South Jersey Breast Cancer Coalition**, talked about the Procrit ads, saying "Sales of these drugs have skyrocketed…because they make chemotherapy look easy and promising…Cancer is big business…The drugs are being marketed to consumers directly …but are they safe?...What don't we know? We don't know if fewer patients are receiving transfusions…What happens to the tumor and to the cancer patient using these drugs?"

PANEL DISCUSSION

Questions focused on quality of life, primary endpoints, amount of usable data received, study design, breast cancer patients, and TVE risks. Panel members expressed skepticism about current studies and safety. It seemed that the companies' answers to several questions did not inspire much confidence, as the companies ducked and bobbed around questions.

Before voting, the chair summarized the discussion: "Many of us on the committee had a lot of questions about trial design, specifically some of the endpoints that were utilized, accessibility of data, and many questions as to why data haven't been available to scrutinize. Many of us are confused about quality of life, fatigue, and patient outcomes data and why that wasn't part of the label. It's interesting that the data would have not been available or at least to the level to reach those kinds of conclusions. Many of us see marketing to be revolving around that (patient reported data). There is little known about the dosing of the agent, and I didn't hear much about why the doses utilized were quite a bit higher than what was on the label."

Too much advertising?

Some panel members complained about TV ads touting ESAs as ways to increase energy and well-being. The FDA's Dr. Pazdur said, "There is a lot of concern (about the advertisements)…We are looking into the issue of why these ads were allowed to go on, and the FDA is responsible for giving the American public the reason why."

Why no quality of life indication?

Dr. Kathy Albain, a medical oncologist, asked about Phase II trial endpoints (quality of life) that led to the embracing of ESAs. A J&J official said there is a body of evidence showing improved patient-reported outcomes from controlled, clinical studies in CIA, and he discussed the INT-10 trial, which he said showed significant improvement in cancer-related fatigue, ability to perform daily activities, and energy level. The discussion focused on the study's methodology, and panel members raised questions about the study's validity. The J&J official said that there are two meta-analyses that have looked at patient-reported outcomes, and both concluded that, despite limitations with the instruments, there was an overall positive effect with ESAs.

Dr. Silvana Martino, director of the Breast Cancer Program at the Angelis Clinic and Research Institute in Santa Monica CA, asked, "Why don't we have quality of life as one of the approved values of this therapy? Is it because nothing has been brought forth? What is the issue?" An FDA official said that it had to do with presentation of data and the study designs, and she didn't think quality of life could have been interpreted in a heterogeneous population as in the INT-10 trial.

Study designs and results

Dr. Anthony Murgo of the National Cancer Institute (NCI) asked Amgen about Study 103's baseline characteristics. He noted a difference in sample sizes in the study and asked for an explanation. He also wanted to know if there were patients who were randomized but who didn't receive treatment. An Amgen speaker said "It was a pre-specified alteration in randomization after hitting a pre-specified transfusion point that was prospectively defined."

Dr. Michael Perry, an oncologist from the University of Missouri, wanted to know how a trial would be designed to pick up TVEs, "What is an ideal design to do that? Are we talking about angiograms every six months? I look at the list included under TVEs, and I'd like some definition of what you think is important and how the companies should prospectively look at them." The FDA's Dr. Juneja responded: "One study specifically asked patients for clinical signs and symptoms related to TE (thromboembolic) events on a regular scale, and that has not been a component of these other studies presented."

Helen Schiff, the patient representative on the panel, asked about the results of the BEST trial. A J&J official said, "This is a review of the BEST study conducted outside the U.S. by a company in a patient population of women with metastatic breast cancer. The primary endpoint was 12-month survival. There is a difference at the 12-month survival point; 115 subjects in the placebo group had died whereas 148 women in the EPO treated group had died. Survival was 1.37 favoring the placebo group patients. We continued to follow the subjects enrolled in INT-76. Although the curves had separated and reached maximal separation by four months after drug treatment started, they continued parallel until 12 months where they started to converge and from that point forward are super-imposable." The J&J official said the survival curves converged after the patients stopped their EPO.

This exchange was interesting:

- *Dr. Otis Brawley, a professor of hematology, oncology, and epidemiology at Grady Memorial Hospital in Georgia:* "What was the hypothesis (in study 145)?"
- *Amgen:* "It was designed to show superiority."
- *Panel member:* "But it did not show superiority."
- *Amgen:* "That is correct."
- *Dr. Brawley:* "Is it fair to say it did not show a decrease in survival?"
- *Amgen:* "The 145 was a superiority trial…The fact that a trial designed to show superiority failed did not mean that the trial showed non-inferiority."
- *Panel member:* "Do you really believe that?" (*audience laughter*)

Another interesting exchange was:

- *Patient representative:* "Given the fact we knew in 1992 there was a hypothetical risk of tumor promotion and then discovered higher risk of TVEs, I can't understand why there were no studies done and now there's only one that's done according to the label?"
- *Amgen official:* "It's important to keep in mind that the label has changed over time. I also think it's very important to place this in the appropriate historical perspective. Potential concerns with regard to thromboembolic events have been known for a long time, and we've done a great deal of work to see the effect of ESAs on tumor progression…We also have a very deep analysis in pre-clinical that show EPOs do not stimulate tumor progression. Again, I'd point out that we don't have data that suggest that tumor progression is an issue as a result of epoetin treatment."
- *Panel member:* "You don't have data to suggest it isn't, either."
- *Amgen official:* "It's extremely hard for us to prove a negative…There are no data to support the view that there is an effect on tumor progression in that setting. We don't have a signal."

Do ESAs stimulate tumors?

Panel members were concerned that ESAs may promote tumor growth. Dr. Brawley said, "I'm concerned that this compound (ESA) is a stimulant, a tumor fertilizer for epithelial cancers – lung, head and neck, carcinoma of the lungs. What data do you have to assure me that this is not 'Miracle Gro for cancer?'" Dr. Martino said, "We know that there may or may not be EPO receptors on tumors, and if they exist it appears the consensus is that they're not a way to stimulate a tumor. Do we not know that there are receptors on an epithelial cell? And then what do we know about angiogenesis?" An Amgen official responded, "The EPO receptors are expressed in low abundance on the surface. That makes it impossible to detect them. It hasn't been possible to detect an EPO-driven effect, and it's speculation on whether there is an effect. You can't find that." An FDA official chimed in, "There is extensive literature that EPO receptors are evident on tumors, breast included."

Pre-clinical and clinical data overload?

Dr. Martino said that there is almost too much data, "There really are too many studies, and they become jumbled in the mind. I'm struggling with the following: If there's an issue that you're decreasing survival, what studies are there where survival was the primary – not secondary, not tertiary – end-point that met approval and for which we have data?...Is there such a study, and is there more than one. This hodgepodge of things presented to me makes our jobs complex and nearly impossible." An FDA official responded, "The only such trial is the BEST trial in breast cancer where the primary endpoint was survival ≥12 months. Amgen said the 145 study had survival as a co-primary endpoint." An Amgen speaker added, "The 145 study…result was neutral. Those data have been made available to the FDA. The 145 study is 'extremely reassuring.'"

Other comments included:

- *Chair:* "The preclinical (data) are pretty well laid out, but I'd prefer clinical data."
- *Amgen official:* "The original approval was based on study 297…What we see is that the survival curves are in fact separating, and Aranesp actually seems to do better. That's what led us to look at small cell lung cancer. As for the solid tumor evidence, we have a significant body of clinical trial data that look at the CIA setting for a number of solid tumors."
- *Asked why some data have not been turned over to the FDA*, an Amgen official said, "Clinical trial work occurs in many arenas. Investigators do clinical trials which don't get turned over to the FDA. There is clearly an evidence base that is more than what the FDA has in its position. We have turned up all primary data we have, but there is a much larger body of trials which, in fact, most of you sitting here participated in."
- *FDA official:* "I think that deserves an answer from the FDA. There was, especially after the 2004 (ODAC) meeting, considerable controversy about the safety of the drug, which led to the 2004 meeting. These are not just studies out there being done by investigators. The two sponsors were supposed to answer the questions posed by the committee. In subsequent conferences, they said they didn't have access to the data from the studies. If these studies were being done to answer the questions, they had an obligation to work with the investigators after the 2004 meeting to provide us with all of the data."

- *David Harrington Ph.D., statistician at Dana-Farber Cancer Institute:* "I'd like to know from the FDA what studies are excluded, and, finally, for me there's this mysterious DAHANCA study in Denmark. The FDA has actual p-values and hazard ratios, but where is that data, and is it in the public domain yet?"
- *Amgen official:* "As for the DAHANCA trial, the trial was stopped for futility, and preliminary interim results were communicated with a p-value. The primary researcher said that he is reluctant to provide more information until it is properly collected from all 500+ patients. He said that he doesn't think the trial would come out in favor of Aranesp, but it is too early to call the study negative (i.e., survival decreasing). However, he said that he didn't think the study would be positive, either."
- *FDA official:* "Some of the studies included did not have adequate follow-up."

Breast Cancer

Some panel members were especially concerned about the use of ESAs in chemotherapy regimens that do not require blood transfusions, particularly breast cancer. An Amgen official said, "We don't have access to the RTOG and CN-20 studies until the data are published…The EPO-CAN-17 trial…didn't demonstrate any safety signals…It was a quality of life study in breast cancer patients receiving chemotherapy. In overall survival, women survived for two years in this study. Eight percent of patients were treated in the adjuvant setting – 20% had metastatic disease and had an additional 12 weeks of chemotherapy. Women were randomized into the study when their Hb fell below 12 and were targeted between 12 and 14. The quality of life results were significantly in favor of the Eprex-treated women. As for safety, there was a slight increase in thromboembolic events…There are three other studies in breast cancer – two are in the adjuvant setting, and one (BRAVE) was conducted in women with metastatic breast cancer…The MOBUS breast cancer study is being conducted in Germany…Two-year disease free survival (DFS) was to be reported…Some of this will be presented at ASCO (in June 2007)."

FDA Questions to the Committee

1a. More **label restrictions.** The FDA revised product labeling in March 2007. **Should further marketing authorization be contingent upon additional restriction in product labeling?** **15 Yes, 2 No**

Panel member comments included:

- *Chair:* "I don't want to go back to the Dark Ages and take a step backward. This is a valuable supportive (drug)."
- *Patient representative:* "I haven't seen any data showing this (an ESA) is safe."
- "It says there are TVEs. No one is ignoring it. It's there."
- "I see nothing that says it (an ESA) is for adjuvant breast cancer."
- "There is a lot of sleight of hand here with how the drug is used and what the drug is used for, and I think that's a real problem."
- "When talking about additional restrictions, the focus is on the black box…Does this include the labeled indication for cancer patients? It's very loose." (An FDA official responded: "Yes, it could.")

1b. More **trials. Should further marketing authorization be contingent upon additional trials?** **Unanimously YES**

Panel member comments included:

- "The burning question is: Does this actually kill people in the doses that you think are reasonable and appropriate? And I haven't seen anything that has an answer. I'd put a stop to all the trials that use higher doses than the recommended doses. They're going to continue to confuse us and waste patient resources."
- "How do we know we're going to get the data for new trials if we don't have data we've been asking for?"
- "To be fair to the sponsor, it's very difficult to accrue to these trials. Why does a patient want to take the chance (of getting a placebo)? They (the companies) are doing the best they can, and they can't accumulate patients. What we need is a large simple trial. If you make it too cumbersome, you can't sell it to the patients."

2. Restrict ESA use in specific tumors. Decreased survival signals were noted in trials enrolling patients with homogeneous tumor types including BEST, ENHANCE, and EPO-CAN-20. Other trials showing decreased survival signals that were conducted in heterogeneous tumor types are 161 and 103. Decreased locoregional control rates were observed in the DAHANCA and ENHANCE trials. Several of these trials employed a treatment strategy to achieve and maintain hemoglobin >12 g/dL.

Should labeling specifically state that ESAs are not indicated for use in 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.)* **12 Yes, 5 No**

Panel member comments included:

- "I think unless it's a clinical trial in the adjuvant setting, and I can go colon or GI or something like that, not metastatic disease, these are people probably cured by the initial therapy."

- "I think because of the BEST trial, we should not use this in breast cancer. What we heard from the breast cancer advocacy group would indicate to us that breast cancer patients are not enthusiastic about receiving EPO…Why would I treat somebody if I don't have a compelling reason to give it? There's no evidence for quality of life. I don't see an added value to treating breast cancer patients."
- "I'm concerned about the…group of adjuvant patients where there seemed to be a difference in survival early on."
- "Two women who spoke today were metastatic, and they both lived for eight years. I don't know why we'd take them out of the (approved use) list."
- "I'll be impolitic. A lot of people get it (an ESA) because doctors make $1,200 a shot off of it, not because they need it."
- "Now, you're going to say that between Hb 10 and 12, it (an ESA) shouldn't be used…That doesn't make sense to me."
- "For the amount of information that needs to be put in here for prescribers, to understand what's meant by specific tumor types, they need to know a lot of detail… even within these tumor types there will be patients where administration of ESA would be indicated. I'm struggling with how this is going to look. In my opinion, there has to be a lot of thought given as to how this will be put in a package insert."
- *Chair:* "It could be complicated when it comes to writing the label."

3. **Put recommended Hb levels in labeling.** RBC transfusions are generally given if Hg is <8 g/dL unless the patient is symptomatic, and RBC transfusions are rarely given when Hg is >10 g/dL.

   Should product labeling define a Hb level in asymptomatic patients at which ESAs should be initiated? 15 Yes, 2 No

Comments included:

- *FDA:* "There are physicians that believe you are eligible for ESA when your Hb level reaches 11.9."
- "Everyone is saying, 'I think they give EPO'…(but) are there data that suggest what people are actually doing?"
- "Does the company have the data? Is 40% of EPO use off-label?"
- *Amgen official:* "The vast majority of ESA use is, in fact, within the label, and it's extraordinarily rare to take it when Hb is above 12. We've looked at late intervention, starting at Hb 10.5-12, and there's a transfusion benefit to early intervention. ASH suggests 10, and ACC (American College of Cardiology) suggests 11."
- *Patient representative:* "The problem is that a lot of doctors give it (an ESA) in terms of prevention, as opposed to when you're anemic."
- *Chair:* "This is not exactly rocket science. The idea is whether we think it's important in the label to define a lower threshold. No means it would be given according to the current guidelines set up by other societies."

4. **Titrate dosing.** 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.

   Should dosing be titrated to avoid transfusions, generally aiming at a lower Hb level, e.g. 9 or 10 g/dL? 11 No, 6 Yes

Comments included:

- *FDA official:* "We have looked at a lot of the quality of life data associated with some of these studies and the measures that are used. We have problems with the measures of these quality of life data. We don't always know what the measure is capturing and what it is not capturing. When we talk about fatigue and vitality, those are very hard to measure. There is consensus that this is a problem, and there are two separate consortia of drug companies that are trying to develop measures of cancer-related fatigue, chemotherapy-related fatigue. Patients don't talk about fatigue and vitality, they talk about weakness and depression, and all of these things have to be sorted out in order for us to be confident."
- "Is there similar data on why it is better to be at Hb of 11 than something else? So we know how to set the bar?" An FDA official responded, "You'd get that from placebo-controlled trials, which we haven't seen. We don't know if the risk factor is driven by the Hb itself or if risks of ESAs are partly driven by dosing."
- "I have problems interpreting those types of data. Sure, people who get anemic have fatigue and don't feel well, but the drop in Hb sometimes may go hand-in-hand with the other effects of chemotherapy that they're getting. I don't think you can relate the level of Hb with quality of life. The bigger problem is interpreting what it's doing to hemoglobin and what the other effects of the chemotherapy are doing on a patient's status."

5. **Limitations on duration of therapy.** Studies of ESAs supporting approval were generally limited to a 12-16 week course of chemotherapy. The FDA is concerned that even when 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)?
16 Yes, 1 No

Panel member comments included:

- "I don't think you need to (recommend discontinuation at a given point). Most people would go to 11 or 12 (weeks). This isn't a very important question compared to the others."
- *Chair:* "A lot of clinics' support staff end up giving these agents after completed chemotherapy because they still continue to have an abnormal hemoglobin…We have conceptually agreed that there should be a limit."

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. Study 103 showed decreased survival in patients receiving ESAs who were not receiving concomitant chemotherapy. The FDA is concerned that adequate attention is not currently directed at the distinction between the 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.**

Panel member comments included:

- *Chair:* "Could you do something like they do with cigarettes?"
- "Something can be done but it's probably beyond the scope of the (FDA's) Office of Oncology."
- *Patient representative:* "We have to reach the advocacy groups. I found that the warnings are not on some of the oncology websites. I think we should ask for ads on TV that are specifically corrective ads that say what was done in the past was wrong. We have to get patients re-educated…Does the FDA have authority to ask for a corrective ad?" An FDA official responded that he will have to check into that.
- "Myelodysplastic syndrome falls into this category, and we need to recognize them as a group. They are transfusion-dependent for a long time, which is different circumstances than people in hospice mode…Just don't lump those (MDS) patients into this category. The problem has been that physicians have also been sold the concept, rightly or wrongly, that quality of life is improved as you use these agents. If grandpa is about to die tomorrow, but I can make his last two hours a little better, then surely I should do that. But there are studies that say that he might die sooner. I think somehow getting the pharma companies to say, 'We're sorry we misled you,' ain't gonna happen."
- "Maybe some communications can be placed on the FDA website. I think they can and that could be a place where patients could get access to information."

7. **Additional oncology trials needed.** 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…**Additional safety data has emerged since ODAC 2004. Please discuss trials needed to investigate these safety concerns and identify barriers to timely accrual of these trials.**

Panel member comments included:

- "The obvious one (trial to recommend) is a placebo-controlled ESA study. Maybe piggyback it onto other trials. You can't have somebody taking the great chance of placebo; it has to be piggybacked."
- "We've seen a lot of sleight of hand here – trials that don't meet their endpoint. What we need is a well set out trial with one endpoint. That is probably the best thing we can do for public health."
- "Most (trials) are going to be Phase III randomized (studies), which are usually evaluating standard therapy and new therapy, and now you'll have two variables."
- "I'd like to see trials that get rid of doses we're not going to accept. That would be my thought. I'm seeing a lot of (needless) working being done."
- "The best possible trial would be the placebo-controlled trial, but I think it would be very hard to do that, so I guess I'd urge a trial of dose reduction or a trial of lower targets for lower Hb, and let's back our way down, see if we can begin to reduce the exposure burden and maybe begin to see a dose relationship."

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