

Appendix: FDA Questions to the Committee and Voting Outcome

1. *Considering all the available data on the benefit and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for the indications listed above? (YES or NO)*

Vote: YES

2. If you recommend that the current indication should be retained, should the FDA require that product labeling be modified? Below are four potential approaches to mitigating risks through revised labeling. Please address each of them separately.

a) To date, only clinical trials in small cell lung cancer have reasonably excluded an increased risk for death among patients receiving ESAs. Trials have demonstrated an increased risk of death and/or tumor promotion in head/neck, non-small cell lung cancer, breast (neoadjuvant and metastatic settings), lymphoid malignancies, and cervical cancers. Tumor types, other than those listed above, have not been adequately studied. *Should the current indication be modified to restrict use only to patients with small cell lung cancer? (YES or NO)*

Vote: NO

b) The PREPARE trial demonstrated decreased relapse-free and overall survival in breast cancer patients receiving neoadjuvant chemotherapy. The risk/benefit assessment is different for patients receiving neoadjuvant and adjuvant chemotherapies than for patients with metastatic or incurable cancers. *Should the current indication be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments? (YES or NO)*

Vote: YES

c) Although increased tumor promotion and/or decreased survival have been demonstrated in several tumor types, adverse findings have been duplicated in two malignancies—breast cancer and head and neck cancer. *Should the current indication be modified to include a statement that ESA use is not indicated for patients with metastatic¹ breast and/or head & neck cancers? (YES or NO; if yes, please specify breast and/or head & neck cancer.)*

Vote: YES [for both breast and head & neck cancers]

d) The only objective evidence of efficacy demonstrated for ESAs has been avoidance of RBC transfusions; however, not all patients with anemia require an RBC transfusion. Product labeling does not specify the hemoglobin level at which ESA treatment should be

¹ The original question did not include the word “metastatic”; the Committee asked that it be added, because with the vote to restrict use in potentially curative settings, non-metastatic breast and head & neck were already covered.

initiated. *Assuming a patient is asymptomatic and has no co-morbid conditions, please specify the hemoglobin level at which initiation of an ESA is appropriate.*

Non-Voting Question. Suggestions were made, but the Committee did not appear to reach consensus.

3. If the Committee recommends that the indication for treatment of anemia due to concomitant chemotherapy should be retained (as currently approved or with additional labeling changes as above), discuss additional strategies that FDA could require to minimize risk. Below are two options that could be considered. If you have other suggestions, please state them.

- a) An informed consent/patient agreement would explicitly require the oncology patient's authorization or agreement to undergo treatment with an ESA. Both patient and physician (or designate) signatures would be required. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy and alternative treatments. *Should the FDA require the implementation of an informed consent/patient agreement for the treatment of chemotherapy induced anemia? (YES or NO)*

Vote: YES

- b) Examples of restricted distribution programs include STEPS (thalidomide), RevAssist (lenalidomide), and iPLEDGE (isotretinoin). Restricted distribution systems link product access to planned safe and effective use. These programs may require identification and enrollment of healthcare providers who agree to prescribe only in accordance with product labeling and who commit to patient education regarding safe use. Registration of patients may also be required. Certain patient characteristics would be recorded at individual patient registrations (e.g., hemoglobin, chemotherapy type, malignant diagnosis). *Should FDA mandate a restricted distribution system for oncology patients receiving ESAs? (YES or NO)*

Vote: NO