Cancer-related anemia is a very serious issue that often arises during the management of cancer patients. It has implications not only for the patient's treatment, influencing the selection and administration of chemotherapeutic agents, but also affects his or her quality of life during and after the treatment.

Prior to discussing the use of biological agents in treating CA-related anemia, it is worthwhile to briefly review the hematopoietic process.

The maturation pathway in the bone marrow is as follows:
- **stem cells** --> **blast-forming-units (BFU)** --> **colony-forming-units (CFU)** and eventually to basophilic erythroblasts

The process then continues in the peripheral circulation as follows:
- **erythroblasts** --> **reticulocytes** --> **red blood cells (RBCs)**

It is important to note that the only erythropoietin (EPO)-dependent part of this pathway is BFU --> CFU --> erythroblast. Thus, EPO has no action on stem cells, reticulocyte release, or circulating RBCs, with resulting implications on the use of EPO-based treatment for anemia.

There is evidence showing a blunted response of endogenous EPO to anemia in patients with cancer as compared to iron-deficient patients without cancer (Miller et al. NEJM 1990:322). Typically when hemoglobin (Hb) levels fall < 12 g/dL, the average person launches an increase in endogenous EPO, but a patient with CA-related anemia shows a suppressed EPO response, and thus a relative deficiency of this hormone. Giving exogenous forms of EPO is an attempt to overcome this problem.

There are also data linking increased carbohydrate content of EPO (specifically, the number of sialic acid residues) with an increased half-life, decreased clearance, and greater biologic efficacy (Ergie J et al. Br J CA 2001). However, recombinant human EPO (rHuEPO), considered the current standard for treating CA-related anemia, has a theoretical maximum of only 14 sialic acid molecules. This has led to the development of a newer compound, darbepoetin alfa (DPO) with 2 additional carbohydrate binding sites (distinct from the EPO receptor binding site) and up to 22 sialic acid residues, raising the carbohydrate content from 40% with rHuEPO to 52% with DPO. This molecular change has indeed translated into the expected clinical change. Preliminary data from Hartley et al presented at the ASCO 2002 meeting showed more rapid Hb response and improved pharmacokinetics (decreased clearance) using DPO compared to rHuEPO, with a half-life of >50 hrs following subcutaneous administration of DPO 6.75 mcg/kg.

As increasing data comparing rHuEPO and DPO is compiled in the future, it is important to understand not only the endpoints of interest, but the analytical methods used. The three major endpoints for anemia are based on a) transfusion-need, b) Hb response (absolute or relative), or c) patient-reported outcomes (ie: FACT survey). The two analytical methods typically employed are "intent-to-treat" (ITT) and "available data" (AD). It is imperative to note that comparing results from two different studies is only valid if the same analytical method is used in both. This is because the ITT approach emphasizes the role of transfusion over that of growth factor in raising the Hb levels, while the AD approach can be adjusted for the use of transfusion, thus allowing more emphasis of the growth factor component.

Thus far, data comparing high-dose DPO (4.5 mcg/kg) to standard dose rHuEPO has shown an increased cumulative percentage of patients responding in the DPO group. However, if more comparable doses are evaluated (DPO 2.25 mcg/kg vs. rHuEPO 40,000 U/qwk), the response rates are in fact similar. Of note, significant improvement in Hb levels have also been
shown with every 2-week dosing of DPO, prompting more questions for future research.