Proposed Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N)

Decision Summary

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, reduced survival) have prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). The initial scope of this national coverage analysis (NCA) was "non-renal" uses. Current non-renal indications for ESA use that are approved by the FDA are: cancer treatment related anemia (erythropoietin, darbepoetin), AZT-induced anemia in HIV-AIDS (erythropoietin only), and prophylactic use for select patients undergoing elective orthopedic procedures with significant expected blood loss (erythropoietin only) (Aranesp® drug label; Procrit® drug label). Because there is a preponderance of emerging data for ESA use in the oncology setting, the focus of the NCA will be ESA use in cancer and related conditions. The other non-renal uses may be addressed in future NCAs. We expect that our future reviews will also include the more adequately powered study of ESA use in spine surgery patients. In the interim, local Medicare contractors may continue to make reasonable and necessary determinations on all non-cancer and non-neoplastic conditions as well as other non-renal uses of ESAs.

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. the anemia of myelodysplasia
3. the anemia of myeloid cancers
4. the anemia associated with the treatment of myeloid cancers or erythroid cancers
5. the anemia of cancer not related to cancer treatment
6. any anemia associated with radiotherapy
7. prophylactic use to prevent chemotherapy-induced anemia
8. prophylactic use to reduce tumor hypoxia
9. patients with erythropoietin-type resistance due to neutralizing antibodies
10. patients with treatment regimens including anti-angiogenic drugs such as bevacizumab
11. patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor
12. anemia due to cancer treatment if patients have uncontrolled hypertension
13. patients with thrombotic episodes related to malignancy

We also propose that ESA treatment is only reasonable and necessary under specified conditions for the treatment of anemia in those types of cancer in which the presence of erythropoietin receptors on either normal tissue/cell lines or malignant tissue/cell lines has been reported in the literature. These cancer types include but are not necessarily limited to:

- bone (sarcoma),
- brain-neurologic,
- breast,
- cervical,
- colo-rectal,
- gastric,
- head-and-neck (squamous cell),
- hepatic,
- lung,
- lymphoma
- melanoma,
- multiple myeloma
- muscle including cardiac,
- ovarian,
- pancreatic (exocrine),
- prostate,
- retinal, and
- uterine.

For patients undergoing treatment for these cancers, we propose ESAs are reasonable and necessary with the following limitations:

1. the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be <9 g/dl/27% in patients without known cardiovascular disease and <10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (The latter patients should be alerted to the increased potential for thrombosis and sequelae.) (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae.)
2. the maximum covered treatment duration is 12 weeks/year;
3. the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin;
4. continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise <1 g/dl/<3%) after 4 weeks of treatment;
5. continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment; and
6. continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit >1 g/dl/>3% after 2 weeks of treatment.

Local contractors may make reasonable and necessary determinations for all uses of ESA therapy for beneficiaries with cancer whose condition is not addressed above.

We are requesting public comments on this proposed determination pursuant to section 1862 as revised by 731 of the Medicare Modernization Act. In light of the issues discussed in our review of the evidence and serious safety concerns voiced in the May 10, 2007 FDA Oncologic Drugs Advisory Committee (ODAC) meeting we are also interested in public comment on whether coverage for ESA therapy for Medicare

beneficiaries with cancer should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

Proposed Decision Memo

TO:	Administrative File: CAG #000383N The Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions
FROM:	Steve Phurrough, MD, MPA Director, Coverage and Analysis Group Louis Jacques, MD Director, Division of Items and Devices Maria Ciccanti, RN Lead Analyst LCDR Tara Turner, PharmD Analyst Elizabeth Koller, MD, FACE Medical Officer Shamiram Feinglass MD, MPH Medical Officer
SUBJECT:	Proposed Coverage Decision Memorandum for the Use of Erythropoiesis Stimulating Agents in Cancer and Related Neoplastic Conditions
DATE:	May 14, 2007

I. Proposed Decision

Emerging safety concerns (thrombosis, cardiovascular events, tumor progression, reduced survival) have prompted CMS to review its coverage of erythropoiesis stimulating agents (ESAs). The initial scope of this national coverage analysis (NCA) was "non-renal" uses. Current non-renal indications for ESA use that are approved by the FDA are: cancer treatment related anemia (erythropoietin, darbepoetin), AZT-induced anemia in HIV-AIDS (erythropoietin only), and prophylactic use for select patients

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- cervical,
- colo-rectal,
- hepatic,
- lung,
- lymphoma
- melanoma,
- multiple myeloma
- pancreatic (exocrine),
- prostate,
- retinal, and
- uterine.

- gastric,
- head-and-neck (squamous cell),
- muscle including cardiac,
- ovarian,

For patients undergoing treatment for these cancers, we propose ESAs are reasonable and necessary with the following limitations:

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II. Background

In this section, we describe the technological developments that gave rise to the use of genetically engineered (recombinant) erythropoietin and related ESAs. We then describe the anemia for which ESAs are prescribed in oncologic conditions, with an emphasis on solid tumors which constituted the majority of tumors in the studies upon which FDA approval was based. For purposes of this discussion, therapy for a medical condition

includes treatment for the signs and symptoms of the underlying condition and treatment for the signs and symptoms of oncologic treatment. Though we have tried to simplify the discussion for the lay reader, the topic is scientifically complex and we believe that an overly simplistic treatment would ultimately be detrimental to the understanding of our review.

A. Biochemical Background

Erythropoietin is a 34-kDa glycoprotein produced primarily, but not exclusively, in the kidney and to a lesser extent in the liver (Dame 1998, Ebert 1999, Eckardt 1992, 2005, Jelkmann 2001, Koury 1991, Moritz 1997, Rankin 2007, Tam 2006, Zanjani 1981). The native protein is a 193 amino acid peptide sequence from which a 27 amino acid peptide leader sequence is removed from the N-terminus. An arginyl residue at the carboxyl terminus also appears to be cleaved during post-translation processing. The mature protein consists of a 165 amino acid backbone with 2 disulfide bonds, three N-linked carbohydrate chains, and one O-linked carbohydrate chain. The major side chains, sialated tetraantennary saccharides, contribute to in vivo stability (Elliott 1996, Faulds 1989, Narhi 1991, 1997, 2001, Sytkowski 1991, Toyoda 2000).

In the classic hormone pathway, erythropoietin regulates erythrocyte production by stimulating progenitor cell proliferation and differentiation in the bone marrow. Hypoxia plays a major role in the feedback loop (Ebert 1999). Erythropoietin activity is mediated through the erythropoietin receptor. The expression of erythropoietin receptors on erythroid progenitor cells is well known (Constantinescu 2003, D'Andrea 1989, 1991; Fraser 1988, Jones 1990; Winkelman 1990). Less well appreciated is the presence of erythropoietin receptors on other tissues including cardiac myocytes, macrophages, neurons, vascular endothelial cells (Anagnostou 1990, 1994; Digicaylioglu 1995; Haroon 2003; Lappin 2003, Masuda 1993; Wright 2004), and cancers/cancer cell lines (bone sarcoma, breast, cervical, colon, gastric, head-neck [squamous cell], hepatoblastoma, melanoma, ovarian, pediatric, renal, retinal, and uterine (Acs 2001, 2002, 2003; Arcasoy 2003, 2005; Batra 2003; Farrell 2004, Fraser 1989; Henke 2006, Jones 1990, Kumar 2006, Lappin 2003, Masuda 1993, Mioni 1992, Ogilvie 2000 Ribatti 2003; Selzer 2000; Westenfelder 2000; Yasuda 2001, 2006). Also less well understood is the role erythropoietin appears to play in angiogenesis (blood vessel formation) in wounds and the female reproductive tract (Haroon 2003; Yasuda 1998). Tumors differ in the extent of erythropoietin receptor and erythropoietin expression (Lai 2005). Metastatic tumors may express erythropoietin receptors and erythropoietin to a greater extent than primary tumor (Lai 2005). Erythropoietin, through its receptor, appears to activate several signaling pathways that are operational in cancer JAK-STAT (Janus kinase-Signal Transducer and Activator of Transcription), MAPK (mitogen-activated protein kinase), NFκ B (nuclear factor-kappa B), and PI3K-Akt (phosphatidylinositol 3-kinase-Akt) (Barber 1994, 1997, Bittorf 2001, Constantinescu 2003, Kumar 2006, Lai 2005, Lester 2005, Linnekin 1992, Mohyeldin 2005, Xia 1996)

Several forms of recombinant human erythropoietin have been developed (Table 1). They differ in their carbohydrate structure. The most common species are erythropoietin-alpha

and beta (Deechongkit 2006, MacDougall 2002). The pharmacokinetic half-life of these products is 6 to 8 hours after IV injection (Halstenson 1991). Because the pharmacodynamic response on the bone marrow is prolonged, dosing regimens vary from 3 times weekly to once weekly. Peak serum levels are higher with the weekly dosing regimens (Cheung 1998, 2001, FDA Procrit Clinical Pharmacology Review 2004, Kryzanski 2005, Ramakrishnan 2004). Dosing via the intravenous route may require 10 to 25% more drug for the same hematologic effect compared to subcutaneous administration (Kaufman 1998, McMahon 1990, Salmonson 1990). The erythropoietin molecule has been modified by the addition of 2 N-linked carbohydrate chains to form darbepoietin. The additional sialic acid residues decrease pharmacokinetic clearance by the body and permit weekly and semi-weekly dosing (MacDougall 1999). More recently, the erythropoietin molecule has been modified by the addition of a methoxy-poly-ethylene glycol polymer chain (pegylation) via a succinimidyl butanoic acid linker (MacDougall 2003, 2005). These changes further decrease pharmacokinetic clearance by the body and permit weekly and even monthly dosing (MacDougall 2005). Although the molecular modifications decrease the affinity of the compound for the erythropoietin receptor in vitro, the increased residence time results in increased exposure of the compound to the erythropoietin receptor and increased erythropoietin-type activity in vivo (MacDougall 2003).

Recombinant erythropoietin was initially used as a replacement for missing hormone in select patients with anemia of end-stage renal disease. Use of ESAs has been extended to a variety of anemic conditions including the anemia of chronic renal disease (not yet on dialysis), anemia secondary to chemotherapy of solid tumors, anemia secondary to AZT therapy, and prophylactic use during the peri-operative period to reduce the need for allogenic blood transfusions (Aranesp label, Danna 1990, Fischl 1990, Laupacis 1993, Procit label). Exploratory work for ESA use treating the anemia of solid tumors and the chemotherapy-induced anemia of hematologic cancers has been undertaken (Dammacco 2002, Gagnon 2003, Patrick 1996, Quirt 2001, Straus 2003)

Table 1: Erythropoiesis Stimulating Agents

Compound	Drug Names	Manufacturer	Production Site	Supplier	Distribution Sites
Erythropoietin-α	Epogen	Amgen	USA	Amgen	USA
Erythropoietin-α	Procrit	Amgen	USA	Ortho Biotech	USA
Erythropoietin-α (w/o serum albumin)	Eprex Epypo Epopen Epoxitin Globuren	J&J subsidiary (Otho Biologics)	Puerto Rico	Cilag Janssen	Europe, Canada (Some of these no longer distributed)

Erythropoietin-ß	(Neo)Recormon	Roche	Germany	Roche	Europe Recormon no longer marketed
Erythropoietin-ß	Erantin			Boehringer Mannheim (Spain), Roche (Spain)	Discontinued or no longer marketed
Erythropoietin-ß	Epoch	Chugai	Japan		Under development
Erythropoietin-δ In human cell lines	Dynepo Gene Activated Erythropoietin	Aventis Transkaryotic Therapies		Shire	Europe (not yet launched) Patent issues
Erythropoietin-Ω	Epomax Hemax Hemax-Eritron	Baxter		Cryopharma (Mexico) Lek (Czech) Sidus (Argentina) Bio Sidus (Thailand) Biosintetica (Brazil)	Countries outside USA
Modified erythropoietin-α Darbepoietin	Aranesp	Amgen	USA	Amgen	USA, Europe
Modified erythropoietin-α Darbepoietin	Nespo	Amgen		DompÃ© Biotec S.p.A.	Europe
Modified Erythropoietin-ß Continuous Erythropoietin Receptor Activator (Pegylation)	Mircera	Roche			Under development

B. Disease Summary

Anemia occurs with varying degrees of frequency and severity in cancer. It is most

frequent in genitourinary, gynecologic, lung, and hematologic malignancies (Barrett-Lee 2006, Groopman 1999, Ludwig 2004, Moullet 1998, Tas 2002). Anemia may be directly related to cancer (type, stage) or to its treatment (type, dose). Co-morbid conditions as well as age can aggravate the anemia (Lipschitz 1995).

Oncologic anemia occurs by a variety of mechanisms (Birgegard 2005, Mercadante 2000). Poor oral intake or altered metabolism may reduce nutrients (folate, iron, vitamin B-12) essential for the proliferation and differentiation of erythroid progenitor cells (Borelli 2007). Antibodies in chronic lymphocytic leukemia (CLL), lymphoma, and some solid tumors may cause increased erythrocyte destruction through hemolysis (Rytting 1996). Tumors may cause blood loss via tissue invasion, e.g. gastrointestinal bleeding from colon cancer. Other neoplasms, particularly hematologic malignancies (leukemia, lymphoma, multiple myeloma) can invade the bone marrow and disrupt the erythropoietic microenvironment (Munker 1995, Skilling 1995). In more advanced cases, there is marrow replacement with tumor or amyloid. Marrow dysfunction can occur, however, even in the absence of frank invasion (Faquin 1992, Mikami 1998). Inflammatory cytokines from interactions between the immune system and tumor cells are thought to cause inappropriately low erythropoietin production and poor iron utilization as well as a direct suppression of erythroid progenitor proliferation (Faquin 1992, Miller 1990, Spivak 2002, Ward 1971).

The treatment of cancer may also cause anemia (Barrett-Lee 2000, 2006, Coiffier 2001, Harrison 2000, Ludwig 2004, Skilling 1999). Radical cancer surgery can result in acute blood loss. Radiotherapy and many cytotoxic chemotherapeutic agents cause marrow suppression to some degree. Damage is due to a variety of mechanisms. For example, alkylating agents cause cumulative DNA damage, anti-metabolites damage DNA indirectly, and platinum-containing agents appear to damage erythropoietin-producing renal tubule cells (Girdwood 1976, Horiguchi 2000).

The level at which anemia requires intervention is not well established. By tradition, patients have been transfused at the hemoglobin level of 7 or 8 g/dl to avoid symptoms and physiologic complications. A transfusion of 2 or more units would result in an increase of at least 2 g/dl of hemoglobin (6 units of hematocrit). Indeed, one of the endpoints for pharmaceutical registration, "need for transfusion", employed an 8% hemoglobin cut-off (FDA Medical Officer Review, Aranesp 2002). Most of these practices, however, are based on empiric observations and not clinical trials. In one of the few studies, Carson et al. found that hip-fracture patients transfused to hemoglobin levels in excess of 10 g/dl did not have more exercise tolerance than non-transfused patients who were transfused after hemoglobin levels dropped to below 8 g/dl or patients became symptomatic (Carson 1998).

The British Blood Transfusion Society has delineated the weaknesses in our knowledge base (Murphy 2001). Their guidelines state that transfusions are indicated in patients with hemoglobin levels less than 7 g/dl and that transfusion should not be undertaken for hemoglobin levels greater than 10 g/dl. They indicate that management of patients with hemoglobin levels between 7 and 10 remains unclear although the hemoglobin threshold

for the treatment of patients with co-morbid conditions with probably higher than 7 g/dl. The College of American Pathologists (CAP) no longer issues transfusion practice guidelines although they have done so in the past (CAP 2002).

Other groups have developed definitions for anemia and have been cited for these definitions, but these definitions cannot be extrapolated into guidelines for oncologic treatment. The World Health Organization (WHO) definitions for anemia were developed for surveillance of anemia due to nutritional deficiency and parasitic infections (WHO 1994, 2001). The National Cancer Institute (NCI) has information on anemia, but does not issue treatment guidelines (Robin Bason 301-594-9051; NCI anemia information from web). Both the NCI and WHO consider hemoglobin levels less than 6.5 g/dl to be life-threatening.

III. History of Medicare Coverage

Prior to this National Coverage Analysis, there was no National Coverage Decision (NCD) concerning the use of ESAs for the indications discussed in this Proposed Decision Memorandum. Currently, Medicare payment for ESAs for end-stage renal disease (ESRD) related anemia is outlined in the Medicare Benefit Policy Manual, Chapter 15, Section 50.5.2. For other indications, Medicare coverage of ESAs administered incident to a physician service for other indications under Part B is determined by local Medicare contractors.

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. ESAs fall within the benefits categories specified in 1861(s)(2)(A) & 1861(s)(2)(B) of the Social Security Act.

IV. Timeline of Recent Activities

March 14, 2007
CMS opened an internally generated National Coverage Decision (NCD) to to evaluate coverage of uses of ESAs in non-renal disease applications.

The initial 30-day comment period began.

April 13, 2007
The public comment period closed; 69 timely comments were received.

V. FDA Status

A. Erythropoietin-alpha was the first ESA approved by the FDA for use in renal failure (1989). Subsequently 2 ESAs were approved for the management of the anemia of cancer treatment (chemotherapy) of non-myeloid neoplastic disease: erythropoietin (1993) and darbepoietin (2002).

B. The FDA reviewed results of the Breast Cancer Erythropoietin Trial (BEST) and

Henke studies. Concerns regarding an increased rate of tumor progression and increased mortality were incorporated into the Precautions Section of product labeling in 2004.

C. The FDA convened a meeting of the Oncologic Drugs Advisory Committee 5/4/2004 to discuss safety issue for ESAs. The briefing information and transcript for the meeting is available at www.fda.gov/ohrms/dockets/ac/cder04.html#Oncologic.

D. In conjunction with the FDA, Amgen issued a "Dear Doctor Letter" regarding the use of ESAs for anemia management in the absence of chemotherapy was sent 1/26/2007. (See www.fda.gov/medwatch/safety/2007/safety07.htm#Aranesp)

E. Serial FDA ALERTS regarding ESA safety information were issued: 11/16/2006, 2/16/2007, and 3/09/2007.

F. The FDA strengthened its warning about cardiovascular and thrombotic events in a variety of populations via a BLACK BOX warning. The FDA included BLACK BOX warnings for tumor progression and decreased survival in cancer patients undergoing cancer treatment. The FDA also warned that ESAs are not indicated for anemic cancer patients not undergoing treatment and that mortality is increased when ESAs are used by this population. Specific warnings on the use of ESAs included that they:

- shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to target a hemoglobin of greater than 12 g/dL,
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a hemoglobin of greater than 12 g/dL,
- increased the risk of death when administered to target a hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for this population.

VI. General Methodologic Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that are used to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that

improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, the blinding of readers of the index test and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence that we considered during our review. We will, of course, consider additional evidence submitted through the public comment period.

Emerging data suggest that ESAs are associated with increased mortality and morbidity despite the alleviation of anemia. The evidence reviewed in this NCA includes the literature on ESA therapy in cancer and focuses on the safety considerations. Most of the studies address the use of ESAs for the treatment or prophylactic management of cancer therapy-related anemia. Select studies address the use of ESAs to treat tissue hypoxia in cancer and thereby attempt to improve response to cancer treatment. Still other studies addressed the use of ESAs in cancer patients without clinically significant anemia. Because of the nature of the findings, literature sources other than the standard medical journals were used when necessary.

B. Discussion of evidence reviewed

1. Questions

1. Is the evidence sufficient to conclude that erythropoiesis stimulating agent (ESA) therapy affects health outcomes when used by Medicare beneficiaries with cancer and related neoplastic conditions?

2. If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable or unfavorable health outcome?

<u>Outcomes</u>

We preface our consideration of the questions with a discussion of the evidence regarding appropriate outcomes (endpoints) for trials of ESA treatment. Because of concern about serious adverse effects including death, we are focusing on evidence of morbidity and

mortality. Most trials have enrolled subjects with a variety of underlying diseases, especially in the trials of cancer where multiple cancer types are represented by the subjects. In light of evidence that the ESA effect may vary by cancer type, it is possible that trials may dilute and thereby underestimate the effect of ESA usage in some cancers.

We are concerned that a number of trials have been terminated, suspended, or otherwise not completed, possibly due to signals of harm, and that the existing fund of published evidence may reflect a bias toward ESA use. For example, the Securities and Exchange Commission (Atlanta bureau) is reported to be investigating Amgen for failure to disclose to investors until 2/2007 that a Danish study of darbepoietin use in head-and-neck cancer was terminated in 10/2006 for safety reasons. The SEC request was disclosed in the annual report recently filed with the Agency (NY Times 3/1/07; USA Today 3/11/07).

CMS, as a public health agency, is aware that many clinical trials are statistically powered for efficacy and not for safety. The absence of adverse events in a setting of potential harm with an absence of adequate safety data cannot be interpreted as proof of no harm.

ESA use may impact a beneficiary in many ways. Thus, we believe that the broad questions above are appropriately addressed by reviewing the evidence for the following questions:

1. Do ESAs (individually or as a class) cause morbidity and mortality?
2. Do ESAs contribute to morbidity and mortality?
3. Are morbidity and mortality related to baseline hemoglobin/hematocrit levels, achieved hemoglobin/hematocrit levels, rate of change in hemoglobin/hematocrit levels, dose levels, or stratified hematologic response to dosages?
4. Are morbidity and mortality with ESAs associated with certain cancers?
5. Do ESAs negatively interact with certain cancer treatments?
6. Do comorbidities common in the Medicare population, such as ischemic disease and congestive heart failure, contribute to this putative morbidity and mortality?

2. External Technology Assessments

We are aware of several external assessments of ESAs and describe them below briefly.

National Institute for Health and Clinical Excellence (NICE)

In 3/2006, the National Institute for Health and Clinical Excellence in the United Kingdom issued a final appraisal determination for "Erythropoietin for Anemia Induced by Cancer Therapy" (Nice, 2006). This was followed by an Appeals Panel that convened in 6/2006 (Nice, 2006 B). The Cochrane Collaboration, an independent, international, not-for-profit organization that prepares and disseminates systematic reviews of healthcare interventions and promotes the search for evidence, prepared an analysis for NICE (Bohlius, 2007). NICE concluded that "Erythropoietin is recommended for use in the management of anaemia only as part of ongoing or new clinical trials that are

constructed to generate robust and relevant data in order to address the gaps in the currently available evidence as outlined in Section 5. Research is needed to confirm the benefits and risks associated with erythropoietin in the management of anaemia induced by cancer treatment (specifically mortality benefits and risks) and to identify patient subgroups (including those with different tumour types) in whom the possible risks are acceptable."

Cochrane Collaboration

(See above.)

Agency for Healthcare Research and Quality (AHRQ)

The AHRQ analysis was structured to assess comparative efficacy for the two FDA approved ESAs, erythropoietin and darbepoetin (BC-BS contract #29020026). The authors concluded that there were not definitive data to indicate that ESA use improved tumor response to treatment and that enhancement of tumor progression was uncertain. The authors indicated that none of the studies, including the unpublished work presented by pharmaceutical sponsors at the 2004 ODAC meeting were designed to test survival.

3. Internal Technology Assessment

Systematic reviews are based on a comprehensive search of published materials to answer a clearly defined and specific set of clinical questions. A well-defined strategy or protocol (established before the results of individual studies are known) is optimal.

CMS staff extensively searched Medline (1988 to present) for primary studies evaluating ESA therapy in cancer. The emphasis was on studies structured to assess adverse events and mortality. CMS staff likewise searched the Cochrane collection, National Institute for Health and Clinical Excellence (UK) appraisals, and the Agency for Healthcare Research and Quality library for systematic reviews and technology assessments. Systematic reviews were used to help locate some of the more obscure publications and abstracts. Preference was given to English publications.

Because much of the material remains outside the domain of the published medical literature, additional sources were used. CMS examined FDA reviews of the registration trials for erythropoietin and darbepoetin as well as the FDA safety data for erythropoietin and darbepoetin. CMS reviewed the transcripts and briefing documents (FDA and pharmaceutical sponsor) from the 2004 FDA Oncologic Drug Advisory Committee meeting on ESA safety. CMS reviewed the FDA ESA drug safety alerts and label changes. CMS searched the National Institutes of Health Clinical Trials.gov database for ongoing/completed trials of ESAs. CMS used internet searches to identify websites with clinical trial results, press releases for clinical trial termination, and U.S. government regulatory action.

Keywords used in the searches included: erythropoietin and survival, darbepoietin and

survival, epoetin and survival, erythropoietin and mortality, darbepoietin and mortality, epoetin and mortality, erythropoietin and thrombosis, darbepoietin and thrombosis, epoetin and thrombosis, erythropoietin and tumor progression, darbepoietin and tumor progression, epoetin and tumor progression, erythropoietin and cardiovascular, darbepoietin and cardiovascular, and epoetin and cardiovascular.

Despite an exhaustive search, we identified no high quality, randomized clinical trials that were of sufficient duration and powered to definitely determine the risk of adverse events including death, tumor progression, and cardiovascular-thromboembolic events in cancer patients, particularly geriatric cancer patients, using ESAs. No trials were structured to assess these hard endpoints in patients with different cancers, cancers at various stages, cancers treated with different modalities or drugs, variable ESA dose responses, and variable comorbidities. We did identify one high quality published trial that was structured to assess locoregional progression (Henke 2003). It did adjust for baseline tumor stage, but was not powered to assess risk for the various tumor stages. Also, in this study, erythropoietin was employed to putatively enhance radiotherapy through a reduction in hypoxia and not to just alleviate anemia. We did identify multiple studies that were terminated for safety reasons. Most of these were never published as full-length articles in Medline journals.

A. Registration Trials

The clinical trials of ESAs that were submitted for FDA approval (registration) were of relatively short duration (12-16 weeks) and focused on non-survival endpoints, specifically reduction of the need for transfusion, change in hemoglobin, and quality-of-life. [Table 2A and 2B in Appendix B]. Many were very small and assessed heterogenous patient populations, primarily those with solid tumors. Indeed the initial erythropoietin approval was based on a composite of 72 non-platinum chemotherapy treated patients from 3 studies and a composite of 59 platinum chemotherapy treated patients from 3 studies in which the primary endpoint, transfusions, was not attained. In a post hoc analysis, transfusions were reduced during the 2nd and 3rd months of treatment. Furthermore, the data from the most extensive blinded, placebo controlled studies of lymphoproliferative disease (darbepoetin #20000161) submitted to the FDA was not included in the FDA label. In addition, the inclusion critieria for most studies included an expected lifespan of at least 3-6 months or an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less (ECOG website, Aranesp Medical Officer Review 2002, 2006, Procrit 1993 FDA Summary basis of approval, Procrit 2004 Medical Officer Review). Significant cardiac disease and hypertension were generally excluded. As such, these studies were not structured to assess mortality and more chronic morbidity. Of note, however, a FDA integrated summary of safety for darbepoetin performed with pooled data from 7 studies suggested that fluid overload is more common in oncologic patients on either darbepoetin (n=975) or erythropoietin (n=115) than placebo (n=221) and that a rapid rise in hemoglobin may be associated with fluid overload, hypertension, and thrombosis.

B. Early Promising Studies

Three early studies by Glaser et al. and Littlewood et al. and Antonadou et al. suggested that ESA therapy might contribute to improved survival and tumor control (Antonadou et al., Glaser 2001, Littlewood 2001). The first was a retrospective review of a small population (n=191) of head-and-neck cancer patients who underwent surgical resection after external beam radiation and adjuvant chemotherapy (mitomycin and 5-flourouracil) (Glaser 2001). Patients were stratified by tumor stage, baseline hemoglobin, and use of erythropoietin. A pre-treatment hemoglobin level of 14 g/dl or greater portended a better prognosis than lower levels. Patients with hemoglobin levels under 14.5 g/dl who were treated with erythropoietin (150 U/kg TIW) had greater likelihood of survival (50/57) than those who did not receive erythropoietin (52/87; p=0.001). Loco-regional control was also better (p=0.001). This study was complicated by the lack of randomization.

The second study was a prospective, blinded study in 375 patients with a variety of cancers who were randomized to erythropoietin (150 U/kg TIW) or placebo for up to 28 weeks (Littlewood 2001). The dose could be doubled in poor responders. The primary endpoint was the fraction of patients who received transfusions after 4 weeks of ESA treatment. The study was later amended to include survival. The follow-up period was 12 months after the last patient completed the study. There was a trend towards improved survival in the erythropoietin group: 37% vs 33%; p=0.13. The median survival was 17 months in the erythropoietin group vs 11 months in the placebo group. The study was complicated by a high drop-out rate (159 of 375), the absence of a treatment protocol for patients with iron deficiency, variable doses, variable duration of follow-up, and the admixture of tumors. The solid tumors were comprised primary of breast and gastrointestinal tumors whereas the hematologic tumors included chronic lymphocytic leukemia, non-Hodgkinâ€™s lymphoma, Hodgkinâ€™s lymphoma, and multiple myeloma. Survival was greater in patients with hematologic cancers.

The third study was a prospective study in 385 patients with pelvic malignancies treated with radation (Antonadou 2001). Patients were randomized to erythropoietin or placebo. The primary endpoints were changes in hemoglobin and local tumor control. The secondary endpoints included disease-free survival and overall survival. Reportedly disease-free survival at 4 years was better in the erythropoietin group. Unfortunately, this study has only been published as an abstract despite its completion in 2000 or 2001. As such there are many outstanding questions about the studyâ€™s design, e.g., inclusion-exclusion criteria, blind status, drug dose escalation, stratification by disease and stage, treatment duration, follow-up strategy, power calculations, and statistical plan, as well as study results, e.g. baseline characteristics, drop-out rate, and intent-to-treat analyses.

A fourth study, by Vansteenkiste et al., was constructed to assess a 50% reduction in the proportion of patients with at least 1 transfusion during week 5 until the end of the 12 week double-blind, placebo-controlled, treatment phase in anemic patients (hemoglobin $\leq$ 11 g/dl) randomized to darbepoetin (2.25 mcg/kg/wk initial dose; 4.5 mcg/kg/wk in poor responders) or placebo (Vansteenkiste 2002). Patients were followed for another 4 weeks and then for another unspecified duration. The manuscript reports that survival and tumor progression did not differ by treatment cohort as of 8/2001, a mean duration of follow-up of 1 year. Criteria for follow-up and drop-out rates during this phase of the trial were not

reported. Publications of future planned analyses could not be located.

C. Other Published Trials

More than 100 papers on ESA use in cancer and related disorders have been published. Most studies have not been structured to assess survival, tumor progression, and adverse events. Many studies enrolled patients with a variety of tumors. Others enrolled patients with a variety of tumor stages. Many studies included patients on a variety of chemotherapy or radiation treatment regimens. Many of the studies were not randomized, double-blind placebo controlled trials. Active control with another ESA was common. Most studies did not employ fixed ESA doses; instead doses could be titrated upwards in poor responders. Concomitant iron administration was sometimes limited to patients in the ESA cohort. Study endpoints were generally hemoglobin thresholds, changes in hemoglobin, transfusion requirements (without a protocol defining transfusion requirement), or quality-of-life. Many studies did not declare a primary endpoint. Survival and/or tumor progression were secondary or add-on endpoints. No studies presented *a priori* power calculations for the numbers of patients and the study duration required to show a clinically significant survival difference for the specified neoplastic disease. No studies presented *a priori* methods for assessment of tumor progression. Any putative risk was presumed not to vary by tumor type or stage, treatment modality, ESA dose, or ESA response to dose. (See Table 3 in Appendix)

D. Terminated Trials

Emerging data suggest that ESA use may be associated with increased morbidity and mortality. The events are not limited to any single pharmacologic agent, to any specific tumor, or to concomitant use with any single therapeutic regimen (Table 4). Complete data from these studies are lacking. Several of these studies were initiated in response to phase 4 commitments to the FDA because of concerns about tumor progression and mortality. Available data are delineated below.

Table 4: Terminated Trials

Cancer Tx	Cancer	Drug	Investigator/Study #/Author	Complete Published Study
Chemotherapy	Lung (non-small cell)	Pegylated Epo ß	Unknown	No
	Lung (small cell)	Epo α	Vercammen in J&J briefing document N93-004 Grote published 2003 abstract & 2005 paper	Yes, under Grote et al.
	Breast	Epo α	Leyland-Jones	Yes, letter 2005

				article 2005
	Breast	Epo α	Rosenzweig	Yes, 2004
Immunotherapy	Colon	Darbe α	Unknown	No
Radiotherapy	Head-neck	Darbe α	Danish Head & Neck Cancer 10 Study Group	No
	Head-neck	Epo α	Machtay	No
	Head-neck	Epo ß	Henke	Yes, 2003
	Head-neck	Epo α	Johnson & Johnson EPO-GBR-7	No Reportedly terminated bc of slow enrollment at 301 of 800 in 2002. 5 yr f/u pending.
Chemo-Radiotherapy	Gastric/Rectal	Epo α	Vadhan-Raj PR00or1-03-006	No
	Cervical	Epo α	Unspecified investigators for investigator initiated protocol Johnson & Johnson PR01-04-005/GOG-0191	No
	Lung (small cell)	Epo α	Wright Johnson & Johnson EPO-CAN-15	Yes, 2007
None	Lung (non-small cell)	Epo α	Unknown	No
None	Assorted	Darbe	Unknown	No

Tx= treatment Epo= erythropoietin Darb= darbepoetin bc= because fu= follow-up

Non-small Cell Lung Cancer, Receiving Chemotherapy, Pegylated Erythropoietin ß (Hoffmann-LaRoche Funding) (FDA Alert)

A prospective, 4-arm, dose-finding trial was conducted in anemic Stage III or IV non-small cell lung cancer patients undergoing first-line chemotherapy. Pegylated erythropoietin was titrated to achieve hemoglobin levels between 11 and 13 g/dl. The study was terminated after enrollment of 153 patients because of increased mortality in the experimental treatment arms.

Breast Cancer, Receiving Chemotherapy, Erythropoietin α
(Ortho Biotech/Johnson & Johnson Funding)

(Published letter and paper- Leyland-Jones 2003 and 2005) (FDA review-2004)

This prospective, placebo-controlled, randomized, non-U.S. study (Breast Cancer Erythropoietin Trial [BEST] [EPO-INT-76]) (n=939) in minimally anemic (hemoglobin ≤ 13 g/dl) metastatic breast cancer patients, who were on first line chemotherapy/hormone (but not homogeneous) therapy and whose disease was stratified for metastasis location, was structured for survival analysis. These patients with ECOG scores ≤ 2 received erythropoietin (40,000-60,000 U/week) or placebo for 12 to 24 weeks to achieve target hemoglobin levels 12-14 g/dl (Oken 1982). Enrollment began in 2000. The treatment arms were well balanced with regard to baseline demographic features, tumor-related characteristics, and hematologic values. (Only 21% of the study population was 66 or older; 4% 76 or older, and 2% from minority groups.) A data safety monitoring board was instituted 1/2002 at the behest of German and British ethics committees. An unplanned interim analysis and eventually trial termination resulted. 59% of hemoglobin values in erythropoietin treated patients were within target vs 45% in placebo treated patients. The erythropoietin cohort experience decreased survival at 12 months: 70% vs 76% (p= 0.012) (Table 5). The increased mortality occurred primarily during the first 4 months. Most of the early deaths were attributable to early disease progression: 6% vs 3%. Others were attributable to vascular and thrombotic events: 1% vs 0.2%. Persistently low hemoglobin levels portended reduced survival regardless of treatment cohort. Reportedly, an analysis of cardiovascular/thrombotic events and absolute hemoglobin levels could not be undertaken because of insufficient data. The principal investigator criticized the study for its inability to collect data on potential prognostic variables (Leyland-Jones 2003). More complete study results were published in 2005 (Leyland-Jones 2005). Its results prompted the FDA 2004 ODAC meeting.

Table 5: Death Profile in BEST

	Erythropoietin α (n=469)		Placebo (n=470)	
	4 months	12 months	4 months	12 months
Died	41	148	16	115
Disease Progression	28	126	13	105
Thrombotic/Vascular Event	5	6	1	3
Chemo Toxicity	NA	8	NA	1

Breast Cancer, Receiving Chemotherapy, Erythropoietin α
(*Ortho Biotech/Johnson & Johnson Funding) (Published article-Rosenzweig et al. 2004)*

Mildly anemic (hemoglobin <12 g/dl) metastatic breast cancer patients were randomized to usual care or usual care plus open-label subcutaneous erythropoietin for a 12 week study. The initial dosing was 40,000 U per week. At week 4, if the hemoglobin had not

increased by at least 1 g/dl, the dose was increased by 50%. If patients continued to be unresponsive to erythropoietin at week 8, the drug was discontinued. The trial was terminated by the investigators after recruitment of only 27 patients when 4 thrombotic events (deep vein thrombosis, pulmonary embolism with deep vein thrombosis, pulmonary embolism with deep vein thrombosis 1 month after drug discontinuation, and brachial vein thrombosis with an infected Mediport) occurred in the experimental arm. In addition, hypertension contributed to the discontinuation by 1 patient in the erythropoietin cohort. Disease progression was similar for the 2 treatment arms (Rosenzweig 2004).

Colon Cancer, Receiving Immunotherapy, Darbepoietin α
(Amgen Funding) (Press release)

Colon cancer patients treated with Vectibix (panitumumab, the human monoclonal antibody directed against epidermal growth factor receptor) (but not chemotherapy or radiotherapy) and darbepoetin-alfa) experienced decreased survival within 16 weeks. The need for transfusion did not differ between those who received darbepoietin and those who did not.

Head-and-neck Cancer, Receiving Radiotherapy, Darbepoietin α
(Amgen Funding)
(Danish Head and Neck Cancer Group website publication:conman.au.dk/dahanca)

Advanced stage head-neck cancer patients treated with radiotherapy and randomized to open-label darbepoietin (vs placebo) in the Danish Head and Neck Cancer 10 Study (N=600 planned, 522 randomized, 516 eligible, 484 with sufficient study time for interim analysis) experienced worse clinical outcomes despite target hemoglobin levels of 14.0 to 15.5 g/dl during radiation therapy. Loco-regional disease progression was greater at 3 years (p=0.01). Overall mortality also tended to be greater (p=0.08). The findings were thought to be significant enough to result in trial termination. Studies on erythropoietin receptor tissues numbers will be undertaken 5/2007. It should be noted that this study was conducted to fulfill a phase 4 commitment to the FDA for the study of tumor progression and survival. Before the trial was terminated, a report to the FDA was originally due 9/2008.

Head-and-neck Cancer, Receiving Radiotherapy, Erythropoietin α
Drug supplied by Ortho Biotech)
(Non-Medline published abstract-Machtay et al. 2004; RTOG 99-03 website)

The study was an international, prospective, randomized, phase III NCI study (PR99-03-046) to assess the role of erythropoietin (40,000 U/wk SQ x 8-9 weeks) in anemic patients (hemoglobin <12.5 g/dl in women and ,13.5 g/dl in men) with Stage I-IV head-and-neck cancer treated with radiotherapy. The hypothesis was that reduction of hypoxia with an erythrocyte stimulating agent would enhance radiosensitivity. Concomitant platin therapy was not mandated, but permitted. The endpoint was death or local-regional failure (persistent or recurrent disease in the primary tumor or regional nodes). An

interim analysis was prompted by the Henke study (Henke 2003). There was a trend towards a less favorable outcome in patients in the erythropoietin arm, but statistical significance was not reached. The investigators, the Radiation Therapy Oncology Group, suspended study enrollment in 11/2003 after entering 148 of 372 planned patients. Erythropoietin dosing was immediately discontinued. The investigators recognized the statistical power losses introduced by the early termination.

Head-and-neck Cancer, Receiving Radiotherapy, Erythropoietin ß
(Hoffman LaRoche Funding) (Published article- Henke et al. 2003)

Three hundred fifty-one advanced head-neck squamous cell cancer patients with mild anemia (hemoglobin <12 g/dl [women]; <13 g/dl [men]) were randomized to erythropoietin-beta (300 U/kg TIW) or placebo prior to and during radiotherapy (60 or 70 Gy) in a prospective, blinded, randomized, placebo controlled study (MF-4449; ENHANCE) (n=351) by Henke et al. The erythropoietin group experienced more local progression over time (relative risk: 1.69; p=0.007) and reduced survival (relative risk: 1.39; p=0.02) than those who did not receive erythropoietin. This pattern was present regardless of tumor resection status, and occurred despite anemia correction. Eighty-two percent of patients on erythropoietin vs only 26% of patients on placebo achieved hemoglobin levels >15 g/dl (men) or >14 g/dl (women). Prognosis was in part related to hemoglobin concentration at baseline and response to fixed dose therapy, i.e., 300 u/kg/TIW during radiation. Patients on erythropoietin also appear to experience more vascular disorders (hypertension, hemorrhage, venous thrombosis and pulmonary embolism, and cerebrovascular disease) (11% vs 5%). Of the 15 cardiac deaths, 10 occurred in the erythropoietin treatment arm.

Gastric/Rectal Cancer, Receiving Chemo-radiotherapy then Surgery, Erythropoeitin α
(Johnson & Johnson Funding)
(Published Non-Medline Abstract-Vadhan-Raj et al. 2004)
(Johnson & Johnson FDA briefing document)

Patients with rectal or gastric cancer with hemoglobin levels 10 to <15 g/dl were randomized to erythropoietin 40,000 U/wk or placebo in a double-blind, prospective, double-blind study in which patients underwent chemo (fluoropyramide)-radiotherapy prior to surgical resection. If the hemoglobin remained below 13 after 4 weeks, the dose was increased by 50%. The study was terminated because of increased thrombo-embolic-vascular events. Data were reportedly available for 59 of the planned 184 patients. Eleven percent (6/53) of the events occurred in patients with rectal cancer; 33% (2/6) occurred in patients with gastric cancer. Twenty-one percent (6/28) of events (primarily serious deep vein thromboses) occurred in patients on epoetin; 6% (2/31) occurred in patients on placebo. Twenty-one percent (7/35) of patients with hemoglobin levels in excess of 13 g/dl experienced; 4% (1/24) occurred in patients with lower levels. The small numbers preclude more extensive analysis.

Lung Cancer, Receiving Chemo-radiotherapy, Erythropoeitin α
(Johnson & Johnson Funding) (Briefing document for FDA meeting)

This study was a double-blind, randomized, placebo-controlled study (EPO-CAN-15) in which patients with limited small cell lung cancer treated with combined chemo-radiotherapy were randomized 1:1 to erythropoietin (40,000 U/wk). The initial treatment target was hemoglobin levels 14-16 g/dl. This was later lowered to 13-14 g/dl. The study appears to have been terminated following thrombo-embolic-vascular events and related deaths. Data were reportedly available for 106 of the planned 620 patients. Nineteen events occurred in the epoetin arm (albeit 2 prior to treatment); 3 occurred in the placebo arm. Four of the epoetin patients with thrombo-embolic-vascular events died. Fourteen of sixteen patients with thrombo-embolic-vascular events were randomized when the hemoglobin target level was 14-16 g/dl. The small numbers preclude more extensive analysis.

Breast Cancer, Receiving Chemotherapy & Later Radiation, Erythropoietin α
(Ortho Biotech/Johnson & Johnson Funding)
(Published paper- Grote et al. 2005)

A prospective, double-blind trial (N93-004) was conducted in small cell lung cancer patients who were to receive up to 12 cycles of chemotherapy; at least 3 of these being etoposide/cis-platinum. Radiation therapy could be added after the third chemotherapy cycle. Patients were randomized to placebo or erythropoietin α 150 U/kg TIW during and for 3 weeks after the completion of chemotherapy. Because the study was to fulfill a 1993 phase 4 safety commitment to the FDA, patients were to be followed for an additional 3 years. The study was structured as a non-inferiority trial. Tumor responses were categorized as complete remission, partial remission, no response, or disease progression. The study was reportedly terminated at 224 of 400 because of slow enrollment. It should be noted that a divergence in survival, in favor of placebo, could be noted at 16-20 months and persisted. With the truncated enrollment, this finding did not reach statistical significance.

The 2004 ODAC Briefing Document and transpscripts were initially available as an internal pharmacologic industry document: Vercammen E, Sullivan D, Matone P. The effect of r-HuEPO in patients with small cell lung cancer (SCLC): A randomized, double-blind, placebo-controlled trial. Protocol N93-004; Phase 4. Document ID No. EDMS-USRA-8057829:4.0. Sept. 26, 2002. This information was later presented in the 2004 J&J ODAC briefing document and at the meeting (2004 ODAC briefing document & transcript). There was no subsequently published study by this author in Medline (Accessed 4/9/07). There is a publication by Grote et al. that describes this study (Grote 2005).

Non-small Cell Lung Cancer, Not Receiving Chemotherapy, Erythropoietin α
(Funded by Ortho Biotech/Johnson & Johnson Funding)
(Briefing document for FDA meeting) (FDA Alert)

A prospective, double-blind, placebo controlled trial (EPO-CAN-20) was conducted in anemic non-small cell lung cancer patients not undergoing chemotherapy. Erythropoietin was titrated to achieve hemoglobin levels between 12 and 14 g/dl. The endpoint was

quality of life. Planned enrollment was 300 patients. Study enrollment was terminated after 70 patients because of increased mortality in the experimental treatment arm. The median time-to-death was shorter in the erythropoietin cohort: 68 days vs 131 days; p=0.04. The increased mortality was attributed primarily to disease progression. Quality of life and the need for transfusion were not better in the erythropoietin arm. Reportedly enrollment was terminated in 12/2003. Preliminary results were included in the briefing document, but apparently FDA was not notified of additional study analyses until 2/2007.

Assorted Cancers, Not Receiving Chemotherapy, Darbepoietin
(Funded by Amgen)
(Press release; American Association for Cancer Research Annual Meeting Webcast)

Patients (N=989) with a variety of active cancers, including hematologic cancers, who were anemic (hemoglobin <11 g/dl), but were not undergoing myelosuppressive chemotherapy or radiotherapy, were randomized to darberpoietin or placebo in a 16 week, double-blind trial with follow-up. Patients were to have a life expectancy greater than 4 months and an ECOG score of 2 or less. There was stratification by entry hemoglobin (<10 g/dl or ≥10 g/dl). The primary endpoint was transfusion rate between weeks 5 to 17. Other endpoints included hemoglobin change and quality of life. The patients receiving darbepoietin did not receive fewer transfusions (18% vs 24%; p=0.15, although reportedly fewer patients on darbepoetin would have met the protocol criteria for transfusions. Patients experienced more mortality (136/515 vs 94/470; p<0.05 CI1.04-1.51). The statistical significance in the preliminary analysis reportedly decreased with adjustments for baseline and prognostic characteristics, but still did not favor the ESA. Subgroup analysis suggested that the results varied by tumor. Reportedly the rate of hemoglobin increase, whether induced by drug or not, did not correlate with survival outcome. Poor response rate may have some predictive value. Thrombotic events were somewhat greater in the darbepoetin group (9.7% vs 7.7%). It should be noted that this study was conducted to fulfill a phase 4 commitment to the FDA for the study of tumor progression and survival. A report to the FDA is due 10/2007.

Cervical Cancer, Receiving Chemotherapy & Radiotherapy, Erythropoeitin α
(Funded by Johnson & Johnson) (Briefing document for FDA meeting)

An open-label randomized study (PR01-04-005/GOG-0191) in which patients with cervical cancer treated with concomitant radiotherapy and cisplatin and with hemoglobin levels <14 g/dl were randomized to receive erythropoietin (40,000 U/wk). The dose was increased 50% in poor responders after 4 weeks. The study appears to have been terminated because of excess numbers of thrombo-embolic-vascular events. Data were reportedly available for 79 of the planned 460 patients. 17% (10/58) of events (primarily venous thromboses) occurred in patients on epoetin; 9% (5/55) occurred in patients on placebo. The small numbers preclude more extensive analysis.

E. Ongoing Studies

We identified 17 reportedly ongoing studies in patients with non-myeloid cell line tumors

(16 solid tumors, 1 large B cell lymphoma, 1 chronic lymphocytic leukemia) (Table 5). Despite the antiquated start dates for many of the studies, we were unable to locate Medline publications as of 3/28/07. One study investigator, however, has published a discussion paper on the subject. Several studies were initiated as phase 4 commitments to the FDA. Several studies, but not all, are registered with Clinical Trials.gov.

Table 6: Ongoing Studies

Cancer	Drug	Investigator/Study Name	Outcome	Start Date	Clin Trial #
Breast	Epo α	A Howell	Overall survival	2000	
Breast	Darb α	German Gynecological Oncology Study Group â€œPREPAREâ€ Study DE-2001-0033	Relapse-free survival	2001 1 published article on cognitive function**	Phase 4 Report to FDA due 11/2007*
Breast	Darb α	West German Study Group DE-2002-0015 ARA-03	Event-free survival (death, relapse, 2nd primary)	2002	Phase 4 Report to FDA due 11/2007*
Breast	Darb α	U Nitz Heinrich-Heine University, Duesseldorf	Disease-free & overall survival at 6 mo to 5 yrs after tx	2004	NCT00309920[a]
Breast	Epo α	Johnson & Johnson	Progression-free survival	2006	NCT00338286[b]
Cervical	Epo α	NCI/NIC of Canada GM Thomas/PS Craighead	Progression-free survival Overall survival	2001 No longer recruiting	NCT00017004[c]
Cervical	Epo	JCA Dimopoulos/ Richard Poetter	Remission rate Local control Disease-free survival	2000 Expected completion 2008	NCT00348738[d]
Cervical	Epo α	Blohmer AGO/NOGGO	Relapse-free survival 5 yrs	1999 Abstract published at 2 yrs #	
Cervical	Epo	H Koelbl	Tumor response	2002	NCT00046969[e]

	ß	AGO Ovarian Cancer Study Group		(Reportedly still recruiting)	
Head-neck	Epo	P Lambin EORTC 229996-24002	Loco-regional control Overall survival	1999	
Head-neck	Epo α	JS Stewart	Local tumor control Disease-free survival Overall survival	1999	
Head-neck LOOK	Epo α	Cross Canada Institute Parliament	Local tumor control Overall survival	Not known	
Lung	Epo α	M 'Brien	Response to chemotherapy	1998	
Lung (non-small cell)	Epo	AR Blackstock	Tumor response rate Overall survival	2002	
Lung (small cell)	Darb α	Amgen 20010145	Survival time	2002 No longer recruiting	NCT00119613[f]
Pelvic	Epo α	D Antonadou	Disease-free survival	Not known # #	
Leukemia (chronic lymphocytic)	Darb α	M Hallek German CLL Study Group	Multiple endpoints including survival	2004	NCT00281892[g]
Lymphoma (large B-cell)	Darb α	A Bosley/R Delarue Group d'Etude des Lymphomes de l'Adulte FR-2003-3005 GELA LNH03-6B	Event-free survival	2003 Expected completion 2008	Phase 4 Due 8/1010* NCT00144755[h]

*It should be noted that this study is being conducted to fulfill a phase 4 commitment to the FDA for the study of tumor progression and survival

**Hermelink K, Untch M, Lux MP, Kreienberg R, Beck T, Bauerfeind I, Munzel K. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. Cancer. 2007;March 9 E-pub.

Blohmer J, et al. Impact of epoetin alpha on disease-free survival in high risk cervical cancer patients receiving sequential adjuvant chemotherapy. ECCO abstract Sept 2003. GET Nothing on Medline since 4/9/07
Antonadou 2001 abstract
a--www.clinicaltrials.gov/ct/show/NCT00309920
b--www.clinicaltrials.gov/ct/show/NCT00338286
c--www.clinicaltrials.gov/ct/show/NCT00017004
d--www.clinicaltrials.gov/ct/show/NCT00348738
e--www.clinicaltrials.gov/ct/show/NCT00046969
f--www.clinicaltrials.gov/ct/show/NCT00119613
g--www.clinicaltrials.gov/ct/show/NCT00281892
h--www.clinicaltrials.gov/ct/show/NCT00144755

4. Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)

A MEDCAC meeting was not convened for this issue.

5. Evidence Based Guidelines/Professional Society Position Published Statements

a. American Society of Hematology (ASH)
Guidelines for ESA use in cancer patients were issued in conjunction with the American Society for Clinical Oncology. They are available as a 2002 publication by Rizzo et al. (Rizzo 2002). The Society has indicated that "Since the publication of this guideline, the product labeling for erythropoiesis stimulating agents has been significantly revised based on emerging safety data." The Society directs site users to the 3/9/ 2007 FDA alert via a web link.

b. American Society for Clinical Oncology (ASCO)
Guidelines for ESA use in cancer patients were issued in conjunction with the American Society of Hematology. They are available as a 2002 publication by Rizzo et al. via request from the Society (Rizzo 2002). The Society has indicated that "Since the publication of this guideline, the product labeling for erythropoiesis stimulating agents has been significantly revised based on emerging safety data." The Society directs website users to the FDA website.

c. National Comprehensive Cancer Network (NCCN)
The National Comprehensive Cancer Network issued updated guidelines from 2/2006 in 1/2007 and 2/2007. Additional revisions are underway. Identification of non-cancer related causes of anemia and appropriate treatment is promoted. It states that cancer-related fatigue is multifactorial, that anemia is only one of the causes, and that this is an active area of investigation. It states that the relationship between anemia and treatment outcome is poorly characterized. It recommends assessment of clinical risk before initiating treatment and determining treatment targets. It acknowledges that "high risk" patients are poorly characterized and that there is a paucity of prospective data regarding their management. It encourages ESA discontinuation in poor responders and dose lowering in brisk responders. Most recently, it has strengthened its warnings about ESA-

associated thrombosis based on the meta-analysis by Bohlius et al. and noted the paper's identification of a trend towards reduced survival (Bohlius 2006). It also recommended that physicians not use ESAs in cancer patients with anemia not due to concurrent chemotherapy if the patients are similar to those enrolled in the Amgen trial. The NCCN "believes that the best management of any patient is in a clinical trial. Participation in clinical trials is especially encouraged."

d. European Organization for Research and Treatment of Cancer (EORTC)
The European Organisation for Research and Treatment of Cancer last prepared an update for ESA use in 2006 prior to the emergence of new data (Bokemeyer 2006/7).

> "The addition of further level I studies confirms our recommendation that, in cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a hemoglobin level of 9-11 g/dl based on anemia related symptoms rather than a fixed hemoglobin concentration..."
>
> "We do not recommend the prophylactic use of erythropoietic proteins to prevent anemia in patients undergoing chemotherapy or radiotherapy..."
>
> "There is only indirect evidence that patients with chemotherapy-induced anaemia or anaemia of chronic disease initially classified as non-responders to standard doses proceed to respond to treatment following a dose increase. None of the studies addressed the question in a prospective, randomised fashion, and so the Taskforce does not recommend dose escalation as a general approach in all patients who are not responding..."
>
> "This analysis confirms that there are no baseline predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice if functional iron deficiency or vitamin deficiency is ruled out; a low serum erythropoietin (EPO) level (only in haematological malignancies) appears to be the only predictive factor to be verified in Level I studies. Further studies are needed to investigate the value of hepcidin, C-reactive protein, and other measures as predictive factors..."
>
> "There is still insufficient data to determine the effect on survival following treatment with erythropoietic proteins in conjunction with chemotherapy or radiotherapy..."
>
> "Likewise, we found no clear link between erythropoietic therapy and other endpoints such as local tumour control, time to progression, and progression-free survival..."
>
> "There is Level I evidence that the risk of thromboembolic events and hypertension are slightly elevated in patients with chemotherapy-induced anaemia receiving erythropoietic proteins."

7. Public Comments

We received 66 topical comments during the initial public comment period. Of the public commenters who furnished this information, 37 were from providers, 5 were from caregivers, 1 was from a patient, 13 were from professional organizations, 7 were from patient advocacy groups, 1 was from a national oncology policy consulting group and 2 were from pharmaceutical companies. Two comments regarding the use of ESAs for renal disease and two related to code assignments are included in the 70, both topics are outside the scope of this NCD.

The majority of commenters requested CMS to provide coverage of ESAs for all non-renal FDA approved indications. Several commenter included studies and scientific literature with their comments.

Finally, several commenters requested that CMS delay rendering a proposed decision until after the FDA Oncology Drug Advisory Committee (ODAC) meeting scheduled for May 11, 2007. Commenters suggested that CMS review the literature and data distributed at the ODAC meeting prior to rendering the proposed decision. CMS' final decision will be published after the ODAC meeting. CMS will as usual consider additional timely evidence furnished after the publication of the proposed decision.

8. Expert Opinion

CMS has solicited external expert opinion and anticipates receiving responses before the publication of the final decision memorandum.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member' (§ 1862(a)(1)(A)). This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions:

> *1. Is the evidence sufficient to conclude that erythropoiesis stimulating agent (ESA) therapy affects health outcomes when used by Medicare beneficiaries with cancer and related neoplastic conditions?*
>
> *2. If the answer to Question 1 is affirmative, what characteristics of the patient, the disease, or the treatment regimen reliably predict a favorable or unfavorable health outcome?*

In the classic paradigm, physiologic replacement of a missing hormone should result in normalization. Indeed many, albeit not all, patients with end-stage renal disease are deficient in erythropoietin because of damage to the renal parenchyma. Their anemia is secondary to and highly responsive to low doses of ESAs. In the non-classic paradigm, a hormone is used at higher than physiologic levels because of hormone resistance or to supplement endogenous pathways to achieve superphysiologic or accelerated physiologic responses.

Early ESA drug development was based on the classic paradigm of erythropoietin action. The endpoints in the clinical trials were reduction in the transfusion rate, quality of life, absolute hemoglobin level, and change in hemoglobin level. The hemoglobin parameters were surrogate endpoints. Because anemia portended poor clinical outcome (Dunphy 1989, Fein 1995, Obralic 1990, Oehler 1990, Reed 1994), it was hypothesized that reversal of anemia itself would improve long-term clinical status. It was presumed that the primary risk was thrombo-embolic-vascular events, and that these were related to hemoglobin level rather than to drug dose and/or response to drug dose. As such, most of the registration trials for FDA approval were relatively small and conducted in patient heterogeneous populations with a mixture of primarily solid tumors at various stages and undergoing treatment with a variety of regimens. (See tables 2A and 2B.) The relative risks and benefits for patients with lymphoproliferative disease are not addressed in the drug label and anecdotal evidence suggest that ESA use in hematologic disease may increase the risk for transformation to plasma leukemia, increased light chain excretion, and decrease the remission interval (Caillette 1993, Olujohungbe 1996, Rogers 1990). The studies were of relatively short duration (12-16 weeks). In addition, entry criteria excluded patients who were sicker because of their oncologic disease or their co-morbidities. Typically life expectancy was to be at least 6 months and/or an Eastern Cooperative Oncology Group (ECOG) performance score of 2 or lower (Oken 1982; ECOG website). In general, patients with New York Heart Association (NYHA) classifications 3 and 4 were excluded. Geriatric patients constituted a relatively small proportion of patients in the registration trials.

Emerging data suggest that ESA use may be associated with increased morbidity and mortality in a variety of patient populations despite the alleviation of anemia. Although the features and exact mechanisms of the increased mortality require better delineation, both thrombo-embolic-vascular disease and tumor progression appear to be involved.

Indeed thrombosis was observed in the early trials in renal patients (the first approved indication for ESAs (Winearls 1986). It was also observed retrospectively (adjusted odds ratio 15.3) in cervical cancer patients. (Wun 2003) More recently thrombosis was observed in patients who received ESAs for spinal and cardiac surgery (D'Ambra 1997, FDA Alert 2007, Procrit label). These data suggest that the thrombotic phenomenon is related to the pharmacologic agent and cannot be entirely attributed to the underlying disease condition.

Etiologic attribution of thrombotic-vascular disease in oncology and cancer treatment, however, is particularly challenging in the absence of randomized clinical trials stratified

for a variety of variables because cancer is a hypercoagulable state (Alacay 2006, Chew 2006, 2007, De Cicco 2004, Grudeva-Popova 2005, Semrad 2007, White 2005). Typically the venous system is involved, but arterial thrombosis does occur. Tumor cells release cysteine proteases that activate coagulation cascade factor X and tissue factor (TF) that activates factor VII (Kakkar1995). Sialic chains on the mucin from adenocarcinomas activate factor X (Donati 1984, Pineo 1973). Cancer cells interacting with monocytes and macrophages induce the release of interleukins (IL)(1,6) and tumor necrosis factor (TNF) (De Cicco 2004, Edwards 1981, Rickles 2001, Schwartz 1981). Furthermore, cancer treatment, including radiotherapy and surgery, can also contribute to thrombosis (Hallahan 1999, Schreiber 1986, Wilson 1987). Growth-factors, high dose fluorouracil, L-asparaginase, mitomycin, platinum compounds, and tamoxifen have all been implicated (Deshmukh 1995, Falanga 2001, Feffer 1989, Fisher 1990, Kuzel 1990, Lee 1999, 2006, Levine 1988, Lipton 1984, Pritchard 1996, Rella 1996, Rivkin 1994, Rogers 1988, Saphner 1991, Weitz 1997). Central line catheter surfaces can activate platelets and factors X and XII (Bern 1990, Bona 1999, De Cicco 124, Lockich 1983, Monreal 1991). Infections of such catheters can result in the release of mucopolysaccharides (gram positive organisms) and endotoxins (gram negative organisms) that activate factor XII, IL-1, TF, and TNF. Venous stasis due to immobility and drug therapy also contributes to thrombosis (De Cicco 2004, Kessler 1989, Levine 1993, Sue-Ling 1986, Walsh 1974).

Several studies in cancer patients were terminated because of thrombo-embolic-vascular events. The FDA has strengthened its warnings for these types of events in the ESA drug labels. The mechanism(s) by which ESAs might cause or aggravate thrombosis are not known. ESA-induced hyperviscosity has been postulated as a cause in patients with high hematocrit levels (Begg 1966; Lage 2002; Turito 1980). Hematocrit elevation, however, cannot be the sole cause of thrombosis because platelet number is increased, function altered, and bleeding time shortened even prior to the erythrocytic rise (Akizawa 1991; Ando 2002; Aranesp™ package insert; Homonchick 2004, Kooistra 1994; Malyszko 1995, 1996; Pirisi 1994; Roger 1993, Sharpe 1994; Stohlawetz 2000). Alterations in other coagulation factors (decreased proteins C and S; increased Factor VIII, thrombin-antithrombin (TAT) III complex, thrombin activatable fibrinolytic inhibitor, and von Willenbrand factor) have been reported (Akizawa 1991; Macdougall 1991, Malyszko-A 1995, Taylor 1992, Tobu 2004). It is known that ESAs cause fluid retention and hypertension (Malyszko -B 1995, Maschio 1995, Roger 1996, Winearls 1986). Both of these can precipitate congestive heart failure and resulting venous stasis. Regardless of the cause(s), only careful prospective trials controlled for the various thrombotic risk factors associated with vascular-thrombotic-embolic disease of cancer will delineate the magnitude of risk attributable to ESAs for the various oncologic populations. Medicare beneficiaries may be at increased risk for such events because of increased cardiovascular disease, increased co-morbidity, and decreased mobility.

At the time of initial drug approvals for cancer-treatment associated anemia, the FDA had concerns about ESA mediated tumor initiation or promotion. The FDA requested post-approval phase 4 commitments in 1993 and 2002 to explore this putative risk promotion because the registration studies were not structured to assess overall survival, cause-

specific mortality, cause-specific morbidity, tumor-free survival, and tumor progression. The post approval studies permitted heterogeneous patient populations because it was presumed that the risk benefit ratio would be similar for all tumors at all stages, for all treatment modalities, and in all adult patient populations.

In many of the terminated trials, there was a signal suggesting decreased survival. Attribution for the precise determination of mortality cause was often not done or not done rigorously. Nonetheless, results from studies that attempted to assess cancer disease-free survival or changes in locoregional tumor control, suggest that tumor progression plays a more significant role than vascular-thrombotic events in the apparent decreased survival observed with ESA use for the anemia secondary to cancer chemotherapy, an FDA approved indication. A signal for decreased survival was also observed with ESA use for the anemia of cancer (but no therapy) and to reduce tissue hypoxia during radiation treatments, neither of which are FDA approved indications. These observations have resulted in FDA Black Box warnings.

Tumor progression might occur via a number of avenues. Malignant cells could be transformed, or their milieu enriched. The first mechanistic pathway includes the ability of malignant cells to survive via decreased programmed cell death (apoptosis), the ability to survive through resistance to chemo/immuno/radiotherapy, increased proliferation leading to greater tumor burden, enhanced invasiveness, and improved migratory or metastatic travel capacity. Another mechanistic pathway includes decreased tissue hypoxia and increased nutrient supply via a more extensive vascular network (angiogenesis) and increased erythrocyte number.

There is a significant amount of in vitro work to support the first pathway, and this might inform CMS in its coverage decision in the absence of definitive clinical data (Acs 2001, 2002, 2003; Anagnostou 1990, 1994; Arcasoy 2003, 2005; Batra 2003; D'Andrea 1989; Digicaylioglu 1995; Farrell 2004, Fraser 1989; Haroon 2003; Henke 2006, Jones 1990; Kumar 2006, Lai 2005; Lappin 2003, Masuda 1993; Mioni 1992, Ogilvie 2000, Ribatti 2003; Rossert 2005, Selzer 2000; Westenfelder 2000; Wright 2004; Winkelman 1990 Yasuda 1998, 2001, 2006). Indeed, elements of the erythrocyte receptor signaling cascade are similar to those of epidermal growth factor (EGF) receptor, a target against which immunotherapeutic agents are being developed (Wakao 1997, Zhang 2006). Locoregional progression of head-and-neck cancer was increased in patients with tumors positive for erythropoietin receptors and who were treated with erythropoietin (Henke 2006). There is a trend for such progression even in the patients with erythropoietin receptors who did not receive erythropoietin suggesting that endogenous erythropoietin might be variable and able to impact clinical outcome (Henke 2006). Cultured cells (cervical cancer line HT100 and glioma line U87) developed resistance to ionizing radiation and cis-platinum after exposure to erythropoietin (Belenkov 2004, Yasuda 2003). Incubation with an inhibitor to the erythropoietin receptor's JAK-STAT pathway, typhostin (AG490), could reverse this resistance (Belenkov 2004).

The picture, however, is not straightforward. As such, universal statements about ESA use in oncology cannot be made. Erythropoietin receptor number may change with the

cell cycle (Acs 2001, Broudy 1991). The number may increase with the stage of the tumor (Acs 2001). Some cell lines do not exhibit proliferation in response to erythropoietin exposure (Wesphal 2002). Indeed, Henke et al. found that locoregional progression of head-and-neck cancer was not increased in erythropoietin-treated patients lacking erythropoietin receptors (Henke 2006). Mittelmann et al. even found that myeloma regression in mice after ESA treatment (Mittelmann 2001). Tovari et al. found that ESA treatment might enhance sensitivity to 5-fluorouracil chemotherapy (Tovari 2005).

There is also a significant amount of in vitro work that supports the second mechanistic pathway. Microvascular density and tumor stage (for neuroblastomas and hepatocellular carcinomas) have been found to correlate with both erythropoietin and erythropoietin receptor expression (Ribatti 2007 A&B). This suggests that there is tumor secretion of erythropoietin that binds to erythropoietin receptors on vasculature which, in turn, proliferates and further promotes tumor growth (Ribatti 2007 A&B). Secretion of pro-angiogenic factors and recruitment of vascular endothelium has also been observed with human mesenchymal stem cells (which, like cancer cells, are less differentiated than normal cells) (Zwezdaryk 2007). There has even been a report of the conversion of myelodysplastic syndrome (MDS) to leukemia attributed to erythropoietin's angiogenic effects on the bone marrow (Bunworasate 2001, Ribatti 2002). Indeed anti-angiogenic monoclonal antibody therapy has been approved for colon cancer and is under development for other tumors (Panares 2007). Nonetheless, erythropoietin-induced angiogenesis has not been found in all cancers or test models (Hardee 2005).

Oncology patients may be exposed to supraphysiologic ESA doses. Many cancer patients manifest erythropoietin resistance, i.e., they have an inappropriately low endogenous erythropoietin response to anemia (Ward 1977) and do not respond to low exogenous dose levels (Miller 1990). This is likely to be compounded in geriatric patients who are known to have reduced hematopoietic reserve (Miller 1990). Less frequent dosing regimens, although equivalent to more frequent dosing regimens on the basis of a hematologic response, result in higher peak blood levels of hormone (Chung 1998, 2001, Kryzunski 2005, Ramakrishnan, 2004). It is not known whether supraphysiologic ESA blood levels would increase the likelihood of spill-over from the classic high affinity erythropoietin receptor binding sites in the bone marrow to non-marrow receptors with different binding constants where it can act as a growth factor (Fraser 1988, 1989, Masuda 1993, Hardee 2006) or whether excess hormone is bound by the soluble erythropoietin receptors secreted by some tumors (Harris 1996; Maeda 2001, Wesphal 2002).

Regardless of the cause(s), careful prospective trials controlled for the tumor, tumor stage and perhaps tumor cell cycle, cancer treatment, and perhaps endogenous systemic or paracrine/autocrine erythropoietin production and the presence of erythropoietin receptor on tumors and as soluble elements in the blood are needed to inform CMS determinations as to whether ESAs provide a meaningful clinical benefit for the various oncologic populations. Careful trials would also assess the effects of dose including doses in patients who exhibit a poor hematologic response to low doses as well as the effects of

long-term dosing and repeated dosing.

Summary

We cannot be sure of the completeness of the evidentiary database because of the question of unpublished data. Negative studies were frequently not available as full published reports on Medline. The early termination of studies by data safety monitoring boards, investigators, and/or pharmaceutical sponsors because of a safety concern does not permit complete appraisal of the magnitude of safety risk. Early termination may reduce the statistical power of a safety finding. Nonetheless, evidence of harm is apparent despite these limitations. ESA treatment is associated with an increased risk of thrombotic-vascular disease, tumor progression, and decreased survival. Furthermore there are potential mechanisms that could explain the etiology of the harm.

Although the data are less robust than we would like, particularly for geriatric patients, they are sufficient to identify patient characteristics and treatment practices that increase the likelihood of unfavorable clinical outcomes. Increased thrombotic-vascular disease, tumor progression, and/or decreased survival occurred with ESA use to prevent or treat anemia secondary to cancer, cancer chemotherapy, or radiotherapy or to improve tissue hypoxia in an attempt to enhance tumor sensitivity to therapy.

From the evidence reviewed, we believe that:

- cancers with erythropoietin receptors-especially when coupled with extensive exogenous ESA exposure may predict increased risk for tumor progression and/or decreased survival.
- the risk:benefit profile is less defined for hematologic cancers because FDA reviewed studies are lacking and patients with myelogenous cancers were excluded from studies.
- a variety of factors including a rapid rise in hemoglobin, a normalized hemoglobin, and a high ESA dose requirement may contribute to or portend increased risk for thrombotic-vascular events
- patients with poorly controlled hypertension, fluid retention, congestive heart failure, and prior thrombo-embolic events are at increased risk for future thrombotic-vascular events with ESA use.
- ESAs may negate the therapeutic utility of anti-angiogenesis and anti-EGF receptor agents.
- bone marrow or progenitor cells within the bone marrow damaged by proliferative or scarring disease have not been adequately shown to respond to low ESA doses without sequelae.

Especially in the setting of potential harm, we believe ESA treatment is not a reasonable substitute for targeted therapy addressing the underlying cause(s) of the anemia. Anemia due to vitamin or mineral deficiency should be addressed by supplementation of those nutritional deficiencies. We believe that ESA use is reasonable and necessary only in clinically significant anemias due to chemotherapy when used at low doses for short

durations. In particular, appropriate limitations should be applied to ESA use by beneficiaries with tumors with erythropoietin receptors. ESA use is not reasonable and necessary in beneficiaries with a poor hemoglobin response.

IX. Conclusion

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that erythropoiesis stimulating agent (ESA) treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

1. any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis
2. the anemia of myelodysplasia
3. the anemia of myeloid cancers
4. the anemia associated with the treatment of myeloid cancers or erythroid cancers
5. the anemia of cancer not related to cancer treatment
6. any anemia associated with radiotherapy
7. prophylactic use to prevent chemotherapy-induced anemia
8. prophylactic use to reduce tumor hypoxia
9. patients with erythropoietin-type resistance due to neutralizing antibodies
10. patients with treatment regimens including anti-angiogenic drugs such as bevacizumab
11. patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor (EGF) receptor
12. anemia due to cancer treatment if patients have uncontrolled hypertension
13. patients with thrombotic episodes related to malignancy

We also propose that ESA treatment is only reasonable and necessary under specified conditions for the treatment of anemia those types of cancer in which the presence of erythropoeitin receptors on either normal tissue/cell lines or malignant tissue/cell lines has been reported in the literature. These cancer types include but are not necessarily limited to:

- bone (sarcoma),
- brain-neurologic,
- breast,
- cervical,
- colo-rectal,
- gastric,
- head-and-neck (squamous cell),
- hepatic,
- lung,
- lymphoma
- melanoma,
- multiple myeloma
- muscle including cardiac,
- ovarian,
- pancreatic (exocrine),
- prostate,
- retinal, and
- uterine.

For patients undergoing treatment for these cancers, we propose that ESA use is reasonable and necessary with the following limitations:

1. the hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be < 9 g/dl/27% in patients without known cardiovascular disease and < 10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion (We suggest that patients, especially those in the latter category, be alerted to the increased potential for thrombosis and sequelae).
2. the maximum covered treatment duration is 12 weeks/year;
3. the maximum covered 4 week treatment dose is 126,000 units for erythropoietin and 630 Î¼g for darbepoietin;
4. continued use of the drug is not reasonable and necessary if there is evidence of poor drug response (hemoglobin/hematocrit rise < 1 g/dl/< 3%) after 4 weeks of treatment;
5. continued administration of the drug is not reasonable and necessary if there is an increase in fluid retention or weight (5 kg) after 2 weeks of treatment; and
6. continued administration of the drug is not reasonable and necessary if there is a rapid rise in hemoglobin/hematocrit > 1 g/dl/> 3% after 2 weeks of treatment.

Local contractors may continue to make reasonable and necessary determinations for all uses of ESA therapy for beneficiaries with cancer whose condition is not addressed above.

We are requesting public comments on this proposed determination pursuant to section 1862 as revised by 731 of the Medicare Modernization Act. In light of the issues discussed in our review of the evidence and serious safety concerns voiced in the May 10, 2007 FDA Oncologic Drugs Advisory Committee (ODAC) meeting we are also interested in public comment on whether coverage for ESA therapy for Medicare beneficiaries with cancer should occur only within appropriately designed clinical research studies where informed consent and safety monitoring can be assured. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

Appendices

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Appendix B: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS normally divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits. The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough

documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. **Generalizability of Clinical Evidence to the Medicare Population**
3.

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important

that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

4. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Improved health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix
Table 2
Studies with ESAs Not Structured to Provide Survival, Thrombosis, and Tumor Progression Data for Cancer by Stage and Type—Papers[1]

Author	Disease Type	Prospectively Stratified for Type/ Stage	Single Cancer Tx Regimen	Single ESA Regimen	Placebo-controlled, Double-blind, Randomized	Sufficient Duration for Dx & Endpoint	Sufficient Power for Endpoint	Endpoint
Randomized-Concurrent Control-Monotherapy-Malignant Conditions								
Abels 1992 Paper Medline (yes)	No Excluded acute leukemia or myeloid ca See Abels 1996 & Henry 1994	No Hb ≤10.5 g/dl or Hct ≤32% Excluded cerebral metastases Performance status: ECOG ≤3 Life expectancy ≥3 mo	1 cohort w no chemotherapy 1 w non-platinun, 1 w platinum tx	Chemo group treated 8 wks; other groups treated 12 wks Titration permitted *	Yes	NA 8 or 12 wks+open label phase	NA N=124 No cheno N=132 Platinum N=157 Non-platinum Excluded pts if ESA tx <15 days	1º Hct level ≥38% or Hct change ≥6% Transfusion need 2º QOL
Abel 1993 Paper Medline (yes)	No Excluded acute leukemia & myeloid ca See Abels 1992, 6 & Henry 1994	No Hb ≤10.5 g/dl or Hct ≤32% Excluded cerebral metastases, renal dysfunction Performance status: ECOG ≤3 Life expectancy ≥3 mo	1 cohort w no chemotherapy 1 w non-platinun, 1 w platinum tx	Chemo group treated 8 wks; other groups treated 12 wks Titration permitted *	Yes	NA 8 or 12 wks+open label phase	NA N=124 No cheno N=132 Platinum N=157 Non-platinum Excluded pts if ESA tx <15 days	1º Hct level ≥38% or Hct change ≥6% Transfusion need 2º QOL
Abels 1996 Paper Medline (yes)	No Excluded acute leukemia & myeloid ca See Abels 1992, 1993, Henry 1994	No Hb ≤10.5 g/dl or Hct ≤32% Excluded cerebral metastases, renal dysfunction Performance status: ECOG ≤3 Life expectancy ≥3 mo	1 cohort w no chemotherapy 1 w non-platinun, 1 w platinum tx	Chemo group treated 8 wks; other groups treated 12 wks Titration permitted *	Yes	NA 8 or 12 wks+ open label phase	NA N=124 No cheno N=132 Platinum N=157 Non-platinum Excluded pts if ESA tx <15 days	Hct change Transfusion need QOL
Aravantinos 2003 Paper Medline (?)	No	No Hb <10.5 g/dl Performance status: ECOG ≤3 Life expectancy ≥3 mo	Platinum tx At various stages in chemotherapy	Yes *	No Open-label	NA Unspecified duration	NA N=47	1º Transfusion need 2º Hb change

Auerbach 2004 Paper Medline (?)	No Excluded lymphoma invasive of marrow & primary marrow maliganacy except CML & MM	No Hb <10.5 g/dl Performance status: ECOG ≤2 Life expectancy ≥6 wks	Anemia could be due to cancer & not tx	Yes, fixed ESA dose ± IV Fe	No Open-label of various Fe tx Not study of Epo per se	NA 6 wks	NA N=157	1° Fe effect on hb 2° QOL
Bamias 2003 Paper Medline (?)	No Solid ca	No Hb ≤13 g/dl Stratified by ca Performance status: WHO ≤3 Life expectancy ≥6 mo Excluded cerebral mets, marrow infiltration, renal dysfunction	Platinum tx	No Variable time Dose ↑ permitted q3-4 wks *	No Open-label	NA Duration of chemotherapy	NA N=144	1° Transfusion need 2° Hb <10 g/dl
Boogaerts 2003 Paper Medline (?)	No	No Hb ≤11 g/dl Performance status: WHO ≤2 Life expectancy >6 mo Excluded seizure, renal dysfunction	No	No Dose ↑ permitted *	No Open-label	NA 12 wks	NA N=262	1° QOL 2° Hb change Transfusion need
Buyukpamukcu 2002 Paper Medline (yes)	No Solid ca (Pediatric)	No Hb >11 g/dl prior to chemo & <10 g/dl w chemo Excluded hepatic, renal dysfunction	No	Yes	Unknown if blind	NA 8 wks	NA N=34	Hb change Transfusion need
Cascinu 1994 Paper Medline (?)	No	No Hb >11 g/dl prior to chemo & <9 g/dl w chemo Excluded cardiac, hepatic, renal dysfunction	Platinum tx Excluded hormone tx	Yes *	Yes	NA 9 wks	NA N=100	1° Hb >10 g/dl at 3 wks 2° Transfusion need
Case 1993 Paper Medline (yes)	No Excluded acute leukemia & myeloid ca	No Hb <10.5 g/dl Performance status: ≤3 Life expectancy >3 mo Excluded cerebral mets, renal dysfunc-	No	Yes *	Yes	NA ≤12 wks or until hct 38-40%	NA N=153	1° Hct >38% or 6% change 2° Transfusion need QOL

		tion						
Cazzola 1995 Paper Medline (yes)	No MM, NHL-low, intermediate grade	Low-intermediate grade Hb ≤11 g/dl Performance status: WHO ≤2 Life expectancy >3 mo Excluded seizure, hepatic dysfunction	Tx not required	Yes 4 doses+placebo *	No Open-label	NA 8 wks	NA N=146	1° Mean weekly hb change: ≥2 g/dl EPO level
Chan 1995 Letter Medline (?)	No Excluded hematologic dx	No Hb ≤10.5 g/dl Excluded cerebral metastases	No	Yes	Unknown if blind	NA 16 wks	NA N=20	Hb change
Chang 2005 Paper Medline (?)	Yes Breast ca See Chang abstract	No Hb <12 g/dl Life expectancy >6 mo	No	No Dose ↑ permitted post 4 or 6 wks *	No Open-label	NA 16 wks or until 4 wks after chemotherapy completion	NA N=354	1° QOL at 12 wks 2° Hb >12 g/dl
Dammacco 1998 Paper Medline (?)	Yes Refractory MM	Stage 2 or 3a Not stratified by tx status Hb <10 g/dl &/or trans-fusion dependence Performance status: Karnofsky >40% Excluded renal dysfunction	No growth factors Not required, but permitted-including XRT	No ESA SQ 150 U/kg TIW Dose ↑ permitted *	No Open-label	NA 24 wk	NA N=71	1° Transfusion need 2o Complete response: Hb change ≥2 g/dl &/or reduced transfusion need QOL
Dammacco 2001 Paper Medline (yes)	Yes MM	No Hb <11 g/dl after ≥6 mo chemotherapy Performance status: ECOG ≤3 Life expectancy ≥3 mo	No	No 2 formulations ESA SQ 150 U/kg TIW Dose ↑ permitted at 4 wks *	Yes Except 2 ESA formulations used	NA 12 wks + 12 wks open-label extension	NA N=155 N=144 evaluated	1° Transfusion need 2° Hb change ≥2 g/dl or level ≥12 g/dl QOL
Daneryd 1998 Paper Medline (no)	No Cachexia due to solid ca primarily GI ca	No Stratified by tumor type, stage Life expectancy ≥6 mo Excluded brain mets, hepatic, renal dysfunction	Stratified by prior tumor tx Tx=indomethicin± EPO	No ESA only if hb <12.8/ 12 g/dl for M/F & until hb normal	Unknown if blind	NA Tx till death or unable to take indomethicin	NA N=108	1° Nutritional state Calorimetry Exercise tolerance 2 ° Survival
De Campos	Yes	No	No	Yes *	Unknown if blind	NA	NA	Time of hb nadir

1995 Paper Medline (yes)	Small cell lung ca	Performance status: Manchester ≤2 Excluded brain mets, cardiac, hepatic, renal dysfunction	Sites differed by # cycles & time of brain XRT Excluded androgen tx	2 doses+placebo		Through multiple tx cycles	N=36	Transfusion need (RBC & PLT) Clonogenic assay
Del Mastro 1997 Paper Medline (no)	Yes Breast ca Anemia prevention	Stage 2 Hb ≤12 g/dl	Yes, except tamoxifen added if receptor + Tx included GCSF	Yes *	Unknown if blind	NA 6 chemo cycles & 36 Epo tx	NA N=62	Hb >10 g/dl EPO levels Fe parameters QOL
Dunphy 1999 Paper Medline (yes)	No Head & neck or non small cell lung ca Appears to be a subset of a phase II trial	No Head & neck stages 3-4 Lung ca stage 4 Life expectancy ≥4 mo Performance status: Zubrod ≤2 Excluded renal dysfunction	No Chemotherapy the same, but the # of regimens differed by disease. XRT or surgery added for head-neck pts depending on response	No Dose ↑ permitted at the end of each chemotherapy round *	No Open-label	NA Variable duration ESA appears to have been used only during chemotherapy phase	NA N=30	1º Hb change >2.5 g/dl
Fallowfield 2002 Paper Medline (yes)	No Non-myeloid ca Subset of Littlewood 2001 data	No Stratified by solid or hematologic ca Hb <10.5 g/dl or changed >1.5 g/dl	No Platinum txed pts excluded	No Variable duration	Yes	NA Tx 16-28 wks	NA N=375	2º QOL
Gamucci 1993 Paper Medline (?)	No Advanced ca	No Stratified by tx Hb <11 g/dl Excluded cardiac, renal dysfunction	Prior tx excluded Platinum tx	Yes (included Fe)	Unknown if blind	NA 12 wks	NA N=38 Preliminary data	Hb change
Garton 1995 Paper Medline (yes)	Yes MM	No Excluded HTN & other comorbid dx not 2º to MM	No No recent androgens Assorted chemotherapy	No Epo SQ 150 U/kg TIW Dose ↑ permitted at 6 wks *	Yes Blinded for 12 wks	NA After 12 wks, placebo group switched to Epo w dose ↑ permitted at 6 wks Tx DC in non-responders	NA N=25	Complete response: Hct 38% Partial: Hct change ≥6%
Hedenus 2002 Paper Medline (yes)	No CLL, HD, MM, low or intermediate grade NHL	No Reportedly stratified by lymphoma vs MM Performance status: ECOG ≤2 Life expectancy ≥6 mo Excluded hepatic,	No	Yes * 3 ESA & 1 placebo doses	Yes	NA 12 wks tx+4 wk f/u	NA	Hb ≥12 g/dl or change ≥2 g/dl

		renal dysfunction						
Hedenus 2003 Paper Medline (yes)	No CLL, HD, NHL, MM	No Hb ≤11 g/dl Performance status: ECOG ≤3 Life expectancy ≥4 mo Excluded CNS, cardiac, hepatic, renal dysfunction	No	No Dose ↑ permitted at 4 wks *	Yes	NA 12 wks+4 wk f/u	NA N=349	1° Hb change >2 g/dl 2° Transfusion need after 4 wks tx QOL
Henry 1994 Letter Medline (yes)	No Assorted ca See Abels 1992, 1993, 1996 Post hoc analysis	No Hb ≤10.5 g/dl or Hct ≤32% Performance status: ECOG ≤3 Life expectancy ≥3 mo Excluded cerebral metastases	1 cohort w no chemotherapy 1 w non-platinun, 1 w platinum tx	Chemo group treated 8 wks; other groups treated 12 wks Titration permitted *	Yes	NA 8 or 12 wks+open label phase	NA N=206 Post hoc analysis on subset of larger study	Predictors of hb change
Henry 1995 Paper Medline (yes)	No Excluded acute leukemia & myeloid ca See Abels 1992, 1993, 1996	No Performance status: ECOG ≤3 Excluded cerebral metastases, seizure, renal dysfunction	Platinum tx	Yes *	Unknown if blind	NA ≤12 wks or until hct 38-40%	NA N=132	Hb change Transfusion need QOL
Henry 2006B Paper Medline (yes)	No Non-myeloid ca	No Hb <11 g/dl Performance status: ECOG ≤2 Life expectancy ≥24 mo Excluded hepatic, renal dysfunction	No	No IV Fe, po Fe, no Fe; all +EPO, but EPO dose↑ permitted at 4 wks *	No Open-label	NA 8 wks tx+ 4 wks f/u	NA N=187	Hb change Fe parameters
Hermelinke 2007 Paper Medline (yes)	Yes Breast ca	No ≥2 cm or inflammatory lesions No metatases	Yes 1 of 2 regimens in PREPARE w sub-randomization to ±ESA	Yes *	Unknown if blind	NA 5 mo	NA N=109	Cognitive function
Iconomou 2003 Paper Medline (?)	No Solid ca	No Hb ≤11 g/dl	No	No Dose ↑ permitted at 4 wks *	Unknown if blind	NA 12 wks	NA N=122	Hb change QOL
James	Yes	No	Platinum tx	Yes *	No	NA	NA	1° Transfusion need

1992 Paper Medline (?)	Ovarian ca	Stages 2-4			Open-label	6 mos	N=21 of 30 enrolled Preliminary data	2° Hb change
Kotasek 2003 Paper Medline (yes)	No Solid ca See Kotasek abstract	No Hb ≤11 g/dl Performance status: ECOG ≤2 Life expectancy ≥6 mo Excluded CNS, cardiac dysfunction	No	Yes 6 fixed ESA doses & placebo *	Yes Part 2: optional open-label extension	NA 12 wk double-blind phase; 8 wk f/u OR 11 wk extension+8 wk f/u	NA N=248	Hb change (power calculation done) QOL Safety (but no power calculations)
Kunikane 2001 Paper Medline (yes)	Yes Non-small cell lung ca	No Performance status: ECOG ≤2 Life expectancy ≥3 mo Excluded massive bone metastases, renal dysfunction	2 platinum tx	Yes 2 fixed ESA doses & placebo *	Yes	NA 6 wks	NA N=72 High drop-out for of exclusion violations	Hb change Hb nadir Transfusion need
Kurz 1997 Paper Medline (yes)	No Gynecologic ca (cervival, ovarian, uterine)	No Hb <11 g/dl Life expectancy >3 mo Excluded hepatic, renal dysfunction	No Polychemotherapy w platinum	No Dose ↑ permitted at 4 wks	Yes	NA 12 wks	NA N=35	Hb change Transfusion need QOL (unvalidated test)
Lindholm 2004 Paper Medline (no)	No W cachexia due to primarily GI ca See Daneryd	No Life expectancy >6 mo	Not current tx	No Indomethicin±variable ESA doses (if needed) until hb normalized	Unknown if blind	NA Tx till death or unable to take indomethicin	NA N=108	1° Relationship between hb & exercise power or physical functioning 2° Survival
Littlewood 2006 Paper Medline (yes)	No CLL, HD, NHL, MM See Hedenus	No Performance status: ECOG ≤3 Excluded hepatic, renal dysfunction	No	No Dose ↑ permitted at 4 wks *	Yes	NA 12 wks+4 wk f/u	NA N=344	QOL
Markman 1993 Paper Medline (yes)	Yes Ovarian ca Composite of 2 trials	No Hb <10.5 g/dl Performance status: Karnofsky >60 Life expectancy ≥2 mo Excluded hepatic, renal dysfunction	Yes Platinum tx W chemotherapy dose adjusted to WBC/PLT	No ESA dose could be ↑ or ↓ per response 3 pts did not receive full ESA regimen bc supply gone	Unknown if blind	NA ESA tx: 3 wks during each of 6 cycles	NA N=62	Hb level Transfusion need
Mirtsching 2002	No	No Hb <11 g/dl	No	No ESA dose ↑ permitted *	No Open-label	NA 13 wks	NA N=375	Hb level ≥12 g/dl or change ≥2 g/dl

Paper Medline (yes)	3 pooled studies-using interim data from 1 study See Glaspy 2001, 2002	Excluded hepatic, renal dysfunction					Pooled data from 3 studies-including preliminary data	Time to target hb Transfusion need
Mystakidou 2005 Paper Medline (?)	No Solid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2 Excluded seizures, renal dysfunction	No chemotherapy or XRT	No Variable tx duration Dose ↑ permitted *	Unknown if blind	NA Up to 24 wks	NA N=100	1° Hb change 2° QOL
O'Shaugh-nessy 2002 Paper Medline (?)	Yes Breast ca	No Performance status: Karnofsky ≥70	Yes Doxorubicin/cyclophosphamide	No Dose ↑ permitted *	Yes Part 2: uncontrol-led extension	NA 12 wks controlled; then 6 mo uncontrol-led	NA N=100	Cognitive function QOL
O'Shaugh-nessy 2005 Paper Medline (?)	Yes Breast ca See O'Shaughnessy	No Stages 1-3	No Anthracycline tx±taxane	No Dose ↑ permitted at 5 wks *	Yes Part 2: uncontrol-led extension	NA 12 wks controlled; then 6 mo uncontrol-led	NA N=100	Cognitive function bf cycle 4 & 6 mo after ESA tx done Hb change QOL
Oberhoff 1998 Paper Medline (?)	No Solid ca	No Hb ≤11 g/dl or 1.5 g/dl change	No	Yes	No Open-label Part 2: uncontrol-led extension	NA 12 wks controlled; then 12 wks uncon-trolled	NA N=227	1° Transfusion vol-ume/ 4 wk intervals
Osterborg 1996 Paper Medline (?)	No MM, NHL±CLL (Low-grade NHL, but many had advanced disease)	No Hb <10.5 g/dl Performance status: WHO ≤2 Life expectancy >2 mo	No (In various tx stages too)	No 3 arms: Fixed dose until hb reached, escalating titration, & placebo * DCed if nonresponder	Unknown if blind Active & placebo controls	NA 24 wks	NA N=121	Time to hb changee Hb change Transfusion need
Osterborg 2002 Paper Medline (yes)	No CLL, MM, NHL (low grade)	No Performance status: WHO ≤3 Life expectancy >4mo Low EPO level	No	No Dose ↑ permitted at 4 wks *	Yes	NA 16 wks	NA N=349	1° Transfusion free interval 2° Hb change ≥2 g/dl QOL
Osterborg 2005 Paper Medline	No CLL, MM, NHL See Osterborg 2002	No Performance status: WHO ≤3 Life expectancy >4	No	Previously treated in placebo controlled trial. Unknown if additional ESA tx given during f/u	Unknown if blind continued after tx phase	In 2nd study part, pts to be followed ≥1 yr; most followed ≥17.5 mo; most pts stable/	NA N=349	Survival not 1° endpoint

(?)		mo Low EPO level				in partial remission after 1st study part		
Porter 1996 Paper Medline (yes)	No Sarcomas (pediatric)	No Hb <10.5 g/dl Excluded cerebral mets, bone mets, seizures, renal dysfunction	No	No Dose ↑ until transfusion independence achieved or 300 U/kg used IV or SQ ESA	Yes	NA 16 wks	NA N=24	Transfusion need
Razzouk 2004 Paper Medline (yes)	No No myeloid or brain ca (pediatric) See Razzouk 2004	No Stratified by solid tumor/HD vs ALL/ NHL Hb <10.5-12 depend-ing on age/sex Excluded renal dys-function	No	No Dose ↑ permitted at 3-4 wks *	Yes	NA 16 wks	NA N=224	1° QOL 2° Hb change
Rosen 2003 Paper Medline (?)	Head-neck	Stage 3 if involved tongue base or hypo-pharynx; Stage 4 Hb ≤16 g/dl Performance status: Karnofsky ≥60 Excluded distant metatases	No prior tx Yes, same chemo-therapy program + XRT Surgery variable	Yes	Unknown if blind	NA 18 wks	NA N=90 Median survival not yet attained	1° Hct change 2° Survival & tumor progression Transfusion need
Savonije 2005 Paper Medline (yes)	No Solid ca See Savonije 2006A,B	No Hb <12 g/dl Performance status: ECOG ≤3 Life expectancy ≥5 mo	Platinum tx	No Dose ↑ permitted at 4 & 8 wks *	No Open-label	NA Tx until 4 wks after last chemo cycle Survival assessed 12 mo after study done	NA N=316	1° Transfusion need 2° Hb change QOL
Savonije 2006A Paper Medline (yes)	No Solid ca See Savonije 2005, 2006B	No Hb <12 g/dl Performance status: ECOG ≤3 Life expectancy ≥5 mo	Platinum tx	No Dose ↑ permitted at 4 & 8 wks *	No Open-label	NA 4 weeks after last chemo cycle	NA N=316	QOL (2° endpoint, but focus of this paper)
Savonije 2006B Paper Medline (yes)	No Solid tumor See Savonije 2005, 2006A	No Hb <12 g/dl Performance status: ECOG ≤3 Life expectancy ≥5 mo	Platinum tx	No Dose ↑ permitted at 4 & 8 wks *	No Open-label	NA 4 weeks after last chemo cycle	NA N=316 Post hoc analysis	Post hoc analyses including transfu-sion need based on initial hb level
Silvestris 1995B Paper Medline (yes)	Yes MM-Melphalan-prednisone resistant	No Stages 1-3A Hb ≤8 g/dl Performance status: Karnofsky ≤50	No	Yes Dose ↑ at 6 wks	Unknown if blind	NA 24 wks	NA N=54	Hb change Transfusion need

		Excluded renal dys-function						
Smith 2003 Paper Medline (yes)	No Non-myeloid ca See Smith 2002	No Hb ≤11 g/dl Performance status: ECOG ≤2 Excluded hepatic, renal dysfunction	Not receiving chemotherapy or XRT	Part 1: 4 doses q wk Part 2: 1 dose q 3 wk+2 doses q 4 wks +2 placebo regimens *	Part 1: open-label Part 2: double-blind	NA Double-blind part 12 wks +optional uncon-trolled 12 wk exten-sion phase w 4 wk f/u	NA N=96 part 1, 86 part 2	Hb change QOL PK data
Ten Bokkel 1998 Paper Medline (yes)	Ovarian ca	No Stages 2B-4 Hb <13 g/dl Performance status: WHO ≤2 Life expectancy >2 mo	Platinum tx	No 2 fixed ESA doses+ pla-cebo Variable duration	No Open-label	NA Up to 6 cycles + 3-24 wks after last tx cycle	NA N=122	1° Transfusion need Time to transfusion
Thatcher 1999 Paper Medline (yes)	Yes Small cell lung ca	No Hb ≥105 g/dl prior to tx (ESA started bf more anemia) Performance status: WHO ≤2	Platinum tx	Yes 2 ESA doses + placebo*	No Open-label	NA Up to 26 wks	NA N=130	1° Hb level ≥10 g/dl 2° Transfusion need QOL
Tsukuda 1998 Paper Medline (?)	Yes Head-neck ca-advanced	No Stage 3-4	Yes Platinunm+5FU	Yes 3 fixed dose arms+pla-cebo when Hb <11.5 g/dl & then given for 8 wks	Unknown if blind	NA 8 wk	NA N=22	Hb change
Vansteen-kiste 2002A (CONSORT) Paper Medline (yes)	Yes Lung ca	Hb ≤11 g/dl Performance status: ECOG ≤2 Excluded brain mets, hepatic, renal dys-function	Platinum tx	No Dose ↑ permitted at 7 wks	Yes	NA 12 wks+4 wk f/u ≥12 mo survival & tumor progression. Preliminary data shown.	NA N=320	1° Transfusion need 2° Hb change Survival
Vansteen-kiste 2004 Paper Medline (yes)	Yes Lung ca Post hoc analysis on another study See Vansteenkiste 2002	Reportedly stratifi-cation by entry hb Hb ≤11 g/dl Performance status: ECOG ≤2 or 3 Life expectancy ≥6 mo Excluded hepatic, renal dysfunction	Platinum tx	No Dose ↑ permitted at 7 wks	Yes	NA 12 wks+4 wk f/u ≥12 mo urvival & tumor progression. Preliminary data shown.	NA N=320 Post hoc analysis	1° Transfusion need after 4 wks of tx 2° Response by initial hb level QOL Dx progression
Varan 1999 Paper Medline	No Solid ca (pediatric)	No Excluded hepatic, renal dysfunction	No Chemotherapy ± XRT	Yes	Unknown if blind	NA 8 wks	NA N=34	Hb level Transfusion need

(yes)								
Wagner 2004 Paper Medline (yes)	Metastatic neuroblas-toma (pediatric)	Yes Stratified by stage C or D, but analysis does not include stage	Yes Induction/consoli-dation chemother-apy, surgery, & interferon similar	No GCSF+ESA tx arms ESA dose adjusted per hb level *	Unknown if blind	Variable time for 7 cycles of chemo-therapy & other tx Followed after tx un-til death	NA N=38	1º transfusion need 2º survival, pro-gresssion free
Welch 1995 Paper Medline (yes)	Ovarian ca-advanced	Stage 2-4 Performance status: WHO ≤2 Excluded cerebral mets	Platinum tx	Yes *	No Open-label	NA W 6 chemothrapy cycles	NA N=30	Hb level Hb change Transfusion need
Wilkinson 2006 Paper Medline (yes)	Ovarian ca	Hb ≤12 g/dl Performance status: ECOG ≤3 Life expectancy ≥6 mo	Platinum tx	Dose ↑ permitted at 4 wks *	No Open-label	NA ≤28 wks including 4 wks after last chemo-therapy dose	NA N=182	1º Hb change ≥1 g/dl over 4 wks (complete re-sponse) 2º QOL Tumor response
Witzig 2005 Paper Medline (yes)	No Incurable ca	No Reported stratifica-tion in analysis Hb ≤11.5 g/dl M, <10.5 g/dl F Performance status: ECOG ≤1 Life expectancy ≥6 mo Excluded untreated brain mets, hepatic, renal dysfunction	No	No Dose ↑ permitted at 4 wks *	Yes	NA 16 wks	NA N=344	Hb level Transfusion need QOL
Wurnig 1996 Paper Medline (yes)	Yes 1º bone ca	No Hb ≤11g/dl	No	IV ESA given when hb <11 g/dl & DC when hb ≥13.5 g/dl	Yes	NA 20 wks	NA N=30	Hb/Hct levels Transfusion need
Randomized-Concurrent Control-Monotherapy-Pre-malignant								
Italian Cooperative Study Group (Grossi) 1998 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	Stratified by MDS type <10% blasts Performance status: Unspecified scale <3 Life expectancy ≥6 mo Excluded renal dys-function No splenomegaly ≥10 cm	No cytotoxic or steroid tx	Epo SQ 150 u/kg/d x8 wks then 150 or 300 u/kg qOD (depending on prior response) for wks 9-24	Yes, for 1st 8 wks During wks 9-24 all pts on open-label drug w dose dependent on response	No 8 wks placebo controlled; then 24 wks w various doses & no control	NA N=87 N=75 evaluated ITT analysis not performed; 1 pt excluded for poor response 1st 8 wks: CVA, dx progression x1 Wks 9-20: DC 43	Hb change ≥1-2 g/dl or transfusion need (≥50% change x2 mo) Predictive value of EPO & transferrin receptor levels

							primarily for no response, dx progression x1, arterial thrombosis x1	
Stein 1991 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts	<10% blasts Hct <32% Performance status: Unspecified type ≤3 Life expectancy ≥6 mo Excluded cardiac, HTN, tumor involvement of CNS, seizure, HTN, infection, hepatic, renal dysfunction	No recent androgens or experimental cytokines Corticosteroids could be used	No Epo IV (initially) 50 U/kg/2x wk Dose ↑ permitted q 4 wks	Yes (for 12 wks)	No 12 wk controlled tx + 12-24 wk optional uncontrolled, open-label tx	NA N=20 Transformation to acute nonlymphocytic leukemia x1 in each tx group	Hct change ≥4% or transfusions eliminated
Randomized-Concurrent Control-Combination Therapy-Malignant Conditions								
Sweeney 1998 Paper Medline (yes)	No (breast, cervix, lung, prostate, uterus)	No Metastatic disease excluded for lung primaries or if CNS involvement	Various XRT Chemotherapy not prohibited	ESA tx ≤7 wks until hb target reached * Fe only given to pts in tx arm	No Open-label	NA 7 wks	NA N=48	Mean hb QOL
Vijayakumar 1993 Paper Medline (yes)	No Breast, lung, prostate, uterus ca	No Stratified by tx site Performance status: Karnofsky ≥70 Life expectancy ≥3 mo Excluded cerebral metastasis	No XRT±chemotherapy Excluded androgen tx	ESA given unti l target hb reached, then maintenance dose given Only tx arm received Fe	No Open-label	NA At least 4 wks	NA N=26 Preliminary results	Hb change WBC change QOL
Randomized-Concurrent Control-Combination Therapy-Pre-malignant Conditions								
Bessho 1997 Paper Medline (?)	Aplastic anemia-variable severity	Hypocellular marrow	Prior tx w corticosteroids or anabolic steroids allowed to continue	No GCSF (2 different formulations) (dose titrated) in all 3 arms x12 wks + Epo SQ 0 or 200 or 400 U/kg x12 wks If responsive, then Epo continued	No Part 1 randomized & controlled. Not blinded. Part 2 only for responders	NA 12 wks for all 24 wks if response	NA N=131 N=110 evaluated for efficacy; not ITT; excluded it adverse events or protocol violations Transformation to AML x1, HTN x2	Hb change >1 g/dl or transfusion need (>50% change) Predictive value of anemia severity, ret count, EPO level, & transferrin receptor level
Bowen 2006 Letter Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No <10% blasts High predicted response rate-per Hellstrom	NA	No GCSF+EPO vs placebo Epo: different formulations, doses (minimum 9000 U TIW), regimens	No Single-blind for 1 dose pharmacodynamic phase; unknown if blind	No 20 wks if responder; 8 wks if non-responder	NA N=21completed part 1	Predictive value of change in hb, retic count, & transferrin receptor level. Predictive value of

				used during part 1. E po dose ↓ during part 2. GCSF (titrated) Combo tx DCed at 8 wks (end part 1) for non responders.	for therapeutic phase			EPO levels & kary-otypes
Casadevall 2004 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No <10% blasts EPO levels <500U/l Performance status: ECOG ≤4 Life expectancy ≥6 mo (Excluded cardiac, hepatic, pulmonary, neurologic, renal dysfunction & HTN)	NA No chemotherapy in last 3 mo No growth factor tx in last 2 mo	No GCSF+EPO vs placebo Epo SQ 20,000 U TIW GCSF titrated. Used during in combo for 12 wks. Then DCed, but could be restarted dur-ing next 40 wks.	No Unknown if blind	No 12 wks for all. Responders followed for 52 wk	No N=60 N=50 reached 12 wks	1º Hb change (≥1.5 g/dl) & transfusion need (eliminated) at 12 wks 2º QOL at 52 wks 2º Direct costs at 52 wks Evaluated only if received tx ≥12wks Not ITT
Randomized-Active Control-Malignant Conditions								
Canon 2006 Paper Medline (yes)	No Non-myeloid ca	No Hb <11 g/dl Performance status: ECOG ≤2 Excluded seizure, he-patic, renal dysfunc-tion	No	Yes * Weight based dose vs non-weight based dose	No Active-control Rx regimen	NA 15 wk tx+ 2 wk f/u	NA N=705	1º Transfusion need after 4 wks of tx 2º Hb >11 g/dl & maintenance Hb 11-13 g/dl QOL Non-inferiority
Cazzola 2003 Paper Medline (yes)	No CLL, MM, low grade NHL	No Stratified by ca type Hb 9-11 g/dl EPO ≤100 mU/ml Performance status: WHO ≤2 Life expectancy >6 mo	Tx not required, but permitted	No 2 dose regimens Dose ↑ permitted post 4 wks *	No Active control	NA 16 wks	NA N=241	1º Hb AUC change 2º Transfusion need
Dmoszynska 2007 Paper Medline (yes)	MM	No Hb <11 g/dl Performance status: WHO ≤2 Life expectancy >6 mo	No	No CERA SQ 1, 2, 3.5, 4.2, 5, 6.5, 8 mg/kg q3 wks* Dose ranging	No Open-label Active control	NA 6 wks	NA N=64	1º Hb change using AUC 2º Hb ≥2 g/dl w/o transfusion Transfusion need PK data
Glaspy 2001 Paper Medline (yes)	No Solid ca Excluded CNS ca	No Hb ≤11 g/dl Excluded seizure	No	No Cohort dose-escalation study *	No No control except lower dose	NA 12 wks	NA N=107 High drop-out rate Preliminary data	Hb change ≥2 g/dl Transfusion after 4 wks tx
Glaspy 2002B	No Solid ca	No Hb ≤11 g/dl	No	No Part 1: 6 darbe vs 2 epo	No Open-label	NA Each part w 12 wk tx	NA N=269	Hb change ≥2 g/dl

Paper Medline (yes)		Performance status: ECOG ≤2 Excluded renal dys-function		doses (1 per study w ↑ permitted at 8 wks; 1 per individual doctor) Part 2: 4 darbe doses vs 1 epo dose (latter w ↑ permitted at 6 wks)	Active control Dose adjustments for epo permitted	period & 4 wk f/u period		
Glaspy 2002C Paper Medline (yes)	No Solid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2 Excluded renal dys-function	No	No 1 initial darbe dose w 4 subsequent maintenance doses vs 1 epo dose w ↑ permitted at 6 wks *	No Unknown if blind Active control Dose adjustments for epo permitted	NA Each part w 12 wk tx period & 4 wk f/u period	NA N=160	Hb change ≥2 g/dl
Glaspy 2003 Paper Medline (yes)	No Solid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2 Excluded renal dys-function	No	No 1 loading darbe vs 1 epo dose followed by 1 of 3 lower darbe doses vs 1 epo dose (latter w ↑ permitted)	No Unknown if blind Active control	NA 12 wk tx period & 4 wk f/u period	NA N=122	Hb change ≥2 g/dl Time to hb change QOL
Glaspy 2005 Paper Medline (yes)	No Non-myeloid ca	No Hb ≥9 & ≤11 g/dl Performance status: ECOG ≤2 Excluded seizures, cardiac, hepatic, renal dysfunction	No	Yes for primary 6 wk endpoint, but not later endpoints Dose ↑ permitted at 6 wks *	No Open-label Active control (asynchronous vs synchronous doses)	NA 16 wks	NA N=81	Hb change at 6 wks PK parameters
Glaspy 2006 Paper Medline (yes)	No Non-myeloid a	No Stratified by entry hb & tx Hb ≤11 g/dl Excluded cardiac, hepatic, renal dys-function	No	No Comparison of 2 ESAs Dose ↑ permitted at 5 wks *	No Open-label Active control	NA 1st 12, then 16 wks	NA N=1220	1° transfusion need after 4 wks ESA tx 2° Hb change QOL
Glimelius 1998 Paper Medline (?)	No Gastrointestinal ca-noncurable Symptomatically progressive	No Hb <13 g/dl M & 11.5 g/dl F if chemo Hb <11.5 g/dl M & <10.5 g/dl F if no chemo	Chemotherapy not required	Yes 2 ESA doses	Unknown if blind Active control	NA 18 wks	NA N=100 84 chemo 16 no chemo	1° Hb change >1 g/dl 2° QOL
Granetto 2003 Paper Medline (yes)	No Solid ca	No Hb <10.g g/dl or change 1.5 g/dl Performance status: ECOG ≤3 Life expectancy ≥3 mo	Platinum tx	No Comparison of wt based vs 1 non-wt based dose regimen Dose ↑ permitted *	No Open-label Active control	NA 12 wks	NA N=546	1° Transfusion need after 4 wks tx 2° Hb change QOL
Henry	No	No	No	No	No	NA	NA	1° Hb change

2006A Paper Medline (yes)	Non-myeloid ca	Hb ≤11 g/dl Performance status: ECOG ≤2 Life expectancy ≥6 mo Excluded CNS mets, seizures, hepatic, renal dysfunction		2 dose regimens Dose ↑ permitted at 4 wks for the q/wk, but not q/2wk cohort *	Open-label Active control	12 wks tx	N=298 Non-inferiority	2º Transfusion need
Hesketh 2004 Paper Medline (yes)	No No myeloid ca	No Stratified by entry hb & weight Hb <11 g/dl	No	Yes Wt based & non-wt based regimens w cor-rection+maintenance phases *	No Open-label Active control	NA 16 wks+4 wk f/u	NA N=243	1º Hb change >2 g/dl or Hb ≥12 g/dl 2º Time to Hb change
Hirsh 2007 Paper Medline (yes)	Yes Non-small cell lung ca	Stage 3B or 4 Performance status: ECOG ≤2 Life expectancy >6 mo Excluded cerebral mets, seizure, renal dysfunction	No	Yes 3 doses q/wk or 3 doses q/3wk *	No Open-label Active control	NA 12 wks	NA N=218	1º Mean hb 2º Hbchange PK parameters
Johansson 2001 Paper Medline (yes)	Yes Prostate ca -hormone refractory-metastatic	Hb ≤10.5 g/dl Life expectancy ≥3 mo	No current chemo-therapy	No 2 ESA doses Dose ↑ permitted at 8 wks in high dose arm *	Unknown if blind Active control	NA 12 wks	NA N=180	Hb change >2 g/dl Transfusion need QOL (powered for this)
Justice 2005 Paper Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2 Excluded seizure, he-patic, renal dysfunc-tion	No Anemia of cancer not exluded	Yes * Comparion of IV vs SQ of ESA given as loading phase 4.5 ug/kg/wk followed by same dose q3 wks	No Open-label Active control	NA 18 wks	NA N=120	1º Hb change 2º PK data Anti-ESA antibody
Olsson 2002 Paper Medline (yes)	Yes Breast ca-metastatic	Hb ≤11 g/dl Life expectancy ≥3 mo	Chemo or hor-monal tx	No 1 ESA arm dose fixed Higher ESA dose arm permitted dose ↑ *	No Open-label Active control (Post hoc non-ran-domized no ESA cohort established)	NA 24 wks	NA N=180	Hb change Transfusion need QOL
Oster 1990 Paper Medline	No MM, NHL MM=1	Marrow involvement Excluded renal dys-function	No tx	No Epo IV 150, 300, 450 U/kg/2x/wk Dose escalation	No Open-label Active control No randomization	No 4-6 wks	NA N=6	Hb change Ferritin change
Osterborg 2007 Paper	Yes B-cell NHL	Intermediate/high grade Hb <11 g/dl	No	Yes 3 ESA dose levels *	No Open-label Active control	NA 12 wks	NA N=93	1º Hb change ≥2 g/dl 2º Hb level

Medline (yes)		Performance status: ECOG ≤2 Life expectancy >6 mo						Time to hb change
Platanias 1991 Paper Medline (yes)	No	No Hb <11 g/dl Performance status: ECOG ≤2 Life expectancy >6 mo Excluded cardiac, hepatic, renal dysfunction	No Not platinum tx	Yes 5 IV ESA dose levels in escalation study	No Open-label Active control	NA 4 wks	NA N=30	Mean hb levels
Schwartzberg 2004 Paper Medline (yes)	No 3 concurrent & later combined trials each w 1 "cancer": breast, non-small cell lung, gynecologic (cervix, ovary, uterus)	No Hb ≤11 g/dl Performance status: Karnofsky ≥50 Excluded hepatic, renal dysfunction	No	Yes Fixed doses of 2 ESAs	No Open-label Active control	NA Up to 16 wks of tx w 3-4 wks of f/u	NA N=312	1° QOL validation of specific metric 2° Hgb change Transfusion need
Senecal 2005 Paper Medline (yes)	Breast ca See Schwartzberg 2004	No Hb <11 g/dl Performance status: Karnofsky ≥50 Excluded hepatic, renal dysfunction	No	Yes Fixed doses of 2 ESAs	No Open-label Active control	NA Up to 16 wks of tx w 3-4 wks of f/u	NA N=141	1° QOL validation of specific metric 2° Hgb ≥12 g/dl or change ≥2 g/dl Transfusion need
Steemsa 2003 Paper Medline (yes)	No Non-myeloid ca	No Hb ≤12 g/dl M, ≤11 g/dl F Performance status: Zubroc ≤2 Life expectancy >6 mo Excluded seizures	Need not be receiving chemotherapy Excluded anemia from cancer tx	Yes * rison of regimens w same initial dosing followed by maintence dosing given q wk or q3 wks	No Open-label Active control	NA 24 wks tx F/u at 55 wks, but not powered for survival	N=365	1° Transfusion need 2° Hb change QOL Powered to detect 13% difference in transfusions; not powered for survival
Straus 2006 Paper Medline (yes)	No CLL, HD, MM, NHL MM=17	No Hb ≤12 g/dl in early group & <9 g/dl in delayed group Performance status: Karnofsky ≥70 Life expectancy ≥6 mo Excluded other current or recent ca	No Myelosuppressive chemo No prior lymphoid radiation	No Dose ↑ permitted at 3- 4 wks * Delayed tx group not given Epo SQ until hb <9 g/dl	No Open-label Randomized to early tx (hb <12 g/dl) or late tx (hb <9 g/dl)	NA No Variable duration ≤16 wks	NA N=424 enrolled N=269 randomized N=234 evaluated (If Enrollee's hb did not reach threshold not randomized)	1° QOL (uncertain when assessed) 2° Hb ≥12 g/dl or change ≥2 g/dl Transfusion need Tumor response
Vansteen-	No	No	No	No	No	NA	NA	Hb change

kiste 2002B Paper Medline (yes)	Pooled data 4 studies See Glaspy 2002, Hedenus 2002, Vansteenkiste 2002	Hb ≤11 g/dl Performance status: ECOG ≤2 or 3	Anemia could be due to tx or ca	Different doses & regimens in 4 pooled studies Dose ↑ permitted in 2 studies	3 studies blinded & placebo controlled, but 1 study open & used active control	12 wks	Post hoc analysis Pooled data	Time to hb change Transfusion need
Waltzman 2005 Paper Medline (yes)	No Solid ca	No Reported stratified by tx type Hb ≤11 g/dl Performance status: ECOG ≤2 Life expectancy >6 mo Excluded untreated brain mets, hepatic, renal dysfunction	No	No Dose ↑ permitted at 4 or 6 wks depending on ESA type *	No Open-label Active control	NA 16 wks	NA N=358	1º Hb change >1 g/dl in 4 wks 2º Transfusion need QOL
Yilmaz 2004 Paper Medline (?)	No Hematologic, solid ca (pediatric)	No	No	1 of 2 ESA doses	No Open label Active control Randomized to 2 ESA doses Age matched control	NA 12 wks	NA N=41	Hb change Transfusion need
Randomized-Active Control-Pre-malignant Conditions								
Balleari 2006 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± refractory cytopenia	No <10% blasts Hb <10 g/dl or transfusion dependent	NA	Yes Epo SQ 10,000 U TIW GCSF 300 mg 1-2x/wk GCSF is experimental agent	No Epo in both arms Unknown if blind Poor responders to ESA alone crossed over to GCSF combo tx	NA 8 wks for all Continued tx for responders	NA N=30 8 wks N=20 longer tx Progression to leukemia 13%	Hb change ≥1-2 g/dl QOL
Hellstrom-L 1998 Paper Medline (no)	MDS Refractory anemia ± ringed sideroblasts ± blasts See Hellstrom-Lindberg 1997A&B	Hb <10 g/dl or transfusion need	NA	No Epo SQ 5-10,000 U/d GCSF SQ 30-150 ug/d 1 rx started 4-6 wks prior to the other rx ↑ dose for each rx permitted	No Randomized Unknown if blind Active control	No 16 or 18 wks (long-term f/u done on subsets of pts from this [n=50] & another study [n=21])	NA N=56 N=47 evaluated N=21 from prior study During study or extended f/u, death from CHF x1 dx progression x1, splenomegaly x2, increased blasts x3, transformation to AML x4)	Complete hb ≥11.5 g/dl. Partial hb change ≥1.5 g/dl or trans-fusion need (100% change) Survival f/u
Thompson	MDS	Stratified by EPO	No recent cyto-	No	Yes	No	NA	1º Hb change, % w

2000 Paper Medline (yes)	Refractory anemia ± ringed sideroblasts ± blasts	level Hb <10 g/dl & transfusion dependent ≤5% blood blasts Neutropenic Performance status; Zubrod ≤2 Excluded ca, hepatic, renal dysfunction, recent infection , recent thromboembolic dx	toxic tx, corticosteroids, anabolic steroids, experimental rx, cytokine tx	Epo SQ 150 U/kg TIW +GMCSF 0.3-0.5 mg/kg/d OR Placebo + GMCSF 0.3-0.5 mg/kg/d	Active agent in both tx arms ESA in 1 arm	12 wks	N=66 N=18 withdrawals Transformation to AML, CVA, other ca, splenomegaly occurred	transfusion need 2º Hb change >2 g/dl, PLT change, correction of neutronphils
Non-randomized-Monotherapy-Malignant Conditions								
Arslan 2004 Paper Medline (?)	No Solid ca	No Stratified by entry hb Excluded seizures, hepatic, renal dysfunction Performance status: Karnofsky ≥80	Platinum tx Excluded prior XRT or chemotherapy	Yes, w/in tx groups *	No Open-label No control No randomization	NA 12 wks for 2 groups & continued for 3 wks after chemotherapy completion in others	NA N=99 Excluded=22	1º Hb change 2º Transfusion need
Boccia 2006 Paper Medline (yes)	No Non-myeloid ca	No Hb <11 g/dl Excluded hepatic, renal dysfunction	No	No Dose ↑ permitted at 6 wks *	No Open-label No control Not randomized	NA Tx ≤13 wks+3 wk f/u	NA N=1493	1º Hb >11 g/dl & maintenance 11-13 g/dl range 2º Transfusion need QOL
Cascinu 1993 Paper Medline (yes)	No	No Hb >11 g/dl prior to chemo & <9 g/dl w chemo Excluded cardiac, hepatic, renal dysfunction	Platinum tx Excluded hormone tx	No Dose ↑ permitted post 3 wks ESA DCed if transfusion or failure to respond	No Open-label No control No randomization	NA ≥3 wks Endpoint at 3 wks	NA N=20	1º Hb >10 g/dl at 3 wks
Cascinu 1995 Paper Medline (?)	No	No >70 yrs Hb >11 g/dl prior to chemo & <9 g/dl w chemo Excluded cardiac, hepatic, renal dysfunction	Platinum tx Excluded hormone tx	Variable duration *	No Control=young pts Matched control	NA At least 9 wks	NA N=42 elderly	1º Hb >10 g/dl at 9 wks 2º Response by age
Cazzola 1992 Paper Medline (yes)	No Hematologic dx including MDS & MM	No Hb <10 g/dl	Tx not required, but permitted	No Dose ↑ permitted post 4 wks * DCed if no response by 16 wks	No Open-label No control No randomization	NA At least 16 wks	NA N=25 N=17 evaluable Transformation to AML x1, dx pro-	Complete response: Hb≥10 g/dl w/o transfusion Partial: Reduction in transfusion Predictive value of

							gression, splenomegaly x1, bleeding x1	EPO level Change transferrin receptor
Cazzola 1996 Paper Medline (yes)	No Includes MDS, MM, NHL, solid ca	No Hb <10 g/dl	Tx not required	No Dose ↑ permitted post 4 wks	No Retrospective No control No randomization	NA 8 wks	NA N=58	1° Hb change ≥2 g/dl w/o transfusion Predictors of ESA response
Crawford 2002A Paper Medline (yes)	No Non-myeloid ca Pooled data	No Life expectancy >6 mo	No	No Dose ↑ permitted * Different dose regimens for 2 studies	No Retrospective Data from open-label, non-randomized studies	NA Unspecified duration	NA N=4382 Post hoc analysis	QOL
Crawford 2002B Paper Medline (yes)	Yes Subset of trial w assorted ca->Lung ca Pooled data 3 studies	No	No	No Dose ↑ permitted Different dose regimens for studies *	No Subset of pooled data from open-label, non-randomized studies	NA 16 wks	NA N=1748 Pooled data Post hoc subset analysis	Hb change QOL
Demetri 1998 Paper Medline (yes)	No Non-myeloid ca, includes hematologic ca	No Hb ≤11 g/dl Life expectancy ≥6 mo	No	No Dose ↑ permitted at 4 wks * ESA DCed at 8 wks for non-response	No Open-label No control Non-randomized	NA 16 wks	NA N=2370	Hb change Transfusion need QOL
Demetri 2002 Paper Medline (yes)	Yes Subset of trials w assorted ca->breast ca Pooled data 3 studies	No Hb ≤11 g/dl Life expectancy ≥6 mo	No	No Dose ↑ permitted Different dose regimens for studies *	No Subset of pooled data from open-label, non-randomized studies	NA ≤16 wks	NA N=1280 Pooled data Post hoc subset analysis	Hb change QOL
Gabrilove 2001 Paper Medline (yes)	No Non-myeloid ca, including hematologic & unknown types of ca	No Hb <11 g/dl Life expectancy >6 mo	No Permitted XRT	No Dose ↑ permitted at 4 wks *	No Open-label No control Non-randomized	NA 16 wks	NA N=3012	Hb/Hct change Transfusion need QOL
Glaser 2001 Paper Medline (?)	Yes Oral squamous cell ca	No Stages T 2-4, N 0-3 Stratification by entry hb & ESA use Hb <12.5 g/dl	Yes Included chemotherapy, XRT & later sugery	No Dose ↑ permitted	No Retrospective No control No randomization	NA Variable tx period F/u >21 mo or un til death	NA N=191	Hb change Tumor control Survival
Glaspy 1997 Paper Medline (yes)	No Non-myeloid ca, including hematologic ca	No Life expectancy >6 mo	No	No Dose ↑ permitted at 8 wks *	No Open-label No control Non-randomized	NA 4 mo	NA N=2342 High drop-out rate	Hb change QOL
Glaspy	No	No	No	No	No	NA	NA	Hb/Hct change

2002A Paper Medline (yes)	Pooled data (See Glaspy 1997, Demetri 1998)	Stratified by non-platinumn vs platinum		Dose ↑ permitted at 4 or 8 wks * Different dose regimens for 2 studies (1 wt based; 1 non-wt based)	Retrospective sub-analysis of 2 uncontrolled studies	4 mo	N=4712 High drop-out rate	Transfusion need (but no criteria for transfusion) QOL
Herrington 2005 Paper Medline (yes)	No	No Hb ≤11 g/dl Excluded use of both ESAs Excluded patients w <12 wks f/u	No	No Dose ↑ was observed for both ESAs	No Retrospective description of ESA use No control No randomization	NA 12 wks f/u	NA N=2785	Hb levels & transfusion needs associated w most frequent doses
Jitnuyanont 2001 Paper Medline (?)	No Excluded acute leukemia & myeloid ca Marrow invasion by tumor permitted	No Hb ≤10.5 g/dl Performance status: ECOG ≤3 Life expectancy ≥3 mo Excluded cerebral metastses, renal dysfunction	No Included pts not on chemotherapy & pts on platinum & non platinum chemotherapy Excluded androgen tx	No Duration different on chemotherapy or not	No Open-label No randomization	NA 8 wks if no chemotherapy 12 wks if chemotherapy	NA N=24	Hb change Transfusion need QOL
Kasper 1997 Paper Medline (no)	No Agnogenic myeloid metaplasia, CLL, HD, lym-phoma, MM, MDS, solid ca, Waldenstrom's dx MM=15	No Hb <10 g/dl Performance status: WHO ≤1 Excluded HTN, renal dysfunction seizure	On chemo >3 mo or off for >6 wks	No * Epo SQ 2000 U/d at start Dose ↑ permitted q4 wks Tx DC permitted at 12 wks for non responders	No Open-label No control No randomization	NA 12 wks for all Up to 20 wks of tx for some	NA N=60 N=48 evaluable; no ITT Dx progression x5, HTN x2, DVT x2, splenomegaly x2	Hb >2 g/dl w/o transfusion Predictive value of EPO level
Katodritou 2006 Paper Medline (no)	MM	Excluded inflammation, renal dysfunction	No Assorted myelosuppressive tx	No Epo SQ 30,000 U/wk x6 wks Then +Fe IV x4 wks if no response	No Open-label No control No randomization	NA 6 wks	NA N=26	Hb change ≥2 g/dl at 6 wks Hb change >1.5 g/dl after Epo & addition of IV Fe Predictive value of transferrin receptor, ret hb, hypochromic RBCs,
Lavey 1993 Paper Medline (yes)	No Tumor above diaphragm-could be pituitary adenimas	No Hb <13.5 g/dl Excluded distant metastases, seizures	No Variable duration XRT, but no chemotherapy	No * Sequential ESA dose regimen w a variable duration of the 2nd dose	No Open-label Controlled, but not randomized	NA ~6-9 wks	NA N=40	Hb change
Leitgeb 1994 Paper Medline	No	No Hb <11 g/dl Life expectancy ≥3 mo	Tx not required	No Dose ↑ permitted at 6 wks	No Open-label No randomization No control	NA 12 wks	NA N=54	QOL change in responders vs non-responders

(?)		Excluded cerebral metastases			Comparison of responders & non-responders			
Leon 1998 Paper Medline (yes)	No Solid ca (pediatric)	No Hb <10.5 g/dl	No	Yes	No Open-label Historical control	NA 12 wks	NA N=25	Hb change >2 g/dl Transfusion need QOL
Libretto 2001 Paper Medline (yes)	No	No	No	No	No Case series	NA	NA N=11	NA
Ludwig 1990 Paper Medline (no)	Yes MM	No Advanced dx Not stratified by tx Hb <11 g/dl	No Prior cytostatic tx Could include XRT Tx ongoing 9/13	No Epo SQ 150 U/kg TIW Dose ↑ permitted at 3 & 6 wks * Variable duration	No Open-label No randomization No control	NA ≥6 mo	NA N=13	Hb change ≥2 g/dl Transfusion need # erythroid burst forming units # granulocyte colony forming units
Ludwig 1993A Paper Medline (?)	No Included hematologic ca, MDS, CML	No	No Could include XRT; some not w tx	No Dose ↑ permitted q 3 wks	No Open-label No control No randomization	NA 12 wks unless pt requested longer-up to 58 wks	NA N=67 enrolled at that point N=60 evaluable	Hb change ≥2 g/dl Transfusion need QOL Survival (Survival analysis compared responders vs non-responders)
Ludwig 1993B Paper Medline (no)	No Included hematologic ca, MDS	No	No Could include XRT	No Dose ↑ permitted at 6 wks	No Open-label No randomization No control	NA 12 wks unless pt requested longer	NA N=42	Hb change QOL Survival (Survival analysis compared responders vs non-responders)
Ludwig 1993C Paper Medline (yes)	No Squamous cell ca, MM Selected subsets of a larger trial & preliminary data	No Hb <11 g/dl Excluded brain mets, seizure, renal dysfunction	Tx may not have been required	No Dose ↑ permitted at 6 wks	No No randomization No control	NA 12 wks	NA N=34	Hb change ≥2 g/dl Traits of responders QOL
Ludwig 1994 Paper Medline (no)	No Included hematologic ca, MDS	No Hb <11 g/dl Life expectancy ≥3 mo	Tx may not have been required Most w XRT or chemo in	No Dose ↑ permitted at 6 wks *	No Open-label Algorithm for response in ½ group tested on 2nd ½	NA 12 wks	NA N=80	Hb change ≥2 g/dl Identification of response predictors

Ludwig 1995A Paper Medline (no)	No No acute leukemia or myeloid ca, but included CLL, HD, MM, NHL, solid ca	No Hb <11 g/dl Excluded intracranial mets, seizures, renal dysfunction	No Included pts not on chemotherapy	No Dose ↑ permitted at 6 wks *	No Open-label No randomization No control Comparison of responders vs no responders	NA 12 wks unless pt requested longer	NA N=102	Hb change ≥2 g/dl Transfusion need EPO levels QOL Comparison of responders vs no responders
Ludwig 1995B Paper Medline (?)	MM	No	Unclear	No Dose ↑ permitted at 6 wks * Variable duration	No Open label No randomization No control	NA 3-12 mo	NA N=20	Bone marrow cellularity Responders vs nonresponders
Maisnar 2004 Paper Medline (?)	No CLL, NHL, MM, MDS, Walden-strom dx, other MM=11	No Hb ≤10 g/dl or transfusion dependent Excluded HTN, renal dysfunction, seizure	Could be undergoing chemotherapy	No Epo SQ 150 U/kg TIW Dose ↑ permitted *	No Open-label No control No randomization	NA At least 3 mo Up to 12 mo	NA N=134 N=127 ITT not done. Excluded included pts w dx progression x3, pulmonary embolism x1	Hb level Transfusion need QOL
Mittleman 1997 Paper Medline (?)	MM	Stage 2-3 Hb <11 g/dl Excluded HTN, MDS	No Assorted tx 15/17	No Epo SQ 150 U/kg TIW Dose ↑ permitted at 4 wks & Fe added *	No Open-label No control No randomization	No 12 wks for all Longer if response	NA N=17 Transformation ot leukemia x1, progressive dx	Hb change >1-2 g/dl &/or transfusion need ≥50% change Predictive value of EPO level
Molica 1993 Letter Medline (?)	CLL, MM MM=8	No Hb <9 g/dl	No Assorted tx including IFN	No Epo SQ 50 U/kg TIW Dose ↑ permitted q4 wks DC if no response	No Open-label No control No randomization	No At least 16 wks	NA N=11	Hb ≥10 g/dl w/o transfusion
Quirt 2001 Paper Medline (yes)	No No acute leukemia & myeloid ca	No Hb ≤11 g/dl Life expectancy >6 mo	½ w chemo tx ½ w XRT or hormonal tx or w/o tx	No Dose ↑ permitted at 4 wks *	No Open-label Each cohort served as own control	NA 16 wks	NA N=218 chemo tx N=183 no chemo tx	1° Transfusion need 2° Hb ≥2 g/dl QOL
Quirt 2006 Paper Medline (yes)	No Pooled studies See Chang, Quirt 2001	No	Some did not receive chemotherapy	No Dose ↑ permitted * Dose regimens not the same for all studies	No Open-label Pooled data from 3 studies: 2 not randomized &1 study used only Canadian pts from a global study	NA Up to 16 wks	NA N=665 3 pooled studies Post hoc analysis	Identification of predictive factors for transfusion
Reinhardt	No	Hb 9-12 g/dl	Can include XRT	Appears to be fixed	No	NA	NA	1° QOL

2003 Paper Medline (yes)	Hematologic, solid ca	Performance status: ECOG ≤3	Excluded hormone tx	dose *	Open-label No control No randomization	8-18 wks tx	N=702	2° Hb change
Schwartz-berg 2003 Paper Medline (yes)	No	No Excluded f/u <12 wk & exposure to other ESA	No	NA Initial dose of 1 ESA vs initial dose of another ESA	No Retrospective at-tempt to compare 2 ESA No control No randomization	NA 12 wks	NA N=1293	Describe doses for each ESA Describe frequency of change for most common ESA dose Hb change
Shasha 2003 Paper Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl Life expectancy ≥6 mo	Current XRT w chemotherapy at some point	No Dose ↑ permitted at 4 wks *	No Open-label No control No randomization	NA 16 wks	NA N=777 Only 57% (442/777) found to be evaluable	Hb ≥12 g/dl or change ≥2 g/dl Transfusion need
Shasha 2006 Paper Medline (yes)	No Non myeloid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2	No tx	No Dose ↑ permitted at 4 wks *	No Open-label No control No randomization	NA 12 wk tx+4 wk f/u	NA N=98	1° Hb change 2° Transfusion need QOL
Silvestris 1995A Paper Medline (no)	Yes MM	Unspecified	Unspecified	Combinations of Epo & alpha interferon & placebo	Unknown if blind or randomized	NA 24 wk	NA Epo + IFN N=5 Epo alone N=11 IFN alone=3 Double placebo N=12	T cell proliferation Ig secretion
Tsukuda 1993 Paper Medline (?)	Yes Head-neck ca + tonsillar lymphoma	No	No Chemo &/or XRT	2 fixed IV ESA doses	No Unknown if blind Unknown if any randomization ESA pt given 1 of 2 fixed doses 3 not given ESA considered place-bo controls	NA During 2-3 cycles of chemo &/or XRT & 3 additional wks	NA N=29	Hb change WBC, PLT change
Vadhan-Raj 2003 Paper Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl Performance status: ECOG ≤1	No	No Dose ↑ permitted at 6 wks *****	No Open-label No control No randomization	NA 16 wks	NA N=1173	Hb change Transfusion need QOL
Non-randomized-Monotherapy-Pre-malignant Conditions								
Aloe-Spiriti 1993 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No ≤10% blasts	NA	No Epo SQ 400 U/kg 2x/wk Then after 3 mo, 600 U/kg 2x/wk	No Open-label No control No randomization	NA 6 mo	NA N=16	Hb level

Aloe-Spiriti 2005 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No ≤10% blasts Hb ≤10 g/dl Life expectancy ≥6 mo Excluded serious comorbid dx	NA No recent chemotherapy, steroids, growth factors	No Epo SQ 40,000 U 2x/wk Then after 4 wks, 40,000 U/wk *	No Open-label No control No randomization	NA 8 wks for all pts ≤24 wks for responders	NA N=133 (Transformation to AML, CVA, HTN, venous thrombosis each x1) N=103 for QOL	Hb change >1-2 g/dl Transfusion need (>50% change) QOL
Bessho 1990 Paper Medline (advice from company)	Aplastic anemia MDS Refractory anemia ± ringed sideroblasts ± excess blasts± transformation	Performance status: Karnofsky >50 Life expectancy ≥3 mo Excluded hepatic, renal function dysfunction Median age 36	NA	No Epo IV 3000 or 6000 U/kg Dose ↑ permitted	No Open-label No control No randomization	NA ≥4 wks	NA N=12	Hb change ≥1.5 g/dl or transfusion need ≥50% change Ferrokinetic studies EPO level change
Boschetti 2004 Paper Medline (?)	Paroxysmal nocturnal hemoglobinuria (Subtypes: hemolytic or aplastic anemia) Pt w PNH+ MDS not treated w ESA	NA	Androgens, anti-lymphocyte globulins, anticoagulants, cyclosporin, steroids permitted	No Descriptive study	No Open-label No control for rx (Control for DNA) No randomization	NA Variable	NA N=7 w ESA tx	Clinical outcomes Genetic mutations Change in PIG-A-negative clone DNA content w ESA tx & withdrawal
Bucalossi 1996 Letter Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No Excluded renal dysfunction	No other tx	No Epo SQ 150 U/kg at start. Dose ↑ permitted post 4 wks	No Open-label No control No randomization	NA 2 mo	NA N=11	Hb change ≤1 g/dl or transfusion need (≤50% change) Predictive value of EPO level, ret index, & transferrin receptor level
Casadevall 1992 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No Transfusion dependent	NA	Yes * Epo IV 100,000 U/2x/wk	No Open-label No control No randomization	NA 12 wks	NA N=14 (8 evaluated)	Hb level (9-11 g/dl) or transfusion need (unspecified reduction) Bone marrow response Predictive value of EPO levels
Cazzola 1992 Paper Medline (yes)	Refractory anemia from lymphoma, monoclonal gammopathy, & hematopoietic stem cell dx	No	NA	No Epo SQ 50 u/kg/5x/wk at start. Dose ↑ q 4 wks for non-response Dose ↓ prn once target reached * Tx DCed at 16 wks for non responders	No Open-label No control No randomization	NA 16 wks Unclear if additional tx & f/u	NA N=25 (17 evaluated) (DC for dx progression x3, progression to AML x1, ↑ LFTs x1, splenomegaly x1, splenic infarction	Complete response Hb level ≥10 g/dl w/o transfusion Partial: any reduction in transfusion need Predictive value of EPO level, ret count, & transferrin

							x1)	receptor level
Cazzola 1996 Paper Medline (yes)	No Refractory anemia from MDS, MM, NHL, solid ca	No Hb <10 g/dl	NA	No Epo SQ 375 U/kg/wk Dose ↑ permitted at 4 wks	No Retrospective Open-label No control No randomization	NA 8 wks	NA N=58 (48 evaluated; no ITT)	Hb change ≥2 g/dl w/o transfusion Predictive value of hb change, EPO level, ret count, & transferrin receptor level
Cermak 2006 Paper Medline (no)	MDS-Refractory anemia ± ringed sideroblasts & thalassemia	No Transfusion dependent	NA	Yes Fe chelation ≥26 mo Followed at 1 mo of tx by Epo SQ 150 U/kg/ TIW x24 mo	No Open-label No control No randomization	Yes 24 mo	NA N=6	Complete response: Hb level ≥11.5 g/dl w/o transfusion Partial: hb change ≥1.5 w/o transfusion need Fe mobilization
Clavio 2004 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No <10% blasts Hb ≤10 g/dl Life expectancy >6 mo Excluded bad HTN, ca, neurologic dx, some rx	No prior tx w steroids, growth agents, cytotoxic agents, or experimental rx	No Epo SQ 40,000/2x/wk Dose ↓ 40,000 U/wk for wks 12-24 if response * Tx DCed at 12 wks for non-responders	No Open-label No control No randomization	NA 12 wks for all 24 wks if response	NA N=11 (10 evaluated-bc of 1 leukemic conversion)	Hb level >12 g/dl QOL Brain function (including EEG, neurosonsology, neuropsych tests)
Depaoli 1993 Paper Medline (no)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts± transformation or chronic myelomonocytic leukemia	Stratification by hb level Only transfusion dependent received Epo	NA	No Epo SQ 150 U/kg TIW for ≥2 mo Dose ↓ to 2x/wk for responders	No Open-label No control No randomization	NA ≥2 mo Unclear duration of tx & f/u	NA N=38, but only 14 given Epo bc of transfusion dependence	Hb >1 g/dl & transfusion need (≥50% change) Predictive value of EPO level, marrow cellularity, platelet response
DiRaimondo 1996 Paper Medline (no)	MDS Refractory anemia	No <5% blasts Hb ≤8 g/dl WBC ≥3000/ mm3 PLT ≥75,000/ mm3 LDH level normal Dx ≤1 yr Performance status: Karnofsky ≤40 or WHO ≥3 Excluded cardiac/ hepatic/renal dysfunction	NA No current steroids or differentiating agents	No Epo SQ 150 U/kg TIW Dose ↑ permitted at 4 wks	No Open-label No control No randomization	NA 8 wks	NA N=12	Hb >1 g/dl & transfusion need (≥50% change) Predictive value of EPO level
Giraldo 2006 Paper	MDS Refractory anemia ± ringed sideroblasts ±	No Stratified by prior ESA use/response,	GCSF permitted	No Darbe dose changes & different doses per-	No Retrospective Open-label	NA 16 wks	NA N=81 (69 evaluated)	Hb change ≥1 g/dl &/or transfusion need ≥50% change

Medine (yes)	excess blasts± transformation or chronic myelomonocytic leukemia	but no tests of statistical significance performed Performance status: ECOG ≤3 for 55 with such classification		mitted GCSF used by some	No control No randomization			
Goy 1993 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No ≤20% blasts Transfusion dependent Exluded HTN, cardio/ pulmonary/ neurologic/hepatic/ renal dysfunction	No recent growth factors or anabolic steroids	No * Epo IV 100,000 U/2x/ wk x12 wks Dose ↓ 10,000 U/qd via SQ route x another 12 wks if a responder	No Open-label No control No randomization	NA 12 wks for all 24 wks for responders	NA N=17	Hb level 9-11 g/dl &/or transfusion need (≥30% change) Predictive value of EPO levels
Hast 2001 Paper Medline (no)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No Required response to prior Epo therapy by reaching hb target >15 g/dl or eliminating transfusion need	NA	No If responded to EPO SQ 10,000 U TIW, epo continued x2 mo, followed by individual taper. If anemia recurred, Epo reinitiated at 30, 000 U TIW	No Open-label No control No randomization	NA Variable duration of f/u	NA N=18 During study or f/u: cardiac failure x3, transformation to AML x3, death from brain tumor x1, other ca x2. Mortality (8/18)	Duration of initial response Need for 2nd course of high dose tx Response to 2nd course of ESA tx
Hellstrom 1991 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No Hb <9 g/dl (or hb <10 g/dl w sx) or transfusion dependent Excluded ca, HTN, seizure	No current cytostatic tx	No Epo IV 200 U/kg TIW in 11 Dose ↑ permitted at 4 & 8 wks Epo SQ 80 U/kg/d in 1	No Open-label No control No randomization	NA 12 wks	NA N=12 N=10 evaluated Marrow fibrosis ↑ in 4/11, HTN, rx related aggravation of thrombocytopenia & bleeding	Hb level ≥11.5 g/dl & change ≥1.5 g/dl or transfusion need ≥50% change
Herrmann 1991 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation or chronic myelomonocytic leukemia	No Exclusion for bone marrow transplant eligible Performance status: Karnofsky >80%	No recent antileukemic rx	No Epo SQ 10,000 U/5x/wk (n=9) or IV 150 U/kg (n=10) at start Dose ↑at 6 & 10 wks for non-response	No Open-label No control No randomization Descriptive study	NA 14 wks	NA N=19	Hb change >1.5 g/dl Transfusion need Predictive value of EPO level Ferritin level & ret count change
Hirashima 1991 Paper Medline (?)	Aplastic anemia or MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-	Performance status: Karnofsky >50% Life expectancy ≥3 mo Excluded hepatic/	No recent chemotherapy or anti-lymphocytic globulin	No Epo IV 3000 or 6000 U/d at start Dose ↑ permitted	No Open-label No control No randomization	NA 8 wks	NA N=12	Hb change ≥1.5g/dl or transfusion need (≥50% change) Predictive value of EPO levels

	tion	renal dysfunction						Ferrokinetic studies Colony forming unit
Isnard 1993 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts See Isnard 1991	No	No recent androgens or cytokines	No Epo SQ 40 U/kg/TIW Dose ↑ per forced titration Dose ↓ in responders to determine maintenance dose	No Open-label No control No randomization	NA 3 mo for all F/u for at least 21 mo for some responders During extended f/u, transformation to AML x1	NA N=20	Complete response Hb level (normal) Partial: hb change ≥2.5g/dl w/o transfusion or change in transfusion need (≥50% change) Predictive value of EPO levels & medullary erythroblasts Colony forming units
Kasper 1997 Paper Medline (no)	No Agnogenic myeloid metaplasia, CLL, HD, lymphoma, MM, MDS, solid ca, Waldenstrom's dx	No Hb <10 g/dl Performance status: WHO ≤1 Excluded HTN, renal dysfunction seizure	On chemo >3 mo or off for >6 wks	No * Epo SQ 2000 U/d at start Dose ↑ permitted q4 wks Tx DC permitted at 12 wks for non responders	No Open-label No control No randomization	NA 12 wks for all Up to 20 wks of tx for some	NA N=60 N=48 evaluable; no ITT Dx progression x5, HTN x2, DVT x2, splenomegaly x2	Hb >2 g/dl w/o transfusion Predictive value of EPO level
Kurzrock 1991 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation	No Hb <10 g.dl Life expectancy ≥3 mo Excluded hepatic & renal dysfunction	No recent tx	No Epo 50 U/kg/d, but variable tx duration	No Open-label No control No randomization	No At least 8 wks w unspecified duration of tx & f/u	NA N=16 Symptomatic dx progression x1, thrombocytopenia reversed w rx DC x3, splenomegaly x1	Ret count ↑ x2 + hb change >2 g/dl or transfusion need eliminated Ferritin & transferrinFe studies Predictive value of EPO levels
Ludwig 1993-A Paper Medline (yes)	No Included hematologic ca, MDS MM=18	No Hb <11 g/dl	No Could include XRT	No Epo SQ 150 U/kg TIW Dose ↑ permitted q 3 wks	No Open-label No randomization No control	No 12 wks unless pt requested longer-up to 58 wks Survival analysis compared responders vs non-responders	NA N=67	Hb change Transfusion need QOL Survival
Ludwig 1993-B Paper Medline (yes)	No Included hematologic ca, MDS MM=18	No	No Could include XRT	No Epo SQ 150 U/kg TIW Dose ↑ permitted at 6 wks	No Open-label No randomization No control	No 12 wks unless pt requested longer Survival analysis compared responders vs non-responders	NA N=42	Hb change QOL Survival
Ludwig	No	No	No	No	No	No	NA	Hb change

1994 Paper Medline (yes)	Included hematologic ca, MDS MM=20	Hb <11 g/dl Life expectancy >3 mo	Could include XRT	Dose ↑ permitted at 6 wks *	Open-label Algorithm for response in ½ group tested on 2nd ½	12 wks	N=80	Identification of response predictors
Maisnar 2004 Paper Medline (no)	No CLL, NHL, MM, MDS, Waldenstrom dx, other	No Hb ≤10 g/dl or transfusion dependent Excluded HTN, renal dysfunction, seizure	Could be undergoing chemotherapy	No Epo SQ 150 U/kg TIW Dose ↑ permitted *	No Open-label No control No randomization	NA At least 3 mo	NA N=134 N=127 ITT not done. Excluded included pts w dx progression x3, pulmonary embolism x1	Hb level Transfusion need QOL
Marques da Costa 1994 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation or chronic myelomonocytic leukemia	No Transfusion dependent No hepatic/renal dysfunction	NA	Yes Epo SQ 10,000 U TIW	No Open-label No control No randomization	NA 12 wks Some post cessation f/u	NA N=9 Dx progression x1	Hb change ≥1 g/dl or transfusion need (>50% change) Predictive value of EPO levels & marrow content of red cell progenitors
Mohr 1993 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts	Hb <10 g/dl or transfusion dependence Excluded hepatic, renal dysfunction	No recent chemotherapyor growth factor tx	Yes * Epo SQ 30 or 60 U/k/d Dose ↑ permitted	No Open-label No control No randomization	NA 12 wks	NA N=10 Dx progression x5	Hb >11 g/dl &/or ↓ transfusion need
Musto 1994A Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No Transfusion dependent	NA	No Epo ≤1050 U/kg/wk ≥2 mo	No Retrospective Open-label No randomization Normal control population for TNF values	NA ≥2 mo	NA N=26	Hb change >2 g/dl w/o transfusion Predictive value of TNF-1-beta & IL-1
Musto 1994B Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No Transfusion dependent	NA	No Epo SQ 450 U/kg TIW Dose ↑ permitted Epo ≥2 mo	No Open-label No control No randomization	NA ≥2 mo	NA N=25	Hb >8 g/dl w/o transfusion Change in soluble transferrin level, fluorescent ret count, hypochromic erythrocyte level
Musto 2003 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts	No Could have received ESA previously	NA	Epo SQ 40,000 U/wk x ≥8 wks Tx DCed for non-response	No Open-label No control No randomization	NA ≥8 wks Variable duration of f/u in responders	NA N=13	Hb change >2 g/dl &/or transfusion free
Musto 2004 Paper	MDS, RCMD Refractory anemia ± ringed sideroblasts ±	Modest renal dysfunction not excluded	NA	Darbe SQ 150 ug/wk x≥12 wks	No Open-label No control	NA ≥12 wks Variable duration of	NA N=37	Hb change ≥1-2 g/dl &/or transfusion need (>50%

Medline (yes)	blasts Refractory cytopenia w multilineage dys plasia ± ringed sideroblasts Dx could be 2° to prior chemo for other ca				No randomization	f/u in responders	Withdrawal for lack of efficacy x 22/37 During f/u, relapse x1, death cause not provided x1	change) Predictive value of EPO, blast, hypoplastic marrow, & transfusion levels
Patton 2005 Paper Medline (yes)	MDS Otherwise unspecified	Currently on Epo	NA	Switch study from 1 ESA to another Titrated as needed	No Retrospective Rx switch study Open-label Active control No randomization	NA 16 wks	NA N=142 switch N=102 naive	Hb change ≥1-2 g/dl OR transfusion need (>50% change)
Rafanelli 1992 Paper Medline (no)	MDS, Anogenic myeloid metaplasia Refractory anemia ± ringed sideroblasts ± blasts	No Performance status: Unspecified: ≤2 Life expectancy >6 mo W/o major hepatic/ renal dysfunction	No recent chemotherapy, retinoids, vitamin D3, glucocorticoids	Yes Epo SQ 150 U/kg/d x3 mo. Responders could continue.	No Open-label No control No randomization	NA ≥3 mo w unspecified duration of tx & f/u	NA N=10	Complete response: Hb change ≥1 g/dl Partial response: Transfusion need (>50% change) Change in burst forming units, colony forming units, & ret count Predictive value of EPO level
Razzano 1991 Letter Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation See Razzano 1993	<30% marrow blasts Hb <10 g/dl & transfusion dependent Life expectancy >3 mo	NA	No Epo SQ 6000 U TIW Dose ↑ permitted q 4 wks	No Open-label No control No randomization	NA Unspecified tx & f/u period	NA N=19 N=17 evaluated Transformation to leukemia x1, CVA x1	Hb change ≥1 g/dl & transfusion need (>50% change) Response duration Predictive value of EPO level
Razzano 1993 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation See Razzano 1991	<30% marrow blasts Hb <10 g/dl & transfusion dependent Life expectancy >3 mo	NA	No Epo SQ 6000 U TIW Dose ↑ permitted q 4 wks	No Open-label No control No randomization	NA Unspecified tx & f/u period	NA N=19 N=17 evaluated Transformation to leukemia x1, CVA x1	Hb change ≥1 g/dl & transfusion need (>50% change) Change in burst forming units & colony forming units Response duration RNA expression of GCSF & GMCSF Predictive value of EPO level
Rose 1995 Paper Medline	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-	<10% marrow blasts Hb <8 g/dl (hct <25%) EPO level <500	NA	No Epo SQ 150 U/kg TIW Dose ↑ permitted q 4 wks	No Open-label No control No randomization	NA No specified duration	NA N=116 N=100 evaluable ITT not done; not	Hct change 6% or transfusion need (≥50% change) in last 3 mo of tx

(yes)	tion or chronic myelomonocytic leukemia	mU/ml Excluded renal dysfunction			Compassionate use trial		evaluated if tx <4 wks Splenomegaly ± pain ± thrombocytopenia x8, transformation to leukemia x5	Predictive value of EPO level
Schouten 1991 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation	Hb <6.5 mmol/l or transfusion dependent Performance status: Karnofsky >60% Life expectancy >3 mo Excluded cardiovascular, hepatic, renal dysfunction	No recent chemotherapy	No Epo SQ 40 U/kg TIW at start Dose ↑ (doubling) permitted q 6 wks x4	No Open-label No control No randomization	No 6 wks for 1st endpoint Appears up to 30 wks	NA N=14 Transformations to AML x3 , death from sepsis & 5% blasts x1	Hb change 15% Predictive value of EPO level
Shapiro 1993 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts ±	Transfusion dependent	NA	No Epo IV 120 U/kg TIW at start Dose ↑ permitted q 4 wks Then highest dose SQ x4 wks	No Open-label No control No randomization	NA Unspecified	NA N=5	Erythrocyte density distribution Phagocytosis of erythrocytes
Shepherd 1992 Letter Medline (?)	MDS Refractory anemia ± blasts	No	NA	No * Epo SQ 100 U/kg TIW Dose ↑ permitted at 4 & 8 wks	No Open-label No control No randomization	NA 24 wks	NA N=6 N=5 evaluated (1 excluded bc of non-compliance) DVT x1	Undefined erythrocyte response
Stasi 1997A Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation or chronic myelomonocytic leukemia See Stasi 1997B	Hb <10 g/dl or transfusion dependent Performance status: ECOG ≤2 Excluded cardiac, CNS, ca, HTN, infection, hepatic, renal dysfunction	No recent cytostatic or growth factor tx	No Epo SQ 150 U/kg TIW Dose ↑ (doubling) permitted at 6 wks	No Open-label No control except for cytokines No randomization	No 6 or 12 wks for all 6 more months for responders	NA N=25	Hb change ≥1-2 g/dl or transfusion need ≥50% change Predictive value of TNF-alfa & IL-1-beta
Stasi 1997B Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation or chronic mye-	Hb <10 g/dl or transfusion dependent Performance status: ECOG ≤2 Excluded cardiac,	No recent cytostatic or growth factor tx	No Epo SQ 150 U/kg TIW Dose ↑ permitted at 6 wks 6 more months for	No Open-label No control No randomization	No	NA N=43	Hb change ≥1-2 g/dl or transfusion need ≥50% change Predictive value of EPO level, ery-

	lomonocytic leukemia See Stasi 1997A	CNS, ca, HTN, infection, hepatic, renal dysfunction		responders				throid burst forming units, & bone marrow hyperplasia
Stasi 2004 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts	<10% blasts Hb <10 g/dl or transfusion dependent Performance status: ECOG ≤2 Excluded cardiac, CNS, ca, HTN, infection, hepatic, renal dysfunction Unresponsive to Epo 20,000 U TIW	No prior MDS tx except Epo	No Epo SQ 40,000 U/wk Dose ↑ permitted at 6 wks Extended tx for responders	No Open-label No control No randomization	No 12 wks for all pts Unspecified additional tx & f/u for responders	NA N=48	Hb change ≥1-2 g/dl or transfusion need ≥50% change Ret count change Predictive value of EPO, erythroid blast forming unit , & karyotype levels Apoptosis Durability of response
Stasi 2005 Paper Medline (?)	MDS, RCMD Refractory anemia ± ringed sideroblasts ± blasts Refractory cytopenia w multilineage dys plasia ± ringed sideroblasts	<10% blasts Hb <10 g/dl or transfusion dependent Performance status: ECOG ≤2 Excluded cardiac, CNS, ca, HTN, infection, hepatic, renal dysfunction	No prior chemotherapy & radiotherapy	No Darbe SQ 150 mcg/wk Dose ↑ permitted at 12 wks *	No Open-label No control No randomization	NA 24 wks Could be extended	NA N=53 N=48 evaluated Dx progression x1	Hb change ≥1-2 g/dl or transfusion need ≥50% change Predictive value of EPO levels Apoptosis QOL
Stebler 1990 Paper Medline (yes)	MDS, Anemia from PNH	Hb <9 g/dl	Prior tx w cyclosporine & danazol continued	No Epo IV (initially) 50 U/kg TIW Dose ↑ permitted	No Open-label No control No randomization	NA 56 wks	NA N=4 Relapse x1	Not specified; description of hb, ret count, transfusion need change
Stenke 1993 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts	Hb <10.5 g/d +sx	NA	Yes Epo SQ 150 U/kg TIW until response	No Open-label No control No randomization	NA 6-14 wks Additional tx appears to have been given	NA N=29 N=27 evaluated Transformation to AML x1, aortic rupture x1	Hb change >1.5 g/dl & level ≥10.5 g/dl or transfusion need 100% change Predictive value of MDS subtype Tine to response
Stone 1994 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transformation or chronic myelo-monocytic leukemia	Hct <28% x1 or <32% x2 Performance status: ECOG <3 Life expectancy >2 mo Excluded cardiac, CNS, hepatic, renal dysfunction HTN,	No recent chemotherapy, radioherapy, experimental tx, (anti) androgen tx	No Epo SQ 100 or 200 or 400 U/kg TIW x6 wks then 0 x2 wks, then resume dose x 6 mo	No Open-label No control No randomization	NA ≤30 wks	NA N=20 Transforamtion to AML x1, TIA x1	Hb change 1.2 g/dl Transfusion need ≥50% change Ret count change Fe studies Predictive value of EPO & hematologic parameters

		infection						
Terpos 2002 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No <20% marrow blasts Hb <10 g/dl & sx or transfusion dependent Performance status: Karnofsky >60% Life expectancy ≥6 mo Excluded cardiac, CNS, hepatic, pulmonary, renal dysfunction Excluded ca, bleeding, transfusion dependent thrombocytopenia	No prior cytotoxic or steroid tx	Yes Epo SQ 150 U/kg TIW Scheduled tx 26 wks, but could be longer	No Open-label No control No randomization	NA 26 wks Longer permitted Observation: median 38 mo, ≤68 mo)	N=292 Transformation to AML 4/281 (26 wks) & 61/281 (observation period)	Hb change ≥1-2 g/dl or transfusion need ≥50% change Predictive value of EPO levels, karyotype, & transfusion status Time to response
Van Kamp 1991 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts	≤10% blasts Hb <10 g/dl or transfusion dependent Excluded hepatic, renal dysfunction	No recent chemotherapy, growth factors or anabolic factors	No Epo SQ 50 U/kg TIW Dose ↑ permitted q 3 wks up to 250 U/kg	No Open-label No control No randomization	No 15 wks	NA N=12 Cytopenia progression x1	Hb change >1.5 g/dl Change in burst forming units, colony forming units, myeloid progenitors, ret count, karyotype, RBC survival
Verhoef 1992 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts See Verhoef 1991	No Transfusion dependent No renal dysfunction	No other tx	No Epo SQ 100 U/kg TIW Dose ↑ q 4 wks	No Open-label No control No randomization	No 12 wks	NA N=10 Dx progression x1, transient blast ↑	Hb change >1 g/dl or transfusion need >30% change Ret count change Ferrokinetic change RBC survival Predictive value of EPO level Marrow change Predictive value of EPO level
Vinh 2003 Abstract Non-Medline (yes)	MDS	NA	NA	No Observed doses of 2 ESAs	No Retrospective chart review	NA	NA N=15	Descriptive data Dose of 1 ESA to maintain Hb>12 g/dl after switch from another ESA
Wallvick 2002 Paper	MDS Refractory anemia ± ringed sideroblasts ±	No Hb <10 g/dl & sx	NA	No Epo SQ 150-200 U/kg TIW	No Open-label No control	NA ≥6 wks Responders offered	NA N=68 N=66 evaluable	Hb change >1.5 g/dl or elimination of transfusion

Medline (no)	blasts Appears to be f/u from prior study				No randomization	additional tx Variable duration of f/u (4-72 mo for re-sponders)	Transformation to AML x1, aneur-ysm rupture x1	Predictive value of EPO level, transfu-sion need, karyo-type
Yoshida 1993 Paper Medline (?)	Aplastic anemia, MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-tion	No Hb <9 g/dl Performance status: Unspecified type ≤3 Life expectancy >3 mo	No recent growth factors	No Epo IV 6000 U/kg TIW (2 used SQ) Dose ↑ q 8 wks x2	No Open-label No control No randomization	NA 24 wks scheduled if required escalation Poorly specified tx & f/u periods	NA N=21 Transformation to AML x3, dx pro-gresssion x1, CVA (extended f/u) x1	Hb change >1.5 g/dl &/or transfu-sion need >50% change Predictive value of EPO levels Change in colony forming units
Ziegler 1993 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	<10% blasts Hb <9 g/dl Transfusion depen-dent Performance status: ?ECOG ≤2 Cardiac/pulmonary/re nal dysfunction ex-cluded Pt w HTN, seizures, recent thrombosis excluded	No recent growth factors permitted	No ESA dose 500 U/kg TIW IV x3 mo Dose ↑ permitted at 3 mo *	No Open-label No control No randomization	No At least 2 months Duration of follow-up unspecified	NA N=16 (Not considered evaluable unless tx >2 mo. N=13 evaluable) Disease progres-sion, reproducible splenic pain x1	Hb change >2 g/dl Transfusion need (≥50% change) Predictive value of EPO level & splenomegaly
Non-randomized-Combination Therapy-Malignant Conditions								
Dunphy 1997 Paper Medline (yes)	Yes Head-neck ca	No Stages 3-4 Life expectancy ≥4 mo Performance status: Zubrod ≤2 Excluded hepatic, renal dysfunction	No Pre-operative carboplatin (vari-able dose) +pacli-taxel XRTcould be sub-stituted for sur-gery if good chemo response	No Dose ↑ permitted during chemo cycles 2 & 3 * ESA group given Fe & folate	No Unknown if blind Only part of con-trol randomized	NA 3 wks for each of 2 or 3 chemocycles	NA N=37	Hb change Transfusion need
Dusenbery 1994 Paper Medline (yes)	Yes Cervical ca	No Stage 1B, 2AB, 3B Hb <12.5 g/dl	No All external beam, but not all intraca-vitary XRT Some given radio-sensitizing cis-pla-tinum	No 10 fixed doses daily -> 3x wk until target hb reached or XRT done * All current patients giv-en Fe	No Open-label Many controls his-torical; concurrent controls non-ran-domized	NA ~6 wks	NA N=20	Retic change Hb change
Lavey 2004 Paper Medline (yes)	Cervical ca (diease inside pelvis)	No Stages 2B-4A Variable histogic dx	Yes Received both chemo-therapy & XRT	Fixed doses given until target hb reached or XRT complete * Also given Fe	No Open-label No randomization Comparator cohort from another trial	NA Tx up to ~7 wks Survival (over-all, progression free) f/u done for apparently	NA N=53	Hg change Hg target Survival

					used for survival	72 mo		
Levine 1999 Paper Medline (yes)	Yes Rectal ca-amenable to pre-op chemoXRT	No Hb ≤15 g/dl	Yes Received both chemotherapy & XRT	Yes 1dose before & others during chemoradiation & pre/peri-op period * Tx group also received Fe	No Open-label No randomization Historical control	NA 12 wks	NA N=10	Hb change Hb level Transfusion need
Malik 1998 Paper Medline (yes)	No Non-hematologic ca	No Hb <10.5 g/dl Performance status: ECOG ≤3 Life expectancy ≥4 mo Excluded cerebral mets, renal dysfunction	Platinum tx Androgen tx excluded	Yes Fe also given	No Open-label No control No randomization	NA At least 10 wks	NA N=23	Hb level >12 g/dl change ≥2 g/dl Transfusion need QOL
Non-randomized-Combination Therapy-Pre-malignant Conditions								
Bernell 1996 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No Hb <11.5 g/dl (M) Hb <10.5 g/dl (F) or requiring bi-monthly transfusions (Excluded CHF, hepatic/renal dysfunction)	NA	Yes * Epo SQ 10,000 U TIW for all wks 1-6 GMSCF 200 ug/d added wks 5-14 in non-responders	No Open-label No control No randomization	NA Part 1: 6 wks (pts continued Epo outside study) Part 2: 14 wks (non-responders)	NA N=37 Part 1 (Conversion to AML/RAEB-t x2; cancer, tumor, MI x1) N=18 Part 2 combo tx (5 excluded-including 1 each for thrombosis & CVA)	Hb level >15 g/dl or transfusion need Predictive value of EPO & LDH levels
Besa 1998 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts No chronic myelomonocytic leukemia	No Myeloblasts ≤20% Not transfusion dependent (Excluded cancer & hepatic/renal dysfunction)	NA No prior chemotherapy or differentiating rx	No * Retinoic acid + vitamin E (fixed doses) Epo SQ 150 U/kg/ TIW at start Dose ↑ at 2 mo for non-response Drug DCed in poor responders	No Open-label No control No randomization	NA ≤6 mo	NA N=24	Hb change >2 g/dl & level (normal) or transfusion need (eliminated) Predictive value of EPO levels
Bessho 1992 Paper Medline (no)	Aplastic anemia MDS MDS=8 See Bessho 1994	No	No	No Epo IV 3000 or 6000 U/d Dose ↑ permitted for non-response	No Open label No control No randomization	NA ≥4 wks	NA N=12	Hb change
Bessho 1994	Aplastic anemia MDS-refractory	No Require RBC or	No Assorted prior tx	No Epo SQ 120 or 240	No No control	NA Duration not stated	NA N=17	Hb level >10 g/dl & transfusion need

Paper Medline (?)	anemia See Bessho 1992 See Matsuda	platelet transfusion Performance status: Karnofsky >50% Excluded hepatic/ renal dysfunction	could be continued	U/kg/ TIW at start Dose ↑ permitted for non-response Dose ↓ prn once target reached GCSF (variable initial disease & dose titrated)	No randomization			(eliminated)(need based on hb levels for individual patients) Predictive value of EPO levels
Economopoulos 1999 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No <10% blasts Hb <10.5 g/dl Dx ≤1 yr Performance status: Karnofsky <50 Hepatic/renal dys-function	Could have failed chemotherapy or be contraindicated for chemotherapy. Chemotherapy need to be given ≥2 mo prior.	No Epo SQ 60 U/kg 3d/wk Dose ↑ permitted post 6 wks for hb change ≤1.5 g/dl GMCSF 3 ug/kg 2d/wk	No Open-label No control No randomization	NA 12 wks Median duration of extended f/u=22 mo	NA N=19 During extended f/u, leukemic transformation (5/19)	Hb change ≥1 g/dl or transfusion need (>50% change) Predictive value of EPO level
Grossi 2002 Letter Medline (?)	MDS Refractory anemia ± excess blasts	No Blasts can be >10% 11/12 transfusion de-pendent	Could have used ESAs	Yes Epo SQ 150 U/kg qOD Amifostine IV 200 mg/m2 3x/wk	No Open-label No control No randomization	NA Tx x6 wks F/u at 60 days & longer	NA N=12 During extended f/u, 2 died from AML	Cheson 2000 end points
Hansen 1993 Paper Medline (no)	MDS Refractory anemia ± blasts ± ringed sideroblasts	No Hb <9 g/dl Performance status: Karnofsky >50 Excluded ca, HTN, seizure, hepatic, renal dysfunction	No recent cytosta-tic, hormone, in-terferon tx	GMCSF SQ 1.5-3 ug/d SQ (titrated) x6 wks Then + Epo 60 U/kg/d Dose ↑ permitted at 6 & 8 wks in non-responders	No Open-label No control No randomization	NA 6 wks on GM-CSF, then ESA added for 12 wks	NA N=13	Hb change >1.5 g/dl or transfusion need Marrow morpho-logy
Hellstrom-L 1993 Paper Medline (?)	MDS Refractory anemia ± blasts ± ringed sideroblasts	No Hb <10 g/dl Excluded HTN, cur-rent ca, seizure	No recent chemo-therapy No prior tx w Epo or GCSF	No GCSF SQ 0.3 ug/d at start. Prn ↑ at 2 & 4 wks. Epo SQ 60 U/kg/d started at 6 wks Dose ↑ permitted at 12 & 14 wks in non-re-sponders	No Open-label No control No randomization Comparison of responders & non-responders	NA 12 wks Epo tx 18 wks total tx	NA N=22 N=21 evaluated During f/u, trans-formation to AML x1	Hb level >10 g/dl wo transfusion or change in Hb ≥1.5 g/dl Granulocyte re-sponse Bone marrow com-position & cellular-ity Predictive value of EPO levels
Hellstrom-L 1997A Paper Medline (no) 2 trials-1 in-complete	MDS Refractory anemia ± ringed sideroblasts ± excess blasts See Hellstrom-Lind-berg 1993,6 & Ne-	Hb <10 g/dl or trans-fusion need	NA	No Epo SQ 5-10,000 U/d or 60-120 U/kg/d GCSF SQ 30-150 ug/d or 0.3-3 ug/kg/d 1 rx started 4-6 wks prior to the other rx	No 1 study open label & no control 1 study random-ized, but to same 2 compounds in op-posite order	NA 18 wks	NA N=58 N=51 evaluated	Complete response: Hb 11.5 g/dl Partial: hb change >1.5 g/dl or trans-fusion need (100% change) Bone marrow cellu-

	grin 1993,6				Pooled data			larity & apoptosis
Hellstrom-L 1997B Paper Medline (yes) From prior trials	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-tion See Hellstrom-Lindberg 1993,6 & Negrin 1993,6	Hb <10 g/dl or trans-fusion need	NA	No Epo SQ 5-10,000 U/d or 60-120 U/kg/d GCSF SQ 30-150 ug/d or 0.3-3 ug/kg/d 1 rx started 4-6 wks prior to the other rx	No 1 study open label & no control 1 study random-ized, but to same 2 compounds in op-posite order Pooled data	No At least 16 wks	NA N=98	Post hoc composite definition of ESA response: Complete hb ≥11.5 g/dl. Partial hb change ≥1.5 g/dl or trans-fusion need (100% change) Predictive value of EPO levels
Hellstrom-L 2003 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts See Hellstrom-Lind-berg 1998	Hb <10 g/dl or trans-fusion need	NA	No Epo SQ 10,000 U/5 d/wk w prn dose reduce-tion x12 wks. GCSF SQ 30-150 ug/3 or 7 d/wk x12 wks. If response, then tx for another 16 wks	No In this study: Open-label No control No randomization Pooled data from other studies	No Tx in this study : 12 wks all 28 wks responders Median f/u in cuurent study 41 mo; in prior studies 43 mo	NA N=63 N=47 responders	Complete hb ≥11.5 g/dl. Partial hb change ≥1.5 g/dl or transfusion need (100% change) QOL
Imamura 1994 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-tion	No	NA	GCSF IV 400 ug/d x10 wks. EPO SQ 100 U/kg/d wks 3-10. Dose ↑ permitted for both	No Open-label No control No randomization	NA 10 wks	NA N=10 Not ITT, excluded if dose violations	Hb change >1-2 g/dl in graded levels PLT & granulocyte change in graded levels
Imamura 1995 Paper Medline (yes)	Aplastic anemia	No	Prior tx w steroids (anabolic, cortico-teroid), cyclospor-ine, Epo (mono-therapy), GCSF (monotherapy) anti-lymphocytic globulin	GCSF IV 400 ug/d x10 wks. EPO SQ 100 U/kg/d wks 3-10. Dose ↑ permitted for both	No Open-label No control No randomization	NA 10 wks with extended tx prn	NA N=32 N=27 after exclu-sion for bleeding, infection Shock, hepatic dysfunction x1	Hb change >1-2 g/dl in graded levels PLT & granulocyte change in graded levels
Jadersten 2005 Paper Medline (no)	MDS Refractory anemia ± ringed sideroblasts ± blasts See Hellstrom-Lind-berg 1993, 1998, 2003	Hb <10 g/dl or trans-fusion dependent Exclusion for bone marrow transplant eligibility & trans-fusion dependent thrombocytopenia	NA	No Composite 3 studies: GCSF SQ 30-150 ug/d x4 wks + Epo SQ 5000-10000 U/d wks 5-16 OR Epo SQ 5000-10000 U/d wks 8 wk + GCSF SQ 30-150 ug/d wks 9-18 OR Epo SQ 10000 U 5x/wk + GCSF SQ 75-300 ug	No Open-label No randomization Non-concurrent control (n=334) from database	No 12-18 wks in original studies 49 mo f/u	NA N=141 from 3 studies N=123 considered for evaluation; 4 excluded for dx progression & 4 for transformation to AML	1st studies Hb change ≥1.5g/dl or transfusion need (100% change) F/u study Response duration Survival Change to AML

				/TIW OR GCSF SQ 0.3-3 ug/kg/d x6 wks +Epo SQ 60 U/kg/d wks 7-12 Dose ↑ permitted				
Mannone 2006 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts or chronic myelomonocytic leukemia See Mannone 2004	No Hb <10 g/dl or transfusion depen-dent <10% blasts EPO <500 mU/ml Excluded ca	Prior ESA expo-sure permitted	Darbe 300 ug/wk x12 wks +GCSF 150 ug TIW for poor response. Combo for another 12 wks	No Open-label No control No randomization	NA 12 wks initial tx 12 more wks if com-bo tx started Then unspecified per-iod of maintenance	NA N=62, but not ITT bc not evaluated bc of sepsis x2 &CHF x1 N=40 completed 12 wks	Hb change ≥1-2 g/dl (if t=0 hb <11 g/dl) or transfusion need ≥50% change Predictive value of EPO level , karyo-type, transfusion need Cost analysis
Mantovani 2000 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No <20% blasts Hb <9 g/dl or transfusion depen-dent Bicytopenia or hx severe infections	No recent growth factors	No Epo SQ 200 U/kg TIW Epo ↑ permitted at 6 wks * +GCSF SQ 1.5 ug/kg/d (titrated prn)	No Open-label No control No randomization	NA 36 wks of tx unless pt requested longer Extended f/u	NA N=33 N=25 evaluable Transformation to AML 7/33	Endpoints at 12 & 36 wks Hb change ≥1-2 g/dl 12 wks or transfusion need ≥50% change Response durability Time to AML Survival (1 & 2 yr)
Matsuda 2002 Paper Medline (?)	Aplastic anemia, MDS Refractory anemia See Bessho 1992,4	NA	NA	No Epo SQ 120 or 240 U/kg TIW Dose ↑ permitted +GCSF SQ 5 or 10 ug/kg TIW (titrated prn)	No Open-label No control No randomization	NA Variable duration of tx & f/u	NA N=20 Transformation to AML x2, death from another ca x1	Hb level 10 g/dl w/o transfusion Granulocytes >2000/ul Platelet >70 $x10^9$/L Dx progression Survival
Maurer 1995 Paper Medline (no)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No	No recent rx for at least 4 wks	No Vit E PO 400 mg/d +Retinoic acid PO 25-45 mg/m2/d +GCSF 1 ug/kg/d SQ at start & titrated +Epo SQ 5000 U/d SQ Epo dose ↑ permitted at 4 wks	No Open-label No control No randomization	NA 12 wks	NA N=10	Hb level WBC level Burst forming units Lymphocyte types Cytokine levels
Miller 1999 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No	NA	IL-3 SQ 3 ug/kg x28 d (↓ prn) Then + EPO SQ 150 U/kg TIW 12 wks & if tolerated for 8 or 12 more wks	No Open-label No control No randomization	NA 28 d on IL-3, then 12 wks on IL-3+Epo tx. Then +2-3 mo tx if no major toxicity	NA N=22 Leukemic trans-formation x1, CVA x1, pul-	Hb change ≥2 g/dl for non-transfused pts & >2 g/dl in transfused pts Ret count change PLT & neutrophil

							monary edema	change Progenitor change
Musto 1994 Letter Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	Transfusion depen-dent	Refractory to Epo	GCSF SQ 300 ug/qD or OD Then 2-4 wks later +Epo SQ 300 U/kg TIW Combo for ≥ 8 wks	No Open-label No control No randomization	NA ≥10-12 wks	NA N=12	Hb level or trans-fusion need Transferrin recap-tor & ret count change
Musto 2001 Paper Medline (no)	MDS Refractory anemia ± ringed sideroblasts ± blasts	Hb <8 g/dl Transfusion depen-dent ≤20% blasts Non-responsive to 2 mo of Epo	Washout x 3 mo	Epo SQ 300 U/kg TIW wks 3-10 1 of the following wks 1-10: GCSF 300 ug/d OR n=27 GMCSF 300 ug/d OR n=23 IL-3 5 ug/kg/d N=10	No Open-label 3 experimental tx arms No randomization	NA 10 wks	NA N=60 N=50 completed 1 of 3 tx Transformation to AML x2, aplasia x1, splenomegaly x2	1° Hb level >8.5 g/dl w/o transfusion 2° changes in ret count & transferrin receptor
Musto 2006 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	<10% blasts Transfusion depen-dent Prior non-response to either ESA or thali-domide Stratified by prior tx	Prior non-response to either ESA or thalidomide alone. Washout x 3 mo	EPO SQ 40,000 U/wk +Thalidomide 200 mg/d x12 wks Then if monotherapy if response Then combo therapy if response lost	No Open-label No control No randomization	No Part 1: 12 wks on combo tx Part 2: ≤12 wks on compo-nent of combo tx not previously failed Part 3 12 wks of combo tx if part 2 failed	NA N=30 N=27 after exclu-sion for AE N=7 after exclu-sion for non-re-sponse to combo tx)	Hb change ≥1-2 g/dl &/or trans-fusion need (>50% change)
Negrin 1993 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-tion See Negrin 1996	Hb <10 g/dl (hct <31%) or anemia sx Excluded cardiac, he-patic, renal dysfunc-tion	Recent chemo-therapy or XRT Current lithium, steroids including danazol, vitamin (A or D)	No GCSF SQ 1 ug/kg (prn titration) When neutrophils ↑, +Epo SQ 100 U/kg/d w escalation to 300 U/kg/d over 16 wks.	No Open-label No control No randomization	No 16+ wks	NA N=28 N=24 evaluated. ITT not done Transformation to AML x1, splenic pain x3	Hb change ≥1-2 g/dl &/or trans-fusion need (>50% change) Ret count Neutrophil ct Predictive value of EPO level & karyo-type
Negrin 1996 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-tion	Hb <10 g/dl (hct <31%) or anemia sx Excluded cardiac, he-patic, renal dysfunc-tion	Recent chemo-therapy or XRT Current lithium, steroids including danazol, vitamin (A or D)	No GCSF SQ 1 ug/kg (prn titration) x 2 wks, +Epo SQ 100 U/kg/d w escalation to 300 U/kg/d over 16 wks. Responders treated 8	No Open-label No control No randomization	No Tx could be 34 wks in some patients Variable duration of extended f/u	NA N=55 Short-term: ↑ myeloblasts x5, metastatic ca x1, thrombocytopenia	Hb change ≥1-2 g/dl &/or trans-fusion need (>50% change) Ret count Neutrophil ct Predictive value of

	See Negrin 1993			more wks of combo tx. These responders treated to 8 more wks of Epo tx.			x1 Long-term: Transformation to AML x2, marrow fibrosis x1, cardiac death x2, thrombo-cytopenia x1	EPO level & karyo-type
Neumeister 2001 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-tion Could be 2° to other dx	Hb <105 g/dl or transfusion dependent	NA	Amfostine IV 250 mg/m2 TIW x 4 wks tx & 2 wks no tx +ESA SQ 150 U/kg/d x 6 wks Cycle repeated. G-CSF SQ 1 ug/kg/d added for non-responders	No Open-label No control No randomization	No 12 wks	NA N=10 DVT x1	Hb change >1.4 g/dl or transfusion need (>50% change) PLT & neutrophil change
Remacha 1999 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts	Hb ≤10 g/dl or trans-fusion dependent EPO ≤ 250 U/L	NA	Epo SQ 300 U/kg TIW x8 wks & tapered over 16 wks if response +GCSF SQ 1 ug/kg TIW at 8 wks for no/ partial response for an-other 8 wks & another 8 wks for partial response	No Open-label No control No randomization	No 24 wks partial/non-responders	NA N=32 (6 with-drawals) Response lost x3, transformation to leukemia x1	Hb change ≥1-2 g/dl or transfusion need (>50% change)
Rigolin 2004 Paper Medline (no)	MDS Refractory anemia ± ringed sideroblasts ± blasts ± transforma-tion Cytogenetic changes	≤10% marrow blasts Hb <9 g/dl or trans-fusion dependent Performance status: Karnofsky >60% Life expectancy >6 mo Prior Epo exposure w/o response or loss of response	Epo washout x≥3 wks No chemotherapy	Yes Epo SQ 10,000 TIW G-CSF SQ 300 U/kg 2x/ wk	No Open-label No control No randomization	No 16 wks	NA N=13	Hb change ≥1-2 g/dl or transfusion need (>50% change) Abnormal CD34+ cells Cell apoptosis
Runde 1995 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts	<15% blasts Hb <10 g/dl PLT ≥20 x10^9/l Performance status: Karnofsky >50% Life expectancy >6 mo Excluded ca, car-diac, CNS, HTN, he-patic, renal dysfunc-tion	NA	No GMCSF SQ 150 ug/ m^2/d days 1-10 Then Epo SQ 100 U/kg/d day 11 x8 wks Then 3 continued at ↑ dose	No Open-label No control No randomization	No 8 wks for most	NA N=10 Heart failure death x1, blast ↑ x1	Hb change ≥1.5 g/dl or transfusion need (>50% change) WBC doubling
Stasi 1999 Paper Medline	MDS Refractory anemia ± ringed sideroblasts ±	≤10% blasts Hb <10 g/dl Performance status: ECOG ≤2	No chemotherapy. Prior ESA therapy not excluded	No Epo SQ 150 U/kg TIW Epo dose ↑ permitted at 6 wks	No Open-label No control No randomization	No 12 wks	NA N=31 N=26 evaluated ITT not done; not	Hb change ≥1-2 g/dl or transfusion need (≥50% change)

(yes)	blasts	Excluded cardiac, CNS, ca, HTN, infec-tion, hepatic, renal dysfunction		+ GMCSF SQ 1 ug/kg/d SQ at start (titrated prn)			evaluated if ≥6 wks tx not com-pleted Dx progression x1, splenic pain & HTN x1	Neutrophil change Predictive value of EPO, TNF-alfa , & marrow infiltration
Stasi 2002 Paper Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts	<10% blasts Hb <10 g/dl Performance status: ECOG ≤2 Excluded cardiac, CNS, ca, HTN, infec-tion, hepatic, renal dysfunction	No prior chemo-therapy	No Epo SQ 150 U/kg TIW ESA dose ↑ permitted at 6 wks +Retinoic acid PO 80 mg/m2/d x7 days q other wk x12 wks w ≥6 mo for responders	No Open-label No control No randomization	No 12 wks for all ≥6 more months for responders	NA N=27	Hb change ≥1-2 g/dl or transfusion need (≥50% change) Ret count, neutron-phil, platelet, ery-throid blast for-ming unit change Apoptosis
Steurer 2003 Paper Medline (?)	MDS "Low-intermediate risk groups"	Excluded prior or current cancer & serious comorbid dx	NA	Darbe SQ 2.25 ug/kg/ wk +Thalidomide PO 100 mg/d	No Open-label No control No randomization	NA Planned duration un-specified	Study DCed after 3/7 developed thrombosis in the absence of protein C & S deficiency, Leiden factor, pro-thrombin gene mutation, surgery, catheters, hormone tx, or PNH	NA Thrombotic events could occur in ab-sence of hb re-sponse
Tsiara 2001 Paper Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts	Transfusion dependent despite EPO 10,000 U/TIW No ca, inflammation, hepatic, renal dys-function	NA	No Epo SQ 10,000 U/TIW Amifostine IV 300 mg/m^2 TIW But variable tx duration x≥4 wks	No Open-label No control No randomization	NA ≥4 wks Unspecified duration of tx & f/u	NA N=7 Transformation to leukemia x1, pul-monary edema, x1 myocardial in-farction x1	Hb level >11.5 g/dl w/o transfusion

1-Did not include papers using ESAs during high dose chemotherapy prior to bone marrow/stem cell transplantation

*Dose discontinuation or reduction for rapid increase in hemoglobin (or hematocrit) or reaching a normal or relatively high hemoglobin (or hematocrit) threshold

(financial contribution by pharmaceutical sponsor)

ALL=acute lymphocytic leukemia Ca=cancer CERA=continuous erythropoietin receptor activiator Chemo=chemotherapy CLL= chronic lymphocyte leukemia CML=chronic myelogenous leukemia CNS=central nervous system D=day(s) Darbe=Darbepoetin DC=discontinued ECOG=Eastern Cooperative Oncology Group Epo=Erythropoietin drug EPO=Erythropoeitin blood/serum levels F=female Fe=iron treatment F/u=follow-up GCSF=Granulocyte colony stimulating factor GI=gastrointestinal GMCSF=Granocyte-Myelocyte colony stimulating factor Hb=hemoglobin Hct=hematocrit HD=Hodgkin's disease HTN=hypertension IL=interleukin ITT=intent to treat analysis IV=intravenous M=male Mets=metastases MDS=myelodysplasic syndrome MM=multiple myeloma Mo=month NA=not applicable NHL=Non-Hodgkin's lymphoma PK=Pharmacokinetic PLT=platelet PMN= polymorphonuclear leukocyte count PNH=paroxsysmal nocturnal hemoglobinuria q=each QOL=quality of life or performance level or fatigue level RBC=red blood cell or erythrocyte Retic=reticulocyte count SQ=subcutaneous TIW=three times per week Tx=Treatment WBC=white blood cell count WHO=Word Health Organization Wk=wk(s) XRT=Radiation therapy

Appendix
Table 3
Studies with ESAs Not Structured to Provide Survival, Thrombosis, and Tumor Progression Data for Cancer by Stage and Type—Abstracts[1]

Author	Disease Type	Prospectively Stratified for Type/ Stage	Single Cancer Tx Regimen	Single ESA Regimen	Placebo-controlled, Double-blind Randomized	Sufficient Duration for Dx & Endpoint	Sufficient Power for Endpoint	Endpoint
Randomized-Placebo Control-Monotherapy-Malignant Conditions								
Aziz 2001 Abstract Non-Medline (?)	Yes Head-neck	No Squamous cell Hb <11 g/d	XRT	Loading dose followed by a maintenance dose	Unknown if blind	No F/u 1 mo post unspecified tx period	NA N=60 N=50 evaluable	Hb level Local reactions Tumor response
Beggs 2003 Abstract Non-Medline (yes)	Unresectable non-small cell lung ca	No Performance status: Karnofsky ≥80	Paclitaxel + platinum then chemo-radiation	Reported fixed dose	Yes	NA 13 wks Unspecified period of f/u	NA N=21	IL-6 levels Correlation w QOL
Carabantes 1999 Abstract Non-Medline (?)	No Ovarian & small cell lung ca	No Hb ≤11.5 g/dl	Platinum tx	No Dose ↑ permitted post 3-4 wks	Unknown if blind	No Randomized when anemic & treated for remainder of 6 chemo cycles+1 mo	NA N=35	Transfusion need QOL
Chang 2002 Abstract Non-Medline (yes)	Breast ca See Chang 2003	No Hb ≤12 g/dl	No	Reported fixed dose	No Open-label	NA 16 wks	NA N=110 Interim analysis N=350 planned	Hb >12 g/dl Transfusion need QOL
Chang 2003 Abstract Non-Medline (yes)	Breast ca See Chang 2002	No Hb ≤12 g/dl	No	Reported fixed dose	No Open-label	NA 16 wks	NA N=261 Interim analysis N=350 planned	Hb >12 g/dl Transfusion need QOL
Chang 2004 Abstract Non-Medline (yes)	Breast ca	No	No	Reported fixed dose	No Open-label	NA 16 wks	NA N=Unspecified	QOL
Cortesi 2005 Abstract Non-Medline	No	No Hb ≤9.5g/dl	No	Comparison of standard ESA dose vs loading dose & maintenance dose	Unknown if blind	NA Unspecified duration 1 endpoint 2 wks	NA N=64 Interim analysis N=202 recruited	2 wk hb change

(?)								
Crawford 1997 Abstract Non-Medline (yes)	Small cell lung ca	No	No	Dose fixed during blinded phase. After that, placebo patients switched to ESA & dose of ESA pts ↑	No Blinded only until hct <32% & transfusion to be given	No Through ≤ 6 chemotherapy cycles	NA N=28	Hct <32% Ret count Anemia prevention QOL
Crawford 2003 Abstract Non-Medline (yes)	Non-small cell lung ca	No Chemotherapy naïve Stage 3B, Stage 4 Hb 11-<15 g/dl	No	No Dose ↑ permitted for non-response *	No Open-label Control switched to ESA if Hb ≤10 g/dl	NA ≤16 wks	NA N=216	Hb level Hb change QOL
Elandt 2006 Abstract Non-Medline (?)	No Urogenital ca	No Hb 10-12 g/dl Performance status: ECOG ≤2	No	Front loaded ESA vs ESA tx w Hb <10 g/dl or sx	No Open-label	NA Unspecified	NA N=68	Hb level Transfusion need Dose needs
Faust 2001 Abstract Non-Medline (yes)	Lung ca See Pirker abstract	No Hb ≤11 g/dl	Platinum tx	No Dose ↑ permitted for non-response *	Yes	NA 12 wks	NA Unspecified	Hb level Transfusion need QOL
Hedenus 2004 Abstract Non-Medline (yes)	No Lymphoproliferative, lymphoid, lung, & others Pooled studies	No	No	Doses not stated Duration of tx 12 or 16 wks	Composite of 4 placebo controlled studies Unknown if blind for 2 studies Post-hoc analysis	No Variable duration of f/u	NA N=658 longer term data Post hoc analysis	Ca progresssion Survival
Henze 2002 Abstract Non-Medline (yes)	No ALL vs non ALL ca (Pediatric) See Henze paper	No Stratification by ca group	No	1 of 2 doses or placebo	Unknown if blind	NA 20 wks	NA N=232	1^{o} transfusion need after 4 wks tx 2^{o} hb change
Iconomou 2002 Abstract Non-Medline (?)	No Solid ca See Iconomou paper	No Hb <11 g/dl	No	No Reported fixed dose	Unknown if blind	No 12 wks	NA	Hb change QOL
Janinis 2003 Abstract Non-Medline (?)	No See Bamias	No Hb ≤11 g/dl Reportedly stratified either pre or post hoc for tx type	No	Reported fixed dose	Unknown if blind	NA Unspecified	NA N=372 evaluable for tumor response Other enrollment information not available	Hb change Transfusion need QOL Tumor response
Kotasek 2002 Abstract	No Solid ca	No Hb ≤11 g/dl	No	No Dose ranging; fixed doses	Yes	NA 12 wks	NA N=155	Hb change

Non-Medline (yes)	See Kotasek 2003							
Malik 2003 Abstract Non-Medline (?)	Ovarian ca Anemic prior to surgery & chemotherapy	Anemic prior to surgery & chemotherapy	Anemic prior to surgery & chemotherapy w paclixatel+carboplatin	Reported fixed dose	Unknown if blind	NA 4-6 wks tx Some later f/u	NA N=22	Hb change Survival
Marinaccio 2003 Abstract Non-Medline (?)	Ovarian ca Anemic prior to surgery & chemotherapy	Anemic prior to surgery & chemotherapy	Anemic prior to surgery & chemotherapy w paclixatel+carboplatin	Reported fixed dose	Unknown if blind	NA 4-6 wks tx Some later f/u	NA N=22	Hb change Survival
Marinaccio 2004 Abstract Non-Medline (?)	Ovarian ca Anemic prior to surgery & chemotherapy	Anemic prior to surgery & chemotherapy	Anemic prior to surgery & chemotherapy w paclixatel+carboplatin	Reported fixed dose	Unknown if blind	NA 4-6 wks tx Some later f/u	NA N=42	Hb change Survival
Moebus 2001 Abstract Non-Medline (?)	Yes Breast ca w 3+ nodes	Yes	Yes Dose dense sequential tx+GCSF vs conventional tx	Unspecified ESA regimen	Unknown if blind 2nd randomization for ESA	No Unspecified	NA N=281 enrolled N=97 in preliminary analysis	Hb change Transfusion need
Osterborg 2006 Abstract Non-Medline (?)	No Non-myeloid ca	No Hb $\geq$8.5 & $\leq$10.5 g/dl	Platinum tx excluded	Novel ESA Sequential dose escalation	Unknown if blind Some randomization	NA 6 wks tx + 3 wks observation	NA N=48	Hb change
Pirker 2001 Abstract Non-Medline (yes)	Lung ca See Faust abstract	No Hb $\leq$11 g/dl	Platinum tx	No Dose $\uparrow$ permitted for non-response *	Yes	NA 12 wks	NA Unspecified	Hb level Transfusion need QOL
Pirker 2002 Abstract Non-Medline (yes)	No	No Hb $\leq$11 g/dl Stratified by entry hb	No	Reported fixed dose	Unknown if blind	NA 12 wks	NA N=320	Hb level Transfusion need Effect of entry hb
Prozanto 2002 Abstract Non-Medline (?)	Breast ca	No	No	Unclear if multiple fixed doses or if dose changes permitted w/in a range	No Open-label	NA Up to 24 wks on chemotherapy +4 wks later	NA N=223 Preliminary data N=178	Hb level Transfusion need QOL
Quirt 1996 Abstract Non-Medline	No Lymphoma & solid ca	No Hb change 1.5 g/dl	No	No Dose $\uparrow$ permitted at 4 wks	Yes	No 16 wks	NA N=56	Transfusion need QOL Cost

(yes)								
Razzouk 2004 Abstract Non-Medline (yes)	No (Pediatric)	Stratified by solid ca+Hodgkins vs ALL+NHL	No	Reported fixed dose	Yes	NA 16 wks	NA N=222	1° QOL 2° Hb level Transfusion need
Sakai 2004 Abstract Non-Medline (?)	Lung ca, lymphoma	No Hb ≤11 g/dl	No	3 fixed doses	Yes	NA 12 wks	NA N=86	Hb change ≥2 g/dl QOL correlation w dose & hb change
Savonjie 2004 Abstract Non-Medline (?)	No Solid ca	No Hb ≤12 g/dl	Platinum tx	No Dose ↑ permitted for non-response	Unknown if blind	NA 4 wks after last cycle	NA N=315	Hb >12 g/dl Hb change Transfusion need QOL
Silberstein 2002 Abstract Non-Medline (?)	No	No Hb ≤11 g/dl M & <10 g/dl F Performance status: ECOG ≤1 Life expectancy ≥6 mo	No	No Dose ↑ permitted for non-response	Unknown if blind	NA 16 wks	NA N=344 Preliminary results	Hb change Transfusion need QOL Toxicity
Strauss 2005 Abstract Non-Medline (?)	Cervical ca-advanced	No Stage 2B-4A Hb 9-13 g/dl	Platinum tx + radiotherapy	Reported fixed dose	Unknown if blind	NA 12 wks F/u 6 mo	NA N=74	1° Correlation between anemia correction & tumor response 2° Dx progression Survival Hb change
Thomas 2002 Abstract Non-Medline (?)	No	No Hb ≤12 g/dl	No	Reported fixed dose	Unknown if blind	NA 12 wks	NA N=130	Hb change >1 g/dl QOL
Throuvalas 2000 Abstract Non-Medline (?)	No Bladder or cervical ca See Throuvalas 2004	Bladder Stages B2-C Cervix Stages 1B-3B	Platinum +XRT (intracavitary XRT also for cervical ca)	Yes	Unknown if blind	No Unspecified duration	NA N=55	Hb change Transfusion need Tumor response Tumor control
Throuvalas 2004 Abstract Non-Medline (?)	No Bladder or cervical ca See Throuvalas 2000	Bladder Stages B2-C Cervix Stages 1B-3B	Platinum +XRT (intracavitary XRT also for cervical ca)	Yes	Unknown if blind	No Unspecified duration of tx & f/u	NA N=55	Hb change Transfusion need Tumor response Tumor control Survival
Vandebroek	No	No	No	Reported fixed ESA	No	NA	NA	Hb ≥11 g/dl

2006 Abstract Non-Medline (?)	Non-myeloid ca	To be strtatified by tumor type To be stratified by entry hb		dose ± IV Fe (vs no or oral Fe)	Open-label	16 wks	N=114 Interim results N=400 planned	Adverse events
Randomized-Placebo Control-Monotherapy-Pre-malignant Conditions								
Randomized-Placebo Control-Combination Therapy-Malignant Conditions								
Blohmer 2004 Abstract Non-Medline (?)	Yes Cervical ca	No Included 1 high risk feature	Yes Includes XRT	No ESA pts only given Fe	No 2 variables in tx Open-label	No Tx up through 4 cycles	NA N=257 Power calculations not provided	1° Relapse free-survival 2° Transfusion need QOL
Randomized-Placebo Control-Combination Therapy-Pre-malignant Conditions								
Mannone 2004 Abstract Non-Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts or chronic myelomonocytic leukemia See Mannone 2006A	No Hb <10 g/dl or transfusion dependent <10% blasts EPO <500 mU/ml Excluded ca	Prior ESA exposure permitted	Darbe 300 ug/wk x12 wks + GCSF 150 ug TIW for poor response. Combo for another 12 wks	No	NA 12 wks initial tx 12 more wks if combo tx started Then unspecified period of maintenance	NA N=55, but not ITT bc preliminary data or not evaluated bc of sepsis N=40 completed 12 wks	Hb change ≥1-2 g/dl (if t=0 hb <11 g/dl) or transfusion need ≥50% change Predictive value of EPO level , karyotype, transfusion need
Randomized-Active Control-Monotherapy-Malignant Conditions								
Albertsson 2002 Abstract Non-Medline (?)	Breast ca-metastatic	No	No	2 fixed ESA doses	No Unknown if blind Active control	NA 24 wks	NA N=180	Hb change QOL
Alexopoulos 2004 Abstract Non-Medline (?)	No Non-hematologic ca	No Hb <11 g/dl or change >1.5 g/dl	No	No Dose ↑ permitted at 4 wks	Unknown if blind Active control	No 8 wks	NA N=50	Hb change Transfusion need QOL
Bindi 2004 Abstract Non-Medline (?)	No	No Classified by asthenia	No	Fixed doses of 2 ESAs	No Randomization for active control in patients with symptoms Placebo control had no symptoms	NA 8 wks	NA N=42	Hb change Ret count change QOL change
Canon 2005 Abstract Non-Medline (yes)	No Non-myeloid ca See Vansteenkiste	No Hb ≤11 g/dl	No	Comparison of 2 dosing regimens	No Active control Non--inferiority	NA 15 wks	NA N=705 randomized; 672 analyzed Not ITT; excluded early drop-outs	1° Transfusion need after 4 wks of tx 2° Hb ≥11g/dl Hb change QOL
Chang 2005	No	No	No	Randomization to 1 of 3 loading doses followed	No Unknown if blind	NA 16 wks	NA N=18	QOL

Abstract Non-Medline (?)				by 2 maintenance doses	Active control		Interim analysis N=? planned	
Charu 2004 Abstract Non-Medline (yes)	No Assorted cancers	No	No tx	Reported 2 fixed doses	No Active control	NA 21 wks tx or 12 wks observation+9 wks tx	NA N=170 Preliminary analysis of study w N=298	Hb change Transfusion need Hospitalization QOL
Delarue 2006 Abstract Non-Medline (yes)	Diffuse large B cell lymphoma	No	Randomization to an experimental chemoimmunotherapy vs a more conventional therapy	Second randomization to 1 ESA w hb target 13-15 g/dl vs more conventional use of another ESA	No Unknown if blind Active control	NA Variable duration for 8 cycles	NA N=130 Preliminary data including survival at 1 yr	Mean hb Survival
Fujisaka 2004 Abstract Non-Medline (?)	Yes Lung ca	No Hb ≤11 g/dl	No	Yes 3 fixed dose levels	Unknown if blind 3 fixed dose levels, but no placebo	No 8 wks	NA N=15	PK data
Glaspy 2002 Abstract Non-Medline (yes)	No See Glaspy paper See Kallich abstract	No Hb ≤11 g/dl	No	Loading doses followed by maintenance doses	No Active control	NA 12 wks	NA N=92	Hb change
Glaspy 2003 Abstract Non-Medline (yes)	No 2 pooled studies	No	No	Front loaded ESA vs another ESA	No Unknown if blind Active control 2 pooled studies	NA 12 weeks	NA N=178 2 pooled studies Post hoc analysis	QOL
Glaspy 2003 Abstract Non-Medline (yes)	No Non-myeloid ca See Glaspy 2005	No Hb ≥9-≤11 g/dl	No	Timing of ESA dose on days 1 vs 15 of chemotherapy	No Open-label Active control	NA 16 wks	NA N=81	Hb change PK data
Glaspy 2005 Abstract Non-Medline (yes)	No Non-myeloid ca	No Stratified by entry hb Stratified by tx type Hb ≤11 g/dl Performance status: ECOG ≤2	No	No Comparison of 2 ESAs Dose ↑ permitted for non-response	No Open-label Active control Non--inferiority	NA 16 wks	NA N=1220 randomized; 672 analyzed Not ITT; excluded early drop-outs	1° Transfusion need after 4 wks of tx 2° Hb 11-13 g/dl Hb change Time to Hb QOL
Glaspy 2006 Abstract Non-Medline (yes)	No	No	No	No Multiple dose regimens	No Active control; limited placebo control Pooled data 20 trials	NA Unpsecified	NA N=? Pooled data 20 trials; post hoc analysis	1° Hb ≥11 g/dl 2° Transfusion need QOL
Henry	No	No	No	Early vs later front-	No	NA	NA	Hb level

2003 Abstract Non-Medline (yes)				loading ESA regimens compared	Open-label Active control	15 wks	N=25	Hb change Transfusion need PK data
Henry 2006 Abstract Non-Medline (?)	No Non-myeloid ca	No Hb ≤11 g/dl	No	No 2 dose regimens * Dose ↑ permitted for non-response	No Open-label Active control	NA 13 wks	NA N=298	1° Hb change Transfusion need Dose changes
Heras 2006 Abstract Non-Medline (?)	No Solid ca	No Hb <11 g/dl	No	2 reportedly fixed doses	No Active control	NA 12 wks	NA N=50	Hb level Transfusion need QOL
Jacubowski 2003 Abstract Non-Medline (yes)	No Solid ca	No	No	Comparison of 2 ESAs Dose ↑ permitted at 4 or 6 wks *	No Open-label Active control	No Up to 16 wks Only preliminary data in abstract	NA N=81 randomized Interim analysis N=300 planned	Hb change >1 g/dl at 4 wks Transfusion need QOL at 16 wks
Justice 2003 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2	No	No Front loaded dosing f/u maintenance given either SQ or IV	No Open-label Active control	NA 15 wks	N=60	Hb change Hb level
Justice 2004 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2	No	No Fixed IV vs SQ doses	No Open-label Active control	NA 15 wks	NA N=?	Hb change
Kallich 2002 Abstract Non-Medline (yes)	No Solid ca See Glaspy paper	No Hb ≤11 g/dl	No	No Loading doses followed by maintenance doses Epo dose ↑ permitted for non-response	No Active control	NA 12 or 16 wks	NA N=99	QOL
Kotsori 2006 Abstract Non-Medline (yes)	No	No Hb ≤11 g/dl	No	Comparison of 2 ESAs Dose ↑ permitted for non-response	No Open-label Active control	NA 8 wks	NA N=110	Hb change Transfusion need Dose need QOL
Reardon 2004 Abstract Non-Medline (yes)	No	No	No	Early (hb 10.5-12 g.dl) or late (≤10 g/dl) initiation of ESA	No Open-label Active control	NA Unspecified	NA N=204 Preliminary data	Hb level Transfusion need QOL
Schwartz-berg	No Non-myeloid ca	No	No	Front loading doses that are fixed or based on	No Open-label	NA Variable	NA N=477	Hb change Time to Hb change

2003 Abstract Non-Medline (yes)	Pooled from 3 studies			weight followed by maintenance regimen	Active control		Pooled from 3 studies Post hoc analysis	
Schwartz-berg 2004 Abstract Non-Medline (yes)	No (breast, lung, gyneco-logic)	No Hb ≤11g/dl Performance status: Karnofsky ≥50 Excluded hepatic & renal dysfunction	No	No 2 ESAs Dose ↑ permitted for non-response	No Open-label Active control	NA 16 wks	NA N=210 after some pt exclusion	Hb level Transfusion need
Schwartz-berg 2006 Abstract Non-Medline (?)	No Pooled from 8 studies	No Post hoc stratification by disease state	No	8 dose regimens Otherwise unspecified	No Unknown if blind Active control Pooled data 8 trials	NA Unspecified	NA Unspecified	1º Hb ≥11 g/dl 2º Transfusion need Hb change QOL
Smith 2002 Abstract Non-Medline (yes)	No	No	No	Dose ranging; fixed doses	No Open-label Active control	NA 12 wks	NA N=79	Hb change PK data
Tchekme-dyian 2002 Abstract Non-Medline (yes)	No Solid ca	No Hb ≤11 g/dl	No	Reportedly 3 fixed doses of 1 ESA & 1 fixed dose of another ESA	No Active control	NA 7 wks	NA N=76	Hb change
Waltz man 2004 Abstract Non-Medline (yes)	No Solid ca	No Hb ≤11 g/d	No	No 2 ESAs Dose ↑ permitted for non-response	No Open-label Active control	NA 16 wk tx	NA N=123 Preliminary data for study to have ≥300	Hb change Time to hb Transfusion need
Welslau 2004 Abstract Non-Medline (?)	No Solid, hematologic ca See Harousseau	No Hb <12 g/dl	No	No Non-weight based dose or weight based dose Dose ↑ permitted at 4-6 wks *	No Open-label Active control	No ESA up to 28 wks Endpoint at 12 wks	NA N=736	Hb change Transfusion need QOL
Randomized-Active Control-Monotherapy-Pre-malignant Conditions								
Not Randomized-Monotherapy-Malignant Conditions								
Abbrederis 2006 Abstract Non-Medline (?)	Esophagogastric ca	No Hb <12 g/dl	No	Reported fixed dose	No Open-label Only 2 in concur-rent control; 29 in historical No randomization	NA Unspecified	NA N=24	Hb change

Antonadou 2006 Abstract Non-Medline (?)	No	No Hb 10-12 g/dl Performance status: ECOG ≤1 Life expectancy >6 mo	6 wk XRT	Reported fixed ESA dose	No Open-label No control No randomization	NA 6 wks	NA N=140 entered N=116 evaluated	Hb level Transfusion need (hb <9 g/dl) QOL
Arslan 2002 Abstract Non-Medline (?)	No	No	Platinum tx	Front loaded in 1 group, tx for anemia after 1 cycle, tx for anemia during 3rd cycle. Last 2 groups divided so that ESA tx DCed after chemo DCed vs continued	Not clearly specified	NA Unspecified	NA N=117	Serial hb values ESA duration
Ault 2003 Abstract Non-Medline (?)	CML	No	Imatinab variable doses	Fixed ESA dose	No Open-label No control No randomization	NA ? wks	NA N=7	Hb change
Baz 2005 Abstract Non-Medline (?)	MM	No	No	No	No Chart review No randomization	NA	NA N=245	Descriptive statistics Survival ESA vs non-ESA users
Baltz 2004 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb <11 g/d	No	Loading dose followed by maintenance dose if response	No Open-label No control No randomization	NA Unspecified tx duration Observed for ≤24 wks	NA Planned N unclear N=55 Preliminary results	1° Hb ≥12 g/dl or Hb change ≥2 g/dl
Beer 2006 Abstract Non-Medline (?)	Prostate ca w bone metastasis	No Hb <11 g/d	Androgen deprivation ± chemotherapy	No Dose ↑ permitted for non-response	No Open-label No control No randomization	NA 6 mo	NA N=16	1° Hb >12.5 g/dl
Belon 2004 Abstract Non-Medline (?)	No	No	No	No Dose ↑ noted Variable duration of tx	No Retrospective survey No control	No Mean tx of 8 wks	NA	Hb change Descriptive
Blayney 2003 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/d Performance status: ECOG ≤1 Excluded cardiac, hepatic, & renal dysfunction	No	Reported fixed dose	No Open-label No control No randomization	NA 17 wks	NA N=254	Oxygen carrying capacity QOL

Boccia 2005 Abstract Non-Medline (?)	No	No	No	No Dose ↑ permitted for non-response *	No Open-label No control No randomization	NA 16 wks	NA N=634 Preliminary data	1° Hb 11-12 g/dl 2° Hb change Transfusion need QOL
Boccia 2006 Abstract Non-Medline (?)	No Non-myeloid ca	No Hb <11 g/dl	No	Reported fixed dose	No Open label No control No randomization	NA 16 wks	NA N=1493 Post hoc analysis by age & hb	Hb ≥11g/dl Time to hb Transfusion need QOL
Ceccherini 2004 Abstract Non-Medline (?)	No Solid ca	No Hb ≤10.5 g/dl	No	Yes Loading dose over 3 days	No No control	No F/u at mean 7.1 wks	NA N=30	Hb change >1 g/dl at day 15
Cella 2004 Abstract Non-Medline (yes)	No Assorted cancers	No Hb ≤11 g/dl	No	No dose information	No Open-label No control No randomization	NA 17 wks	NA N=1558	QOL
Chap 2002 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl	No	Reported fix dose *	No Open-label No control No randomization	NA 16 wks	NA N=11 Interim analysis N=20 planned	Hb change
Cleeland 2004 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl	No	Reported fixed dose	No Open-label No control No randomization	NA 26 wks, but only 17 wks in this abstract	NA N=1053 Preliminary analysis of study w N=2423 Not ITT excluded those who did not reach 16 wks of tx	QOL Correlation w Hb change
Dicato 2005 Abstract Non-Medline (?)	No Post hoc analysis	No	No	Fixed dose regimen by weight cohort	No Retrospective No control No randomization	NA Duration not speci-fied	NA N=168 ESA Post hoc analysis	Likelihood of hb change ≥2 g/dl or hb ≥12 g/dl by body weight Transfusion need
Fastenau 2004 Abstract Non-Medline (yes)	No Pooled trials Post hoc analysis	No Hb ≤11 g/dl	No	Each study w a reported fixed dose regimen	No Unspecified 2 pooled trials	NA Unspecified	NA N=Unspecified 2 pooled trials Post hoc analysis	Time to hb rise Correlation w QOL
Gabrilove 2003 Abstract	No Solid ca	No Excluded AML, CML, MDS	No	No Dose ↑ permitted for non-response *	No Open-label No control	NA 24 wks	NA N~250 Preliminary	QOL Correlation w Hb change

Non-Medline (yes)		Performance status: Karnofsky ≥50 Excluded infection, hepatic & renal dysfunction			No randomization		analysis	
Glaser 1999 Paper Medline (?)	Yes Head-neck ca See Glaser 2001	No Stages T 2-4, N 0-3 Hb <12.5 g/dl	Yes Included chemo-therapy, XRT & later sugery	No Dose ↑ permitted	Study design not specified	Tx 4-5 wks F/u 17 mo	NA N=37 Preliminary data	Hb target Fe/anemia markers Tumor response Time to recurrence
Glaspy 2001 Abstract Non-Medline (yes)	No Solid ca	No Hb ≤11 g/dl Performance status: ECOG ≤2	No	No Part A Reported 7 fixed doses of 1 ESA & titrated dose other ESA Epo dose ↑ permitted for non-response Part B Randomized to ESA 1 fixed doses or ESA 2 that could be titrated	No Open-label No control	NA Unspecified for both parts	NA Part A N=239 Part B N=176 Preliminary data for 83	Hb ≥12 g/dl Hb change Transfusion need QOL
Grosbach 2004 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl	No	Loading dose followed by maintenance dose if response Withdrawn for poor response in maintenance	No Open-label No control No randomization	NA Tx duration unclear Observed x 24 wks	NA N=36 “evaluable” Preliminary data N=130 planned	Hb ≥12 g/dl or Hb change ≥2 g/dl
Harousseau 2004 Abstract Non-Medline (?)	No Solid, hematologic ca	No Hb <12 g/dl	No	No Initial weight based dose vs flat dose Dose ↑ permitted	No Open-label No control No randomization	No 12 wks	NA N=736	1º QOL 2º Hb change
Hernadez 2006 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl	No	8 dose regimens Otherwise unspecified	No 1 trial uncontrolled and open-label Pooled data 2 trials	NA 13 or 16 wks	NA 1686 Pooled data 2 trials	1º Hb ≥11 g/dl 2º Transfusion need Hb change QOL
Hesketh 2004 Abstract Non-Medline (yes)	No	No	No	Fixed or weight based loading doses followed by lower maintenance doses	No Open-label No control	NA 16 wks	NA N=241	Hb change & level
Huddart 2002 Abstract Non-Medline	No Solid ca	No Hb ≤10.5 g/dl	Platinum tx	No Dose ↑ permitted for non-response		Until 4 weeks after last cycle	NA N=90	Hb change ≥2 g/dl Transfusion need Ret count QOL

(yes)								
Hudis 2002 Abstract Non-Medline (yes)	Breast ca	No	Adjuvant tx	No Dose ↑ permitted for non-response	No Open-label No control No randomization	NA 24 wks	NA N=721 for interim evaluation	Hb change QOL
Hudis 2003 Abstract Non-Medline (yes)	Breast ca	No	Adjuvant tx	No Dose ↑ permitted for non-response	No Open-label Historical control No randomization	NA 24 wks	NA N=1597 "evalu-able" pts	Hb change QOL
Juan 2002 Abstract Non-Medline (?)	No Solid ca	No Hb <11 g/dl	No	Fixed ESA dose + IV Fe	No Open-label No control No randomization	NA 8 wks	NA N=20	Hb change Transfusion need
Libutti 2004 Abstract Non-Medline (?)	No Assorted ca	No Hb ≥9 & ≤11 g/dl	No Could be under-going chemo or radiotherapy	Unknown	No Open-label No control No randomization	NA N=12 wks	NA N=48	QOL Correlation w Hb
Malik 2006 Abstract Non-Medline (?)	No Gastrointestinal ca Is a subset of a larger study	No Reportedly stratified by tumor type	No	Unknown	No Open-label No control No randomization	NA N=16 wks	NA N=360 Is a subset of a larger study N=1493	1º Hb 11-13 g/dl 2º Time to hb
Malmstrom 2003 Abstract Non-Medline (?)	Ovarian ca	No Advanced ca	No	Unspecified dosing	No Open-label Healthy normal controls not re-ceiving ESA	NA 24 wks	NA N=40 ca pts N=15 normals	Memory tests QOL Correlation w hb change
Migliori 2004 Abstract Non-Medline (?)	Lung ca	No Advanced/metastatic Hb ≤10.5 g/dl or hb decrease >1.5 g/dl w chemotherapy Performance status: ECOG ≤1 Stratified by plati-num tx ot not & prior Epo exposure	No Could be under-going chemo or radiotherapy	Reported fixed dose	No Open-label Historical control No randomization	NA 4 wks	NA N=24	Hb change at 2 & 4 wks
Mirtsching 2003 Abstract Non-Medline	No Non-myeloid ca	No Hb ≤11 g/dl	No	No 2 ESAs Dose ↑ permitted for non-response	Pooled data from 3 studies	Not specified Pooled data	NA N=396	Hb change Transfusion need

(yes)								
Ordonez 2004 Abstract Non-Medline (?)	No Solid ca	No Hb ≤13 g/dl M or ≤12 g/dl F	Platinum tx	No Dose ↑ permitted at 4 wks Variable duration of tx; mean 72 days	No Observational	No Variable duration of tx; mean 72 days	No Interim analysis of N=136	Hb change >1 g/dl Transfusion need QOL
Ordonez 2005 Abstract Non-Medline (?)	No Solid ca	No Hb ≤13 g/dl M or ≤12 g/dl F	Platinum tx	No Dose ↑ permitted for non-response	No Open-label No control Not randomized	NA 4 wks after last chemotherapy tx	NA N=270 enrolled N=255 evaluable	Hb change >1 g/dl QOL
Pantellakos 2002 Abstract Non-Medline (?)	No	No Hb 9-11 g/dl	XRT			NA 6-8 wks	NA N=151	Hb change Transfusion need QOL
Pappalardo 2003 Abstract Non-Medline (?)	No Non-myeloid & advanced ca	Performance status: ECOG 3-4 Life expectancy short	No tx	ESA dose 1 on days 1 & 2, then dose 2 on days 3 to 8	No Open-label No control No randomization	NA 15 days	NA N=28	Hb change Transfusion need QOL
Patton 2002 Abstract Non-Medline (yes)	No Non-myeloid ca See Patton abstract 2003	No Hb ≤11 g/dl	No	Reported fixed dose x 8 wks * & less frequent dose if responsive	No Open-label No control No randomization	NA 24 wks	NA N=13 Interim analysis N=20 planned	Hb change
Patton 2003 Abstract Non-Medline (yes)	No Non-myeloid ca See Patton abstract 2002	No Hb ≤11 g/dl	No	Reported fixed dose x 8 wks * & less frequent dose if responsive	No Open-label No control No randomization	NA 24 wks	NA N=20	Hb change
Peterson 2003 Abstract Non-Medline (yes)	No	No Excluded pts receiving transfusion	No	No Front loaded regimen vs other regimens vs another ESA	No Retrospective chart review Open-label No control No randomization	NA 5 wks	NA N=217	Early Hb response
Reed 2005 Abstract Non-Medline (?)	Ovarian ca Post hoc analysis	No Hb ≤13 g/dl	Platinum tx	Reportedly 2 fixed doses or placebo	No Retrospective	NA Duration unspecified	NA N=120 Post hoc analysis	Tumor progression Survival Thrombotic events Transfusion need
Rushing 2003 Abstract Non-Medline	No Colo-rectal ca Subset of larger study	No	Chemo or radia-tion tx	Reported fixed dose	No Retrospective subset analysis	NA 16 wks	NA N=244 Subset of larger	Hb level Transfusion need QOL

(yes)	See Gabrilove paper 2001						study. Pos hoc analysis	
Samantas 2006 Abstract Non-Medline (yes)	No Solid ca, lymphoma	No Hb <12 g/dl Performance status: ECOG ≤2 Life expectancy >6 mo	No	Reported fixed ESA dose	No Open-label No control No randomization	NA ≥12 wks	NA N=56	1° Hb >12 g/dl 2° QOL
Shasha 2006 Abstract Non-Medline (?)	No Non-myeloid ca	No Hb ≤11g/dl	No tx	No Dose ↑ permitted for non-response *	No Open-label No control No randomization	NA 12 wks	NA N=57	1° Hb ≥12 g/dl or change ≥2 g/dl
Spiridonidis 2002 Abstract Non-Medline (yes)	No	No	No	No Variable doses & dura-tion	No Retrospective chart review	NA Variable	NA N=101	Hb ≥2 g/dl Time to response
Steinmetz 2006 Abstract Non-Medline (yes)	No Solid ca	No Hb <11 g/dl or de-crease >1.5 g/dl Performance status: ECOG ≤2	No	No Dose ↑ permitted for non-response	No Open-label No control No randomization	NA 12 wks	NA N=196	Response rate Hb change Hb ≥12 g/dl Predictive value of EPO levels, ret count, soluble transferrin receptor
Tarabay 2004 Abstract Non-Medline (yes)	No Non-myeloid	No Hb ≤11 g/dl	No	Loading dose regimen	No Open-label No control No randomization	NA 12 wks	NA N=16 Preliminary results N=60 planned	1° Hb change ≥1-2 g/dl (minor) or >2 g/dl (major)
Tarantolo 2004 Abstract Non-Medline (yes)	No Non-myeloid ca	No Hb ≤11 g/dl	No	Loading doses followed by maintenance doses * Withdrawal for poor response 2 part study	No Open-label No control No randomization	NA 16 wks	NA N=24 Preliminary results for Part A	Hb change >1 g/dl
Thames 2003 Abstract Non-Medline (yes)	No	No Hb ≤11 g/dl or Hct <33%	No	No ESA switch study Dose ↑ permitted for non-response	No Retrospective chart review-US Oncology No blind No control No randomization	NA 12 wks	NA N=296	Hb change
Vadhan-Raj 2003 Abstract Non-Medline	No Non-myeloid ca	No Hb ≤11 g/d Performance status: ECOG ≤1	No	Reported fixed dose	No Open-label No control No randomization	NA 12 wks	NA N=128 Preliminary data from a study with	QOL

(yes)		Excluded cardiac, hepatic, & renal dysfunction					700	
Van den Bosch 2005 Abstract Non-Medline (?)	No	No Hb ≤11.3 g/d Minimun ESA tx 4 wks	No	Variable doses & regimens	No Retrospective chart review Open-label No control No randomization	NA Variable duration	NA N=781	Effect if ESA started bf anemia of chemotherapy Time to hb
Vasu 2006 Abstract Non-Medline (?)	No Non-myeloid ca, solid ca	At least 1 dose ESA	No	Epo or Darbe Dose ↑ permitted for non-response	No Retrospective chart review Open-label No randomization	NA 8 wks	NA N=109	Hb change Transfusion need
Vekeman 2006 Abstract Non-Medline (?)	No	No ESA use during hospitalization Excluded dialysis	No	Variable doses & regimens of 2 ESAs	No Open label Retrospective	NA	NA Epo=24,814 Darbe=2,990	Transfusion need (unclear if is during hospitalization or during what time period)
Villar 2001 Abstract Non-Medline (?)	Yes Head-neck ca-advanced	No Stages 3-4	Yes Platinum tx +XRT +Carbogen breathing	Reported fixed dose	No Appears to be a case series in which ESA tx was introduced after 20 of 56 pts	NA 7 wk tx w 1 yr f/u	NA N=56	Hb level Transfusion need Survival
Wagner 2006 Abstract Non-Medline (?)	Non-small cell lung ca	No Stage 3A-B	Chemo-radiation tx	Preventive tx w reported fixed dose	Unknown if blind & randomized Placebo control	NA Unspecified	NA N=51	Hb change Time to hb
Not Randomized-Monotherapy-Pre-malignant Conditions								
Finelli 2004 Abstract Non-Medline (?)	MDS Low or inter-mediate risk	Hb <10 g/dl & sx EPO <200 U/l	NA	No Epo 40,000 U 2x/wk x8 Then 40,000 U 1x/wk	No Open-label May be case series No control No randomization	NA ≥8 wks	NA N=18	Hb >1 g/dl Transfusion need
Gabrilove 2005 Abstract Not-Medline (yes)	MDS (Low or intermediate risk-IPSS definition) See Gabrilove 2006A,B	No Hb ≤11 g/dl Stratified by prior ESA use)	NA	No Darbe SQ 500 ug q3 wk Dose frequency ↑ permitted at 7 wks	No Open-label No control No randomization	NA 13 wks (See Gabrilove 2006 extension study)	NA Interim analysis N=100 (planned enrollment 200)	1° Hb change ≥2 g/dl or transfusion need elimination
Gabrilove 2006A Abstract Not-Medline	MDS (Low or intermediate risk-IPSS definition)	No Hb ≤11 g/dl Stratified by prior ESA use)	NA	No Darbe SQ 500 ug q3 wk Dose frequency ↑ permitted at 7 wks	No Open-label No control No randomization	NA 53 or 55 wks depending on dose frequency	NA N=148 N=98 ESA naive	2° Hb change Transfusion need QOL ESA naïve re-

(yes)	See Gabrilove 2005,6BC			Study duration longer for pt w >frequent dosing		(See Gabrilove 2005 primary study)		sponse
Gabrilove 2006B Abstract Not-Medline (yes)	MDS (Low or intermediate risk-IPSS definition) See Gabrilove 2005,6A	No Hb ≤11 g/dl Stratified by prior ESA use)	No chemotherapy. GCSF only for infection	No Darbe SQ 500 ug q3 wk	No Open-label No control No randomization	No 13 wks	NA Interim analysis N=100 (planned enrollment 200)	1° Erythroid response 2° Hb change Transfusion need QOL ESA naïve pt response
Gabrilove 2006c Abstract Not-Medline (yes)	MDS (Low or intermediate risk) See Gabrilove 2005,6AB	No Hb ≤11 g/dl Stratified by prior ESA use)	NA	No Darbe SQ 500 ug q3 wk Dose frequency ↑ permitted at 7 wks	No Open-label No control No randomization	NA 53 or 55 wks depending on dose frequency (See Gabrilove 2005 primary study)	NA N=209 enrolled Preliminary data from interim analysis N=189	1° Erythroid response 2° Hb change Transfusion need QOL ESA naïve pt response
Ghio 1993 Abstract Not-Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± excess blasts	No Hb <10 g/dl or transfusion dependent Excluded ca, HTN, seizures, hepatic, renal dysfunction	No cytostatic, growth, anabolic steroid tx	No Epo SQ 75 U/kg TIW Dose ↑ permitted q 4 wks up to 250 U/kg Dc if not response at max dose	No Open-label No control No randomization	NA 16 wks for all 24 wks responders	NA N=13 Dx progression x1	Hb change >1.5 g/dl &/or transfusion need >50% change Ret count, burst forming unit, colony forming unit, transferrin receptor change Predictive value of EPO level
Isnard 1991 Abstract Non-Medline (?)	MDS Refractory anemia ± ringed sideroblasts See Isnard 1993	No Hb <10 g/dl	NA	No Epo SQ 40 U/kg/TIW Dose ↑ per forced titration Dose ↓ in responders to determine maintenance dose	No Open-label No control No randomization	NA 3 mo for all F/u for at least 21 mo for some responders	NA N=20	Complete response Hb level (normal) Partial: hb change ≥2.5g/dl w/o transfusion or change in transfusion need (≥50% change) Predictive value of EPO levels & medullary erythroblasts
La Porte 1991 Abstract Non-Medline (?)	MDS Refractory anemia ± ringed sideroblasts	NA	NA	Epo SQ 40 U/kg TIW & ↑ incrementally to 300 U/kg TIW Dose ↓ in responders at 3 mo	No Open-label No control No randomization	No 3 mo + unspecified maintenance period	NA N=6	Not clearly stated: Hb change & level Transfusion need
Paquette 2006	MDS Low-intermediate	Stratified by prior ESA exposure	NA	ESA dose	No Open-label	NA 52 wk	NA N=209 enrolled	1º Hb change at 13 wks

Abstract Non-Medline (?)	risk	Hb <11 g/dl			No control No randomization		Preliminary data from interim analysis N=129	2º QOL
Petti Abstract Non-Medline (yes)	MDS Refractory anemia ± ringed sideroblasts ± blasts	No	NA	No Epo ≤400 U/kg/2x wk Dose ↑ permitted Rx DCed for non-response	No Open-label No control No randomization	NA Tx 3 mo all Tx 6 mo responders Variable extended f/u	N=16	Hb change >1 g/dl &/or transfusion need (>50% change) Ret count change
Verhoef 1991 Abstract Non-Medline (?)	MDS Unspecified See Verhoef 1992	No Transfusion dependent	NA	No Epo SQ 100 U/kg TIW Dose ↑ q 4 wks	No Open-label No control No randomization	No 12 wks	NA N=10 Dx progression x1, transient blast ↑	Transfusion need Ferrokinetic change RBC survival Predictive value of EPO level
Non-randomized-Combination Therapy-Malignant Conditions								
Non-randomized-Combination Therapy-Pre-malignant Conditions								
Mannone 2004 Abstract Non-Medline (?)	MDS Refractory anemia ± ringed sideroblasts ± blasts or chronic myelomonocytic leukemia See Mannone 2006A	No Hb <10 g/dl or transfusion dependent <10% blasts EPO <500 mU/ml Excluded ca	Prior ESA exposure permitted	Darbe 300 ug/wk x12 wks + GCSF 150 ug TIW for poor response. Combo for another 12 wks	No	NA 12 wks initial tx 12 more wks if combo tx started Then unspecified period of maintenance	NA N=55, but not ITT bc preliminary data or not evaluated bc of sepsis N=40 completed 12 wks	Hb change ≥1-2 g/dl (if t=0 hb <11 g/dl) or transfusion need ≥50% change Predictive value of EPO level , karyotype, transfusion need
Not randomized-Active Control-Monotherapy-Malignant Conditions								
Case 2005 Abstract Non-Medline (?)	Gynecologic ca	No Hb ≤10 g/dl	No	Variable doses & regimens for 2 ESAs	No Retrospective chart review Active control No randomization	NA Variable duration	NA N=123	Hb change Transfusion need
Pujade-Lauraine 2004 Abstract Non-Medline (yes)	No Solid, hematologic ca	No ESA tx x ≥8 wks	No	Assorted ESAs Variable tx duration	No Retrospective Active control	No Variable duration	NA N=125	Dose to achieve given hb change
Smith 2001 Abstract Non-Medline (yes)	No	No	No	No Comparison of 2 regimens Dose ↑ permitted for non-response	No Open-label Active control Unknown if randomized	NA Variable duration	NA N=290	Hb ≥12 g/dl or Hb change ≥2 g/dl Transfusion need
Vercammen 2005 Abstract Non-Medline	No Pooled data	No	No	Fixed dose regimens vs weight based regimens	No Retrospective Active control No randomization	NA Duration not specified	NA N=3908 9 studies pooled	Likelihood of hb change >2 g/dl by body weight

(?)								
Not Randomized-Active Control-Monotherapy-Pre-malignant Conditions								

1-Did not include papers using ESAs during high dose chemotherapy prior to bone marrow/stem cell transplantation
*Dose discontinuation or reduction for rapid increase in hemoglobin (or hematocrit) or reaching a normal or relatively high hemoglobin (or hematocrit) threshold
(financial contribution by pharmaceutical sponsor)
ALL=acute lymphocytic leukemia Ca=cancer CERA=continuous erythropoietin receptor activator Chemo=chemotherapy CLL= chronic lymphocyte leukemia CML=chronic myelogenous leukemia CNS=central nervous system D=day(s) Darbe=Darbepoetin DC=discontinued ECOG=Eastern Cooperative Oncology Group Epo=Erythropoietin drug EPO=Erythropoeitin blood/serum levels F=female Fe=iron treatment F/u=follow-up GCSF=Granulocyte colony stimulating factor GI=gastrointestinal GMCSF=Granocyte-Myelocyte colony stimulating factor Hb=hemoglobin Hct=hematocrit HD=Hodgkin's disease HTN=hypertension IL=interleukin ITT=intent to treat analysis IV=intravenous M=male Mets=metastases MDS=myelodysplasic syndrome MM=multiple myeloma Mo=month NA=not applicable NHL=Non-Hodgkin's lymphoma PK=Pharmacokinetic PLT=platelet PMN= polymorphonuclear leukocyte count PNH=paroxsysmal nocturnal hemoglobinuria q=each QOL=quality of life or performance level or fatigue level RBC=red blood cell or erythrocyte Retic=reticulocyte count SQ=subcutaneous TIW=three times per week Tx=Treatment WBC=white blood cell count WHO=Word Health Organization Wk=wk(s) XRT=Radiation therapy