Table 2A: Studies Submitted to the FDA (Studies in children not included)

Drug	Cancer-type	Cancer Tx	N=	Design	Endpoint	Inclusion Criteria	Exclusion Criteria
Epo α 1992 3 pooled trials I87-016 I87-017 I87-037	Assorted cancers	Non-platin	72 (49+22+1) from 3 studies	Double-blind (1st phase) Placebo-controlled	Transfusion need	See comments * ??Hgb<10.5	See comments *
Epo α 1992 3 pooled trials I88-018 I88-019 I87-036	Assorted cancers	Platin-based	59 from 3 studies	Double-blind (1st phase) Placebo-controlled	Transfusion need	See comments * ??Hgb<10.5	See comments *
Epo α 1992 2 pooled trials H87-014 H87-032	Assorted cancers	None	76 (52+24) from 2 studies	Double-blind (1st phase) Placebo-controlled	Hct change	??Hgb<10.5	
Epo α 2004 PR98-27-008	Breast, CNS, GI, GU, GYN, Head-neck, Lung, Lymph Nodes, Melanoma, Other	Platin (17%) Non-platin (83%)	344	Double-blind Placebo-control Stratified by hgb <(g/dl or higher Stratified by use of concurrent XRT (only 10% of population) LOOK at analysis	1º Transfusion rate (changed from QOL) 2º QOL 3º Survival 1 year p randomization	Hgb<10.5 W <11.5 M	Uncontrolled HTN MDS Metabolic anemia Bleeding Hemolysis
Epo α 2004 EPO-CA-480	Solid tumors	Platin	NA	Open-label 6-arm	NA	NA	NA
Darb 2001 980297 Phase III	Lung cancer	Platin	320 but 6 with-drew bf 1st dose	Double-blind Placebo-control Stratified by SCLC (29%) vs NSCLC (71%) Stratified by worldwide (non-US) geography	1º Transfusion rate	Hgb <11.5 After screening, baseline values were done: 42 vs 20 patients had values ≥11g/dl (Imbalance)	Uncontrolled HTN Uncontrolled angina CHF >Class 2 or RF <40% CNS malignancy Primary hematologic disorder Metabolic anemia Bleeding Hemolysis
Darb 2001 990146	Non-myeloid	Multi-cycle chemo	29	Oprn-label No control Pharmacokinetic study	Pharmacokinetic data	NA	NA
Darbe 2001 990174	Solid tumors	Chemotherapy	92 Darb 20 Epo	Active control	NA	NA	NA
Darb 2001 980290	Breast, GI, GU, GYN, Lung, Other solid tumors	Multi-cycle chemo Permitted pelvic radiation (30	211 qWk tx 119 q 2 Wk tx 344 Darb 85 Epo	Open-label Multiple doses/ 2 regimens Active control Dose-ranging	Dose-ranging Antibodies	Hgb ≤11.0 (initially 10)	Metabolic anemia Bleeding Hemolysis

		gy)		study			
Darbe 2001 980291	Breast , GI, GU, GYN, Lung, Other solid tumors	Multi-cycle chemo	208 Darb (10 of these did not get rx) 51 placebo	Double-blind Placebo-control Dose-ranging	Dose at which ≥50% had hgb increase ≥2 g/dl & at which ≤20% had high hgb (>14 & 15 g/dl for women & men resprectively)	Hgb ≤11.0	Metabolic anemia Bleeding Hemolysis
Darbe 2001 990114	Lymphoproliferative	Chemotherapy	66	Blinded Placebo control Dose-ranging Stratification by lymphoma & myeloma	Increase in hgb >2 g/dl Hgb >12 g/dl for 28 days Transfusion	Hgb ≤11.0	Metabolic anemia Bleeding Hemolysis
Darbe Between 2001 & 2005 Phase III Not included in label	Lymphoproliferative	Chemotherapy	349	Blinded Placebo control Stratification by lymphoma & myeloma	1º increase hgb ≥2 g/dl 2º transfusion need	Hgb ≤11.0	Incomplete information available from FDA registration trial reviews. Data not included in label.
Darbe 2001 990111	Non-myeloid cancer	NO chemotherapy	102	Open-label No control Dose-ranging	Increase in hgb >2 g/dl Unspecified Hgb correction Transfusion	Hgb ≤11.0	Metabolic anemia Bleeding Hemolysis
Darbe 2006 20030231 Phase III	Non-myeloid cancer Including MM HD	Multi-cycle chemo	705 randomized 672 in per protocol analysis	Double-blind Active control Stratified by tumor type, hgb (<10 g/dl), geography	1º Transfusion (changed from 2º) 2º Hgb change (changed from 1º)	Hgb <11.0 ECOG states 0-2	Recent ESA use Recent transfusion EPO antibobodies Hematologic disorder , except non-myeloid ca, causing anemia Inflammatory disease Uncontrolled HTN Uncontrolled angina, dysrhythmia CHF >Class 2

*FDA medical officer review not available for examination. Statistical review available.
*Studies complicated by the use of 2 formulations of erythropoietin: Procrit and Eprex. Only patients receiving Procrit appear to have been included in the FDA analysis.

Table 2B: Studies Submitted to the FDA (continued)

Drug	Dose	Duration	Comments
Epo α 1992 3 pooled trials	Non-platinum chemotherapy 150 U/kg TIW Open-label phase up to 300 U/kg	12 weeks Open-label phase up to 6 months	Drop-out rate 17%; Epo drop-out 2x placebo 1º endpoint, transfusion requirement, not lower; 2º endpoint, hct change, statistically significant; QOL data collection incomplete Other clinical information, including ECOG status, not available because FDA medical officer review not available & pooled data from otherwise unspecified trials used *
Epo α 1992 3 pooled trials	Non-platinum chemotherapy 150 U/kg TIW Open-label phase up to 300 U/kg	12 weeks Open-label phase up to 6 months	Sample size for 2 studies not justified by investigators Drop-out rate 34% . Discontinuation due to disease progression: Epo 5.9%, placebo 2.9% 1º endpoint, transfusion requirement, not lower; 2º endpoint, hct

			change, statistically significant; QOL p=0.05 Other clinical information, including ECOG status, not available because FDA medical officer review not available & pooled data from otherwise unspecified trials used *
Epo α 1992 2 pooled trials	No chemotherapy 100 U/kg TIW	8 weeks	Drop-out rate 33% 1^{o} endpoint, hct change, statistically significant; 2^{o} endpoint, transfusion requirement, not lower Other clinical information, including ECOG status, not available because FDA medical officer review not available & pooled data from otherwise unspecified trials used*
Epo α 2004 PR98-27-008	40,000 U/wk Increased to 60,000 U/wk if did not increase hgb by 1% or required transfusion	16 weeks	Actual baseline hgb 9.5 g/dl Change 2.8 vs 0.9; p<0.0001 All given Fe Fewer transfusion required (25/170 vs 48/170; p=0.001) 43% did not respond to lower dose No information on how many responded to higher dose No information on those who were responders No information on effect of XRT Thrombotic events 10 (8 persons) vs 6 (5 persons) HTN D 5 v 3 persons Not sufficient hgb data to determine relationship between level or change and thrombosis Recommended to have plan for thrombotic events and potential tumor growth No clear differences in survival, but not structured for this endpoint Tmor progression not structured
Epo α 2004 EPO-CA-480	150 U/kg TIW vs 300 U/kg/wk vs 450 U/kg/wk vs 600 U/kg/wk vs 900 U/kg/wk	12 weeks	Discontinued because of poor enrollment (n=54)
Darb 2001 980297	2.25 ug/kg/wk Increased to 4.5 mcg/kg/week if did not increase hgb by 1g/dl at 6 weeks	12 weeks	1/3 of patients withdrew-primarily because of death, disease progression, treatment change Mean hgb baseline not provided. 85% of patients had hgb levels $\geq$9 gl/dl Fewer transfusion required (39/148 vs 74/149; p<0.001) (Reportedly no different by tumor type) 43% did not respond to lower dose. 28% of poor responders responded to a doubled dose; Mean 2.4 g/dl. Patient s with the lowest hgb levels had the best response to treatment-although it is not clear which dose was required. Reportedly patients with the highest EPO levels had the highest transfusion needs, but there was no analysis assessing the concomitant hgb level and whether the EPO response was appropriate or sufficient for the hgb level. and whether relative EPO response to hgb predicted response to exogenous ESA. Pulmonary embolism occurred only in patients on drug. HTN rx started 19 vs 13. Death 22 vs 19 ??16 weeks.
Darb 2001 990146	2.25 ug/kg/wk Increased to 4.5 mcg/kg/week if did not increase hgb by 1g/dl at 6 weeks	12 wks+4 wk f/u Could enter 12 wk IV phase if responder (N=15)	Reported no dose accumulation Pharmacokinetics reportedly time-linear
Darbe 2001 990174	Darbe 4.5 ug/kg/wk to hgb 12 then 1.5 ug/kg/wk Darbe 4.5 ug/kg/wk x4 wks then 2.25 ug/kg/wk x8 wks Darbe 4.5 ug/kg/wk x4 wks then 3 ug/kg/wk x8 wks EPO 40,000 U/wk x 12 wks	12 weeks	NA
Darb 2001 980290	Part 1-Darbe-7 weekly doses 0.5--8.0 ug/kg Epo-150 U/kg TIW (Could double 7 weekly doses 0.5--8.0 ug/kg Epo-150 U/kg TIW Part 2-	12 wks+4 wk f/u	Transfusion policy changed from a protocol to guidelines # with poor response to Epo not delineated Peak SQ absorption at 72 hours Multiple doses did not double serum levels Pharmacokinetics reportedly time-linear Data not considered sufficient for q 2 weeks dosing because lack of

	4 semi-weekly doses 3-9.0 ug/kg Epo-40,000 U/kg/wk Could increase to 60,000 if did not increase hgb by 1g/dl at 6 weeks		clinical endpoint & low numbers
Darbe 2001 980291 Kotasek 2003	6 q 3 week doses 4.5—15 ug/kg q	12 weeks+8 weeks f/u	20% drop-out Wide dose range with significant hgb response Data not considered sufficient for q 2 weeks dosing because lack of clinical endpoint & low numbers
Darbe 2001 990114	1, 2.25, or 4.5 ug/kg/wk	12 weeks	Rx better than placebo No linear dose effect on hgb or transfusion; highest dose tended to be better than lowest dose Suggestion of different response rates for different diseases
Darbe Between 2001 & 2005 Phase III Not included in label	2.25 ug/kg/wk Could increase to 4.5 ug/kg/wk for poor response	12 weeks	Rx better than placebo Complete review of study not provided by FDA
Darbe 2001 990111	0.5, 1.0, 2.25, or 4.5 ug/kg/wk	12 week+4 week f/u	NA-Redacted
Darbe 2006 20030231 Phase III	500 ug q 3 wks (max 5 dozes) vs 2.25 ug/kg/wk	15 weeks+2 weeks f/u	Specified non-inferiority margin not acceptable to FDA. Limited clinical differences 254 patients ≥65 years. 60 of these were ≥75 years 27% drop-out FACT-F analysis invalid per FDA Patients with baseline hemoglobins <10 g/dl had higher death and serious adverse event rates

Table 3

Author	Single Tumor Type	Single Tumor Stage or Prospectively Stratified for Stage	Single Cancer Tx Regimen	Single ESA Regimen	Placebo-controlled Double-blinded Randomized	Sufficient Duration for Dx & Endpoint	Sufficient Power for Endpoint	Endpoint
Abels 1992	No No acute leukemia or myeloid ca No cerebral metas-tases See Abels 1996 & Henry 1994	No	1 cohort w no che-motherapy 1 w non-platinun, 1 with platinum tx	No chemo group treated 8 wks; other groups treated 12 wks *	Unknown if blind	No 8 or 12 wks	NA	Hct level Transfusion need QOL
Abel 1993	No No acute leukemia or myeloid ca No cerebral metas-tases See Abels 1992, 6 & Henry 1994	No	1 cohort w no che-motherapy 1 w non-platinun, 1 with platinum tx	No chemo group treated 8 wks; other groups treated 12 wks *	Yes	No 8 or 12 wks+open label phase	NA	Hct level Transfusion need QOL
Abels 1996	No No leukemia/ myeloid ca See Henry 1994	No	No	Yes w/in tx groups *	Yes	No 8 or 12 wks	NA	Hct change Transfusion need QOL
Aravan tinos 2003	No	No	Various platinum At various stages in chemotherapy	Yes	No Open-label	Not stated	NA N=47	1o transfusion need 2o hb change
Arslan 2004	No Solid tumors	No	Various platinum	Yes w/in tx groups *	No No control	No 12 wks for 2 groups Uncertain for 1	NA	Hb change
Auerba ch 2004	No	No	No	Yes	No Open-label of various Fe tx	Not study of EPO per se	NA	Effect of Fe on hb QOL
Ayash 1994	No Solid tumors	No	No High dose chemo-therapy (1 of 3 regimens) & bone marrow transplant	Yes * IV administration x 28 d	No No control	No 160 days	NA N=10 IV dose	Transfusion need Time to hct 30%
Bamias 2003	No	No	No	No * Variable time	No Open-label	No	NA	Transfusion need
Beggs 2003	Yes Non-small cell lung ca	No Stages 2-3B Unresectable	Yes Includes XRT	Yes	Unknown if blind	No 13 wks	NA N=21	Fatigue Hb level IL-6 level
Bessho 1997	NA Aplastic anemia	NA	NA	No Dose-ranging Variable time depending on response	No Open-label	No	NA	Hb change Transfusion need
Bindi 2004	No	No Classified by as-thenia	No	Yes	No Unknown if blind Pts randomized to 1 of 2 ESAs had asthenia "Control" pts did not have asthenia	No 8 wks	NA	Hb change Retic change Hematologic traits of responders
Blohm er 2004	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 Power calculations not provided in abstract	1o relapse free-survival 2o transfusion need QOL
Boccia 2006	No Non-myeloid ca	No	No	No Dose ↑ permitted at 6 wks *	No Open-label Not randomized	No Tx up to 16 wks+3 wk f/u	NA	Hb target

					No control			
Boogaerts 2003	No	No	No	No Dose ↑ permitted *	No Open-label	No 12 wks	NA	QOL
Bowen 2006	MDS 3 low risk subtypes	<10% blasts	No	No In tx group, different ESA drug formulations, doses, regimens used Tx group also given variable doses of GCSF Tx dced at 8 wks for non responders	No Single-blind for 1 dose pharmaco-dynamic phase; unknown if blind for therapeutic phase	No 20 wks if responder; 8 wks if non-responder	NA	Hematologic para-meters including ret count
Buyukpa-mukcu 2002	No Solid tumors	No	No	Yes *	Unknown if blind	No 8 wks	NA	Hb change Transfusion need
Canon 2006	No Non-myeloid	No	No	Yes *	No Active-control Rx regimen	No 15 wks	NA	Transfusion need Non-inferiority
Carabantes 1999	No Ovarian & small cell	No	Various platinum	No Dose ↑ permitted post 3-4 wks	Unknown if blind	No Randomized when became anemic and treated for remainder of 6 chemo cycles+1 mo	NA	Transfusion need QOL
Casadevall 2004	No MDS 3 subtypes	<10% blasts	No	GCSF dose could be adjusted & could be reinstituted , in the combination tx group if anemia recurred ESA dose fixed	No GCSF+EPO vs placebo	No Responders in combo tx arm by 12 wks given EPO alone x 40 wks; Double placebo control followed 52 wks	No N=60 N=50 reached 12 wks	Hb change QOL Evaluated only if received tx >12wks
Cascinu 1993	No	No	Various platinum	No Dose ↑ permitted post 3 wks	No No control	No 3 wks	NA	Hb change at 3 wks Transfusion need
Cascinu 1994	No	No	Various platinum	Yes *	Yes	No 9 wks	NA	Hb change at 3 wks Transfusion need
Cascinu 1995	No	No	Various platinum	Variable time *	No Control=young pts	No At least 9 wks	NA	Hb change at 9 wks
Case 1993	No No leukemia/ myeloid ca	No	No	Yes *	Yes	No 12 wks	NA	Hb change Transfusion need QOL
Cazzola 1992	No Hematologic dx including benign	No	No	No Dose ↑ permitted post 4 wks *	No No control	No At least 16 wks	NA	Hb>10 g/dl w/o transfusion
Cazzola 1995	No MM/NHL	Low/intermediate grade	No	Yes 4 doses+placebo *	No Open-label	No 8 wks	NA	Hb change
Cazzola 1996	No Includes MDS	No	No	No Dose ↑ permitted post 4 wks	No Retrospective	No 8 wks	NA	Hb Δ>2 g/dl w/o transfusion Predictors of ESA response
Cazzola 2003	No MM/NHL/CLL	Low-grade	Not required	No Dose ↑ permitted post 4 wks *	No Active control 2 dose regimens	No 16 wks	NA	Hb AUC change
Chan 1995	No No hematologic dx	No	No	Yes	Unknown if blind	No 16 wks	NA	Hb change

Chang 2005	Yes Breast ca	No	No	No Dose ↑ permitted post 4 or 6 wks *	No Open-label	No At least 12 wks	NA	QOL at 12 wks
Crawford 1997	Yes Small cell lung ca	No	No	Dose fixed during blind-ed phase. After that, pla-cebo patients switched to ESA & dose of ESA pts ↑	No Blinded only until hct <32% & trans-fusion to be given	No Through < 6 chemo-therapy cycles	NA	Anemia prevention QOL
Crawford 2002-A	No	No	No	No Dose ↑ permitted Different dose regimens for 2 studies	No Retrospecti ve study of pooled data from open-la-bel, non-random-ized study	Unstated duration	NA	QOL
Crawford 2002-B	Yes Subset of trial with assorted ca->Lung ca	No	No	No Dose ↑ permitted Different dose regimens for 2 studies *	No Subset study of pooled data from open-label, non-randomized study	No 16 wks	NA	Hb change QOL
Crawford 2003	Yes Non-small cell lung ca	No Stage 3B & 4	No	No Dose ↑ permitted at 4 wks *	No Open-label Control pts receiv-ed ESA if hb <10 g/dl	No Up to 16 wks	NA N=216	Hb change Transfusion need QOL Survival
Dammacco 1998	Yes Refractory MM	Stage 2 or 3	Not required, but permitted	No Dose ↑ permitted *	No Open-label	No 24 wk	NA N=71	Hb change Transfusion need QOL
Dammacco 2001	Yes MM	No	No	No Dose ↑ permitted at 4 wks *	Yes	No 12 wks + 12 wks open-label extension	NA	Transfusion need
Danery d 1998	No With cachexia due to primarily GI ca	Stratified	Stratified by prior tumor tx Tx=indomethicin+EPO	No EPO only if hb <12.8/ 12 for M/W & until hb normal	Unknown if blind	Survival=2 o endpoint Tx till death or un-able to take indome-thicin	No N=108	Nutritional state Calorimetry Exercise tolerance
De Campos 1995	Yes Small cell lung ca	Better Manchester score	No Sites differed by # cycles & time of brain XRT	Yes * 2 doses+placebo	Unknown if blind	No Through multiple cycles of chemo	No N=36	Time of hb nadir Transfusion need (RBC & PLT) Clonogenic assay
Del Mastro 1997	Yes Breast ca Anemia prevention	Stage 2	Yes except tamox-ifen added if re-ceptor +	Yes *	Unknown if blind	No 6 chemo cycles & 36 EPO tx	No N=62	Hb>10 g/dl
Demetri 1998	No Non-myeloid ca, but appears to include hematologic ca	No	No	No Dose ↑ permitted at 4 wks *	No Open-label Non-randomized Tx DCed at 8 wks for non-responders	No 4 mo	NA	QOL
Dunphy 1997	Yes Head & neck ca	No Stages 3-4	No Pre-operative carboplatin (vari-able dose) +pacli-taxel Radiation could be substituted 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	No 3 wks for each of 2 or 3 chemocycles	NA	Hg change Transfusion need
Dunphy 1999	No Head & neck or non small cell lung ca	No Head & neck stages 3-4	No Chemotherapy the same, but the # of regimens	No Dose ↑ permitted at the end of each	No Open-label	No Variable duration	NA N=30	1o hb change

	Appears to be a sub-set of a phase II trial	Lung ca stage 4	differed by disease. XRT or surgery added for head-neck pts depending on re-sponse	chemo-therapy round *		ESA appears to have been used only dur-ing chemothera py phase		
Dusenb ery 1994	Yes Cervical ca	No	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	No ~6 wks	NA	Retic change Hb change
Fallowf ield 2002	No Non-myeloid ca Subset of Littlewood 2001	No Stratified by solid or hematologic	No Platinum treated pts in Littlewood excluded	No Variable duration	Yes	No 16-28 wks	NA	2o QOL
Gabrilo ve 2001	No Non-myeloid ca, but appears to include hematologic & unknown types of ca	No	No Permitted XRT	No Dose ↑ permitted at 4 wks *	No Open-label Non-randomized No control	No Maximum tx 16 wks	NA	Hb/hct change Transfusion need QOL
Gamuc ci 1993	No	No Advanced tumor	De novo tx Various platinum (Says stratified, but n=57)	Yes (included Fe)	Unknown if blind	No 12 wks Written bf all enrol-led pts completed	NA	Hb change
Garton 1995	Yes MM	No	No	No Dose ↑ permitted at 6 wks *	Yes	No After 12 wks, place-bo group switched to ESA	NA	Hct change
Glaser 2001	Yes Head & neck ca	No	Yes Includes XRT	No Dose ↑ permitted at 1 wk Variable tx period; tx started with hb <12.5 g/dl	No Retrospecti ve No randomizati on Stratificatio n by entry hb & ESA use	No Followed for >21 mo or un til death	NA	Hb change Tumor control Survival
Glaspy 1997	No Non-myeloid ca but appears to include hematologic ca	No	No	No Dose ↑ permitted at 8 wks *	No Open-label Non-randomized No control	No Up to 4 mo High drop-out rate	NA	Hb change QOL
Glaspy 2001	No Solid tumor	No	No	No Dose-escalation study #	No No control except lower dose	No 12 wks High drop-out rate Written bf study done	NA	Hb change
Glaspy 2002-A	No Retrospective sub-analysis. See Glaspy 1997, Demetri 1998	No	No Stratified by non-platinumn vs plati-num	No Dose ↑ permitted at 4 or 8 wks * Different dose regimens for 2 studies (1 wt based; 1 non-wt based)	No Retrospecti ve sub-analysis of 2 un-controlled studies	No Up to 4 mo High drop-out rate	NA	Hb/hct change Transfusion need (but no criteria for transfusion) QOL
Glaspy 2002-B	No Solid tumor	No	No	No Part 1: 6 darbe vs 2 epo doses (1 per study w ↑ permitted at 8 wks; 1 per individual doctor) Part 2: 4 darbe doses vs 1 epo dose (latter w ↑ per-mitted at 6 wks)	No Open-label "Active control", but dose adjust-ments for epo permitted	No Each part w 12 wk tx period & 4 wk f/u period	NA	Hb change
Glaspy 2002-C	No Solid tumor	No	No	No 1 initial darbe dose w	No Unknown if	No Each part w	NA	Hb change QOL

				4 subsequent maintenance doses vs 1 epo dose w ↑ permitted at 6 wks *	blind Active control	12 wk tx period & 4 wk f/u period		
Glaspy 2003	No Solid tumor	No	No	No Part 1: 3 darbe vs 1 epo doses (w ↑ permitted) Part 2: 4 darbe doses vs 1 epo dose (latter w ↑ permitted at 6 wks)	No Unknown if blind Active control	No Each part w 12 wk tx period & 4 wk f/u period	NA	Hb change Transfusion need
Glaspy 2005	No Non-myeloid	No	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)	No	NA N=81	Hb change at 6 wks
Glaspy 2006	No Non-myeloid	No	No	No Dose ↑ permitted at 5 wks *	No Open-label Active control	No 1st 12, then 16 wks	NA	1o transfusion need 2o Hb change QOL
Glimelius 1998	No GI ca	Surgically incurable, Symptomatically progressive	No	Yes (High & low rx doses)	Unknown if blind Active control	No 18 wks	NA	Hb change
Glossmann 2003	No Relapsed HL or 1st relapse of aggressive NHL	Relapsed at various stages	Yes (additional tx if some response)	Yes	Unknown if blind	End of tx cycles	NA	Transfusion need
Granetto 2003	No Solid tumor	No	Various platinum	No Dose ↑ permitted * Different dose regimens:1 wt based; 1 non-wt based	Open-label Active control	No 12 wks	NA	Transfusion need
Hedenus 2002	No Lymphoproliferative Reportedly stratified by lymphoma vs MM	No	No	Yes * 3 darbe & 1 placebo doses	Yes	No 12 wks+4 wk f/u	NA	Hb change
Hedenus 2003	No CLL, HD, NHL, MM	No	No Extent of prior tx	No Dose ↑ permitted at 4 wks *	Yes	No 12 wks+4 wk f/u	NA	Hb change Transfusion need
Hellstrom-L 1993	No Refractory anemia + blasts	No	No	No GCSF dose ↑ permitted at 2 & 4 wks ESA dose started at 6 ks & dose ↑ permitted at 12 wks in non-responders & 14 weeks in responders	No Open-label No control No randomization Comparison of responders & non-responders	No 12 wks ESA tx	NA	Hg target Bone marrow exam Traits of responders
Hellstrom-L 1997	No MDS 4 subtypes See Hellstrom-Lindberg 1993,6 & Negrin 1993,6	No	No	No Tx w GCSF + ESA Doses & regimens dif-fered for the contribut-ing studies *	No Open-label No control No randomization Pooled data	No At least 10 wks	NA N=98	Post hoc composite definition of ESA response
Hellstrom-L 1998	No MDS 3 subtypes	No	No	No 2 dose regimens of GCSF+EPO ↑ dose for each rx per-mitted	No Active control	No 16 or 18 wks (long-term f/u done on subsets of pt from this & another study)	NA	Hb change
Henry 1994	No Assorted cancers See Abels 1991	No	No Some no tx Some assorted chemo including platinum	1 dose & duration if no chemotherapy; another if chemotherapy	Yes	No 8 wks if no tx 12 wks if chemother-	NA	Hb change

						apy given		
Henry 1995	No Not acute leukemia or myeloid ca	No	Various platinum	Yes *	Unknown if blind	No Up to 12 wks	NA	Hb change Transfusion need QOL
Henry 2006	No Non-myeloid ca	No	No	No 2 dose regimens Dose ↑ permitted at 4 wks for the q/wk, but not q/2wk cohort *	No Open-label Active control	No Up to 12 wks tx & 13 wks of f/u	NA	Hb change
Henry 2006	No Non-myeloid ca	No	No	No IV Fe, po Fe, no Fe; all +EPO, but EPO dose↑ permitted at 4 wks *	No Open-label	No 12 wks	NA	Hb change
Hermel inke 2007	Yes Breast ca	>2 cm or inflamma-tory No metatases	Yes 1 of 2 regimens in PREPARE w sub-randomization to +darbe	Yes *	Unknown if blind	No 5 mo	NA N=109	Cognitive function
Herring ton 2005	No No pts who used both ESAs No patients w <12 wks f/u	No	No	No Dose ↑ was observed for both ESAs	No No control No randomizati on No blind Retrospecti ve des-cription of ESA use	No 12 wks f/u	NA	Hb levels & trans-fusion needs asso-ciated w most fre-quent doses
Hesket h 2004	No No myeloid ca	No	No	Yes Wt based and non-wt based regimens w cor-rection+maintenance phases *	No Open-label Active control	No 16 wks+4 wk f/u	NA	Hb change Time to Hb change
Hirsh 2007	Yes Non-small cell lung ca	Yes Stage 3B or 4	No	Yes 3 q/wk doses, 3 q/3wk doses *	No Open-label	No Up to 12 wks tx & 13 wks of f/u	NA	Hb change
Iconom ou 2003	No Solid tumor	No	No	No Dose ↑ permitted at 4 wks *	Unknown if blind	No 12 wks	NA	Hb change QOL
Italian Cooper ative Study Group 1998	Yes Stratified by 3 types of low risk MDS	No	No	Yes	Yes	No 8 wks placebo controlled; then 24 wks w various doses & no control	NA	Hb change Transfusion need
Jacubo wski 2003	No Solid tumors	No	No	Dose ↑ permitted at 4 wks (the time of the 1o endpoint) *	No Open-label	No Up to 16 wks Only preliminary data in abstract	NA	Hb change at 4 wks QOL at 16 wks
James 1992	Yes Ovarian ca	No Stages 2-4	Various platinum	Yes *	No Open-label	No 6 mos	NA N=21 of 30 enrol-led; written bf study done	Transfusion need
Janinis 2003	No	No	Stratified by platinum & non platinum chemo-therapy use	Yes	No Open-label	No Unspecified & vari-able (dosing started only w hb trigger level)	NA	Transfusion need QOL
Jitnuya nont 2001	No No acute leukemia or myeloid ca No cerebral metastses Marrow invasion by tumor permitted	No	No Included pts not on chemotherapy & pts on platinum & non platinum chemotherapy	No Duration different on chemotherapy or not	No Open-label No randomizati on	No 8 wks if no chemo-therapy 12 wks if chemo-therapy	NA N=24	Hb change Transfusion need QOL
Johanss	Yes	Hormone	No	No	Unknown if	No	NA	Hb change

on 2001	Prostate ca	refractory Metastatic		Dose ↑ permitted at 8 wks in high dose arm *	blind Active control (2 doses of ESA)	12 wks		Transfusion need QOL (powered for this)
Kajikawa 1993	No Cirrhosis, Hepatocellular ca	No	NA Hepatectomy	Yes	Autologous blood transfusion +ESA vs No autologous blood transfusion Unknown if ESA segment blinded	No ~4 wk study	NA	Hct change Transfusion need
Kotasek 2003	No Solid tumor	No	No	Yes 6 fixed ESA doses & placebo *	Yes Part 2: optional open-label extension	No 12 wk double-blind phase; 8 wk f/u OR 11 wk extension+ 8 wk f/u	NA	Safety (but no power calculations) Hb change (power calculation done)
Kotsori 2006	No	No	No	No Dose ↑ permitted at 4 wks for 2 ESAs	No Unknown if blind Active control	No 8 wks	NA	Hb change Transfusion need QOL
Kunikane 2001	Yes Non-small cell lung ca	No massive bone metastases	2 platinum tx	Yes 2 fixed ESA doses & placebo *	Yes	No 6 wks High drop-out bc of exclusion violations	NA	Hb change/nadir
Kurz 1997	No Gynecologic ca (cervival, ovarian, uterine)	No	No Polychemotherapy	No Dose ↑ permitted at 4 wks	Yes	No 12 wks	NA	Hb change Transfusion need QOL (unvalidated test)
Lavey 1993	No Tumor above diaphragm-could involve pituitary adenomas	No No distant metastases	No Variable duration XRT, but no chemotherapy	No Sequential dose regimen w a variable duration of the 2nd dose *	No Open-label Controlled, but not randomized	No ~6-9 wks	NA N=40	Hb change
Lavey 2004	Cervical ca (diease inside pelvis)	No FIGO 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 used for survival	No Tx up to ~7 wks Survival (over-all, progression free) f/u done for apparently 72 mo	NA N=53	Hb change Hb target
Leitgeb 1994	No	No	No	No Dose ↑ permitted at 6 wks	No Open-label No randomization No control Comparison of responders & non-responders	No 12 wks	NA	QOL change in responders vs non-responders
Leon 1998	No Solid tumor (pediatric)	No	No	Yes	No Open-label Historical control	No 12 wks	NA (pilot study)	Hg change Transfusion need QOL
Levine 1999	Yes Rectal Amenable to pre-op XRT	No	Yes Received both chemo-therapy & XRT	Yes 1dose before & others during chemoradiation & pre/peri-op period *	No Open-label No randomization	No 12 wks	NA	Hg change Transfusion need

				Tx group also received Fe	Historical control			
Librett o 2001	No	No	No	No	No Case series	No	NA N=11	NA
Lindho lm 2004	No With cachexia due to primarily GI ca See Daneryd	No	Not currently being treated	No Indomethicin+variabl e ESA doses (if needed) until hb normalized	Unknown if blind	Survival=2 o endpoint Tx till death or un-able to take indome-thicin	NA N=108	Relationshi p be-tween hb & exer-cise power or phys-ical functioning
Littlew ood 2006	No CLL, HD, NHL, MM See Hedenus	No	No Extent of prior tx	No Dose ↑ permitted at 4 wks *	Yes	No 12 wks+4 wk f/u	NA	QOL
Ludwig 1990	Yes MM	No Advanced	No Could include XRT	No Dose ↑ permitted at 3 & 6 wks * Variable duration	No Open-label No randomizati on No control	No 6 mo	NA N=13	Hb change Transfusion need # erythroid burst forming units # granulocyte col-ony forming units
Ludwig 1993-A	No Included hematologic ca, MDS	No	No Could include XRT	No Dose ↑ permitted q 3 wks	No Open-label No randomizati on 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	No Included hematologic ca, MDS	No	No Could include XRT	No Dose ↑ permitted at 6 wks	No Open-label No randomizati on No control	No 12 wks unless pt requested longer Survival analysis compared responders vs non-responders	NA N=42	Hb change QOL Survival
Ludwig 1993-C	No Squamous cell ca, MM Selected subsets of a larger trial & pre-liminary data	No	No	No Dose ↑ permitted at 6 wks	No No randomizati on No control	No Variable duration	NA N=34	Hb change Traits of responders QOL
Ludwig 1994	No Included hematologic ca, MDS	No	No Could include XRT	No Dose ↑ permitted at 6 wks *	No Open-label Algorithm for re-sponse in ½ group tested on 2nd ½	No 12 wks	NA	Hb change Identificatio n of response predictors
Ludwig 1995	No No acute leukemia or myeloid ca, but CLL, HD, MM, NHL per-mitted No intracranial in-volvement	No	No Included pts not on chemotherapy Some stratification in analysis	No Dose ↑ permitted at 6 wks *	No Open-label No randomizati on No control Compariso n of re-sponders vs no re-sponders	No 12 wks unless pt requested longer	NA	Hb change Transfusion need QOL Comparison of responders vs no responders
Malik	No	No	Various platinum	Yes	No	No	NA	Hb change

1998	No hematologic ca No cerebral mets			Fe also given	Open-label No randomization No control	At least 10 wks	N=23	Transfusion need QOL
Mangiameli 2002	Lung ca	No Advanced	Various platinum				NA N=10	Neurotoxicity protection Hb change
Mantovani 2000	No MDS: 3 subtypes: RA/ RARS bicyto-penia or infection; RAEB w <20% blasts	No	No	No Tx w titrated GCSF ESA dose ↑ permitted at 6 wks *	No Open-label No randomization No control	36 wks unless pt requested longer	NA N=33	Hb change 12 wks Hb change 36 wks Response durability Time to AML Survival
Markman 1993	Yes Ovarian ca failed platinum or w recur-rence	No	Yes 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	No ESA tx: 3 wks during each of 6 cycles	NA	Hb level Transfusion need
Mirtsching 2002	No (3 pooled studies-using interim data from 1 study) See Glaspy 2001, 2	No	No	No ESA dose ↑ permitted *	No Open-label Pooled data from 3 studies-including preliminary data	No 13 wks	NA	Hb level Time to target hb Transfusion need
Mystakidou 2005	No Solid tumors	No	No chemotherapy or XRT	No Variable tx duration	Unknown if blind	No Up to 24 wks	NA N=100	Hb change QOL
Negrin 1993	No MDS Assorted subtypes	No	No	No GCSF dose titrated ESA dose escalated to 300 U/kg/d.	No Open-label No control No randomization	No 16 wks	NA	Hb change Transfusion need
Negrin 1996	No MDS Assorted subtypes	No	No	No GCSF dose titrated ESA dose escalated to 300 U/kg/d. Responders treated 8-16 more wks	No Open-label No control No randomization	No Tx could be >32 wks in some patients	NA N=55	Hb change Transfusion need
O'Shaugh-nessy 2002	Yes Breast ca	No	Yes Doxorubicin/cyclophosphamide	No Dose ↑ permitted *	Yes Part 2: uncontrol-led extension	No 12 wks controlled; then 6 mo uncontrol-led	NA (pilot study)	QOL-fatigue
O'Shaugh nessy 2005	Yes Breast ca	No Stages 1-3	No Anthracycline tx+taxane	No Dose ↑ permitted at 5 wks *	Yes Part 2: uncontrol-led extension	No 12 wks controlled; then 6 mo uncontrol-led	NA (pilot study)	Cognitive function bf cycle 4 & 6 mo after ESA tx done
Oberhoff 1998	No Solid tumor	No	No	Yes	No Open-label Part 2: uncontrol-led extension	No 12 wks controlled; then 12 wks uncon-trolled	NA	Transfusion vol-ume/ 4 wk intervals
Olsson 2002	Yes Breast ca	Metastatic	No	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)	No 24 wks	NA	Hb change Transfusion need QOL
Osterborg 1996	No MM/NHL+CLL	Low-grade NHL, but many actually	No (In various tx stages too)	3 arms: Fixed dose until hb reached, escalating titration, &	Unknown if blind Active &	No 24 wks	NA N=121	Time to hb response

		had advanced disease		placebo *	placebo controls			
Osterb org 2005	No CLL, MM, NHL (See Osterborg)	No	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/ in partial remission after 1st study part	NA Unclear if any pts lost to f/u N=343	Survival not 1o endpoint
Osterb org 2007	Yes B-cell NHL	Intermediate/high grade	No	Yes 3 ESA dose levels *	No Open-label Active control	No 13 wks	NA	Hb change
Pawlicki 1997	No		No	Yes	No Open-label No control	No 16 wks	NA	Hb change Transfusion need QOL
Perillo 2001	Yes Ovarian ca	No Stages 3B & C—4 Residual tumor <1 cm after cytoreduc-tive surgery	Yes Includes transplan-tation	GCSF+EPO+GMCSF	Unknown if blind EPO not the ex-perimental agent	No Unspecified duration	NA	CD34+ cell mobilizatio n Hematopoietic re-overy
Perillo 2004	No Gynecologic ca	No Cervical: stage 2B-4A Ovarian: stage 3C-4	No	No Fixed GCSF dose in control arm 3 variable GCSF arms + same dose ESA (but 3 or 4 d regimens)	No Unknown if blind Active control	No 3-4 days	NA	# of peripheral blood progenitor cells collected via aphaeresis for auto-logous transplant
Pierelli 1994	Yes Ovarian ca	Stage 3BC-4 w <1 cm residual tumor post cytoreductive surgery	Yes Platinum	GCSF in all pts ESA in ½ pts	No Not randomized 5 consecutive pts given 1 tx; 5 con-secutive pts given other tx	No Until day 14 after multiple chemothera -py cycles	NA	Haematipoietic progenitors & myeloid different-tiation
Pierelli 1999	Yes Ovarian ca	Stage 3BC-4 w <1 cm residual tumor post cytoreductive surgery	Yes	No Fixed GCSF dose + fixed ESA dose-but given only when Hct <30 until Hct 35%	Unknown if blind	No 10-12 days for each of 3 chemothera py cycles	NA	# of peripheral blood progenitor cells collected via aphaeresis for auto-logous transplant WBC & PMN counts
Platanias 1991	No	No	No Not platinum	Yes 5 IV ESA dose levels in escalation study	No Open-label Active control	No 4 wks IV dose	NA IV dose	Hb change
Porter 1996	No Sarcomas (pediatric)	No	No	No Dose ↑ until transfusion independence achieved or 300 U/kg used IV or SQ ESA	Yes	No 16 wks IV dose	NA IV dose	Transfusion need
Quirt 2001	No No acute leukemia or myeloid ca	No	½ w/o tx ½ w variety of tx	No Dose ↑ permitted at 4 wks *	No Open-label Each cohort	No 16 wks	NA	Transfusion need

					serv-ed as own control			
Quirt 2006	No 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 ran-domized & 1 study used only Cana-dian pts from a global study	No Up to 16 wks	NA	Identificatio n of predictive factors for transfusion
Razzou k 2004	No No myeloid or brain ca Stratified by solid tumor/HD vs ALL/NHL	No	No	No Dose ↑ permitted at 3-4 wks *	Yes	No 16 wks	NA	QOL
Rose 1994	No MDS Assorted subtypes	<10% marrow blasts	No	No Dose ↑ permitted q 4 wks *	No Open-label No control Compassio nate use trial	No No specified duration	NA	Transfusion need in last 3 mo of tx
Rosen 2003	Yes Head-neck No distant metatases	Stage 3 if involved tongue base or hypo-pharynx; Stage 4	Yes	Yes for chemotherapy Surgery variable	Unknown if blind	No 18 wks	NA N=90	1o Hct change 2o Survival & tumor progression
Savonij e 2005	No Solid tumor	No	Various platinum	No Dose ↑ permitted at 4 & 8 wks *	No Open-label	No Tx until 4 wks after last chemo cycle Survival assessed 12 mo after study done	NA N=316	Transfusion need
Savonij e 2006-A	No Solid tumor See Savonije 2005	No	Various platinum	No Dose ↑ permitted at 4 & 8 wks *	No Open-label	No 4 weeks after last chemo cycle	NA	QOL (2o endpoint, but focus of this paper)
Savonij e 2006-B	No Solid tumor See Savonije 2005	No	Various platinum	No Dose ↑ permitted at 4 & 8 wks *	No Open-label	No 4 weeks after last chemo cycle	NA	Post hoc analyses including transfu-sion need based on initial hb level
Schwar tz-berg 2003or 4	No	No	No	NA	No No control No randomizati on No blind Retrospecti ve at-tempt to compare 1 epo dose w an-other darbe dose	No 12 wks	NA	Hb change
Schwar tz-berg 2004	No 3 concurrent & later combined trials each w 1 "cancer": breast, non-small cell lung, gynecologic (cervix, ovary, uterus)	No	No	Yes 2 fixed doses of ESAs	No Open-label Active control	No Up to 16 wks of treatment w 3-4 wks of f/u	NA	1o QOL validation of specific metric 2o Hgb change Transfusion need
Scott 2002	Yes Head-neck ca	No	Yes-surgery	Yes 3 pre-operative doses	Unknown if blind	No 3 pre-operative doses	NA	Hb/hct/ret change Transfusion need

Senecal 2005	Yes Breast ca See Schwartzberg 2004	No	No	Yes 2 fixed doses of ESAs	No Open-label Active control	No Up to 16 wks of treatment w 3-4 wks of f/u	NA	1o QOL validation of specific metric 2o Hgb change Transfusion need
Shasha 2003	No Non-myeloid ca	No	Current XRT w chemotherapy at some point	No Dose ↑ permitted at 4 wks *	No Open-label No randomization No control	No 16 wks Only 57% (442/777) found to be evaluable	NA	Hb/Hct change Transfusion need
Shasha 2006	No No myeloid	No	No tx	No Dose ↑ permitted at 4 wks *	No Open-label No randomization No control	No 12 wk tx+4 wk f/u	NA	Hb change
Silvestris 1995	Yes MM Melphalan-predni-sone resistant	No Stages 1-3A	No	Yes Dose ↑ at 6 wks	Unknown if blind	No 24 wks	NA N=54	Hb change Transfusion need
Sloan 2002	No	No	No		Yes	No	NA	Transfusion need QOL
Smith 2003	No Non-myeloid ca	No	Not then receiving chemo/ radio tx	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	No Double-blind part 12 wks +optional uncon-trolled 12 wk exten-sion phase w 4 wk f/u	NA	Hb change
Stein 1991	No MDS 2 subtypes- some transfusion depen-dent	<10% blasts	No Corticosteroids could be used	No Dose ↑ permitted q 4 wks * IV ESA	Yes	No 12 wk controlled tx + 12-24 wk optional uncontrolled, open-label tx IV ESA	NA	Hb change, but in transfusion depen-dent pts
Straus 2002	No CLL, HD, MM, NHL	No Pts who did not de-velop hb <12 g/dl not randomized	No	No Dose ↑ permitted at 3- 4 wks * Pts in delayed tx group not given ESA until hb <9 g/dl	No Open-label	No Pts received tx of variable duration up to 12 wks	NA	QOL (uncertain when assessed)
Sweeney 1998	No (breast, cervix, lung, prostate, uterus)	No Metastatic disease excluded for lung primaries or if CNS involvement	Various XRT Chemotherapy not prohibited	ESA tx given <7 wks until hb target reached Fe only given to pts in tx arm	No Open-label	No 7 wks	NA	Hb change QOL
Ten Bokkel 1998	Yes Ovarian cs	No Stages 2B-4	Various platinum	No 2 fixed ESA doses+ pla-cebo Variable duration	No Open-label	No Up to 6 cycles + 3-24 wks after last tx cycle	NA N=122	Transfusion need Time to transfusion
Thatcher 1999	Yes Small cell lung ca	No	Various platinum	Yes 2 ESA doses + placebo*	No Open-label	No Up to 26 wks	NA N=130	Hb level
Thompson 2000	No MDS Assorted subtypes	No	No	Yes Variable doses of GM-CSF	Yes	No 85 days	NA	Hb change Transfusion need
Tsukuda 1993	Yes Head-neck ca	No	No	No Could include XRT	No Unknown if blind Unknown if any randomization ESA pt	No During 2-3 cycles of chemo and/or XRT and 3 additional wks	NA	Hb change WBC, PLT change

					given 1 of 2 fixed doses 3 not given ESA considered place-bo controls			
Tsukuda 1998	Yes Head-neck ca	Yes Stages 3-4	Yes	Yes 3 fixed dose arms+pla-cebo when Hb <11.5 g/dl & then given for 8 wks	Unknown if blind	No 8 wk	NA	Hb change
Vadhan-Raj 2003	No Non-myeloid ca	No	No	No Dose ↑ permitted at 6 wks *	No Open-label No control No randomization	No Up to 16 wks	NA	Change in fatigue & function Transfusion need QOL
Vansteen-kiste 2002 (CONSORT)	Yes Lung ca	Reportedly stratify-cation by tumor type	Various platinum	No Dose ↑ permitted at 7 wks	Yes	No 12 wks+4 wk f/u >12 mo survival & tumor progression . Preliminary data shown.	NA N=320	Transfusion need
Vansteen-kiste 2002	No No CNS ca See Glaspy 2002, Hedenus 2002, Vansteenkiste 2002	No	No Anemia could be due to tx or ca	No Different doses & regi-mens in 4 pooled studies Dose ↑ permitted in 2 studies	No 3 studies blinded & placebo control-led, but 1 study open & used ac-tive control	No 12 wks	NA	Post hoc analysis on pooled data Hb change Time to hb change
Vansteen-kiste 2004	Yes Lung ca See Vansteenkiste 2002	Reportedly stratify-cation by tumor type	Various platinum	No Dose ↑ permitted at 7 wks	Yes	No 12 wks+4 wk f/u >12 mo urvival & tumor progression . Preliminary data shown.	NA N=320	Post hoc analyses including transfu-sion need based on initial hb level
Varan 1999	No Solid tumors (pediatric)	No	No	Yes	Unknown if blind	No 2 mo	NA	Hb change Transfusion need
Vijayakumar 1993or4	No Selected breast, lung, prostate, uterus	No Stratified by tx site	No XRT was tx	Yes * Only tx arm received Fe	No Open-label	No At least 4 wks (preliminary results)	NA N=26 (preliminary results)	Hb change WBC change
Wagner 2004	Yes Metastatic neuro-blastoma (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
Waltzman 2005	No Solid tumor No untreated brain mets	No	Reportedly stratified by platinum vs non-platinum	No Dose ↑ permitted at 4 or 6 wks depending on ESA type *	No Open-label Active control	No 9 wks	NA	Hb change
Welch 1995	Yes Ovarian	Advanced FIGO stage 2-4	Various platinum	Yes *	No Open-label	No W 6 chemothrapy cycles	NA N=30	Hb change Transfusion need
Witzig 2005	No Incurable ca	No	No	No Dose ↑ permitted at 4 wks *	Yes	No 16 wks	NA	Hb change Transfusion need QOL
Wurnig 1996	Yes 1o bone ca	No	No	IV ESA given when hb <11 g/dl & dc when hb >13.5 g/dl	Yes	No 20 wks	NA	Hb/hct levels Transfusion

								need
Yilmaz 2004	No Hematologic ca Solid tumors include-ing sarcomas Pediatric	No	No	1 of 2 ESA doses	Unknown if blind Active control Randomize d to 2 ESA doses	No 12 wks	NA	Hb change Transfusion need
Zagari 2003	No	No	Various platinum		No Open-label	No	NA	

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

Δ=delta ALL=acute lymphocytic leukemia AUC=area under the curve Ca=cancer D=day(s) Darbe=darbeoetin epo=erythropoietin Fe=iron treatment F/u=follow-up GCSF=Granulocyte colony stimulating factor

GMCSF=Granocyte-Myelocyte colony stimulating factor Hb=hemoglobin Hct=hematocrit HD=Hodgkin's disease

IL=interleukin IV=intravenous MDS=Myelodysplastic disorder MM=multiple myeloma Mo=month

NHL=Non-Hodgkin's lymphoma PLT=platelet PMN= polymorphonuclear leukocyte count

QOL=quality of life or performance level RBC=red blood cell count Retic=reticulocyte count

SQ=subcutaneous Tx=Treatment WBC=white blood cell count Wk=wk(s) XRT=Radiation therapy

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

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.

3. 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.