Table S1. Systematic review characteristics

Citation	Type of Analysis	Time-Period	Study Designs	Sample Characteristics	ESA	Indication	Data Available	Number of Trials	Author Conclusions/ Interpretation	Comments
Bohlius et al, Lancet, 2009; Bohlius et al, Lancet, erratum 2009; Bohlius et al, Cochrane, 2009[9,10]	Meta-analysis (IPD)/CR	Jan 1, 1985-Jan 31, 2008	RCTs (prevention or tx of anemia: ESAs + transf *v* transf only)	Adults or peds with Ca (regardless of tx status)	EPO-α EPO-β DAR	(Not specified) CT-induced anemia and anemia of Ca	Mortality during active study period, survival during longest f/up	53 trials	ESAs increased mortality during active study periods and worsened OS.	• Meta-analysis with individual patient data. • ESA type not separated. • Only mortality/ survival data. • Meta-regression for several explanatory variables.
Glaspy et al, BJC, 2010[29]	Meta-analysis (IPD/LBR)	Jan 1, 1985–Mar 31, 2008	RCTs (prevention or tx of anemia: CT, RT/CT, RT only, anaemia of cancer)	Adults or peds with Ca (regardless of tx status)	EPO-α EPO-β DAR	(Not specified) CT-induced anemia and anemia of Ca	Survival, disease progression, risk of VTEs	60 trials	No significant effect of ESAs on survival or disease progression. Future RCTs will examine safety and efficacy of ESAs when used according to the revised labeling information.	• Literature-based review. • Refer to guideline manuscript text for highlighted differences with other meta-analyses.
Bennett et al, JAMA, 2008a, 2008b[8,28]	Meta-analysis (LBR)	Jan 1, 1985–Oct 31, 2008	RCTs (ESAs for tx of anemia in oncology)	Non-myeloid malignancies; CT-induced anemia	EPO-α EPO-β DAR	CT-induced anemia	Survival, VTE	53 trials (Survival) 38 trials (VTE)	ESAs increased risks of VTE and mortality.	• Literature-based review. • ESA type not separated.
Lambin et al, Cochrane, 2009[30]	Meta-analysis (LBR)/CR	No limit–Feb 24, 2009	RCTs (RT with or without ESAs)	Pts of any age with head and neck Ca	EPO-α EPO-β DAR	Not specified	OS, DFS, local tumor recurrence, toxicity of tx	5 trials	Worse outcomes for RT plus EPO compared to RT alone. High target Hb may have had significant role.	• Literature-based review; Cochrane review. • Evidence tables note limitations.

Citation	Type of Analysis	Time-Period	Study Designs	Sample Characteristics	ESA	Indication	Data Available	Number of Trials	Author Conclusions/ Interpretation	Comments
Tonelli et al, CMAJ, 2009[31]	Meta-analysis (LBR)	1950–Oct 22, 2007	RCTs (ESA vs no ESA or PLA)	Adults with Ca-related anemia (results included pts with solid tumors, and hematological malignancies)	EPO-α EPO-β DAR	CT-induced anemia and anemia of Ca	Mortality; CVEs and hypertension; HRQOL; transf; tumor response; SAEs	52 trials 28 trials (Mortality)	ESAs improved some disease-specific QOL; decreased transf; increased risk death, SAEs. ESAs should not be used as alternative to transf in pts with Ca-related anemia.	• Studies poor to moderate quality; short duration (mdn f/up 12 wks); pts often aware of tx group. • Subgroup analyses of baseline Hb also provided.
Newland & Black, Ann Pharma, 2008[33]	Systematic Review	1950–Aug, 2008	RCTs (ESA increased tumor progression or death from disease progression)	Head and neck, breast, cervical, NSCLC, non-myeloid, lympho-proliferative	EPO-α EPO-β DAR	Not specified	Tumor progression; Survival	10 trials	Absolute conclusions about tumor progression cannot be drawn. Ten trials investigating off-label use of ESAs in pts with Ca, report increased risk of tumor progression and/or tx-associated death. Two reported worse OS with ESA compared with PLA; another reported shorter time to death with tx. Poor quality data basis for FDA's warnings/ labeling.	• Data were not pooled. • Data for this review were not extracted to evidence tables.

Citation	Type of Analysis	Time-Period	Study Designs	Sample Characteristics	ESA	Indication	Data Available	Number of Trials	Author Conclusions/ Interpretation	Comments
Ross et al, Oncologist, 2007[32]	Systematic Review (plus meta-analysis [LBR] of Hb response rates)	1980-Dec 15, 2005	Controlled trials (randomized or not) plus observational studies (retrospective or not)	Adults with primary MDS	EPO-α EPO-β DAR	Anemia of MDS	Hb changes; transfusions; number of pts with Hb response; QOL; AEs	59 trials (4 RCTs, 1 non-RCT, 54 uncontrolled case series)	ESAs are efficacious in anemia of MDS. Hb response appears higher in DAR *v* EPO arms. Safety data seem comparable, but DAR data are sparse, and there were no direct comparison studies.	Included retrospective observational uncontrolled studies but kept single-arm data separate from controlled trials (4 randomized, 1not)

Abbreviations: ESA, erythropoiesis-stimulating agent; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; PLA, placebo; Hb, hemoglobin; CR, Cochrane Review; IPD, individual patient data analysis; LBR, literature-based review; MDS, myelodysplastic syndrome; Hb, hemoglobin; Ca, cancer; RT, radiation therapy; f/up, follow-up; OS, overall survival; DFS, disease-free survival; AEs, adverse events; SAEs, serious adverse events; QOL, quality of life; RCTs, randomized controlled trials; CVE, cardiovascular events; transf, transfusions; tx, treatment; VTE, venous thromboembolic event

Table S2. Randomized controlled trial characteristics

Trial	Primary Endpoint	Category (Design)	Population	Intervention/ Regimen	Sample Size (by arm)	Author Conclusions	Comments
Schouwink et al, Eur J Cancer, 2008[47]	• Change in Hb • Proportion of pts transfused	Initiation threshold	Pts receiving chemo	EPO-α immediate *v* delayed (until Hb <=10)	N=110 n=55 (early) n=55 (standard)	• Percent transfusions similar • Amount transfused almost twice as high in standard group. • Early EPO significantly improves Hb.	• Open label, adequate randomization, exclusions detailed.
Glaspy et al, Cancer, 2009[42]	• Efficacy in Hb maintenance • Safety	Initiation threshold	Non-myeloid malignancies	EPO-α immediate *v* delayed (until Hb < 11)	N=186 n=68 (early) n=68 (standard) n=50 (non-randomized)	• Both early and standard EPO increased and maintained Hb (11.0-13.0 g/dL) in pts with CIA.	• Open label, adequate randomization, exclusions described.
Vansteenkiste, BMC, 2009[49]	• Transfusion rates	Dose comparison with stratification by BL Hb (≥ 10 g/dL *v* < 10 g/dL)	Pts with CIA, non-myeloid malignancies	DAR-α (500µg Q3W *v* 2.25 µg/kg QW)	N=705 n=353 (500µg Q3W) n=352 (2.25 µg/kg QW)	• DAR- α Q3W and QW raised Hb levels and maintained mean Hb at <12 g/dL in both baseline-Hb groups. The ≥10 g/dL baseline-Hb group had fewer transfusions and faster anemia correction.	• Post-hoc re-analysis to examine results for patients with baseline Hb ≥ 10 g/dL *v* < 10 g/dL. • Initial report Canon et al, JNCI, 2006.
Pedrazzoli et al, JCO, 2008[45]	• Hematopoietic response	Iron supplement	Pts with CIA and without iron deficiency	DAR-α +/- sodium ferric gluconate IV	N=149 n=73 (IV iron) n=76 (DAR)	• IV iron supplementation significantly reduces DAR tx failures without additional toxicity.	• Open label, randomization not described, exclusions described.
Bastit et al, JCO, 2008[41]	• Hematopoietic response	Iron supplement	Pts with CIA, non-myeloid malignancies	DAR-α + IV iron *v* po/ no iron	N=398 n=201 (IV iron) n=197 (DAR)	• IV iron well tolerated • Improved hematopoietic response rate, lower incidence of transfusions compared with DAR.	• Open label, adequate randomization.
Hedenus et al, Leukemia, 2007[51]	• Change in Hb	Iron supplement	Pts with moderate anemia and indolent NHL, CLL, or myeloma, not requiring CT	EPO-β *v* EPO-β + IV iron (iron sucrose; Venofer)	N=67 n=34 (EPO) n=33 (EPO+iron)	• Hb increase and response significantly greater with the addition of IV iron. Lower EPO dose needed with addition of IV iron.	
Heras et al, Eur	• Change in Hb	Dose finding	Pts with CIA, solid	EPO-β 30,000	N=50	• Improvements in FACT-	• Double-blind,

Trial	Primary Endpoint	Category (Design)	Population	Intervention/ Regimen	Sample Size (by arm)	Author Conclusions	Comments
J Cancer Care, 2008[44]			tumors	IU *v* EPO-β 20,000 IU + iron 800 mg po bid	n=30 (EPO-β30) n=20 (EPO-β20)	F significantly (p< 0.001) correlated with increases in Hb • No dose-dependent adverse events.	randomization not described, no withdrawals.
Volgger et al, Anticancer Res, 2008[52]	• Hematopoietic response, transfusion rates, QOL, change in Hb	Dose finding	Pts with gynecological or breast malignancies	EPO-β 10,000 IU TIW *v* EPO-β 20,000 IU BIW	N=119 n=60 (EPO-β TIW) n=59(EPO-β BIW)	• Similar improvements in Hb level and QOL. Further investigation needed to determine whether less frequent dosing regimens may result in increased rates of thromboembolic events.	
Tsuboi et al, Jpn JCO, 2009[48]	• Change in Hb	Efficacy/Safety	Pts with CIA, lung cancer or lymphoma	EPO-β *v* PLA	N=122 n=63 (EPO-β) n=59 (PLA)	• EPO significantly increased Hb, ameliorated decline of QOL.	• Double blind, adequate randomization, exclusions described.
Aapro et al, EJC, 2009[40]	• Risk factors for TVEs and the effect of antithrombotic treatment on incidence of TVEs • (OS primary endpoint in trial)	Efficacy/Safety	Pts with metatastic breast cancer receiving CT	EPO-β *v* CTL	N=463 n=231 (EPO-β) n=232 (CTL)	• Several risk factors may impact the risk of TVEs with ESA use. Antithrombotic therapy may have potential to reduce risk of TVEs under epoetin therapy.	• Retrospective analysis of BRAVE trial
Gupta et al, Cancr Bio Ther, 2009[43]	• Effect of EPO-β on Hb/anemia	Efficacy/Safety	Pts with previously untreated advanced cervical cancer (stages IIB to IIIB) receiving concurrent CT plus RT	EPO-β *v* CTL	N=120 n=60 (EPO-β) n=60 (CTL) Note: 5 pts "absconded" during tx. "Evaluable": n=58 (EPO-β) n=57 (CTL)	• EPO-β safely and effectively corrects anemia in pts with advanced cervical cancer receiving CT plus RT and is not associated with adverse effects on response rate, OS, DFS and treatment-related toxicities.	• Inclusion criteria required baseline Hb 10-11 g/dL, but range in CTL goes up to 12.5 and in EPO goes down to 9.5. • Also assessed OS, DFS, safety, and QOL
Greenberg et	• Effect of EPO	Efficacy/Safety	Pts with	EPO	N=110 (118)	• There was similar OS and	• 118 pts were

Trial	Primary Endpoint	Category (Design)	Population	Intervention/ Regimen	Sample Size (by arm)	Author Conclusions	Comments
al, Blood, 2009[50]	on clinical outcomes (erythroid response, survival		myelodysplastic syndrome	+ SC *v* SC only	n=53 (EPO+SC) n=57 (SC only)	transformation of acute myeloid leukemia in EPO *v* SC arms. Improvements in multiple QOL domains in EPO arm. Increased survival in erythroid responders *v* non-responders.	randomized, but 8 were "unevaluable" because of insufficient data. Do not report the distribution of these 8 pts into arms at randomization.
Pfeffer et al, NEJM, 2009 ("TREAT")[46]	• Effect of DAR on clinical outcomes	Subset analysis of renal patients with malignancy	Pts with diabetes, chronic kidney disease	DAR-α *v* PLA (offered DAR "rescue")	N= 2,038 **Cancer Subset** n= 188 (DAR-α) n= 160 (PLA)	• Not applicable.	• Double blind, adequate randomization.

Abbreviations: ESA, erythropoiesis-stimulating agent; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; PLA, placebo; G-CSF, granulocyte colony-stimulating factor; SC, supportive care; OS, overall survival; CT, chemotherapy; RT, radiotherapy

Table S3. Summary of systematic review outcomes: transfusions

Author		Event Rate		Relative Risk (95% CI)	Number of Trials	Comments
		ESA	Control			
Tonelli et al, CMAJ, 2009[31]	*Overall*	707/2,882	952/2,439	0.64 (0.56 to 0.73)	24	• ESAs reduced transfusions. • Random effects models; I^2 not reported. • Many studies did not specify criteria for administering transfusions.
	EPO v none	579/2,229	739/1,892	0.65 (0.56 to 0.75)	21 (28 comparisons; multiple arms)	
	DAR v none	128/653	213/547	0.58 (0.41 to 0.83)	3	
Ross et al, Oncologist, 2007[32] (MDS only)		35/45	19/21	OR 0.3 (0.1 to 1.6)	1	• Patients with MDS only.

Abbreviations: ESA, erythropoiesis-stimulating agent; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; MDS, myelodysplastic syndrome

Table S4. Summary of systematic review outcomes: survival

Author		Event Rate		Hazard Ratio (95% CI)	Number of Trials	Comments
		ESA	Control			
Bohlius et al, Lancet, 2009; Bohlius et al, Cochrane, 2009[9,10]	***Mortality during active study period*** [a]					• Little evidence of heterogeneity across trials. • *Additional data to consider.* Results for mortality also stratified by study characteristics (Fig 4, p1537) and pt characteristics (Fig 5, p1538).
	Overall	865/7,634	665/6,299	1.17 (1.06 to 1.30); *P* = .003	53	
	Chemotherapy	605/5,676	490/4,765	1.10 (0.98 to 1.24); *P* =.12	38	
	Overall survival (until last date of follow-up) [a]					
	Overall	2,643/7,634	2,350/6,299	1.06 (1.00 to 1.12); *P* =.046	53	
	Chemotherapy	1,888/5,676	1,667/4,765	1.04 (0.97 to 1.11); *P* =.263	38	
Bennett et al, JAMA, 2008[8,28]	*Overall*	NP	NP	1.09 (1.01 to 1.18); *P* = NR	53	• Random effects models; no significant heterogeneity. • Most trials had limited ability to evaluate survival or tumor progression.
	Anemia of cancer	NP	NP	1.19 (1.01 to 1.40); *P* = NR	6	
	Tx-related anemia	NP	NP	1.09 (1.00 to 1.19); *P* = NR	47	
Lambin et al, Cochrane, 2009[30]	*Overall*	355/705	398/692	*OR 0.73 (0.58 to 0.91); *P* =.005	5	• Variability in follow-up times reported. • Fixed effect models; 2 studies accounted for 68% of weight; I^2=41%. • Weight for Overgaard was 40.5%.
	Local regional PFS	242/554	299/543	*OR 0.63 (0.49 to 0.80); *P* =.0002	4	• Local regional PFS not defined. • Fixed effect models; I^2=47%.
Tonelli et al, CMAJ, 2009[31]	*Overall (all-cause)*	515/3,789	360/2,736	RR 1.15 (1.03 to 1.29); *P* = NR	28 (31 comparisons; multiple arms)	• Stratified data comparable (i.e., type of Ca, target Hb). • Random effects models; I^2=0%. • Effect in DAR arm (Smith et al, 2008).
	EPO v none	291/2,163	207/1,581	RR 1.12 (0.97 to 1.29); *P* = NR	21	
	DAR v none	224/1,626	153/1,155	RR 1.22 (1.01 to 1.47); *P* = NR	7	
Glaspy, BJC, 2010[29]	*Overall*	NP	NP	OR 1.06 (0.97 to 1.15); *P* = NR	60	• Used on-study mortality for 34 studies and long term follow-up (>6 months) for 26 studies in a single analysis. • Used modified ITT. • Did not use meta-regression and tests of interaction to evaluate the influence of potentially explanatory variables.
	Anemia of Cancer	NP	NP	OR 1.09 (0.87 to 1.36); *P* = NR	9	
	RT only	NP	NP	OR 1.18 (0.95 to 1.47); *P* = NR	4	
	Chemotherapy	NP	NP	OR 1.03 (0.93 to 1.13); *P* = NR	47	
Ross et al, Oncologist, 2007[32] (MDS only)	*Overall (all-cause)*	(6/119)	2/94	OR 1.7 (0.4 to 7.4); *P* = NR	NR (of 5)	• Patients with MDS only.

Abbreviations: ESA, erythropoiesis-stimulating agent; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; PLA, placebo; MDS, myelodysplastic syndrome; OS, overall survival; PFS, progression free survival; NR, not reported; NS, not significant; NP, sum not provided in table or text, individual trial event rates are available in review; ARR, Absolute risk reduction

[a]Defined mortality during active study period as death from any cause between date of randomization and 28 days after end of active study phase; and OS as death from any cause between date of randomization and date of last available follow-up. *The Lambin meta-analysis calculates the point estimate and CI for survival (hence is <1.0), whereas the others calculate point estimates and CIs for mortality (hence are all >1.0).

Table S5. Summary of systematic review outcomes: tumor response

Author		Event Rate		Relative Risk (95% CI)	Number of Trials	Comments
		ESA	Control			
Lambin et al, Cochrane, 2009[30]	*Local regional tumor control*	412/658	450/649	0.92 (0.81 to 1.03); *P* = .15	4	• Random effects model; I^2=54%. • Tumor response not defined and schedule of assessment or follow-up unclear.
Tonelli et al, CMAJ, 2009[31]	*Complete response*	NR	NR	0.88 (0.69 to 1.12); *P* = NR	2	• Random effects models; I^2=0%.
	Partial response	NR	NR	0.70 (0.44 to 1.11); *P* = NR		

Abbreviations: ESA, erythropoiesis-stimulating agent; NR, not reported

Table S6. Summary of systematic review outcomes: thrombosis

Author	Event Rate		Relative Risk (95% CI)	Number of Trials	Comments
	ESA	Control			
Bennett et al, JAMA, 2008[28]	334/4,610	173/3,562	1.57 (1.31 to 1.87)	38	• VTE definitions varied across trials. • VTE rates not predefined primary outcome measure in any of the trials.
Tonelli et al, CMAJ, 2009[31]	NR	NR	1.69 (1.27 to 2.24)	13	• 13 trials of 14 comparisons. • Random effects model; I^2=0%.
Glaspy et al, BJC, 2010[29]	NR	NR	*Overall:* OR 1.48 (1.28 to 1.72)	44	• VTE definitions varied across trials. Similar findings when analyzed 18 chemotherapy studies with long-term follow-up and "the most consistent" definitions of VTE. • Random effects model; I^2=0%.
	NR	NR	*Anemia of cancer:* OR 1.36 (0.68 to 2.74)	6	
	NR	NR	*RT only:* OR 1.84 (0.78 to 4.35)	3	
	NR	NR	*CT:* OR 1.48 (1.27 to 1.72)	35	
Ross et al, Oncologist, 2007[32] (Note: MDS only)	0	0	NA	NR (of 5)	• Patients with MDS only.

Abbreviations: ESA, erythropoiesis-stimulating agent; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; MDS, myelodysplastic syndrome; VTE, venous thromboembolic event; NR, not reported; NA, not applicable; RT, radiotherapy; CT, chemotherapy

Table S7. Summary of systematic review outcomes: adverse events

Author		Event Rate		Relative Risk (95% CI)	Number of Trials	Comments
		ESA	Control			
Lambin et al, Cochrane, 2009[30]	*Acute toxicity*	47/223	44/218	1.03 (0.78 to 1.35); *P* = .86	2	• Assume toxicity is due to RT?
Tonelli et al, CMAJ, 2009[31]	*Overall SAEs*	1,123/3,307	787/2,584	1.16 (1.08 to 1.25)	21	• Effect of tx with ESAs *v* no treatment. • SAEs labeled as such by primary paper authors, or if severity unspecified but AE led to withdrawal from tx. • Random effects models; I^2=0%. • Data for cardiovascular events and hypertension available, but not significant.
	EPO v none SAEs	545/1,911	374/1,510	1.17 (1.05 to 1.30)	16	
	DAR v none SAEs	578/1,396	413/1,074	1.15 (1.04 to 1.27)	5	
Ross et al, Oncologist, 2007[32] (MDS only)	*Any AE*	13/44	18/43	OR 0.6 (0.2 to 1.4)	NR (of 5)	• Patients with MDS only.
	Progression to AML	1/110	8/97	OR 0.2 (0.0 to 1.2)	NR (of 5)	

Abbreviations: ESA, erythropoiesis-stimulating agent; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; SAEs, serious adverse events; RT, radiotherapy; NR, not reported; MDS, myelodysplastic syndrome

Table S8. Summary of systematic review outcomes: quality of life

Author		Sample Size		Difference (95% CI)	Number of Trials	Comments
		ESA	Control			
Tonelli et al, CMAJ, 2009[31]	*FACT-Anemia (Total Score)*	310	216	14.66 (-1.09 to 30.41) I^2=93%	3	• LASA scores also available for 7 trials (p4). • Pooled results using random effects models. I^2 noted. • Considered only measures used in >1 study in each comparison, since various QOL measures reported across studies. • Results by baseline Hb also available (Table 2 in paper).
	FACT-Anemia (General Score)	454	255	4.11 (2.00 to 6.22) I^2=0%	3	
	FACT-Anemia: Fatigue Subscale	1,798	1,371	3.00 (1.36 to 4.64) I^2=73%	10	
	FACT-Anemia: Anemia Subscale	795	625	3.90 (1.63 to 6.16) I^2=84%	7	

Abbreviations: ESA, erythropoiesis-stimulating agent; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; NR, not reported; FACT, Functional Assessment of Cancer Therapy

Table S9. Trials evaluating thresholds for initiating treatment*

Author	Number Randomized		Malignancy	Drug and Treatment Duration	Hb when EPO/DARB Initiated (g/dL)		Pts Given EPO/DARB (%)		Transfused (%)		Differences in FACT Measures from Baseline	Thrombo-embolic Events (%)		Deaths	
	I	D			I	D	I	D	I	D		I	D	I	D
Schouwink et al, Eur J Cancer, 2008[47]	55	55	NR (solid tumors only?)	EPO-α ≤ 24 wks AND iron supplement TID	11.2 (0.8)**	≤ 10	92.7%	0%	ITT: 27.3% PP: 29.4%	ITT: 27.3% PP: 27.8%	NR	ITT: 7.3% PP: 7.8%	ITT: 3.7% PP: 3.7%	ITT: 14.5% PP: 15.7%	ITT: 9.1% PP: 9.3%
Glaspy et al, Cancer, 2009[42]	Ran: 68 Non: 50	68	non-myeloid malignancy	EPO-α ≤ 16 wks + iron therapy	Ran: 11.5 (0.3)* Non: 10.1 (0.6)**	<11	Ran: 100% Non: 98%	75%	Ran: 9% Non: 24%	ITT: 5.9%	Ran: 1.5 Standard: -2.6 Non: 1.2	Ran: 5.9% Non: 8%	ITT: 8.8%	Ran: 2.9% Non: 10%	ITT: 2.9%
Charu, Oncologist, 2007[39] [b]Rearden, 2004~[38]	102	102	non-myeloid malignancy	DAR-α ≤ 22 wks	11.1 (0.7)**	< 10	97.1%	62.7%	ITT: 16.7% (9%-25%) PP: 17%	ITT: 26% (16%-35%)	NR	ITT: 9.8% PP: 10.1%	ITT: 2.0%	ITT: 7.9% PP: 6.1%	ITT: 6.9% PP: 7.8%
[b]Straus, 2006[57]	135	134	hematologic	Epoetin </=16 weeks	11.1 ± 0.7[3]	<9	100	19.4	17.8	26.1	FACT-An 8.22 (2.62) unadjusted mean, 6.67 (2.25) estimated mean†, **, FACT-fatigue 3.13 (1.16) unadjusted mean, 2.67 (0.94) estimated mean†, **	11.1	3†	2.2%	3.0%
[b]Crawford,	109	107	non-small cell	Epoetin 16	13.1	≤10[5]	100	46.0	12.3	20.0	NS	12	15	5.5%	4.7%

Author	Number Randomized		Malignancy	Drug and Treatment Duration	Hb when EPO/DARB Initiated (g/dL)		Pts Given EPO/DARB (%)		Transfused (%)		Differences in FACT Measures from Baseline	Thrombo-embolic Events (%)		Deaths	
	I	D			I	D	I	D	I	D		I	D	I	D
2007[56]			lung cancer	weeks (D group – from 1st administration to end of study	± 1.0[3]										

Abbreviations: I, erythropoietic stimulant therapy begun immediately after randomizations; D, erythropoietic stimulant therapy delayed until Hb falls to threshold; EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; NR, not reported; Ran, randomized; Non, non-randomized; FACT, Functional Assessment of Cancer Therapy; ITT, intention to treat; PP, per protocol

* Statistics reported where available, **Mean (standard deviation)

[π] At screening, pts with Hb< 11g/dL not randomized, but treated immediately with EPO. Pts with Hb 11-12.0 g/dL randomized. Outcomes data for non-randomized group followed and reported "Non."

~Available in abstract form only

[1] I=erythropoietic stimulant therapy begun immediately after randomizations; D= erythropoietic stimulant therapy delayed until Hb falls to threshold; [2] transfusion data include 22 weeks follow-up as patients received chemotherapy throughout; [3] mean ± standard deviation; [4] mean ± standard error; [5]Included 7 participants who recived epo despite having Hb > 10 g/dL, † statistically significant differences; ** estimated mean based on the treatment effect using a random coefficient linear growth curve model; NS= no significant difference; NR=not reported

[b]Source: Based on original work done by: Seidenfeld J, Piper M, Bohlius J, Weingart O, Trelle S, Engert A, Skoetz N, Schwarzer G, Wilson J, Brunskill S, Hyde C, Bonnell C, Ziegler KM, Aronson N. Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment. Comparative Effectiveness Review No. 3. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center

Table S10. Trials evaluating ESAs +/– intravenous iron supplementation*

Trial	Intervention	Number Randomized		Malignancy	Hb Response** (%)		Transfused (%)		Deaths		Adverse Events (%)		Comments
		Iron	No Iron		Iron	No Iron	Iron	No Iron	Iron	No Iron	Iron	No Iron	
Pedrazzoli et al, JCO, 2008[45]	DAR-α +/- sodium ferric gluconate IV	73 PP: 53	76 PP: 50	lung, GYN, breast, colorectal	ITT: 76.7% PP: 92.5%	ITT: 61.8% PP: 70%	NR	NR	ITT: 22.1% PP: 7.5%	ITT: 3.9% PP: 6%	ITT: 9.6% PP: 13.2%	ITT: 7.9% PP: 12%	
Bastit et al, JCO, 2008[41]	DAR-α + IV iron *v* po/ no iron	201 PP: 200 Safety: 203	197 PP: 193 Safety : 203	non-myeloid	ITT: 85.6% PP: 86%	ITT: 72.6% PP: 74.1%	ITT: 16.0% PP: 16%	ITT: 25.4% ACTP: 25.4%	ITT: 10.4% Safety: 10.3%	ITT: 7.6% Safety: 7.8%	ITT: 79.1% Safety: 78.3% **VTE** ITT: 6.0% Safety: 5.9%	ITT: 81.2% Safety: 82.9% **VTE** ITT: 6.1% Safety: 6.2%	**QOL** With iron: FACT-F mean △ 2.40; Without iron: FACT-F mean △2.17
Hedenus et al, Leukemia, 2007[51]	EPO-β *v* EPO-β + IV iron	33	34	indolent NHL, CLL, or myeloma, not requiring chemotherapy	ITT: 87% PP: 93% *P* < .001 (ITT and PP)	ITT: 53% PP: 53%	ITT: 6%	ITT: 3%	ITT: 0%	ITT: 11.8%	Not reported by allocated treatment		Mean △ in Hb to end of treatment 0.99 g/dL (95% CI, 1.61to 0.37; *P* = .0023)

Abbreviations: GYN, gynecological; NR, not reported; QOL, quality of life; VTE, venous thromboembolic events; ITT, intention to treat; PP, per protocol; SAEs, serious adverse events; FACT, Functional Assessment of Cancer Therapy

* Statistics reported where available

**Response: > 12 g/dL or Hb increase > 2 g/dL without transfusions, except for Hedenus et al, where response defined as increase in Hb of ≥2.0 g/dL versus baseline without transfusion until end of treatment at week 15

Table S11. "Other" RCTs*

Author	Malignancy	Drug and Treatment Duration	Number Randomized		Hb Response Rates (%)		Transfused (%)		Thromboembolic Events (%)		Differences in FACT Measures from Baseline		Note
			Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	
Vansteenkiste, BMC, 2009[49]	non-myeloid malignancies	ARM 1: DAR-α 500 ug Q3W ARM 2: DAR-α 2.25 ug/kg QW	353 BL Hb < 10 g/dL (n=176) BL Hb ≥ 10 g/dL (n=177)	352 BL Hb < 10 g/dL (n=175) BL Hb ≥ 10 g/dL (n=177)	Hb < 10 g/dL: 54% (95% CI, 46 to 62) Hb ≥ 10 g/dL: 90% (95% CI, 85 to 94)	Hb < 10 g/dL: 57% (95% CI, 49 to 65) Hb ≥ 10 g/dL: 85% (95% CI, 79 to 90)	Hb < 10 g/dL: 44% (95% CI, 37 to 52) Hb ≥ 10 g/dL: 14% (95% CI, 8 to 21)	Hb < 10 g/dL: 47% (95% CI, 39 to 54) Hb ≥ 10 g/dL: 26% (95% CI, 18 to 33)	[v]Hb < 10 g/dL: 11 (6%; 95% CI, NR) [v]Hb ≥ 10 g/dL: 19 (11%; 95% CI, NR)	[v]Hb < 10 g/dL: 11 (6%; 95% CI, NR) [v]Hb ≥ 10 g/dL: 17 (10%; 95% CI, NR)	NR	NR	On study deaths: ARM 1: Hb < 10 g/dL: 24 (14%); Hb ≥ 10 g/dL: 14 (8%) ARM 2: Hb < 10 g/dL: 32 (18%); Hb ≥ 10 g/dL: 20 (11%) Incidence of SAEs (not nec tx-related): Hb < 10 g/dL: 48% Hb ≥ 10 g/dL: 31% (95% CI, NR)
Gupta et al, Cancr Bio Ther, 2009[43]	advanced cervical cancer (stages IIB to IIIB)	ARM 1: EPO-β 10,000 IU 3x/wk ARM 2: standard supportive care	60	60	NR	NR	PP: 15.5% ITT: 15.0%	PP: 43.9% ITT: 41.7%	0	0	NR	NR	QOL: used LASA and found difference in change scores in favor of EPO (*P* < .01). 2-year survival: ARM 1: 67%; median 21

Author	Malignancy	Drug and Treatment Duration	Number Randomized		Hb Response Rates (%)		Transfused (%)		Thromboembolic Events (%)		Differences in FACT Measures from Baseline		Note
			Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	
													months ARM 2: 65%; median 20 months 2-year DFS: ARM 1: 62% ARM 2: 60% Incidence of AEs: $P > .05$
Tsuboi et al, Jpn JCO, 2009[48]	lung cancer, malignant lymphoma	ARM 1: EPO-β 8 wks ARM 2: PLA	63	59	ITT: 41.4% PP: 42.6%	ITT: 1.7% PP: 1.8%	ITT: 11.1% PP: 11.5%	ITT: 11.9% PP: 12.5%	1.2%	0%	**FACT-Anemia**		1 yr survival from K-M: EPO 64.9%, Pla 65.9%. HR 0.94 (95% CI, 0.57 to 1.53)
											-0.5 ± 9.4	-3.6 ± 9.0	
Heras et al, Eur J Cancer Care, 2008[44]	solid tumor	ARM 1: 30,000 IU EPO-β + iron ARM 2: 20,000 IU EPO-β ≤ 12 wks + iron	30	20	78.3%	66.7%	**First 4 wks**		NR	NR	NR	NR	Survival NR
							0%	16.8%					
Volgger et al, Anticancer Res, 2008[52]	gynecological and breast cancer	ARM 1: EPO-β 10,000 IU TIW ARM 2: EPO-β 20,000 IU BIW	60	59	45%	56%	12%	15.6%	0%	15.25%[+]	**FACT-Anemia**		FACT changes are baseline to end of study; differences between arms, NS
					$P = .257$						51.2 to 55.2	55.1 to 57.3	
											FACT-G[≠]		
											18.2 to 20.7	20.9 to 21.5	
Pfeffer et al,	diabetes, chronic	ARM 1:	2,012	2,016	NR	NR	14.8%	24.5%	10.9%	8.4%	**FACT-Fatigue**		Death (any

Author	Malignancy	Drug and Treatment Duration	Number Randomized		Hb Response Rates (%)		Transfused (%)		Thromboembolic Events (%)		Differences in FACT Measures from Baseline		Note
			Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	
NEJM, 2009 ("TREAT")[46]	kidney disease, and anemia	DAR-α ARM 2: PLA (DAR "rescue" if Hb < 9.0g/dL)	**History of Malignancy**				**Entire sample** HR 0.56 (95% CI, 0.49 to 0.64) *P* < .001				**(entire sample)**		cause) among pts w/ hx of malignancy DAR-α: 60/188 PLA: 37/160
			188	160							4.2 ± 10.5	2.8 ± 10.3	
											-3.3 (26.41)	-5.2 (27.43)	*P* =.13
Greenberg et al Blood, 2009[50]	myelodysplastic syndrome	ARM 1: EPO + SC ARM 2: SC only	53	57	34%	5.8%	29%	51%	1.9%	0	No significant differences reported between arms.		OS, *P* = .28

Abbreviations: EPO-α, Epoetin α; EPO-β, Epoetin β; DAR, Darbepoetin; PLA, placebo; NS, not statistically significant; NR, not reported; OS, overall survival; SC, supportive care; FACT, Functional Assessment of Cancer Therapy

* Statistics reported where available

[+]One patient experienced a deep vein thrombosis and a pulmonary embolism

*Patients who achieved >= 11 g/dL between week 1 and end of time period

[#]FACT-G subscale: physical well-being

[v]Authors report a total of 73 thromboembolic events during study (64% [47] occurred in patients with baseline Hb ≥10 g/dL) and does not separate by dosing regimen. Table 5 of Vansteenkiste (p10) indicates 58 thromboembolic events overall, and separates by dosing regimen.

Table S12. Costs of ESAs

Medicare Plan B Average Sales Price (as of March 1, 2010)

Agent	HCPCS Code Dosage	Medicare Payment Limit ($USD)	Initial Dose[≠]	Regimen[¥]	Price Per 3-Week Cycle
Darbepoetin alfa (non-esrd)	1 µg	2.83	2.25 µg/kg SC	Weekly (SC)	$2.83 x 2.25 x (patient weight in kg) x 3
			500 µg SC	Every 3 weeks (SC)	$2.83 x 500
Epoetin alfa (non-esrd)	1000 U	9.537	150 U/kg	3 times weekly (SC)	$9.537 x (150 x (patient weight in kg) ÷ 1000) x 9
			40,000 U	Weekly (SC)	$9.537 x 40 x 3

ESA, erythropoiesis-stimulating agent; HCPCS, Healthcare Common Procedure Coding System; SC, subcutaneously; U, units

[¥]Adult dosing

[≠]Refer to Table 2 for dose modifications.

NOTE. Drug prices were estimated from a third-party payor perspective, based on reimbursement rates from the Centers for Medicare and Medicaid Services that are widely accepted by providers, computed at the manufacturer's average sales price. Other treatment-related direct and indirect costs were not considered, such as diagnostic laboratory tests. Actual treatment costs and reimbursement will vary considerably across regions, payors, institutions, and practices, as well as over time, and the reader should consult current local cost information specific to their practice setting. Costs were based on Medicare Part B payment allowance limits effective March 1, 2010 (with no administration fees or other adjustments; Medicare Part B Drug Average Sales Price: http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/01a19_2010aspfiles.asp#TopOfPage).

Table S13. MEDLINE search terms

("erythropoietin, recombinant"[MeSH Terms] OR erythropoietin, recombinant[nm] OR "erythropoiesis/drug effects"[MAJR] OR "erythropoiesis/physiology"[MAJR] OR "erythropoietin/therapeutic use"[MAJR] OR "epoetin alfa"[MeSH Terms] OR epoetin alfa[nm] OR "epoetin beta"[Substance Name] OR "darbepoetin alfa"[Substance Name] OR Aranesp[tw] OR Eprex[tw] OR Procrit[tw] OR Epogen[tw] OR Neorecormon[tw] OR "ESA"[tiab]) AND (neoplasms[mh] OR neoplas*[tw] OR tumor[tw] OR tumors[tw] OR tumour[tw] OR tumours[tw] OR malignan*[tw] OR Cancer*[tw] OR Oncolog*[tw] OR Bone marrow diseases[mh] OR myelodysplas*[tw] OR Myeloproliferat*[tw] OR Sarcoma*[tw] OR Leukemi*[tw] OR Leukaemi*[tw] OR Lymphoma*[tw] OR (Hodgkin*[tw] AND (disease[tw] OR lymphoma[tw])) OR "NHL"[tw] OR Carcinom*[tw] OR adenocarcinom*[tw] OR antineoplastic agents[mh] OR antineoplastic protocols[mh] OR chemotherapy, adjuvant[mh] OR chemotherap*[tw] OR antineoplastic*[tw] OR drug therapy, combination[mh] OR stem cell transplantation[mh] OR (("bone marrow"[tw] OR "stem cell"[tw]) AND transplant*[tw]) OR "HSCT"[tw] OR "PBSCT"[tw] OR radiotherapy[mh] OR radiotherapy[tw] OR (radiation[tw] AND (therapy[tw] OR therapeutic[tw] OR treatment[tw] OR treated[tw])) OR combined modality therapy[mh]) AND ((((clinical trial[pt] OR clinical trial, phase II[pt] OR clinical trial, phase III [pt] OR clinical trial, phase IV[pt] OR randomized controlled trial [pt] OR "multicenter study"[pt] OR controlled clinical trial [pt] OR clinical trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR "clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR evaluation studies[pt] OR "evaluation studies as topic"[mh] OR follow-up studies[mh] OR prospective studies[mh] OR cohort studies[mh] OR control[tw] OR controlled[tw] OR controls[tw] OR prospectiv*[tw] OR volunteer*[tw])) NOT (animals[mh] NOT human[mh])) OR (("systematic review*"[tw] OR "systematic literature review*"[tw] OR meta-analysis[pt] OR meta-analysis[ti] OR metaanalysis[ti] OR meta-analyses[ti] OR evidence-based medicine[tw] OR (evidence-based[tw] OR evidence based[tw] AND (guideline[tw] OR guidelines[tw] OR recommendation*[tw])) OR consensus development conference[pt] OR health planning guidelines[tw] OR guideline[pt] OR practice guideline[pt] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR evid based dent[ta] OR evid based nurs[ta] OR evid based ment health[ta] OR clin evid[ta]) OR ((systematic[tw] OR systematically[tw] OR critical[tw] OR (study[tiab] AND selection[tiab]) OR (predetermined[tw] OR inclusion[tw] AND criteri*[tw]) OR exclusion criteri*[tw] OR "main outcome measures"[tw] OR "standard of care"[tw]) AND (survey[tw] OR surveys[tw] OR overview*[tw] OR review[tw] OR reviews[tw] OR search*[tw] OR (handsearch[tw] OR hand search[tw]) OR analysis[tw] OR critique[tw] OR appraisal[tw] OR (reduction[tw] AND risk[tw] AND (death[tw] OR recurrence[tw]))) AND (literature[tw] OR articles[tw] OR publications[tw] OR publication[tw] OR bibliography[tw] OR bibliographies[tw] OR published[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tw] OR internet[tw] OR textbooks[tw] OR references [tw] OR trials [tw] OR meta-analysis [mh] OR (clinical [tw] AND studies [tw]) OR treatment outcome[tw])) NOT (case report[ti] OR editorial[ti] OR editorial[pt] OR letter[pt] OR newspaper article[pt]))) NOT (animals[mh] NOT human[mh])) AND English[lang] AND ("2007/01/01"[PDAT] : "2010/01/31"[PDAT])