

**SUPPLEMENT TO BACKGROUND INFORMATION**

**FOR THE**

**ONCOLOGIC DRUGS ADVISORY COMMITTEE**

**13 March 2008**

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Procrit<sup>®</sup>/Epogen<sup>®</sup> (Epoetin alfa)**

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**List of Abbreviations**

BEST	Breast Cancer Erythropoietin Survival Trial (Study EPO-INT-76)
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
HR	hazards ratio
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development, LLC
LTFU	long-term follow up
NSCLC	non-small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee
OR	odds ratio
PRO	patient-reported outcomes
RR	relative risk
SCLC	small-cell lung cancer

This document provides supplemental information to the briefing material provided by Amgen Inc. and Johnson & Johnson Pharmaceutical Research & Development, LLC (J&JPRD) for the United States Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) meeting to be held on 13 March 2008.

**1. Section 3.3.2 (Impact of ESAs on Symptoms of Anemia)**

Section 3.3.2 (Impact of ESAs on Symptoms of Anemia) of the meeting briefing document references studies that have suggested a relationship between treatment of anemia with ESAs and corresponding improvements in anemia-related symptoms and fatigue/energy. These studies are tabulated in Appendix 2 of the briefing document. As a point of clarification, information on the dates that data from these studies were submitted to FDA is provided in [Supplement Table 1](#). It is emphasized that the submitted studies do not meet FDA's current standards for the registration of patient-reported outcome (PRO) endpoints, although they do support labeling in other countries and have been incorporated into treatment guidelines.

**Supplement Table 1. Effect of Epoetin Alfa Treatment on Symptoms of Anemia in Patients Receiving Cancer Chemotherapy (Summary of Results From 5 Studies)**

Study/Tumor Type	Epoetin Alfa Dose Regimen	Treatment Groups	Measures	Results	General Comments	Data submitted to FDA
<a href="#">Case et.al, 1993/ Varied</a>	150 IU/kg SC TIW x 12 weeks	Non-cisplatin or Cisplatin + EPO (n=63) or placebo (n=61)	LASA-Energy, Daily Activities and Overall QOL	ESA-treated patients had significant improvements in Energy and Daily Activities (P<0.05), and Overall QOL (P=0.083) as compared to baseline values	No intergroup comparisons between EPO-treated and placebo groups conducted	CSR 7/30/92 (PLA 103234) Datasets 7/30/92
<a href="#">Littlewood et.al. 2001/Varied</a>	150 IU/kg SC TIW x 6 cycles + 4 wk post-CT	Nonplatinum + EPO (n=238) or placebo (n=111)	LASA Energy, Daily Activities, Overall QOL, FACT-G, FACT-F, FACT-An, SF-36	ESA-treated patients had significant improvements in LASA Energy P<0.001, Daily Activities P<0.01, Overall QOL P=0.01, FACT-G P<0.05, FACT F P<0.01, FACT-An P<0.01, SF-36 NS	Adjustments for covariates not included.	CSR 2/11/08 Dataset 2/11/08 CSR 12/20/07 CSR 10/11/02 Datasets 10/11/02
<a href="#">Chang et.al, 2005 / Breast</a>	40K SC QW x 16 weeks (QOL at 12 weeks)	Nonplatinum+ EPO 40K QW (n=168), or SOC (n=170)	FACT-An, FACT-F, LASA Energy, Daily Activities, Overall QOL	ESA-treated patients had significant improvements in FACT-An and FACT-F P<.0001; LASA Energy P<.014, Daily Activities P<.01, Overall QOL P<.001		CSR 2/4/08 Dataset 2/4/08 CSR 3/28/07 SN 1265 Datasets 3/28/07 SN 1265
<a href="#">Thatcher et.al, 1999/ SCLC</a>	150 IU/kg SC TIW X 6 cycles or 300 IU/kg SC TIW x 6 cycles	Platinum or Nonplatinum+EPO 150 IU TIW (n=42),EPO 300 TIW (n=44), or SOC (n=44)	LASA Energy, Daily Activities, Overall QOL, WHO Performance Score	Significant improvements in overall QOL P<0.05 for EPO 150 IU/kg group. All others NS	Open label design	N/A
<a href="#">Witzig et.al. 2005/ Varied</a>	40K SC QW x 16 weeks	Platinum or Nonplatinum+ EPO (n=154) or placebo (n=151)	LASA Overall QOL, FACT-An, Symptom Distress Scale	ESA-treated patients had significant improvements in LASA Overall QOL P=0.27, FACT-An P=0.18, SDS NS	QOL higher in placebo group at baseline. Effect of increased transfusion rate in placebo group on Hb could have masked true QOL differences between groups.	CSR 8/29/03 Datasets 8/29/03 (BLA 103234)

CT=chemotherapy; EPO=epoetin alfa; FACT= Functional Assessment of Cancer Therapy; FACT-AN = FACT-anemia; FACT-F=FACT=fatigue; FACT-G= FACT-general; Hb=hemoglobin; LASA=linear analog self-assessment; NS=not significant; SC=subcutaneous; SOC=standard of care; QOL=quality of life; QW=once weekly SCLC=small-cell lung cancer; SDS=Symptom Distress Scale; SF-36; TIW=3 times weekly; 40K=40,000 IU

## 2. Table 2 (Safety Data of Concern)

For the BEST study, it is noted that Table 2 in the briefing document includes overall survival data based on the 12-month timepoint (the primary endpoint of the study) as well as data based on a protocol-specified long-term follow-up analysis (after 75% of subjects had died). The companies believe it is necessary to include all data from the BEST study so that the results may be evaluated in a comprehensive manner.

However, it is acknowledged that the long-term follow-up data may be confounded by post-study chemotherapy or the “crossover” of subjects in the control group to receive ESAs.

For the EPO-CAN-20 study, it is noted that Table 2 of the briefing document includes data that differs from that in the current product labeling. The data in Table 2 are based on the final analysis of 70 subjects rather than the Data Safety Monitoring Committee analysis of 66 subjects that led to discontinuation of the study (which is included in the product labeling).

For Amgen Study 20010103, it is noted that the hazards ratio (HR) for overall survival differs from that in the current product labeling. The HR (darbepoetin alfa vs placebo) for overall survival in the product labeling (1.30, 95% CI: 1.07, 1.57) corresponds to the analysis based on the original cutoff date for the Study 20010103 clinical study report (07 November 2006). The HR presented in Table 2 of the briefing document (1.22; 95% CI: 1.03, 1.45) corresponds to a later analysis of a more complete dataset that included updated survival data from the optional rollover protocol (Study 20020149), in which subjects could receive an additional 16 weeks of their originally assigned blinded treatment (darbepoetin alfa or placebo) ([Smith et al, 2008](#)).

For study GOG-191, it is noted that subjects received chemoradiotherapy, not chemotherapy alone.

## 3. Table 3 (Other Informative Controlled Clinical Studies) and Table 4 (Additional Controlled Studies)

The following clarifications to Table 3 in the briefing document are noted:

- FR-2003-3005 (GELA): Subjects in the control arm were allowed to receive ESAs for symptomatic anemia.
- Study 20030232: Follow-up for deaths was 19 weeks.

- EPO-GBR-7: Data were presented in the 10 May 2007 ODAC briefing document.
- RTOG-99-03: Subjects could receive radiotherapy or chemoradiotherapy.
- EPO-GER-22: Data were presented at the German Medical Sciences meeting in 2006 (Debus et al, 2006).
- EPO-GER-8/AGO-NOGGO: Subjects received sequential chemotherapy and radiotherapy.

In Table 4 of the briefing document, it is noted that data for Study EPO-CAN-15 have been published in abstract format ([Goss et al, 2005](#)).

The timeline for submission of outstanding clinical data considered to be potentially informative was shared with the May 2007 ODAC and with FDA in August 2007. All of these data have now been provided to FDA. The companies acknowledge that FDA has not had time to review all of these data given the timing of the current ODAC. Thus, Tables 3 and 4 of the briefing document have been modified to include only published or publicly presented data ([Supplement Table 2](#) and [Supplement Table 3](#)).

**Supplement Table 2. Other Informative Controlled Clinical Studies**

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Data Reported to FDA
20010145 <a href="#">Pirker et al, 2007</a> (Amgen) Postmarketing commitment	Extensive stage SCLC receiving chemotherapy (n = 600)	Randomized, double-blind, placebo-controlled	13 g/dL	At median follow-up of 2.5 years, ESA and placebo had similar PFS: HR 1.02; 95% CI: 0.86, 1.21  and overall survival: HR 0.93; 95% CI: 0.78, 1.11	Report and datasets 10/07
FR-2003-3005 LNH03-6B <a href="#">Delarue et al, 2006; ODAC Briefing Materials, 2007</a> (GELA) Postmarketing commitment	Diffuse Large B-cell Lymphoma receiving chemotherapy (n = 458/660 planned)	Randomized, controlled open-label (control group was allowed to receive ESA for symptomatic anemia)	13 to 15 g/dL initially  11 to 13 g/dL in protocol amendment	At 1 year, ESA and control groups had similar overall survival (78% vs 70%)  RR 0.75; 95% CI: 0.44, 1.76  and event-free survival (73% vs 64%) RR 0.75; 95% CI: 0.44, 1.26	N/A (study ongoing)
980297 <a href="#">Vansteenkiste et al, 2002; ODAC Briefing Materials, 2007</a> (Amgen)	SCLC and NSCLC receiving chemotherapy (n = 314)	Randomized, double-blind, placebo-controlled	13 to 14 g/dL (women)  13 to 15 g/dL (men)	After median follow-up of ~8 months, ESA and control had similar overall survival: HR 0.77 (95% CI: 0.59, 1.01)  and PFS HR 0.79 (95% CI: 0.62, 1.00)	Report and datasets 4/05  Long-term follow-up datasets 3/07
20030232 <a href="#">Taylor et al, 2005</a> (Amgen)	Nonmyeloid malignancy, receiving chemotherapy (n = 391)	Randomized, double-blind, placebo-controlled	11 to 13 g/dL	ESA and placebo groups had similar incidence of on-study death (9% ESA, 10% placebo); total follow-up was 19 weeks.	Report 8/06 Datasets 3/07

<sup>a</sup> Study terminated early

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**Supplement Table 2. Other Informative Controlled Clinical Studies**

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Data reported to FDA
EPO-GER-7 <a href="#">Möbus et al, 2007</a> (AGO)	Breast cancer receiving adjuvant chemotherapy (n = 643)	Randomized, controlled, open-label	12.5 to 13 g/dL	At median follow-up of 62 months, ESA and control groups had similar disease-free survival (72% vs 71%; p = 0.86) and overall survival (81% vs 83%; p = 0.89)	Report and datasets 2/08
EPO-GBR-7 <a href="#">ODAC Briefing Materials, 2007</a> (J&JPRD)	Head and neck cancer receiving radiation alone (n = 301) <sup>a</sup>	Randomized, controlled, open-label	12 g/dL withheld > 15 g/dL and restarted at < 14.5 g/dL at 50% of dose	1-year survival similar between ESA and control: (77.3% ESA, 79.9% control) p = 0.867	Report 1/08 Datasets 2/08
N93-004 <a href="#">Grote et al, 2005</a> (J&JPRD)  Postmarketing commitment	SCLC receiving chemotherapy (n = 224)	Randomized, double-blind, placebo-controlled	14 to 16 g/dL	3-year mortality similar between ESA and placebo: (91.7% ESA, 87.8% placebo)  Final overall tumor response similar between groups: (60% ESA, 56% placebo)	Report and datasets 10/02
EPO-CAN-17 <a href="#">Chang et al, 2005</a> (J&JPRD)	Breast cancer receiving chemotherapy (n = 354)	Randomized, controlled, open-label	12 to 14 g/dL	Deaths similar between ESA and control (24 deaths ESA, 27 deaths control)	Report and datasets 2/08

<sup>a</sup> Study terminated early

**Supplement Table 2. Other Informative Controlled Clinical Studies**

Study Designation(s) (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Data reported to FDA
RTOG-99-03 <a href="#">Machtay et al, 2007</a> (J&JPRD)	Head and neck, radiotherapy or chemo-radiotherapy (n = 148) <sup>a</sup>	Randomized, controlled, open-label	13.5 to 16 g/dL (men) 12 to 14 g/dL (women)	3-year mortality similar between ESA and placebo (56% ESA, 57% control) 3-year locoregional PFS similar between ESA and placebo (47% ESA, 52% control)	Report 1/08 Datasets 2/08
EPO-GER-22 (J&JPRD) <a href="#">Debus et al, 2006</a>	Inoperable Stage III NSCLC receiving chemotherapy (n = 385) <sup>a</sup>	Randomized, controlled open-label	13 g/dL initially <12 g/dL (withhold at > 13 g/dL, resume at < 12 g/dL) in amendment	Median survival time was similar for ESA (338 days) and control (299 days): p = 0.61	Report 2/08 Datasets 2/08
EPO-GER-8/ AGO-NOGGO <a href="#">Blohmer et al, 2004</a> (AGO)	High risk cervical cancer receiving sequential chemotherapy and radiotherapy (n = 250)	Randomized, controlled, open-label	13 to 14 g/dL	Relapse or death events: 19 ESA vs 31 control Deaths: 16 ESA vs 23 control	Report and datasets 02/08

<sup>a</sup> Study terminated early

**Supplement Table 3. Additional Controlled Studies**

Study Designation(s) Publication (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Data reported to FDA
HD-15 <a href="#">Engert, 2007</a> (GHSG)	Advanced Hodgkin's lymphoma receiving chemotherapy (n = 688/1500 planned)	Randomized, double-blind, placebo- controlled	During chemotherapy period: 12 to 14 g/dL initially (13 g/dL in protocol amendment)  After chemotherapy: ≤12 g/dL	Interim data from 688 subjects:  30-month overall survival similar (ESA vs control): OR 1.21; 95% CI: 0.32, 4.55  30-month freedom-from-treatment failure similar between ESA and control	N/A (study ongoing)
BRAVE <a href="#">Aapro et al, 2008</a> (Hoffman La Roche)	Metastatic breast cancer receiving chemotherapy (n = 463)	Randomized, controlled, open-label	ESA withheld at ≥ 15 g/dL and reinstated at < 13 g/dL	After 18 months, ESA and control groups had similar overall survival HR 1.07; 95% CI 0.87, 1.33; p = 0.522  and PFS HR=1.07; 95% CI 0.89, 1.30; p = 0.448.	N/A (Amgen or J&JPRD does not have access to data)
EPO-CAN-15 <a href="#">Goss et al, 2005</a> (J&JPRD)	Limited disease SCLC receiving chemotherapy (n = 104)	Randomized, double-blind, placebo- controlled	ESA treated patients 12 to 14 g/dL	No significant difference in time to progression (p = 0.8291) or overall survival (p = 0.2260) between ESA and placebo.	Report and datasets 02/08

**Supplement Table 3. Additional Controlled Studies**

Study Design(s) Publication (Sponsor)	Tumor type (n)	Study Design	Hemoglobin Target	Published Results for Survival and/or Disease Progression	Data reported to FDA
EPO-INT-45 <a href="#">Wilkinson et al, 2006</a> (J&JPRD)	Ovarian cancer receiving chemotherapy (n= 182)	Randomized, controlled, open-label	12 to 14 g/dL	At the end of treatment, investigator assessed tumor evaluation in the 2 groups was similar for complete response, partial response, or no response.  More patients had progressive disease in the ESA group versus control (11.4% versus 1.7%, respectively), but the difference was not statistically significant p=0.425).  Three patients (in the ESA group) died during the study.	Study summary and datasets 2/08
EPO-INT-47 <a href="#">Pronzato et al, 2002</a> (J&JPRD)	Breast cancer receiving chemotherapy (n = 220)	Randomized, controlled	12 g/dL to 14 g/dL	No differences between ESA and control groups in tumor response or overall survival	Study summary and datasets 2/08
EPO-INT-49 <a href="#">Milroy et al, 2003</a> (J&JPRD)	NSCLC (stage IIIb, IV) receiving chemotherapy (n = 424)	Randomized, controlled	≤ 15 g/dL (men) ≤ 14 g/dL (women)	No differences in survival between treatment groups	Study summary and datasets 2/08

#### 4. Section 4.4 (Updated Overall Assessment of Risk)

##### Clarification of Statistical Methods

In the updated study-level meta-analysis of mortality, which was based on the methods used in the Cochrane Collaboration report ([Bohlius et al, 2006](#)), it is noted that studies where ESAs may have been administered to the control arm as part of standard medical care were excluded (eg, GELA; [Strauss et al, 2007](#)). In general, small studies ( $\leq 10$  subjects per study arm) were excluded. Since the published data inconsistently reported results (a mix of percentages, number of events, and in rare cases, odds ratio [OR], relative risk [RR], or HR estimates), the OR was selected as the summary measure after consultation with an external expert in meta-analyses; these were generated using the Comprehensive Meta Analysis (V2) software. This varied from the Cochrane Collaboration approach, which reported either the Peto OR or a combination of reported and estimated HRs.

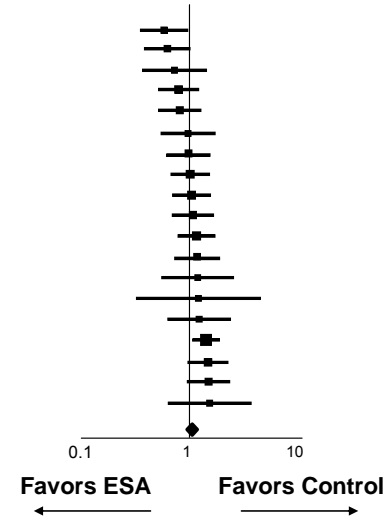
While Amgen and J&JPRD have conducted these meta-analyses to further evaluate the nature and consistency of the safety signals that have been observed, the companies acknowledge that results of meta-analyses should not minimize the safety concerns raised by individual studies. These meta-analyses are, however, useful for summarizing the most recent data across studies and evaluating these safety concerns within the context of the overall available data.

##### Meta-analyses Using the BEST 1-year Data

In the meta-analyses presented in the briefing document, the long-term follow-up data from the BEST study were used for consistency with the other studies included in the analysis, with results using the 1-year data provided in text and in footnotes. For completeness, these meta-analyses are provided below using the 1-year data rather than the long-term follow-up data ([Supplement Figure 1](#) and [Supplement Figure 2](#)). Sensitivity analyses have been done that use the long-term follow-up data for the BEST study rather than the 1-year data for that study.

**Supplement Figure 1. Study-level Meta-analysis of Overall Death  
 19 CIA Studies (including 3 Chemoradiotherapy\*) with LTFU  
 (n = 8071; 4149 ESA, 3922 Control)**

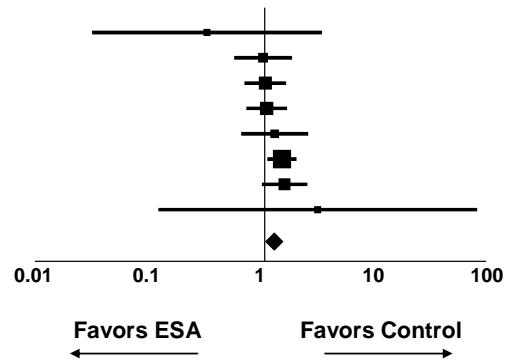
Study name	Odds ratio	95% CI	
		Lower limit	Upper limit
* EPO-GER-022	0.58	0.35	0.96
Vansteenkiste (AMG 980297)	0.62	0.38	1.01
* Blohmer (AGO-NOGGO)	0.73	0.37	1.44
Pirker( AMG 20010145)	0.79	0.52	1.21
Littlewood	0.81	0.52	1.28
Chang 2005 (EPO-CAN-17)	0.97	0.55	1.73
Witzig 2005	0.98	0.62	1.55
Aapro 2006 (BRAVE)	1.02	0.67	1.53
Mobus	1.05	0.70	1.57
Osterborg 2005	1.08	0.69	1.67
Milroy (INT-49)	1.16	0.79	1.72
Savonije 2005	1.18	0.73	1.90
* Thomas (GOG-0191)	1.19	0.55	2.56
Engert 2007 (HD 15 IA)	1.21	0.32	4.55
Prozanto (INT-47)	1.23	0.63	2.39
Leyland-Jones (1 year ITT)	1.42	1.07	1.90
Hedenus 2003 (AMG 20000161)	1.48	0.97	2.27
PREPARE	1.50	0.96	2.36
Grote 2005 (N93-004)	1.54	0.64	3.72
<b>Random Effects Model</b>	<b>1.04</b>	<b>0.92</b>	<b>1.19</b>



I<sup>2</sup> = 27.5%; Fixed Effects Model = 1.06 (0.95, 1.18)  
 If 1-year BEST data are used, the Overall I<sup>2</sup> = 12.3%; Random Effects Model = 1.00 (0.89, 1.12) with Fixed Effects Model = 1.00 (0.89, 1.11)  
 \*: CTx RTx studies

**Supplement Figure 2. Study-level Meta-analysis of Overall Death  
 8 Breast Cancer Studies (n = 3517; 1748 ESA, 1769 Control)**

Study name	Odds ratio	95% CI	
		Lower limit	Upper limit
Del Mastro	0.31	0.03	3.17
Chang 2005 (EPO-CAN-17)	0.97	0.55	1.73
Aapro 2006 (BRAVE)	1.02	0.67	1.53
Mobus	1.05	0.70	1.57
Prozanto (INT-47)	1.23	0.63	2.39
Leyland-Jones (1 year ITT)	1.42	1.07	1.90
PREPARE	1.50	0.96	2.36
O'Shaughnessy 2005	2.94	0.12	73.93
<b>Random Effects Model</b>	<b>1.22</b>	<b>1.03</b>	<b>1.45</b>



**Includes BEST 1-year Data**

I<sup>2</sup> = 0%; Fixed Effects Model = Random Effects Model  
 If 1-year BEST data are used, the Overall I<sup>2</sup> = 0%; Random Effects Model = Fixed Effects Model = 1.04 (0.88, 1.24)  
 Meta Analysis Using OR

**Sensitivity Analyses:**

Excluding O'Shaughnessy (weight < 1%): OR 1.22 (1.03, 1.44)  
 Excluding O'Shaughnessy and Del Mastro (combined weight < 1%): OR 1.23 (1.03, 1.46)

### Meta-analyses Using Different Statistical Methods

To address concerns regarding use of the OR as a point estimate for meta-analyses, primary data from 16 Amgen and J&JPRD studies in CIA in which long-term ( $\geq 6$  months) follow-up information was collected were combined and HRs were calculated for each study and across all studies combined (with study as a stratification factor) using an unadjusted Cox proportional hazards model. Primary data were not available for 3 studies included in the original analysis in the briefing document and thus could not be included in this patient-level analysis ([Engert, 2007](#) [HD-15]; [Österborg et al, 2005](#); and [Aapro et al, 2008](#)); details of these studies are provided in [Supplement Table 4](#).

**Supplement Table 4. Studies Excluded from the Patient-level Analysis**

	Estimated OR (original analysis)	Available data	Values in Sensitivity Analysis 3
Aapro 2008	1.02 (0.67, 1.53)	HR; # events	1.07 (0.87, 1.33)
Engert 2007 (HD-15)	1.21 (0.32, 4.55)	# events	1.21 (0.32, 4.49)*
Österborg 2005	1.08 (0.69, 1.67)	HR; # events	1.04 (0.80, 1.36)

\*recalculated

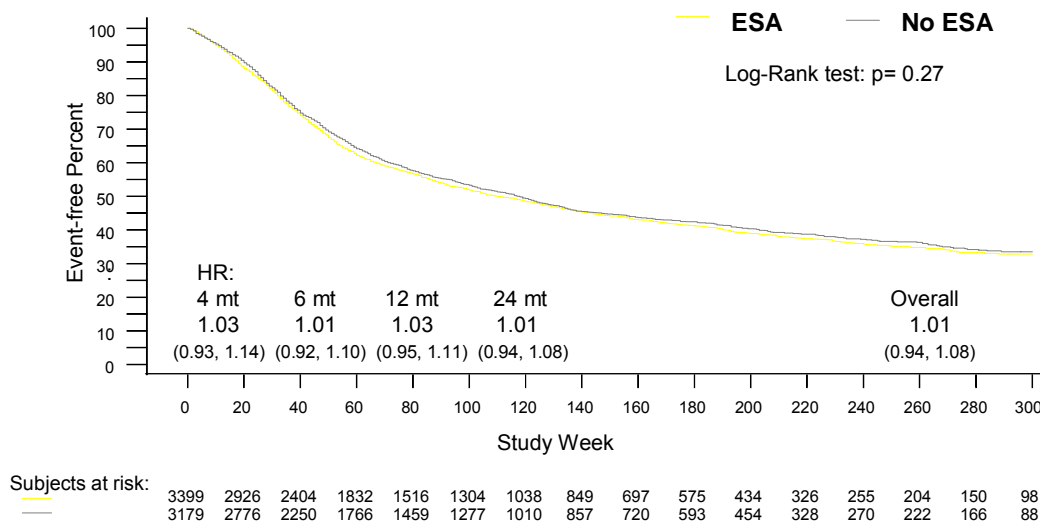
However, since HRs were provided in the published manuscripts for two of these studies, additional sensitivity analyses including the published HRs for [Aapro et al \(2008\)](#) and [Österborg et al \(2005\)](#) were done (including and excluding data from HD-15). In addition, sensitivity analyses were done using both the primary 1-year survival data from the BEST study as well as using additional information collected during the longer-term follow-up period for that study. The results of these multiple sensitivity analyses are provided in [Supplement Table 5](#). The estimates summarizing results across studies appear to be consistent. The small variations observed are unlikely to change any conclusions that may be drawn from these data.

**Supplement Table 5. Sensitivity Analysis for CIA studies with LTFU Using Different Statistical Approaches**

# studies	Metaanalysis Type	Summary Estimate Used	Point Estimate (random effects)	95% CL
<b><i>Analyses using BEST 12-month data</i></b>				
19	Study-level	OR	1.04	0.92, 1.19
19	Study-level	HR for 18; OR for 1 study (Engert)	1.04	0.96, 1.13
18	Study-level	HR (excludes Engert)	1.04	0.95, 1.14
16	Study-level	OR	1.04	0.89, 1.21
16	Study-level	HR	1.04	0.94, 1.15
16	Patient-level	HR (censors BEST at 1 year)	1.03	0.95, 1.11
<b><i>Analyses using BEST LTFU data</i></b>				
19	Study-level	OR (BEST LTFU)	1.00	0.89, 1.12
19	Study-level	HR for 18 (BEST LTFU); OR for 1 study (Engert)	1.02	0.95, 1.10
18	Study-level	HR (BEST LTFU) (excludes Engert)	1.02	0.95, 1.10
16	Study-level	OR	0.99	0.86, 1.14
16	Study-level	HR	1.01	0.93, 1.11
16	Patient-level	HR	1.01	0.94, 1.08

The Kaplan-Meier plot of the patient-level analysis of CIA studies with long-term follow up is provided in [Supplement Figure 3](#), with HR estimates for time to death at 4 months, 6 months, 12 months, 24 months, and overall.

**Supplement Figure 3. Time to Death Including LTFU  
 (Patient-level Analysis of 16 CIA Studies with LTFU)**



The median time (95% CI) to death including long-term follow up in weeks was 110 (101, 1 23) for ESA and 118 (108, 125) for No ESA.

### Meta-analyses Excluding Smaller Studies With Few Events

To address concerns related to the inclusion of studies with either a small sample size or few events, sensitivity analyses including or excluding the results of smaller studies are provided using the breast cancer meta-analysis as an example. It should be noted that there is only a minimal impact to the summary point estimates when smaller studies that contribute little weight overall are excluded. In addition, the measures of statistical heterogeneity of findings across trials (eg,  $I^2$ ) do not indicate more than a very modest degree of statistical heterogeneity when results of these smaller studies are included in the analysis.

The originally presented meta-analysis of breast cancer studies (Figure 8 in the briefing document) included 8 studies identified using the study selection criteria. The exclusion of smaller studies (ie, O'Shaughnessy et al, 2005, Del Mastro et al, 1997) does not change the summary estimate since the weights for these studies are low (in this case, ie, <1 % for each study), as shown in Supplement Table 6.

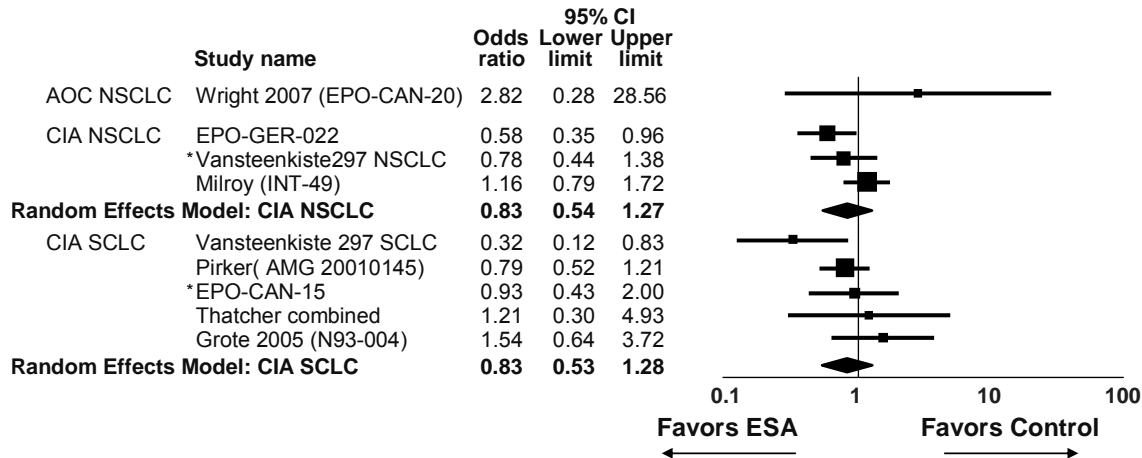
**Supplement Table 6. Sensitivity Analysis for Studies of Breast Cancer Patients Including or Excluding Smaller Study Results**

	BEST 1-Year estimate		BEST LTFU estimate	
	OR	95% CL	OR	95% CL
OR (8 studies):	1.22	(1.03, 1.45)	1.04	(0.88, 1.24)
OR excluding O'Shaughnessy	1.22	(1.03, 1.44)	1.04	(0.88, 1.24)
OR excluding O'Shaughnessy and Del Mastro	1.23	(1.03, 1.49)	1.05	(0.88, 1.25)

**Meta-analysis of Lung Cancer Studies**

As the meta-analyses of overall death in lung cancer included subjects with small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), an updated forest plot is provided by specific tumor type and treatment setting (Supplement Figure 4). It is noted that in Supplement Figure 4, the SCLC and NSCLC subsets are analyzed separately for Study 980297.

**Supplement Figure 4. Study-level Meta-analysis of Overall Death 8 Lung Cancer Studies (n = 2247; 1143 ESA, 1104 Control)**

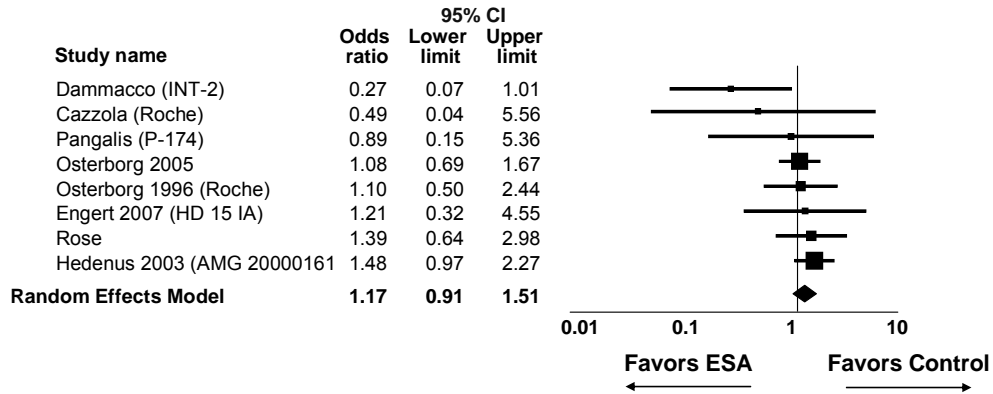


For CIA NSCLC: I<sup>2</sup> = 57.6%; Fixed Effects Model = 0.87 (0.66, 1.14)  
 For CIA SCLC: I<sup>2</sup> = 34.4%; Fixed Effects Model = 0.82 (0.60, 1.12)  
 Overall I<sup>2</sup> = 32.9%; Random Effects Model = 0.85 (0.62, 1.15); Fixed Effects Model = 0.85 (0.70, 1.05)  
 Meta Analysis Using OR  
 \* = Radiochemotherapy study

**Meta-analysis of Lymphoid Malignancy Studies**

Figure 10 in the briefing document has been updated to include more recent data (Supplement Figure 5).

**Supplement Figure 5. Study-level Meta-analysis of Overall Death  
 9 Lymphoid Tumor Studies (n = 2142; 1205 ESA, 937 Control)**



I<sup>2</sup> = 0.0%; Fixed Effects Model = Random Effects Model  
 Meta Analysis Using OR  
 1 study (Hedenus AMG 990114; not plotted) had no deaths in either group

**Head and Neck Cancer Studies**

In Section 4.4.4 (ESA Safety in Specific Cancers, Head and Neck Cancer), it should be noted that RTOG-9903 was discontinued by the Data Monitoring Committee after an unplanned interim analysis indicated a non-significant trend toward lower locoregional control and an imbalance in survival favoring the control group.

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