# Epoetin Beta (NeoRecormon®) Therapy in Patients with Solid Tumours Receiving Platinum and Non-platinum Chemotherapy: a Meta-analysis

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**Abstract.** *Background: Anaemia is a common complication of chemotherapy (CT), including both non-platinum (Pt)-based as well as Pt-based CT. Patients and Methods: Patients from three controlled trials with solid tumours receiving either Pt- or non-Pt-based CT, who had been randomised to epoetin beta treatment or standard care, were included in this meta-analysis (n=255, n=199, respectively), to see if epoetin beta was equally effective in both CT types. The primary end-point was haemoglobin (Hb) change. Secondary end-points included transfusion requirement, adverse events (AEs), survival, time to tumour progression and thromboembolic events (TEEs). Results: All patients responded rapidly to epoetin beta treatment, showing a median Hb increase of ≥1 g/dl from baseline at week 4. A median Hb of 12.2, 12.5 and 11.8 g/dl was achieved in all patients, those receiving Pt-based CT and those receiving non-Pt-based CT, respectively, after 16 weeks of treatment. Transfusion risk reductions associated with epoetin beta treatment of 53% (p<0.0001), 61% (p<0.0001) and 26% (non significant) were observed for all patients, Pt- and non-Pt-based CT patients, respectively. Overall, for all three populations, there were no risks identified for tumour progression or overall survival. There was a statistically non-significant incidence of TEEs (5.9% versus 4.5%) and no marked differences were observed between groups for frequency or type of AEs reported. Conclusion: The type of CT has no impact on the ability of epoetin beta to rapidly increase Hb in patients with solid tumours and CT-induced anaemia.*

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Patients with cancer often experience anaemia as a consequence of the malignancy or resulting from the myelosuppressive effects of the chemotherapy (CT) they receive. A recent survey revealed that 75% of patients with solid or lymphoid malignancies who received chemotherapy were anaemic (1). Anaemia is particularly common in patients who receive platinum (Pt)-based CT, which has led to a vast amount of research into the use of recombinant human erythropoietin (rHuEPO) in patients receiving this type of CT. However, anaemia is not exclusive to patients receiving Pt-based CT and is, in fact, a common complication of all forms of CT (2).

Anaemia may be temporarily corrected by red blood cell (RBC) transfusions; although these are usually reserved for patients with severe anaemia (haemoglobin [Hb] <8 g/dl). Also, RBC transfusions are inconvenient and not without complication, so that the introduction of rHuEPO has improved the way in which anaemia is managed in patients with cancer. Recently published guidelines from the European Organization for Research and Treatment of Cancer (EORTC) advocate early treatment of cancer-associated anaemia with erythropoietic proteins at Hb levels of 9–11 g/dl (3). The guidelines also suggest that the aim of rHuEPO treatment should be to increase Hb levels to a target range of 12–13 g/dl and then continue treatment so that Hb is maintained at this level. Maintaining Hb levels of between 11 g/dl and 13 g/dl has been shown to correlate with a maximum benefit in quality of life (QoL) for the patient (4).

Table I. *Details of studies included in the meta-analysis.*

| Study | Study design | Diagnosis | No. of patients included inanalysis (epoetin beta/control) | Epoetin beta dosage | Control | Duration |
|---|---|---|---|---|---|---|
| ten Bokkel Huinink *et al.,* 1998 (9) | R O PG; 3-arm | Ovarian cancer; anaemia (Hb <13 g/dl) | 83/37 | 150 or 300 IU/kg body weight 3 x weekly | Standard therapy only | 6 months |
| Oberhoff *et al.,* 1998 (8) | R PG | Solid organ tumours; anaemia (Hb <11 g/dl) | 114/104 | 5,000 IU daily | Standard therapy only | 12 24 weeks |
| Boogaerts *et al.,* 2003 (13) | R O PG | Malignant disease; anaemia (Hb <11 g/dl) | 131/128 | 150 IU/kg body weight 3 x weekly; adjusted according to Hb | Standard therapy only | 12 weeks |

R=randomised; PG=parallel-group; O=open label; Hb=haemoglobin.

Many patients with solid and lymphoid tumours, receiving either Pt-based or non-Pt-based CT, have benefited from treatment with erythropoietic agents (5-15). Epoetin beta has been shown to improve Hb levels rapidly and effectively, reduce RBC transfusion requirements and improve QoL in patients with solid and haematological malignancies (8, 9, 11, 13-15).

None of these studies have shown by direct comparison how Pt-based and non-Pt-based CT affect the efficacy of rHuEPOs. However, a study by Abels *et al.* (16) showed that patients receiving epoetin were likely to respond, by a change in haematocrit, in a similar manner whether receiving cisplatin CT, non-cisplatin CT or no CT. In addition, a retrospective sub-analysis of the studies by Glaspy *et al.* (17) and Demetri *et al.* (7) showed increases in Hb, reduction in RBC transfusion requirement and improvements in QoL, regardless of the CT in patients with solid and haematological malignancies (17).

This meta-analysis investigated whether there is any difference in efficacy resulting from the CT type (Pt-CT *versus* non-Pt-CT), using the pooled results of three controlled clinical trials (8, 9, 13) in patients with solid tumours treated with epoetin beta.

## Patients and Methods

The data were pooled from three controlled clinical studies of epoetin beta (NeoRecormon®; performed by F. Hoffmann-La Roche or Boehringer Mannheim) and included in this meta-analysis. A summary of the studies included in the analysis is provided in Table I. In these studies, patients were randomised to epoetin beta treatment or standard care. Data on all randomised, controlled patients with solid tumours and undergoing CT were included in the analysis. Only those epoetin beta patients who had received at least one dose of study medication were included in the analysis. Patients were assigned to treatment groups according to the treatment actually received.

Patients in the control group were treated according to standard care, which included RBC transfusions. In one study (8), 29 patients received standard care in the first treatment phase and were allowed to cross over to epoetin beta in the second phase. These patients were censored at the time of initiation of epoetin beta treatment (day 84).

*Efficacy measures.* In all three studies, Hb was measured at regular intervals and at the same time-points in both the epoetin beta and control groups. Assessment of Hb was the primary end-point of the current analysis. Baseline Hb was defined as the mean of all available Hb values prior to baseline. For other analyses, baseline was defined as the time of the first dose of epoetin beta in the epoetin beta treatment group or the day of randomisation for the control group.

Transfusions were carefully recorded in all studies as part of the efficacy analysis. For this analysis, patients who did not receive a transfusion were censored at the last entry in the drug log or the last visit date (as defined by the last available Hb value) plus 28 days, in the knowledge that transfusions taking place in this time frame would have also been recorded.

For the assessment of secondary end-points such as survival, time to tumour progression and time to thromboembolic events (TEEs), no further follow-up was performed beyond study treatment plus a standard 28-day follow-up period, during which serious adverse events (AEs) including deaths were recorded. Deaths reported outside this period were not included in the analysis. In order to assess the time to malignancy progression retrospectively, all AEs were carefully reviewed for signs of progression with reviewers blinded to the treatment assignment. The onset date of the earliest of these events was used as the time of the first sign of tumour progression. Events were included in the analysis if observed during the study treatment or during the standard 28-day follow-up period. Patients without events were censored as they were for survival, at the time of last entry into the drug log plus 28 days.

All AEs reported during the treatment period and for a further 28 days were included in the assessment.

*Statistical analysis.* For statistical modelling, Hb post-baseline values were summarised in the form of area under the curve (AUC) values for an observed period, calculated by the trapezoidal

Table II. *Baseline demographics for all patients with solid tumours.*

| | Epoetin beta (n=255) | Control (n=199) |
|---|---|---|
| Sex, n (%) | | |
| Male | 40 (16) | 46 (23) |
| Female | 215 (84) | 153 (77) |
| Median (range) age, years | 57.0 (20-85) | 58.0 (19-77) |
| Median (range) weight, kg | 63.0 (42.0-105.0) | 63.55 (38.5-114.0) |
| n | 254 | 198 |
| Median (range) height, cm | 164.0 (142.0-190.0) | 164.0 (142.0-186.0) |
| n | 255 | 197 |
| Chemotherapy, n (%) | | |
| Pt-based | 195 (76.5) | 137 (68.8) |
| Non-Pt | 60 (23.5) | 62 (31.2) |
| Median (IQR) Hb, g/dl | | |
| All patients | 10.3 (9.3-11.4) | 10.1 (9.3-10.8) |
| Pt CT | 10.5 (9.6-11.8) | 10.2 (9.4-10.9) |
| Non-Pt CT | 9.6 (8.4-10.6) | 9.9 (8.8-10.4) |

Hb=haemoglobin; Pt=platinum; CT=chemotherapy; IQR=interquartile range.

rule and standardised by baseline values and time. Analysis of covariance (ANCOVA) was used with baseline and treatment as additional factors in the $Hb_{AUC}$ model. The hypothesis for HbAUC was tested using an F-test (type 3). Overall, progression-free and transfusion-free survival were analysed by Kaplan–Meier estimates, log-rank testing and Cox regression analysis. TEEs were summarised in terms of crude rates independently of onset. Three general hypotheses were tested using the log-rank method.

Subgroup analyses were performed for three subpopulations: all patients with solid tumours treated with Pt-based or non-Pt-based CT; all patients with solid tumours treated with Pt-based CT; all patients with solid tumours treated with non-Pt-based CT.

## Results

The baseline demographics were mostly well matched and are shown in Table II. In the pooled population, the two treatment groups were well balanced with respect to race, age and weight. Hb values at baseline were also well balanced between the two treatment groups. A difference seen in baseline gender was caused by a 2:1 randomisation, favouring the epoetin beta treatment group, from the study in patients with ovarian cancer (9). The patients underwent treatment (plus follow-up) for a mean duration of 140 and 115 days in the epoetin beta and control treatment arms, respectively.

In the overall population, the median increase in Hb level from baseline to week 16 was 1.5 g/dl in the epoetin beta group compared with no change in the control group. Similar findings were observed in patients receiving Pt-based CT at week 16. In this subpopulation, the median increase in Hb level was 1.4 g/dl in the epoetin beta group, with a decrease in median Hb of 0.2 g/dl being observed over this time-period in the control group. In patients receiving non-Pt-based CT, there was a median increase in Hb level at week 16 of 1.9 g/dl, compared with 0.6 g/dl in the control group. Patients receiving epoetin beta achieved median Hb levels after 16 weeks of treatment of 12.2, 12.5 and 11.8 g/dl in all patients and subpopulations receiving Pt-based and non-Pt-based CT, respectively (Figure 1). In contrast, Hb levels only reached 10.4, 10.3 and 10.6 in the respective control groups. All patients responded rapidly, showing a median increase of at least 1 g/dl in Hb from baseline at week 4 (Figure 2).

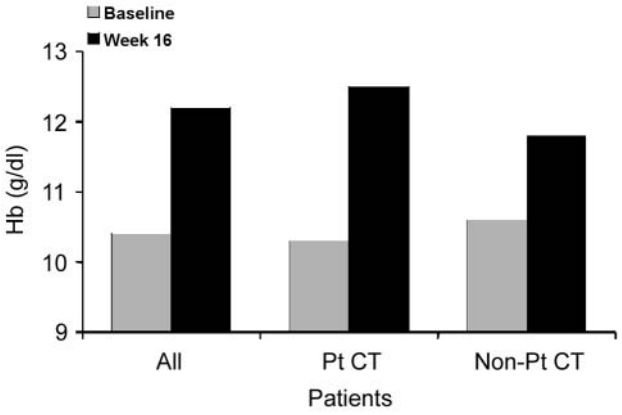


Figure 1. *Median haemoglobin (Hb) levels of patients with solid tumours and subpopulations of those receiving non-platinum (Pt)-based chemotherapy (CT) and those with platinum-based chemotherapy at baseline and after 16 weeks of treatment with epoetin beta.*

For patients in the epoetin beta group compared with the control, least square mean estimates of baseline-adjusted mean change in Hb levels were significant in all patients overall (1.1 *versus* 0.1 g/dl) and patients who received Pt-based CT (1.1 *versus* –0.1 g/dl) and non-Pt-based CT (1.2 *versus* 0.6 g/dl). The model for all the groups analysed contained both treatment and baseline Hb as factors, which were statistically significant in all cases ($p<0.05$ for the treatment effect). Changes in Hb levels in the epoetin beta group were similar for all patients and the subpopulations. Direct comparison of Hb levels between patients receiving Pt-based and non-Pt-based CT by ANCOVA highlighted an interaction term ($p=0.043$). However, least squares mean assessment confirmed this to be an imbalance in the control groups of the subpopulations.

Fewer blood transfusions occurred in the epoetin beta group than in the control group (Table III). Cox regression

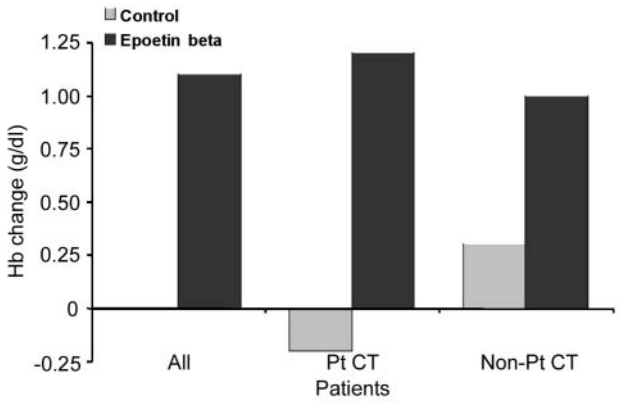


Figure 2. *Change in median haemoglobin (Hb) levels after 4 weeks of treatment for all patients and those receiving platinum (Pt)-based and non-platinum-based chemotherapy (CT).*

Table III. *Transfusion events stratified for patients with solid tumour and chemotherapy type.*

| Patients | Epoetin beta | Control | Relative risk[a] | *p*-value |
|---|---|---|---|---|
| Overall, n | 255 | 199 | | |
| Number of events (%) | 67 (26.3) | 90 (45.2) | 0.47 | <0.0001 |
| Pt CT, n | 195 | 137 | | |
| Number of events (%) | 42 (21.5) | 62 (45.3) | 0.39 | <0.0001 |
| Non-Pt CT, n | 60 | 62 | | |
| Number of events (%) | 25 (41.7) | 28 (45.2) | 0.74 | NS |

[a]Relative risk as assessed by Cox regression analysis.
Pt=platinum; CT=chemotherapy; NS=non significant.

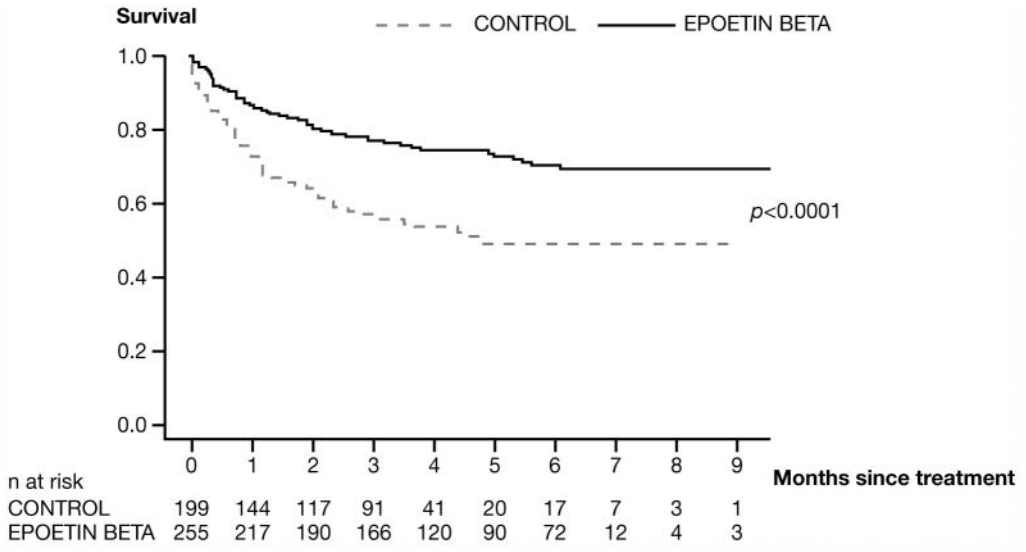


Figure 3. *Kaplan-Meier curve showing transfusion-free survival in all patients.*

analysis for all patients, patients receiving Pt-based CT and patients receiving non-Pt-based CT showed transfusion risk reductions of 53% (log-rank test $p<0.0001$), 61% (log-rank test $p<0.0001$) and 26% respectively, associated with epoetin beta treatment (Table III; Figure 3).

For all three populations, no risks were identified with regard to tumour progression or overall survival. Cox regression analysis for all patients, and those receiving Pt-based CT or non-Pt-based CT showed non-significant risk reductions associated with epoetin beta treatment of 29%, 26% and 22%, respectively, for tumour progression, and 23%, 30% and 3%, respectively, for overall survival.

A total of 192 out of 255 patients (75%) in the epoetin beta group and 142 out of 199 patients (71%) in the control group reported at least one AE. No marked differences were observed between the treatment groups in terms of the frequency or types of AEs reported. An equal percentage of patients in both the epoetin beta (73/255 patients; 29%) and control (57/199 patients; 29%) groups experienced at least one serious AE. There were no obvious differences in the

types or frequencies of any particular serious AE between the two groups. A slightly lower percentage of patients in the epoetin beta group (21/255 patients; 8%) experienced an AE leading to death compared with patients in the control group (26/199 patients; 13%). There was a slight, though statistically non-significant, difference in the incidence of TEEs between groups. In all patients, 5.9% (15/255) of patients in the epoetin beta-treated group experienced at least one TEE compared with 4.5% (9/199) of patients in the control group. Patients underwent treatment (excluding 28 days of follow-up) for a mean duration of 140 and 115 days in the epoetin beta and control treatment arms, respectively, which may explain why there were slightly fewer TEEs measured in patients from the control group.

## Discussion

The results of this meta-analysis show that treatment with epoetin beta resulted in statistically significant ($p<0.05$) improvements in Hb in patients with solid tumours, regardless of the CT these patients received. The magnitude of the Hb increases observed was similar in patients overall and in those receiving Pt-based CT or non-Pt-based CT. Increases in Hb associated with epoetin beta treatment were rapid; a change from baseline of at least 1 g/dl was seen after 4 weeks in all populations analysed. Once-weekly epoetin beta (30,000 IU) in patients with haematological malignancies has also shown rapid improvements in Hb level of a similar magnitude (14). Furthermore, in patients following this once-weekly regimen, Hb continued to improve, with a 2 g/dl increase being achieved at a median time of 8.1 weeks.

As well as experiencing a rapid response, all patients in the current meta-analysis achieved a mean Hb of approximately 12 g/dl after 16 weeks of epoetin beta treatment, regardless of the CT type they received. It is important for patients to achieve and maintain a Hb level of this magnitude so that they have the opportunity of benefiting from maximum improvements in QoL (4). Moreover, maintaining a Hb level within the target range of 12–13 g/dl has been advocated by the recent EORTC guidelines (3).

Other than maintaining Hb levels within the target range in order to improve overall QoL, another of the major goals suggested by the EORTC guidelines, is to reduce transfusion requirements (3). In this meta-analysis, transfusion requirements were reduced in patients with solid tumours, similar to previous epoetin beta studies in patients with haematological malignancies (11, 14).

For over a decade, patients have received the benefits epoetin beta therapy offers in terms of improved Hb, reduced transfusion requirements and, most of all, improved QoL. However, there are some studies that have shown a slightly higher incidence of TEEs in patients with cancer, who are receiving erythropoietic proteins compared with standard therapy (12, 18-21). Consequently, the occasional occurrence of TEEs with erythropoietic proteins has been reflected in the product labels for this class of drug. In this study, the incidence of TEEs in the epoetin beta group was low and similar to that of the control group. Further evidence that TEEs do not appear to have a major impact in patients taking epoetin beta is shown in a meta-analysis from nine studies on epoetin beta (21). Slightly lower percentages of patients with TEEs were seen in the current study (5.9%, epoetin beta *versus* 4.5%, control), which only considered patients with solid tumours rather than the wider range of tumour types analysed previously (5.9 *versus* 4.2% of patients with at least one event) (22). In addition, TEE-related mortality in patients with cancer is not associated with epoetin beta treatment (21).

Epoetin beta has the same structure and function as endogenous erythropoietin. Therefore, it is expected that the mode of action of epoetin beta would be independent of the CT type administered to the patient. The results of this meta-analysis confirmed that epoetin beta is effective and safe, regardless of the CT employed in anaemic patients with solid tumours. In particular, there was no increase in risk of tumour progression and overall survival.

In conclusion, epoetin beta, as shown previously (13, 15), is effective at rapidly increasing Hb levels in patients with solid tumours. Improvements in Hb levels were shown to be irrespective of the type of CT received by this patient group. Furthermore, this meta-analysis provides further evidence on the safety of epoetin beta in patients with solid tumours.

## References

1 Ludwig H, Van Belle S, Barrett-Lee P, Birgegard G, Bokemeyer C, Gascon P, Kosmidis P, Krzakowski M, Nortier J, Olmi P, Schneider M and Schrijvers D: The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer *40*: 2293-2306, 2004.

2 Groopman JE and Itri LM: Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst *91*: 1616-1634, 1999.

3 Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Österborg A, Repetto L and Soubeyran P: EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. Eur J Cancer *40*: 2201-2216, 2004.

4 Crawford J, Cella D, Cleeland CS, Cremieux PY, Demetri GD, Sarokhan BJ, Slavin MB and Glaspy JA: Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. Cancer *95*: 888-895, 2002.

5 Del Mastro L, Venturini M, Lionetto R, Garrone O, Melioli G, Pasquetti W, Sertoli MR, Bertelli G, Canavese G, Costantini M and Rosso R: Randomized phase III trial evaluating the role of erythropoietin in the prevention of chemotherapy-induced anemia. J Clin Oncol *15*: 2715-2721, 1997.

6 Glaspy J, Bukowski R, Steinberg D, Taylor C, Tchekmedyian S and Vadhan-Raj S: Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. J Clin Oncol *15*: 1218-1234, 1997.

7 Demetri GD, Kris M, Wade J, Degos L and Cella D: Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a prospective community oncology study. Procrit Study Group. J Clin Oncol *16*: 3412-3425, 1998.

8 Oberhoff C, Neri B, Amadori D, Petry KU, Gamucci T, Rebmann U, Nowrousian MR, Voigtmann R, Monfardini S, Armand JP, Herrmann R, Netter-Pinon J, Tubiana-Mathieu N and Zwierzina H: Recombinant human erythropoietin in the treatment of chemotherapy-induced anemia and prevention of transfusion requirement associated with solid tumors: a randomized, controlled study. Ann Oncol *9*: 255-260, 1998.

9 ten Bokkel Huinink WW, de Swart CA, van Toorn DW, Morack G, Breed WP, Hillen HF, van der Hoeven JJ, Reed NS, Fairlamb DJ, Chan SY, Godfrey KA, Kristensen GB, van Tinteren H and Ehmer B: Controlled multicentre study of the influence of subcutaneous recombinant human erythropoietin on anaemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based chemotherapy. Med Oncol *15*: 174-182, 1998.

10 Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E and Einhorn LH: Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol *19*: 2875-2882, 2001.

11 Österborg A, Brandberg Y, Molostova V, Iosava G, Abdulkadyrov K, Hedenus M and Messinger D for the Epoetin Beta Hematology Study Group: Randomized, double-blind, placebo-controlled trial of recombinant human erythropoietin, epoetin beta, in hematologic malignancies. J Clin Oncol *20*: 2486-2494, 2002.

12 Vansteenkiste J, Pirker R, Massuti B, Barata F, Font A, Fiegl M, Siena S, Gateley J, Tomita D, Colowick AB and Musil J for the Aranesp 980297 Study Group: Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst *94*: 1211-1220, 2002.

13 Boogaerts M, Coiffier B and Kainz C for the Epoetin beta QOL Working Group: Impact of epoetin beta on quality of life in patients with malignant disease. Br J Cancer *88*: 988-995, 2003.

14 Cazzola M, Beguin Y, Kloczko J, Spicka I and Coiffier B: Once-weekly epoetin beta is highly effective in treating anaemic patients with lymphoproliferative malignancy and defective endogenous erythropoietin production. Br J Haematol *122*: 386-393, 2003.

15 Bogdanos J, Karamanolakis D, Milathianakis K, Repousis P, Chloraki-Bobota A, Majed H, Pagalou-Thoua E, Tsintavis A and Koutsilieris M: Epoetin beta (NeoRecormon) corrects anaemia in patients with hormone-refractory prostate cancer and bone metastases. Anticancer Res *24*: 1957-1961, 2004.

16 Abels RI, Larholt KM, Krantz KD and Bryant EC: Recombinant human erythropoietin (rHuEPO) for the treatment of the anemia of cancer. Oncologist *1*: 140-150, 1996.

17 Glaspy J, Degos L, Dicato M and Demetri GD: Comparable efficacy of epoetin alfa for anemic cancer patients receiving platinum- and nonplatinum-based chemotherapy: a retrospective subanalysis of two large, community-based trials. Oncologist *7*: 126-135, 2002.

18 Littlewood TJ, Bajetta E, Nortier JW, Vercammen E and Rapoport B for the Epoetin Alfa Study Group: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol *19*: 2865-2874, 2001.

19 Leyland-Jones B for the BEST Investigators and Study Group: Breast cancer trial with erythropoietin terminated unexpectedly. Lancet Oncol *4*: 459-460, 2003.

20 Bohlius J, Langensiepen S, Schwarzer G, Seidenfeld J, Piper M, Bennet C and Engert A: Erythropoietin for patients with malignant disease. Cochrane Database Syst Rev *3*: CD003407, 2004.

21 Coiffier B, Boogaerts M, Aapro M, Huber M and Burger H-U: Thromboembolic events in patients with cancer treated with NeoRecormon (epoetin beta): a meta-analysis of controlled clinical trials. Ann Oncol *15(Suppl 3)*: Abstract 840P, 2004.

22 NeoRecormon Summary of Product Characteristics. Roche Registration Ltd, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, UK (July 2005).

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