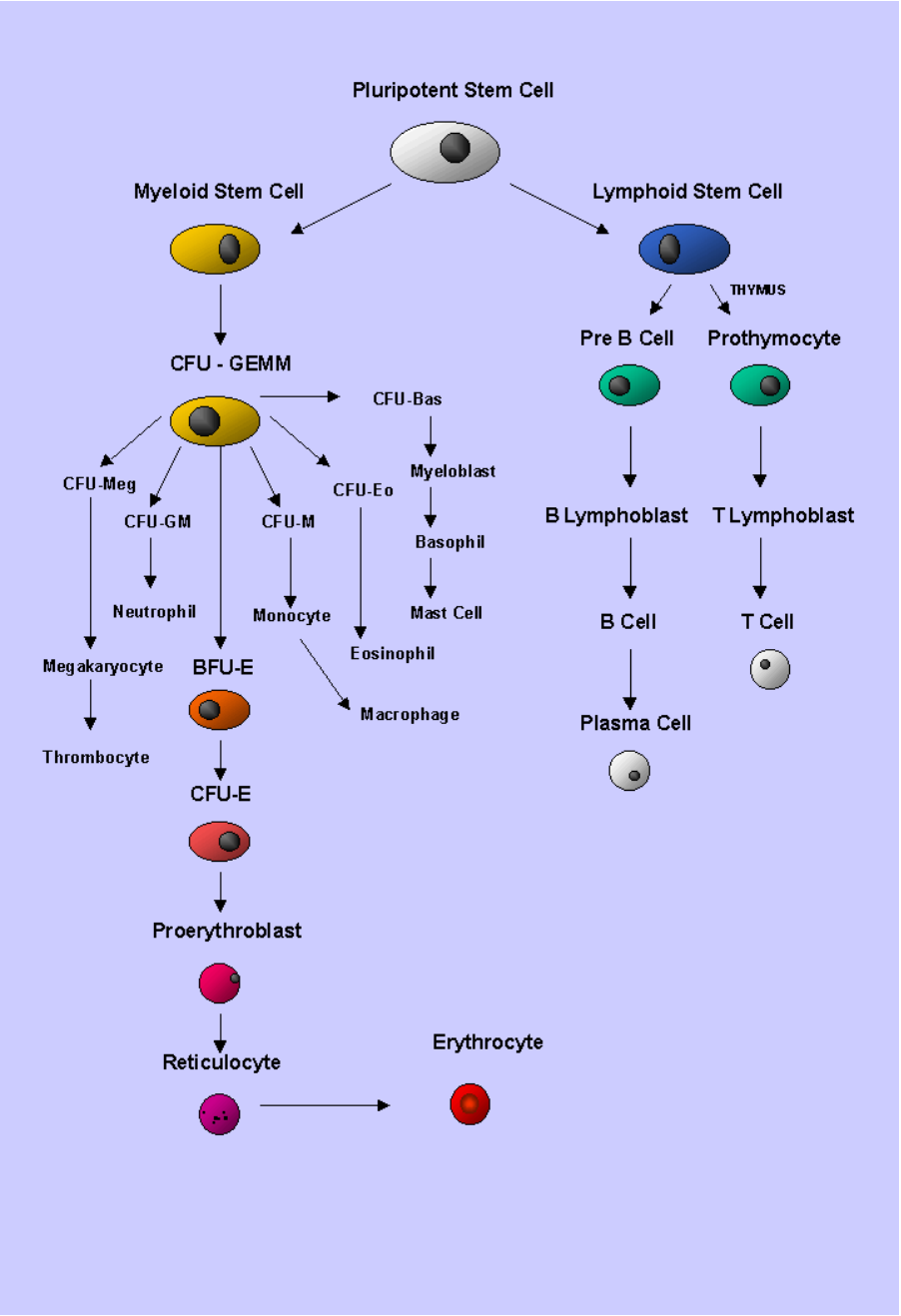
# Chemotherapie geïnduceerde anemie: actuele visie op toepassing van recombinant Epo en ijzertherapie

**Dr. L. Dirix,**
**Medische Oncologie - Inwendige Ziekten,**
**GZA Ziekenhuizen, Antwerpen.**

# Erythropoiesis

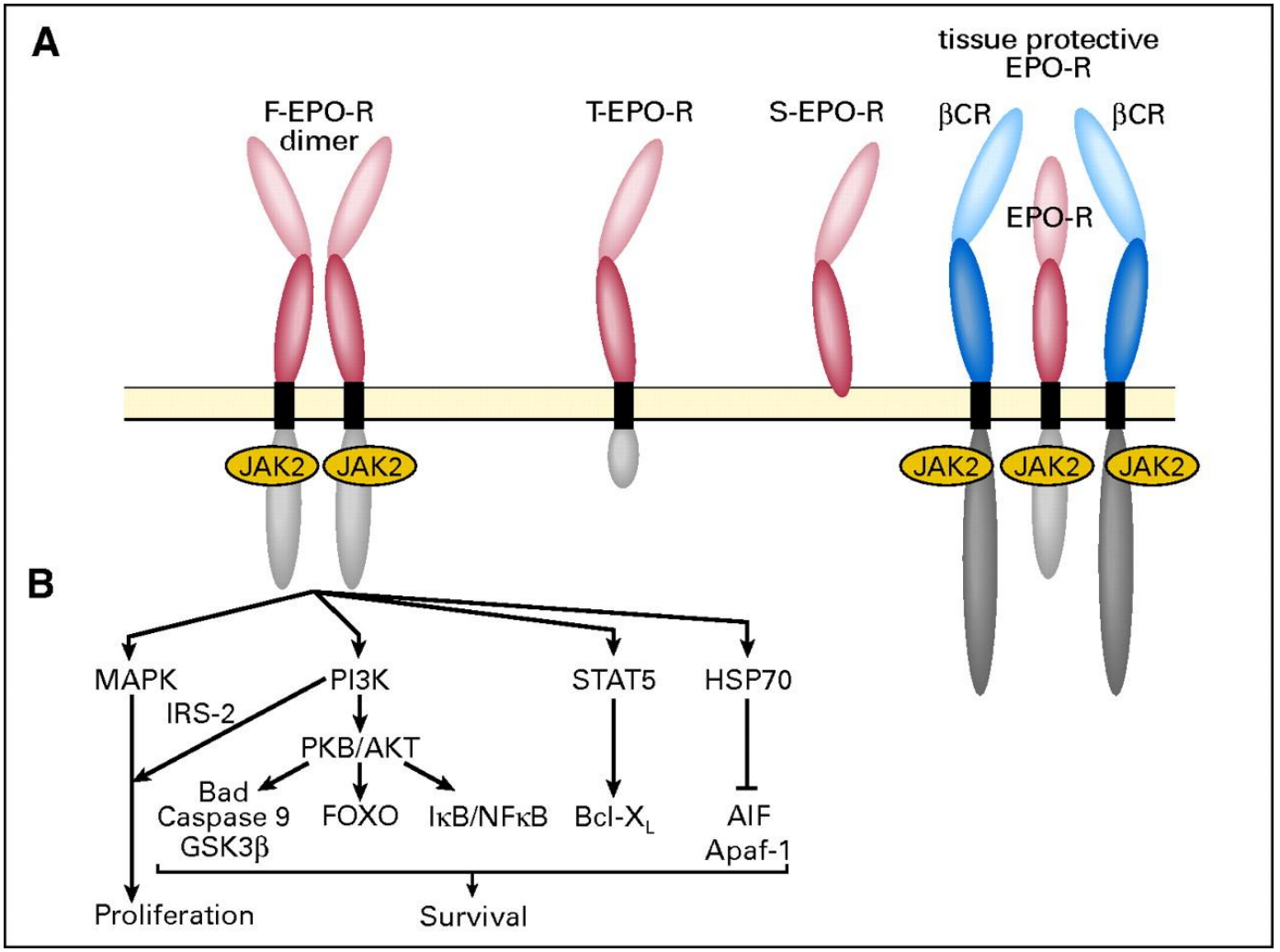
- 2.3 million red blood cells produced every second in human bone marrow
- 138 million every minute
- 42 billion between now and dinner-time!
- Main regulator is **erythropoietin (EPO)**



# EPO

- Glycoprotein essential survival, proliferation, differentiation erythrocytic precursors
- Deficient in CKD
- EPO in CKD = hormone replacement therapy
- Interacts EPO-R
- Determination EPO-R
  - Unreliable IHC
  - Cytoplasmatic versus membrane
  - RT-PCR, Western blot, Northern Blot

# Erythropoietine (EPO) en de EPO receptor (EPO-R) signaalweg




Hadland, B. K. et al. J Clin Oncol; 27:4217-4226 2009

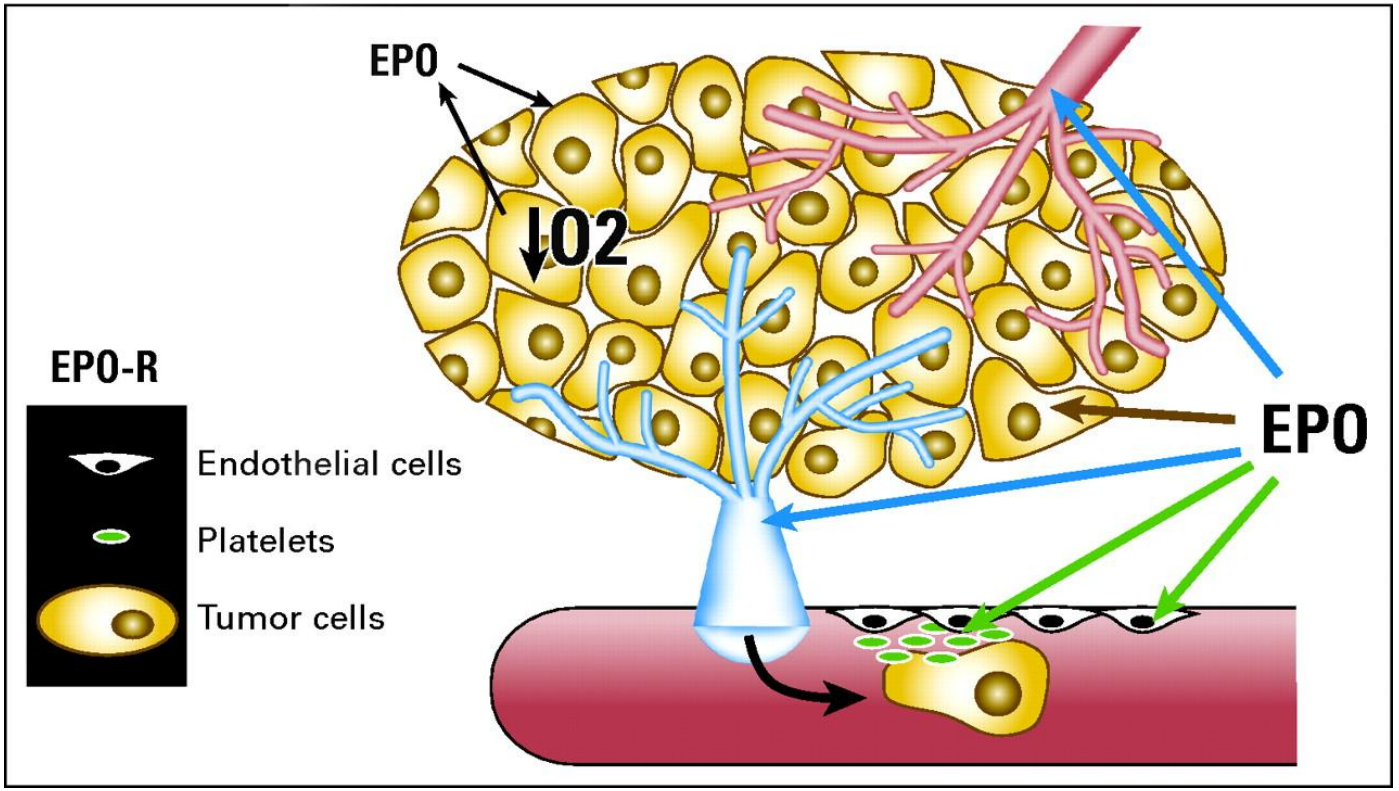
# EPO-R in niet-maligne, niet-hematopoiëtisch weefsel

- Hart
- Bloedvaten
- Nieren
- CZS
- PZS

# EPO-R in tumoren

- EPO-R in tumor biopsies
- Humane kanker cellijnen
- Diermodellen

# Rol van erythropoietine (EPO) in tumor progressie




Hadland, B. K. et al. J Clin Oncol; 27:4217-4226 2009

# Pathogenese van bloedarmoede bij patiënten met kanker.

- Tekort aan EPO
- ↑ Inflammatoire cytokines ( IL-1, TNF, IFN-$\gamma$)
- ↓ Aantal rode precursoren
- ↓ Gevoeligheid van rode precursoren aan EPO
- Nierfalen
- Infecties
- Chemo-radiotherapie
- Hypervolemie
- Beenmerg infiltratie
- Bloeding
- Hemolyse
- Vit. B12 tekort
- Folium tekort
- ijzertekort en/of ijzergebruiksstoornissen

# Consequences and treatment of anemia

- Untreated anemia leads to symptoms that diminish QoL:
  - Fatigue
  - Impaired cognitive function
  - Depression
  - Unable to work
  - Social isolation
  - Reduced sexual activity
  - Unable to complete daily activities
- Unfavorable prognostic factor for clinical outcome
- Treatment options
  - Red blood cell transfusions
  - Erythropoiesis stimulating agents (ESAs)
  - Iron for iron-deficiency anemia

# Potential risks of red blood cell transfusions vs ESAs

- Transfusions have well-recognized liabilities
  - Infections: HIV 1:1.000.000, others.., ? unknown…
  - Acute lung injury: whole blood 1:432, RBC 1:557000
  - Volume overload
  - Acute and delayed reactions
  - Alloimmunization
  - Iron overload
  - Suggestions of adverse cancer-related outcomes
- Demand on blood supply would intensify
- Multiple transfusions needed to maintain Hb level sufficient to minimize signs and symptoms of anemia
- Inconvenience for the patient

# ESAs

- 1989: chronisch nierfalen
- 1993: niet-myeloide kanker: anemie tgv chemotherapie
- Contraindicatie: ongecontroleerde AHT
- Patient Safety : TE, overleving
- FDA ODAC Meetings 2004, 2007, 2008

# Recombinante humane ESAs in de oncologie

- Epoetin alfa (Eprex, Procrit, Epogen,...)
- Epoietin beta (NeoRecormon)
- Darbepoietin alfa (Aranesp)
- Biosimilars
- ASCO/ASH 2007: based on a comprehensive systematic review comparing outcomes of epoietin and darbepoeitin in patients with chemotherapy-induced anemia and on identical cancer-related indications, warnings, and cautions in the relevant FDA-approved package inserts, the Update Committee considers these agents to be equivalent with respect to effectiveness and safety.

# ESAs in de Oncologie

- 1. Efficaciteit : Hb
- 2. Relatie QoL
- 3. Behandeling met ijzer
- 4. TV-events
- 5. Overleving
- 6. Huidige richtlijn

# Recombinante humane ESAs in de hematologie-oncologie: Efficaciteit

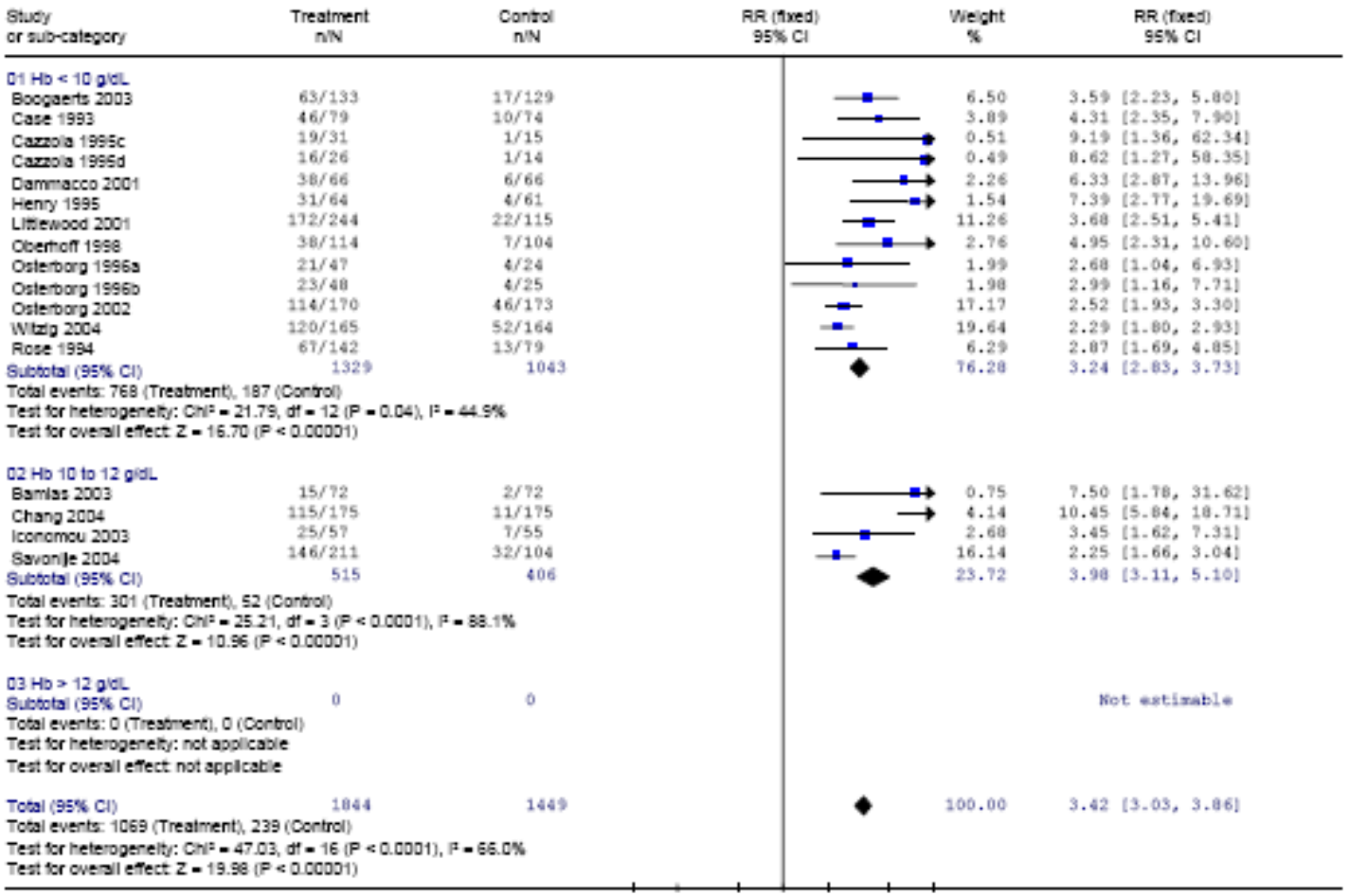
- BohliusJ, et al JNCI 2006;98:708
- 42 studies Epo vs placebo
- Bij 2/3 HB stijging
- RR voor TRF 0.64.
- Verhouding voor aantal TRF 2/1
- Ongeveer 1/3 geen effect
- 3x/week iv, sc, 1x/week
- Effect dosis escalering  bij non-responders: onduidelijk (verschil ASCO/ASH vs andere
- BSMO richtlijn : geen escalatie.

# Proven hematologic response with epoetin

**Figure 4. Fixed-Effects Meta-Analysis of Data on Hematologic Response Rates from 15 RCTs of Epoetin versus Control**

Comparison: Epoetin vs. Control

Outcome: Hematologic response




**RR 3.42 (95%CI 3.03 – 3.06)**

# Monitoring en toediening van ijzer

- Auerbach et al. : 157 ptn
  - Geen ijzer vs oraal ijzer 325 mg 2x/dag vs IV ijzer
  - Hb < 10.5 gr/dL en Tsat < 20%
  - Iedereen 40 000 IU Epo alfa
  - 6 weken
  - Hb 0.9 vs 1.5 vs 2.5
- Henry et al : 187 ptn
  - 125 mg IV ijzer/week vs 325 mg oraal 3x/dag vs nil
  - Hb < 11 gr/dL en Ferritine > 100 en Tsat > 15%
  - Epo alfa 40.000 IU
  - 4 weken : Hb 2.4 vs 1.6 vs 1.5
- Hedenus et al. : 67 ptn
  - IV ijzer 100 mg/week w1-6 vs nil
  - Epo beta 30.000 IU/week
  - Hb 9-11, ijzer in BM
  - 2.76 vs 1.56

# Monitoring en toediening van ijzer

- Predrazolli et al. JCO, 2008;
- N = 149
- Hb < 11 gr/dL
- Ferritine > 100 ng/mL
- Tsat > 20 %
- IV ijzer 125 mg/week w1-w6 versus nil
- Darbopoietine 150 microgram/week
- HB + 2 gr/dL en/of > 12 gr/dL
- 76,7% versus 61.8%

# Monitoring en toediening van ijzer: conclusie

- Toediening van ijzer verhoogt het effect van ESAs
- De IV route lijkt meest werkzaam
- Effect lijkt maar beperkt afhankelijk van ijzerstatus
- Is er een effect separaat van ESAs bij nl Tsat ?
- De drempel om IV ijzer te gebruiken is de afgelopen jaren sterk verlaagd.
- Dosering 100 mg/week of 200-300 mg / 2 weken

# Epoetin alfa: 40,000 IU qw verhoogt Hb en verbetert levenskwaliteit

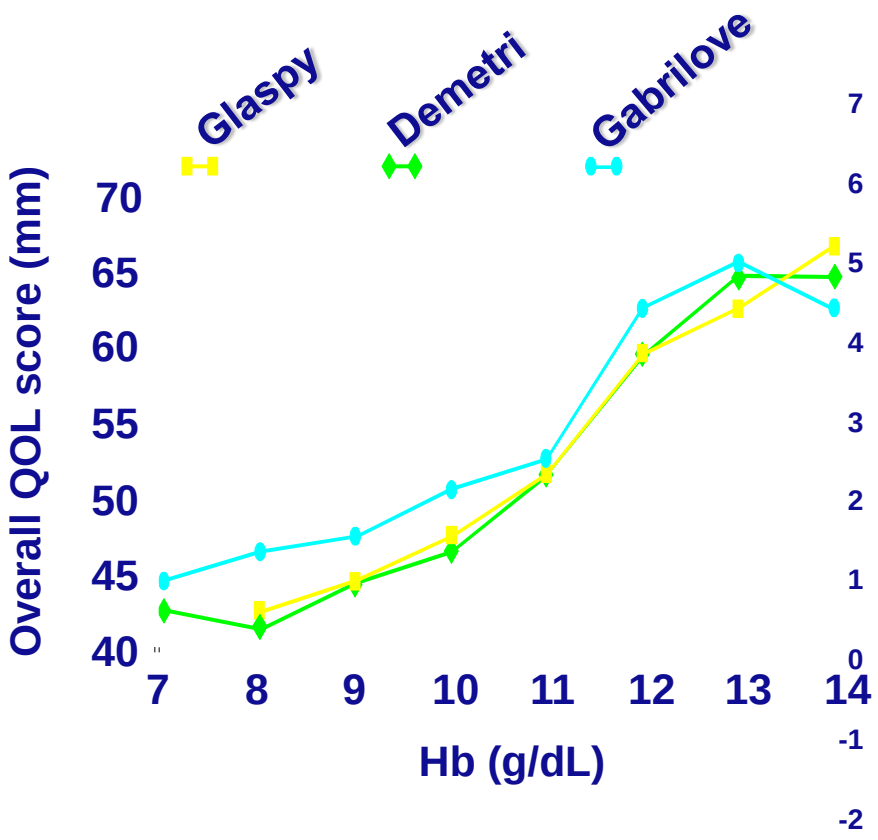
| | Evaluable patients (n) | Regimen tiw / qw | Hb ↑ *P* value | Transfusion ↓ *P* value | QoL ↑ *P* value |
|---|---|---|---|---|---|
| Littlewood | 375 | tiw | <0.001 | =0.006 | <0.01 |
| Gabrilove | 2964 | qw | <0.001 | <0.007 | <0.001 |
| Shasha | 442 | qw | <0.05 | <0.05 | <0.05 |
| Crawford | 216 | qw | =0.0001 | =0.089 | <0.05 |
| Straus | 269 | qw | <0.0001 | <0.0001 | <0.05 |
| EPOLYM | 540 | qw | <0.001 | <0.008 | <0.05 |
| Witzig | 330 | qw | <0.001 | =0.005 | =0.006* |

**Littlewood *et al. J Clin Oncol* 2001;19:2865–74; Gabrilove *et al. J Clin Oncol* 2001;19:2875–82; Shasha *et al. Cancer* 2003;98:1072–9; Crawford *et al. Proc ASCO* 2003;22:628(abstract 2527) Straus *et al. Blood* 2003;102:497a(abstract 1811); Dammacco *et al*. *Hematol J* 2004;5 (Suppl 2):S177(abstract 515); Tesch *et al. Hematol J* 2004;5(Suppl 2):S177(abstract 514); Witzig *et al. J Clin Oncol* 2005;23:2606–17**

# Recombinante humane ESAs in de hematologie-oncologie: Efficaciteit-QoL

- Kritisch en m.i. onderschat onderdeel van de discussie
- Geldt ook voor TRF
- Blijft onduidelijk na (minstens?) 4 meta-analyses
- QoL toename
  - De “hoegrootheid”
  - Duur van het effect
  - Relatie tot HB stijging
  - Relatie tov startwaarde; maw vanaf wanneer is “cancer related anemia ” symptomatisch
- Cancer related fatigue = multifactorieel en anemie is hier een onderdeel van
- Allicht is co-mobiditeit een co-determinant
- Maw : When to start treatment of CRA.

# Relatie tussen Hb en LK scores




Glaspy (150 IU/kg tiw);
Demetri (10K tiw); Gabrilove (40K qw)

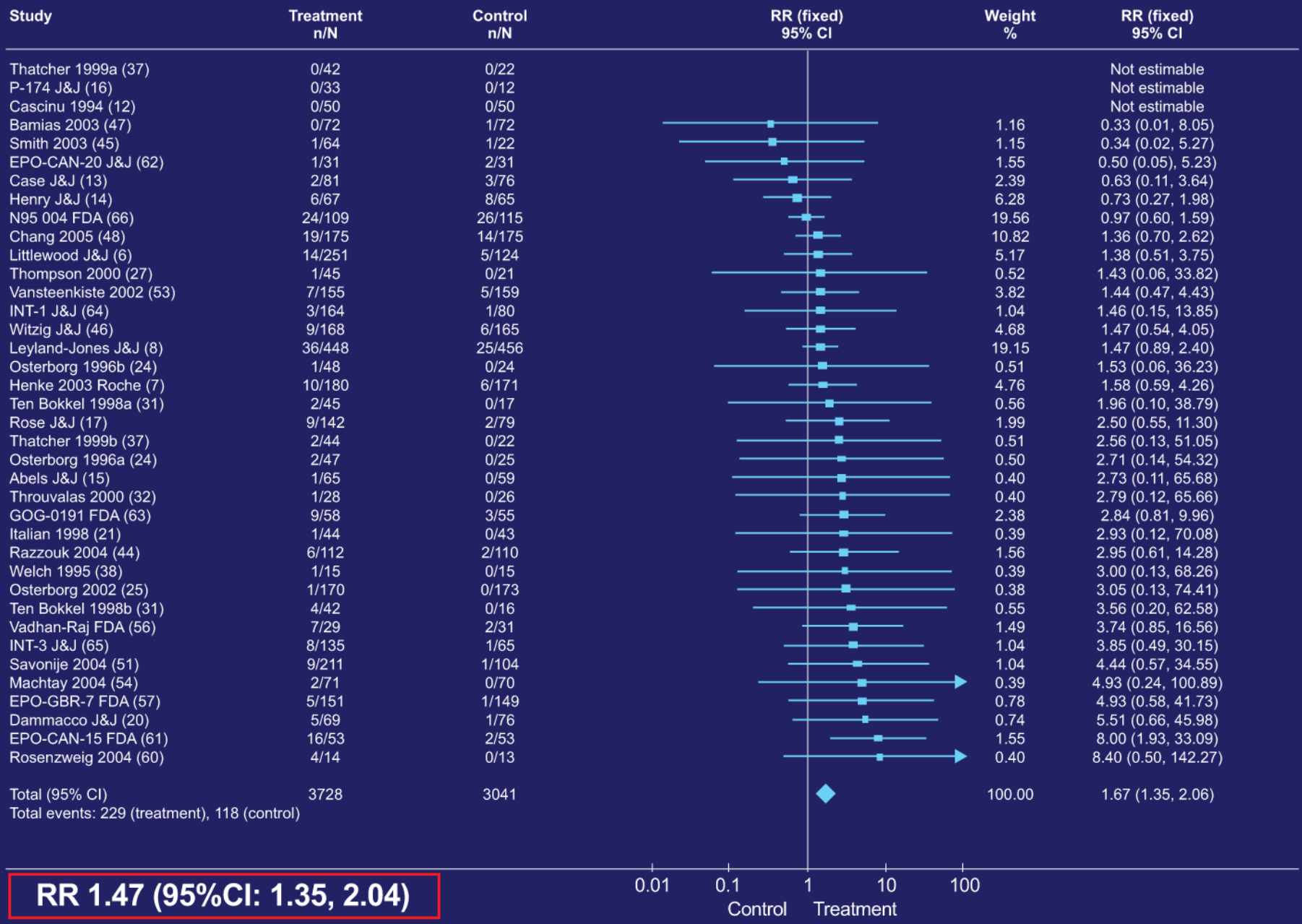

Data from patients with baseline Hb ≤10.5 g/dL
QoL, quality of life

Glaspy (1997); Demetri (1998); Gabrilove (2001)

Littlewood *et al. J Clin Oncol* 2001;19:2865–74
Nortier *et al. Ann Oncol* 2000

# Patient Safety :
# TE, DFS en OS en ESAs

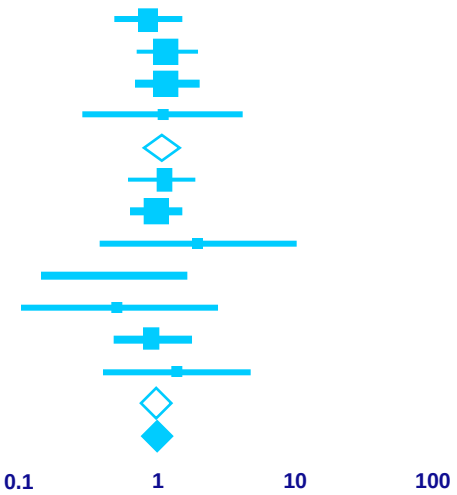
# Cochrane *JNCI* meta-analysis 2006: VTE




**RR 1.47 (95%CI: 1.35, 2.04)**

# No effect on VTE by ESA dose – active controlled CIA studies

| | | | Peto odds ratio | Lower limit | Upper limit | Z value | P value |
|---|---|---|---|---|---|---|---|
| 2 FL | CT_20020118 | 2 FL | 0.849 | 0.490 | 1.471 | -0.584 | 0.559 |
| 2 FL | CT_20010101 | 2 FL | 1.158 | 0.710 | 1.890 | 0.588 | 0.556 |
| 2 FL | CT_20020139 | 2 FL | 1.157 | 0.670 | 1.996 | 0.524 | 0.601 |
| 2 FL | CT_20000174 | 2 FL | 1.095 | 0.290 | 4.140 | 0.133 | 0.894 |
| 2 FL | | | 1.055 | 0.785 | 1.419 | 0.355 | 0.723 |
| 3 LFD | CT_20030231 | 3 LFD | 1.075 | 0.628 | 1.838 | 0.263 | 0.793 |
| 3 LFD | CT_20030125 | 3 LFD | 0.975 | 0.658 | 1.445 | -0.128 | 0.899 |
| 3 LFD | CT_20020152 | 3 LFD | 1.911 | 0.374 | 9.753 | 0.779 | 0.436 |
| 3 LFD | CT_20020165 | 3 LFD | 0.473 | 0.143 | 1.569 | -1.223 | 0.221 |
| 3 LFD | CT_20020166 | 3 LFD | 0.502 | 0.095 | 2.649 | -0.811 | 0.417 |
| 3 LFD | CT_20040262 | 3 LFD | 0.898 | 0.489 | 1.650 | -0.347 | 0.729 |
| 3 LFD | CT_980290 Q23 | LFD | 1.345 | 0.408 | 4.439 | 0.487 | 0.626 |
| 3 LFD | | | 0.965 | 0.744 | 1.252 | -0.267 | 0.789 |
| Overall | | | 1.003 | 0.825 | 1.220 | 0.034 | 0.973 |




**Meta-analysis of embolism / thrombotic events by randomized treatment group**

**Front-loaded dosing: RR 1.055 (95% CI: 0.785 – 1.419)**

**Less frequent dosing: RR 0.965 (95% CI: 0.744 – 1.252)**

**Over all studies RR 1.003 (95% CI: 0.825 – 1.220)**

# Risk of thrombotic event by target Hb (stopping level) from AHRQ

| Dose withholding Hb (g/dL) | Relative Risk (TE event) | 95% Confidence level |
|---|---|---|
| <12 | Not estimable | NA |
| >12 to ≤ 13 | 0.70 | 0.29 – 1.67 |
| >13 to ≤ 14 | 1.71 | 1.23 – 2.40 |
| >14 to ≤ 15 | 1.92 | 1.22 – 3.02 |
| >15 to ≤ 16 | 1.66 | 1.08 – 2.54 |

# Thrombo-embolie(TE) Risico en ESAs

- Eerder onderschat (rapportering)
- Arteriële en veneuse thrombosen (LE, AMI, TIA, DVT)
- Meta-analyse : RR 1,67
- NNH : 75 bij basisrisico 2%
- NNH : 7.5 bij basisrisico 20%
- Nefrologie: relatie hogere Hct hoger risico op TE
- Thrombogeen effect is meer dan enkel effect op Hb
- Van Steenkiste: darbopoeitin vs placebo 4,5% vs 3.0% (NS)
- 147 dames cervixcarcinoom: CT+RT+/-ESA (RR=10)
- Effect van LMWH en anti-aggregantia = ?

# ESAs en DFS en OS

- Bloedarmode ongunstige prognostische faktor
- Suggestie dat correctie anemie per se aanleiding zou geven tot verbeterde OS was niet onlogisch
- Littlewood JCO, 2001.
    - n=275; mixed bag
    - Non-platinum CT
    - Hb< 10.5 gr/dL en/of val met =/> 1.5 gr/dL
    - Epo alfa 150IU/kg 3x/we, 12-14 weken `
    - 17/12 versus11/12
- Meta-analyse 19 RCT (n=2805), OS voordeel 0.81(0.67-0.99)
- Geen enkele individuele studie was bedoeld om DFS of OS te beoordelen.

# ESAs en DFS en OS

- Hoofd-en Hals kanker
- Borstkanker
- Longkanker
- Lymfoproliferatieve kanker
- Geen anti-kanker therapie
- Meta-analyse

# ESAs en DFS en OS: Hoofd-en Hals Kanker

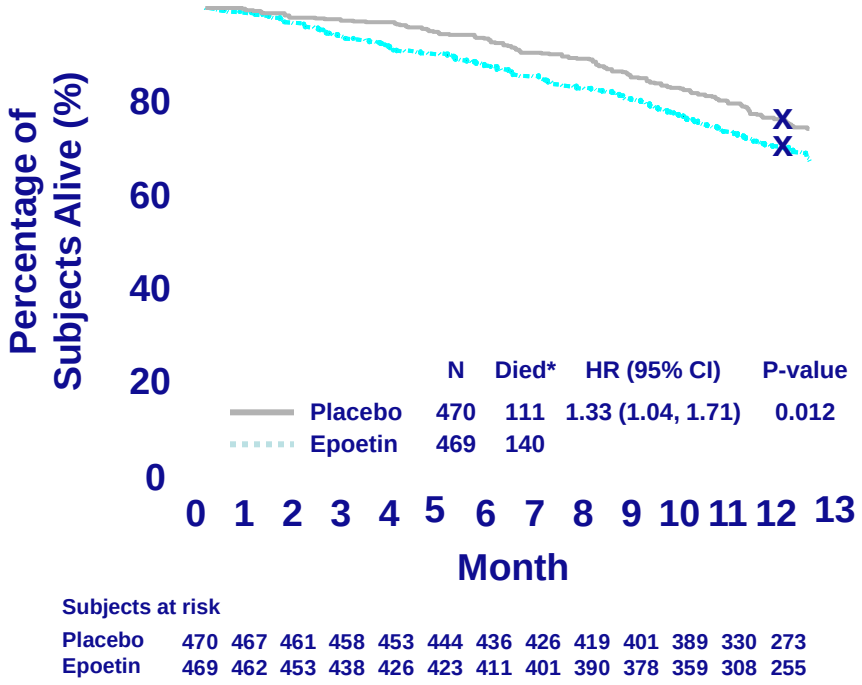
- 5 studies met specifieke vraagstelling; anemie per se + hypoxie
- ENHANCE: RT + epo beta of placebo (n=351)
  - lokale PFS,  Hb  naar 14-15  gr/dL
  - AHT+bloeding+TE  11% vs 5%
  - PFS 1.69 (1.16-2.47) p 0.007
  - OS 1.39 (1.05-1.84) p 0.02
- DAHANCA: T1-T4NX niks versus darbepoietine (n=522)
  - Hb < 14.5 nooit hoger dan 15.5 gr/dL
  - DFS 1.44  significant
  - OS 1.28 NS
- RTOG 99-03 (n=148) RT+/- CT +/-EPO alfa
  - DFS at 1 Y 63 vs 70%

# ESAs en DFS en OS: Borstkanker

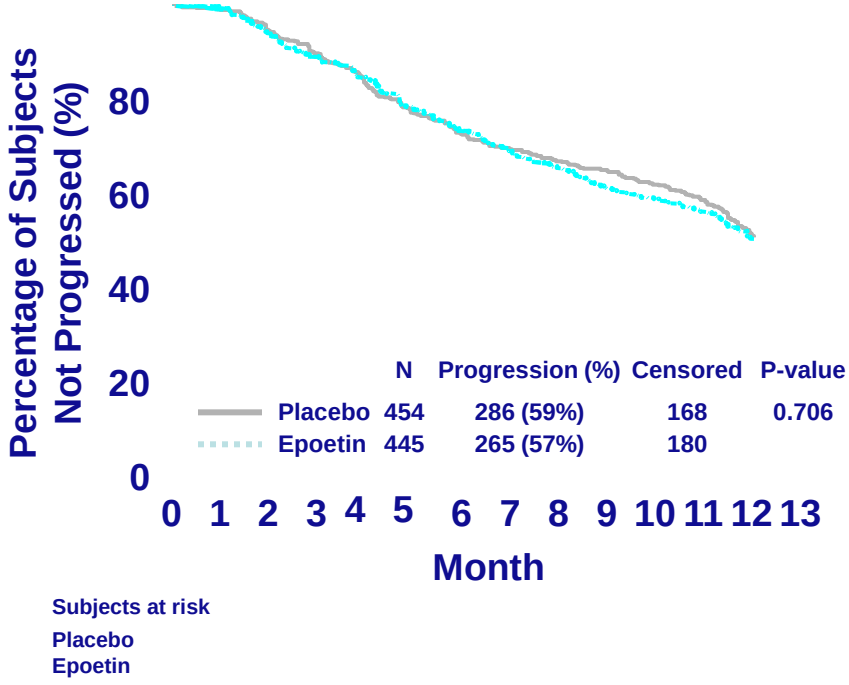
- 2 grote studies bij M+
- BEST: Epo alfa 40.000 IU/ week vs placebo (n=939)
  - Eerste 4 maanden
  - OS 1.37 (1.07-1.74)  p 0.01
  - 41 vs 16 overlijdens
  - Vroegtijdig gestopt
- BRAVE: open-label MBC (n=463), Epo beta
  - DFS en OS identiek

# BEST: Cause of Death Attributed to Disease Progression

- No difference in time to tumor progression between groups




**Time to Death within 12 mo after Randomization**
**BEST (EPO-INT-76)**
**(Intent-to-treat subjects)**




**Time to Tumor Progression**
**BEST (EPO-INT-76)**

***Prior to 12 months (+ 2 weeks) after randomization**

# ESAs en DFS en OS: andere M

- Longkanker
  - NSCLC Hb 12-14 houden  EPO alfa HR 1.84 OS
  - NSCLC+SCLC : darbepoeitine vs nil geen effect
- Lymfoproliferatieve ziekten (n=349)
  - MM/CLL/HL,NHL,Wa  Darbepoietine vs nil
  - OS HR 1.37 p 0.037
  - Geen verschil in PFS
  - TVE 3.4% vs 0.6%
- Geen therapie studies
  - 20010103: placebo-gecontroleerd
  - Darbepoietine vs nil Hb < 11 , Hb 12-13 houden
  - OS HR 1.3 p 0.008
  - Geen verschil in TRF !!!!!
  - TVE 3.1% vs 1.3%

# ESAs en DFS en OS: Meta-analyse

- Bohlius et al. Lancet 2009; 373:1532-1542
- N = 13933 patienten
- 53 trials
- Vaak korte FU
- Mixed bag tumoren, therapie, start Hb, doel Hb
- ESAs
  - Tijdens therapie : sterfte HR  1.17
  - Bij pten met CT : HR 1.1

# ESAs in de Hemato-oncologie : Conclusies

- Er is een beperkt ongunstig effect op OS.
- Het blijft onduidelijk of dit gevolg is van TVE en/of progressie.
- Dit effect is groter bij patienten die geen chemotherapie krijgen. (kinetiek effect ?)
- Nefrologie heeft geleerd dat hoog Hb gehalte nastreven met ESA’s de mortaliteit verhoogt.
- Dus: aanpassen label FDA

# ESAs in de Hemato-oncologie : BSMO richtlijn

- Chemotherapie geïnduceerde anemie
- Symptomatisch en Hb < 11 gr/dL
- Uitsluiten andere oorzaken anemie, Tsat < 20% IV Fe
- Standaarddoses gebruiken
- 8 weken; geen stijging met 1 gr/dL = STOP
- Enkel gebruik tijdens CT periode
- Stop bij Hb 13 gr/dL
- Geen dosisescalering
- Geen onderscheid platinum/geen platinum
- Geen onderscheid tumorsoorten

# ESAs in de Hemato-oncologie : eindbemerkingenn

- Curatief versus palliatief
- Inschatten thrombotisch risico
  - Glioblastoom
  - EOC
  - Pancreascarcinoom
- Levenskwaliteit
  - Co-morbiditeit
  - Cardiovasculair-respiratoir-renaal
- Kost tov TRF
- Safety tov TRF

# Current reimbursement criteria in onco-hemato: platinum chemotherapy (Pt)

| Eprex® / Binocrit® | NeoRecormon® | Aranesp® |
|---|---|---|
| Treatment of secondary anemia induced by platinum CT in **adult cancer patients** | Treatment of secondary anemia induced by platinum CT in **adult patients with solid tumours** | Treatment of secondary anemia induced by platinum CT in **adult cancer patients** |

– Exclusion of other causes of anemia (occult hemorrhage, iron deficiency, hemolysis,...)

– Need for upfront demand to medical advisor

– Reimbursement given for 12 months after authorization of medical advisor

– Possibility of prolongation for 12 months

⇨ No specific criteria regarding initial Hb level, dose, duration of treatment,

⇨ Doubling of dose allowed if the increase in hemoglobin is inadequate

# Current reimbursement criteria in onco-hemato: non-platinum chemotherapy (non-Pt)

| | Eprex® / Binocrit® | NeoRecormon® | Aranesp® |
|---|---|---|---|
| – Secondary anemia in pts with solid or hematological tumors treated with CT<br>– Hb level < 11 g/dl<br>– Exclusion of all other causes of anemia | | | |
| **Initial treatment** | Dose : 150 IU/kg 3x/week or 450 IU/kg QW (equivalent to 40.000 IU fixed dose) | Dose : 450 IU/kg per week | **Weekly dose** : 2.25 µg/kg |
| | Duration : 4 weeks for solid tumors, 8 weeks for hematological tumors | | |
| **If increase in Hb level ≥ 1 g/dL without any transfusion after initial treatment** ↓ | | | |
| **Continuation of treatment = 8 weeks** | Dose : 150 IU/kg 3 x /week or 450 IU/kg QW (equivalent to 40.000 IU fixed dose)* | Dose : 450 IU/kg QW | Dose : 2.25 µg/kg QW |
| • No need for upfront demand to medical advisor<br>• Keep all justifications (tumor type, chemotherapy, Hb level,…) at disposition of medical advisor<br>• Reimbursement max. 2 x per 12 months | | | |

# Indications approved in onco-hematology (original EU labels)

| Epoetin alfa (Eprex® / Binocrit® ) | NeoRecormon® | Aranesp® |
|---|---|---|
| **Treatment of anemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumors, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy)** | **Treatment of symptomatic anemia in adult patients with non-myeloid malignancies receiving chemotherapy** | **Treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy** |

**Eprex a Binocrit SmPCs have not yet been updated following the new EMEA recommendations**

# Updated dosage recommendations in onco-hematology

| | Eprex® / Binocrit® | NeoRecormon® | Aranesp® |
|---|---|---|---|
| Hb threshold | Anaemia<br>(e.g. Hb ≤ 10 g/dL ) | Symptomatic anaemia (e.g. Hb ≤ 10 g/dL ) | |
| Target Hb | 10 – 12 g/dL<br>A sustained Hb > 12g/dL should be avoided | | |
| Initial dose | 150 IU/kg 3x/week<br>or 450 IU/kg QW | 30,000 IU (450IU/kg) per week in 1 injection or in 3 to 7 injections | 500 µg (6.75 µg/kg) Q3W<br>or 2.25 µg/kg QW |
| Dose increase in non-responders | - If increase in Hb is < 1g/dL after 4 weeks ⇨ double the dose<br>(max 300 IU 3x/week) (max 60000 IU/week)<br>- If increase in Hb is < 1g/dL after 8 weeks ⇨ treatment should be discontinued | | No.<br>If clinical response is inadequate after 9 weeks, further therapy may not be effective |
| Dose adjustment | - if ↗ in Hb > 2g/dL in 4 weeks or Hb > 12g/dL⇨ ↙ dose by 25 to 50%<br>- if Hb ≥ 13g/dL discontinue until Hb = 12g/dL ⇨ ↙ dose by 25% | - once therapeutic objective achieved ⇨ ↙ dose by 25 to 50%<br>- if Hb > 12g/dL or if ↗ in Hb > 2g/dL in 4 weeks ⇨ ↙ dose by 25 to 50%<br>- if Hb ≥ 13g/dL discontinue until 12g/dL ⇨ ↙ dose by 25% | |

**Eprex & Binocrit SmPCs have not yet been updated following the new EMEA recommendations**