"BIOSIMILARI, QUESTI SCONOSCIUTI"

Hospital meeting

10 GIUGNO 2010, ore 14.30

Dr Maria Sofia Rosati

Biosimilari, questi sconosciuti

Maria Sofia Rosati

Hospital Meeting, Roma, 10 Giugno 2010

Ripasso generale!

NCCN® Practice Guidelines in Oncology – v.1.2010

Myeloid Growth Factors

Guidelines Index
Myeloid Growth Factors TOC
Discussion, References

EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE[a]

RISK ASSESSMENT FOR FEBRILE NEUTROPENIA[c]

Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignancies[b]

- Disease
- Chemotherapy regimen[d]
  - High dose therapy
  - Dose dense therapy
  - Standard dose therapy
- Patient risk factors[d]
- Treatment intent (curative vs palliative)

→ High[e] (> 20%)

→ Intermediate (10 - 20%)

PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA[c,f,g]

CHEMOTHERAPY TREATMENT INTENT		
CURATIVE/ ADJUVANT[h]	PROLONG SURVIVAL/ QUALITY OF LIFE	SYMPTOM MANAGEMENT QUALITY
CSF (category 1 for G-CSF)[i]	CSF (category … for …	

[a] The NCCN Myeloid Growth Factors Guidelines … patients.

[b] For use of growth factors in Myelod… Myelodysplastic Guidelines … see the NCCN Acute M…

[c] Febrile neutro… over 1 h…

…Cycles

…ing agent dose, radiation …tors use on the slight excess risk …d with these agents and modalities are …elated risk of leukemia and MDS has been …c studies, but has not been observed in the available …zed studies.

…gory 1 evidence for G-CSF for a reduction of: risk of febrile …penia, hospitalization, intravenous antibiotics during the course of therapy. There is category 2A evidence for G-CSF for a reduction in infection related mortality during the course of treatment. (See discussion for further detail.)

[j] Only consider CSF if patients are at significant risk for serious medical consequences of febrile neutropenia, including death.

[k] The use of CSF in this setting is a difficult decision and requires careful discussion between the physician and the patient. If patient risk factors determine the risk is10 -20%, CSF is reasonable. However, if the risk is due to the chemotherapy regimen, other alternatives such as the use of less myelosuppressive chemotherapy or dose reduction, if of comparable benefit, should be explored.

…complication …nsity. …otherapy for solid tumors …n Factors for Prophylaxis and …enance of Scheduled Dose Delivery …Factors (MGF-D).

…ations are category 2A unless otherwise indicated.
…NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

RISCHIO ELEVATO DI SVILUPPO DI LEUCO-NEUTROPENIA FEBBRILE!!!!
> 20%

Myeloid Growth Factors

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Examples of Disease Settings and Chemotherapy Regimens with a High Risk of Febrile Neutropenia (> 20%)

- *This list is not comprehensive*, there are other agents/regimens that have a high risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia MGF-B)
- Pegfilgrastim has not been documented to have benefit in regimens given under a 2 week duration.
- Note: The references listed for each regimen are limited by the specific populations studied, methods, and collection of data for febrile neutropenia in the clinical trial.

Bladder Cancer
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)[1]

Breast Cancer
- Docetaxel + trastuzumab (metastatic or relapsed)[2]
- Dose dense AC → T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)[3]
- AT (doxorubicin, paclitaxel) (metastatic or relapsed)[4]
- AT (doxorubicin, docetaxel) (metastatic or relapsed)[5]
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)[6]

Esophageal and Gastric Cancer
- Docetaxel/cisplatin/fluorouracil[7]

Kidney Cancer
- Doxorubicin/gemcitabine[8]

Non-Hodgkin's Lymphoma
- ICE (ifosfamide, carboplatin, etoposide) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphomas, 2nd line, salvage)[9]
- RICE * (rituximab, ifosfamide, carboplatin, etoposide)[10]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone)[11]
- MINE (mesna, ifosfamide, novantrone and etoposide) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphomas, 2nd line, refractory)[12]
- DHAP (dexamethasone, cisplatin, cytarabine) (Peripheral T-cell Lymphomas, Diffuse Large B-Cell Lymphoma, 2nd line)[13]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (Diffuse Large B-Cell Lymphoma, Peripheral T-cell Lymphoma, 2nd line, recurrent)[14]
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[15]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[16,17]

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)[18]
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)[18]

Multiple Myeloma
- Modified HyperCVAD[19]

Myelodysplastic syndrome
- Antithymocyte globulin, rabbit/cyclosporine[20]
- Decitabine[21]

Ovarian Cancer
- Topotecan[22]
- Paclitaxel[23]
- Docetaxel[24]

Pancreatic Cancer
- Gemcitabine/docetaxel[25]

Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[26]
- Doxorubicin[27]

Small Cell Lung Cancer
- Topotecan[28]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[29]
- VIP (etoposide,ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[30]

*In general, dose dense regimens require growth factor support for chemotherapy administration.

See Chemotherapy Regimen References MGF-A (3 of 5)

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk of Febrile Neutropenia MGF-A (2 of 5)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

MYELOID GROWTH FACTORS FOR PROPHYLAXIS AND TREATMENT OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim (category 1)
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.
  - Start 24-72 h after completion of chemotherapy and treat through post-nadir recovery. Administration of growth factor on same day as chemotherapy is not recommended.
- Pegfilgrastim (category 1) (For prophylactic use only)
  - One dose of 6 mg per cycle of treatment.
  - Start 24-72 h after completion of chemotherapy. Administration of growth factor on same day as chemotherapy is not recommended.[1]
  - There is evidence to support use for chemotherapy regimens given every 3 wks (category 1).
  - Phase II studies demonstrate efficacy in chemotherapy regimens given every 2 wks.
  - There are insufficient data to support dose and schedule of weekly regimens or chemotherapy schedules less than 2 weeks and these cannot be recommended.

Filgrastim (Categoria 1)

- Dose giornaliera 5 mcg/Kg iniziando 24/48 ore dopo la CHT fino al post-nadir o al raggiungimento di una ANC vicino alla norma
- NO filgrastim lo stesso giorno della CHT
- NO uso concomitante a CHT e/o RT

Therapeutic Use of CSFs (MGF-3)

Compared to prophylactic use, there is less evidence supporting therapeutic use of CSFs for FN as an adjunctive to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials [46], Clark and colleagues reported a shorter length of hospitalization (HR = 0.63; 95% CI, 0.49 to 0.82; P = 0.0006), shorter time to neutrophil recovery (HR = 0.32; 95% CI, 0.23 to 0.46; P < 0.00001), but no improvement in overall survival associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al [47] again found no difference in mortality, but they were unable to assess other clinical benefits. Of note,

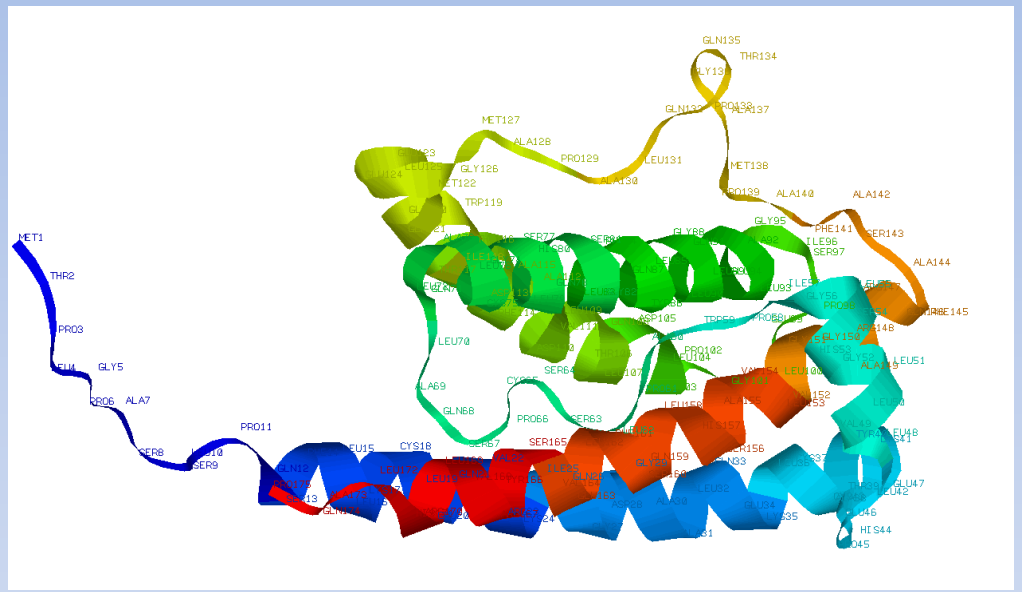
Considerazioni

- Profilassi primaria: la neutropenia febbrile (FN) è attesa, per il protocollo in esame, in >20% dei casi; indicazione: filgrastim (gg 2→nadir) o peg-filgrastim (6 mg entro le 24 ore dal trattamento)
- Profilassi secondaria: quando la FN è un evento atteso < 20% nel protocollo in esame, ma il/la paziente ha sviluppato l'evento al I ciclo; indicazione: filgrastim (gg 2→nadir) o peg-filgrastim (6 mg entro le 24 ore dal trattamento)

Considerazioni

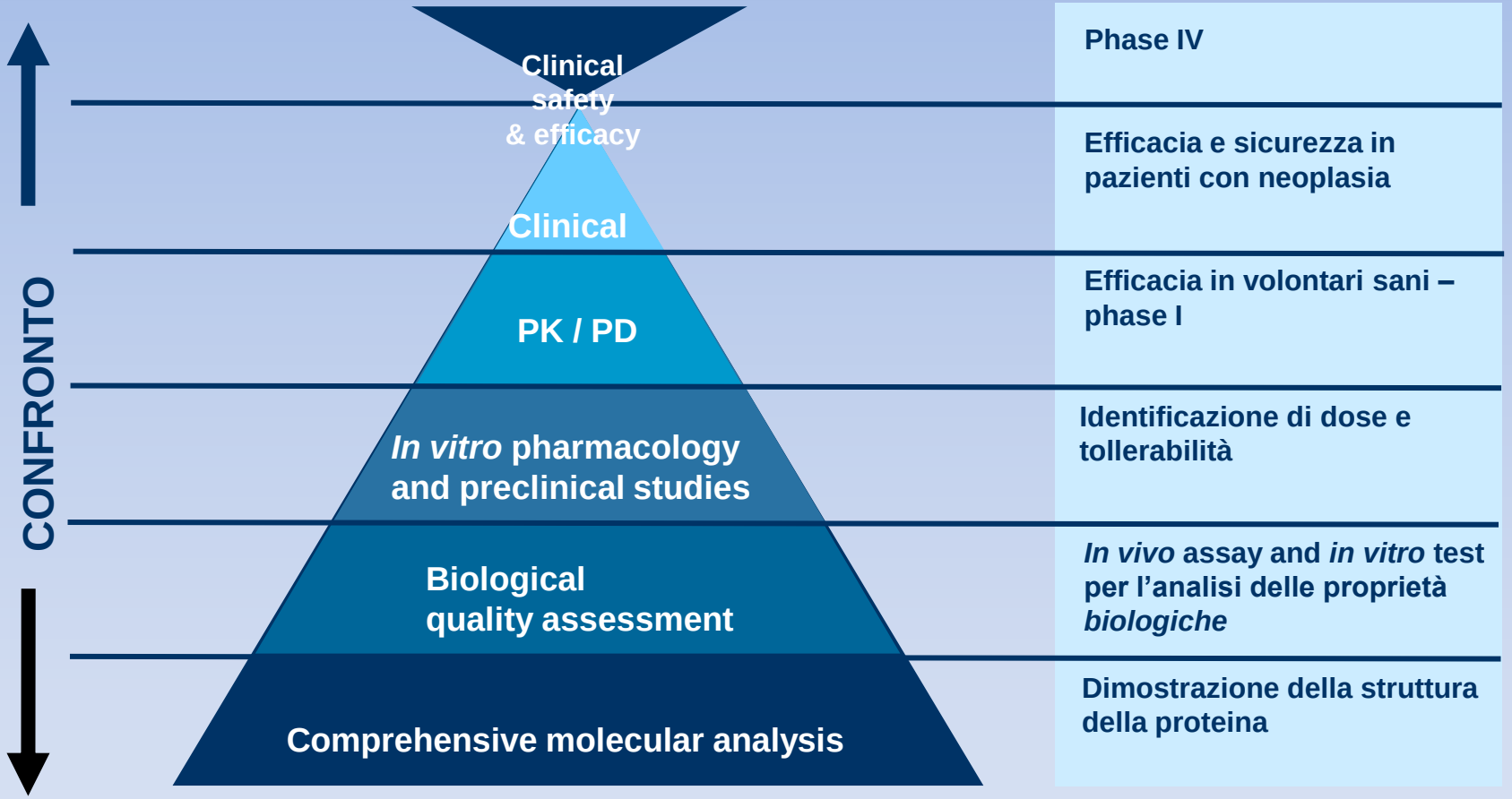
- Utilizzo terapeutico: quando il/la pz presenta FN, utile supporto con terapia antibiotica. L'utilizzo dei CSF non migliora il recupero
- Leuco-neutropenia NON febbrile: NON VA TRATTATA CON CFS!!!!!!!!!!!!!
- Opportuno eseguire esame emocromocitometrico intorno al NADIR del primo ciclo per prevederne l'andamento successivo.

Zarzio®



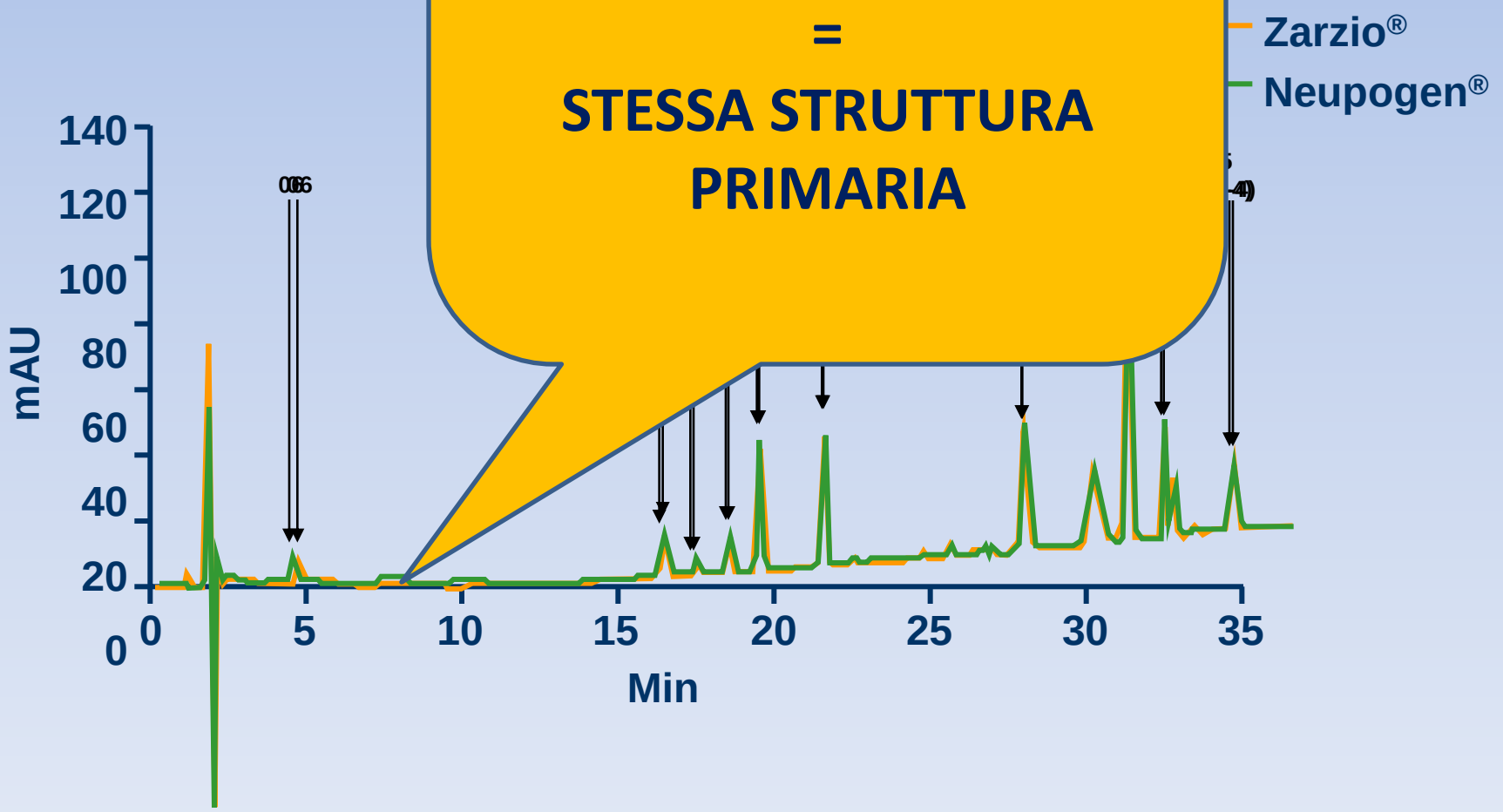
Filgrastim

Zarzio®: programma di sviluppo



Map

PERFETTA SOVRAPPOSIZIONE DI MAPPAGGIO PEPTIDICO = STESSA STRUTTURA PRIMARIA



CONFRONTO FISICO-CHIMICO

Molecular attribute	Methods	Zarzio®	Reference product	International standard
Composition, primary structure	Peptide map (LC-MS), peptide mass fingerprint (MALDI-MS), MALDI-TOF, sequencing	✓	✓	✓
Higher-order structure, conformation	Far and near UV CD spectr[illegible]py, thermal stability, NMR, S[illegible]A	✓	✓	✓
Polarity, charge, isoforms	RP-HPLC, CZE	✓	✓	✓
Size, aggregates, physical conditions	SDS-PAGE/Coomassi[illegible] AF4, AUC	✓	✓	✓
Binding	[illegible]	[illegible]	[illegible]	✓
Biological activity				✓

STRUTTURA PRIMARIA IDENTICA
STRUTTURA SECONDARIA SIMILE
STRUTTURA TERZIARIA SIMILE
MASSA MOLECOLARE ≈ IDENTICA
CARICA SIMILE
AFFINITA' DI LEGAME IDENTICA
BIOATTIVITA' IDENTICA

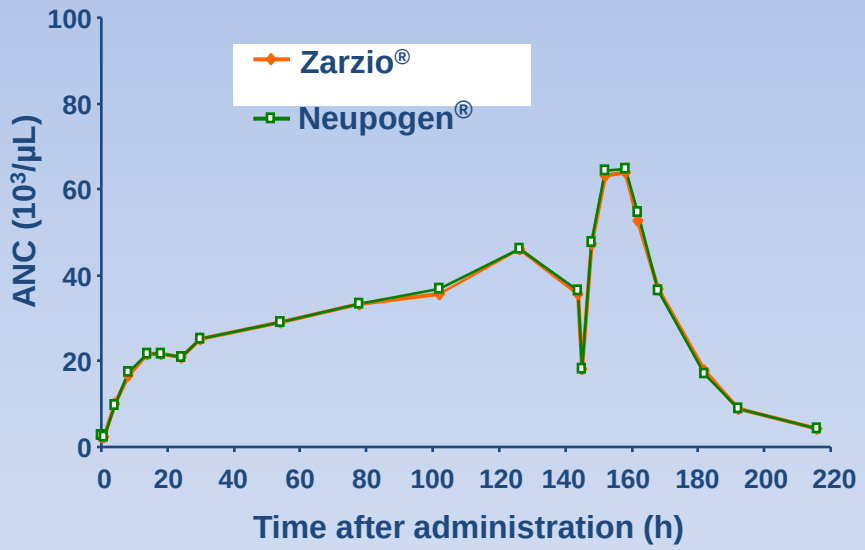
Efficacia e sicurezza
Studi di Fase I

Study	EP06-101	EP06-102	EP06-103	EP06-105
Type of study	Randomised, double-blind, 2-way crossover	Randomised, double-blind, 2-way crossover	Randomised, double-blind, 2-way crossover	Randomised, double-blind, 2-way crossover
No. of subjects (146)	40	26	56	24
Age (range), race, gender	25-45 years, 100% Caucasian 52.5% male	23-39 years 100% Caucasian 54% male	21-54 years 100% Caucasian 59% male	21-53 years 100% Caucasian 54% male
Dose	10 μg/kg	5 μg/kg	5 μg/kg	1 μg/kg
Frequency of dosing	Multiple SC injections for 7 days	Single IV injection	Multiple SC injections for 7 days	Single SC injection
Objectives	Primary: PK bioequivalence Secondary: PD, safety, local tolerance	Primary: PK bioequivalence Secondary: PD, safety	Primary: PD bioequivalence Secondary: Safety, local tolerance, PK	Primary: PD bioequivalence Secondary: Safety, local tolerance, PK

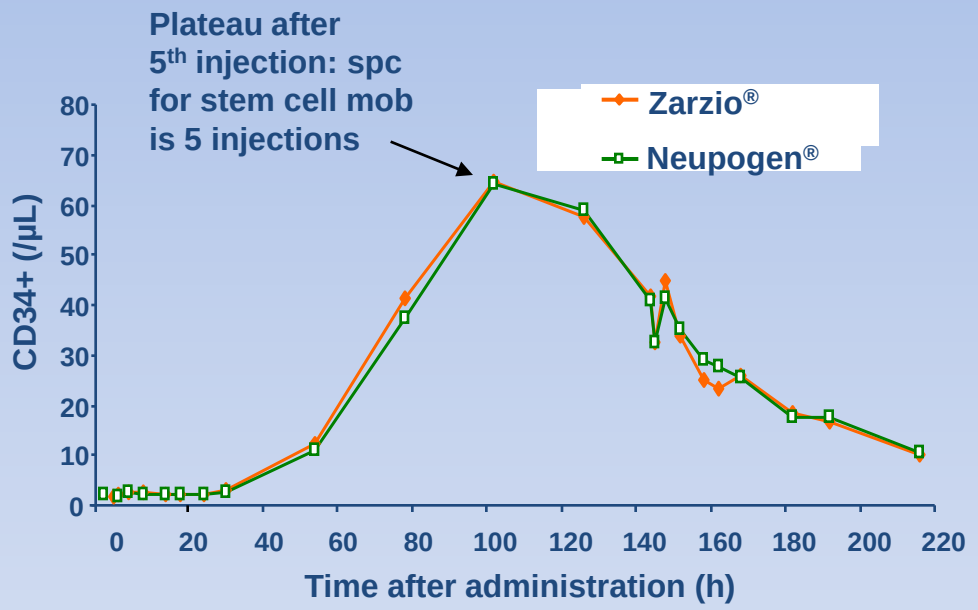
Gascon P et al. *Ann Oncol*, Dec 09

Phase I:
Studio EPO6-101

Development of absolute neutrophil count (ANC)



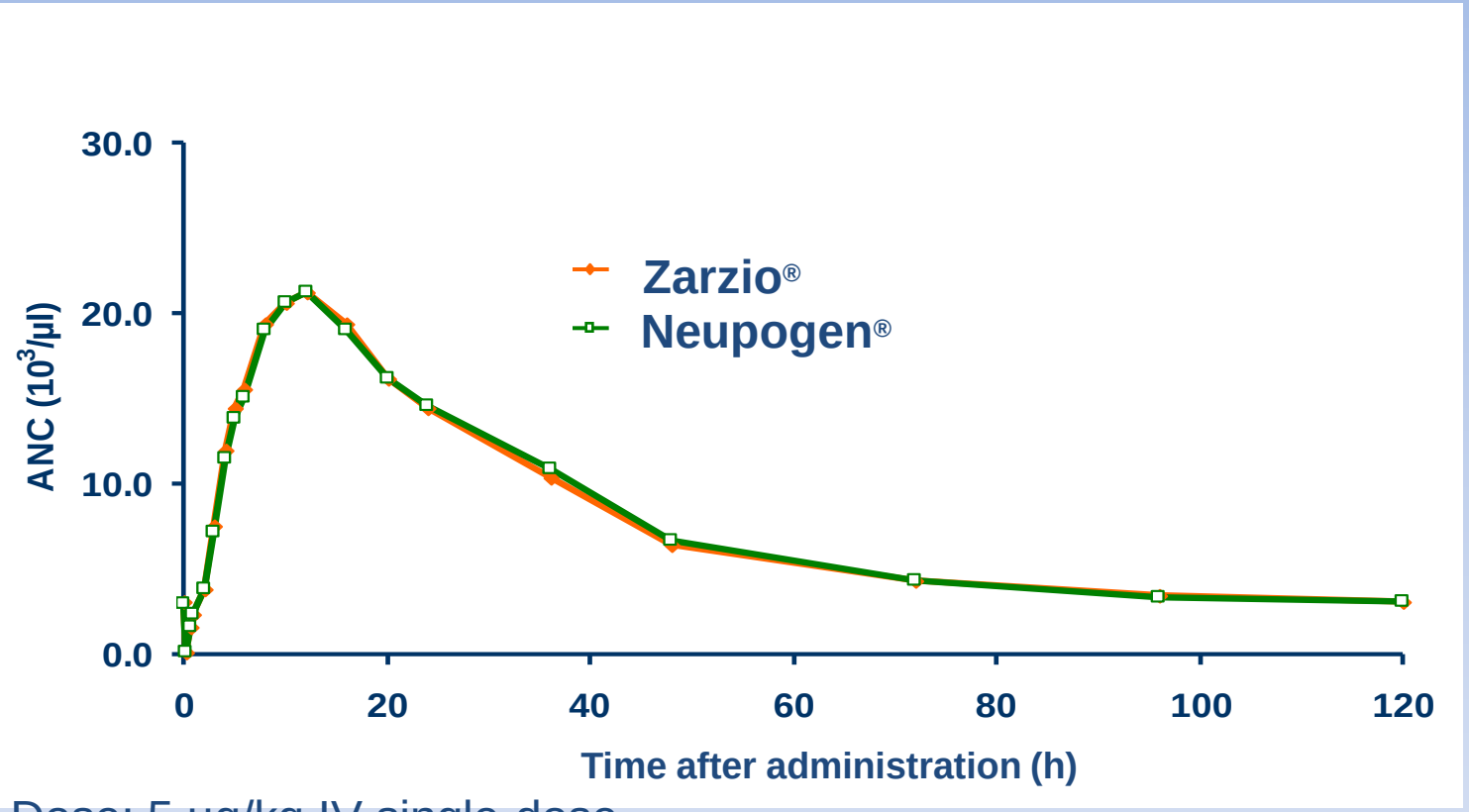
Development of CD34⁺ cells



- Dose: 10 µg/kg SC for 7 days
- CD34⁺ count = surrogate marker for efficacy in stem cell mobilisation
- Curves for both ANC and CD34⁺ cells superimposable for Zarzio® and Neupogen®

Gascon P et al. *Ann Oncol*, Dec 09

Phase I:
Studio EPO6-101



- Dose: 5 µg/kg IV single-dose
- ANC curves superimposable for Zarzio® and Neupogen®
- Zarzio® and Neupogen® show comparable pharmacodynamics after a single IV dose

Gascon P et al. *Ann Oncol*, Dec 09

Studi di Fase I: sommario

- Gli eventi avversi farmaco-correlati conZarzio® nei volontari sani (es: dolore muscolo-scheletrico) sono sovrapponibili a quelli di Neupogen®

- Nessuna differenza per frequenza, severità, relazione di causalità

http://www.emea.europa.eu/humandocs/Humans/EPAR/zarzio/zarzio.htm

Gascon P et al. *Ann Oncol*, Dec 09

...o® profilo

IN

...dotto usando la tecnologia del DNA ricombinante in

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Formulazione

- Soluzione per iniezione-infusione
- Somministrazione parenterale (S...

Stabilità

- 30 mesi
- Dopo diluizione: 24 hours at 2-8°...

Anemia: indagare le cause!!

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Cancer- and Chemotherapy-Induced Anemia

NCCN Guidelines Index
Anemia Table of Contents
Discussion

Primo check! Conta RETICOLOCITARIA ED MCV

Indagare possibili cause:

Emorragie (sangue occulto, es. Endoscopici)

Emolisi (Test di coombs, DIC, aptoglobina)

Fattori nutrizionali (sideremia, ferritina, B12 e folati)

Ereditarietà

Funzionalità renale (GFR< 60)

Ripasso generale!!

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011
Cancer- and Chemotherapy-Induced Anemia

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MANAGEMENT OF FUNCTIONAL IRON DEFICIENCY IN PATIENTS RECEIVING ESAs

Iron studies:
Iron panel (serum iron, total iron binding capacity, serum ferritin)

- **Functional iron deficiency (ferritin ≤ 800 ng/mL and transferrin saturation < 20%)** → **Consider IV iron supplementation[m,n,o] with erythropoietic therapy**
- **No iron deficiency (ferritin > 800 ng/mL or transferrin saturation ≥ 20%)** → **IV or oral iron supplementation is not needed**

See Parenteral Iron Preparations (ANEM-E)

RECOMMENDATIONS FOR ADMINISTERING PARENTERAL IRON PRODUCTS[1-6] (2 of 3)

	Iron Dextran†	Ferric gluconate†	Iron sucrose†
Test dose	Required 25 mg slow IV push and wait 1 hr before giving main dose	MD discretion 25 mg slow IV push or infusion	MD discretion 25 mg slow IV push
Dosage[9]	100 mg IV over 5 min • Repeated dosing once weekly for 10 doses to achieve total dose of 1 g or • Total dose infusion given over several hours*	125 mg IV over 60 min • Repeated dosing given once weekly for 8 doses or 200 mg IV over 3-4 hrs • Repeated every 3 weeks for 5 doses • Individual doses above 200 mg are not recommended[10] • Maximum total dose = 1000 mg	200 mg IV over 2-5 min • Repeated dosing given every 1- 4 weeks • Individual doses above 300 mg are not recommended[11] • Maximum total dose = 1000 mg
Routes	IV infusion IM (INFed®) (not recommended)	IV injection/infusion	IV injection/infusion

†Examples of adverse events associated with FDA approved doses of parenteral iron preparations include: hypotension, hypertension, nausea, vomiting, diarrhea, pain, fever, dyspnea, pruritis, headaches, and dizziness.

*Dose = 0.0442 (Desired Hgb - Observed Hgb) X LBW + (0.26 X LBW). LBW = Lean Body Weight
If dose exceeds 1000 mg, remaining dose may be given after 4 wks if inadequate hemoglobin response.

See References (ANEM- E 3 of 3)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

NCCN Guidelines™ Version 1.2011
Cancer- and Chemotherapy-Induced Anemia

ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 OF 5)

Cancer Patient Survival

- Studies have reported possible decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in cancer patients receiving erythropoietic drugs for correction of anemia and target hemoglobin levels of >12 g/dL.[1-8] One analysis in patients with cancer not receiving active therapy found decreased survival in ESA treated patients.[6] Please refer to the FDA website for additional information: http://www.fda.gov/cder/drug/infopage/RHE/default.htm. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa) to patients outside of the treatment period of cancer-related chemotherapy. A treatment period is defined as anemia following initiation of therapy and continuing approximately 6 weeks after the completion of treatment.
- While three meta-analysis updates on survival have indicated an increased mortality risk with the use of ESAs,[9,10,11,12] two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.[13,14]
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to a target hemoglobin of < 12 g/dL.
- Additional prospective clinical trials designed and powered to measure cancer patient survival are ongoing to provide clinicians with data to guide optimal use of erythropoietic agents.
- Because of the above issues, providers should inform patients of risks and benefits of ESA therapy versus red blood cell transfusion. (See Comparison of Risks and Benefits of ESA Use Versus Red Blood Cell Transfusion - ANEM-D).

Thrombosis

- Early trials of recombinant human erythropoietin reported that a high target hematocrit (42 ± 3%) was found to have an increased number of vascular events (arterial and venous).
- Erythropoietin has a thrombogenic potential independent of hemoglobin levels.[15] Patients with previous risk factors for thrombosis may be at higher risk for thrombosis with the use of ESAs. If considering use of ESAs, evaluate the risk factors for thrombosis: history of thromboembolism, heritable mutation, hypercoagulability, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. (See NCCN Venous Thromboembolic Disease Guidelines)
- A meta-analysis update on thrombotic complications confirms an increased thrombosis risk in cancer patients with use of erythropoietic agents.[9]
- A clinical trial in chronic kidney disease patients demonstrated an increased risk of stroke with darbepoetin alfa.[16]

Erythropoietic Therapy - Adverse Effects continued (ANEM-B 4 of 5)

See References (ANEM- B 5 of 5)

Note: All recommendations are category 2A unless otherwise indicated.
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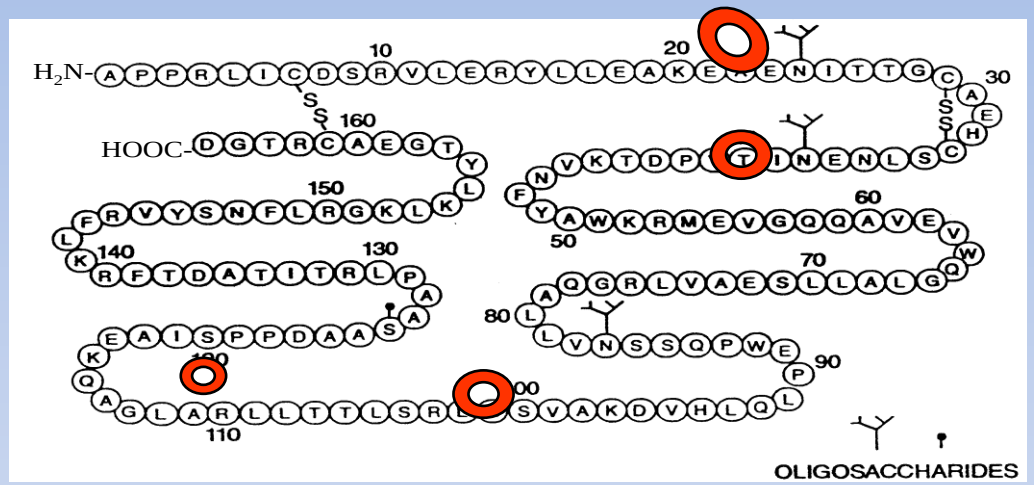
Binocrit®

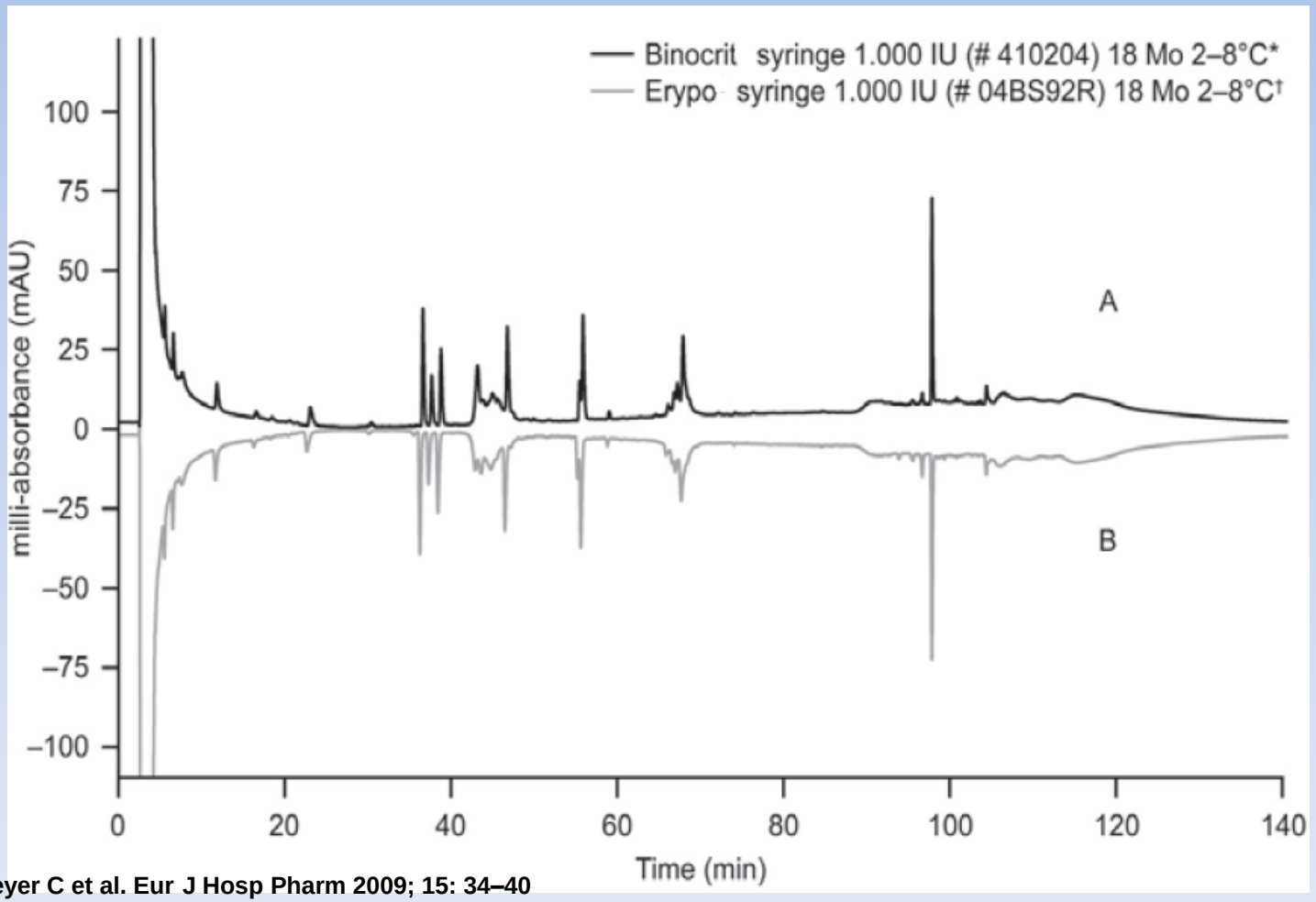


Mod. Gilg et al, Pharmaceutica Acta Helvetiae 71,1996

Eritropoietina α

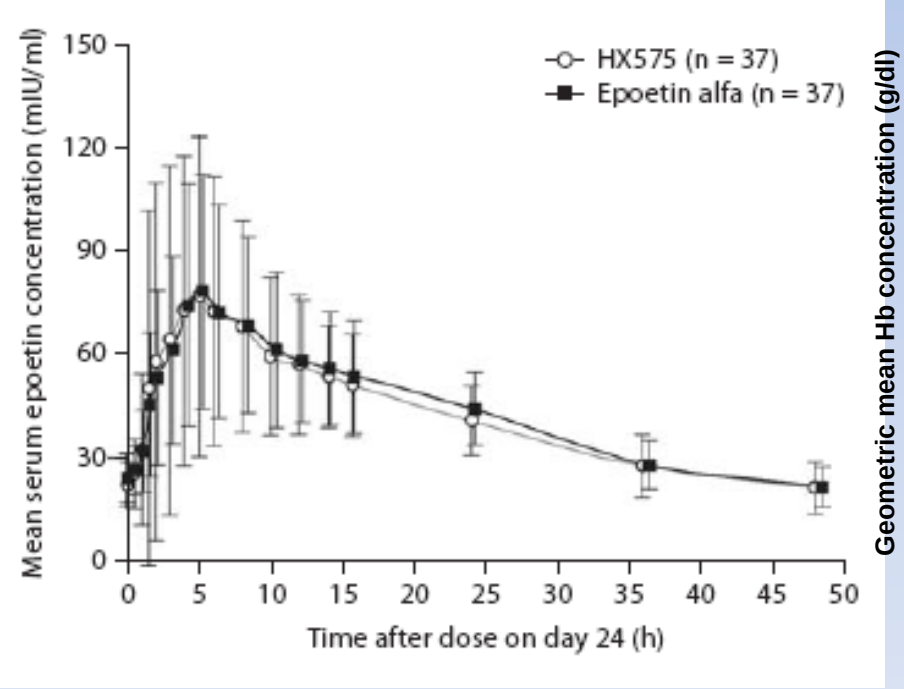
Sequenza peptidica

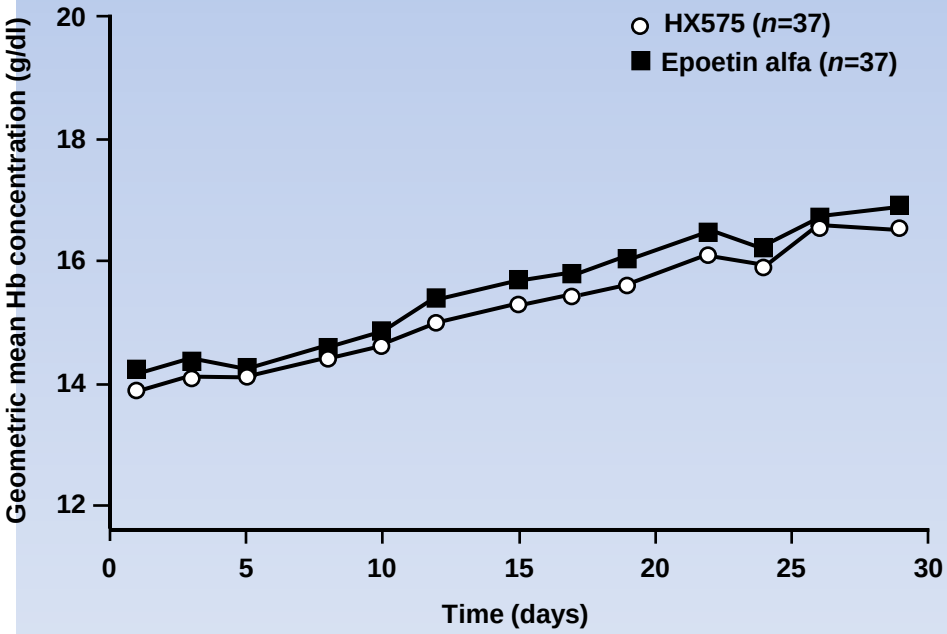
- **Struttura primaria**



Brockmeyer C et al. Eur J Hosp Pharm 2009; 15: 34–40

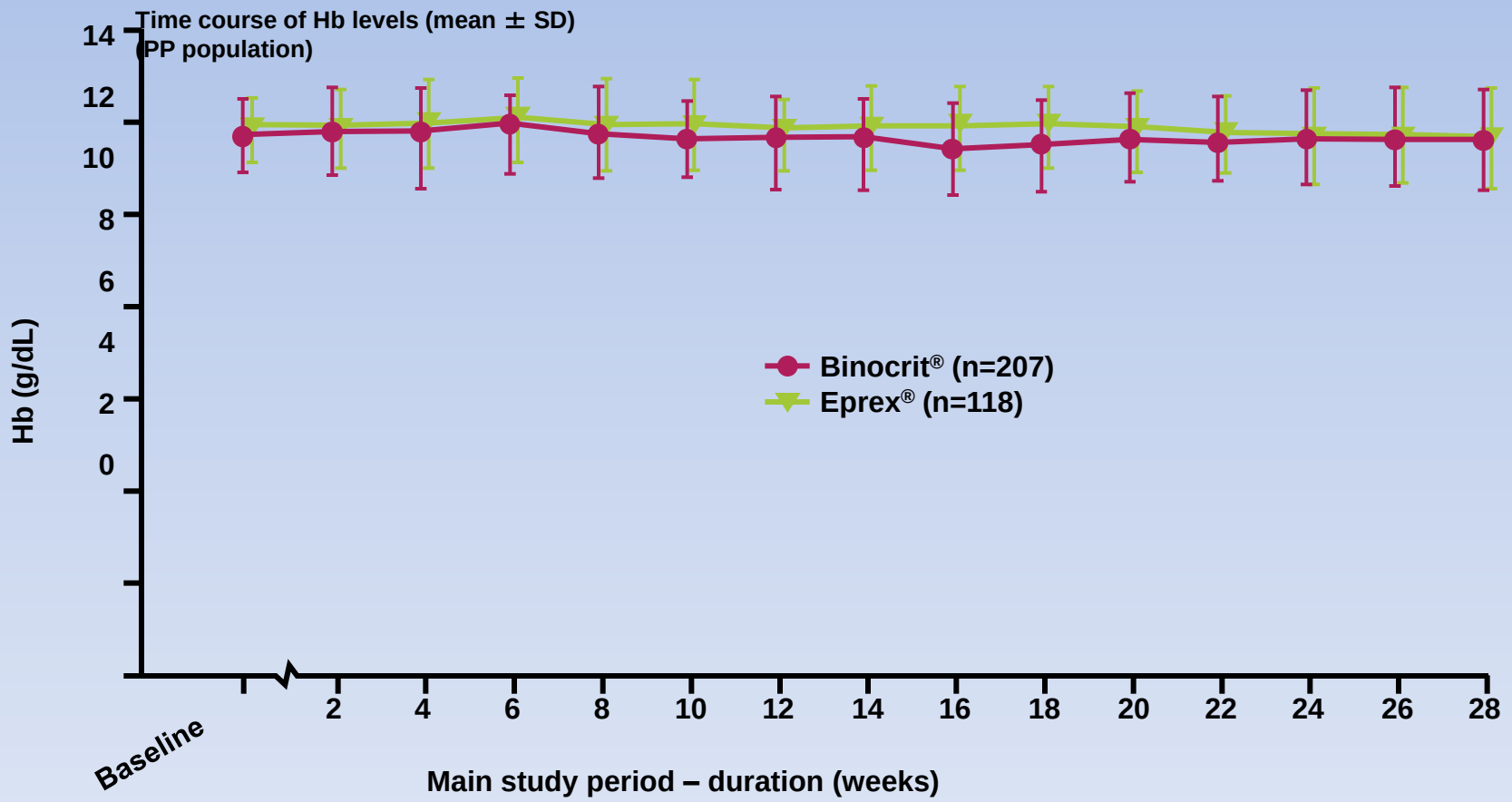
PD e PK: Studi di fase I
INJ-12





Sörgel F *et al*. Pharmacology 2009; 83: 122–30

Studio INJ-9: Binocrit® and Eprex® iv



Haag-Weber M *et al*. Clin Nephrol 2009; 72: 380–90

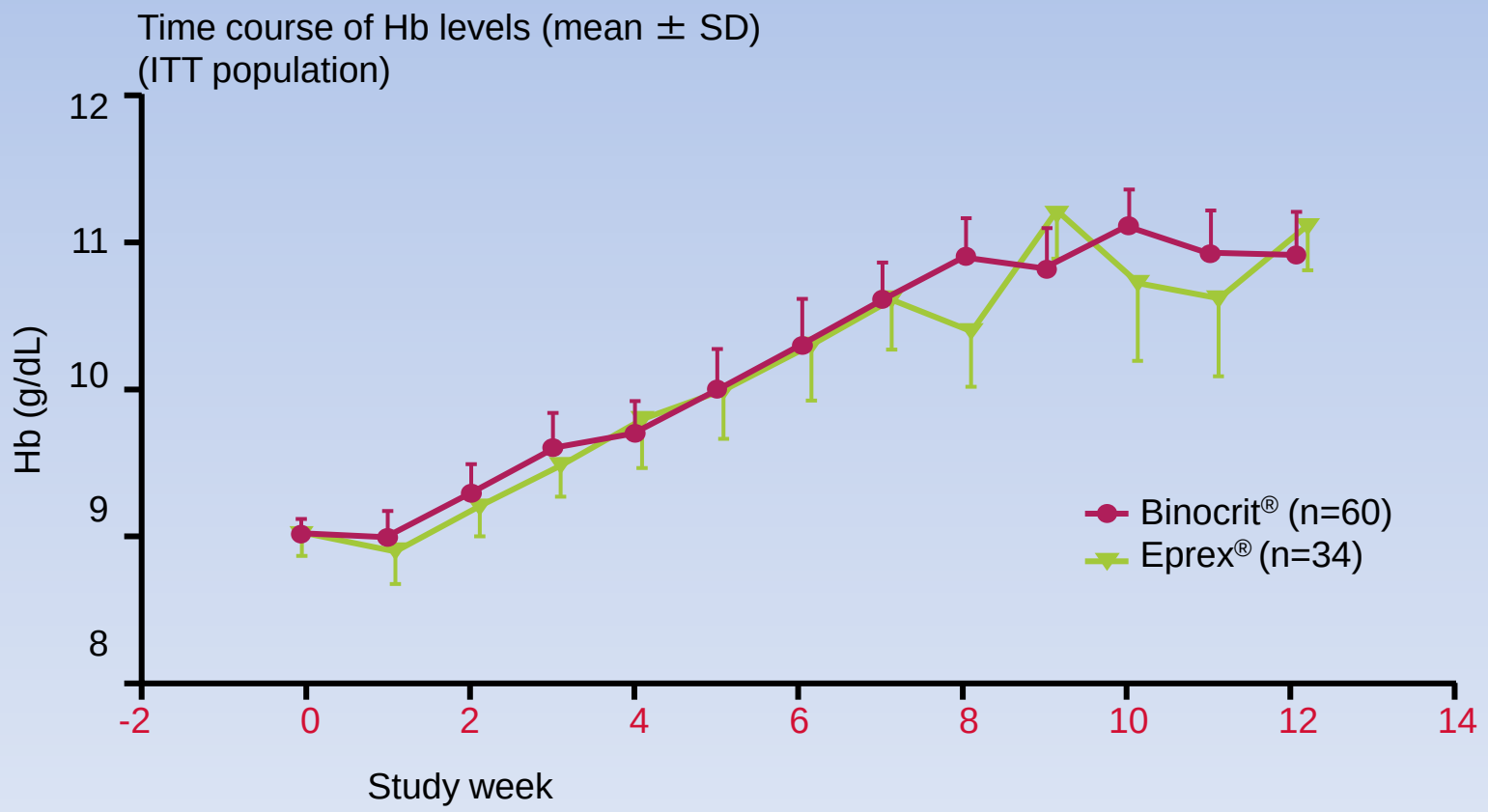
INJ-9: tollerabilità Binocrit® e Eprex®

	Binocrit® (n=314)		Eprex® (n=164)	
	n	%	n	%
Non-site specific procedural complications	94	29.9	46	28.0
Muscle-related signs and symptoms	78	24.8	39	23.8
Upper respiratory tract infections	71	22.6	41	25.0
Diarrhoea (excl. infective)	63	20.1	22	13.4
Nausea/vomiting	52	16.6	30	18.3
Lower respiratory tract/lung infections	44	14.0	29	17.7
Cardiac/vascular procedural complications	45	14.3	25	15.2
Vascular hypotensive disorders	48	15.3	21	12.8
Musculoskeletal/connective tissue signs and symptoms	41	13.1	24	14.6

Haag-Weber M *et al*. Clin Nephrol 2009; 72: 380–90

INJ-11: Binocrit®

Trattamento sc 3x settimana a dosi standard (150 IU/kg) corregge efficacemente l'anemia.



Weigang-Köhler K *et al*. Onkologie 2009; 32: 168–74

INJ-11 Conclusioni: Binocrit® in pazienti con anemia indotta da chemioterapia

- **Binocrit® vs controllo mostra equivalenza in termini di efficacia a parità di profilo di sicurezza.**
- **Nessuna differenza clinica tra i due gruppi**

Weigang-Köhler K *et al*. Onkologie 2009; 32: 168–74

: profilo

la tecnologia del DNA ricombinante in cellule

in pz con IRC in emodialisi (i.v.)
on IRC (i.v.)
nti affetti da cancro in corso di CHT (s.c.)

Dosaggi/ Forme

- Dose iniziale: 3x/settimana per IRC ici in CHT
- Cut off di Hb: 12

Formulazione

- Siringhe pre-riempite
- CKD – ev
- CIA - s.c.

Stabilità

- 24 mesi
- Dopo diluizione: 24 ore a 2-8°C

GRAZIE