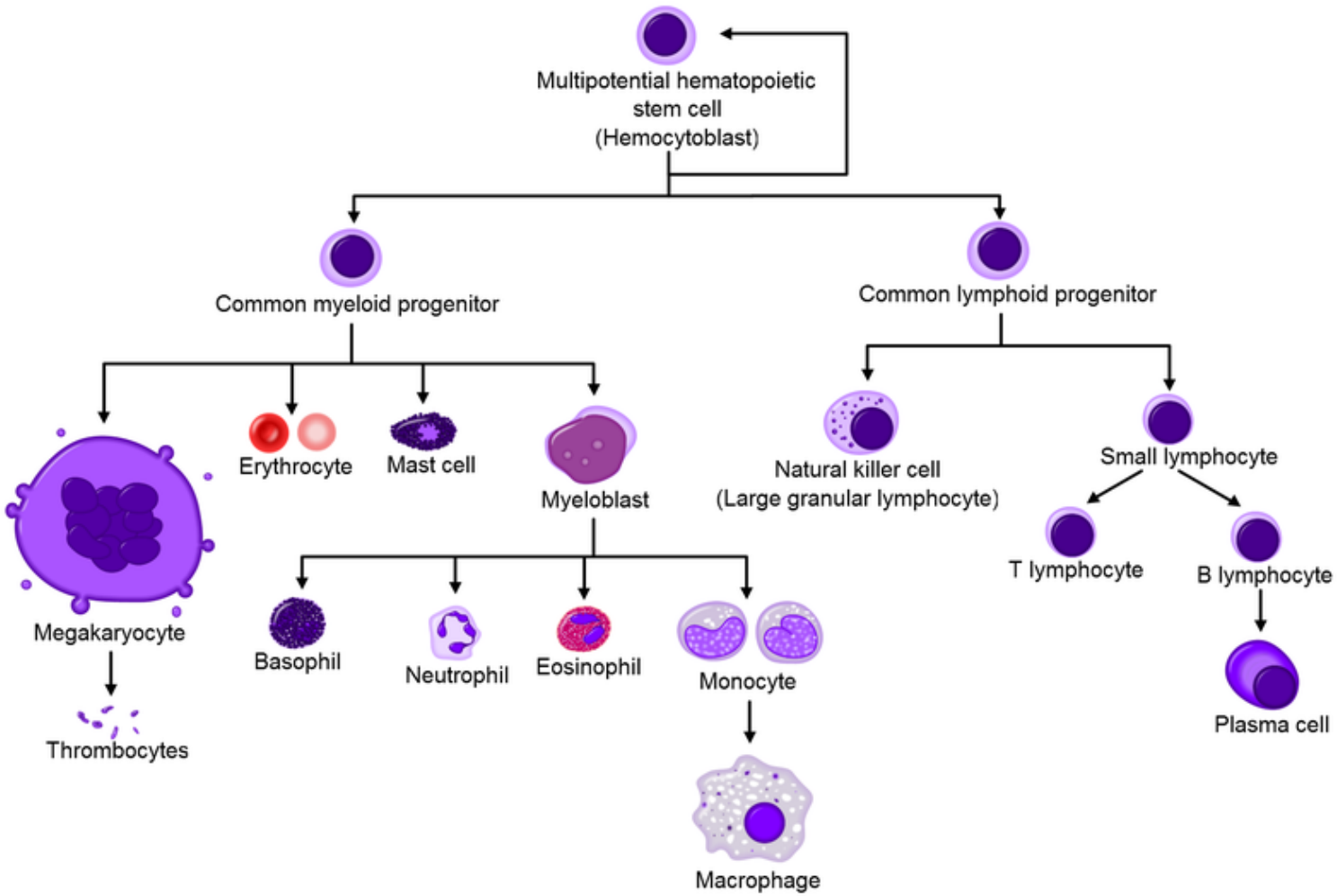
LIMBURGS ONCOLOGISCH CENTRUM vzw

Hematopoietic growth factors

Koen Theunissen
Hematologie
Jessa Ziekenhuis – Hasselt
Limburgs Oncologisch Centrum

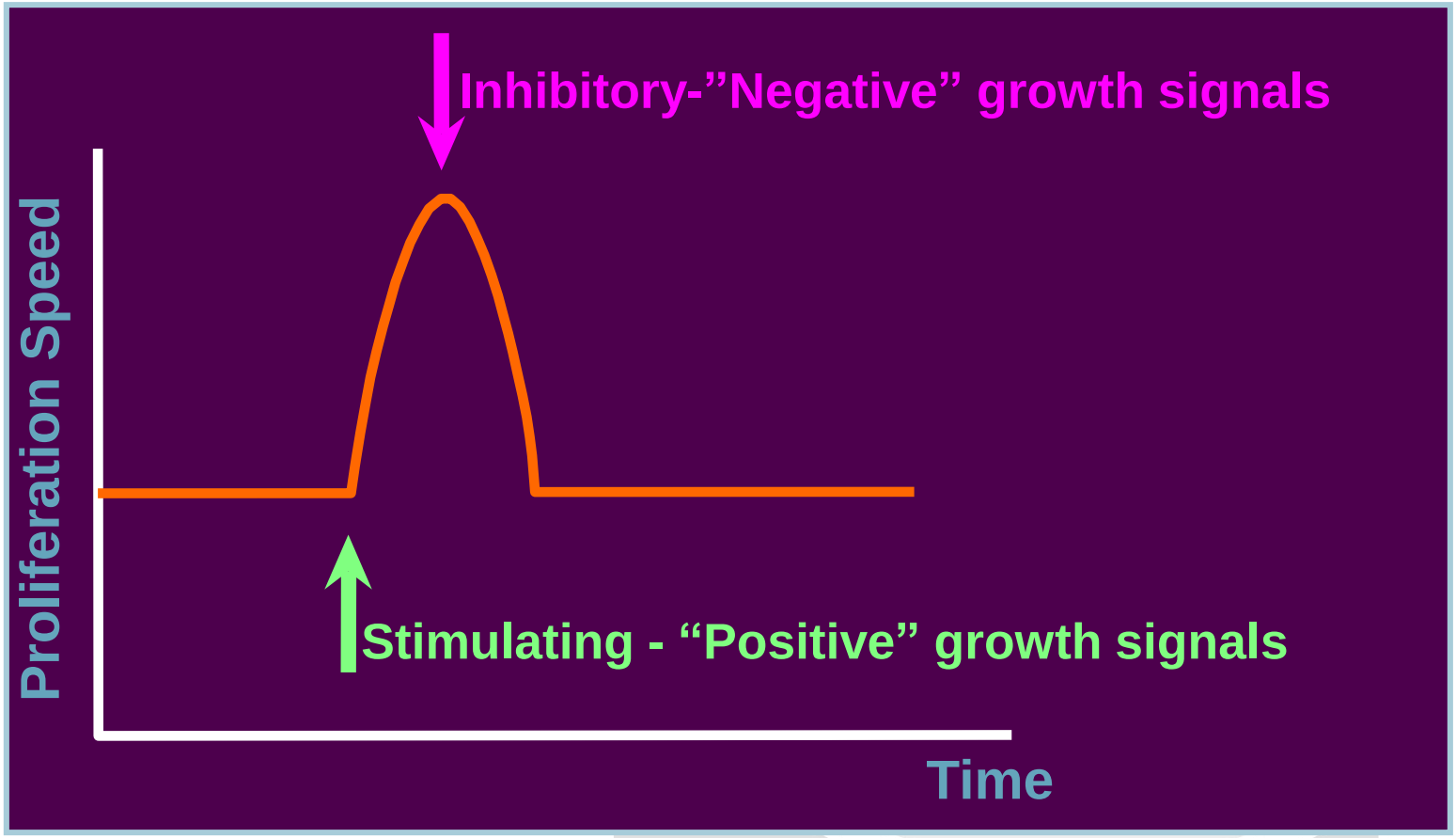
Hematopoiesis : stem cell differentiation



Peripheral Blood

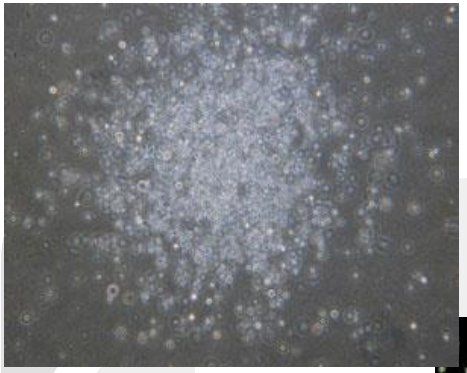
Hemoglobin		14	-	18	g/dl
Hematocrit		0.40	-	0.54	
RBC		4.50	-	6.00	x 1012/l
WBC		4	-	10	x 109/l
neutrophil rods	0	-	5%	(0 - 0.2)	
neutrophils	40	-	70%	(1.8 - 7)	
eosinophils	0	-	4%	(0.0 - 0.4)	
basophils	0	-	2%	(0.0 - 0.2)	
lymfocytes	20	-	45%	(1.5 - 3.5)	
monocytes	2	-	10%	(0.2 - 0.8)	
Thrombocytes		150	-	450	x 109/l

Regulation of Hematopoiesis

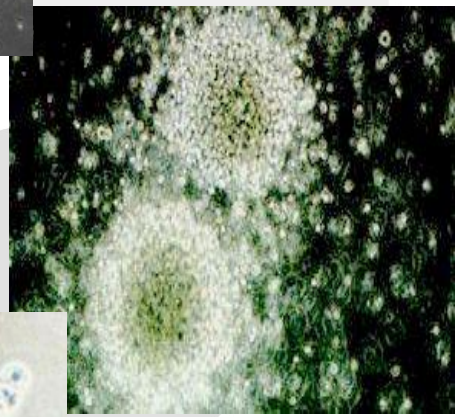


History of Hematopoietic growth factors

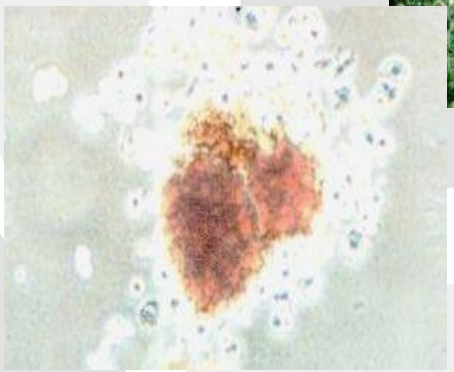
- Pluznik et al (1965), Metcalf et al (1966)
  - Bone marrow cultures in "conditioned medium" and agarose
  - Bone marrow cells form colonies of more mature cells (CFU : "colony forming units")



CFU-G



CFU-GM



CFU-GEMM

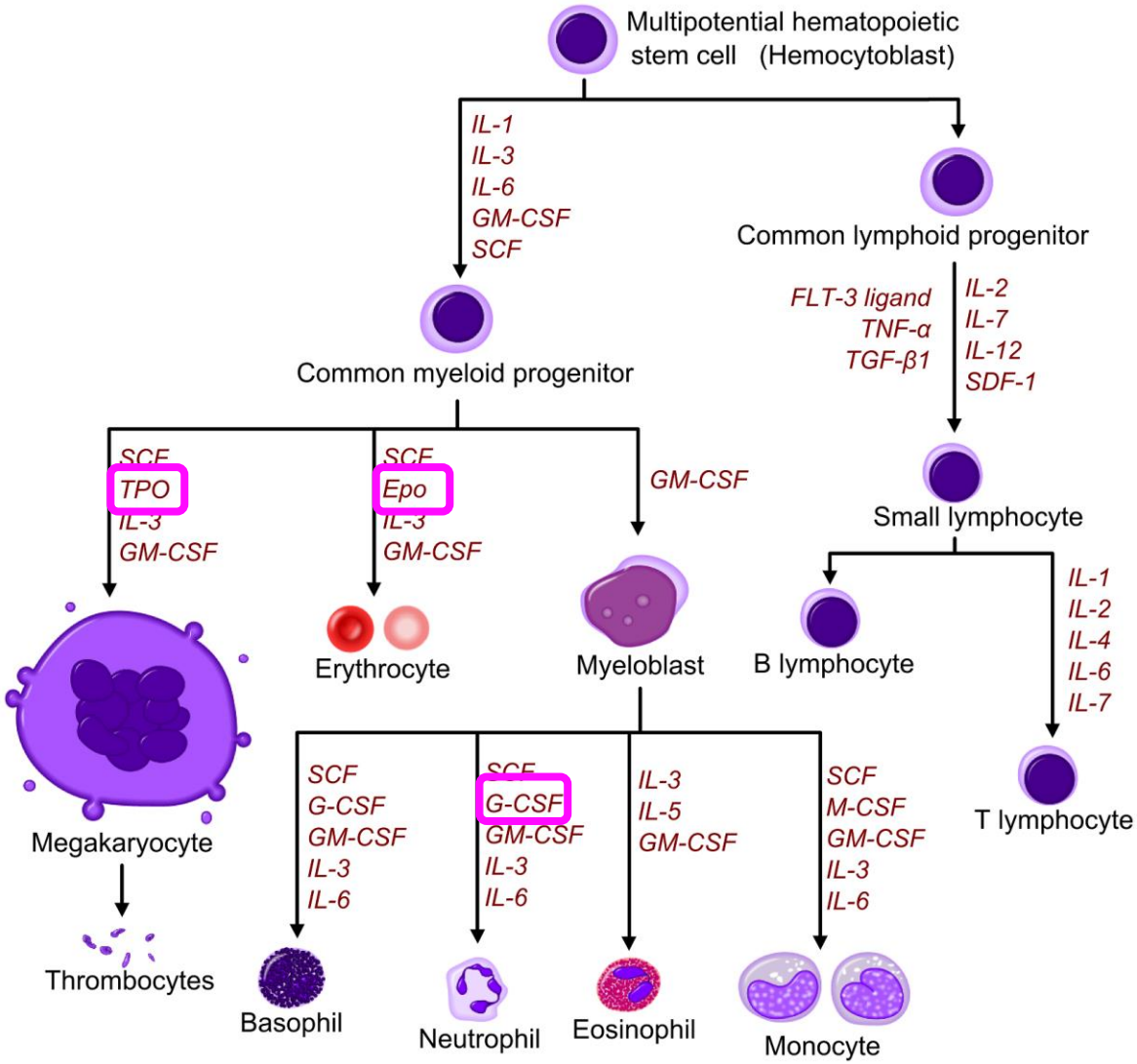
History of Hematopoietic growth factors

- Soluble factors = CSF ("colony stimulating factors"
- 1970-1980 : different kinds of CSF
  - Nomenclature depending on type of colony grown in cultures
  - Hypothesis : Growth and differentiation are regulated by exposition of stem and progenitor cells to different "CSF"

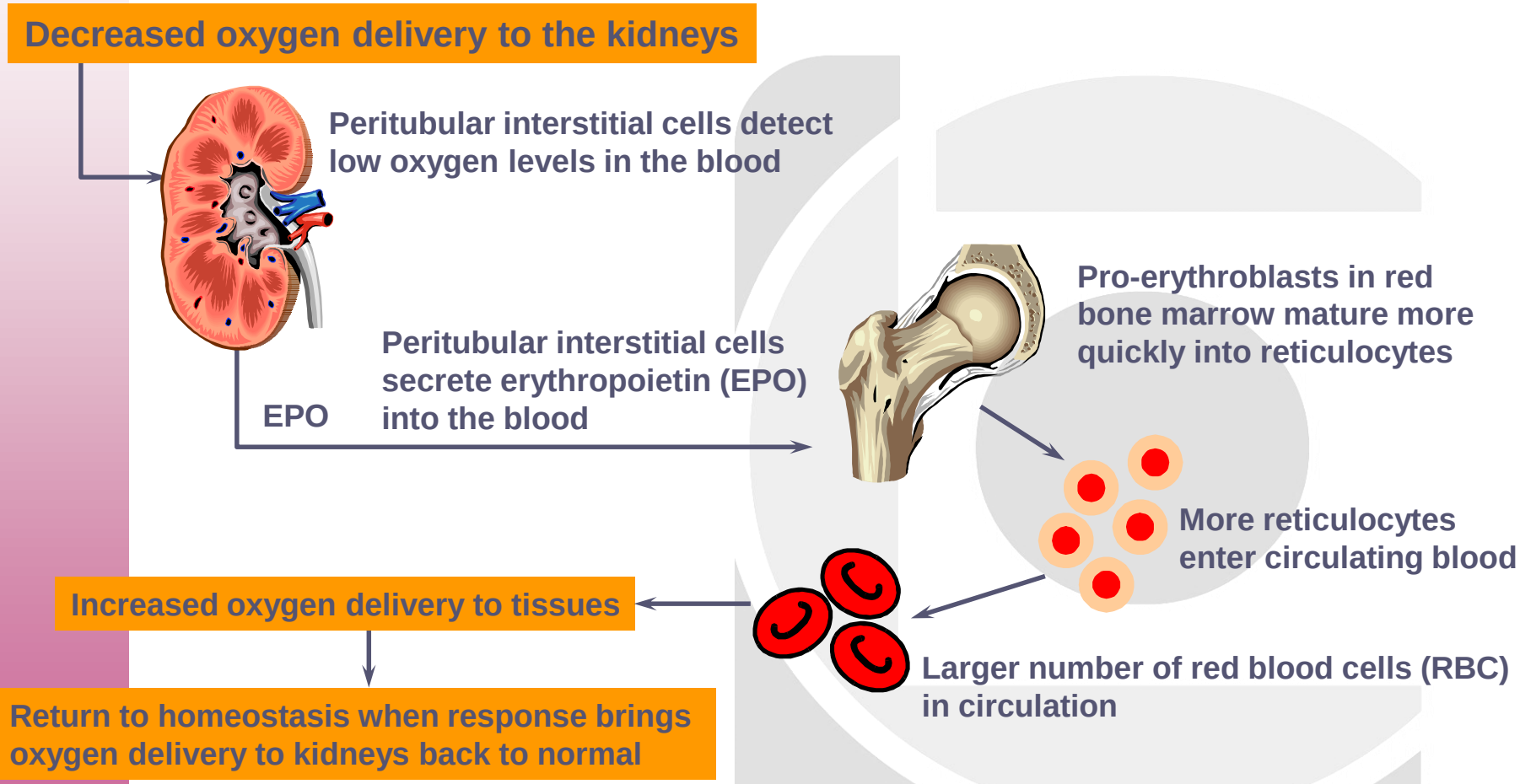
History of Hematopoietic growth factors

- 1980-1990 : molecular cloning of responsible genes and recombinant DNA technology
  - Cytokines : Large family of regulating molecules
    - Interferons
    - Interleukines
    - Tumor necrosis factors
    - Hematopoietic growth factors
  - Control the hematopoietic and the immune system, and their interactions with other systems

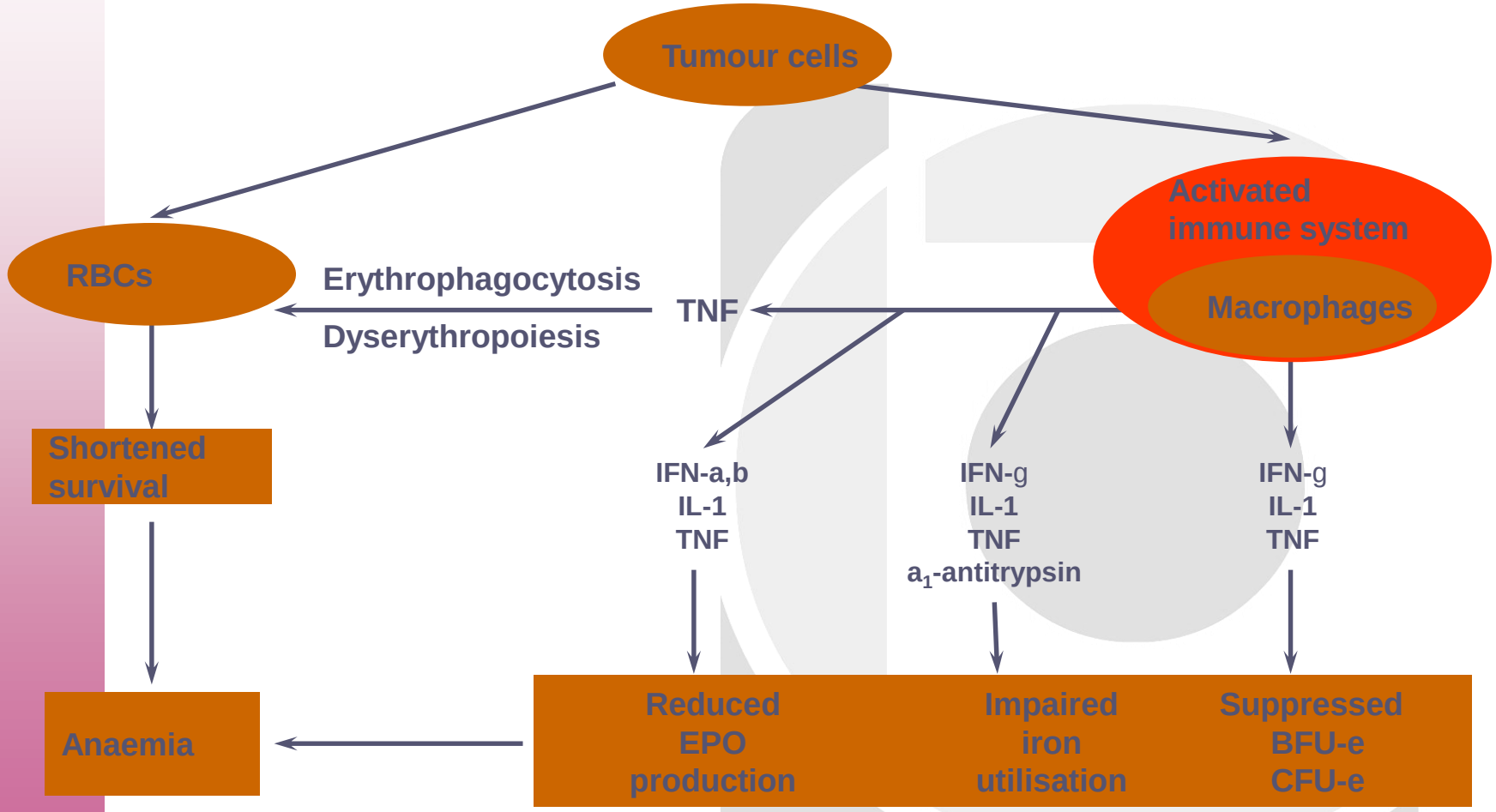
Hematopoietic growth factors



Fysiological role of EPO



Anemia in cancer patients



Nowrousian MR. Med Oncol 1998;15(Suppl. 1):S19–28

Influence of anemia on response

Low hemoglobin level

↓

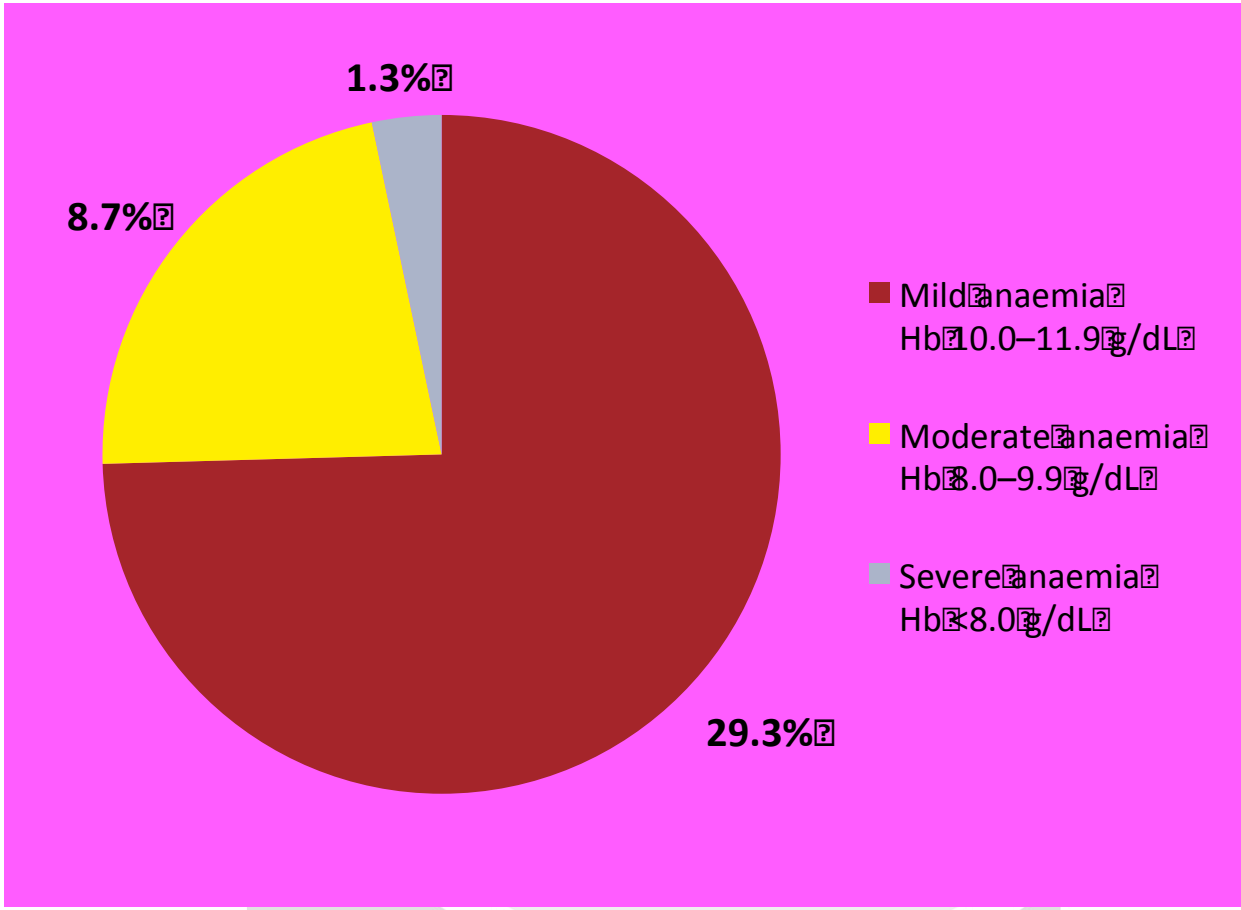
Poor tumor oxygenation - Intratumoral hypoxia

- treatment → radiotherapy, chemoradiotherapy, chemotherapy → **Resistance**
- genetic instability → aggressiveness → **Development of an aggressive phenotype**
- oxygen-related proteins → metastasis → **Development of an aggressive phenotype**
- stimulation of angiogenesis → progression → **Development of an aggressive phenotype**

Molls M. et al :Strahlenther. Onkol. 1998;174: Suppl IV:13 -16

Anemia is Common in Cancer Patients of all Tumour Types and Disease Status

- 39.3%[a] of all patients anemic at enrolment
- 67%[b] anemic at some point during the 6-month study
- 50.3% of patients receiving chemotherapy were anemic
- 38.9%[b] received treatment for anemia



[a]Denominator = 14,520 patients
[b]Denominator = 13,628 patients

*Anaemia defined as haemoglobin (Hb) <12 g/dL

Ludwig H et al. *Eur J Cancer* 2004;40:2293–2306

Why Does Anemia Need To Be Treated?

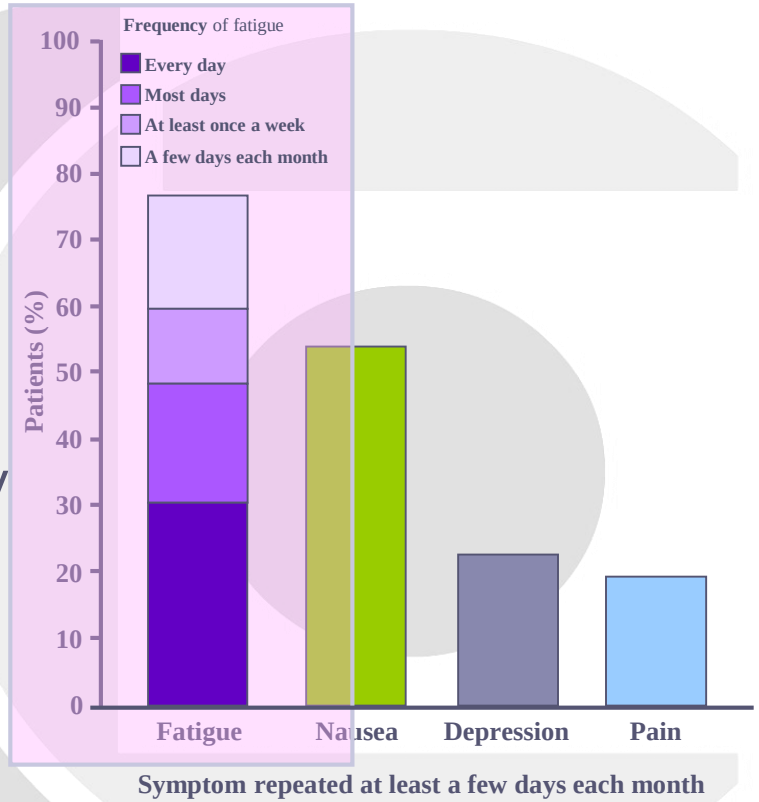
- Anemia is associated with poor prognosis in cancer patients[1]
- The ability to complete chemotherapy regimens on time and with full dose might be compromised[2]
  - A significant association ($p<0.001$) between chemotherapy dose delays and reductions, and anemia has been observed
- Patient quality of life (QoL) becomes impaired with low Hb levels[3]
- Patients can also suffer from cancer-related fatigue (CRF)[4]

1. Caro JJ et al. Cancer 2001;91:2214–2221; 2. Repetto L, CIPOMO Investigators. *Crit Rev Oncol Hematol* 2009;72:170–179; 3. Ludwig H et al. *Eur J Cancer* 2004;40:2293–2306; 4. NCCN. Cancer-related fatigue v.1.2011 www.nccn.org

CRF is a Common Side Effect in Chemotherapy-treated Cancer Patients

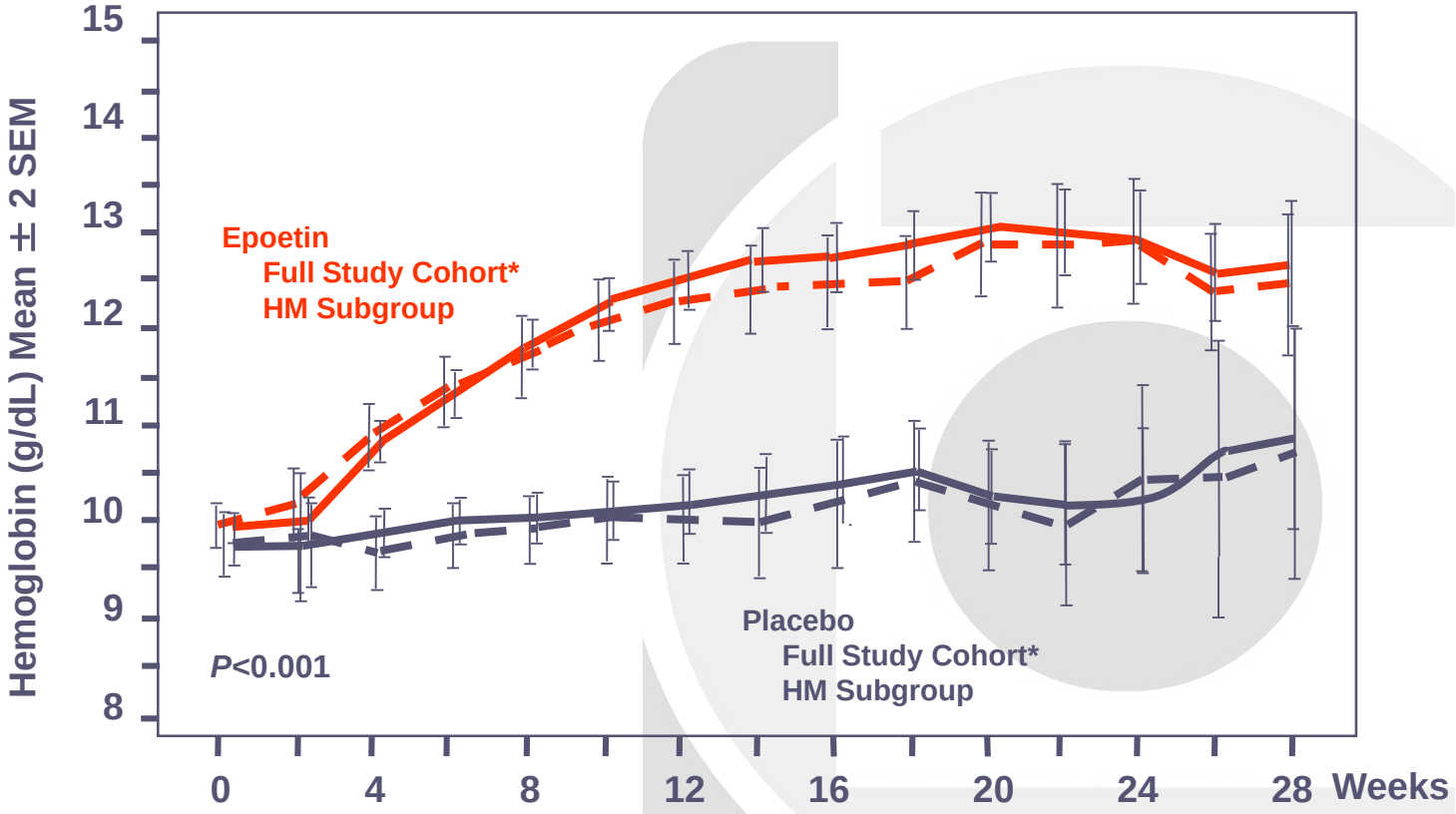
- ~70–100% of patients with cancer are affected by fatigue[1,2]
- 30% of patients experience fatigue on a daily basis[2]
- 95% of patients undergoing chemotherapy or radiotherapy anticipate CRF[3]

Frequency of side effects experienced by chemotherapy-treated patients (n=379)[3]



1. NCCN. Cancer-related fatigue v.1.2011 www.nccn.org
2. Curt GA et al. *Oncologist* 2000;5:353–360
3. Hofman M et al. *Oncologist* 2007;12:4–10

EPO alpha for treatment of anemia in cancer patients



Littlewood 2001; Littlewood 2000.

IMPACT NHL Study: Objectives and Protocol

- Multicentre, international, retrospective and prospective observational study non-Hodgkin's lymphoma patients receiving CHOP-14 or CHOP-21 (with or without rituximab)
- **Primary objective:** To assess neutropenia prophylaxis
- **Secondary objective:** To investigate anemia and ESA administration
- This study presents results of the secondary outcome evaluations

Haioun C et al. *Leuk Lymphoma* 2011;52:796–803

IMPACT NHL Study: Baseline Characteristics

- The full analysis set included 1829 patients:
  - 404 (22%) received an ESA
  - 1425 (78%) received no ESA
- Patients receiving an ESA were generally older, female and had more advanced disease
- The most frequently prescribed ESA was DA (n=207), followed by epoetin beta (n=105) and epoetin alfa (n=89)
  - Three patients received an ESA other than these agents
  - 14 patients switched ESA during the study

Haioun C et al. *Leuk Lymphoma* 2011;52:796–803

Administration of an ESA was Associated with an Increase in Hb

	Darbepoietin	Epoetin alfa	Epoetin beta
Patients with baseline Hb <10 g/dL*	**n=89**	**n=37**	**n=33**
Achieved Hb ≥10g/dL, KM % (95% CI)	**95 (87, 103)**	**90 (73, 106)**	**93 (80, 106)**
Achieved Hb 10–12 g/dL, KM % (95% CI)	**92 (78, 105)**	**78 (46, 110)**	**81 (63, 99)**
Patients with baseline Hb <11 g/dL*	**n=155**	**n=58**	**n=58**
Achieved Hb ≥11g/dL, KM % (95% CI)	**88 (74, 101)**	**79 (60, 99)**	**76 (61, 91)**
Patients with baseline Hb <12 g/dL*	**n=182**	**n=64**	**n=71**
Achieved Hb ≥12g/dL, KM % (95% CI)	**62 (41, 82)**	**80 (61, 98)**	**64 (49, 80)**
Achieved Hb 12–13g/dL, KM % (95% CI)	**42 (26, 59)**	**78 (46, 110)**	**77 (74, 110)**

*Patients who remained in study at Week 5

Haioun C et al. *Leuk Lymphoma* 2011;52:796–803

Effects and side effects

- Bohlius et al, J Nat Cancer Institute 2006; Cochrane Database Syst Rev 2006
  - 57 trials, 9353 anemic cancer patients
  - Significant reduction of transfusions (RR 0,64)
  - Baseline Hb<12 : higher likelihood of response
  - Higher risk of tromboembolism (6,1% vs 3,8%)
  - Trend towards more hypertension
  - Positive effect on QOL

Effects and side effects

- Bennett et al, JAMA 2008
  - Tromboembolism increased
    - 38 phase 3 trials, 8172 patients
    - 7,5 vs 4,9%; RR 1,57
  - Hazard rate for mortality significantly increased!
    - 51 phase 3 trials, 13611 patients
    - HR 1,1

Effects and side effects

- Bohlius et al, Lancet 2009
  - 53 studies, 13933 patients
  - Increased on study (+17%) and overall mortality (+6%)
  - Not statistically significant when limited to patients receiving chemotherapy

ASH/ASCO guidelines 2010 (Rizzo et al, Blood 2010 and JCO 2010)

- Exclude other cause of anemia
- Epoietin and Darbepoietin are equivalent
- Hb level < 10, chemotherapy induced
  - Hb 10-12 if symptomatic can be considered
- Consider trombo-embolic risk
- Starting dose:
  - Epoietin 150U/kg 3x/week or 40000 U weekly
  - Darbepoietin 2,25mcg/kg weekly, 500mcg q3W
  - Lowest possible dose to be pursued
- Discontinue if no response

ASH/ASCO guidelines 2010 (Rizzo et al, Blood 2010 and JCO 2010)

- Hb to be increased to the lowest level to avoid transfusion
- Monitor iron parameters
  - Supplementation if necessary
- Not if no concurrent chemotherapy
  - Exception : low risk MDS
- Nonmyeloid hematological malignancies
  - First try chemotherapy alone
  - Particular care in chemotherapy and malignancies associated with increased risk of tromboembolism
- Treatment with curative intent (cf black box warning FDA) ???

Granulocyte-Colony Stimulating Factor

- G-CSF:
  - Mice without G-CSF :
    - chronic neutropenia in varying degrees
    - Decreased numbers of myeloid progenitors in the bone marrow
  - Primary effect : increase of differentiation of CFU-G into polymorphonuclear cells
  - In clinical practice:
    - Fast increase in the number of neutrophils
    - Increased survival in peripheral blood
    - Increased functionality: diapedesis, chemotaxis, phagocytosis

Chemotherapy Induced Neutropenia

- Neutropenia is the most frequent dose limiting toxicity of chemotherapy
- Consequences of CIN:
  - Infections
  - Hospitalization
  - Administration of (IV) broad-spectrum antibiotics
  - Decreased QOL
  - Delay/ dose reduction of chemotherapy
  - Decreased efficiency of treatment
  - Increase health care cost
- Risk of CIN depends on:
  - Grade of neutropenia
  - Duration of neutropenia

2010 Update EORTC G-CSF Guidelines

EUROPEAN JOURNAL OF CANCER xxx(2010)xxx–xxx

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journal homepage: www.ejconline.com

Position Paper

2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours

M.S. Aapro [a,,m], J. Bohlius [b,n], D.A. Cameron [c,o], Lissandra Dal Lago [d,p], J. Peter Donnelly [e,q], N. Kearney [f,r], G.H. Lyman [g,s], R. Pettengell [h,t], V.C. Tjan-Heijnen [i,u], J. Walewski [j,v], Damien C. Weber [k,w], C. Zielinski [l,x]*

2010 Update EORTC G-CSF Guidelines

STEP 1
Assess frequency of FN associated with planned chemotherapy regimen

- **FN risk ≥20%** → Prophylactic G-CFS recommended
- **FN risk 10-20%** → Step 2
- **FN risk <10%** → G-CSF prophylaxis not indicated

Step 2
Assess factors that increase the frequency/risk of FN

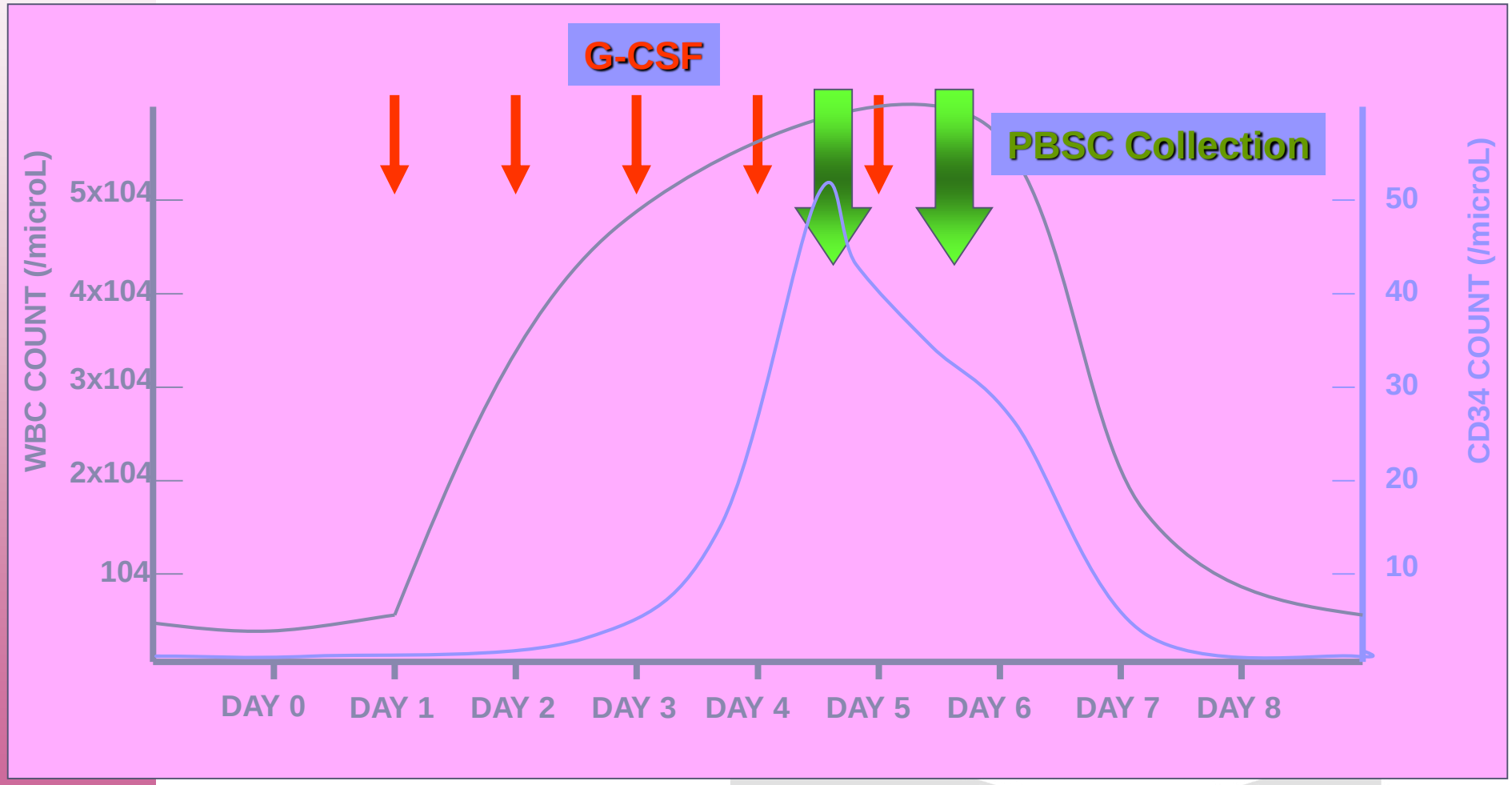
High risk	Age >65 years
Increased risk (level I and II evidence)	Advanced disease, History of prior FN No antibiotic prophylaxis, no G-CSF use
Other factors: (level III and IV evidence)	Poor performance and/or nutritional status Female gender Haemoglobin <12g/dL Liver, renal or cardiovascular disease

STEP 3
Define the patient's overall FN risk for planned chemotherapy regimen

- Overall FN risk ≥ 20% → Prophylactic G-CFS recommended
- Overall FN risk < 20% → G-CSF prophylaxis not indicated

REASSESS AT EACH CYCLE

Peripheral Blood Stem Cell Harvest

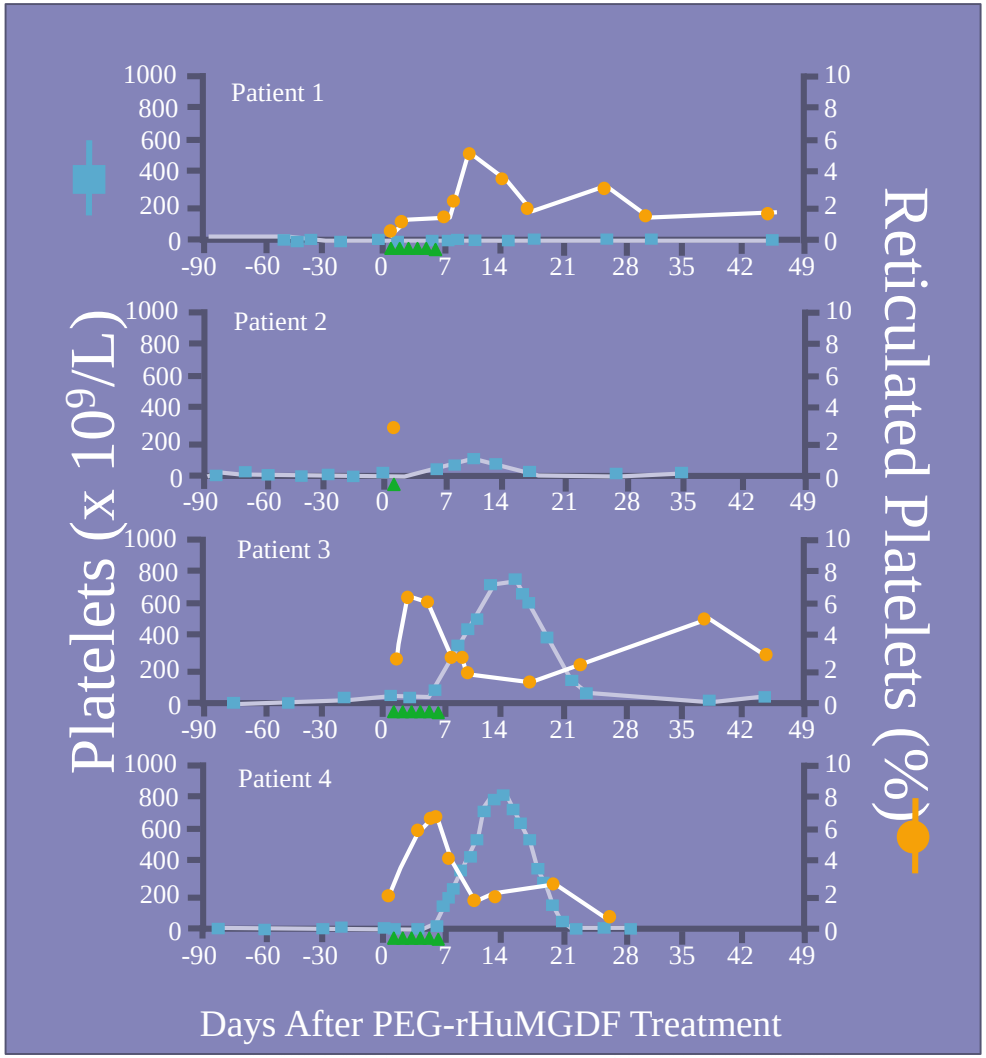


Biosimilars

- Erythropoëtins
  - Darbepoëtine alpha, Epoëtine alpha, Epoëtine beta
- G CSF
  - Short acting : filgrastim and lenograstim
  - Long acting : pegfilgrastim
- "Biosimilars" or follow-on biologicsbiologic medical products whose active drug substance is made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene expression methods.
  - Efficacy?
  - Immunogenicity?
  - Biosimilarity does not imply interchangeability!

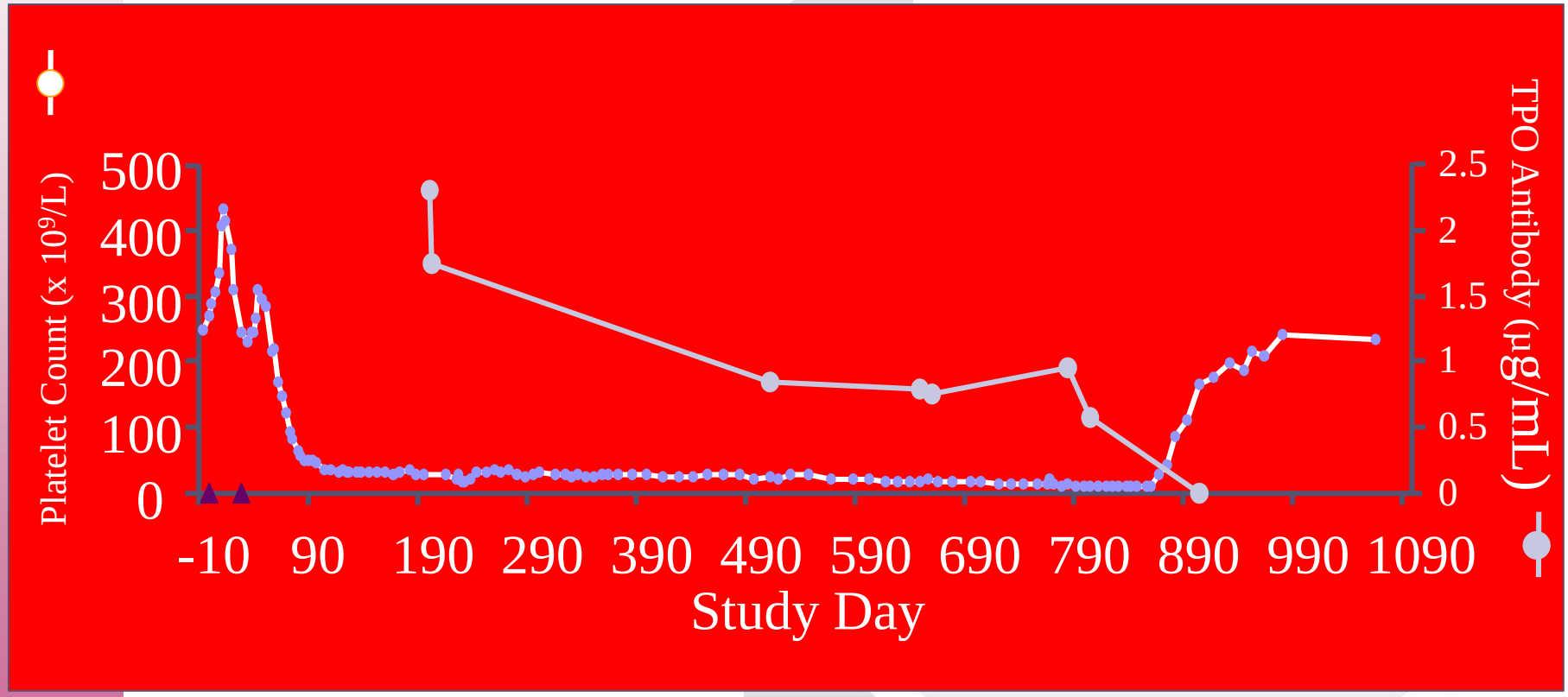
PEG-rHuMGDF in ITP

- ▲ Indicates days of 0.5 µg/kg PEG-rHuMGDF dosing
  - Patients 1 and 3 received 7 days of dosing
  - Patient 2 received only 1 day of dosing because of adverse events
  - Patient 4 received 6 days of dosing because of adverse events



Nomura S, et al. Blood. 2002;100:728-730. This research was originally published in Blood. © the American Society of Hematology.

PEG-rHuMGDF Antibody Formation

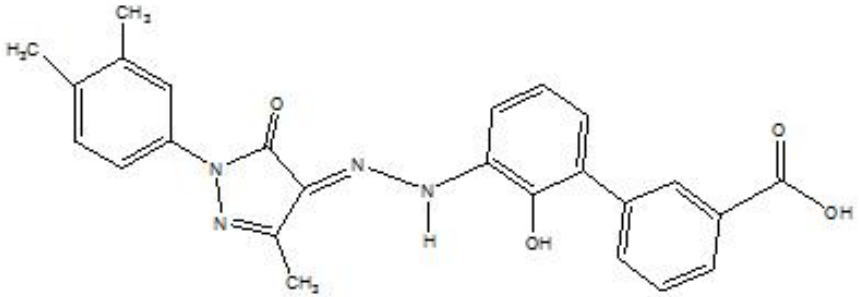


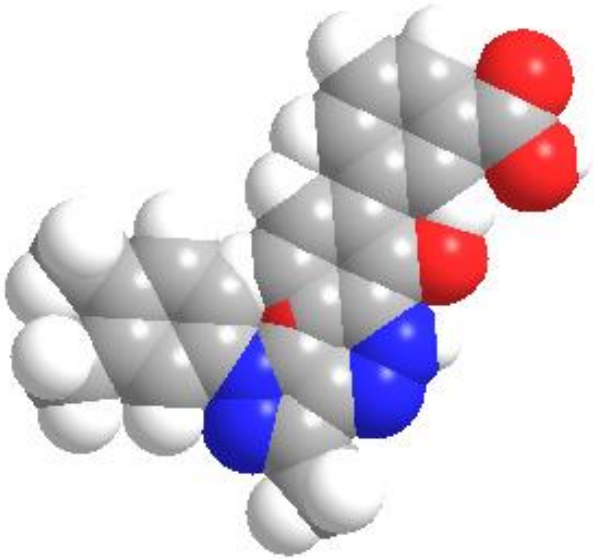
Li J, et al. Blood. 2001;98:3241-3248. This research was originally published in Blood. © the American Society of Hematology.

Second-Generation Thrombopoietic Growth Factors

- TPO peptide mimetics
  - Romiplostim : Nplate, SC, 1x/week
- TPO nonpeptide mimetics
  - Eltrombopag : Revolade, oral, daily
  - AKR501
  - LGA-4665
  - S-888711
- TPO agonist antibodies

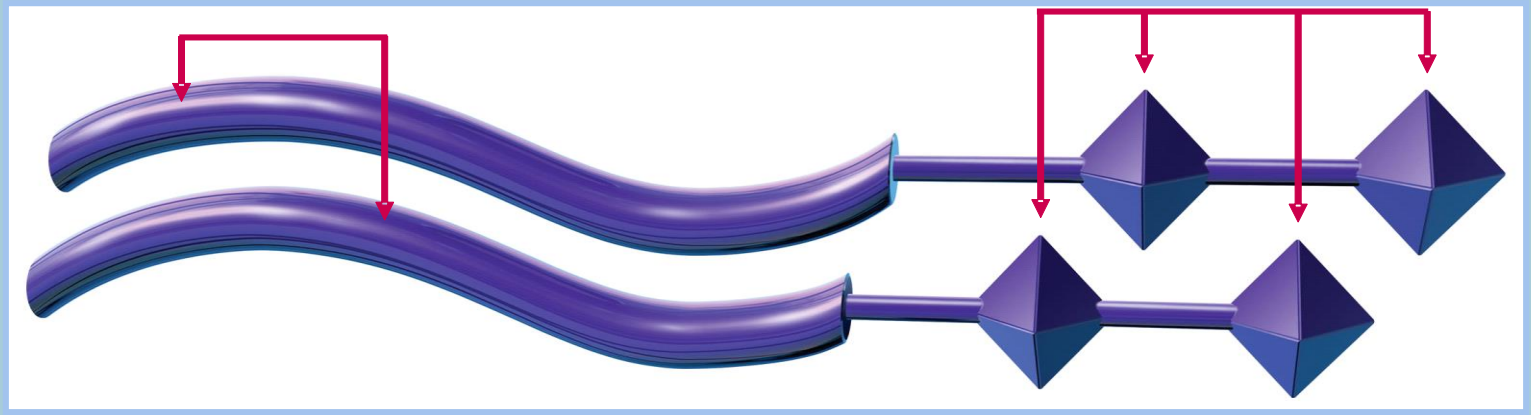
Eltrombopag (Revolade)





Romiplostim: Structure

Fc carrier domain **Peptide-containing domain**

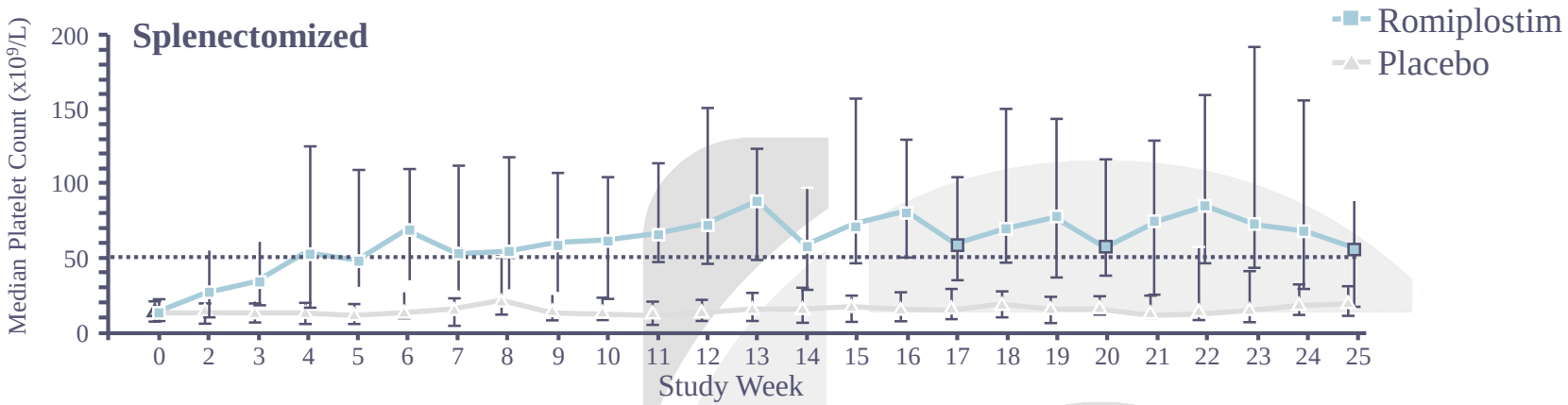


Romiplostim is a 'peptibody' with two domains

- A peptide TPO receptor binding domain that imparts the biologic activity
  - No sequence homology to endogenous thrombopoietin
- An antibody Fc domain that increases the half life in the bloodstream

Bussel et al. *N Engl J Med.* 2006;355:1672–1681.

Romiplostim Phase 3 study



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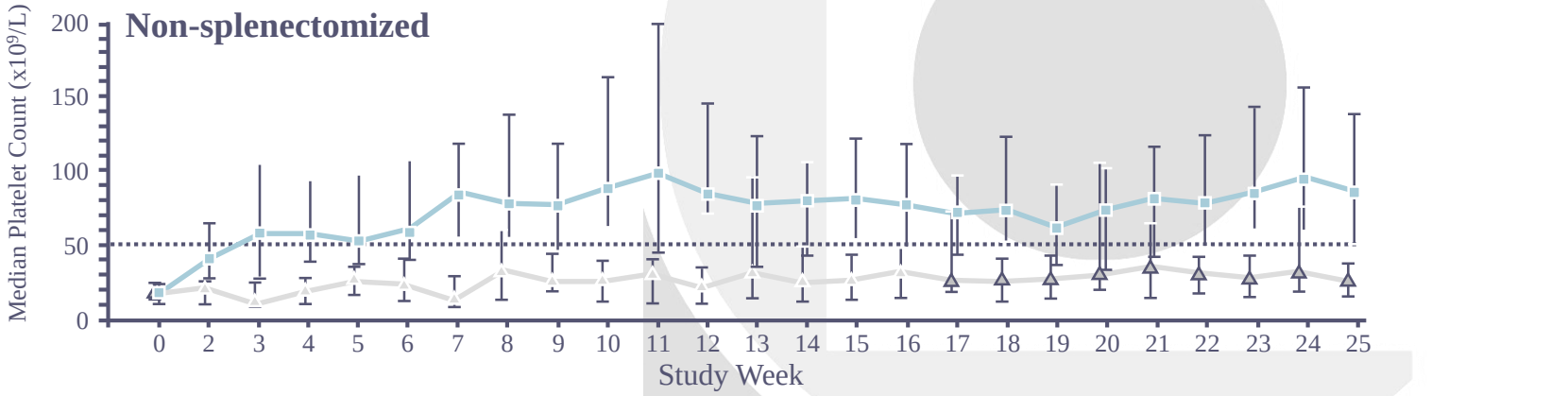
Placebo*	21	21	21	21	21	21	21	21	21	21	20	20	20	20	20	20	20	20	18	19	18	18	19	17	19
Romiplostim*	42	42	42	42	42	42	41	42	41	41	40	39	41	39	40	40	39	40	39	39	40	38	38	39	40



	0	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Placebo*	21	21	21	21	21	21	21	20	18	19	19	19	18	18	18	18	18	18	18	18	18	18	17	16	17
Romiplostim*	41	41	41	41	41	41	40	41	41	40	40	37	40	38	40	38	39	39	38	39	38	36	38	39	39

*Number available for measurement

Kuter et al. *Lancet*. 2008;371:395–403.

Romiplostim Phase 3. Two Parallel 24-week Studies in Adult Patients with ITP: Summary

In non-splenectomized patients:

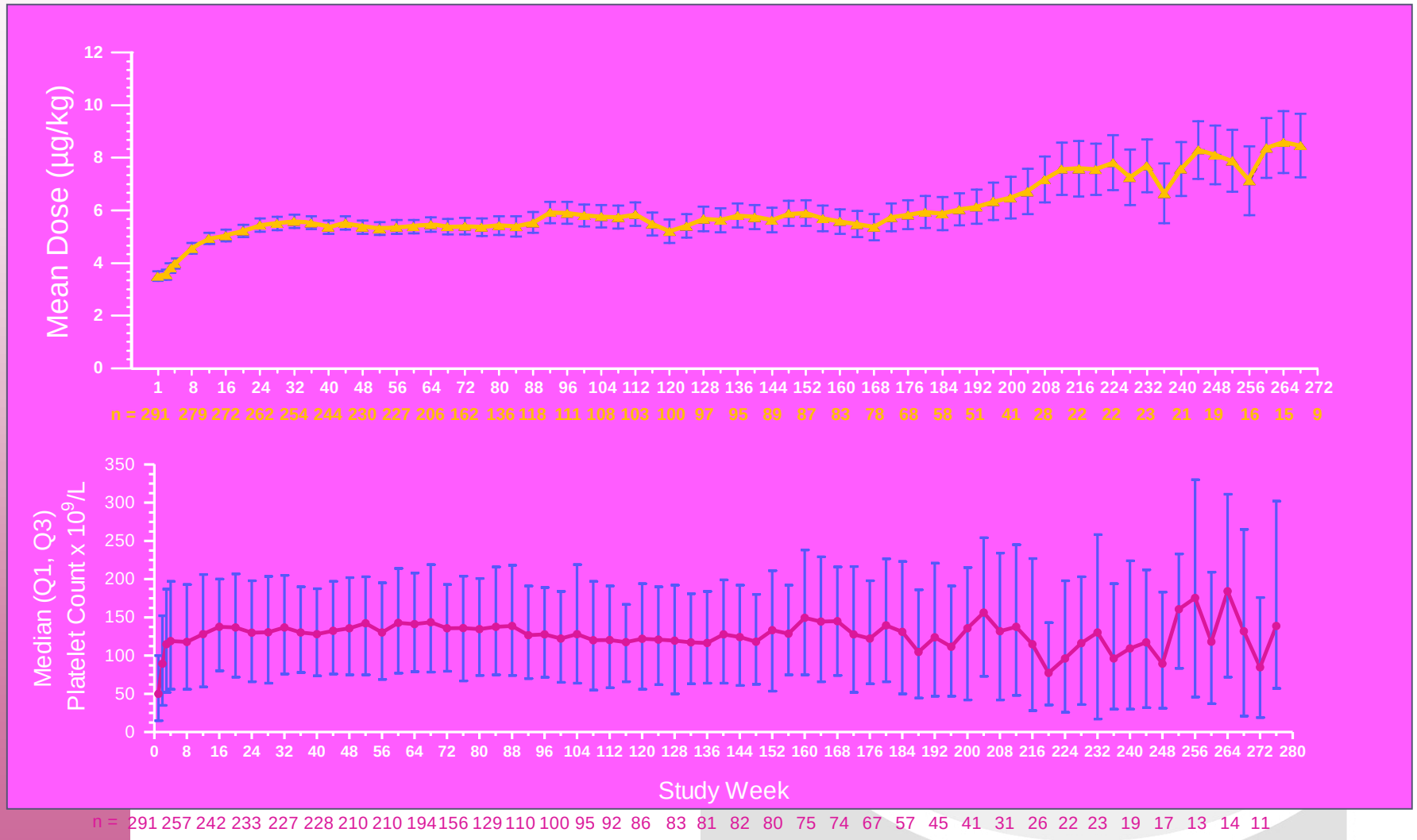
- 88% overall response, 61% durable response
- Increased and maintained platelet counts over 24 weeks
- Rescue medications significantly decreased
- 73% of romiplostim patients discontinued or reduced concurrent ITP therapy (corticosteroids, azathioprine, danazol)

In splenectomized patients:

- 79% overall response, 38% durable response
- Platelet counts increased and maintained over 24 weeks
- Rescue medications significantly decreased
- All romiplostim patients discontinued or reduced concurrent ITP therapy

Kuter et al. *Lancet.* 2008;371:395–403.

Stability of Platelet Counts and Romiplostim Dose Over Time



Kuter et al. *Blood* (ASH Annual Meeting Abstracts) 2010;116:68 (Oral presentation).

The Most Frequently-Reported Adverse Events Were Mild to Moderate

	Placebo n = 41 [n (%)]	Romiplostim n = 84 [n (%)]
Patients with any adverse event	39 (95)	84 (100)
Headache	13 (32)	29 (35)
Fatigue	12 (29)	28 (33)
Epistaxis	10 (24)	27 (32)
Arthralgia	8 (20)	22 (26)
Contusion	10 (24)	21 (25)
Petechiae	9 (22)	14 (17)
Diarrhea	6 (15)	14 (17)
Upper respiratory tract infection	5 (12)	14 (17)
Dizziness	0	14 (17)
Insomnia	3 (7)	13 (16)
Myalgia	1 (2)	12 (14)
Back pain	4 (10)	11 (13)
Nausea	4 (10)	11 (13)
Pain in extremity	2 (5)	11 (13)
Cough	7 (17)	10 (12)
Anxiety	5 (12)	9 (11)
Gingival bleeding	5 (12)	9 (11)
Abdominal pain	0	9 (11)
Nasopharyngitis	7 (17)	7 (8)
Ecchymosis	6 (15)	6 (7)

Adverse events occurring in at least 10% of patients in either treatment group

Kuter et al. *Lancet.* 2008;371:395–403.

Summary of Adverse Events

	n = 291 % (n)
Adverse events	98% (284)
Serious adverse events	40% (117)
Treatment-related adverse events	35% (103)
Treatment-related serious adverse events	8% (24)
Deaths	5% (16)
Thrombotic events	9% (25)
Neutralizing antibodies to romiplostim – Absent on retesting after drug withdrawal – No cross-reactive antibodies to eTPO	1% (2)

Kuter et al. Blood (ASH Annual Meeting Abstracts) 2010;116:68 (Oral presentation).

Hematopoietic Growth factors Conclusions

- Epo is indicated in chemotherapy induced anemia
  - Side effects exist
  - Black box warnings – guidelines to be observed
- G CSF
  - For the prevention of CIN and FN in selected patients and chemotherapy regimens
  - For peripheral blood progenitor cell mobilisation
    - With/without chemotherapy
    - Poor mobilizers : plerixafor associated in lymphoma/myeloma
- Thrombopoietin mimetics
  - In splenectomized chronic ITP patients
  - Side effects exist!
  - Other indications under investigation