SAMSUNG MEDICAL CENTER

Clinical Practical Guideline for Using Growth Factor

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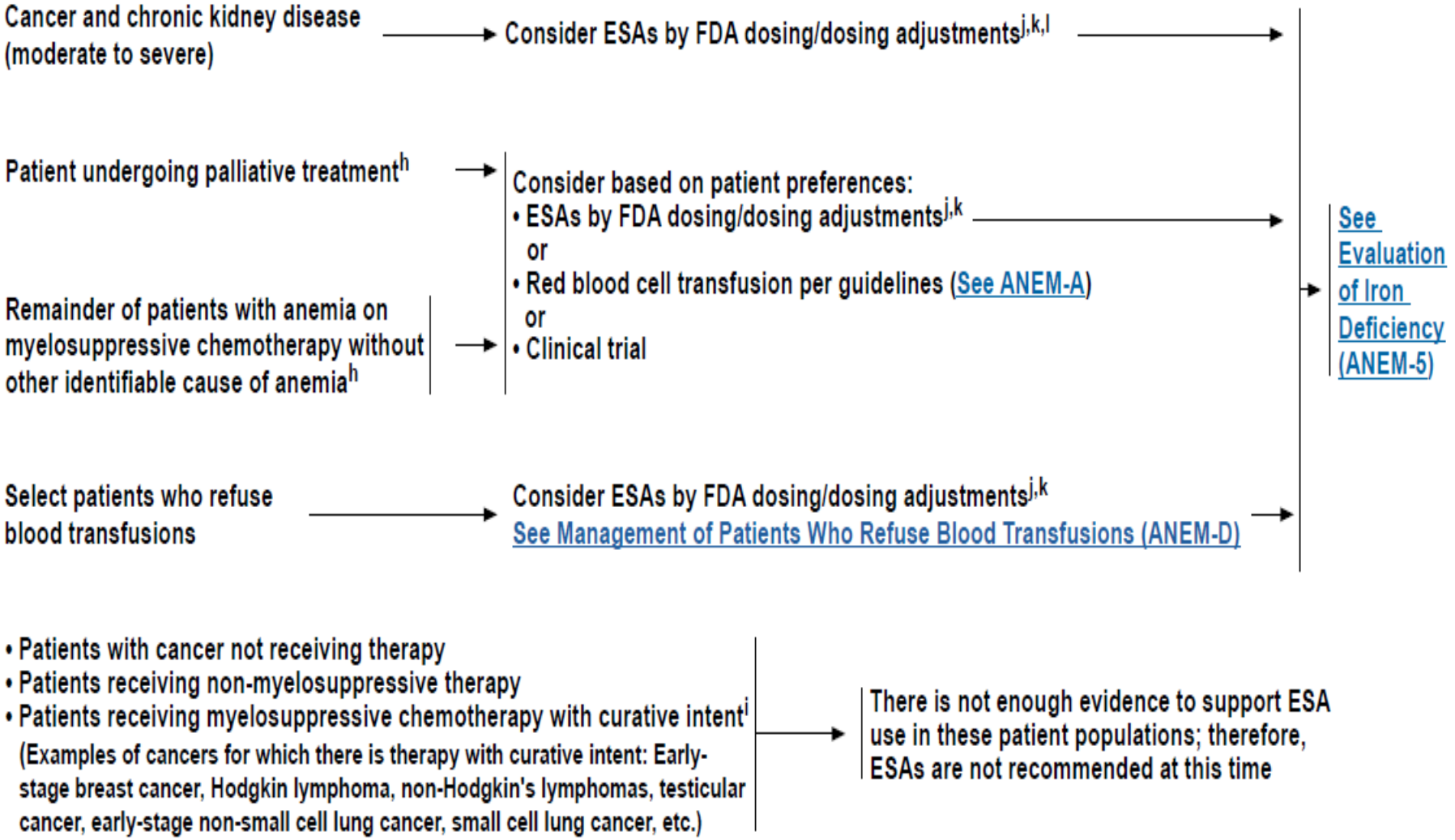
Clinical Use of Growth Factors

1. Erythropoietin
2. Thrombopoietin (TPO receptor agonist)
3. G-CSF

Clinical Use of Erythropoietin

Special Categories in Considering ESA Use

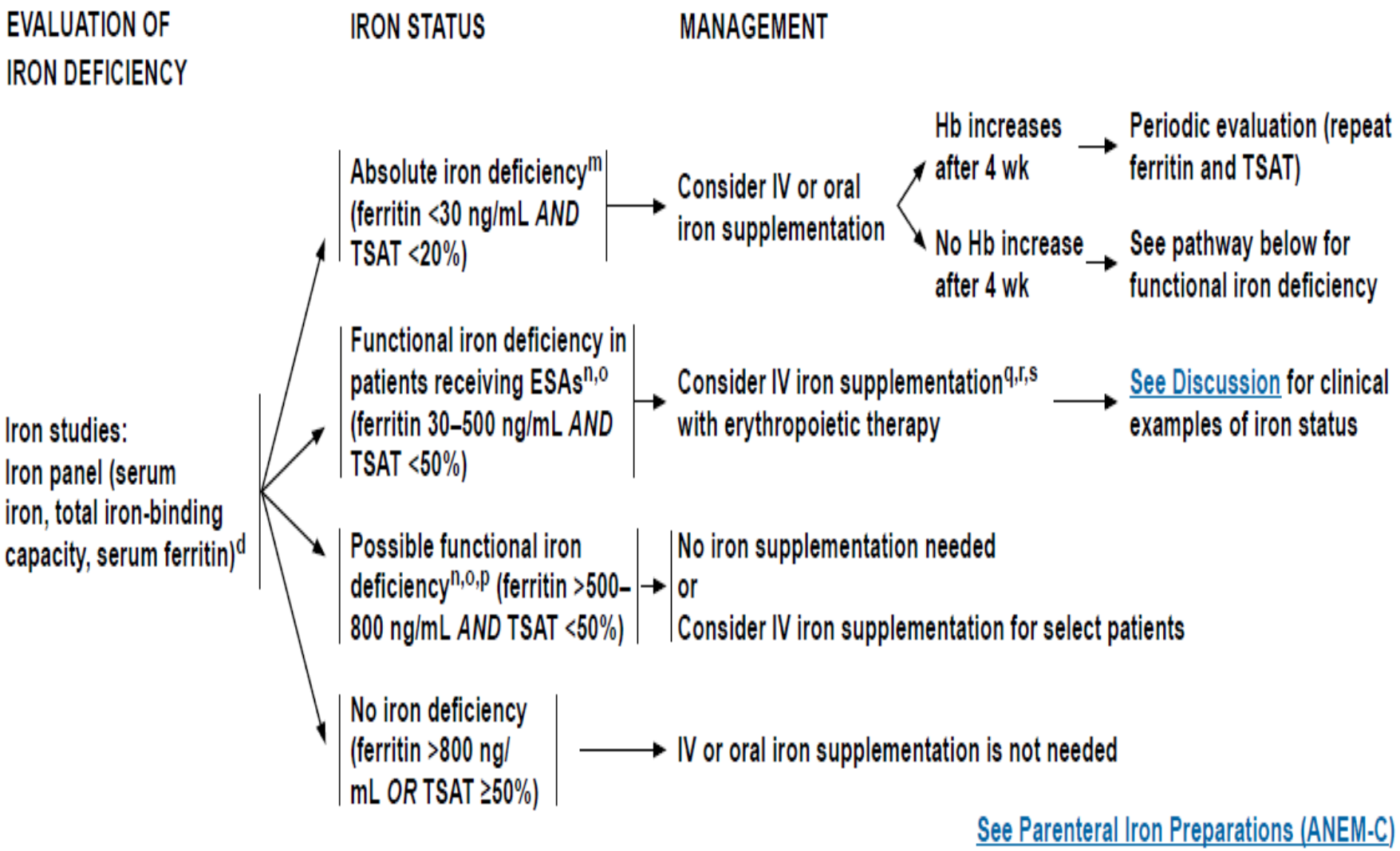


Comparison of Risk and Goals of ESA vs Transfusion

Discuss the following risks and goals with patients when considering anemia treatment options:

	ESA in the Cancer Setting	Red Blood Cell Transfusion
Risks	• Increased thrombotic events • Possible decreased survival • Time to tumor progression shortened	• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury) • Transfusion-associated circulatory overload (TACO) • Virus transmission (eg, hepatitis, HIV) • Bacterial contamination • Iron overload • Increased thrombotic events • Possible decreased survival • Alloimmunization • Increased risk of poor response to future platelet transfusions due to HLA immunization
Goals	• Transfusion avoidance • Gradual improvement in anemia-related symptoms	• Rapid increase of Hb and hematocrit levels • Rapid improvement in anemia-related symptoms

Special Categories in Considering ESA Use



Functional Iron Deficiency

Table 1 Study parameters used to diagnose FID and AID

Study	Functional iron deficiency	Absolute iron deficiency
Ludwig [2]	TSAT < 20% and ferritin ≥ 30 ng/ml	TSAT < 20% and ferritin < 30 ng/ml
Bach [19]	TSAT < 16% and ferritin > 100 ng/ml (mild) or serum ferritin 30–100 ng/ml (moderate)	
Gilreath [9]	TSAT 20–50% and ferritin 30–800 ng/ml	TSAT < 20% and ferritin < 30 ng/ml
Ludwig [20]	TSAT < 20% and ferritin > 30 ng/ml and >100 ng/ml in cancer patients	TSAT < 20% and ferritin < 30 ng/ml (those with cancer ferritin < 100 ng/ml)
Hedenus [21]	TSAT < 20% and ferritin > 30 ng/ml (women) or >40 ng/ml (men)	NA

NA not available

Neoh K, et al. Support Care Cancer 2016 Nov. Epub

sTfR/log ferritin value ≥ 1.03

Kanuri G, et al. PLOS One 2016 Sep. Epub

SMC Cancer Anemia Study

Primary end point

- Defining the causes of anemia in cancer patients via comparison of more relevant biochemical parameters (including sTfR and hepcidin) between anemic and non-anemic patients with cancer

Secondary end point

- Assessment of the anemia related biochemical characteristics in cancer patients via comparison of parameters to reference value in general population

- Defining the correlation of each parameter and clinical characteristics

Correlation of each parameter and clinical characteristics

- The correlation between parameters and clinical features are as below
  - metastatic disease ∝ higher CRP
  - chemotherapy within 6 months ∝ higher CRP, hepcidin
  - age ↑∝higher sTfR
  - MCV ↑∝higher ferritin, hepcidin
  - CRP, ferritin and hepcidin were positively correlated with each other

➔ Ferritin and hepcidin are markers for inflammation, but the level of those parameters are also possibly affected by iron status

➔ Advanced disease and recent chemotherapy seems to promote inflammatory condition

Comparison of parameters between anemic vs non-anemic cancer pts

- Among the cancer patients, anemic patients showed significantly higher level of sTfR compared to non-anemic patient (p=0.011)
- Although not statistically significant, the level of ferritin, CRP, and hepcidin was more elevated in anemic patients.

➔ Consistent with common belief, cancer anemia seems to be closely related to inflammatory process (ACD) according to higher ferritin, CRP and hepcidin level in this population

➔ Of note, however, iron deficiency and/or iron restricted erythroiesis also contributes considerably to pathogenesis of anemia in cancer patient

Iron deficient erythropoiesis might play key role in development of anemia in cancer patients

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Keywords: *cancer, anemia, soluble transferrin receptor, hepcidin*

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ABSTRACT

Introduction: Multifactorial pathogenesis is involved in anemia of cancer patients and defining the causes of anemia is not always simple.

Methods: The incidence of anemia among 4 major cancers (gastric, colorectal, lung cancer and hepatocellular carcinoma), and biochemical features of anemia using ferritin, CRP, hepcidin and soluble transferrin receptor (sTfR) were assessed. Anemia was defined either by hemoglobin (Hb) ≤11 g/dL or a drop of Hb 2 g/dL or more during anticancer treatment.

Results: Among the 345 patients including 152 lung cancer, 101 gastric cancer, 69 colorectal cancer and 23 hepatocellular carcinoma, 49 patients (14.2%) had anemia at their initial diagnosis of cancer. During treatment, 129 (37.4%) experienced anemia, and 34 (26.4%) were treated mostly by transfusion. Biochemical feature of anemia was examined with 39 patients' samples. When comparing to the reference value from general population, cancer patients showed numerically higher ferritin, sTfR, CRP and hepcidin level. Among the cancer patients, anemic patients had significantly higher ferritin ($p = 0.050$) and sTfR ($p = 0.009$) level compared to non-anemic patients.

Conclusion: Anemia is a common issue in cancer patients and is largely undertreated with sub-optimal diagnoses of cause. The rates of anemia increase significantly during anti-cancer treatment and appear to be largely associated with iron deficiency.

Proposed Cancer Anemia Treatment

Cancer Anemia

Anemia assessment with CBC, iron profile, sTfR, hepcidin, IL-6…

IDA

FID

ACD

(Ferinject®)

The Efficacy of Intravenous Iron for the Treatment of Anemia in Cancer Patients

This study is currently recruiting participants.

See ▶ **Contacts and Locations**

Verified February 2017 by Jun Ho Jang, Samsung Medical Center

Sponsor:
Samsung Medical Center

Information provided by (Responsible Party):
Jun Ho Jang, Samsung Medical Center

ClinicalTrials.gov Identifier:
NCT02599012

First received: October 7, 2015
Last updated: February 7, 2017
Last verified: February 2017
History of Changes

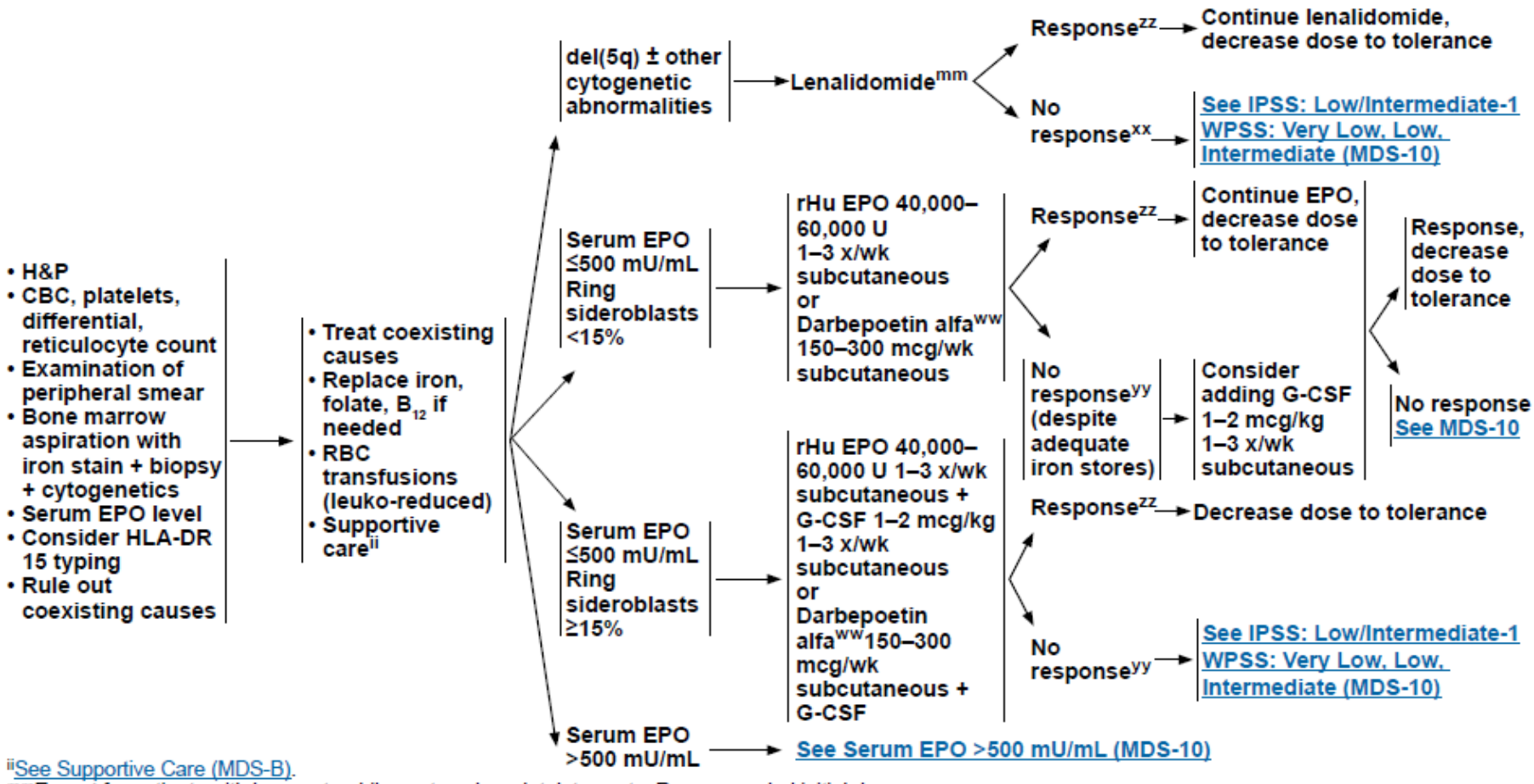
▶ Purpose

- Multifactorial pathogenesis is involved in anemia of cancer patients and defining the causes of anemia is not always simple.
- Currently, treatment options available for anemia in cancer patients include red blood cell (RBC) transfusion, erythropoietin stimulating agent (ESA), and **iron** supplementation, accompanying considerable pros and cons for each treatment.
- Previous studies have demonstrated benefit when treating with **IV iron** in combination with ESA and, more recently, evidence is emerging to suggest a role for **IV iron** alone.
- In this study, investigator will assess the efficacy of intravenous **iron** for the treatment of anemia in cancer patients.

NCCN Guidelines Version 1.2016
Myelodysplastic Syndromes

NCCN Guidelines Index
MDS Table of Contents
Discussion

EVALUATION OF RELATED ANEMIA | **TREATMENT OF SYMPTOMATIC ANEMIA** | **FOLLOW-UP**



[ii] See Supportive Care (MDS-B).

[mm] Except for patients with low neutrophil counts or low platelet counts. Recommended initial dose is: 10 mg/d for 21 out of 28 days or 28 days monthly for 2 to 4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤500 mU/mL.

[ww] In some institutions, darbepoetin alfa has been administered using doses up to 500 mcg weekly; also, note that darbepoetin alfa 300 mcg every other week is equivalent to 150 mcg weekly.

[xx] Lack of 1.5 gm/dL rise in Hb or decreased RBC transfusion requirement by 3 to 4 months of treatment.

[yy] Lack of 1.5 gm/dL rise in Hb or decreased RBC transfusion requirement by 6 to 8 weeks of treatment.

[zz] Target Hb range 10 to 12 g/dL; not to exceed 12 g/dL.

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.

Erythropoietin for LR-MDS

- **Erythrocyte-stimulating agents (ESA)**
  - *1st-line treatment for symptomatic anemia*
  - ***40~60% of HI-E up to 18~24 months***
  - *Addition of G-CSF may be synergistic*
  - *Long-acting darbepoietin alfa*

ESA ± G-CSF		No.	RR	Leukemic TF.	Duration of Res.
Hellstrom-Lindberg	Phase II	50 (L+H)	**38%**	28% @43 mos	**median 24 months**
Jadersten	Phase II	121 (vs.237)	**39%**	Not increased	**median 23 months**
Park	Retrospect.	403	**50%**	N/A	**20~24 months**
Kelaidi	Phase II	99	**56%**	14.5% @ 3yr	**Not reached @ 52wks**

Hellstrom-Lindberg E, et al. *Blood*. 1998;92:68-75
Jadersten M, et al. *J Clin Oncol*. 2008;26:3607-13
Park S, et al. *Blood.* 2008;111:574-82
Kelaidi C, et al. *Ann Hematol*. 2013;92:621-31

Erythropoietin for LR-MDS to Whom & How?

- **Who will benefit from ESA?**

  Serum EPO < 500 U/L
  Low serum ferritin
  Lower pre-treatment RBC transfusion (< 2u/month)
  Lower IPSS(-R) risk patients (RA or RARS; low blast percentage)
  Normal cytogenetics
  Absence of aberrant CD5/CD7 expression
  Activated ERK pathway (pERK+)

- **Risk of ESA**
  - ***↑mortality & VTE in non-MDS pts. if Hb target > 12 g/dL (2007 U.S. FDA)***
    : Use with caution, to LR-MDS patients, targeting Hb of 10~12 g/dL

Therapeutic aims in Lower risk MDS

✓ Symptomatic anemia

- Erythropoietin level is important
- EPO < 500 mIU/ml - → EPO use at least 16 weeks
- Responder - → continue until no response
- Non Responder -- →consider other treatment

Study for Optimal Dosing of Darbepoetin in MDS patients

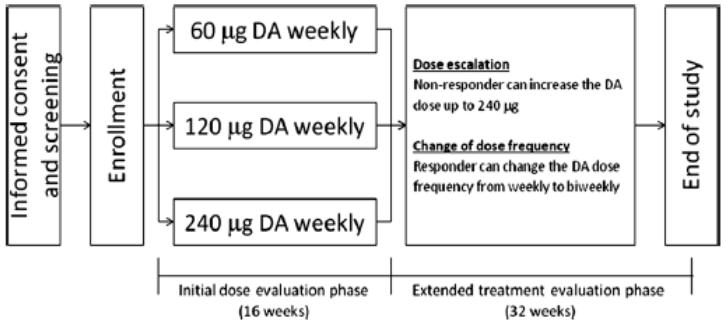
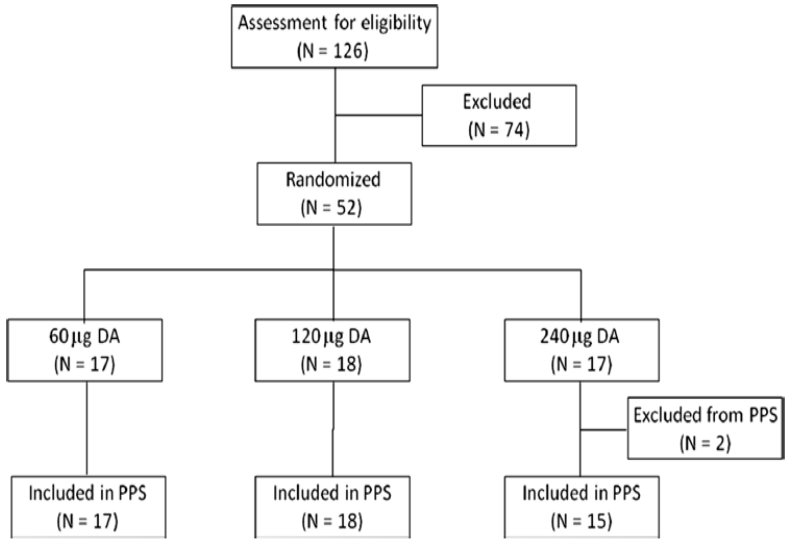
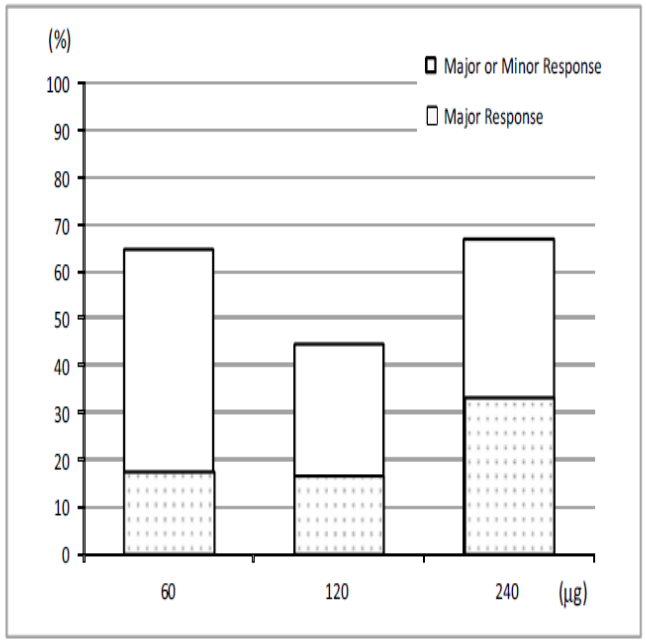
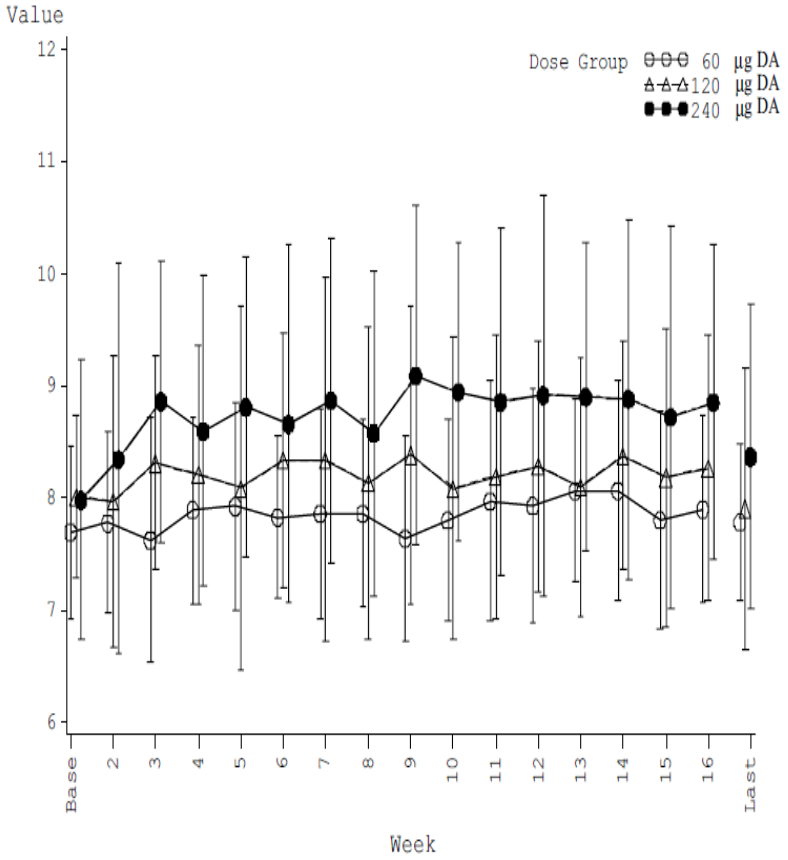


Fig. 1 Study design. *DA* darbepoetin alfa





		60 μg DA	120 μg DA	240 μg DA
	N	17	18	15
Major or Minor Response	n (%)	11 (64.7 %)	8 (44.4 %)	10 (66.7 %)
	95% CI	(38.3, 85.8)	(21.5, 69.2)	(38.4, 88.2)
Major Response	n (%)	3 (17.6 %)	3 (16.7 %)	5 (33.3 %)
	95% CI	(3.8, 43.4)	(3.6, 41.4)	(11.8, 61.6)



Int J Hematol (2015) 102:401–412
DOI 10.1007/s12185-015-1862-5

ORIGINAL ARTICLE

A randomized controlled trial comparing darbepoetin alfa doses in red blood cell transfusion-dependent patients with low- or intermediate-1 risk myelodysplastic syndromes

Jun Ho Jang[1] · Hironori Harada[2,8] · Hirohiko Shibayama[3] · Ryutaro Shimazaki[4] · Hyeoung-Joon Kim[5] · Kenichi Sawada[6] · Kinuko Mitani[7]

Received: 8 June 2015 / Revised: 16 August 2015 / Accepted: 25 August 2015 / Published online: 1 September 2015

Abstract Darbepoetin alfa (DA) is a standard treatment for anemia in lower-risk MDS. However, to date there has been no comparative study to investigate the initial dosage. We, thus, conducted a randomized controlled trial to elucidate the optimal initial dosage of DA. International Prognostic Scoring System low or intermediate-1 risk MDS patients with hemoglobin levels ≤9.0 g/dL, serum erythropoietin levels ≤500 mIU/mL, and red blood cell transfusion dependency were enrolled. Patients were randomized to receive DA either at 60, 120, or 240 μg/week for 16 weeks followed by continuous administration with dose adjustment up to 48 weeks. Of 17, 18, and 15 patients in the 60, 120, and 240 μg DA groups included in the efficacy analysis, 64.7, 44.4, and 66.7 %, respectively, achieved the primary endpoint (major or minor erythroid response), while 17.6, 16.7, and 33.3 % achieved major erythroid responses in the initial 16-week period. No clinically significant safety concerns were identified. DA reduced the transfusion requirements effectively and safely in transfusion-dependent, lower-risk MDS patients. Given the high-

Therapeutic aims in Lower risk MDS

✓ Symptomatic anemia

- Darbepoetin 240 mcg (up to 300 mcg) weekly for at least 16 weeks
- EPO < 100 mIU/ml - → 75% of patients response to Darbepoetin
- 100 < EPO < 500 mIU/ml - → 25% of patients response to Darbepoetin
- EPO > 500 mIU/ml - → less than 2% of patients response to Darbepoetin

Clinical Use of TPO-RA

History of TPO-Receptor agonist (TPO-RA)

- Thrombopoietin --- in 1958 by Kelemen
- In 1994

  recombonant human thrombopoietin (rhTPO)

  pegylated, recombinant, human megakaryocyte growth and development factor (PEG-rhMGDF)
- 2nd generation TPO receptor agonist

  Romiplostim

  Eltrombopag

Structure of TPO

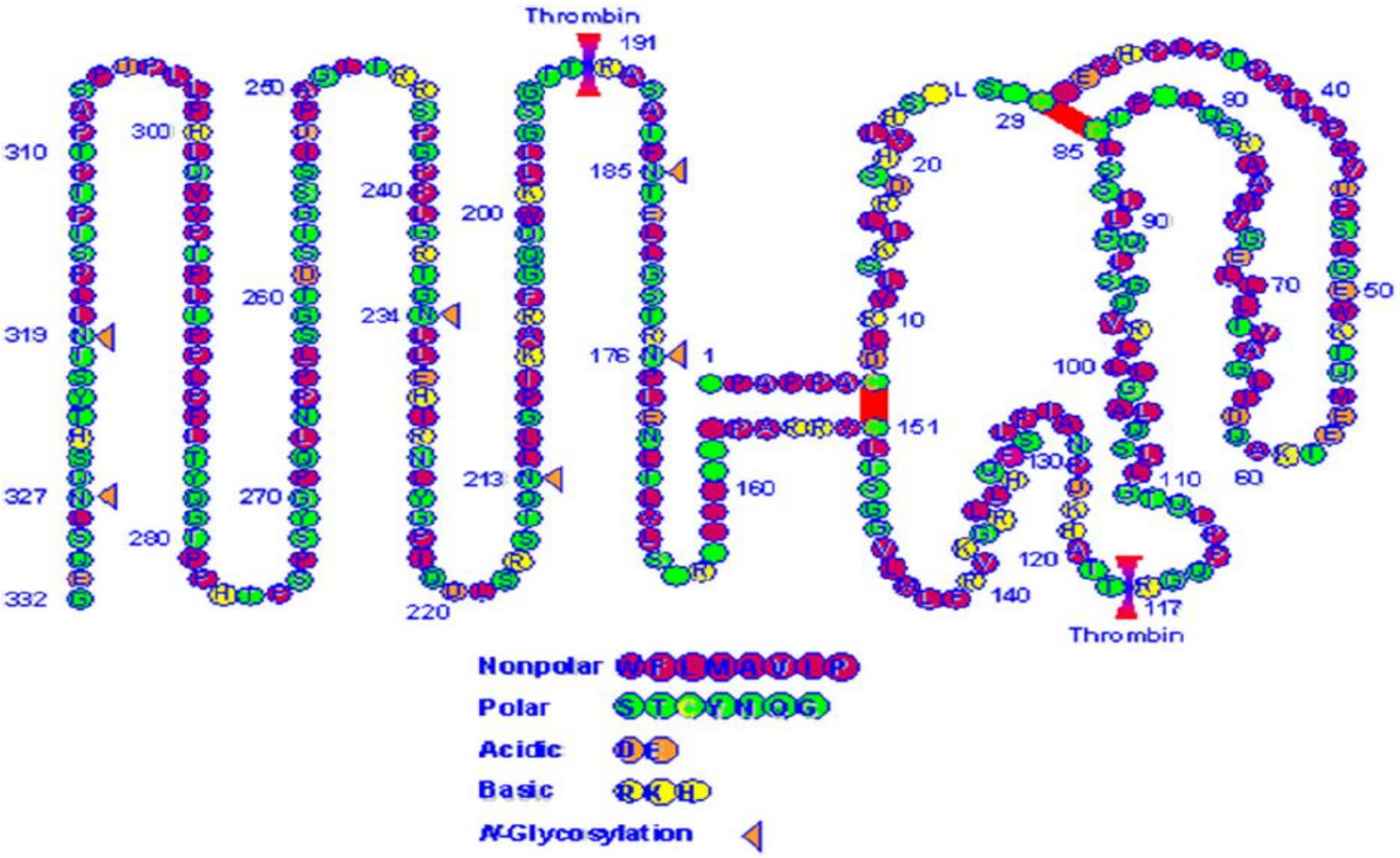
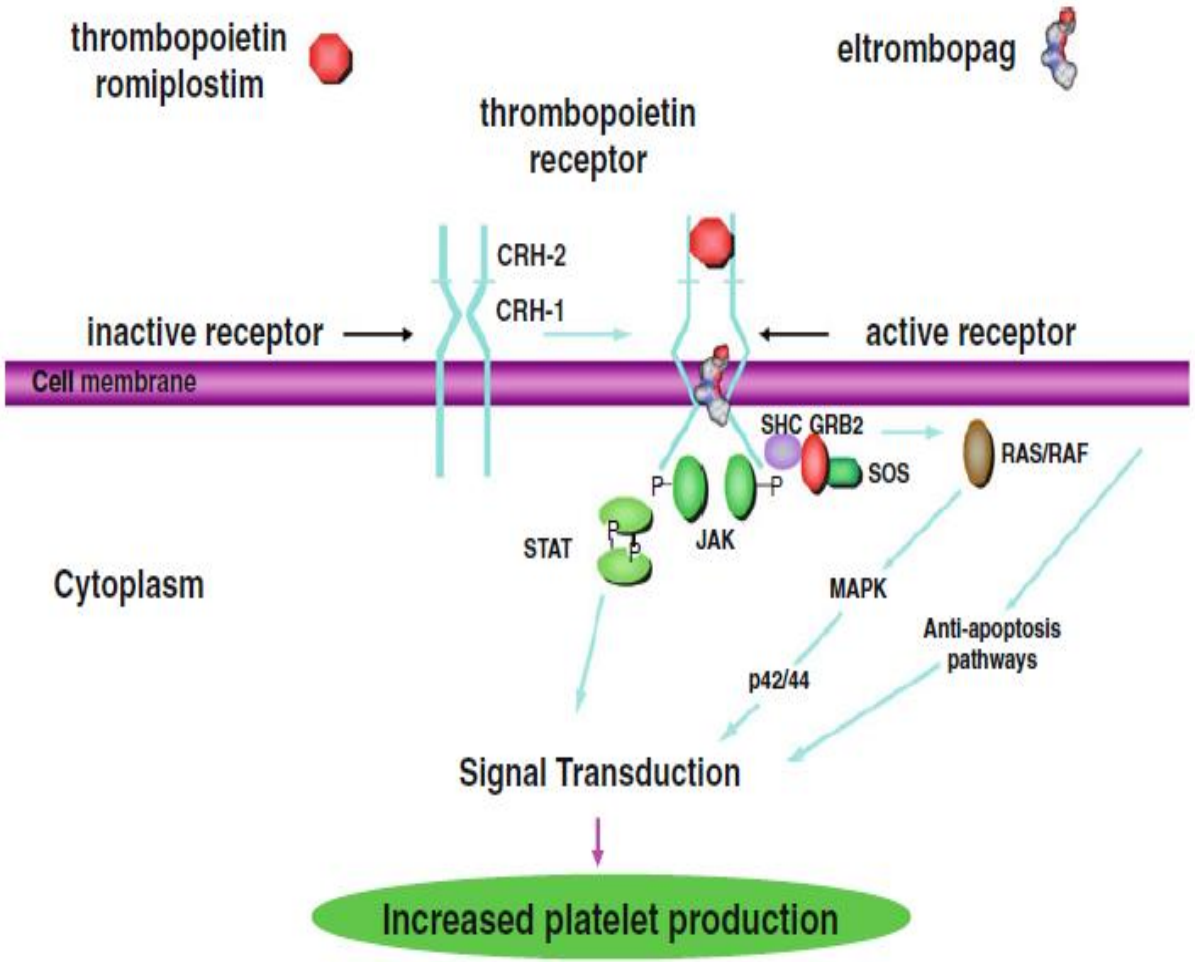


Fig. 1 Thrombopoietin (TPO) structure. Amino acids 1–153 define the "EPO-like" domain which binds the TPO receptor. Amino acids 154–332 define the "carbohydrate-rich" domain that provides stability. Sites of potential thrombin cleavage are indicated. *Red bars* indicate known disulphide linkages (Courtesy of Dr. T. Kato, Pharmaceutical Research Laboratory, Kirin Brewing Company, Takasaki, Gunma, Japan)

Kuter D. Int J Hematol (2013) 98:10–23

Activation of the TPOR by TPO or TPO-RA



Kuter D. Int J Hematol (2013) 98:10–23

TPO-R agonists

Revolade

- TPO non-peptide agonist:[1]
  - May have an effect additive to TPO
- Stimulates growth and differentiation of megakaryocytes and increases platelet production[3] – activates the TPO-R in a manner that is similar to but different from recombinant human TPO

Romiplostim

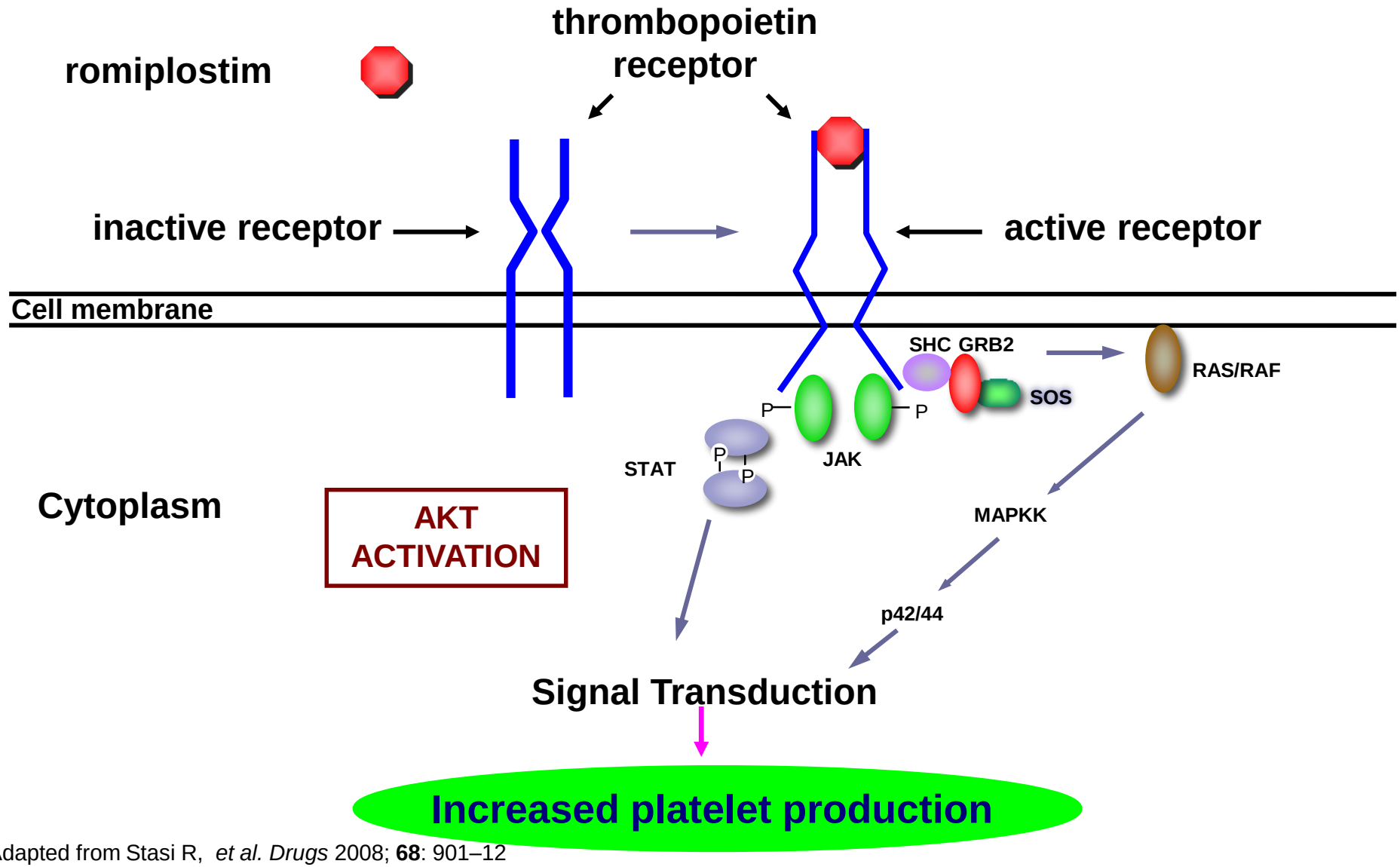
- TPO-peptide agonist[1]
- Stimulates megakaryopoiesis in the same manner as endogenous TPO[1]
  - Structurally unrelated to TPO[1]
  - Competes with TPO for binding to TPO-R[2]
- Stimulates growth and differentiation of megakaryocytes and increases platelet production[3] – binds to same site on the human TPO-R as endogenous TPO[1]

EMA has approved TPO-R agonists for adult chronic ITP if splenectomy has failed or is contraindicated

EMA, European Medicines Agency

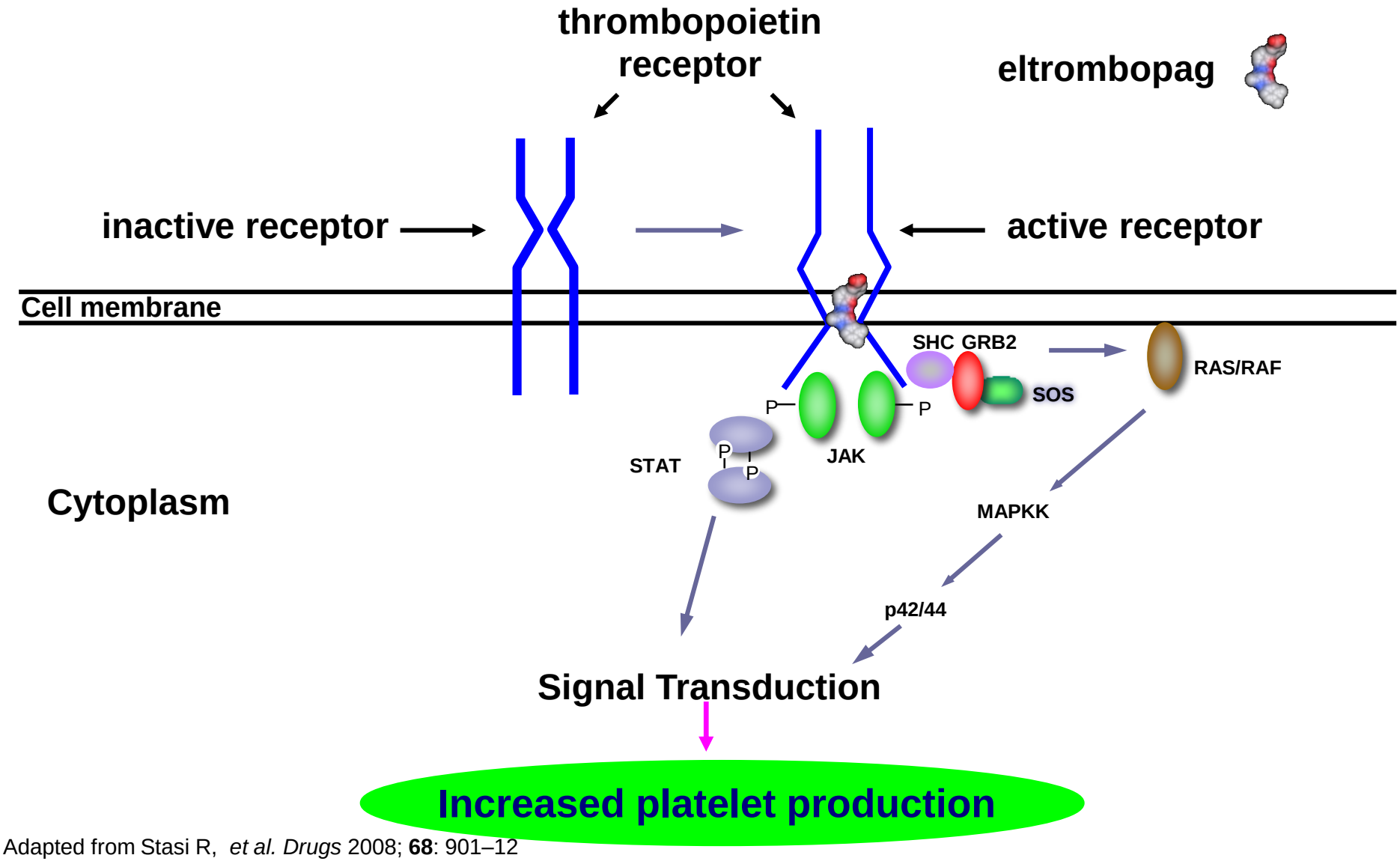
1. Kuter D. *Blood* 2007; **109**: 4607–16; 2. Broudy V, Lin N, *Cytokine* 2004; **25**: 52–60; 3. EMA. Revolade Summary of Product Characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001110/WC500089964.pdf [Accessed 2011]

Romiplostim: Mechanism of Action



Adapted from Stasi R, *et al. Drugs* 2008; **68**: 901–12

Eltrombopag: Mechanism of Action



Adapted from Stasi R, *et al. Drugs* 2008; **68**: 901–12

ASH (2011): guidelines for patients failing first-line therapies

Clinical situation	Therapy option
First-line treatment in newly diagnosed patients	

Treatment for patients unresponsive to/relapsed following corticosteroid therapy	**Recommended options**
	(based on evidence level 1B)
	• **Splenectomy**
	• **TPO-R agonists** (*Revolade* [eltrombopag] and *Nplate* [romiplostim])
	  • In patients at risk of bleeding who relapse after splenectomy
	  • In patients contraindicated for splenectomy who have failed at least one other therapy

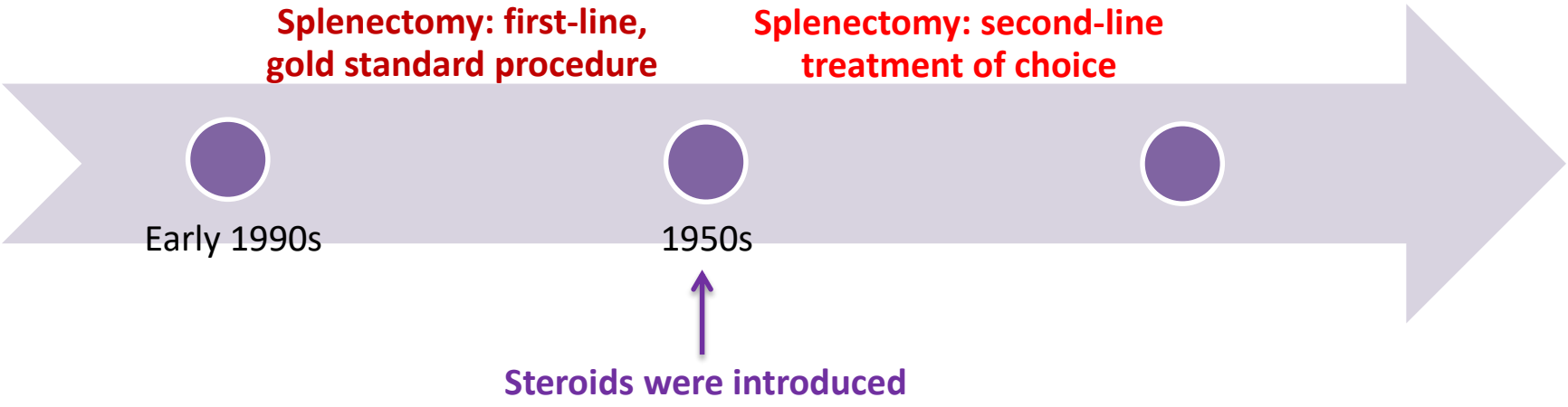
EMA has approved TPO-R agonists if splenectomy has failed or is contraindicated

EMA, European Medicines Agency

Adapted with permission from Neunert C, *et al. Blood* 2011; **117**: 4190–207

Still do we need splenectomy in ITP patients?

Treatment of ITP



First-line	Second-line	TPO mimetics	B-cell targeted treatment	Immunosuppressive/cytotoxic/other agents
Corticosteroids IVIg IVAnti-D	Splenectomy	Romiplostim Eltrombopag	Rituximab	Azathioprine, Cyclophosphamide, Cyclosporin A, Danazol, Dapsone, Mycophenolate Mofetil, Vinca alkaloids

Stasi R, *et al. Ann Hematol* 2010;89:1185-95.

Contraindications to splenectomy

- Elderly (relative contraindication)(>65?)
- DM, Hypertension, Cardiac disorder
- Asthma, COPD, Common variable immune disease
- Extensive abdominal surgery
- Extremely Obese
- Allergy to Vaccine
- Poor responder to IVIg

Impact of patient age & activity level

Patient considerations

- **Risk of fatal haemorrhage greatest in older patients:**[1]
  - 0.4% per year in patients <40 years
  - 1.2% per year in patients 40–60 years
  - 13% per year in patients >60 years
- **Energetic lifestyles require 'safer' platelet counts**

Platelet >20–30 x 10^9/L

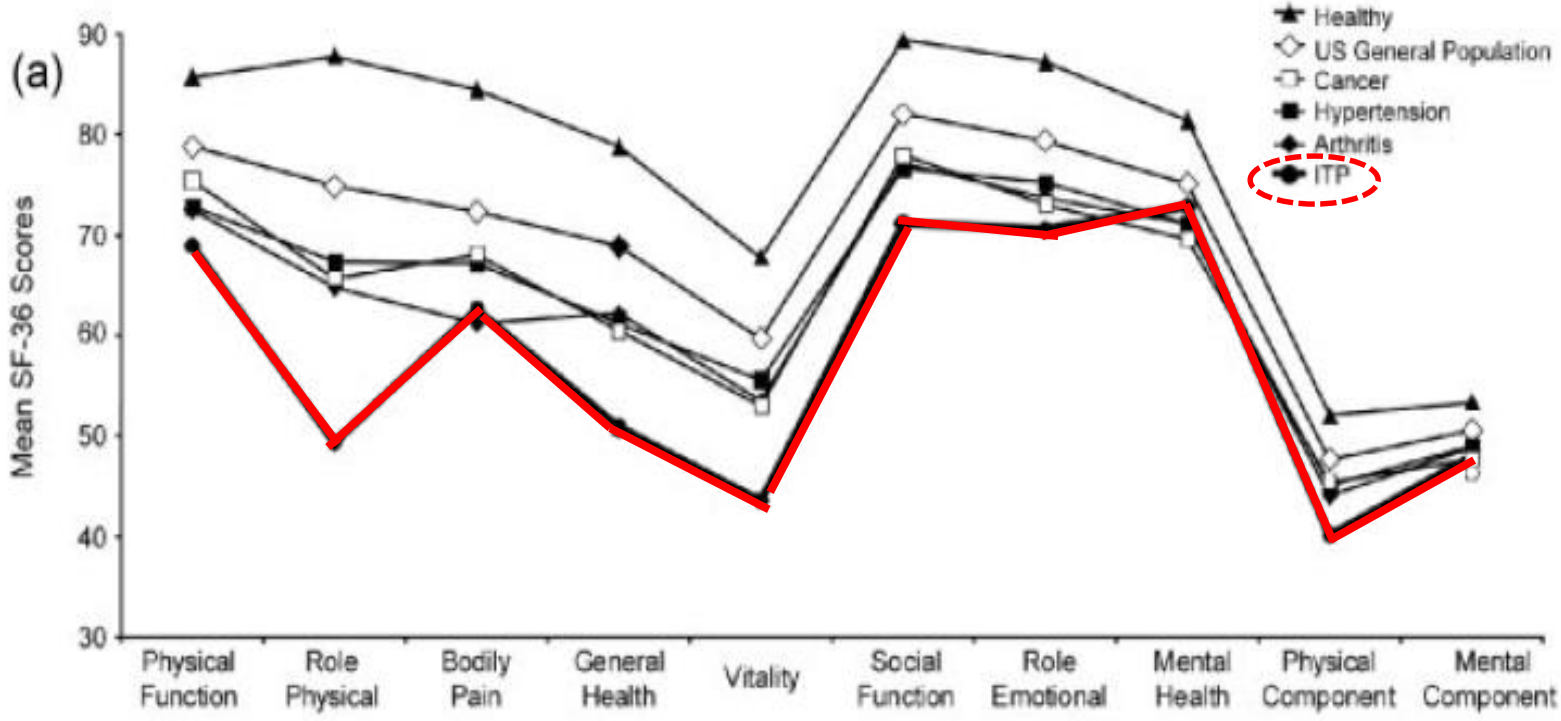
Platelet >50 x 10^9/L

Platelet >80 x 10^9/L

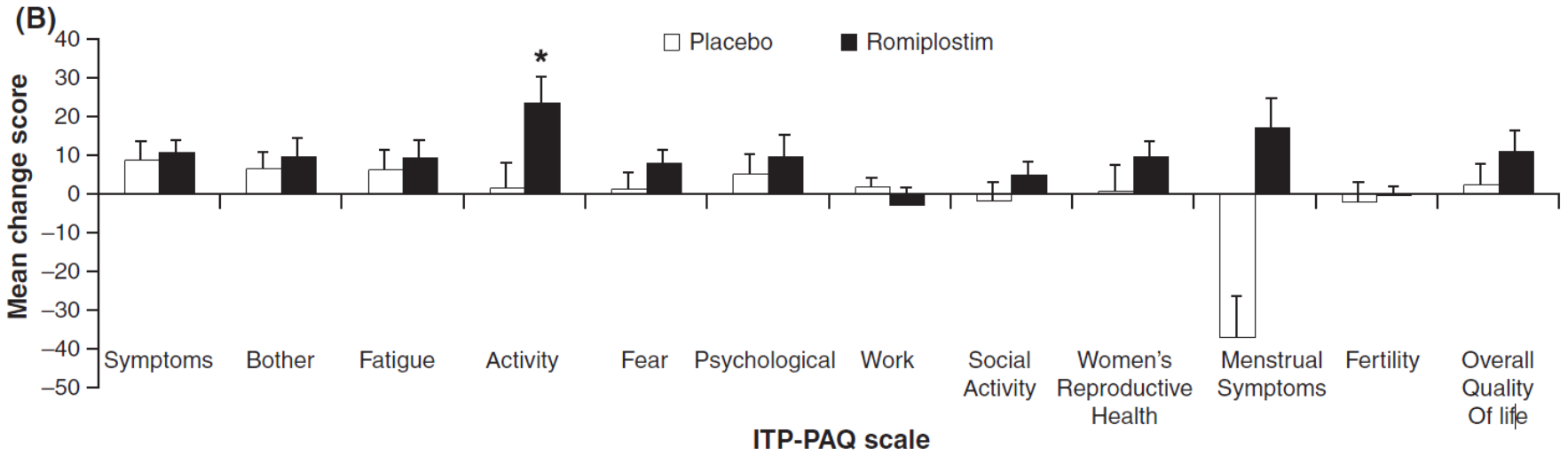
Cohen et al. Arch Intern Med 2000;160:1630–1638

Impact Of ITP on Quality of Life (1)

- HRQOL of ITP patients is worse than that of the general population, healthy subjects, and patients with hypertension, arthritis or cancer. [1]

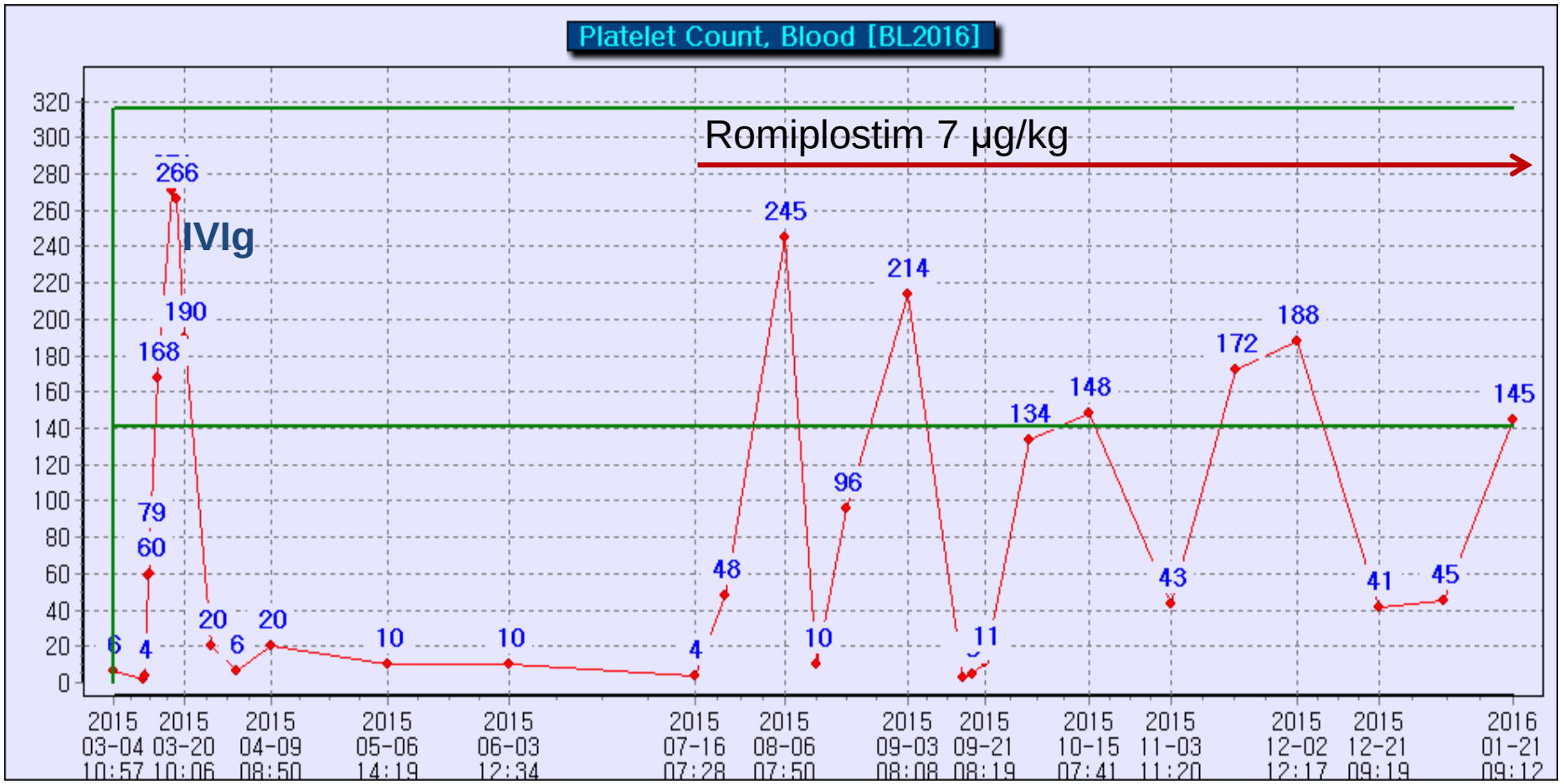


Romiplostim: QOL



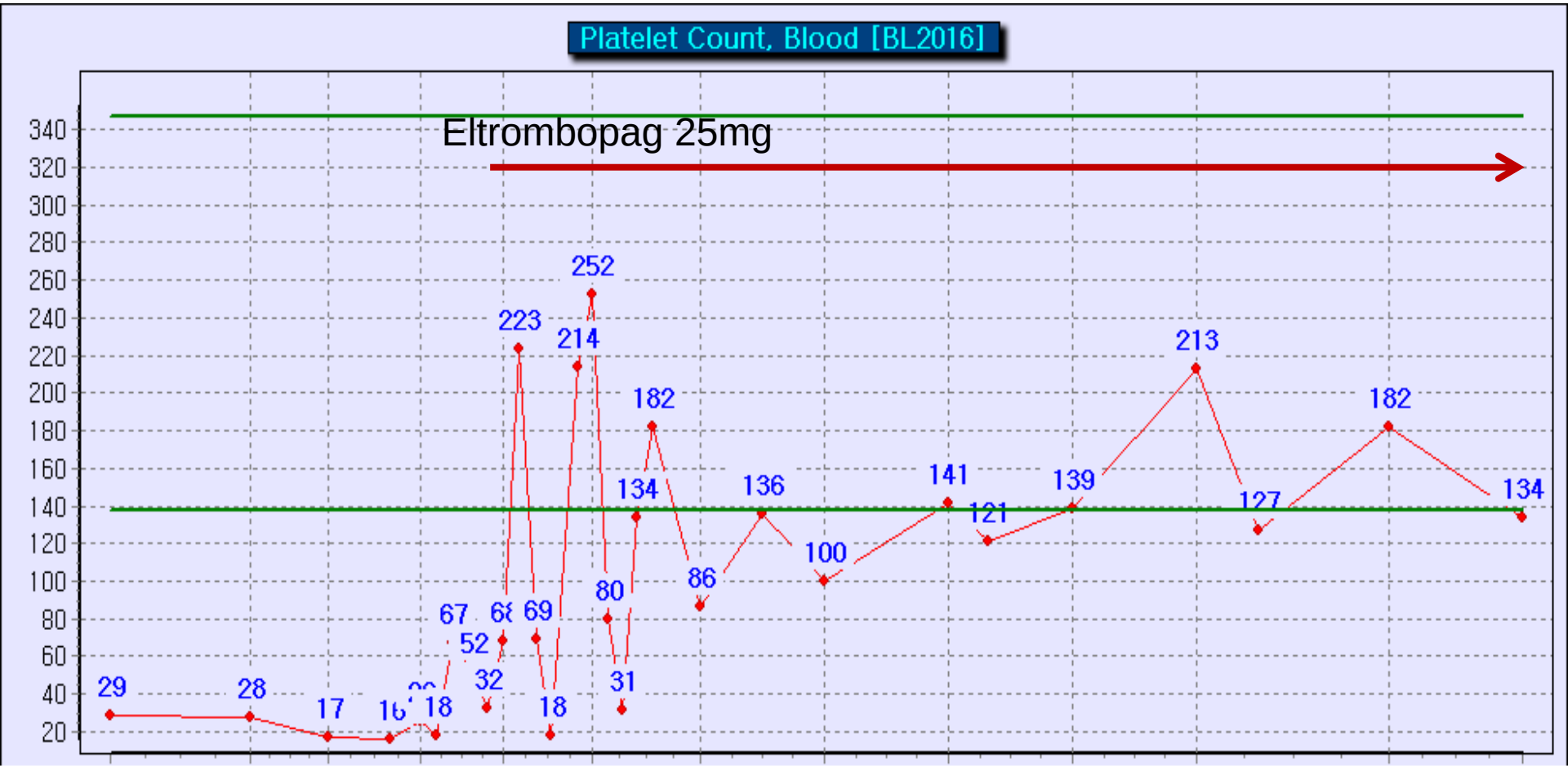
(George et al. Br J Haematol, 2009;144:409)

Do we need weekly romiplostim or daily eltrombopag?

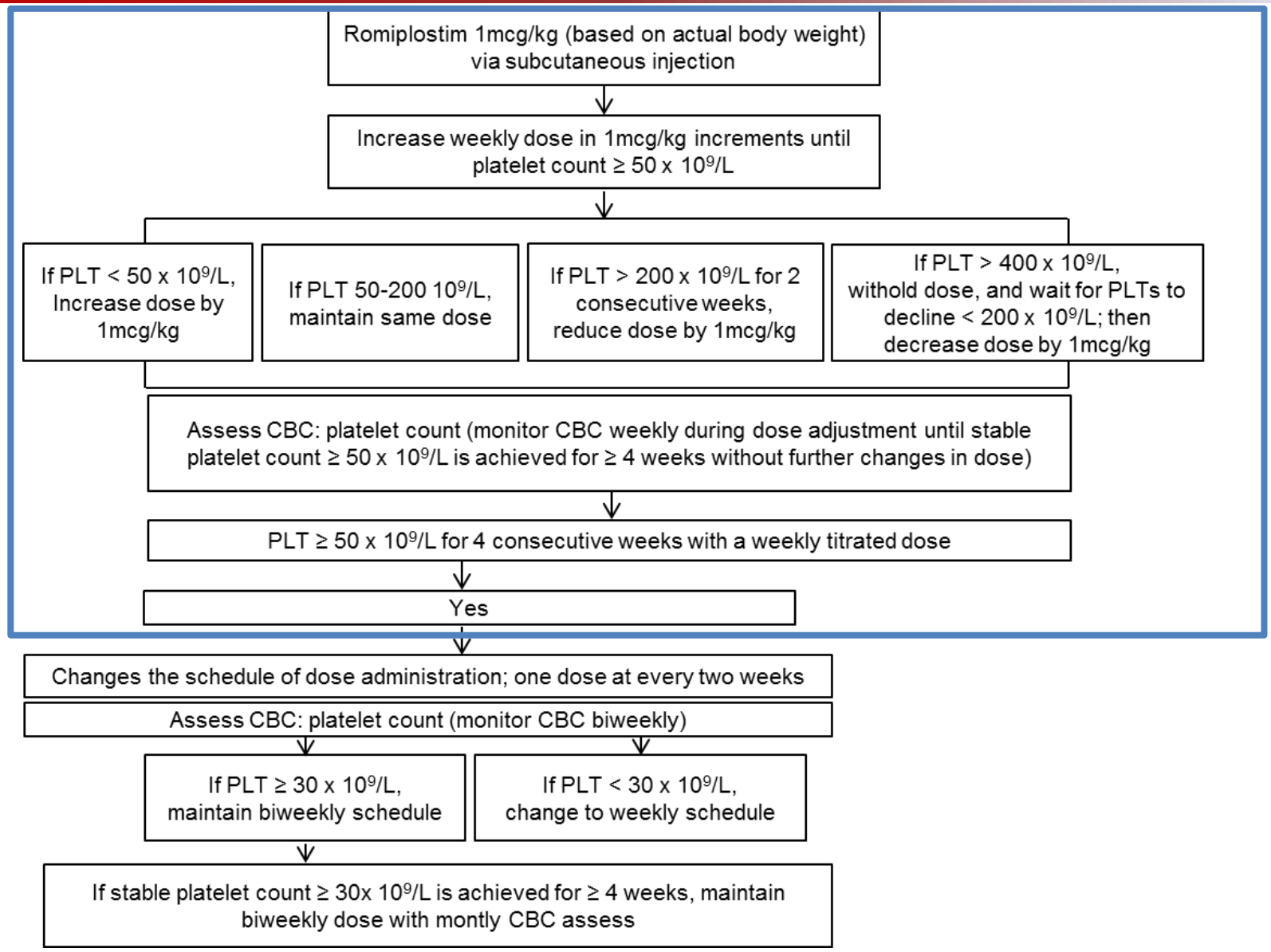


Do we need weekly romiplostim or daily eltrombopag?

F/36 steroid refractory ITP



Biweekly Romiplostim Study



Do we need weekly romiplostim or daily eltrombopag?

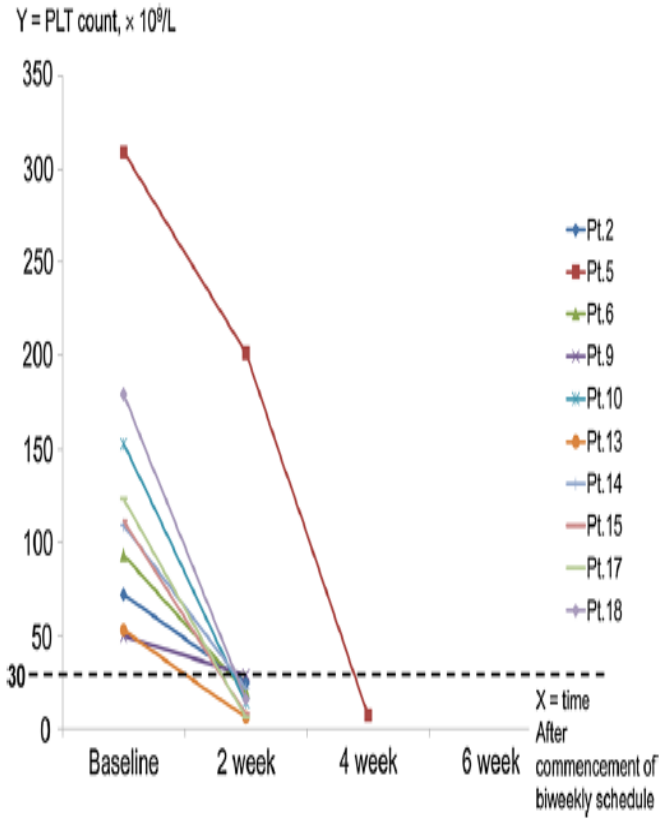


Fig. 2 Serial platelet counts after first biweekly romiplostim injection

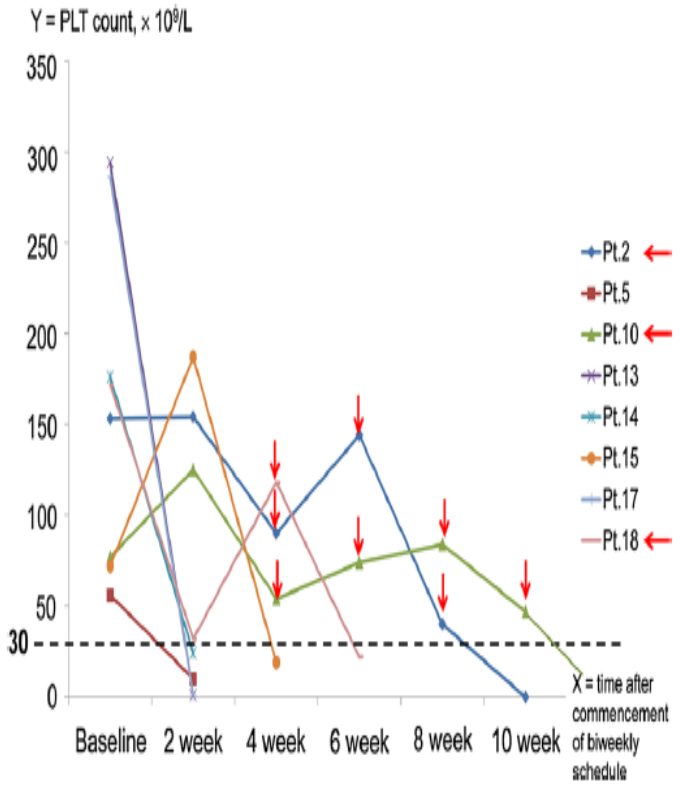


Fig. 3 Serial platelet counts after second biweekly romiplostim injection

- Biweekly administration of romiplostim in adult chronic ITP was not effective in maintaining PLT counts more than ≥ 30 x 10^9/L.

- When returning to weekly administration after failing the biweekly schedule, substantial patients exhibited labile and insufficient PLT response to the previously titrated doses, thus, required higher weekly doses in turn.

- As a result, it seems to be hard to recommend lengthening the dose interval of romiplostim more than a week; weekly schedule should be used as standard at least within 6 months after commencing treatment

Int J Hematol (2016) 103:44–52
DOI 10.1007/s12185-015-1889-7

ORIGINAL ARTICLE

Multicenter, prospective study to evaluate the efficacy of biweekly romiplostim administration in patients with immune thrombocytopenia

Silvia Park[1] · Sung Soo Yoon[2] · Jung Hee Lee[3] · Joon Seong Park[4] · Jun Ho Jang[1] · Jong Wook Lee[5]

Received: 16 June 2015 / Revised: 18 October 2015 / Accepted: 22 October 2015 / Published online: 28 October 2015

Abstract Multicenter, prospective study was conducted to evaluate the efficacy of biweekly romiplostim in maintaining platelet $\geq 30 \times 10^9$/L for at least 4 weeks. Treatment was started with a weekly injection (1 mcg/kg), and the dose was escalated until a titrated dose was achieved that maintained a platelet 50–200 $\times 10^9$/L for four consecutive weeks. Patients were scheduled to a biweekly schedule, and returned to a weekly schedule if platelets fell to $<30 \times 10^9$/L. Eighteen patients were enrolled (median platelet, 14×10^9/L). After the first weekly schedule, ten of eighteen (55.6 %) attained a median titrated dose of 3 mcg/kg and proceeded to the first biweekly schedule. However, all failed to maintain a platelet $\geq 30 \times 10^9$/L for at least 4 weeks, and returned to a second weekly schedule, where eight of the ten achieved a titrated dose (median, 5 mcg/kg) and moved to a second schedule of biweekly romiplostim. Three of the eight (37.5 %) showed platelet $\geq 30 \times 10^9$/L for 4, 8, and 10 weeks, but all eight patients eventually experienced a drop in platelets. Lengthening the dose interval of romiplostim to greater than a week is not feasible to maintain stable platelet count.

Keywords Immune thrombocytopenia · Romiplostim · Biweekly schedule

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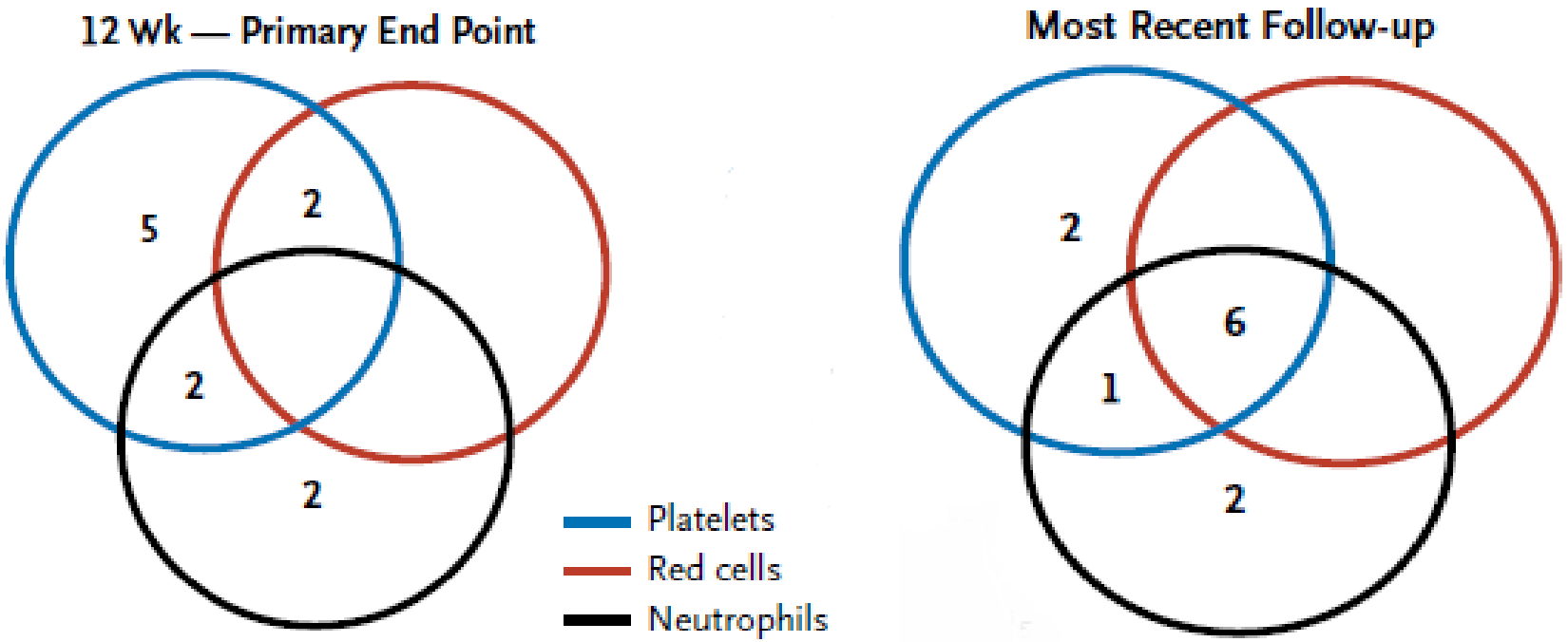
Introduction

Primary ITP is a common cause of thrombocytopenia in both adults and children, with an estimated prevalence of 5–20 per 100,000 persons and an estimated incidence of 1–3 per 100,000 persons [1–5]. The prevailing hypothesis to explain the pathophysiology of primary ITP is accelerated platelet destruction by platelet autoantibodies [6–8]. However, platelet autoantibodies are detectable in only approximately 60 % of patients [9], and a subset of patients do not respond to medical or surgical inhibition of antibody-mediated platelet clearance or B cell suppression, suggesting the possible involvement of alternative mechanisms [10]. Accumulated evidence from studies of platelet

Promising Treatment of Aplastic Anemia

- 11 of 25 patients (44%) met primary response criteria in at least one lineage 12 weeks



Olnes MJ, et al. NEJM 367:11, 2012

Title

- **Efficacy and Safety of Romiplostim (AMG531) in Patients With Aplastic Anemia Refractory to Immunosuppressive Therapy:**
  A 1-Year Interim Analysis of a Phase 2 Clinical Trial

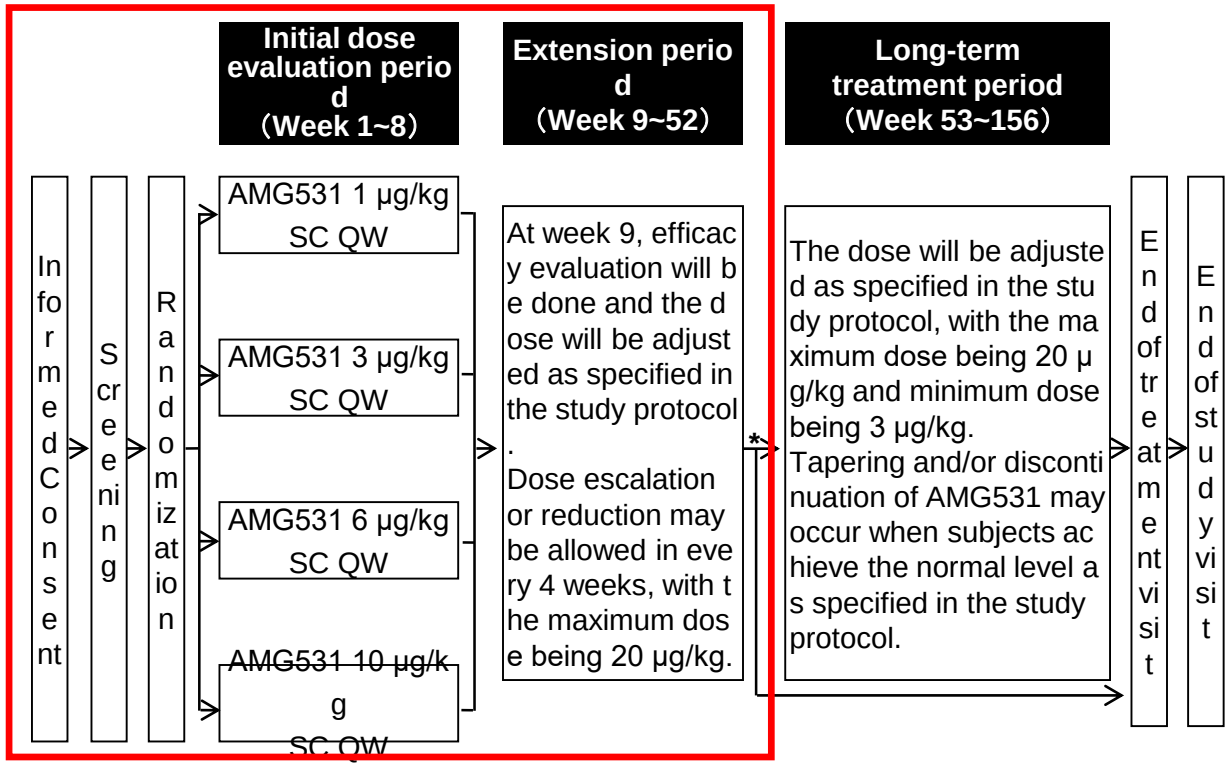
Methods

- **Endpoints**
- Primary endpoint : The proportion of subjects achieving a platelet response at Week 9
- Secondary endpoints :
  - •The proportion of subjects achieving a platelet response
  - •The proportion of subjects who become independent of platelet transfusion
  - •The proportion of subjects achieving an erythroid response and/or neutrophil response
  - •Changes in platelet count, hemoglobin concentration, and neutrophil count as continuous variables
  - •The proportion of subjects achieving tri-lineage responses
  - •Others
- Safety: Adverse events and antibody formation of antibodies against AMG531 and TPO

Methods

- **Study Design**

- A multicenter, randomized, open-label, parallel, comparative, dose-finding study



*Subjects who meet the criteria specified below moved to Long-term treatment period.

1) Subjects with platelet responses confirmed during 8 weeks prior to Week 53 (Week 46-Week 53)

2) Subjects who do not have any significant changes in medical condition during the initial evaluation period and extension period (Week 1-Week 52) including bone marrow stem cell disorders or new active malignancies

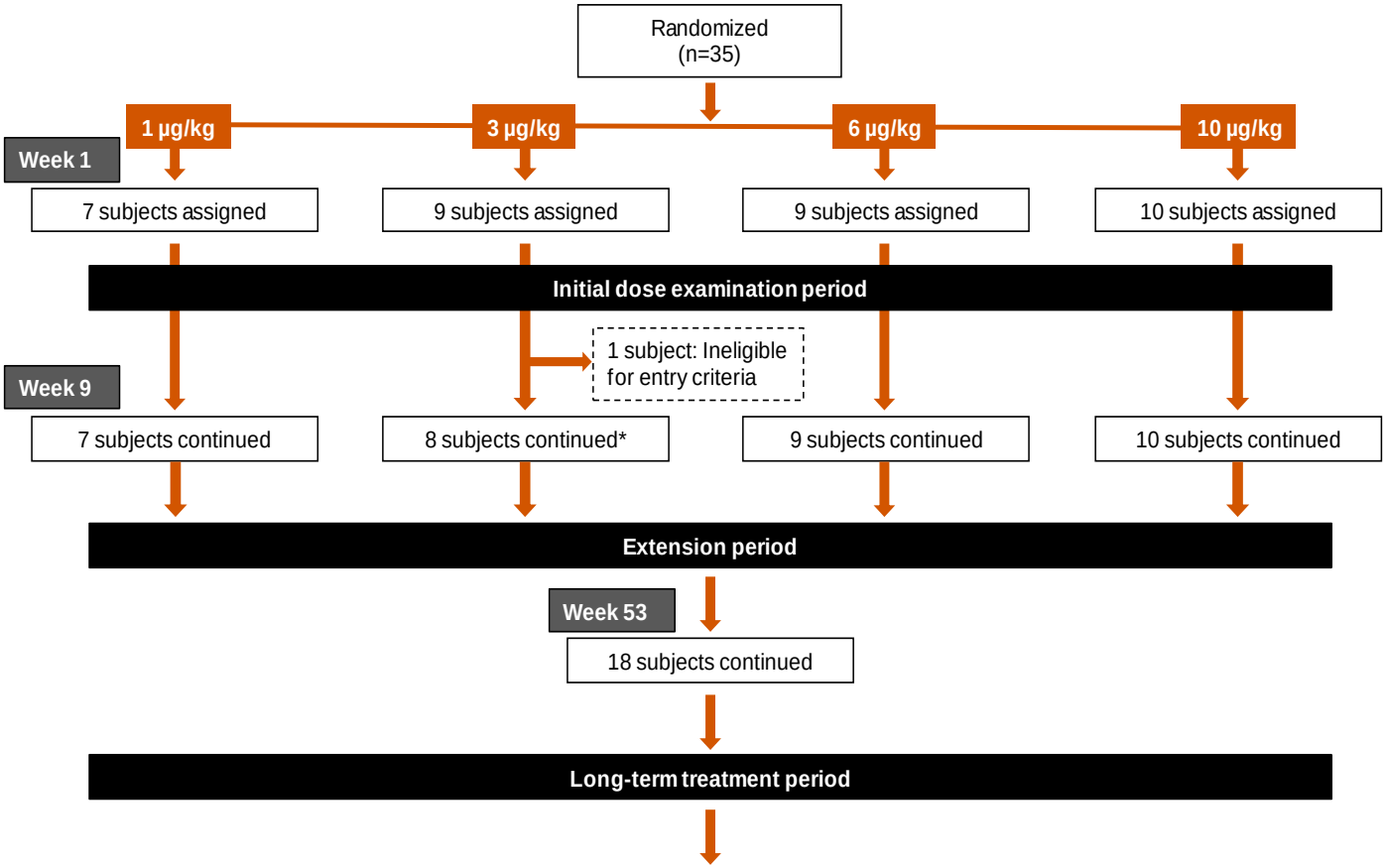
Methods

- **Key Eligibility Criteria**

- Patients with AA and refractory to immunosuppressive therapy (IST)
- Platelets with a platelet counts of ≤ 30×10^9/L
- Patients who gave voluntary written informed consent for study participation
- Patients who were previously treated with at least one course of antithymocyte globulin (ATG) with cyclosporine
- Patients aged ≥19 years
- Patient without other cause of thrombocytopenia

Results

Patient Flow



*1 subject receiving 3 µg/kg AMG531 who moved to the extension period w as excluded from the analysis set because of poor AMG531 compliance duri ng the initial dose examination period.

Patient Demographics

Initial dose of AMG531 (μg/kg)		1	3	6	10	Total
(N)		7	7	9	10	33
Age (years)	Mean	44.9	45.1	46.1	50.9	47.1
	SD	11.0	11.3	15.1	12.5	12.4
Gender	F / M	2 / 5	5 / 2	4 / 5	6 / 4	17 / 16
BMI (kg/m^2)	Mean	23.83	23.03	23.96	23.09	23.47
	SD	2.55	3.08	2.85	2.08	2.54
Time since diagnosis (months)	Mean	130.3	146.7	126.8	134.5	134.1
	SD	80.6	65.4	134.3	83.9	92.5
Severity of aplastic anemia	Non severe (%)	3 (42.9)	4 (57.1)	5 (55.6)	3 (30.0)	15 (45.5)
	Severe (%)	4 (57.1)	3 (42.9)	3 (33.3)	7 (70.0)	17 (51.5)
	Very severe (%)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.0)
Number of ATG cycles	Mean	1.0	1.1	1.2	1.1	1.1
	SD	0.0	0.4	0.4	0.3	0.3
Time since last dose of ATG (months)	Mean	114.6	114.3	66.3	113.3	101.0
	SD	80.5	79.9	60.7	86.1	76.7
Platelet transfusion	Yes* (%)	6 (85.7)	4 (57.1)	7 (77.8)	6 (60.0)	23 (69.7)
RBC transfusion		5 (71.4)	7 (100.0)	9 (100.0)	8 (80.0)	29 (87.9)

* Transfused in the previous 8 weeks prior to the initial dose of AMG531

The patient demographics indicate that each value was well-balanced among all dose groups.

Baseline Characteristics

Initial dose of AMG531 (μg/kg)		1	3	6	10	Total
Platelet count ($\times 10^9$/L)	N	7	7	9	10	33
	Mean	7.5	10.9	10.7	9.8	9.8
	SD	3.6	9.2	6.9	5.1	6.2
Hemoglobin concentration (g/dL)	N	4	5	4	6	19
	Mean	6.7	6.5	6.0	6.5	6.4
	SD	0.6	0.8	1.0	2.1	1.3
Neutrophil count ($\times 10^6$/L)	N	7	7	9	10	33
	Mean	890	961	875	922	911
	SD	361	579	500	384	438

The patient demographics indicate that each value was well-balanced among all dose groups.

Primary Endpoint: Platelet Response at Week 9

Initial dose of AMG531 (μg/kg)		1	3	6	10	Total
N		7	7	9	10	33
Platelet response	N (%)	0 (0.0)	0 (0.0)	3 (33.3)	7 (70.0)	10 (30.3)
	95% CI	0.0, 41.0	0.0, 41.0	7.5, 70.1	34.8, 93.3	15.6, 48.7

95% CI: Two-sided Exact 95% Confidence Interval

- No subject in the 1 and 3 μg/kg group achieved the platelet response.
- The platelet response was the highest in the 10 μg/kg group

Platelet Transfusion Independency

Initial dose of AMG531 (μg/kg) (N)			1 7	3 7	6 9	10 10	Total 33
Platelet transfusion independency	by Week 9	N %	1 (14.3)	2 (28.6)	1 (11.1)	2 (20.0)	6 (18.2)
	by Week 53	N %	3 (42.9)	2 (28.6)	4 (44.4)	6 (60.0)	15 (45.5)
NA		N	1	3	2	4	10

NA: the subjects who were independent of platelet transfusion at base line.

By Week 53, 45.5% (15/33) of the subjects were independent of platelet tran sfusion

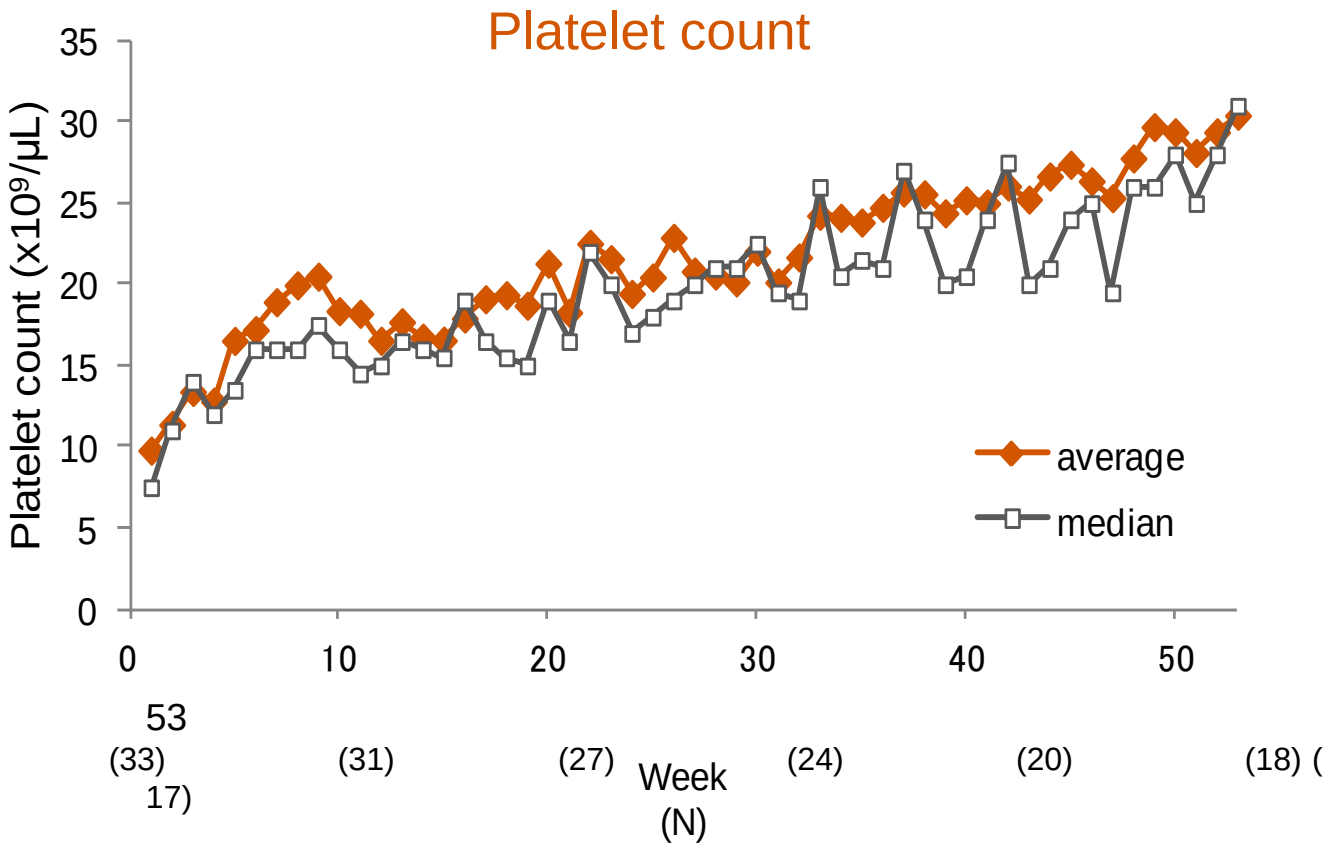
Tri-lineage Response ~~at/by~~ Week 53

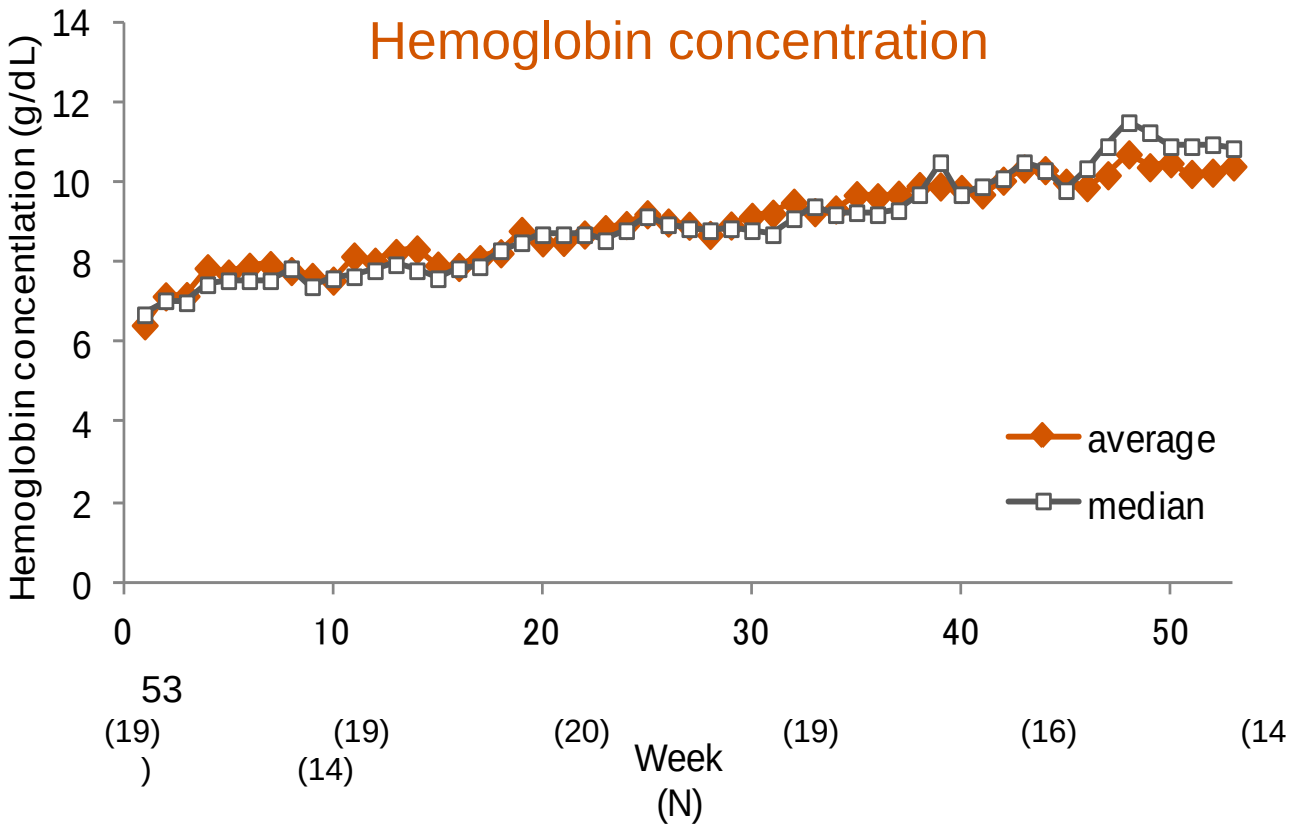
		N=33	
		N	%
Tri-lineage Response	at Week 53	5	15.2
	by Week 53	11	33.3
NA		12	-

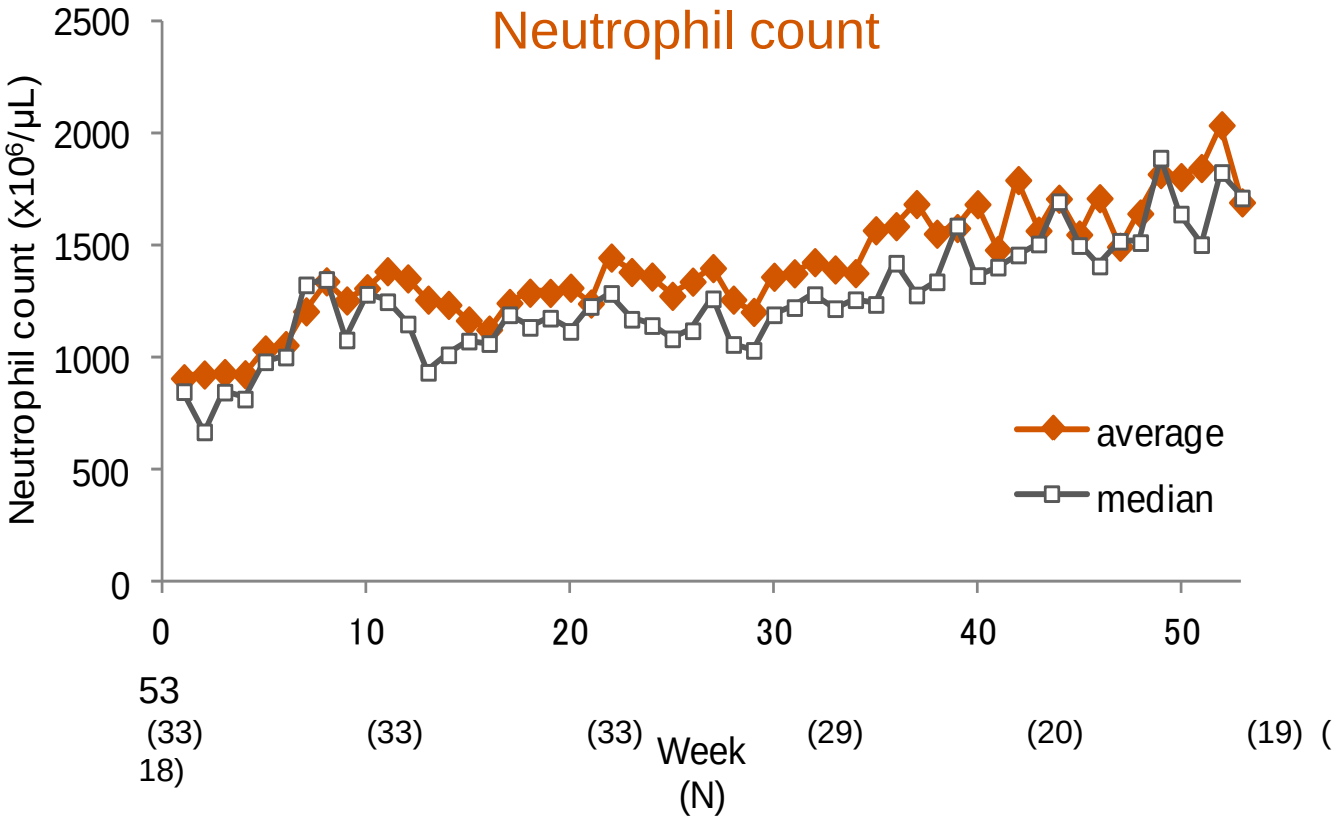
NA: any one or more of baseline values of three blood cells did not m eet the response definitions.

By Week 53, 33.3% (11/33) of the subjects achieved the tri-lineage respo nse.

Changes in Blood Cell Counts by Week 53




Hemoglobin concentration
Hemoglobin concentlation (g/dL)
14
12
10
8
6
4
2
0
0
10
20
30
40
50
average
median
53
(19)
)
(19)
(14)
(20)
Week
(N)
(19)
(16)
(14



We observed a continuous increasing trend of each blood cell res ponse
until Week 53.

Safety

TEAEs observed in >10% of patients	Total (N=35)	
	N	%
Subjects with any events	30	85.7
Upper respiratory tract infection	12	34.3
Fatigue	8	22.9
Myalgia	6	17.1
Transfusion reaction	6	17.1
Dyspepsia	4	11.4

Drug-related TEAEs in >5% of patients	Total (N=35)	
	n	%
Subjects with any events	3	8.6
Myalgia	3	8.6
Fatigue	2	5.7

CTCAE grade ≥3 TEAEs in >5% of patients	Total (N=35)	
	n	%
Subjects with any events	14	40.0
Transfusion reaction	6	17.1
Purpura	2	5.7

TEAEs: Treatment-emergent adverse events
The terms were coded on MedDRA version 18.1 .
CTCAE: The National Cancer Institute Common Terminology Criteria for Adverse Events (Versio n 4.0) was used to grade TEAEs.

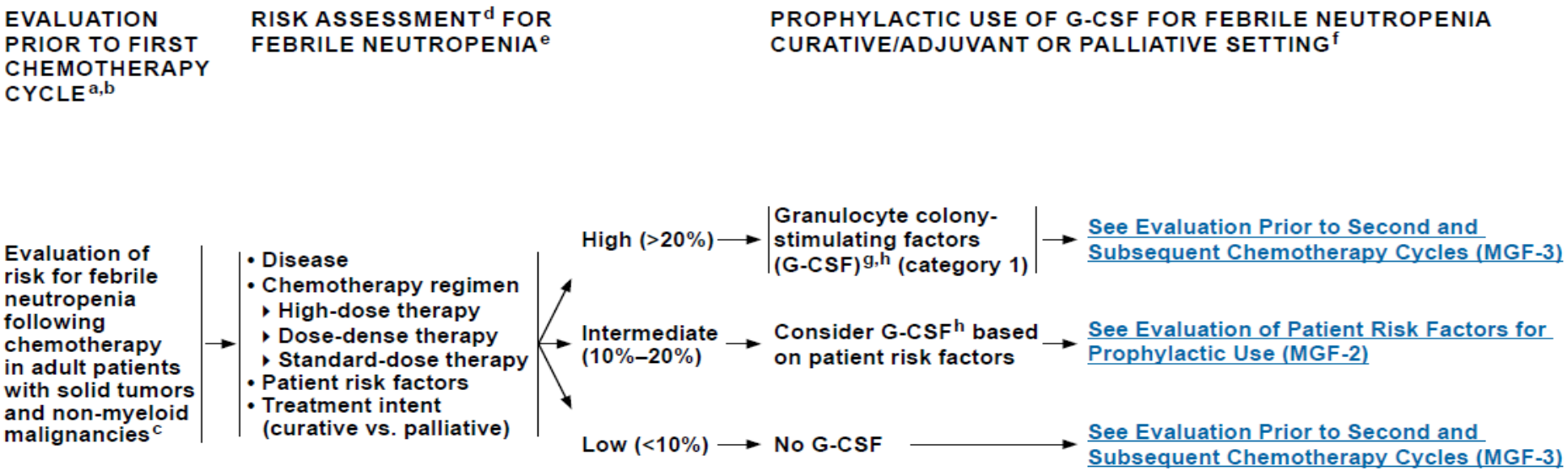
Conclusion in Romiplostim Study

- These results show that AMG531 is effective and safe for 1 year in AA patients refractory to IST.
- On the basis of efficacy and safety determined in the initial dose evaluation period, we selected 10 μg/kg as an optimal initial dose of AMG531 for patients with AA.
- A clinical study to confirm the efficacy and safety of AMG531 in patients with AA is currently ongoing (NCT02773290).

Clinical Use of G-CSF

NCCN Guidelines Version 1.2017
Myeloid Growth Factors

NCCN Guidelines Index
Table of Contents
Discussion



[a]The NCCN Guidelines for Myeloid Growth Factors were formulated in reference to adult patients.
[b]Patients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with MGF as clinically indicated, unless precluded by trial specifications.
[c]For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for Myelodysplastic Syndromes, and in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia.
[d]There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (See MGF-A) and patient risk factors (See MGF-2).
[e]Febrile neutropenia is defined as single temperature: ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[f]See Toxicity Risks with Myeloid Growth Factors (MGF-E).
[g]G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).
[h]There is category 1 evidence for G-CSF for a reduction of: risk of febrile neutropenia, hospitalization, and 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 details).

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

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- ***This list is not comprehensive***; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for treatment by cancer site are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-2)
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients). (See MGF-1)

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (See NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC[b] (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Breast Cancer
- Dose-dense AC followed by T[b] (doxorubicin, cyclophosphamide, paclitaxel)[2]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[3]
- TC[a,c] (docetaxel, cyclophosphamide)[4]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[5]

Hodgkin Lymphoma
- Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[7]

Kidney Cancer
- Doxorubicin/gemcitabine[8]

Non-Hodgkin's Lymphomas
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[9]
- ICE (ifosfamide, carboplatin, etoposide)[a,10,11]
- Dose-dense CHOP-14[a,b] (cyclophosphamide, doxorubicin, vincristine, prednisone)[12,13]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[14]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[15]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[16]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[17,18]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[19]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[20] ± bortezomib (VTD-PACE)[21]

Ovarian Cancer
- Topotecan[a,22]
- Docetaxel[23]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[24]
- Doxorubicin[a,25]
- Ifosfamide/doxorubicin[26]

Small Cell Lung Cancer
- Topotecan[27]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[28]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)[29,30]
- TIP (paclitaxel, ifosfamide, cisplatin)[31]

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 4)

See References, MGF-A (3 of 4)

[a]Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for treatment by cancer site.
[b]In general, dose-dense regimens require growth factor support for chemotherapy administration.
[c]Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

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

Myeloid growth factor for therapeutic use

Possible Indications for the Initiation of Therapeutic MGF for Management of Febrile Neutropenia[a,b]

- Sepsis syndrome
- Age >65 years
- Absolute neutrophil count [ANC] <100/mcL
- Neutropenia expected to be more than 10 days in duration
- Pneumonia or other clinically documented infections
- Invasive fungal infection
- Hospitalization at the time of fever
- Prior episode of febrile neutropenia

MGF Doses for Therapeutic Use:[c]

- Filgrastim or filgrastim-sndz[d]
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits).
  - Continue until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.
- Sargramostim
  - Used in clinical trials at a dose of 250 mcg/m^2/d (rounding to the nearest vial size by institution-defined weight limits).
  - Continue until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.

MGF in mobilization and post HSCT

Mobilization of Hematopoietic Progenitor Cells in Autologous Setting

- Single-agent growth factor:[1-3]
  - Filgrastim or filgrastim-sndz[a] or tbo-filgrastim
    - Dose: 10–32 mcg/kg/d by subcutaneous injection, in daily or twice-daily dosing. Begin apheresis on day 4 or 5 and continue until leukapheresis.
- Combination chemotherapy followed by filgrastim/filgrastim-sndz[a]/tbo-filgrastim with the goal of mobilization during count recovery.[4-6]
  - Filgrastim/filgrastim-sndz[a]/tbo-filgrastim is started about 24 hours after completion of chemotherapy.
- Concurrent filgrastim/filgrastim-sndz[a] + sargramostim (category 2B)
  - Filgrastim/filgrastim-sndz[a] 7.5 mcg/kg each morning, sargramostim 7.5 mcg/kg each evening, and leukapheresis beginning on day 5.[7]
- Filgrastim/filgrastim-sndz[a]/tbo-filgrastim + plerixafor (for selected patients with non-Hodgkin's lymphoma or multiple myeloma)[8-10]
  - Plerixafor is indicated for:
    - Patients who were heavily pre-treated[11] or had prior treatment with >10 cycles of cytotoxic chemotherapy, or those who have failed prior collection attempts or exhibit risk factors for being poor mobilizers due to more than 6 cycles of lenalidomide or fludarabine, or radiation to the pelvis.
    - As "just in time" or "rescue" in the case of suboptimal peripheral CD34+ count.[12-14]
  - Dosing:
    - Filgrastim/filgrastim-sndz[a]/tbo-filgrastim dose: 10 mcg/kg/d x 4 days. On the evening of day 4, start plerixafor by subcutaneous injection 11 hours prior to day 5 collection (the next morning).
    - Plerixafor dose: 0.24 mg/kg/d for patients weighing >83 kg; 20 mg (fixed dose), or 0.24 mg/kg/d for patients weighing ≤83 kg, maximum 4 doses (if creatinine clearance >50 mL/min, maximum dose 40 mg/d)

MGF in mobilization and post HSCT

Mobilization of Allogeneic Donors

- Allogeneic hematopoietic cell donors:[15-18]
  - Filgrastim (preferred) or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)
    - Dose: 10 mcg/kg/d by subcutaneous injection, start collection on day 4 or 5.[19-21]
  - Plerixafor (category 2B): Use in normal donors is under study.[22,23]
- For granulocyte transfusion:
  - Filgrastim or filgrastim-sndz[a] (category 2B) or tbo-filgrastim (category 2B)
    - Single dose: 5 mcg/kg subcutaneously with dexamethasone 10 mg PO 8–24 hours prior to collection.[24]

Supportive Care Options

- Filgrastim[b,25] or filgrastim-sndz[a] or tbo-filgrastim
  - Post autologous hematopoietic cell or cord blood transplant
  - 5 mcg/kg/d. Begin day +5 post transplant until recovery of ANC (eg, >1.5 x 10^9/L x 2 d).[c]
- Sargramostim[26-28]
  - Post autologous hematopoietic cell transplant or delayed hematopoietic engraftment after transplant
  - 250 mcg/m^2/d until ANC >1.5 x 10^9/L x 3 d.
- Pegfilgrastim[29]
  - Post autologous hematopoietic cell transplant

Use of Growth factors after induction therapy

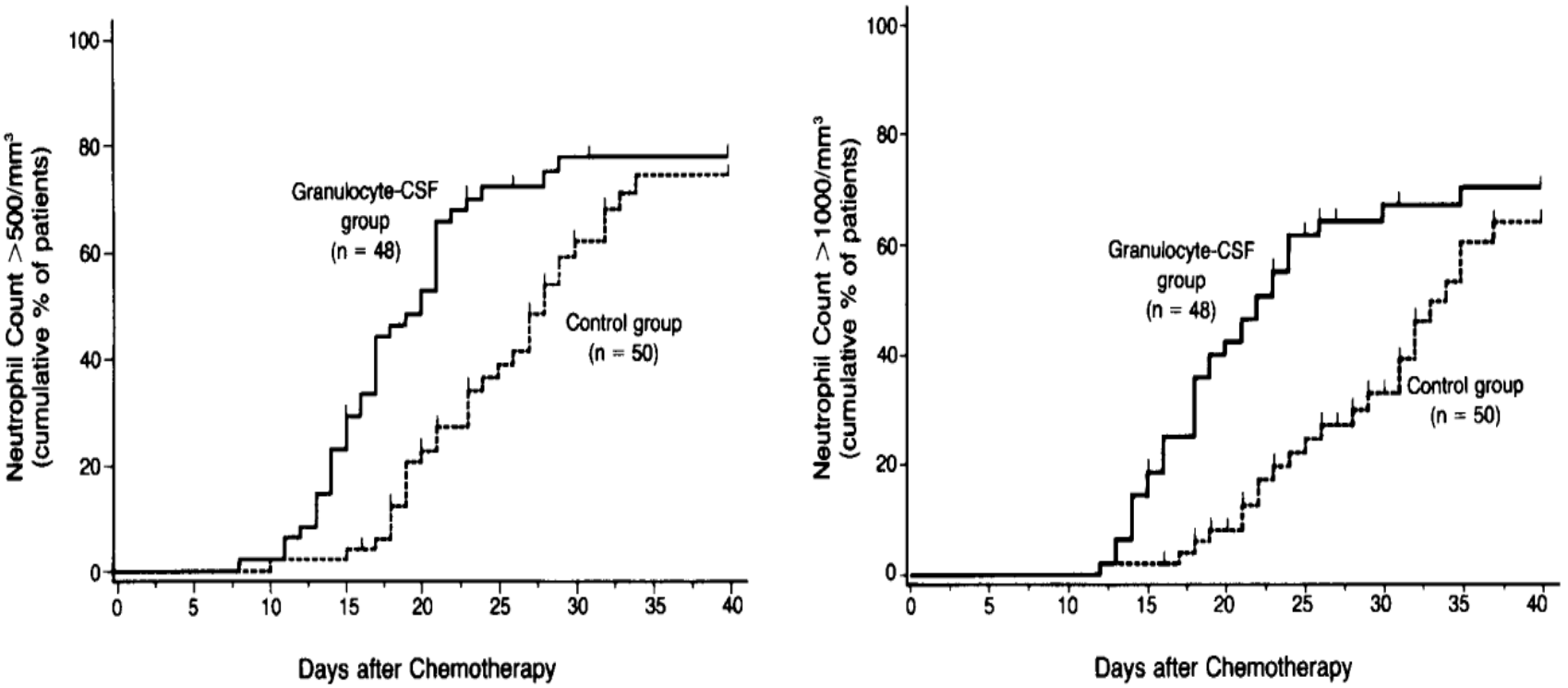


Figure 1. Recovery of the Neutrophil Count to More Than 500 (Left Panel) or 1000 (Right Panel) per Cubic Millimeter after Induction Therapy.

For the left panel, P = 0.0002 by generalized Wilcoxon test and 0.009 by log-rank test, and for the right panel the corresponding P values are 0.0002 and 0.0091.

Ohno R et al. NEJM 1990; 323: 871-7

Use of Growth factors after induction therapy

Table 2. Febrile Episodes and Documented Infections after Randomization.

VARIABLE	GRANULOCYTE-CSF GROUP	CONTROL GROUP
	no. of patients	
Afebrile before randomization	27	33
Became febrile	23	32
Remained afebrile	4	1
Documented infection	5	15*
Septicemia	3	6
Pneumonia	1	4
Septicemia and pneumonia	0	1
Perianal abscess	1	0
Cellulitis	0	1
Gingivitis and pharyngitis	0	2
Cystitis	0	1
Fever of unknown origin	18	17
	no. of days	
Febrile days		
Mean ±SD	5.7±7.0	6.5±4.4
Median (range)	3 (0–31)	7 (0–14)

*P = 0.028 for the comparison with the granulocyte-CSF group.

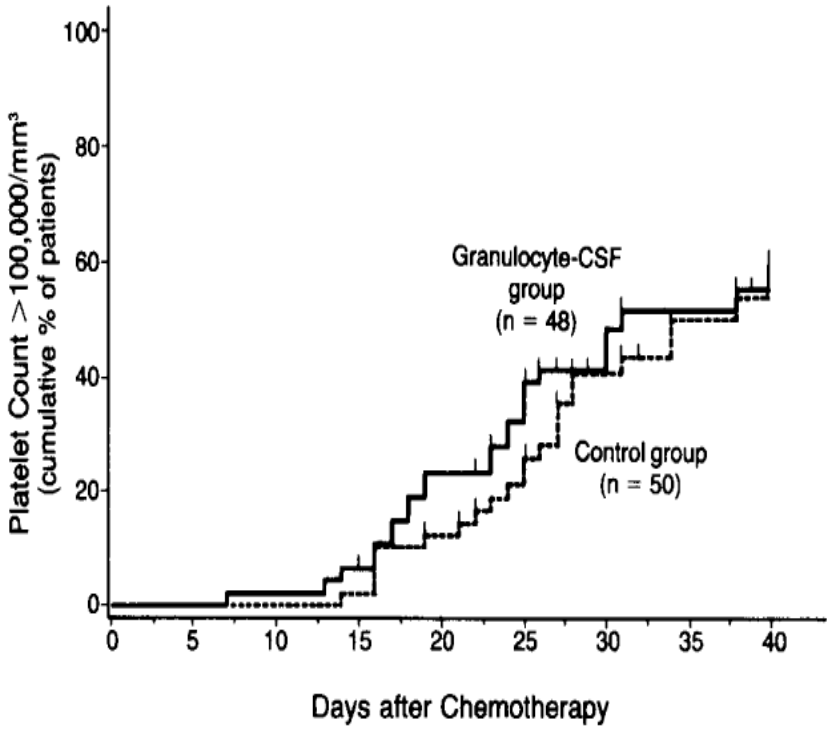


Figure 2. Recovery of the Platelet Count to More Than 100,000 per Cubic Millimeter after Chemotherapy.
P = 0.4745 by generalized Wilcoxon test and 0.3648 by log-rank test.

Ohno R et al. NEJM 1990; 323: 871-7

Use of Growth factors after induction therapy

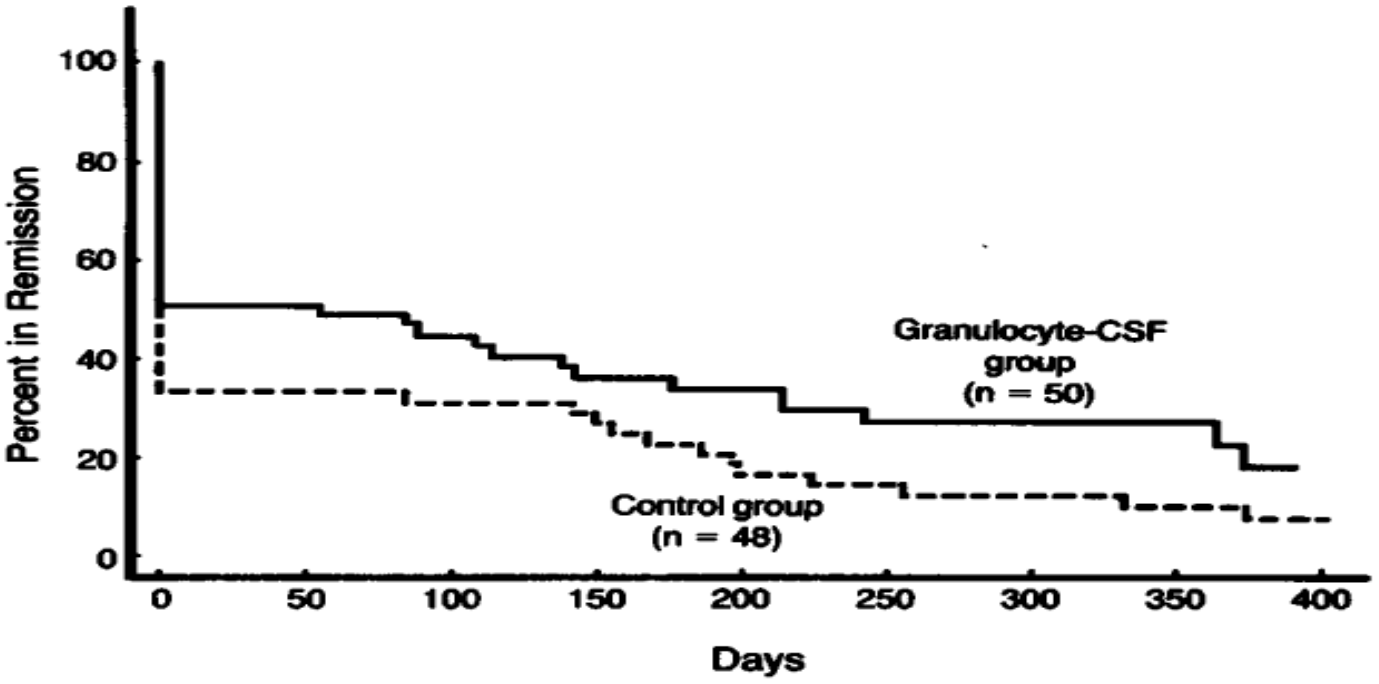


Figure 4. Kaplan–Meier Curve of the Percent in Remission. Patients who did not have complete remission were assigned a duration of zero. P = 0.0752 by generalized Wilcoxon test and 0.0995 by log-rank test.

Ohno R et al. NEJM 1990; 323: 871-7

Conclusion

1. Many growth factors are useful for hematology – oncology area

2. Several growth factors are promising in hematology – oncology area