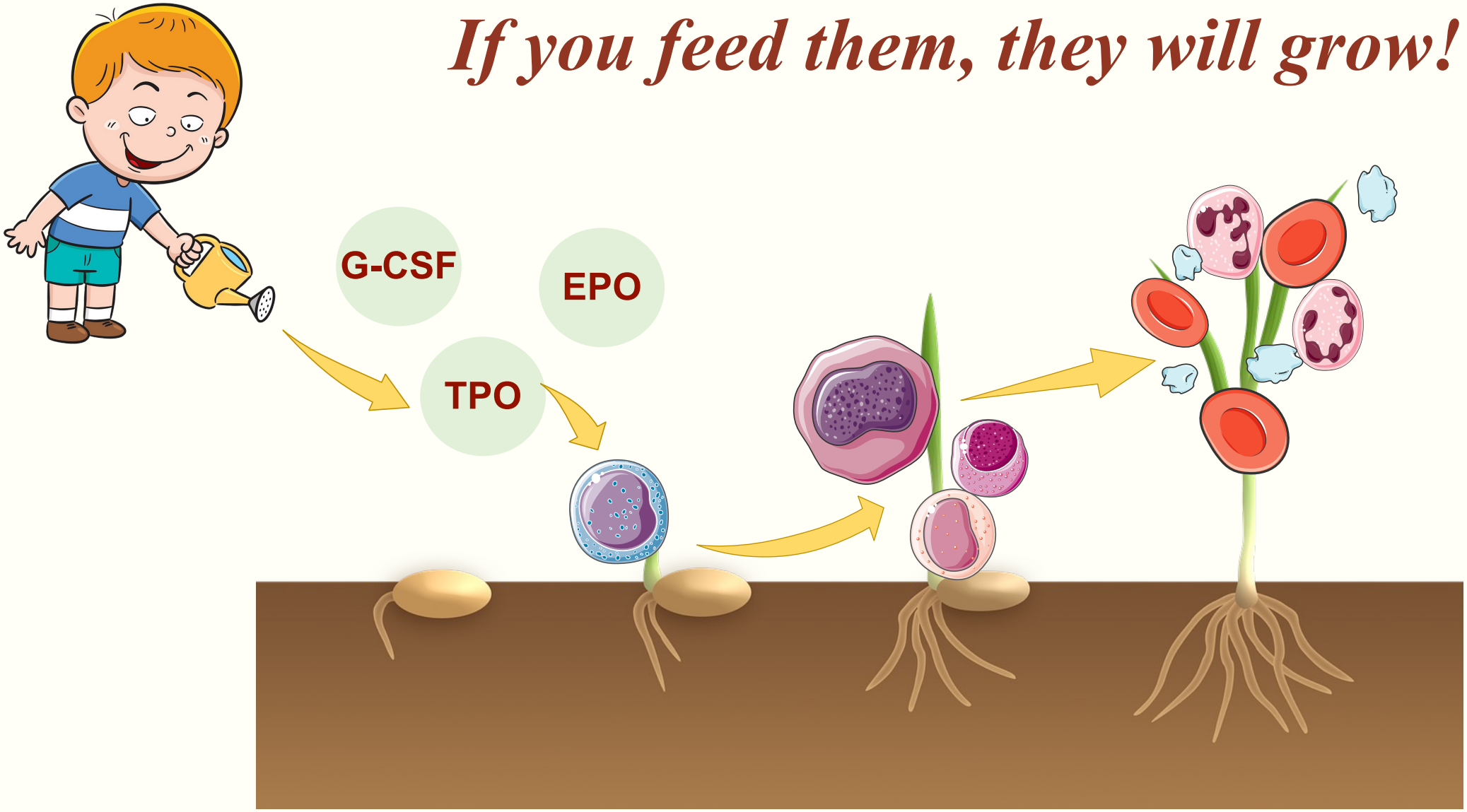
Cytopenia In Cancer:
Use of Growth Factors in Patients With Cancer

Hanny Al-Samkari, M.D.
Hematology Oncology Division
Massachusetts General Hospital
hal-samkari@mgh.Harvard.edu

Gerald A. Soff MD
Chief, Classical Hematology Service
Sylvester Comprehensive Cancer Center,
University of Miami Health System
gas199@Miami.edu

If you feed them, they will grow!



Disclosures

Gerald Soff, M.D

- Research Support (Past 5 years):
  - Amgen
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Anthos Therapeutics
- Advisory Boards (Past 5 years)
  - Janssen Scientific Affairs
  - Sobi/Dova Pharmaceuticals
  - Luzsana (HengruiUSA) Biotechnology
  - Sanofi

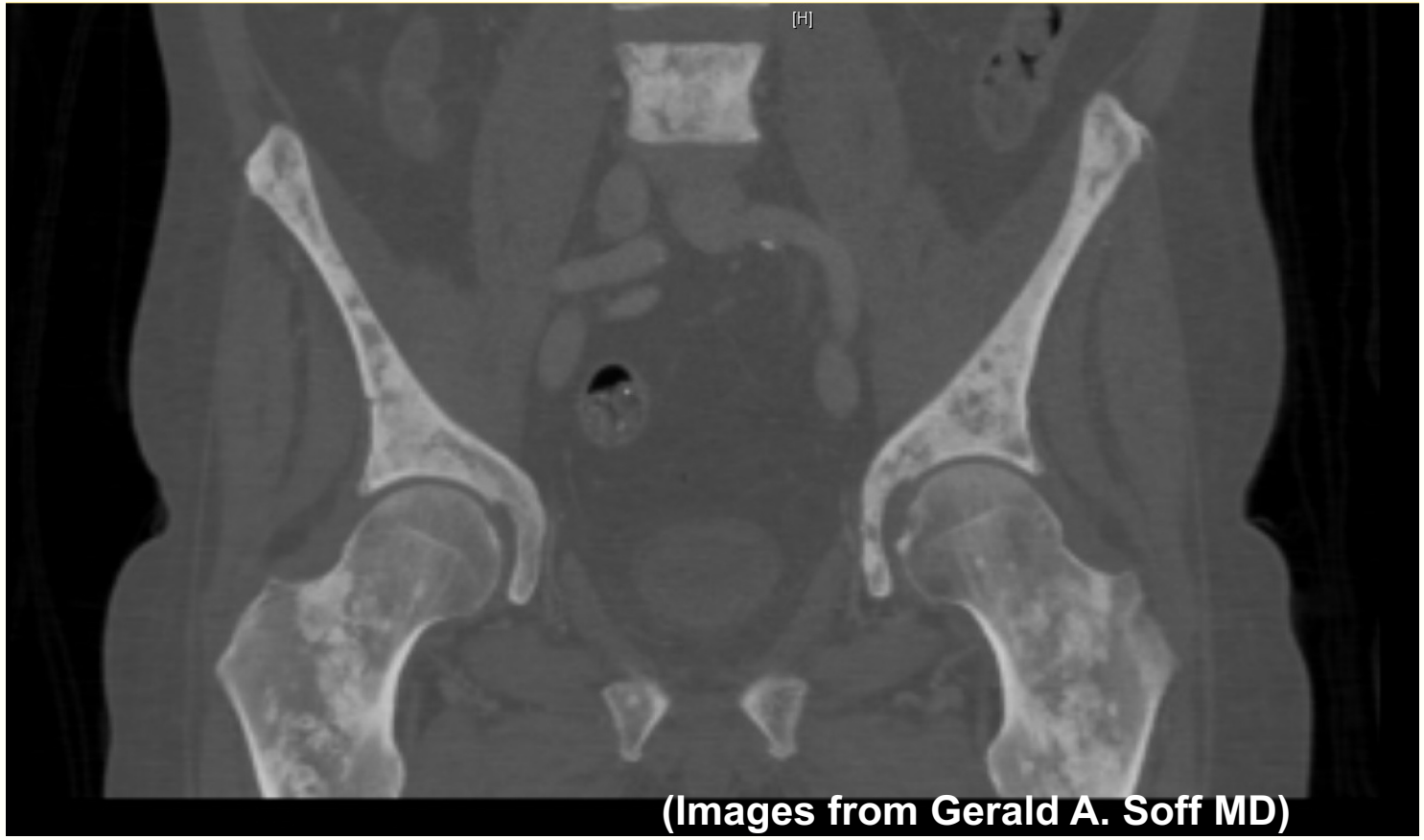
Hanny Al-Samkari, M.D.

- Research Support:
  - Agios
  - Dova/Sobi
  - Amgen
- Consultancy
  - Agios
  - Dova/Sobi
  - Argenx
  - Rigel
  - Moderna
  - Novartis
  - Forma

Pancytopenia From Cancer

- Obvious chemotherapy nadir
- Marrow infiltration
- Sepsis
- Other drugs

Bone Metastasis ~ Bone Marrow Invasion

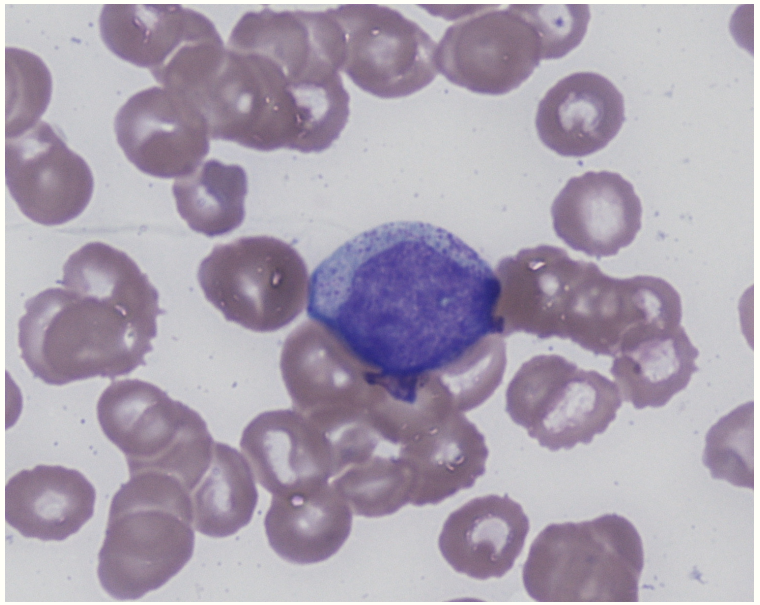


63 yr. old man, with bone metastases from prostate cancer and pancytopenia.

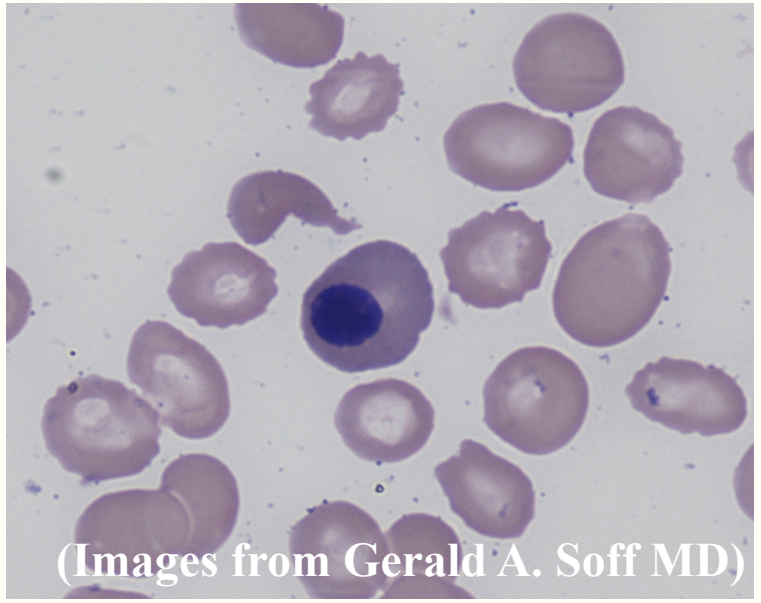
Leukoerythroblastosis/Myelophthisis

- Marrow invasion with abnormal cells (carcinoma, advanced myeloproliferative disease, fibrosis, etc.)
- Immature red and white cells (promyelocytes, myelocytes, metamyelocytes, nucleated cells.

Myelocyte

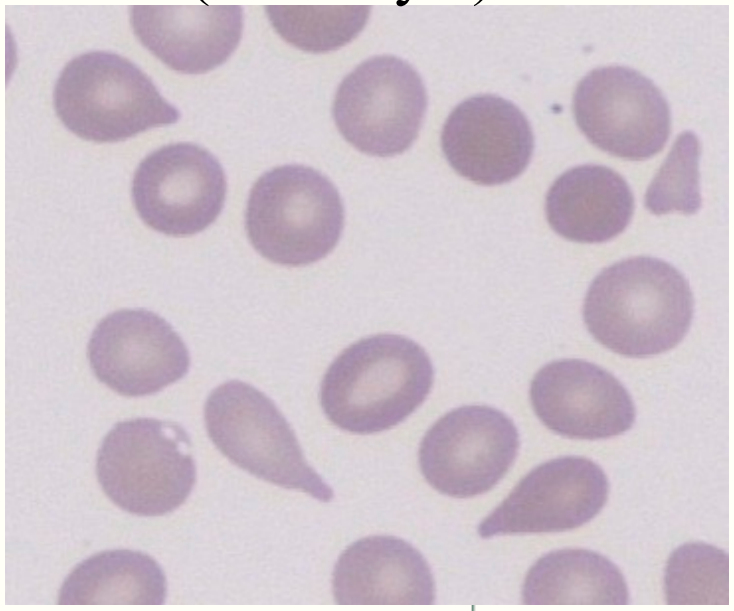


Nucleated rbc



(Images from Gerald A. Soff MD)

Teardrop Cells
(Dacrocyte)

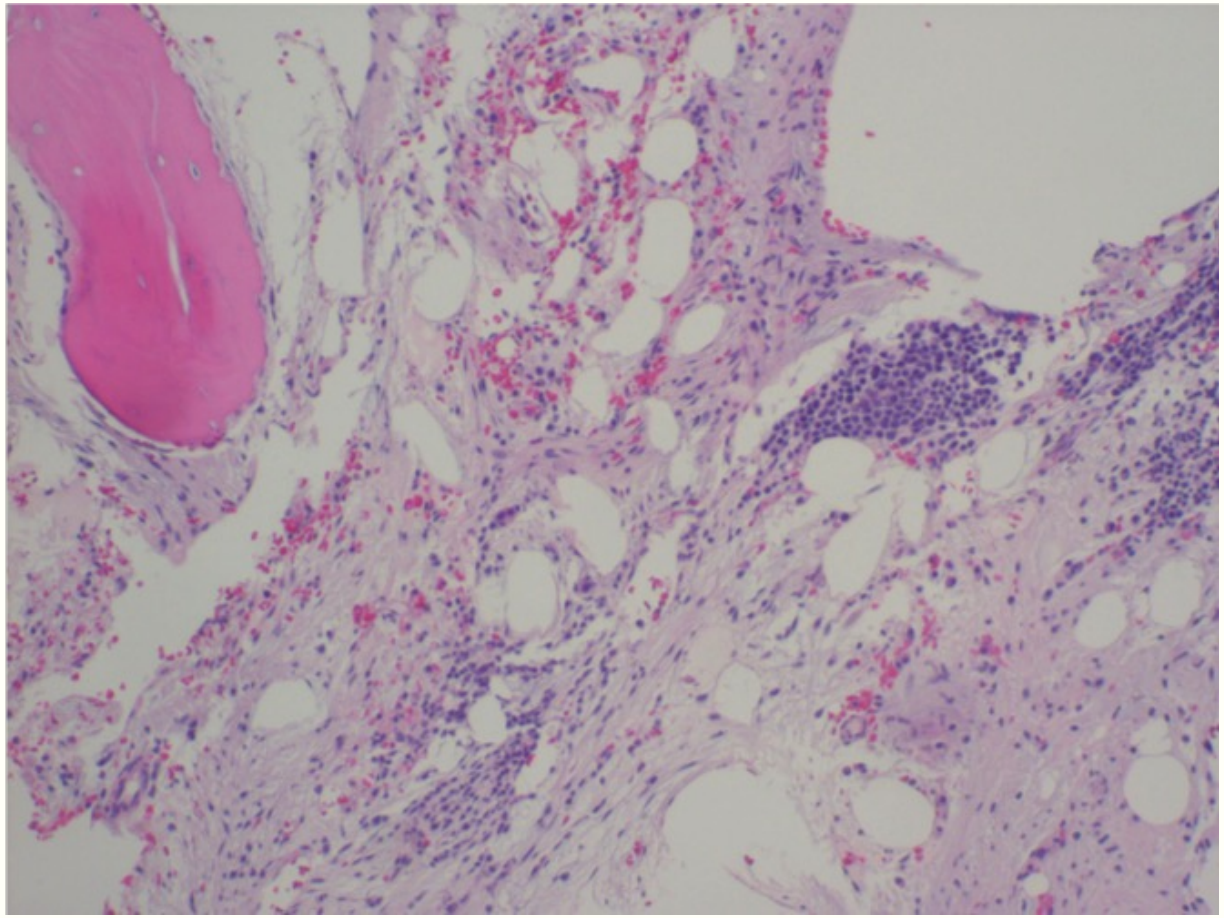


Myelophthisis vs. Leukoerythroblastosis

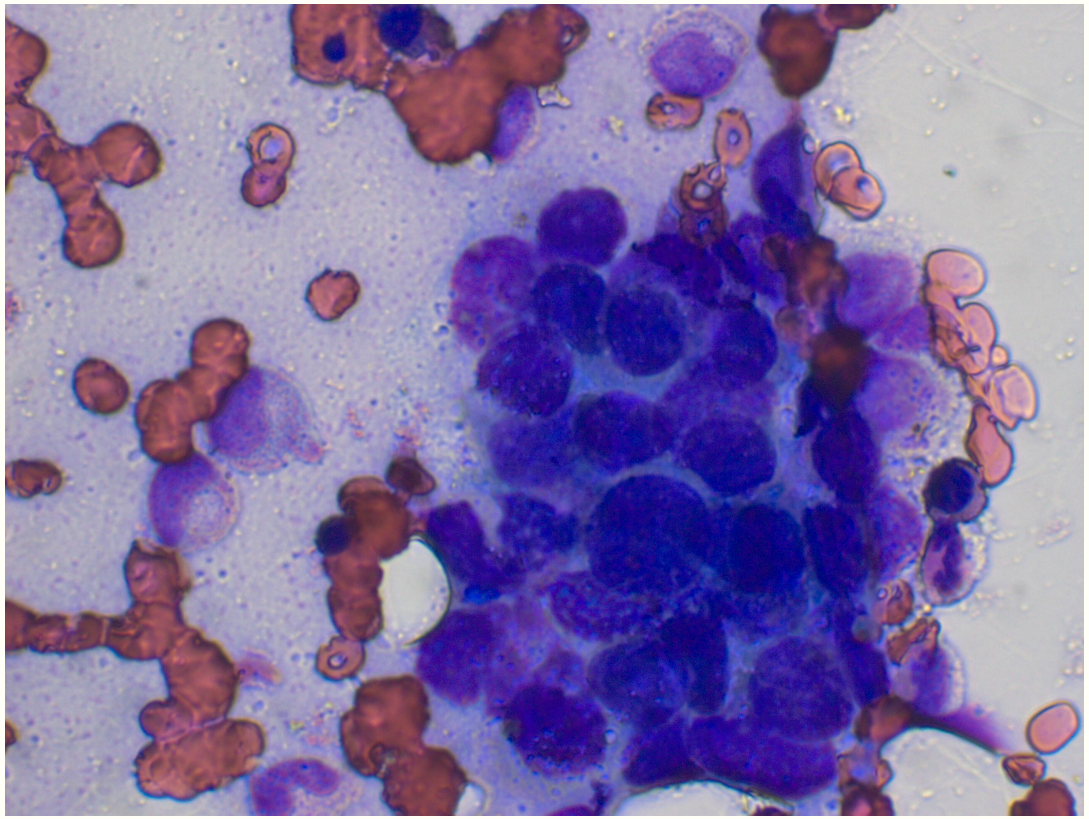
- Myelophthisis:
  - Refers to the displacement of hemopoietic bone-marrow tissue by fibrosis, tumors, or granulomas

- Leukoerythroblastosis:
  - Peripheral blood morphologic findings, indicative of marrow infiltration.
  - Immature cells of the myeloid series
  - Nucleated red cells
  - Teardrop red cells (Dacrocyte)

Cancer Cells in Bone Marrow



"Grape Clusters"

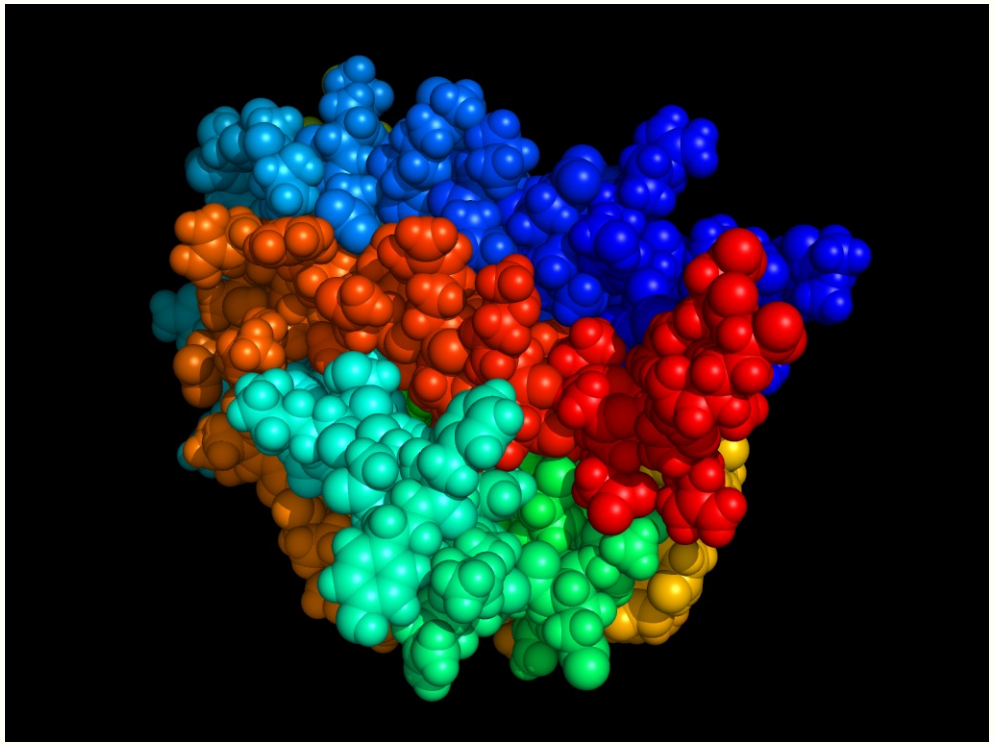


(Images from Gerald A. Soff MD)

Bone Marrow Biopsy in Cancer Patient with Pancytopenia

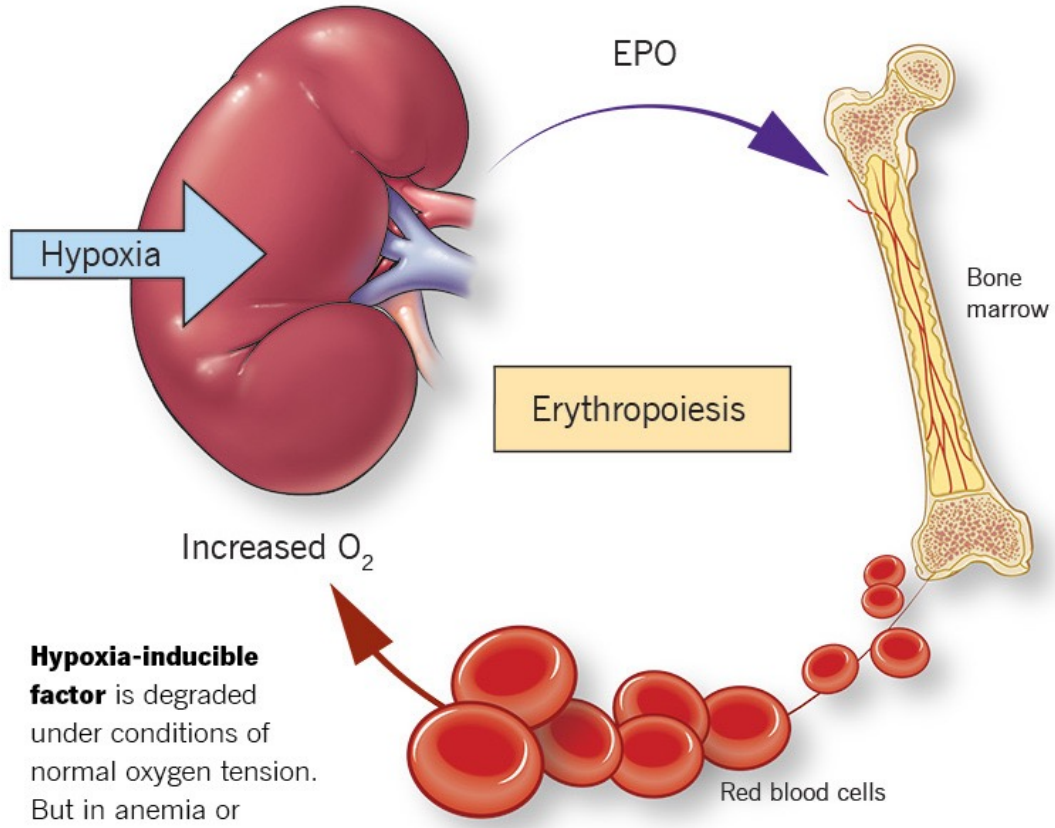
- As a general rule, if a patient has bone metastases sufficient to lead to cortical bone destruction, a bone marrow biopsy is not indicated.
- If results are negative, “we probably missed one of the affected areas.”
- If results are positive, “we already knew it.”
- If one suspects a secondary MDS/leukemia, start with peripheral blood cytogenetic evaluation.

Erythropoietin



- https://en.wikipedia.org/wiki/Erythropoietin
- https://consultqd.clevelandclinic.org/anemia-of-chronic-kidney-disease/

Erythropoietin (EPO) promotes production of mature red blood cells in the bone marrow. More red blood cells in the circulation leads to increased oxygenation and lower levels of hypoxia-inducible factor, suppressing EPO production.



Hypoxia-inducible factor is degraded under conditions of normal oxygen tension. But in anemia or hypoxia, it promotes gene transcription of erythropoietin (EPO), necessary for maturation of red blood cells.

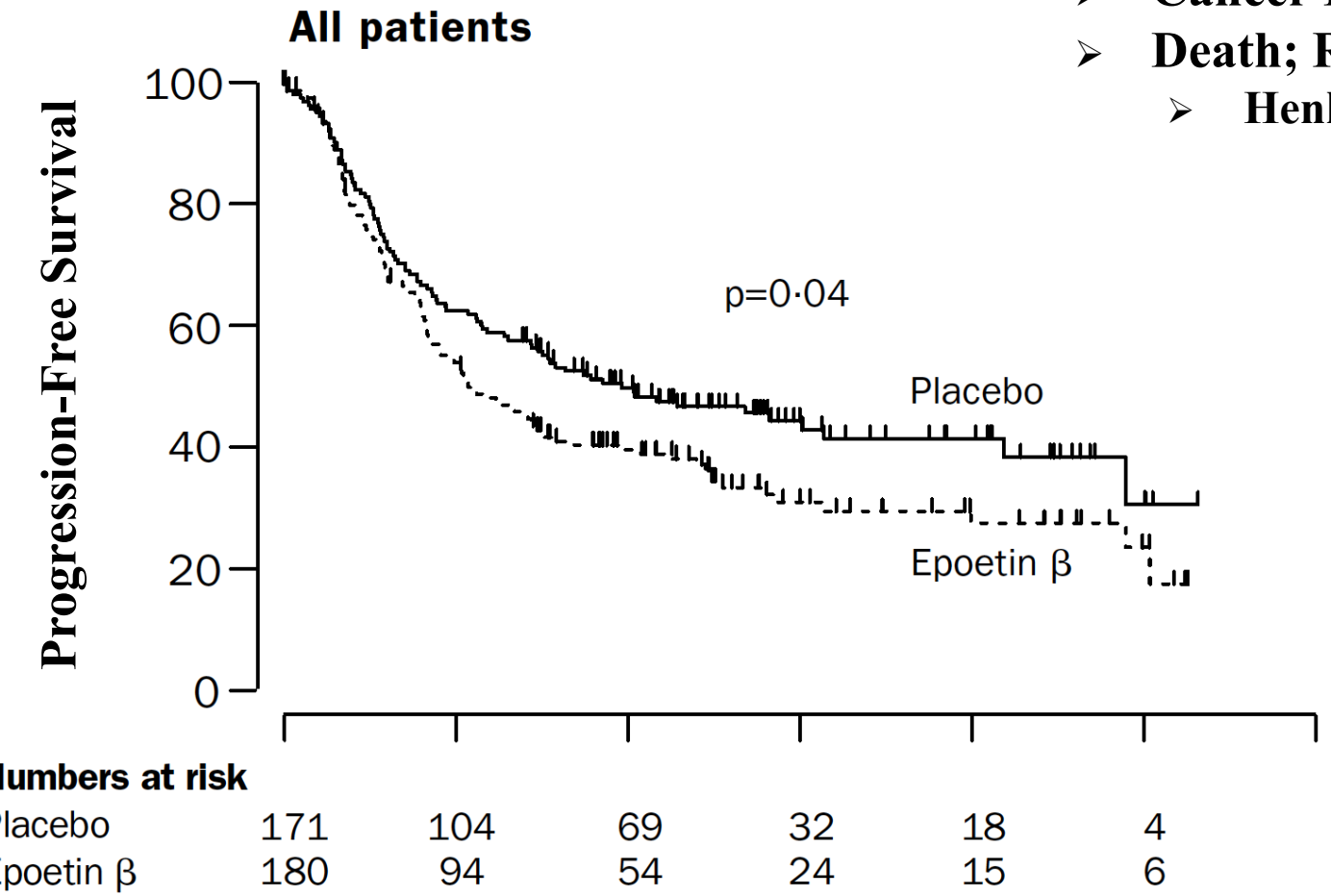
Iron is necessary as well for red blood cell production. Its absorption and transport are also promoted by hypoxia-inducible factor (see **Figure 2**).

Medical Illustrator: Beth Halasz CCF ©2016

Role Of Erythropoiesis-Stimulating Agents (ESAs): Epoetin Alfa and Darbepoetin Alfa

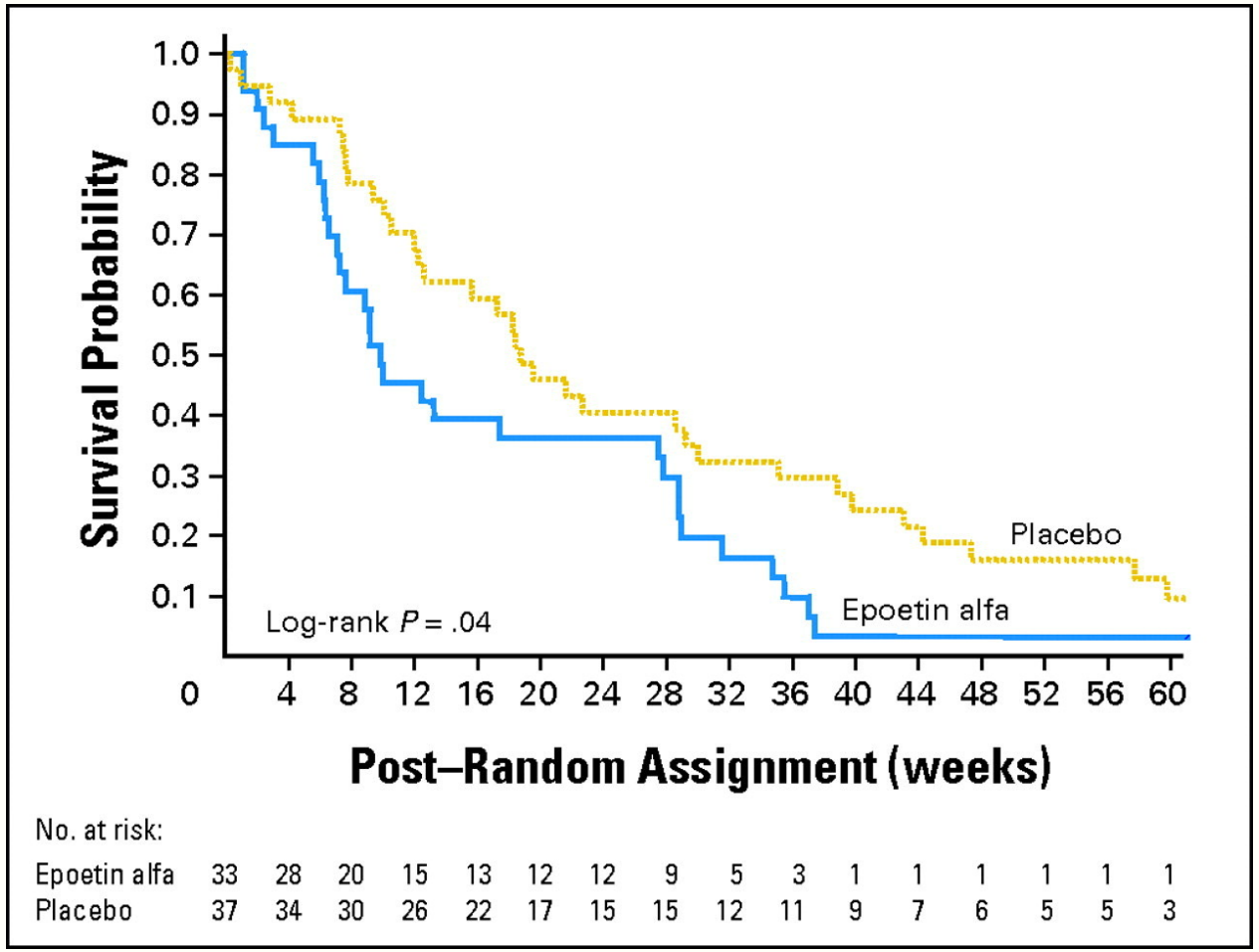
- ESAs were first used in the 1980s to treat anemia in patients with chronic renal failure, including those on hemodialysis.
- Subsequent trials indicated that ESAs were effective in increasing Hgb in patients with cancer and cancer treatment-related anemia.
- But after 2005, their use became more "controversial" because of data linking ESA use to inferior survival and worse cancer outcomes.
- Debate if risk is only with Hgb corrections to > 12 gm/dL.
- Mechanism of poor outcomes not resolved:
  - A. Increased oxygen deliver to cancer?
  - B. Does EPO stimulate cancer growth?
  - C. Other?

Head And Neck Cancer with Anemia Undergoing Radiotherapy:



- Cancer Progression; RR 1.69 (p=0.007)
- Death; RR 1.39 (p=0·02)
  - Henke et al. Lancet 2003; 362: 1255–60.

Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non–Small-Cell Lung Cancer With Disease-Related Anemia.



Hgb (gm/dL)	Placebo	Epoetin Alpha
Baseline	10.3	10.3
4 weeks	10.3	11.8
8 weeks	10.7	11.8
12 weeks	10.5	12.4

Wright et al. J Clin Oncol 25:1027-1032. 2007

FDA Guidance for Epoetin Alfa

PROCRIT® (epoetin alfa) injection, for intravenous or subcutaneous use
Initial U.S. Approval: 1989

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE
See full prescribing information for complete boxed warning.

Chronic Kidney Disease:
- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks (2.2).
- Use the lowest PROCRIT dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).

Cancer:
- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (5.2).
- Use the lowest dose to avoid RBC transfusions (2.4).
- Use ESAs only for anemia from myelosuppressive chemotherapy (1.3).
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure (1.5).
- Discontinue following the completion of a chemotherapy course (2.4).

Perisurgery:
- Due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended (5.1).

https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Epogen/epogen_pi_hcp_english.pdf

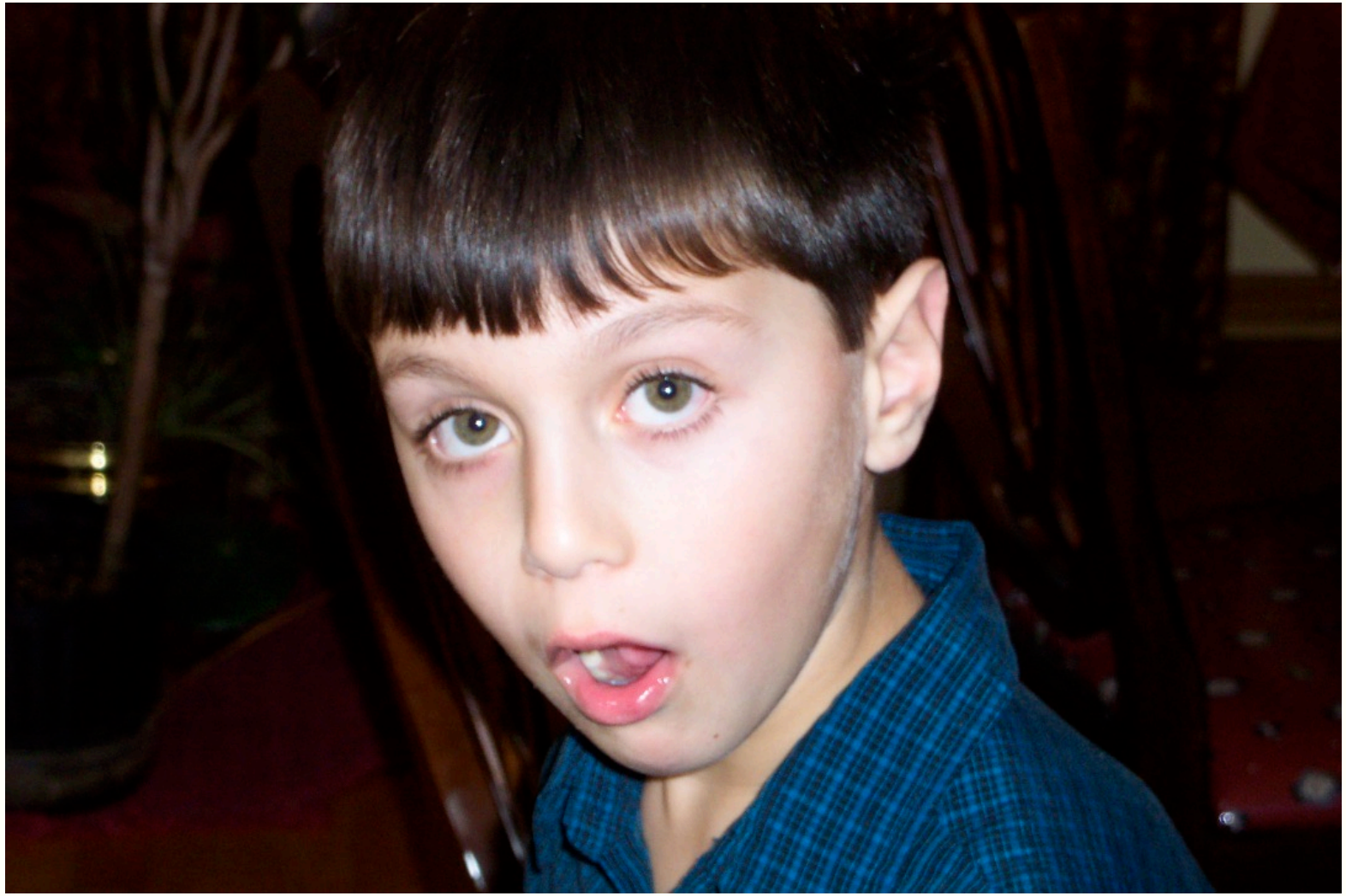
Cancer:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.
- Use the lowest dose to avoid RBC transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.

FDA: ESAs in Anemia Associated With Myelosuppressive Chemotherapy:

- "The serious risks of shortened overall survival and/or increased risk of tumor progression or recurrence associated with these drugs remain."
- The prescribing information continues to note an increased risk of tumor progression or recurrence, as well as death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.
- Health care providers are encouraged to discuss the risks and benefits of using ESAs with each patient before initiating use.

Are You Serious?



SPECIAL CATEGORIES IN CONSIDERING ERYTHROPOIESIS-STIMULATING AGENT (ESA) USE

Cancer and chronic kidney disease (moderate to severe) → **Consider ESAs by FDA dosing/dosing adjustments[j,m,n,o]** →

Patient undergoing palliative treatment[k] →

Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia[k] →

Consider based on patient preferences:
- **ESAs by FDA dosing/dosing adjustments[j,m,n]**
  or
- **RBC transfusion per AABB Guidelines**
  or
- **Clinical trial**

→ **Evaluation of Iron Deficiency (ANEM-4)**

Select patients who refuse blood transfusions → **Consider ESAs by FDA dosing/dosing adjustments[j,m,n]** → **Management of Cancer- and Chemotherapy-Induced Anemia for Patients Who Refuse Blood Transfusions (ANEM-C)**

- **Patients with cancer not receiving therapy**
- **Patients receiving non-myelosuppressive therapy**
- **Patients receiving myelosuppressive chemotherapy with curative intent[l]**
  (Examples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin lymphomas, testicular cancer, early-stage non-small cell lung cancer, and small cell lung cancer)

→ **There is not enough evidence to support ESA use in these patient populations; therefore, ESAs are not recommended at this time**

ERYTHROPOIETIC THERAPY - ADVERSE EFFECTS (3 of 5)

Survival of Patients with Cancer

- Studies have reported possible decreased survival in patients with cancer receiving erythropoietic drugs for correction of anemia. Analyses of eight studies in patients with cancer found decreased survival in patients receiving erythropoietic drugs for correction of anemia and target Hb levels of >12 g/dL.[1-7,10] One analysis in patients with cancer not receiving active therapy found decreased survival in patients treated with ESAs.[6] Please refer to the FDA website for additional information: https://www.fda.gov/drugs/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers. Unless new evidence demonstrates a change in benefit:risk estimates, physicians should be advised not to administer ESAs (darbepoetin alfa, epoetin alfa, or epoetin alfa-epbx) 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,[8-11] two meta-analyses have indicated that ESA use did not significantly affect mortality or disease progression.[12,13]
- Recent pharmacovigilance trials have reported no adverse effects on survival in patients with cancer with chemotherapy-induced anemia receiving ESAs.[14-16]
- The risks of shortened survival and tumor progression have not been excluded when ESAs have been dosed to a target Hb of <12 g/dL.
- Additional prospective clinical trials designed and powered to measure survival of patients with cancer 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 RBC transfusion (see Discussion for comparison of risks and benefits of ESA use versus RBC transfusion).
- Recent studies suggest that use of ESAs may be deleterious when used in patients with metastatic breast cancer. See Discussion.

ASCO/ASH Clinical Practice Guideline Update on Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents:

- PURPOSE:
  - Update ASCO/ASH recommendations for use of erythropoiesis-stimulating agents (ESAs) in patients with cancer.
- METHOD:
  - PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) and meta-analyses of RCTs in patients with cancer published from January 31, 2010, through May 14, 2018.
  - ASCO and ASH convened an Expert Panel to review the evidence and revise previous recommendations as needed.
- Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents: ASCO/ASH Clinical Practice Guideline Update.
  - Bohlius et al, JCO 37:1336-1351. 2019
  - Bohlius et al, Blood Adv 3 (8): 1197–1210. 2019

ASCO/ASH Clinical Practice Guideline Update on Management of Cancer-Associated Anemia With Erythropoiesis-Stimulating Agents:

- RESULTS:
  - The primary literature review included 15 meta-analyses of RCTs and two RCTs.
  - A growing body of evidence suggests that adding iron to treatment with an ESA may improve hematopoietic response and reduce the likelihood of RBC transfusion.
  - The biosimilar literature review suggested that biosimilars of epoetin alfa have similar efficacy and safety to reference products, although evidence in cancer remains limited.

- Bohlius et al, JCO 37:1336-1351. 2019
- Bohlius et al, Blood Adv 3 (8): 1197–1210. 2019

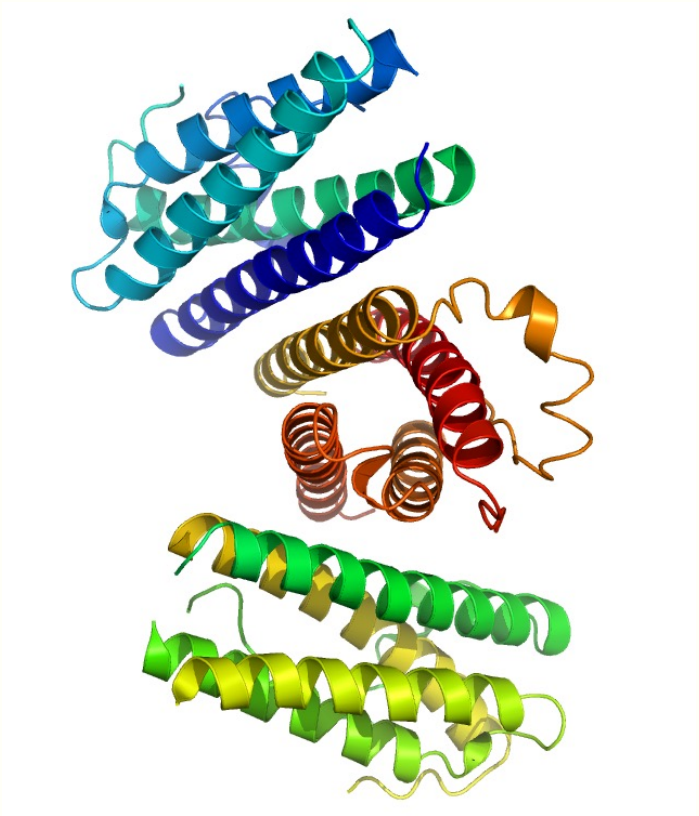
RECOMMENDATIONS:

1. ESAs (including biosimilars) may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin has declined to < 10 g/dL.
2. RBC transfusion is also an option.
3. With the exception of selected patients with myelodysplastic syndromes, ESAs should not be offered to most patients with nonchemotherapy-associated anemia.
4. During ESA treatment, hemoglobin may be increased to the lowest concentration needed to avoid transfusions.
5. Iron replacement may be used to improve hemoglobin response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency.

- Additional information is available at
- https://www.asco.org/practice-patients/guidelines/supportive-care-and-treatment-related-issues
- www.hematology.org/guidelines.

Myeloid Growth Factor/G-CSF:

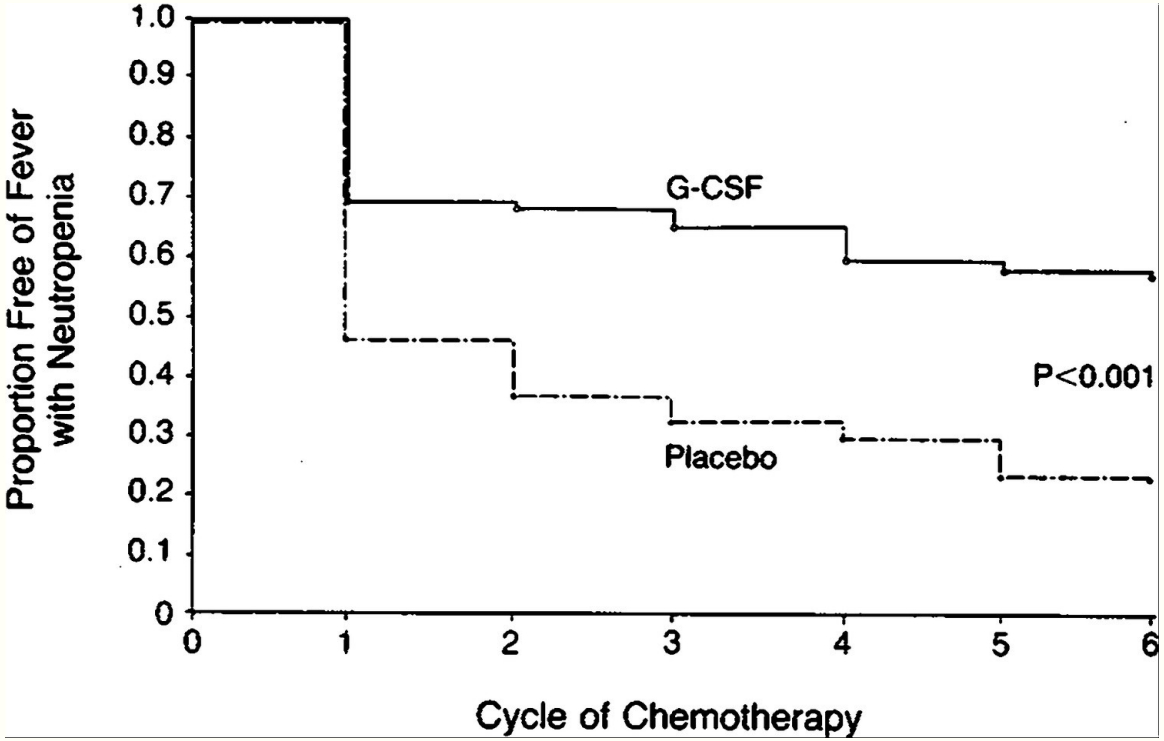
Granulocyte Colony Stimulating Factor (G-CSF)



https://en.wikipedia.org/wiki/Granulocyte_colony-stimulating_factor

- Early studies (1988-1991) indicated reduced fever/neutropenia and depth of neutrophil nadir.

Reduction by G-CSF of Fever and Neutropenia Induced by Chemotherapy in Patients with Small-Cell Lung Cancer



- Kaplan–Meier Curve for the Proportion of Patients Remaining Free of Fever with Neutropenia, According to Treatment Cycle.
- Crawford J et al. N Engl J Med 1991;325:164-170.

Primary Prophylaxis Use of Granulocyte Colony Stimulating Factors (G-CSFs)

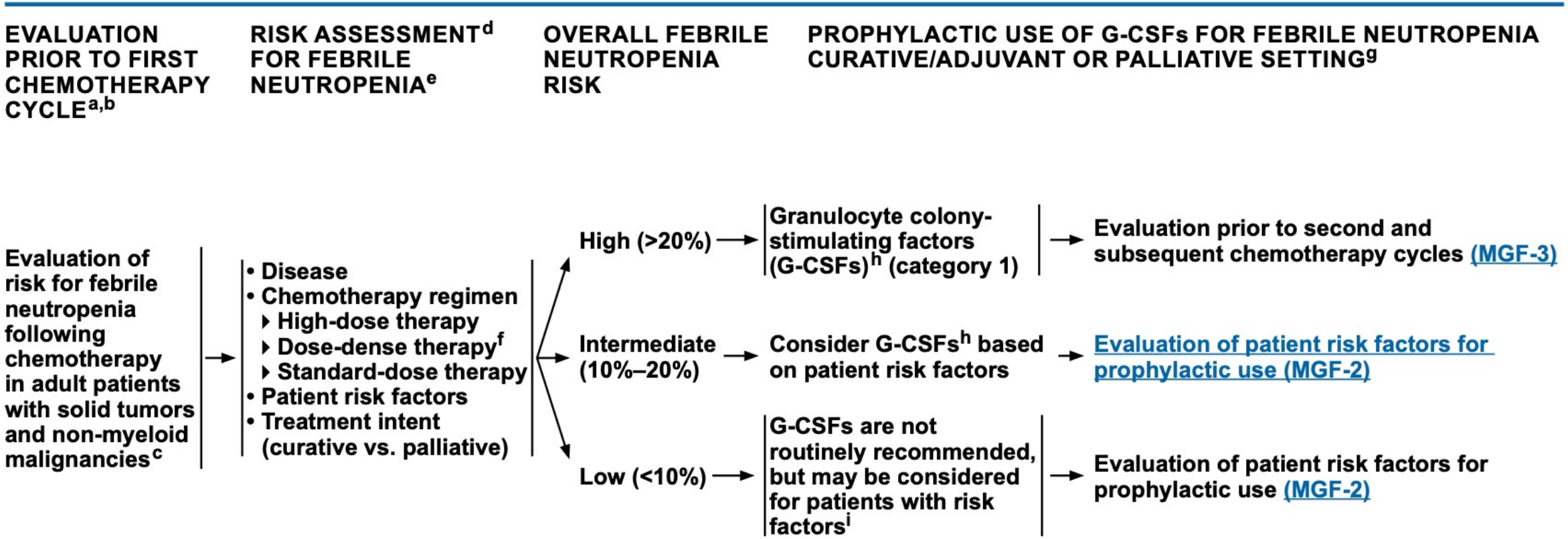
- Meta-analysis in 17 randomized controlled trials of primary prophylaxis:
- Febrile-Neutropenia: [RR] 0.54, 95% CI 0.43-0.67)
- Infection-related mortality: [RR] 0.55, 95% CI 0.33-0.90)
- All-cause mortality during the chemotherapy period: [RR] 0.60, 95% CI 0.43-0.87)
- "This meta-analysis was not able to address the impact of primary prophylaxis on disease-free or cancer-specific survival."
  - Kuderer NM, et al J Clin Oncol. 2007;25(21):3158.

- Guidelines from the ASCO, European Society for Medical Oncology (ESMO), Infectious Diseases Society of America (IDSA), and National Comprehensive Cancer Network (NCCN).
- Recommend primary prophylaxis when the anticipated incidence of neutropenic fever is approximately > 20% with a given regimen.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Hematopoietic Growth Factors

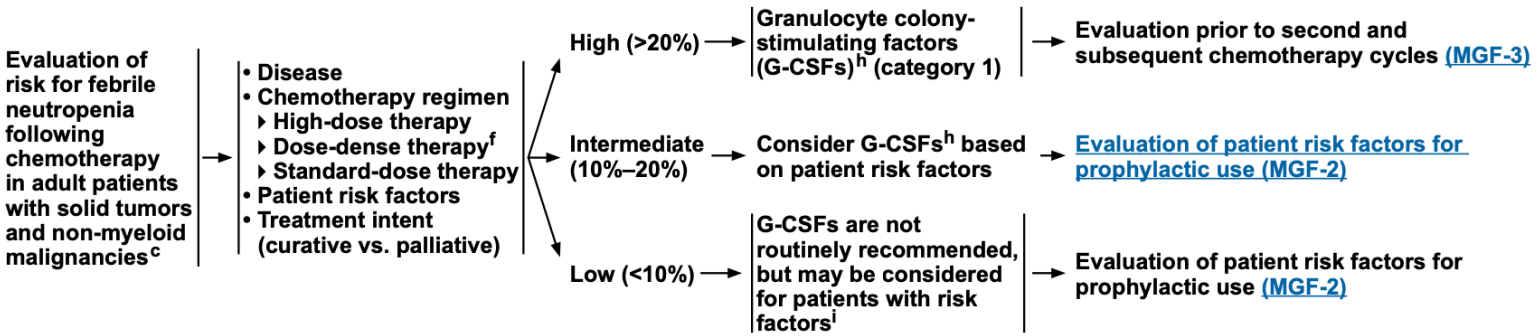
NCCN Guidelines Index
Table of Contents
Discussion



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Hematopoietic Growth Factors

NCCN Guidelines Index
Table of Contents
Discussion



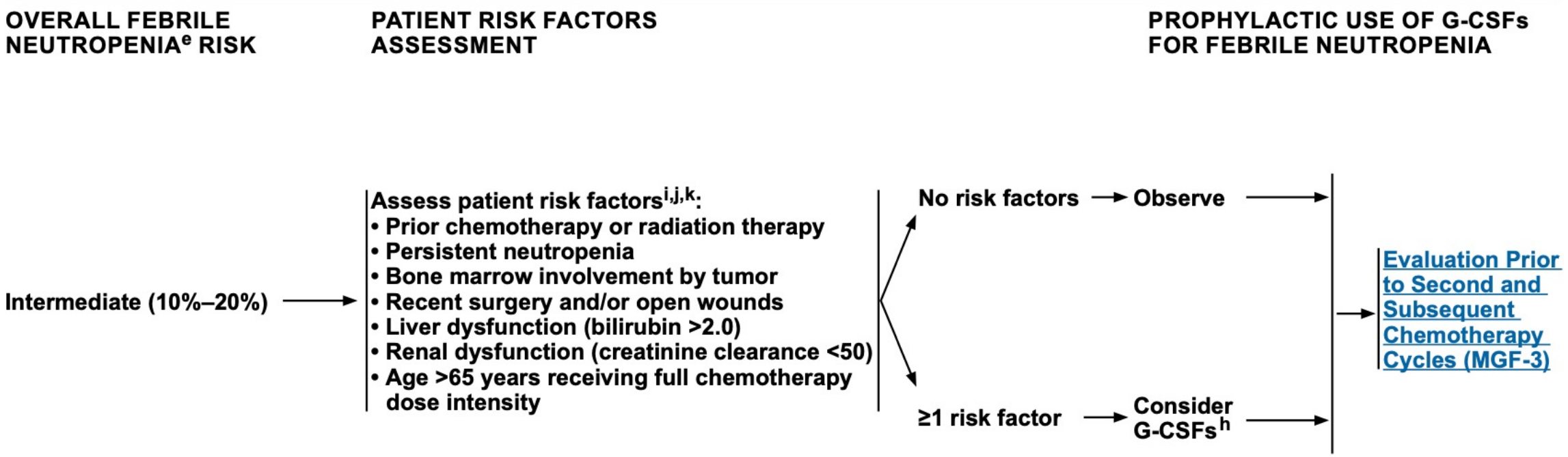
[a] The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.
[b] Patients receiving cytotoxic chemotherapy as part of a clinical trial may be evaluated for prophylaxis with myeloid growth factors (MGFs) as clinically indicated, unless precluded by trial specifications.
[c] For use of growth factors in myelodysplastic syndromes (MDS), see the NCCN Guidelines for Myelodysplastic Syndromes; in acute myeloid leukemia (AML), see the NCCN Guidelines for Acute Myeloid Leukemia; in chronic myeloid leukemia (CML), see the NCCN Guidelines for Chronic Myeloid Leukemia; in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), see the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. For use of growth factors in other cancer types, refer to the appropriate Guidelines.
[d] There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen (MGF-A) and patient risk factors (MGF-2).
[e] Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; and neutropenia: <500 neutrophils/mcL or <1000 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] In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.
[g] Toxicity Risks with MGFs (MGF-C).
[h] G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).
[i] G-CSFs may be considered for patients receiving low-risk regimens who have 2 or more patient-related risk factors (MGF-2). Use of G-CSF in this setting is based on clinical judgment.

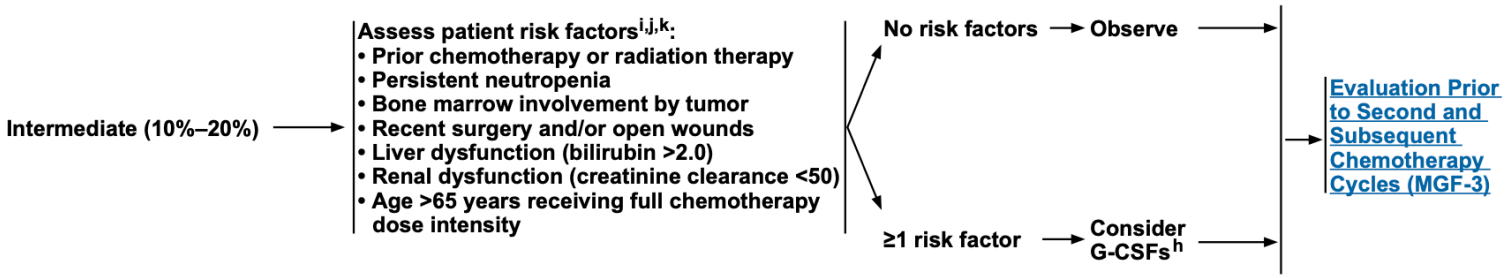
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Hematopoietic Growth Factors

NCCN Guidelines Index
Table of Contents
Discussion





[e] Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; and neutropenia: <500 neutrophils/mcL or <1000 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.

[h] G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[i] G-CSFs may be considered for patients receiving low-risk regimens who have 2 or more patient-related risk factors. Use of G-CSF in this setting is based on clinical judgment.

[j] Other possible patient risk factors for febrile neutropenia may include poor performance status or human immunodeficiency virus (HIV) infection (in particular, patients with low CD4 counts). The listed patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory cancer patients receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoietic cell transplant (Lyman GH, et al. Crit Rev Oncol Hematol 2014;90:190-199).

[k] Other factors may warrant the use of G-CSFs (eg, chronic immunosuppression in the post-transplant setting, including organ transplant).

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.

G-CSF Dosing (NCCN)

Filgrastim

- 5 mcg/kg daily (Rounded to Nearest vial size) until ANC recovery to normal or near normal.
- Vials:
  - 300 mcg/0.5 mL
  - 480 mcg/0.8 mL
  - (~ 80 KG is tipping point between doses).

Pegfilgrastim

- 6 mg SC, once per chemotherapy cycle, the day after chemotherapy.
  - FDA-approved delivery device in order to deliver the full dose of Pegfilgrastim the following day. (Onpro®)
- Do not administer between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

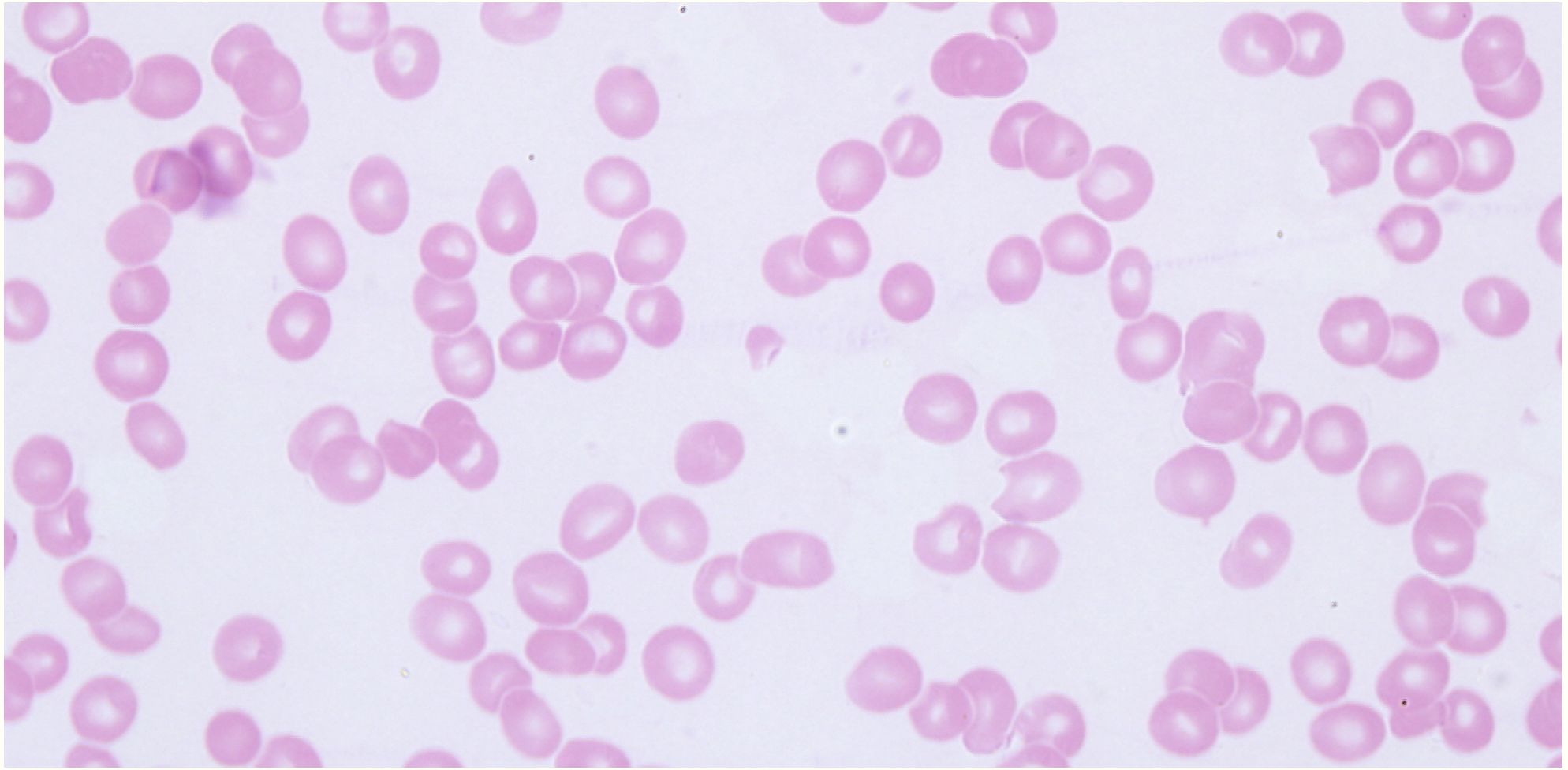
G-CSF And Overall Survival

- "With an average follow- up of 5 years, G-CSF support associated with a 3.4% reduction in absolute risk of mortality and an RR of 0.9 for all-cause mortality.
- Notably, the degree of survival benefit correlated with the chemotherapy dose intensity."
  - NCCN Guidelines Version 3.2024 Hematopoietic Growth Factors
  - (https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf)

G-CSF Adverse Events

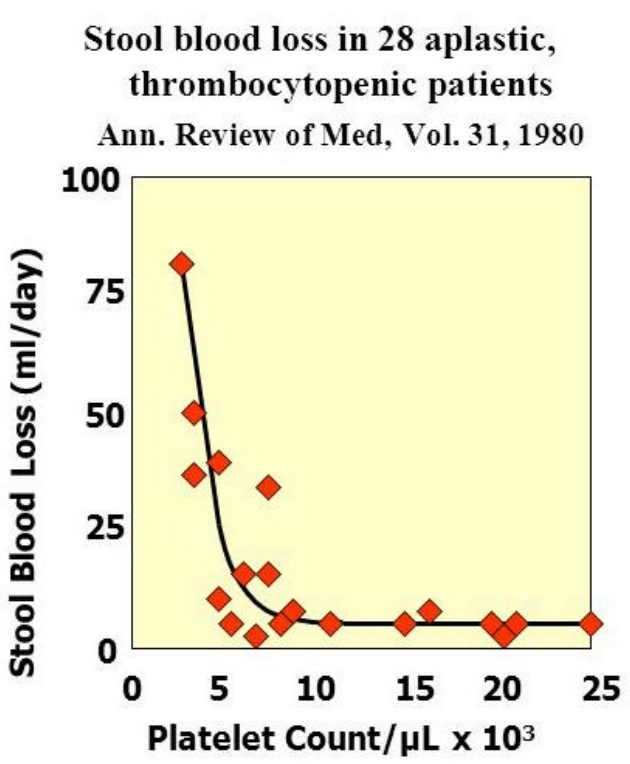
- Bone Pain: Most common
- Allergic Reactions:
  - Rash, urticaria, facial edema, wheezing, respiratory distress, etc.
- Splenic Rupture
- Acute Respiratory Distress Syndrome

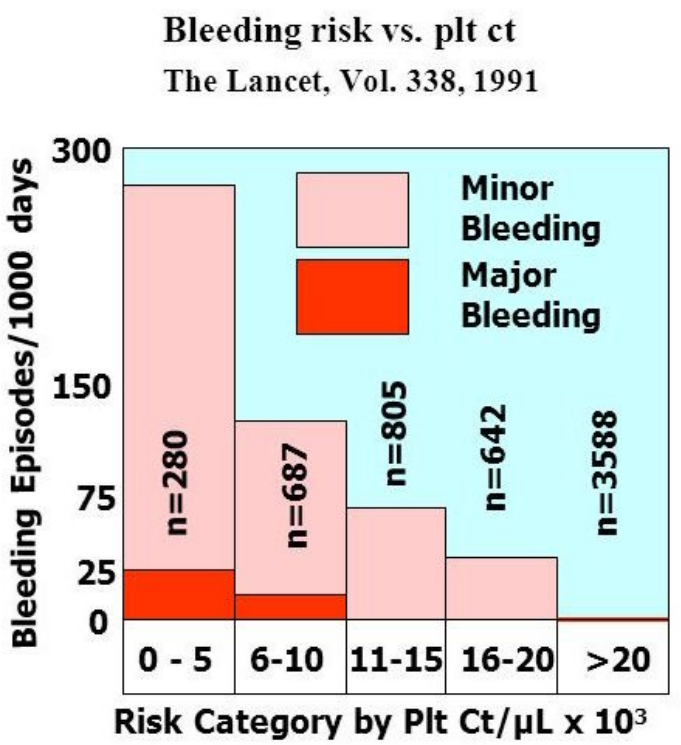
Thrombocytopenia



Risk of Bleeding & Platelet Count

- "Normal": Approximately 140,00-450,000/mcL
- Clinically significant spontaneous bleeding: less than 10-20,000/mcL





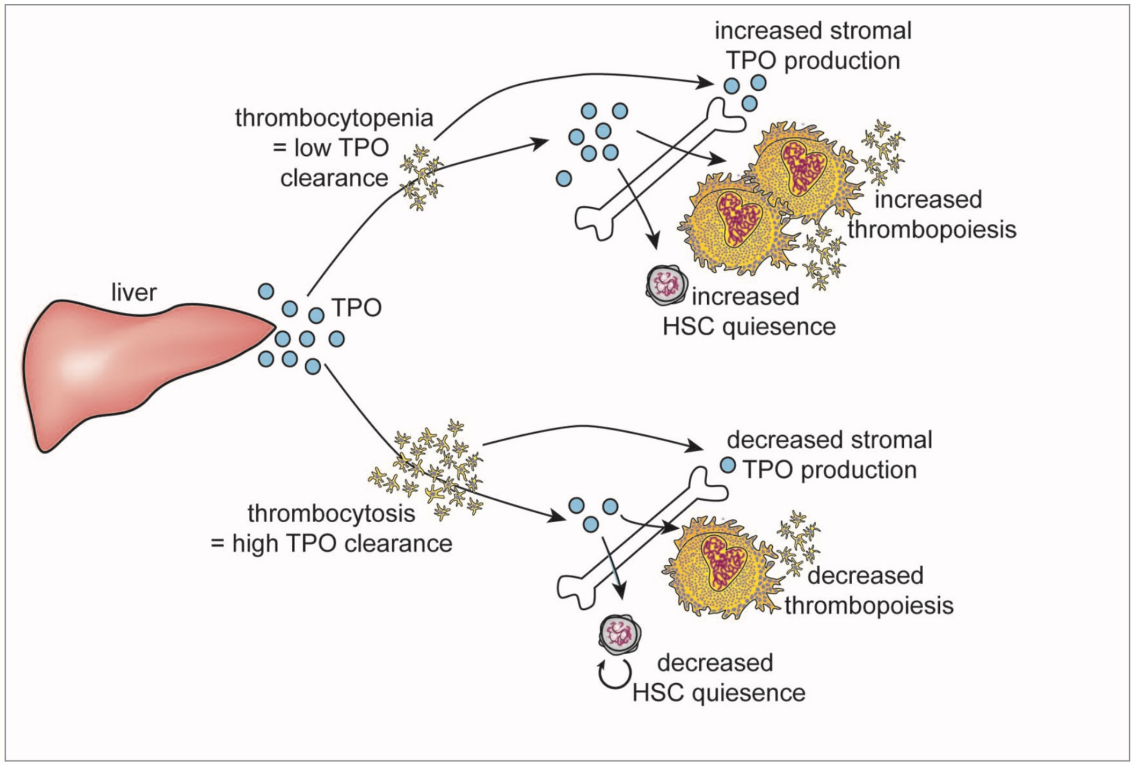
http://images.slideplayer.com/14/4494169/slides/slide_13.jpg

Causes Of Thrombocytopenia In Cancer Patients

Causes of Thrombocytopenia	%
Chemotherapy	78.6
Mixed Causes	9.3
Infection	7.9
Myelophthisis	2.9
Graft Versus Host Disease	0.7
Liver Disease	0.7

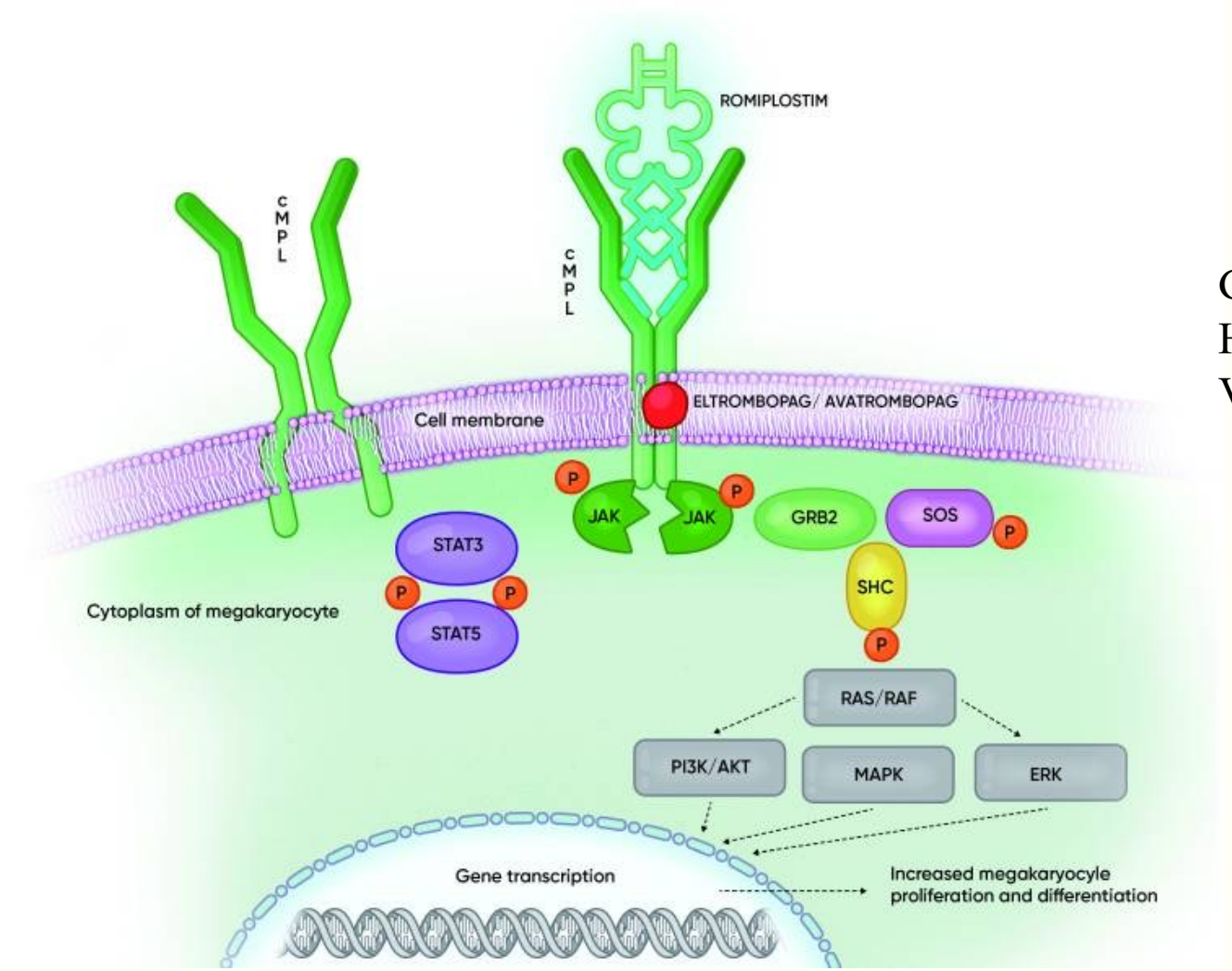
Mantha et al, Journal of Thrombosis and Thrombolysis, 43: 514–518, 2017

TPO Regulation And Activity



- TPO synthesis, primarily in liver.
- Early experience with rTPO resulted in some cases of formation of autoantibody to endogenous TPO and severe thrombocytopenia.

Thrombopoietin Mimetics and their Cellular Mechanisms of Action

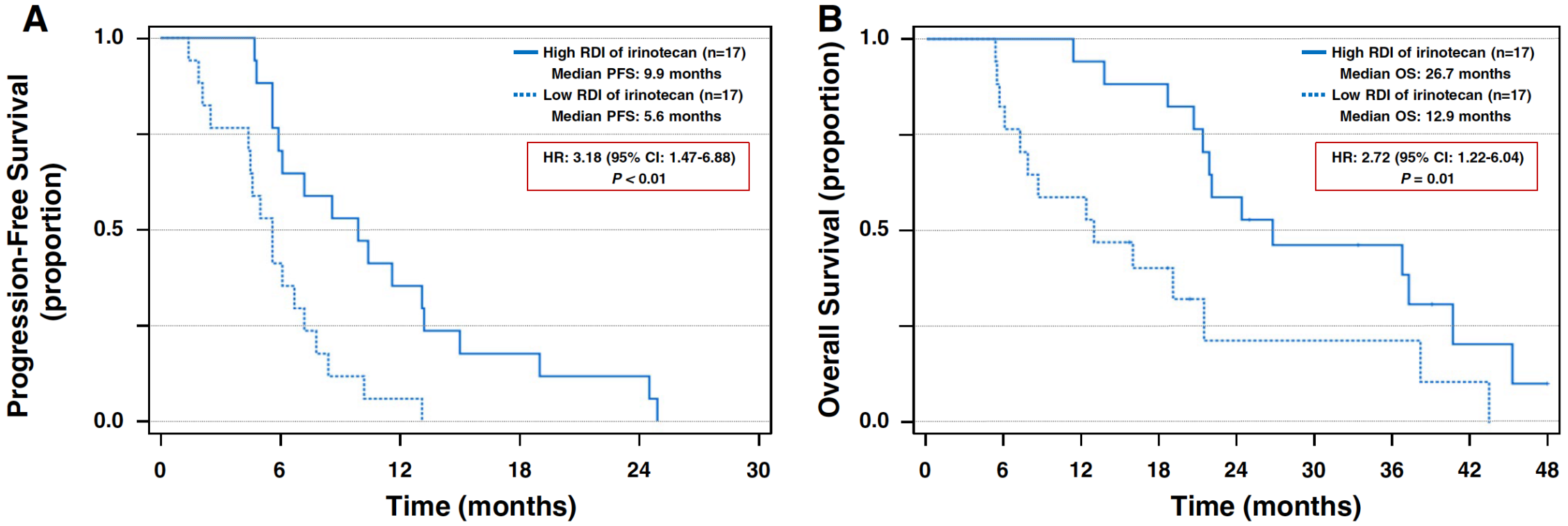


Ghanima et al.
Haematologica 2018
Volume 104(6):1112-1123

Chemotherapy-Induced Thrombocytopenia

- Chemotherapy-induced thrombocytopenia (CIT) is common.
  - Can lead to chemotherapy dose delay and/or dose reduction, possibly impacting cancer outcomes.
  - i.e. 37% in FOLFOX4 study.
- Two main types of CIT:
  - Persistent CIT: Platelet count does not recover to acceptable level (>75-100K) by day 1 of next cycle (or beyond)
  - Nadir CIT: Deep nadirs (<25-50K) are observed midcycle, with acceptable recovery by day 1 of next cycle

The Impact of Relative Dose Intensity On Outcomes In Metastatic Colorectal Cancer



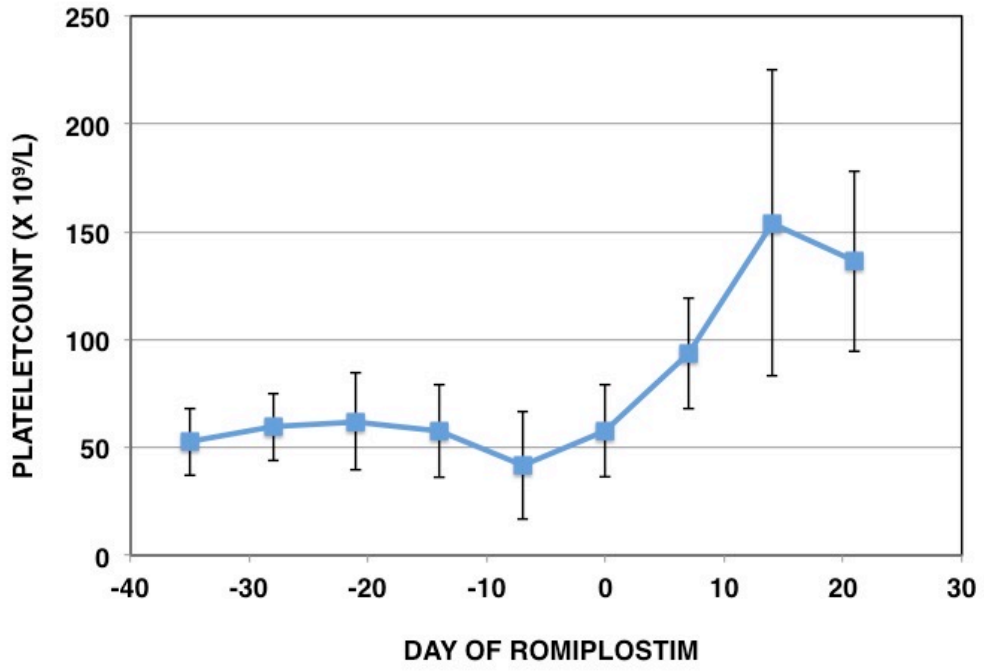
- Relative Dose Intensity (RDI), High >80%, Low, <80%
- Nakayama et al. Cancer Chemotherapy and Pharmacology. 73:847-855, 2014.

What Is Goal Of Treatment of Chemotherapy-Induced Thrombocytopenia?

- Bleeding, even without intervention, is rare.
- Oncologists/Patients care for ability to maintain “Full Dose” chemotherapy.
- Target is platelet count at beginning of cycle.
- Avoid dose reduction/dose in chemotherapy.
- No established, FDA approved intervention!

Persistent Chemotherapy Induced Thrombocytopenia

- Case series of 20 solid tumor patients with CIT, successfully treated with romiplostim (thrombopoietin receptor agonist).
  - Used "ITP" regimen of weekly, titrated doses.
  - Mean Dose: 2.9 mcg/kg (range 1.0–5.1).

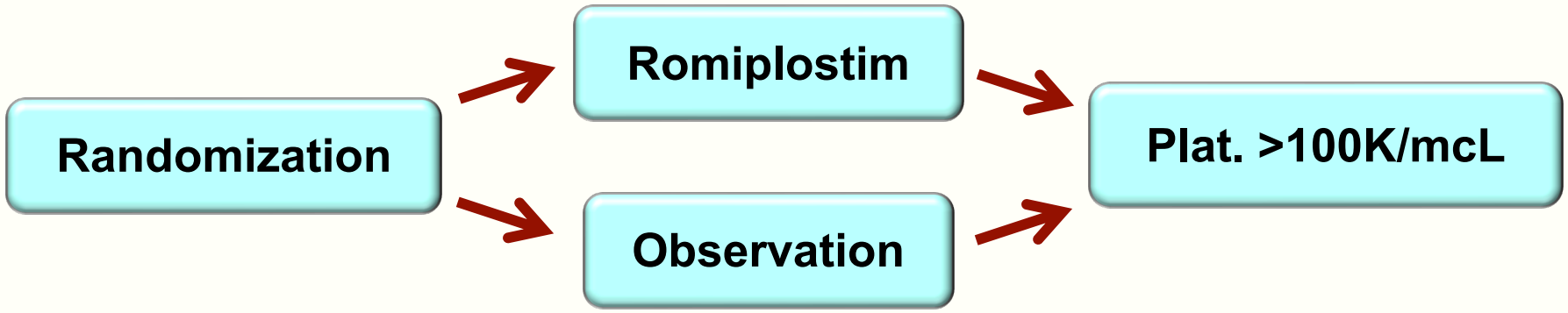


Parameswaran et al, Supportive Care in Cancer (2014).

Phase II Trial: Design

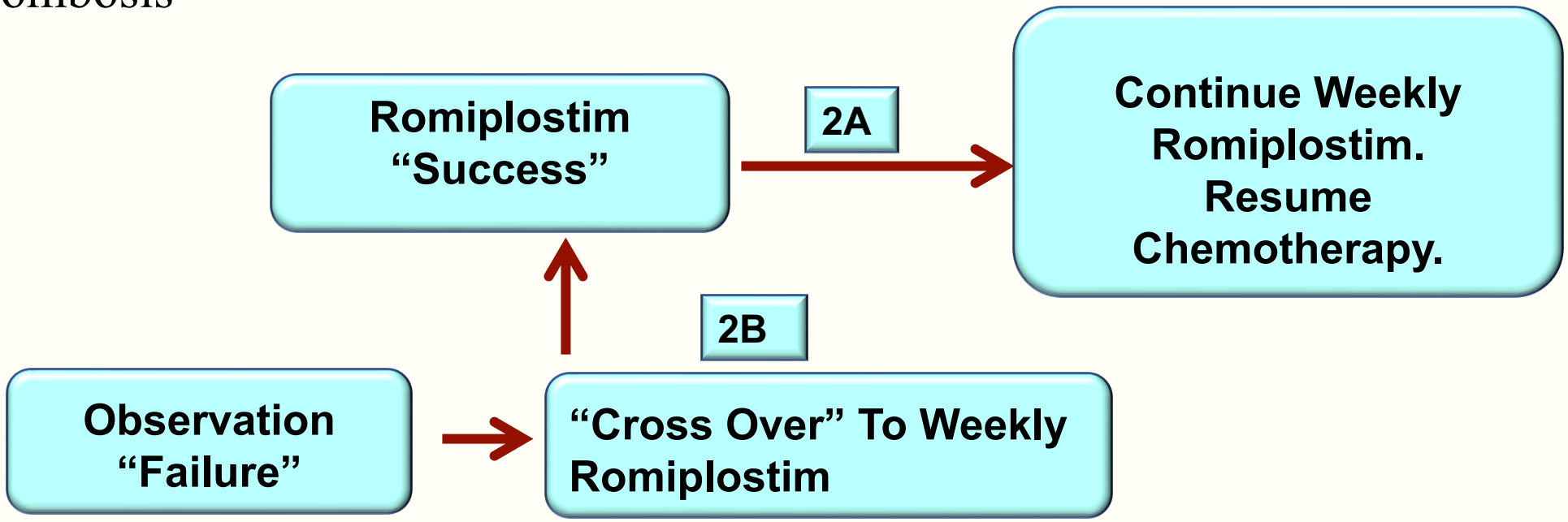
- Single Center: MSKCC
- Solid tumor patients. (Stage III or IV).
- No chemotherapy for past 14+ days.
- Persistent CIT: >4 weeks of platelets <100,000/mcL, despite reduction or delay in chemotherapy.
- ANC > 1.0, Hgb >8.0 g/dL.
- Randomized, 2:1 to weekly romiplostim versus observation.
- Primary Endpoint (3 weeks): Platelet recovery (>100,000/mcL).

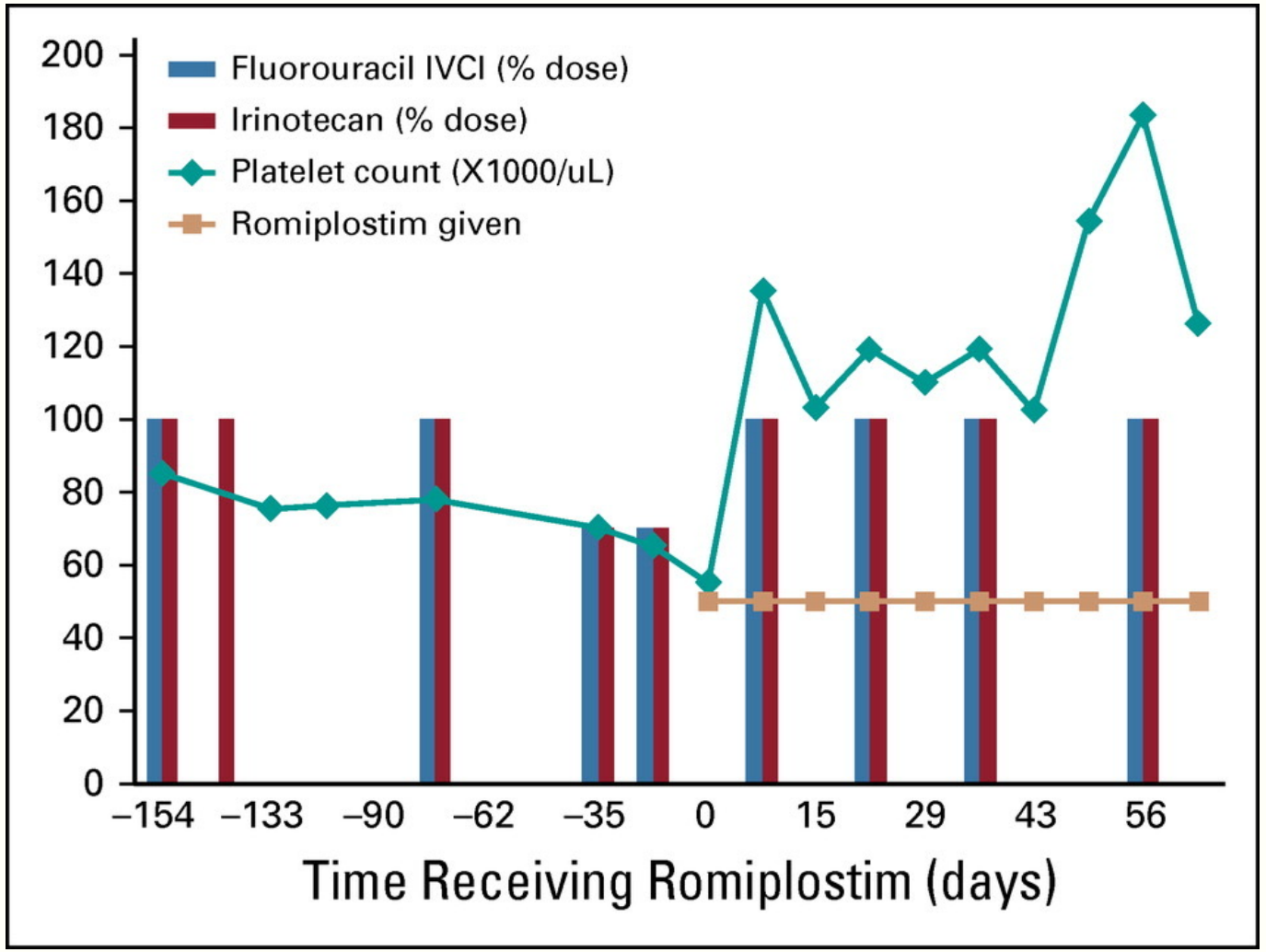
Primary Endpoint (3 weeks)



Phase II Trial: Secondary Endpoints

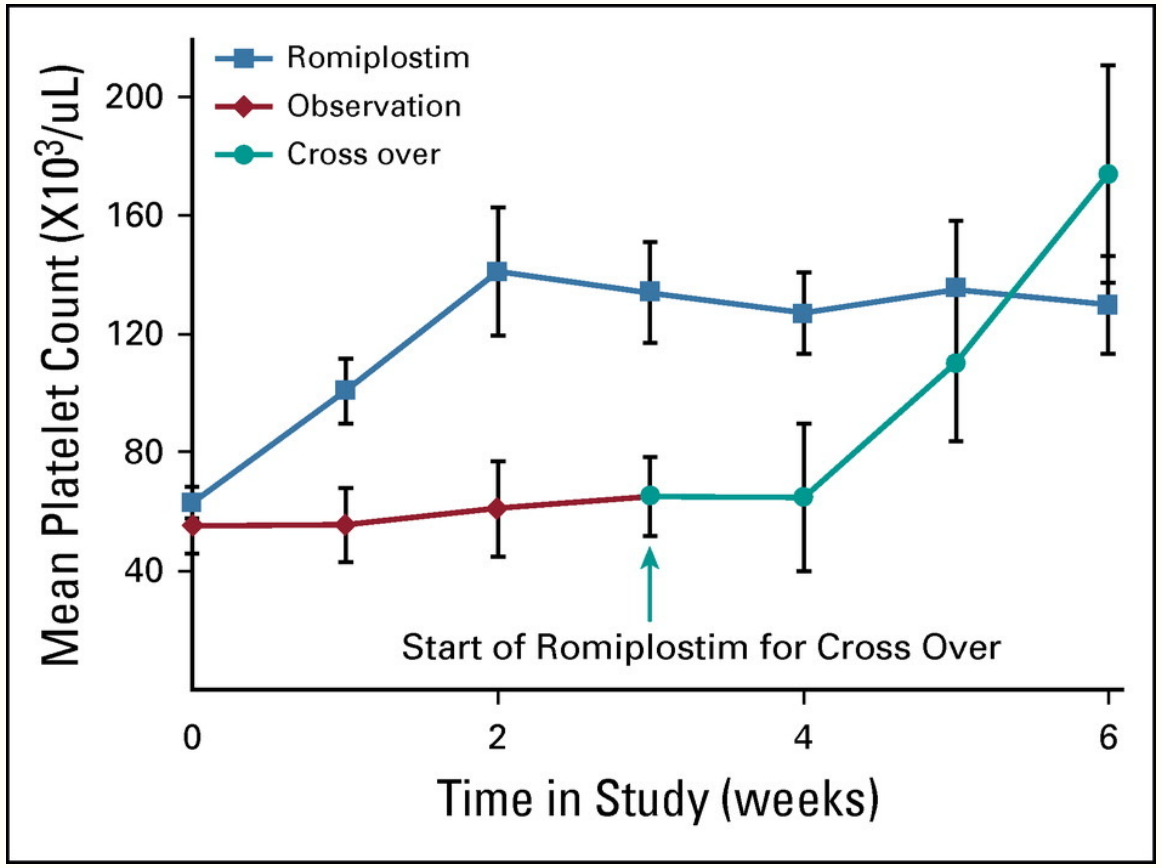
- 2A: Romiplostim-Treated Patients:
  - Upon correction of platelets, resume chemotherapy at discretion of oncologist.
  - Continue weekly romiplostim indefinitely, while on chemotherapy.
- 2B: Observation patients:
  - If failed to correct their platelet counts at 3 weeks, eligible to cross-over to receive romiplostim.
- Safety: Thrombosis





- Soff et al, *J Clin Oncol 37:2892-2898. 2019 (*DOI: 10.1200/JCO.18.01931).

Romiplostim For CIT: Results



- Correct the platelet count:
  - 2.6 mcg/kg (95% CI, 2.4 to 2.8 mcg/kg)
- Maintain platelet count during the resumption of chemotherapy:
  - 3.3 mcg/kg (95% CI, 2.7 to 3.8 mcg/kg)
- No patient became refractory or resistant to romiplostim.

- Soff et al, *J Clin Oncol 37:2892-2898. 2019 (*DOI: 10.1200/JCO.18.01931).

Final Primary Endpoint All Patients (N=60) (ITT)

	>100,000/mcL, within 3 wk	Fail To Correct within 3 wk	Total
Romiplostim	**44 (85%)**	**8***	**52**
Observation	**1 (12.5%)**	**7**	**8**

(P<0.001)

- *Of the 8 failures:
- 2 patients were protocol violations because chemotherapy was prematurely resumed prior to platelet correction.
- 1 did not complete 3 weeks.
- 93% response "on specified protocol treatment."

- Soff et al, *J Clin Oncol 37:2892-2898. 2019 (*DOI: 10.1200/JCO.18.01931).

Safety: Venous Thromboembolic Events

- VTE during the first 12 months of romiplostim treatment: 6/59 (10.2%)
  - Pulmonary Embolism: 2
  - Proximal DVT: 2
  - Calf DVT: 2
  - Romiplostim was not discontinued on the development of a VTE.
- Arterial Events
  - 1 Patient with small cell lung cancer experienced MI (3 months) and CNS-metastasis associated CVA (>12 months).

Romiplostim for chemotherapy-induced thrombocytopenia: Efficacy and safety of extended use

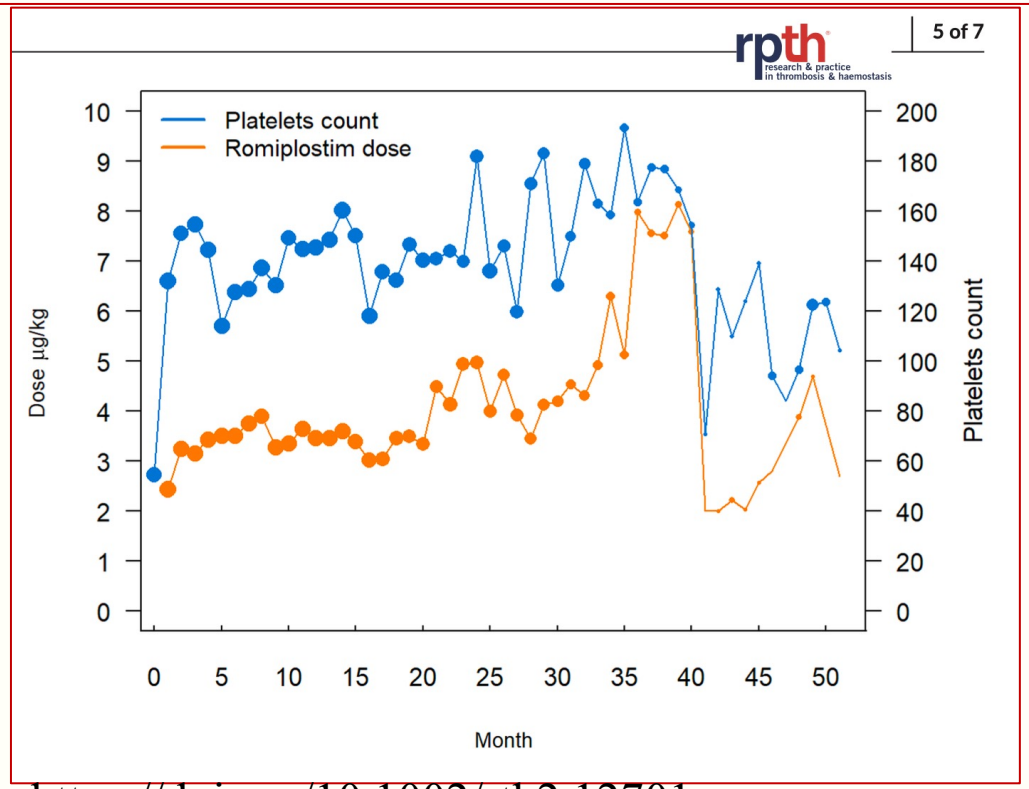
Efficacy and safety of romiplostim in the patients in the phase 2 study, who received romiplostim for ≥1 year.

- No episode of recurrent CIT: 70% (N=14/20).
- Single chemotherapy dose delay due to CIT: 20% (N=4)
- Chemotherapy dose reduction: 10% (N=2)

- DVT: 1
- Tumor-related ischemic events: 1

- **Conclusions:** Long-term use of romiplostim for treatment of CIT was effective and safe, with no evidence of resistance or increased risk of thrombosis.

Mean monthly romiplostim dose and mean monthly platelet counts while in the study.



Wilkins CR, et al. Res Pract Thromb Haemost. 2022;6:e12701. https://doi.org/10.1002/rth2.12701

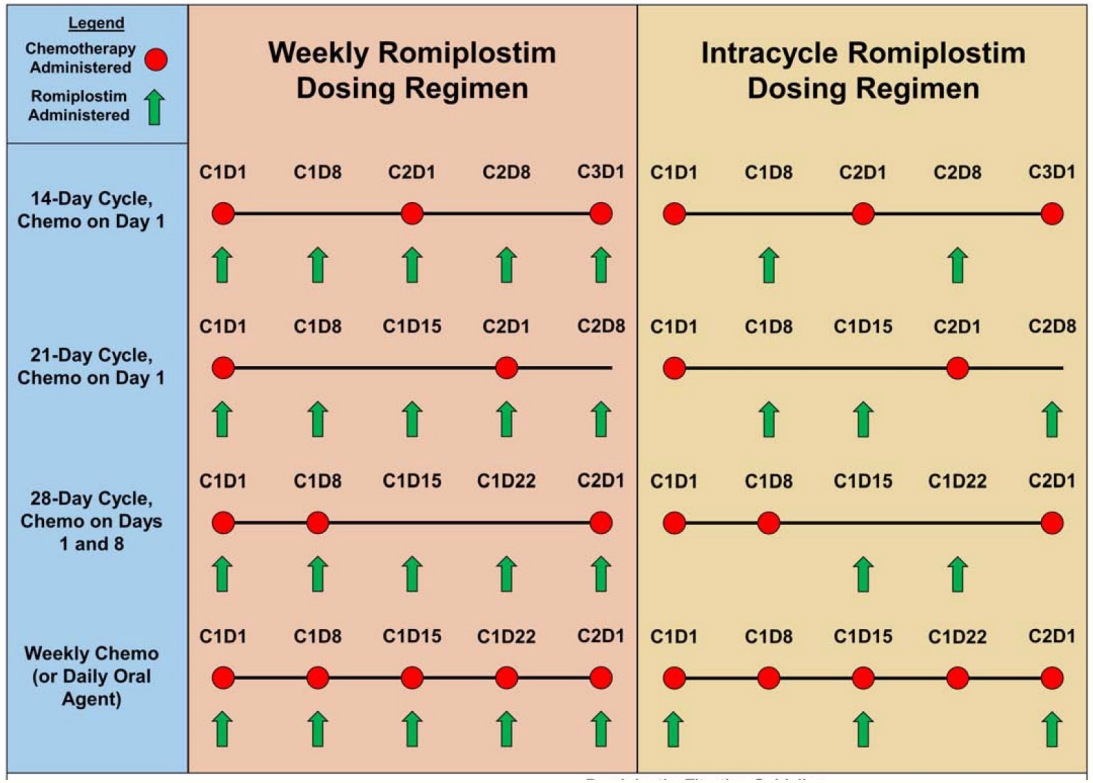
A Multicenter Study of Romiplostim for CIT in Solid Tumors and Hematologic Malignancies

- Retrospectively evaluated patients with CIT treated on institutional romiplostim treatment pathways at 4 US centers
- **Primary outcome** was achievement of a romiplostim response (median on-romiplostim platelet count $\geq 75 \times 10^9$/L and $\geq 30 \times 10^9$/L above baseline)
- **Secondary outcomes** included time to platelet count $\geq 100 \times 10^9$/L and rates of:
  - Platelet count $< 100 \times 10^9$/L
  - Platelet count $< 75 \times 10^9$/L
  - Platelet count $< 50 \times 10^9$/L
  - Thrombocytosis
  - Chemotherapy dose reduction/treatment delay
  - Platelet transfusion
  - Bleeding
  - Thromboembolism

Al-Samkari H, et al. Haematologica 2021 Volume 106(4):1148-1157

Eligibility/Study Design

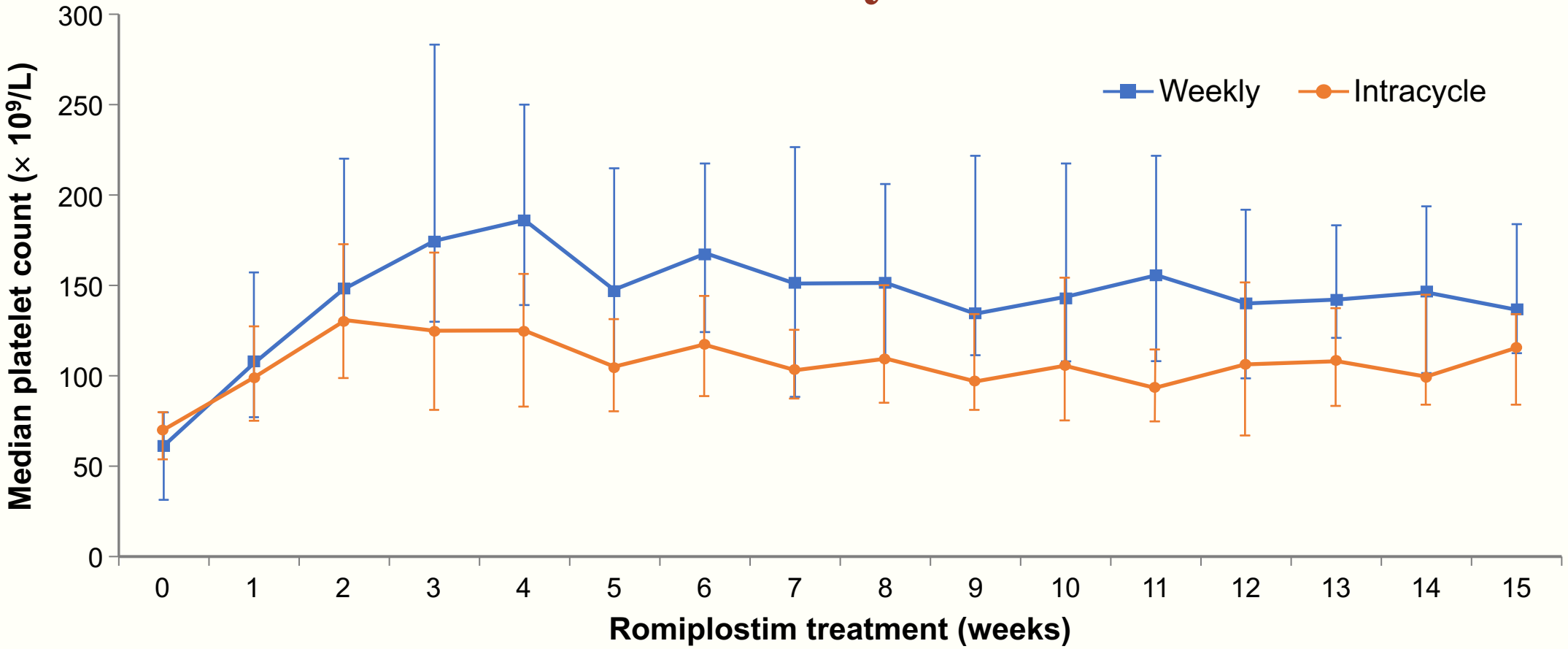
- Eligibility: persistent thrombocytopenia (platelet count < 100×10^9/L) at least 3 weeks from the date of the last chemotherapy administration or after a delay in chemotherapy regimen initiation for ≥ 1 week due to thrombocytopenia



- Weekly romiplostim
  - 2 institutions used a weekly romiplostim CIT pathway
  - Romiplostim was administered irrespective of timing of chemotherapy
- Intracycle romiplostim
  - Romiplostim was administered primarily on chemotherapy off-weeks, twice per month on average

Al-Samkari H, et al. Haematologica 2021 Volume 106(4):1148-1157

Weekly romiplostim is more effective than "intracycle"



Al-Samkari H, et al. Haematologica 2021 Volume 106(4):1148-1157

A multicenter study of romiplostim for CIT in solid tumors and hematologic malignancies (cont.)

- 71% of patients achieved a romiplostim response
- 79% of patients avoided chemotherapy dose reductions/treatment delays
- 89% of patients avoided platelet transfusions
- Median per-patient platelet count on romiplostim was significantly higher than baseline (116,000/μL vs 60,000/μL; $p < 0.001$)
- Bone marrow tumor invasion, prior pelvic irradiation, and prior temozolomide were predictive of no response to romiplostim
- Bleeding rates were lower than historical CIT cohorts and thrombosis rates were not elevated
- Weekly dosing was superior to intracycle dosing, with higher response rates and fewer chemotherapy dose reductions/treatment delays

Al-Samkari H, et al. Haematologica 2021 Volume 106(4):1148-1157

Futility

- 3 variables were predictive of a significantly lower likelihood of romiplostim response
  1. Bone marrow tumor invasion: odds ratio 0.029, $p < 0.001$
  2. Prior pelvic irradiation: odds ratio 0.078, $p = 0.048$
  3. Prior temozolomide: odds ratio 0.24, $p = 0.043$

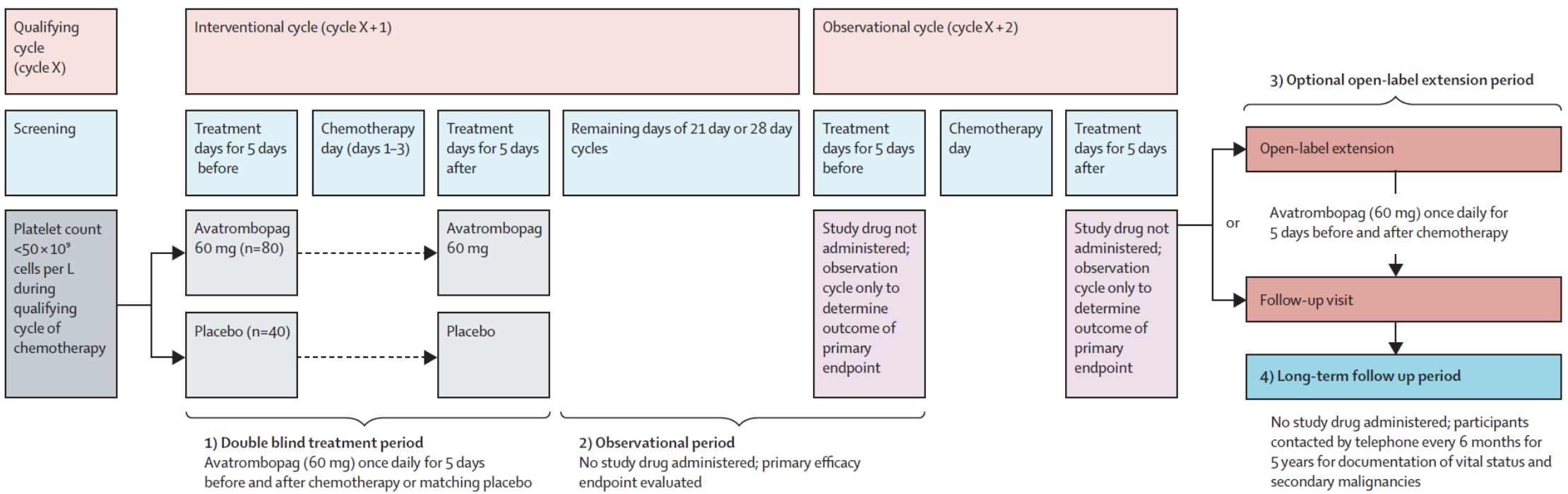
Al-Samkari H, et al. Haematologica 2021 Volume 106(4):1148-1157

Avatrombopag for Nadir CIT: International, Randomized, Double-Blind Phase 3 Trial

- 122 patients randomized 2:1 to avatrombopag or placebo
- Patients had to have Plt <50 x2 measurements any time during chemo cycle to qualify
- Patients with prior CIT or >2 prior chemo regimens were *excluded* (per regulatory agency request)
- Composite primary endpoint: Proportion of responders not requiring Plt transfusion or either a 15% or more chemotherapy dose reduction or 4-day or more chemotherapy delay due to CIT following study drug admin until the start of next cycle

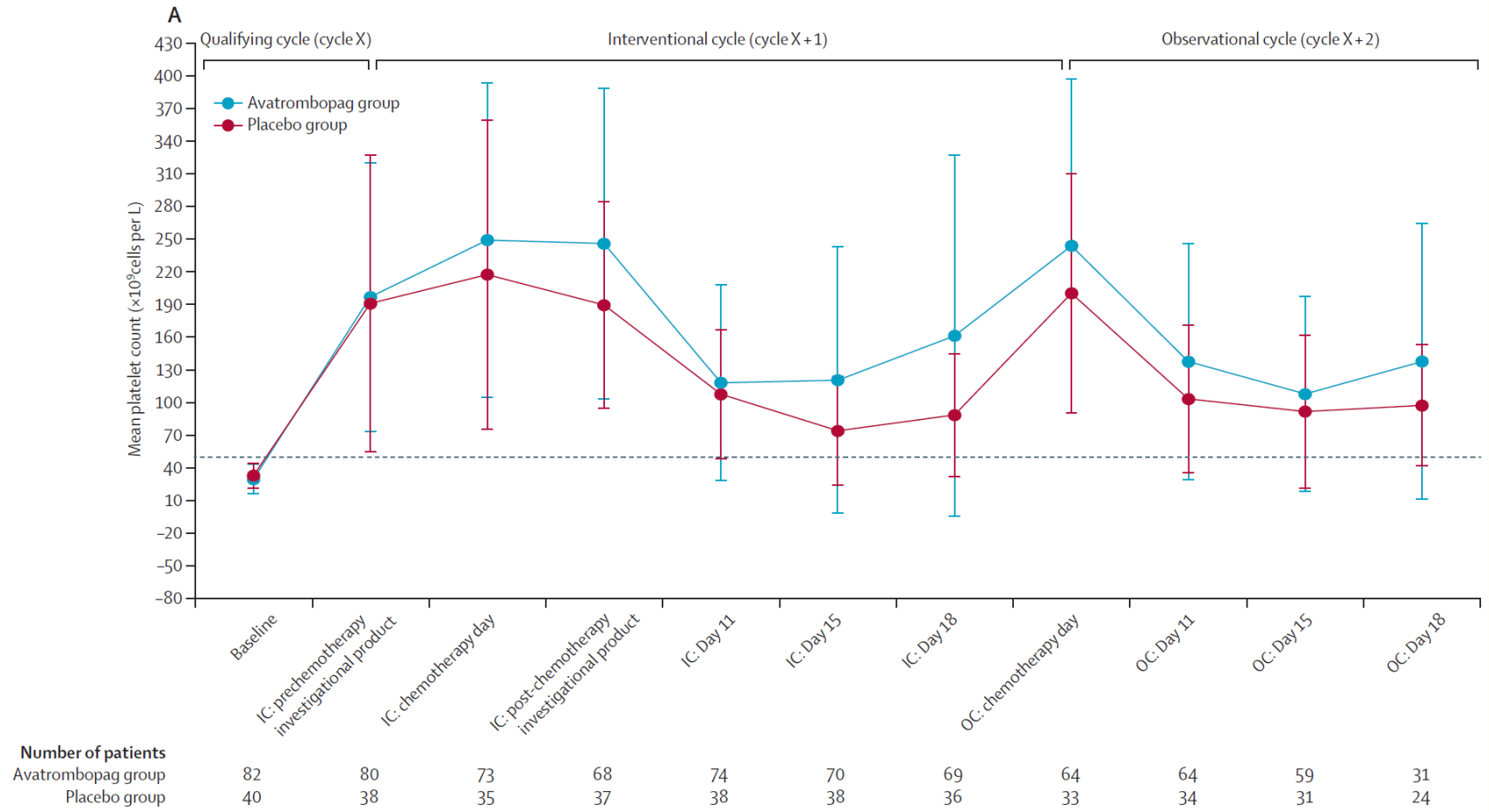
Al-Samkari H, Lancet Haematol. 2022;9(3):e179-e89.

Avatrombopag for Nadir CIT: International, Randomized, Double-Blind Phase 3 Trial



Al-Samkari H, Lancet Haematol. 2022;9(3):e179-e89.

Avatrombopag Effective in Raising Platelet Count



Number of patients											
Avatrombopag group	82	80	73	68	74	70	69	64	64	59	31
Placebo group	40	38	35	37	38	38	36	33	34	31	24

Al-Samkari H, Lancet Haematol. 2022;9(3):e179-e89.

Avatrombopag Safety in Cancer Patients

- 2 VTEs in avatrombopag arm (2%) versus 1 patient in placebo arm (3%)
- Bleeding events all minor
- Very few adverse events considered related to study drug treatment.

Al-Samkari H, Lancet Haematol. 2022;9(3):e179-e89.

BUT, Study was NEGATIVE

- Due to high rates of *spontaneous recovery* of platelet count in placebo arm
- 70% of avatrombopag patients and 73% of placebo patients achieved primary endpoint of avoiding Plt txf, chemo dose reduction or delay

- Take-home: Nadir CIT does not require treatment in most patients, especially in those relatively chemotherapy-naïve

Al-Samkari H, Lancet Haematol. 2022;9(3):e179-e89.

Conclusions: Based on Existing Studies

- TPO-RAs are effective in treating persistent CIT in solid tumor patients (probably not needed for most nadir CIT)
- TPO-RA maintenance in persistent CIT allows for resumption of chemotherapy with a reduced rate of CIT
- No evidence of increased thrombotic risk
- Poor efficacy
  - Bone marrow tumor invasion
  - Prior pelvic irradiation
  - Prior temozolomide

CIT: Current Knowledge/Knowledge Gaps

- CIT is common
- CIT can impact the RDI of chemotherapy
- Most situations of reduced RDI are not due to isolated CIT
- It is not known under which circumstances reduced RDI may impact cancer control (i.e. metastatic pancreatic cancer vs testicular cancer)
- There is no standard, approved intervention
- Treatment and prevention of recurrent CIT are important unmet needs
- TPO-RAs are effective in increasing platelet counts and preventing recurrence of CIT
- Continuous therapy appears to be superior to intracycle therapy for persistent CIT
- Primary or metastatic cancer of the liver is associated with a higher rate of CIT
- Bone marrow tumor invasion, prior pelvic irradiation, and prior temozolomide are predictive of no response to romiplostim.

Use of Thrombopoietin Receptor Agonists (TPO-RA) in Patients With Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Hematopoietic Growth Factors

NCCN Guidelines Index
Table of Contents
Discussion

USE OF THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RA) IN PATIENTS WITH CANCER

PRESENTATION | **ASSESSMENT** | **MANAGEMENT**

Suspected chemotherapy-induced thrombocytopenia (CIT)[a] ★ →

Evaluate for other potential causes of thrombocytopenia as indicated
- **First check**
  - Complete blood count (CBC) with differential, including evaluation for other cytopenias
  - Blood smear morphology, including evaluation for platelet clumping
- **Then consider other potential etiologies, including:**
  - Nutritional deficiencies
  - Medications and supplements suppressing platelet production
  - Infection (including viral reactivation)
  - Disseminated intravascular coagulation (DIC)
  - Immune thrombocytopenia
  - Heparin-induced thrombocytopenia (HIT)
  - Radiation-induced myelosuppression
  - Bone marrow involvement by underlying malignancy
  - Hematologic malignancy (including therapy-related myeloid neoplasia)
  - Hemolytic anemia
  - Consumption of platelets secondary to blood loss
  - Antiphospholipid syndrome (APLS)
  - Hypersplenism
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Thrombotic microangiopathies (TMAs) such as thrombotic microangiopathic anemia, thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS)

→ **Treat underlying cause(s) as indicated**

→ **CIT** → **Consider**
- **Platelet transfusion per Association for the Advancement of Blood & Biotherapies (AABB) guidelines**
- **Chemotherapy dose reduction or change in treatment regimen**
- **Clinical trial of TPO-RA[b]**
- **Romiplostim[b,c,d,e,f]** ★

Thrombocytopenia post-hematopoietic cell transplant[a,g] →

- **Evaluate for other potential causes of thrombocytopenia as indicated, including examples above, as well as primary or secondary graft failure, graft-versus-host disease (GVHD), relapse of hematologic malignancy, and transplant-associated TMA (TA-TMA).**

→ **Treat underlying cause(s) as indicated**

→ **Primary or secondary failure of platelet recovery without other clear underlying causes** → **Consider**
- **Platelet transfusion per AABB guidelines**
- **Clinical trial of TPO-RA[b]**
- **Eltrombopag[h]**

Known MDS → NCCN Guidelines for Myelodysplastic Syndromes

Known myeloid malignancy or ALL → **Treat underlying disease per** NCCN Guidelines

★ **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.

Footnotes and References on TGF-2

TGF-1

Chemotherapy Induced Thrombocytopenia For Hematologic Malignancies

- Currently no evidence of efficacy in:
  - Myeloid Leukemia
  - Lymphoid Leukemia
  - Lymphoma
  - Stem Cell Transplant
  - High-risk MDS
- Adverse safety signal in AML and high-risk MDS.
  - "The TPO receptor (also referred to as c-MPL or CD-110) is expressed on approximately 60% of AML blast cells as well as some patients with high-risk myelodysplastic syndrome."
  - Increased Progression of Disease in studies of eltrombopag in AML and high-risk MDS. (Soff et al, J Thromb Haemost. 2024;22:53–60).

Received: 14 June 2023 | Revised: 8 September 2023 | Accepted: 25 September 2023

https://doi.org/10.1016/j.jtha.2023.09.031

jth

ISTH GUIDANCE AND GUIDELINES

Management of chemotherapy-induced thrombocytopenia: guidance from the ISTH Subcommittee on Hemostasis and Malignancy

Gerald Soff[1] | Avi Leader[2] | Hanny Al-Samkari[3] | Anna Falanga[4] | Anthony Maraveyas[5] | Kristen Sanfilippo[6] | Tzu-Fei Wang[7] | Jeffrey Zwicker[2]

Management of chemotherapy-induced thrombocytopenia: guidance from the ISTH Subcommittee on Hemostasis and Malignancy Soff et al, J Thromb Haemost. 2024;22:53–60.

Guidance statements for thrombocytopenia receptor agonists for CIT in solid tumors

1. If considering use of a TPO-RA, we suggest enrollment in a clinical trial as preference.
2. If unable to enroll in a clinical trial, we suggest consideration of a TPO-RA in the setting of inadequate platelet recovery at day 1 of a chemotherapy cycle to avoid chemotherapy dose reduction or a delay of ≥7 d (assuming adequate neutrophil and hemoglobin recovery).
   a. Potential use of a TPO-RA should be in patients with solid tumors where full-dose chemotherapy is expected to achieve or maintain a clinically relevant response (note that the use of TPO-RA has not been studied in an adjuvant setting).
   b. Goals of therapy for use of a TPO-RA should be to achieve an adequate platelet count to avoid reduced chemotherapy dose intensity in future cycles.
   c. Once initiated, a TPO-RA should be continued for the duration of chemotherapy, with titration to the lowest dose to maintain a target platelet count between 100 and 200 $\times$ 10^9/L (or titrate to the platelet count to allow full relative dose intensity chemotherapy) at the beginning of each chemotherapy cycle.
3. When considering off-label use of TPO-RA (not in the setting of a clinical trial), we recommend use of romiplostim over other TPO-RAs.
4. We recommend against the initiation of TPO-RA during chemotherapy nadir of index episode as there are no data to indicate shortening of the depth or duration of an acute nadir, and there are no data on safety in this setting.

Conclusions

- G-CSF is highly effective in preventing Febrile-Neutropenia.
- EPO is effective in increasing Hgb, but evidence from a number of studies indicating at cost of cancer progression and poorer overall survival.
- TPO Receptor Agonist, romiplostim, is effective in increasing platelet count and preventing recurrent Chemotherapy-Induced Thrombocytopenia.
  - Not yet FDA approved, but NCCN endorsed (level 2A).
- Clinical trials of TPO-RAs in CIT are ongoing now.


"That's all Folks!"