혈소판과 적혈구의 수혈대체요법

조선대학교 병원
혈액종양내과 박치영

Anemia Toxicity Scales(Hb level)

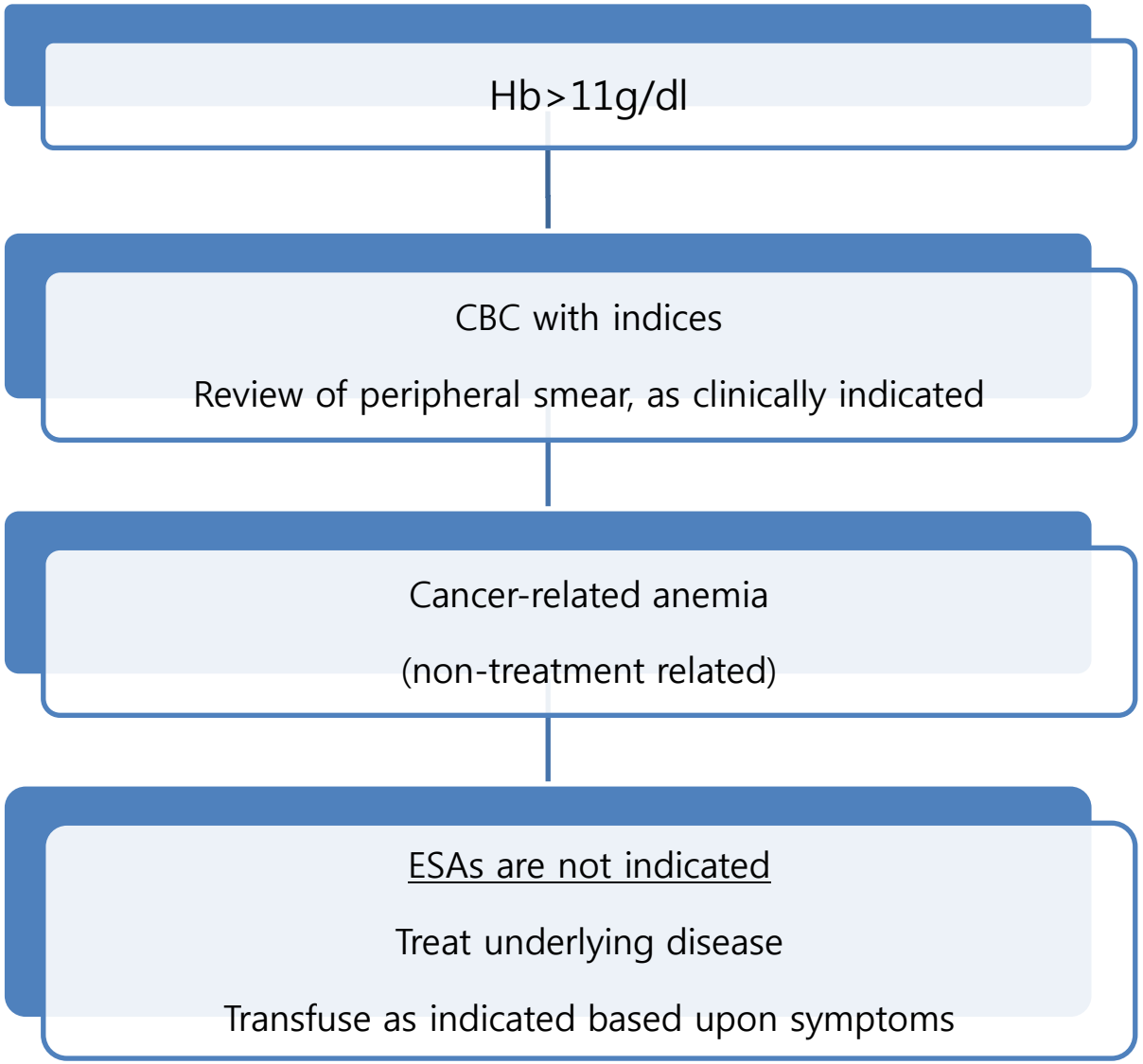
Severity	NCI/WHO scale
none	Normal
Mild	10 ~ normal
Moderate	8 ~ < 10
Severe	6.5 ~ < 8
Life-threatening	< 6.5

Comparison of risks and benefits of **ESA** use vs **RBC** transfusion

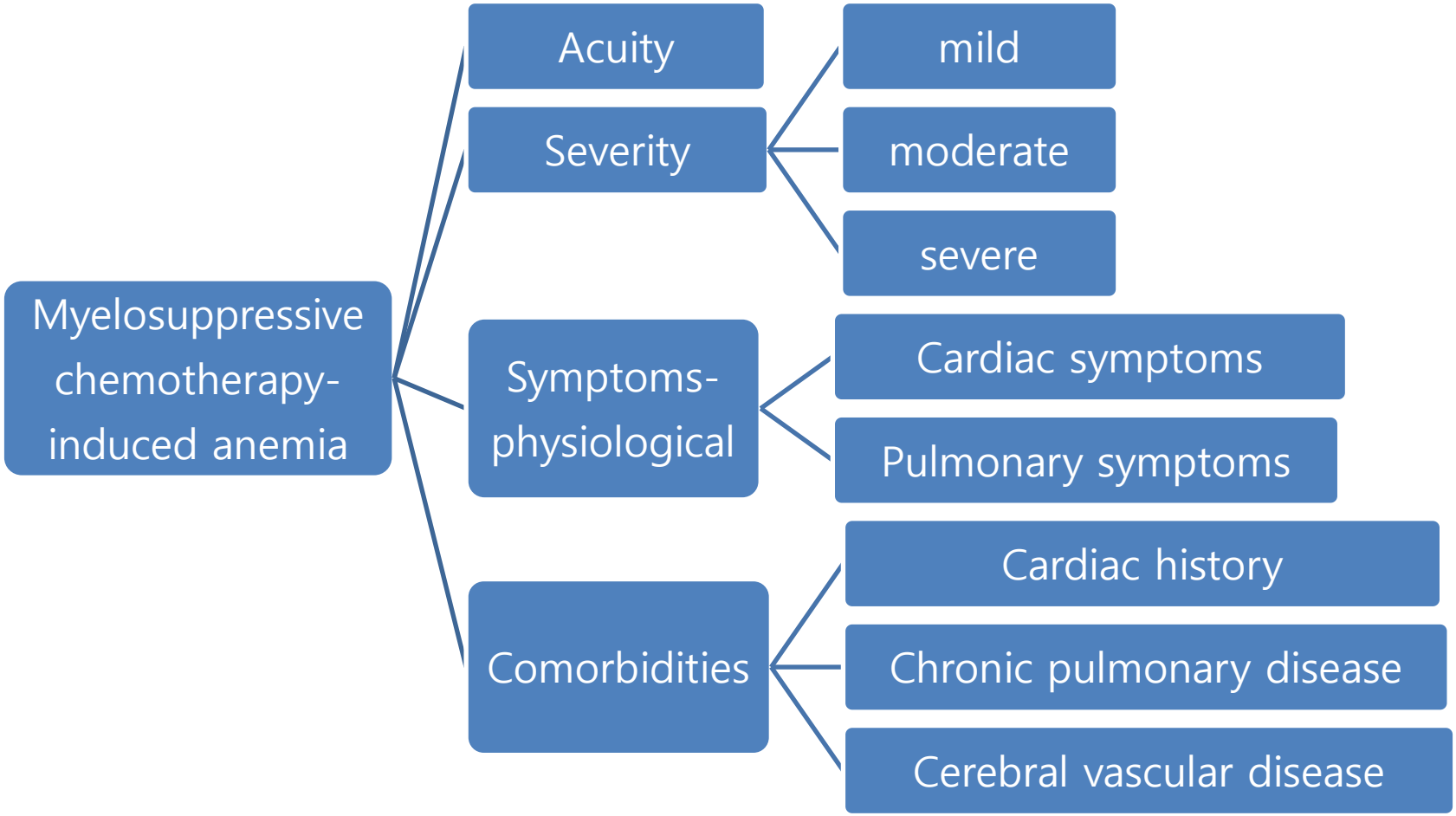
Risks & Benefits of the use of ESA in the cancer setting		**Risks & Benefits of the use of red blood cell transfusion**	
Risks	•Increased thrombotic events •Decreased survival •Time to tumor progression shortened	Risks	•Transfusion reactions •Congestive heart failure •Virus transmission •Bactrerial contamination •Iron overload
Benefits	•Transfusion avoidance •Gradual improvement in fatigue	Benefits	Rapid increase of Hb Rapid improvement in fatigue

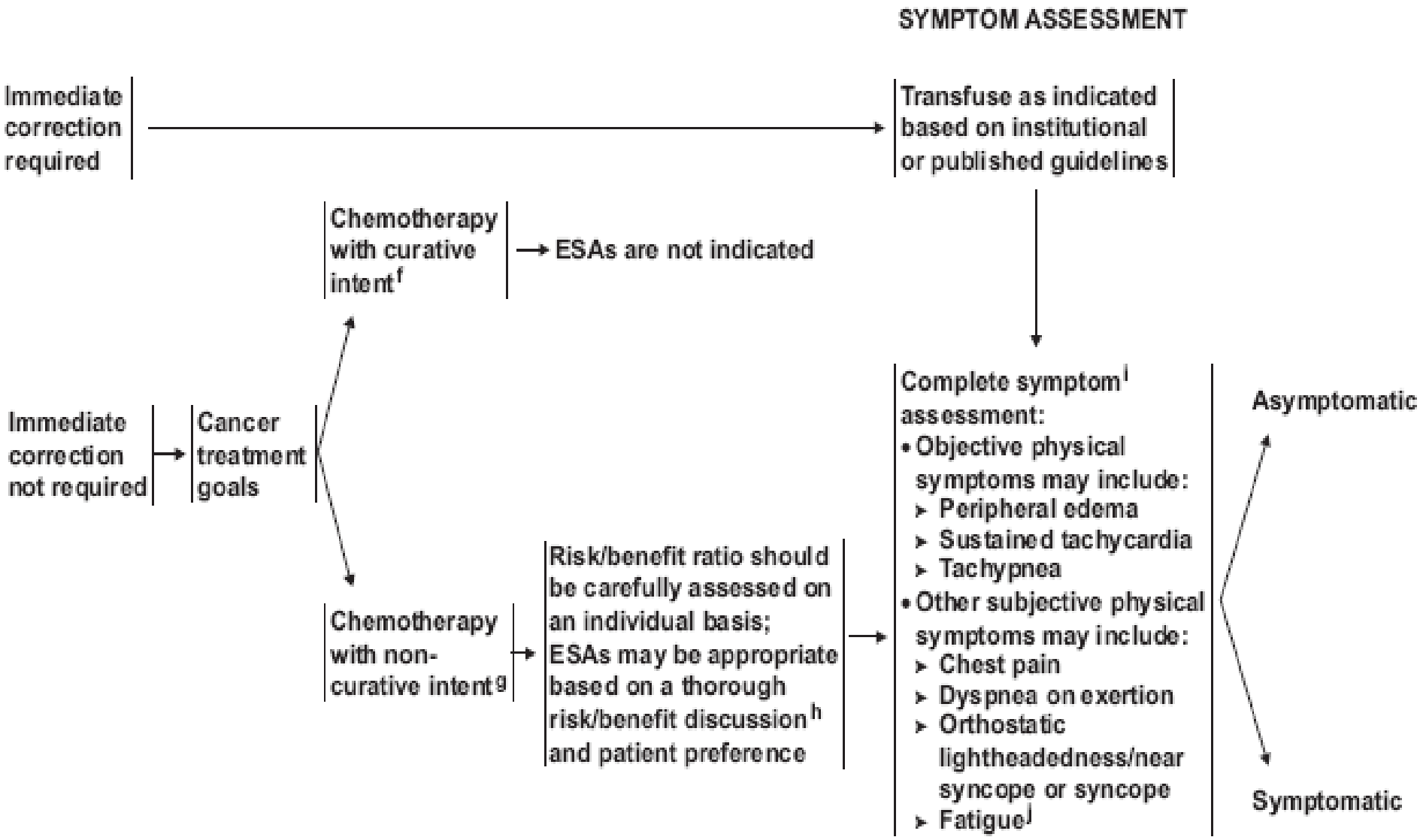
CANCER- and CHEMOTHERAPY -induced ANEMIA

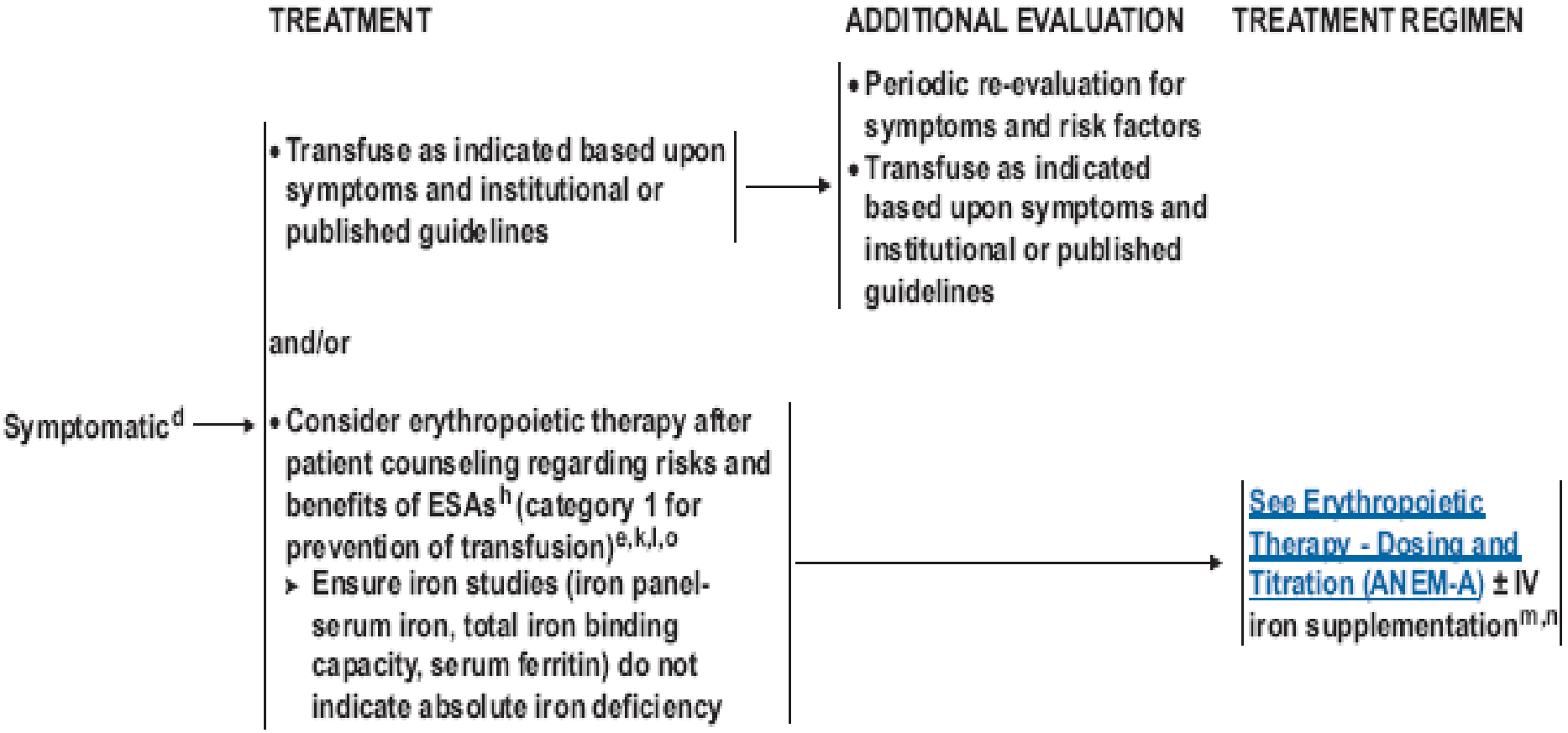
Cancer related anemia(Non treatment related)



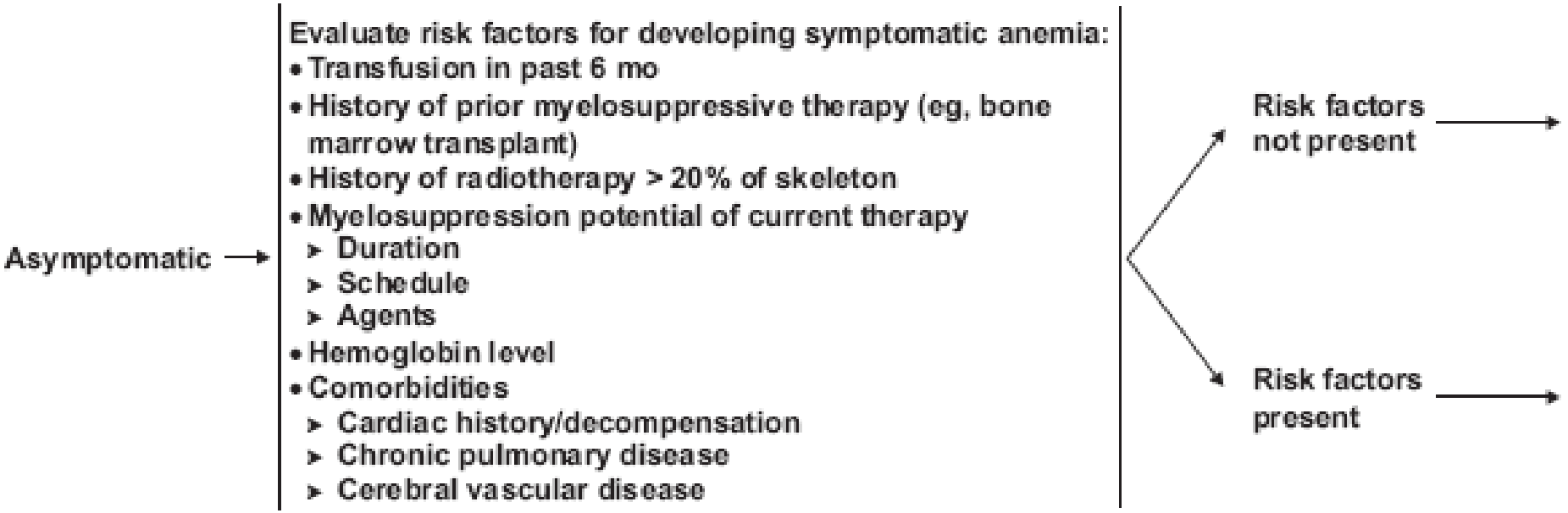
Chemotherapy related anemia

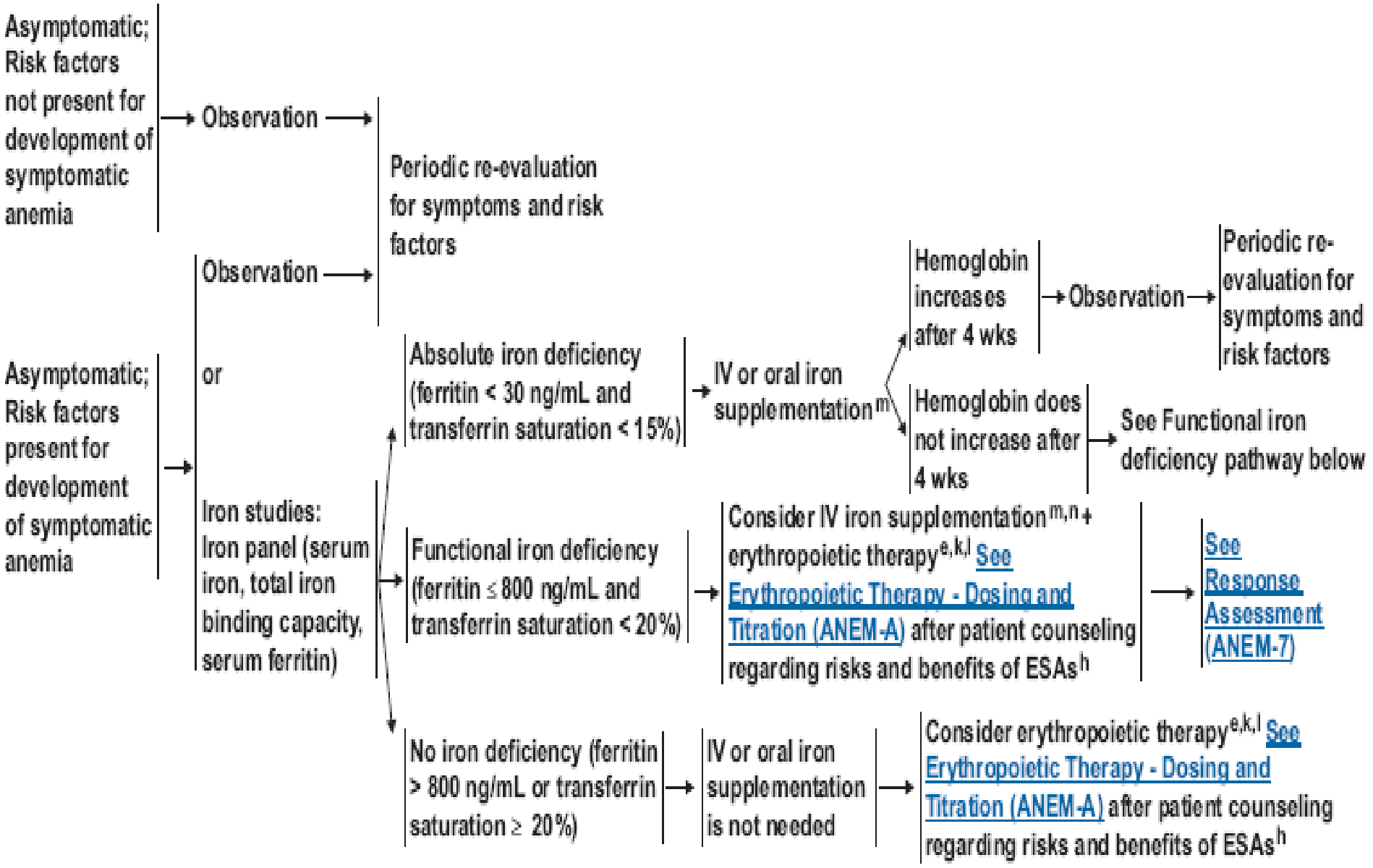



SYMPTOM ASSESSMENT
Immediate correction required
Transfuse as indicated based on institutional or published guidelines
Chemotherapy with curative intent[f]
ESAs are not indicated
Immediate correction not required
Cancer treatment goals
Chemotherapy with non-curative intent[g]
Risk/benefit ratio should be carefully assessed on an individual basis; ESAs may be appropriate based on a thorough risk/benefit discussion[h] and patient preference
Complete symptom[i] assessment:
• Objective physical symptoms may include:
▸ Peripheral edema
▸ Sustained tachycardia
▸ Tachypnea
• Other subjective physical symptoms may include:
▸ Chest pain
▸ Dyspnea on exertion
▸ Orthostatic lightheadedness/near syncope or syncope
▸ Fatigue[j]
Asymptomatic
Symptomatic


TREATMENT
ADDITIONAL EVALUATION
TREATMENT REGIMEN
• Transfuse as indicated based upon symptoms and institutional or published guidelines
• Periodic re-evaluation for symptoms and risk factors
• Transfuse as indicated based upon symptoms and institutional or published guidelines
and/or
Symptomatic[d]
• Consider erythropoietic therapy after patient counseling regarding risks and benefits of ESAs[h] (category 1 for prevention of transfusion)[e,k,l,o]
▸ Ensure iron studies (iron panel-serum iron, total iron binding capacity, serum ferritin) do not indicate absolute iron deficiency
See Erythropoietic Therapy - Dosing and Titration (ANEM-A) ± IV iron supplementation[m,n]

EVALUATION FOR SYMPTOMATIC ANEMIA RISK AMONG CANCER PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY WITHOUT CURATIVE INTENT




Asymptomatic; Risk factors not present for development of symptomatic anemia
Observation
Periodic re-evaluation for symptoms and risk factors
Asymptomatic; Risk factors present for development of symptomatic anemia
Observation
or
Iron studies: Iron panel (serum iron, total iron binding capacity, serum ferritin)
Absolute iron deficiency (ferritin < 30 ng/mL and transferrin saturation < 15%)
IV or oral iron supplementation m
Hemoglobin increases after 4 wks
Observation
Periodic re-evaluation for symptoms and risk factors
Hemoglobin does not increase after 4 wks
See Functional iron deficiency pathway below
Functional iron deficiency (ferritin ≤ 800 ng/mL and transferrin saturation < 20%)
Consider IV iron supplementation m,n + erythropoietic therapy e,k,l See Erythropoietic Therapy - Dosing and Titration (ANEM-A) after patient counseling regarding risks and benefits of ESAs h
See Response Assessment (ANEM-7)
No iron deficiency (ferritin > 800 ng/mL or transferrin saturation ≥ 20%)
IV or oral iron supplementation is not needed
Consider erythropoietic therapy e,k,l See Erythropoietic Therapy - Dosing and Titration (ANEM-A) after patient counseling regarding risks and benefits of ESAs h

INITIAL DOSING	TITRATION FOR NO RESPONSE	TITRATION FOR RESPONSE

PACKAGE INSERT DOSING SCHEDULE

Epoetin alfa 150 units/kg 3 times wk by subcutaneous injection	→	Increase dose of epoetin alfa to 300 units/kg 3 times wk by subcutaneous injection
or		
Epoetin alfa 40,000 units every wk by subcutaneous injection	→	Increase dose of epoetin alfa to 60,000 units every wk by subcutaneous injection
or		
Darbepoetin alfa 2.25 mcg/kg every wk by subcutaneous injection	→	Increase darbepoetin alfa to up to 4.5 mcg/kg every wk by subcutaneous injection
or		
Darbepoetin alfa 500 mcg every 3 wks by subcutaneous injection		

- The dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.
- If hemoglobin increases by more than 1 g/dL in a 2 week period, dose should be reduced by 25-50% of the prior dose.

ALTERNATIVE REGIMENS

Darbepoetin alfa 100 mcg fixed dose every wk by subcutaneous injection	→	Increase darbepoetin alfa to up to 150-200 mcg fixed dose every wk by subcutaneous injection[6]
or		
Darbepoetin alfa 200 mcg fixed dose every 2 wks by subcutaneous injection[7]	→	Increase darbepoetin alfa to up to 300 mcg fixed dose every 2 wks by subcutaneous injection[7]
or		
Darbepoetin alfa 300 mcg fixed dose every 3 wks by subcutaneous injection	→	Increase darbepoetin alfa to up to 500 mcg fixed dose every 3 wks by subcutaneous injection[8]
or		
Epoetin alfa 80,000 units every 2 wks by subcutaneous injection[9]		
or		
Epoetin alfa 120,000 units every 3 wks by subcutaneous injection[10]		

See Footnotes and References (ANEM-A 2 of 5)

See Adverse Effects of Erythropoietic Therapy (ANEM-A 3 of 5)

Epoetin alfa

Anemia with Cancer Chemotherapy non-myeloid CA:
Usual dose is 150 units/kg SC three times per week. If response is poor after 8 weeks, the dose may be increased up to as much as 300 units/kg three times per week.
Alternative regimen: 40,000 IU SC weekly. If response is poor after 4 weeks, dose may be increased to 60,000 IU weekly.

Anemia – Chronic Renal Failure (for dialysis or non-dialysis patients):
Usual dose is 50-100 units/kg IV or SC three times per week. If response is poor after 4 weeks, dose can be increased by 25%. If Hgb is approaching 12 g/dL, reduce dose by 25%. Dose increases should not be made more than every 4 weeks. Maintenance doses range from 12.5 to 525 units/kg (median 75 units/kg) three times per week. Once weekly SC dose of entire week's dosage may be efficacious in some patients.
Pediatric dose: 50 units/kg IV or SC three times weekly

Anemia – HIV infection associated with zidovudine (AZT):
Starting dose is 100 units/kg IV or SC three times per week for 8 weeks. If response is poor after 8 weeks, the dose may be increased by 50-100 units/kg three times per week up to 300 units/kg three times per week. Discontinue use if Hgb exceeds 13 g/dL and reinitiate at dose 25% lower once Hgb drops below 12 g/dL.

Anemia – surgery (reduction of allogeneic blood transfusions):
300 units/kg/day SC for 10 days prior to surgery, on the day of surgery, and 4 days after surgery.
Alternative regimen: 600 units/kg SC once per week (21, 14, and 7 days before surgery) with a fourth dose on the day of surgery.

Dose should be adjusted for each patient to achieve and maintain a target Hgb of 10 to 12 g/dL. Reduce the dose by 25% if Hgb approaches 12 g/dL or increases > 1 g/dL in any 2-week period.

Darbepoetin alfa

Anemia – Chronic Renal Failure:
Starting dose is 0.45 mcg/kg IV or SC once weekly. Titrate doses to not exceed a target hemoglobin concentration of 12 g/dL. Some patients have been successful with once every 2 weeks administration.
Anemia – Cancer Patients Receiving Chemotherapy:
Starting dose is 2.25 mcg/kg SC once weekly. Dose should be adjusted to achieve and maintain a target hemoglobin.

Do not increase doses more frequently than once a month.
If the hemoglobin is increasing and approaching 12 g/dL, reduce the dose by 25%. If the hemoglobin continues to increase, withhold doses temporarily until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose 25% below the previous dose.

Adverse Effects of ESA

- Thrombosis
- Hypertension
- Seizure
- ESA Neutralizing antibodies(PRCA)
- Cancer patient survival

Table 3. Summary of randomized trials that showed adverse health effects with ESA.

Study/Tumor/(n)	ESA treatment, duration	Hb start value (g/dL)	Hb target value (g/dL)	Adverse Outcome
Chemotherapy				
PREPARE,[43] breast cancer, n=733	Darbepoetin alfa (4.5 µg/kg/2 wk), Not reported	Mean 13.6	≥13	Decreased OS, 14% vs 10% death; faster tumor growth
BEST,[45] metastatic breast cancer, n=939	Epoetin alfa (40 000 U/wk), 12 months	≤ 13	>14	Decreased 12-month survival, 70% vs 76%, P = 0.01
20000161,[46] lymphoid malignancy, n=344	Darbepoetin alfa (2.25 µg/kg/wk), 12 wk	≤11	≥14 (women) ≥15 (men)	Decreased OS, HR for death = 1.37, P = 0.04
Radiotherapy				
ENHANCE,[47] head and neck, n=351	Epoetin beta (300 IU/kg x 3/wk), 7-9 wk	<12 (women) <13 (men)	≥14 (women) ≥15 (men)	Decreased OS, HR for death = 1.39, P = 0.02; locoregional progression, HR = 1.69, P = 0.007
DAHANCA 10,[48] head and neck, n=522	Darbepoetin alfa (150 µg/wk), Terminated early	≤14.5	>15.5	Increased locoregional failure, RR = 1.44, P = 0.03
Chemoradiotherapy				
GOG-191,[51] cervical cancer, n=113	Darbepoetin alfa (40 000 U/wk), Terminated early	<12	>14	Decreased OS, 61% vs 75%; decreased PFS, 58% vs 65%
No therapy/palliative radiotherapy				
EPO-CAN-20,[49] non-small cell lung cancer, n=70	Epoetin alfa (40 000 U/wk), 12 wk	<12.1	>14	Decreased OS, HR for death = 1.84, P = 0.04
Amgen 103,[50] non-myeloid cancer, n=989	Darbepoetin alfa (6.75 µg/kg/4 wk), 16 wk	≤11	>13	Decreased OS, HR for death = 1.3, P = 0.008

Hb = hemoglobin; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

Thrombopoeitin Stimulating Agents

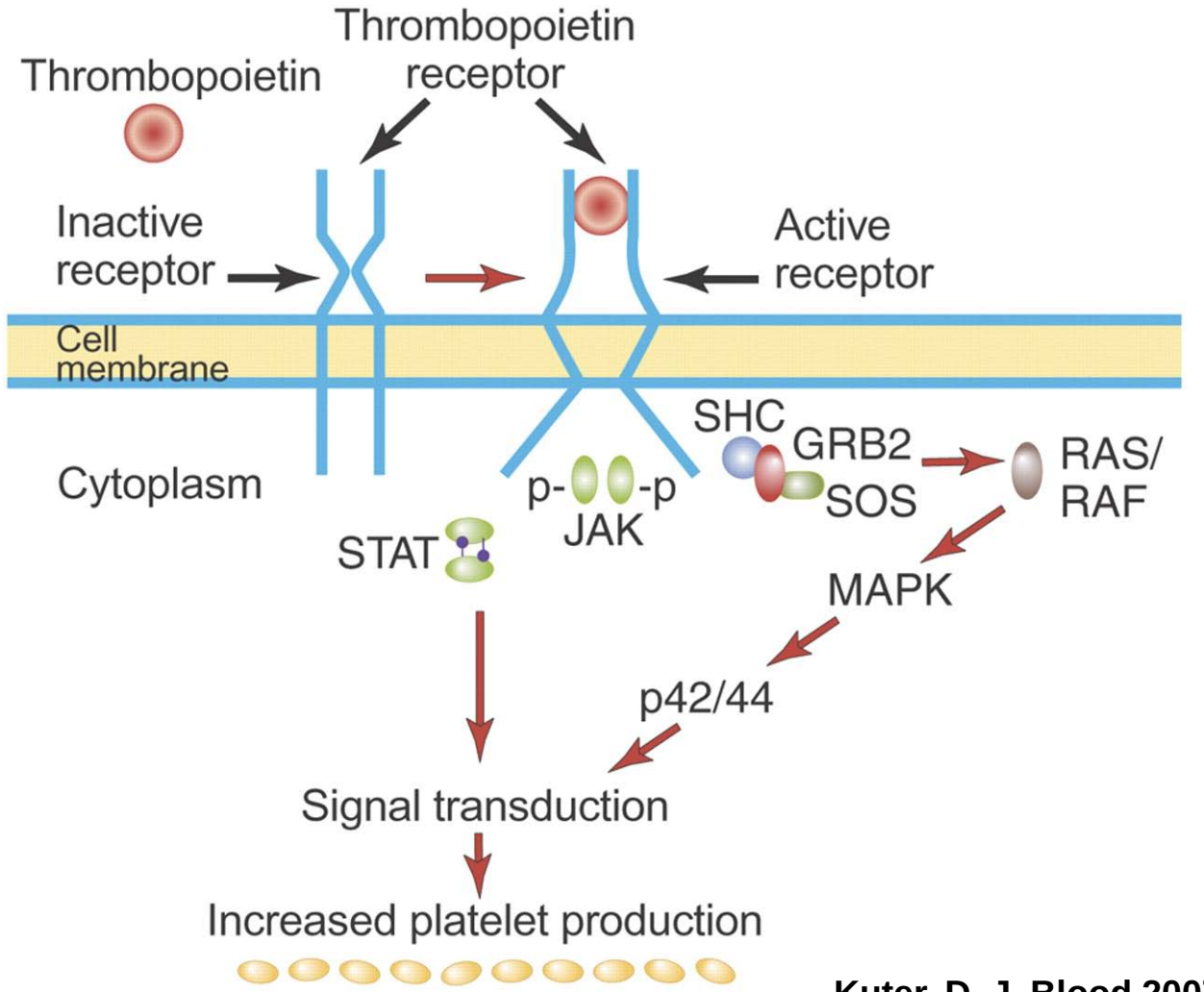
First-generation thrombopoietic growth factors

- Recombinant human thrombopoietins
  - rhTPO
  - PEG-rHuMGDF
- Recombinant TPO fusion proteins
  - Promegapoietin (TPO/IL3 fusion protein)

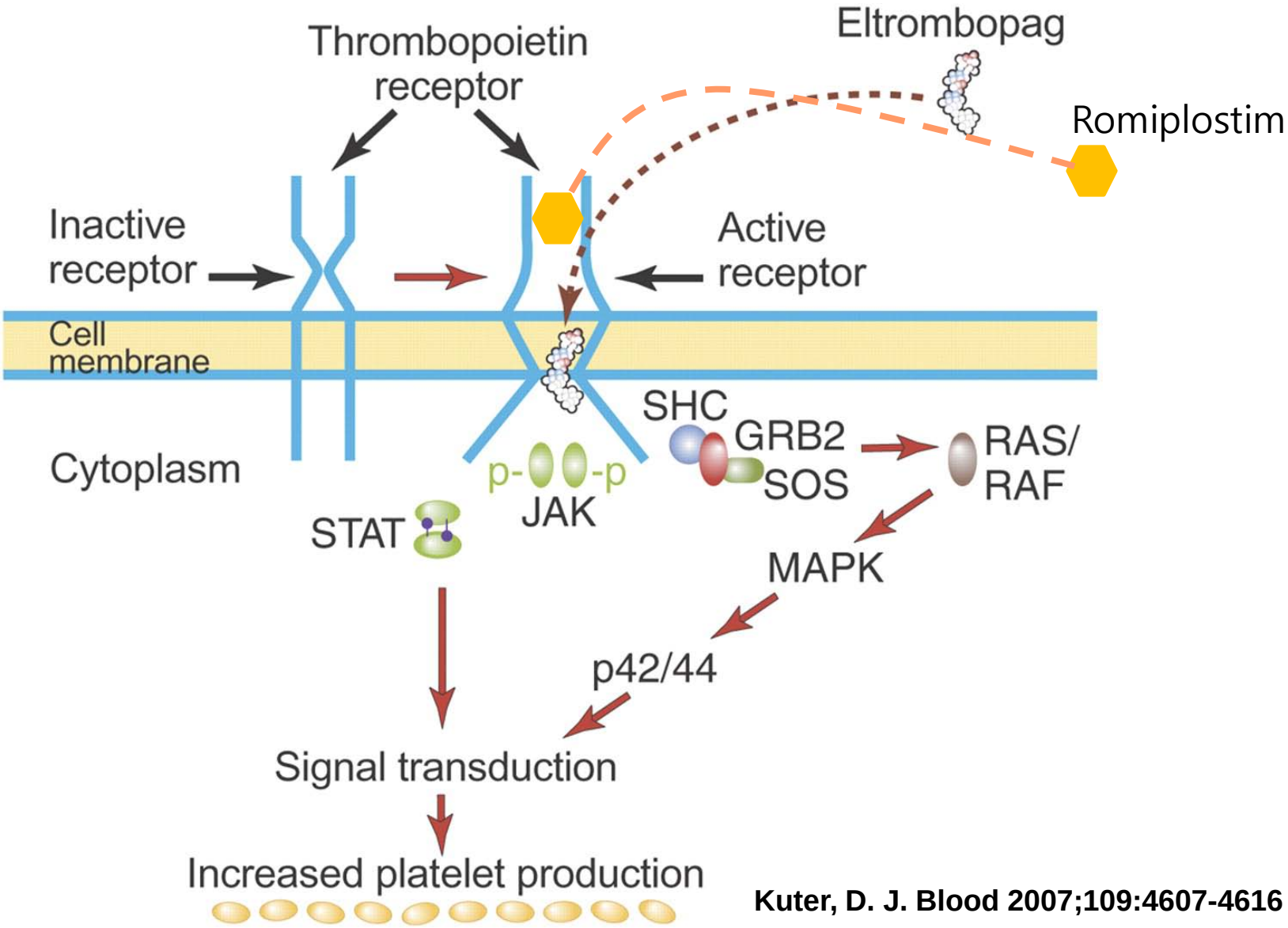
Second-generation thrombopoietic growth factors

- TPO peptide mimetics
  - Fab 59
  - AMG 531
  - Peg-TPOmp
- TPO nonpeptide mimetics
  - Eltrombopag (SB497115, Promacta)
  - AKR-501
- TPO agonist antibodies
  - Minibodies [VB22B sc(Fv)2]
  - Domain subclass-converted TPO agonist antibodies (MA01G4G344)

Mechanism of activation of the TPO receptor by TPO



Kuter, D. J. Blood 2007;109:4607-4616



Kuter, D. J. Blood 2007;109:4607-4616

Thrombopoietin-Stimulating agonist

- Eltrombopag for Thrombocytopenia in Patients with Cirrhosis Associated with Hepatitis C – NEJM 2007;357:2227-2236

- Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura -- NEJM 2007;357:2237-2247

TPO and ITP

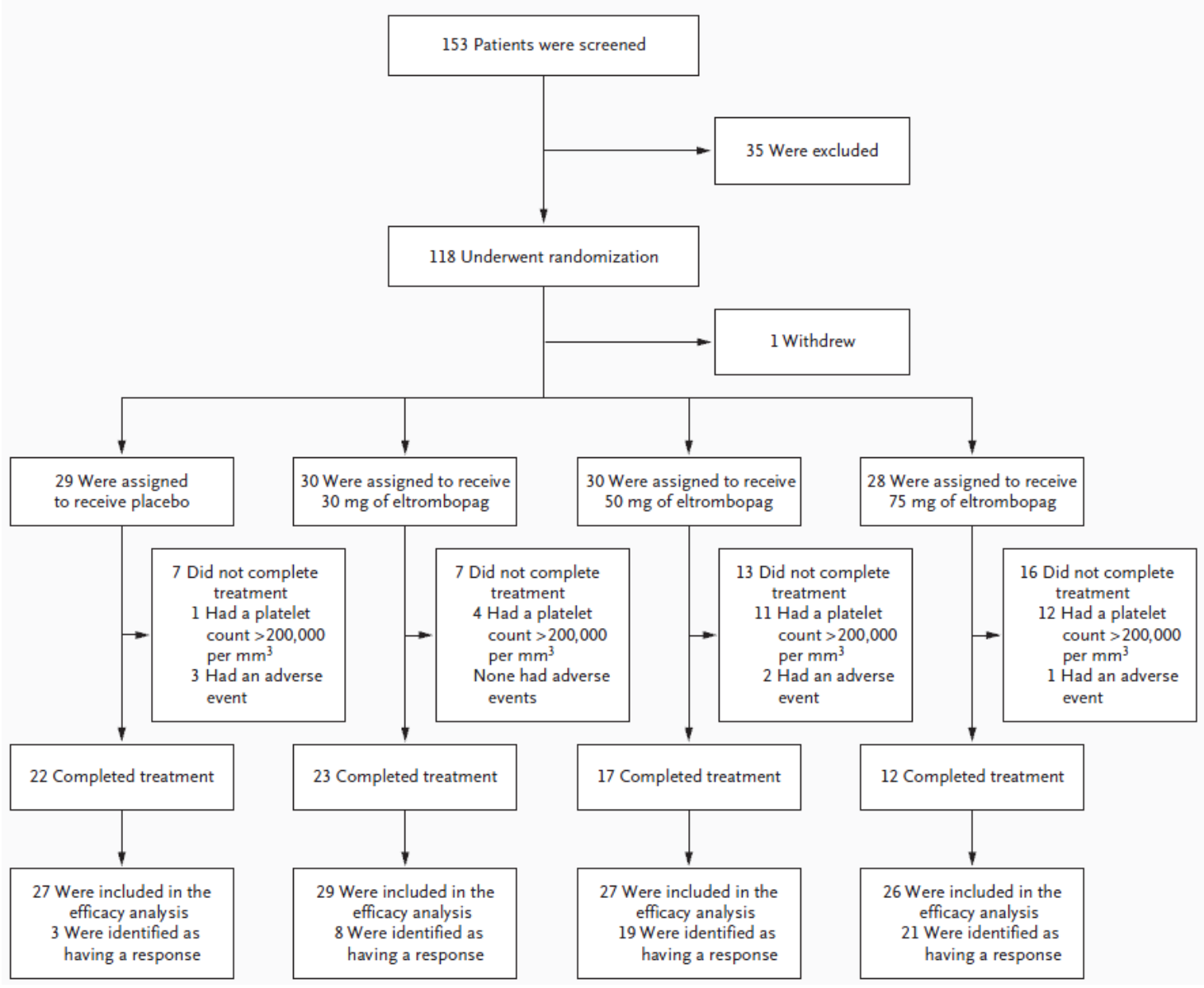
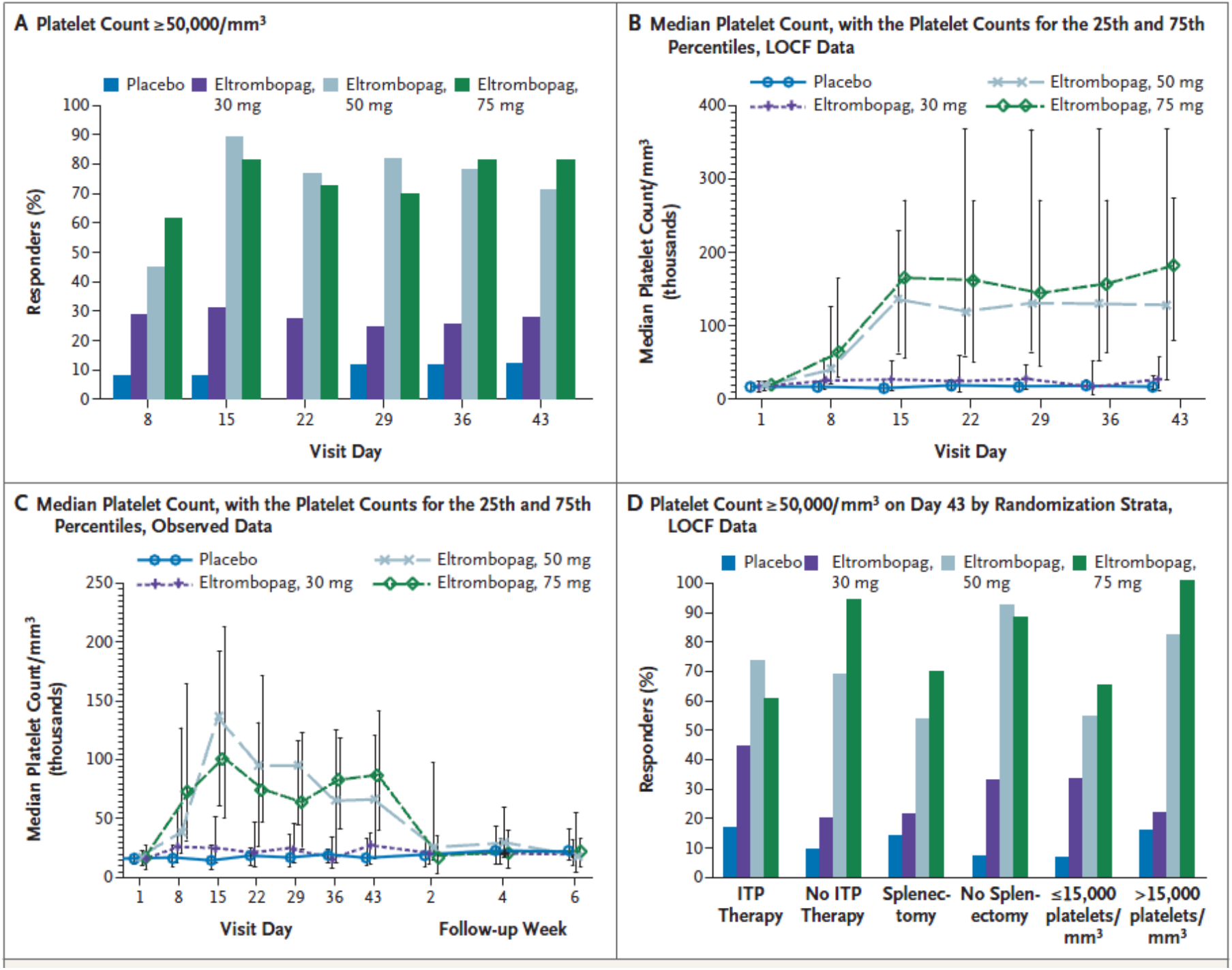

153 Patients were screened
35 Were excluded
118 Underwent randomization
1 Withdrew
29 Were assigned to receive placebo
30 Were assigned to receive 30 mg of eltrombopag
30 Were assigned to receive 50 mg of eltrombopag
28 Were assigned to receive 75 mg of eltrombopag
7 Did not complete treatment
1 Had a platelet count >200,000 per mm3
3 Had an adverse event
7 Did not complete treatment
4 Had a platelet count >200,000 per mm3
None had adverse events
13 Did not complete treatment
11 Had a platelet count >200,000 per mm3
2 Had an adverse event
16 Did not complete treatment
12 Had a platelet count >200,000 per mm3
1 Had an adverse event
22 Completed treatment
23 Completed treatment
17 Completed treatment
12 Completed treatment
27 Were included in the efficacy analysis
3 Were identified as having a response
29 Were included in the efficacy analysis
8 Were identified as having a response
27 Were included in the efficacy analysis
19 Were identified as having a response
26 Were included in the efficacy analysis
21 Were identified as having a response

Table 1. Demographic and Clinical Characteristics at Baseline.

Characteristic	Placebo (N=29)	Eltrombopag			Total (N=117)	P Value
		30 mg (N=30)	50 mg (N=30)	75 mg (N=28)		
Age — yr						0.04*†
Median	42	51	45	55	50	
Range	18–85	23–79	23–81	18–85	18–85	
Sex — no. (%)						0.33‡
Female	16 (55)	16 (53)	21 (70)	20 (71)	73 (62)	
Male	13 (45)	14 (47)	9 (30)	8 (29)	44 (38)	
Race — no. (%)§						0.02†‡¶
Black	1 (3)	1 (3)	—	—	2 (2)	
Asian	2 (7)	4 (13)	12 (40)	3 (11)	21 (18)	
White	25 (86)	25 (83)	18 (60)	25 (89)	93 (79)	
Mixed	1 (3)	—	—	—	1 (<1)	
Stratification variables — no. (%)						
Splenectomy	14 (48)	15 (50)	15 (50)	11 (39)	55 (47)	0.82‡
Concomitant ITP medication	6 (21)	10 (33)	12 (40)	10 (36)	38 (32)	0.43‡
Platelets ≤15,000/mm^3	14 (48)	15 (50)	12 (40)	15 (54)	56 (48)	0.82‡
Prior therapies — no. (%)						0.52‡‖
≥1	28 (97)	29 (97)	30 (100)	26 (93)	113 (97)	
≥2	21 (72)	26 (87)	24 (80)	16 (57)	87 (74)	
≥3	14 (48)	17 (57)	18 (60)	11 (39)	60 (51)	
≥4	12 (41)	12 (40)	12 (40)	6 (21)	42 (36)	


A Platelet Count ≥50,000/mm³
Placebo
Eltrombopag, 30 mg
Eltrombopag, 50 mg
Eltrombopag, 75 mg
Responders (%)
Visit Day
B Median Platelet Count, with the Platelet Counts for the 25th and 75th Percentiles, LOCF Data
Placebo
Eltrombopag, 30 mg
Eltrombopag, 50 mg
Eltrombopag, 75 mg
Median Platelet Count/mm³ (thousands)
Visit Day
C Median Platelet Count, with the Platelet Counts for the 25th and 75th Percentiles, Observed Data
Placebo
Eltrombopag, 30 mg
Eltrombopag, 50 mg
Eltrombopag, 75 mg
Median Platelet Count/mm³ (thousands)
Visit Day
Follow-up Week
D Platelet Count ≥50,000/mm³ on Day 43 by Randomization Strata, LOCF Data
Placebo
Eltrombopag, 30 mg
Eltrombopag, 50 mg
Eltrombopag, 75 mg
Responders (%)
ITP Therapy
No ITP Therapy
Splenectomy
No Splenectomy
≤15,000 platelets/mm³
>15,000 platelets/mm³

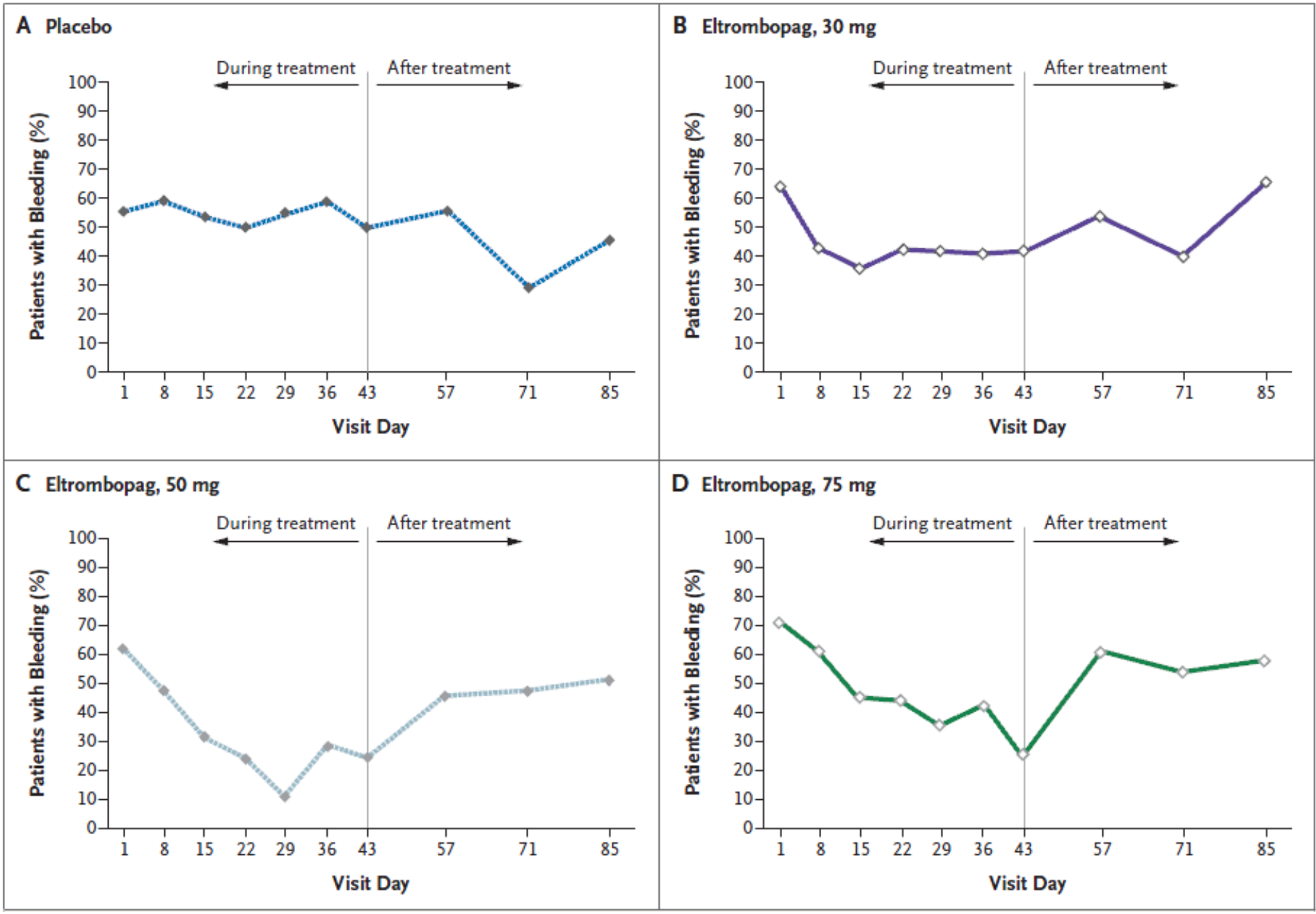

A Placebo
During treatment
After treatment
Patients with Bleeding (%)
100
90
80
70
60
50
40
30
20
10
0
1
8
15
22
29
36
43
57
71
85
Visit Day
B Eltrombopag, 30 mg
During treatment
After treatment
Patients with Bleeding (%)
Visit Day
C Eltrombopag, 50 mg
During treatment
After treatment
Patients with Bleeding (%)
Visit Day
D Eltrombopag, 75 mg
During treatment
After treatment
Patients with Bleeding (%)
Visit Day

Table 2. Adverse Events in 5% or More of Patients in Any Study Group.

Event	Placebo (N=29)	Eltrombopag		
		30 mg (N=30)	50 mg (N=30)	75 mg (N=28)
Total*	17 (59)	14 (47)	14 (47)	17 (61)
Total grade 3 or 4 events†	4 (14)	2 (7)	4 (13)	3 (11)
Headache	6 (21)	4 (13)	3 (10)	6 (21)
Aspartate aminotransferase elevation	—	1 (3)	—	2 (7)
Constipation	2 (7)	1 (3)	—	2 (7)
Fatigue	5 (17)	—	1 (3)	2 (7)
Rash	1 (3)	1 (3)	—	2 (7)
Anemia	2 (7)	1 (3)	1 (3)	1 (4)
Diarrhea	2 (7)	—	—	1 (4)
Peripheral edema	2 (7)	—	1 (3)	1 (4)
Taste disturbance	2 (7)	—	—	1 (4)
Abdominal distention	2 (7)	1 (3)	—	—
Arthralgia	3 (10)	1 (3)	—	—
Epistaxis	—	4 (13)	—	—
Hemorrhoids	2 (7)	—	—	—
Pain in extremity	1 (3)	2 (7)	—	—

TPO and other diseases(Liver cirrhosis)

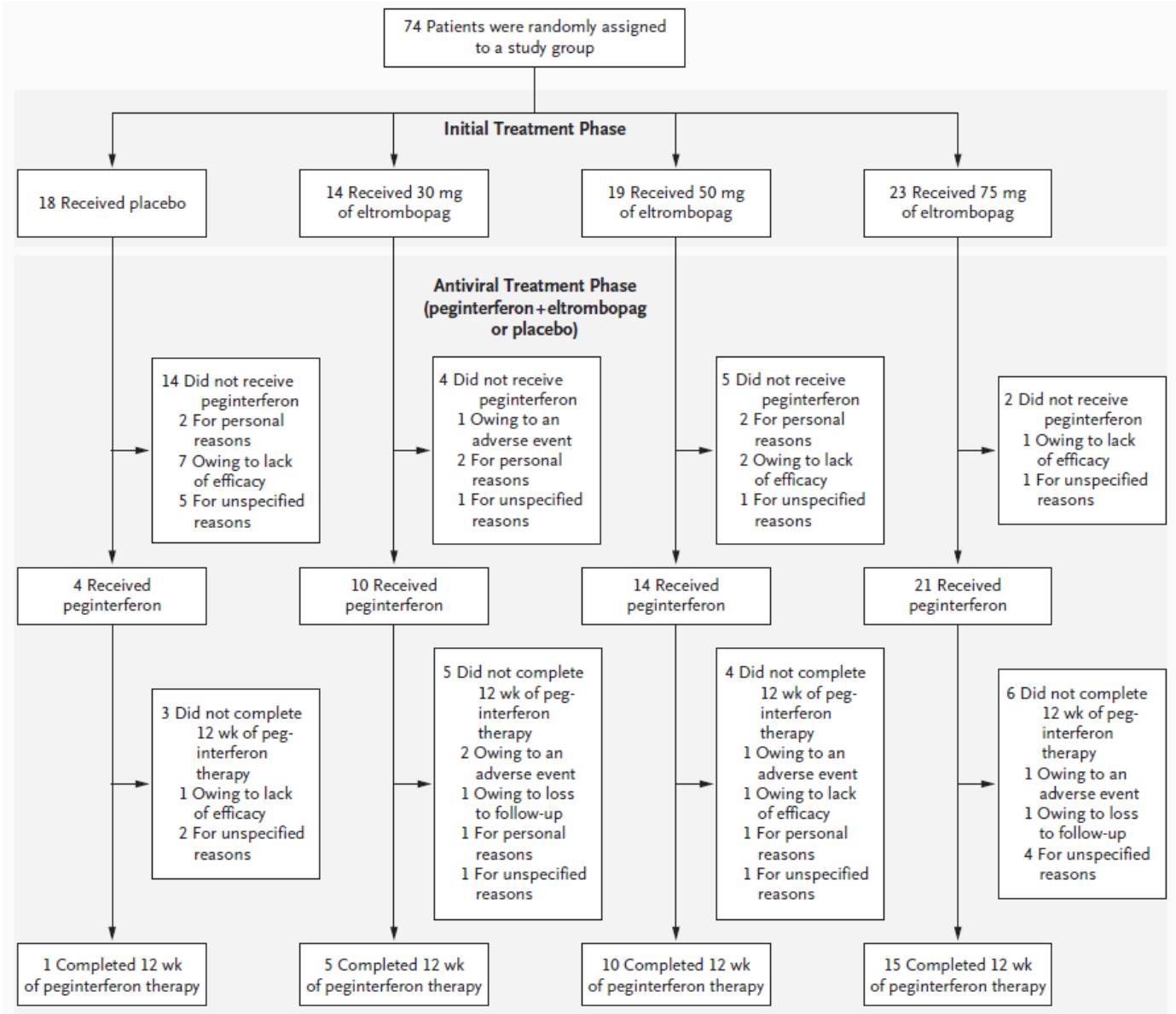


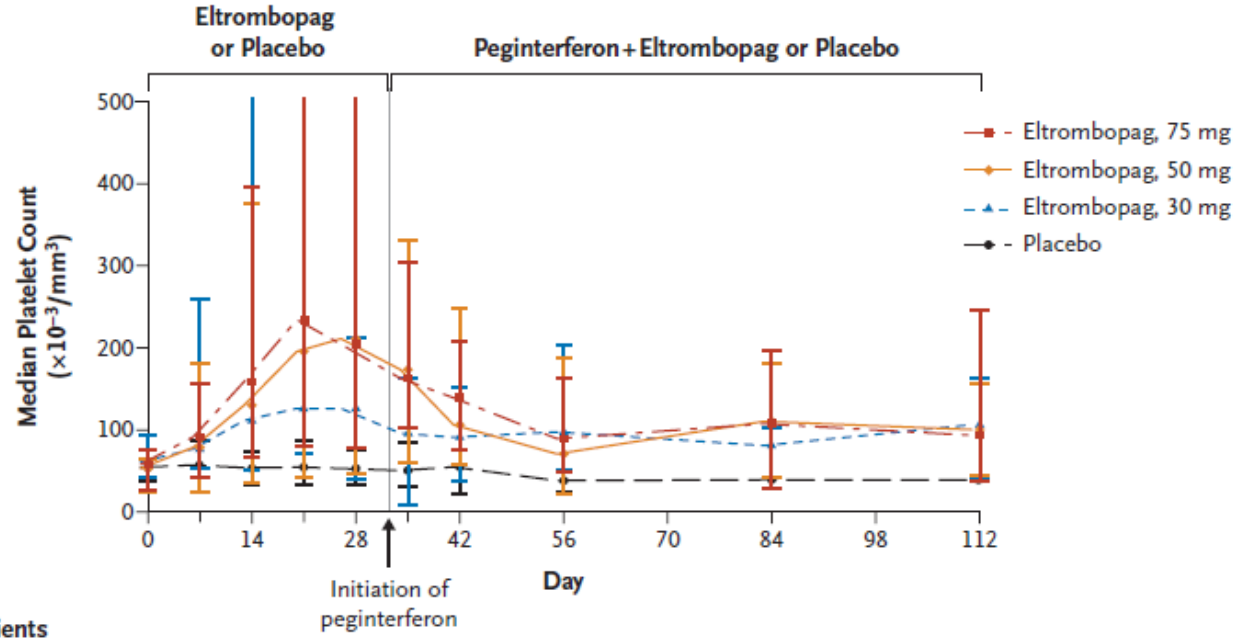
Table 1. Baseline Characteristics of the Patients.*

Characteristic	Eltrombopag			Placebo (N=18)	All (N=74)
	30 mg (N=14)	50 mg (N=19)	75 mg (N=23)		
Age — yr					
Median	56	50	51	52	51
Range	43–74	30–72	38–60	41–71	30–74
Sex — no. (%)					
Male	10 (71)	12 (63)	19 (83)	11 (61)	52 (70)
Female	4 (29)	7 (37)	4 (17)	7 (39)	22 (30)
Race — no. (%)†					
Black	0	2 (11)	1 (4)	1 (6)	4 (5)
Asian	0	1 (5)	0	1 (6)	2 (3)
White	13 (93)	16 (84)	22 (96)	16 (89)	67 (91)
Platelet count					
Median — per mm^3	59,000	52,000	54,000	55,000	55,000
Range — per mm^3	34,000–94,000	26,000–66,000	28,000–75,000	27,000–75,000	26,000–94,000
20,000 to <50,000/mm^3 — no. (%)	5 (36)	7 (37)	8 (35)	6 (33)	26 (35)
≥50,000 to <70,000/mm^3 — no. (%)	7 (50)	12 (63)	13 (57)	11 (61)	43 (58)
≥70,000/mm^3 — no. (%)	2 (14)	0	2 (9)	1 (6)	5 (7)
HCV genotype — no. (%)					
1 or 4	10 (71)	11 (58)	14 (61)	10 (56)	45 (61)
2 or 3	4 (29)	8 (42)	8 (35)	7 (39)	27 (36)
Unknown	0	0	1 (4)	1 (6)	2 (3)
Albumin — g/liter	35.8±6.8	33.8±4.9	36.6±5.7	36.4±5.8	35.7±5.7
Alanine aminotransferase — IU/liter	120.6±51.4	117.8±67.5	117.0±69.3	120.5±70.7	118.8±64.2
Aspartate aminotransferase — IU/liter	123.3±68.1	127.4±67.3	128.6±104.1	129.5±72.8	127.5±79.2
Total bilirubin — μmol/liter	25.3±11.5	25.1±14.1	24.9±16.3	27.7±14.0	25.7±14.4

Table 2. Median Platelet Counts at the End of the Initial Treatment Phase and the End of the Antiviral Treatment Phase.*

Variable	Eltrombopag			Placebo (N=18)
	30 mg (N=14)	50 mg (N=19)	75 mg (N=23)	
End of initial treatment phase				
Platelet count				
No. of patients with data	11	16	22	14
Median — per mm³	125,000	212,000	204,000	53,000
Range — per mm³	40,000 to 214,000	47,000 to 599,000	78,000 to 527,000	34,000 to 74,000
Change from baseline				
No. of patients with data	12	16	22	14
Median — per mm³	74,000	152,000	151,000	−3,000
Range — per mm³	6,000 to 155,000	10,000 to 540,000	45,000 to 473,000	−22,000 to 13,000
≥100,000/mm³ — no. of responders/total no. of patients who could be evaluated (%)	9/12 (75)	15/19 (79)	20/21 (95)	0/17
≥200,000/mm³ — no. of responders/total no. of patients who could be evaluated (%)	3/12 (25)	9/19 (47)	11/21 (52)	0/17
End of antiviral treatment phase				
Platelet count				
No. of patients with data	2	7	8	1
Median — per mm³	106,000	100,000	92,000	39,000
Range — per mm³	43,000 to 164,000	46,000 to 156,000	38,000 to 245,000	39,000 to 39,000
Change from baseline — per mm³				
Median	31,000	54,000	31,000	−25,000
Range	−18,000 to 122,000	8000 to 97,000	−23,000 to 191,000	−25,000 to −25,000

A



No. of Patients										
Placebo	18	18	18	17	14	3	3	4	2	1
Eltrombopag, 30 mg	14	14	14	12	11	10	10	9	7	6
Eltrombopag, 50 mg	19	19	17	16	15	12	14	12	10	10
Eltrombopag, 75 mg	23	23	22	22	20	18	20	18	17	15

B

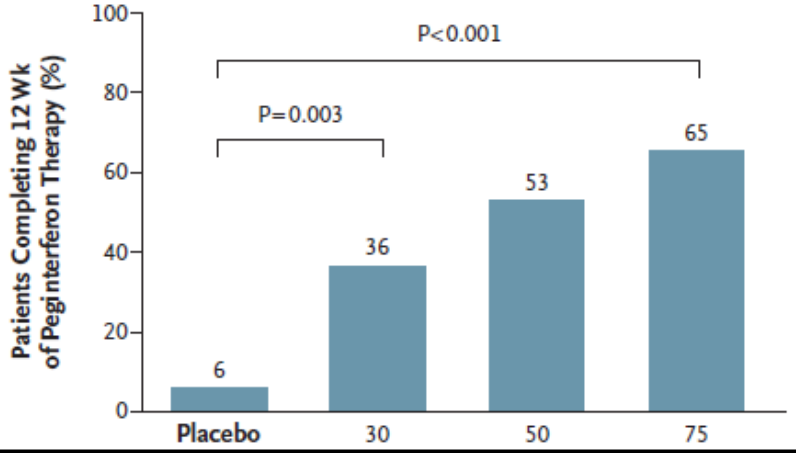


Table 3. Most Common Adverse Events during the Initial Treatment Phase and the Antiviral Treatment Phase.*

Event	Eltrombopag			Placebo (N=18)
	30 mg (N=14)	50 mg (N=19)	75 mg (N=23)	
	number of events (percent)			
Initial treatment phase				
Any	11 (79)	10 (53)	13 (57)	10 (56)
Headache	5 (36)	3 (16)	4 (17)	3 (17)
Dry mouth	2 (14)	2 (11)	2 (9)	1 (6)
Upper abdominal pain	2 (14)	2 (11)	0	0
Nausea	1 (7)	2 (11)	1 (4)	0
Antiviral treatment phase				
Any	9 (64)	13 (68)	17 (74)	3 (17)
Influenza-like illness	4 (29)	5 (26)	8 (35)	1 (6)
Fatigue	4 (29)	5 (26)	5 (22)	1 (6)
Chills	0	6 (32)	2 (9)	1 (6)
Headache	3 (21)	3 (16)	3 (13)	0
Arthralgia	3 (21)	1 (5)	2 (9)	1 (6)
Depression	2 (14)	1 (5)	4 (17)	0
Myalgia	3 (21)	2 (11)	2 (9)	0
Nausea	3 (21)	3 (16)	1 (4)	0
Anemia	2 (14)	2 (11)	2 (9)	0
Pyrexia	1 (7)	3 (16)	2 (9)	0
Diarrhea	0	1 (5)	3 (13)	1 (6)
Irritability	2 (14)	0	1 (4)	1 (6)
Pruritus	1 (7)	2 (11)	0	1 (6)
Rash	0	3 (16)	1 (4)	0

결 론

- Erythropoietin-stimulating agents와 Thrombopoietin-stimulating agents를 사용하여 수혈을 하지 않고 빈혈과 혈소판감소증을 조절 할수 있는 경우가 많아졌다.

- 단, 이러한 cytokine의 사용에 따른 발생가능한 부작용은 충분히 고려되어야 한다.