A role for recombinant G-CSF and GM-CSF in lung cancer

대구가톨릭의대 호흡기내과
정치영

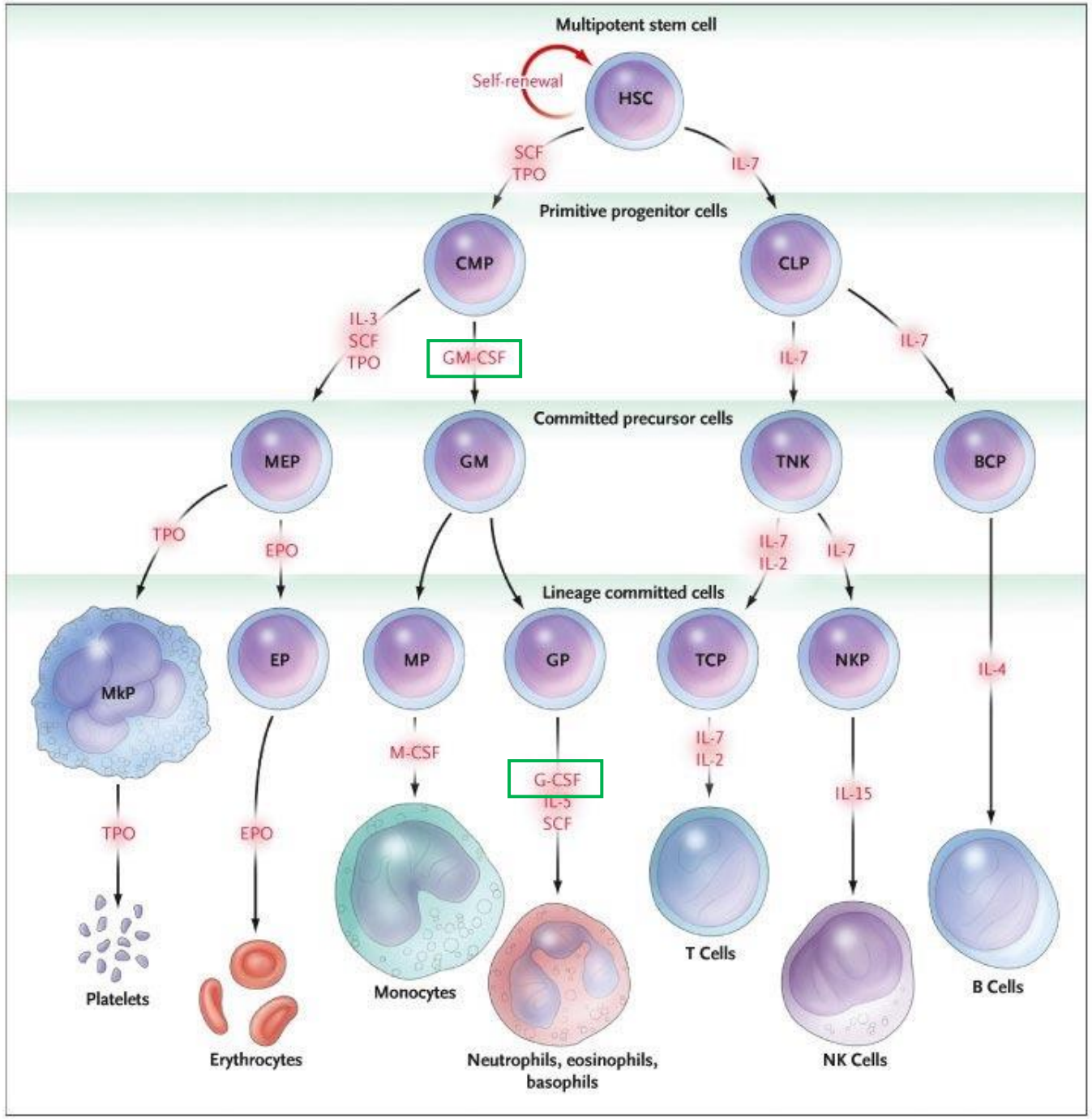
Contents

- **G-CSF/ GM-CSF**

- **Recombinant G-CSF**
  - **: Primary prophylaxis & secondary prophylaxis**
  - **: Neutropenic fever**

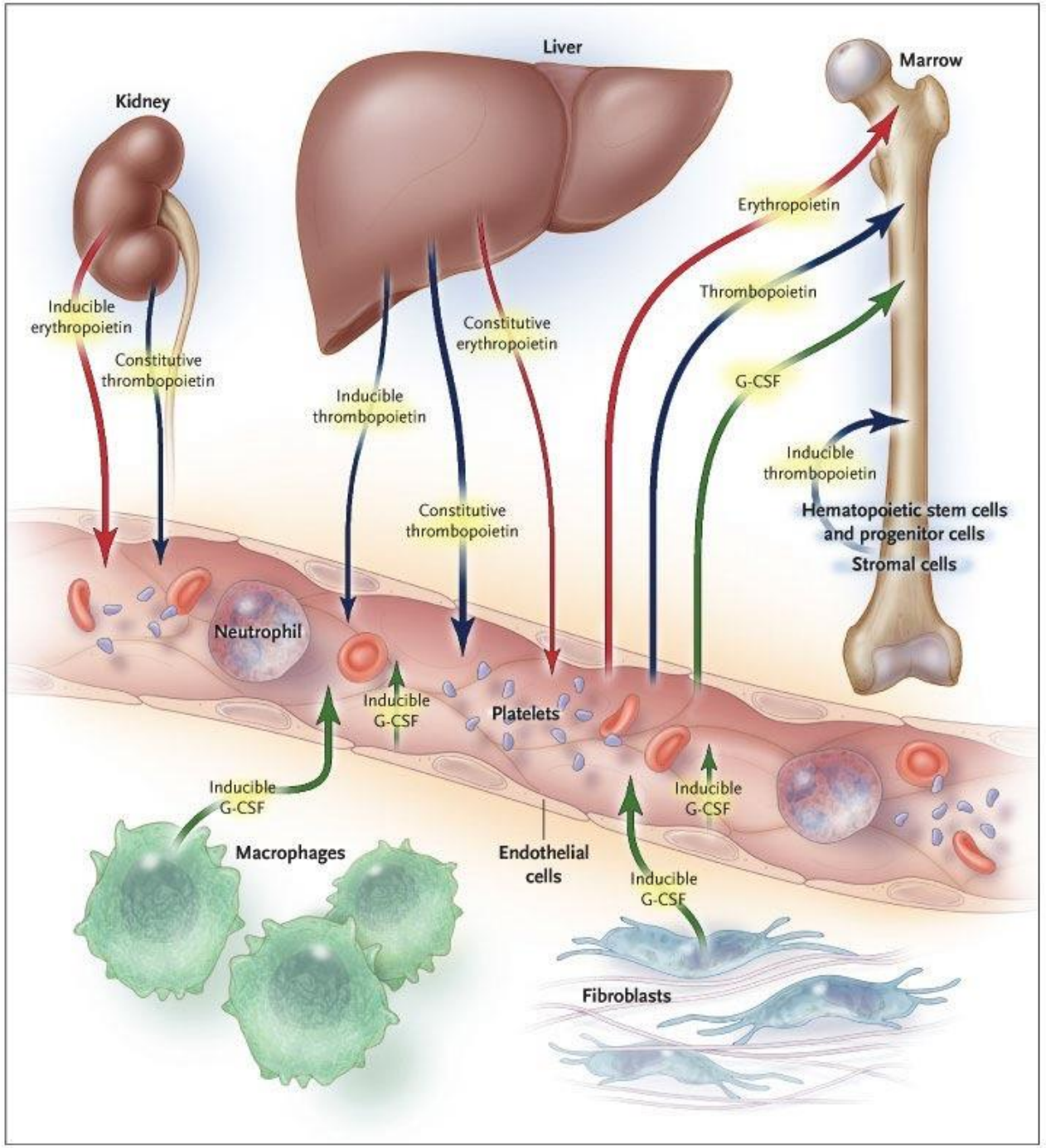
- **G-CSF vs. GM-CSF/ long- vs. short-acting G-CSF**

Hematopoiesis



N Engl J Med. 2006;354:2034-45.

Regulation of the production of hematopoietic growth factors

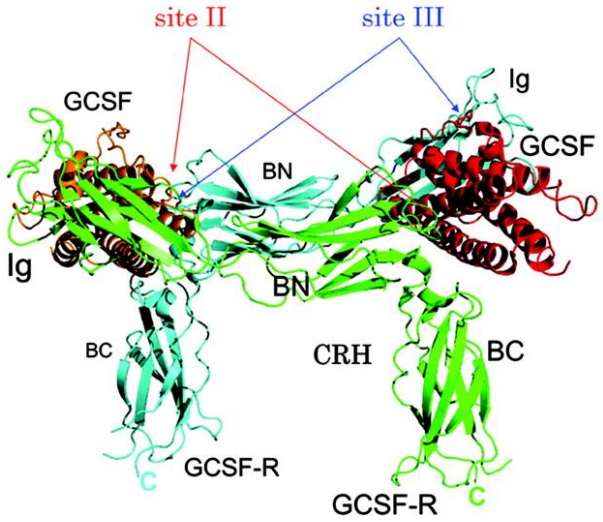


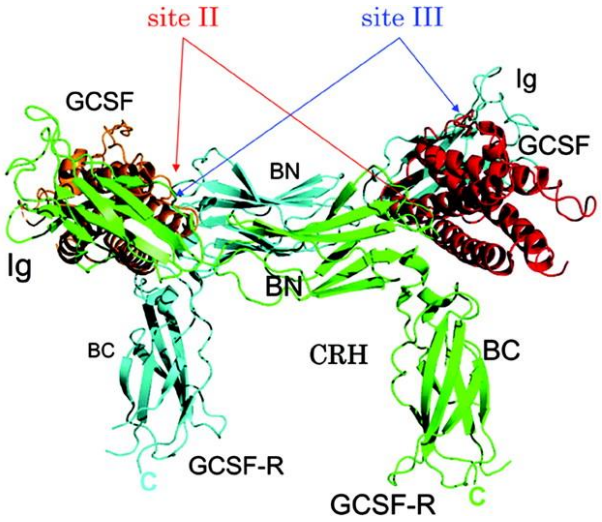
Inflammatory mediators
: IL-1, IL-6, TNF α

N Engl J Med. 2006;354:2034-45.

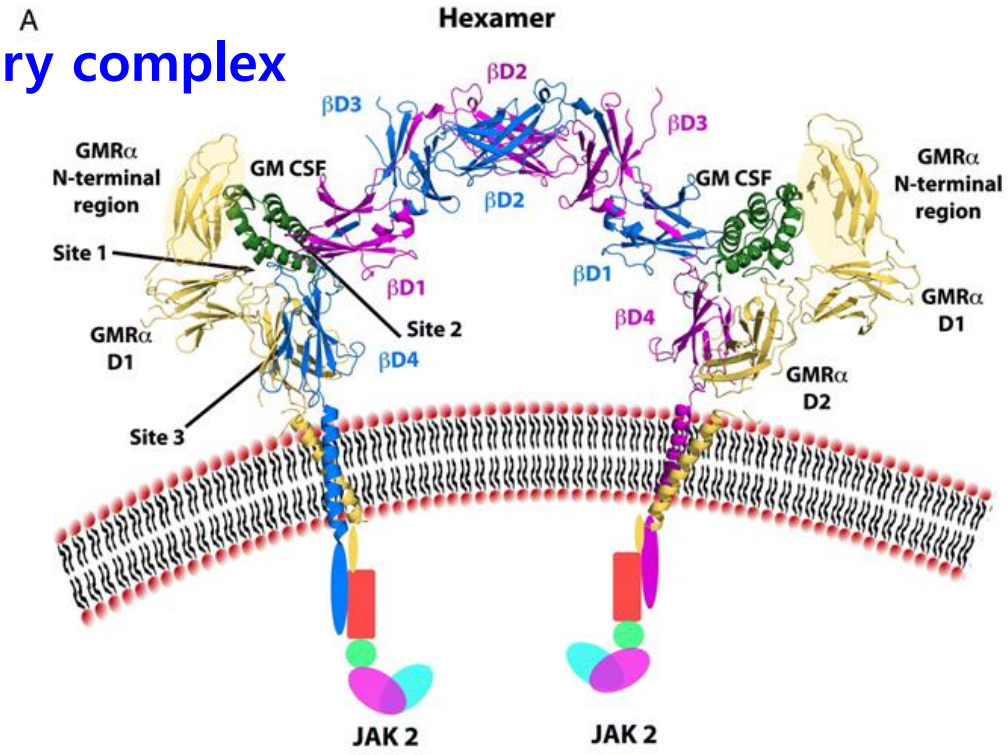
G-CSF & GM-CSF structure

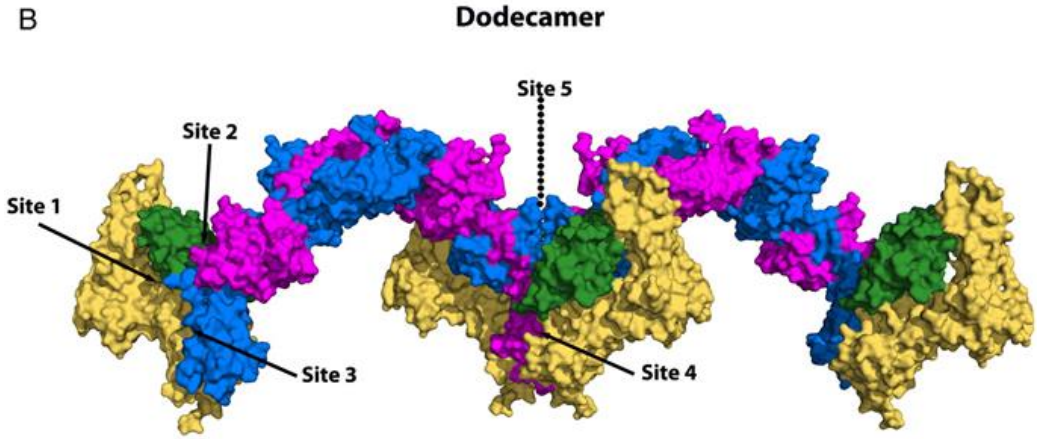
G-CSF tetramer





GM-CSF ternary complex

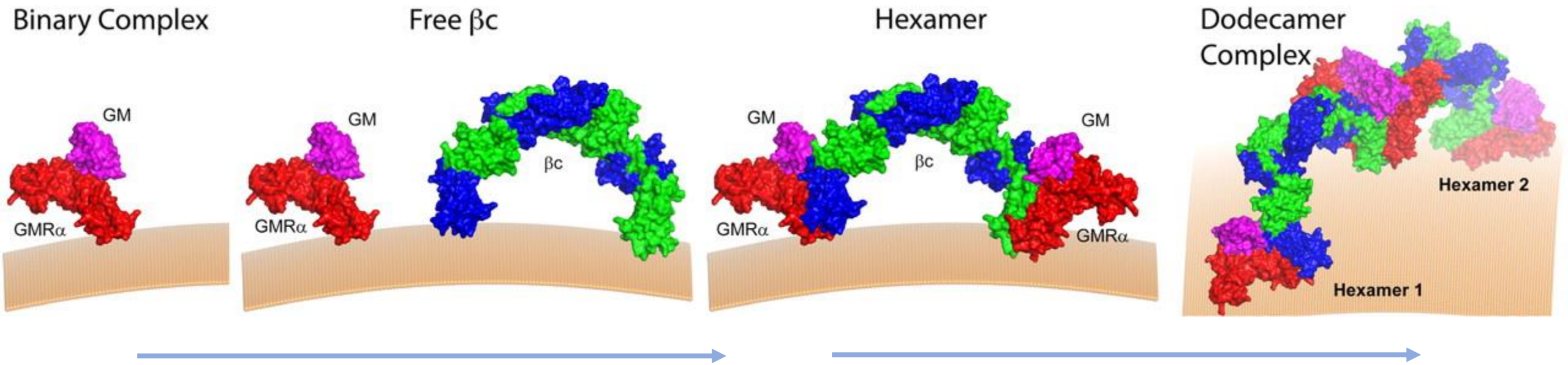




Proc Natl Acad Sci U S A. 2006 Feb 28;103(9):3135-40.

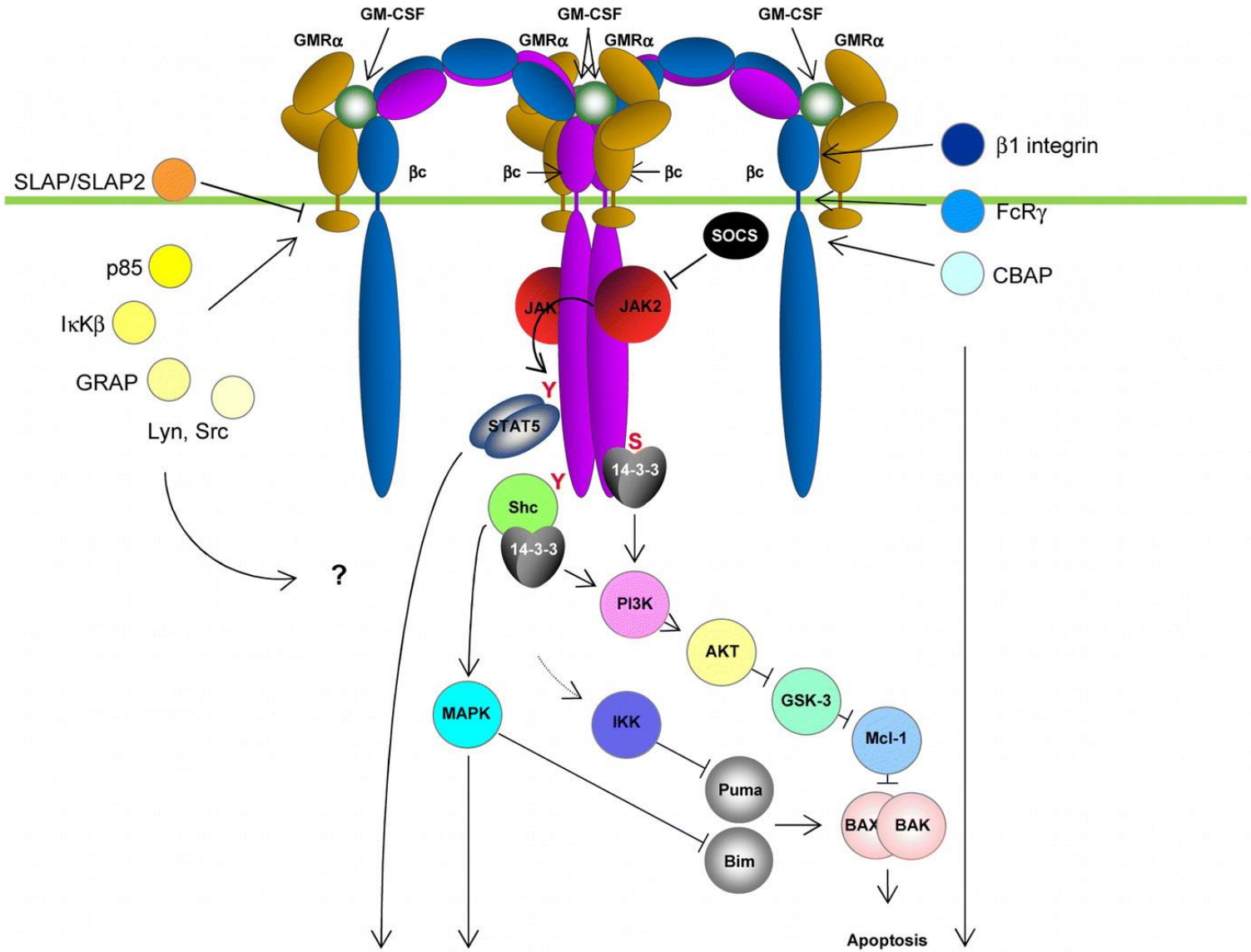
Growth Factors. 2012 Apr;30(2):63-75.

GM-CSF receptor activation



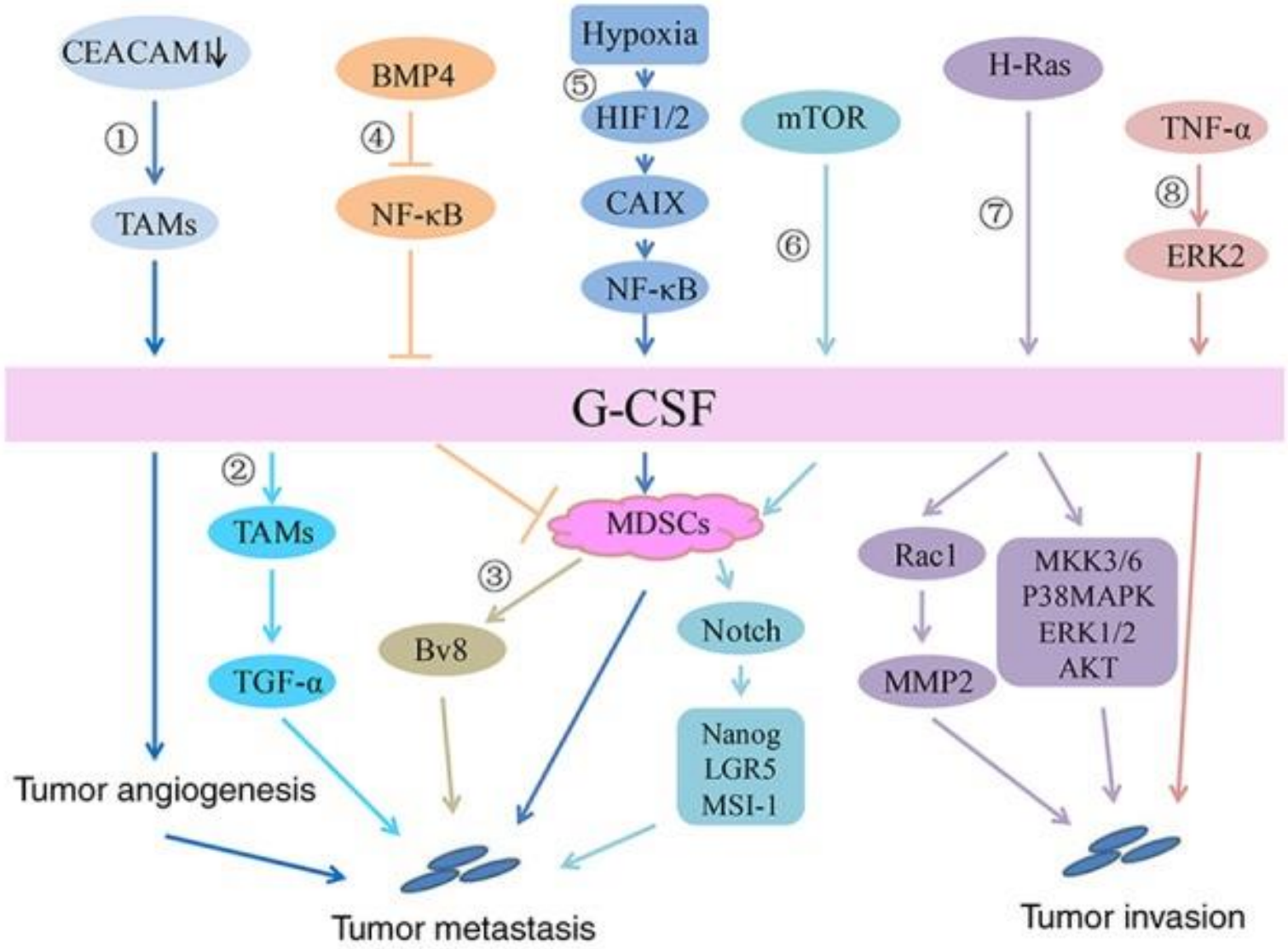
Blood. 2009 Aug 13;114(7):1289-98.

GM-CSF receptor complex: signaling pathways



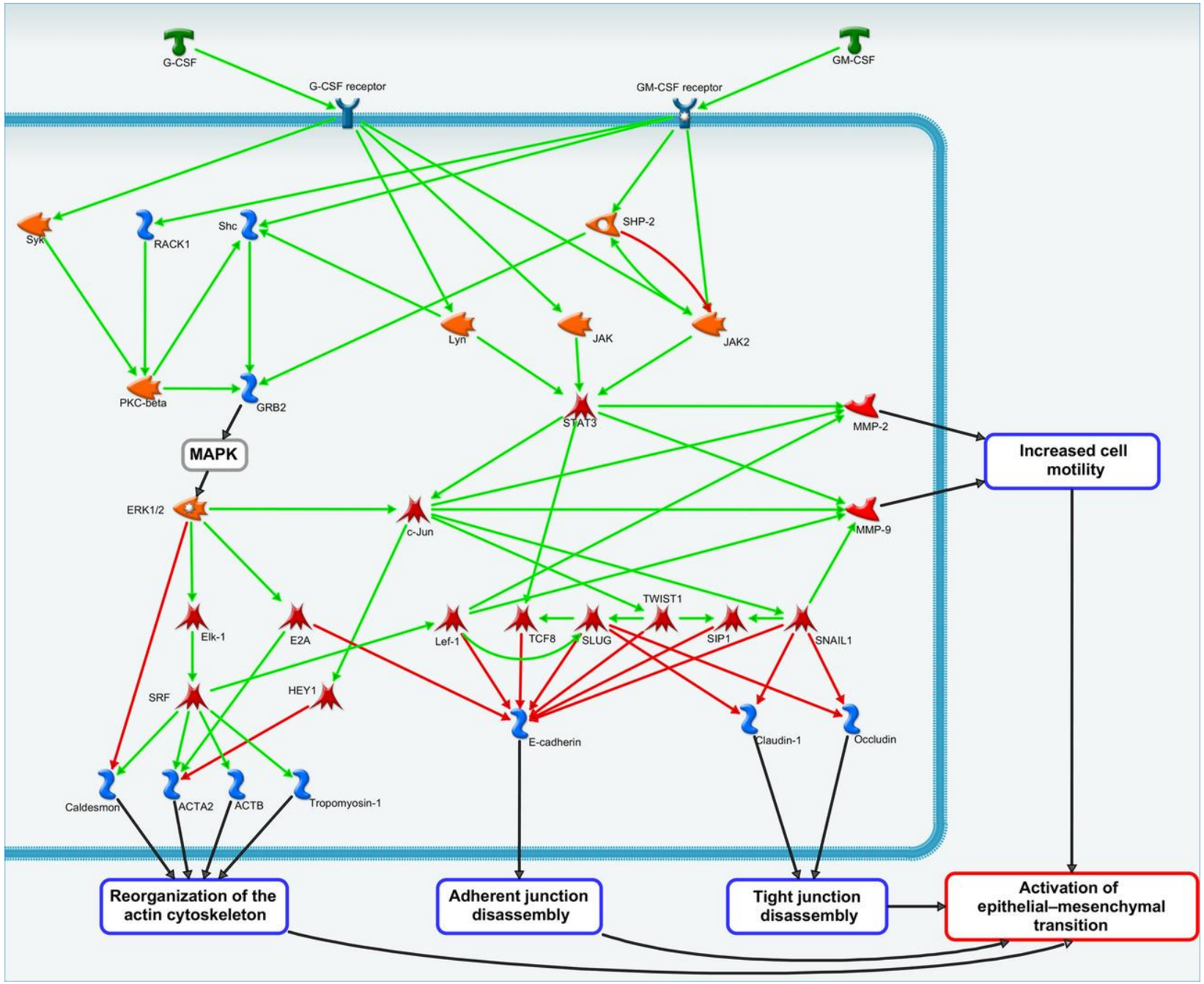
Growth Factors. 2012 Apr;30(2):63-75.

G-CSF signaling pathways



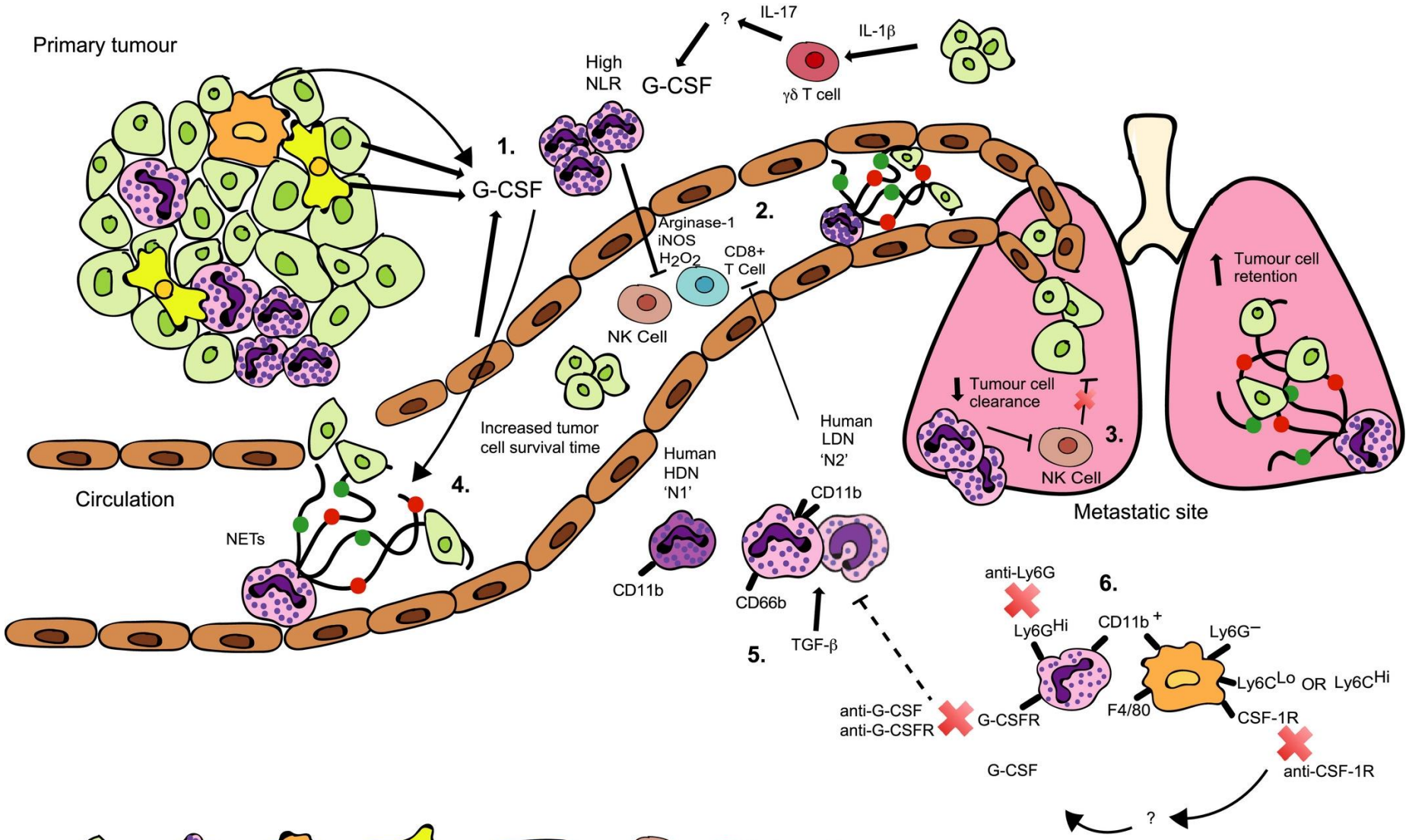
Mol Med Rep. 2020 May; 21(5): 2019–2029.

Putative signal pathways: EMT



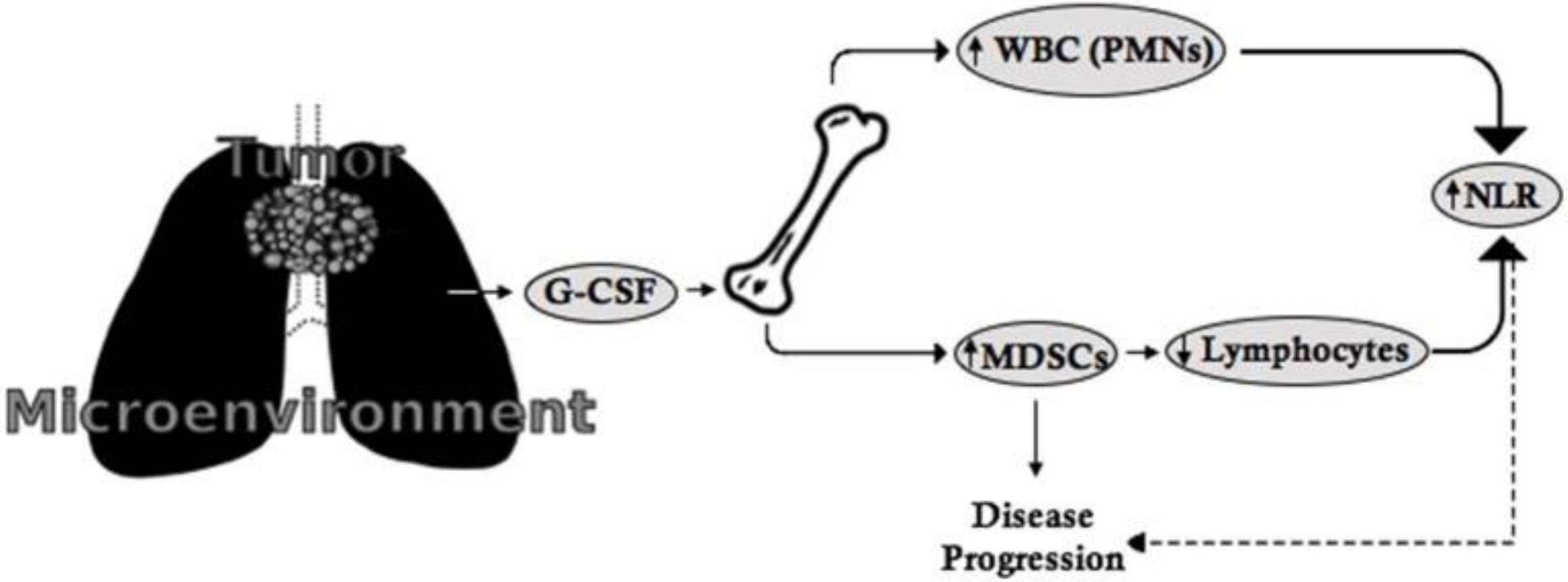
Cancer Medicine 2014;3(4):737–746.

G-CSF facilitates metastasis via tumour-promoting neutrophils



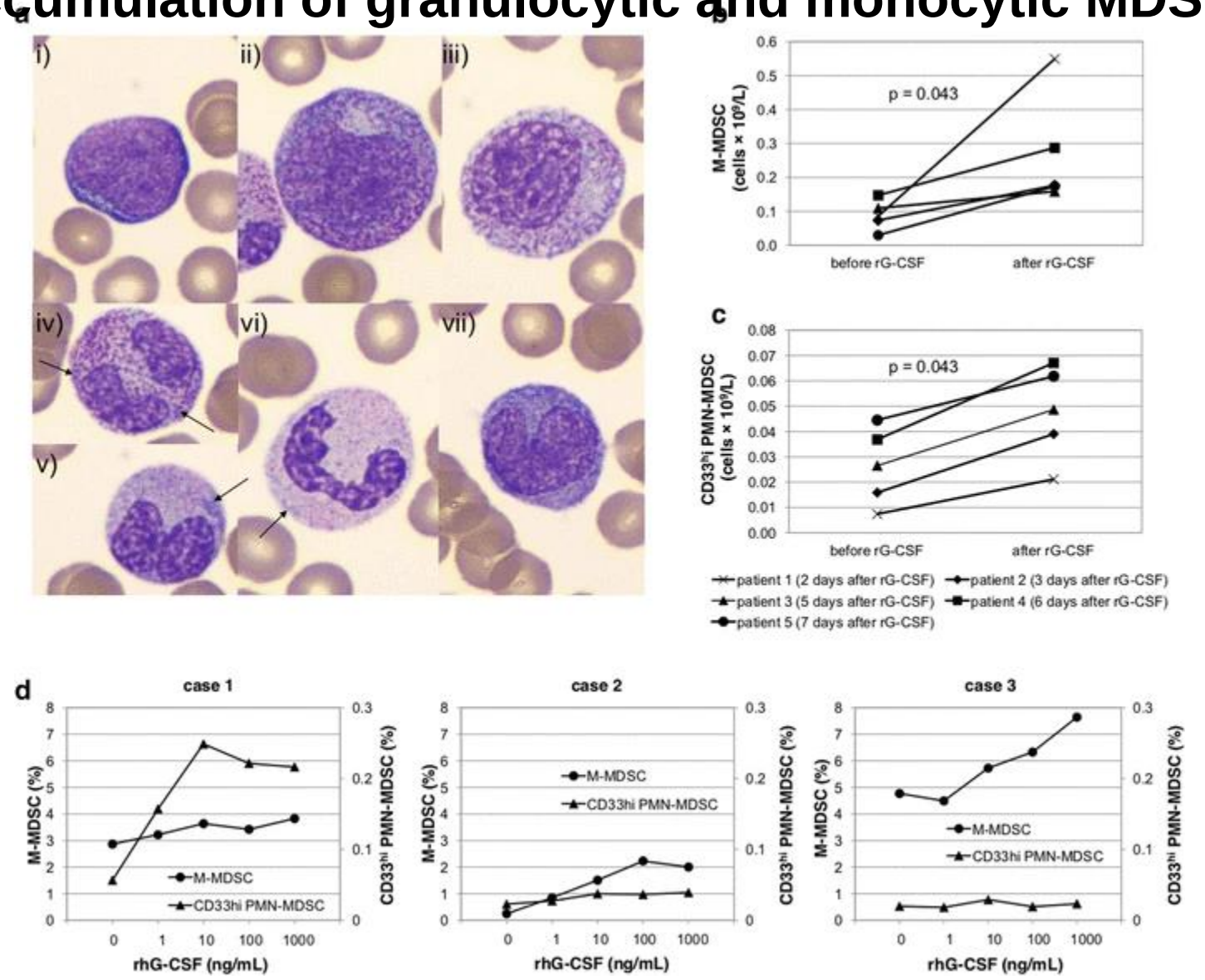
FEBS J. 2018 Feb;285(4):665-679.

G-CSF–MDSC–NLR paradigm



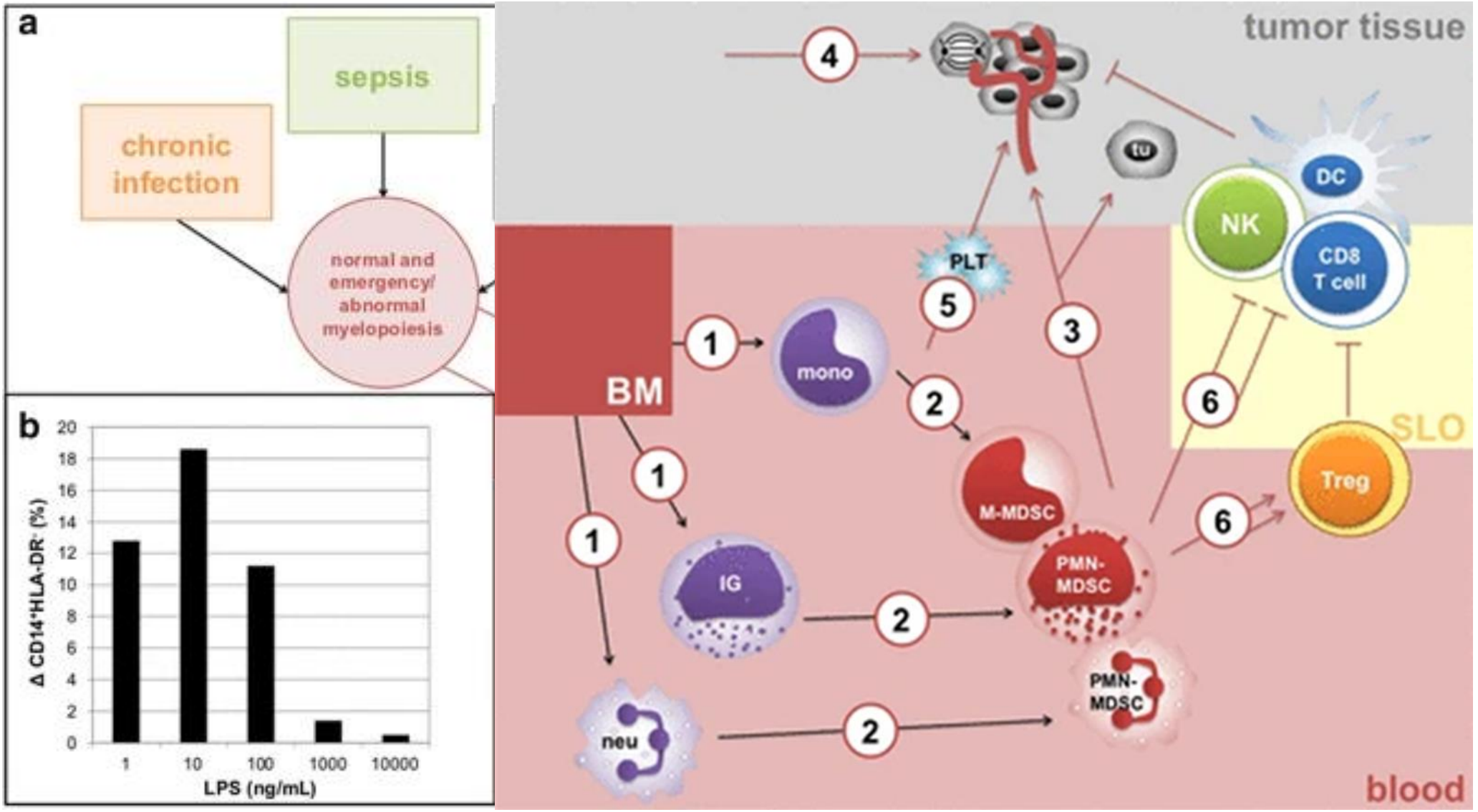
Front Oncol. 2019 Apr 26;9:295.

rhG-CSF triggers ‘emergency’ myelopoiesis and accumulation of granulocytic and monocytic MDSCs



Cancer Immunol Immunother. 2018;67:1919-1929.

rhG-CSF immunosuppressive and tumor-promoting actions



Cancer Immunol Immunother. 2018;67:1919-1929.

Pro- and antitumorigenic roles of G-CSF & GM-CSF

Tumor type	G-CSF	GM-CSF
NSCLC	**Angiogenic, immunosuppressive via MDSC**	
Glioma	Auto-/paracrine growth stimulation	
Bladder carcinoma	Auto-/paracrine growth stimulation	?
Colorectal cancer	Tumorigenic	Immune-mediated and immune-in dependent tumor suppression
Melanoma	Tumorigenic	Antiangiogenic via soluble VEGFR Tumorigenic via MDSC
Skin cancer	Synergistically tumorigenic and angiogenic	
Bone metastases	Sustain cancer stem cell phenotype	

Cancer Medicine 2014;3(4):737–746.

Introductions

- **Cytotoxic chemotherapy**
  → profound & sometimes prolonged **“neutropenia”**
  → **hospitalization** for treatment of **fever**
  /potentially **fatal infection**

- **Neutropenia:** pre-engraftment phase of HCT,
  induction therapy for acute leukemia
  → can also occur in standard-dose chemotherapy for other neoplasms

Definitions

- **Neutropenia**

  Severe neutropenia:

  ANC < 500/mm^3 or

  ANC that is expected to decrease to < 500/mm^3 during the next 48 hours

  Profound neutropenia: ANC < 100/mm^3

- **Fever**

  single temperature ≥ 38.3℃ or

  temperature ≥ 38℃ sustained over a 1 hour period

WBC growth factors, colony-stimulating factors

- **Recombinant human granulocyte colony stimulating factor (G-CSF):** filgrastim, pegfilgrastim

- **Granulocyte-macrophage colony stimulating factor (GM-CSF):** sargramostim

Definitions

- **Primary prophylaxis**

  : prophylactic use following the administration of chemotherapy when neutropenia is anticipated

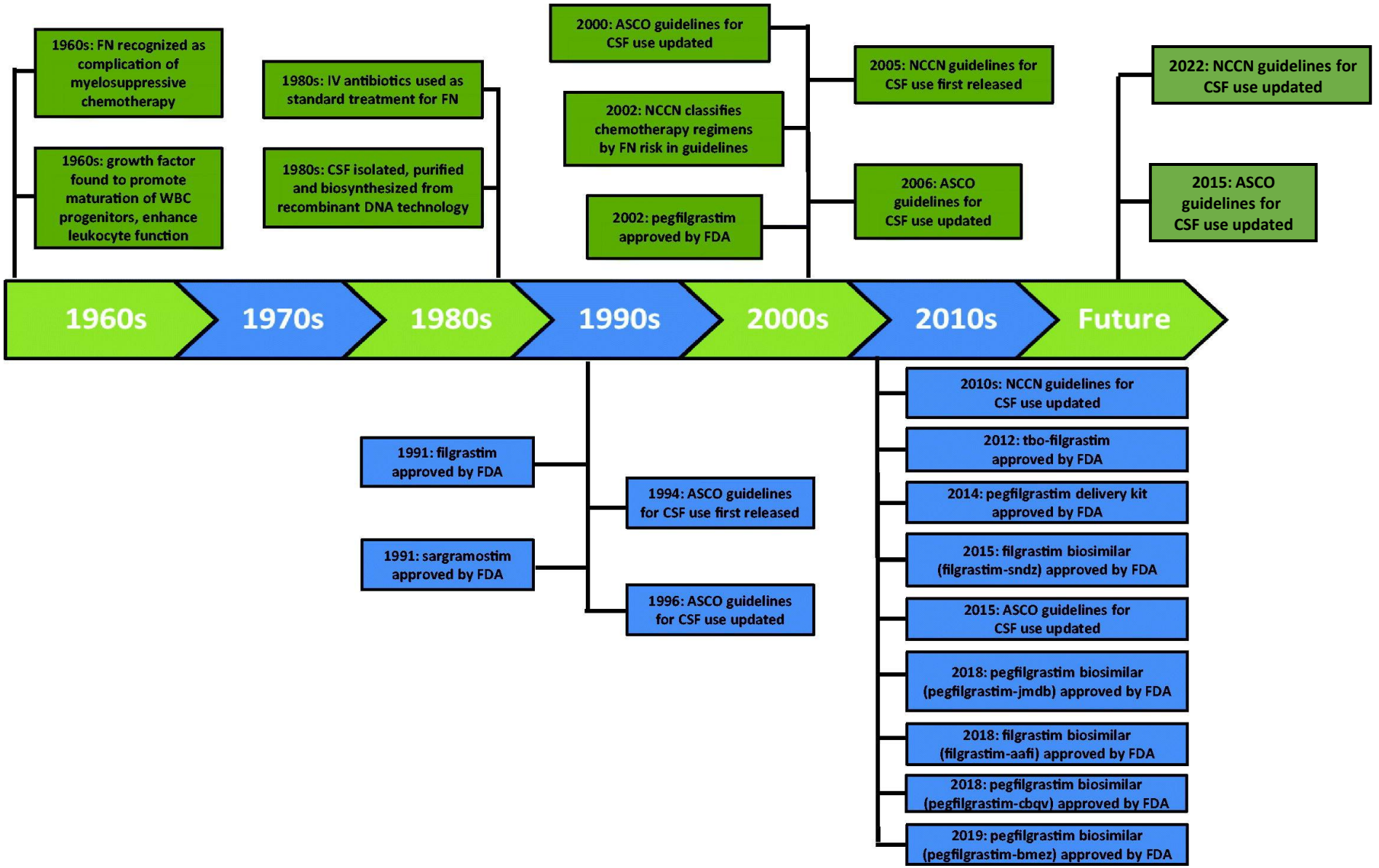
  : initiation of G-CSF during the first cycle and continuing through subsequent cycles of chemotherapy

- **Second prophylaxis**

  : prophylactic use during retreatment after a previous cycle of chemotherapy that causes neutropenic fever

  : administration of a G-CSF in subsequent chemotherapy cycles after neutropenic fever has occurred in a prior cycle

Evolution of CSF use



Curr Med Res Opin. 2020 Mar;36(3):483-495.

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Growth Factors

Version 1.2022 — December 22, 2021

NCCN.org

VOLUME 33 · NUMBER 28 · OCTOBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

Thomas J. Smith, Kari Bohlke, Gary H. Lyman, Kenneth R. Carson, Jeffrey Crawford, Scott J. Cross, John M. Goldberg, James L. Khatcheressian, Natasha B. Leighl, Cheryl L. Perkins, George Somlo, James L. Wade, Antoinette J. Wozniak, and James O. Armitage

Thomas J. Smith, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Kari Bohlke, American Society of Clinical Oncology, Alexandria; Scott J. Cross, Virginia Oncology Associates, Norfolk; James L. Khatcheressian, Virginia Cancer Institute, Richmond, VA; Gary H. Lyman, Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA; Kenneth R. Carson, Washington

A B S T R A C T

Purpose

To update the 2006 American Society of Clinical Oncology guideline on the use of hematopoietic colony-stimulating factors (CSFs).

clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v248–v251, 2010
doi:10.1093/annonc/mdq195

Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications

J. Crawford[1], C. Caserta[2] & F. Roila[2]

On behalf of the ESMO Guidelines Working Group*

[1]*Division of Medical Oncology, Department of Medicine, Duke University Medical Center, Durham, USA;* [2]*Department of Medical Oncology, S. Maria Hospital, Terni, Italy*

clinical review

Optimal Management of Neutropenic Fever in Patients With Cancer

Andrea J. Zimmer, MD[1] and Alison G. Freifeld, MD[1]

abstract

Febrile neutropenia remains an important complication of treatment with cytotoxic chemotherapy. It is often the first and sometimes the only sign or symptom of infection in this vulnerable patient population. Urgent and appropriate evaluation and treatment are imperative because delay in initiating appropriate antibiotic therapy may be life threatening. Selection of antibiotics should be based on the patient's symptoms, previous culture data, and institutional antibiograms. Ongoing therapy should be guided by culture and clinical data. Antimicrobial resistance is of great concern, particularly in this population, so careful attention to antibiotic selection and duration is needed.

J Oncol Pract 15:19-24.

IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v111–v118, 2016
doi:10.1093/annonc/mdw325

Management of febrile neutropaenia: ESMO Clinical Practice Guidelines†

J. Klastersky[1], J. de Naurois[2], K. Rolston[3], B. Rapoport[4], G. Maschmeyer[5], M. Aapro[6] & J. Herrstedt[7] on behalf of the ESMO Guidelines Committee*

[1]Institut Jules Bordet—Centre des Tumeurs de l'ULB, Brussels, Belgium; [2]St Luke's Cancer Centre, Royal Surrey County Hospital, Guildford, UK; [3]M.D. Anderson Cancer Center, Houston, TX, USA; [4]Medical Oncology Centre of Rosebank, Johannesburg, South Africa; [5]Department of Hematology, Oncology and Palliative Care, Ernst von Bergmann Hospital, Potsdam, Germany; [6]Multidisciplinary Institute of Oncology, Clinique de Genolier, Genolier, Switzerland; [7]Department of Oncology, Odense University Hospital (OUH), Odense, Denmark

Primary prophylaxis

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NCCN Guidelines Version 1.2022
Management of Neutropenia

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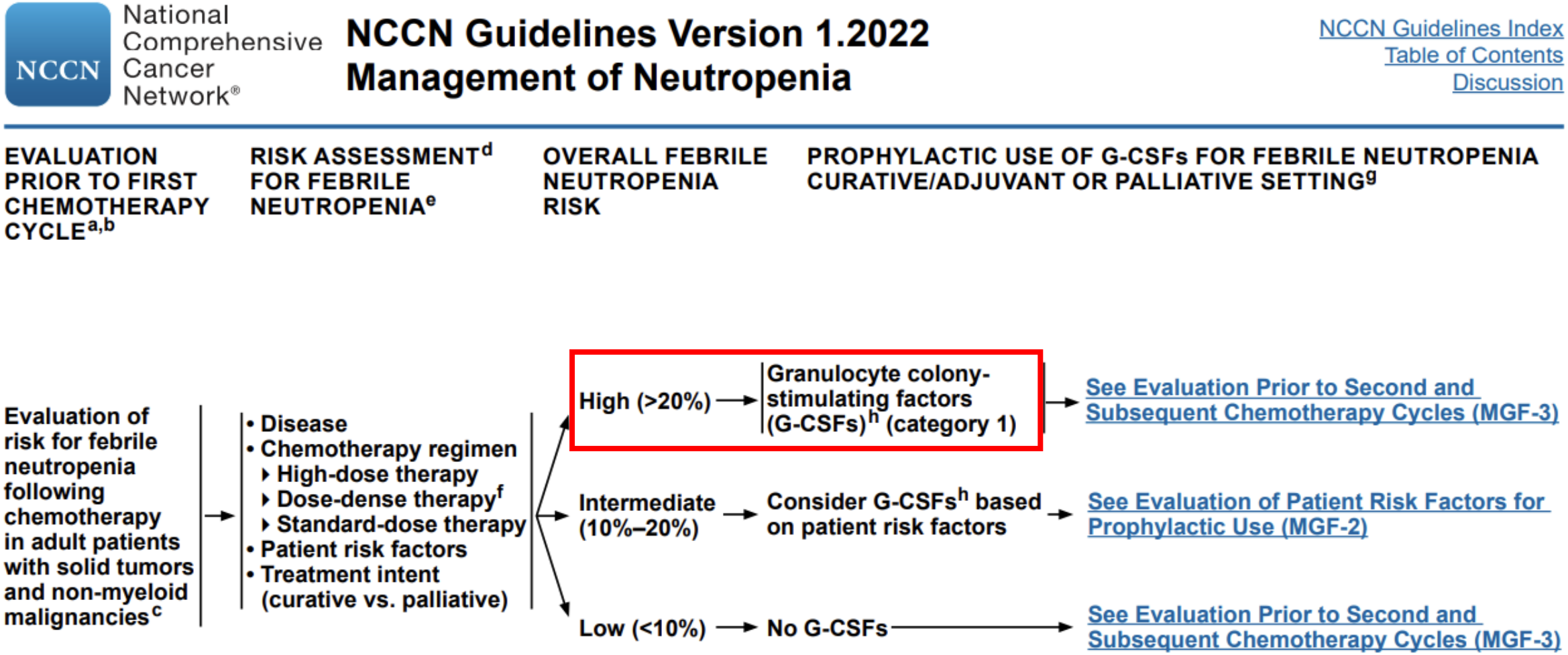


EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- *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 of Cancer by 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)
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

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

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

Bone Cancer
- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7,b]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,c] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Colorectal Cancer
FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)[11,d]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[12-14]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[15]
- Escalated BEACOPP[e] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[16]

Kidney Cancer
- Doxorubicin/gemcitabine[17]

Non-Hodgkin Lymphomas
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[18]
- ICE (ifosfamide, carboplatin, etoposide)[a,19,20]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[21,22]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[23]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[24]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[25]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[26,27]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[28]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[29] ± bortezomib (VTD-PACE)[30]

Ovarian Cancer
- Topotecan[a,31]
- Docetaxel[32]

Pancreatic Cancer
FOLFIRINOX[f] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[33]
- Doxorubicin[a,34]
- Ifosfamide/doxorubicin[35]

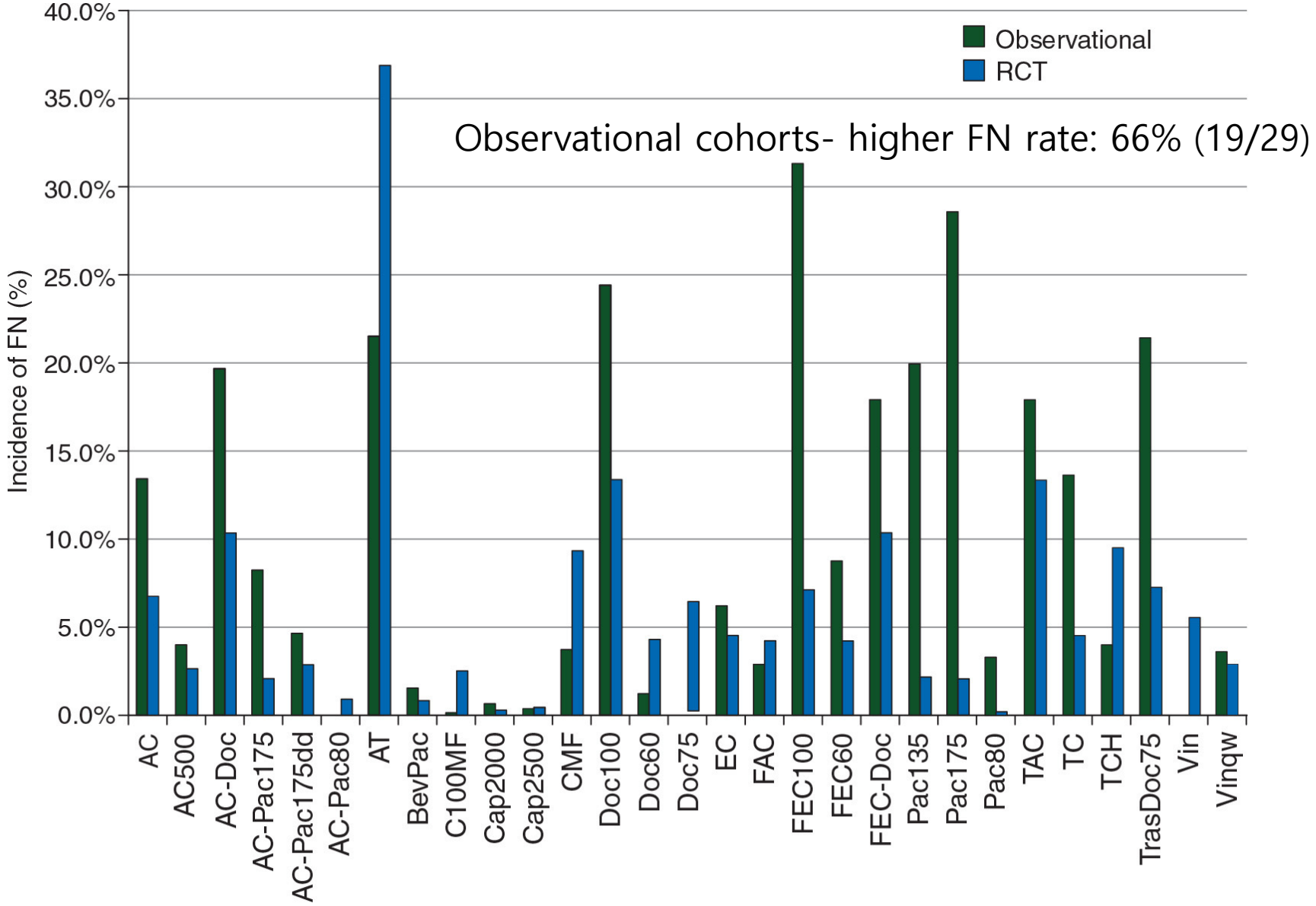
Small Cell Lung Cancer[g]
- Topotecan[36]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[37]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[38]

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

[e] Risk of bleomycin-induced pulmonary toxicity may be increased in patients

Incidence of FN for all chemotherapy regimens



*breast cancer-related chemotherapies

Ann Oncol. 2016 Apr;27(4):608-18.

Primary prophylaxis

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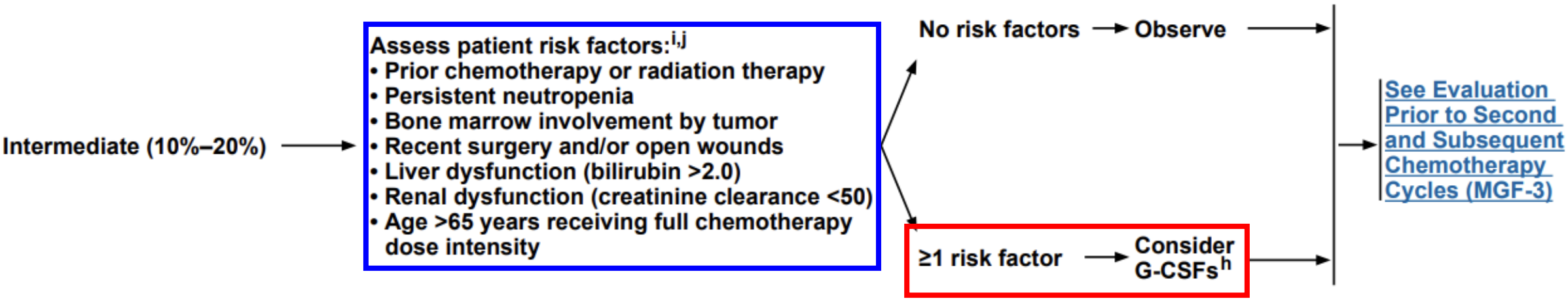


EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH AN INTERMEDIATE RISK FOR FEBRILE NEUTROPENIA (10%–20%)[a]

- ***This list is not comprehensive***; there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment of Cancer by 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)
- In general, dose-dense regimens require myeloid growth factor support to maintain dose intensity and schedule.

Occult Primary- Adenocarcinoma
- Gemcitabine/docetaxel[41]

Breast Cancer
- Docetaxel[a,42,43]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)[a,44]
- Paclitaxel every 21 days[a,45]

Cervical Cancer
- Cisplatin/topotecan[46-48]
- Paclitaxel/cisplatin[a,48]
- Topotecan[49]
- Irinotecan[50]

Colorectal Cancer
- FOLFOX[a] (fluorouracil, leucovorin, oxaliplatin)[h,51]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,52]

Non-Hodgkin Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,53]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[54,55] including regimens with pegylated liposomal doxorubicin[56,57]
- Bendamustine[a]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[58]
- Cisplatin/vinorelbine[59]
- Cisplatin/docetaxel[58,60]
- Cisplatin/etoposide[61]
- Carboplatin/paclitaxel[a,i,62]
- Docetaxel[60]

Ovarian Cancer
- Carboplatin/docetaxel[63]

Prostate Cancer
- Cabazitaxel[j,64]

Small Cell Lung Cancer[g]
- Etoposide/carboplatin[65]

Testicular Cancer
- BEP[e] (bleomycin, etoposide, cisplatin)[66-68]
- Etoposide/cisplatin[69]

Uterine Sarcoma
- Docetaxel[70]

ASCO guideline 2015

CLINICAL QUESTION 1

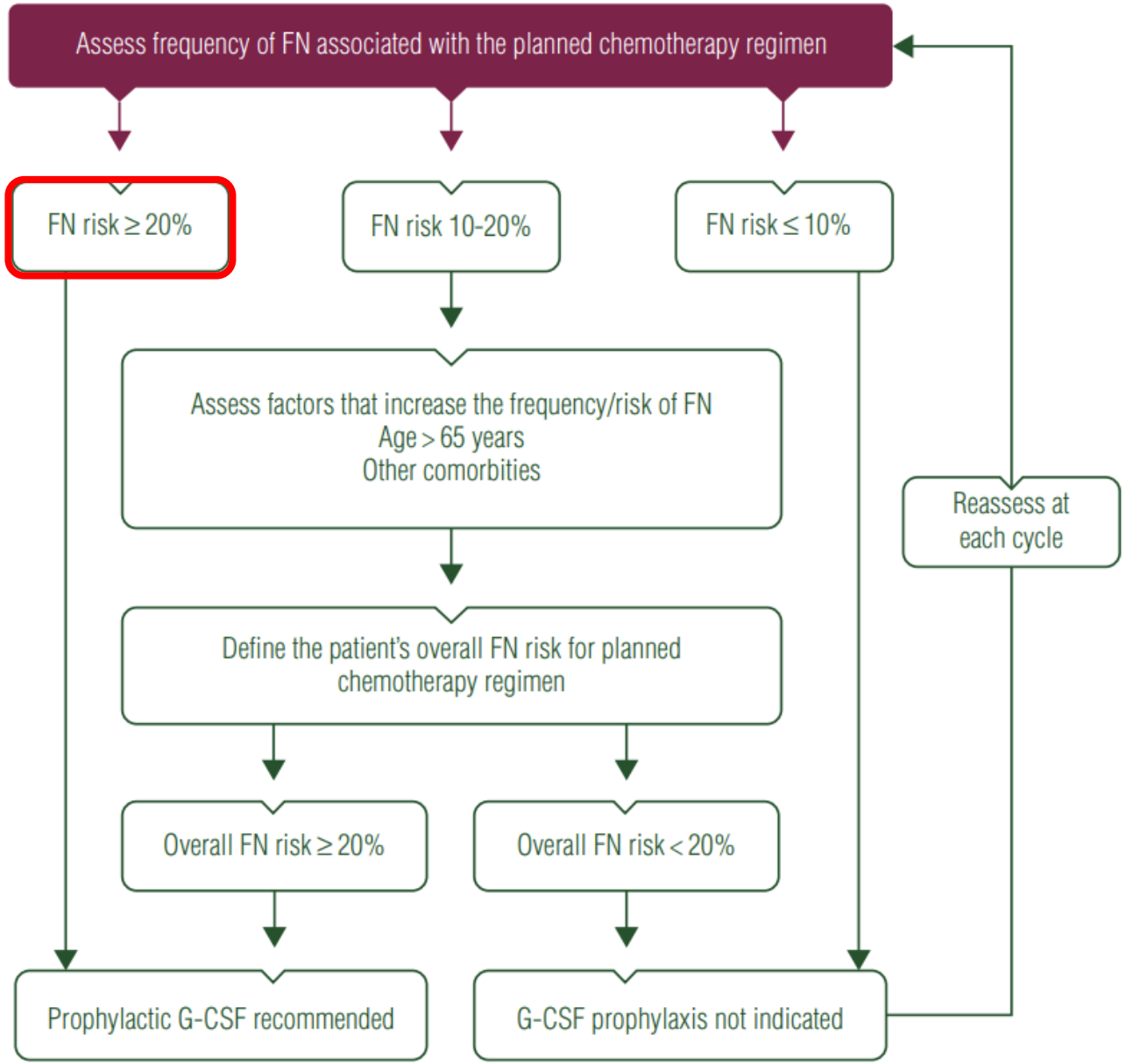
In adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians consider when selecting patients for primary prophylaxis of febrile neutropenia with a CSF?

Recommendation 1

Primary prophylaxis with a CSF starting in the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia on the basis of patient-, disease-, and treatment-related factors. Primary CSF prophylaxis should also be administered in patients receiving dose-dense chemotherapy when considered appropriate. Consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSF support when available. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

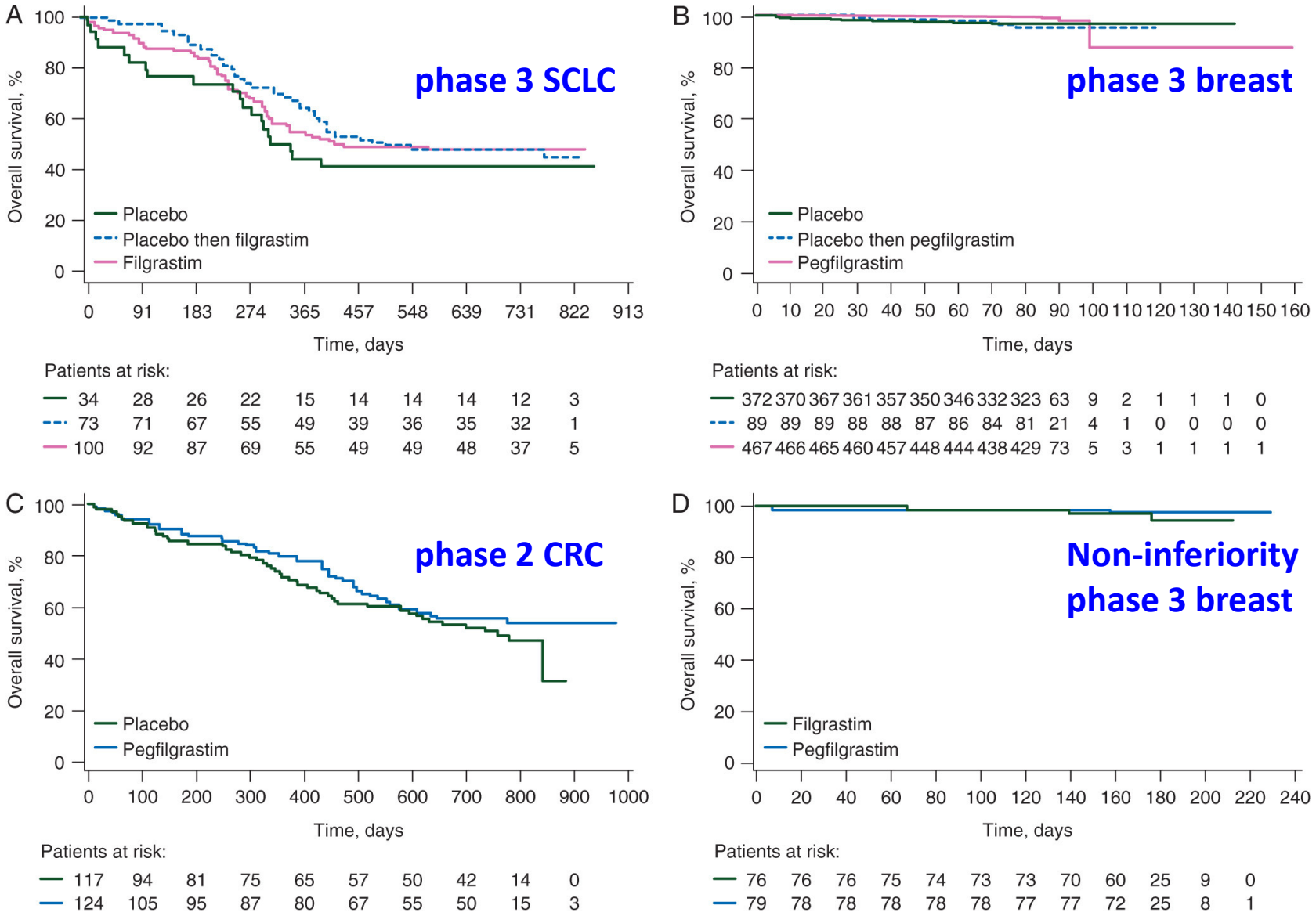
ESMO guideline 2015

Algorithm to decide primary prophylaxis



ESMO guideline 2016

Overall survivals: G-CSF vs. placebo



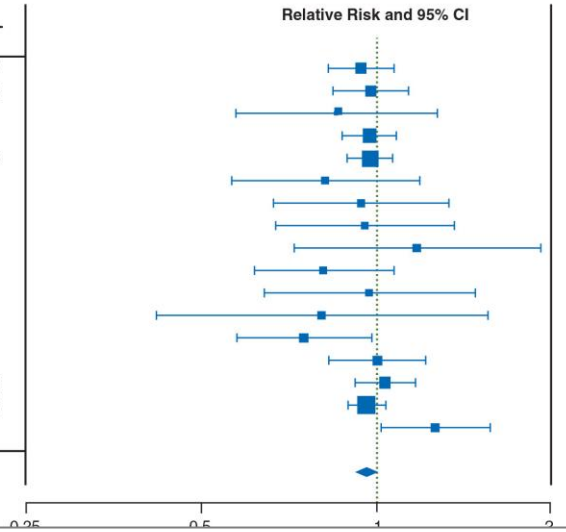
Ann Oncol. 2015 Jul;26(7):1452-8.

Mortality: Primary G-CSF support vs. Control

A

Statistics for each study

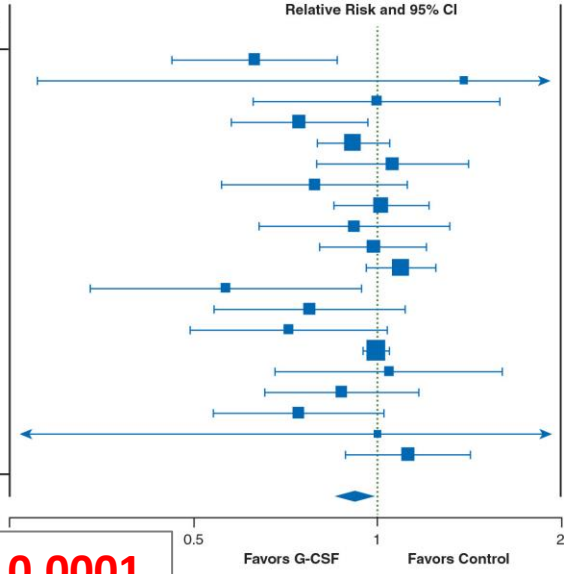
	Relative Risk	Lower Limit	Upper Limit	*P*-value	Dead/Total G-CSF	Dead/Total Control
Burton	0.94	0.82	1.07	0.33	199/387	218/397
Doorduijn	0.97	0.84	1.13	0.74	123/197	123/192
Fossa	0.85	0.57	1.27	0.42	32/129	38/130
Fukuoka	0.97	0.87	1.08	0.57	30/32	30/31
Gatzemeier	0.97	0.88	1.06	0.52	120/141	122/139
Gisselbrecht	0.81	0.56	1.18	0.28	30/82	36/80
Papaldo	0.94	0.66	1.33	0.72	49/254	50/243
Pettengell	0.95	0.67	1.36	0.78	24/41	24/39
Veyret	1.17	0.72	1.91	0.53	23/61	19/59
Woll	**0.81**	**0.61**	**1.07**	**0.13**	**23/34**	**26/31**
Zinzani	0.97	0.64	1.48	0.89	28/77	27/72
Fridrik	0.80	0.41	1.55	0.51	11/38	13/36
Osby	0.75	0.57	0.98	0.03	45/101	62/104
Osby	1.00	0.82	1.21	1.00	69/103	67/100
Smith	1.03	0.91	1.17	0.63	184/282	176/278
Pinter	**0.96**	**0.89**	**1.04**	**0.29**	**312/422**	**326/423**
Shah	**1.26**	**1.01**	**1.56**	**0.04**	**27/31**	**38/54**
RE Model	0.97	0.93	1.01			



C

Statistics for each study

	Relative Risk	Lower Limit	Upper Limit	*P*-value	Dead/Total G-CSF	Dead/Total Control
Diehl	0.63	0.46	0.86	0.003	55/466	88/469
Pan	1.38	0.28	6.91	0.69	3/13	2/12
Pfreundschuh	0.99	0.62	1.58	0.98	30/195	30/194
Ardizzoni	0.74	0.58	0.96	0.05	41/67	23/28
Bonomi	0.91	0.79	1.04	0.17	114/191	251/383
Del Mastro	**1.06**	**0.79**	**1.41**	**0.70**	**44/77**	**40/74**
Dhingra	0.79	0.55	1.12	0.18	34/100	44/102
Forastiere	1.01	0.85	1.21	0.89	72/101	69/98
Fountzilas	0.92	0.64	1.31	0.63	35/93	37/90
Heigener	0.98	0.81	1.20	0.88	33/40	31/37
Henderson	1.09	0.96	1.24	0.20	260/1033	482/2088
Masutani	0.57	0.34	0.94	0.02	13/38	23/38
Masutani	0.77	0.54	1.11	0.16	24/50	31/50
Moebus	**0.72**	**0.49**	**1.04**	**0.08**	**43/585**	**60/584**
Omura	0.99	0.95	1.05	0.82	157/166	156/164
Ray-Coquard	1.04	0.68	1.60	0.85	26/73	28/82
Riccardi	0.87	0.65	1.17	0.36	24/36	29/38
Untch	0.74	0.54	1.03	0.07	52/330	71/335
Dhanraj	**1.00**	**0.14**	**6.91**	**1.00**	**2/74**	**2/74**
Hertzberg	**1.12**	**0.88**	**1.42**	**0.35**	**71/126**	**60/120**
RE Model	0.92	0.85	0.99			

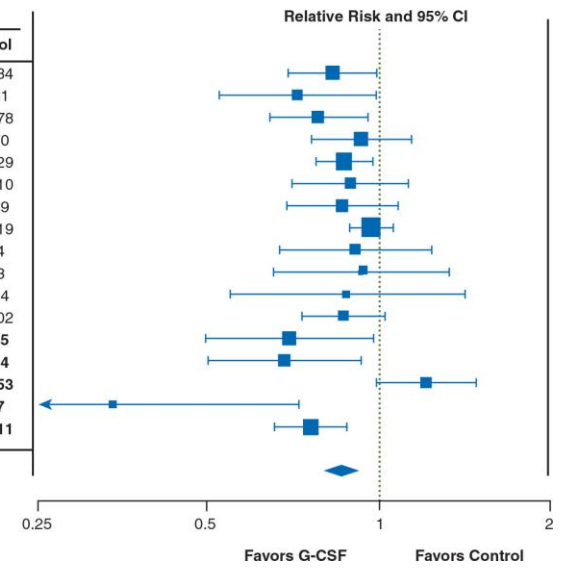


RR=0.92; 95% CI 0.90–0.95; ARD=−3.3%; 95% CI −4.2–−2.4; P < 0.0001

B

Statistics for each study

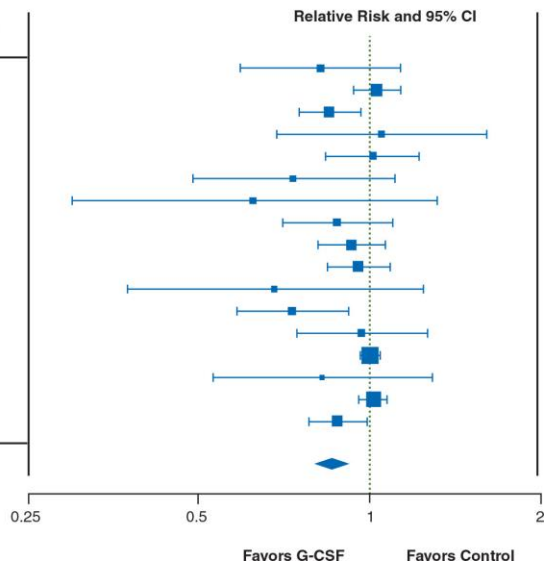
	Relative Risk	Lower Limit	Upper Limit	*P*-value	Dead/Total G-CSF	Dead/Total Control
Citron	0.83	0.69	1.00	0.05	168/988	202/984
Pfreundschuh	0.72	0.52	0.99	0.04	52/349	75/361
Pfreundschuh	0.78	0.64	0.95	0.01	80/172	106/178
Pfreundschuh	0.93	0.76	1.14	0.48	85/169	92/170
Sternberg	0.87	0.77	0.98	0.02	101/134	112/129
Venturini	0.89	0.70	1.13	0.34	104/604	118/610
Verdonck	0.86	0.69	1.08	0.20	85/238	99/239
Ardizzoni	0.97	0.89	1.06	0.51	109/125	107/119
Capotorto	0.91	0.66	1.24	0.54	26/42	30/44
De Boer	0.93	0.65	1.33	0.69	11/14	11/13
Economopoulos	0.88	0.54	1.42	0.59	23/103	29/114
Thatcher	0.87	0.73	1.03	0.10	106/201	123/202
Del Mastro	**0.69**	**0.49**	**0.98**	**0.04**	**48/502**	**75/545**
Del Mastro	**0.68**	**0.50**	**0.93**	**0.02**	**55/500**	**88/544**
Lin	**1.21**	**0.99**	**1.49**	**0.07**	**132/349**	**110/353**
Payandeh	**0.34**	**0.16**	**0.72**	**0.002**	**7/66**	**25/77**
Moebus	**0.76**	**0.65**	**0.88**	**0.0002**	**199/641**	**251/611**
RE Model	0.86	0.80	0.92			



D

Statistics for each study

	Relative Risk	Lower Limit	Upper Limit	*P*-value	Dead/Total G-CSF	Dead/Total Control
Burnell	0.82	0.59	1.13	0.23	47/701	115/1403
Fleming	1.03	0.93	1.13	0.59	136/160	130/157
Fleming	0.85	0.75	0.96	0.01	97/134	110/129
Fumoleau	1.05	0.68	1.61	0.83	28/76	26/74
Therasse	1.01	0.83	1.22	0.92	109/224	108/224
Brodin	0.73	0.49	1.10	0.11	11/18	20/24
Frasci	0.63	0.30	1.31	0.21	10/100	16/100
Furuse	0.88	0.70	1.10	0.25	61/114	69/113
Georgoulias	0.93	0.81	1.06	0.28	115/167	113/152
Homesley	0.95	0.84	1.09	0.48	72/88	78/91
Kummel	0.68	0.37	1.24	0.21	15/108	22/108
Maurel	0.73	0.58	0.92	0.01	39/65	55/67
Mavroudis	0.97	0.74	1.26	0.80	38/62	45/71
Niell	1.00	0.96	1.04	0.99	265/283	264/282
Sekine	0.82	0.53,	1.28	0.39	21/55	25/54
Sledge	1.01	0.95	1.07	0.77	202/230	389/447
Goto	**0.88**	**0.78**	**0.99**	**0.03**	**72/90**	**82/90**
RE Model	0.94	0.89	0.99			



Ann Oncol. 2018;29:1903-1910.

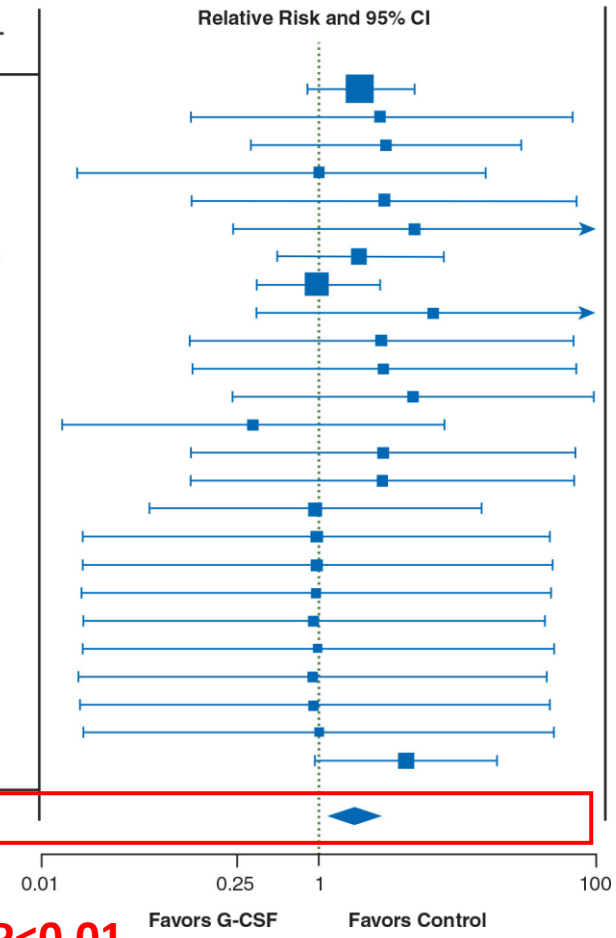
Secondary malignancies: Primary G-CSF support vs. Control

All eligible studies

A

Statistics for each study

	Relative Risk	Lower Limit	Upper Limit	*P*-value	Event/Total G-CSF	Event/Total Control
Diehl	2.01	0.82	4.94	0.13	14/466	7/469
Pettengell	2.86	0.12	68.10	0.52	1/41	0/39
Pfreundschuh	3.10	0.32	29.69	0.33	3/349	1/361
Pfreundschuh	1.02	0.06	16.25	0.99	1/341	1/348
Verdonck	3.01	0.12	73.58	0.50	1/238	0/239
Pfreundschuh	4.97	0.24	102.95	0.30	2/195	0/194
Burnell	2.00	0.50	7.98	0.33	4/701	4/1403
Citron	1.00	0.35	2.83	0.99	7/988	7/984
Fumoleau	6.82	0.36	129.76	0.20	3/76	0/74
Papaldo	2.87	0.12	70.13	0.52	1/254	0/243
Therasse	3.00	0.12	73.25	0.50	1/224	0/224
Veyret	4.84	0.24	98.71	0.31	2/61	0/59
Fossa	0.34	0.01	8.17	0.50	0/129	1/130
Fleming	2.94	0.12	71.73	0.51	1/160	0/157
Fleming	2.89	0.12	70.27	0.51	1/134	0/129
Sternberg	0.96	0.06	15.23	0.98	1/134	1/129
Fukuoka	0.97	0.02	47.41	0.99	0/32	0/31
Gatzemeier	0.99	0.02	49.34	0.99	0/141	0/139
Gisselbrecht	0.98	0.02	48.60	0.99	0/82	0/80
Pan	0.93	0.02	43.49	0.97	0/13	0/12
Venturini	1.01	0.02	50.81	1.00	0/604	0/610
Woll	**0.91**	**0.02**	**44.74**	**0.96**	**0/34**	**0/31**
Zinzani	0.94	0.02	46.56	0.97	0/77	0/72
Untch	1.02	0.02	51.01	0.99	0/330	0/335
Moebus	**4.29**	**0.93**	**19.77**	**0.06**	**9/641**	**2/611**
RE Model	1.85	1.19	2.88			



RR=1.85; 95% CI 1.19–2.88;

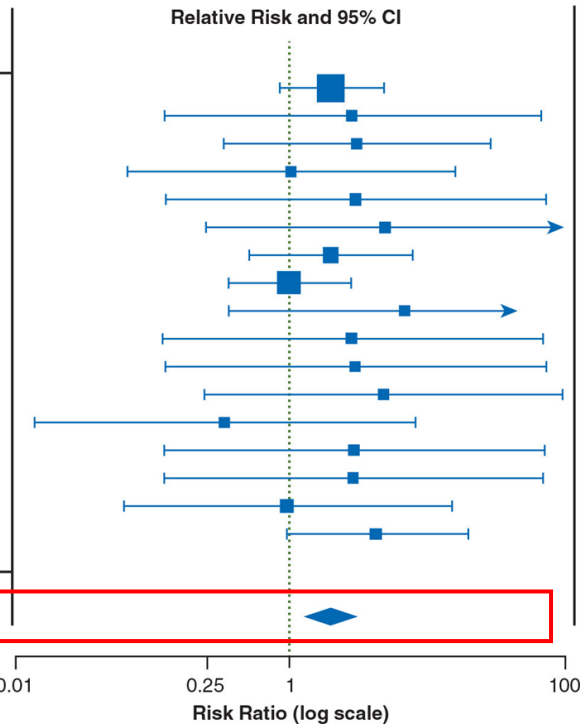
ARD=0.47; 95% CI 0.21–0.73; P<0.01

Excluding studies with zero cases

B

Statistics for each study

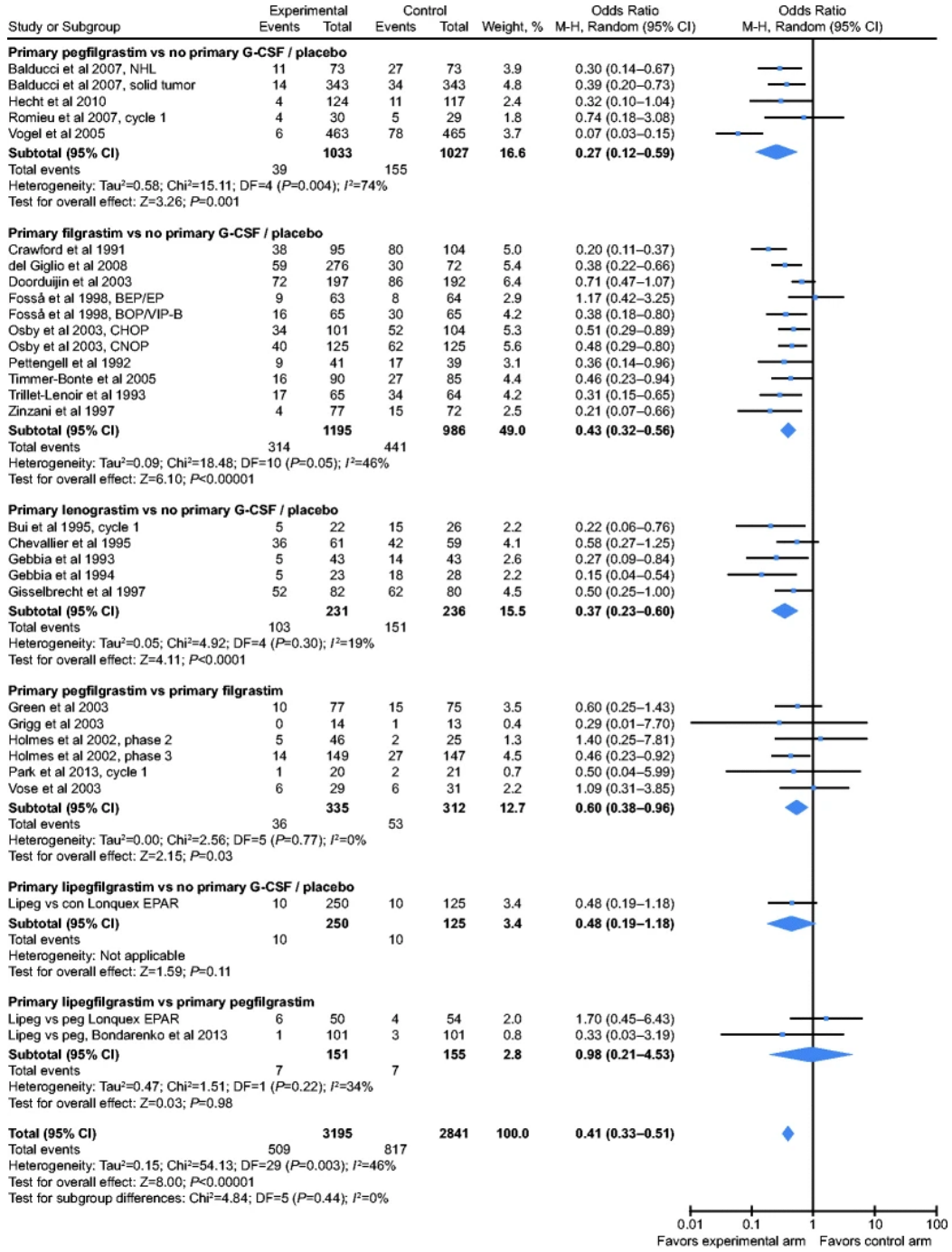
	Relative Risk	Lower Limit	Upper Limit	*P*-value	Event/Total G-CSF	Event/Total Control
Diehl	2.01	0.82	4.94	0.13	14/466	7/469
Pettengell	2.86	0.12	68.10	0.52	1/41	0/39
Pfreundschuh	3.10	0.32	29.69	0.33	3/349	1/361
Pfreundschuh	1.02	0.06	16.25	0.99	1/341	1/348
Verdonck	3.01	0.12	73.58	0.50	1/238	0/239
Pfreundschuh	4.97	0.24	102.95	0.30	2/195	0/194
Burnell	2.00	0.50	7.98	0.33	4/701	4/1403
Citron	1.00	0.35	2.83	0.99	7/988	7/984
Fumoleau	6.82	0.36	129.76	0.20	3/76	0/74
Papaldo	2.87	0.12	70.13	0.52	1/254	0/243
Therasse	3.00	0.12	73.25	0.50	1/224	0/224
Veyret	4.84	0.24	98.71	0.31	2/61	0/59
Fossa	0.34	0.01	8.17	0.50	0/129	1/130
Fleming	2.94	0.12	71.73	0.51	1/160	0/157
Fleming	2.89	0.12	70.27	0.51	1/134	0/129
Sternberg	0.96	0.06	15.23	0.98	1/134	1/129
Moebus	**4.29**	**0.93**	**19.77**	**0.06**	**9/641**	**2/611**
RE Model	1.99	1.25	3.18			



RR=1.99; 95% CI 1.25–3/18

Ann Oncol. 2018;29:1903-1910.

Risk of febrile neutropenia
G-CSF: meta-analysis



Support Care Cancer. 2015;23:3131-40.

"과립세포군 촉진인자(G-CSF) 주사제의 건강보험 확대를 통해 암환자의 치료율 향상 기대"
-보건복지부 고시 (2016. 8. 31.)

약제명	현 행	개 선
· Pegfilgrastim (품명:뉴라스타프리필드시린지주) · Pegteograstim (품명:뉴라펙프리필드시린지주) · Tripegfilgrastim (품명:듀라스틴주사액프리필드시린지) · Lipegfilgrastim (품명:롱퀵스프리필드주) • Eflapegrastim (2021.10.28.) (품명: 롤론티스프리필드시린지주)	예방적 투여가 가능한 대상 총 5개 암종 11개 요법 1) 발열성 호중구 감소증 위험이 20% 이상 ▪ 유방암 2개 요법 ▪ 비호지킨림프종 5개 요법 ▪ 호지킨림프종 1개 요법 ▪ 생식세포종양 1개 요법 ▪ 고환암 3개 요법 (생식세포종양과 1개 요법 동일)	예방적 투여가 가능한 대상 총 10개 암종 40개 요법 1) 발열성 호중구 감소증 위험이 20%이상(암종, 요법 확대) ▪ 유방암 2개 요법 ▪ 비호지킨림프종 6개 요법 ▪ 호지킨리프종 2개 ▪ 생식세포종양 3개(고환암 포함) ▪ 방광암 1개 ▪ 골암 6개 ▪ 중추신경계암 2개 ▪ 연조직육종 4개 ▪ 횡문근육종 2개 ▪ 신경모세포종 1개 2) 발열성 호중구 감소증 위험이 10-20%(신설) - 65세 이상 또는 이전 항암요법 투여시 발열성 호중구감소증 등이 있었던 환자 ▪ 유방암 6개 ▪ 방광암 1개 ▪ 비호지킨림프종 2개 ▪ 호지킨림프종 1개 ▪ 생식세포종양 1개
· Filgrastim (품명:그라신주 등) · Lenograstim (품명:뉴트로진주)	예방적 투여는 불인정 급여기준의 호중구수 수치에 해당하는 경우 인정	소아 암환자의 예방적 투여 인정. ▪ 성인과 동일한 요법

Secondary prophylaxis

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Management of Neutropenia

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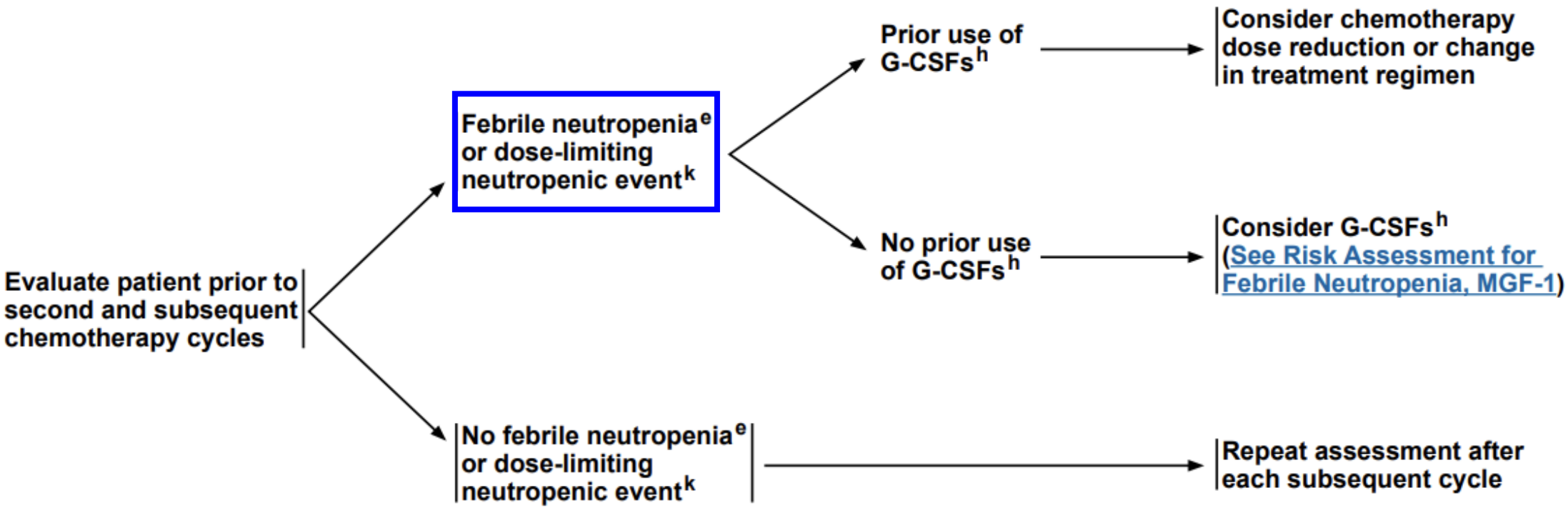
EVALUATION PRIOR TO SECOND AND SUBSEQUENT CHEMOTHERAPY CYCLES

SECONDARY PROPHYLAXIS



ASCO guideline 2015

CLINICAL QUESTION 2

Among adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians use to select patients for secondary prophylaxis of febrile neutropenia with a CSF?

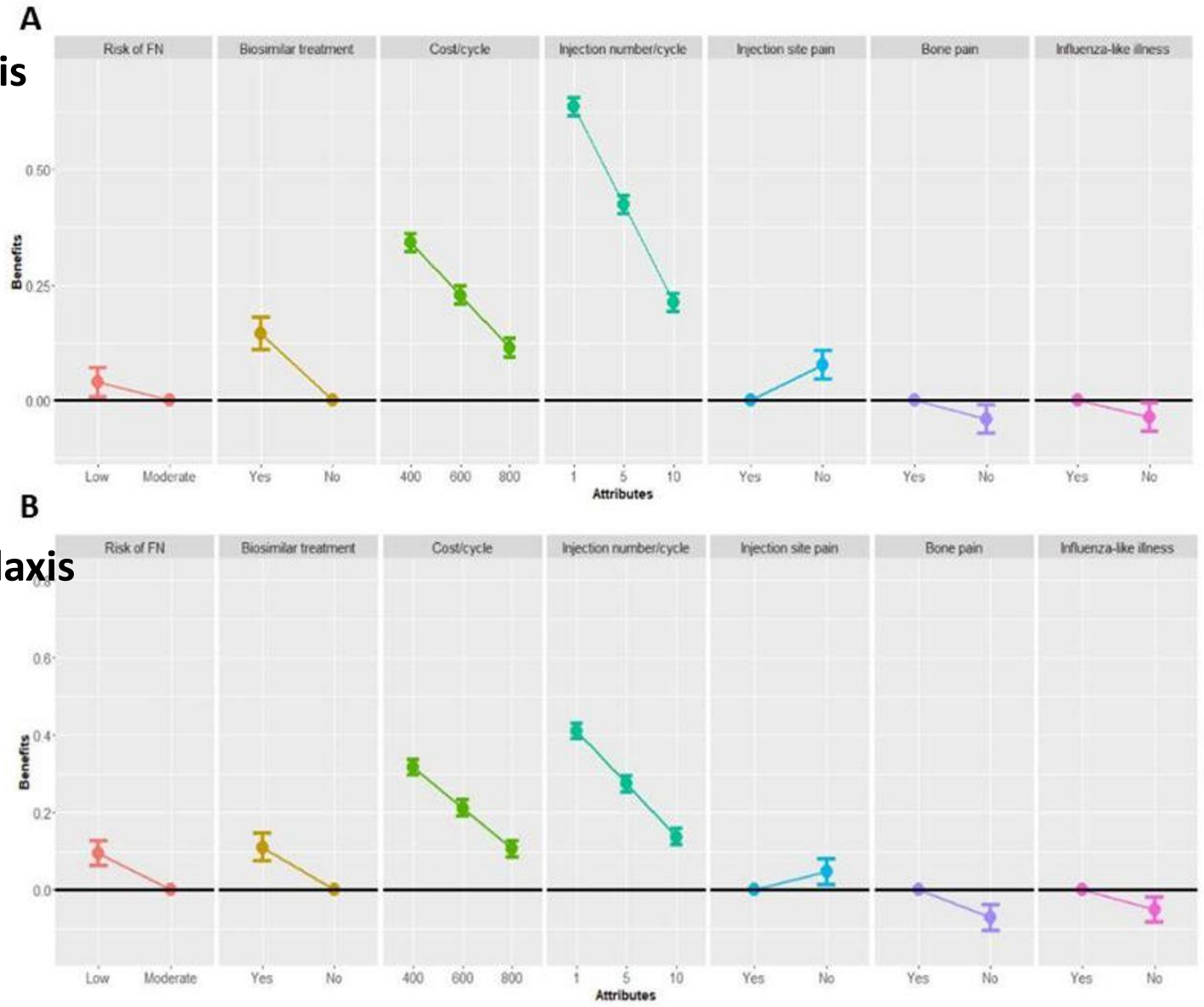
Recommendation 2

Secondary prophylaxis with CSFs is recommended for patients who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or OS or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

Physicians' preferences for G-CSF

Primary prophylaxis

Secondary prophylaxis



BMJ Support Palliat Care. 2021 Oct 27;bmjspcare-2021-003082.

Febrile neutropenia

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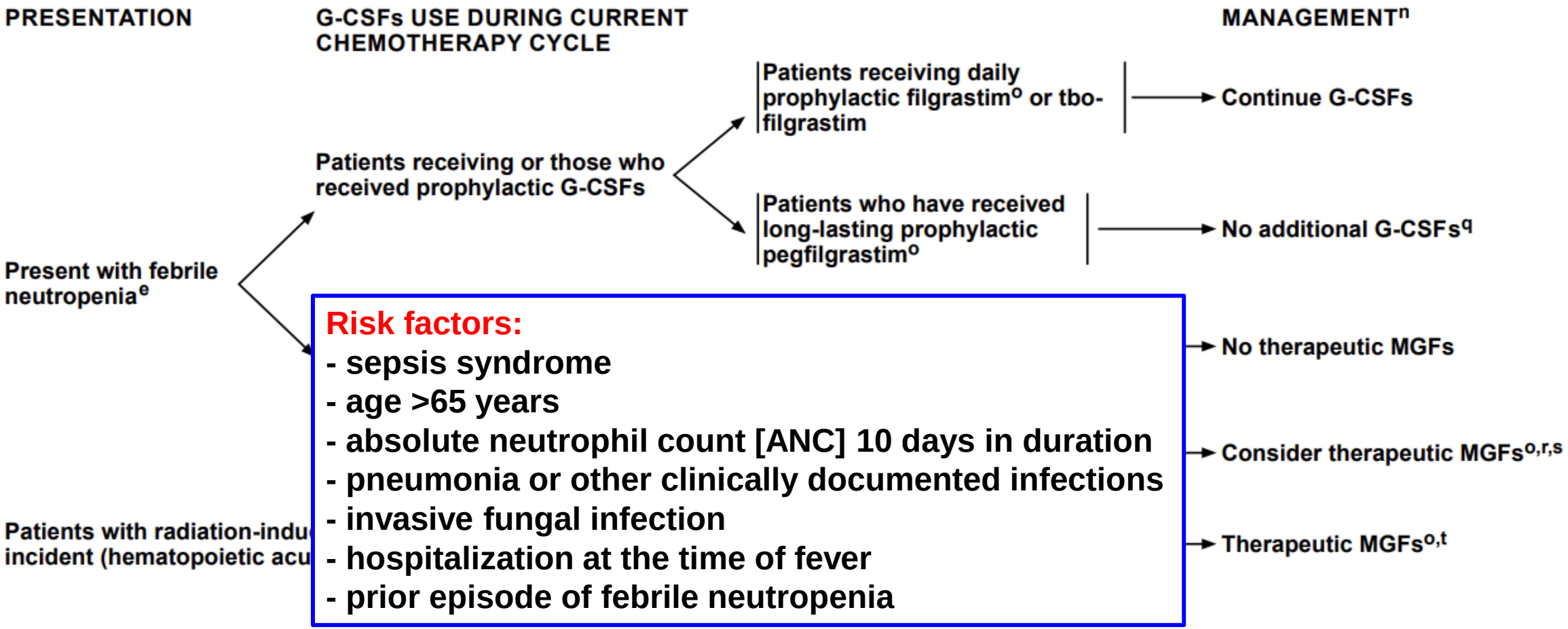
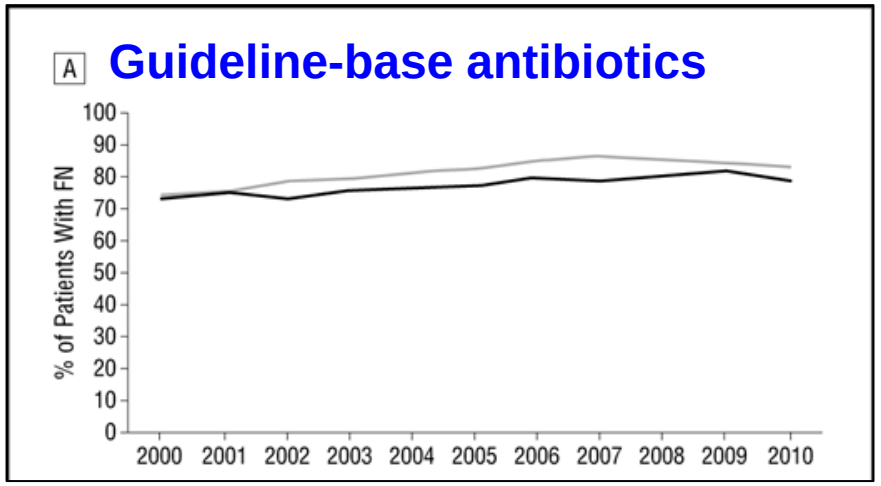
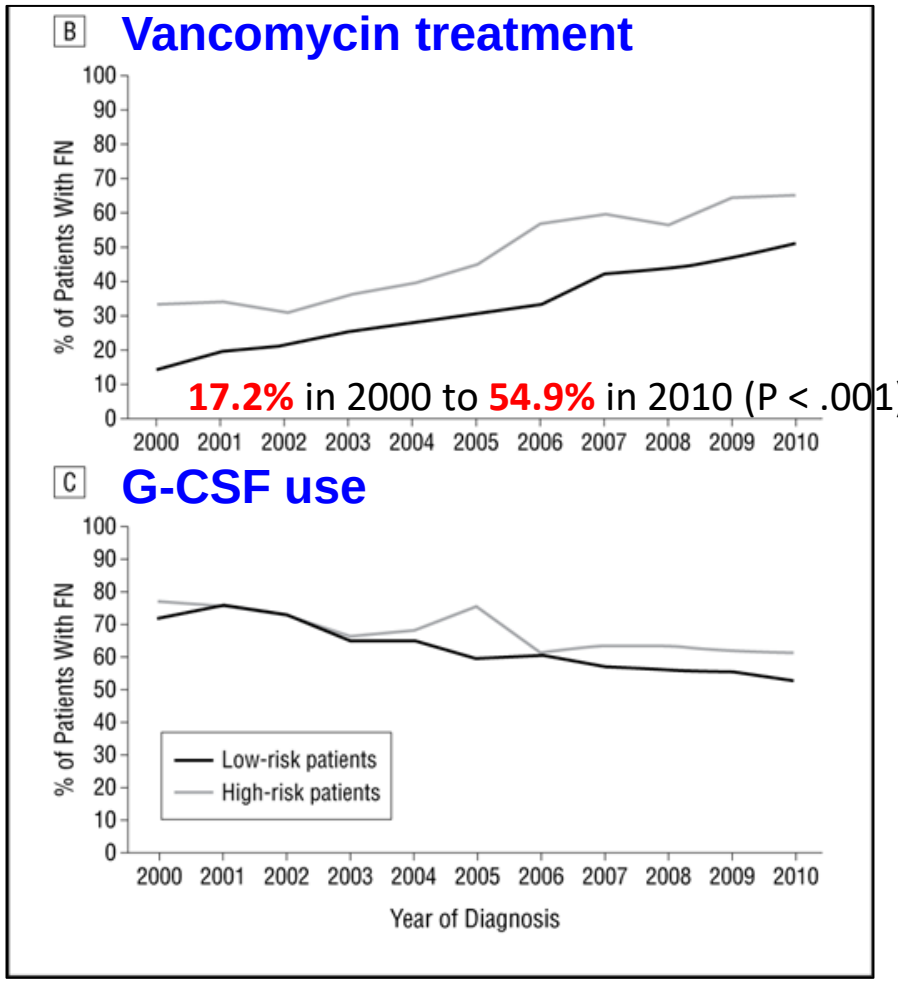
THERAPEUTIC USE OF MYELOID GROWTH FACTORS (MGFs)[e,l,m]



Use of guideline- & nonguideline-based treatment for FN



73.4% in 2000 to **80.3%** in 2010 (P < .001)



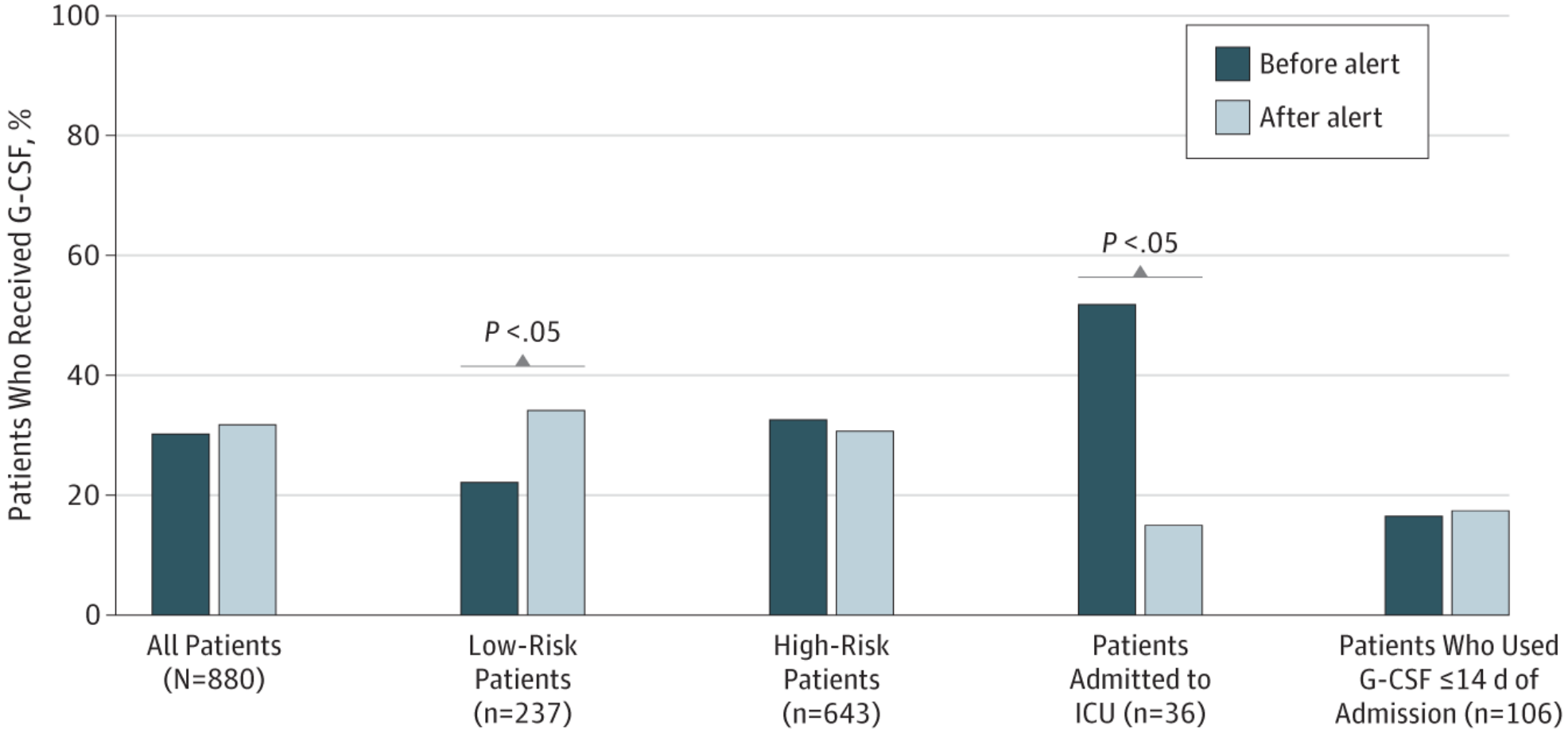
17.2% in 2000 to **54.9%** in 2010 (P < .001)

72.5% in 2000 to **55.0%** in 2010 (P < .001)

JAMA Intern Med. 2013;173(7):559-568.

Use of G-CSF in hospitalization with febrile neutropenia

Electronic health record (HER) alert: Before vs. After



*Clinician selected G-CSF indication: **febrile neutropenia (40.7%)**

JAMA Oncol. 2018;4(7):996-998.

Dose & schedule

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G-CSFs FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim[a] (category 1) or tbo-filgrastim[b] (category 1)
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.
  - Start the next day or up to 3–4 days after completion of myelosuppressive chemotherapy and treat through post-nadir recovery.[c,d,1]
- Pegfilgrastim[a] (category 1)
  - One dose of 6 mg
    - Based on clinical trial data, pegfilgrastim[a] can be administered the day after myelosuppressive chemotherapy (category 1).[2] There are data for and against same-day dosing but the FDA-approved dosing schedule is still recommended.[3-6]
    - There should be at least 12 days between the dose of pegfilgrastim[a] and the next cycle of chemotherapy.
    - If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim[a] may be given after each chemotherapy treatment.
    - For patients who cannot return to the clinic for next-day administration, there is an FDA-approved delivery device available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application).[e,7-12]
    - Administration of pegfilgrastim[a] up to 3–4 days after chemotherapy is also reasonable based on trials with filgrastim.
  - There is evidence to support use for chemotherapy regimens given every 3 weeks (category 1).
  - There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 weeks.
  - There are insufficient data to support use for cytotoxic chemotherapy regimens administered every week; therefore, pegfilgrastim should not be used.
- Caution should be exercised when administering prophylactic G-CSF in patients given concurrent chemotherapy and radiation.[13]
- Subcutaneous route is preferred for all G-CSFs listed above.
- For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Toxicity risks

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TOXICITY RISKS WITH MYELOID GROWTH FACTORS

Filgrastim,[a] Pegfilgrastim,[a] and Tbo-filgrastim[b,c,d,e]

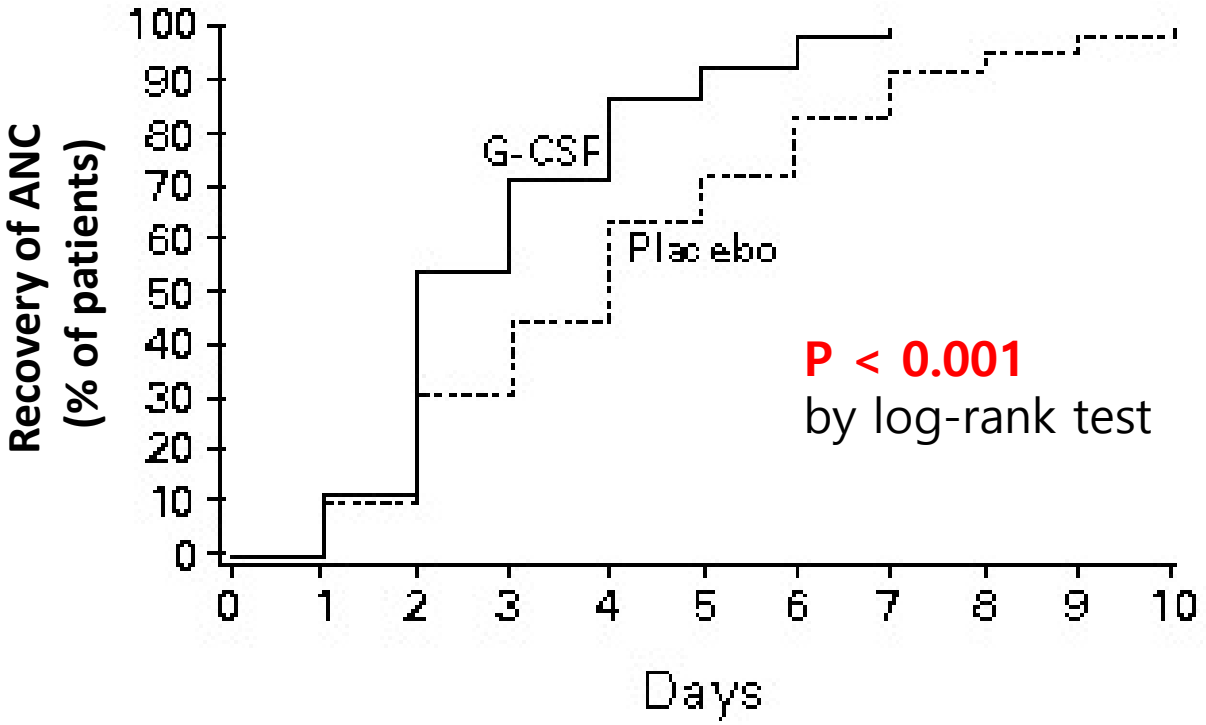
- Warnings
  - Allergic reactions
    - Skin: rash, urticaria, facial edema
    - Respiratory: wheezing, dyspnea
    - Cardiovascular: hypotension, tachycardia, anaphylaxis
  - Bleomycin-containing regimens: pulmonary toxicity[d]
  - Splenic rupture[f]
  - Acute respiratory distress syndrome
  - Alveolar hemorrhage and hemoptysis
  - Sickle cell crises (only in patients with sickle cell disease)
  - MDS and AML[g]
- Precautions
  - Cutaneous vasculitis
  - Immunogenicity
- Adverse reactions
  - Bone pain[f,h]

Sargramostim[b,d]

- Warnings
  - Fluid retention
  - Respiratory symptoms
  - Cardiovascular symptoms: Use with caution in patients with preexisting cardiac disease.
  - Renal and hepatic dysfunction: Monitor patients who display renal or hepatic dysfunction prior to initiation of treatment.
- Adverse events occurring in >10% of patients receiving sargramostim
  - AML - fever, skin reactions, metabolic disturbances, nausea, vomiting, weight loss, edema, anorexia
  - Autologous hematopoietic cell transplant or peripheral blood progenitor cell transplant - asthenia, malaise, diarrhea, rash, peripheral edema, urinary tract disorder
  - Allogeneic hematopoietic cell transplant or peripheral blood progenitor cell transplant - abdominal pain, chills, chest pain, diarrhea, nausea, vomiting, hematemesis, dysphagia, GI hemorrhage, pruritus, bone pain, arthralgia, eye hemorrhage, hypertension, tachycardia, bilirubinemia, hyperglycemia, increased creatinine, hypomagnesemia, edema, pharyngitis, epistaxis, dyspnea, insomnia, anxiety, high blood urea nitrogen (BUN), and high cholesterol

G-CSF vs. placebo in afebrile neutropenia

Time to recovery of ANC > 500/mm³



Median: **2 days** vs. 4 days

Hospitalization & Culture-positive infections

End Point	G-CSF (N = 71)	Placebo (N = 67)
No. hospitalized		
For infectious complications	8	9
For other reasons	1	2
Percent hospitalized*		
For infectious complications	11 (5–21)	13 (6–24)
For any reason	13 (6–23)	16 (8–27)
Days hospitalized†		
Median	6	5
Range	2‡–21	4‡–23
Days receiving parenteral antibiotics†		
Median	5	5
Range	1‡–8	0–12
No. of patients with positive cultures†	5	5

*Values in parentheses are 95 percent confidence intervals.

†All hospitalizations are included.

‡Data were censored because of death.

N Engl J Med. 1997 Jun 19;336(25):1776-80.

ASCO guideline 2015

CLINICAL QUESTION 3

Are there circumstances in which CSFs should be considered for the treatment of neutropenia in adults with cancer?

Recommendation 3.1

Therapy for patients with afebrile neutropenia. CSFs should not be routinely used for patients with neutropenia who are afebrile. (Type: evidence based, benefits outweigh harms. Evidence quality: high. Strength of recommendation: strong.)

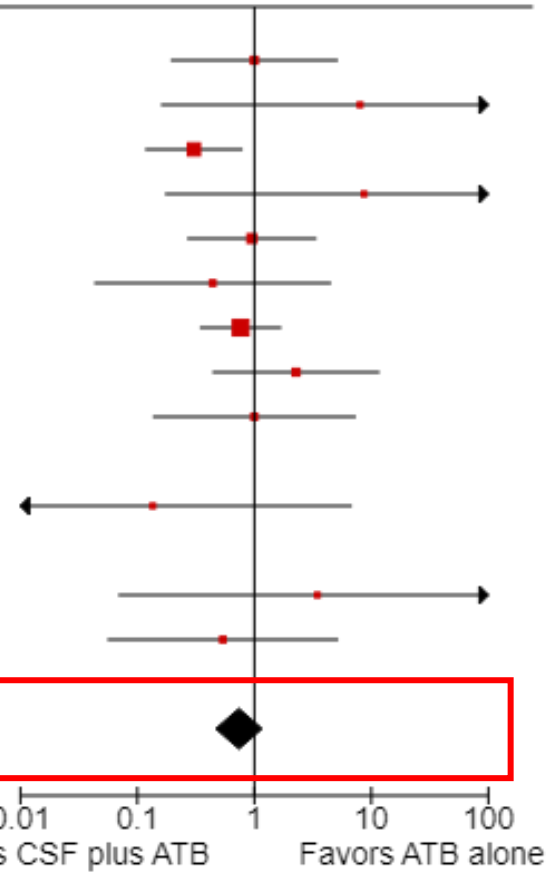
Overall mortality: G-CSF + antibiotics vs. antibiotics alone

Study or Subgroup	log[Hazard Ratio]	SE	CSF plus ATB Total	ATB alone Total	Weight	Hazard Ratio IV, Random, 95% CI
Anaissie 1996	0	0.84	50	50	7.6%	1.00 [0.19 , 5.19]
Arnberg 1998	2.08	2	14	15	1.3%	8.00 [0.16 , 403.40]
Aviles 1996	-1.19	0.49	61	58	22.2%	0.30 [0.12 , 0.79]
Biesma 1990	2.16	2	12	14	1.3%	8.67 [0.17 , 437.00]
Garcia-Carbonero 2001	-0.05	0.65	104	99	12.6%	0.95 [0.27 , 3.40]
Lopez-Hernandez 2000	-0.82	1.19	21	19	3.8%	0.44 [0.04 , 4.54]
Maher 1994	-0.27	0.41	109	107	31.8%	0.76 [0.34 , 1.71]
Mayordomo 1995	0.82	0.84	39	22	7.6%	2.27 [0.44 , 11.78]
Mayordomo 1995	0	1.02	39	21	5.1%	1.00 [0.14 , 7.38]
Mitchell 1997	0	0	94	92		Not estimable
Ravaud 1998	-2	2	34	34	1.3%	0.14 [0.00 , 6.82]
Riikonen 1994	0	0	28	30		Not estimable
Rodriguez 2005	1.24	2	18	17	1.3%	3.46 [0.07 , 174.15]
Vellenga 1996	-0.62	1.16	65	69	4.0%	0.54 [0.06 , 5.23]
Total (95% CI)			**688**	**647**	**100.0%**	**0.74 [0.47 , 1.16]**

Heterogeneity: Tau² = 0.00; Chi² = 9.96, df = 11 (P = 0.53); I² = 0%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable



Cochrane Database Syst Rev. 2014 Oct 30;2014(10):CD003039.

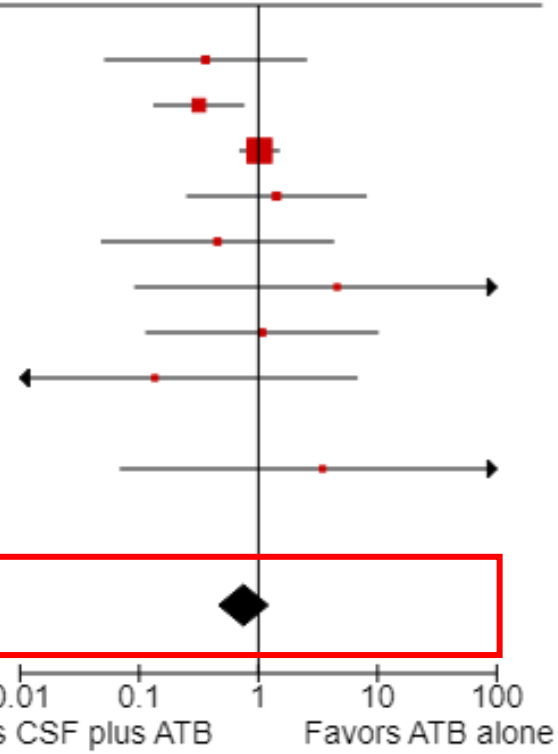
Infection-related mortality: G-CSF + antibiotics vs. antibiotics alone

Study or Subgroup	log[Hazard Ratio]	SE	CSF plus ATB Total	ATB alone Total	Weight	Hazard Ratio IV, Random, 95% CI
Anaissie 1996	-1.02	1	50	50	5.5%	0.36 [0.05 , 2.56]
Aviles 1996	-1.15	0.45	61	61	21.6%	0.32 [0.13 , 0.76]
Biesma 1990	0.02	0.2	12	14	53.3%	1.02 [0.69 , 1.51]
Garcia-Carbonero 2001	0.35	0.89	104	99	6.8%	1.42 [0.25 , 8.12]
Lopez-Hernandez 2000	-0.79	1.15	21	19	4.2%	0.45 [0.05 , 4.32]
Mayordomo 1995	1.52	2	39	21	1.4%	4.57 [0.09 , 230.43]
Mayordomo 1995	0.07	1.15	39	22	4.2%	1.07 [0.11 , 10.22]
Ravaud 1998	-2	2	34	34	1.4%	0.14 [0.00 , 6.82]
Riikonen 1994	0	0	28	30		Not estimable
Rodriguez 2005	1.24	2	18	7	1.4%	3.46 [0.07 , 174.15]
Vellenga 1996	0	0	65	69		Not estimable
Total (95% CI)			**471**	**426**	**100.0%**	**0.75 [0.47 , 1.20]**

Heterogeneity: Tau² = 0.07; Chi² = 9.09, df = 8 (P = 0.33); I² = 12%

Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Not applicable



Cochrane Database Syst Rev. 2014 Oct 30;2014(10):CD003039.

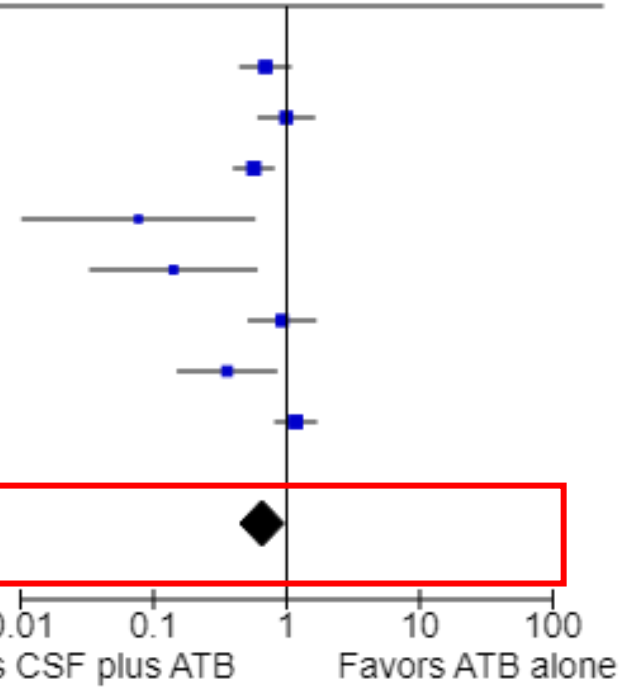
Hospitalization > 10 days: G-CSF + antibiotics vs. antibiotics alone

Study or Subgroup	CSF plus ATB Events	CSF plus ATB Total	ATB alone Events	ATB alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Anaissie 1996	18	50	26	50	16.4%	0.69 [0.44 , 1.09]
Garcia-Carbonero 2001	24	104	23	99	15.6%	0.99 [0.60 , 1.64]
Maher 1994	30	109	52	107	17.9%	0.57 [0.39 , 0.81]
Mayordomo 1995	1	39	7	21	3.0%	0.08 [0.01 , 0.58]
Mayordomo 1995	2	39	8	22	5.2%	0.14 [0.03 , 0.61]
Mitchell 1997	17	94	18	92	14.0%	0.92 [0.51 , 1.68]
Riikonen 1994	5	28	15	30	10.1%	0.36 [0.15 , 0.85]
Yoshida 1999	39	102	33	101	17.8%	1.17 [0.81 , 1.70]
Total (95% CI)		**565**		**522**	**100.0%**	**0.65 [0.44 , 0.95]**
Total events:	136		182			

Heterogeneity: Tau² = 0.18; Chi² = 22.50, df = 7 (P = 0.002); I² = 69%

Test for overall effect: Z = 2.21 (P = 0.03)

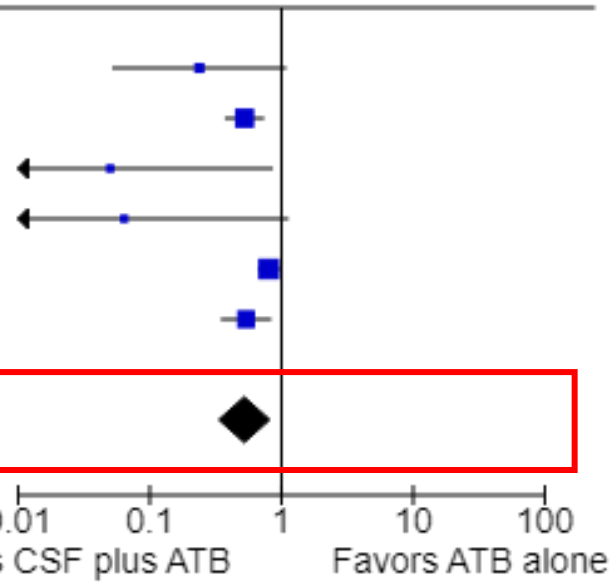
Test for subgroup differences: Not applicable



Cochrane Database Syst Rev. 2014 Oct 30;2014(10):CD003039.

Time to neutrophil recovery: G-CSF + antibiotics vs. antibiotics alone

Study or Subgroup	CSF + ATB Events	CSF + ATB Total	ATB alone Events	ATB alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Garcia-Carbonero 2001	2	104	8	99	6.8%	0.24 [0.05 , 1.09]
Maher 1994	31	109	58	107	29.2%	0.52 [0.37 , 0.74]
Mayordomo 1995	0	39	5	21	2.2%	0.05 [0.00 , 0.86]
Mayordomo 1995	0	39	4	22	2.2%	0.06 [0.00 , 1.13]
Mitchell 1997	58	94	71	92	33.3%	0.80 [0.66 , 0.97]
Ravaud 1998	14	34	26	34	26.2%	0.54 [0.35 , 0.84]
Total (95% CI)		**419**		**375**	**100.0%**	**0.52 [0.34 , 0.81]**
Total events:	105		172			



Heterogeneity: Tau² = 0.14; Chi² = 16.49, df = 5 (P = 0.006); I² = 70%

Test for overall effect: Z = 2.89 (P = 0.004)

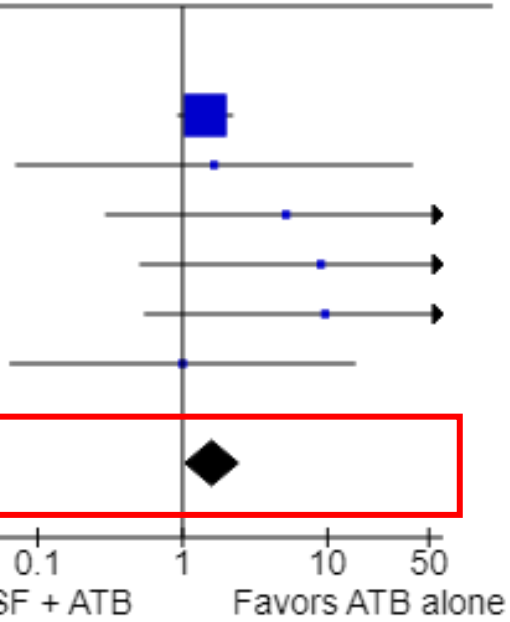
Test for subgroup differences: Not applicable

Cochrane Database Syst Rev. 2014 Oct 30;2014(10):CD003039.

Bone/joint pain of flu-like sx.: G-CSF + antibiotics vs. antibiotics alone

Study or Subgroup	CSF + ATB Events	CSF + ATB Total	ATB alone Events	ATB alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Arnberg 1998	0	14	0	15		Not estimable
Maher 1994	35	109	24	107	89.4%	1.43 [0.92 , 2.24]
Mayordomo 1995 (1)	1	39	0	21	1.8%	1.65 [0.07 , 38.82]
Mayordomo 1995 (2)	4	39	0	22	2.1%	5.17 [0.29 , 91.86]
Ravaud 1998	4	34	0	34	2.1%	9.00 [0.50 , 160.96]
Riikonen 1994	4	28	0	30	2.1%	9.62 [0.54 , 170.96]
Vellenga 1996	1	65	1	65	2.3%	1.00 [0.06 , 15.65]
Total (95% CI)		**328**		**294**	**100.0%**	**1.59 [1.04 , 2.42]**
Total events:	49		25			

Risk Ratio M-H, Random, 95% CI



Heterogeneity: Tau² = 0.00; Chi² = 4.18, df = 5 (P = 0.52); I² = 0%

Test for overall effect: Z = 2.14 (P = 0.03)

Test for subgroup differences: Not applicable

Footnotes

(1) G-CSF

(2) GM-CSF

Cochrane Database Syst Rev. 2014 Oct 30;2014(10):CD003039.

IDSA guideline 2011

X. What Is the Role of Hematopoietic Growth Factors (G-CSF or GM-CSF) in Managing Fever and Neutropenia?

Recommendations

41. Prophylactic use of myeloid colony-stimulating factors (CSFs; also referred to as hematopoietic growth factors) should be considered for patients in whom the anticipated risk of fever and neutropenia is ⩾20% (**A-II**).

42. CSFs are not generally recommended for treatment of established fever and neutropenia (**B-II**).

Clinical Infectious Diseases 2011;52(4):e56–e93

ASCO guideline 2015

CLINICAL QUESTION 3

Are there circumstances in which CSFs should be considered for the treatment of neutropenia in adults with cancer?

Recommendation 3.2

Therapy for febrile patients with neutropenia. CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSFs should be considered in patients with fever and neutropenia who are at high risk for infection-associated complications or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features in-

J Clin Oncol 33:3199-3212.

ASCO guideline 2015

Table 2. Patient Risk Factors for Poor Clinical Outcomes Resulting From Febrile Neutropenia or Infection[28]

Risk Factor
Sepsis syndrome
Age > 65 years
Profound neutropenia (absolute neutrophil count < 0.1×10^9/L)
Neutropenia expected to last > 10 days
Pneumonia
Invasive fungal infection
Other clinically documented infections
Hospitalization at time of fever
Prior episode of febrile neutropenia

J Clin Oncol 33:3199-3212.

Therapeutic use

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Management of Neutropenia

NCCN Guidelines Index
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THERAPEUTIC USE OF MYELOID GROWTH FACTORS (MGFs)[e,l,m]

PRESENTATION	G-CSFs USE DURING CURRENT CHEMOTHERAPY CYCLE	MANAGEMENT[n]
Present with febrile neutropenia[e]	Pati… rece…	…ontinue G-CSFs
		…o additional G-CSFs[q]
	Pati… prophylactic G-CSFs	…o therapeutic MGFs
	Risk factors present for an infection-associated complication[p]	Consider therapeutic MGFs[o,r,s]
Patients with radiation-induced myelosuppression following a radiologic/nuclear incident (hematopoietic acute radiation syndrome [H-ARS])[o]		Therapeutic MGFs[o,t]

Risk factors:
- sepsis syndrome
- age >65 years
- absolute neutrophil count [ANC] 10 days in duration
- pneumonia or other clinically documented infections
- invasive fungal infection
- hospitalization at the time of fever
- prior episode of febrile neutropenia

가. filgrastim(품명: 그라신주 등), lenograstim(품명: 뉴트로진주)

1) 암환자에게 아래와 같은 기준으로 투여하는 경우에 요양급여를 인정함
(제2006-3호: 2006.4.1, 개정 제2006-4호: 2006.5.1, 개정 제2016-242호: 2016.9.1.)

- 아 래 -

○ 혈액종양에 대해 항암요법을 받고 있는 환자의 호중구감소증의 경우 호중구수가 1,000/㎣ 미만일 경우 투여를 시작하여 3,000/㎣까지 투여하는 경우 인정

○ 고형암에 대해 항암요법을 받고 있는 환자의 호중구감소증의 경우 호중구수 500/㎣미만에서 시작하여 1,000/㎣까지 투여하는 경우 인정
단, 발열을 동반한 호중구감소증(febrile neutropenia)환자에서는 시작시기를 호중구수 1,000/㎣ 미만, 종료 시기를 3,000/㎣까지 인정

○ 골수형성이상증후군에 따른 호중구감소증의 경우 호중구수가 1,000/㎣미만일 경우 투여를 시작하여 3,000/㎣까지 투여하는 경우 인정

○ 조혈모세포이식의 경우 이식 후 투여를 시작하여 호중구수가 3,000/㎣까지 투여하는 경우 인정

GM-CSF (Sargramostim) vs. G-CSF (Filgrastim)

Patient characteristics

Characteristic	No. of patients (%)	
	Sargramostim (RhuGM-CSF)	Filgrastim (RhuG-CSF)
Total no. of patients	79	102
Age (yrs)		
Median	57.2	54.2
Range	30–70	35–72
Gender (%)		
Female	62 (78)	73 (72)
Male	17 (22)	29 (27)
Primary neoplasm (%)		
Breast cancer	21 (26)	24 (23)
Lymphoma	26 (33)	24 (23)
Lung cancer	12 (15)	17 (17)
Ovarian cancer	3 (4)	13 (13)
Other	17 (22)	24 (23)
ANC at enrollment (%)		
0–100	17 (22)	32 (31)
101–200	14 (17)	16 (16)
201–300	17 (22)	13 (13)
301–400	15 (19)	25 (24)
401–500	16 (20)	16 (16)
Mean ANC at enrollment	277/μL	282/μL

Results

Endpoint	Sargramostim (RhuGM-CSF) $n = 79$	Filgrastim (RhuG-CSF) $n = 102$	p Value
Mean (± SEM) days on growth factor	5.7 ± 0.23	4.6 ± 0.14	0.0001
Mean (± SEM) days to ANC of			
500/μL	3.3 ± 0.16	3.6 ± 0.16	0.32
1000/μL	5.1 ± 0.22	4.5 ± 0.13	0.009
1500/μL	5.7 ± 0.23	4.6 ± 0.14	0.0001
Hospitalization with neutropenic fever or for IV antibiotics			
No. of patients (%)	5 (6.3)	8 (7.8)	0.46
Mean LOS ± SEM (days)	4.8 ± 0.58	5.6 ± 1.1	0.58
Mean duration of fever ± SEM (days)	1.6 ± 0.60	3.6 ± 0.92	0.14

LOS = length of stay.

Cancer Invest. 1998;16(6):366-73.

GM-CSF (Sargramostim) vs. G-CSF (Filgrastim)

Group	No. Days with Indicated Maximum Body Temperature[a]			
	Grade 0, <100.4 °F (<38.0 °C)	Grade 1, 100.4–100.8 °F (38.0–38.2 °C)	Grade 2, 100.9–101.2 °F (38.3–38.4 °C)	Grade 3, ≥101.3 °F (≥38.5 °C)
Maximum Temperature				
Sargramostim	221	34	26	105
Filgrastim	183[b]	42	28	116
Maximum Temperature within Four hr of Drug Administration				
Sargramostim	26	6	9	21
Filgrastim	21	11	4	16

[a]The total number of evaluable treatment days was 386 for sargramostim and 369 for filgrastim.

[b]Significantly different from corresponding value for sargramostim (p = 0.01).

Am J Health Syst Pharm. 2005 Jan 1;62(1):83-7.

GM-CSF (Sargramostim) vs. G-CSF (Filgrastim/Pegfilgrastim)

Comparison Group	Outcome Event	Sargramostim		Comparison Group		Univariate		Multivariate	
		No. of Events*	Incidence Rate of Event (95% CI)	No. of Events*	Incidence Rate of Event (95% CI)	Incidence Rate Ratio (95% CI)	*P*	Adjusted Incidence Rate Ratio (95% CI)	*P*
Sargramostim vs. filgrastim	Infection-related hospitalizations	10	0.12 (0.05-0.20)	22	0.26 (0.15-0.37)	0.46 (0.22-0.97)	.0422	0.44 (0.20-0.94)	.0333
	Febrile neutropenia -related hospitalizations†	4	0.05 (0.01-0.12)	7	0.08 (0.03-0.17)	0.58 (0.17-1.98)	.3837	0.61 (0.17-2.15)	.4448
Sargramostim vs. pegfilgrastim	Infection-related hospitalizations	10	0.12 (0.05-0.20)	37	0.24 (0.16-0.31)	0.52 (0.26-1.04)	.0628	0.44 (0.21-0.90)	.0256
	Febrile neutropenia -related hospitalizations†	4	0.05 (0.01-0.12)	9	0.06 (0.03-0.11)	0.85 (0.26-2.75)	.7827	0.74 (0.22-2.50)	.6235

Cancer. 2009 Oct 15;115(20):4839-48.

ASCO guideline 2015

CLINICAL QUESTION 7

Should CSFs be avoided in patients receiving concomitant chemotherapy and radiation therapy?

Recommendation 7

CSFs should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSFs may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected. (Type: evidence based. Evidence quality: high. Strength of recommendation: strong.)

J Clin Oncol 33:3199-3212.

CONVERT: G-CSF with CCRT in LS-SCLC

Incidence of hematological toxicity, infections and hospitalization

	Naïve group (n = 307), all CTx cycles, n (%)		proG-CSF group (n = 180)				
			all CTx cycles,n (%)	cycles with G-CSF, n (%)	cycles without G-CSF, n (%)	Primary proG-CSF sub-group (n = 60) all cycles, n (%)	Secondary proG-CSF sub-group (n = 120) all cycles, n (%)
Febrile Neutropenia	52 (**17**)		53 (**29**)	18 (**10**)	40 (**22**)	11 (**18**)	42 (**35**)
p value		*<0.001*			*0.002*		*0.029*
Infections*	29 (**9**)		29 (**16**)	14 (**8**)	22 (**12**)	6 (**10**)	23 (**19**)
p value		*0.043*			*0.165*		*0.168*
Anaemia*	35 (**11**)		29 (**16**)	19 (**11**)	19 (**11**)	11 (**18**)	18 (**15**)
p value		*0.180*			*>0.999*		*0.709*
Blood transfusion	94 (**31**)		92 (**51**)	66 (**37**)	45 (**25**)	32 (**53**)	60 (**50**)
p value		*<0.001*			*0.017*		*0.793*
Thrombocytopenia*	46 (**15**)		50 (**28**)	36 (**20**)	20 (**11**)	9 (**15**)	41 (**34**)
p value		*0.001*			*0.029*		*0.009*
Platelet transfusion	18 (**6**)		15 (**8**)	12 (**7**)	7 (**4**)	4 (**7**)	11 (**9**)
p value		*0.388*			*0.346*		*0.796*
Hospitalization	207 (**67**)		138 (**77**)	118 (**66**)	103 (**57**)	45 (**75**)	93 (**78**)
p value		*0.038*			*0.129*		*0.844*

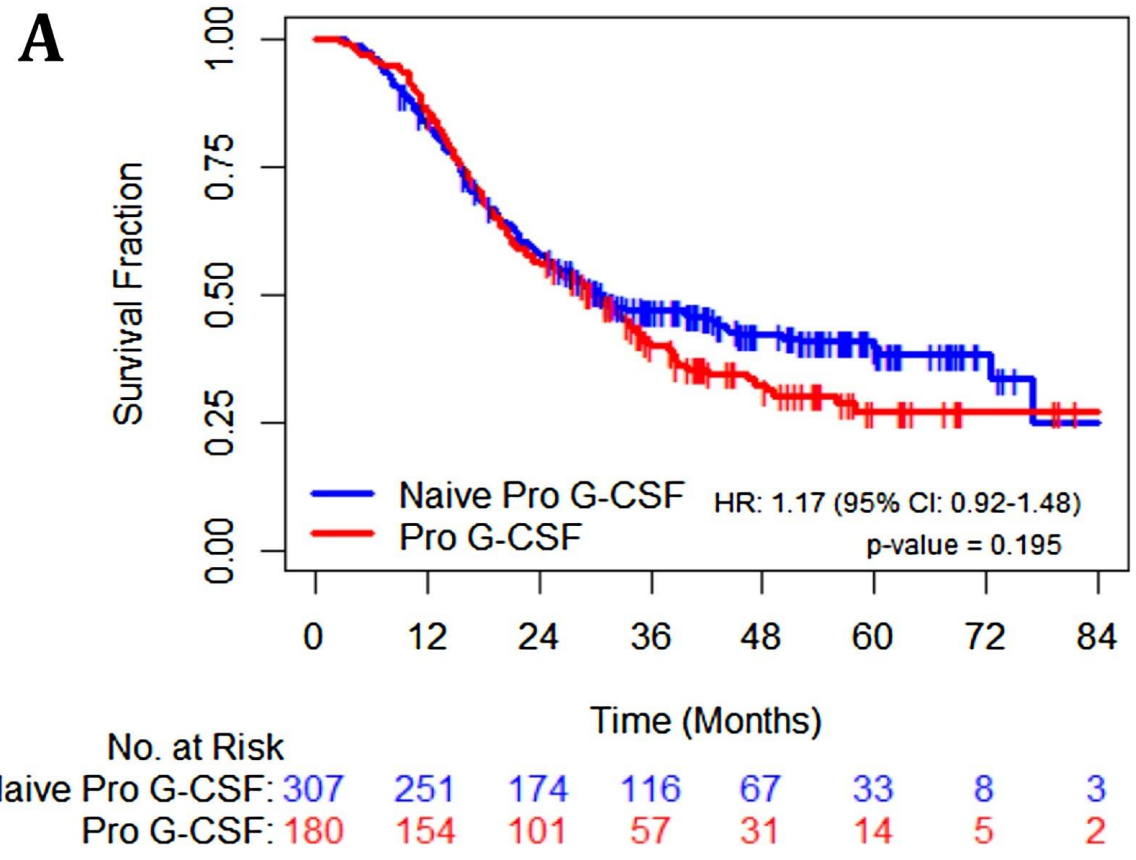
Abbreviations: CTx, chemotherapy; proG-CSF, prophylactic granulocyte-colony stimulating factor.

* grade.3–4.

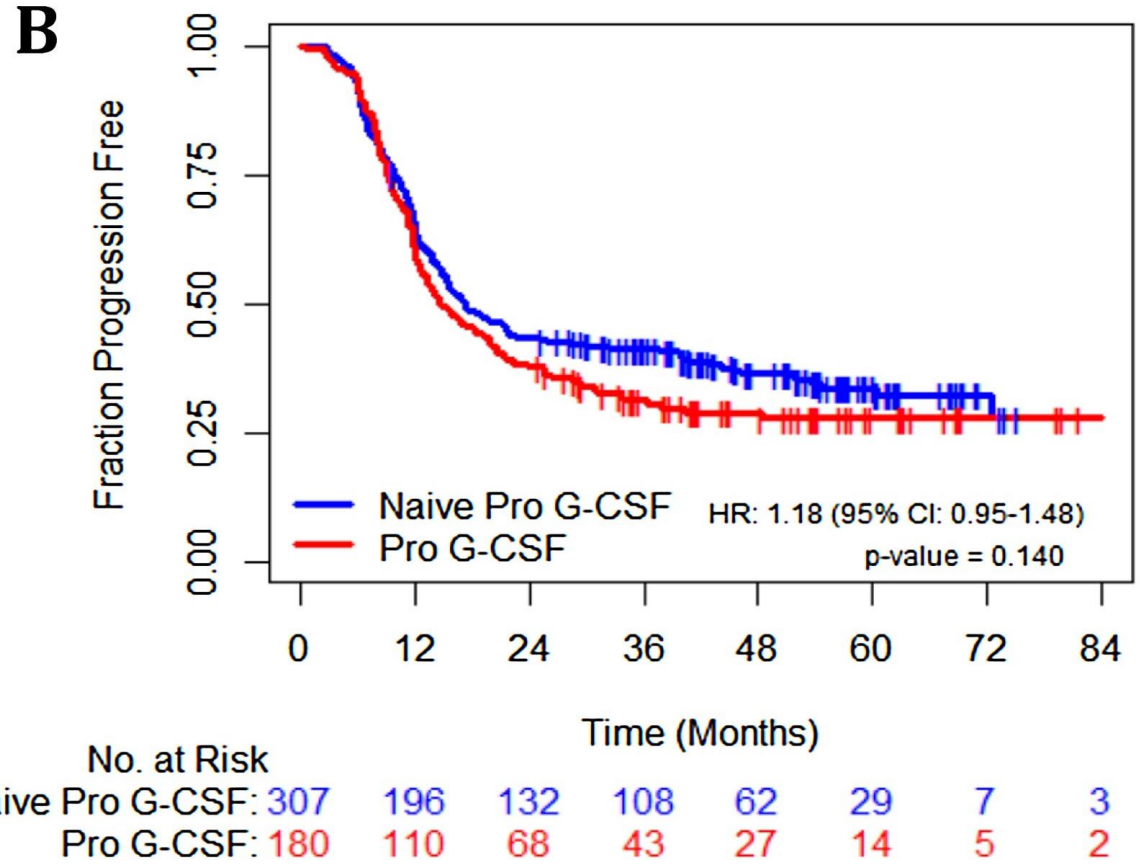
Lung Cancer. 2021;153:165-170.

CONVERT: G-CSF with CCRT in LS-SCLC

Overall survival



Progression free survival



Lung Cancer. 2021;153:165-170.

Dose & schedule

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NCCN Guidelines Version 1.2022
Management of Neutropenia

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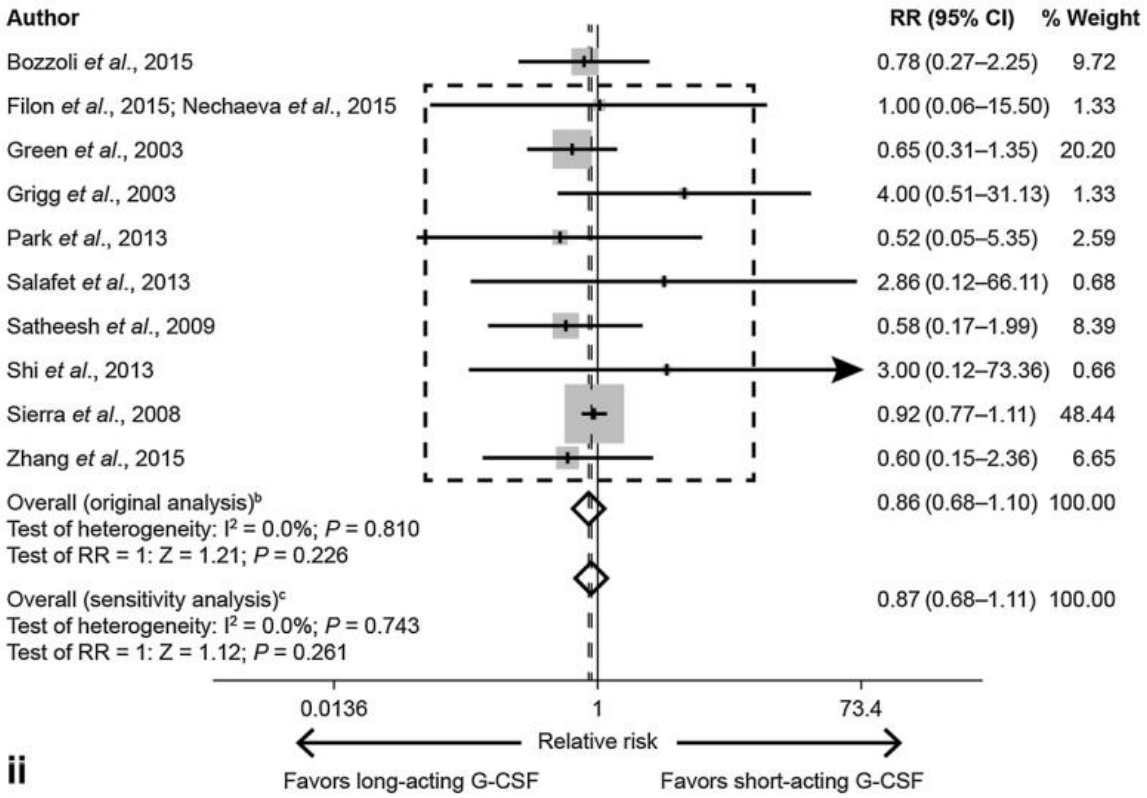
G-CSFs FOR PROPHYLAXIS OF FEBRILE NEUTROPENIA AND MAINTENANCE OF SCHEDULED DOSE DELIVERY

- Filgrastim[a] (category 1) or tbo-filgrastim[b] (category 1)
  - Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards.
  - Start the next day or up to 3–4 days after completion of myelosuppressive chemotherapy and treat through post-nadir recovery.[c,d,1]
- Pegfilgrastim[a] (category 1)
  - One dose of 6 mg
    - Based on clinical trial data, pegfilgrastim[a] can be administered the day after myelosuppressive chemotherapy (category 1).[2] There are data for and against same-day dosing but the FDA-approved dosing schedule is still recommended.[3-6]
    - There should be at least 12 days between the dose of pegfilgrastim[a] and the next cycle of chemotherapy.
    - If the treatment cycle includes chemotherapy administration on days 1 and 15, pegfilgrastim[a] may be given after each chemotherapy treatment.
    - For patients who cannot return to the clinic for next-day administration, there is an FDA-approved delivery device available that can be applied the same day as chemotherapy in order to deliver the full dose of pegfilgrastim the following day (approximately 27 hours after application).[e,7-12]
    - Administration of pegfilgrastim[a] up to 3–4 days after chemotherapy is also reasonable based on trials with filgrastim.
  - There is evidence to support use for chemotherapy regimens given every 3 weeks (category 1).
  - There are phase II studies that demonstrate efficacy for chemotherapy regimens given every 2 weeks.
  - There are insufficient data to support use for cytotoxic chemotherapy regimens administered every week; therefore, pegfilgrastim should not be used.
- Caution should be exercised when administering prophylactic G-CSF in patients given concurrent chemotherapy and radiation.[13]
- Subcutaneous route is preferred for all G-CSFs listed above.
- For information regarding prophylactic anti-infectives (ie, viral, fungal, bacterial), see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Febrile neutropenia: long- vs. short-acting G-CSF

RTCs



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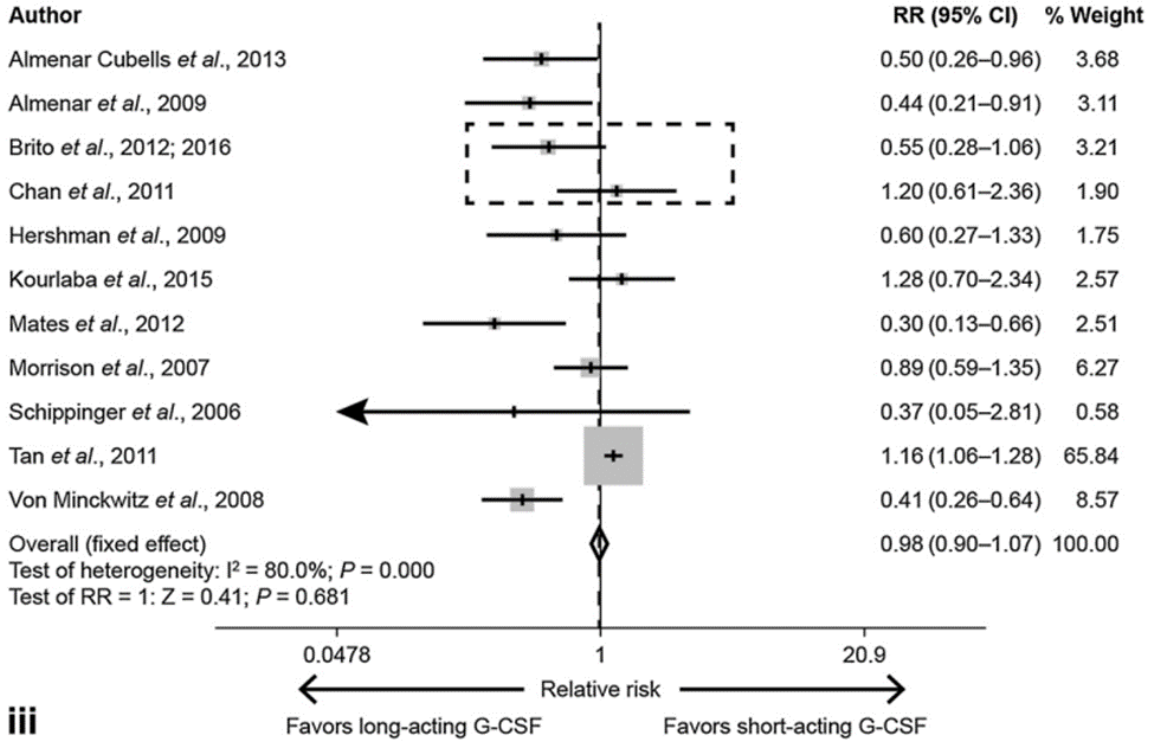
Non-RTCs



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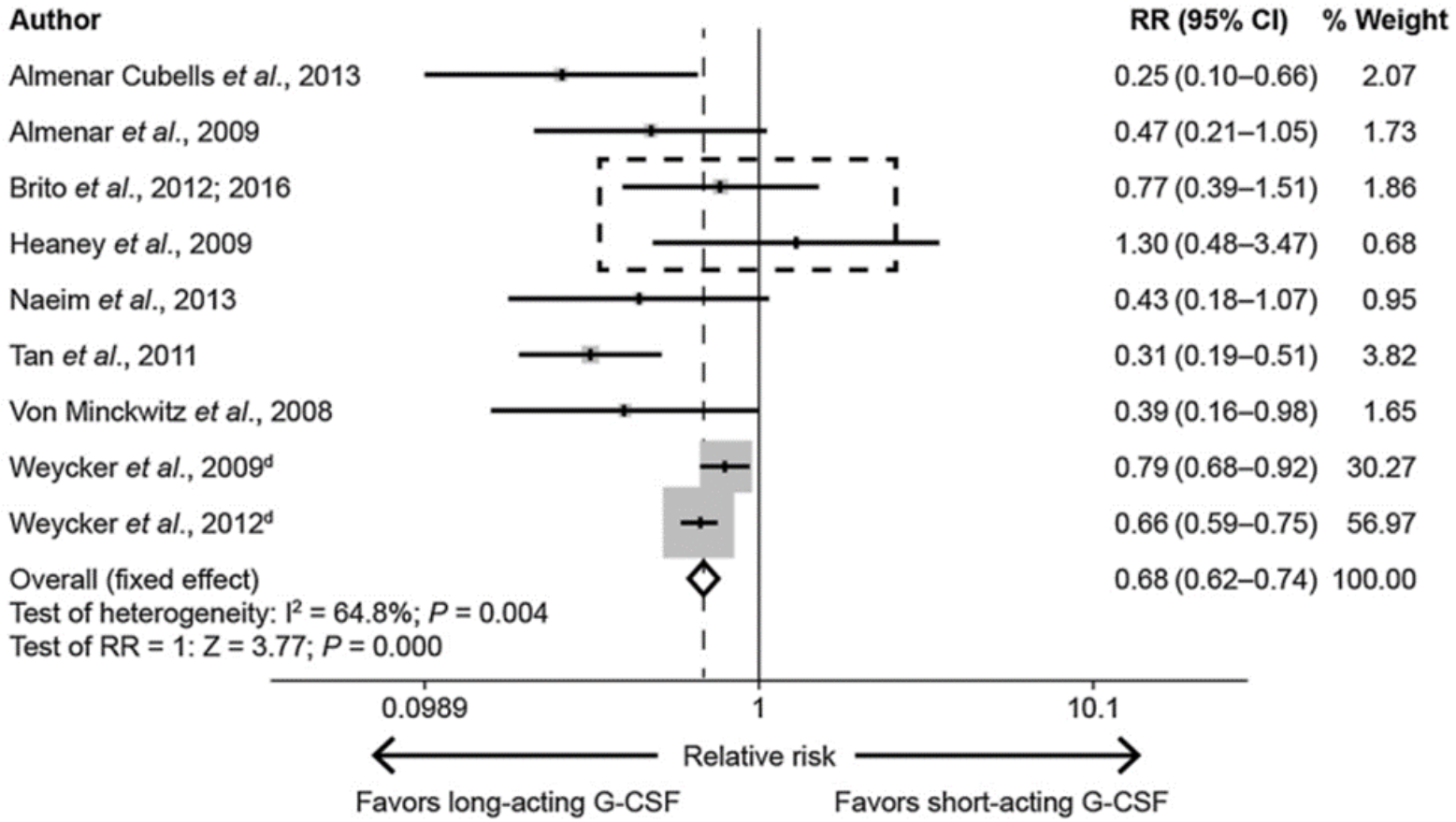
Adv Ther. 2018 Nov;35(11):1816-1829.

FN-related hospitalization: long- vs. short-acting G-CSF

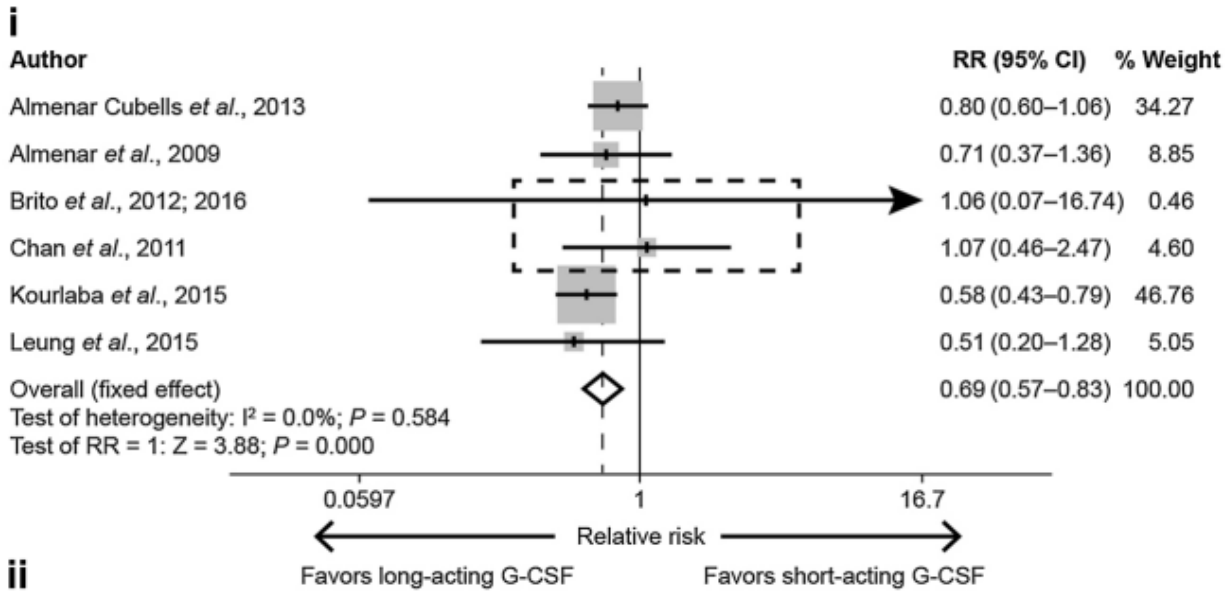
Non-RTCs



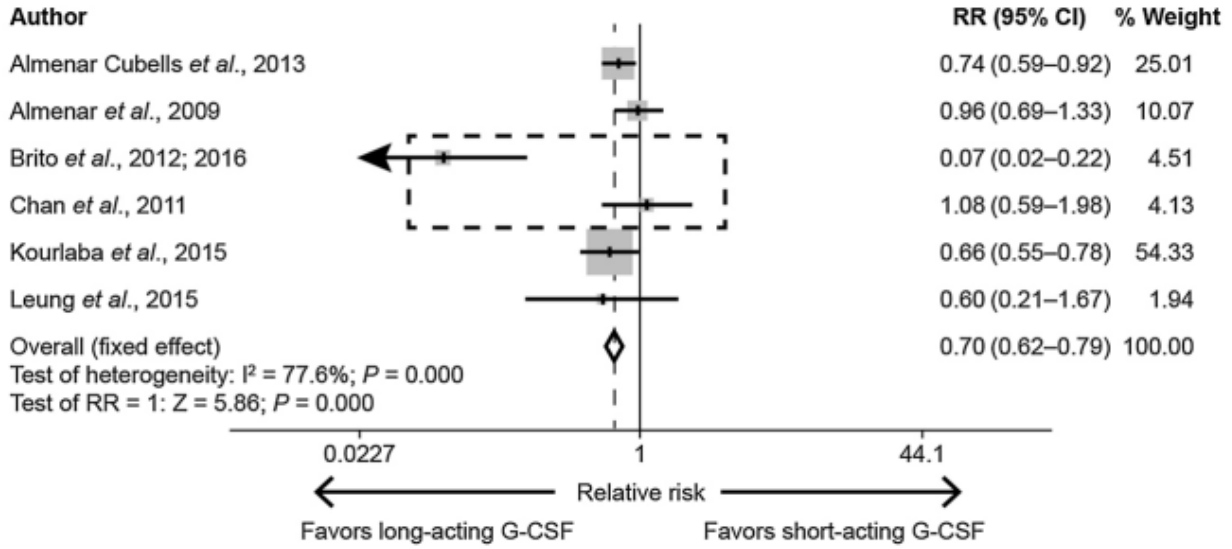
Adv Ther. 2018 Nov;35(11):1816-1829.

CTx dose reduction & delay: long- vs. short-acting G-CSF

Chemotherapy dose reductions

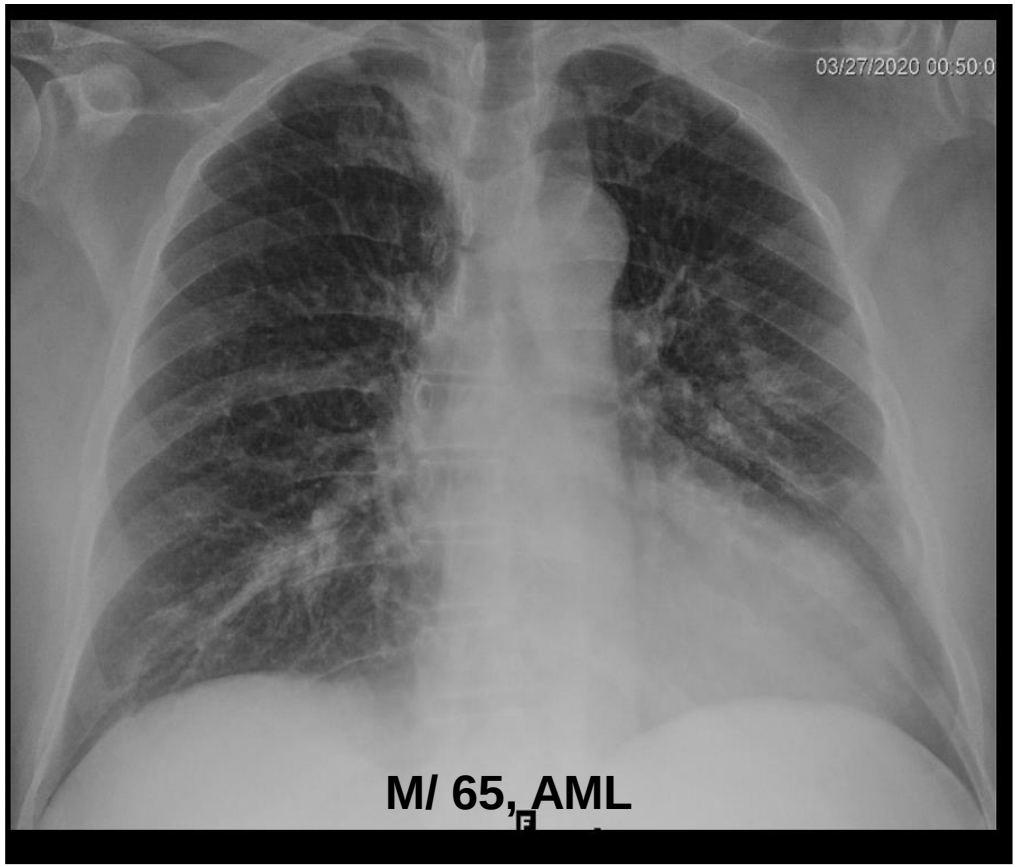


Chemotherapy dose delays



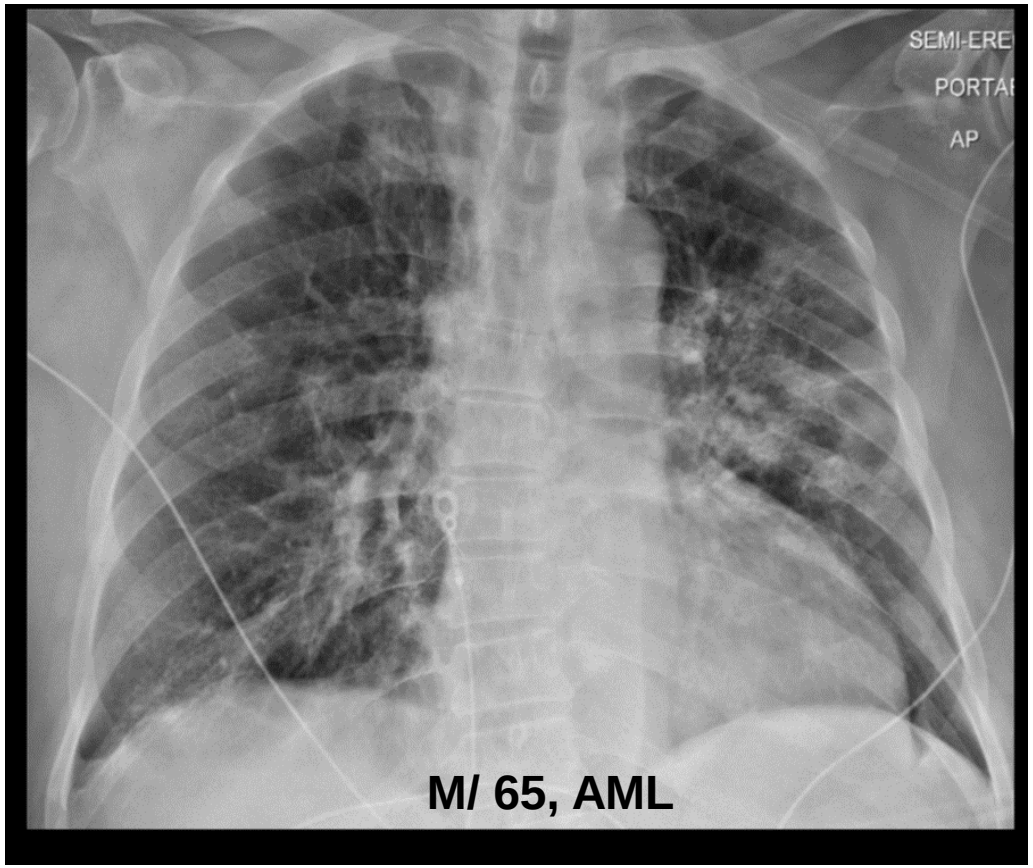
Adv Ther. 2018 Nov;35(11):1816-1829.

G-CSF for neutropenic fever in COVID-19



G-CSF administration

ANC 300/mcL

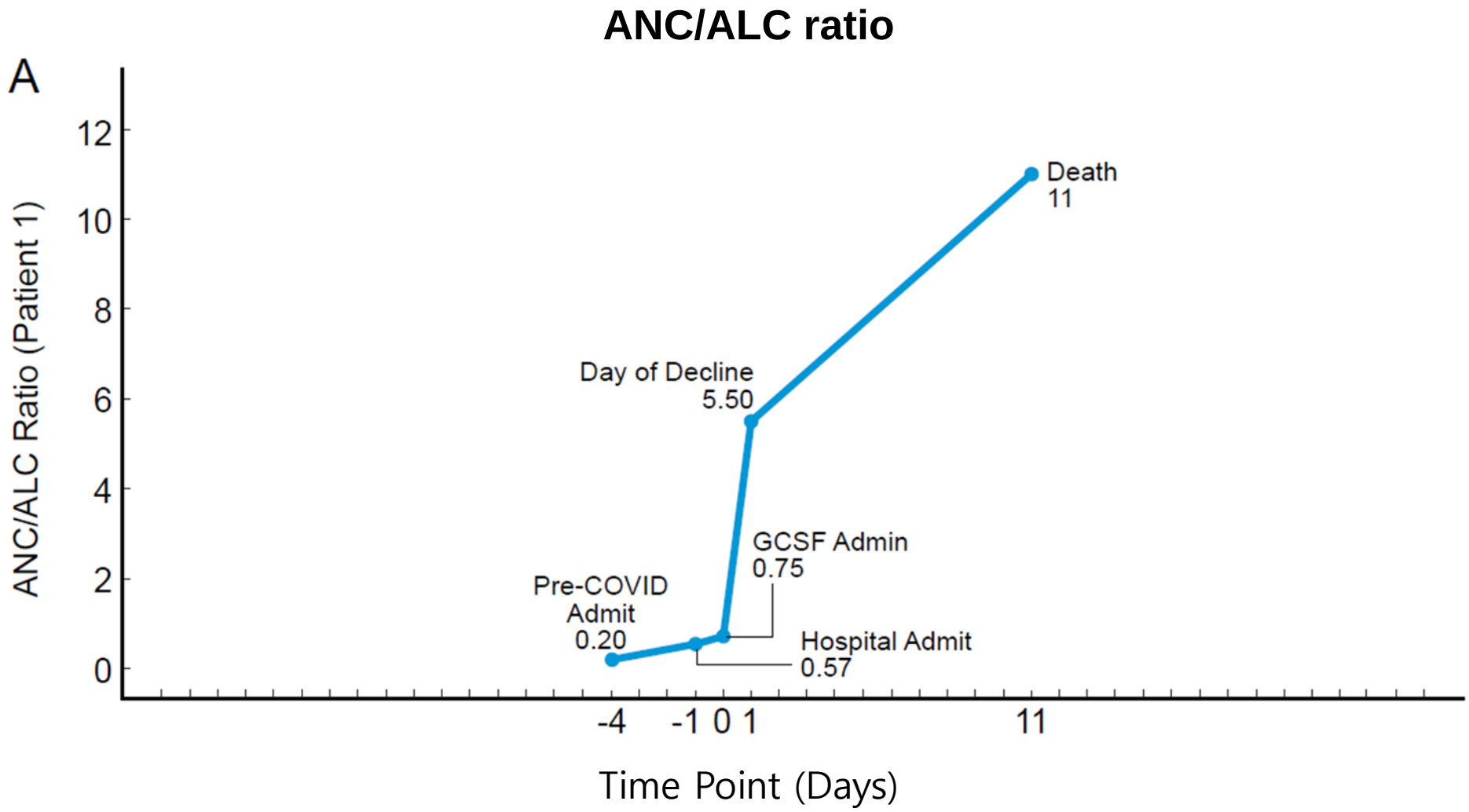


1 day after

ANC 2,200/mcL

Am J Hematol. 2020 Aug; 95(8): E210–E213.

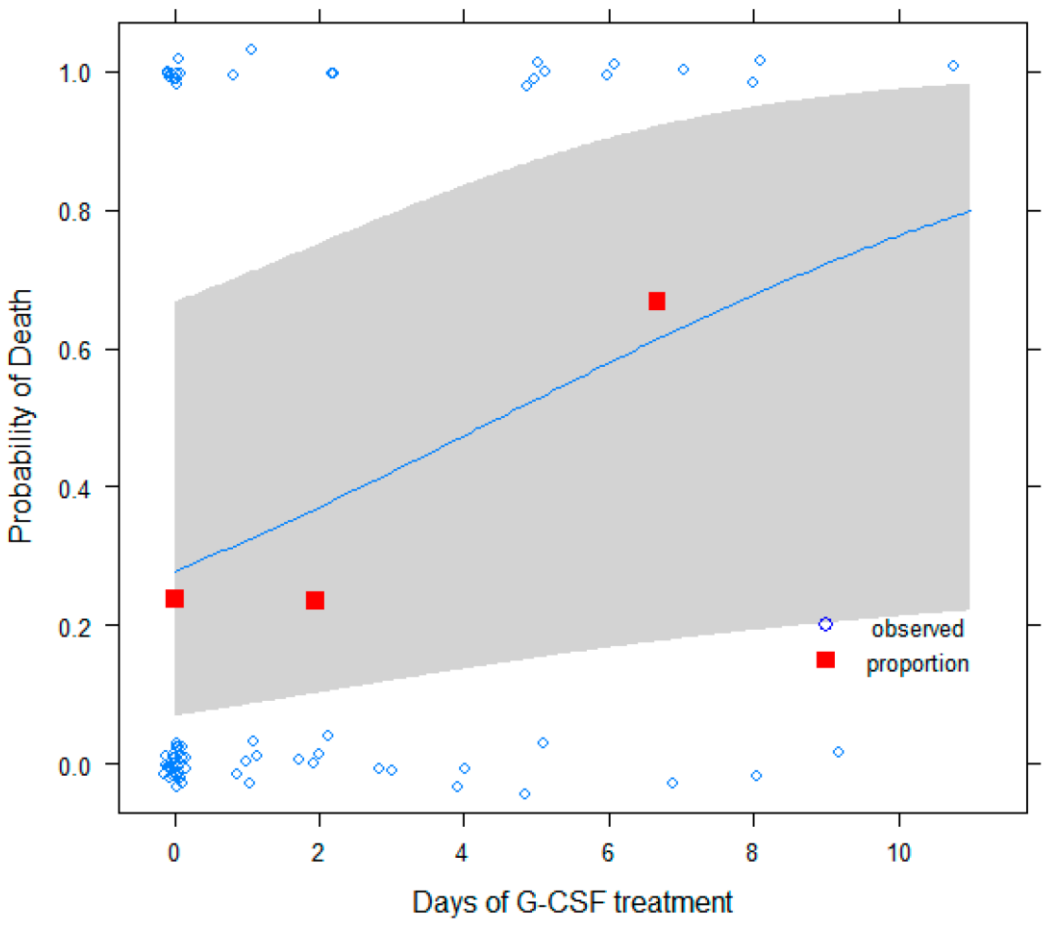
G-CSF for neutropenic fever in COVID-19



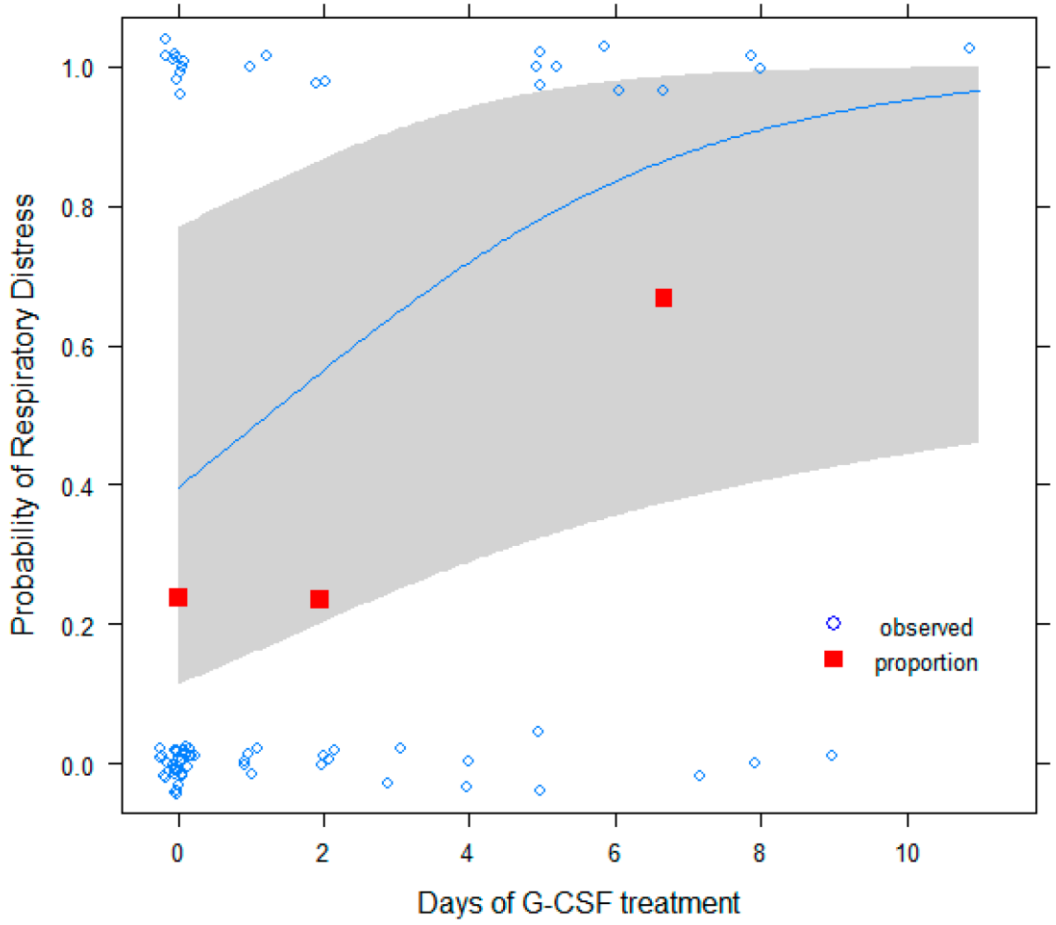
Am J Hematol. 2020 Aug; 95(8): E210–E213.

G-CSF: Cancer patients with neutropenia and COVID-19

Death



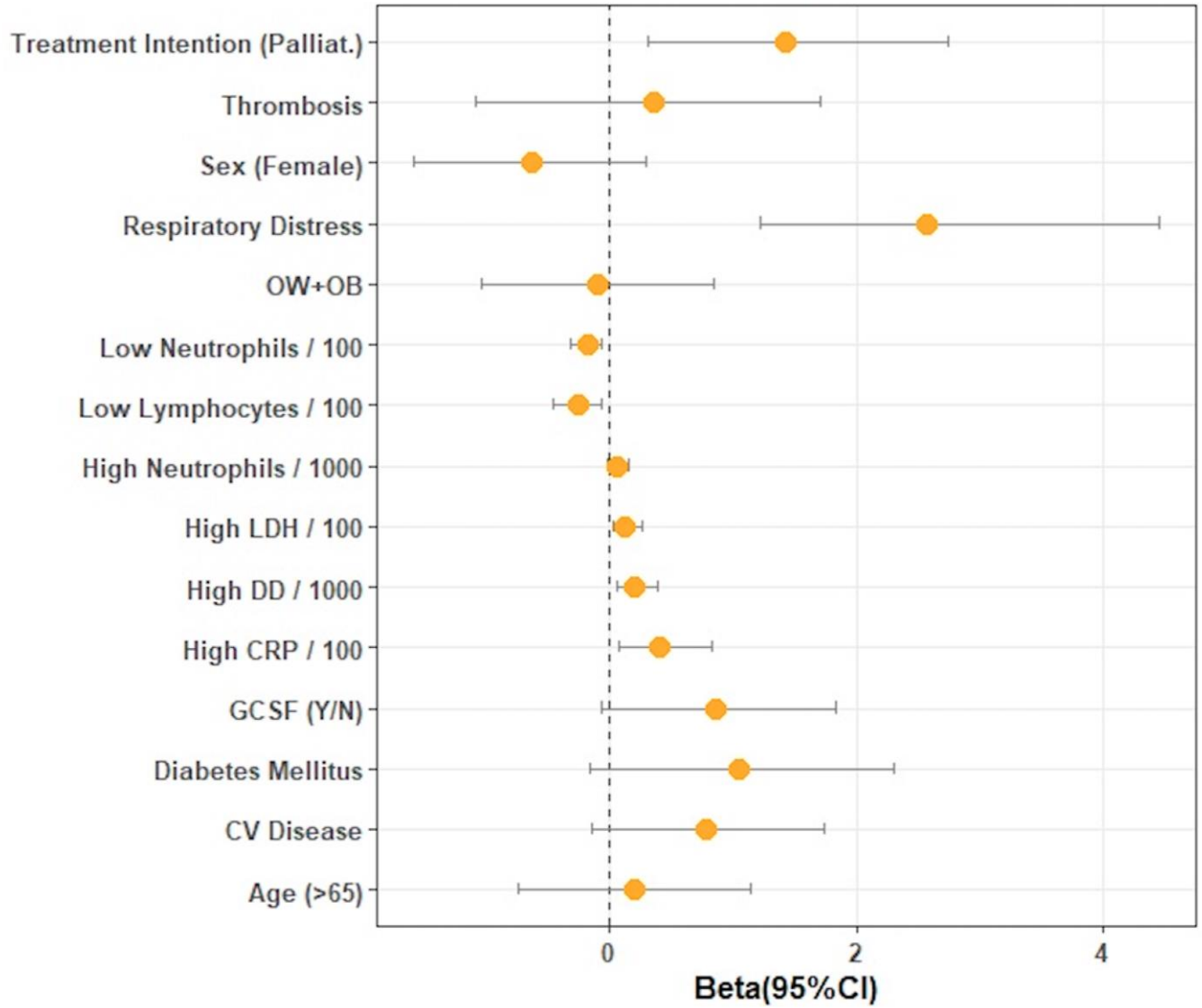
Respiratory distress



Cancers (Basel). 2021 Aug 20;13(16):4205.

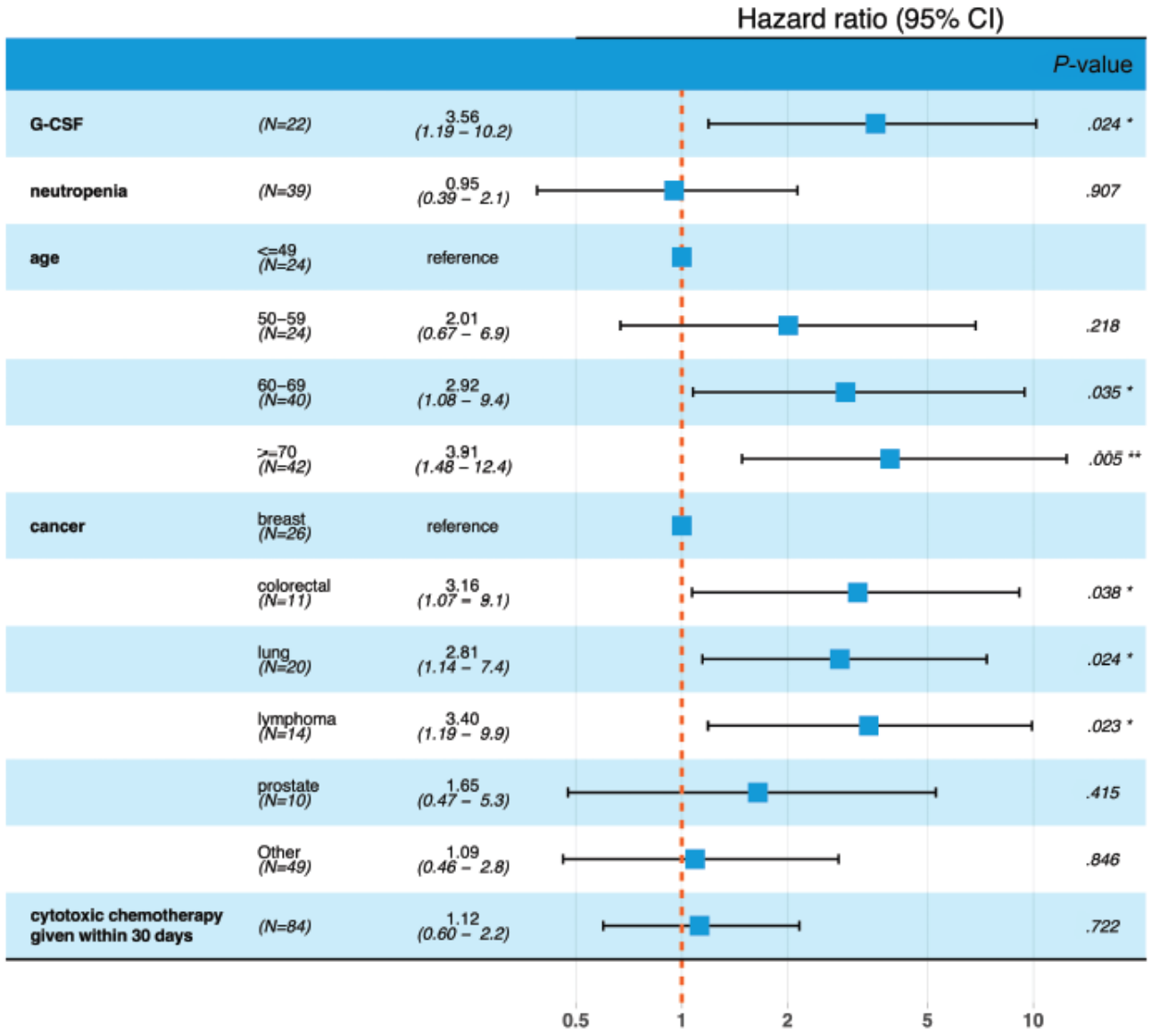
G-CSF: Cancer patients with neutropenia and COVID-19

Mortality according to different variables



Cancers (Basel). 2021 Aug 20;13(16):4205.

G-CSF: Respiratory failure or death in COVID-19



CID. 2022;74(4):567–74

Summary

- **Recombinant G-CSF** was associated with a high risk of developing secondary malignancies (AML/MDS) and may carries risks of disease progression.

- **Primary prophylaxis:** > 20% risk of febrile neutropenia
  10-20% risk of FN & high risk factors

- **Afebrile neutropenia:** G-CSFs should not be routinely used

Summary

- **Neutropenic fever:**

  G-CSFs should not be routinely used

  as adjunctive treatment with antibiotic therapy

  G-CSFs should be considered in patients with high risk of

  infection-associated complication & poor prognosis

  (eg. age >65, ANC <100, pneumonia, sepsis…)

- Concerns for patients with COVID-19