III Simpósio Internacional de Onco-Hematologia

12, 13 E 14 MARÇO DE 2020

Hotel Pullman São Paulo Vila Olímpia

Uso Racional de Fatores de Crescimento Granulocítico na Hematologia

SANTA CASA de São Paulo

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Inovação e compromisso

Conflitos de Interesses

Rodolfo D. Cançado CRM 56697/SP

De acordo com a resolução do Conselho Federal de Medicina nº 1595/2000 e Resolução da Diretoria Colegiada da ANVISA nº 96/2008, eu declaro que:

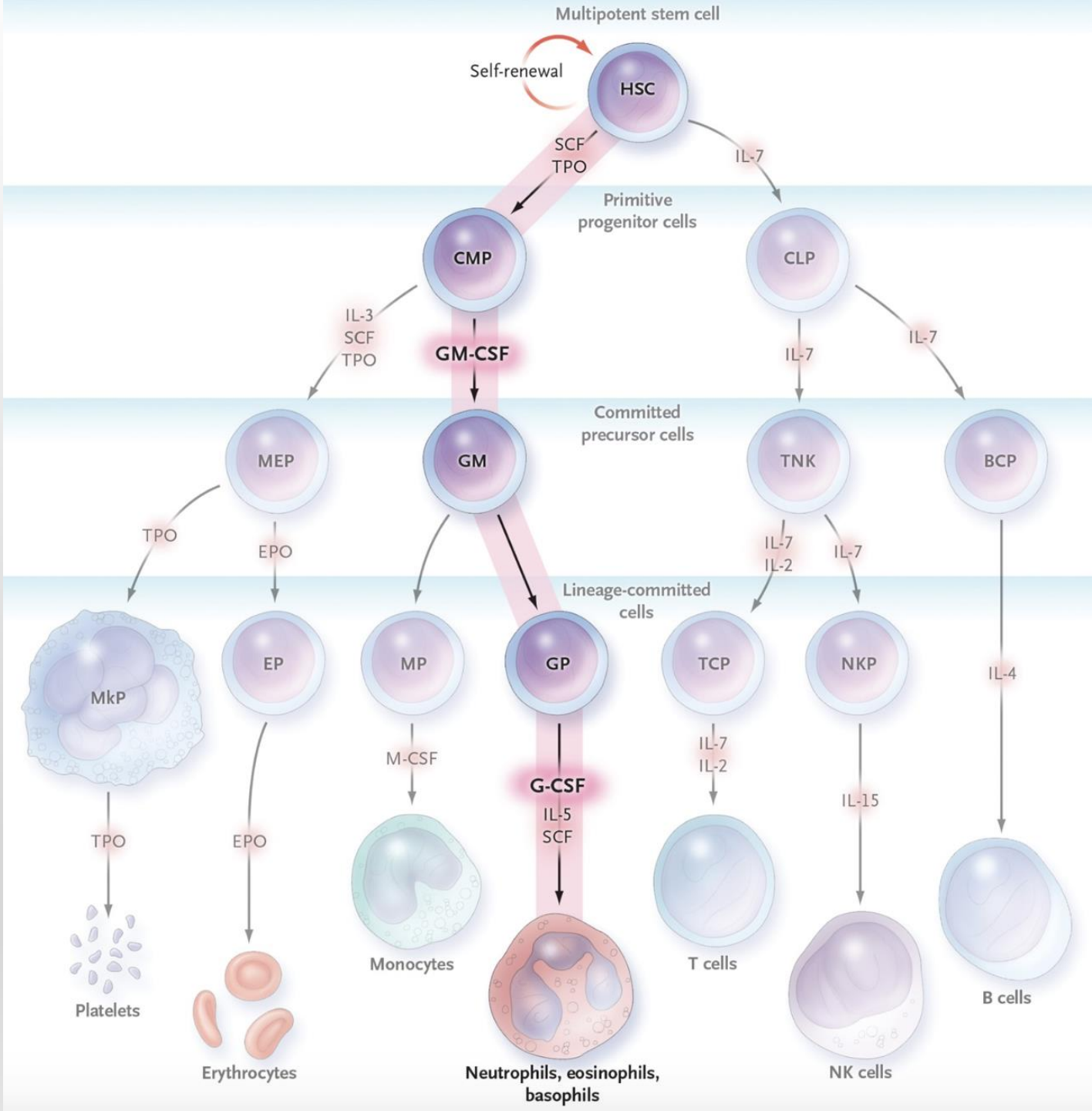
- Pesquisa Clínica – Como investigador: AstraZeneca, Novartis
- Apresentações científicas – Como palestrante: Novartis, Takeda, Farmoquimica, AstraZeneca, Amgen
- Atividades de Consultoria – Como membro de Advisory Boards: Novartis

Declaro não ter ações em bolsa de valores das empresas supracitadas.

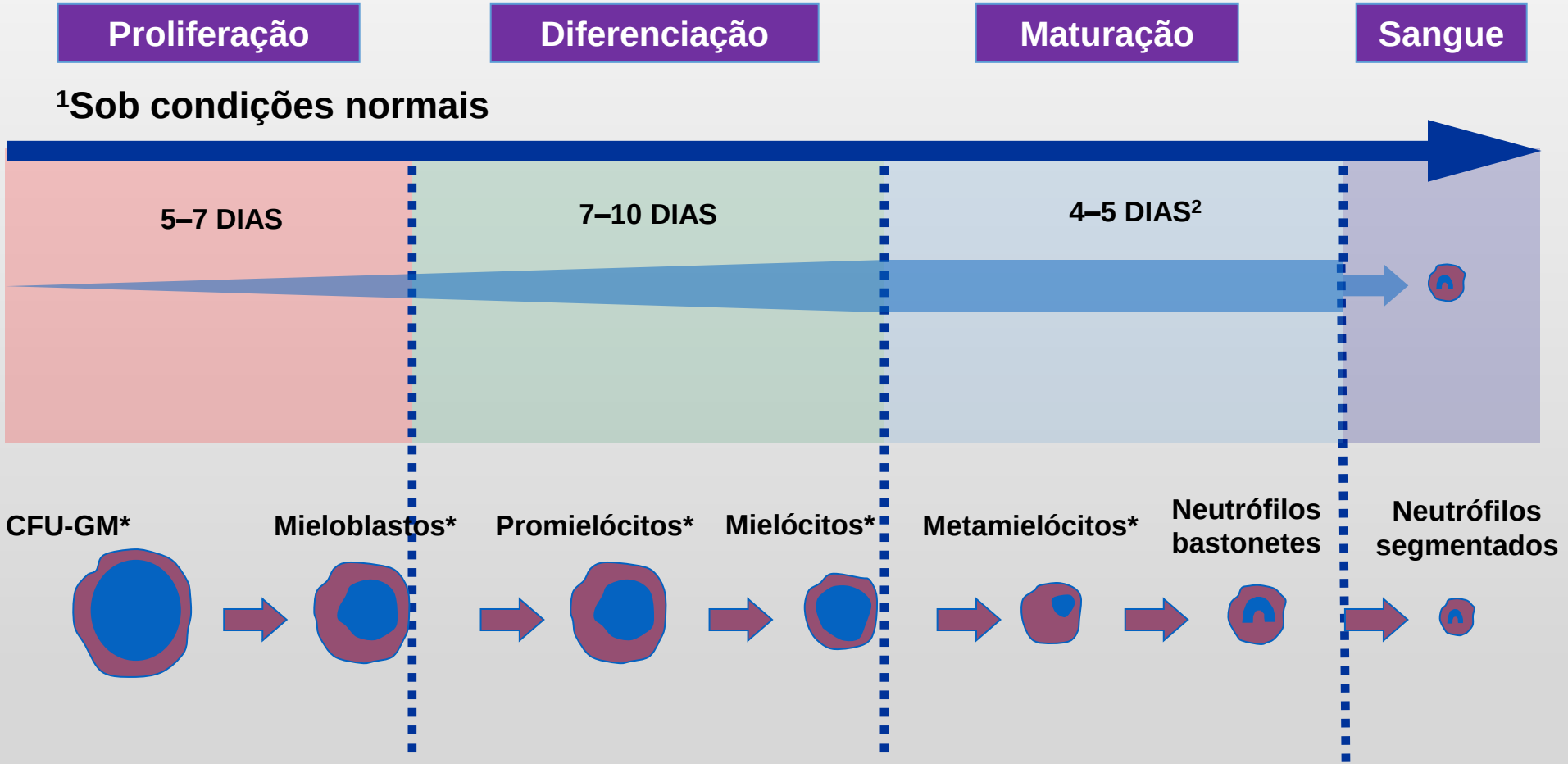
Meus pré-requisitos para participar destas atividades são o intercâmbio científico, a autonomia do pensamento científico, independência de opinião e liberdade de expressão, aspectos estes respeitados pela Novartis.

As informações fornecidas neste material podem incluir recomendações que não constam na bula aprovada de nossos produtos. Estas informações têm o intuito de fornecer a você os dados científicos pertinentes para tirar suas próprias conclusões e para tomar suas próprias decisões. Estas informações não são destinadas à promoção ou recomendação de nenhuma indicação, dose ou outra alegação não incluída na bula do produto. A Novartis não corrobora a promoção de seus produtos de uma forma que não esteja de acordo com suas bulas aprovadas.

Hematopoese e Fatores de Crescimento Hemotopoéticos no processo de Proliferação e Diferenciação das Células Hematopoéticas



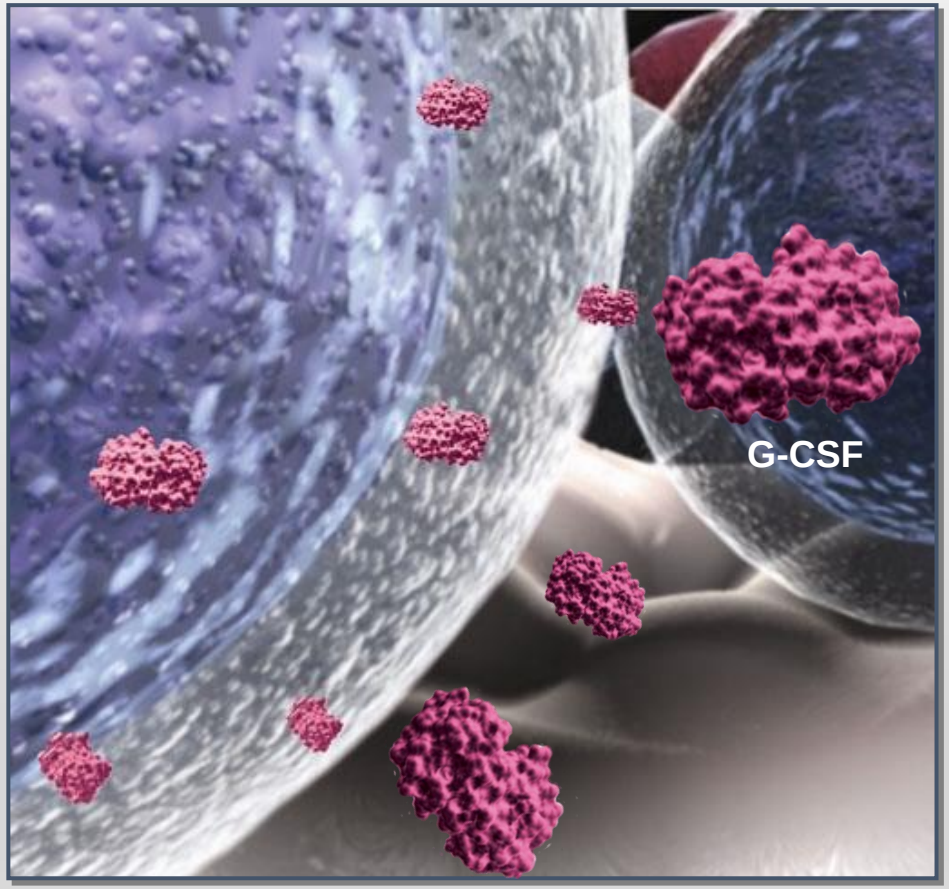
Granulocitopoese



Adaptado de: 1. Silvia FM et al. Development and maturation of neutrophils. Veterinary Quarterly 1994 (16); 4: 220-5. 2. Lord et al. The kinetics of human granulopoiesis following treatment with granulocyte colony-stimulating factor in vivo Proc. Natl. Acad. Sci. USA 86, 9499- 9503 (1989).

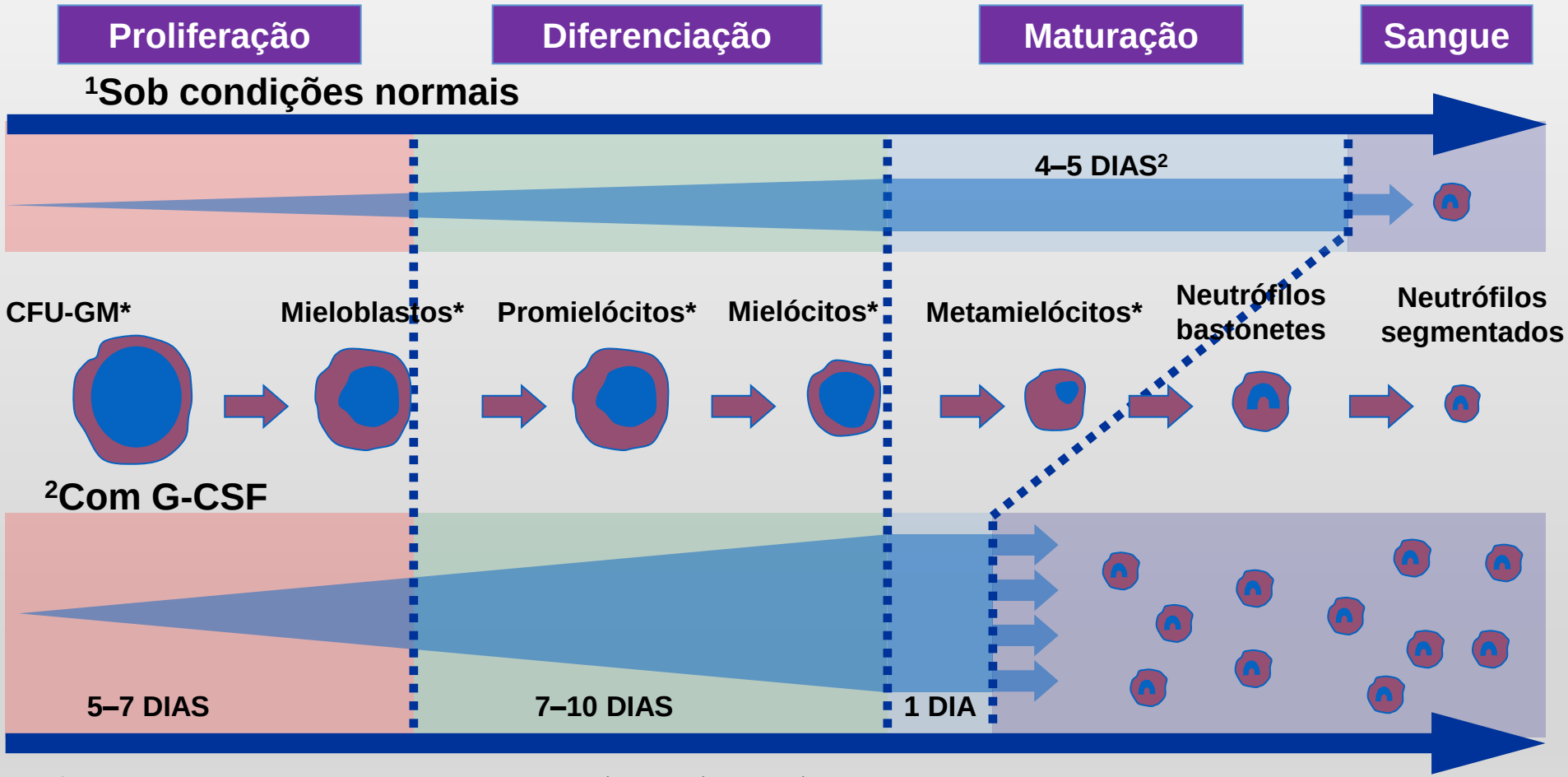
Fator de Crescimento Granulocítico (G-CSF) Endógeno

- ✓ Liga-se aos receptores das células precursosas de neutrófilos
- ✓ Estimula a proliferação e diferenciação de células imaturas para formar os neutrófilos maduros



Adaptado de Núñez C, et al. *Hematopoietic Lineages in Health and Disease.* 1997;49−55.

Granulocitopoese com G-CSF



*A referência baseada em animais foi somente para ilustrar o ciclo de maturação dos neutrófilos. Foi incluído um comentário no slide.

Adaptado de: 1. Silvia FM et al. Development and maturation of neutrophils. Veterinary Quarterly 1994 (16); 4: 220-5. 2. Lord et al. The kinetics of human granulopoiesis following treatment with granulocyte colony-stimulating factor in vivo Proc. Natl. Acad. Sci. USA 86, 9499- 9503 (1989).

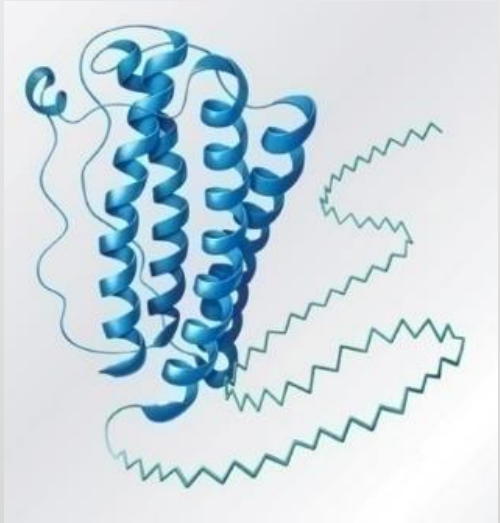
Fatores de Crescimento Granulocítico Exógenos

G-CSF diário: filgrastim[1,3,4]

Filgrastim : fator de crescimento recombinante, FDA (1991)

Lenograstim
GM-CSF (sargramostim)
GMCSF derivado da E. coli (molgramostim)

Pegfilgrastim[2,3,4]



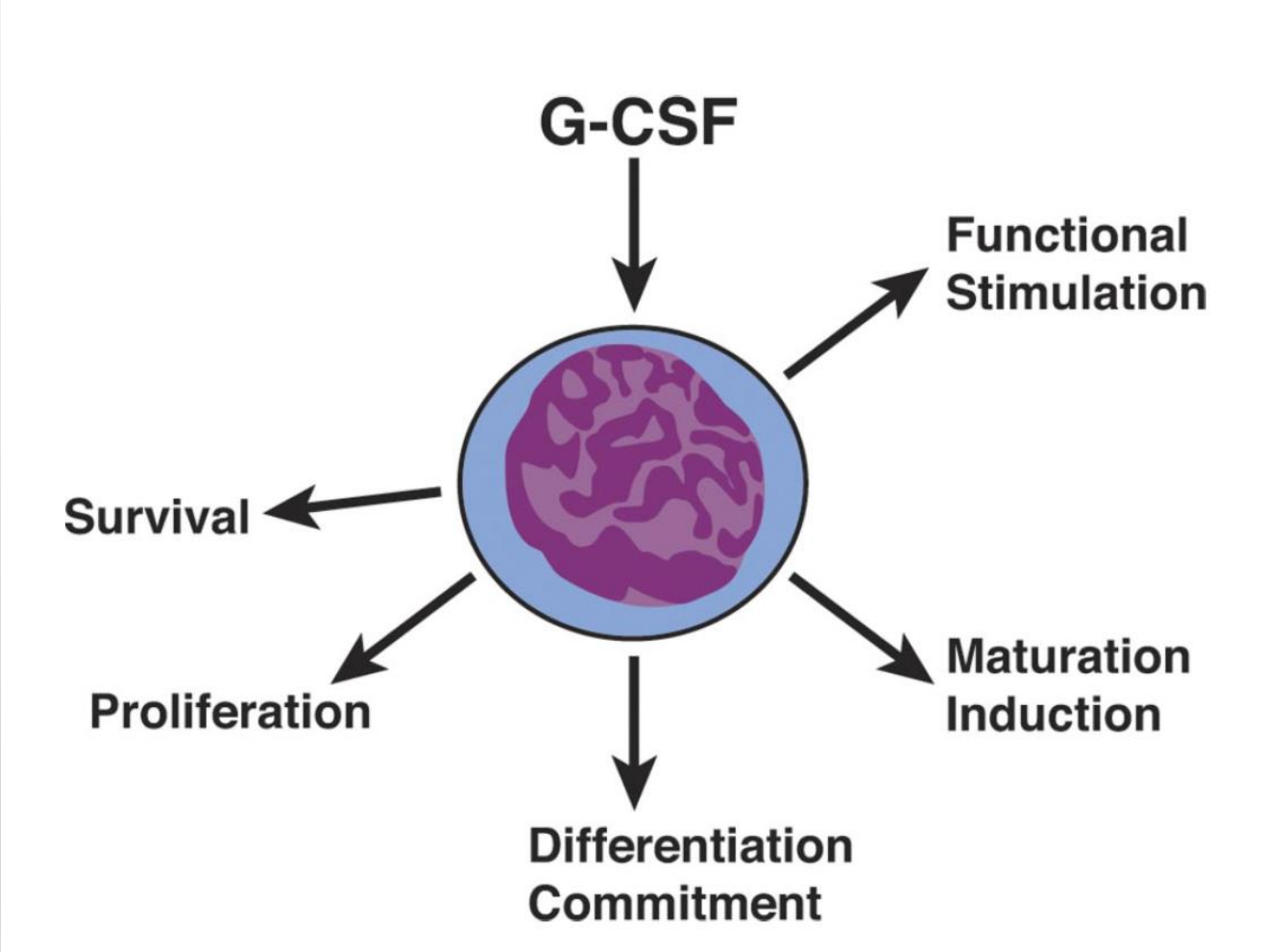
Pegfilgrastim: adição de um grupo de polietileno glicol (PEG) ao N-terminal de filgrastim, FDA (2002)

Lipegfilgrastim
Balugrastim

Adaptado de: 1. Filgrastim. Bula aprovada pela ANVISA em 24/01/2019. 2.Pegfilgrastim. Bula aprovada pela ANVISA em 20/02/2019. 3. Komrokji RS, et al. The colony-stimulating factors: Opinion use to prevent and treat neutropenia and its complications. *Expert Opin Biol Ther* 2004;4:1897-910. 4. Green MD et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy *Annals of Oncology* 2003;14:29–35.

Filgrastrim (Granulokine®, Neupogen®)

- Meia-vida: 2 – 4 horas
- Eliminado principalmente por filtração glomerular e excreção renal

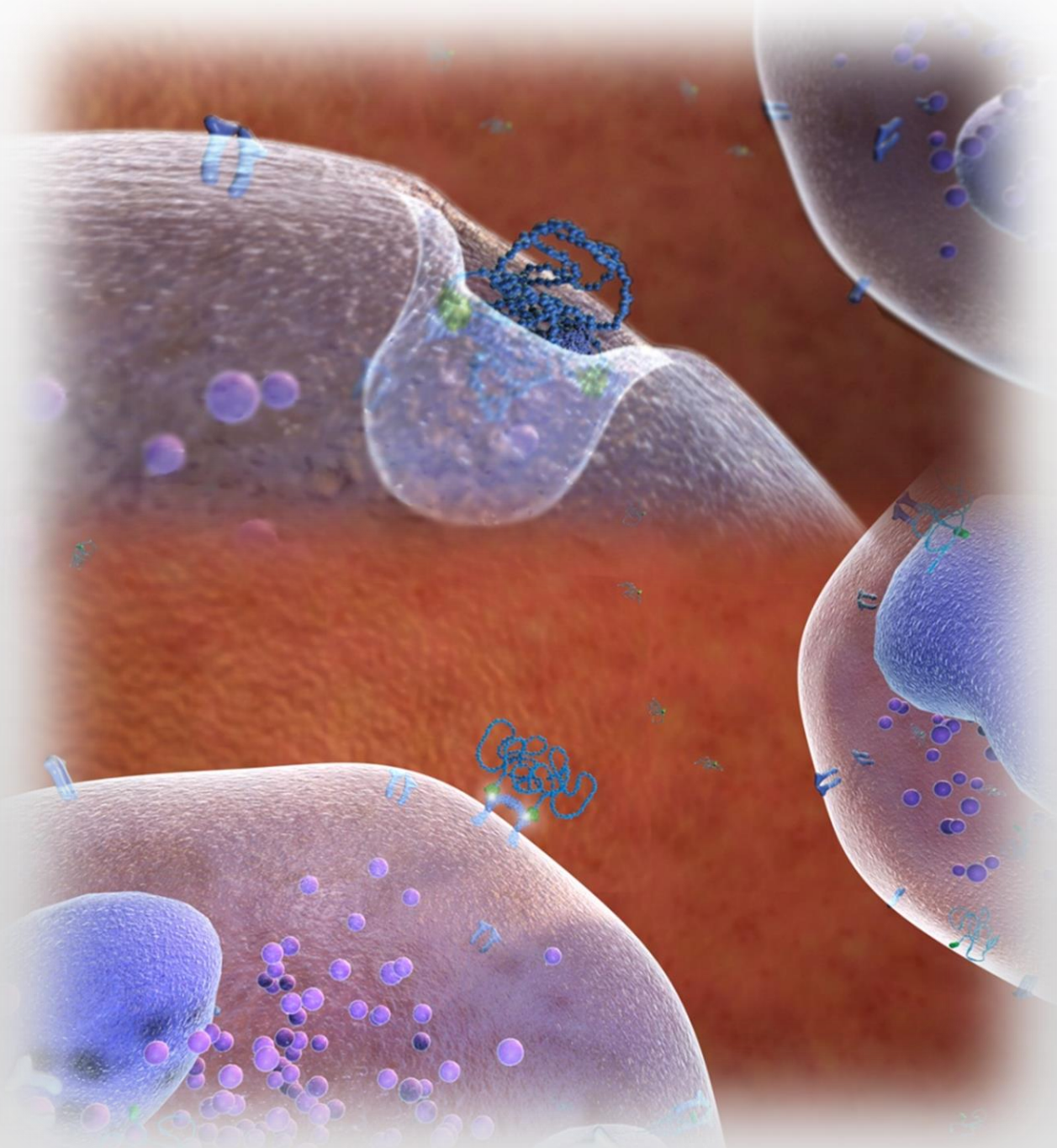


Jordan K et al. Dtsch Arztebl Int 2017; 114: 481–7.

Adaptado de: Yang BB, Kido A, Shibata A, et al. Serum pegfilgrastim concentrations during recovery of absolute neutrophil count in patients with cancer receiving pegfilgrastim after chemotherapy. *Pharmacotherapy*. 2007;27:1387-1393.

Pegfilgrastim: Neulastim®
Depuração mediada por neutrófilos

- Pegfilgrastim liga-se ao receptor de G-CSF presente na superfície do neutrófilo
- O complexo resultando receptor-G-CSF é internalizado e metabolizado

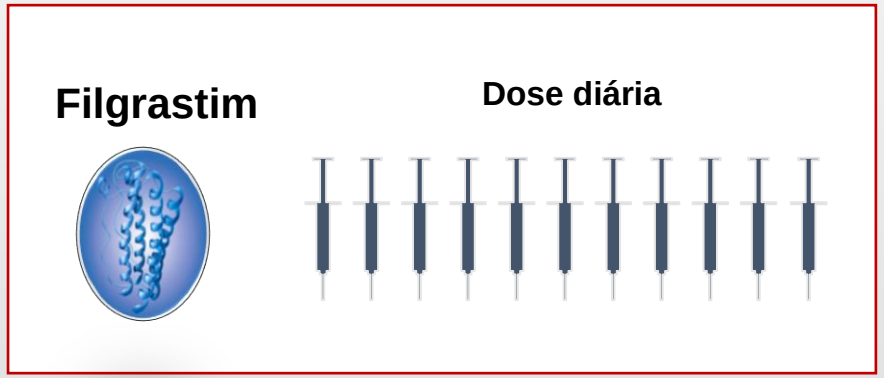


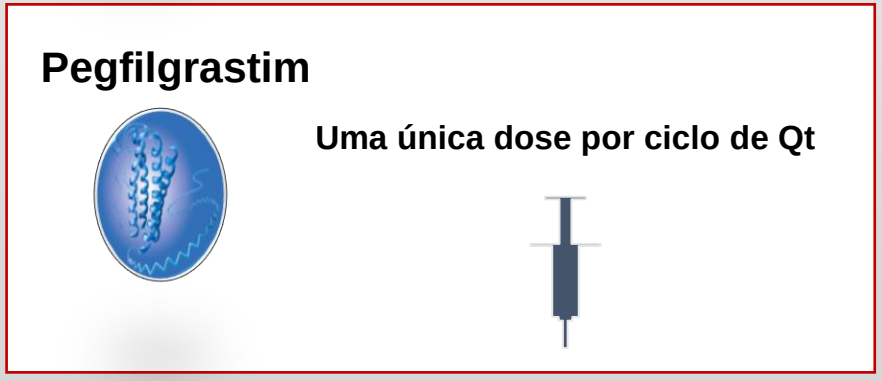
Luftner D, Possinger K. Pegfilgrastim-Rational drug design for the management of chemotherapy-induced Neutropenia. *Onkologie*. 2005;28:595−602.
Yang BB, Kido A, Shibata A, et al. Serum pegfilgrastim concentrations during recovery of absolute neutrophil count in patients with cancer receiving pegfilgrastim after chemotherapy. *Pharmacotherapy*. 2007;27:1387-1393.

Vantagens da Peguilação

- Aumento do tempo de meia-vida
  - ✓ **2 - 4 horas (filgrastim)** vs

    46 - 62 horas (pegfilgrastim)
- Menor frequência de administração
- Maior adesão
- Melhor qualidade de vida
- Menor/melhor custo-efetividade

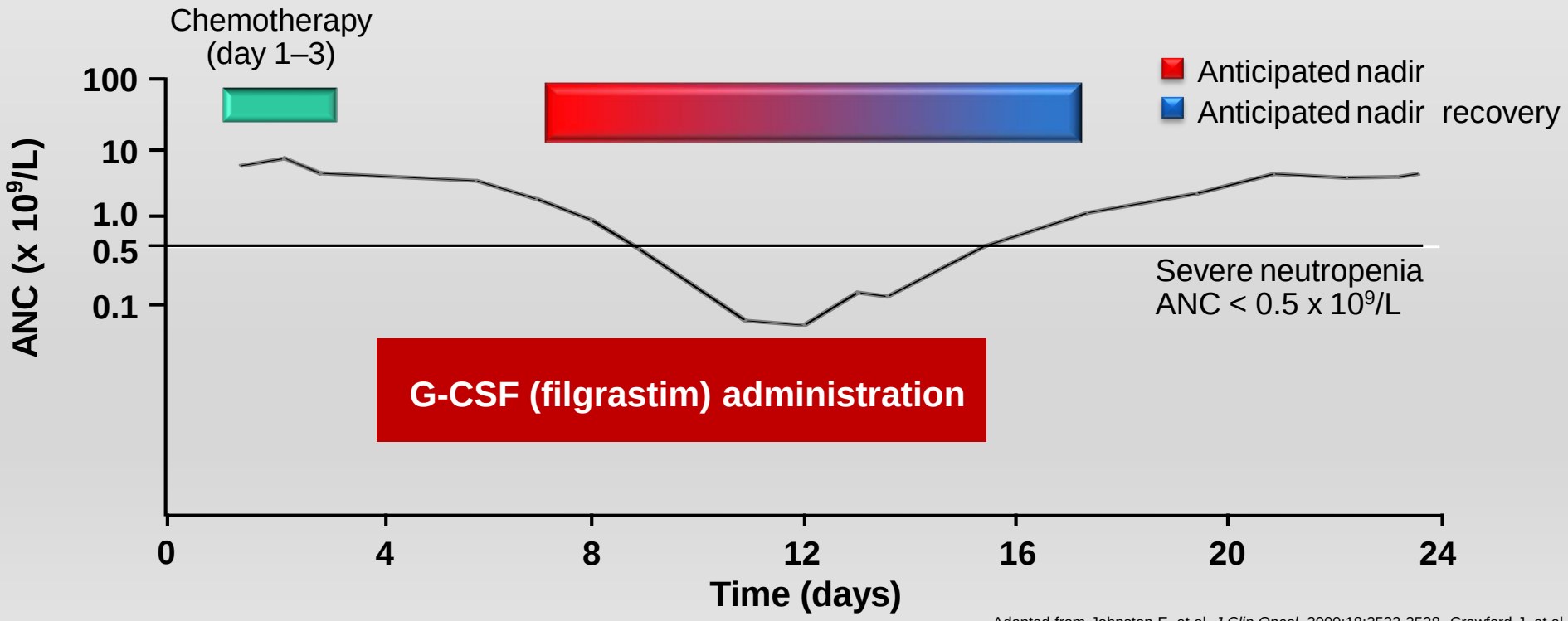




Adaptado de: Green MD et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy *Annals of Oncology* 2003;14:29–35;

Filgrastrim (Granulokine®, Neupogen®)

- Deve ser iniciado 24 horas após o término da Qt citotóxica
- Dose: 5 µg/kg/d administrado via SC ou IV
- Mantido até pós-nadir



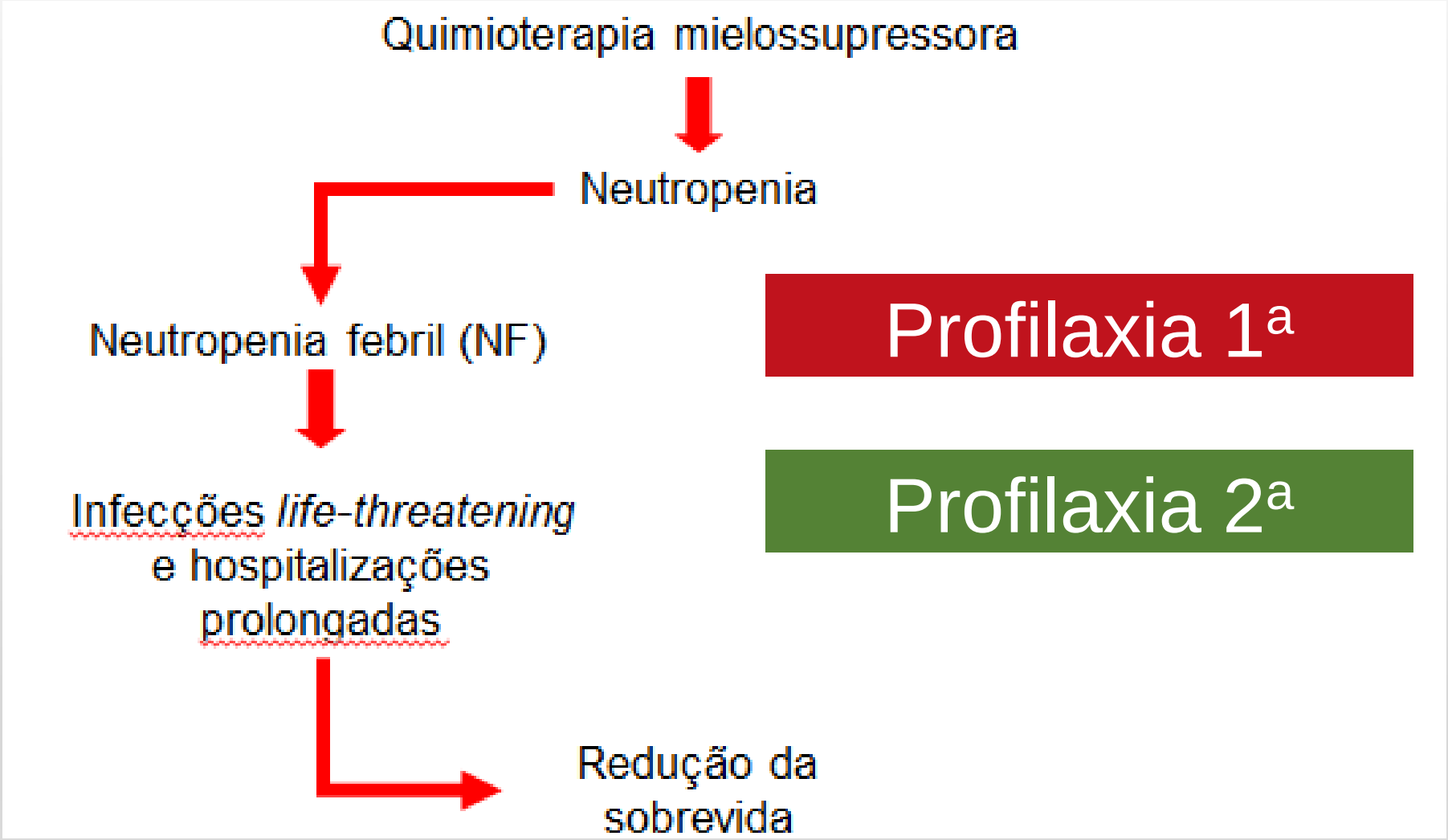
Adapted from Johnston E, et al. *J Clin Oncol*. 2000;18:2522-2528. Crawford J, et al. *N Engl J Med*. 1991;325:164–170

Pegfilgrastrim (Neulastim®)

- Deve ser iniciado 24 horas o término da quimioterapia citotóxica
- Dose: 6 mg (seringa preenchida) administrada via SC
- Recomendada uma dose para cada ciclo de Qt

Porquê?

Uso Racional de G-CSF



Adaptado de:

1. Kuderer NM, et al. Mortality, Morbidity, and Cost Associated with Febrile Neutropenia in Adult Cancer Patients*Cancer* 2006;106:2258–2266; 2. Chirivella I, et al. Impact of chemotherapy dose-related factors on survival in breast cancer patients treated with adjuvant anthracycline-based chemotherapy Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 24, No 18S (June 20 Supplement), 2006: 668 *J Clin Oncol* 2006;24:Abstract 668; 3. Bosly A, et al. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. *Hematol* 2007, advance access published October 20, 2007; doi:10.1007/s00277-007-0399-y

Neutropenia Induzida por QT e suas Complicações

- National Cancer Institute (NCI)
  - ✓ 60.000 pacientes admitidos por NF por ano
  - ✓ Aprox. 8 casos/1000 pacientes em Qt
- Neutropenia (>10-14 dias) predispõe:
  - ✓ Infecção grave
  - ✓ Óbito (pode chegar a 15% por evento)
- Custo ($13,372 - $19,110)

Bennetti CL , New England Journal Medicine,, 2013; 368;12.

>50% de todas as neutropenias (G3-4) ocorrem no primeiro ciclo em vários tipos de tumor

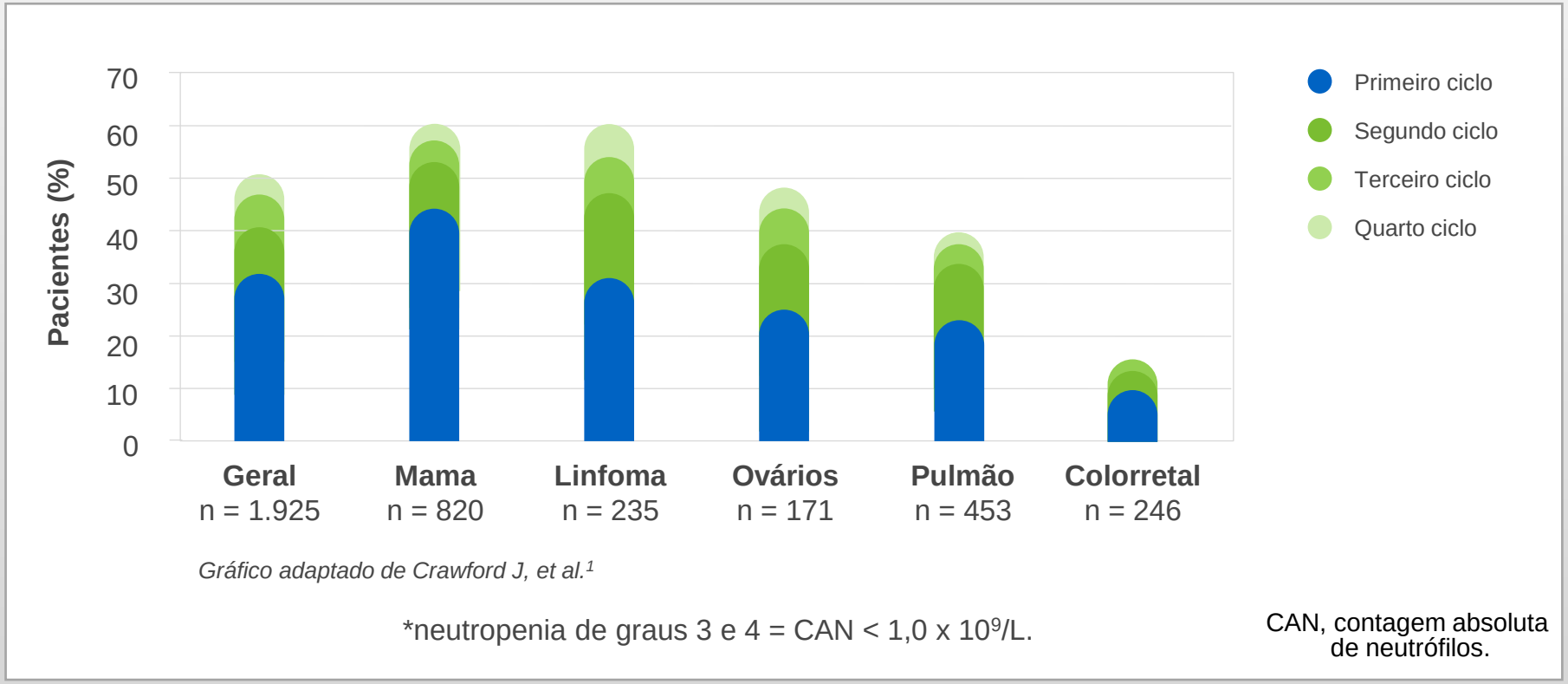


Gráfico adaptado de Crawford J, et al.[1]

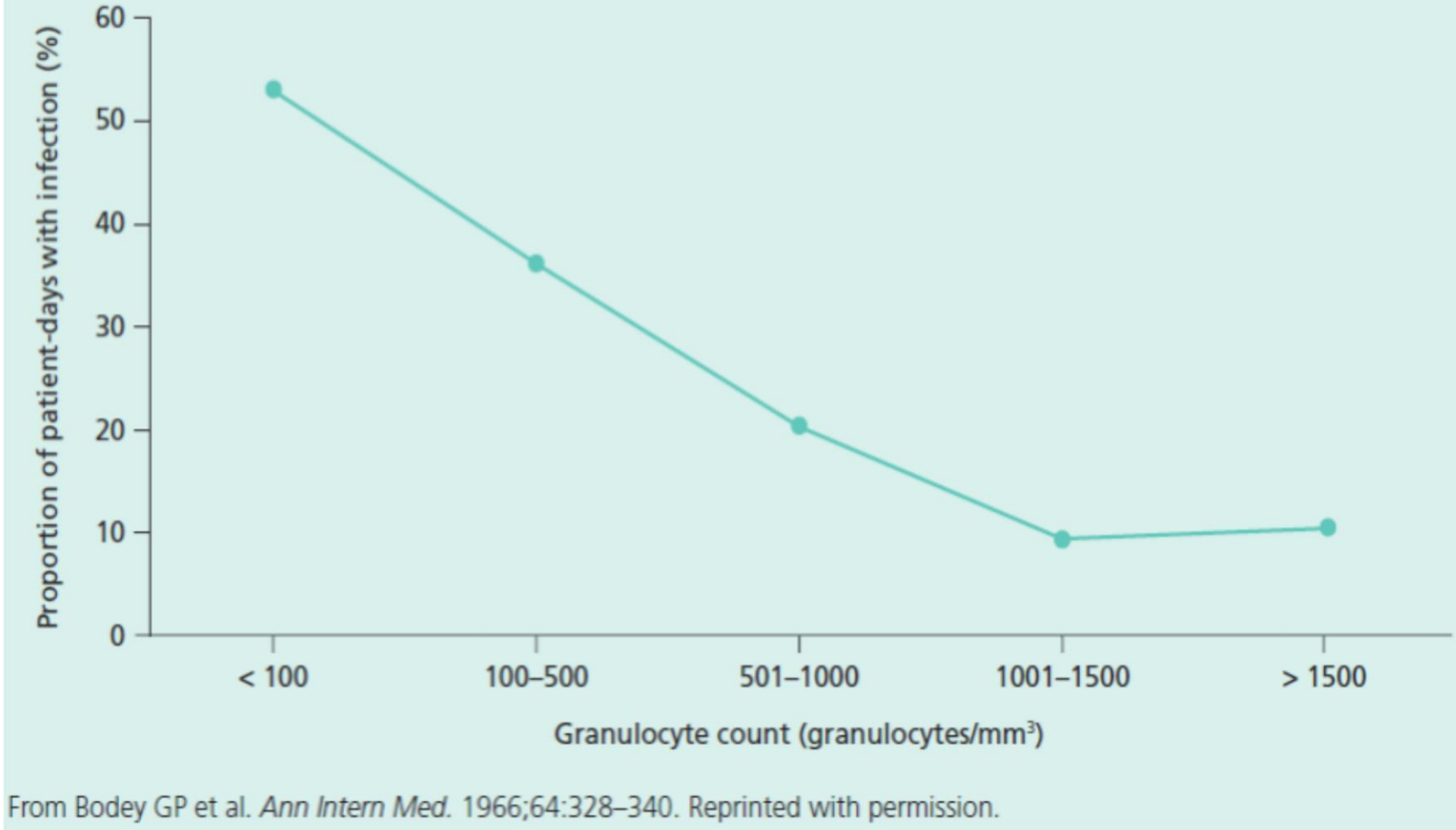
*neutropenia de graus 3 e 4 = CAN < 1,0 x 10^9/L.

CAN, contagem absoluta de neutrófilos.

Eventos neutropênicos de graus 3/4 podem levar a atraso ou redução de dose

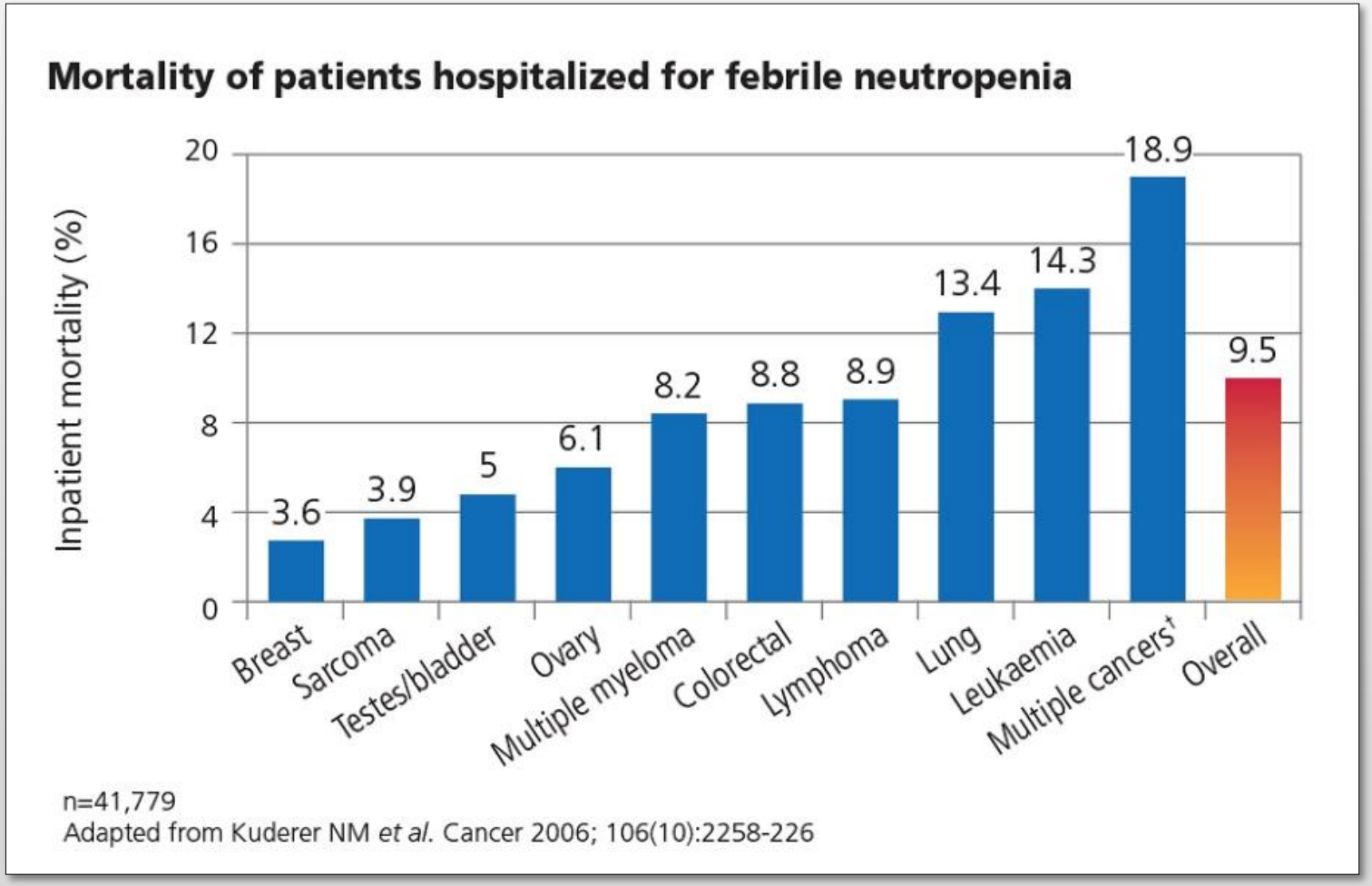
1. Crawford J, et al para o CAN Study Group. Painel apresentado no: 46º Encontro Anual da Sociedade Americana de Hematologia; 4 a 7 de dezembro de 2004; San Diego, Califórnia. Painel 2210;
2. Dale DC, et al. *J Natl Compr Cancer Netw*. 2003;1:440-454.

Risco de Infecção e Contagem Absoluta de Neutrófilos em pacientes com Leucemia Aguda em tratamento Qt

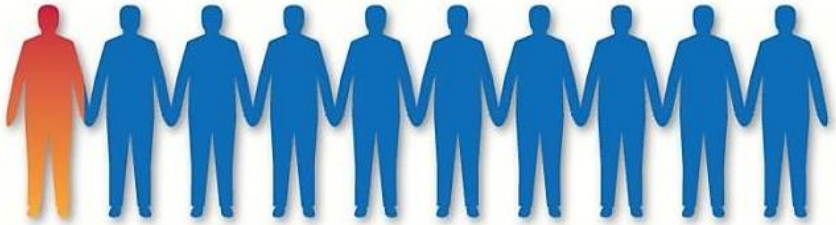


From Bodey GP et al. *Ann Intern Med.* 1966;64:328–340. Reprinted with permission.

Neutropenia Febril e Risco de Morte



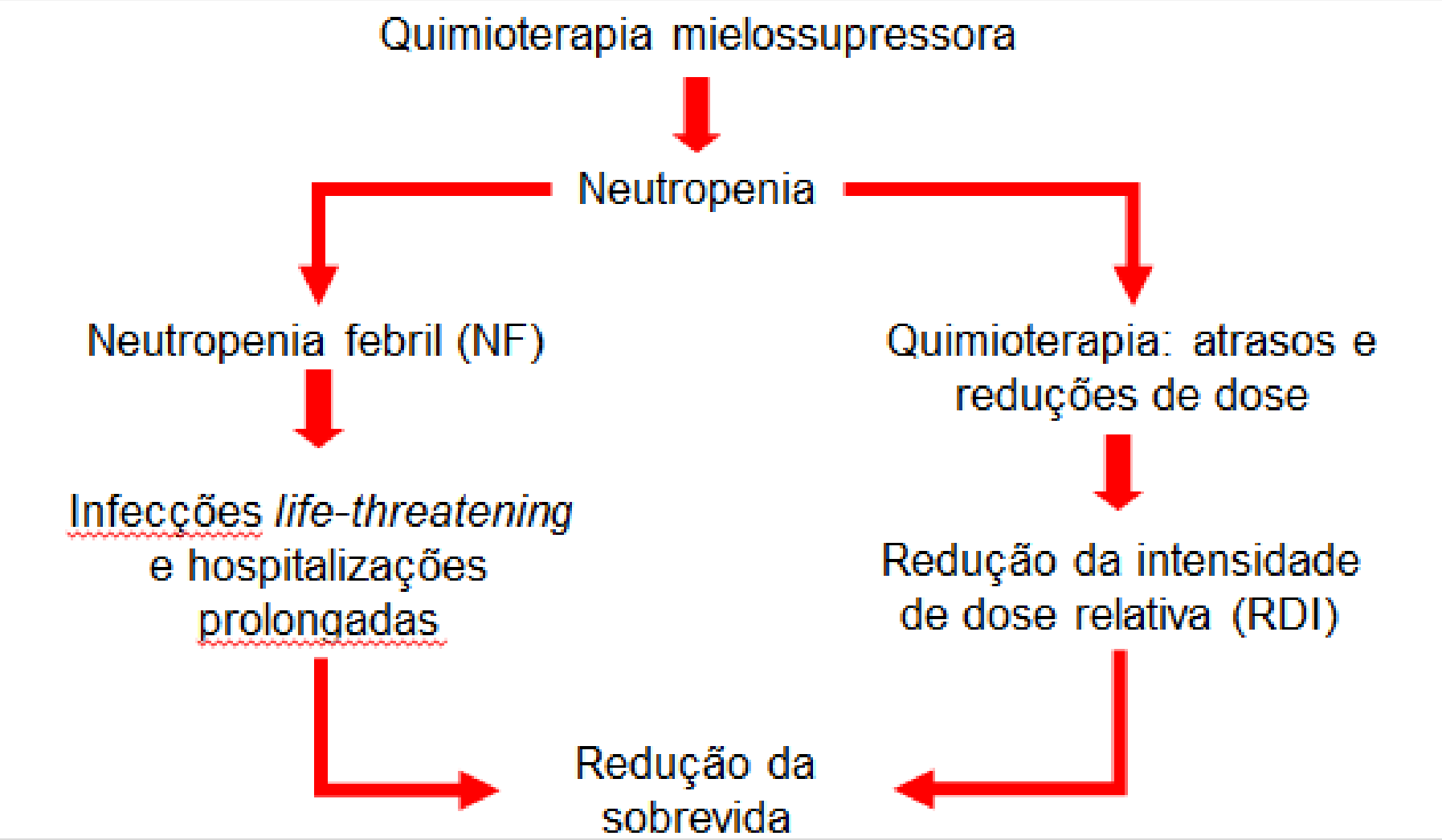
1 in 10 Patients hospitalized for FN die[1]



In this study using a large longitudinal database of 41,779 adult cancer patients who were hospitalized for febrile neutropenia, the overall risk of mortality was 1 in 10 patients. The longitudinal discharge database derived from 115 US medical centers was used to study all adult cancer patients hospitalized with FN between 1995 and 2000, comprising a total of 41,779 patients. Primary outcomes included mortality, length of stay (LOS), and cost per episode.

Porquê?

Uso Racional de G-CSF



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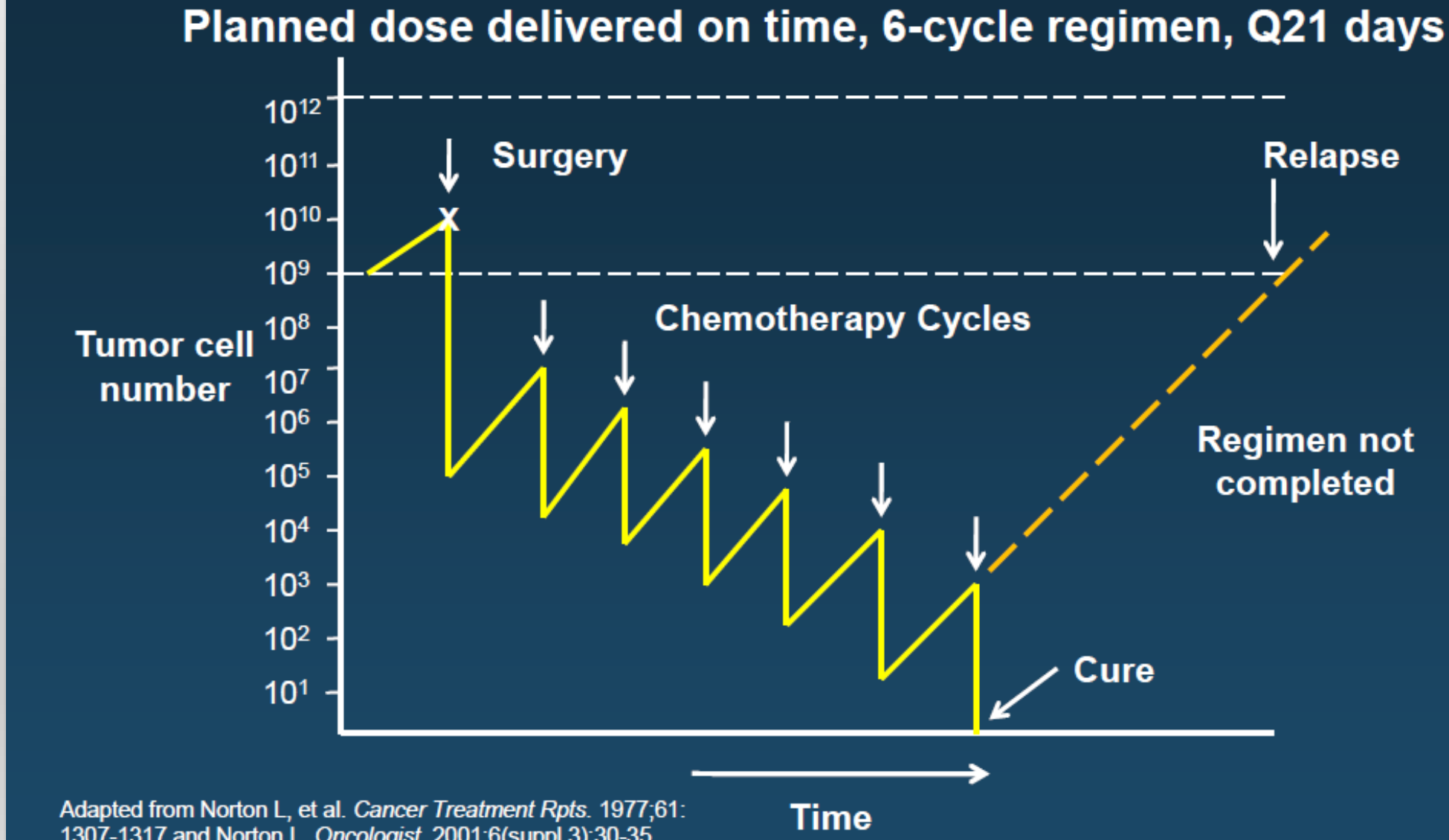
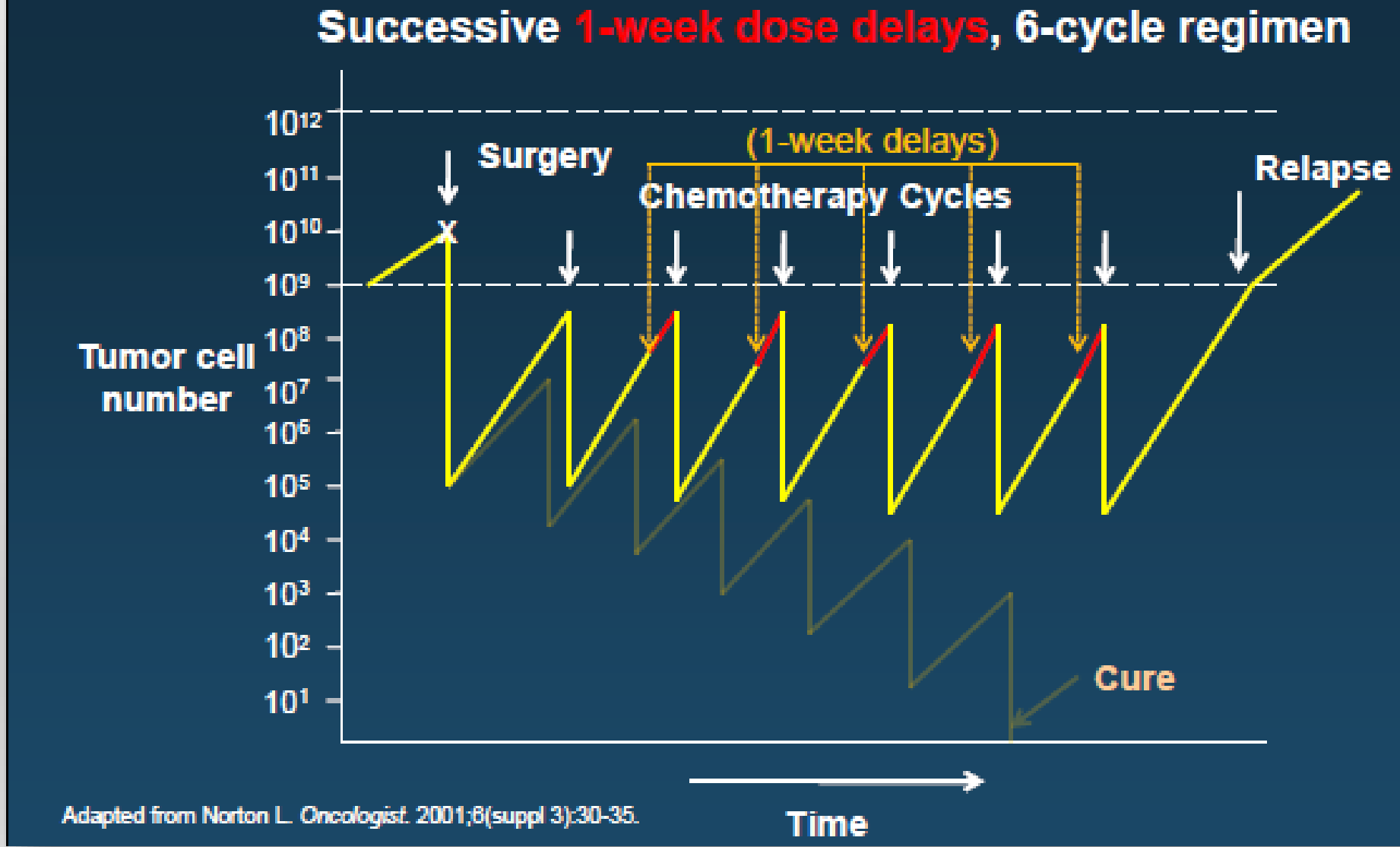
Tumor Growth Between Cycles



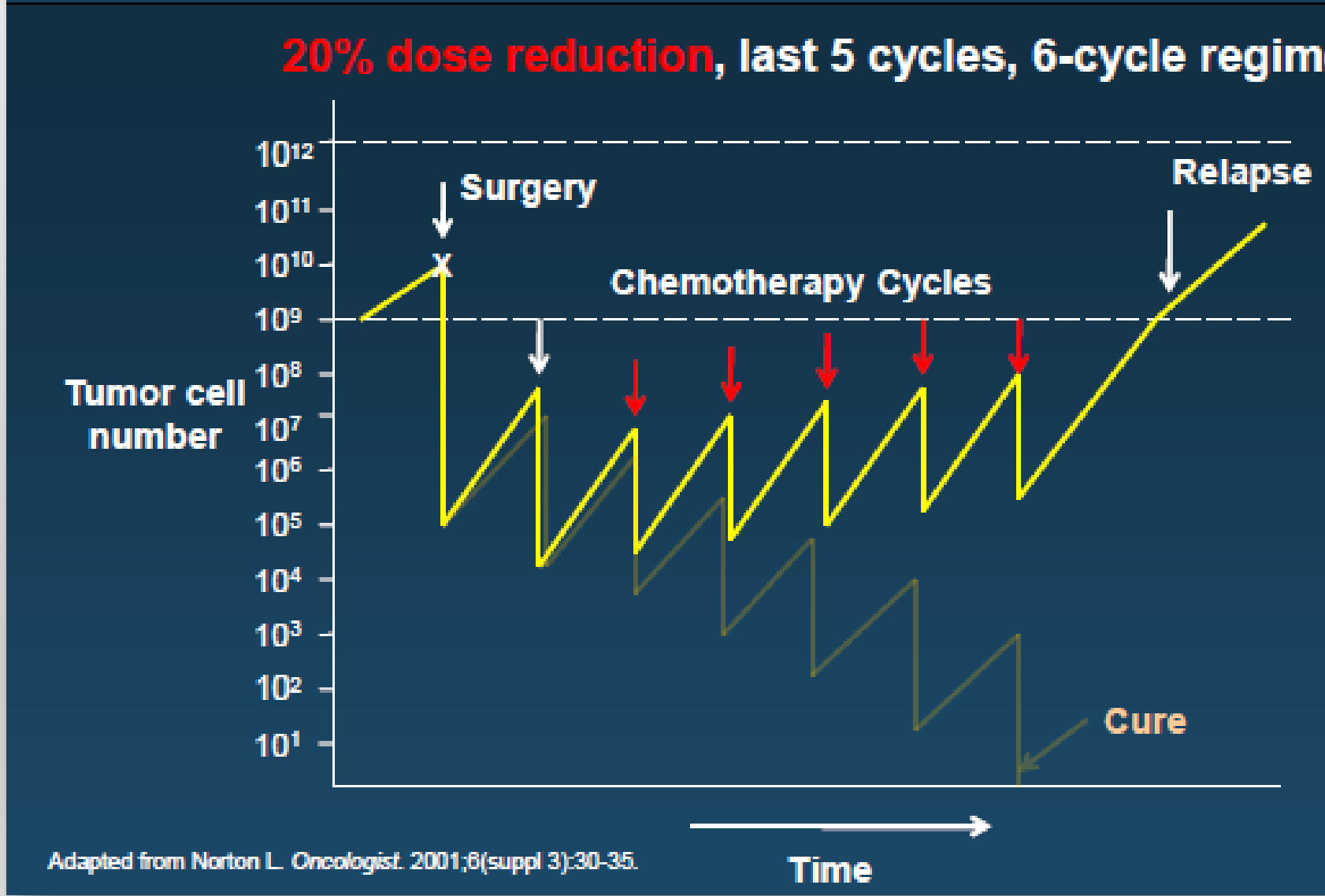
Adapted from Norton L, et al. *Cancer Treatment Rpts.* 1977;61: 1307-1317 and Norton L. *Oncologist.* 2001;6(suppl 3):30-35.

Theoretical Relapse With Suboptimal Adjuvant Chemotherapy Due to Dose Delays



Adapted from Norton L. *Oncologist*. 2001;6(suppl 3):30-35.

Theoretical Relapse With Suboptimal Adjuvant Chemotherapy Due to Dose Reductions



Adapted from Norton L. *Oncologist*. 2001;6(suppl 3):30-35.

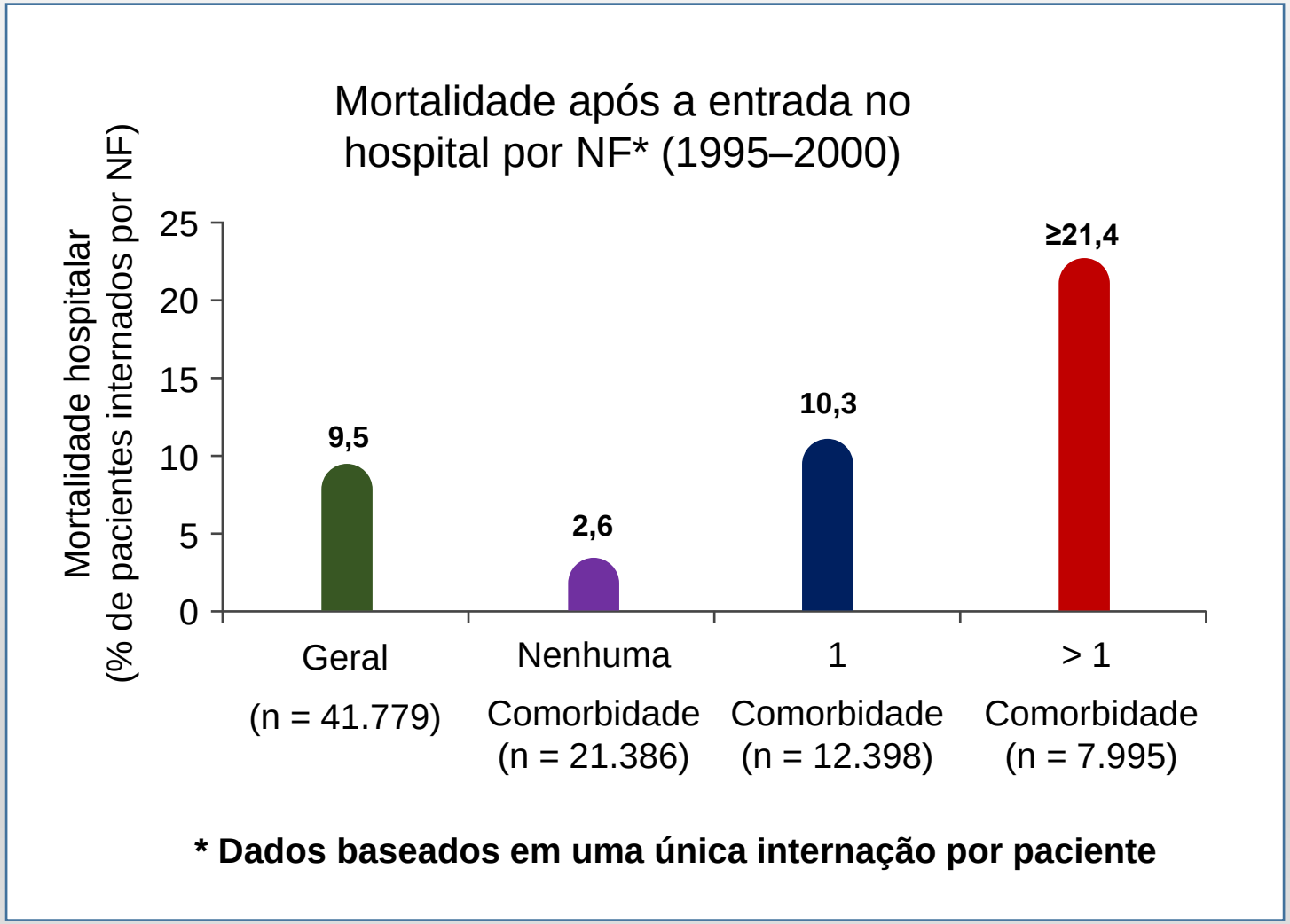
Uso Racional de G-CSF: Principais Fatores de Risco

Para Quem?

- Regime Qt e intenção do tratamento
- > 65 anos de idade
- Baixo *Performance Status*
- Fatores coexistentes (comorbidade)
  - ✓ Disfunção Renal (Clcreat < 50), Hepática, Cardíaca [NYHA III/IV], DPOC
- Fatores pré-existentes
  - ✓ Infecção, cirurgia recente, comprometimento da MO e/ou Rdt
- Pacientes que não fizeram profilaxia primária no 1º ciclo e não obtiveram recuperação granulocítica adequada no tempo planejado
- Anemia, linfopenia (<700/mm^3), hipoalbuminemia, bilirrubina > 2

Bennetti CL , New England Journal Medicine,, 2013; 368;12.

Relação entre Neutropenia febril, Risco de Morte e Comorbidade



NF, neutropenia febril; UHC, University HealthSystem Consortium.
Adaptado de: Kuderer NM, et al. *Cancer*. 2006;106:2258-2266.

National Comprehensive Cancer Network®

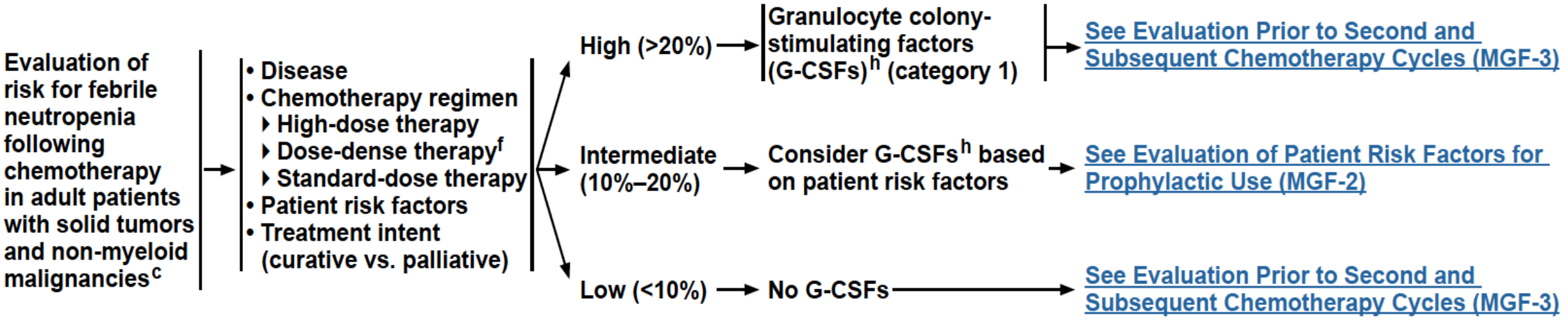
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hematopoietic Growth Factors

Version 2.2020 — January 27, 2020

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Management of Neutropenia



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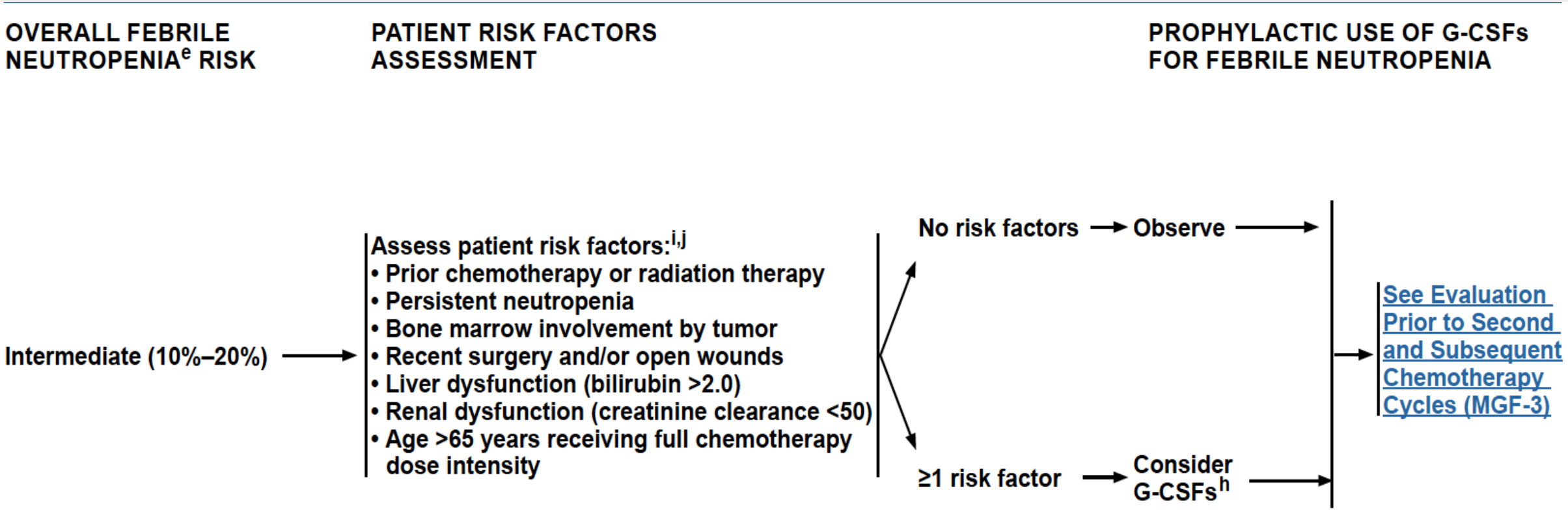
NCCN Guidelines Version 2.2020
Management of Neutropenia



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NCCN Guidelines Version 2.2020
Management of Neutropenia

Example of Disease Settings and Chemotherapy Regimens with an Intermediate Risk For Febrile Neutropenia (10%-20%)

Non-Hodgkin's Lymphomas

- GDP (gemcitabine, dexamethasone, cisplatin/ carboplatin)[a,54]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[55,56] including regimens with pegylated liposomal doxorubicin[57,58]
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Bendamustine[a]

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Management of Neutropenia

Example of Disease Settings and Chemotherapy Regimens with a High Risk For Febrile Neutropenia (>20%)

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]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]

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

Kidney Cancer
- Doxorubicin/gemcitabine[17]

Non-Hodgkin's Lymphomas
- 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]

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[d] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

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

Small Cell Lung Cancer
- Topotecan[36]

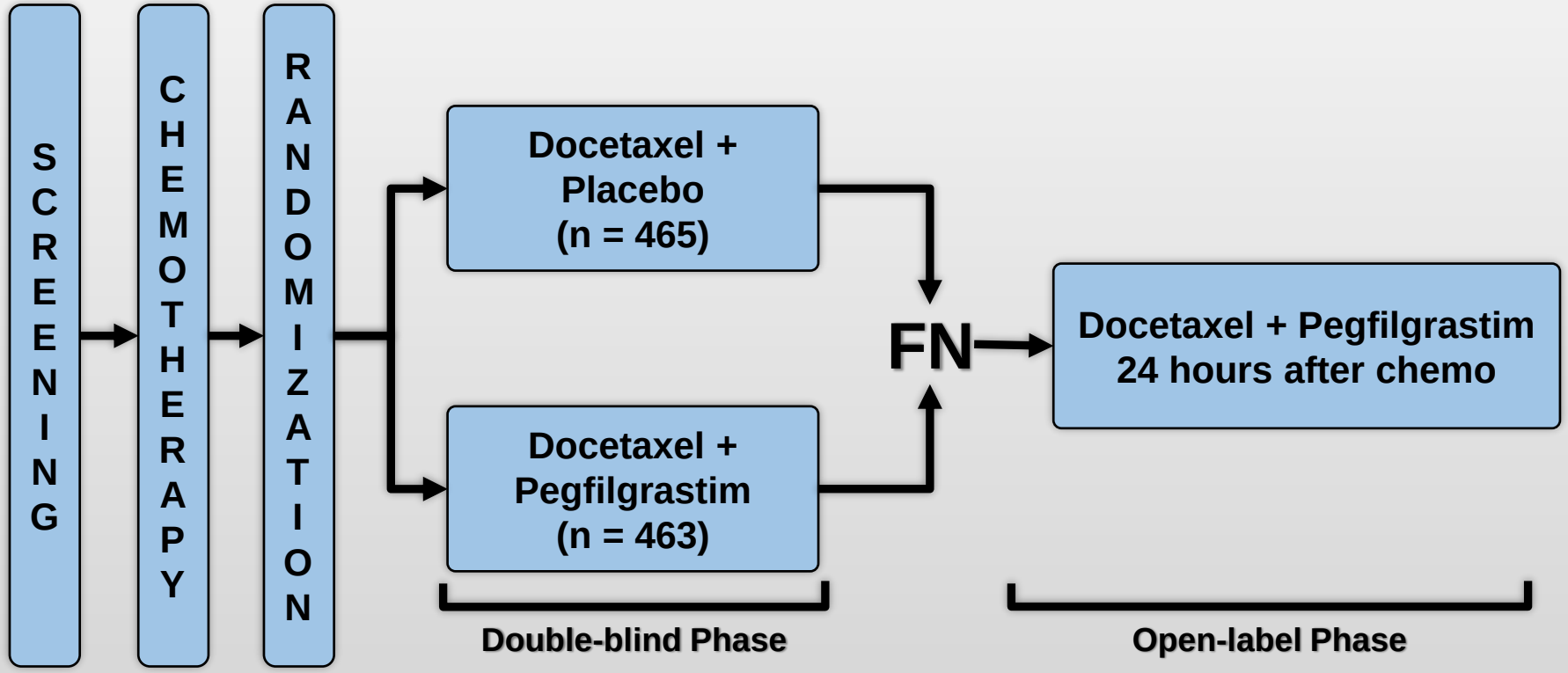
Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[37]
- VIP (etoposide, ifosfamide, cisplatin)

Benefícios Clínicos associados à Profilaxia Primária com G-CSF

- ✓ ⬇ risco de NF (até 94%)
- ✓ ⬇ risco de hospitalização por NF (até 93%)
- ✓ ⬇ uso de antimicrobianos (até 80%)
- ✓ ⬇ mortalidade precoce por infecção
- ✓ ⬇ atraso de ciclos e redução de doses

Adaptado de:
1. Kuderer NM, et al. Impact of Primary Prophylaxis With Granulocyte Colony- Stimulating Factor on Febrile Neutropenia and Mortality in Adult Cancer Patients Receiving Chemotherapy: A Systematic Review*J Clin Oncol* 2007;25:3158-67.
2. Pinto L, et al. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials Lionel P into a, Zhimei Liu a, Quan*Curr Med Res Opin* 2007;23:2283-95.
3. Von Minckwitz G, et al. Pegfilgrastim *6* ciprofloxacin for primary prophylaxis with TAC (docetaxel/doxorubicin/cyclophosphamide) chemotherapy for breast cancer. Results from the GEPARTRIO study*Ann Oncol* 2008;19:292-8.
4. Aapro M, et al. Pegfilgrastim primary prophylaxis vs. current practice neutropenia management in elderly breast cancer patients receiving chemotherapy *Crit Rev Oncol Hematol* 2010;74:203-10.
6. Lyman GH, et al. Acute Myeloid Leukemia or Myelodysplastic Syndrome in Randomized Controlled Clinical Trials of Cancer Chemotherapy With Granulocyte Colony-Stimulating Factor: A Systematic Review*J Clin Oncol* 2010;28:2914-24.
7. Lyman G, et al. Overall survival in randomized controlled trials of chemotherapy (CT) with or without GCSF support: A systematic review.*J Clin Oncol* 2010;28:15s (suppl; abstr 9141).
8. Bula Granulokine Roche: Aprovada em 02/09/2013;9. Bula Neulastim Roche: Aprovada em 31/03/2014; 9. Vogel CL, et al. *J Clin Oncol*. 2005;23:1178-1184.

Phase 3 Study to Evaluate the Efficacy of Pegfilgrastim in Reducing FN Incidence in Patients With Breast Cancer

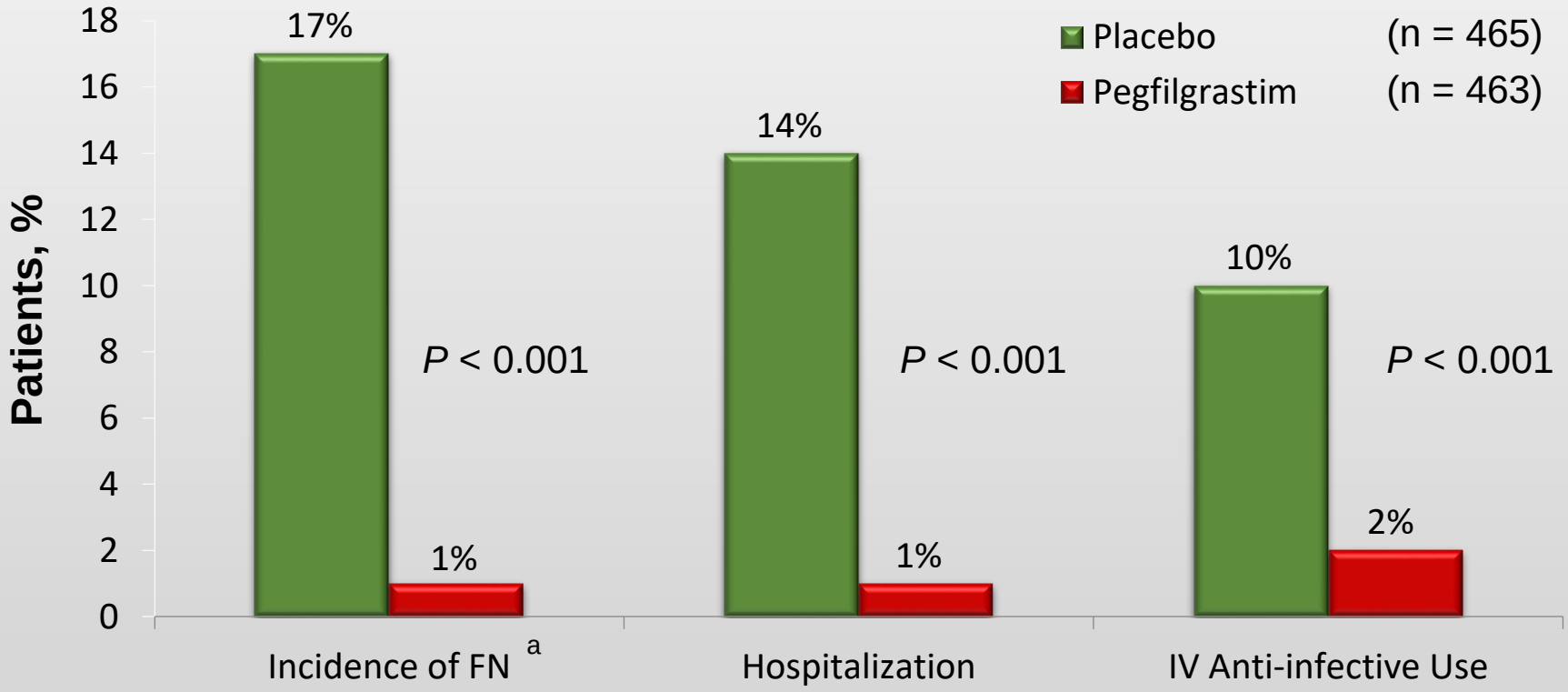


Phase 3 study design in breast cancer:
Phase 3, multicenter, multinational, double-blind, placebo-controlled trial of patients with breast cancer receiving 100 mg/m^2 docetaxel every 21 days for up to four cycles. The study included 928 patients randomized (1:1) to placebo or pegfilgrastim. Primary endpoint was percentage of patients who developed FN. Secondary endpoints were incidence of FN-related hospitalization and incidence of FN-related anti-infective use.

Febrile Neutropenia, FN = absolute neutrophil count < 0.5 x 10^9/L and temperature ≥ 38.2°C

Vogel CL, et al. *J Clin Oncol*. 2005;23:1178-1184.

Incidence of FN and FN-Related Complications: Pegfilgrastim vs Placebo

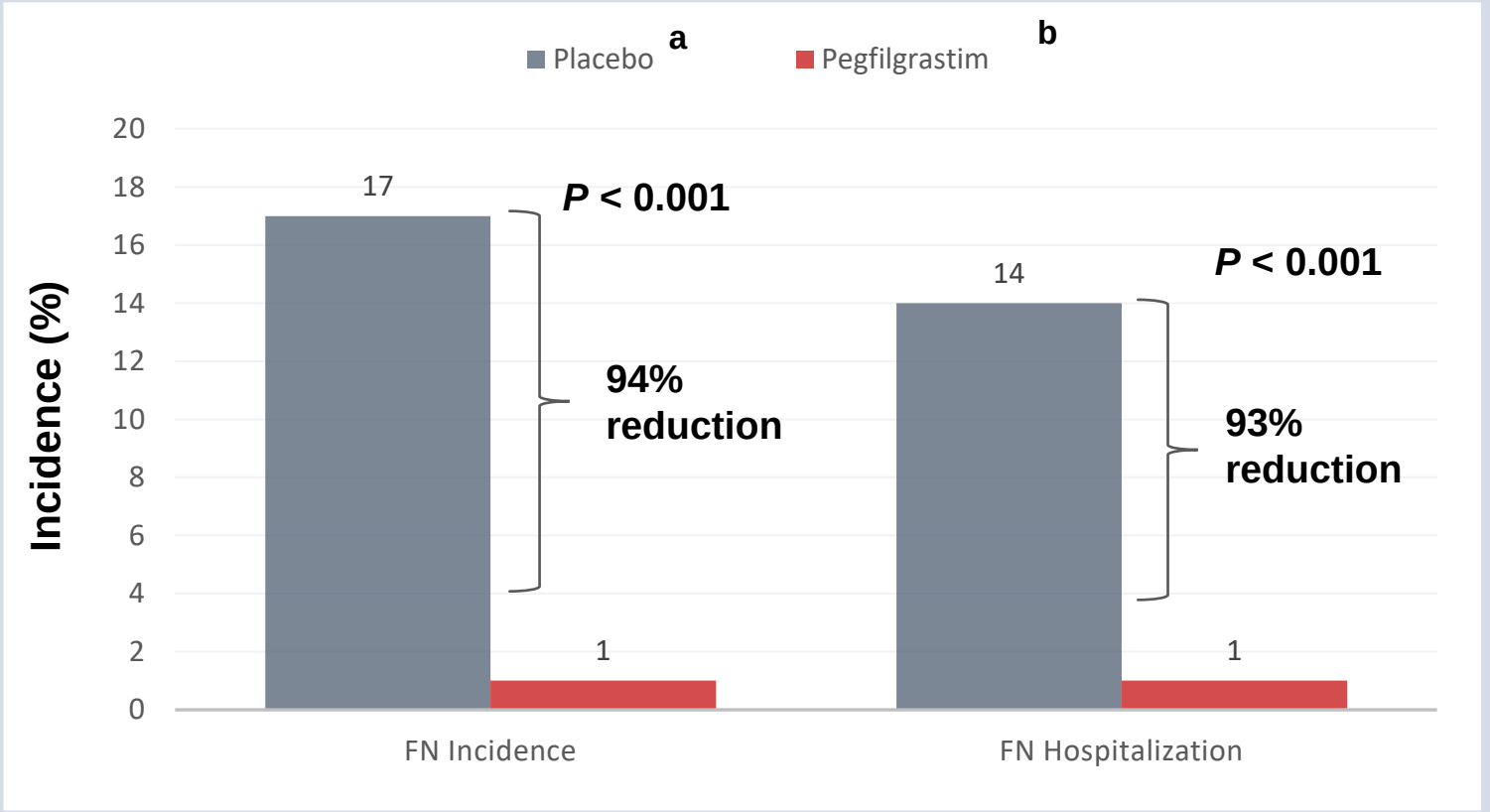


67% of FN events occurred during the first cycle in the placebo group

FN = febrile neutropenia; IV = intravenous

Vogel CL, et al. *J Clin Oncol*. 2005;23:1178-1184.

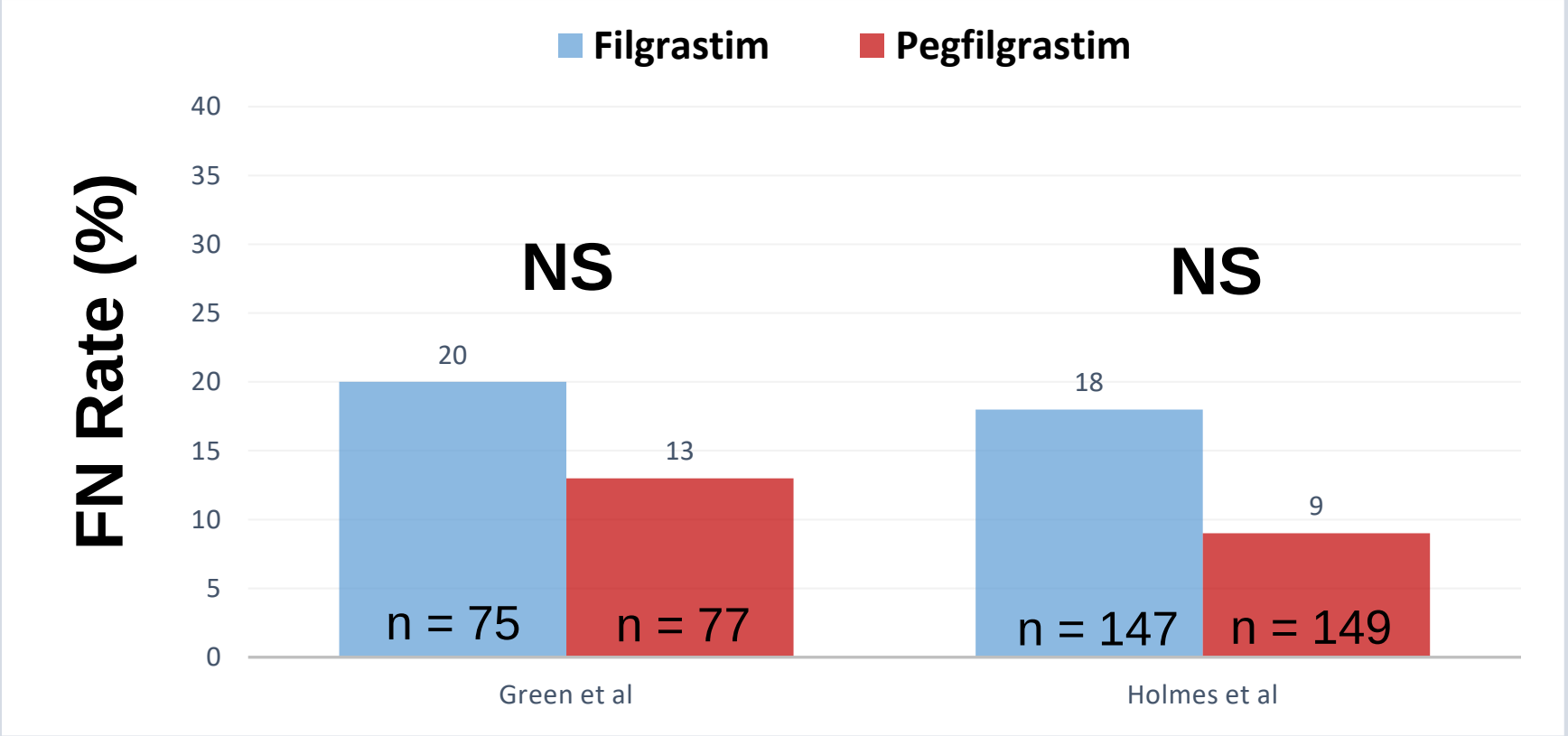
Incidence of FN and FN Hospitalization: Pegfilgrastim vs Placebo



N = 928 patients with breast cancer; docetaxel 100 mg/m^2 every 3 weeks for up to four cycles.
[a]Primary endpoint: incidence of FN (temperature ≥ 38.2°C and ANC < 0.5 x 10^9/L).
[b]Secondary endpoint: FN hospitalization.

Vogel CL, et al. *J Clin Oncol.* 2005;23:1178-1184.

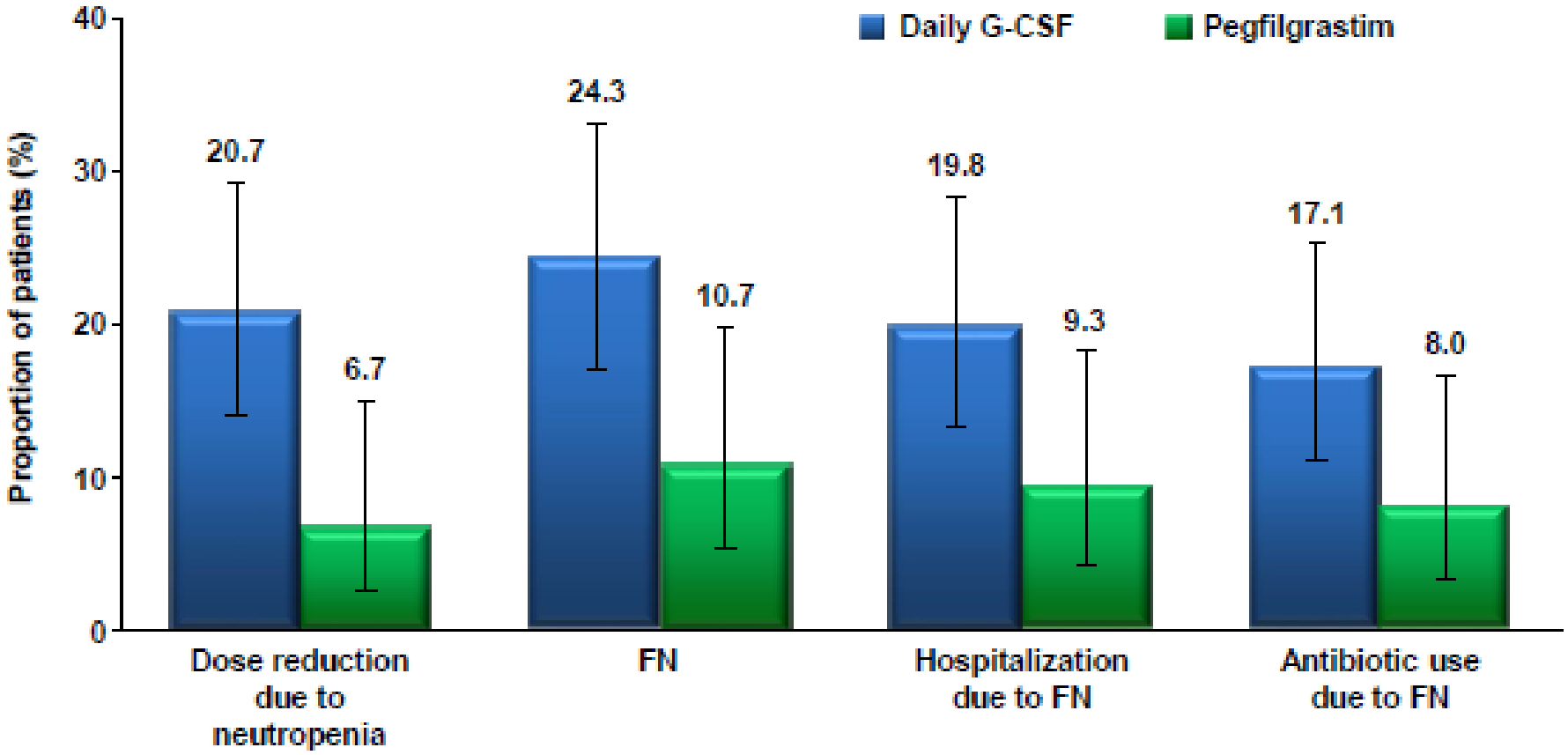
Incidence of FN: Pegfilgrastim *versus* Filgrastim



Doxorubicin 60 mg/m^2 Q3W + docetaxel 75 mg/m^2 Q3W. This study was designed to investigate the noninferiority of filgrastim to pegfilgrastim. No claims of superiority can be made[2,3]

Green MD, et al. *Ann Oncol.* 2003;14:29-35, Holmes FA, et al. *J Clin Oncol.* 2002;20:727-731.

Pegfilgrastim *versus* Filgrastim



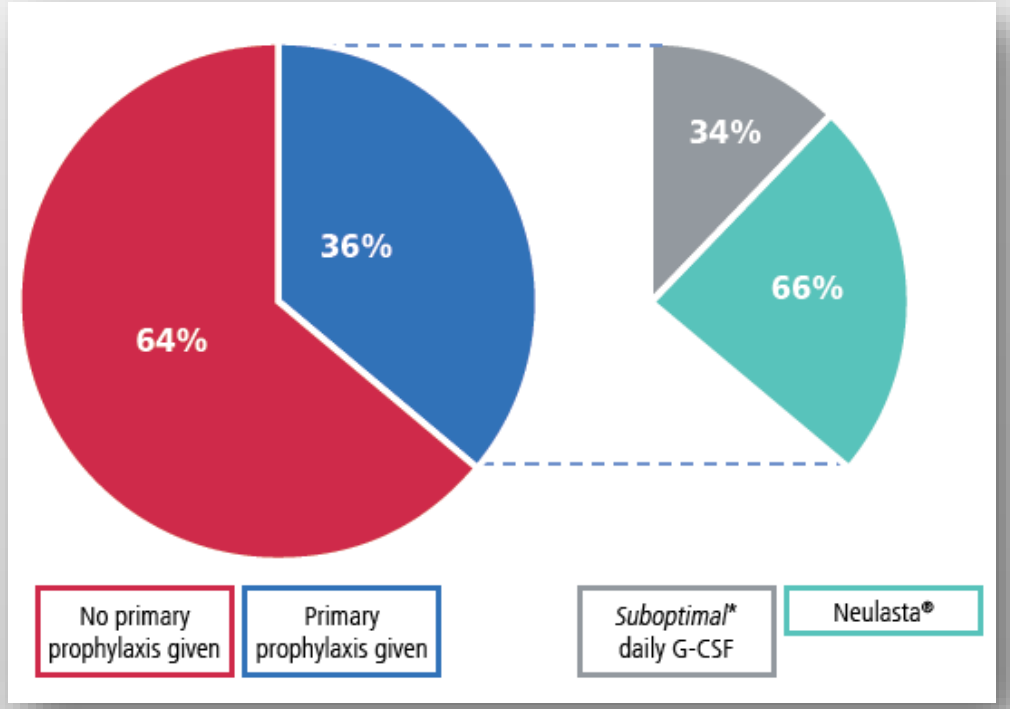
Incidência de NF foi 15% menor com Pegfilgrastim *versus* Filgrastim

FN = febrile neutropenia; IV = intravenous

Almenar D et al Eur J Cancer Care, 2009; 18:280-6.

Estudo Observacional: LNH (LDGCB) – RCHOP-21

- 702 pacientes
- 19% de NF em algum momento
  - 47% no 1o ciclo
  - apenas 36% receberam profilaxia primária, apesar de múltiplos fatores de risco para NF (66% pegfilgastrim)
  - 34% dose subótima (média de 5 doses por ciclo)
- Taxa de hospitalização: (80% vs 20%)
- Atraso de ciclo (55% vs 40%)

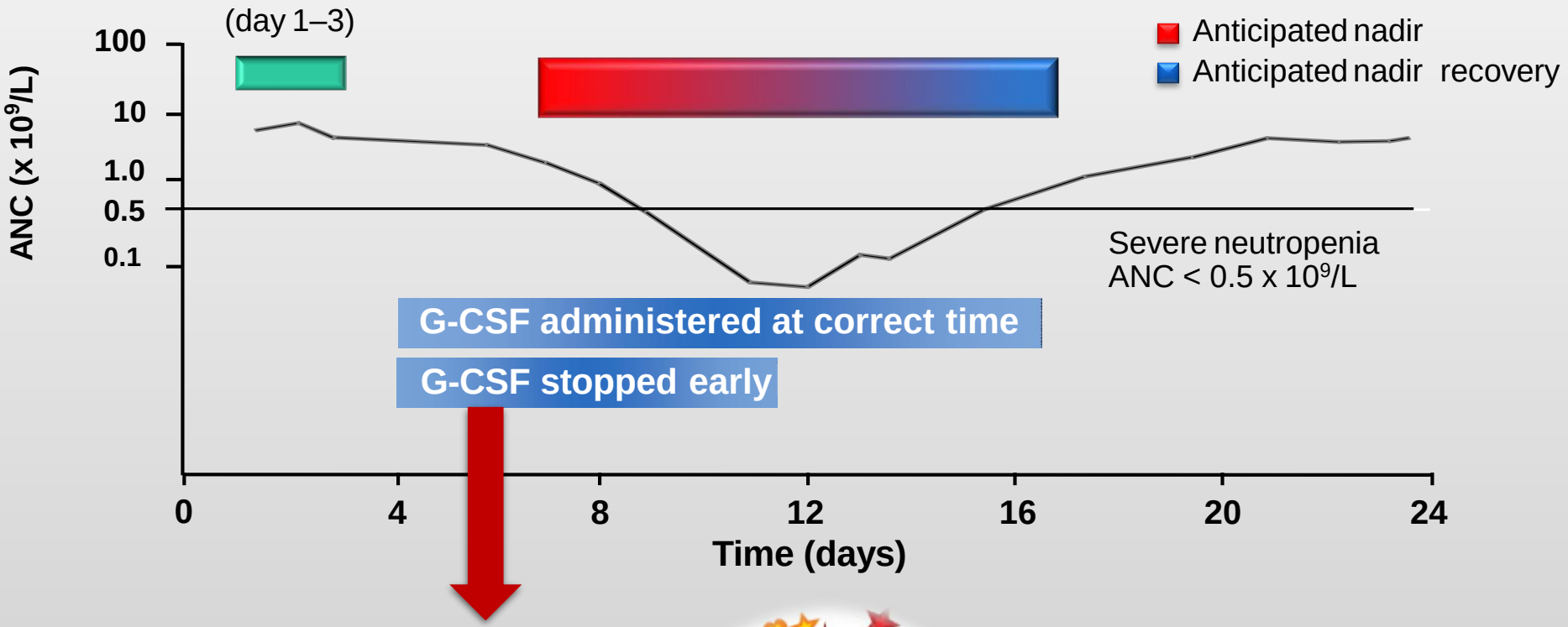


ANC, absolute neutrophil count; DLBCL, Diffuse large B-cell lymphoma; FN, febrile neutropenia; PP, primary prophylaxis; RDI, relative dose intensity; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone

1. Pettengell R *et al.* Support Care Cancer 2012; 20(3):647-52 **2.** Aapro MS *et al.* Euro J Cancer 2011; 47:8-32 3.

O risco de Neutropenia Febril aumenta se o uso de G-CSF for interrompido antes ou iniciado depois

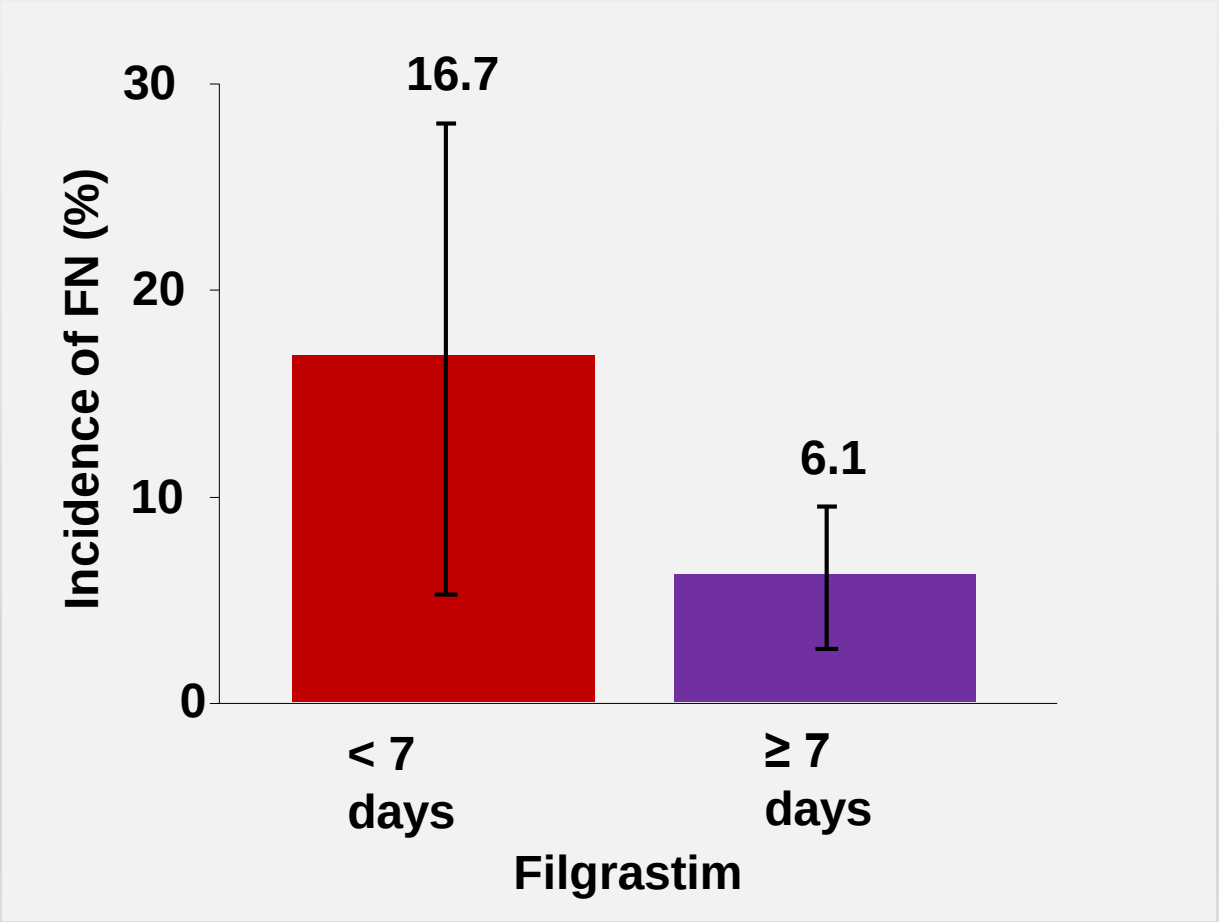
Quando e Como?



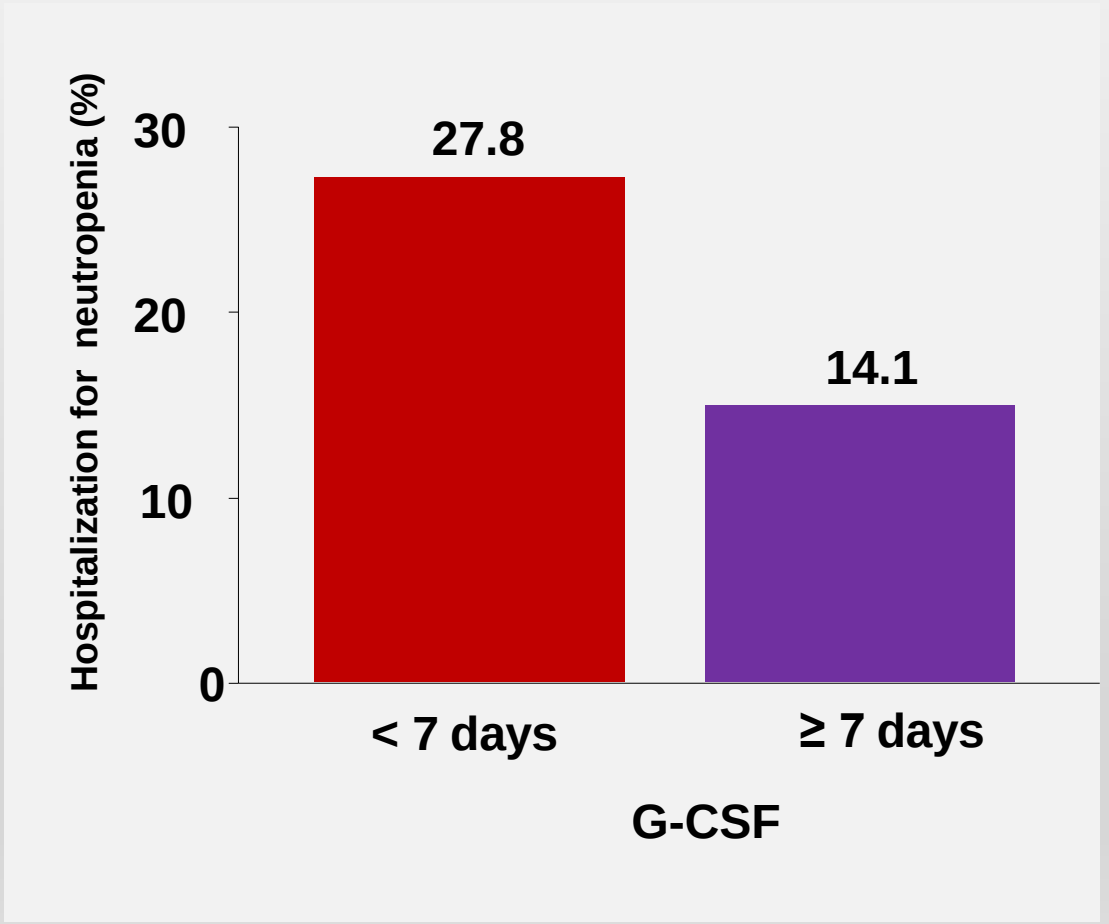
Interromper precocemente: pode não impedir a Neutropenia Febril

Diminuir a administração de G-CSF diário aumenta o risco de NF em pacientes com Linfoma Não-Hodgkin

170 patients were treated with 652 cycles of CHOP chemotherapy with filgrastim prophylaxis

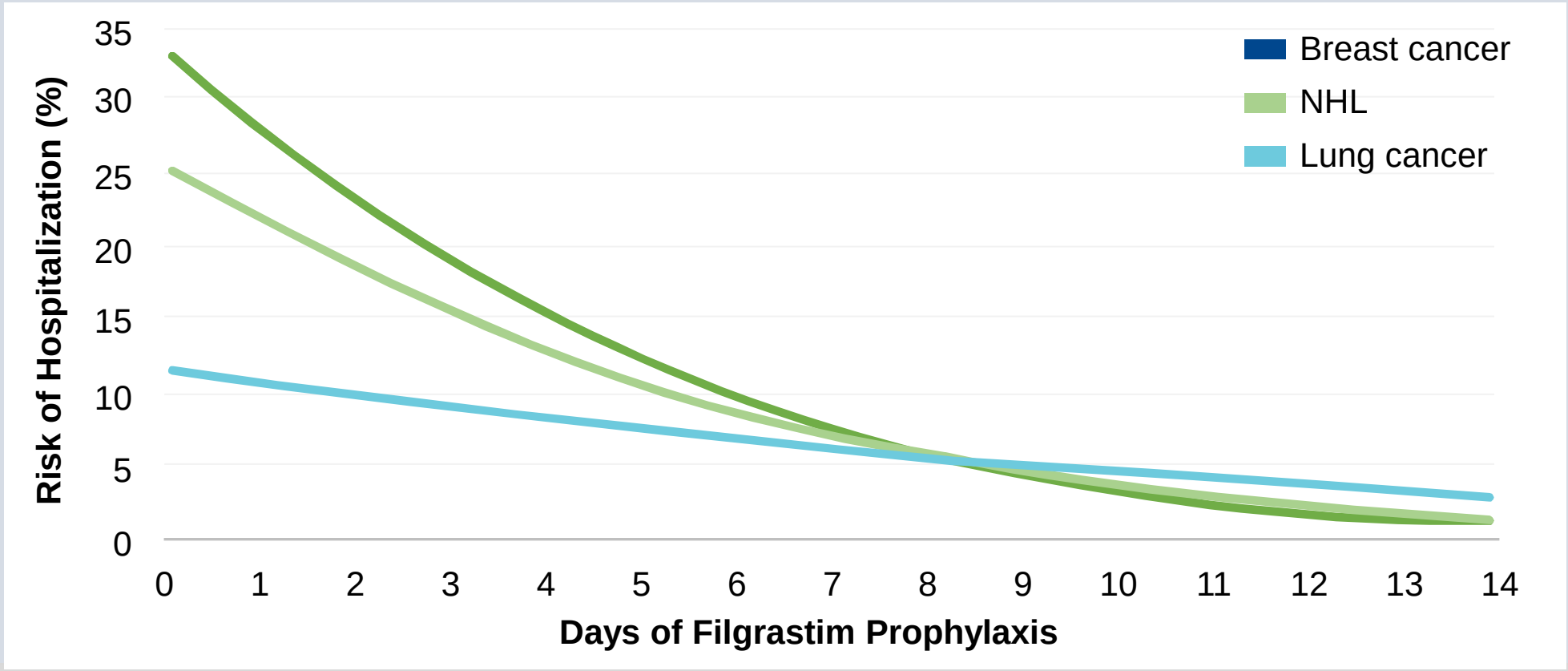


Adaptado de Scott SD *et al. J Manag Care Pharm* 2003;9(suppl):15–21



Adaptado de Chrischilles EA *et al. Blood* 2003;102:Abstract 1817

Increased Risk of Hospitalization With Shorter Courses of Filgrastim Across Multiple Tumors

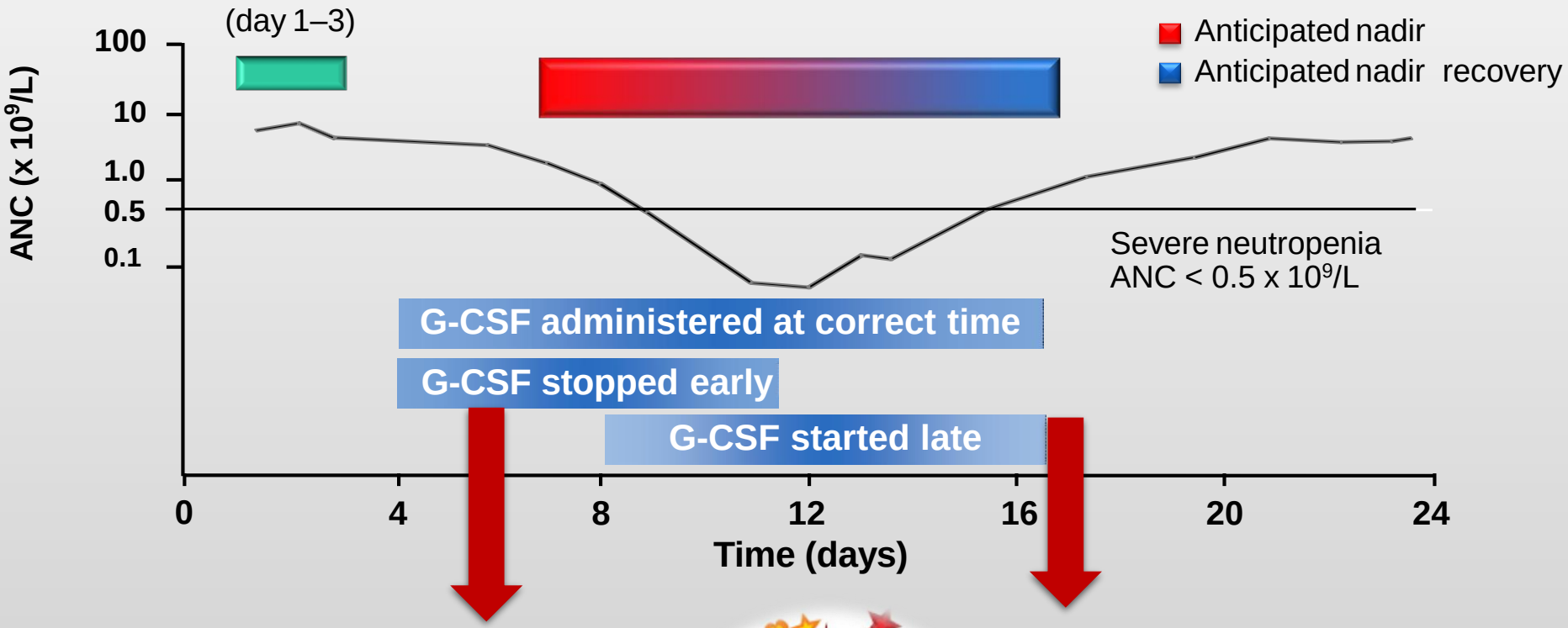


Predicted risk of hospitalization for neutropenia or infection. Based on coefficients from generalized estimating equation model and assuming mean Charlson Comorbidity Index, cycle 1, and no recent history of hospitalization or anemia.This study used ICD-9-CM codes for neutropenia or infection as no such code exists for FN.

Weycker D, et al. *Ann Pharmacother.* 2006;40:402-407.
Graph adapted from Figure 1 of reference.

O risco de Neutropenia Febril aumenta se o uso de G-CSF for interrompido antes ou iniciado depois

Quando e Como?



Interromper precocemente: pode não impedir a Neutropenia Febril

Iniciar tardiamente: pode não haver células precursoras suficientes para garantir a recuperação hematológica adequada

Atraso para iniciar a profilaxia com G-CSF aumenta a incidência e a duração da NF

Time of G-CSF administration	24 hours after CT	48 hours after CT	72 hours after CT	96 hours after CT	If WBC ≤ 1 x 10^9/L	No G-CSF
Incidence of FN (% of cycles)	16%	33%	25%	66%*	75%*	75%*
Duration of FN (days)	0	0	0	2*	4*	3*
Duration of G-CSF support (days)	11.5	12.0	13.5	15.5*	17.0*	–

* $p \leq 0.05$ vs the other groups

CT, chemotherapy WBC, white blood cell

Adaptado de Koumakis G *et al. Oncol* 1999;56:28–35

Considerações Finais

- O uso racional de G-CSF é fundamental para reduzir NF e suas complicações, e assegurar melhor resposta ao tratamento quimioterápico proposto
- G-CSF é custo-efetivo
- O importante é saber/entender: para quem, quando, como e até quando, e seguir as recomendações previstas em “bula”

Obrigado

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