VIATRIS 曄致

Fulphila
福富血注射劑
(pegfilgrastim-jmdb) injection
Pegylated Granulocyte Colony Stimulating Factor Injection (PEG-GCSF Injection) 6 mg / 0.6 mL

長效型白血球生長激素

短效型白血球生長激素

Refining the role of pegfilgrastim for prevention of chemotherapy-induced neutropenia

2023-9-17 彰基血腫 曾若涵

PEG-2022-0334-202212

Table of contents

ADC, antibody-drug conjugate; ESMO, European Society for Medical Oncology; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NCCN, National Comprehensive Cancer Network; vs, versus.

Part 1
Introduction of neutropenia and febrile neutropenia (FN)

FN, febrile neutropenia.

Introduction of neutropenia and febrile neutropenia (FN)

Neutropenia

- **< 500** neutrophils/mcL

Or

- **< 1,000** neutrophils/mcL and a **predicted decline to ≤ 500** neutrophils/mcL **over the next 48 hours**

Febrile neutropenia

- Single temperature: **≥ 38.3˚C** orally

Or

- **≥ 38.0˚C over 1 hour**

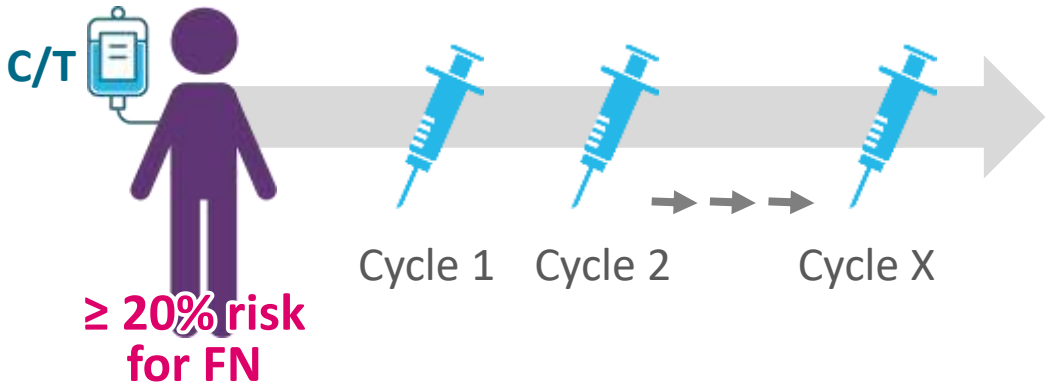
And

- Neutropenia

FN, febrile neutropenia; NCCN, National Comprehensive Cancer Network.
NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022.

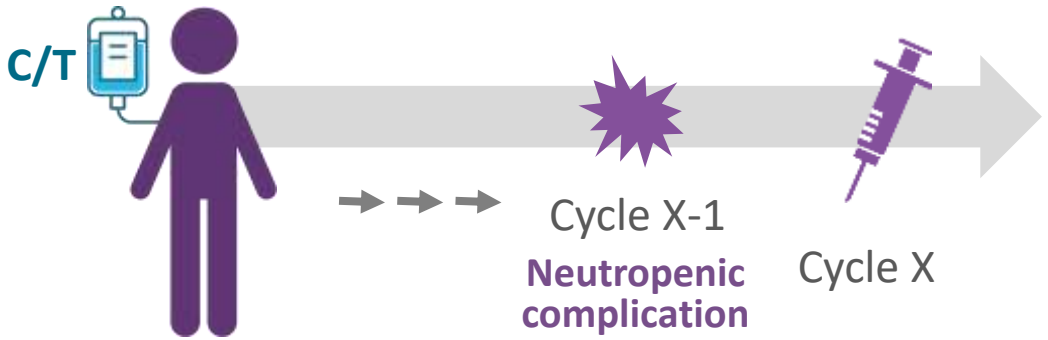
Prophylactic use of CSFs to reduce the risk of FN is warranted when the risk of FN is approximately 20% or higher

Primary prophylaxis



Primary prophylaxis with a CSF starting with the **first cycle and continuing through subsequent cycles of chemotherapy (C/T)** is recommended in patients who have an **approximately 20% or higher risk for FN based** on patient-, disease- and treatment-related factors.

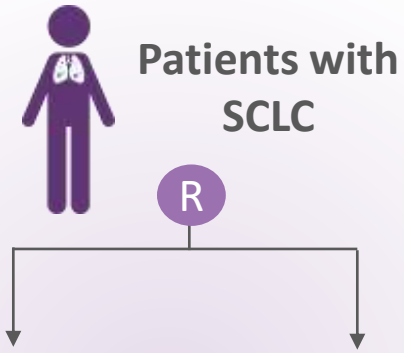
Secondary prophylaxis



Secondary prophylaxis with a CSF is recommended for patients who **experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received)**, in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome.

ASCO, American Society of Clinical Oncology; CSF(s), colony-stimulating factor(s); C/T, chemotherapy; FN, febrile neutropenia.
Smith TJ, et al. J Clin Oncol. 2015;33(28):3199-3212.

G-CSF reduces the duration of neutropenia caused by C/T in SCLC patients

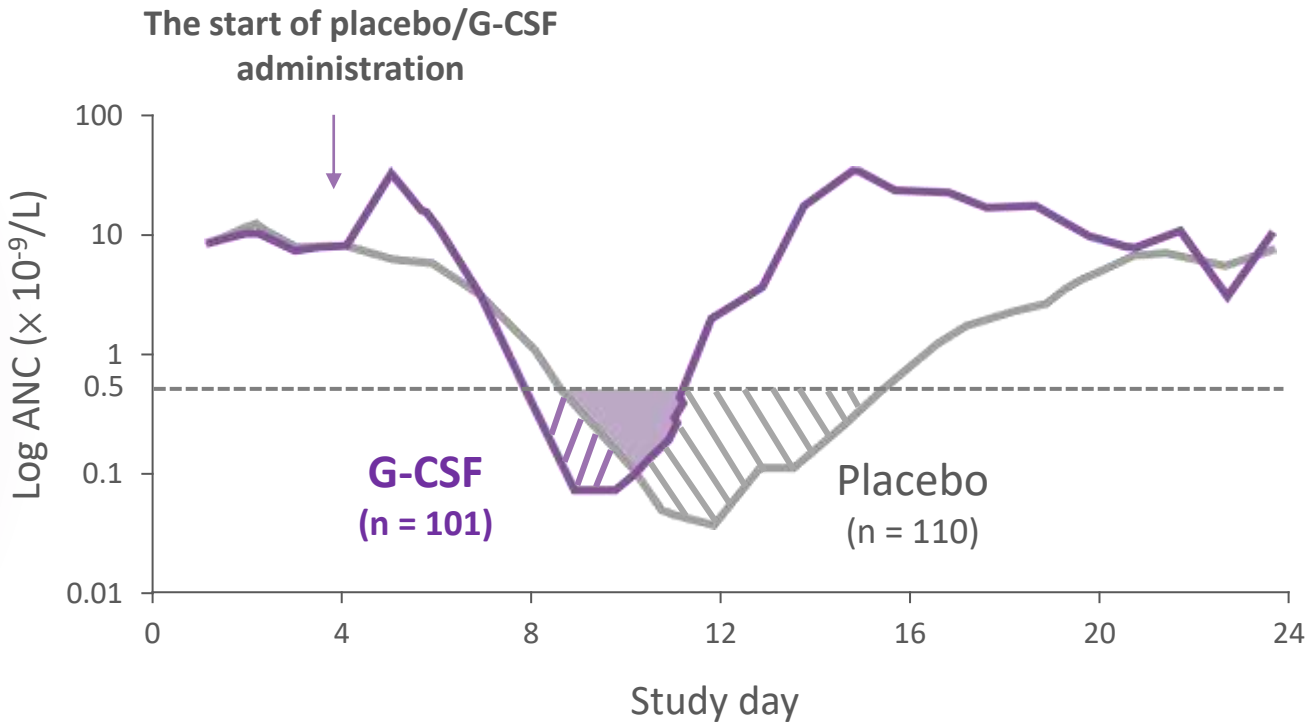


Treatment **beginning on day 4** and **continuing through day 17 of a 21-day cycle**

up to 6 cycles of C/T with CDE

Study the incidence of infection as manifested by **fever with neutropenia**

Median ANC during cycle 1



G-CSF decrease the depth and duration of neutropenia

ANC, absolute neutrophil count; CDE, cyclophosphamide, doxorubicin, and etoposide; C/T, chemotherapy; G-CSF, granulocyte colony-stimulating factor; R, randomized; SCLC, small cell lung cancer.

Crawford J, et al. N Engl J Med. 1991;325(3):164-170.

Part 1
Guideline recommendations from NCCN & ESMO

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.

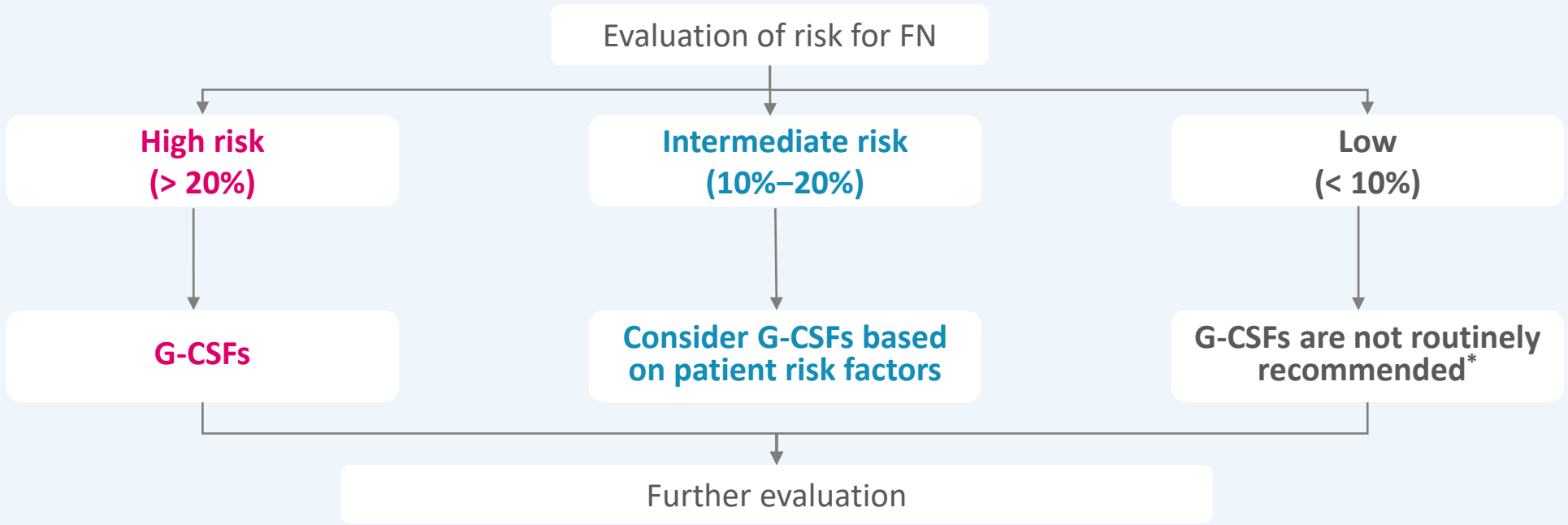
Evaluation prior to first chemotherapy cycle

NCCN

Primary prophylaxis

- Prophylactic use of G-CSFs for FN is recommended in **patients with high risk** and **prophylactic use is considered in patients with intermediate risk** based on patient risk factors.
- An **FDA-approved biosimilar** is an appropriate substitute for filgrastim and pegfilgrastim.

Evaluation in patients with risk for FN



* May be considered for patients with risk factors.

FDA, United States Food and Drug Administration; FN, febrile neutropenia; G-CSFs, granulocyte colony-stimulating factors; NCCN, National Comprehensive Cancer Network.

NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022.

Disease settings and chemotherapy regimens with high risk for FN (> 20%)

NCCN

Primary prophylaxis

Examples of disease settings and chemotherapy regimens with a high risk for FN (> 20%)

- **Acute lymphoblastic leukemia (ALL)**
  - Select ALL regimens as directed by NCCN treatment protocol
- **Bladder cancer**
  - Dose-dense MVAC
- **Bone cancer**
  - VAI, VDC-IE, cisplatin/doxorubicin, VDC, or VIDE
- **Breast cancer**
  - Dose-dense AC followed by dose-dense paclitaxel
  - TAC, TC , or TCH
- **Head and neck squamous cell carcinoma**
  - TPF
- **Hodgkin lymphoma**
  - Brentuximab vedotin + AVD
  - Escalated BEACOPP
- **Kidney cancer**
  - Doxorubicin/gemcitabine
- **Non-Hodgkin lymphomas**
  - CHP, dose-adjusted EPOCH, ICE, dose-dense CHOP-14, MINE, DHAP, ESHAP, or HyperCVAD
- **Melanoma**
  - Dacarbazine-based combination with IL-2, INF-α
- **Multiple myeloma**
  - DT-PACE ± bortezomib
- **Ovarian cancer**
  - Topotecan or docetaxel
- **Soft tissue sarcoma**
  - MAID, doxorubicin, or ifosfamide/doxorubicin
- **Small cell lung cancer**
  - Topotecan
- **Testicular cancer**
  - VeIP, VIP, TIP

AC, doxorubicin and cyclophosphamide; ALL, acute lymphoblastic leukemia; AVD, doxorubicin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CHOP-14, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; DHAP, dexamethasone, cisplatin, and cytarabine; DT-PACE, dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ESHAP, etoposide, methylprednisolone, cisplatin, and cytarabine; FN, febrile neutropenia; HyperCVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE, ifosfamide, carboplatin, and etoposide; IL-2, interleukin-2; INF-α, interferon-α; MAID, mesna, doxorubicin, ifosfamide, and dacarbazine; MINE, mesna, ifosfamide, mitoxantrone, and etoposide; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NCCN, National Comprehensive Cancer Network; TAC, docetaxel, doxorubicin, and cyclophosphamide; TC, docetaxel and cyclophosphamide; TCH, docetaxel, carboplatin, and trastuzumab; TIP, paclitaxel, ifosfamide, and cisplatin; TPF, docetaxel, cisplatin, and 5-fluorouracil; VAI, vincristine, doxorubicin/dactinomycin, and ifosfamide; VDC, cyclophosphamide, vincristine, and doxorubicin/dactinomycin; VDC-IE, vincristine, doxorubicin/dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide; VeIP, vinblastine, ifosfamide, and cisplatin; VIDE, vincristine, ifosfamide, doxorubicin/dactinomycin, and etoposide; VIP, etoposide, ifosfamide, and cisplatin.

NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022.

Prophylactic use of G-CSFs in patients with intermediate risk of FN

Primary prophylaxis

Risk factors in patients with intermediate risk of FN

Adult patients with **intermediate risk (10%–20%)** of FN

Assess patient risk factors:

- **Prior chemotherapy or radiation therapy**
- **Persistent neutropenia**
- **Bone marrow involvement by tumor**
- **Recent surgery and/or open wounds**
- **Liver dysfunction (bilirubin > 2.0)**
- **Renal dysfunction (creatinine clearance < 50)**
- **Age > 65 years receiving full chemotherapy dose intensity**

≥ 1 risk factor
Consider G-CSFs

No risk factors
Observe

Further evaluation

FN, febrile neutropenia; G-CSFs, granulocyte colony-stimulating factors; NCCN, National Comprehensive Cancer Network.
NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022.

Chemotherapy regimens with an intermediate risk for FN (10%–20%)

Primary prophylaxis

Examples of disease settings and chemotherapy regimens with an intermediate risk for FN (10%–20%)

- **Occult primary-adenocarcinoma**
  - Gemcitabine/docetaxel
- **Breast cancer**
  - Docetaxel
  - AC + sequential docetaxel (taxane portion only)
  - Paclitaxel every 21 days
- **Cervical cancer**
  - Cisplatin/topotecan
  - Paclitaxel/cisplatin
  - Topotecan
  - Irinotecan
- **Colorectal cancer**
  - FOLFIRINOX
- **Esophageal and gastric cancers**
  - Irinotecan/cisplatin
- **Non-Hodgkin lymphomas**
  - GDP
  - CHOP including regimens with pegylated liposomal doxorubicin
  - Bendamustine
- **Non-small cell lung cancer**
  - Cisplatin/paclitaxel
  - Cisplatin/vinorelbine
  - Cisplatin/docetaxel
  - Cisplatin/etoposide
  - Carboplatin/paclitaxel
  - Docetaxel
- **Ovarian cancer**
  - Carboplatin/docetaxel
- **Pancreatic cancer**
  - FOLFIRINOX
- **Prostate cancer**
  - Cabazitaxel
- **Small cell lung cancer**
  - Etoposide/carboplatin
- **Testicular cancer**
  - BEP
  - Etoposide/cisplatin
- **Uterine sarcoma**
  - Docetaxel

AC, doxorubicin and cyclophosphamide; BEP, bleomycin, etoposide, and cisplatin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; FN, febrile neutropenia; FOLFIRINOX, fluorouracil, leucovorin, oxaliplatin, and irinotecan; GDP, gemcitabine, dexamethasone, and cisplatin/carboplatin; NCCN, National Comprehensive Cancer Network.

NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022.

G-CSFs for prophylaxis of FN and maintenance of scheduled dose delivery (1/2)

NCCN

Filgrastim (category 1) or tbo-filgrastim (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.

Pegfilgrastim (category 1)

- **One dose of 6 mg**
- There is evidence to support use for chemotherapy regimens given every 3 weeks (category 1).
- There are insufficient data to support use for cytotoxic chemotherapy regimens administered every week; therefore, pegfilgrastim should not be used.

ANC, absolute neutrophil count; FN, febrile neutropenia; G-CSFs, granulocyte colony-stimulating factors; NCCN, National Comprehensive Cancer Network.
NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022.

G-CSFs for prophylaxis of FN and maintenance of scheduled dose delivery (2/2)

Pegfilgrastim (category 1)

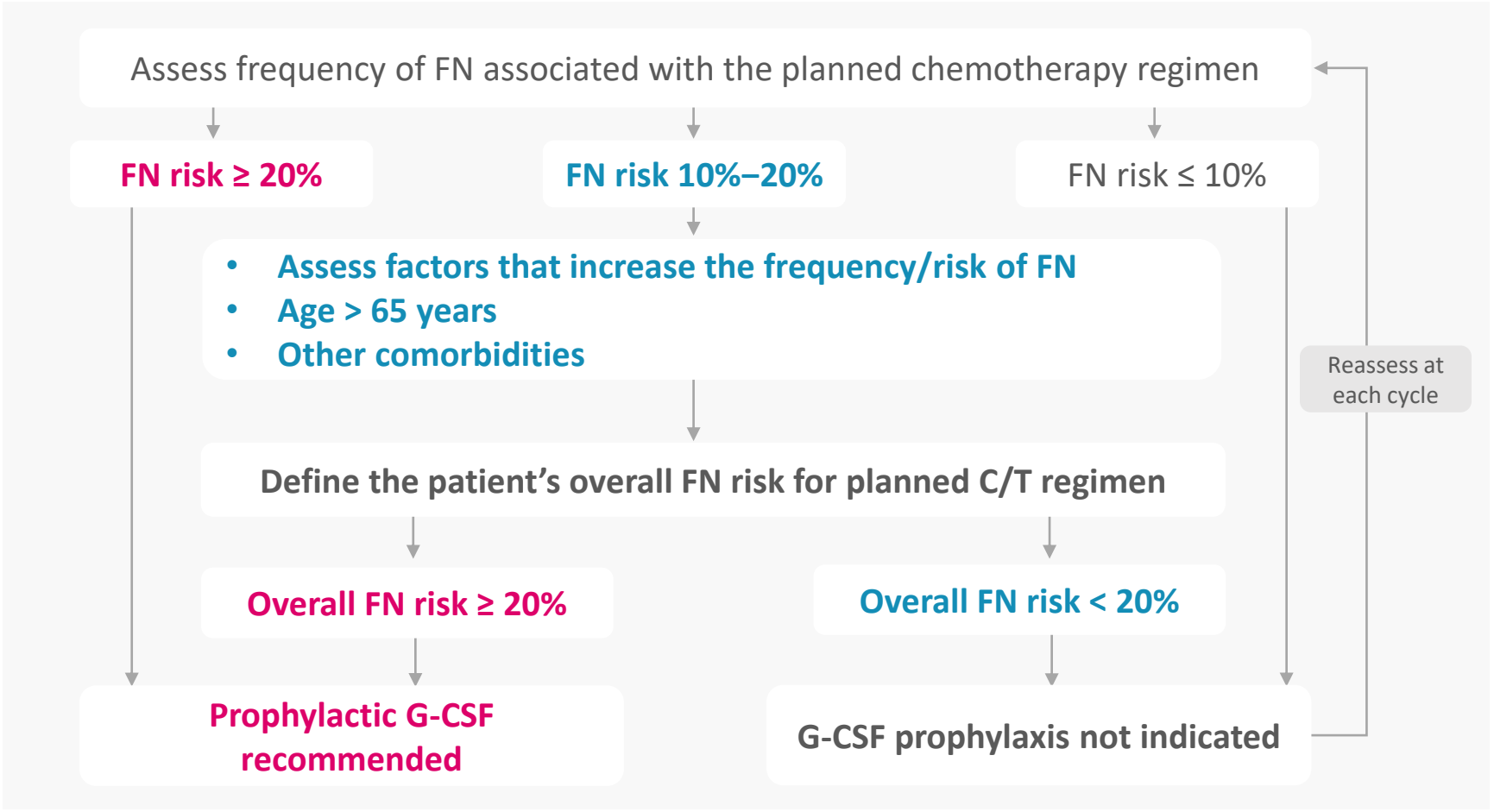
- Based on clinical trial data, pegfilgrastim can be administered the day after myelosuppressive chemotherapy (category 1). There are data for and against same-day dosing but the FDA-approved dosing schedule is still recommended.
- If the treatment cycle includes **chemotherapy administration on days 1 and 15, pegfilgrastim may be given after each chemotherapy treatment.**
- Administration of pegfilgrastim up to 3–4 days after chemotherapy is also reasonable based on trials with filgrastim.

- Caution should be exercised when administering prophylactic G-CSF in patients given concurrent chemotherapy and radiation.
- Subcutaneous route is preferred for all G-CSFs listed above.

FDA, United States Food and Drug Administration; FN, febrile neutropenia; G-CSF(s), granulocyte colony-stimulating factor(s); NCCN, National Comprehensive Cancer Network.
NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022.

G-CSF usage is recommended in patients receiving C/T with a > 20% risk of developing FN and in those with risk factors

Algorithm to decide primary prophylactic G-CSF usage



Secondary prophylaxis (i.e. **G-CSF given for a course of C/T following a course with FN***):

Is indicated if dose reduction below threshold or delay of C/T is not desirable (e.g., treatment with a curative intent).

Dose schedule, route of application of pegfilgrastim:

Pegfilgrastim, injected sc as a single dose of either 100 µg/kg (individualized) or of a total dose of 6 mg (general approach)

* FN is defined as an oral temperature of > 38.3°C or two consecutive readings of > 38.0°C for 2 hours and an ANC of < 0.5×10^9/L, or expected to fall below 0.5×10^9/L.

ANC, absolute neutrophil count; C/T, chemotherapy; ESMO, European Society for Medical Oncology; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; sc, subcutaneous.

Klastersky J, et al. Ann Oncol. 2016;27(suppl 5):v111-v118.

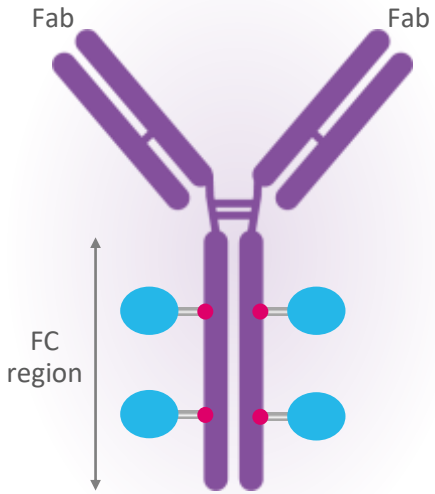
Part 1
ADC-induced neutropenia

ADC, antibody-drug conjugate.

Neutropenia is a common adverse event in cancer patients treated with ADC[1]

- **Antibody-drug conjugates (ADC)** are monoclonal antibodies attached to biologically active drugs through chemical linkers that deliver and release cytotoxic agents at the tumor site, reducing the likelihood of systemic exposure and therefore toxicity.[2]

Antibody-drug conjugate structure[3]



Antibody
- Chimeric or humanized antibodies
- Antibody fragments
- Bispecific antibodies

Linkers
- Cleavable linkers: acid sensitive, protease-sensitive or glutathione sensitive
- Non-cleavable linkers

Cytotoxic payloads
Examples:
- DNA targeting payloads
- Tubulin inhibitors

Conjugation technology
- Non-specific modification of lysine or cysteine residues
- Site selection conjugation

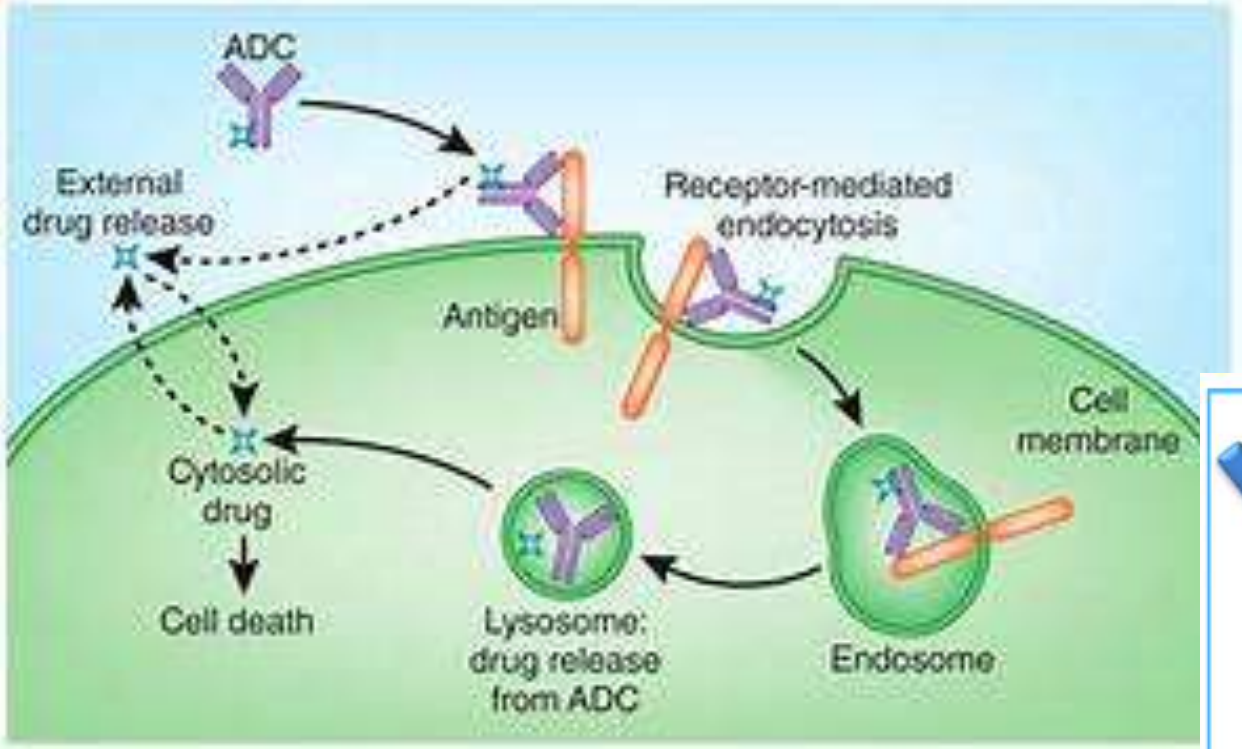
Mechanism of ADC-induced neutropenia[4]

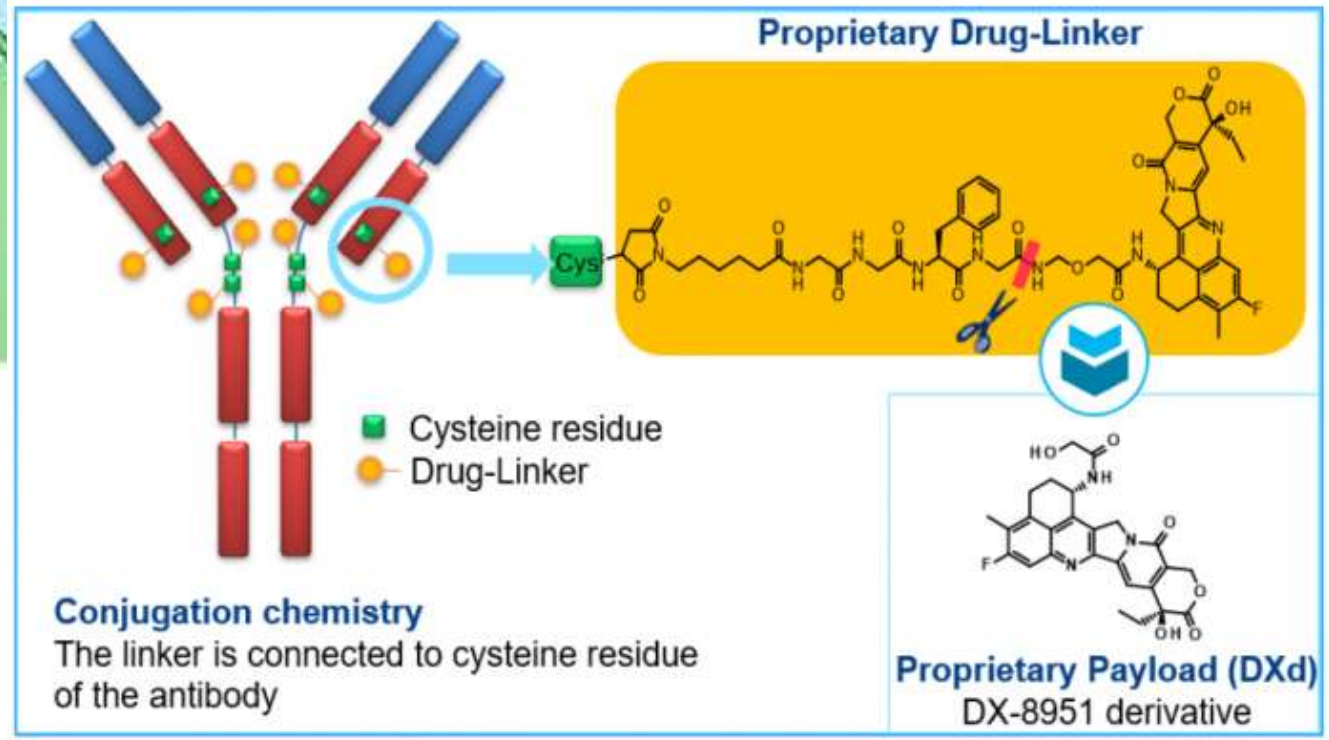
Disruption of microtubule function during mitosis in the bone marrow results in neutropenia.

The reduced neutrophil counts increase the incidence of infections, including FN and sepsis.

ADC, antibody-drug conjugate; Fab, antigen binding fragment; Fc, constant fragment; FN, febrile neutropenia.

1. Zhao H, et al. Mol Cancer Ther. 2017;16(9):1866-1876. **2.** Wolska-Washer A and Robak T. Drug Saf. 2019;42(2):295-314. **3.** Hafeez U, et al. Molecules. 2020;25(20):4764. **4.** Donaghy H. MAbs. 2016;8(4):659-671.


ADC
External drug release
Receptor-mediated endocytosis
Antigen
Cell membrane
Cytosolic drug
Cell death
Lysosome: drug release from ADC
Endosome


Proprietary Drug-Linker
Cys
Cysteine residue
Drug-Linker
Conjugation chemistry
The linker is connected to cysteine residue of the antibody
Proprietary Payload (DXd)
DX-8951 derivative

FDA approved ADC drug[1] with incidence of decreased neutrophil count > 20%

	Fam-trastuzumab deruxtecan-nxki[2]								
Study	DESTINY-Breast01 and Study DS8201-A-J101	DESTINY-Breast03		DESTINY-Breast04		DESTINY-Lung02	DESTINY-Gastric01		
Inclusion criteria	Unresectable or metastatic HER2-positive BC	Unresectable or metastatic HER2-positive BC		Unresectable or metastatic HER2-low BC		Unresectable or metastatic HER2-mutant NSCLC	Locally advanced or metastatic gastric cancer		
Median cycles (range)	NA								
Enhertu® usage	Once every 3 weeks								
Median duration of treatment in the Enhertu® arm, months (range)	7 (0.7 to 31)	14 (0.7 to 30)		8 (0.2 to 33)		19% of patients were exposed for greater than 6 months	4.6 (0.7 to 22.3)		
Decreased neutrophil count	**Fam-trastuzumab deruxtecan-nxki 62%** (N = 234)	**Fam-trastuzumab deruxtecan-nxki 70%** (N = 257)	Ado-trastuzumab emtansine 30% (N = 261)	**Fam-trastuzumab deruxtecan-nxki 64%** (N = 371)	C/T 73% (N = 172)	**Fam-trastuzumab deruxtecan-nxki 52%** (N = 101)	**Fam-trastuzumab deruxtecan-nxki 72%** (N = 125)	Irinotecan or paclitaxel 45% (N = 62)	

ADC, antibody-drug conjugate; BC, breast cancer; C/T, chemotherapy; HER2, human epidermal growth factor receptor 2; FDA, United States Food and Drug Administration; NA, not available; NSCLC, non-small cell lung cancer.

1. Tong JTW, et al. Molecules. 2021;26(19):5847. **2.** Enhertu® FDA package insert.

FDA approved ADC drug[1] with incidence of neutropenia > 20% (1/2)

	Brentuximab vedotin[2]									
Study	Study 1	Study 2	Study 3 AETHERA		Study 4 ALCANZA		Study 5 ECHELON-1		Study 6 ECHELON-2	
Inclusion criteria	Relapsed classical Hodgkin lymphoma	Relapsed systemic anaplastic large cell lymphoma	Classical Hodgkin lymphoma post-auto-HSCT consolidation		Primary cutaneous anaplastic large cell lymphoma and CD30-expressing mycosis fungoides		Previously untreated stage III or IV classical Hodgkin lymphoma		Previously untreated systemic anaplastic large cell lymphoma or other CD30-expressing peripheral T-cell lymphomas	
Median cycles (range) in the Adcetris® arm	9 (1 to 16)	7 (1 to 16)	15 (1 to 16)		12 (1 to 16)		6 (1 to 6)		6 cycles: 70% of patients 8 cycles: 18% of patients	
Incidence of neutropenia	**Brentuximab vedotin 54%** (N = 102)	**Brentuximab vedotin 55%** (N = 58)	**Brentuximab vedotin 78%** (N = 167)	Placebo 34% (N = 160)	**Brentuximab vedotin 21%** (N = 66)	Methotrexate or bexarotene 24% (N = 62)	**Brentuximab vedotin + AVD 91%** (N = 662)	ABVD 89% (N = 659)	**Brentuximab vedotin + CHP 59%** (N = 223)	CHOP 58% (N = 226)

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; ADC, antibody-drug conjugate; AVD, doxorubicin, vinblastine, and dacarbazine; CD, cluster of differentiation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHP, cyclophosphamide, doxorubicin, and prednisone; FDA, United States Food and Drug Administration; HSCT, hematopoietic stem cell transplantation.

1. Tong JTW, et al. Molecules. 2021;26(19):5847. **2.** Adcetris® FDA package insert.

FDA approved ADC drug[1] with incidence of neutropenia > 20% (2/2)

	Sacituzumab govitecan-hziy[2]		Polatuzumab vedotin-piiq[3]		Loncastuximab tesirine-lpyl[4]	Inotuzumab ozogamicin[5]	
Study	Study ASCENT	Study IMMU-132-01	Study GO29365		Studies ADCT-402-201 (LOTIS-2) and ADCT-402-101	INO-VATE ALL trial	
Inclusion criteria	mTNBC who had previously received a taxane and at least 2 prior therapies	mTNBC who had received at least 2 prior treatments for metastatic disease	R/R B-cell lymphomas		DLBCL	R/R ALL	
Median cycles (range) in the ADC arm	NA	NA	5 (49% receiving 6 cycles)		3 (1 to 15)	3	
Incidence of neutropenia	**Sacituzumab govitecan-hziy 64%** (N = 258)	C/T* 44% (N = 224)	**Sacituzumab govitecan-hziy 64%** (N = 108)	**Polatuzumab vedotin-piiq + BR 49%** (N = 45)	BR 44% (N = 39)	**Loncastuximab tesirine-lpyl > 20%** (N = 215)	**Inotuzumab ozogamicin 49%** (N = 164)	FLAG, MXN/Ara-C, or HIDAC 45% (N = 143)

ADC, antibody-drug conjugate; ALL, acute lymphoblastic leukemia; BR, bendamustine and rituximab; C/T, chemotherapy; DLBCL, diffuse large B-cell lymphoma; FDA, United States Food and Drug Administration; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; HIDAC, high dose cytarabine; mTNBC, metastatic triple-negative breast cancer; MXN/Ara-C, mitoxantrone and cytarabine; NA, not available; R/R, relapsed or refractory.

* Eribulin, capecitabine, gemcitabine, or vinorelbine.

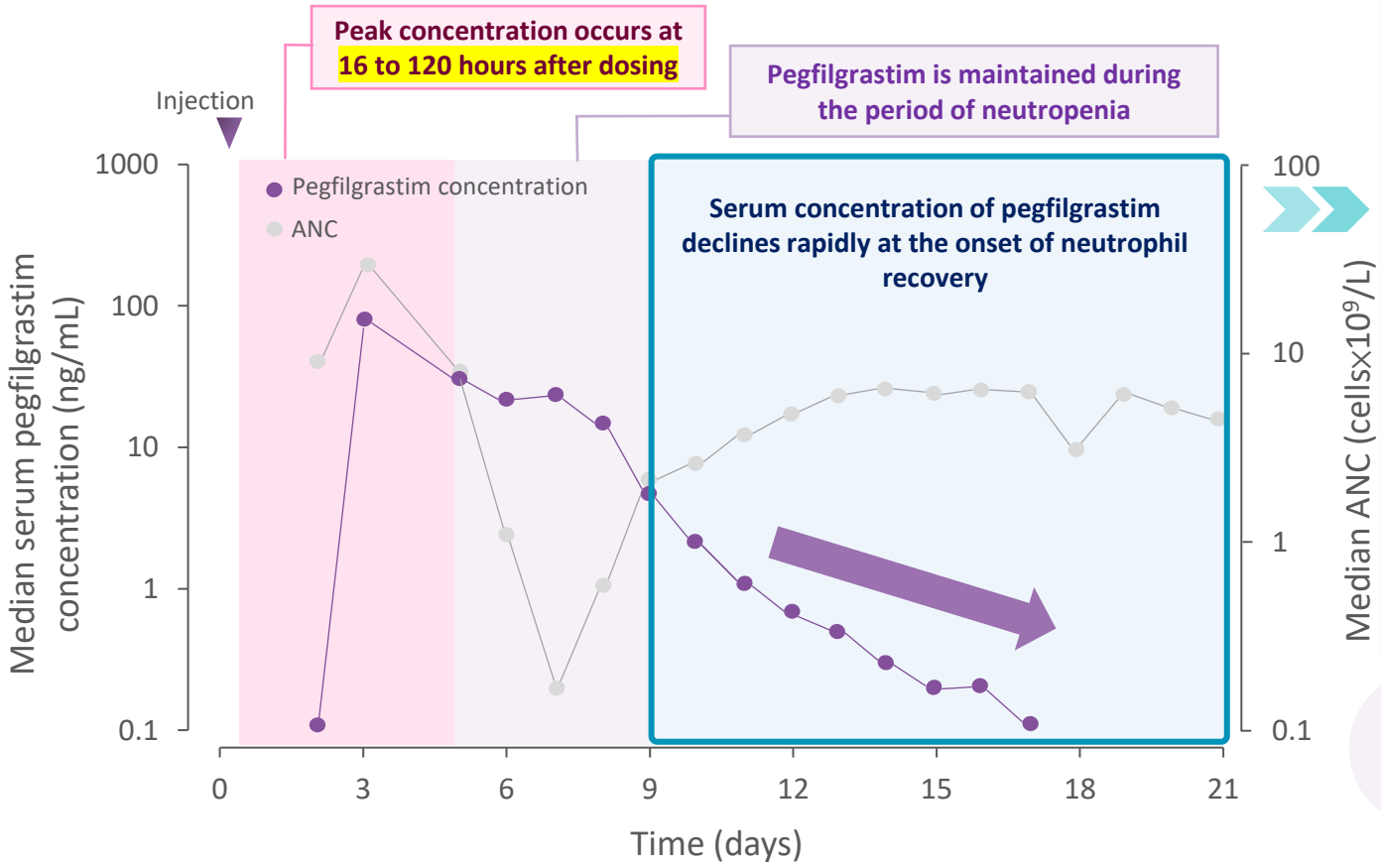
1. Tong JTW, et al. Molecules. 2021;26(19):5847. **2.** Trodelvy® FDA package insert. **3.** Polivy® FDA package insert. **4.** Zynlonta® FDA package insert. **5.** Besponsa® FDA package insert.

Part 1
The difference between short-acting and long-acting G-CSF

G-CSF, granulocyte colony-stimulating factor.

Pegfilgrastim has a self-regulating clearance mechanism that results in a smooth recovery of neutrophil levels[1]

Profile of median pegfilgrastim serum concentration and ANC in C/T treated patients after a single 6 mg injection[2]



Self-regulating clearance mechanism of pegfilgrastim[3]

Pegfilgrastim effectively eliminates the renal clearance, and implicates a **neutrophil-mediated mechanism** as the primary clearance of the molecule

ANC recovery

Decrease of pegfilgrastim in the serum

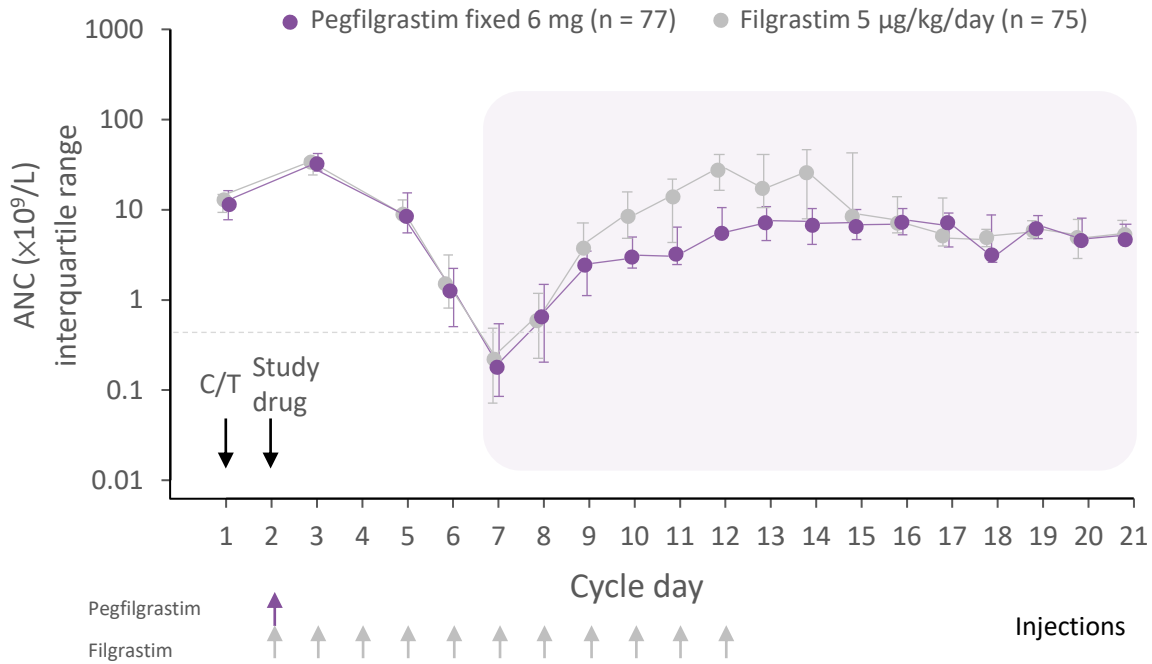
"Self-regulating" clearance of pegfilgrastim results in a smooth recovery of neutrophil levels[1]

ANC, absolute neutrophil count; C/T, chemotherapy.

1. Waladkhani AR. Eur J Cancer Care (Engl). 2004;13(4):371-379. **2.** European Medicines Agency. Fulphila® summary of product characteristics. **3.** Holmes FA, et al. Ann Oncol. 2002;13(6):903-909.

Pegfilgrastim is as effective as filgrastim and has a similar safety profile to filgrastim

A single dose of pegfilgrastim vs. 11 daily injections of filgrastim[1]



A single injection of pegfilgrastim was as effective as daily injections of filgrastim for all cycles[2]

Safety outcomes[2]

Pegfilgrastim vs. filgrastim
Similar safety profile

AE possibly related to the study drug
Pegfilgrastim (**57%**) vs. filgrastim (**58%**)

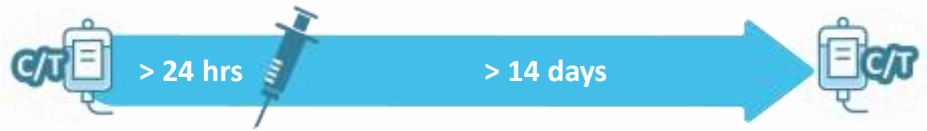
The most frequently reported AE: Bone pain
Pegfilgrastim (**37%**) vs. filgrastim (**42%**)

Pegfilgrastim vs. filgrastim
No patients developed **neutralizing antibodies**

AE, adverse event; ANC, absolute neutrophil count; C/T, chemotherapy; vs, versus.

1. Roth K, et al. Generics and Biosimilars Initiative Journal (GaBI Journal). 2017;6(4):185-187. **2.** Green MD, et al. Ann Oncol. 2003;14(1):29-35.

The difference between short-acting and long-acting G-CSF

	Long-acting G-CSF (pegfilgrastim)	Short-acting G-CSF (filgrastim)
Half-life	15–80 hrs[1]	3–4 hrs[2]
Administration	SC[1]	SC or IV[3]
Dosage	Once per chemotherapy cycle[1] 	Daily injection[3] 
Efficacy	Pegfilgrastim ≒ 11 days' filgrastim[4]	
Adverse reactions	Bone pain and pain in extremity[1,3]	
Patient compliance	Better[2]	Worse[2]
Burden for patients and HCPs	Lower[2]	Higher[2]
Advantages over filgrastim	• Once-per-cycle dosing may be more convenient for patients[4] • Maintaining chemotherapy RDI, thus significantly reducing healthcare costs and improving cancer survival[5] • Lower risk of hospitalization for neutropenic complications during cancer chemotherapy[6]	
Cost (reimbursement)	Dosage: 6 mg/0.6 mL • Neulasta®: 6 mg/0.6 mL[7] → NTD 17,490[8] • **Fulphila®: 6 mg/0.6 mL[9] → NTD 15,229[8]** • Ziextenzo®: 6 mg/0.6 mL[10] → NTD 14,866[8]	• Filgrastim®: 300 μg/0.7 mL → NTD 1,745[11] • Granocyte®: 250 μg → NTD 1,782[12] • Nivestim®: 600 μg/mL → NTD 1,559[13]

C/T, chemotherapy; FDA, United States Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; HCPs, healthcare professionals; hrs, hours; IV, intravenous; RDI, relative dose intensity; SC, subcutaneous.

1. Fulphila® FDA package insert. **2.** Green MD, et al. Ann Oncol. 2003;14(1):29-35. **3.** Neupogen® FDA package insert. **4.** Aapro M, et al. Support Care Cancer. 2017;25(11):3295-3304. **5.** Cornes P, et al. Future Oncol. 2022;18(16):1979-1996. **6.** Weycker D, et al. Am J Clin Oncol. 2012;35(3):267-274. **7.** Neulasta® 中文仿單（版本：Amgen PI 2019/04 V24）。**8.** 全民健康保險藥物給付項目及支付標準（發文日期：中華民國 111 年 5 月 13 日）。**9.** Fulphila® 中文仿單。**10.** Ziextenzo® 中文仿單（版本：TWI-240421）。**11.** Filgrastim® 健保給付價格。**12.** Granocyte® 健保給付價格。**13.** Nivestim® 健保給付價格。

The reimbursement criteria of long-acting G-CSF are more restricted than short-acting G-CSF

The different reimbursement criteria for short-acting and long-acting G-CSF

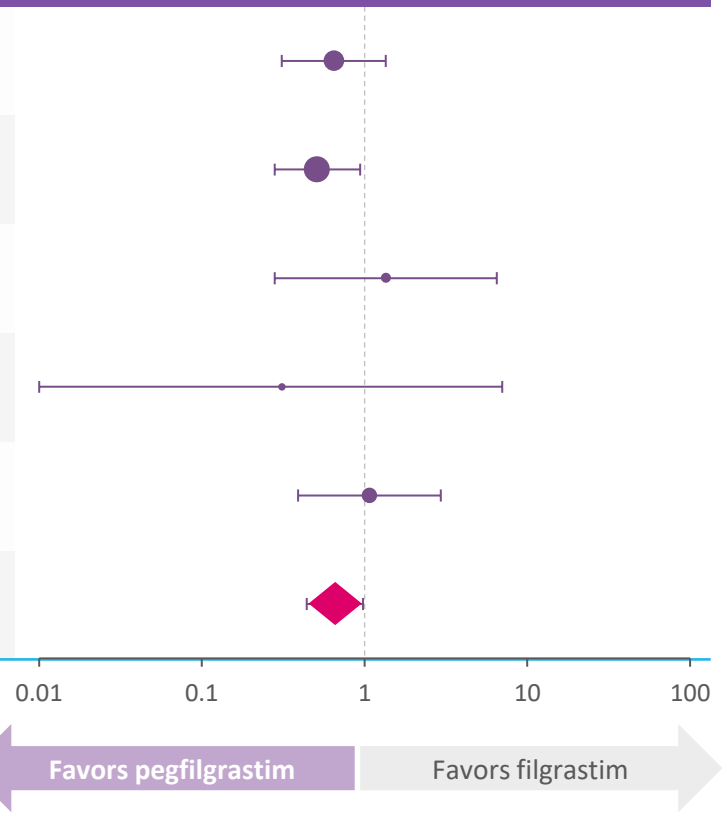
	長效型 G-CSF	短效型 G-CSF
健保給付規範	**健保給付規範較嚴格** • 限**非骨髓性癌症合併有骨髓侵犯**之患者，**在骨髓抑制性抗癌藥物治療後**，且**曾經發生白血球少於 1000/cumm**，或**中性白血球（ANC）少於 500/cumm 者使用**。	**健保給付規範較寬鬆** 1) 用於造血幹細胞移植患者。 **2) 血液惡性疾病接受靜注化學治療後。** 3) 先天性或循環性中性白血球低下症者（當白血球數量少於 1000/cumm，或中性白血球（ANC）少於 500/cumm）。 **4) 其他惡性疾病患者在接受化學治療後，曾經發生白血球少於 1000/cumm，或中性白血球（ANC）少於 500/cumm** 者，即可使用。 5) 重度再生不良性貧血病人嚴重感染時使用，惟不得作為此類病人之預防性使用。 6) 化學治療，併中性白血球缺乏之發燒，若中性白血球小於 100/cumm、癌症不受控制、肺炎、低血壓、多器官衰竭或侵犯性黴菌感染等危機程度高之感染。 7) 對於骨髓造血功能不良症候群（MDS）的病人，若因嚴重性的中性白血球過低（ANC < 500/cumm）而併發感染時，可間歇性使用 G-CSF，但不得作為長期且常規性使用。 8) 週邊血液幹細胞的趨動–不論在自體或異體幹細胞的收集，應於收集前之 4–5 日開始皮下注射 G-CSF，其劑量為 10 μg/kg/day。

ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; MDS, myelodysplastic syndrome.
衛生福利部中央健康保險署。藥品給付規定。第 4 節 血液治療藥物。（111. 08. 23 更新）。

Systematic review and meta-analysis revealed FN incidence was significantly lower for pegfilgrastim than filgrastim (1/2)

Pegfilgrastim vs. filgrastim: FN incidence

Study or subgroup	Pegfilgrastim		Filgrastim		Weight	Risk ratio (95% CI)
	Events	Total	Events	Total		
Green 2003 (breast)	10	77	15	75	30.5%	0.65 (0.31–1.35)
Holmes 2002 (breast, phase 3)	14	149	27	147	45.1%	0.51 (0.28–0.94)
Holmes 2002 (breast, phase 2)	5	46	2	25	6.7%	1.36 (0.28–6.50)
Grigg 2003 (NHL)	0	14	1	13	1.7%	0.31 (0.01–7.02)
Vose 2003 (NHL, HL)	6	29	6	31	16.1%	1.07 (0.39–2.94)
Total		315		291	100%	**0.66** (0.44–0.98)



CI, confidence interval; FN, febrile neutropenia; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; vs, versus.

Cooper KL, et al. BMC Cancer. 2011;11:404.

Effectiveness of daily vs. non-daily G-CSFs in patients with solid tumors undergoing C/T

Multicenter, retrospective, observational study

Solid tumors
(excluding BC)
N = 391

Inclusion criteria

- ≥ 18 years old
- Undergone C/T with at least one concomitant G-CSF (daily or non-daily) administration more than 2 months ago

Pegfilgrastim
(n = 180)

Daily G-CSF*
(n = 211)

* 196 with filgrastim and 15 with lenograstim
Median days of administration of G-CSF (range): 5 (1 to 18)

Primary outcome measure

- The percentage of patients with grade 3–4 neutropenia

Secondary outcome measures

- Incidence of FN
- The percentage of patients with C/T dose delays or reductions
- Response to C/T treatment according to physician's criterion

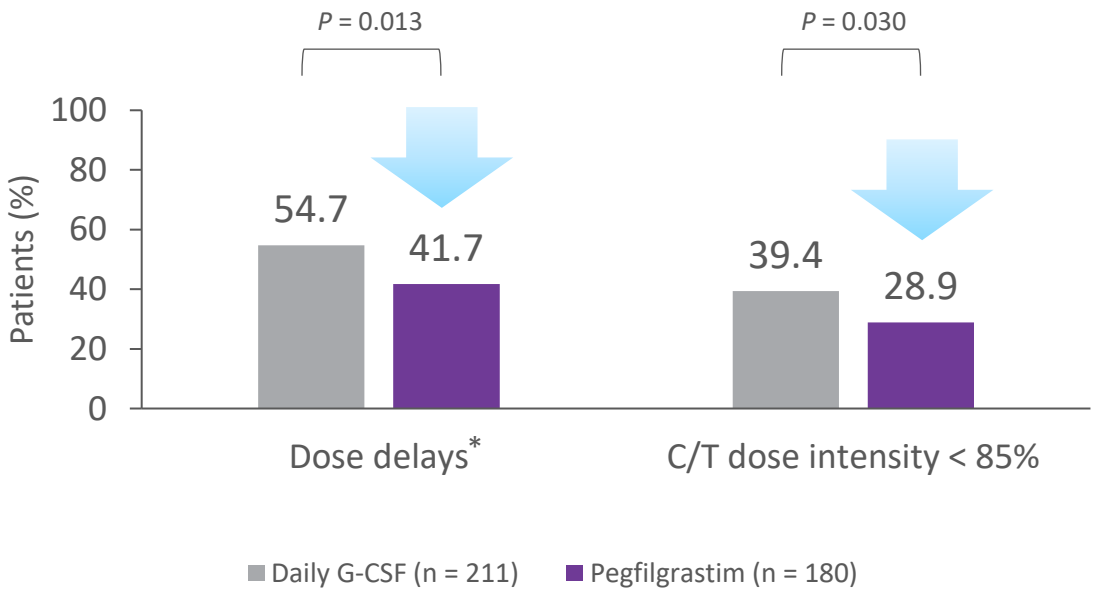
- 47.3% of patients received primary prophylaxis and 26.3% of patients received secondary prophylaxis.

BC, breast cancer; C/T, chemotherapy; FN, febrile neutropenia; G-CSF(s), granulocyte colony-stimulating factor(s); vs, versus.
Almenar Cubells D, et al. Eur J Cancer Care (Engl). 2013;22(3):400-412.

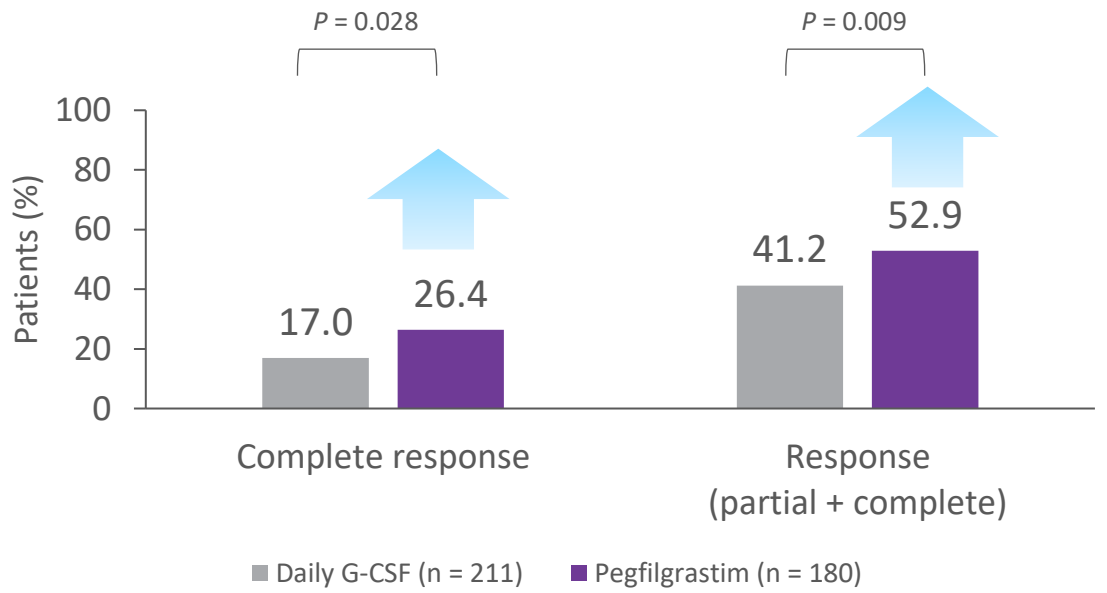
Patients who received a daily G-CSF suffered more C/T dose reductions, delays, and presented a lower response rate

- Rate of dose delays and C/T dose intensity (< 85%) were significantly less with pegfilgrastim than with filgrastim/lenograstim.
- Rate of complete response to C/T was significantly higher with pegfilgrastim than with filgrastim/lenograstim.

C/T dose delays and reductions in patients who received pegfilgrastim or daily G-CSF



Response rate in patients who received pegfilgrastim or daily G-CSF



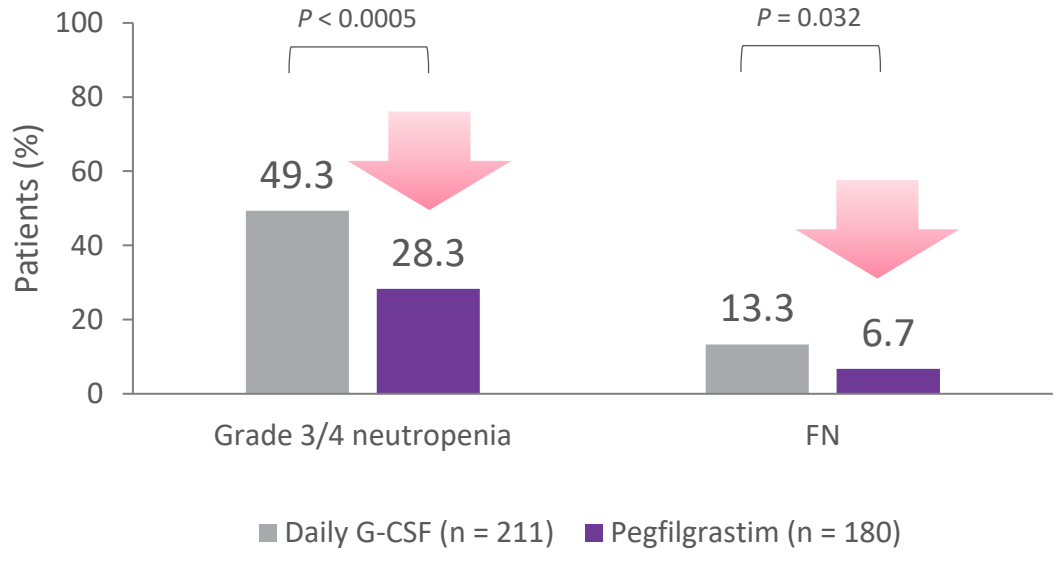
* > 3 days delay in any cycle.
C/T, chemotherapy; G-CSF, granulocyte colony-stimulating factor.
Almenar Cubells D, et al. Eur J Cancer Care (Engl). 2013;22(3):400-412.

Compared to pegfilgrastim, patients with daily G-CSF suffered more FN, hospitalizations, and antibiotics use due to FN

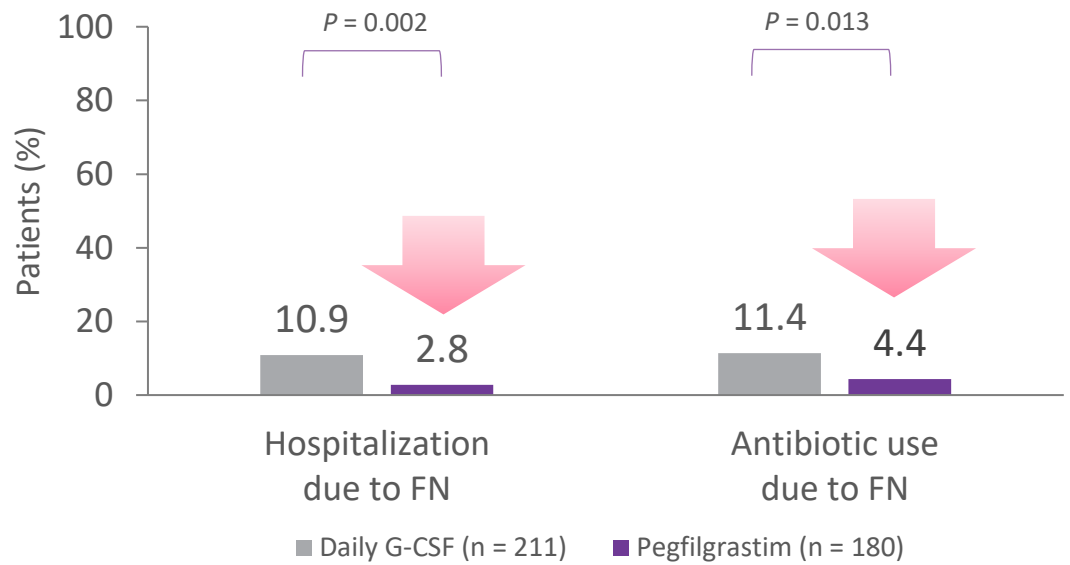
- Rate of severe neutropenia (grade 3 or 4) and FN were significantly less in patients receiving pegfilgrastim compared with patients receiving filgrastim/lenograstim.

- Rate of hospitalization due to FN and antibiotic use due to FN were significantly less in patients receiving pegfilgrastim compared with patients receiving filgrastim/lenograstim.

Pegfilgrastim is more effective in preventing FN



Pegfilgrastim with lower incidence of hospitalization and antibiotic use due to FN



FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor.

Almenar Cubells D, et al. Eur J Cancer Care (Engl). 2013;22(3):400-412.

Use of pegfilgrastim vs. short-acting G-CSF

An international panel of experts convened to develop guidance on appropriate use of pegfilgrastim:

Refining the role of pegfilgrastim (a long-acting G-CSF) for prevention of chemotherapy-induced febrile neutropenia: consensus guidance recommendations

Evidence level	Consensus reached	Statement
I	91%	• Clinical trial data suggest a similar efficacy and safety profile with **pegfilgrastim** and **11 days' filgrastim**. • If 11 days' filgrastim is not utilized, pegfilgrastim should be given in preference to a reduced duration of daily filgrastim.
V	100%	• Based on the **convenience** and patient **adherence**, **pegfilgrastim** may be preferred to 11 days' filgrastim for prevention of chemotherapy-induced FN. This is particularly the case in **frail** or **elderly** patients.

G-CSF, granulocyte colony-stimulating factor; FN, febrile neutropenia; vs, versus.

Aapro M, et al. Support Care Cancer. 2017;25(11):3295-3304.

Special considerations for patients with hematologic malignancies

Evidence level	Consensus reached	Statement
II	100%	• In newly diagnosed patients with acute myeloid leukemia (AML) receiving induction therapy, filgrastim could be considered. • In patients receiving **consolidation chemotherapy with curative intent**, **pegfilgrastim** may be **preferred** to filgrastim.
IV	100%	• In patients with **lymphoma/chronic lymphocytic leukemia**, or **MM** receiving targeted treatments, **pegfilgrastim** or short acting G-CSF can be considered if needed to continue treatment.

AML, acute myeloid leukemia; G-CSF, granulocyte colony-stimulating factor; MM, multiple myeloma.
Aapro M, et al. Support Care Cancer. 2017;25(11):3295-3304.

Brief summary

Primary prophylaxis

- G-CSF is recommended for patients with **high risk** of developing FN[1,2]
- G-CSF is considered for patients with **intermediate risk** of developing FN **≥ 1 risk factor**[1]

Secondary prophylaxis

- G-CSF is recommended for patients with **FN** or **dose-limiting neutropenic event** prior to second and subsequent chemotherapy cycles[1]

Benefits of long-acting G-CSF (pegfilgrastim) vs. short-acting G-CSF (filgrastim)

- Better **adherence** and **convenience**[3]
- **Lower risk** for **FN**[4]
- **Lower risk** of **hospitalization** for neutropenic complications[5]

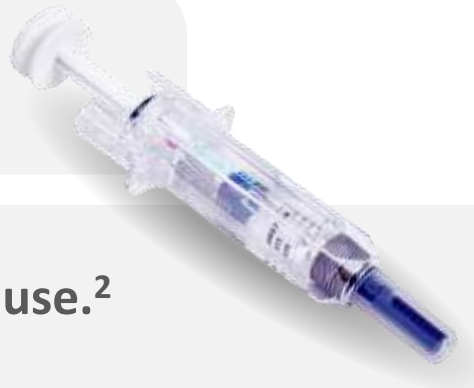
ESMO, European Society for Medical Oncology; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NCCN, National Comprehensive Cancer Network; vs, versus.

1. NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022. **2.** Klastersky J, et al. Ann Oncol. 2016;27(suppl 5):v111-v118. **3.** Aapro M, et al. Support Care Cancer. 2017;25(11):3295-3304. **4.** Cooper KL, et al. BMC Cancer. 2011;11:404. **5.** Weycker D, et al. Am J Clin Oncol. 2012;35(3):267-274.

Part 2
Introduction and benefits of pegfilgrastim-jmdb

Product characteristics of Fulphila®

The FDA approved Fulphila® (pegfilgrastim-jmdb) as the first biosimilar to Neulasta (pegfilgrastim).[1]



- UltraSafe Plus™ ergonomic design aims to support **injection comfort, ease of use.[2]**
- Provides confidence against **needlestick injury.[2]**

- Fulphila® is a long-acting G-CSF.[3,4]
- PEG chains increased serum half-life means that dosing intervals can be increased, improving patient convenience.[5]
- Fulphila®, a pegfilgrastim biosimilar demonstrated equivalent efficacy and similar safety to reference pegfilgrastim.[6,7]

FDA, United States Food and Drug Administration; G-CSF, granulocyte colony-stimulating factor; PEG, polyethylene glycol.

1. FDA NEWS RELEASE. FDA approves 1st biosimilar to Neulasta to help reduce the risk of infection during cancer treatment. **2.** BD UltraSafe Plus™ Passive Needle Guard. **3.** Roth K, et al. Generics and Biosimilars Initiative Journal (GaBI Journal). 2017;6(4):185-187.
4. Fulphila® 中文仿單。**5.** Waladkhani A-R. Eur J Cancer Care (Engl). 2004;13(4):371-379. **6.** Waller CF, et al. Ann Hematol. 2019;98(5):1217-1224. **7.** Hoy SM. BioDrugs. 2019;33(1):117-120.

UltraSafe PlusTM

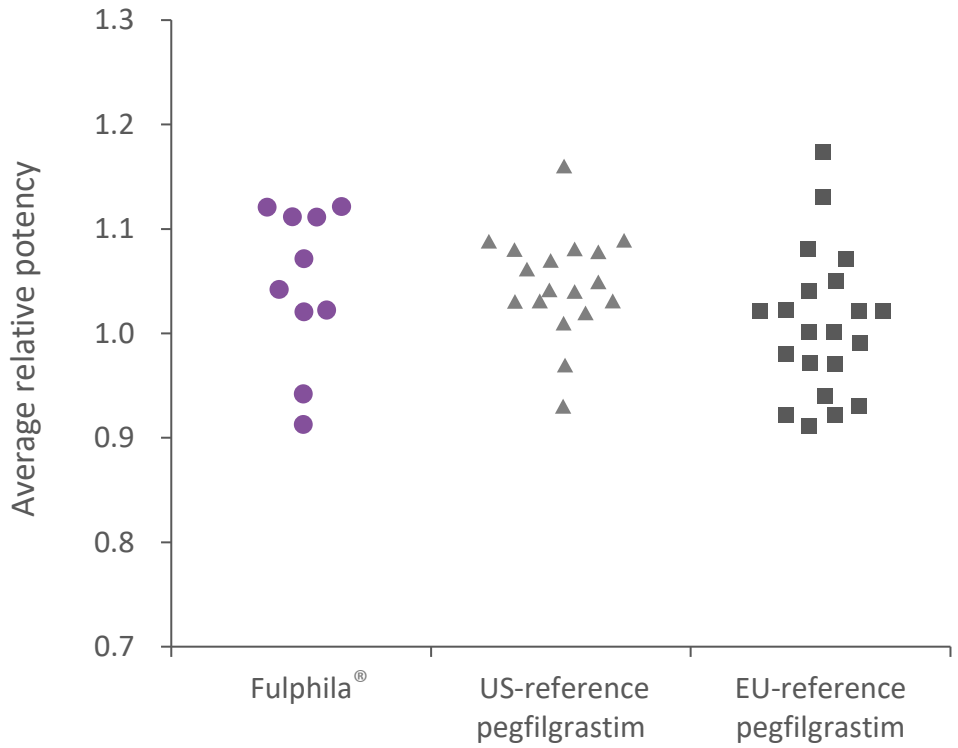
Indication, mechanism, and administration of Fulphila®

Approved indication and posology of Fulphila® in Taiwan

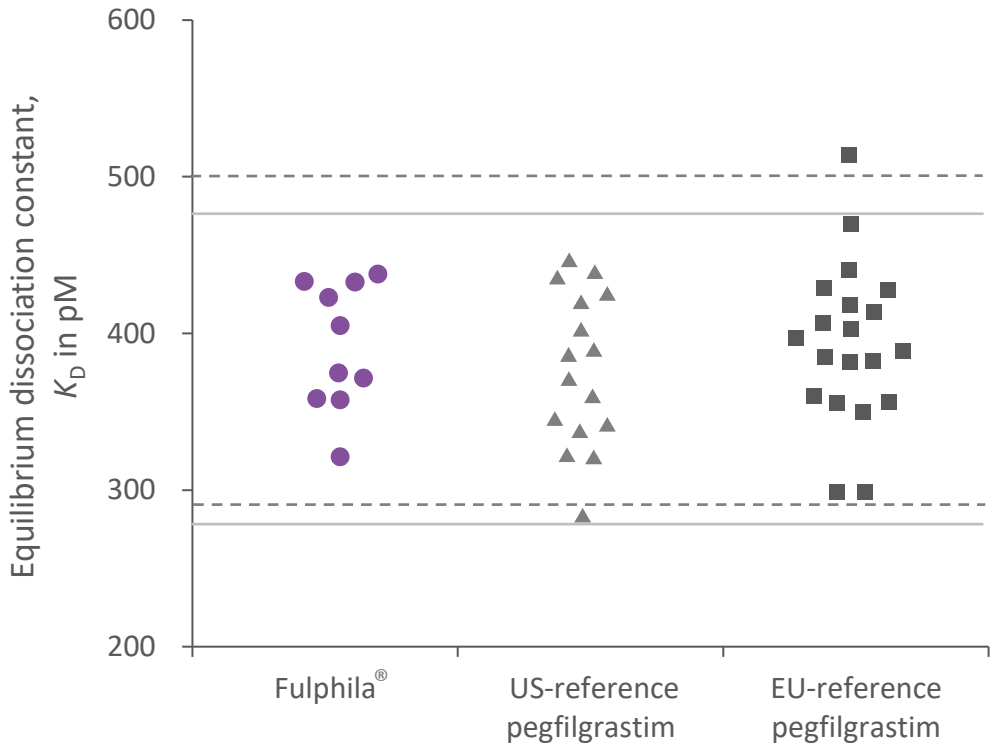
適應症	• 適用於非骨髓性癌症病人在接受易引起臨床上有顯著發生率的嗜中性白血球減少症合併發燒之骨髓抑制性抗癌藥物治療時，以降低嗜中性白血球減少症合併發燒為表現之感染發生率。 • Fulphila® 不可用於造血幹細胞移植時動員周邊血液前趨細胞。
作用機轉	Pegfilgrastim 為群落刺激因子，作用在造血細胞上，經由與專一性的細胞表面受體結合後，因而刺激增生、分化、分化專一性及最終細胞功能活化。
用法用量	Fulphila® 的成人建議劑量為每一化學療法週期單一皮下注射 6 mg。

MYL-1401H (Fulphila®) showed high similarity to reference pegfilgrastim lots in the potency assay and G-CSF receptor binding[1,2]

Scatter plot of the relative potency for various lots of Fulphila® and reference pegfilgrastim[1]



Scatter plot for the equilibrium dissociation constant (K_D) of G-CSF receptor binding with Fulphila® and reference pegfilgrastim[1]



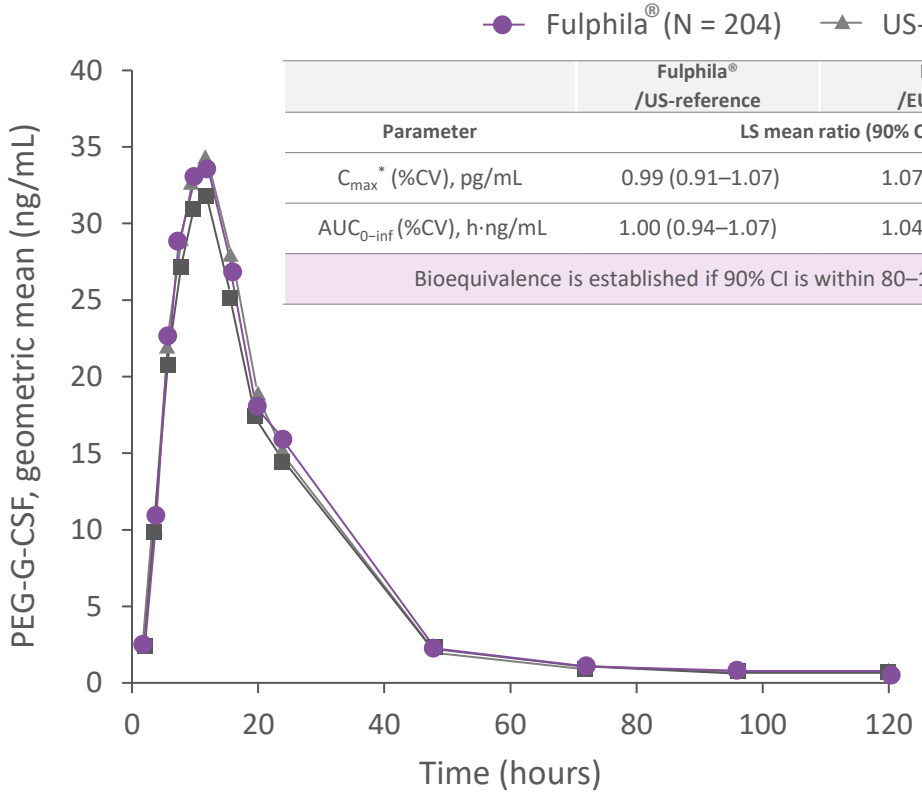
The lines represent the ranges from the observed data for the EU-reference pegfilgrastim (– – –) lots and US-reference pegfilgrastim (——) lots.

EU, European Union; G-CSF, granulocyte colony-stimulating factor; K_D, equilibrium dissociation constant; US, United States.

1. Waller CF, et al. J Cancer Res Clin Oncol. 2018;144(6):1087-1095. **2.** Hoy SM. BioDrugs. 2019;33(1):117-120.

The PK and PD analysis were similar among Fulphila®, US-reference pegfilgrastim, and EU-reference pegfilgrastim

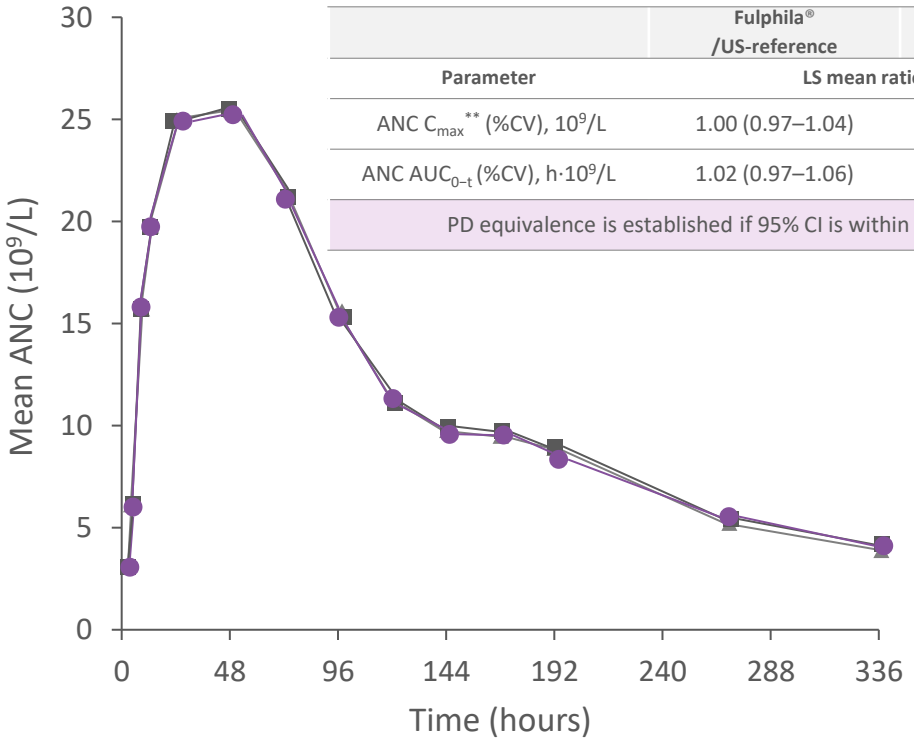
Mean serum pegfilgrastim concentration vs. time profile (PK analysis set)



Parameter	Fulphila® /US-reference LS mean ratio (90% CI)	Fulphila® /EU-reference LS mean ratio (90% CI)
C_{max}* (%CV), pg/mL	0.99 (0.91–1.07)	1.07 (0.98–1.16)
AUC_{0-inf} (%CV), h·ng/mL	1.00 (0.94–1.07)	1.04 (0.98–1.11)

Bioequivalence is established if 90% CI is within 80–125%

ANC vs. time profile (PD analysis set)



Parameter	Fulphila® /US-reference LS mean ratio (95% CI)	Fulphila® /EU-reference LS mean ratio (95% CI)
ANC C_{max}** (%CV), 10^9/L	1.00 (0.97–1.04)	0.99 (0.96–1.03)
ANC AUC_{0-t} (%CV), h·10^9/L	1.02 (0.97–1.06)	1.00 (0.96–1.05)

PD equivalence is established if 95% CI is within 85–117.65%

ANC, absolute neutrophil count; AUC_{0-inf}, area under the curve from the time of dosing to infinity; AUC_{0-t}, area under the curve above baseline; CI, confidence interval; C_{max}*, observed maximum serum concentration; ANC C_{max}**, maximum change from baseline for ANC; %CV, coefficient of variation; EU, European Union; LS, least squares; PD, pharmacodynamics; PEG-G-CSF, pegylated granulocyte colony-stimulating factor; PK, pharmacokinetics; US, United States; vs, versus.

Waller CF, et al. J Cancer Res Clin Oncol. 2018;144(6):1087-1095.

Pegfilgrastim biosimilar Fulphila® in the prophylactic treatment of chemotherapy-induced neutropenia

Objective To evaluate safety and efficacy of Fulphila® and European Union-sourced reference pegfilgrastim in patients with BC.

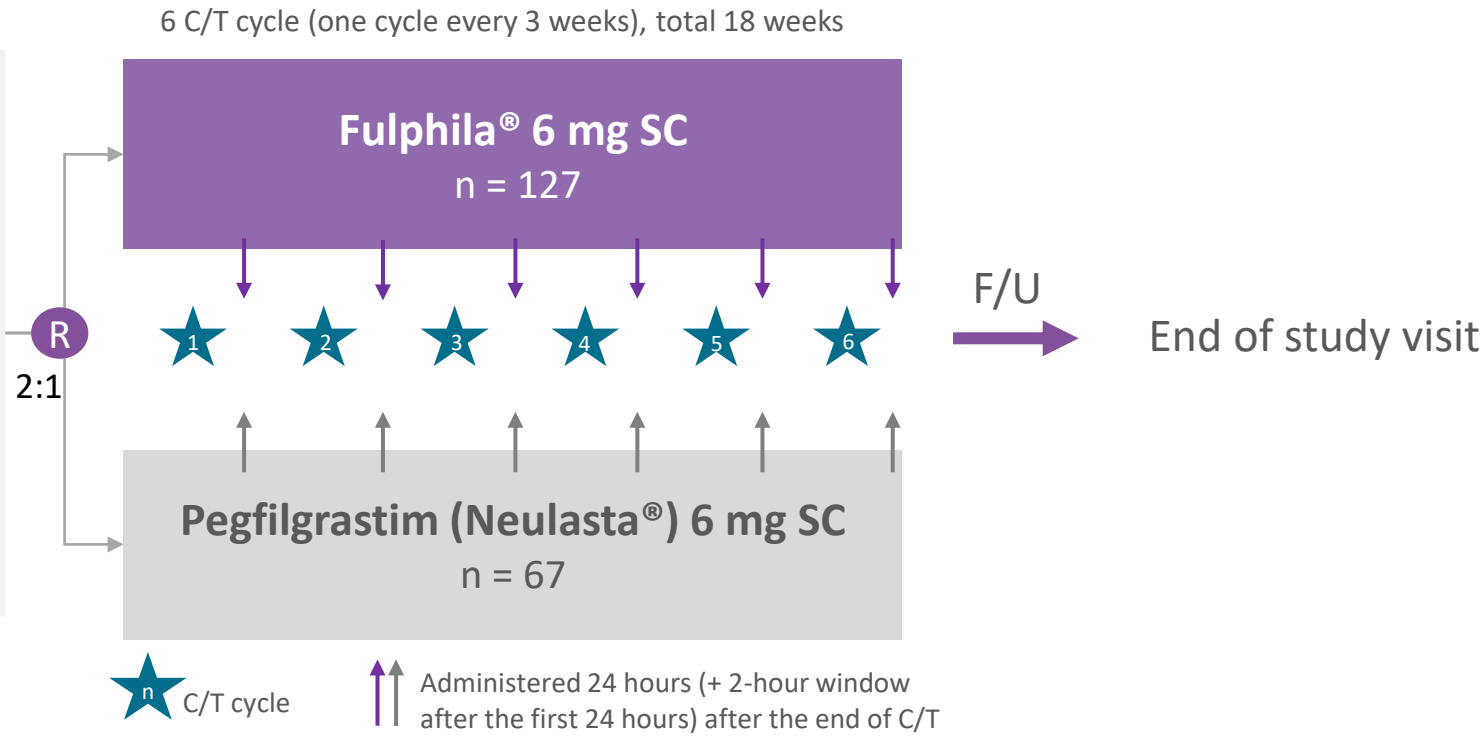
Phase 3, randomized, double-blind, parallel-group equivalence trial

BC patients

N = 194

Inclusion criteria

- BC eligible to receive neoadjuvant or adjuvant TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2)



BC, breast cancer; C/T, chemotherapy; F/U, follow-up; R, randomized; SC, subcutaneous; TAC, docetaxel, doxorubicin, and cyclophosphamide.

Waller CF, et al. Ann Hematol. 2019;98(5):1217-1224.

Primary endpoint was duration of severe neutropenia and equivalence was declared if the CI was completely within the range of ± 1 day

Primary endpoint

The duration of severe neutropenia (DSN) in cycle 1, defined as days with ANC < 0.5 × 10^9/L*

* Equivalence was declared if the 2-sided 95% CI was within the range of ± 1 day

Secondary endpoints

- Frequency of grades 3-4 neutropenia
- Depth and time to ANC nadir and rate of recovery
- Rate of FN
- Delay, reduction, and omission of chemotherapy doses

Safety endpoints

Adverse events

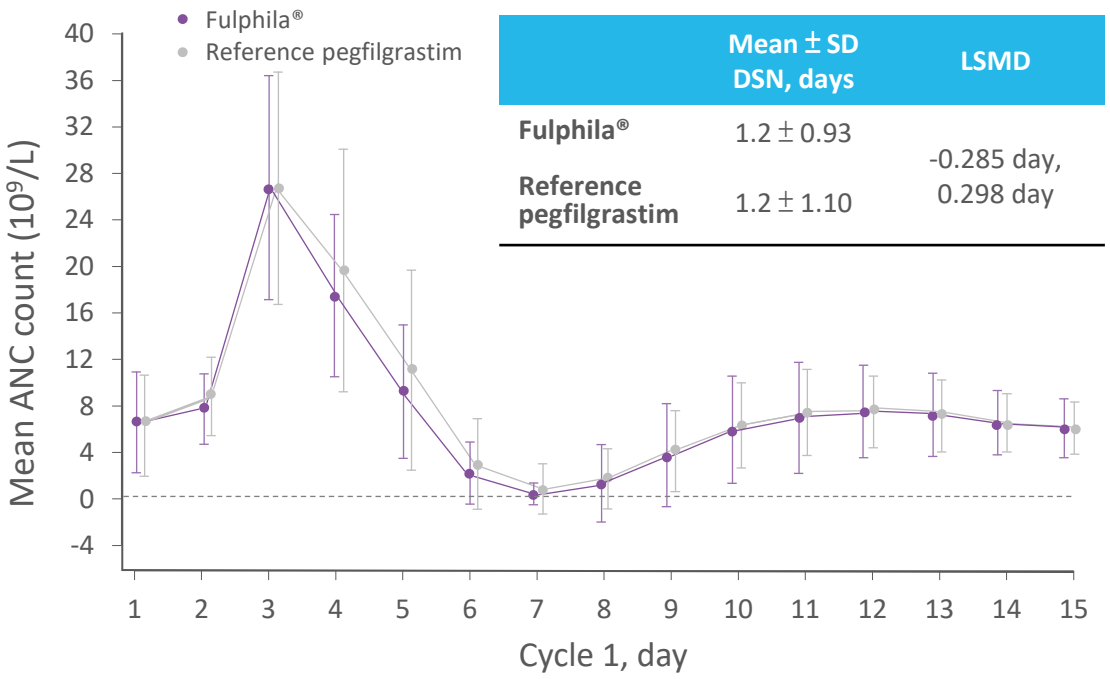
Including:

- Bone pain
- Injection site reactions
- NAb

ANC, absolute neutrophil count; CI, confidence interval; DSN, duration of severe neutropenia; FN, febrile neutropenia; NAb, neutralizing antibody.
Waller CF, et al. Ann Hematol. 2019;98(5):1217-1224.

The mean ANC profiles among patients treated with Fulphila® and reference pegfilgrastim were similar

Mean ANC over time by treatment in cycle 1 (PP population)



	Mean ± SD DSN, days	LSMD
Fulphila®	1.2 ± 0.93	-0.285 day, 0.298 day
Reference pegfilgrastim	1.2 ± 1.10	

Efficacy endpoints

Frequency, depth, and time of neutropenia in cycle 1 (PP population)	Fulphila® (N = 126)	Reference pegfilgrastim (N = 67)
DSN, mean (SD), days	1.2 (0.9)	1.2 (1.1)
DSN, LS mean (SE), days	1.3 (0.1)	1.3 (0.2)
Grade 3 neutropenia, n (%)[a,b]	20 (15.9)	12 (17.9)
Grade 4 neutropenia, n (%)[b,c]	94 (74.6)	43 (64.2)
ANC nadir, mean (SD), 10^9/L	0.40 (0.5)	0.78 (1.4)
ANC nadir, median (range), 10^9/L	0.21 (0.0–2.5)	0.27 (0.0–6.7)
Duration of post-nadir ANC recovery within ≤ 3 days, n (%)	121 (97)[d]	67 (100)
Rate of FN in cycle 1 (ITT population)	**Fulphila® (N = 127)**	**Reference (N = 67)**
Rate of FN, n (%)	5 (4)	1 (2)
Frequency of neutropenia across all cycles (ITT population)	**Fulphila® (N = 127)**	**Reference (N = 67)**
Grade 3 neutropenia, n (%)[a,b]	17 (13)	7 (10)
Grade 4 neutropenia, n (%)[b,c]	103 (81)	49 (73)
FN, n (%)[e]	7 (6)	1 (2)
Frequency of chemotherapy doses reduced, omitted, or delayed across all cycles (ITT population)	**Fulphila® (N = 127)**	**Reference (N = 67)**
Related to neutropenia, FN, or documented infections, n (%)	5 (4)	1 (2)

[a] ANC < 1.0 × 10^9 /L; [b] Only the highest grade neutropenia experienced was reported; [c] ANC < 0.5 × 10^9 /L; [d] Percentage calculated using the 125 patients with a confirmed post-nadir ANC recovery; [e] Out of 8 patients with FN, 3 met the ESMO definition, 1 patient did not, and 4 other patients had insufficient data to confirm FN, but all patients were considered to have FN for the data analysis.

ANC, absolute neutrophil count; DSN, duration of severe neutropenia; ESMO, European Society for Medical Oncology; FN, febrile neutropenia; ITT, intention-to-treat; LS, least squares; LSMD, least squares mean difference; PP, per protocol; SD, standard deviation; SE, standard error.

Waller CF, et al. Ann Hematol. 2019;98(5):1217-1224.

The overall safety profiles of Fulphila® and reference pegfilgrastim were comparable

TEAEs occurring in ≥ 5% of patients in either treatment group

	Fulphila® (N = 127)	Reference (N = 67)
TEAEs, n (%)	114 (90)	58 (87)
Alopecia	76 (60)	36 (54)
Bone pain	**51 (40)**	**24 (36)**
Nausea	37 (29)	25 (37)
Asthenia	23 (18)	10 (15)
Fatigue	19 (15)	16 (24)
Diarrhea	16 (13)	12 (18)
Thrombocytopenia	14 (11)	6 (9)
Anemia	14 (11)	9 (13)
Vomiting	12 (9)	7 (10)
Headache	12 (9)	8 (12)
Stomatitis	11 (9)	2 (3)
Thrombocytosis	8 (6)	0 (0)
Decreased appetite	8 (6)	0 (0)
Febrile neutropenia	7 (6)	1 (1)
ALT increased	7 (6)	8 (12)
AST increased	7 (6)	7 (10)
Platelet count decreased	7 (6)	5 (7)
Pyrexia	3 (2)	5 (7)
Abdominal pain	3 (2)	4 (6)

Bone pain:

Bone pain reported by patients **was similar between groups**, and no patients discontinued because of bone pain.

Injection site reaction:

- **No Fulphila®–treated patients reported an injection site reaction.**
- One (2%) patient receiving reference pegfilgrastim had injection site redness on day 2, cycle 2.

Immunogenicity results:

- **The Fulphila® group had no treatment-induced ADA-positive patients.**
- Only 1 (2%) ADA-positive result for reference pegfilgrastim was due to seroconversion.

ADA, antidrug antibody; TEAEs, treatment-emergent adverse events.
Waller CF, et al. Ann Hematol. 2019;98(5):1217-1224.

Part 2
Unmet needs in the treatment of neutropenia in Taiwan

Reimbursement criteria regarding pegfilgrastim use in Taiwan is stricter than other guidelines

Gap between indication, NCCN & ESMO guidelines, and NHI reimbursement guidelines of pegfilgrastim

	Indications
NCCN guidelines[1]	**Primary prophylaxis:** • G-CSF is recommended for patients with high risk of developing FN. • G-CSF is considered for patients with intermediate risk of developing FN including ≥ 1 risk factor. **Secondary prophylaxis:** • G-CSF is considered in patients with FN (≥ 38.3°C orally or ≥ 38.0°C over 1 hour; and neutropenia: < 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 hours) / dose-limiting neutropenic event (could be a nadir count or day of treatment count that could otherwise impact planned dose of chemotherapy) and no prior use of G-CSFs.
ESMO guidelines[2]	**Primary prophylaxis:** • FN can be effectively prevented by the use of G-CSFs; it is recommended to use these agents in patients receiving chemotherapies with a > 20% risk of developing FN and in those having serious comorbidities and/or aged > 60 years. **Secondary prophylaxis** (i.e., G-CSF given for a course of C/T following a course with FN [oral temperature of > 38.3°C or two consecutive readings of > 38.0°C for 2 hours and an ANC of < 0.5×10^9/L, or expected to fall below 0.5×10^9/L]): • Is indicated if dose reduction below threshold or delay of C/T is not desirable (e.g., treatment with a curative intent).
Approved indication in Taiwan[3]	• 適用於**非骨髓性癌症病人**在**接受**易引起臨床上**有顯著發生率的嗜中性白血球減少症合併發燒之骨髓抑制性抗癌藥物治療時**，以降低嗜中性白血球減少症合併發燒為表現之感染發生率。 • Fulphila® 不可用於造血幹細胞移植時動員周邊血液前趨細胞。
NHI reimbursement guidelines[4]	• 限**非骨髓性癌症合併有骨髓侵犯**之患者，在**骨髓抑制性抗癌藥物治療後**，且**曾經發生白血球少於 1000/cumm，或中性白血球（ANC）少於 500/cumm** 者使用。

ANC, absolute neutrophil count; C/T, chemotherapy; ESMO, European Society for Medical Oncology; FN, febrile neutropenia; G-CSF(s), granulocyte colony-stimulating factor(s); NCCN, National Comprehensive Cancer Network; NHI, National Health Insurance.

1. NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022. **2.** Klastersky J, et al. Ann Oncol. 2016;27(suppl 5):v111-v118. **3.** Fulphila® 中文仿單。
4. 衛生福利部中央健康保險署。藥品給付規定。第 4 節 血液治療藥物。（111. 08. 23 更新）。

Pegfilgrastim is only reimbursed for patients who have bone marrow involvement as secondary prophylaxis

- NCCN and ESMO guidelines recommended pegfilgrastim be a primary prophylaxis and secondary prophylaxis.

	Primary prophylaxis	Secondary prophylaxis
NCCN guidelines[1]	✓	✓
ESMO guidelines[2]	✓	✓
Approved indication in Taiwan[3]	✓	✓
NHI reimbursement guidelines[4]	✗	✓ 限非骨髓性癌症合併有骨髓侵犯之患者，在骨髓抑制性抗癌藥物治療後，且曾經發生白血球少於 1000/cumm，或中性白血球（ANC）少於 500/cumm 者使用。

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NHI, National Health Insurance.

1. NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022. **2.** Klastersky J, et al. Ann Oncol. 2016;27(suppl 5):v111-v118. **3.** Fulphila® 中文仿單。
4. 衛生福利部中央健康保險署。藥品給付規定。第 4 節 血液治療藥物。（111. 08. 23 更新）。

Role of Fulphila® to improve patient access to medicines

針對**符合適應症但不符合健保給付**的中高風險嗜中性白血球低下症病患，**NCCN 和 ESMO guidelines** 仍建議治療

暉致提供**病患支持計畫**給符合條件的癌症病人，減輕病人醫療負擔，增加對安全有效的生物製劑的可近性

- **初級預防**

或

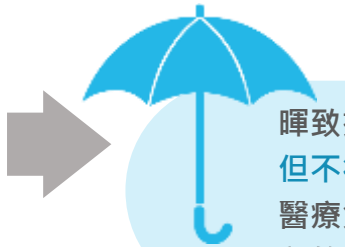
- **無骨髓侵犯的次級預防的非骨髓性癌症病人等**

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.

Summary

	Primary prophylaxis	Secondary prophylaxis
NCCN guidelines[1]	✓	✓
ESMO guidelines[2]	✓	✓
Approved indication in Taiwan[3]	✓	✓
NHI reimbursement guidelines[4]	✗	✓ 限非骨髓性癌症合併有骨髓侵犯之患者，在骨髓抑制性抗癌藥物治療後，且曾經發生白血球少於 1000/cumm，或中性白血球（ANC）少於 500/cumm 者使用

- The FDA approved **Fulphila® (pegfilgrastim-jmdb)** as the **first biosimilar** to Neulasta® (pegfilgrastim) to decrease the incidence of infection, as manifested by febrile neutropenia.[5,6]
- Fulphila® is **equivalent** in efficacy to originator pegfilgrastim and with no clinically meaningful differences in safety.[7]
- PEG biosimilars may provide opportunities to **optimize FN management** in patients with **intermediate-to-high FN risk** in the real-world data.[8]
- Fulphila® can be offered at a **lower price** than the reference drug and **increase patient access** to pegfilgrastim treatment.
  - **Fulphila® :** NTD 15,229 (6 mg/0.6 mL)[3,9]
  - **Neulasta® :** NTD 17,490 (6 mg/0.6 mL)[9,10]



暉致提供病患支持計畫給符合適應症但不符合健保給付的病患，減輕病人醫療負擔，增加對安全有效的生物製劑的可近性

ESMO, European Society for Medical Oncology; FDA, United States Food and Drug Administration; NCCN, National Comprehensive Cancer Network; NHI, National Health Insurance; PEG, pegfilgrastim.

1. NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1. 2023 — December 2, 2022. **2.** Klastersky J, et al. Ann Oncol. 2016;27(suppl 5):v111-v118. **3.** Fulphila® 中文仿單。 **4.** 衛生福利部中央健康保險署。藥品給付規定。第 4 節 血液治療藥物。（111. 08.23 更新）。 **5.** Fulphila® FDA package insert. **6.** FDA NEWS RELEASE. FDA approves 1st biosimilar to Neulasta to help reduce the risk of infection during cancer treatment. **7.** Waller CF, et al. Ann Hematol. 2019;98(5):1217-1224. **8.** Cornes P, et al. Future Oncol. 2022;18(16):1979-1996. **9.** 全民健康保險藥物給付項目及支付標準（發文日期：中華民國 111 年 5 月 13 日）。**10.** Neulasta® 中文仿單（版本：Amgen PI 2019/04 V24）。

Fulphila® Risk Management Plan（風險管理計畫）

衛福部核准適應症

適用於非骨髓性癌症病人在接受易引起臨床上有顯著發生率的嗜中性白血球減少症合併發燒之骨髓抑制性抗癌藥物治療時，以降低嗜中性白血球減少症合併發燒為表現之感染發生率。

建議參考劑量

- Fulphila 的成人建議劑量為每一化學療法週期單一皮下注射 6 mg。請勿在使用細胞毒性化學療法前 14 天到細胞毒性化學療法後 24 小時的期間給予 Fulphila。
- 在小於 18 歲的兒童或青少年，Fulphila 的安全性與有效性尚未確立。

常見副作用

- 肌肉骨骼副作用：骨頭痛（25～45%）、四肢疼痛。

少見但嚴重之副作用

- 心血管副作用：微血管滲漏症候群。
- 血液學副作用：白血球增多症（小於 1％）、脾臟破裂、 鐮狀細胞危象。
- 免疫系統副作用：嚴重過敏反應。
- 腎臟副作用：腎損傷（腎絲球腎炎）。
- 呼吸道副作用：急性呼吸窘迫症候群（ARDS）。
- 其他：對於惡性細胞的腫瘤生長刺激效果的潛在作用。

注意事項

- 單次使用預充填針筒上的針蓋還有乾的**自然橡膠（乳膠）**，對於該物質**過敏的人不可使用。**
- **懷孕：**對於懷孕婦女沒有足夠及控制良好的試驗。
- **授乳：**Pegfilgrastim 是否會分泌至乳汁中是未知的， 其他重組 G-CSF 很少被分泌於乳汁中及新生兒不會口服吸收 G-CSF。當給予授乳婦女時須注意。

病患教育

- 藥品盒內附有 "病患用藥須知"
- 提醒病人可能潛在的不良反應。
- 若病人需自行注射時，務必參考 “病患用藥須知”於操作前進行指導。
- 若錯過施打的時間，請病人與醫療人員聯繫。
- 提醒病人發生疑似不良反應時請立即告訴醫師、藥師或醫療人員。其中包含任何沒有列在病人用藥手冊或仿單中之不良反應。

藥物不良反應通報方式

- 疑似藥物不良反應報告撰寫 加註 *藥品商品名、批號、適應症*。
- 全國藥物不良反應通報系統，電話：02-2396-0100，傳真：02-235-84100，網站：https://adr.fda.gov.tw/ ，電子郵件：adr@tdrf.org.tw。
- 您也應該向暉致醫藥股份有限公司-藥品安全監視部門通報任何不良反應，電話：02-6603-1688 以及電子郵件：pv.taiwan@viatris.com

Fulphila® 福富血 處方資訊摘要

本品 Fulphila 為 Neulasta 的生物相似性藥品。

〔成分含量與劑型〕

注射劑，Fulphila 是 6 mg（0.6 mL）pegfilgrastim 裝於預充填針筒內，並附有 27 號、1/2 英吋針頭及 UltraSafe® 針頭保護物。

〔適應症〕

適用於非骨髓性癌症病人在接受易引起臨床上有顯著發生率的嗜中性白血球減少症合併發燒之骨髓抑制性抗癌藥物治療時，以降低嗜中性白血球減少症合併發燒為表現之感染發生率。

Fulphila 不可用於造血幹細胞移植時動員周邊血液前趨細胞。

〔用法與用量〕

•Fulphila 的成人建議劑量為每一化學療法週期單一皮下注射 6 mg。請勿在使用細胞毒性化學療法前 14 天到細胞毒性化學療法後 24 小時的期間給予 Fulphila。 •在小於 18 歲的兒童或青少年，Fulphila 的安全性與有效性尚未確立。 •使用前，請將裝有 Fulphila 預充填針筒的小盒由冰箱取出，讓 Fulphila 預充填針筒放置室溫中（至少 30 分鐘）。放置於室溫下超過 48 小時則須丟棄。 •在溶液及容器許可的狀況下，給藥前應目視檢查顆粒物質及變色。當發現顆粒物質或變色時，請勿使用。注意：單次使用的預充填針筒的針頭蓋含有乾燥的天然橡皮（衍生自乳膠）；對乳膠過敏的人不可使用本產品。

〔禁忌事項〕

•對於 pegfilgrastim 或 filgrastim 有嚴重過敏反應病史的病人禁止使用 Fulphila。

〔警語與注意事項〕

•脾臟破裂：給予 pegfilgrastim 後可能發生包括致命案例的脾臟破裂。
•急性呼吸窘迫症候群（ARDS）：使用 pegfilgrastim 的病人可能會發生急性呼吸窘迫症候群（ARDS）。
•嚴重過敏反應：使用 pegfilgrastim 的病人可能會發生包括全身性過敏反應（anaphylaxis）的嚴重過敏反應。
•鐮狀細胞疾病的病人的使用：鐮狀細胞疾病的病人使用 pegfilgrastim 可能會發生嚴重的鐮狀細胞危象。
•腎絲球腎炎：使用 pegfilgrastim 的病人發生過腎絲球腎炎。
•白血球增多：在使用 pegfilgrastim 的病人中觀察到白血球（WBC）計數為 100×10^9/L 以上。
•微血管滲漏症候群（Capillary leak syndrome, CLS）：曾有投與顆粒性白血球群落刺激因子（Granulocyte-colony stimulating factor, G-CSF）後發生微血管滲漏症候群的案例報告，其症狀為低血壓、低白蛋白血症、水腫和血液濃縮。
•對於惡性細胞的腫瘤生長刺激效果的潛在作用：Pegfilgrastim 及 filgrastim 作用的 G-CSF 受體已被發現存在於腫瘤細胞株上。

〔不良反應〕

•安慰劑對照組的臨床試驗中，pegfilgrastim 組 ≥ 5% 病人最常發生及群組之間差異 ≥ 5% 的不良反應是骨痛及四肢痛。
•脾臟破裂 •急性呼吸窘迫症候群（ARDS）•嚴重過敏反應 •鐮狀細胞疾病的病人的使用 •腎絲球腎炎 •白血球增多 •微血管滲漏症候群 •對於惡性細胞的腫瘤生長刺激效果的潛在作用。

備註：*此為處方資訊摘要，完整處方資訊請詳閱仿單。