REGIONE LAZIO

REGIONE LAZIO

Direzione Regionale: SALUTE E INTEGRAZIONE SOCIOSANITARIA

Area: POLITICA DEL FARMACO

DETERMINAZIONE

N. G14608 **del** 23 NOV. 2015 **Proposta n.** 18320 **del** 23/11/2015

Oggetto:

recepimento Linee di indirizzo regionali per l'uso appropriato dei fattori di crescita leucocitaria (G-CSF) nel Lazio.

Proponente:

Estensore	DENARO RITA	
Responsabile del procedimento	MECOZZI ALESSANDRA	
Responsabile dell' Area	L. LOMBARDOZZI	
Direttore Regionale	F. DEGRASSI	
Protocollo Invio		
Firma di Concerto		

Richiesta di pubblicazione sul BUR: NO

OGGETTO: recepimento Linee di indirizzo regionali per l'uso appropriato dei fattori di crescita leucocitaria (G-CSF) nel Lazio.

IL DIRETTORE DELLA DIREZIONE SALUTE E INTEGRAZIONE SOCIOSANITARIA

Su proposta del Dirigente dell'Area Politica del Farmaco;

VISTA la legge statutaria 11 novembre 2004, n. 1 "Nuovo Statuto della Regione Lazio";

VISTA la legge regionale n. 6 del 18 febbraio 2002, avente ad oggetto "Disciplina del sistema organizzativo della Giunta e del Consiglio e disposizioni relative alla dirigenza ed al personale regionale", e successive modificazioni;

VISTO il regolamento regionale del 16 aprile 2015, n. 3, concernente: "Modifiche al regolamento regionale 6 settembre 2002, n. 1 (Regolamento di organizzazione degli uffici e dei servizi della Giunta Regionale) e successive modificazioni;

VISTA la deliberazione di Giunta regionale n. 111 del 29 maggio 2013 con la quale è stato conferito alla dott.ssa Flori Degrassi l'incarico di Direttore della Direzione regionale "Salute e integrazione sociosanitaria";

VISTE le azioni previste nei Programmi Operativi 2013-2015 a salvaguardia degli obiettivi strategici di Rientro dai disavanzi sanitari della Regione Lazio relative alla promozione dei farmaci biosimilari al fine di razionalizzarne l'uso e la spesa;

VISTA la scadenza brevettuale di molecole biologiche ad alto impatto e la necessità di coniugare i risparmi perseguibili con la peculiarità delle molecole biologiche;

CONSIDERATO necessario predisporre delle linee di indirizzo regionali sui farmaci biosimilari al fine di armonizzare e declinare a livello regionale le disposizioni AIFA, regolamentare l'appropriatezza d'uso di tali farmaci e l'accesso;

VISTA la determinazione Dirigenziale n. G05686 del 12/05/2015 Costituzione Gruppo di Lavoro "Farmaci biosimilari" e le successive determinazioni dirigenziali nn. G07923 e G08694 del 26/06/2015 di integrazioni del Gruppo di Lavoro.

CONSIDERATO che il Gruppo di Lavoro dopo numerosi incontri ha elaborato le Linee di indirizzo regionali per l'uso appropriato dei fattori di crescita leucocitaria (G-CSF) nel Lazio;

CONSIDERATO necessario recepire le suddette Linee di indirizzo che costituiscono parte integrante e sostanziale del presente atto

DETERMINA

Per le motivazioni indicate in premessa, che si intendono integralmente riportate:

- di recepire le Linee di indirizzo regionali per l'uso appropriato dei fattori di crescita leucocitaria (G-CSF) nel Lazio.

IL DIRETTORE
(dott.ssa Flori Degrassi)

DIEP Lazio
Dipartimento di Epidemiologia
del Servizio Sanitario Regionale
Regione Lazio

SISTEMA SANITARIO REGIONALE
ASL ROMA E

REGIONE LAZIO

Linee di indirizzo per l'uso appropriato dei fattori di crescita leucocitaria (G-CSF) nel Lazio

9 novembre 2015

GRUPPO DI LAVORO REGIONALE *FARMACI BIOSIMILARI* [1]

DIREZIONE REGIONALE SALUTE E INTEGRAZIONE SOCIOSANITARIA

Lorella Lombardozzi, Alessandra Mecozzi - Area Politica del Farmaco, Direzione Regionale Salute e Integrazione Sociosanitaria, Regione Lazio

CLINICI INDIVIDUATI ALL'INTERNO DEL SERVIZIO SANITARIO REGIONALE (SSR) DEL LAZIO

Alessandro Andriani, specialista in ematologia, ASL RM A; referente per il Lazio della Società Italiana di Ematologia

Salvatore Di Giulio, specialista in nefrologia, A.O. San Camillo Forlanini

Teresa Gamucci, specialista in oncologia, ASL Frosinone; coordinatore regionale A.I.O.M.

Antonio Gasbarrini, specialista in gastroenterologia, professore ordinario di Gastroenterologia, Policlinico Gemelli - Università Cattolica del Sacro Cuore

Anna Kohn, specialista in gastroenterologia, A.O. San Camillo Forlanini

Andrea Mengarelli, specialista in ematologia, I.F.O.

Giovanni Minisola, specialista in reumatologia, A.O. San Camillo Forlanini; presidente della Società Italiana di Reumatologia

Maurizio Simmaco, specialista in biologia molecolare; professore ordinario di Biologia molecolare, Università La Sapienza

Guido Valesini, specialista in reumatologia, Policlinico Umberto I; professore ordinario di Reumatologia; Direttore della Scuola di specializzazione in reumatologia, Università La Sapienza

Germano Zampa, specialista in oncologia, ASL RM A

SEGRETERIA SCIENTIFICA DEL GRUPPO DI LAVORO

Antonio Addis, Laura Amato, Monica Pirri, Rosella Saulle, Francesco Trotta - Dipartimento di Epidemiologia del Servizio Sanitario Regionale del Lazio

Rita Denaro, Area Politica del Farmaco, Direzione Regionale Salute e Integrazione Sociosanitaria, Regione Lazio

(1) Determinazioni della Direzione Regionale Salute e Integrazione Sociosanitaria del Lazio nn. G05686 del 12/05/2015, G07923 del 26/06/2015, G08694 del 13/07/2015

Preambolo

Il presente documento ha l'obiettivo di illustrare il percorso adottato dal Gruppo di lavoro sui biosimilari per formulare le linee di indirizzo sull'uso appropriato dei fattori di crescita leucocitaria (G-CSF) nella pratica clinica della Regione Lazio.

Gli elementi considerati ai fini dello sviluppo delle linee di indirizzo sono i seguenti:

1) analisi dei farmaci autorizzati e delle rispettive indicazioni terapeutiche;
2) analisi dei dati di utilizzo del G-CSF e confronti intra- e inter-regionali;
3) dati epidemiologici relativi alle condizioni per le quali il G-CSF è indicato;
4) analisi delle evidenze disponibili in letteratura e delle principali Linee Guida.

1) Analisi dei farmaci autorizzati e delle rispettive indicazioni terapeutiche

In Italia risultano commercializzate 8 specialità medicinali appartenenti alla classe dei fattori di crescita mieloidi (G-CSF) (Tabella 1). In particolare, esistono 4 diverse formulazioni dei G-CSF: 1) il filgrastim, di cui esistono 4 biosimilari e 1 originator; 2) il lenograstim, che è la forma glicosilata del filgrastim; 3) il pegfilgrastim, che è la forma pegilata del filgrastim; 4) il lipegfilgrastim, ovvero la forma glicopegilata di filgrastim.

In generale, dall'analisi delle indicazioni autorizzate riportate nei Riassunti delle Caratteristiche del Prodotto (RCP) delle specialità considerate, emerge che le 5 indicazioni del filgrastim originator sono perfettamente sovrapponibili a quelle dei filgrastim biosimilari. Viene riportato di seguito il dettaglio dell'analisi comparativa dei G-CSF per ogni indicazione autorizzata.

a) Profilassi neutropenia febbrile (NF) da chemioterapia

Limitando il confronto alla popolazione di pazienti adulti e anziani nell'indicazione alla profilassi della neutropenia febbrile da chemioterapia, si osserva che l'indicazione di filgrastim è del tutto sovrapponibile a quelle del lenograstim, pegfilgrastim e lipegfilgrastim.

Nel complesso della popolazione pediatrica, il filgrastim è il fattore di crescita indicato per la profilassi della neutropenia febbrile da chemioterapia; il lenograstim non prevede esplicitamente l'uso (per questa indicazione) nei bambini fino a due anni d'età. Pegfilgrastim e lipegfilgrastim non prevedono l'uso nei bambini (in tutte le fasce d'età) per questa specifica indicazione.

b) *Riduzione della durata di NF in terapia mieloablativa seguita da trapianto del midollo osseo*
c) *Mobilizzazione delle cellule staminali periferiche*

Filgrastim e biosimilari hanno indicazioni interamente sovrapponibili; lenogastrim è sovrapponibile a filgrastim per entrambe le indicazioni ad esclusione dei pazienti fino a due anni d'età (per i quali non è indicato); pegfilgrastim e lipegfilgrastim non sono autorizzati per queste due indicazioni.

d) *Neutropenia congenita*
e) *Neutropenia HIV correlata o correlata ai farmaci anti-HIV*

Solo il filgrastim (originator e biosimilare) è autorizzato per il trattamento della neutropenia in questi sottogruppi specifici di pazienti. Non esistono differenze nelle indicazioni autorizzate tra originator e biosimilari.

2) Analisi dei dati di utilizzo del G-CSF e confronti intra- e inter-regionali

a) I dati italiani

I dati italiani, estratti dal rapporto Osmed 2014, mostrano che nella classe dei fattori della crescita (G-CSF) oltre il 75% della spesa e il 68% dei consumi (come DDD) è rappresentato da lenograstim, pegfilgrastim e lipegfilgrastim. Poco meno del 25% della spesa e del 32% dei consumi è invece dovuto al filgrastim (sia come originator che come biosimilare) (Tabella 2).

Se si analizzano in dettaglio i dati nazionali del filgrastim e in particolare si effettua il confronto tra originator e biosimilare, emerge che i biosimilari di filgrastim rappresentano il 56% della spesa e l'81% dei consumi (Tabella 3).
L'analisi temporale mostra un costante e significativo aumento dei biosimilari a partire dal 2011 sia in termini di spesa che di consumi (Figure 1, 2).

b) G-CSF: Il confronto inter-regionale

I dati delle diverse Regioni italiane (fonte: Ministero Salute - tracciabilità del farmaco, 2014) mostrano una evidente eterogeneità nei consumi di biosimilari e, in generale, delle diverse formulazioni disponibili di G-CSF (l'analisi non include il lipegfilgrastim).
In particolare, nel Lazio si registrano consumi di biosimilari molto bassi, attestati attorno al 10%, che sono molto distanti anche dalla media italiana dei consumi di biosimilari (che è di oltre il 20%) (Figura 3). Da notare che sono ben 7 le Regioni in cui l'uso del biosimilare è oltre il 50% (VdA, Bz, Tn, Veneto, FVG, Emilia-Romagna e Umbria).
La quota di filgrastim originator usata nel Lazio, pari a circa il 5% dei consumi dei G-CSF, risulta essere nella media dei consumi italiana (Figura 3). Risulta molto elevato invece il consumo di pegfilgrastim, che nel Lazio rappresenta il 75% dei consumi (nelle regioni più virtuose il consumo di pegfilgrastim è circa il 20% dei consumi di G-CSF).
Se si analizzano i dati puntuali dei consumi, appare evidente come nella Regione Lazio la pratica clinica faccia registrare in assoluto consumi maggiori di G-CSF, in particolare di pegfilgrastim, rispetto alle altre Regioni (Figura 4).
Ovviamente, si dà per scontato che non esistono differenze tra Lazio e altre Regioni nella prevalenza o incidenza delle patologie per le quali è indicato il trattamento con G-CSF.
L'analisi dei costi medi delle DDD dei G-CSF evidenzia che nel Lazio, a fronte di un consumo di G-CSF che è il più elevato di Italia, il costo medio di una DDD è di oltre 37 euro, 60% in più rispetto alle regioni più virtuose (23 euro), nelle quali si registra anche un consumo assoluto inferiore di G-CSF (Figura 5).

3) Dati epidemiologici relativi alle condizioni per le quali il G-CSF è indicato

a) Neutropenia febbrile da chemioterapia

L'incidenza dei tumori stimata in Italia nel 2014 è di circa 366.000 casi (AIRTUM).
La neutropenia febbrile (NF) è uno degli eventi frequenti nel corso delle chemioterapie per il trattamento dei tumori. L'incidenza di NF è stimata tra il 10% e il 57% dei pazienti trattati [1]. Inoltre il rischio di mortalità associato a NF è stimato intorno al 5% per tumori solidi e arriva all'11% per tumori ematologici [2].
Le linee guida AIOM del 2014 sulla gestione della tossicità ematopoietica in oncologia [3] identificano (anche in accordo alle principali LG internazionali dell'ASCO e dell'ESMO) i sottogruppi di pazienti per i quali è raccomandato il trattamento profilattico (sia come profilassi primaria che secondaria) con G-CSF per ridurre il rischio di NF. I diversi sottogruppi di pazienti, per i quali è raccomandata la profilassi, sono identificati sulla base dell'incidenza attesa di NF a seguito delle chemioterapie somministrate ai pazienti, tenendo conto dell'età e delle co-morbidità.

Si riprendono di seguito le raccomandazioni dell'AIOM:

- Profilassi primaria:
  - il G-CSF è raccomandato in profilassi primaria in pazienti che ricevono chemioterapia ad alto rischio di NF (>20%);
  - l'utilizzo del G-CSF in caso di un rischio di NF compreso tra il 10% e il 20% è raccomandato in presenza di fattori di rischio paziente e malattia dipendenti (età, comorbidità, ecc.). Questi vanno riconsiderati ad ogni ciclo di trattamento;
  - la profilassi primaria nei pazienti con rischio ipotizzato di NF inferiore al 10% non è raccomandata.

- Profilassi secondaria:

  il G-CSF si deve utilizzare in profilassi secondaria nei pazienti con un precedente episodio di NF, nei casi in cui non sia raccomandata una riduzione di dose.

- Uso terapeutico del G-CSF:

  l'uso terapeutico di G-CSF non è raccomandato nelle seguenti condizioni:

  - in pazienti con neutropenia non febbrile;
  - in associazione ad antibioticoterapia.

Esiste una debole evidenza per l'uso di G-CSF nel ridurre la durata della neutropenia febbrile. In ogni caso, l'appropriatezza del trattamento con G-CSF per quest'ultima indicazione va valutata sul singolo paziente.

b) Mobilizzazione delle cellule periferiche per trapianto di midollo

Secondo i dati GITMO in Italia [4] nel 2014 sono avvenuti circa 4900 trapianti di cellule staminali emopoietiche (autologo o allogenico). Nel 55% dei casi di trapianto allogenico la fonte di cellule staminali proveniva da sangue periferico (PBSC).

c) *Neutropenia congenita*

È una malattia rara [5]. La neutropenia congenita grave è un'immunodeficienza, caratterizzata da livelli bassi di granulociti (< 200/mm3), in assenza di un concomitante deficit dei linfociti. La prevalenza nella popolazione generale è stimata in 1-1,7:333.300. L'incidenza annuale è circa 1:250.000 nati.

d) Neutropenia da HIV o da farmaci anti-HIV

Nel Lazio si stimano circa 600 nuovi casi di HIV nel 2014 (incidenza: 10,3 per 100.000 residenti)[6]. In Italia sono state stimate 123.000 (range 115.000-145.000) persone che vivono con l'infezione da HIV, con una prevalenza pari a 0,28 (range 0,24-0,32) per 100 persone residenti con età maggiore di 15 anni.

4) Analisi della letteratura e delle principali Linee Guida pubblicate

- *Analisi della letteratura*

Da una ricerca condotta sulle principali banche dati bibliografiche (Pubmed, EMBASE e Cochrane Library) fino a luglio 2014, sono state selezionate 49 referenze in cui vi è un confronto tra i G-CSF usati nelle diverse indicazioni (Allegato).
Gli studi clinici in cui viene effettuato un confronto testa a testa tra differenti specialità di G-CSF confermano la sostanziale sovrapponibilità per quanto riguarda il profilo beneficio/rischio delle varie specialità.

- *Analisi delle principali Linee Guida (LG) pubblicate*

A partire dalle ultime raccomandazioni degli oncologi americani (ASCO) pubblicate online lo scorso luglio 2015 [7], è stata condotta una ricerca bibliografica su Pubmed ristretta a "Government Publications", "Guideline", "Technical Report" pubblicati negli ultimi anni (dal 2012) relativi ai G-CSF. Sono state selezionate 3 LG che includono raccomandazioni sull'uso dei G-CSF in setting diversi; il gruppo di lavoro ha evidenziato la disponibilità di una quarta LG sviluppata per il setting della mobilizzazione, per cui sono state considerate complessivamente 4 LG pubblicate [7-10].

➢ *G-CSF in oncologia* [7]: *Quesito clinico*: I vari G-CSF si differenziano in termini di efficacia?
Raccomandazione: Pegfilgrastim, filgrastim, TBO-filgrastim e filgrastim-sndz (e altri biosimilari appena disponibili) possono essere utilizzati per la prevenzione della neutropenia febbrile correlata al trattamento. La scelta dell'agente dipende da convenienza, costo e situazione clinica.

➢ *G-CSF per mobilizzazione cellule staminali* [8,9]:
Il GM-CSF ha dimostrato di essere inferiore a G-CSF in termini di numero di cellule staminali raccolte e in esiti post-trapianto di recupero ematopoietico, supporto trasfusionale e antibiotico, episodi febbrili, e ospedalizzazioni. I dati sull'uso di pegfilgrastim per la mobilizzazione sono ancora limitati. Filgrastim e

lenograstim sono i G-CSF di scelta per mobilizzare le cellule progenitrici emopoietiche tanto nel donatore sano che nel paziente.

- *G-CSF per neutropenia (congenita e acquisita) in pediatria* [10]:

  Sono disponibili tre prodotti a base di G-CSF nel nostro Paese: lenograstim (glicosilato), filgrastim (non glicosilato), e pegfilgrastim. È stata riportata una superiorità della forma non glicosilata rispetto alla glicosilata nell'aumentare la conta dei neutrofili (ANC). Tuttavia, gli esperti concordano sulla non superiorità di lenograstim vs. filgrastim poiché il numero di infezioni era simile nei pazienti trattati con le due preparazioni. L'uso di pegfilgrastim nella neutropenia è stato raramente riportato in età pediatrica.

Le raccomandazioni riportate nelle quattro LG selezionate sono pubblicate su riviste internazionali peer-reviewed e in due LG è riportato il metodo utilizzato per la ricerca delle evidenze in letteratura. Tuttavia, in tre LG il metodo di lavoro adottato per la approvazione dei documenti era costituito dalla convocazione di expert panel (Tabella 4).

La qualità delle 4 LG incluse è stata valutata utilizzando la checklist AGREE (Appraisal of Guidelines for Research & Evaluation) [11]. Sulla base dei punteggi ricevuti, solo la LG di Smith TJ et al. [7] è ritenuta fortemente raccomandata nella pratica clinica (Tabella 4).

In generale, tutte le LG concordano sul fatto che in oncologia tutti i G-CSF sono equivalenti; in pediatria (neutropenia congenita e acquisita) i dati supportano una maggiore preferenza per l'uso di filgrastim rispetto agli altri tipi di G-CSF. Solo per quanto riguarda la mobilizzazione è stata registrata una sostanziale equivalenza tra filgrastim e lenograstim sia per il setting allogenico che per quello autologo.

Conclusioni del Gruppo di lavoro

Sulla base dell'analisi della letteratura e tenendo conto delle indicazioni terapeutiche registrate dei diversi principi attivi rientranti nella categoria dei fattori di crescita leucocitaria, dopo ampio confronto svolto nell'ambito del Gruppo di lavoro sui biosimilari istituito dalla Regione Lazio, viene approvata all'unanimità la seguente linea di indirizzo:

L'uso dei principi attivi pegfilgrastim, lenograstim, lipegfilgrastim, filgrastim (originator e biosimilare), è considerato sovrapponibile dal punto di vista della sicurezza ed efficacia nella comune indicazione terapeutica *profilassi della neutropenia febbrile da chemioterapia* nei pazienti adulti e anziani; solo filgrastim (originator e biosimilari) è indicato per questa indicazione in tutte le fasce pediatriche. Altre indicazioni terapeutiche, quali *terapia mieloablativa* e *mobilizzazione cellule staminali*, vengono coperte dal filgrastim (originator e biosimilare) e lenograstim nelle principali fasce d'età (il lenograstim non è indicato nei bambini da 0 a 2 anni).

Le rimanenti indicazioni *neutropenia congenita* e *neutropenia da HIV* sono coperte solo da filgrastim (originator e biosimilare) (Tabella 1).

Non vi sono evidenze che sostengano la preferenza di uno dei fattori di crescita leucocitaria rispetto agli altri (incluso il biosimilare), diverse da quelle economiche o legate a singole e documentabili situazioni cliniche. Per tale ragione il fabbisogno di terapie con G-CSF può essere soddisfatto, indistintamente e con una quota non inferiore all'80% della richiesta, da uno dei principi attivi indicati nella Tabella 1. La rimanente quota (fino al 20%) sarà sufficiente a garantire il trattamento delle situazioni cliniche eccezionali documentate.

Sulla base di quanto detto, la Regione deve favorire, tra questi principi attivi, l'uso del farmaco più vantaggioso, anche dal punto di vista economico, secondo l'indicazione terapeutica registrata. In questo modo sarà sicura di garantire, sulla base delle attuali conoscenze, lo stesso livello di efficacia e sicurezza per il paziente e al tempo stesso di favorire il risparmio delle risorse per il SSR.

Monitoraggio dell'aderenza alle linee di indirizzo

E' previsto che l'implementazione delle linee di indirizzo sia monitorata attraverso uno specifico indicatore. A partire dalla data di pubblicazione dell'atto regolatorio regionale, con cui verranno adottate le linee di indirizzo, saranno verificati i consumi dei G-CSF su base semestrale nel periodo seguente attraverso i flussi informativi sanitari disponibili presso la Regione Lazio.

In particolare sarà utilizzato il seguente indicatore di aderenza alle linee di indirizzo:

- *percentuale di utilizzo del filgrastim nella principale indicazione autorizzata, ovvero la profilassi della neutropenia febbrile da chemioterapia.*

I consumi dei vari G-CSF saranno calcolati come DDD/1000 abitanti die e sarà effettuata l'analisi della variabilità regionale tra i diversi centri prescrittori.

Nel primo anno di adozione delle linee di indirizzo il risultato atteso è quello di avere almeno il 60% di consumo di filgrastim sul totale dei G-CSF.

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Tabella 1. Analisi delle indicazioni terapeutiche riportate negli RCP(1) dei G-CSF(2) commercializzati.

Indicazioni: per esteso	**Indicazioni: titolo breve**	**Principio attivo** *(Nome commerciale)*							
		Filgrastim *(Granulokine)*	**Filgrastim** *(Nivestim)*	**Filgrastim** *(Ratiograstim)*	**Filgrastim** *(Tevagrastim)*	**Filgrastim** *(Zarzio)*	**Lenograstim** *(Myelostim/ Granocyte)*	**Pegfilgrastim** *(Neulasta)*	**Lipegfilgrastim** *(Lonquex)*
indicato nel ridurre la durata della neutropenia e l'incidenza della neutropenia febbrile in pazienti trattati con chemioterapia citotossica standard per affezioni maligne (con l'eccezione della leucemia mieloide cronica e delle sindromi mielodisplastiche)	Profilassi della neutropenia febbrile da chemioterapia	**X**	**X**	**X**	**X**	**X**	**X** [a]	**X** [b]	**X** [b]
indicato nel ridurre la durata della neutropenia in pazienti sottoposti a terapia mieloablativa seguita da trapianto di midollo osseo considerati a maggior rischio di neutropenia severa prolungata. La sicurezza e l'efficacia sono simili negli adulti e nei bambini trattati con chemioterapia citotossica	Terapia mieloablativa seguita da trapianto di midollo osseo	**X**	**X**	**X**	**X**	**X**	**X** [a]		
indicato per la mobilizzazione delle cellule progenitrici del sangue periferico (PBPC)	Mobilizzazione di cellule staminali periferiche	**X**	**X**	**X**	**X**	**X**	**X** [a]		
in pazienti, bambini o adulti, con neutropenia grave congenita, ciclica o idiopatica, con una CAN (conta assoluta dei neutrofili) < 0,5 x 109/l e una storia di infezioni gravi o ricorrenti, una somministrazione a lungo termine di filgrastim è indicata per incrementare la conta dei neutrofili e per ridurre l'incidenza e la durata delle complicanze infettive	Neutropenia congenita	**X**	**X**	**X**	**X**	**X**			
indicato nel trattamento della neutropenia persistente (CAN uguale o minore di 1,0 x 109/l) in pazienti con infezione da HIV avanzata, per ridurre il rischio di infezioni batteriche quando non siano appropriate altre opzioni per controllare la neutropenia	Neutropenia HIV correlata o correlata ai farmaci antiretrovirali	**X**	**X**	**X**	**X**	**X**			

Originator; Biosimilari; [a]Esclusi bambini 0-2 anni; [b] Solo per popolazione adulta

(1) RCP = Riassunto delle Caratteristiche del Prodotto; **(2)** G-CSF = Fattori di crescita leucocitaria

Dati italiani sui biosimilari (Osmed 2014)

Tabella 2. Biosimilari, erogazione attraverso le strutture pubbliche e prescrizione territoriale SSN nel 2014

	Sottogruppo	Spesa pro capite	Inc. %	Δ % 14-13	DDD/1000 ab die	Inc. %	Δ % 14-13
Epoetina	**Totale**	**4,65**	**100,0**	**-3,0**	**2,9**	**100,0**	**6,6**
	Originator[1]	1,57	33,7	-8,4	1,1	35,9	-5,5
	Biosimilari[2]	0,58	12,4	86,3	0,6	21,1	111,6
	Altre epoetine[3]	**2,51**	**53,9**	**-9,7**	**1,3**	**43,0**	**-6,3**
Fattori della crescita	**Totale**	**1,39**	**100,0**	**-11,0**	**0,1**	**100,0**	**-1,3**
	Originator[4]	0,15	10,9	-23,3	<0,1	5,8	-24,9
	Biosimilari[5]	0,19	13,9	22,1	<0,1	25,3	33,7
	Altri fattori della crescita[6]	**1,05**	**75,2**	**-13,3**	**0,1**	**68,9**	**-7,7**
Somatotropina	**Totale**	**1,76**	**100,0**	**4,7**	**0,3**	**100,0**	**-2,5**
	Originator[7]	0,44	25,3	36,3	<0,1	17,3	-7,3
	Biosimilari[8]	0,10	5,4	6,5	<0,1	8,5	4,3
	Altre somatotropine[9]	**1,22**	**69,3**	**-3,6**	**0,2**	**74,1**	**-2,0**

[1] Eprex®; [2] Abseamed®, Binocrit®, Retacrit®; [3] Aranesp®, Eporatio®, Mircera®, Neorecormon®; [4] Granulokine®; [5] Nivestim®, Ratiograstim®, Tevagrastim®, Zarzio®; [6] Neulasta®, Myelostim®, Lonquex®, Granocyte®; [7] Genotropin®; [8] Omnitrope®; [9] Humatrope®, Norditropin®, Nutropinaq®, Saizen®, Zomacton®;

Tabella 3. Biosimilari, erogazione attraverso le strutture pubbliche e prescrizione territoriale SSN nel 2014: confronto biosimilare versus farmaco originator*

Gruppo	Sottogruppo	Spesa pro capite	Inc. %	Δ % 14-13	DDD/1000 ab die	Inc. %	Δ % 14-13
Epoetina	**Totale**	**2,15**	**100,0**	**6,1**	**1,7**	**100,0**	**18,9**
	Originator[1]	1,57	73,1	-8,4	1,1	63,0	-5,5
	Biosimilari[2]	0,58	26,9	86,3	0,6	37,0	111,6
Fattori della crescita	**Totale**	**0,35**	**100,0**	**-3,1**	**0,0**	**100,0**	**16,6**
	Originator[3]	0,15	43,9	-23,3	<0,1	18,7	-24,9
	Biosimilari[4]	0,19	56,1	22,1	<0,1	81,3	33,7
Somatotropina	**Totale**	**0,42**	**100,0**	**29,9**	**0,1**	**100,0**	**-3,8**
	Originator[5]	0,33	82,3	36,3	<0,1	67,0	-7,3
	Biosimilari[6]	0,09	17,7	6,5	<0,1	33,0	4,3

[1] Eprex®; [2] Abseamed®, Binocrit®, Retacrit®; [3] Granulokine®; [4] Nivestim®, Ratiograstim®, Tevagrastim®, Zarzio®; [5] Genotropin®; [6] Omnitrope®
*il farmaco utilizzato come confronto nello studio clinico

Figura 1. Incidenza (%) dei farmaci biosimilari sulla spesa dei farmaci biosimilari e del farmaco originator

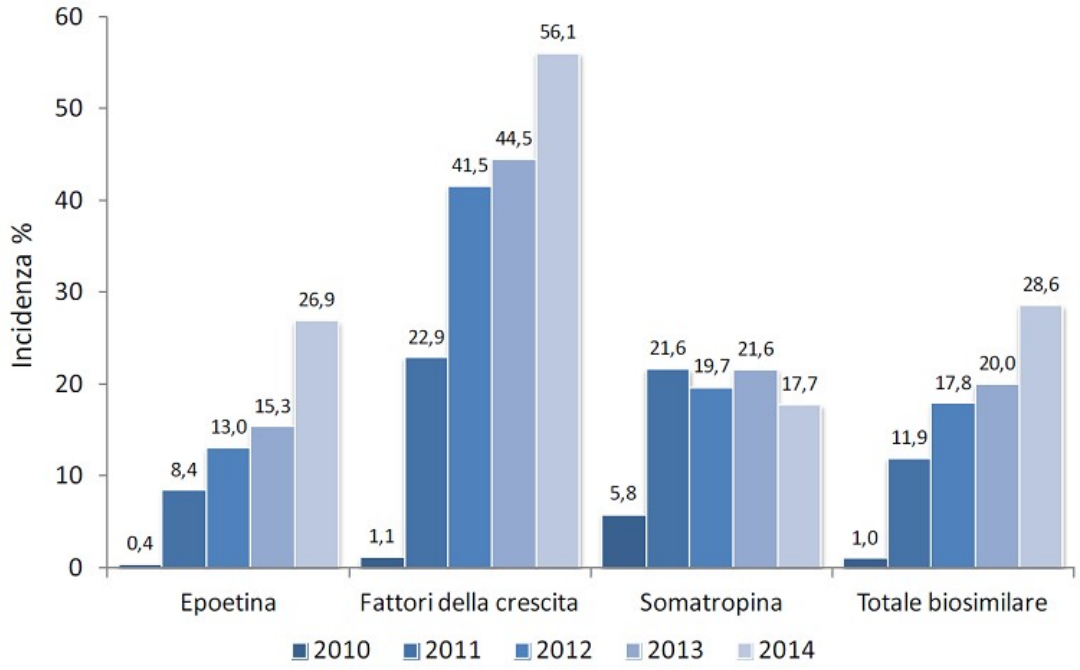

Figura 2. Incidenza (%) dei farmaci biosimilari sui consumi dei farmaci biosimilari e del farmaco originator

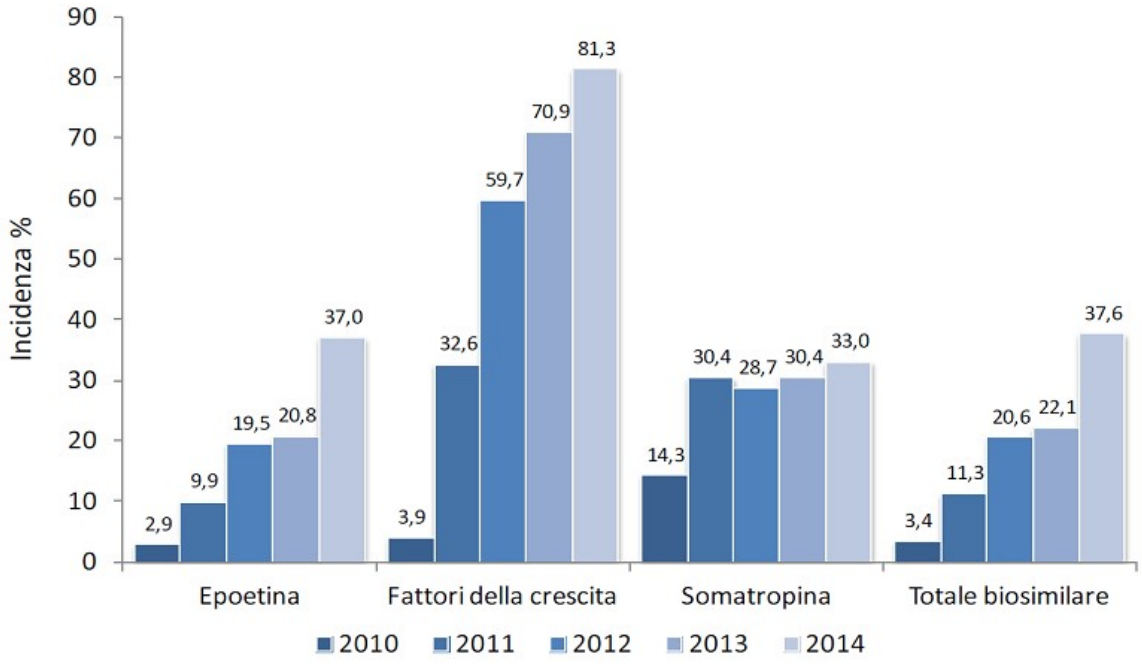

Figura 3. Consumi (*Defined Daily Doses*) dei G-CSF: confronto inter-regionale (Tracciabilità del farmaco, MinSal, 2014)

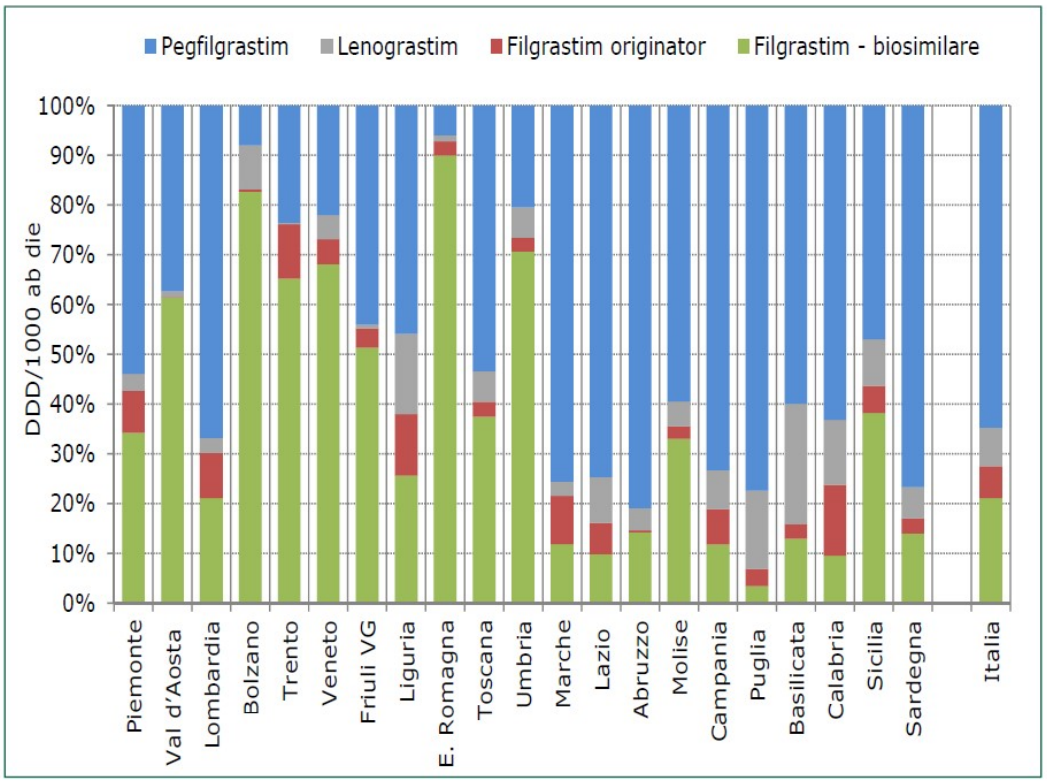

Figura 4. Consumi (*Defined Daily Doses*) dei G-CSF: confronto inter-regionale (Tracciabilità del farmaco, MinSal, 2014)

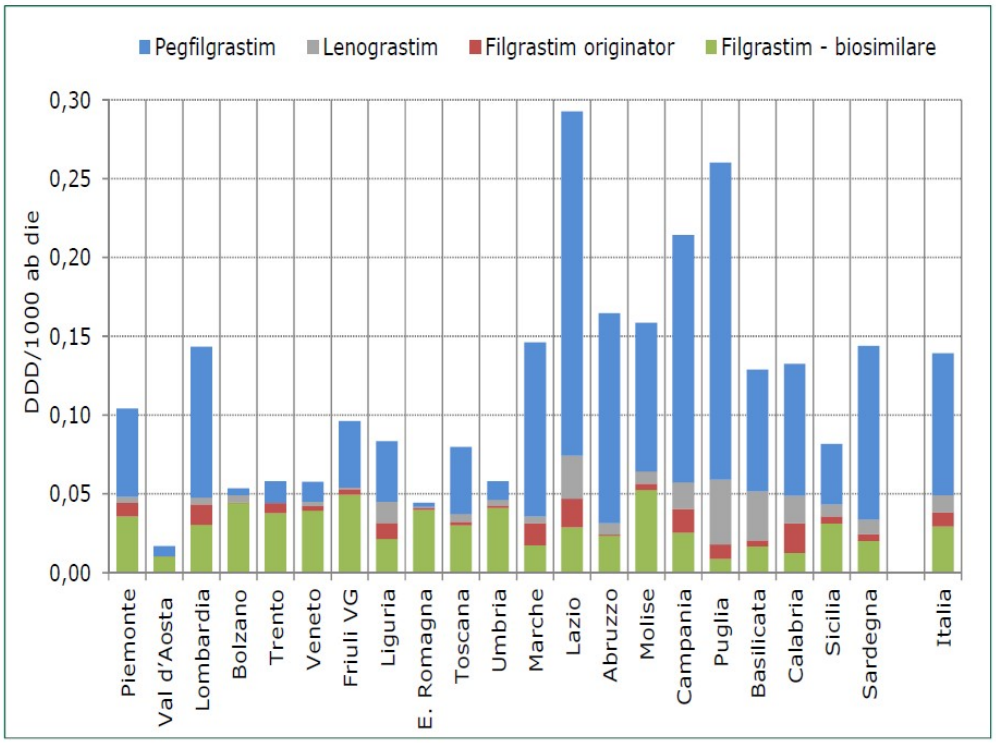

Figura 5. Costo medio per DDD dei G-CSF : confronto inter-regionale (Tracciabilità del farmaco, MinSal, 2014)

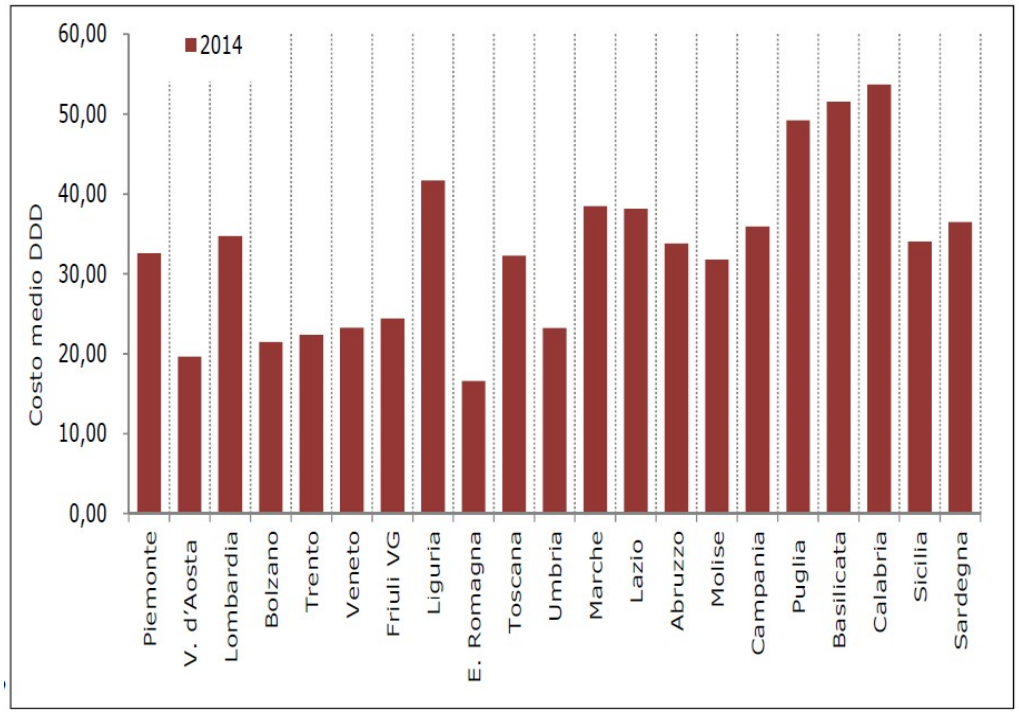

Tabella 4. Caratteristiche delle principali Linee Guida sui G-CSF[(1)] ed esito della valutazione con metodo AGREE

Linee Guida (LG)	Approvazione delle LG	Metodo	Pubblicazioni selezionate	Referenze	AGREE score	Giudizio complessivo
Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update	2 independent commitee	Raccomandazione basata su revisione sistematica RCT di fase III, revisioni sistematiche, meta-analisi e pratica clinica	66	Smith TJ et al. JCO 2015 33(28):3199-212.	77/92	Fortemente raccomandata
Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations	Expert panel	Revisione delle evidenze disponibili by consensus	Not reported	Giralt S, etal.Biol Blood Marrow Transplant. 2014 Mar;20(3):295-308.	49/92	Non raccomandata
Best practice for peripheral blood progenitor cell mobilization and collection in adults and children: results of a Società Italiana Di Emaferesi e Manipolazione Cellulare (SIDEM) and Gruppo Italiano Trapianto Midollo Osseo (GITMO) consensus process	Expert panel	Revisione delle evidenze disponibili by consensus	Not reported	Pierelli L, et al. Transfusion. 2012 Apr;52(4):893-905.	53/92	Non raccomandata
Congenital and acquired neutropenias consensus guidelines on therapy and follow-up in childhood from the Neutropenia Committee of the Marrow Failure Syndrome Group of the AIEOP (AssociazioneItalianaEmato-OncologiaPediatrica)	Expert panel; AIEOP Board	Raccomandazione basata su revisione sistematica della letteratura	59	Fioredda F, et al. Am J Hematol. 2012 Feb;87(2):238-43.	64/92	Raccomandata (con riserva)

(1) G-CSF = Fattori di crescita leucocitaria

Strategia di ricerca e risultati relativi a equivalenza terapeutica dei fattori di crescita delle colonie granulocitarie (filgrastim, filgrastim biosimilari, lenograstim e pegfilgrastim).

Ricerca bibliografica

La ricerca è stata effettuata sulle principali banche dati bibliografiche (The Cochrane Library, PubMed, Embase) e su siti di agenzie governative (CRD -Centre for Reviews and Dissemination, HTA - Health Technology Assessment, NHSEED - NHS Economic Evaluation Database).

Per ciascuna banca dati sono state sviluppate specifiche strategie di ricerca, senza applicare alcuna restrizione di lingua o data di pubblicazione.

The Cochrane Library (issue 7/2014)

1. MeSH descriptor: [Neoplasms by Histologic Type] explode all trees
2. MeSH descriptor: [Neoplasms by Site] explode all trees
3. (neoplasm* OR cancer* OR carcino* OR malignan* OR leukemi* OR leukaemia* OR tumour* OR tumor*OR neutropeni* OR adenocarcinoma* OR lymphoma* OR chemo*):ti,ab,kw (Word variations have been searched)
4. #1 or #2 or #3
5. filgrastim and (biosimilar* or lenograstim or pegfilgrastim)
6. pegfilgrastim and (biosimilar* or lenograstim or filgrastim)
7. biosimilar* and (filgrastim or lenograstimor or pegfilgrastim)
8. #5 or #6 or #7
9. #4 and #8

PubMed (from January 1966 to July 2014)

(((((biosimilar* AND (filgrastim OR lenograstim OR pegfilgrastim))) OR (pegfilgrastim AND (biosimilar* OR lenograstim OR filgrastim))) OR (filgrastim AND (biosimilar* OR lenograstim OR pegfilgrastim)))) AND ((((("Neoplasms"[Mesh]) OR "LEUKEMIA"[Mesh]) OR "LYMPHOMA"[Mesh]) OR (neoplasm* OR cancer* OR carcino* OR malignan* OR leukemi* OR leukaemia* OR tumour* OR tumor* OR neutropeni* OR adenocarcinoma* OR lymphoma* OR chemo*))

EMBASE (from (January 1988 to July 2014)

1. neoplasm*:de,ab,ti OR cancer*:de,ab,ti OR carcino*:de,ab,ti OR malignan*:de,ab,ti
2. leukemi*:de,ab,ti OR leukaemia*:de,ab,ti
3. tumour*:de,ab,ti OR tumor*:de,ab,ti
4. neutropeni*:de,ab,ti
5. adenocarcinoma*:de,ab,ti

6. lymphoma*:de,ab,ti
7. chemo*:de,ab,ti
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. biosimilar*:de,ab,ti AND (filgrastim:de,ab,ti OR lenograstimor:de,ab,ti OR pegfilgrastim:de,ab,ti)
10. pegfilgrastim:de,ab,ti AND (biosimilar*:de,ab,ti OR lenograstim:de,ab,ti OR filgrastim:de,ab,ti)
11. filgrastim:de,ab,ti AND (biosimilar*:de,ab,ti OR lenograstim:de,ab,ti OR pegfilgrastim:de,ab,ti)
12. #9 OR #10 OR #11
13. #8 AND #12 AND [humans]/lim

La ricerca della letteratura ha portato all'identificazione di 668 articoli (dopo eliminazione di duplicati). Di questi, in base al titolo e all'abstract, sono stati esclusi 613 articoli perché non pertinenti.
Il risultato è di 49 referenze da poter considerare.

Di seguito i risultati da noi ottenuti:

Referenze

1. Aksu G, Corapcioglu F, Fayda M, Basar EZ, Mutlu A, Ince Z. The comparison of the preventive effects of filgrastim and lenograstim in pediatric cancer patients treated with chemotherapy and radiotherapy. [Turkish]. 22. 2007:63-8.
Abstract: Objectives: To compare the preventive effects of filgrastim and lenograstim in pediatric cancer patients treated with chemotherapy and radio-therapy. Methods: Eighty-two patients treated with myelosuppressive chemotherapy and/or radiotherapy in Pediatric Oncology and Radiation Oncology Departments of Kocaeli University, Faculty of Medicine between September 2005 and March 2007 were randomized to filgrastim and lenograstim arms. Radiotherapy doses and fields 3 weeks prior to the therapy, age, gender, histopathological type of the tumor, stage and chemotherapy protocols were recorded. Patients with bone marrow infiltration due to the tumoral invasion and patients receiving steroid including chemotherapy regimens were excluded from the study. Equivalent doses of two hematopoetic growth factors (filgrastim 5 mug/kg/day, S.C; lenograstim 150 mug/m²/day, S.C) were applied beginning 24 hours following the completion of the chemotherapy till leukocyte count reached 10.000/mm³. Results: Delay in the new chemotherapy cure following chemotherapy protocol was median 5 days in lenograstim arm (16 patients, 37%) while it was 3 days in filgrastim arm (10 patients; %25) however the difference was not statistically significant (p=0.188). In lenogastrim arm, febrile neutropenia occurred in 6 patients and infections without neutropenia were seen in 4 patients (pneumonia in 2 patients, otitis media in 1 patient and pharengitis in 1 patient). In filgrastim arm, febrile neutropenia occurred in 3 patients and gingivitis and gastroenteritis in 2 patients and the difference between two groups was also not significant (p=0.258). However, bone pain was present in 2 patients in lenograstim arm while it was seen in 10 patients in filgrastim arm with a significant difference (p=0.008). Conclusion: Although preventive effects of filgrastim and lenograstim on febrile neutropenia and non-neutropenic infections in patients receiving radiotherapy and chemotherapy are not significantly different, delay in the new chemotherapy cure following chemotherapy protocol is shorter in filgrastim arm. However, bone pain is also significantly higher in filgrastim arm. US: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/166/CN-00642166/frame.html

2. Bosi A, Szer J, Kassis J, Sierra J, Desborough C, Buchanan K. A multicenter, double-blind, randomized, phase II trial comparing pegfilgrastim with filgrastim as an adjunct to chemotherapy for acute myeloid leukemia. 3. 2005:42-3.

3. Brito M, Esteves S, Andre R, Isidoro M, Moreira A. Comparison of efficacy of primary prophylaxis with pegfilgrastim filgrastrim and a biosimilar filgrastim in TAC regimen (docetaxel doxorubicin and cyclophosphamide). Cancer Res. 2012; 72(24).
Abstract: Background: Febrile neutropenia (FN) is a major toxicity of myelosupressive chemotherapy. Primary prophylactic use of granulocyte colony stimulating factors (G-CSF) is recommended in high risk FN regimens. The comparison of pegfilgrastim (Peg) and filgrastim (Fil) FN prophylactic effectiveness is still an issue of debate. Very recently Nivestim (Niv), a new biosimilar filgrastim, has also become commercially available. We aimed to compare the efficacy of the 3 mentioned types of G-CSF in the primary prophylaxis of FN. Methods: Single-center, retrospective study to evaluate the incidence of FN in women with breast cancer treated with adjuvant or neo-adjuvant TAC (FN risk 20%). Patients (Pt) were divided in 3 consecutive cohorts according to G-CSF primary prophylaxis (Fil, Peg and Niv) FN was defined as axillary temperature 38,3 (degrees)C and absolute neutrophil count < 500/ul. Results: We included a total of 421 women (median age 51 y, 25-76) with Stage II (56%) and Stage III (44%) breast cancer. Age and stage distribution were similar in the 3 cohorts. A single dose of Peg was administered in all 767 cycles (cy). The standard dose of Fil and Niv was 7 daily injections, only in in 13% Fil pt and 10% Niv pt < 7 administrations were done. The incidence of FN per patient and per cycle is presented in Table 1. In all cohorts, approximately half of NF episodes occurred in the 1st cycle (48% Fil, 59% Peg, 42% Niv). (Figure Presented) Conclusions: No differences in terms of efficacy existed between Biosimilar Niv and original biological reference Fil. Seven daily injections of Fil and Niv seem equivalent to single dose Peg. Besides efficacy, questions like cost-effectiveness and convenience of administration should be taken into account when approaching this topic. Our data showed a predominance of events in the 1st cycle (regardless of the type of G-CSF). This has been consistently described in the literature and may support the necessity to recommend other NF preventive measures in this cycle.

4. Camara JIM, Pousa AL, Garcia EG et al. Economic evaluation of the use of pegfilgrastim vs filgrastim in primary prevention in breast cancer patients in Spain with risk of febrile neutropenia: Evaluacion economica del uso de pegfilgrastim frente a filgrastim en profilaxis primaria en pacientes con cancer de mama con riesgo de padecer neutropenia febril en Espana. Pharmacoecon. Span. Res. Artic. 2008; 5(3):71-81.
Abstract: Objectives. Pegfilgrastim and filgrastim are two recommended treatments to reduce the incidence of febrile neutropenia (FN) subsequent to cancer chemotherapy. With neutrophil-regulated kinetics, pegfilgrastim is effective with an only administration throughout the period of myelosuppression, while filgrastim must be administered daily until neutrophil levels recover. The present model evaluates the cost-effectiveness in Spain of pegfilgrastim 6 mg given once per cycle compared with filgrastim used for 6 or 11 days/cycle in 45-year-old women with stage II breast cancer receiving four cycles of chemotherapy with an overall FN risk of ~20% or higher. Methods. An analytical model was developed from the perspective of the Spanish National Health System (SNS). Efficacy data included in the model were obtained through medical literature. Costs per patient were calculated using the drug cost, drug administration cost and the hospitalization cost. Relative efficacy was measured using the life year gained (LYG) and the years of life adjusted for quality (QALY), while cost-effectiveness was assessed through an incremental cost-effectiveness ratio (ICER). Results. Pegfilgrastim was cost-saving compared to filgrastim used for 11 days/cycle - assuming the absolute risk of FN decreased by 5.5%, pegfilgrastim was associated with 0.06 LYG per patient and achieved a saving of 17 (euro). Pegfilgrastim was shown to reduce the absolute FN incidence by 10.5% compared to 6 days of filgrastim per cycle, resulting in 0.111 LYG. The mean cost per patient treated with pegfilgrastim was 4242 (euro) and 2779 (euro) for those who received filgrastim 6 days/cycle. Pegfilgrastim was therefore cost-effective compared to filgrastim 6 days/cycle with an ICER of 13.180 (euro)/LYG and 13.933 (euro)/QALY gained. Conclusions. In this model of breast cancer patients at high risk of FN (greater-than or equal to) 20%) in Spain,

primary prophylaxis with pegfilgrastim 6 mg per cycle was cost-saving compared to filgrastim used for 11 days/cycle and cost-effective compared with filgrastim 6 days/cycle. (copyright) 2008 Adis Data Information BV.
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5. Caruso D, Rossi L, Tomao F et al. Lenograstim (L) versus pegfilgrastim (P) in management of chemotherapy related neutropenia (CRN) in non metastatic breast cancer patients (NMBCP). Int. J. Gynecol. Cancer 2012; 22:E930.
Abstract: Background and aims: CRN is associated with morbidity, costs, and chemotherapy reductions. This retrospective study compared P (6 mg) with L (263 (mu)g) to prevent CRN in NMBCP especially at first and last cycle of treatment. Methods: 50 women (median age 54) underwent to median 6 CT doses (antracyclines+/-taxanes). At every cycle, 28 pts received daily L (5 injections from day 5 to 9), while 22 single P on day 2. Absolute neutrophil count, incidence of G3/G4-CRN, bone pain (BP: NRS>7) and cost-effectiveness were evaluated. Results: During first and last cycle of chemotherapy, G3/G4-N was 28.5% and 11% in L, while was 23% and 0% in P. At first and last cycle of FEC100 (patients: 10 L vs 9 P) G3/G4-CRN was 20% and 0% in L, versus 22% and 0% in P. At first and last cycle of TAC/AC+T (patients: 18 L vs 13 P) G3/G4-CRN was 33% and 17% in L, versus 23% and 0% in P. Chemotherapy reduction occurred in 10 patients of L and 9 of P. Two and three Febrile-CRN (FCRN) occurred in L and P. BP was 18% in P vs 36% in L. In Italy cost of 1 P and 5 L was about 1489,00 and 655,00 euro. Conclusions: At first cycle there is no difference between L and P respect to CRN. In TAC/AC+T P was more effective than L to prevent CRN especially at last cycle, despite major costs. No difference was found about FCRN incidence, safety and chemotherapy reduction.

6. Castagna L, Bramanti S, Levis A et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. Ann Oncol 2010; 21(7):1482-5.
Abstract: BACKGROUND: American Society of Clinical Oncology guidelines recommend the use of growth factor after high-dose chemotherapy (HDC) and peripheral blood stem cell (PBSC) support. This randomized trial aims to demonstrate the noninferiority of pegfilgrastim (PEG) compared with filgrastim (FIL) after HDC. PATIENTS AND METHODS: Eighty patients were assigned to FIL at a daily dose of 5 mug/kg or a single fixed dose of PEG (6 mg) 1 day after PBSC. The primary end point was the duration of neutropenia both in terms of absolute neutrophil count (ANC) <0.5 x 10(9)/l and of days to reach an ANC >0.5 x 10(9)/l. RESULTS: The mean duration of neutropenia was 6 and 6.2 days and the mean time to reach an ANC >0.5 x 10(9)/l was 11.5 and 10.8 in the FIL and PEG group, respectively. No differences were observed in the mean time to reach an ANC >1.0 x 10(9)/l (12.2 versus 12.0 days) in the incidence of fever (62% versus 56%) and of documented infections (31% versus 25%). The mean duration of antibiotic therapy was 5.7 and 4.0 days in FIL and PEG group, respectively. CONCLUSION: PEG is not inferior to FIL in hematological reconstitution and represents an effective alternative after HDC and PBSC.

7. Cesaro S, Nesi F, Tridello G et al. A randomized, non-inferiority study comparing efficacy and safety of a single dose of pegfilgrastim versus daily filgrastim in pediatric patients after autologous peripheral blood stem cell transplant. PLoS One 2013; 8(1):e53252.
Abstract: PURPOSE: To assess the non-inferiority of pegfilgrastim versus filgrastim in speeding the recovery of polymorphonuclear cells (PMN) in pediatric patients who underwent autologous peripheral blood stem cell transplant (PBSCT). METHODS: The sample size of this randomized, multicenter, phase III study, was calculated assuming that a single dose of pegfilgrastim of 100 ug/kg was not inferior to 9 doses of filgrastim of 5 ug/kg/day. Randomization was performed by a computer-generated list and stored by sequentially numbered sealed envelopes. RESULTS: Sixty-one patients, with a median age of 11.5 years, were recruited: 29 in the filgrastim arm and 32 in the pegfilgrastim arm. Twenty percent were affected by lymphoma/leukaemia and eighty percent by solid tumors. The mean time to PMN engraftment was 10.48 days (standard deviation [SD] 1.57) and 10.44 days (SD 2.44) in the filgrastim and pegfilgrastim arms, respectively. Having fixed a non-inferiority margin Delta of 3, the primary endpoint of non-inferiority was reached. No differences were observed for other secondary endpoints: platelet engraftment, mean time to

platelet recovery (28 days vs. 33 days), fever of unknown origin (79% vs. 78%), proven infection (34% vs. 28%), mucositis (76% vs. 59%). After a median follow-up of 2.3 years (95% C.I.: 1.5, 3.3), 20 deaths were observed due to disease progression. CONCLUSIONS: We conclude that pegfilgrastim was not inferior to daily filgrastim in pediatric patients who underwent PBSCT. EU CLINICAL TRIAL REGISTER NUMBER: 2007-001430-14.

8. Cesaro S, Nesi F, Tridello G et al. A non-inferiority study comparing efficacy and safety of a single dose of pegfilgrastim versus daily filgrastim in paediatric patients after autologous peripheral blood stem cell transplant. Bone Marrow Transplant. 2012; 47:S372.
Abstract: Objectives: To assess the efficacy of pegfilgrastim vs. daily filgrastim in pediatric patients who underwent peripheral blood stem cell transplant (PBSCT) by a randomized, multicenter, phase III, non inferiority study. Methods: The primary endpoint was the time to polimorphonuclear cell (PMN) engraftment. Patient sample size was calculated on the hyphotesis that a single dose of pegfilgrastim of 100 ug/kg was not inferior to 9 or more doses of filgrastim of 5 ug/kg/day as time of PMN recovery. Platelet (PLT) engraftment, iatrogenic toxicity, and safety were secondary endpoints. Results: From May 2007 to June 2011, 61 patients (pts), 38 M, 23 F, were recruited in 4 centres: 29 pts were randomized to filgrastim arm and 32 pts to the pegfilgrastim arm. Median age at PBSC transplantation was 11.5, range 1.6- 17.4; median body weight was 36, range 9.6-106; 20% of patients were affected by lymphoma/leukaemia, 80% by solid tumours; 79% of patients were in complete remission (32) or in very good partial remission (16) at PBSC infusion. The median value of CD34+ infused was 6.4x 106/kg, range 3-300. The mean time to PMN engraftment was 10.48 days (standard deviation (SD) 1.57) and 10.44 days (SD 2.44) in filgrastim and pegfilgrastim group, respectively. Having fixed a non inferiority margin Delta = 3, the primary endpoint was reached, determining the non inferiority of pegfilgrastim. Other enpoints in the filgrastim and pegfilgrastim group were as follows: PLT engraftment, 100% vs. 97%; median time to recovery to PLT > 50 x 109/L, 22 days, range 10-84 vs. 28 days, range 10-132; one or two episodes of FUO, 79% vs. 78%; proven infection, 34% vs.28%; WHO grade II-IV mucositis, 76% vs. 59%. No significant differences were found in terms of toxicity between 2 arms and no toxic death was reported within the first 100 days post-PBSCT. After a median follow-up of 2.3 years (95% C.I.: 1.5-3.3), 20 deaths were observed, 9 in the filgrastim and 11 in the pegfilgrastim group, all due to progression of disease. Conclusion: A single dose of pegfilgrastim is not inferior to daily filgrastim in pediatric patients who underwent PBSCT.

9. Chan A, Leng XZ, Chiang JY et al. Comparison of daily filgrastim and pegfilgrastim to prevent febrile neutropenia in Asian lymphoma patients. Asia Pac J Clin Oncol 2011; 7(1):75-81.
Abstract: AIM: Febrile neutropenia (FN) is a highly prevalent complication of chemotherapy, particularly in patients with non-Hodgkin's lymphoma. This study aimed to compare the efficacy of filgrastim and pegfilgrastim in Asian lymphoma patients by evaluating the incidence of FN and associated complications. METHODS: This was a single-center, retrospective cohort study in Asian lymphoma patients who received chemotherapy with primary prophylactic granulocyte colony-stimulating factors support between January 2008 and August 2009. Data were analyzed using an intent-to-treat approach, which aimed to reflect actual prescribing practices. RESULTS: A total of 204 Asian lymphoma patients were included in this study, with 81 patients in the filgrastim arm and 123 patients in the pegfilgrastim arm. Overall, the incidence of breakthrough FN was similar between the two groups of patients (13.6%: filgrastim arm vs 16.3%: pegfilgrastim arm; P=0.69). Neutropenic complications such as chemotherapy treatment delay and chemotherapy dose reduction were similar between the two arms. CONCLUSION: In Asian patients, pegfilgrastim prophylaxis did not show a therapeutic advantage for preventing neutropenic outcomes compared with filgrastim prophylaxis.

10. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer 2011; 11:404.
Abstract: BACKGROUND: Febrile neutropenia (FN) occurs following myelosuppressive chemotherapy and is associated with morbidity, mortality, costs, and chemotherapy reductions and

delays. Granulocyte colony-stimulating factors (G-CSFs) stimulate neutrophil production and may reduce FN incidence when given prophylactically following chemotherapy. METHODS: A systematic review and meta-analysis assessed the effectiveness of G-CSFs (pegfilgrastim, filgrastim or lenograstim) in reducing FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. G-CSFs were compared with no primary G-CSF prophylaxis and with one another. Nine databases were searched in December 2009. Meta-analysis used a random effects model due to heterogeneity. RESULTS: Twenty studies compared primary G-CSF prophylaxis with no primary G-CSF prophylaxis: five studies of pegfilgrastim; ten of filgrastim; and five of lenograstim. All three G-CSFs significantly reduced FN incidence, with relative risks of 0.30 (95% CI: 0.14 to 0.65) for pegfilgrastim, 0.57 (95% CI: 0.48 to 0.69) for filgrastim, and 0.62 (95% CI: 0.44 to 0.88) for lenograstim. Overall, the relative risk of FN for any primary G-CSF prophylaxis versus no primary G-CSF prophylaxis was 0.51 (95% CI: 0.41 to 0.62). In terms of comparisons between different G-CSFs, five studies compared pegfilgrastim with filgrastim. FN incidence was significantly lower for pegfilgrastim than filgrastim, with a relative risk of 0.66 (95% CI: 0.44 to 0.98). CONCLUSIONS: Primary prophylaxis with G-CSFs significantly reduces FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. Pegfilgrastim reduces FN incidence to a significantly greater extent than filgrastim.

11. Costa LJ, Hogan K, Kramer C et al. Comparison between pegfilgrastim and filgrastim-based autologous hematopoietic stem cell mobilization in the setting of patient adapted (nullJust in Timenull) plerixafor: Efficacy and cost analysis. Blood 2011; 118(21).
Abstract: Background: Autologous hematopoietic stem cell (AHSC) mobilization is often performed utilizing filgrastim (G-CSF) without prior chemotherapy. The CXCR4 inhibitor plerixafor enhances the ability of filgrastim to mobilize CD34+ cells but adds substantial cost to the mobilization. Several algorithms have been proposed utilizing the patient's actual capacity to mobilize CD34+ cells to determine the need to add plerixafor after filgrastim has been initiated. The pegylated form of filgrastim (pegfilgrastim) has been used as an alternative and more convenient method of mobilization and has in a few instances been utilized with plerixafor. We hypothesize that replacing weight-based filgrastim with flat dose pegfilgrastim in a validated cost-saving mobilization algorithm for patient-adapted use of plerixafor will add convenience without increase in cost. Methods: Single center retrospective analysis comparing mobilization outcomes and estimated total cost of mobilization in two consecutive cohorts undergoing filgrastim mobilization (FIL) or pegfilgrastim mobilization (PEG) prior to AHSCT for multiple myeloma (MM) or lymphoma (LY). Subjects in FIL received filgrastim 10 mcg/kg/day subcutaneously continuing until completion of collection while subjects in PEG received one flat dose of 12 mg of pegfilgrastim. In both cohorts peripheral blood CD34+ cells (PB-CD34+) enumeration was performed on the fourth day after initiation of growth factor. Subjects surpassing a certain target-specific threshold of PB-CD34+ (e.g 14 cells/mm3 for target of 3 null 106 CD34+/kg and 25 cells/mm3 for target of 6 null 106 CD34+/kg) started apheresis on the same day while subjects with lower PB-CD34+ received plerixafor 240 mcg/kg subcutaneously in the evening of the fourth day and apheresis was started on the fifth day (Figure 1). Decision to use of plerixafor followed the same previously validated algorithm in both cohorts. Apheresis, and growth factor +/- plerixafor were continued until the mobilization target was met. Analysis of estimated total cost of mobilization utilized average wholesale price (AWP) for drugs and institutional average charges for apheresis, cryopreservation and laboratory tests from a representative sample of subjects. Results: Seventy-four consecutive subjects were included in FIL and 47 in PEG. The two cohorts were comparable in terms of age (57.5 vs. 52.2), proportion of patients with diagnosis of MM (63.5% vs.66%), proportion of MM patients previously exposed to lenalidomide (63.8% vs. 51.6%), average body weight (82.9 vs.84 kg) and average mobilization target (4.5 vs. 5 null 106 CD34+/kg). Overall 68/74 in FIL and 43/47 patients in PEG met the mobilization target (Table). Only one patient in each cohort required re-mobilization before proceeding to AHSCT. Median PB-CD34+ on day 4 was significantly higher in PEG. Consequently, by utilizing the same decision algorithm, patients in PEG received fewer subcutaneous injections and were less likely to require administration of plerixafor. Cohorts had near identical average number of apheresis sessions and comparable CD34+ yield. The estimated cost associated with growth factor was on average US$ 3,069 higher in PEG, but it was

counterbalanced by an estimated $4,287 saving in plerixafor cost, resulting in no significant difference in the estimated overall cost of mobilization. Conclusion: Single administration of pegfilgrastim 12 mg is associated with better CD34+ mobilization than filgrastim 10 mcg/kg/day in patients with MM and LY allowing for effective mobilization with less frequent use of plerixafor. Pegfilgrastin with patient adapted used of plerixafor is a reliable, convenient and cost-neutral strategy for AHSC mobilization. [Table Presented].

12. Costa LJ, Kramer C, Hogan KR et al. Pegfilgrastim vs filgrastim-based steady state autologous hsc mobilization in the setting of patient adapted (nulljust in timenull) plerixafor: Efficacy and economic outcomes. Biol. Blood Marrow Transplant. 2012; 18(2):S249.
Abstract: Plerixafor enhances the ability of filgrastim to mobilize CD34+ cells for AHSCT in patients with lymphoma (LY) or multiple myeloma (MM). Single dose of pegfilgrastim has, in some series, been utilized for autologous mobilization for its convenience and possibly greater efficacy. We retrospectively compared two consecutive mobilization cohorts utilizing filgrastim (FIL) 10 mcg/kg/day or pegfilgrastim (PEG) 12 mg (single dose) for steady state mobilization and the same algorithm for nulljust in timenull use of plerixafor. In both cohorts peripheral blood CD34+ cells (PBCD34+) enumeration was performed on the 4th day after initiation of growth factor to determine the immediate initiation of apheresis or administration of plerixafor with apheresis starting in the next day. Decision to use plerixafor was determined by the same previously validated algorithm in both cohorts. Apheresis and growth factor +/- plerixafor were continued until the mobilization target was met. Analysis of estimated total cost of mobilization utilized average wholesale price (AWP) for drugs and average charges for apheresis, cryopreservation and laboratory tests from a representative sample of subjects. Seventy-four consecutive subjects were included in FIL and 57 in PEG. The two cohorts were comparable in terms of age (57.5 vs. 53.7), proportion of patients with diagnosis of MM (63.5% vs.66.7%), proportion of MM patients previously exposed to lenalidomide (63.8% vs. 50%), average body weight (82.9 vs.84 kg) and average mobilization target (4.5 vs. 5 x 106 CD34+/kg). Overall 68/74 in FIL and 52/57 patients in PEG met the mobilization target. Median PB-CD34+ on day 4 was significantly higher in PEG. (Table presented) Patients in PEG received fewer subcutaneous injections and were less likely to require administration of plerixafor. Cohorts had near identical average number of apheresis sessions and comparable CD34+ yield. The estimated cost associated with growth factor was on average US(greater-than or equal to)3,069 higher in PEG, but it was counterbalanced by an estimated (greater-than or equal to)3,546 saving in plerixafor, resulting in no significant difference in the estimated overall cost of mobilization. Single administration of pegfilgrastim is associated with better CD34+ mobilization than daily filgrastim in patients with MM and LY allowing for effective mobilization with less frequent use of plerixafor. Pegfilgrastin with patient adapted used of plerixafor is a reliable, convenient and cost-neutral strategy for AHSC mobilization.

13. Costa LJ, Kramer C, Hogan KR et al. Pegfilgrastim- versus filgrastim-based autologous hematopoietic stem cell mobilization in the setting of preemptive use of plerixafor: efficacy and cost analysis. Transfusion 2012; 52(11):2375-81.
Abstract: BACKGROUND: Plerixafor enhances the ability of filgrastim (FIL) to mobilize CD34+ cells but adds cost to the mobilization. We hypothesized that replacing weight-based FIL with flat-dose pegfilgrastim (PEG) in a validated cost-based mobilization algorithm for patient-adapted use of plerixafor would add convenience without increased cost. STUDY DESIGN AND METHODS: A single-center retrospective analysis compared two consecutive cohorts undergoing FIL or PEG mobilization before autologous hematopoietic stem cell transplantation for multiple myeloma or lymphoma. FIL dose was 10 microg/kg/day continuing until completion of collection and a 12-mg flat dose of PEG. Peripheral blood CD34+ cells (PB-CD34+) enumeration was performed on the fourth day after initiation of growth factor. Subjects surpassing a certain target-specific threshold of PB-CD34+ started apheresis immediately while subjects with lower PB-CD34+ received plerixafor with apheresis starting on the fifth day. RESULTS: Overall 68 of 74 in the FIL group and 52 of 57 patients in the PEG group met the mobilization target. Only one patient in each cohort required remobilization. Median PB-CD34+ on Day 4 was significantly higher in patients in the PEG group (18.1x10(6) vs. 28.7x10(6)cells/L, p=0.01). Consequently, patients in the PEG group were less

likely to require administration of plerixafor (67.5% vs. 45.6%, p=0.01). Cohorts had near identical mean number of apheresis sessions and comparable CD34+ yield. The estimated cost associated with growth factor was higher in patients in the PEG group, but it was counterbalanced by lower cost associated with use of plerixafor. CONCLUSION: Single administration of 12 mg of PEG is associated with better CD34+ mobilization than FIL allowing for effective, convenient mobilization with less frequent use of plerixafor.

14. Dmoszynska A, Manko J, Croneck AW et al. Efficacy and safety of biosimilar G-CSF and originator g-csf for haematopoietic stem cell mobilisation: A randomised comparison. Blood 2011; 118(21).
Abstract: OBJECTIVES: Recombinant granulocyte colony-stimulating factor (G-CSF) is widely used to mobilise haematopoietic stem cells. Biosimilar filgrastim is now available in Europe. No differences were observed between biosimilar filgrastim (n=40) and a retrospective cohort of patients receiving originator filgrastim for stem cell mobilisation in a previous comparison, although no safety findings were reported (Lefrere et al. Adv Ther 2011;28:304-10). We compared the efficacy and safety of a biosimilar filgrastim (EP-2006, Sandoz Biopharmaceuticals) with originator filgrastim (Neupogen(registered trademark), Amgen) in patients with haematological malignancies. METHODS: A total of 108 patients were included in this study, 59 of whom were female (49 male), with an overall median age of 51 years (range 19-69). Patients had multiple myeloma (n=46), Hodgkin's lymphoma (n=26), non-Hodgkin's lymphoma (n=28) or other diagnosis (n=8). Median time from diagnosis to mobilisation was 10 months (range 3-122). After administration of mobilising regimens (primarily high-dose etoposide, high-dose cyclophosphamide, intermediate-dose Ara-C or ESHAP), patients were randomised to a standard daily 10 (mu)g/kg dose of EP-2006 (n=54) or originator filgrastim (n=54). RESULTS: Median duration of G-CSF administration was 8 days with both EP-2006 (range 4-17) and originator filgrastim (range 4-14). Both groups had a median of one apheresis with a median time until first apheresis of 11 days. There were no statistically significant differences between groups in the median (range) number of mobilised CD34+ cells/(mu)L in peripheral blood (EP-2006, 62.0 [2-394]; originator filgrastim, 47.5 [2-370]) or the number of CD34+ cells/kg body weight (EP-2006, 9.1 [0-23]; originator filgrastim, 9.4 [6-48]). Five patients (9%) in each group did not mobilise sufficient CD34+ cells. The adverse event profile was comparable between the EP-2006 and originator filgrastim groups, with similar occurrence of neutropenic fever (9 vs 11 patients) and bone pain (8 vs 6 patients). CONCLUSION: EP-2006 demonstrated similar efficacy and safety as the reference filgrastim in haematopoietic stem cell mobilisation in patients with haematological malignancies.

15. Ferrara F, Izzo T, Criscuolo C et al. Comparison of fixed dose pegfilgrastim and daily filgrastim after autologous stem cell transplantation in patients with multiple myeloma autografted on a outpatient basis. Hematol Oncol 2011; 29(3):139-43.
Abstract: Different authors have explored the feasibility of autografting patients with multiple myeloma (MM) on an outpatient basis. Peg-filgrastim (PEG), a long-acting recombinant G-CSF, has similar efficacy when compared to conventional G-CSF for chemotherapy-induced neutropenia, but little is known about its use in the autologous stem-cell transplantation (ASCT) setting, namely in patients programmed to be autografted on outpatient basis. In this study, we compared therapeutic results in terms of hematopoietic recovery, non-hematologic toxicity, duration of hospitalization and percentage of hospital readmission between patients receiving either conventional G-CSF or PEG. Thirty-eight MM patients (48 autografts) received PEG, given at a single dose of 6 mg at day +5 from stem cell infusion, while 81 (113 autografts) received G-CSF from day + 2 up to stable neutrophil recovery. The conditioning regimen was high dose melphalan in all patients. The median age and the median number of CD34 + cell infused were comparable between the two groups. Overall, a second hospital admission was required in 36 procedures out of 161 (32%). Febrile neutropenia (FN) and severe mucositis were the most frequent causes of hospitalization. There was no statistically significant difference as percentage of hospital readmission is concerned: in the PEG group readmission was needed in 6 out of 48 autografts (12%) as opposed to 30 out of 113 (26%) in the G-CSF subgroup, p: 0.06. The median time of hospital stay for readmitted patients was identical for the two subgroups (9 days vs. 9 days, p:

0.94). Finally, one case of transplant related mortality occurred in the whole patient series (0.6%). In conclusion, ASCT on an outpatient basis is feasible and safe in patients with MM, the majority of whom are manageable at home. The administration of single dose PEG results in no different outcome in terms of safety and efficacy as compared to 8 days of G-CSF.

16. Fox E, Widemann BC, Hawkins DS et al. Randomized trial and pharmacokinetic study of pegfilgrastim versus filgrastim after dose-intensive chemotherapy in young adults and children with sarcomas. Clin Cancer Res 2009; 15(23):7361-7.
Abstract: PURPOSE: To compare the effectiveness, tolerance, and pharmacokinetics of a single dose of pegfilgrastim to daily filgrastim in children and young adults with sarcomas treated with dose-intensive combination chemotherapy. EXPERIMENTAL DESIGN: Patients were randomized to receive a single dose of 100 mcg/kg of pegfilgrastim s.c. or 5 mcg/kg/day of filgrastim s.c., daily until neutrophil recovery after two treatment cycles with vincristine, doxorubicin, and cyclophosphamide (VDC) and two cycles of etoposide and ifosfamide (IE). The duration of severe neutropenia (absolute neutrophil count, < or =500/mcL) during cycles 1 to 4 and cycle duration for all cycles were compared. Pharmacokinetics of pegfilgrastim and filgrastim and CD34+ stem cell mobilization were studied on cycle 1. Growth factor-related toxicity, transfusions, and episodes of fever and neutropenia and infections were collected for cycles 1 to 4. RESULTS: Thirty-four patients (median age, 20 years; range 3.8-25.8) were enrolled, and 32 completed cycles 1 to 4. The median (range) duration of absolute neutrophil count of <500/mcL was 5.5 (3-8) days for pegfilgrastim and 6 (0-9) days for filgrastim (P = 0.76) after VDC, and 1.5 (0-4) days for pegfilgrastim and 3.75 (0-6.5) days for filgrastim (P = 0.11) after IE. More episodes of febrile neutropenia and documented infections occurred on the filgrastim arm. Serum pegfilgrastim concentrations were highly variable. Pegfilgrastim apparent clearance (11 mL/h/kg) was similar to that reported in adults. CONCLUSION: A single dose per cycle of pegfilgrastim was well tolerated and may be as effective as daily filgrastim based on the duration of severe neutropenia and number of episodes of febrile neutropenia and documented infections after dose-intensive treatment with VDC and IE.

17. Green MD, Koelbl H, Baselga J et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003; 14(1):29-35.
Abstract: BACKGROUND: We evaluated the efficacy of a single fixed 6 mg dose of pegfilgrastim (a pegylated version of filgrastim) per cycle of chemotherapy, compared with daily administration of filgrastim, in the provision of neutrophil support. PATIENTS AND METHODS: Patients (n = 157) were randomized to receive either a single 6 mg subcutaneous (s.c.) injection of pegfilgrastim or daily 5 mg/kg s.c. injections of filgrastim, after doxorubicin and docetaxel chemotherapy (60 mg/m(2) and 75 mg/m(2), respectively). Duration of grade 4 neutropenia, depth of neutrophil nadir, incidence of febrile neutropenia, time to neutrophil recovery and safety information were recorded. RESULTS: A single 6 mg injection of pegfilgrastim was as effective as daily injections of filgrastim for all efficacy measures for all cycles. The mean duration of grade 4 neutropenia in cycle 1 was 1.8 and 1.6 days for the pegfilgrastim and filgrastim groups, respectively. Results for all efficacy end points in cycles 2-4 were consistent with the results from cycle 1. A trend towards a lower incidence of febrile neutropenia was noted across all cycles with pegfilgrastim compared with filgrastim (13% versus 20%, respectively). A single fixed dose of pegfilgrastim was as safe and well tolerated as standard daily filgrastim. CONCLUSIONS: A single fixed dose of pegfilgrastim administered once per cycle of chemotherapy was comparable to multiple daily injections of filgrastim in safely providing neutrophil support during myelosuppressive chemotherapy. Pegfilgrastim may have utility in other clinical settings of neutropenia.

18. Grigg A, Solal-Celigny P, Hoskin P et al. Open-label, randomized study of pegfilgrastim vs. daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma. Leuk Lymphoma 2003; 44(9):1503-8.
Abstract: Pegfilgrastim is composed of the protein filgrastim to which a 20-kDa polyethylene glycol (PEG) is covalently bound at the N-terminal residue resulting in decreased renal clearance and

increased plasma half-life compared with filgrastim. This open-label, randomized, phase 2 study compared two doses of single administration pegfilgrastim (60 and 100 microg/kg) with daily doses of filgrastim (5 microg/kg/day) or no cytokine treatment after standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy for non-Hodgkin's lymphoma in 50 elderly patients. The primary endpoint was the duration of grade 4 (severe) neutropenia (absolute neutrophil count < 0.5 x 10(9)/l) in cycle 1. Duration of grade 4 neutropenia in cycle 1 was 2.2 (SD 1.2), 1.5 (SD 1.1), 0.8 (1.2) and 5.0 (2.0) days for patients who received pegfilgrastim 60 microg/kg, pegfilgrastim 100 microg/kg, filgrastim 5 microg/kg and no cytokine, respectively. The baseline characteristics of the pegfilgrastim and filgrastim groups were imbalanced with increased bone-marrow involvement and prior therapy in the former. When the treatment groups were balanced for these risk factors, duration of grade 4 neutropenia was comparable with 2.0 and 3.0 vs. 0.6 and 0.5 days for pegfilgrastim 100 microg/kg and filgrastim patients with and without these risk factors, respectively. The incidence of febrile neutropenia (defined as ANC < 0.5 x 10(9)/l and temperature > 38.2degrees C) was low (10% of patients). Pegfilgrastim was well tolerated with a safety profile similar to daily filgrastim. Once per chemotherapy cycle administration of pegfilgrastim was comparable to filgrastim in this clinical setting.

19. Grigg AP. Advances in hematology. A comparison of pegfilgrastim and filgrastim. Clin. Adv. Hematol. Oncol. 2005; 3(3):176-80.

20. Grigg AP. A comparison of pegfilgrastim and filgrastim. Clin Adv Hematol Oncol 2005; 3(3):176, 179-80.

21. Heaney ML, Toy EL, Vekeman F et al. Comparison of hospitalization risk and associated costs among patients receiving sargramostim, filgrastim, and pegfilgrastim for chemotherapy-induced neutropenia. Cancer 2009; 115(20):4839-48.
Abstract: BACKGROUND: Sargramostim is a granulocyte-macrophage-colony-stimulating factor (GM-CSF). Unlike filgrastim and pegfilgrastim, which are granulocyte-colony-stimulating factors (G-CSFs), sargramostim activates a broader range of myeloid lineage-derived cells. Therefore, GM-CSF might reduce infection risk more than the G-CSFs. This study compared real-world infection-related hospitalization rates and costs in patients using G/GM-CSF for chemotherapy-induced neutropenia. METHODS: This retrospective matched-cohort study analyzed nationally representative health insurance claims in the United States from 2000 through 2007. The sample population included patients who received chemotherapy and G/GM-CSF. G/GM-CSF treatment episodes began with the first administration of G/GM-CSF and ended when a subsequent administration was >28 days after a prior administration. Sargramostim patients were matched 1:1 with filgrastim and pegfilgrastim patients based on gender and birth year. Outcomes included infection-related hospitalization rates and the associated costs. Hospitalization rates were analyzed using univariate and multivariate Poisson methods; covariates included myelosuppressive agents received, tumor type, anemia, and comorbidities. RESULTS: A total of 990 sargramostim-filgrastim and 982 sargramostim-pegfilgrastim matched pairs were analyzed. Cohorts were similar with regard to age, gender, and comorbid conditions. Several differences were observed with regard to tumor type, anemia, and chemotherapy, but no systematic trends were apparent. Sargramostim patients experienced a 56% lower risk of infection-related hospitalizations compared with filgrastim and pegfilgrastim patients. Infection-related hospitalization costs were 84% and 62% lower for sargramostim patients compared with patients treated with filgrastim and pegfilgrastim, respectively. CONCLUSIONS: Among patients with or at risk for chemotherapy-induced neutropenia, these data indicated that use of sargramostim was associated with a reduced risk of infection-related hospitalization and lower associated costs compared with filgrastim or pegfilgrastim.

22. Holmes FA, O'Shaughnessy JA, Vukelja S et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002; 20(3):727-31.

Abstract: PURPOSE: This multicenter, randomized, double-blind, active-control study was designed to determine whether a single subcutaneous injection of pegfilgrastim (SD/01, sustained-duration filgrastim; 100 microg/kg) is as safe and effective as daily filgrastim (5 microg/kg/d) for reducing neutropenia in patients who received four cycles of myelosuppressive chemotherapy. PATIENTS AND METHODS: Sixty-two centers enrolled 310 patients who received chemotherapy with docetaxel 75 mg/m(2) and doxorubicin 60 mg/m(2) on day 1 of each cycle for a maximum of four cycles. Patients were randomized to receive on day 2 either a single subcutaneous injection of pegfilgrastim 100 microg/kg per chemotherapy cycle (154 patients) or daily subcutaneous injections of filgrastim 5 microg/kg/d (156 patients). Absolute neutrophil count (ANC), duration of grade 4 neutropenia, and safety parameters were monitored. RESULTS: One dose of pegfilgrastim per chemotherapy cycle was comparable to daily subcutaneous injections of filgrastim with regard to all efficacy end points, including the duration of severe neutropenia and the depth of ANC nadir in all cycles. Febrile neutropenia across all cycles occurred less often in patients who received pegfilgrastim. The difference in the mean duration of severe neutropenia between the pegfilgrastim and filgrastim treatment groups was less than 1 day. Pegfilgrastim was safe and well tolerated, and it was similar to filgrastim. Adverse event profiles in the pegfilgrastim and filgrastim groups were similar. CONCLUSION: A single injection of pegfilgrastim 100 microg/kg per cycle was as safe and effective as daily injections of filgrastim 5 microg/kg/d in reducing neutropenia and its complications in patients who received four cycles of doxorubicin 60 mg/m(2) and docetaxel 75 mg/m(2).

23. Huttmann A, Schirsafi K, Seeber S, Bojko P. Comparison of lenograstim and filgrastim: effects on blood cell recovery after high-dose chemotherapy and autologous peripheral blood stem cell transplantation. J Cancer Res Clin Oncol 2005; 131(3):152-6.
Abstract: PURPOSE: The aim of the study was to evaluate whether glycosylated granulocyte colony-stimulating factor (G-CSF) (lenograstim) offers a benefit over non-glycosylated G-CSF (filgrastim) in clinically relevant end points after high-dose chemotherapy (HDC) and autologous peripheral blood stem cell transplantation (PBSCT). METHODS: We retrospectively analyzed the outcome of 261 patients treated with either lenograstim (n=68) or filgrastim (n=193). Time to blood cell recovery, toxicities, and infectious complications were analyzed in a total of 469 G-CSF treatment cycles. RESULTS: Mean time to leukocyte recovery was 10.7 days (SD+/-0.9) (lenograstim) and 10.8 days (SD+/-0.6) (filgrastim), respectively. Likewise, time to thrombocyte engraftment, febrile days, duration of therapeutic antibiotic treatment, severity of non-hematological toxicities, duration of in-hospital stay, and duration of G-CSF treatment were similar in both groups. Owing to the physicochemical and pharmacokinetic properties of lenograstim, the required dose until leukocyte recovery was significantly smaller as compared to filgrastim (38.5 vs 54.0 microg/kg of body weight). CONCLUSIONS: Collectively, our data indicate that both G-CSF preparations are equally effective in hastening leukocyte recovery in the setting of high-dose chemotherapy followed by autologous PBSCT.

24. Kim IH, Park SK, Suh OK, Oh JM. Comparison of lenograstim and filgrastim on haematological effects after autologous peripheral blood stem cell transplantation with high-dose chemotherapy. Curr Med Res Opin 2003; 19(8):753-9.
Abstract: OBJECTIVE: To compare the efficacy of lenograstim and filgrastim on haematological recovery following an autologous peripheral blood stem cell transplantation (PBSCT) with high-dose chemotherapy. METHODS: A retrospective case-controlled study. RESULTS: Absolute neutrophil count (ANC) recovery above 0.5 x 10(9)/l and white blood cell (WBC) recovery above 4 x 10(9)/l for 3 consecutive days was achieved earlier with filgrastim than with lenograstim ((13.2 +/- 8.0 vs 19.0 +/- 10.0 days, p = 0.004), (16.9 +/- 9.7 vs 29.9 +/- 16.6 days, p = 0.001), respectively). The platelet recovery above 20 x 10(9)/l was also achieved earlier with filgrastim than with lenograstim (19.5 +/- 11.6 vs 27.2 +/- 13.8 days, p = 0.006). Furthermore, filgrastim-treated patients received fewer days of granulocyte colony simulating factor (G-CSF) administration (12.5 +/- 7.0 vs 18.6 +/- 8.5 days, p = 0.001) and spent less time in hospital (23.7 +/- 10.9 vs 32.0 +/- 17.6 days, p = 0.009). Duration of antibiotic administration was also significantly shorter in the

filgrastim group (13.6 +/- 7.6 vs 29.1 +/- 19.8 days, p = 0.001). CONCLUSION: In patients undergoing PBSCT following high-dose chemotherapy, filgrastim significantly reduced the duration of neutropenia, thrombocytopenia and days of G-CSF administration, and led to earlier hospital discharge compared with lenograstim.

25. Kopf B, De Giorgi U, Vertogen B et al. A randomized study comparing filgrastim versus lenograstim versus molgramostim plus chemotherapy for peripheral blood progenitor cell mobilization. Bone Marrow Transplant 2006; 38(6):407-12.
Abstract: We conducted a prospective randomized clinical trial to assess the mobilizing efficacy of filgrastim, lenograstim and molgramostim following a disease-specific chemotherapy regimen. Mobilization consisted of high-dose cyclophosphamide in 45 cases (44%), and cisplatin/ifosfamide/etoposide or vinblastine in 22 (21%), followed by randomization to either filgrastim or lenograstim or molgramostim at 5 microg/kg/day. One hundred and three patients were randomized, and 82 (79%) performed apheresis. Forty-four (43%) patients were chemonaive, whereas 59 (57%) were pretreated. A median number of one apheresis per patient (range, 1-3) was performed. The median number of CD34+ cells obtained after mobilization was 8.4 x 10(6)/kg in the filgrastim arm versus 5.8 x 10(6)/kg in the lenograstim arm versus 4.0 x 10(6)/kg in the molgramostim arm (P=0.1). A statistically significant difference was observed for the median number of days of growth factor administration in favor of lenograstim (12 days) versus filgrastim (13 days) and molgramostim (14 days) (P<0.0001) and for the subgroup of chemonaive patients (12 days) versus pretreated patients (14 days) (P<0.001). In conclusion, all three growth factors were efficacious in mobilizing peripheral blood progenitor cells with no statistically significant difference between CD34+ cell yield and the different regimens, and the time to apheresis is likely confounded by the different mobilization regimens.

26. Lefrere F, Bernard M, Audat F et al. Comparison of lenograstim vs filgrastim administration following chemotherapy for peripheral blood stem cell (PBSC) collection: a retrospective study of 126 patients. Leuk Lymphoma 1999; 35(5-6):501-5.
Abstract: Mobilization techniques for peripheral blood stem cell (PBSC) collection include the administration of chemotherapy followed by hematopoietic growth factors or growth factors alone. Two forms of recombinant human granulocyte colony-stimulating factor (rhG-CSF) are available for PBSC mobilization: lenograstim and filgrastim which are the glycosylated and non-glycosylated forms respectively. In order to determine the influence of the two forms of G-CSF following chemotherapy on PBSC collection, we conducted a retrospective study in 126 patients with various hematological malignancies: 65 and 61 for the lenograstim and filgrastim groups respectively. No significant differences between the two groups were observed in terms of sex, age and diagnosis. Prior therapies and PBSC mobilization regimen were also equivalent. No significant difference was observed between the groups for the median CD34+ cells harvested. The number of leukapheresis necessary to obtain a minimal number of 3 x 10(6) CD34+ cells/kg was equivalent for the two groups. The proportion of patients affected by a failure in PBSC collection was similar in the two groups. Our data suggest that lenograstim and filgrastim are equivalent for PBSC mobilization after chemotherapy.

27. Lyman GH, Lalla A, Barron RL, Dubois RW. Cost-effectiveness of pegfilgrastim versus filgrastim primary prophylaxis in women with early-stage breast cancer receiving chemotherapy in the United States. Clin Ther 2009; 31(5):1092-104.
Abstract: BACKGROUND: Prophylaxis with granulocyte colony-stimulating factor reduces the risk for febrile neutropenia (FN) in patients receiving myelosuppressive chemotherapy. OBJECTIVE: We estimated the incremental cost-effectiveness of primary prophylaxis (starting in cycle 1 of chemotherapy) with pegfilgrastim versus filgrastim in women with early-stage breast cancer receiving myelosuppressive chemotherapy in the United States. METHODS: A decision-analytic model was constructed from a health payer's perspective with a lifetime study horizon. The model considered direct medical costs and outcomes related to reduced FN and potential survival benefits due to reduced FN-related mortality and on-time receipt of full-dose chemotherapy. Sensitivity analyses were conducted. RESULTS: Pegfilgrastim was cost-saving and more effective (ie,

dominant strategy) than 11-day filgrastim. The incremental cost-effectiveness ratio (ICER) for pegfilgrastim versus 6-day filgrastim was $12,904 per FN episode avoided. Adding the survival benefit due to reduced FN mortality and receipt of optimal chemotherapy dose yielded an ICER of $31,511 per quality-adjusted life year (QALY) gained and $14,415 per QALY gained, respectively. The most influential factors included inpatient FN case-fatality rate, cost of pegfilgrastim and filgrastim, baseline probability of FN, relative risk for FN between filgrastim and pegfil-grastim, and cost of administration of filgrastim. CONCLUSION: Pegfilgrastim was cost-saving compared with 11-day filgrastim and cost-effective compared with 6-day filgrastim from a health payer's perspective for the primary prophylaxis of FN in these women with early-stage breast cancer receiving myelosuppressive chemotherapy.

28. Marchesi F, Gumenyuk S, Vacca M et al. Lenograstim (Myelostim(registered trademark)) vs biosimilar filgrastim (Zarzio(registered trademark)) for autologous peripheral blood stem cells mobilization in adult patients with hematologic malignancies: A single institution experience. Bone Marrow Transplant. 2014; 49:S214.
Abstract: Introduction: Biosimilar Granulocytre Colony-Stimulating Factor (G-CSF) has been approved on the basis of comparable quality, safety and efficacy as the originator product. So far, biosimilar G-CSF Zarzio(registered trademark) has been approved also for autologous peripheral blood stem cell (PBSC) mobilization and for prophylaxis of sever neutropenia duration following conditioning chemotherapy and stem cell infusion. However, there is still general skepticism about safety and efficacy of Zarzio(registered trademark) in these setting of patients. Materials (or patients) and Methods: From March to November 2013, 22 consecutive adult patients with hematologic malignancies (acute leukemia n=5, lymphoma n=13 and multiple myeloma n=4) underwent autologous PBSC mobilization after administration of chemotherapy associated to biosimilar Filgrastim (Zarzio(registered trademark)) in our Institution. Zarzio(registered trademark) was administered according to the study protocol in which patients were enrolled for acute leukemia (5 mcg/Kg/day in 2 patients and 10 mcg/Kg/day in 3 patients), at dosage of 10 mcg/Kg/day for multiple myeloma and 5 mcg/Kg/day for lymphoma. The target of CD34+ cell dose was 4 x 106/Kg recipient body weight. This cohort of 22 patients was retrospectively compared with 53 consecutive patients (acute leukemia n=2, lymphoma n=28 and multiple myeloma n=23) who underwent autologous PBSC mobilization after administration of chemotherapy associated to Lenograstim (Myelostim(registered trademark)) at the same dosage from March 2011 to February 2013. Results: The two groups of patients were similar as baseline clinical features, including sex (P=1), age and body weight at leukapheresis (P=0.124 and 0.357, respectively), bone marrow involvement and disease status at leukapheresis (P=0.451 and 0.501 respectively), previous radiotherapy (P=0.551), previous chemotherapy lines (P=0.977) and mobilization regimes of chemotherapy received (P=0.198), with the only exception for diagnosis distribution (high rate of acute leukemia in the Zarzio(registered trademark) group; P=0.014). As for PBSC collection data, median days of G-CSF administration, median CD34+/mcL number at leukapheresis and median number of CD34+ x 106/Kg collected at first leukapheresis were similar between two groups of patients. However, in group of patients who received Zarzio(registered trademark), we observed an higher rate of mobilization failures (22.7% compared to 3.8% of Myelostim(registered trademark) group; P=0.02), an higher rate of patients unable to reach the target of CD34+ cell planned dose (40.9% vs 7.5%; P=0.001) and an higher (but not statistically significant) rate of patients needing Plerixafor administration (13.6% vs 1.9%; P=0.076). We not observed any adverse effect directly related to Zarzio(registered trademark) administration. Discussion: Despite the limitation due to the low number of patients, our data suggest that Zarzio(registered trademark) could be less effective when compared with Myelostim(registered trademark) for PBSC mobilization after chemotherapy in adult patients with hematologic malignancies and more expensive considering the high rate of patients needing Plerixafor administration. Further studies on a larger number of patients are warrant to better evaluate the role of Zarzio (registered trademark) in this setting.

29. Martinez M, Rivera Fong L, Valero Saldana LM. Comparison of pegfilgrastim vs filgrastim in hematological recovery after high-dose chemotherapy and autologous hematopoietic progenitor cells transplant. Bone Marrow Transplant. 2014; 49:S520-S521.
Abstract: Introduction: The high-dose chemotherapy are followed by ASCT produce various complications that increase morbidity and mortality in transplant patients, the use stimulating factor of Granulocyte colony(G - CSF) favor an early hematologic recovery and is now a standard use. Alternately several studies have used Pegfilgrastim 6 mg single dose with varying results. Materials (or patients) and Methods: A comparative study of a retrospective cohort of 82 patients who were treated with highdose chemotherapy followed by ASCT in the transplant unit of the Instituto Nacional de Cancerologia of Mexico City. 41 patients in the filgrastim group and 41 patients in the Pegfilgrastim group . The applied Filgrastim dose was 10 mcgr/kg/dia, every 12 hours to achieve hematologic recovery and single dose of Pegfilgrastim 6 mg on day +5 after ASCT .Results: The recovery of neutrophils (graft) with Pegfilgrastim was presented with a median at day +11 while with Filgrastim the median was the day + 15, some patients with Pegfilgrastim presented very early recoveries on day +6, whereas filgrastim first recoveries were day +9; in assessing probability of recovery; our patients with Pegfilgrastim have 61% chance to recover for the day +10, whereas with filgrastim they have 30% likely to be recovered in the same time (day +10), the neutrophil engraftment results are statistically signifi- cant, there was no difference in recovery of platelets. Discussion: We conclude with results from our study that a single administration of Pegfilgrastim 6mg is effective in reducing the time to neutrophil recovery without adverse effects on its application, even though the cost is higher than Filgrastim, the decreased hospital stay, infections and transfusion requirements, compensate in an important way. (Figure Presented).

30. Mathew S, Adel N, Rice RD et al. Retrospective comparison of the effects of filgrastim and pegfilgrastim on the pace of engraftment in auto-SCT patients. Bone Marrow Transplant 2010; 45(10):1522-7.
Abstract: The high doses of chemotherapy used for the preparatory regimens before autologous blood or marrow stem cell transplantation leave patients at risk for neutropenic complications. The administration of filgrastim post transplant reduces the time to neutrophil recovery and therefore has become a standard practice at many institutions. In 2006, we implemented a practice change from filgrastim to pegfilgrastim. We present data on 164 consecutive patients (82 patients who received filgrastim compared with 82 patients who received pegfilgrastim) who received an auto-SCT between January 2006 and November 2007. Patients who received pegfilgrastim had faster engraftment (9.6 days compared with 10.9 days, P<0.0001), a lower incidence of febrile neutropenia (59% compared with 78%, P=0.015), as well as shorter hospital stay, fewer days of treatment with i.v. antibiotics (6.3 days compared with 9.6 days, P=0.006), and fewer radiographic tests, which translated to an estimated total cost savings of over $8000 per patient. Overall, there were no differences in toxicity with these two agents. We conclude that a single dose of pegfilgrastim is a safe and efficacious alternative to daily injections of filgrastim and can be a cost-effective approach in auto-SCT patients.

31. Ozer-Deniz S, Taylor DC, Hill G, Skornicki M, Danel A, Kunz E. Clinical consequences of primary prophylaxis with pegfilgrastim versus filgrastim for the prevention of febrile neutropenia in non-Hodgkin lymphoma and stage II breast cancer patients in Germany. Value Health 2010; 13(7):A253.
Abstract: OBJECTIVES: To assess the clinical consequences of primary prophylaxis (PP) with pegfilgrastim versus 6- or 11-day filgrastim (F6, F11) in the prevention of febrile neutropenia (FN) in non-Hodgkin lymphoma (NHL) patients receiving CHOP-14 chemotherapy and in breast cancer (BC) patients receiving TAC chemotherapy in Germany. METHODS: A lifetime Markov model was developed, consisting of two phases: 1) on-chemotherapy phase (OCP), where model cycle length equals chemotherapy cycle length (CHOP-14:14 days, TAC: 21 days), and 2) post-chemotherapy phase (PCP) with annual model cycles. PP is defined as prophylaxis initiated with the first chemotherapy cycle. Cycle 1 FN risk with no prophylaxis (NP) was estimated to be 21% for NHL CHOP-14 and 14% for BC TAC. All cycle relative risk of FN using PP with pegfilgrastim versus no

PP, F6, and F11 was 0.25, 0.87, and 0.61. FN case fatality was estimated (NHL: 8.9%; BC: 3.6%). In PCP, all-cause mortality was estimated from German life-tables; NHL and BC mortality from US data; patients experiencing FN were assumed to have higher mortality due to reduced chemotherapy dose intensity. All inputs were estimated from clinical trials and published literature. The model estimates life-years, number of FNs, and number needed to treat (NNT) to prevent an FN. RESULTS: NNT to prevent an FN were 1.3, 6.2, 2.2 in NHL; 2.3, 11.1, 4.0 in BC for Pegfilgrastim, F6, and F11 compare to NP. Overall, FN episodes per patient were 0.15, 0.76, and 0.47 in NHL; 0.09, 0.43, and 0.27 in BC. Per-patient life-months gained using PP with Pegfilgrastim were 3.4 and 1.8 versus F6 and F11, respectively in NHL, and 2.2 and 1.2 in BC. CONCLUSIONS: Primary prophylaxis with pegfilgrastim results in a lower NNT, fewer FN events, and more life-years than with 6-day filgrastim or 11-day filgrastim in both NHL and BC.

32. Papa A, Rossi L, Tomao F et al. Lenograstim versus pegfilgrastim in management of haematologic toxicities by chemotherapy (CT) in non-metastatic breast cancer (NMBC) patients. Supportive Care Cancer 2012; 20:S101.
Abstract: Objectives: This retrospective study analyzed the efficacy, safety and cost of a single injection of pegfilgrastim (P, 6 mg) compared with daily lenograstim (L, 263 (mu)g) in primary neutropenia's (N) prophylaxis in non-metastatic breast cancer patients during chemotherapy (CT). Methods: Fifty women (median age, 54 years) underwent a median six (range, 4-8) CT doses with antracyclines(plus or minus)taxanes. At every cycle, 28 patients received daily L (median five injections from days 5 to 9) while 22 patients single P on day 2. Absolute neutrophil count, incidence of G3/G4-N, bone pain (BP; Numerical Rate Scale>7), and cost effectiveness (CE) were evaluated. Results: In the overall population, the incidence rates of G3-N and G4- N were 25 and 68 %, respectively in L vs. 22.7 and 41 %, respectively, in P; two and three febrile neutropenia occurred with L and P, respectively. In FEC100 (19 patients, ten L vs. nine P), we observed 0 % of G3-N and 30 % of G4-N in L and 33 % of G3-N and 44 % of G4-N in P. In TAC/AC+T (31 patients, 18 L vs. 13 P), G3-N and G4-N were 38.8 and 66.6 %, respectively, in L vs. 15.3 and 30.7 %, respectively, in P. Of pts in P, 18.2 % had BP vs. 35.7 % in L. CT reduction was observed in 35.7 % in L vs. 41 % in P. In Italy, the cost of one P and five L was about 1489,00(euro) and 655,00(euro), respectively. Conclusions: P was more effective and expensive than L, particularly in TAC/AC+T. In FEC100, L was satisfactory with a good CE profile. No difference was found about NF incidence and safety.

33. Pastore D, Delia M, Carluccio P et al. Comparison of the effects of +3 day post-transplant daily filgrastim doses versus a single pegfilgrastim dose in autologous SCT. Bone Marrow Transplant. 2012; 47:S124-S125.
Abstract: Background: The use of high-dose chemotherapy followed by autologous stem cell transplantation is an important treatment option for selected patients with hematological malignancies. Hovewer, the high chemotherapy doses used for pretransplantation preparation exposes patients to the risk of neutropenic complivations, including bacterial and fungal infections,that in rare cases can be fatal. The post-transplant administration of filgrastim reduced the time to neutrophil recovery and has therefore become standard practice in many institutions. Alternatively, the long-acting filgrastim formulation, pegfilgrastim, can be administered as a single 6 mg dose and has a significantly increased half-life, partly due to a decreased renal clearance. Patients and Methods: In this study, data of 72 consecutive adult patients who received an auto-SCT between January 2009 and May 2011 and filgrastim (40pts) or pegfilgrastim (40pts) after transplantation were retrospectively examined. Diagnoses were non Hodgkin lymphoma (26 pts), Hodgkin lymphoma (24 pts) and Multiple Myeloma (30pts). Standard conditioning regi mens (HD-Melphaln or BEAM) were used. The mean CD34+ stem cell doses infused were 4.1 and 4.9x106/kg (p=ns) for the pegfilgrastim and filgrastim group; the groups were matched for age, sex and underlying disease. Patients of the filgrastim group received daily subcutaneous injections of 5 mg/Kg/day starting at the day +3 after transplantation until ANC >1x109/L; patients of the pegfilgrastim group received a fixed dose of 6 mg subcutaneously on day +3 post-transplantation. Results: The median time to an ANC of 0.5x109/L was 9 and 10 days (p=0.04), respectively, in the pegfilgrastim and filgrastim groups. There was no significant difference in the platelet engraftment

between the pegfilgrastim and filgrastim groups (11 vs 12 days, respectively, p=ns). The median number of days with febrile neutropenia in the pegfilgrastim group was 2 (range 1-5), versus 3 (range 1-6) in the filgrastim group (p=0.09). There was no difference in the incidence of documented infections (22% in the pegfilgrastim vs 25% in filgrastim, p=0.8). Median hospital stay (from day 0) was 15 day for pegfilgrastim and 16 days for the filgrastim group (p=0.2); there was no significant differences in survival at day +100 or at 1 year. Conclusions: We conclude that a single injection of pegfilgrastim administered on post-transplant day+3 shows comparable safety and efficacy profiles to +3 daily injections of filgrastim.

34. Perrier L, Lefranc A, Perol D et al. Cost effectiveness of pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous stem cell transplantation in patients with lymphoma and myeloma: an economic evaluation of the PALM Trial. Appl Health Econ Health Policy 2013; 11(2):129-38.
Abstract: BACKGROUND: Use of the recombinant human granulocyte colony-stimulating factor (rhG-CSF) filgrastim accelerates neutrophil recovery following myelosuppressive chemotherapy. Since filgrastim requires multiple daily administrations, forms of rhG-CSF with a longer half life, including pegfilgrastim, have been developed. Pegfilgrastim is safe and effective in supporting neutrophil recovery and reducing febrile neutropenia after conventional chemotherapy.
Pegfilgrastim has also been successfully used to support patients undergoing peripheral blood stem cell (PBSC) transplantation for haematological malignancies. To our knowledge, no cost-effectiveness analysis (CEA) of pegfilgrastim in this setting has been published yet. OBJECTIVE: We undertook a CEA to compare a single injection of pegfilgrastim versus repeated administrations of filgrastim in patients who had undergone PBSC transplantation for lymphoma or myeloma. The CEA was set in France and covered a period of 100 +/- 10 days from transplant. METHODS: The CEA was designed as part of an open-label, multicentre, randomized phase II trial. Costs were assessed from the hospital's point of view and are expressed in 2009 euros. Costs computation focused on inpatient, outpatient, and home care. Costs in the two arms of the study were compared using the Mann-Whitney test. When differences were statistically significant, multiple regression analyses were performed in order to identify cost drivers. Incremental cost-effectiveness ratios (ICER) were calculated for the major endpoints of the trial; i.e., duration of febrile neutropenia (absolute neutrophil count [ANC] <0.5 x 10(9)/L and temperature >/=38 degrees C), duration of neutropenia (ANC <1.0 x 10(9)/L and ANC <0.5 x 10(9)/L), duration of thrombopenia (platelets <50 x 10(9)/L and <20 x 10(9)/L), and days with a temperature >/=38 degrees C). Uncertainty around the ICER was captured by a probabilistic analysis using a non-parametric bootstrap method. RESULTS: 151 patients were enrolled at ten French centres from October 2008 to September 2009. The mean total cost in the pegfilgrastim arm of the study (n = 74) was <euro>25,024 (SD 9,945). That in the filgrastim arm (n = 76) was <euro>28,700 (SD 20,597). Pegfilgrastim strictly dominated filgrastim for days of febrile neutropenia avoided, days of neutropenia (ANC <1.0 x 10(9)/L) avoided, days of thrombopenia (platelets <20 x 10(9)/L) avoided, and days with temperature >/=38 degrees C) avoided. Pegfilgrastim was less costly and less effective than filgrastim for the number of days with ANC <0.5 x 10(9)/L avoided and the number of days with platelets <50.0 x 10(9)/L avoided. Taking uncertainty into account, the probabilities that pegfilgrastim strictly dominated filgrastim were 67 % for febrile neutropenia, 86 % for neutropenia (ANC <1.0 x 10(9)/L), 59 % for thrombopenia (platelets <20 x 10(9)/L), 86 % for temperature >/=38 degrees C, 32 % for neutropenia (ANC <0.5 x 10(9)/L), and 43 % for thrombopenia (platelets <50 x 10(9)/L). Conversely, the probability that filgrastim strictly dominated pegfilgrastim for neutropenia (ANC <0.5 x 10(9)/L) is 5 %. CONCLUSION: This study found no evidence that the use of pegfilgrastim is associated with greater cost in lymphoma and myeloma patients after high-dose chemotherapy and PBSC transplantation.

35. Pinto L, Liu Z, Doan Q, Bernal M, Dubois R, Lyman G. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. Curr Med Res Opin 2007; 23(9):2283-95.
Abstract: BACKGROUND AND OBJECTIVE: While head-to-head clinical trials demonstrate pegfilgrastim to be as efficacious as filgrastim in reducing chemotherapy-induced neutropenia,

these studies lacked the statistical power to demonstrate better outcomes with one therapy compared to the other. Our objective was to obtain a pooled estimate of the effect of pegfilgrastim compared with filgrastim on incidence of febrile neutropenia (FN), and related outcomes among patients with solid tumors and malignant lymphomas receiving myelosuppressive chemotherapy. RESEARCH DESIGN AND METHODS: We searched PubMed and EMBASE for articles published from January 1, 1990 to August 31, 2006 reporting on randomized controlled trials (RCTs) that compared the efficacy and safety of pegfilgrastim versus filgrastim. We only accepted studies in which filgrastim (5 microg/kg/day) and pegfilgrastim (100 microg/kg or a fixed dose of 6 mg) were administered at approved doses indicated on the package insert. Pooled relative risk (RR) was estimated using the conservative random effects, empirical Bayesian method of Hedges and Olkin. MAIN OUTCOME MEASURES: Rates of grade IV neutropenia and of FN, time to absolute neutrophil count (ANC) recovery, and bone pain. RESULTS: We identified five RCTs, with a total of 617 patients, evaluating the efficacy of a single dose of pegfilgrastim per cycle versus daily filgrastim injections. Although only one study had a statistically significant difference in FN reductions favoring pegfilgrastim over filgrastim (relative risk reduction of 50%; p = 0.027), the pooled RR showed a statistically significant favorable result for pegfilgrastim (RR = 0.64; 95% CI, 0.43-0.97). Grade IV neutropenia rates (for cycle 1: RR = 0.99; 95% CI, 0.91-1.08; cycle 2: RR = 0.88; 95% CI, 0.70-1.11; cycle 3: RR = 0.80; 95% CI, 0.47-1.36; cycle 4: RR = 0.90; 95% CI, 0.71-1.13), time to ANC (SMD = 0.11, 95% CI, -0.34-0.56), and incidence of bone pain (RR = 0.95; 95% CI, 0.76-1.19) were similar between the two G-CSFs. The included trials varied in the type of cancer, chemotherapy regimen and type of trial. CONCLUSION: A single dose of pegfilgrastim performed better than a median of 10-14 days of filgrastim in reducing FN rates for patients undergoing myelosuppressive chemotherapy.

36. Richardson P, Soiffer RJ, Antin JH et al. Defibrotide (DF) for the randomized phase II trial of pegfilgrastim versus filgrastim to treat neutropenia post-autologous peripheral blood stem cell transplant (PBSCT) in patients with non-hodgkins lymphoma [Abstract No. 43]. 108. 2006:17-8.

37. Rifkin R, Beveridge R, Spitzer G et al. Results of a randomized phase II trial of pegfilgrastim versus filgrastim to treat neutropenia post-autologous peripheral blood stem cell transplant (PBSCT) in patients with non-hodgkins lymphoma (NHL) [Abstract No. 4936]. 110. 2007:309b.

38. Sehouli J, Goertz A, Steinle T et al. [Pegfilgrastim vs filgrastim in primary prophylaxis of febrile neutropenia in patients with breast cancer after chemotherapy: a cost-effectiveness analysis for Germany]. Dtsch Med Wochenschr 2010; 135(9):385-9.
Abstract: OBJECTIVE: Febrile neutropenia (FN) is a common toxic side effect of myelosuppressive chemotherapy. The cost-effectiveness of primary prophylaxis (PP) of FN with granulocyte colony stimulating growth factor (G-CSF) filgrastim for six or eleven days was compared to single dose pegfilgrastim in patients with early breast cancer receiving chemotherapy (>or= 20 % FN risk) as simulated in a model. METHODS: Based on a decision-analytical model we conducted a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) from the perspective of the Statutory Health Insurance (SHI) in Germany. The model simulated three clinical alternatives being built on each other, that pegfilgrastim and filgrastim had differential impact on (1) the risk of FN, (2) on FN-related mortality, and (3) on the achieved chemotherapy relative dose
intensity (RDI) leading to gain in long-term survival. RESULTS: Assuming a 5.5 % lower risk of FN for PP with pegfilgrastim than an 11-day course of filgrastim provided - from the perspective of the SHI - a cost saving of Euro 2,229. A gain of 0.039 quality-adjusted life-years (QALY) resulted when the third alternative was used. Assuming a 10.5 % lower risk of FN for PP with pegfilgrastim than a 6-day filgrastim course, the third alternative showed an incremental cost-effectiveness ratio (ICER) of Euro 17.165 per life-year gained (LYG) and Euro 18.324 per QALY with 0.074 QALYs gained. CONCLUSION: These results indicate that PP with pegfilgrastim is cost saving compared to 11-day use of filgrastim and cost-effective compared to 6-day use of filgrastim in patients with breast cancer treated in Germany.

39. Simona B, Cristina R, Luca N et al. A single dose of Pegfilgrastim versus daily Filgrastim to evaluate the mobilization and the engraftment of autologous peripheral hematopoietic progenitors in malignant lymphoma patients candidate for high-dose chemotherapy. Transfus Apher Sci 2010; 43(3):321-6.
Abstract: Pegfilgrastim has equivalent efficacy to daily G-CSF in enhancing neutrophil recovery after chemotherapy, but conclusive data concerning its use for peripheral blood stem cell (PBSC) mobilization are lacking. From 2003 to 2008 we used high-dose chemotherapy in 64 lymphoma patients. At mobilization chemotherapy (ESHAP) the first 26 patients used unconjugated G-CSF, while the remaining 38 patients received Pegfilgrastim. At the time of harvest 25 patients collected stem cells after the use of G-CSF and 36 in the Peg group. No statistical by significant differences were observed in median peripheral CD34+ cells mobilized (77 muL versus 71 muL) and in collected PBSC (12.3 x 10(6)/kg versus 9.4 x 10(6)/kg p = 0.76). In the PEG group all patients collected the target PBSC with a single apheresis with a greater proportion of "optimal" mobilizers (83% versus 64%; p = 0.05). In conclusiona single dose of Pegfilgrastim could be a valid alternative to unconjugated G-CSF to mobilize PBSC in lymphoma patients.

40. Staber PB, Holub R, Linkesch W, Schmidt H, Neumeister P. Fixed-dose single administration of Pegfilgrastim vs daily Filgrastim in patients with haematological malignancies undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2005; 35(9):889-93.
Abstract: Infectious complications are frequent events in patients undergoing high-dose cytotoxic chemotherapy with subsequent autologous peripheral blood stem cell transplantation (PBSCT). To evaluate whether a single subcutaneous injection of pegfilgrastim (6 mg) is as safe and effective as daily filgrastim (5 mug/kg/day), 60 consecutive autologous stem cell transplantations performed for various haematological malignancies have been analysed. In total, 24 patients undergoing 30 consecutive PBSCT received a single subcutaneous injection of 6 mg pegfilgrastim on day 5 after transplantation and were compared retrospectively with 30 patients receiving 5 mug/kg/day of filgrastim starting from day 7 post transplantation. The mean duration of grade 4 neutropenia in the pegfilgrastim and filgrastim groups was 8.3 and 9.5 days, respectively (P=0.047). The results of the two groups were not significantly different for incidence of febrile neutropenia and toxicity profile. However, duration of febrile neutropenia (1.6 vs 3.0 days) and total days of fever (1.73 vs 4.1) were different (P=0.017 and 0.003, respectively), favouring the pegfilgrastim arm. Consequently, a higher incidence of transplants with documented infectious complications associated with the filgrastim group could be observed (56 vs 26%) (P=0.02). A single injection of pegfilgrastim administered at day 5 post transplant shows comparable safety and efficacy profiles to daily injections of filgrastim.

41. Taylor DC, Ozer-Deniz S, Hill G, Skornicki M, Danel A, Kunz E. Cost-effectiveness of primary prophylaxis with pegfilgrastim versus filgrastim for the prevention of febrile neutropenia in non-Hodgkin lymphoma and stage ii breast cancer patients in Germany. Value Health 2010; 13(7):A263-A264.
Abstract: OBJECTIVES: To assess the cost-effectiveness in Germany of primary prophylaxis (PP) with pegfilgrastim versus 6- or 11-day filgrastim (F6, F11) in the prevention of febrile neutropenia (FN) in non-Hodgkin lymphoma (NHL) patients receiving CHOP-14 chemotherapy and in breast cancer (BC) patients receiving TAC chemotherapy. METHODS: A payer perspective Markov model of febrile neutropenia prophylaxis in chemotherapy patients was developed. PP was defined as initiating prophylaxis with the first chemotherapy cycle. Model cycle length matches chemotherapy cycle length (CHOP-14:14 days, TAC: 21 days); model time horizon is the duration of chemotherapy (6 cycles). Cycle 1 FN risk with no prophylaxis was estimated to be 21% for NHL CHOP-14 and 14% for BC TAC; all cycle relative risks of FN versus no prophylaxis for PP using Pegfilgrastim, F6, and F11 were 0.25, 0.87 and 0.61, respectively, based on published literature and meta-analyses. Pegfilgrastim cost was estimated as (euro)1686 per chemotherapy cycle; corresponding costs for F6 and F11 were (euro)1347 and (euro)2469 based on German national pricing. Incremental cost- effectiveness ratios (ICERs) were calculated per FN events avoided. Costs and outcomes were discounted (3%/year). Sensitivity analyses were performed. RESULTS:

For NHL FN events per patient were 0.15, 0.76, and 0.47 for Pegfilgrastim, F6, and F11, respectively. ICER for Pegfilgrastim versus F6 was (euro)1386 per FN avoided. For BC, corresponding FN events per patient were 0.09, 0.43, and 0.27. The ICER for Pegfilgrastim versus F6 was (euro)6651 per FN avoided. Pegfilgrastim was dominant (less costly, more effective) compared with F11 in both populations. Results were most sensitive to baseline risk of FN, cost of prophylaxis and cost of FN events. CONCLUSIONS: Primary prophylaxis with pegfilgrastim costs <(euro)1400 per additional FN avoided compared with 6-day filgrastim for NHL patients treated with CHOP-14, and <(euro)7000 for BC patients treated with TAC. Pegfilgrastim dominated 11-day filgrastim.

42. Teofili L, Izzi I, Nuzzolo ER et al. Chemotherapy-Induced Neutropenia in HIV Positive Patients with Lymphoma: Comparison of Pegfilgrastim with Daily Filgrastim Administration. Mediterr J Hematol Infect Dis 2012; 4(1):e2012062.
Abstract: We retrospectively compared the incidence of neutropenia in two groups of HIV patients with lymphoma, who underwent chemotherapy supported by once-per-cycle administration of pegfilgrastim or by daily subcutaneous injection of filgrastim, respectively. Our findings indicate that pegfilgrastim and filgastrim produce similar results in preventing both neutropenia and febrile neutropenia.

43. Uysal Sonmez O, Guclu E, Turker I et al. Comparison of the effect of filgrastim vs. lenograstim started during febrile neutropenia attack in patients with solid tumors. Eur. J. Cancer 2013; 49:S296.
Abstract: Background: Chemotherapy induced Febrile neutropenia (FN) in solid tumors causes mortality and morbidity at a significant rate. In this study, we aimed to compare the effects of filgrastim or lenograstim started with the first dose of antibiotics in patients diagnosed with FN. Patients and Methods: Between February 2009 and May 2012, one hundred and fifty one patients diagnosed with FN were evaluated retrospectively. Patient's characteristics and other data were collected from patient files. Febrile neutropenia was defined as the number of a single body temperature equal or greater to 38.3(degrees)C measured from mouth or a constant body temperature with equal or greater to 38.0(degrees)C in one hour period in patient with neutropenia which has an absolute neutrofil count less than 500/mm3. Whenever febrile neutropenia was defined antibiotics to gether with granocyte colony stimulating factors(GCSF) either filgrastim or lenograstim started in 30 minutes. Results: In this study 175 febrile neutropenia attacks in 151 patients were examined. Seventy three of the patients were male and 78 of them were women. The median age was 53.6 and 53.6 in male and females respectively. The most common solid tumor was breast carcinoma in 38 (25%) patients. One hundres and five FN patients (58%) were patients who received GCSF as primary propylaxis. Demographic characteristics and laboratory findings of patients given Filgrastim and Lenogastrim are represented in Table 1. (Table presented) Conclusion: Compared to lenograstim filgrastim shortens the duration of hospitalization time during FN attack by correcting neutropenia faster in solid tumors.

44. Volovat C, Buchner A, Bias P, Mueller U. Efficacy of lipeg filgrastim versus pegfilgras tim in patients with breast cancer: Subgroup analysis based on age, weight, and type of treatment. Supportive Care Cancer 2014; 22(1):S233.
Abstract: Background and Aims Background and Aims: Lipegfilgrastim is a long-acting, fixed-dose, glycopegylated recombinant granulocyte colony-stimulating factor developed to reduce the duration of severe neutropenia and the incidence of febrile neutropenia (FN) in adults receiving myelosuppressive chemotherapy with a (greater-than or equal to)20% risk of FN. This analysis evaluated the effects of age, weight, and treatment type (adjuvant vs metastatic disease) on the efficacy of lipegfilgrastim vs pegfilgrastim using data from 2 studies (1 phase II, 1 phase III) in breast cancer patients receiving chemotherapy. Methods Both studies randomized patients to subcutaneous lipegfilgrastim (3, 4.5, or 6 mg, phase II; 6 mg, phase III) or pegfilgrastim (6 mg)(almost equal to) 24 h after chemotherapy (60 mg/m2 doxorubicin/75 mg/m2 docetaxel) for 4 21-day cycles. Blood samples for absolute neutrophil counts (ANC) were obtained 24 h before chemotherapy (cycle 1), daily until day 15, and during cycles 2, 3, and 4. This post hoc analysis,

pooled data from the lipegfilgrastim and pegfilgrastim 6- mg groups from both studies. Study endpoints included duration of severe neutropenia; time to ANC recovery; depth of ANC nadir; and incidence of grade 4 neutropenia stratified by age, weight, and type of treatment. Results Data for stratified efficacy endpoints are summarized in the Table. Conclusions Treatment with lipegfilgrastim limits the extent of neutropenia regardless of patient age, weight, or type of treatment. This post hoc analysis demonstrates a trend for a lower rate of grade 4 neutropenia with lipegfilgrastim treatment that is consistent across all subgroups evaluated.

45. Ziakas PD, Kourbeti IS. Pegfilgrastim vs. filgrastim for supportive care after autologous stem cell transplantation: can we decide? Clin Transplant 2012; 26(1):16-22.
Abstract: Granulocyte-colony-stimulating factors are helpful for the support of patients receiving autologous hematopoietic stem cell transplantation, resulting in faster neutrophil recovery and lower incidence of febrile neutropenia (FN). Our aim was to evaluate the use of pegfilgrastim vs. filgrastim with regard to absolute neutrophil count (ANC) recovery, risk, and duration of FN and length of hospital stay. Mean difference was the summary effect for continuous data, and odds ratio for binary data, using random-effects modeling. MEDLINE, EMBASE, and the Cochrane Registry of Randomized Controlled Trials were included in the search. Randomized controlled trials (RCTs), case-control studies, and studies with historical control group for filgrastim were eligible. Of the initial 114 studies screened, 12 studies were analyzed (four were RCTs, including one phase III trial). The use of pegfilgrastim resulted in a one d gain in ANC recovery (mean difference -0.82, 95% CI -1.07 to -0.57, $p < 0.001$) and duration of FN (-0.67, 95% CI -1.28 to -0.06, $p < 0.001$) but had no effect on the risk of FN or length of stay. Pegfilgrastim was more expensive (baseline marginal cost euro116.97, $p < 0.001$), which was largely determined by the treatment duration and pegfilgrastim cost. Non-randomized setting attenuated the effect on duration of FN whereas delayed onset of filgrastim injections (to pegfilgrastim) overestimated the protective effect on the risk of FN. Both drugs are at least equally effective, though methodology and disease stratification in published trials warrant further improvement.

46 Sarı N, Dalva K, Ilhan IE. Comparison of filgrastim and lenograstim in pediatric solid tumors. Pediatr Hematol Oncol. 2013 Oct;30(7):655-61.
Abstract PURPOSE: Chemotherapy-induced febrile neutropenia (FEN), which causes treatment delays or chemotherapy dose reductions, is a serious side effect of cancer treatment. In Turkey, recombinant G-CSF (rG-CSF) has been used since 2000 to control neutropenia. The purpose of this prospective randomized study is to compare the effectiveness, toxicities and the cost of these two drugs in children. METHODS: Between April and December 2008, 29 patients were administered 40 courses of chemotherapy in each arm. A randomized crossover study was designed. All patients were administered rG-CSF 24 hours after the last day of chemotherapy as a secondary prophylaxis. Complete blood counts as well as peripheral blood progenitor (CD34+) cell levels were measured before G-CSF treatment and on the fifth and the seventh day of treatment. RESULTS: The median duration of neutropenia, FEN, the length of hospitalization, the incidence of FEN, and documented infection was not different between the two rG-CSF treatment groups. Erythrocyte and platelet transfusion rates were also similar. After 7 days, the mean leukocyte (WBC [white blood cell]) and neutrophil count (ANC [absolute neutrophil count]), hemoglobin and platelet levels were not significantly different. However, the CD34+ cell level was significantly higher in the lenograstim group. Lenograstim was also more expensive than filgrastim. No serious side effects were reported for either rG-CSF treatment. CONCLUSIONS: There is no difference following the administration of either lenograstim or filgrastim for the duration of neutropenia, FEN or hospitalization for pediatric cancer patients. For stem cell mobilization, lenograstim was superior to filgrastim.

47 Sourgens H, Lefrère F. A systematic review of available clinical evidence - filgrastim compared with lenograstim. Int J Clin Pharmacol Ther. 2011 Aug;49(8):510-8.
Abstract: BACKGROUND: Filgrastim (Neu-pogen®, Amgen) and lenograstim (Granocyte®, Chugai Pharma) are chemically different granulocyte colony-stimulating factors (G-CSFs). Based on receptor-binding studies and in vitro potency assessment, a clinical superiority of lenograstim

versus filgrastim has been postulated together with potential cost savings favouring lenograstim over filgrastim. *OBJECTIVES*: To compare the clinical efficacy of filgrastim and lenograstim based on current Summaries of Product Characteristics (SPCs) for both products taking into account published clinical trials in patients and healthy volunteers. SEARCH STRATEGY AND SELECTION CRITERIA: PubMed and citation lists of published articles were used to identify clinical trials with direct comparisons of filgrastim and lenograstim. All available clinical information directly comparing filgrastim and lenograstim has been accepted for evaluation. DATA COLLECTION: A total of 16 studies compared filgrastim with lenograstim. Four studies had a randomized, parallel-group design, 4 had a cross-over design and 8 studies were uncontrolled. RESULTS: Available data do not suggest a clinically remarkable difference between filgrastim and lenograstim in chemotherapy-induced neutropenia and the mobilisation of peripheral blood progenitor cells (PBPC) in patients and healthy donors. CONCLUSIONS: Both G-CSFs are recommended for clinical use according to instructions in the respective SPCs; there is no reason to prefer lenograstim over filgrastim in any of the approved indications for both. Costs calculations need to consider the advent of biosimilar filgrastim in Europe.

48 AKSU G, ÇORAPÇIOĞLU F, FAYD M, BAŞAR EZ, MUTLU A, İNCE Z. The comparison of the preventive effects of filgrastim and lenograstim in pediatric cancer patients treated with chemotherapy and radiotherapy. Turkish Journal of Oncology. 2007;22(2)63-68.
Abstract: OBJECTIVES: To compare the preventive effects of filgrastim and lenograstim in pediatric cancer patients treated with chemotherapy and radiotherapy. METHODS: Eighty-two patients treated with myelosuppressive chemotherapy and/or radiotherapy in Pediatric Oncology and Radiation Oncology Departments of Kocaeli University, Faculty of Medicine between September 2005 and March 2007 were randomized to filgrastim and lenograstim arms. Radiotherapy doses and fields 3 weeks prior to the therapy, age, gender, histopathological type of the tumor, stage and chemotherapy protocols were recorded. Patients with bone marrow infiltration due to the tumoral invasion and patients receiving steroid including chemotherapy regimens were excluded from the study. Equivalent doses of two hematopoetic growth factors (filgrastim 5 µg/kg/day, S.C; lenograstim 150 µg/m2/day, S.C) were applied beginning 24 hours following the completion of the chemotherapy till leukocyte count reached 10.000/mm3. RESULTS: Delay in the new chemotherapy cure following chemotherapy protocol was median 5 days in lenograstim arm (16 patients, 37%) while it was 3 days in filgrastim arm (10 patients; %25) however the difference was not statistically significant (p=0.188). In lenogastrim arm, febrile neutropenia occurred in 6 patients and infections without neutropenia were seen in 4 patients (pneumonia in 2 patients, otitis media in 1 patient and pharengitis in 1 patient). In filgrastim arm, febrile neutropenia occurred in 3 patients and gingivitis and gastroenteritis in 2 patients and the difference between two groups was also not significant (p=0.258). However, bone pain was present in 2 patients in lenograstim arm while it was seen in 10 patients in filgrastim arm with a significant difference (p=0.008). CONCLUSION: Although preventive effects of filgrastim and lenograstim on febrile neutropenia and non-neutropenic infections in patients receiving radiotherapy and chemotherapy are not significantly different, delay in the new chemotherapy cure following chemotherapy protocol is shorter in filgrastim arm. However, bone pain is also significantly higher in filgrastim arm.

49 Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. Am J Med. 2002 Apr 1;112(5):406-11.
Abstract: PURPOSE: Several studies have evaluated the efficacy of the recombinant colony-stimulating factors in reducing the severity and duration of neutropenia and the risk of infection associated with dose-intensive cancer chemotherapy. We performed a meta-analysis to define better the magnitude of this effect and to assess the generalizability of the results among different diseases and types of treatment. MATERIALS AND METHODS: We used electronic databases and citation lists to identify controlled clinical trials of the prophylactic efficacy of the colony-stimulating factors on neutropenic complications. We selected randomized trials of the use of recombinant colony-stimulating factors before the onset of fever or neutropenia following systemic

chemotherapy for solid tumors or malignant lymphomas. RESULTS: We identified eight controlled trials (n = 1144 patients) of prophylactic colony-stimulating factors, including five trials of filgrastim (recombinant granulocyte colony-stimulating factors) and three studies of lenograstim (glycosylated granulocyte recombinant colony-stimulating factors). Five trials were double-blind and placebo-controlled; three included untreated controls. Use of recombinant colony-stimulating factors was associated with a reduced risk of febrile neutropenia (odds ratio [OR] = 0.38; 95% confidence interval [CI]: 0.29 to 0.49), documented infection (OR = 0.51; 95% CI: 0.36 to 0.73), and infection-related mortality (OR = 0.60; 95% CI: 0.30 to 1.22), but a greater risk of bone pain (OR = 2.9; 95% CI: 1.6 to 4.8). CONCLUSION: In this meta-analysis, recombinant colony-stimulating factors were effective in reducing the risk of febrile neutropenia and documented infection associated with several malignancies and dose-intensive treatment regimens.