ORIGINAL ARTICLE

Retrospective Analysis of the Safety and Efficacy of Pembroria® During Non-Medical Switching from the Originator Drug Keytruda® in Patients With Various Advanced Malignancies in Real-World Clinical Practice

Liudmila G. Zhukova ✉, **Daria A. Filonenko, Natalya I. Polshina, Sergei A. Smolin, Olga S. Pasechnyuk**
Loginov Moscow Clinical Scientific Center, Moscow, Russia

Abstract

Introduction. The emergence of genetically engineered biological drugs is rightly considered a revolutionary event in medicine. In 2022, the first biosimilar of pembrolizumab, the Russian drug Pembroria®, was approved. One of the study types that can convincingly demonstrate the safety and efficacy of a biosimilar is its use for switching from the originator drug for non-medical reasons (NMS, non-medical switching) according to standard approaches of real-world clinical practice and the drug label.

Aim. To assess the safety of NMS in patients with various advanced malignancies from the originator drug Keytruda® to the biosimilar Pembroria® and evaluate its effectiveness in real-world clinical practice.

Materials and Methods. We analyzed the data of 114 patients with various advanced malignancies who had the last line of treatment with Keytruda® as monotherapy or in combination with other agents within the approved indications and were switched to Pembroria® within NMS. After switching to Pembroria®, patients did not switch to another immune checkpoint inhibitor within this line of therapy.

Results. The incidence of immune-mediated adverse reactions (imARs and ARs) of any severity during treatment with comparators differed slightly: 57% with Keytruda® and 54% with Pembroria®. The majority of imARs with both Keytruda® and Pembroria® were Grade 1 (69% and 86%, respectively). All serious ARs were resolved and did not result in drug discontinuation. When analyzing the best objective response to treatment, complete response, partial response, and stable disease were observed in 9 (7.9%), 28 (24.6%), and 61 (53.5%) cases, respectively, with Keytruda® and 8 (7%), 24 (21%), 52 (45.6%) cases, respectively, with Pembroria®.

Conclusion. The safety profile of Keytruda® and Pembroria® is acceptable and comparable: the imAR rate with Pembroria® when switching from Keytruda® did not exceed that with the originator drug Keytruda®; in most patients, switching from Keytruda® to Pembroria® was not associated with an increase in the imAR rate or severity. The majority of patients maintained disease control when switched to Pembroria®.

Keywords: biosimilar, PD-1 inhibitor, immune-mediated adverse reactions, immune checkpoint inhibitors, immunotherapy, clinical studies, switching from the originator drug, Pembroria, pembrolizumab

For citation: Zhukova LG, Filonenko DA, Polshina NI, Smolin SA, Pasechnyuk OS. Retrospective Analysis of the Safety and Efficacy of Pembroria® During Non-Medical Switching from the Originator Drug Keytruda® in Patients With Various Advanced Malignancies in Real-World Clinical Practice. Journal of Modern Oncology. 2024;26(3):**-**. DOI: 10.26442/18151434.2024.3.203013

Introduction

The emergence of genetically engineered biological drugs (biologics) is rightly considered a revolutionary event in medicine. Modern biotechnologies helped develop effective therapies that changed the fate of many patients. However, the manufacturing of biologics is high-tech and, therefore, requires significant costs, primarily financial, which makes providing these medicinal products to all those in need difficult. Generic originator drugs (ODs) with relatively simple chemical formulas have entered daily clinical practice in all areas of medicine. Meanwhile, as regards generic complex biologics, there is still mistrust and apprehension both regarding the equal efficacy of the original molecule and safety. A biosimilar medicinal product (biosimilar) is a biologic similar in terms of safety, quality and efficacy to the originator biological medicinal product in an equivalent dosage form.

Information about the authors

✉ **Liudmila G. Zhukova** – D. Sci. (Med.), Corr. Memb. RAS, Loginov Moscow Clinical Scientific Center. E-mail: l.zhukova@mknc.ru; ORCID: 0000-0003-4848-6938

Daria A. Filonenko – Cand. Sci. (Med.), Loginov Moscow Clinical Scientific Center. ORCID: 0000-0002-7224-3111

Natalya I. Polshina – oncologist, Loginov Moscow Clinical Scientific Center. ORCID: 0000-0001-5417-0425

Sergei A. Smolin – oncologist, Loginov Moscow Clinical Scientific Center. ORCID: 0000-0001-8887-2660

Olga S. Pasechnyuk – oncologist, Loginov Moscow Clinical Scientific Center. ORCID: 0009-0002-8509-5944

Most of the first approved biosimilars were relatively small therapeutic proteins, such as hormones (e.g., somatotropin and insulin glargine) and growth factors (e.g., filgrastim and epoetin). More complex biosimilars, such as monoclonal antibodies used in rheumatology, gastroenterology, and oncology, have been approved and marketed in recent years [1]. The introduction of biosimilars improves patients' access to biological treatments. Ensuring the consistently high quality, safety, and efficacy of these products is a challenge for both manufacturers and regulators.

There are certain specific features in the marketing authorization of these products due to various factors. The international approach to the study of biosimilars, in

 JOURNAL OF MODERN ONCOLOGY. 2024; 26 (3): 295–299

comparison with the studies of original molecules, includes the following stages:

- detailed comparative study of physicochemical and biological properties;
- comparative preclinical studies on relevant animals;
- comparative study of pharmacokinetics and pharmacodynamics;
- comparative efficacy and safety study;
- possibility to extrapolate data to other indications;
- possibility to reduce the scope of clinical studies of biosimilars in comparison with ODs when equivalent properties have been demonstrated [2].

The clinical study stage may be initiated only if the biosimilar and the originator biologic are similar in terms of quality and functional characteristics, have equivalent pharmacokinetics and, if possible, pharmacodynamics and an identical toxicity profile. In fact, clinical studies are the culmination of a biosimilar's development and, in contrast to studies at this stage, have a limited scope in the development of an originator drug [3]. Since most of the evidence of its similarity to the OD has been accumulated by the time of initiation of clinical studies, it should be understood that clinical studies of the biosimilar are aimed only at proving its therapeutic equivalence to the OD. To this end, studies should be conducted in the patient population that is most sensitive in terms of the effects of the investigational product and as homogeneous as possible (homogeneous in terms of its baseline clinical and demographic characteristics) [4]. No dose-ranging studies or optimal dosing regimen studies are required for a biosimilar, as all these data are already available for the OD. The absence of differences in the efficacy and safety of the biosimilar and the originator drug is proven using primary endpoints reflecting the direct potency of the drug and least affected by external factors. In particular, in a study of a biosimilar used in oncology, it is preferable to compare the efficacy with that of the OD using the overall response rate, rather than the survival rates normally used for antitumor drugs (overall survival, progression-free survival, etc.), as survival rates can be influenced by various factors (tumor spread at study enrollment, prior treatment, severity of concomitant diseases, choice of subsequent treatment, and many more) [5]. The main difference between a comparative efficacy study of a biosimilar and an OD and a Phase III clinical study of an originator drug is that its purpose is not to prove advantages of the biosimilar over placebo or standard therapy, but to prove the absence of differences in efficacy in comparison with the OD, since its superiority over standard therapy has already been proven [6].

Another challenge in the clinical development of biosimilars is to prove that there are no differences with the OD in immunogenicity and safety. Both parameters should be investigated not only in pivotal studies, the sensitivity of which could be limited, e.g., in respect of immunogenicity (e.g., in cancer patients receiving concomitant chemotherapy), but also at the post-marketing stage, since clinical studies are a somewhat simplified experimental model, which does not always reflect the real-world clinical picture [7].

The approved biosimilar is similar to the reference (originator) product in terms of efficacy, safety and quality, and any observed differences are considered clinically insignificant [8]. Therefore, biological treatment of a bionaive patient (i.e., a patient previously untreated with a certain biologic) can start with the relevant biosimilar without any efficacy or safety issues other than those stated for the reference drug. However, the transfer of patients treated with the OD to a biosimilar raises doubts [9, 10]. There have been concerns that switching between very similar but not identical versions of a biologic could lead to an increase in immunogenicity due to subsequent exposure to potentially different sets of epitopes (for example, due to glycosylation profile differences between the products), although this has never been observed in clinical studies. Another concern was the possibility of the formation of antibodies to the biological agent used, which could lead to safety issues or loss of efficacy [11, 12].

These risks can be minimized by conducting preclinical studies comparing biosimilars and reference drugs, as well as post-marketing observational studies that help evaluate the efficacy and safety profile of a biosimilar in real-world settings, and monitoring long-term immunogenicity. Moreover, post-marketing pharmacovigilance data are important to ensure long-term safety and efficacy [13].

One of the research options that can convincingly demonstrate the safety and efficacy of a biosimilar is its use in non-medical switching (NMS) from the OD according to the standard approaches of real-world clinical practice and the Instruction for Medical Use of the drug.

NMS normally means switching a stable patient from a prescribed medicinal product to another medicinal product for reasons other than lack of clinical response, adverse effects, or poor compliance. NMS occurs when a clinically stable patient, whose current therapy is effective and well tolerated, is switched by the physician's decision to another therapeutic alternative. This type of switching is not for higher efficacy, safety and/or convenience, but is usually initiated for organizational/technical reasons and serves to reduce costs or ensure uninterrupted/constant access to the same class of drugs.

International literature already has some publications on switching studies (from OD to biosimilar and between different biosimilars), but only for a few drugs. In particular, 5 studies evaluated the switching from filgrastim (reference drug) to filgrastim biosimilars: A. Engert et al. (2009) - Filgrastim – XM02 [14], U. Gatzemeier et al. (2009 r.) – Filgrastim – XM02 [15], K. Verpoort et al. (2012 r.) – Filgrastim – Zarzio®/Filgrastim Hexal® [16], K. Blackwell et al. (2015 r.) – Filgrastim – EP2006 [17], T. Kobayashi et al. (2017 r.) – Filgrastim – Filgrastim BS [18]. Three of these were Phase III randomized studies, of which one study included multiple switches. The other two studies were retrospective analyses of available databases. In general, none of these studies revealed safety or efficacy issues related to switching from a biologic to another biosimilar [14-18].

For one trastuzumab biosimilar, KANJINTI, switching was carried out during a Phase III study in early breast cancer. The data analysis revealed comparable immunogenicity in the reference drug group and the group with the switch to the biosimilar. No extra adverse events (AEs) were detected [1].

A meta-analysis of studies evaluating the safety of NMS for various drugs was published in 2023 [19]. It included a total of 5252 patients (31 studies for 21 biosimilars), who were switched to a biosimilar from its reference biologic or vice versa. Studies were included if they evaluated biosimilars approved by the US Food and Drug Administration, such as adalimumab (11 studies), epoetin alfa (2 studies), etanercept (3 studies), filgrastim (1 study), infliximab (7

JOURNAL OF MODERN ONCOLOGY. 2024; 26 (3): 295–299

studies), insulin glargine (1 study), rituximab (5 studies), and trastuzumab (1 study).

Clinical study data in this systematic review revealed no differences in terms of major safety parameters, such as mortality, serious adverse reactions (SARs and ARs), and treatment discontinuation, following the switching (to the biosimilar from its reference biologic or vice versa). The result was the same for all switching protocols and did not depend on the drug group, switching direction, or number of switches. The immunogenicity data showed the same frequency of anti-drug antibodies and neutralizing antibodies in patients who were switched to the biosimilar from its reference biologic or vice versa and in patients who were not switched. AEs such as anaphylaxis, hypersensitivity reactions, and injection site reactions were similar in all groups [19].

In the current socio-political situation, the issue of uninterrupted access to therapy is becoming ever more important: in this case, NMS is used due to the absence of the foreign-made originator drug, which precludes further treatment. In this situation, the optimal solution is NMS to a domestically manufactured biosimilar, which will always be available. The common use of immune checkpoint inhibitor (ICI) biosimilars, such as Pembroria®, into the oncology practice allowed to significantly increase the availability of this type of therapy for cancer patients.

A large number of patients have been switched from the OD Keytruda® to the biosimilar Pembroria® for non-medical reasons at the Loginov Moscow Clinical Scientific Center since December 2022; therefore, it was decided to conduct a retrospective analysis of the safety and efficacy of the biologic in patients with various advanced malignancies in real-world clinical practice.

JOURNAL OF MODERN ONCOLOGY. 2024; 26 (3): 295–299

https://doi.org/10.26442/18151434.2024.3.203013

PEMBRORIA, A4

JOURNAL OF MODERN ONCOLOGY. 2024; 26 (3): 295–299

Study aim: To assess the safety of non-medical switching of patients with various advanced malignancies from the OD Keytruda® to the biosimilar Pembroria® in real-world clinical practice; to assess the efficacy of Pembroria® (prescribed for non-medical switching from the OD Keytruda®) in patients who have received the biosimilar Pembroria® for 6 months or more.

Materials and Methods

The analysis included data of 114 patients (36 women and 78 men) with various advanced malignancies (Figure 1), with any previous cytotoxic therapy regimens (including targeted and immuno-oncology drugs) and Keytruda® (at least 1 administration) used in the last line of treatment as monotherapy or in combination with other agents for approved indications, who were switched to Pembroria® (at least 1 administration) for non-medical reasons. After NMS to Pembroria®, patients did not change their biologic to another ICI within this treatment line.

The average age of patients was 65 years (36 to 88).

21 (18.4%) patients had received other ICIs in previous treatment lines; 90 (79%) patients were still on this treatment at the time of data collection. Patients received an average of 8 doses of Pembroria® (minimum 3 administrations, maximum 11 administrations).

Data collection format: systematic collection of individual patient data. Data collection method: interview.

Follow-up period: from December 2022 to September 2023.

Results

Safety Assessment

It is important to note that the total number of drug administrations was different: 1507 administrations (13 on average) for the OD Keytruda® and 871 administrations (8 on average) for the biosimilar Pembroria®.

An infusion-related reaction (IRR) was observed in 1 patient (0.9%) treated with Keytruda® (highest Grade 1, after the 6th administration). No IRRs were observed with Pembroria®.

The frequency of immune-mediated ARs (imARs) of any grade varied slightly with the compared drugs: 57% with Keytruda® and 54% with Pembroria®.

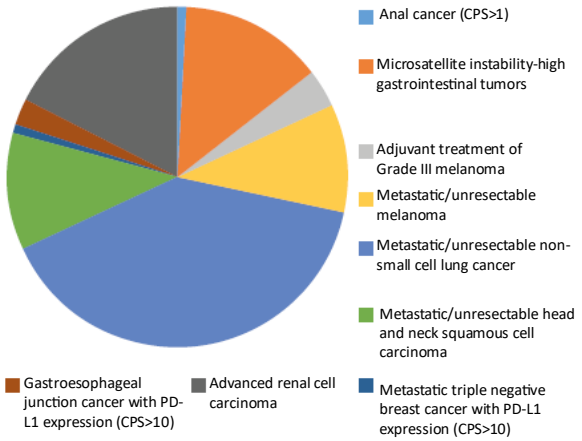
25 (25.4%) patients had no imARs during the entire treatment period. The most common imARs during treatment with Keytruda® and Pembroria® were increased liver enzymes, increased creatinine, asthenia and hypothyroidism (Figure 2).

Following the switch from Keytruda® to Pembroria®, 51 (44.7%) patients had no increase in the frequency or severity of imARs, 3 (2.6%) had an increase in the severity of imARs, and 31 (27.3%) patients developed new imAR(s) (Table 1).

Most imARs were Grade 1 both with the OD Keytruda® and with the biosimilar Pembroria® (69% and 86%, respectively). In 4 patients receiving Keytruda®, Grade 3 imARs were reported: hyperthyroidism in 1 patient and increased liver enzymes in 3 patients. One Grade 3 AR was observed with Pembroria®: increased liver enzymes.

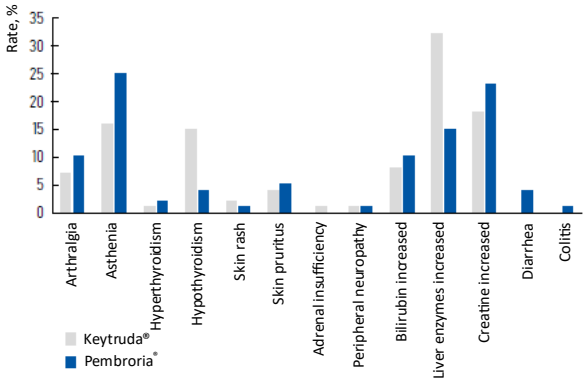
All SARs were relieved and did not lead to treatment discontinuation.

Figure 1. Distribution of Study Subjects by Disease.



Note. CPS, Combined Positive Score; PD-L1, programmed death ligand 1.

Figure 2. ImAR Rate Reported During Therapy.



None of the 114 patients switched from Keytruda® to Pembroria® had imARs not specified in the Instruction for Medical Use; there was no case of subsequent discontinuation of Pembroria® for any reason, including imARs.

Within the framework of this analysis, 4 deaths (3.5%) were revealed. Causes of death: cerebral infarction, brain disease progression with subsequent brain edema; the causes of 2 deaths remained unknown. No deaths related to imARs or imSARs were reported.

Thus, based on the data presented, the safety profiles of Keytruda® and Pembroria® are acceptable and comparable. The switch from Keytruda® to Pembroria® was not associated with an increase in the frequency or severity of imARs in most patients.

Efficacy Assessment

During the treatment with Keytruda® and Pembroria®, their efficacy was evaluated in 98 (86%) and 108 (94%) patients, respectively.

Response was not assessed in 15 patients receiving Keytruda® due to the small number of administrations and in 1 patient for a different reason; 6 patients treated with Pembroria® were also not evaluable as they were lost to follow-up.

JOURNAL OF MODERN ONCOLOGY. 2024; 26 (3): 295–299

Table 1. Time Course of the ImAR Rate and Severity During Switching from Keytruda® to Pembroria®

Changes in the rate and severity of imARs	Number of patients	
	abs.	%
No imARs	29	25.4
No changes	51	44.7
Increased maximum imAR grade	3	2.6
New imAR(s)	31	27.3
Total	114	100

When analyzing the best objective response (OR), complete response (CR), partial response (PR), or stable disease (SD) were observed in 9 (7.9%), 28 (24.6%), and 61 (53.5%) cases, respectively, in patients treated with Keytruda® and 8 (7%), 24 (21%), and 52 (45.6%) cases, respectively, in patients treated with Pembroria®.

Of the 16 patients not evaluable while on treatment with Keytruda®, 7 (43%) had SD, 4 (25%) had PR, 4 (25%) had progressive disease (PD), and 1 patient had no OR assessment after the switch to Pembroria®.

Of the 9 patients who achieved CR with Keytruda®, 7 (77.8%) patients retained it after the switch to Pembroria®, 1 (11.1%) patient had PD and 1 (11.1%) patient had no response assessment.

Among 28 patients with PR on Keytruda®, 20 patients (71.4%) retained PR, 1 (3.5%) patient improved from PR to CR, and 7 (25%) patients had PD.

It was noted that 45 (73.7%) patients with SD achieved on Keytruda® retained it after switching to Pembroria®, 12 (19.7%) patients with SD subsequently had PD, and 4 (6.5%) patients had no OR assessment (Figure 3).

The majority of patients (74%) are still on Pembroria® at the time of data collection, PD has been registered in 24 of 114 (21%) patients.

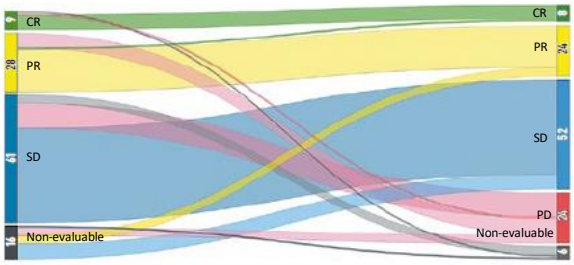
Thus, most patients still had disease control after the Keytruda®/Pembroria® switch.

Conclusion

The analysis did not reveal any evidence that switching from the OD to its biosimilar is unsafe. The results showed that none of the patients developed serious imARs, IRRs or AEs not specified in the Instruction for Medical Use.

It is important to consider that the observed "loss of effect" is most likely due to the "normal" decrease in response over time rather than to the switching process. Therefore, additional long-term studies, including long-term follow-up of patients after a switch to a biosimilar, can provide more detailed information about how treatment efficacy changes over time. Such studies can help distinguish between the effect of switching and the overall decrease in response and assess the real impact of biosimilars on patients. When analyzing the study results, another important aspect must be taken into account: 87% of patients received treatment for metastatic disease (including metastatic gastroesophageal junction cancer, non-small cell lung cancer, head and neck squamous cell carcinoma), which itself determines an unfavorable prognosis and can have a significant impact on treatment efficacy in general. Additional analyses of subgroup data in larger cohorts of patients may provide more data on the efficacy and safety of switching to biosimilars.

Figure 3. Change in the Time Course of Response in Patients Switched from Keytruda® to Pembroria®, Abs.



In turn, an increase in the frequency of imARs can be associated with the duration of immunotherapy. There is considerable evidence in the international literature that the frequency and severity of ARs can vary with the duration of treatment. This should also be taken into account when assessing the safety of switching to biosimilars.

Based on the results of the final assessment of the safety and efficacy of Keytruda® and Pembroria®, the following conclusions can be made:

- The safety profiles of Keytruda® and Pembroria® are acceptable and comparable: the rate of imARs with Pembroria® after the switch from the OD Keytruda® did not exceed that of the latter;
- in most patients, the switch from Keytruda® to Pembroria® was not associated with an increase in the frequency or severity of imARs;
- most patients still had disease control after the switch to Pembroria®.

However, long-term monitoring is necessary to make sure that this switch is safe and effective over a long period of time.

Disclosure of interest. The authors declare that they have no competing interests.

Authors' contribution. The authors declare the compliance of their authorship according to the international ICMJE criteria. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent for publication. Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

Funding source. The authors declare that there is no external funding for the exploration and analysis work.

REFERENCES

1. Barbier L, Ebbers HC, Declerck P, et al. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: A systematic review. *Clin Pharmacol* Ther. 2020;108(4):734-55. DOI:10.1002/cpt.1836
2. Kirchhoff CF, Wang XM, Conlon HD, et al. Biosimilars: Key regulatory considerations and similarity assessment tools. *Biotechnol Bioeng*. 2017;114(12):2696-705. DOI:10.1002/bit.26438
3. Triplitt C, Hinnen D, Valentine V. How similar are biosimilars? What do clinicians need to know about biosimilar and follow-on insulins? *Clin Diabetes*. 2017;35(4):209-16. DOI:10.2337/cd16-0072
4. García JJ, Raez LE, Rosas D. A narrative review of biosimilars: A continued journey from the scientific evidence to practice implementation. *Transl Lung Cancer Res*. 2020;9(5):2113-9. DOI:10.21037/tlcr-20-601

5. Markus R, Liu J, Ramchandani M, et al. Developing the totality of evidence for biosimilars: Regulatory considerations and building confidence for the healthcare community. *BioDrugs*. 2017;31(3):175-87. DOI:10.1007/s40259-017-0218-5
6. Niazi S. Scientific rationale for waiving clinical efficacy testing of biosimilars. *Drug Des Devel Ther*. 2022;16:2803-15. DOI:10.2147/DDDT.S378813
7. Joshi D, Khursheed R, Gupta S, et al. Biosimilars in oncology: Latest trends and regulatory status. *Pharmaceutics*. 2022;14(12):2721. DOI:10.3390/pharmaceutics14122721
8. van Overbeeke E, De Beleyr B, de Hoon J, et al. Perception of originator biologics and biosimilars: A survey among belgian rheumatoid arthritis patients and rheumatologists. *BioDrugs*. 2017;31(5):447-59. DOI:10.1007/s40259-017-0244-3
9. Dylst P, Vulto A, Simoens S. Barriers to the uptake of biosimilars and possible solutions: A Belgian case study. *Pharmacoeconomics*. 2014;32(7):681-91. DOI:10.1007/s40273-014-0163-9
10. Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, et al. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. *Ann Rheum Dis*. 2016;75(9):1693-6. DOI:10.1136/annrheumdis-2015-208684
11. Faccin F, Tebbey P, Alexander E, et al. The design of clinical trials to support the switching and alternation of biosimilars. *Expert Opin Biol Ther*. 2016;16(12):1445-53. DOI:10.1080/14712598.2017.1238454
12. Schellekens H. Immunogenicity of therapeutic proteins: Clinical implications and future prospects. *Clin Ther*. 2002;24(11):1720-40; discussion 1719. DOI:10.1016/s0149-2918(02)80075-3
13. Konstantinidou S, Papaspiliou A, Kokkotou E. Current and future roles of biosimilars in oncology practice. *Oncol Lett*. 2020;19(1):45-51. DOI:10.3892/ol.2019.11105
14. Engert A, Griskevicius L, Zyuzgin Y, et al. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. *Leuk Lymphoma*. 2009;50(3):374-9. DOI:10.1080/10428190902756081
15. Gatzemeier U, Ciuleanu T, Dediu M, et al. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. *J Thorac Oncol*. 2009;4(6):736-40. DOI: 10.1097/JTO.0b013e3181a52964
16. Verpoort K, Möhler TM. A non-interventional study of biosimilar granulocyte colony-stimulating factor as prophylaxis for chemotherapy-induced neutropenia in a community oncology centre. *Ther Adv Med Oncol*. 2012;4(6):289-93. DOI:10.1177/1758834012461330
17. Blackwell K, Semiglazov V, Krasnozhon D, et al. Comparison of EP2006, a filgrastim biosimilar, to the reference: A phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. *Ann Oncol*. 2015;26(9):1948-53. DOI:10.1093/annonc/mdv281
18. Kobayashi T, Kamada I, Komura J, et al. Comparative study of the number of report and time-to-onset of the reported adverse event between the biosimilars and the originator of filgrastim. *Pharmacoepidemiol Drug Saf*. 2017;26(8):917-24. DOI:10.1002/pds.4218
19. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. *PLoS One*. 2023;18(10):e0292231. DOI:10.1371/journal.pone.0292231

Article received: September 01, 2024
Article approved for publication: ##.##.#####