



CrossMark

Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers

Josep Tabernero,¹ Malvika Vyas,² Rosa Giuliani,³ Dirk Arnold,⁴ Fatima Cardoso,⁵ Paolo G Casali,⁶ Andres Cervantes,⁷ Alexander MM Eggermont,⁸ Alexandru Eniu,⁹ Jacek Jassem,¹⁰ George Pentheroudakis,¹¹ Solange Peters,¹² Stefan Rauh,¹³ Christoph C Zielinski,¹⁴ Rolf A Stahel,¹⁵ Emile Voest,¹⁶ Jean-Yves Douillard,² Keith McGregor,² Fortunato Ciardiello¹⁷

To cite: Tabernero J, Vyas M, Giuliani R, *et al.* Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open* 2016;1:e000142. doi:10.1136/esmoopen-2016-000142

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/esmoopen-2016-000142>).

JT and MV contributed equally.

Received 06 December 2016
Accepted 06 December 2016

For numbered affiliations see end of article.

Correspondence to

Josep Tabernero; jtabernero@vhio.net

ABSTRACT

Biosimilars present a necessary and timely opportunity for physicians, patients and healthcare systems. If suitably developed clinically, manufactured to the correct standards and used appropriately, they can positively impact on the financial sustainability of healthcare systems. A critical consideration regarding the introduction of biosimilars into the clinic centres on the required information concerning all the respective procedures. This position paper aims to describe the issues revolving around biosimilars that are relevant to the field of oncology, especially the prescribers. More specifically, we discuss aspects related to definition, forms of biosimilars, labelling, extrapolation, interchangeability, switching, automatic substitution, clinical standards on safety and efficacy, responsibilities among prescribers and pharmacists, potential impact on financial burden in healthcare and the current scenario and future prospects of biosimilars in Europe and the rest of the world.

INTRODUCTION

Biological medicinal products form an integral and effective part of the management of non-communicable and communicable diseases. They are crucial to treating life-threatening conditions in all disease areas, including oncology.

With the anticancer medicines market set to surpass the 140 billion EUR¹ mark by 2020, healthcare decision makers are facing considerable challenges: tackling the issue of sustainability of healthcare systems and improving access to medicines for patients.² Biological medicinal products, or those whose active substance is made by a living organism, will represent 19%–20% of the total global share of pharmaceutical sales by 2017, and thus form an essential part of the anticancer medicines offering.³

Biosimilars (similar versions of the originator biologics) present a necessary

opportunity for physicians, patients and healthcare systems. If properly developed clinically, manufactured to the correct standards and used appropriately (with both the physician and patient being well informed), they can positively impact the financial sustainability of healthcare systems, globally.

The European Union (EU) has been a pioneer in approving biosimilars, with the approval of 23 biosimilars up to 2016.⁴ Prior to the introduction of biosimilars for monoclonal antibodies (moAbs), biosimilars only existed for low molecular weight compounds. In 2013, the European Medicines Agency (EMA) approved two biosimilars for infliximab, an moAb, a large and complex molecule that is widely prescribed for patients in several disease areas, including oncology.⁵ With the majority of moAbs coming off patent by 2020, the oncology landscape will be facing a lot of changes. The introduction of biosimilars, existence of their reference products (originator biologics) and creation of improved versions of existing biologics (biobetters), among others will constitute a challenging environment for all key stakeholders: prescribers, pharmacists, nurses, patients, reimbursing bodies and manufacturers.

To ensure that the patients are being prescribed the safest and most efficacious treatment possible, all key actors including the prescribers and patients will need to understand the complexities of biosimilars and take decisions that will be in the patient's interests.

This paper aims to explore the issues surrounding biosimilars that are relevant to the field of oncology, especially the prescribers.



What are biosimilars?

Biosimilars are medicinal products containing a similar version of the active substance of their originator or reference product (biologic), derived from living organisms. They include hormones, small proteins, vaccines, fusion proteins and moAbs, the latter of particular relevance in the field of oncology.⁶ The registration of biosimilars in Europe follows complex regulatory pathways established by bodies such as the EMA, in line with those of their reference products, including preclinical and clinical studies as well as rigorous comparability exercises.

How are they different from generics?

The difference between biosimilars and generics is extremely important to understand. Generic, or small molecule drugs, are identical copies of their reference products and produced via a chemical synthesis.

When manufacturers seek the approval for a generic, they must establish bioequivalence tests that deem the two identical. Generic products do not require the additional testing requirement of clinical studies since they do not derive from living organisms, unlike biologics. With generics, the responsibility to prescribe lies with the physician, whereas accountability to dispense lies with the delivering pharmacist. Given the widespread use of generics, physicians are being encouraged to prescribe medicines using their international non-proprietary names (INN), as opposed to their commercial ones.

With biosimilars, due to the complexity of recreating a product which is made by living organisms, strict quality, safety and efficacy criteria need to be followed. These criteria include the submission of data from preclinical and clinical studies, among other requirements, to test the degree of similarity to the originator and the consequent safety and efficacy of the final product. Importantly, due to the complexity of the process, different batches of a particular moAb could even be considered biosimilar versions of the moAb given they do not follow a purely chemical pathway but are made from living cells.

Thus, small molecule generics and biosimilars differ immensely since the latter's requirements are similar to those of an originator biologic (including clinical trials and rigorous comparability studies).

Other forms of biosimilars

In addition to biosimilars, the lapse of patents for original biologic products has led to the creation of multiple classes of biologics, in addition to biosimilars.

Non-comparable biologics are those biosimilars that do not meet the requirements of similarity to the original medicinal product since they have not been through the strict requirements including comparability studies among other requirements, as stipulated by the relevant bodies, such as the EMA, the World Health Organization (WHO) or the US Food and Drug Administration (FDA).

Biobetters are superior products to the originator biologic with improved administration of the product, greater stability as well as other better performing indicators.

They are consequently improved versions of the originator and may, for example, increase patient adherence to therapy. They are neither the originator nor their biosimilar, but a novel category of products.

In various regions, biosimilars are also referred to as 'follow-on pharmaceuticals', subsequent entry biologics and biocomparables, among others.

Labelling of biosimilars

Labelling refers to the information that is displayed on the packaging of a product. The topic of labelling is important for biosimilars since both the EMA and FDA adopt the same approach that they apply to generic products, following the bioequivalence route.^{7,8} This implies that the information on the label of a biosimilar should be a copy of the approved label of the reference product. In theory, this justification is valid. However, as biosimilars are not identical copies but the best possible version of their reference products, their labelling is of crucial importance due to the fact that it provides both the physician and the patient with the necessary information about the product and its effects.

More specifically, in the case of biosimilars for moAbs, the submitted information from the clinical studies, including detailed pharmacovigilance plans, needs to be reflected on the label. This is important in the field of oncology, as physicians should be suitably informed regarding (1) the patient population it was tested on (ie, a sensitive patient population) and (2) the sensitivity of endpoints used in the trial to demonstrate the efficacy of the biosimilar for the specific indication.

Furthermore, the correct name of the reference product for a biosimilar is also crucial. Since a biosimilar is not an identical version of its reference product, the label must reflect the brand name of the originator biologic, instead of the INN to correctly track the biosimilar and related adverse events. Contrary to generics that are referenced by their INN, the complexity of a biosimilar, including the recording of related adverse events, means that the label must specify the brand name, as recommended by the EMA, FDA and WHO.⁹⁻¹¹

Thus, the label or summary of product characteristics (SmPC) should clearly reflect the information concerning the product it contains and refer to the appropriate sections of the European Public Assessment Report (EPAR) that are important considerations for the physician. As a biosimilar is not an identical clone of the originator biologic, data concerning the extrapolation, interchangeability, switching and automatic substitution, immunogenicity and traceability should also be detailed appropriately.

Considering the complexity of biosimilars, adequate information is crucial to educating the physician and the patient to inform them about the product they will be administering.

Extrapolation

For prescribers, extrapolation is an extremely important component to the concept of biosimilarity. The EMA



defines extrapolation as ‘extending information and conclusions available from studies in one or more subgroups of the patient population (source population)... to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information... to reach conclusions for the target population ...’¹²

As biosimilars are complex products that undergo new clinical studies in line with those of their reference products, extrapolation of the indications should be permitted if verified scientifically. Analytical, preclinical, pharmacokinetics, pharmacodynamics and clinical data, along with immunogenicity, should be collected if the biosimilar is to be correctly extrapolated to all indications of its reference product.

Thus, extrapolation to all clinical indications may be acceptable in the EU,¹³ and globally, if there are enough relevant data related to the safety and efficacy of the biosimilar, any differences in the data are appropriately justified.¹⁰

Interchangeability, switching and automatic substitution

Interchangeability, switching and automatic substitution are important topics in oncology. In the field of generics, this trio does not represent a serious concern since the products are identical copies of their reference compound. Switching a patient from the original product to its generic version is common practice and, due to its interchange, a different profile of adverse events is not expected.

In biosimilars, it is important for the physician to know if and when a product is being switched (from originator to biosimilar, biosimilar to originator or biosimilar to biosimilar). The decision to change or switch should be taken by the physician having grasped a deep understanding of the product (via the information on the SmPC and EPAR), and subsequently informing the patient (based on all the factual information) and closely monitoring the patient at all times, in collaboration with nursing teams. This is crucial as it will allow the physician and their colleagues to trace any adverse events to the appropriate product. Given the complexity of biosimilars, switching in any of the aforementioned three scenarios might result in different outcomes since every biologic is unique. In theory, although quite improbable, they could provoke certain immune reactions and the effectiveness of a given medicine in patients may be altered if the product is changed during a period of treatment due to the differences from its reference product (immunogenicity).¹⁴

In the EU, interchangeability of medicines is linked to their substitution, which is a Member State competence.¹⁵ However, Member States are advised to consider the precautionary principle as well as the potential risks associated with substituting a reference biological medicinal product with a biosimilar when tendering for hospitals. Nine out of 28 Member States completely prohibit automatic substitution of biosimilars for reference products

by pharmacists^{16 17}. Six out of 28 Member States restrict substitution to ensure the safety of patients and in particular, avoid unforeseen immune responses.^{16 17} There is no clear consensus among Member States concerning this issue, implying that countries may decide whether to implement policies related to automatic substitution or not.¹⁸ The EMA has not underlined any recommendations on interchangeability.¹⁹

Automatic substitution, which might be practice for generics, should therefore be avoided in the field of biosimilars. Interchangeability and switching should only be permitted if: (1) the physician is well-informed about the products; (2) the patient is fully briefed by the physician and (3) a nurse is closely monitoring the changes and tracking any adverse events.

Clinical standards: safety and efficacy of biosimilars

The Directive 2003/63/EC, outlining the community code relating to medicinal products for human use, states that the assessment procedure for applying for a marketing authorisation of a biosimilar should include bioequivalence and bioavailability data as well as pharmaceutical, chemical and biological findings.²⁰ The addition of pharmaceutical, chemical and biological data differentiates their requirements from ‘essential similar’ or generic products, and are in place to improve the safety and efficacy of biosimilars, or ‘similar biological medicinal products’.

In line with these requirements, the EMA provides robust guidelines for the manufacturer, including: a step-wise approach for the design of non-clinical studies; the use of pharmacodynamic markers; study design, choice of appropriate patient population and choice of surrogate and clinical endpoints in efficacy trials; clinical safety (including design of immunogenicity studies), risk management plan and pharmacovigilance; extrapolation of safety and efficacy.²¹

Given the complexity of biosimilars, ensuring their safety and efficacy is critical. The EMA’s guidelines provide a comprehensive dossier that is required for biosimilars, including the data for immunogenicity. Clinical studies are required for biosimilars to ensure that the manufacturing process is sound and does not differ from that of the originator biologic. Furthermore, EMA’s robust comparability study guidelines included in the dossier are essential to establish the safety and efficacy of biosimilar medicinal products.²²

To appropriately capture clinical efficacy and immunogenic reactions, a biosimilar product should be tested in the most sensitive populations and its data are reported clearly. This will contribute to the robustness of its safety and efficacy and therefore build confidence in the physician and patient alike.

Lastly, once a biosimilar is on the market, continuous monitoring to ensure its safety and efficacy is also required. Given that some side effects are only seen after prolonged exposure to the biosimilar and/or after a large number of patients are treated with a certain medicine,



additional pharmacovigilance and phase IV studies are essential.

Responsibilities between prescribers and pharmacists

Conventionally, a pharmacist is a professional who is qualified to prepare and dispense medicinal products, whereas a prescriber is a professional who can select a medicinal product matched to specificities of a given patient. Both are vital in the treatment and care of patients in collaboration with other key professionals and healthcare providers.

Given that pharmacists prepare medicinal products, they can also switch from the original to the similar product, if permitted. For generic products, pharmacists can automatically swap from one to the other, since they are identical.

As biosimilars are complex and unique, pharmacists should not be allowed to automatically switch the biosimilar without the knowledge and consent of both the prescriber and patient.

Prescribers should select the appropriate product based on sufficient data and knowledge and on informing the patient of the changes (original biologic to biosimilar, biosimilar to original, biosimilar to biosimilar). The end goal is to ensure the patient receives the best, safe and efficacious treatment available.

Impact on the financial burden

Globally, the spending on medicinal products will reach 1.3 trillion EUR²³ by 2020, with 225 new cancer treatments expected to be introduced by 2020. With breakthrough therapies in the pipeline, biosimilar medicinal products are particularly appealing in view of their promise to reduce the heavy financial burden faced by healthcare systems worldwide. The introduction of biosimilars is expected to have cumulative potential savings of 50–100 billion EUR by 2020.²⁴ However, the budgetary impact needs to be monitored.

In Europe, price reductions for biosimilars are expected to range from 20% to 40%, with a few cases being higher.²⁴ Given that the current savings do not have a huge budgetary impact, the introduction of more biosimilars and increase in their prescription (based on the choice available) will impact the financial burden of a healthcare system.

Thus, the potential savings will have a direct correlation with (1) the uptake of biosimilars, (2) the negotiations between the Member States and manufacturers and (3) the increase in confidence to prescribe by the physician and acceptance by the patient.

Current situation in EU, Europe and ROW

The EU's executive body, the European Commission and its decentralised body and the EMA have been working with biosimilars for the last 15 years. Since 2006, 23 biosimilars have received marketing authorization in the EU.⁴ As biosimilar medicines represent a rapidly emerging field, the EMA has established an extensive set of guidelines,²⁵

which although neither binding nor mandatory, aim to guide the course of action and support the increasing number of biosimilar applications.²⁶ Currently, no biosimilars have been withdrawn from the market due to safety reasons; however, 1 biosimilar medicinal product was rejected on the basis of differences between the biosimilar and its reference product (such as impurities), as well as stability concerns.²⁷

In the Asia-Pacific region, over 300²⁸ biosimilars (including moAbs) are currently in the pipeline, as compared with 50²⁴ in the USA and EU. With the loss of patents, lower exclusivity periods for branded biologics and high costs, Asia-Pacific countries are slowly and gradually preparing to produce and use biosimilars. Countries such as Australia, Malaysia, South Korea, Japan, China and India already have strict regulatory standards for biosimilars, including guidelines.²⁸ The WHO, with its guidelines, is also assisting the emerging countries, including those in Africa, by guiding them on biosimilars.

Globally, the next 5 years will be important for biosimilars, for their uptake and their impact on healthcare systems.

CONCLUSION

With potential savings, a rapidly increasing range of biologic products and well-informed healthcare professionals and patients, biosimilars do represent one of the ways forward to obtain sustainability. Physicians will make decisions based on what is best for their patients. To ensure that the decision is accurate, information is crucial for the prescriber, pharmacist, nurse and patient. Collecting enough data, including findings from clinical studies, to instill confidence in prescribers, pharmacists and patients concerning the medicinal product and patient monitoring via expert teams will be crucial in the field of biosimilar medicinal products.

The manufacturing of biosimilars must also adhere to the stringent regulations and guidelines stipulated by the WHO, EMA and FDA. Medicinal products that do not follow the appropriate procedures and yet receive approval due to less stringent regulations in certain countries,²⁹ for example, lack of a comparability exercise, otherwise known as non-comparable biologics, biomimics or intended copies of the originator, should not be used. Safety and efficacy standards are essential in biosimilars and should be respected by all entities manufacturing the product, all countries and their regulatory bodies approving the product, all physicians prescribing the product and all pharmacists dispensing the product. The approved product is ultimately prescribed to benefit the patient, and its optimal safety and efficacy is, critically, the shared responsibility of both the manufacturers and the regulatory bodies.

Author affiliations

¹Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Universitat Autònoma de Barcelona, Barcelona, Spain

²European Society for Medical Oncology, Lugano, Switzerland

³Medical Oncology, San Camillo-Forlanini Hospital, Rome, Italy



⁴Cancer Center, CUF Hospitals, Lisbon, Portugal

⁵Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal

⁶Fondazione IRCCS National Cancer Institute, Milan, Italy

⁷Hematology-Medical Oncology Department, Clinic Hospital, Valencia, Spain

⁸Gustave Roussy Cancer Campus Grand Paris, Villejuif, France

⁹Department of Breast Tumors, Cancer Institute "Ion Chiricuta", Cluj-Napoca, Romania

¹⁰Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland

¹¹University of Ioannina, Ioannina, Greece

¹²Oncology Department, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

¹³Department of Hemato-oncology, Hospital Center Emile Mayrisch, Esch/Alzette, Luxembourg

¹⁴Department of Medicine I, Clinical Division of Oncology, Medical University of Vienna, Vienna, Austria

¹⁵Netherlands Cancer Institute, Amsterdam, The Netherlands

¹⁶University Hospital Zürich, Zurich, Switzerland

¹⁷Second University of Naples, Naples, Italy

Competing interests JT serves on advisory boards for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Eli Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho and Takeda. DA has, in the last 2 years, participated in advisory boards and/or acted as a speaker at meetings and/or recipient of travel support for participation in medical meetings for/from Roche, Merck Serono, Amgen, Bayer Healthcare, Sanofi-Aventis, Terumo and Sirtex. AC has acted as a consultant or advisor to Amgen, AstraZeneca, Sanofi-Aventis, Merck Serono, MSD, Genentech and Roche.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

- European Central Bank. <https://www.ecb.europa.eu/stats/exchange/eurofxref/html/eurofxref-graph-usd.en.html> (accessed Nov 2016).
- IMS Institute for Healthcare Informatics. *Global oncology trend report: a review of 2015 and outlook to 2020*. Parsippany: IMS Institute for Healthcare Informatics, 2016.
- IMS Institute for Healthcare Informatics. *The global use of medicines: outlook through 2017*. Parsippany: IMS Institute for Healthcare Informatics, 2013.
- European Medicines Agency. European public assessment reports. http://www.ema.europa.eu/ema/index.jsp?mid=WC0b01ac058001d124&searchType=name&taxonomyPath=&genericsKeywordSearch=Submit&searchGenericType=biosimilars&keyword=Enter+keywords&alreadyLoaded=true&curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&treeNumber=&searchTab=searchByAuthType&pageNo=1 (accessed Nov 2016).
- European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144941.pdf (accessed Dec 2016).
- Lee JF, Litten JB, Grampp G. Comparability and biosimilarity: considerations for the healthcare provider. *Curr Med Res Opin* 2012;28:1053–8.
- Food and Drug Administration. *Scientific considerations in demonstrating biosimilarity to a reference product*. Silver Spring: Food and Drug Administration, 2015.
- European Medicines Agency. *QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product*. London: European Medicines Agency, 2012.
- European Medicines Agency. *Guideline on similar biological medicinal products (revision 1)*. London: European Medicines Agency, 2014.
- World Health Organization. *Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)*. Geneva, Switzerland: World Health Organization, 2016.
- United States Food and Drug Administration. *Non-proprietary naming of biological products: guidance for industry (Draft Guidance)*. Silver Spring: United States Food and Drug Administration, 2015.
- European Medicines Agency. *Concept paper on extrapolation of efficacy and safety in medicine development*. London: European Medicines Agency, 2013.
- European Medicines Agency. *Guideline on similar biological medicinal products containing biotechnology - derived proteins as active substance: clinical and non-clinical issues*. London: European Medicines Agency, 2014.
- European Medicines Agency. *Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins*. London: European Medicines Agency, 2005.
- European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000129.jsp&mid=WC0b01ac0580533e0f (accessed Dec 2016).
- Niederwieser D, Schmitz S. Biosimilar agents in oncology/haematology: from approval to practice. *Eur J Haematol* 2011;86:277–88.
- Agency for Medicinal Products and Medical Devices of Croatia. <http://www.halmed.hr/en/Lijekovi/Informacije-o-lijekovima/Bioloski-i-biosli-cni-lijekovi/> (accessed Nov 2016).
- Kurki P, Ekman N. Biosimilar regulation in the EU. *Expert Rev Clin Pharmacol* 2015;8:649–59.
- European Medicine Agency. *Questions and answers on generic medicines*. London: European Medicines Agency, 2012.
- European Commission. *Commission directive 2003/63/EC of 25 June 2003 amending directive 2001/83/EC of the European parliament and of the council on the community code relating to medicinal products for human use* UK, London: European Commission, 2013.
- European Medicines Agency. *Guideline on similar biological medicinal products containing biotechnology - derived proteins as active substance: clinical and non-clinical issues*. London: European Medicines Agency, 2014.
- European Medicines Agency. *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)*. London: European Medicines Agency, 2012.
- IMS Institute for Health Informatics. *Global medicines Use in 2020: outlook and implications*. Parsippany: IMS Institute for Health Informatics, 2015.
- IMS Institute for Health Informatics. *Delivering on the potential of biosimilar medicines*. Parsippany: IMS Institute for Health Informatics, 2016.
- European Medicine Agency. *Guideline on similar biological medicinal products*. London: European Medicines Agency, 2014.
- European Medicines Agency. *Biosimilar medicinal products*. London: European Medicines Agency, 2011.
- European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000585/human_med_000643.jsp&mid=WC0b01ac058001d124 (accessed Nov 2016)
- Quintiles IMS. Biosimilars by region: Asia Pacific. <http://www.quintiles.com/microsites/biosimilars-knowledge-connect/biosimilars-by-region/asia-pacific> (accessed Nov 2016).
- Castañeda-Hernández G, Szekanecz Z, Mysler E, et al. Biopharmaceuticals for rheumatic diseases in Latin America, Europe, Russia, and India: innovators, biosimilars, and intended copies. *Joint Bone Spine* 2014;81:471–7.



Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers

Josep Taberero, Malvika Vyas, Rosa Giuliani, Dirk Arnold, Fatima Cardoso, Paolo G Casali, Andres Cervantes, Alexander MM Eggermont, Alexandru Eniu, Jacek Jassem, George Pentheroudakis, Solange Peters, Stefan Rauh, Christoph C Zielinski, Rolf A Stahel, Emile Voest, Jean-Yves Douillard, Keith McGregor and Fortunato Ciardiello

ESMO Open 2017 1:
doi: 10.1136/esmoopen-2016-000142

Updated information and services can be found at:
<http://esmoopen.bmj.com/content/1/6/e000142>

These include:

References

This article cites 4 articles, 0 of which you can access for free at:
<http://esmoopen.bmj.com/content/1/6/e000142#BIBL>

Open Access

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[Open access](#) (86)
[Respiratory research](#) (2)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>