

# Biosimilars as a strategy to improve sustainability



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It is clearly acknowledged that competition between branded drugs and lower impact strategies (biosimilars and generics) might potentially represent a key driver to bend cancer-cost curve in the forthcoming future.<sup>1</sup>

In this regard, regulatory agencies (European Medicines Agency (EMA) and Food and Drug Administration) moved towards developing a specific pathway for the approval of biosimilars, although this process is undermined by hazards.<sup>2</sup>

Nevertheless, the way to increase the confidence, the applicability and the clinical relevance of the results of trials (in terms of efficacy, safety and costs) with drugs attempting to change clinical practice (and to enter the market) has become more rigorous and sophisticated across the recent years.

These are the challenging perspectives where the development of biosimilars (and generics) should be addressed in order to maintain the equilibrium between the increasing economic burden of healthcare and the methodological rules in interpreting the results of clinical trials required by regulatory agency (and ethics in general).

This complicated scenario calls for a clear position from scientific associations (as well as from governments and healthcare community), and the European Society for Medical Oncology (ESMO) has replied with a series of clear and precise standpoints, reflecting on all related issues and critical aspects, with a particular focus on the responsibilities behind the whole process, to be equally shared by companies and regulatory agencies.<sup>3</sup>

Although Europe paved the way to biosimilars, and in view of 2020 as a 'horizon' for science and for the market, when many monoclonal antibodies will come off patents, ESMO is pivotally recommending that the complex (and challenging) environment we are going to deal with would be better faced if a team (constituted by prescribers, nurses, patients, pharmacists, reimbursing bodies

and companies) will share together responsibilities and duties.

Key points to be addressed are represented by the extrapolation, the interchangeability, the switching and the automatic substitution.

With regard to the first one, given the intrinsic (and significant) differences with generics, ESMO recommends that extrapolation of the indications should be allowed only if a solid scientific background behind is provided. This is crucial for clinical practice; indeed, the extrapolation (ie, approval of a drug in an indication not tested in clinical trials) of a biosimilar with a proven efficacy in metastatic disease of a poor-prognosis solid tumour to a different disease setting (early disease, adjuvant or neoadjuvant strategy) where the main objective is not palliation, while cure the disease, may have hidden complexities, ranging from pure methodology (choice of endpoints, patients' population) to ethics. Thus, although the European Union (EU) considers 'acceptable' such process, the scientific verification when possible is suggested, and any difference in the available data between the different clinical scenarios must be appropriately justified.

Concerning the other three issues (interchangeability, switching and automatic substitution), these do not represent major issues for generics, but the drug substitution in general is a matter of the overall competence of Member States in the EU; different countries amended different positions, ranging from a 'possible' acceptance to prohibition (with many countries without a definitive decision), and EMA did not to date underline any recommendation. The automatic substitution, which may potentially be established by pharmacists exclusively without consulting prescribers, according to ESMO panellists, should be avoided. A biosimilar could potentially 'interchange' the originator only if the prescribing physician and the nurses taking care of the patients are entirely aware of all



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available data on that biosimilar, and a strict monitoring of adverse events has been shared with the patient, and the patient himself/herself was informed by the clinical staff about the biosimilar he/she is receiving.

Given the intrinsic complexity in the development of biosimilar monoclonal antibodies in oncology concerning their complex molecular structure, the potential for post-translational modifications and multidimensional manufacturing process, prescribing physicians (who are eventually involved in clinical investigations with branded drugs) might have the common feeling that the risk of 'a more permissive' pathway (in comparison with originators) to approval for biosimilars in general is possible.

Indeed, the way to register in a sensitive and homogeneous population a branded (new) drug requires a great superiority following formal and controlled pre-study hypotheses, in progression-free or overall survival, demonstrating large advantages for patients. Conversely, a biosimilar might be potentially tested in a different clinical scenario (and thereafter extrapolated), with an equivalence or non-inferiority trial aimed to intermediate (and not validate) endpoints such as activity (response in general), and not to demonstrate advantages, but rather to tolerate small disadvantages in comparison with the originator.

The example, recently published, of trastuzumab and its biosimilar(s) clearly resembles all these issues.<sup>4</sup> In this trial, patients with HER2-positive metastatic breast cancer (so, a sensitive and homogeneous population as required by regulations) were enrolled in a multicentre, double-blind, parallel-group equivalence study. The primary endpoint was overall response rate (ORR) at 24 weeks. Although EMA identified ORR as a sensitive endpoint for clinical trials of biosimilar antibodies, the current available data indicate that ORR does not always correlate with survival with the strength of a surrogate endpoint.<sup>5</sup>

Following EMA indications, if response has to be chosen, it is likely that pathologically complete response (pCR) in the neoadjuvant setting for HER2-positive breast cancer would have been the most sensitive endpoint, as recently reported by Jackisch *et al.*<sup>6</sup> Indeed, EMA requires that the most sensitive population where the comparison is tested should be that where if there is a difference between the biosimilar and the originators, that difference will most easily be detected (even if dealing with equivalence/non-inferiority). According to Jackisch *et al.*, if we use the same equivalence margins for ORR (metastatic disease) and pCR (for early/locally advanced disease), the predicted maximum loss in long-term efficacy with the biosimilar versus trastuzumab is smaller for pCR than for ORR. In addition, other requirements of EMA for biosimilar context would be more easily satisfied, such as

the treatment-free follow-up phase and the immunogenicity monitoring.

Nevertheless, as physicians treating both the individual patient and the disease in the context of the whole community, we have to recognise the biosimilar clinical development as an opportunity for healthcare in general, in light of the potential savings in a forthcoming future where these drugs would compete for the same patients with originators and so-called biobetters. The issue is to increase the amount of evidence and information regarding biosimilars for increasing confidence in treating physicians and pharmacists. In this regard, the development of serious postmarketing surveillance plan will allow prescribers to more easily adhere to such kind of opportunity in clinical practice. We all should agree that biosimilar (and generic) oncology drugs might potentially represent the so-called 'cost game-changer' in the overall market system.

That is why ESMO identifies the whole group of physicians, pharmacists, patients, companies and agencies as key leaders in assuming this great responsibility for the overall health community in order to guarantee the appropriate development of biosimilars and their use for clinical practice.

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