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Expert Discussion

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Biosimilars in the Treatment of Breast Cancer

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Biosimilars (biologicals) are biological products with no clinically meaningful difference to the reference product in terms of efficacy and safety. They are gaining increasing attention, as they have similar characteristics as the original drugs and have the potential to provide an alternative to these effective yet costly treatments. Regulations on biosimilars are significantly stricter than on other generics and require extensive in vitro and in vivo studies. Therefore, the potential to reduce treatment costs is not as great as with generics, but still may be up to 40% [Schleicher SM, Seidman AD: JAMA Oncol 2017; doi: 10.1001/jamaoncol.2016.6789]. This increases the number of available treatment options in various cancers, including breast cancer.

Question 1: Which Biologicals Do You Consider as Potential Candidates for the Clinical Use in the Treatment of Breast Cancer?

Bartsch: In breast cancer, two types of biological agents are currently being used in clinical routine: monoclonal antibodies as anti-cancer treatment and smaller molecules, such as growth factors, as adjunct treatment for the therapy and prevention of treatment related side-effects. With regards to growth factors, such as erythropoietin and filgrastim, biosimilars have already arrived in breast cancer therapy and are widely used today. So far, no biosimilars to antibodies have been approved in breast cancer, but trastuzumab and – albeit to a lesser extent – bevacizumab seem to be logical candidates for the development of biosimilars. In the future, denosumab, a monoclonal antibody targeting the RANK ligand, may also be of interest for the manufacturers of biosimilars.

Bauernhofer: Monoclonal antibodies as anti-cancer treatment and peptide hormones, such as growth factors, are currently being used in clinical routine. For the latter, e.g. erythropoietin and filgrastim, biosimilars are already used in breast cancer therapy today. The monoclonal antibodies trastuzumab and bevacizumab seem to be candidates for the development of biosimilars in the near future since their patents are about to end; thereafter pertuzumab may be the next step. Also denosumab, a monoclonal antibody targeting the RANK ligand as an osteoprotective agent in case of bone metastases, may be of interest for the manufacturers of biosimilars. Furthermore, pegylated erythropeitin or peg-filgrastim might be interesting compounds, although complicated in the manufacturing process.

Vrbanec: Some biologicals will be off patent. Herceptin (trastuzumab) is the first, as the European patent expired in 2014. The other is bevacizumab for which the patent runs out in 2017. Biosimilars to these antibodies, primarily trastuzumab, will be potential candidates for the clinical use in the treatment of breast cancer. Several biosimilars of trastuzumab are in development and may soon become available. So for example last year the results of 2 studies with biosimilars of trastuzumab – MYL-14010 and ABP 980 – in metastatic and early-stage breast cancer were presented. The results showed that both biosimilars were as effective and safe as trastuzumab.

Vrdoljak: Trastuzumab, pertuzumab, TDM1, and bevacizumab are candidates for the development of biosimilars. Potentially, in triple-negative breast cancer (TNBC), check point inhibitors are possible candidate, but currently sufficient evidence for the use in every day practice is still lacking.

Question 2: What Is the Difference in the Use of Biologicals in the Treatment of Early-Stage and Advanced-Stage Breast Cancer?

Bartsch: Biologicals are widely used in the treatment of early and advanced stage breast cancer and biosimilars to G-CSF are al-

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ready commonly prescribed. As for biosimilars to therapeutic antibodies, such as trastuzumab, the main issue from my perspective is whether the comparability exercise did include a trial conducted in the adjuvant setting. I would assume that many clinicians would accept an extrapolation of adjuvant or neoadjuvant data to the metastatic setting but would be less inclined to use a biosimilar trastuzumab in the adjuvant setting if the clinical activity was only evaluated in patients with metastatic disease.

Bauernhofer: Biologicals are increasingly used in the treatment of early and advanced stage breast cancer and biosimilars to G-CSF – and to a lesser extent erythropoietins – are already commonly prescribed. As pegylated filgrastim has a higher therapeutic index compared to conventional filgrastim, new pegylated filgrastim-biosimilars would have a good market potential. For biosimilars to therapeutic antibodies such as trastuzumab, the main issue besides efficacy is safety since this compound has been licensed in the palliative, neoadjuvant, and adjuvant setting. Comparative studies including large cohorts of patients in at least the metastatic and neoadjuvant settings with a long follow-up period will be necessary to convince me to use it in all indications. Moreover, trastuzumab formulation plays an important role as well. Most patients receive the drug subcutaneously – a biosimilar with i.v. license only will have less market potential due to the much longer treatment duration in the outpatient department.

Vrbanec: Clinical trials with trastuzumab biosimilars are in the late stage and focused on metastatic and early breast cancer. What should be considered in the use of biologicals in the adjuvant setting is that we see the results of our therapy only after a few years. For Herceptin we have data from clinical studies with thousands of women and very long follow-up (10 or 11 years in trials). This is not the case for biologicals. On the other hand in metastatic disease we have to see how the biologicals interact with other monoclonal antibodies, particularly pertuzumab, because the regimens for first-line therapy for metastatic breast cancer involve pertuzumab.

Vrdoljak: I see no difference in use. However, there is a difference in the level of evidence.

Question 3: Where Do You See the Indication for the Use of the Trastuzumab Biological Instead of Herceptin in Your Current Practice?

Bartsch: As stated above, this depends upon the available clinical data. If a biosimilar to trastuzumab was shown to be as effective as the original in the metastatic setting, I would tend to use the biosimilar drug in this specific situation while I would be reluctant to extrapolate clinical data to the adjuvant setting. Another issue is the combination of trastuzumab with pertuzumab as first-line treatment of metastatic breast cancer or in the neoadjuvant setting; in the absence of clinical data, I would still prefer to use original trastuzumab in these circumstances.

Bauernhofer: My decision would depend on the available comparative clinical studies in which the trastuzumab biosimilar has been tested (in the metastatic situation alone, or in the neoadjuvant, and adjuvant setting as well). I would use the drug in the clinical setting it was tested in (e.g. metastatic), but would be reluctant to extrapolate clinical data, e.g. to the neoadjuvant or adjuvant setting.

Vrbanec: In my view, all patients who are eligible for Herceptin treatment are potential candidates for using biologicals.

Vrdoljak: The use of trastuzumab as biosimilar will be based on the level of available evidence and the price of the drug.

Question 4: What Is the Importance of Studies Evaluating the Role of Trastuzumab Biologicals in the Treatment of Breast Cancer, Particularly in the Perspective of Your Country?

Bartsch: The development of generics and biosimilars to originator drugs are an integral part of a drug's life-cycle, as they help in lowering drug prices. This is particularly important in expensive drugs, such as therapeutic antibodies – in limited-resource countries and as well as in industrialized countries.

Bauernhofer: The development of biosimilars to original drugs is important. On the one hand, I would consider biosimilars to be economically important as they help lowering drug prices and force originators to press for innovation. Particularly in expensive drugs, such as therapeutic antibodies, the economic impact will be huge. On the other hand cost is not the only important variable, efficacy and safety must be comparable to the original drug, otherwise I would not use it. Therefore, I consider biosimilars to trastuzumab or other biologicals to be relevant. These drugs may help to provide anti-HER2 treatment to breast cancer patients in limited-resource countries and may also reduce the pressure on healthcare systems in developed countries, such as Austria.

Vrbanec: The biologic drugs for cancer are some of the most expensive medicines today, costing thousands of Euros for 1 patient for a year. If there are multiple drugs and biologicals on the market, the cost will come down. Therefore biologicals have the potential to provide savings for healthcare system in my country. Biologicals can also bring some improvements to patient outcomes by providing more treatment options to physicians.

Vrdoljak: I am aware of studies with trastuzumab biosimilars that have recently been published as abstracts and, of course, these data could be important in the decision-making process of governmental officials when deciding about the licensing of these drugs.

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