The Challenges and Benefits of Biosimilar Drug Development for Trastuzumab, a Precision Medicine

PEER REVIEWED

Monoclonal antibodies (mAb) are among the most promising biologic drugs currently on the market for treatment of life-threatening diseases, such as breast cancer, and chronic diseases, such as rheumatoid arthritis. Since the first monoclonal antibody was manufactured in 1975, there have been multiple efforts to understand the mechanism of action, correlation with structure, and to design mAbs capable of targeting specific receptors.[1,2] The selectivity and specificity of these mAbs resulted in the first generation of targeted therapies. Today this approach is referred to as precision medicine or personalised medicine, which is an innovative approach to disease prevention and treatment that takes into account differences in people's genes, environments and lifestyles.[3,4,5] Trastuzumab, a genetically engineered humanised mAb from Genentech, provided one of the first examples of precision medicine. Under the brand name Herceptin®, it was approved by the US Food and Drug Administration in 1998, and has been marketed in the US since then. Trastuzumab is approved for the treatment of breast and gastric cancers that overexpress HER2.[6,7]

In tandem with the trastuzumab approval, the FDA granted approval to Dako Corporation's HercepTest®, an *in vitro* assay capable of detecting HER2 protein overexpression. This test allows physicians to identify patients who could benefit from trastuzumab treatment as well as those patients who would not benefit from treatment. The trastuzumab approval created a foundation for the further development of drugs associated with HER2 receptor binding, as demonstrated by approval of Genentech's Perjeta® (pertuzumab) in 2012,[8] and Kadcyla® (ado-trastuzumab emtansine) in 2013, both indicated for treatment of HER2 positive breast cancer.[9,10] Pertuzumab is a first-in-class HER dimerisation inhibitor for the treatment of HER2-positive cancers. Ado-trastuzumab ematansine is a HER2 antibody-drug conjugate comprised of Genentech's trastuzumab antibody linked to ImmunoGen's antimitotic agent, emtansine.

As of today, there have been 19 updates to Genentech's trastuzumab labelling information, since its approval in 1998. Trastuzumab's indications evolved from the treatment of metastatic breast cancer patients overexpressing the HER2 to now include adjuvant therapy for breast cancer, and most recently, the treatment of metastatic gastric cancer.[7] Many patients have not benefited from this therapy due to limited global availability and treatment expense; however, this situation is set to change in the US, when the patent for trastuzumab expires in 2019, and biosimilar treatments become available. Biosimilar versions of trastuzumab are currently being developed as lower-cost alternative treatments, with the goal of offering the same therapeutic benefits as the originator product. This paper will discuss the benefits and unique challenges of biosimilar development for trastuzumab. The authors will also discuss how the innovator plans to ensure the continued use of branded Herceptin as combination therapy with pertuzumab.

Clinical Challenges Associated with Trastuzumab Biosimilar Drug Development

Trastuzumab biosimilar Phase I drug development, like that for most other biosimilars, is usually conducted utilising male healthy volunteers (HVs). This represents a more homogenous population compared to breast cancer patients, who have highly variable pharmacokinetic (PK) profiles. Such PK variability is due, in part, to the highly variable nature of HER2 expression, and the fact that the receptor may have a truncated form unable to bind the antibody. Trastuzumab is now approved in the management of breast cancer in three different settings, as well as gastric cancer as follows: 1) Adjuvant setting in early stage HER2 over-expressing breast cancer (US and EU); 2) Locally advanced or metastatic HER2 over-expressing breast cancer (US and EU); 3) Neoadjuvant therapy – where the therapy aims to shrink the tumour prior to surgery – in HER2 over-expressing breast cancer (EU only); 4) HER2 over-expressing metastatic gastric or gastroesophageal junction adenocarcinoma (US and EU). When selecting the most sensitive indication to study a trastuzumab biosimilar, many complex factors must be considered.

Trials in the adjuvant setting are lengthy, as relapse rates are low and occur over a period of several years. Approval of trastuzumab in the adjuvant setting was obtained after the results of three major trials were published, each enrolling over 3000 patients. Follow-up periods of at least two years were required to reach statistical significance in terms of disease-free survival. Demonstrating similar efficacy with a biosimilar version of trastuzumab in this indication would require many thousands of patients to be treated for several years. This is therefore not a viable indication in which to demonstrate biosimilarity.

Until recently, the only other indication option in which to demonstrate biosimilarity was metastatic breast cancer (MBC). The strategy for the MBC clinical programme will generally be proposed for two different treatment regimens – combination with docetaxel, or combination with docetaxel/pertuzumab. The size of the trial is calculated based on realistic equivalence margins while remaining clinically sound. Based on the authors' experience, this has historically required approximately 600 patients and competition for these patients in the clinical trial setting is expected to be fierce. Although these large trials are challenging to conduct, some companies have achieved success using this approach. For example, according to a poster presented at the 2015 American Society of Clinical Oncology (ASCO) annual meeting, Pfizer appears to be studying its trastuzumab biosimilar in both MBC and neoadjuvant settings.[11] Mylan also evaluated a trastuzumab biosimilar (MYL-1401O) for the same MBC indications and presented results at the 2016 ASCO annual meeting. In a Phase III safety and efficacy study, Mylan's proposed trastuzumab biosimilar product, MYL-1401O, was compared with Herceptin® and demonstrated equivalency and comparable safety. Mylan's MYL-1401O could offer another treatment option for HER2-positive breast cancer.[12] It is therefore possible to develop a biosimilar version of Herceptin utilising this indication but for the reasons stated, working in this indication represents a significant challenge.

In the EU, trastuzumab is also approved as a neo-adjuvant treatment for breast cancer. Although not approved for this indication in the US, it is possible that the FDA may consider this indication, especially now that pertuzumab is approved

in combination with trastuzumab for neo-adjuvant treatment. Celltrion is currently conducting a Phase III Efficacy and Safety Study of biosimilar CT-P6 and Herceptin as neoadjuvant and adjuvant treatment.[13] This would be a more favourable indication from a practical standpoint, as a smaller number of patients would be required and it would take less time to measure a response to therapy. Any such proposal to use the neo-adjuvant setting for biosimilar approval in the US would need to be discussed and agreed upon with the Agency.

As pertuzumab is used in tandem with trastuzumab in certain indications, this could have a significant life cycle advantage for the use of trastuzumab. This product is designed to bind to the HER2 receptor and prevent the dimerisation of HER2 with other HER family receptors at the surface of cancer cells. Pertuzumab has been launched in multiple countries in combination with trastuzumab and docetaxel. These current approvals ensure that trastuzumab's medical use will continue even after patent expiry in these regions and that trastuzumab (in combination with pertuzumab) use may even continue to grow. For example, pertuzumab is in Phase III development for HER2-positive breast cancer in combination with trastuzumab as a first-line therapy for metastatic disease; in combination with trastuzumab-MCC-DM1 as first-line therapy for metastatic disease; and as part of an adjuvant regimen for surgically resected early-stage disease. Phase III development of pertuzumab as second-line therapy is also in progress. Phase III development in ovarian cancer is underway in the EU, and Phase III development is also in progress. If pertuzumab use continues in tandem with trastuzumab, it appears likely trastuzumab will remain relevant for the foreseeable future.

Trastuzumab was recently approved for use as a treatment for HER2 over-expressing metastatic gastric or gastroesophageal junction adenocarcinoma. However, because only 10% of gastric tumours over-expressed HER2 protein, an inordinate number of patients need to be screened in order to obtain a statistically powered sample size.

Genentech/Roche have also taken steps to try and prevent erosion of trastuzumab's position in the marketplace. In 2013, a subcutaneous formulation containing 600 mg of trastuzumab was approved in the EU which can be administered in approximately five minutes.[14] The original IV formulation, which contains 150 mg of trastuzumab, was infused over a 30–90 minute timeframe requiring patients to attend an IV clinic to receive their dose every three weeks. The subcutaneous formulation – apart from clearly being much faster to administer – also raises the possibility of self-administration at home. It remains to be seen how effective these protective strategies will be when there are significant differences in the price of the two formulations.

Major Cost Benefits of Diagnostic Tests

Through the early identification and initiation of optimal tests, personalised medicine has the potential to lower the overall cost of healthcare dramatically. Indeed, the cost of diagnostic tests for most personalised medicines – under $1000 for the vast majority – is small when compared with the potential benefits.

Trastuzumab reduced the likelihood of cancer metastasis to other parts of the body by a remarkable 53% at three years, according to a 2005 study.[15] The test to detect whether a breast cancer patient has an overabundance of HER2 protein costs about $400. It is clear that identifying which patients should and should not be treated with trastuzumab can save tens of thousands of dollars, as well as avoiding unnecessary side-effects.

Commercial Considerations

Despite its initial indication within a niche, biomarker-defined subset of patients, trastuzumab achieved nearly $200 million in global sales during its first full year on the market, and exceeded $1 billion in annual global sales by 2006.[16] The approval of trastuzumab demonstrated that therapeutic products addressing niche sub-populations can achieve both regulatory and market success. Targeting an appropriate patient population is now commonplace. In 2014, 35% of all new products approved require the identification of candidate patients using a biomarker. More recently, with patents for trastuzumab nearing expiry, Genentech completed a 2012 launch of pertuzumab, a HER2 receptor antagonist that is administered in combination with, and to enhance the performance of, trastuzumab. Initial indications for pertuzumab are in metastatic breast cancer and early breast cancer.[17]

Although Genentech's overall trastuzumab franchise is projected to lose up to 45% of its worldwide sales with the introduction of biosimilars,[18] pertuzumab may help make up for the shortfall. According to Evaluate Ltd.'s Annual Sales Report for Roche, Genentech's parent company, trastuzumab was launched on October 1, 1998 in the US, and has a US patent expiry of June 18, 2019. Worldwide sales, excluding Japan, China and Saudi Arabia, were $189 million in 1999 and $6.8 billion in 2015, and were projected to peak at just over $7 billion in 2016 and 2017, prior to declining to $4.2 billion by 2022.[19] According to another report by Evaluate Ltd., pertuzumab was launched in the US on June 8, 2012, and has a US patent expiry of June 1, 2025. Worldwide sales were $60 million in 2012 and were projected to dramatically increase through 2022 to almost $5 billion.[20]

Future Perspective

As discussed above, the patents on trastuzumab expired in Europe in July 2014 and are set to expire in the US in June 2019.[21,22] As a result, multiple companies are developing or have developed trastuzumab biosimilars. According to the Generics and Biosimilars Initiative (updated April 8, 2016), at least three trastuzumab biosimilars have been approved to date: Biocon/Mylan [India in 2013], Celltrion [Republic of Korea in 2014], and Biocad [Russia in 2016].[23] According to *Citeline* database there are 25 clinical trastuzumab biosimilar studies, out of which 11 Phase III studies are completed or closed.[24]

The use of trastuzumab is expected to continue after patent expiry, and possibly after pertuzumab patent expiration in June 2025 (per *Evaluate Pharma*). This is due to the product's demonstrated ability to increase survival in HER2-positive breast cancer patients, strong historical performance in the marketplace to date, and its recent approval as a neoadjuvant treatment in patients with early-stage HER2-positive breast cancer in conjunction with pertuzumab and docetaxel (US, EU, Australia, New Zealand, Israel, Mexico, Japan, Switzerland, and Canada). Further supporting the increased adoption of trastuzumab, whether in the form of the originator product or a biosimilar version, will be additional anticipated approvals of pertuzumab. Further demand for less expensive and better performing tests to identify patients who will benefit from the use of trastuzumab (including use with pertuzumab) is likely to evolve the companion diagnostic armamentarium.

Five years from now we can anticipate that trastuzumab in the EU and USA will share a market with several biosimilars, allowing patients to benefit from an interchangeable treatment option at reduced cost. The biosimilar treatment will be prescribed in combination with pertuzumab. We should expect a pipeline of biosimilars-in-development for pertuzumab as well. However, a new breakthrough therapy addressing covered indications – e.g.,

one that has an extraordinary effect on disease progression in HER2 positive patients in addition to demonstrating a statistically justifiable difference in overall survival – could diminish the market opportunity for the current generation of anti-HER2 therapies and undercut the impetus for associated biosimilar development. As such, the development of biosimilars will become increasingly competitive. The sponsor of the most competitive biosimilar product, in terms of price and availability, should invest time in clinical and regulatory intelligence research on the reference product, and should invest money in the development of the best quality product, manufactured with the most efficient process. Moreover, the authors foresee that a similar approach for precision medicine life extension may be taken for other biologics, for example, cetuximab (Erbitux®) or panitumumab (Vectibix®).

Conclusion

Trastuzumab was the first potential mAb oncology precision medicine to be approved by the FDA. As such, biosimilar trastuzumab development sets a precedent for biosimilar products of other precision medicines. Sponsors of trastuzumab biosimilars benefit from the availability of a biomarker that defines the patient population. There is also potential to prolong the life of the trastuzumab biosimilar as pertuzumab (as a combination product with trastuzumab) garners additional indications. In light of the latest approval of pertuzumab – in conjunction with trastuzumab in the neoadjuvant setting – it is possible that the FDA may allow the neo-adjuvant setting for biosimilar development.

Potential trastuzumab biosimilar drug development challenges include:

- Selecting and recruiting the right patient population,
- Competition for breast cancer patients in the clinical trial setting from other sponsors of trastuzumab biosimilars and novel biologics,
- Developing a trastuzumab biosimilar programme to satisfy both the EMA and FDA,
- Developing a trastuzumab biosimilar programme to satisfy non-ICH countries,
- The potential for additional clinical work to be needed for the trastuzumab biosimilar if planned to be used in conjunction with pertuzumab.

Acknowledgements

The authors would like to thank Drs Jeffrey Spaeder, Chief Medical and Scientific Officer, and Brad Smith, Vice President of Advisory Services, Daoying Hu, Associate Director, Global Feasibility and Jill Dawson, Consultant to the Corporate Communications team at QuintilesIMS for their insights and editorial comments.

REFERENCES

1. Siegel R, Ma J, Zou Z & Jemal A. Cancer Statistics, Cancer Journal for Clinicians, CA: A 1–22 (2014): http://onlinelibrary.wiley.com/doi/10.3322/caac.21208/pdf., visited on 30 Aug.2016.
2. Liu JKH. The history of monoclonal antibody development-Progress, remaining challenges and future innovations. Annalsof Medicine and Surgery 3, 113–116, (2014) http://www.ncbinlm.nih. gov/pubmed/25568796, visited on 30 Aug. 2016.
3. FDA Precision medicine: http://www.fda.gov/ScienceResearch/SpecialTopics/PrecisionMedicine/default.htm, visited on 5 Sep.2016.
4. Paving the Way for Personalized Medicine: FDA's Role www.fda.in a New Era of Medical Product Development, 2013: http://gov/in a New Era of Medical Product Development, 2013: http://downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf, visited on 30 Aug. 2016.
5. Aspinall MG & Hamermesh RG. Realizing the Promise of Personalized Medicine, Harvard Business Review, 11pp. (2007):https://hbr.org/2007/10/realizing-the-promise-ofpersonalized-medicine, visited on 30 Aug. 2016.
6. ssa AM. Personalized Medicine and the Practice of Medicine in the 21st Century. Mcgill J Med. 10, 1, 53–57, (2007): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2323540/, visited on 30 Aug.2016.
7. USPI Herceptin, Dated March 2016: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103792s5330lbl.pdf, visited on 5 Sep. 2016.
8. FDA press release, FDA approves Perjeta for type of late-stage breast cancer June 8, 2012: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm307549.htm, visited on 5 Sep. 2016.
9. USPI Perjeta dated March 2016: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125409s109lbl.pdf, visited on 5 Sep. 2016.
10. USPI Kadcyla dated April 2016: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125427s094lbledt.pdf, visited on 5 Sep. 2016.
11. ASCO, 2015: Development of PF-05280014, a potential biosimilar to trastuzumab http://meetinglibrary.asco.org/content/151942-156, visited on 30 Aug. 2016.
12. ASCO, 2016: Heritage: A phase III safety and efficacy trial of the proposed trastuzumab biosimilar Myl-1401O versus Herceptin. http://meetinglibrary.asco.org/content/162159-176, visited on 30 Aug. 2016.
13. ClinicalTrials.gov:https://clinicaltrials.gov/ct2/show/NCT02162667 , visited on 5 Sep. 2016.
14. Herceptin EMA changes since initial authorisation of pages/medicines/human/medicines/000278/human_med_000818jsp&mid=WC0b01ac05-8001d124, visited on 5 Sep. 2016.
15. Carlson RH. Trastuzumab: a major breakthrough for the treatment of breast cancer. Oncology Times UK. 2, 8, 9–10 (2005) ASCO Annual Meeting: http://journals.lww.com/oncotimesuk/Fulltext/2005/08000/Trastuzumab__a_major_breakthrough_for_the.6.aspx, visited on 30 Aug. 2016.
16. Genentech website:http://www.gene.com/about-us/investors/historical-product-sales/herceptin, visited on 15 Jul. 2016.
17. Genentech website:http://www.gene.com/download/pdf/perjeta_prescribing.pdf, visited on 15 Jul. 2016.
18. Deutsche Bank Markets Research, Pharmaceuticals Roche, November 2 2015.
19. Bank of America, Merrill Lynch: Roche Holdings. APHINITY deep dive: biggest pivot in next 12 months. Equity 04 August 2015.
20. Evaluate Ltd: Annual Sales Worldwide. Report date: July 11, 2016
21. http://www.medscape.com/viewarticle/817812, visited on 3 Aug.2016.
22. http://www.gabionline.net/Biosimilars/General/Biosimilarsoftrastuzumab, visited on 3 Aug. 2016.
23. http://adisinsight.springer.com/drugs/800014629, visited on 3Aug. 2016.
24. Citeline: https://citeline.com/, visited on 5 Sep. 2016.

Oxana Iliach
Ph.D., Senior Director, Regulatory Affairs, Biosimilars Center of Excellence, Research & Development Solutions, QuintilesIMS

Raymond A. Huml
MS, DVM, RAC, Vice President, Strategic Drug Development, and Head, Global Biosimilars Strategic Planning, Biosimilars Center of Excellence, Research & Development Solutions, QuintilesIMS

Winfred Shaw
MBA, Head, Precision Medicine Center of Excellence, Research & Development Solutions, QuintilesIMS

Nigel Rulewski
MD, Vice President, Global Strategic Drug Development and Head of QuintilesIMS' Biosimilars Center of Excellence, Research & Development Solutions, QuintilesIMS