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GlobalData
PharmaPoint

HER2-POSITIVE BREAST CANCER – GLOBAL DRUG FORECAST AND MARKET ANALYSIS TO 2023

Executive Summary

HER2-Positive Breast Cancer: Key Metrics in the Eight Major Pharmaceutical Markets, 2013–2023	
2013 Epidemiology	
Breast cancer incident cases	853,902
HER2-positive breast cancer incident cases	182,487
2013 Market Sales	
US	$2.41bn
5EU	$1.99bn
Japan	$126m
China	$425m
Total	**$4.95bn**
Late-Stage Pipeline Assessment	
Number of drugs in Phase III profiled	2
Most Promising Late-Stage Pipeline Drugs	**Peak-Year Sales**
Neratinib (Puma Biotechnology)	$90m
Key Events (2013–2023)	**Level of Impact**
Herceptin (trastuzumab) patent expiry in the 5EU in 2014	↓↓↓
Launch of biosimilar trastuzumab in the 5EU in 2015	↓↓↓
Approval of Perjeta (pertuzumab) in the adjuvant setting in 2017	↑↑
Launch of neratinib in the metastatic setting in 2018	↑↑
Launch of Kadcyla (ado-trastuzumab emtansine, T-DM1) in the adjuvant setting in 2019	↑↑
2023 Market Sales	
US	$7.95bn
5EU	$3.90bn
Japan	$239m
China	$613m
Total	**$12.70bn**

Source: GlobalData
5EU = France, Germany, Italy, Spain, and UK

The table above presents the key metrics for human epidermal growth factor receptor type 2 (HER2)-positive breast cancer in the eight major pharmaceutical markets (US, France, Germany, Italy, Spain, UK, Japan, and China) during the forecast period from 2013–2023.

HER2-Positive Breast Cancer Market to Increase by 2.5-Fold by 2023

In the 8MM in this report, GlobalData valued the HER2-positive breast cancer market at $4.95 billion in 2013, and expects the market to increase to $12.70 billion in 2023, at a Compound Annual Growth Rate (CAGR) of 9.88%. The US contributes almost half of the total market sales in both 2013 and 2023.

The top drivers of growth in the HER2-positive breast cancer market during the forecast period include:

- The rapid uptake of the premium-priced biologics, Perjeta and Kadcyla, in all settings of the disease, where their sales will increase at a CAGR of 30.2% and 35.1%, respectively, during the forecast period. By 2023, together, they will capture 75% of the total HER2-positive breast cancer market.
- The launch of Perjeta and Kadcyla in early disease in the neoadjuvant and adjuvant settings will have the greatest impact on the HER2-positive breast cancer therapeutics market, with both agents capturing 77% of the non-metastatic market by 2023.

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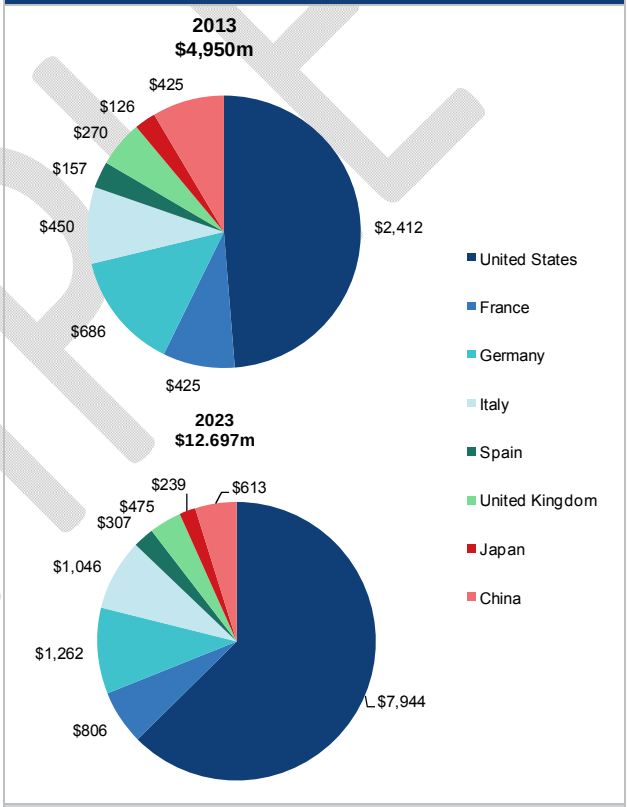
- Combinations of branded therapies in both the early-stage and metastatic settings will inflate the annual cost of therapy (ACOT). For instance, the ACOT for the combination of Perjeta with Herceptin is three times that for Herceptin alone in both adjuvant and metastatic settings in the US.
- A growing aging population and an increasing incidence of HER2-positive breast cancer cases across the 8MM. This is especially the case in urban China, where over the forecast period, the female population will increase faster than in any other market covered in this report, at a CAGR of 2.9%.

Major barriers to growth in the HER2-positive breast cancer market include:

- The patent expiry of Herceptin in the 5EU in 2014, and in the US in 2019, will negatively impact the market, as Herceptin sales will decrease at a CAGR of 4.7% by 2023.
- Tighter control of healthcare total expenditures in the 5EU will be a significant hurdle for the uptake of new premium-priced drugs, especially when they are used in combination. In the US, the Affordable Care Act (ACA) is creating a new cost-conscious environment that could impact the free-pricing system.
- Inconsistent healthcare coverage across China continues to be a barrier to growth in the HER2-positive breast cancer market. In addition, there is low participation in breast screening programs in China, and there are drug reimbursement issues as well.

The figure shown below provides the global sales for HER2-positive breast cancer during the forecast period.

Global Sales for HER2-Positive Breast Cancer by Region, 2013–2023



Source: GlobalData

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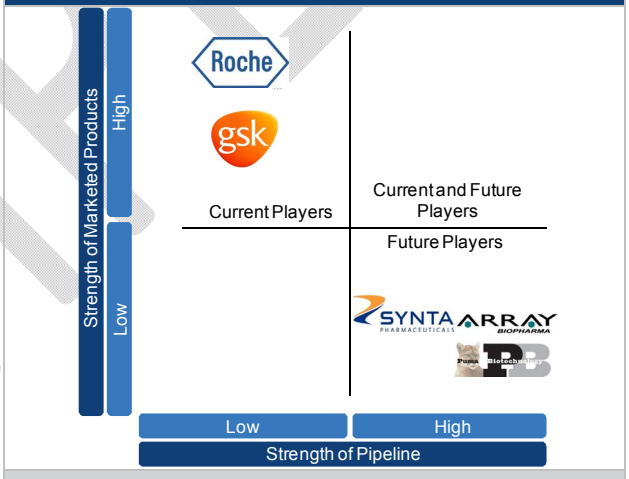
Roche Retains Its Monopoly in the HER2-Positive Breast Cancer Market

In 2013, Roche was the undeniable global leader in the HER2-positive breast cancer market, capturing 95% of the total HER2-targeted drug sales. This leadership was built on the success of Herceptin, which has been the standard of care in all settings of HER2-positive breast cancer since its launch in 1998. Herceptin alone accounted for 84% of the HER2-positive market in 2013. With a looming patent expiry for Herceptin, Roche recently launched two new anti-HER2 monoclonal antibodies (mAbs): Perjeta in 2012, and Kadcyla in 2013. Roche's mAbs have no real competition in the market, and as such, these new agents are forecast to see rapid uptake, thereby maintaining Roche's dominance of the market. By 2023, GlobalData expects that Roche's share of the HER2-positive breast cancer market will exceed $12 billion.

To enter this challenging market, competitors have been focusing on the development of tyrosine kinase inhibitors (TKIs). In 2007, GlaxoSmithKline (GSK) launched Tykerb (lapatinib), the first HER2-targeted TKI. Puma and Boehringer Ingelheim are currently investigating TKIs for breast cancer; however, the role for TKIs remains small, as Tykerb accounted for less than 5% of the HER2-positive market in 2013. Indeed, the role of TKIs in early disease appears very uncertain. GlobalData foresees that TKIs will only be used in later lines of therapy, after the use of Roche's mAbs. By the end of the forecast period in 2023, GlobalData anticipates that the HER2-positive TKI market will have decreased to $198m, from $212m in 2013. Ultimately, GlobalData believes that Roche's monopoly of this market will only be challenged by companies with innovative product portfolios, such as Novartis, and Pfizer.

The figure shown below provides an analysis of the company portfolio gap in HER2-positive breast cancer during the forecast period.

Company Portfolio Gap Analysis in HER2-Positive Breast Cancer, 2013–2023



Source: GlobalData

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Kadcyla Will Experience Strong Uptake Across the 8MM

Since launching for use in the second-line metastatic breast cancer setting in February 2013, Roche's Kadcyla has been rapidly adopted in the US. In 2013, Kadcyla captured 10% of the US market and 5% of the US, 5EU, and Japan. In comparison, only 7% of patients in these markets in which Perjeta was launched received Perjeta in combination with Herceptin in the first-line setting, despite Perjeta having been launched six months before Kadcyla. In fact, key opinion leaders (KOLs) and global prescribers interviewed by GlobalData praised the high efficacy and low side effect profile of Kadcyla, which is expected to result in its continued strong uptake across the 8MM. With expected approval in the first-line setting in 2017, and as an adjuvant therapy in 2019, GlobalData forecasts Kadcyla to become the leader in the HER2-positive market, capturing 38% of the total market by 2023.

Non-Metastatic Breast Cancer Represents the Largest Market for HER2-Targeting Agents

In 2013, the combined sales of anti-HER2 agents used in the neoadjuvant and adjuvant treatment of early-stage (non-metastatic) breast cancer represented 55% of the total market. The use of Herceptin is particularly strong in the adjuvant setting, where its sales contributed to 99% of the total adjuvant market, and 49% of total Herceptin sales, in 2013. During the forecast period, GlobalData expects the adjuvant and neoadjuvant settings to remain the largest markets, and forecasts their sales to reach $8.60 billion in 2023, representing 67% of the total HER2-positive market. This increase in market size will be driven primarily by the uptake of premium-priced therapies, such as Perjeta, which was the first drug to receive approval in the neoadjuvant setting in the US in 2013.

The dynamism of the adjuvant and neoadjuvant markets has prompted many companies to try to position their products in these settings, especially since the early lines of therapy for metastatic disease are considered to be inaccessible due to Roche's monopoly in this area. TKIs were of particular interest, since they offer greater convenience than mAbs, but the negative results for Tykerb in the adjuvant setting, which were released in early 2014, showed that TKIs may not be a good fit for this setting. Generally, TKIs have more side effects, with little efficacy benefit, compared with antibodies. Therefore, GlobalData believes that the adjuvant and neoadjuvant settings will remain an exclusive market for anti-HER2 mAbs, hence constituting the most lucrative opportunity for biosimilar developments. In 2023, GlobalData expects the biosimilar market for trastuzumab to be worth $962m in 8MM, with 65% of sales being in the neoadjuvant and adjuvant settings.

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Better Treatment for Brain Metastases Remains the Most Pressing Unmet Need

Although the efficacy of HER2-targeted therapies substantially improves the life expectancy of patients with HER2-positive disease, by nature, HER2-positive breast cancer is still a more aggressive form of the disease, with a poorer prognosis and worse outcomes than for patients with HER2-negative (and hormone receptor [HR]-positive) disease. Two unmet needs are of high importance to increase survival in HER2-positive disease:

- The effective treatment of central nervous system (CNS) metastases
- The treatment of disease that has become resistant to HER2-targeting therapies

HER2-targeting mAbs have failed to deliver benefits to patients with brain metastases, because they cannot pass the blood-brain barrier. TKIs, such as Tykerb or neratinib, may be effective here; however, resistance to kinase inhibitors is common, so innovative therapies to treat TKI-resistant HER2-positive disease will also be required. The agents in early-stage development that target phosphoinositide 3-kinase (PI3K), such as NVP-BYL719 and the cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor, palbociclib, have both been suggested for use in the treatment of anti-HER2-resistant breast cancer. With impressive results in the HER2-negative setting, as well as some evidence of blood-brain barrier penetration, these agents also have the possibility of addressing the unmet needs that plague the HER2-positive market.

Future Breast Cancer Therapies Will Unite the HER2-Positive and HER2- Negative Markets

The agents in the most advanced stages of development for HER2-positive breast cancer are the TKIs — namely, Boehringer Ingelheim's (BIs) Gilotrif (afatinib) and Puma's neratinib. However, recent study results show that TKIs may not demonstrate a great benefit over the existing therapies. GlobalData foresees that TKIs will be used in these scenarios: almost exclusively in later lines of therapy; after the failure of anti-HER2 therapies in the earlier stages of metastatic disease; or for patients with known brain metastases. Puma is positioning neratinib for use as a later line of therapy, and in this setting (second-line metastatic and beyond), GlobalData forecasts neratinib to generate $128m in sales by 2023.

A very limited number of agents are being developed specifically for HER2-positive breast cancer. For example, Array's ARRY-380 (ONT-380) is another TKI that is currently in Phase I/II for HER2-positive disease, while Galena is developing NeuVax (nelipepimut-S), a vaccine that is also being investigated in HER2-negative disease. In fact, GlobalData believes that the most promising agents for HER2-positive disease are being developed primarily for HER2-negative disease. In particular, KOLs have expressed interest in PI3K

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inhibitors, such as Novartis's BYL-719, as well as in CDK 4/6 inhibitors, such as Pfizer's palbociclib and Novartis's LEE011, in the treatment of HER2-positive disease. Other drugs in the early phases of development include Daiichi Sankyo's patritumab (U3-1287), which is an anti-HER3 mAb, and Syntha's ganetespib (STA-9090), which is a heat shock protein 90 (HSP90) inhibitor. However, the clinical relevance of these agents still remains to be established.

The HER2-positive market has become very mature since the launch of anti-HER2 antibodies. For agents to be successful, the strategy may not be to target HER2 specifically, but rather, to target a separate pathway that is applicable to both HER2-positive and -negative disease, thus unifying the breast cancer market.

"For HER2-negative disease, [there] is much easier uptake [of drugs], so that is why they went there [first]. But obviously, those kinds of drugs could be of high interest in HER2-positive disease, too."

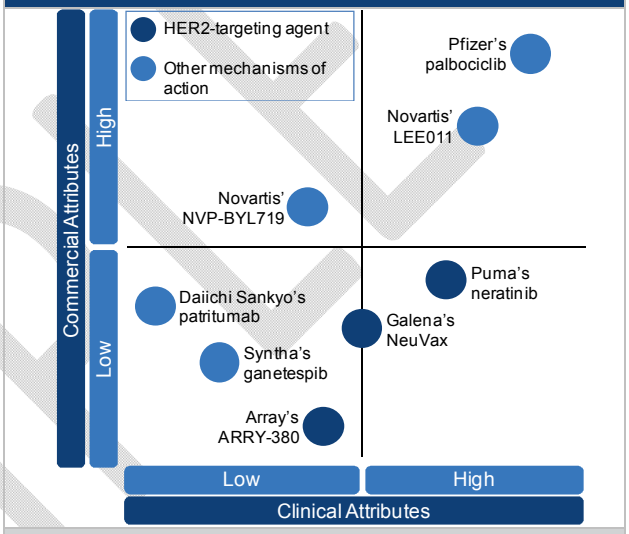
OUS Key Opinion Leader, April 2014

"…drugs like palbociclib will be very interesting in HER2-positive disease, and some of them do cross the blood-brain barrier, so…those might be interesting approaches."

US Key Opinion Leader, January 2014

The figure shown below provides a competitive assessment of the most promising agents for HER2-positive breast cancer during the forecast period.

Competitive Assessment of Most Promising Agents for HER2-Positive Breast Cancer, 2013–2023



Source: GlobalData

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What Do Physicians Think?

KOLs praised the efficacy of Kadcyla for metastatic disease, and are already anticipating its use in earlier settings.

"The effectiveness with the lack of toxicity is one of the big attractions of T-DM1 [Kadcyla]."

OUS Key Opinion Leader, April 2014

"I am a big believer in TDM-1. I did lots of those first trials with TDM-1, and I think it's a great drug. And so, we are very hopeful that it's going to have positive results in the different adjuvant trials that are underway."

US Key Opinion Leader, January 2014

"We are hopeful that HER2-positive disease will be essentially cured in the next decade, or shorter, by the new agents that we have, that all clearly showed a dramatic benefit in patients who had received prior trastuzumab in the case of Kadcyla, and in those who hadn't [been treated with prior trastuzumab] in the case of Perjeta. I mean, there was clearly an improved survival. So, that suggests that by adding those agents in some form in the early-stage setting, that we will cure more patients with HER2-positive disease."

US Key Opinion Leader, January 2014

"If [Kadcyla] turned out to be an active agent in the early-stage setting, that's where it will get used. I mean, ultimately, there is not going to be a desire to hold back on drugs — [that is,] to use better drugs later. We are going to want to use our best drugs up front. If T-DM1 is better, and we can use T-DM1 up front and have a better result in terms of efficacy, and have a lower toxicity, then that's what will be used."

US Key Opinion Leader, December 2013

KOLs still believe there is room for TKIs, especially after disease progression following the use of anti-HER2 mAbs. Neratinib, in particular, is a TKI under development that they are looking forward to using in the metastatic setting.

"What I tell people is, at some point, you should be using a lapatinib combination, either with Herceptin or with Xeloda [(capecitabine)], and then you should be using whatever other chemotherapies with Herceptin that you have still left — eribulin, navelbine, gemcitabine — and I don't think the order matters."

US Key Opinion Leader, January 2014

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"In my opinion, it [Tykerb] has always been a very promising drug, but the promise…has never been held in the clinic, probably because of scheduling, which doesn't allow the full potential of anti-tumor activity because you have to stop at a certain point because of unacceptable toxicity. The same is for neratinib or afatinib; probably playing with the schedule and ensuring optimal exposure of the tumor to optimal saturation of receptors may really reveal additional properties of these drugs in the treatment of trastuzumab-, or antibody-, in general, refractory HER2-positive tumors."

OUS Key Opinion Leader, April 2014

"[Neratinib is] such a potent oral tyrosine kinase inhibitor [that], maybe instead of pitching themselves against Herceptin, they could look at how they are going to work in patients who don't respond, or who have higher-risk disease, or afterwards, etcetera."

US Key Opinion Leader, January 2014

"[Neratinib is a] drug that has a very impressive anti-tumor activity, very impressive. I remember the Phase II study in patients [who were] never treated before with anti-tumor agents, that, as a single agent it, gave a 50% response rate, which is quite remarkable."

OUS Key Opinion Leader, April 2014

"The real difficulty is that the market has moved on so much from when the trials [for neratinib and Gilotrif] have been done, and one assumes these drugs are going to be expensive, with a lot of toxicity, and without a clear data set to support them, because everyone has moved on to giving totally different treatment. I think it's going to be much harder to get those in."

OUS Key Opinion Leader, April 2014

Effective therapies for the treatment of brain metastases remain the biggest unmet need, and KOLs are interested to see how cyclin-dependant kinase inhibitors, which are currently in development for HER2-negative disease, can deliver in this setting.

"…HER2-positive patients very frequently get brain metastases….Radiation is a good treatment, but it doesn't last forever, so progression in the brain after radiation is a real problem. We do not have any good treatments for that; that's an unmet medical need."

US Key Opinion Leader, January 2014

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"Another class of drugs which has activity in HER2-positive disease, but is being pursued in ER [estrogen-receptor]-positive disease, of course, are CDK 4/6 inhibitors, and those are quite interesting….They have the potential of crossing the blood-brain barrier, and are highly effective in ER-positive disease, and I'm hopeful [that we] are going to really change the course of patients who have ER-positive breast cancer."

US Key Opinion Leader, January 2014

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2 Introduction

2.1 Catalyst

HER2-positive breast cancer is the second most common cancer in the world and the most common cancer in women worldwide. When diagnosed at a very early stage, the prognosis is positive, with a five-year survival rate of nearly 100%. However, in the later stages of the disease, survival rapidly decreases. HER2-positive breast cancer is aggressive, and historically, has had a worse overall survival (OS) compared with HER2-negative disease, which is considered to be less aggressive. In 1998, the launch of the first HER2-targeted therapy, Herceptin (trastuzumab), revolutionized the treatment of the disease, bringing the OS close to that of HER2-negative breast cancer. The realization that introducing HER2-targeted therapies earlier into the disease management strategy could improve disease-free survival (DFS) has created a large market for HER2-directed therapies. Today, HER2-positive breast cancer patients are living longer with their disease, thanks to established disease management strategies using numerous combinations of chemotherapy with Herceptin and the tyrosine kinase inhibitor (TKI), Tykerb (lapatinib). During the forecast period from 2013–2023, GlobalData expects that the HER2-positive market will grow due to the aging populations in the US, 5EU, Japan, and China.

The realization that introducing HER2-targeted therapies earlier into the disease management strategy could improve disease-free survival (DFS) has created a large market for HER2-directed therapies.

Furthermore, with the new premium-priced agents, such as Perjeta (pertuzumab) and Kadcyla (ado-trastuzumab emtansine) becoming established in the early lines of metastatic disease, physicians will have additional treatment options for patients. More therapies will be used in the neoadjuvant and adjuvant settings, and several pipeline agents are also being investigated in the non-metastatic market in this disease. A number of these agents are looking to address the greatest unmet need for HER2-positive breast cancer patients — brain metastases — which typically occur in the later lines of metastatic therapy and are caused by increasingly resistant disease.

2.2 Related Reports

- GlobalData (2014). Non-Small Cell Lung Cancer (NSCLC) – Global Drug Forecast and Market Analysis to 2022 – Event-Driven Update, April 2014, GDHC002EPIDR
- GlobalData (2014). Pancreatic Cancer – Opportunity Analysis and Forecasts to 2017, March 2014, GDHC016POA

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- GlobalData (2013). Bladder Cancer – Opportunity Analysis and Forecasts to 2017, December 2013, GDHC014POA

2.3 Upcoming Related Reports

- GlobalData (Q3 2014). HER2-Negative Breast Cancer – Global Drug Forecast and Market Analysis to 2023
- GlobalData (Q3 2014). Renal Cell Carcinoma – Global Drug Forecast and Market Analysis to 2023

Appendix

11.8 About GlobalData

GlobalData is a leading global provider of business intelligence in the healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports, and forecasts. Our analysis is supported by a 24/7 client support and analyst team.

GlobalData has offices in New York, San Francisco, Boston, London, India, Korea, Japan, Singapore, and Australia.

11.9 Disclaimer