Table above presents the key metrics for colorectal cancer (CRC) in the eight major pharmaceutical markets (8MM) (US, France, Germany, Italy, Spain, UK, Japan, and China) during the forecast period from 2013–2023.

**Moderate Growth in the Colorectal Cancer Market Expected from 2013 Through 2023**

GlobalData estimates that the value of the CRC market in the US, 5EU (France, Germany, Italy, Spain, and the UK), Japan, and China in 2013 was $5.02 billion. This market is defined as sales of major branded drugs commonly prescribed for CRC patients across the 8MM. Just under half of these sales, $2.23 billion (45%), were generated in the US, with the 5EU representing the next largest region by sales, estimated at $1.71 billion (34%). Japan and China contributed the smallest proportion of sales to the global CRC market, with 2013 sales of $817m (16%) and $259m (5%), respectively.

By 2023, the end of the forecast period, GlobalData projects CRC sales to rise to $8.11 billion in the 8MM, at a moderate Compound Annual Growth Rate (CAGR) of 4.9%. In particular, GlobalData expects the Chinese CRC market to grow most rapidly, increasing to $1.05 billion (13% share) by 2023, at a robust CAGR of 15.1%. Sales in the other regions are expected to increase by the end of the forecast period, however, the proportion of sales from the US and Japan are forecast to decrease to 40% and 13%, respectively.
respectively, with market share in the 5EU remaining consistent at 34% by 2023.

Major drivers of the growth of the CRC market over the forecast period include:

- Populations are aging and CRC incident case rates are increasing in all the markets covered. Overall, across the 8MM, the incidence of CRC is expected to increase by an Annual Growth Rate (AGR) of 3.4% from 2013-2023. Growth in incidence is forecast to be most pronounced in urban China, where GlobalData expects there to be nearly 432,000 cases in 2023, rising from just over 253,000 in 2013 at an AGR of 7.0%. This increase, coupled with an anticipated increase in branded therapy prescription in China, will drive growth of the Chinese, and ultimately global, CRC market over the forecast period.

- The launch of premium-priced adjuvant/maintenance therapies will extend first-line treatment of metastatic CRC. GlobalData expects Bayer/Onyx’s Stivarga (regorafenib) to garner label extension as an adjuvant treatment for first-line patients after curative resection of liver metastases, and enjoy rapid uptake across the 8MM. Also, Mologen AG’s MGN1703 is expected to launch in the 5EU in 2019 as a maintenance therapy after completion of successful first-line treatment. Overall, this treatment will potentially extend the number of branded treatments provided to patients.

- The launch of premium-priced products for treatment of later-line CRC, including Eli Lilly’s Cyramza (ramucirumab) and Boehringer Ingelheim’s nintedanib, will layer on to or replace cheaper generic chemotherapy regimens. Overall, GlobalData expects the launch of four pipeline agents for second-line and beyond metastatic CRC through 2023. The launch of these agents will ensure that many patients will receive three to four lines of treatment with branded, premium-priced drugs by the end of the forecast period.

Major barriers to the growth of the CRC market will include:

- Lack of development of neoadjuvant/adjuvant pipeline agents for the treatment of resectable, high-risk CRC. The resectable, high-risk CRC setting has significant unmet needs, and represents a lucrative opportunity for developers of efficacious treatments that can improve cure rates for resected patients. With the lack of any new premium-priced agents in this setting, GlobalData expects the status quo of drug treatment to remain with the prescription of generic and relatively cheap neoadjuvant/adjuvant chemotherapy regimens throughout the forecast period.

- Patent expiration of Avastin (bevacizumab), the leading drug in the CRC market, is expected in 2019. GlobalData expects subsequent patient share erosion by biosimilars. In 2023, the end year of the
Executive Summary

In the forecast period, GlobalData forecasts bevacizumab biosimilars to garner approximately $500m in sales, representing 15% of total molecule revenues. With these expected to be priced at a discount to Avastin, GlobalData anticipates the uptake of these biosimilars to negatively impact the growth of the CRC market in the second half of the forecast period.

- Increasing cost-consciousness will limit premium pricing opportunities for pipeline agents in the CRC market. Healthcare austerity measures are being incorporated across the major markets, and drug companies will need to consider the changing reimbursement landscape when determining pricing strategies for their drugs. GlobalData expects that this era of austerity and healthcare reform will negatively affect pharmaceutical companies’ ability to gain reimbursement approval for their new CRC therapies.

The following figure illustrates the global sales for CRC by region during the forecast period.

![Sales for CRC by Region, 2013–2023](Image)
**Executive Summary**

**Roche’s Avastin to Remain the Leader of the Anti-Angiogenesis Space**

Roche’s anti-angiogenesis drug Avastin has been the best-selling brand in CRC for many years, and, after label extension in the second-line continuation setting, is set to remain the market leader across the forecast period. However, competition in this drug class is expected to become more intense, especially in the second-line metastatic setting, as Sanofi/Regeneron’s Zaltrap and Eli Lilly’s pipeline agent Cyramza (ramucirumab) garner uptake across the major markets. Though these latter two drugs have subtly different mechanisms of action to Avastin, interviewed KOLs effectively perceive them as “me-too” drugs. Therefore, these drugs are expected to struggle to overcome oncologists’ deep familiarity and comfort with using Avastin in CRC.

GlobalData expects the next surge of anti-angiogenesis drugs to be focused on the anti-Ang2 inhibitor class. This class is likely to be led by Roche’s dual anti-VEGF/Ang2 inhibiting antibody vanucizumab (RO5520985; RG7221). Roche is currently investigating vanucizumab head-to-head against Avastin in a randomized Phase II study. If this agent is successful in a large, pivotal study, GlobalData anticipates vanucizumab to become a key part of Roche’s strategy to overcome biosimilar erosion of Avastin towards the end of the forecast period. With Sanofi/Regeneron and AstraZeneca also possessing anti-Ang2 drugs in their early-stage pipelines, Roche will be eager to remain the leader of this new drug class and maintain its dominance of the CRC market.

The following figure presents the gap analysis for the forecast period of companies in the CRC space.

**High Unmet Need Remains for Neoadjuvant/Adjuvant Treatments to Improve Cure Rates in Early-Stage, Resectable CRC Patients**

Interviewed experts report high unmet need for novel, efficacious treatments that can improve the cure rates for high-risk stage II and III CRC patients. As no pipeline agents are focused on this setting, GlobalData expects these unmet needs to remain unfilled by the end of the forecast period.
GlobalData’s primary research confirms the status of chemotherapy regimens, such as FOLFOX, as the mainstays of treatment in the neoadjuvant/adjuvant setting for early-stage, high risk, resectable CRC patients. However, despite the established algorithms for the management of these patients, a significant proportion will recur or progress to metastatic disease. Unlike other large oncology indications, such as HER2+ breast cancer, to date no targeted treatments have successfully launched in this setting for CRC. After the high-profile, failed studies for Avastin and Erbitux in the adjuvant CRC setting, it is apparent that developers are continuing to approach this setting with wariness. Due to the high unmet need, GlobalData expects high commercial reward for the developer of an efficacious and well tolerated drug that can improve the cure rate and cater to this large population of patients.

Biomarker-Driven Strategies and Immune Checkpoint Inhibitors to Potentially Shape the Future CRC Market

Interviewed KOLs are enthusiastic about early-stage innovative approaches targeting metastatic CRC patients with BRAF and KRAS mutation-positive disease, and immune checkpoint inhibitors such as the anti-PD1/PDL1 drugs. With Big Pharma taking a leading role, GlobalData expects the targeted, biomarker-driven approach for the treatment of metastatic CRC to become a significant R&D strategy for developers during and beyond the forecast period. In the BRAF mutation-positive setting, a subset with poor prognosis and high unmet need, GlobalData anticipates Roche and GlaxoSmithKline/Novartis to lead the development of exciting, novel combinations of BRAF and MEK inhibitors alongside marketed epidermal growth factor receptor (EGFR) targeting inhibitors, such as Erbitux and Vectibix. Likewise, GSK/Novartis and AstraZeneca are investigating combinations of MEK, PI3K/AKT, and mTOR inhibitors for the treatment of KRAS mutation-positive disease, a segment with far fewer treatment options compared to the KRAS wild-type setting.

Furthermore, as the traditional immunotherapy-sensitive indications such as melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC) become saturated with development, GlobalData expects developers of anti-PD1 and PDL1 immunotherapies to focus on other indications with high incidence and commercial potential, such as CRC. In this regard, the four major players in the field — Bristol-Myers Squibb (BMS), Merck, Roche, and AstraZeneca — are all investigating their anti-PD1/PDL1 assets in early-stage clinical studies in CRC. If these innovative strategies begin to bear fruit, GlobalData anticipates further investment by Big Pharma in late-stage studies in CRC during the forecast period. As these immunotherapies hold the promise of long, durable responses for metastatic patients, they have the potential to ultimately
Executive Summary

revolutionize the CRC metastatic treatment paradigm.

**Label Extention of Stivarga and Launch of MGN1703 in the 5EU to Have a Significant Impact on the CRC Market**

GlobalData expects the approval of two treatments, Stivarga and MGN-1703, in the first-line metastatic CRC setting over the forecast period. Stivarga is forecast to garner label extension in 2019 across the 8MM as an adjuvant treatment for first-line patients after curative resection of liver metastases and neoadjuvant/adjuvant chemotherapy-containing drug treatment. GlobalData’s research finds that a substantial minority of first-line metastatic CRC patients have liver-only metastasis and therefore can be eligible for curative resection. Penetration of Stivarga in this setting is expected to drastically grow the market sales of Stivarga, from $220m in 2013 to $1.69 billion in 2023, a CAGR of 23%, and in the process driving the overall global CRC market. Likewise, GlobalData expects the launch of the immunotherapy MGN-1703 in the 5EU to drive growth of the overall market as this drug will be offered as a maintenance therapy after completion of successful first-line treatment, and therefore will potentially extend the number of branded treatments a patient is likely to be given. As a first-in-class drug, GlobalData expects MGN1703 to command a premium price in the CRC market, and forecasts MGN11703 peak-year sales of over $250m in 2023.

The following figure provides a competitive assessment of the most promising agents for CRC during the forecast period.

![Competitive Assessment of Late-Stage Pipeline Agents in CRC, 2013–2023](image)

**What Do the Physicians Think?**

Key Opinion Leaders (KOLs) do not expect results from the FIRE-3 study comparing Erbitux and Avastin in the first-line KRAS wild-type metastatic setting to have a major impact on prescribing behavior.
“I am not sure [the results from the FIRE-3 study] are going to make a huge difference. I think, in practice at least, in the US, for patients who are KRAS wild-type, the choice of Erbitux vs. Avastin has really been something that the physician has chosen on their own. I think there are some physicians who really like to use Erbitux, and use it up front, and other people who always prescribed Avastin and either don’t use Erbitux at all or really use it more at a later stage.”

US Key Opinion Leader

“Avastin is the standard of care for both KRAS wild-type and KRAS mutated patients. This is the perception right now for the US as a whole. There are pockets, perhaps, where people probably are moving to Erbitux plus FOLFIRI, but I would say majority is still Avastin frontline.”

US Key Opinion Leader

“The reason for using Avastin as a first-line treatment is due to the side-effect profile compared to Erbitux, rather than the efficacy. The side effect of most concern with Erbitux is the rash.”

US Key Opinion Leader

Interviewed KOLs expect Zaltrap and Cyramza (ramucirumab) to struggle to garner much uptake in the second-line metastatic setting.

“In second-line [setting] you have Avastin, Zaltrap, and now, [potentially,] ramucirumab. For ramucirumab, to be honest, I think it will come down to what the survival data looks like. If it’s only as good as or worse than the other two, then, being the third player to join the party, I don’t think it has much chance of becoming a standard of care…”

OUS Key Opinion Leader

“In my view there is no probable advantage [of Zaltrap] over Avastin continuation, and [in my experience] there seems to be more side effects with Zaltrap than Avastin, so I really don’t prefer to use Zaltrap at this time.”

US Key Opinion Leader

Interviewed experts reported high unmet need for targeted treatments for KRAS and BRAF mutation-positive CRC patients.

“Unmet needs in overall survival are greater for KRAS mutated patients. We need to have new drugs to try to increase overall survival in this population. [Overall], I think now we need to have a different strategy for KRAS and for BRAF patients. It’s important to have different strategy.”

OUS Key Opinion Leader
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“BRAF mutant-positive colorectal cancer patients are a subset with very poor prognosis; most patients really have a very rapid and progressive course and it is a pretty nasty disease. But, I think this is probably the area where in the area of targeted therapies we may see perhaps the most exciting developments in the next few years for colorectal cancer”

US Key Opinion Leader

Interviewed KOLs are excited about the potential of kinase inhibitor combinations, such as BRAF/MEK with EGFR inhibitors for BRAF mutation-positive disease, and the immune checkpoint inhibitors, such as the anti-PD1/PDL1 antibodies.

“The high level question is the comparison between the doublet BRAF/EGFR combinations to some of the potential triplet BRAF/MEK/EGFR or BRAF/PI3K/EGFR combinations. If they are tolerable, I really think that those triplets are going to be the better way to go. I am hopeful we could see some, potentially, really exciting advances in the ‘oncogene-addiction’ treatment category.”

US Key Opinion Leader

“The PD1 and PDL1 inhibitors are exciting, and so far, in CRC, they have only been tested in a very small number of patients. But I think there is enough there to warrant the [further] exploration of this space in colorectal cancer. It remains to be seen what happens, but I know there is a lot of excitement about that.”

US Key Opinion Leader
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2 Introduction

2.1 Catalyst

Colorectal cancer (CRC) is the second leading cause of mortality among cancer patients in the world and is the third most diagnosed cancer globally, and thus represents a huge burden on healthcare systems. Despite robust screening programs across most of the 8MM (US, France, Germany, Italy, Spain, UK, Japan, and China), a significant proportion (10-20%) of patients are diagnosed with stage IV metastatic disease and correspondingly poor prognoses, compared to resectable early-stage disease. In terms of targeted treatments, the metastatic CRC treatment landscape is mature, including the branded treatments Avastin (bevacizumab), Erbitux (cetuximab), and Vectibix (panitumumab), treatments that have extended the survival of metastatic patients compared to chemotherapy-only regimens. However, high unmet needs remain for the extension of survival of metastatic patients, and particularly those with KRAS mutation-positive disease, for whom the epidermal growth factor receptor (EGFR) inhibitors Erbitux and Vectibix are not recommended.

The CRC market is expected to grow due to the incorporation of five late-stage pipeline agents during the forecast period, including Mologen’s MGN1703, Eli Lilly’s Cyramza (ramucirumab), and Boehringer Ingelheim’s nintedanib. These pipeline agents will be utilized across different segments of the metastatic population, from the first-line maintenance setting (MGN1703) to the second- and later-line settings (Cyramza and nintedanib). Furthermore, GlobalData expects the label extension of Stivarga as a first-line adjuvant treatment for metastatic CRC patients with resected liver metastases. Stivarga is currently approved for the smaller third- or fourth-line, chemotherapy, and targeted-treatment refractive settings. Ultimately, however, GlobalData expects unmet needs to remain unfulfilled by these pipeline agents, and anticipates that novel, innovative approaches, such as those targeting BRAF mutation-positive disease and immune checkpoint inhibitors, will provide the best opportunity for substantial improvement in the prognosis of advanced CRC patients.
Introduction

2.2 Related Reports


2.3 Upcoming Related Reports

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

- GlobalData (2014). Malignant Melanoma – 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, Boston, London, India and Singapore.

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