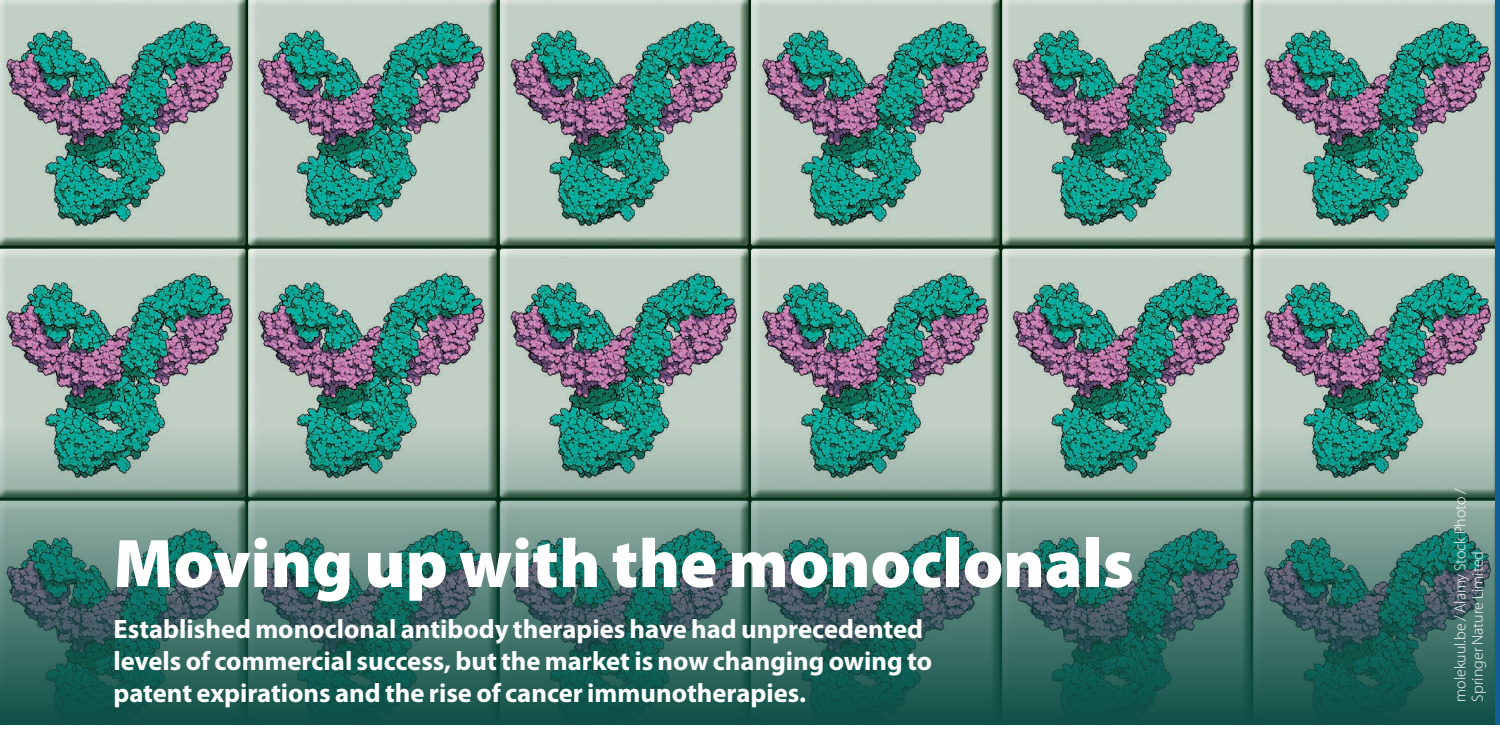

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Moving up with the monoclonals

Established monoclonal antibody therapies have had unprecedented levels of commercial success, but the market is now changing owing to patent expirations and the rise of cancer immunotherapies.

BioPharma Dealmakers

Monoclonal antibodies (mAbs) continue to dominate the pharmaceutical market. Last year, total global sales of mAbs were over $122 billion, and sales are expected to rise to more than $200 billion in 2024 (**Fig. 1**). Seven of the top ten best-selling drugs in 2018 were mAbs, with Humira (adalimumab)—AbbVie's multibillion blockbuster therapy for various immune disorders—in the top spot with sales of $20 billion (*Nat. Rev. Drug Discov.* **18**, 245; 2019). In this feature, we explore the current and forecasted mAb market with the help of Evaluate Ltd.

Core strengths

Since the pioneering mAb approval in 1986, mAbs have matured to become a core therapeutic modality, with more than 80 mAbs now approved for a wide range of diseases.

Two areas have historically seen particular success for therapeutic mAbs. One is oncology, for which total sales of mAbs were around $50 billion in 2018 (**Fig. 2**). Here, mAbs that target cancer cell signaling, such as Roche's human epidermal growth factor receptor 2 (HER2)-specific mAb Herceptin (trastuzumab) for breast cancer and its vascular endothelial growth factor-specific mAb Avastin (bevacizumab) for various cancers, have had many years of commercial success. Both products had sales of more than $5 billion in 2018 (**Fig. 3**). Two more recent entrants into the best-selling mAbs list are also oncology products: Merck and Co.'s Keytruda (pembrolizumab) and Bristol-Myers Squibb's Opvido (nivolumab), which both had sales greater than $5 billion in 2018 too. These mAbs inhibit the immune checkpoint programmed cell death 1, and have been at the forefront of the cancer immunotherapy revolution (see the feature on page B21-23).

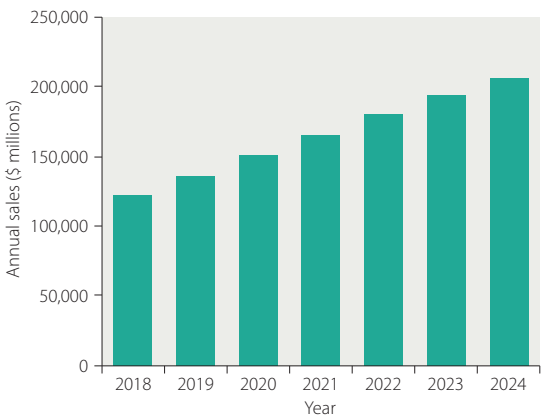

Fig. 1 | Growth in the global sales of monoclonal antibodies from 2018 to 2024. Source: EvaluatePharma, July 2019.

The other highly successful area for mAbs is products that target signaling by inflammatory cytokines such as tumor necrosis factor (TNF) to treat immune disorders. Humira is one of several TNF blockers that have achieved blockbuster status, based on approvals for multiple indications, including rheumatoid arthritis, psoriasis, Crohn's disease and ankylosing spondylitis. Remicade (infliximab), Johnson & Johnson's TNF blocker, is indicated for a similarly wide range of immune disorders, and was still in the top ten-selling mAbs in 2018 (**Fig. 3**) despite growing competition from biosimilar versions. Stelara (ustekinumab), another mAb marketed by Johnson and Johnson that is just ahead in the top ten, targets the interleukins IL-12 and IL-23 to treat diseases including Crohn's disease, psoriasis and psoriatic arthritis, while Novartis's Cosentyx (secukinumab), an IL-17 blocker that is approved for psoriasis, psoriatic arthritis and ankylosing spondylitis, also makes the list.

Evolution of the top ten

In 2018, AbbVie's Humira topped the top ten list of best-selling mAbs by a wide margin, outselling the second-placed Keytruda by more than $10 billion (**Fig. 3**). However, substantial changes to this list are forecasted by 2024, as more of the established products lose patent protection and biosimilar competitors enter the market (**Fig. 4**). For

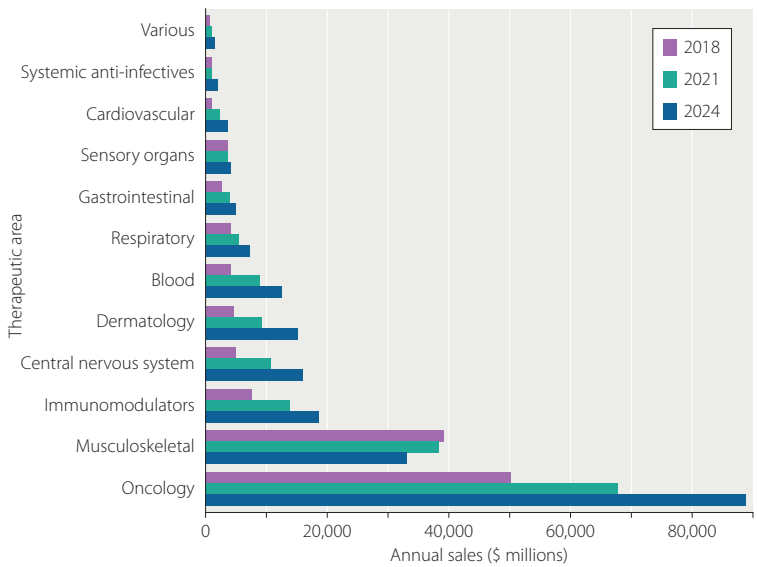

Fig. 2 | Trends in monoclonal antibody sales by therapy area. Source: EvaluatePharma, July 2019.

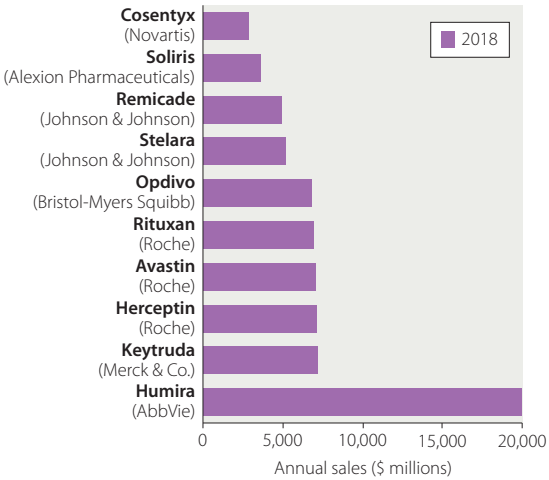

Fig. 3 | Top ten monoclonal antibodies by sales in 2018. Source: EvaluatePharma, July 2019.

Humira, such competitors are not expected until 2023, meaning that it is forecasted to be in second place in 2024. However, products with nearer-term or existing biosimilar competition, such as Remicade, Herceptin, Avastin and Rituxan (rituximab), are set to fall out of the top ten completely (**Fig. 4**).

Humira is forecasted to be replaced at the top of the list by Keytruda, with its sales of more than $15 billion in 2024 reflecting its position as a backbone of cancer immunotherapy strategies in multiple indications. Its competitor Opdivo is also in the top three, but the gap in sales compared with Keytruda is widening, reflecting the greater success of Keytruda in indications such as non-small-cell lung cancer.

New entrants into the top ten in 2024 include Ocrevus (ocrelizumab) developed by Roche (Genentech) for the treatment of multiple sclerosis. The CD20-targeted mAb, which is the first drug to be approved for both relapsing–remitting and primary progressive multiple sclerosis, has had one of the most successful launches ever, reaching blockbuster status only a year after its approval in 2017 (*Nat. Rev. Drug Discov.* **17**, 855; 2018). Roche also has another entrant, Perjeta (pertuzumab), a HER2-targeted mAb for the treatment of breast cancer. Sales from these two products could help the company compensate for the loss of revenue from its current leading mAbs Herceptin, Avastin and Rituxan due to biosimilar competition.

Two other new entrants that are forecast to enter the top 10 are for immuno-inflammatory disorders. Dupixent (dupilumab), developed by Regeneron and Sanofi, is an inhibitor of IL-4 and IL-13 that is approved for atopic dermatitis and asthma, while Takeda's Entyvio (vedolizumab), which targets the integrin α4β7, is approved for Crohn's disease and ulcerative colitis.

Completing the top ten, Johnson & Johnson's Darzalex (daratumumab) is a CD38-targeted mAb that is approved for multiple myeloma. Together with other leading anticancer mAbs, such as Keytruda, Opdivo and Perjeta, it will contribute to the expansion of the overall market for mAbs in oncology to $88 billion in 2024 (**Fig. 2**).

New approvals

In a record-breaking year for US Food and Drug Administration approvals, 2018 saw the approval of 11 mAbs (**Table 1**), representing almost 20% of the total of 57 newly approved drugs (*Nat. Rev. Drug Discov.* **15**, 85–89; 2019). Unusually, many of the new approvals occurred in areas outside of oncology. For example, Trogarzo (ibalizumab), developed by TaiMed Biologics and Theratechnologies, is a CD4-targeted mAb that is the first biologic to be approved for the treatment of HIV. Given the dominance of small-molecule combination therapies in this area though, it is not predicted to be a blockbuster.

The entry of multiple mAbs in the central nervous system area is expected to lead to greater commercial success. Amgen and Novartis were the first to gain approval for a mAb that blocks signaling by calcitonin gene-related peptide (CGRP) to treat migraine with the approval of Aimovig (erenumab), which targets the CGRP receptor.

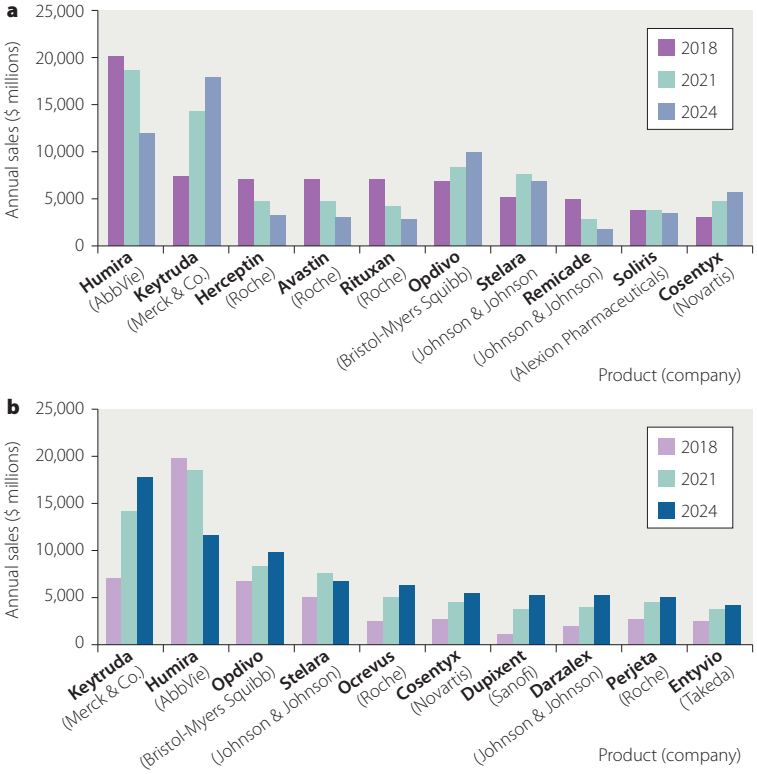

Fig. 4 | Changes in the top ten best-selling monoclonal antibodies. a, Sales of the top ten best-selling monoclonal antibodies in 2018, together with their forecasted sales for 2021 and 2024. **b**, Sales in 2018 of the antibodies that are forecasted to be in the top ten in 2024, ordered by their expected position in 2024. Source: EvaluatePharma, July 2019.

Shortly after, Eli Lilly and Teva had their competitor mAbs—Ajovy (fremanezumab) and Emgality (galcenzumab)—also approved for migraine. Both target CGRP, rather than the CGRP receptor. How differences between these products will play out in the market is not yet clear, but all three mAbs were forecasted at launch to be close to or beyond blockbuster status by 2024.

Finally, there were notable mAb approvals for rare diseases, such as Ultragenyx's Crysvita (burosumab), which targets fibroblast growth factor 23 to treat X-linked hypophosphatemia, and Alexion Pharmaceuticals' Ultomiris (ravulizumab), which targets complement C5 to treat paroxysmal nocturnal hemoglobinuria. Both are expected to become blockbusters.

Table 1 | FDA approvals of monoclonal antibodies in 2018

Drug (brand name)	Developer(s)	Indication
Ibalizumab (Trogarzo)	TaiMed Biologics and Theratechnologies	HIV
Tildrakizumab (Ilumya)	Sun Pharma	Plaque psoriasis
Burosumab (Crysvita)	Ultragenyx Pharmaceutical and Kyowa Hakko Kirin	X-linked hypophosphatemia
Erenumab (Aimovig)	Amgen and Novartis	Migraine
Mogamulizumab (Poteligeo)	Kyowa Hakko Kirin	Mycosis fungoides and Sezary syndrome
Moxetumomab pasudotox (Lumoxiti)	AstraZeneca	Hairy cell leukemia
Fremanezumab (Ajovy)	Teva	Migraine
Galcanezumab (Emgality)	Eli Lilly	Migraine
Cemiplimab (Libtayo)	Regeneron and Sanofi	Cutaneous squamous cell carcinoma
Emapalumab (Gamifant)	Novimmune	Primary hemophagyocytic lymphohistiocytosis
Ravulizumab (Ultomiris)	Alexion Pharmaceuticals	Paroxysmal nocturnal hemoglobinuria

FDA, US Food and Drug Administration.