FROM THE ANALYST'S COUCH

The market for chimeric antigen receptor T cell therapies

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2017 was a landmark year in oncology. The FDA approved the first two CD19-targeted chimeric antigen receptor (CAR) T cell therapies: tisagenlecleucel-T (Kymriah; Novartis) and axicabtagene ciloleucel (Yescarta; Kite Pharma/Gilead Sciences). These therapies have remarkable efficacy in some blood cancers and herald a paradigm shift in oncology treatment.

Pioneering CAR T cell therapies

CAR T cell therapies are produced by collecting a patient's T cells via leukapheresis, followed by an *ex vivo* process that includes T cell activation, transduction with a CAR-containing viral vector and expansion of the CAR-expressing T cells before patient infusion. CARs are composed of an antibody-derived fragment that recognizes tumour antigens coupled to costimulatory molecules that promote T cell expansion and persistence.

In August 2017, Kymriah received FDA approval for paediatric patients and young adults (up to age 25 years) with relapsed or refractory (R/R) B cell acute lymphoblastic leukaemia (ALL). Approval was granted less than 6 months after the FDA accepted the biologics license application under priority review, based on a single arm phase II (ELIANA) trial. Within 3 months of infusion, complete remission (CR) or CR with incomplete blood count recovery (CRi) occurred in 83% of patients. Kymriah is under regulatory review by the FDA for adults with R/R diffuse large B cell lymphoma (DLBCL), an aggressive subtype of non-Hodgkin lymphoma (NHL), and is under review in Europe for R/R B cell ALL and DLBCL. This drug is also being assessed in follicular lymphoma (FL), second-line DLBCL, chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM).

The second-to-market CAR T cell therapy, Yescarta, was granted FDA approval in October 2017, more than 1 month ahead of its target review date. This therapy is approved for adults with R/R B cell lymphoma, including DLBCL and other aggressive NHL subtypes, after at least two lines of systemic therapy, and is under review in Europe for this indication. FDA approval was based on a single arm phase II (ZUMA-1) trial. In an updated analysis, the overall response rate (ORR) was 82%, including a CR rate of 58%. Yescarta has shown promising early data in adults with R/R B cell ALL and is being evaluated in multiple pivotal trials for mantle cell lymphoma (MCL) and indolent NHL subtypes, including FL.

Both Kymriah and Yescarta are available through a restricted programme that includes a risk evaluation mitigation strategy to address the severe and life-threatening side effects of cytokine release syndrome (CRS) and neurotoxicity. The FDA also requires post-marketing studies to assess the long-term safety and risk of secondary malignancies.

The CAR T cell therapy pipeline

The pipeline is rapidly expanding and contains therapies designed to improve safety, target new antigens (including those on solid tumours) and be used off-the-shelf (Table 1).

Phase I (TRANSCEND) data for Juno Therapeutics' CD19-directed lisocabtagene maraleucel (JCAR017), its lead candidate, show promising efficacy (ORR of 74% and CR of 68% at 3 months; at 6 months ORR and CR were both 50%) and manageable side effects (grade 3 or higher CRS and neurotoxicity of 1% and 14%, respectively) in R/R DLBCL, making it a serious contender for Kymriah and Yescarta in this indication. Regulatory submission is expected in 2018. Juno's JCAR015 was discontinued in 2016 following five treatment-related deaths (due to cerebral oedema). Other companies are developing CD19-targeted CAR T cell therapies, including an off-the-shelf version from Cellectis/Pfizer (UCART19). ▸

Table 1 | **Select chimeric antigen receptor T cell therapies in phase I/II development**

Product	Developer (collaborator)	Target(s)	Indication(s)
JCAR017	Juno Therapeutics/Celgene	CD19	B cell NHL (DLBCL)
UCART19	Cellectis/Pfizer	CD19	B cell ALL
bb2121	Bluebird bio	BCMA	Multiple myeloma
LCAR-B38M	Nanjing Legend Biotech	BCMA	Multiple myeloma
KITE-585	Kite Pharma/Gilead Sciences	BCMA	Multiple myeloma
AUTO2	Autolus	BCMA and TACI	Multiple myeloma
MB-102	Mustang Bio	CD123	AML and BPDCN
UCART123	Cellectis	CD123	AML and BPDCN
CD33-targeted CAR	Ziopharm Oncology (Intrexon)	CD33	AML
BPX601	Bellicum Pharmaceuticals	PSCA	Pancreatic cancer
JCAR020	Juno Therapeutics	MUC16	Ovarian cancer
CAR-EGFR/EGFRvIII T	CARsgen Therapeutics	EGFRvIII	Glioblastoma
MB-101	Mustang Bio	IL-13Rα2	Glioblastoma
JCAR023	Juno Therapeutics	L1CAM	Neuroblastoma
CAR CLD18 T cells	CARsgen Therapeutics	Claudin-18.1	Gastric/pancreatic adenocarcinoma
AU105	Aurora Biopharma	HER2 and CMV	Glioblastoma

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BCMA, B cell maturation antigen; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; DLBCL, diffuse large B cell lymphoma; EGFRvIII, epidermal growth factor receptor variant III; HER2, human epidermal growth factor receptor 2; IL-13Rα2, interleukin-13 receptor α2; L1CAM, neural cell adhesion molecule L1, also known as CD171; MUC16, mucin 16; NHL, non-Hodgkin lymphoma; PSCA, prostate stem cell antigen; TACI, transmembrane activator and CAML interactor.

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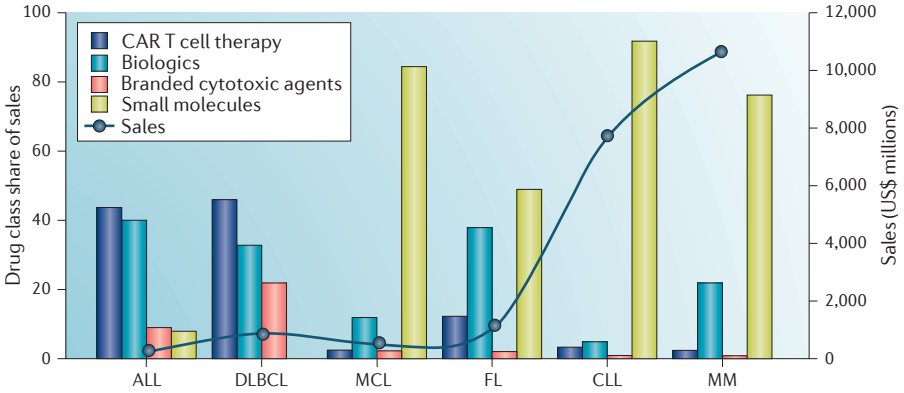

Figure 1 | **2026 sales forecast of branded therapies and market share for each drug class for relapsed or refractory haematologic malignancies.** The figure shows the forecast for the six major markets: United States, France, Germany, Italy, Spain and United Kingdom. Relapsed or refractory (R/R) acute lymphoblastic leukaemia (ALL) (paediatric and young adults), diffuse large B cell lymphoma (DLBCL) (adults), mantle cell lymphoma (MCL), follicular lymphoma (FL) and chronic lymphocytic leukaemia (CLL) include second-, third-line treatments; R/R multiple myeloma (MM) includes second-, third- and fourth-line treatments.

New targets in haematological cells. Utilizing B cell maturation antigen (BCMA), which is expressed on nearly all MM cells but not on normal cells (CD19 is present on both), is a promising future direction. The data set is small, but at 9 months, bb2121 (Bluebird bio/Celgene) has an impressive ORR (94%) and CR (56%) in heavily pretreated patients with R/R MM, with mild and manageable toxicity; LCAR-B38M (Nanjing Legend Biotech) has shown similarly high efficacy. A pivotal phase II trial for bb2121 is now under way. bb2121 was granted breakthrough therapy designation from the FDA and Priority Medicines (PRIME) eligibility from the European Medicines Agency (EMA) in November 2017. Gilead (KITE-585) and Autolus (AUTO2) are also testing BCMA-targeted CAR T cell therapies in MM.

CD123 is widely expressed in haematological malignancies, including acute myeloid leukaemia (AML). CD123-targeted MB-102 (Mustang Bio) and UCART123 (Cellectis) are being evaluated in phase I trials for R/R AML and blastic plasmacytoid dendritic cell neoplasm. Unlike other companies, Cellectis is developing allogeneic CAR T cell therapies using healthy donor T cells that are engineered to avoid graft-versus-host disease. Potential advantages of allogeneic, off-the-shelf products include improved availability, as well as manufacturing consistency, efficiency and cost effectiveness. Although the FDA placed a clinical hold on both UCART123 phase I trials following a patient fatality, the hold was lifted with revisions to the trial protocols, including a lower dose of UCART123. Cellectis is also developing allogeneic CAR T cell therapies targeting CD19, CD22, CD38 and CS1.

Improving safety with gene switches. Ziopharm Oncology is developing a CD33-targeted CAR T cell therapy in which expression of the CAR can be turned off by a small molecule; a phase I trial in R/R AML is ongoing. BPX-601 (Bellicum Pharmaceuticals) targets prostate stem cell antigen (PSCA) and is in phase I for PSCA-positive unresectable pancreatic cancer. This CAR is activated only upon binding to both PSCA and a small molecule. Bispecific AUTO2 (Autolus) targets BCMA and transmembrane activator and CAML interactor (TACI); its safety switch (RQR8) can be induced with rituximab (MabThera; Genentech) to trigger CAR T cell death.

Targets in solid tumours. Many developers are diversifying their pipelines with solid tumour targets (Table 1); a formidable challenge due to antigen heterogeneity, the presence of difficult-to-penetrate stroma and an immunosuppressive tumour microenvironment. In an attempt to boost the immune response in the tumour microenvironment, armoured mucin 16-targeted JCAR020 (Juno Therapeutics) incorporates interleukin-12 to stimulate T cells. Currently, little data support CAR T cell therapy use in solid tumours and the therapeutic potential remains unknown. Targeting more than one antigen (for example, AU105; Aurora BioPharma) or combining CAR T cell therapies with other drugs could unlock their potential in solid tumours.

Market indicators

The list prices for Kymriah (US$475,000) and Yescarta ($373,000) have raised the price ceiling for oncology therapies. In 2026, the market for branded therapies for haematological malignancies — R/R NHL (DLBCL, FL, MCL and CLL) and MM — is estimated to exceed $20 billion, with CAR T cell therapies commanding approximately $1.1 billion (Fig. 1). CAR T cell therapies are expected to capture the largest share of drug sales in paediatric and young adult patients with ALL (44%) or DLBCL (46%). Based on early data that suggested superior efficacy and safety of JCAR017 compared with Kymriah and Yescarta in DLBCL, JCAR017 is expected to see higher uptake in this market. JCAR017 is the sole CAR T cell therapy forecast in the CLL market. CAR T cell therapy sales in MCL and FL comprise Yescarta and Kymriah, respectively. Forecast sales for bb2121 in R/R MM are captured in the fourth line only and thus are expected to be small.

CAR T cell therapy is expected to see greatest uptake in heavily pretreated patients, therefore sales will be constrained by small eligible populations. We forecast up to three lines of treatment in ALL amd NHL subtypes and four lines in MM; additional sales may be realized in later lines. Safety concerns will also limit uptake, notably for Kymriah and Yescarta.

CAR T cell therapy development is still in its infancy and the commercial potential of this class, particularly for off-the-shelf therapies and those targeting solid tumours, is still shrouded with uncertainty.

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Competing interests
The authors declare no competing interests.

FURTHER INFORMATION
Axicabtagene ciloleucel (Yescarta) label:
https://www.fda.gov/downloads/UCM581226.pdf
Tisagenlecleucel-T (Kymriah) label:
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