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Supplementary information

The next-generation CAR-T therapy landscape

In the format provided by the authors

Database assembly

We assembled a consolidated clinical asset database representing 254 distinct CAR-T assets in phase I through phase III of global clinical development, owned by 154 distinct commercial or academic entities. To maximize landscape coverage, the consolidated CAR-T database was assembled via a combination of two independent datasets, both extracted in August 2023: the EvaluatePharma drug asset database and the AdisInsight Pharma drug asset database.

The initial EvaluatePharma database extract was filtered for "Biotechnology" in the "Technology Category" field, and "Gene-Modified Cell Therapy" in the "Technology" field, generating a list of 560 distinct drug assets. Further manual filtering was performed via the "Mechanism of Action" and "Pharmacological Class" fields, to filter for CAR-T cell therapies (that is, CAR-NK cell therapies, TCR cell therapies, and other non-CAR-T cell therapies were excluded from the set). This resulted in a distinct count of 352 CAR-T assets in phase I through phase III of global clinical development.

A similar process was performed with the AdisInsight database, where the initial extract was manually filtered for all CAR-T assets via the "Chemical/Biological Class" field. The AdisInsight database yielded a distinct count of 269 CAR-T assets in phase I through phase III of global clinical development.

Phase I through phase III asset names were then consolidated into a master database (621 assets in total) and prepared to undergo manual verification and classification into six platform type categories (described in Supplementary Table 1) and two cell source categories. Six distinct classifications of CAR-T platforms were evaluated, one of which ("Traditional") includes the cellular engineering build seen in today's six commercialized therapies, as well as the majority of pipeline assets.

Supplementary Table 1 | CAR-T platform types

Platform type	Definition	Example asset(s)	Owner(s)
Armoured	Co-expression of various proteins and ligands, or co-secretion of cytokines with the CAR to enhance CAR-T cell function	BNT 211	BioNTech
		LYL 797	Lyell
		NIB 102	Noile-Immune
Logic-gated	Boolean logic-based signaling to respond to multiple inputs to alter signaling or expression of CAR and/or proteins. Includes "OR", "NOT", and "AND" gates, but not dual targeting, which is categorized under multi-antigen targeting	CCT301 38	Exuma
		CCT301 59	Exuma
		CD19/CD20 Heme bispecific	ImmPACT
Multi-antigen targeting	Simultaneous engagement of multiple antigens for increased specificity	AU 101	Aurora
		bbT369	2seventy
		AUTO 8	Autolus
On/off switch	Ability to turn engagement with target cells "on" or "off" with various mechanisms	AIC 100	AffyImmune
		PRGN-3006	Precigen
		SynKIR 110	Verismo
Switchable	Engagement of multiple antigens using single CAR-T with adaptor moieties	CLBR 001	Calibr
		ACLX 001	Arcellx
		DARIC 33	2seventy
Traditional	Original model present in all currently approved CAR-T therapies. Consists of extracellular single-target CAR and an intracellular co-stimulatory domain	Kymriah	Novartis
		Yescarta	Gilead
		Carvykti	Janssen

CAR-T asset verification and classification

While the insights uncovered in this study relate primarily to the classification of CAR-T assets into their respective platform type and cell source categories, it was vital to the analysis to ensure that all 621 assets were manually verified to both remove any double-counts across databases and to ensure assets were still in the stage of development indicated by our two databases.

Verification and classification were performed in parallel on the consolidated database via use of company websites, ClinicalTrials.gov, press releases, and relevant company literature. For each of the 621 assets, we began the verification process by querying the pipeline section of the company website of each asset owner to confirm the asset's validity and its stage of development. Next, we performed classification by analyzing technical traits about the CAR-T asset and determining the type of platform and cell source used. In most cases, the necessary information to classify an asset was accessible on the company's website; however, in approximately 20% of cases, we also leveraged clinical trial disclosures, press releases, and published literature from the company to obtain sufficient information needed to make issue a classification.

After the consolidated database was verified and classified, 254 distinct assets remained out of the 621 initial assets. The difference is explained primarily by elimination of double-counted assets across the two databases, though there were assets which, upon manual revision, were also found either to no longer be associated with active clinical programs or to not be discoverable online (mainly pertaining to ex-US assets).

Supplementary Table 2 | Number of distinct CAR-T assets in the analysis, by platform type

	Phase I	Phase I/II	Phase II	Phase III	Total
Armoured	15	6	2	0	23
Armoured/on-off switch	3	0	0	0	3
Armoured/ multi-antigen targeting	1	0	0	0	1
Logic-gated	1	4	0	0	5
Multi-antigen targeting	16	15	3	0	33
On/off switch	2	0	0	0	2
Switchable	10	0	1	0	11
Traditional	113	36	33	2	176
Grand total	**156**	**60**	**37**	**2**	**254**

Most common platforms, excluding the traditional build, are armored and multi-antigen targeting, at 11% and 13% of clinical-stage assets, respectively. Traditional CAR-Ts make up 70% of clinical-stage assets.
Note: one traditional, autologous asset is counted twice in phase I and Phase II (different indications).

Supplementary Table 3 | Number of distinct CAR-T assets in the analysis, by cell source

Cell source	Phase I	Phase I/II	Phase II	Phase III	Total
Allogeneic	35	8	4	0	47
Autologous	121	52	33	2	207
Grand total	**156**	**60**	**37**	**2**	**254**

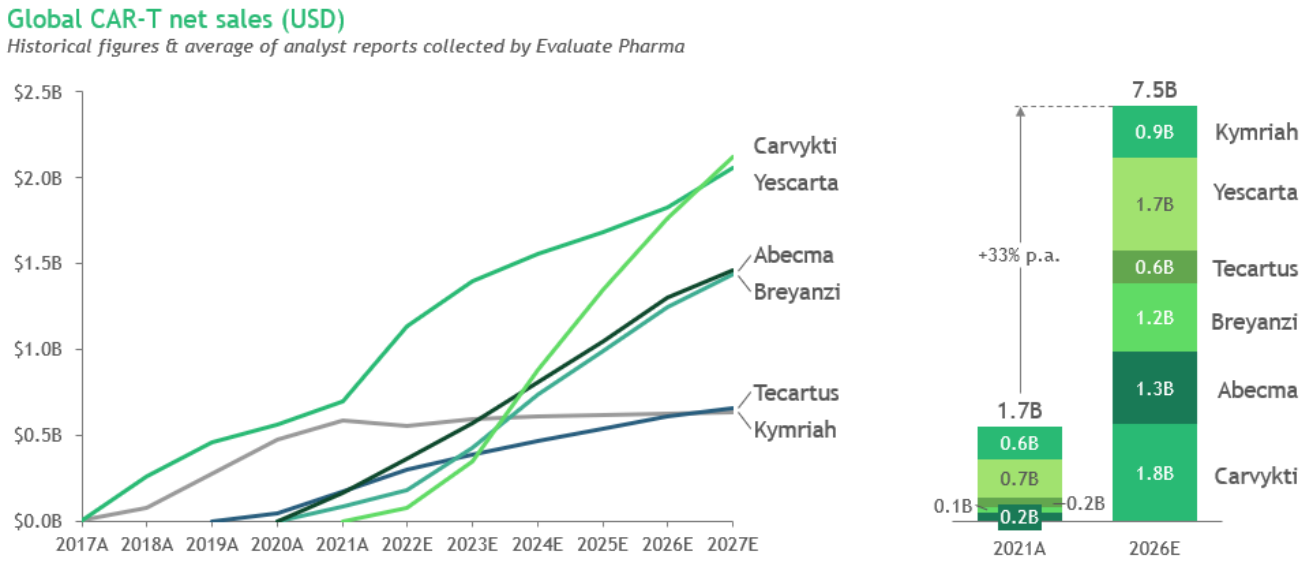
Regarding cell source, clinical-stage CAR-T assets are divided along a 81% and 19% line, in favour of autologous relative to allogeneic.

Note: in Figure 2, if an asset has more than one platform (for example, armoured and multi-antigen targeting), it was counted for each of the platforms.

Current state of CAR-T cell therapy landscape

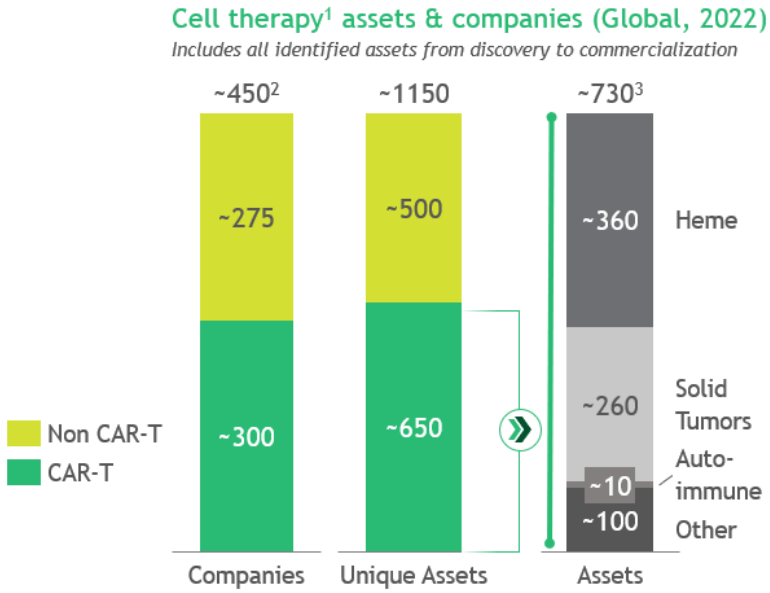
We analysed the net sales of the six US-commercialized CAR-T cell therapy assets, as well as the broader landscape of cell therapy companies and assets. Revenues for commercialized therapies were obtained from EvaluatePharma and triangulated against analyst reports SVB Leerink and BofA Research. Revenue forecasts were obtained from EvaluatePharma.

The first CAR-T cell therapy to be FDA-approved, the CD19-targeted therapy Kymriah (Novartis), was approved in 2017 for acute lymphoblastic leukaemia (ALL). Since then, several CD19-targeted CAR-T therapies have been developed — Yescarta (KITE), Tecartus (KITE) and Breyanzi (Bristol Myers Squibb) — as well as two CAR-T therapies targeting BCMA: Carvykti (J&J) and Abecma (Bristol Myers Squibb). Since the introduction of Kymriah in 2017, the CAR-T market has grown to $1.7 billion in 2021 and is expected to reach $7.5 billion in sales (~35% compound annual growth rate) as existing CD19-targeted and BCMA-targeted therapies penetrate earlier lines of relevant blood cancers. With analysts projecting the use of CAR-T therapies to increase by 10% by 2033, R&D effort has been focused on developing next-generation CAR-T therapies, largely within blood cancer indications, as well as a considerable number of assets that also target solid cancers (Supplementary Figure 1).



Supplementary Figure 1 | Commercialized CAR-T cell therapy landscape. The cumulative market for CAR-T cell therapies is expected to increase to $7.5 billion in net sales, growing at a rate of roughly 33% per annum. By year-end 2022, Kymriah and Yescarta (anti-CD19), the first two approved CAR-T therapies, have the highest net sales run rates for treatment of B-cell lymphomas. By 2027, Carvykti (anti-BCMA and indicated for multiple myeloma) is expected to overtake competing therapies as the highest-selling CAR-T therapy.

Our cell therapy landscape view was informed by EvaluatePharma and includes all identified assets, from discovery to commercialization. We expect this current view to significantly under-count assets in discovery, on account of the lack of public data availability for this low-maturity segment of assets.



Supplementary Figure 2 | Overall cell therapy landscape. Roughly two thirds of cell therapy companies are in the CAR-T space, with CAR-T assets encompassing just over 50% of cell therapy assets. Within the CAR-T space, roughly half of assets seek to treat haematological malignancies, with another third aimed at treating solid tumours.

Supplementary Figure 3 | CAR-T commercial viability framework. The four key dimensions for evaluating the commercial potential of a CAR-T therapy include drug safety, reproducible efficacy against targeted indications, ease of administration and reduction of patient burden and logistical hurdles, and manufacturing efficiency, both in terms of time and labour intensity.