An evaluation of the reimbursement status of CAR-T cell therapies in the EU-4 and UK

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Background

Policymakers in the European Commission recognize cell and gene therapies as a revolutionary modality. Since 2018, six CAR-T cell therapies have obtained EU and UK marketing authorization. However, there is a need for new pricing and reimbursement (P&R) assessment frameworks, as upfront costs and one-time administration schedules create challenges in assessing efficacy, budget impact and cost-effectiveness of CGTs.[1]

Objectives

This research focused on the six CAR-Ts in blood cancer indications, to understand drivers behind HTA evaluations of the main clinical and economic packages and their impact on HTA and reimbursement status in EU-4 and England **(Table 1)**.

Table 1: Industry sponsored CAR-Ts with marketing registration approvals in the EU-4 and UK[2-7]

Brand name	Active substance	Indication(s)	EMA approval date*
KYMRIAH®	**Tisagenlecleucel**	Relapsed or refractory (r/r) acute lymphoblastic leukemia (ALL); r/r diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL)	Aug 2018
YESCARTA®	**Axicabtagene ciloleucel**	r/r Diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL); r/r diffuse primary mediastinal large B-cell lymphoma (PMBCL) and DLBCL; r/r FL	Aug 2018
TECARTUS®	**Brexucabtagene autoleucel**	r/r mantle cell lymphoma; r/r ALL	Dec 2020
Abecma®	**Idecabtagene vicleucel**	r/r multiple myeloma (MM)	Aug 2021
Breyanzi®	**Lisocabtagene maraleucel**	r/r DLBCL, PMBCL and follicular lymphoma grade 3B (FL3B)	Apr 2022
CARVYKTI®	**Ciltacabtagene autoleucel**	r/r MM	May 2022

Source: EMA Sources as of June 2023 *Approval date of first indication, where relevant

Methods

We conducted primary research with 12 payers / proxies with advanced therapy expertise from France, Germany, Spain, Italy and England. This was complemented with information about the main clinical and economic data packages for each submission, based on publicly available HTA reports and other official P&R documents.

Results – HTA landscape

As of June 2023, France had conducted HTA assessments for all six CAR-Ts; Germany had evaluated five; England, Italy and Spain had published evaluations for three **(Table 2)**.[8]

From these evaluations, negative reimbursement decision were seen in France and Spain. The most frequent criticism across all agencies was the use of single arm trials (SATs). The majority of surveyed payers agreed that the use of SATs is a barrier to a positive HTA evaluation.

Table 2: Reimbursement status and HTA pathway/rating of CAR-Ts (per indication where applicable) in the EU-4 and England[9-27]

	KYMRIAH®	YESCARTA®	TECARTUS®	Abecma®	Breyanzi®	CARVYKTI®
(G-BA benefit)	**Non-quantifiable**	**Non-quantifiable**	**Non-quantifiable**	**Non-quantifiable**	**Non-quantifiable**	Under evaluation
(ASMR rating)	**III/IV** **V**	**III** **V**	**III** **V**	**V**	✓	**V**
(HTA pathway)	**STA**	**STA**	**STA**	Under evaluation	Under evaluation	Evaluation suspended*
(HTA rating)	**Innovative**	**Innovative**	**Innovative**	Not yet evaluated	Not yet evaluated	Not yet evaluated
				Under evaluation	Not yet evaluated	Under evaluation

Source: EMA, FDA, country-specific HTA reports and other official sources, as of June 2023. *Manufacturer withdrew submission evidence

Legend: Reimbursed Not Reimbursed ✓ Approved paid early access

Key Insights

Surveyed French and Spanish payers strongly agreed on the difficulty of making P&R decisions based on SATs. For example, the HAS attributed an ASMR rating V (no improvement in actual benefit) for Abecma and Carvykti in multiple myeloma. As such, respective paid early access schemes also became invalid.

Similarly, clinical uncertainty about the long-term response of Tecartus for MCL, combined with a high budget impact, resulted in a negative reimbursement decision in Spain.

In the survey, English and Italian payers also agreed SATs were a key area of criticism from HTA bodies. However, manufacturers have aimed to address these by conducting follow-up clinical trials, submitting real-world evidence (RWE) and enrolling their products in the mandatory AIFA registry, with some success.

After a NICE re-evaluation under the single technology assessment (STA) pathway, Yescarta became the first CAR-T recommended for use for lymphoma in England. This decision was based on RWE collection via the Cancer Drugs Fund and follow-up trial data.

As the latest CAR-T evaluated in Italy, Tecartus secured an innovative status for MCL, funded via the Innovative Medicine Fund, and was added to the AIFA registry to resolve uncertainty about its long-term effects.

In Germany, SATs prevented CAR-Ts from securing a quantifiable additional benefit. However, as orphan drugs, their additional benefit was considered proven up to the annual sales threshold of €30 million (previously €50 million).

Surveyed German payers confirmed a previous G-BA statement that, despite their innovative status, CGTs require controlled comparative studies to achieve a higher benefit rating than 'non-quantifiable benefit'.

> Manufacturers should have comparative trials ready (for CGTs) with appropriate endpoints at the time of launch / HTA assessment
>
> **German payer**

Conclusions

There have been few adaptations to European HTA assessment frameworks to accommodate CAR-T specificities to date. As some CAR-Ts are now already reimbursed, payers expect HTA bodies to demand more strongly that manufacturers provide robust comparative data to achieve favourable P&R outcomes. However, in cases where this is not possible, or the data are not currently available, rigorously designed RWE studies (including use of registry data) and/or indirect comparisons could continue to bridge the evidence gap in certain jurisdictions.

References
1. EFPIA, "Shifting the paradigm for ATMPs", January 2022 **2.** EMA, EPAR Kymriah, August 2018 **3.** EMA, EPAR Yescarta, August 2018, **4.** EMA, EPAR Tecartus, December 2020 **5.** EMA, EPAR Abecma, August 2021 **6.** EMA, EPAR Breyanzi, April 2022 **7.** EMA, EPAR Carvykti, May 2022 **8.** Research Partnership, https://deep-dive.pharmaphorum.com/, August 2023 **9.** G-BA, Kymriah, September 2022 and September 2020 **10.** G-BA, Yescarta, May 2019 **11.** G-BA, Tecartus, August 2021 **12.** G-BA, Abecma, June 2022 **13.** G-BA, Breyanzi, April 2023 **14.** HAS, Kymriah, December 2022, April 2021 and February 2019 **15.** HAS, Yescarta, March 2023 and January 2023 **16.** HAS, Tecartus, March 2023 and May 2021 **17.** HAS, Abecma, January 2022 **18.** HAS, Carvykti, December 2022 **19.** NICE, Kymriah, November 2022, March 2019 and December 2018 **20.** NICE,Yescarta, February 2023 and June 2023 **21.** NICE, Tecartus, June 2023 and February 2021 **22.** AIFA, Kymriah, September 2021 **23.** AIFA, Yescarta, July 2021 **24.** AIFA, Tecartus, December 2022 **25.** AEMPS, Kymriah, February 2019 **26.** AEMPS, Yescarta, October 2019 **27.** AEMPS, Tecartus, June 2022

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