HTA218

Trends in reimbursement mechanisms used by CAR-T therapies in the EU4 and the UK (2018–2023)

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BACKGROUND

Health technology assessment (HTA) bodies face considerable challenges when evaluating advanced therapy medicinal products (ATMPs) due to clinical data limitations and the expected financial risk of high upfront costs. [1]

Alternative reimbursement mechanisms can alleviate these payer concerns. In particular, performance-based reimbursement (PBR) and coverage with evidence development (CED) have been commonly used in European HTAs (Table 1).

This study aims to understand recent trends in reimbursement mechanisms for ATMPs and analyse reimbursement outcomes following re-assessment. As chimeric antigen receptor T-cell (CAR-T) therapies are commonly reimbursed via PBRs and CEDs (and had the most publicly available data at the time of this study), HTA reports on these treatments were reviewed in the EU4 (France, Germany, Spain, Italy) and the UK over a 5-year period (2018–2023). [2]

Table 1. Reimbursement mechanisms used in EU-5 health technology assessments

Mechanism	Definition
PBR	Total amount reimbursed for a therapy is linked to clinical performance.
CED	Access to patients is granted during continued evidence development.
Normal entry	The therapy demonstrates sufficient clinical benefit and/or is cost-effective, leading to standard reimbursement (with or without a confidential discount).

Abbreviations: CED, coverage with evidence development; PBR, performance-based reimbursement.

METHODS

- We identified CAR-T therapies approved in key European markets (EU4 and the UK) by June 2023 using data from HTA reports and the European Medicine Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) websites. [3–9]
- We extracted information on original submission and reimbursement documents from relevant HTA agency or government websites, press releases and news articles from January 2018–June 2023. During data analysis, we sourced additional information on follicular lymphoma reimbursement in Spain (assessed in 2024). We extracted CAR-T re-assessment information up to September 2024.
- Where possible, we investigated access agreement terms used, such as payment structures used in PBRs, and endpoints to be collected by national registries within CED agreements. We also outlined changes to reimbursement approaches (including reimbursement mechanism, list price, clinical benefit rating) following re-assessment of each therapy.

RESULTS

Types of reimbursement mechanisms

- Reimbursement agreements were identified for six CAR-T therapies in the EU4 and the UK with decisions between 2018–2024 (Table 2).
- Three countries used a single reimbursement mechanism:
  - England and France used CEDs. Spain used PBRs.
  - In England, all CEDs were reimbursed via the Cancer Drugs Fund (CDF). In France, all CEDs were reimbursed via the early access scheme.
- Two countries used a mix of reimbursement mechanisms:
  - Italy used PBRs, CED and normal entry; Germany used PBRs and normal entry. Only these countries used the normal entry route for CAR-T access.

Table 2. Reimbursement mechanisms for CAR-T therapies used by HTA bodies in the EU-5[a]

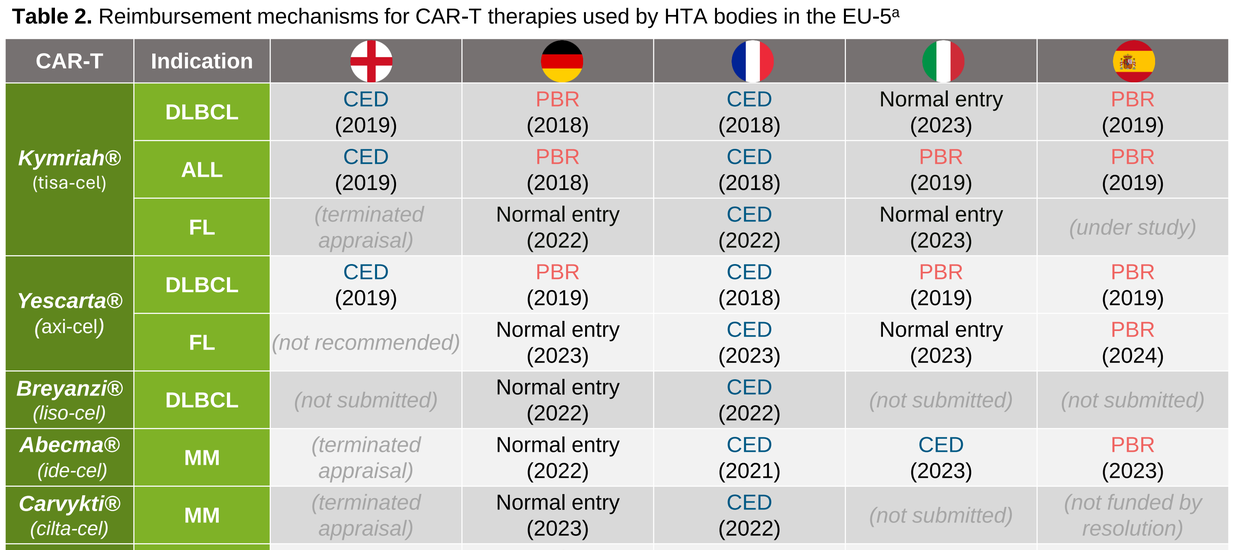
CAR-T	Indication	England	Germany	France	Italy	Spain
Kymriah® (tisa-cel)	DLBCL	CED (2019)	PBR (2018)	CED (2018)	Normal entry (2023)	PBR (2019)
	ALL	CED (2019)	PBR (2018)	CED (2018)	PBR (2019)	PBR (2019)
	FL	*(terminated appraisal)*	Normal entry (2022)	CED (2022)	Normal entry (2023)	*(under study)*
Yescarta® (axi-cel)	DLBCL	CED (2019)	PBR (2019)	CED (2018)	PBR (2019)	PBR (2019)
	FL	*(not recommended)*	Normal entry (2023)	CED (2023)	Normal entry (2023)	PBR (2024)
Breyanzi® *(liso-cel)*	DLBCL	*(not submitted)*	Normal entry (2022)	CED (2022)	*(not submitted)*	*(not submitted)*
Abecma® *(ide-cel)*	MM	*(terminated appraisal)*	Normal entry (2022)	CED (2021)	CED (2023)	PBR (2023)
Carvykti® *(cilta-cel)*	MM	*(terminated appraisal)*	Normal entry (2023)	CED (2022)	*(not submitted)*	*(not funded by resolution)*
Tecartus® *(brexu-cel)*	MCL	CED (2023)	Normal entry (2021)	CED (2021)	CED (2023)	PBR (2022)
	ALL	CED (2023)	PBR (2023)	CED (2023)	Normal entry (2023)	*(not recommended)*

Abbreviations: AEMPS, Spanish Agency of Medicines and Medical Products; AIFA, Italian Medicines Agency, ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell; CED, coverage with evidence development; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; G-BA, Federal Joint Committee; HAS, French National Authority for Health; MCL, mantle cell lymphoma; MM, multiple myeloma; NICE, National Institute of Health and Care Excellence; PBR, performance-based reimbursement.
Notes: [a] NICE (England); G-BA (Germany); HAS (France); AIFA (Italy); AEMPS (Spain)

Terms of agreement

- PBR and CED terms included staged payments, confidential rebates; clinical outcomes criteria included overall survival (OS) only, OS plus overall response rate (ORR), and OS plus additional outcomes (Figure 1). However, 38–70% of data on PBR and CED terms were unavailable.

Figure 1. Reimbursement structures and clinical outcomes measured in PBRs (A, B), and CEDs (C)



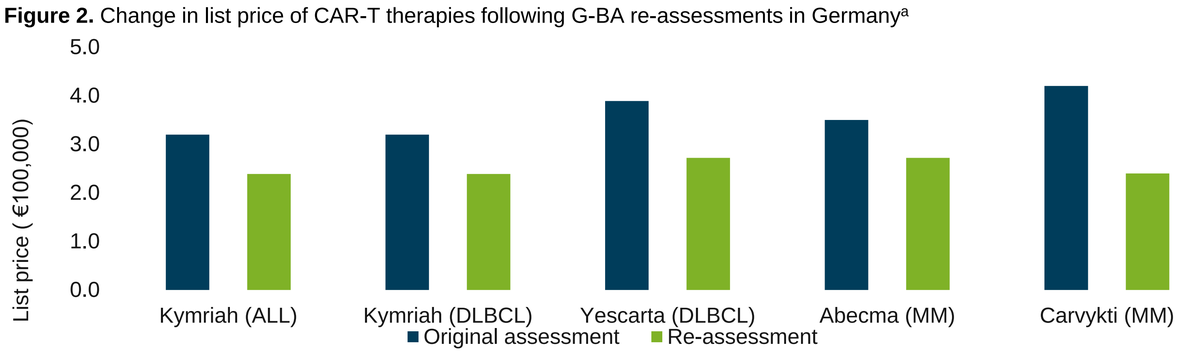
Abbreviations: CAR-T, chimeric antigen receptor T-cell; CED, coverage with evidence development; PBR, performance-based reimbursement; ORR, overall response rate; OS, overall survival.

Trends following re-assessment (France and Germany)

Trends following re-assessment were analysed for select countries only, where information about clinical benefit is rated (France and Germany) and information about pricing is publicly available (Germany only).

- List price (Germany):
  - All CAR-Ts were orphan drugs requiring a full benefit assessment after exceeding the annual revenue threshold. As no added benefit was proven, prices were set at the drug group reference price or capped at the level of their standard comparator, indicated by the list price reductions of 22–43% (Figure 2).

Figure 2. Change in list price of CAR-T therapies following G-BA re-assessments in Germany[a]



Abbreviations: ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell; DLBCL, diffuse large B cell lymphoma; G-BA, federal Joint Committee; MM, multiple myeloma PBR, performance-based reimbursement.
Notes: [a] Original G-BA assessment dates: Kymriah (ALL/DLBCL): 2019; Yescarta: 2019; Abecma: 2022; Carvykti: 2023. G-BA re-assessment dates: Kymriah (ALL/DLBCL): 2024; Yescarta: 2023; Abecma: 2024; Carvykti: 2024

- Clinical benefit (France and Germany):
  - Changes to clinical benefit rating occurred in around 30% of CAR-Ts re-assessed (Table 3):
    - The additional benefit of Yescarta and Abecma were downgraded in Germany, both from *non-quantifiable* to *not proven*.
    - The Amélioration du service médical rendu (ASMR) of Abecma was upgraded in France, from V to IV.
- Reimbursement mechanism (France and Germany):
  - Following re-assessment in France, all CAR-Ts received specialist funding via the liste-en-sus, whether their clinical benefit rating was downgraded or not.
  - Where this data were available, following re-assessment in Germany, all CAR-Ts were reimbursed via normal entry whether their clinical benefit rating was downgraded or not.
  - Carvykti in France was withdrawn from the early access scheme and public reimbursement due to an inadequate level of evidence submitted—specifically, the absence of randomised controlled trial data and reliance on an indirect treatment comparison. It is unclear why the HTA body did not consider the data collected via CED sufficient to compensate for limited trial evidence.

Table 3. Changes to clinical benefit rating and reimbursement mechanism following re-assessment in France and Germany[a]

		France				Germany			
CAR-T	Indication	Original assessment		Re-assessment		Original assessment		Re-assessment	
		ASMR	Mech.	ASMR	Mech.	Benefit rating	Mech.	Benefit rating	Mech.
Kymriah® (tisa-cel)	DLBCL	IV	CED	IV	Specialist funding	Non-quant	PBR	Non-quant	N/A
	ALL	III	CED	III	Specialist funding	Non-quant	PBR	Non-quant	N/A
	FL	V	CED	*Not yet re-assessed*		Hint of non-quant	Normal entry	*Not yet re-assessed*	
Yescarta® (axi-cel)	DLBCL	III	CED	III	Specialist funding	Not proven	PBR	Not proven	N/A
	FL	V	CED	*Not yet re-assessed*		Not proven	Normal entry	*Not yet re-assessed*	
Breyanzi® *(liso-cel)*	ALL	III	CED	*Not yet re-assessed*		Not proven	Normal entry	*Re-assessment ongoing* (exp. Dec 2024)	
Abecma® *(ide-cel)*	MM	V	CED	IV	Specialist funding	Non-quant	Normal entry	Not proven	N/A
Carvykti® *(cilta-cel)*	MM	V	CED	N/A	*Not reimbursed*	Non-quant	Normal entry	Not proven	Normal entry
Tecartus® *(brexu-cel)*	MCL	III	CED	*Not yet re-assessed*		Hint of non-quant	Normal entry	*Not yet re-assessed*	
	ALL	V	CED	*Not yet re-assessed*		Hint of non-quant	PBR	*Not yet re-assessed*	

Abbreviations: ALL, acute lymphoblastic leukaemia; ASMR, Amélioration du service médical rendu; CAR-T, chimeric antigen receptor T-cell; CED, coverage with evidence development; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; Mech, mechanism; MM, multiple myeloma; non-quant, non-quantifiable; PBR, performance-based reimbursement.
Notes: [a] Changes to reimbursement mechanism or clinical benefit rating are highlighted in yellow.

CONCLUSIONS

- Our results demonstrate that there was considerable variation in the type of reimbursement mechanism used for CAR-T access across the EU4 and the UK, likely explained by different evidence requirements and acceptability of clinical endpoints across markets.
- The trends observed reflect the markets' established processes for the assessment of ATMPs: England's CDF and France's DESCAR-T registry permits ongoing data collection via CED. Notably, Italy is an early adopter of alternative reimbursement mechanisms, which may explain the mix of PBRs and CEDs in CAR-T reimbursements. [10]
- Though most clinical benefit ratings remained constant following re-assessment, a minority of CAR-Ts underwent positive or negative rating changes, highlighting the risk and reward of using alternative reimbursement mechanisms.
- Significant gaps remain in publicly available data on reimbursement terms. Greater transparency is needed to support manufacturers in pre-empting terms to satisfy payers and enable better planning for data collection (e.g. earlier registry set-up).

REFERENCES

1. Jørgensen, J., & Kefalas, P. (2021). Regenerative Medicine, 16(4), 405–422. https://doi.org/10.2217/rme-2020-0169
2. EMA (2024) https://www.ema.europa.eu/en/documents/committee-report/
3. European Medicines Agency. European public assessment reports. Available from: https://www.ema.europa.eu/en/medicines/
4. Medicines and Healthcare products Regulatory Agency. Products. Available from: https://products.mhra.gov.uk/substance/
5. National Institute for Health and Care Excellence. Guidance, NICE advice and quality standards. Available from: https://www.nice.org.uk/guidance/
6. Gemeinsamer Bundesausschuss. Beschlüsse des Gemeinsamen Bundesausschusses. Available from: https://www.g-ba.de/beschluesse/.
7. Haute Autorité de Santé. Publications. Available from: https://www.has sante.fr/
8. AIFA. Negotiation and reimbursement. Available from: https://www.aifa.gov.it/
9. AEMPS. Available from: https://www.aemps.gob.es/
10. Jørgensen J, Kefalas P. J Mark Access Health Policy. 2015 Sep 30;3. doi: 10.3402/jmahplglesias-López, Carolina et al. Value in Health, Volume 26, Issue 6, 841 - 853.v3.29321. PMID: 27123175; PMCID: PMC4802687.

ABBREVIATIONS

AEMPS, Spanish Agency of Medicines and Medical Products; AIFA, Italian Medicines Agency; ALL, acute lymphoblastic leukaemia; ASMR, Amélioration du Service Médical Rendu; ATMP, Advanced Therapy Medicinal Product; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; CED, coverage with evidence development; DLBCL, diffuse large B cell lymphoma; EMA, European Medicines Agency; EU-5, France, Germany, Italy, Spain and the United Kingdom; FL, follicular lymphoma; G-BA, Federal Joint Committee; HAS, French National Authority for Health; HTA, Health Technology Assessment; MCL, mantle cell lymphoma; Mech, mechanism; MHRA, Medicines and Healthcare products Regulatory Agency; MM, multiple myeloma; N/A, not available; NICE, National Institute for Health and Care Excellence; Non-quant, non-quantifiable; PBR, performance-based reimbursement

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