Reimbursement of CAR-T cell therapies in Europe: Key challenges from precedents and lessons for the future

Putnam Inizio Advisory

M Kowalska[1], A Koćwin[1], J Żyrek[1], M Dimassi[2], E Hanna[3], C Rémuzat[3], C François[3,4]
[1]Putnam, Cracow, Poland; [2]Putnam, Tunis, Tunisia; [3]Putnam, Paris, France; [4]Aix-Marseille University, Marseille, France

Acceptance code 132523

Background and objective

CAR-Ts are genetically modified T-cells targeting cancer antigens. These therapies have revolutionised haematologic cancer treatment by demonstrating outstanding potential for curing disseminated and aggressive haematologic malignancies (1). Since the approval of the first CAR-T cell therapy in 2018, HTABs have been facing uncertainties related to efficacy and safety of these innovative therapies in addition to affordability challenges. This study aimed to identify the key challenges faced by CAR-Ts at HTA level and provide key learnings for future CAR-Ts in France, Germany, England, and Scotland.

Methods

A comprehensive review of available CAR-Ts HTA reports (cut-off, 30 May 2023) from HTA websites (HAS, G-BA, NICE, and SMC) was performed. HTABs' comments on study designs, submitted evidence, and evidence prerequisites were thoroughly examined to identify critical factors that influence HTA decision-making.

Results

- Thirty-two HTA reports for 6 CAR-Ts [Yescarta™ (axi-cel), Kymriah™ (tisa-cel), Breyanzi™ (liso-cel), Tecartus™ (brexu-cel), Abecma™ (ide-cel), and Carvykti™ (cilta-cel)] for treatment of B-cell malignancies were identified. HAS had the highest number of available reports (13 reports, including 3 reassessments) (Table 1)
- Five of the 6 CAR-T therapies have OD status; the sixth CAR-T therapy (Breyanzi™) lost its OD status in 2022 upon the manufacturer's request
- Ninety-four percent of recommendations were positive, including 7% positive decisions with a restriction of indication; 78% involved an MAA
- Overall, only 2 negative recommendations were issued: a negative recommendation by SMC for Kymriah™ due to inappropriate economic evaluation; and a negative recommendation by G-BA for Breyanzi™ for the lack of comparison with an appropriate comparator therapy, resulting in no proven added benefit

Table 1. Characteristics of CAR-Ts pivotal trials and HTA decisions

Drug	Indication	OD	MA in EU	HAS		G-BA		NICE		SMC		Pivotal study	Design	Initial median follow-up, months	Primary endpoint	Efficacy outcomes on primary endpoint, ITT population % (n/N)
Yescarta™ (axi-cel)	DLBCL, PMBCL, tFL 3L+	Yes	2018	**2018**[a] **SMR:** Important **ASMR:** III	**2021**[a,b,c] **SMR:** Important **ASMR:** III	**2019**[b] **AB:** non-quantifiable 3-year decision	**2022**[c] **AB:** non-quantifiable	**2019** MAA, under CDF, EoL	**2023**[c] MAA, EoL	**2019** PAS, EoL, ultra-orphan criteria		ZUMA-1	SAT	8.7	Overall response rate	77 (85/111)
	DLBCL, HGBL 2L+	Yes	2022	**2023**[b] **SMR:** Important **ASMR:** III		-		*Ongoing*		-		ZUMA-7	**RCT**	24.9	Event-free survival	8.3 mo vs 2 mo, Δ=6.3 mo, **HR=0.40**
	FL 4L	Yes	2022	**2023**[b] **SMR:** Important **ASMR:** V		-		-		-		ZUMA-5	SAT	18.2	Overall response rate	94 (74/79)[d]
Kymriah™ (tisa-cel)	DLBCL 3L+	Yes	2018	**2018**[a] **SMR**: Important **ASMR:** IV	**2021**[a,b,c] **SMR:** Important **ASMR:** IV	**2019**[b] **AB:** non-quantifiable	**2020**[c] **AB:** non-quantifiable	**2019** MAA, under CDF		**2/2019** Not recommended	**8/2019**[c] PAS, EoL, ultra-orphan criteria	JULIET	SAT	13.9	Overall response rate	33.9 (56/165)
	ALL 2L+	Yes	2018	**2018**[a] **SMR:** Important **ASMR:** III	**2021**[a,b,c] **SMR:** Important **ASMR:** III	**2020**[b] **AB:** non-quantifiable		**2018** MAA, under CDF		**2019** PAS, EoL, ultra-orphan criteria		ELIANA	SAT	24.1	Overall remission rate	67 (65/97)
	FL 3L+	Yes	2022	**2022** **SMR:** Important **ASMR:** V		**2022**[b] **AB:** non-quantifiable		*Terminated on the request of the company*		-		ELARA	SAT	28.9	Complete response rate	68.1 (64/94)
Breyanzi™ (liso-cel)	DLBCL, PMBCL, FL3B 3L+	No	2022	-		**2023**[b] **AB:** not proven		-		-		TRANSCEND-NHL-001	SAT	19.9	Overall response rate	*No data*
												TRANSCEND WORLD	SAT	11.6	Overall response rate	*No data*
Tecartus™ (brexu-cel)	MCL 3L	Yes	2020	**2021**[b] **SMR:** Important **ASMR:** III		**2021** **AB:** non-quantifiable		-		**2021** OD, EoL, PAS		ZUMA-2	SAT	*No data*	Overall response rate	85 (63/74)
	ALL 2L	Yes	2022	**2023**[b] **SMR:** Important **ASMR:** V		**2023** **AB:** non-quantifiable		-		*TBC*		ZUMA-3	SAT	16.4	Overall remission rate	54.9 (39/71)
Abecma™ (ide-cel)	MM 4L	Yes	2021	**2021**[b] **SMR:** Important **ASMR:** V		**2022** **AB:** non-quantifiable		*TBC*		-		KarMMa	SAT	11.3	Overall response rate	67 (94/140)
Carvykti™ (cilta-cel)	MM 4L	Yes	2022	**2022**[b] **SMR:** Important **ASMR:** V		*TBC*		*Terminated*		-		CARTITUDE-1	SAT	12.4	Overall response rate	83 (94/113)

[a]Annual data submission
[b]Time-limited decision
[c]Re-evaluation report
[d]Data on inferential population defined as all patients who received axi-cel and who had a minimum duration of follow-up

Colour coding:
Positive decision: HAS: SMR, major to mild; ASMR, major (I) to non-existent (V); G-BA: AB, major to non-quantifiable
Positive decision with restrictions on indication
Negative decision: HAS: SMR: insufficient; G-BA: no AB

1 Single-arm trial as major limitation

SATs were considered a major limitation by all HTABs and associated with a high degree of uncertainty. However, they were accepted in the context of life-threatening disease with high unmet needs. The uncertainties mainly resulted from the impossibility of quantifying the treatment's relative efficacy or safety and the potential risk of bias. In France, lack of comparative evidence did not lead to a downgrade of clinical value of a CAR-T (SMR: important; ASMR: moderate).

In Germany, because all products except Breyanzi were ODs, they were granted an AB (non-quantifiable) through the OD pathway; ODs' AB is proven in the MA process.

In England or Scotland applying an MAA, including a coverage with evidence development agreement, was sufficient for HTABs.

2 Low-credibility indirect treatment comparison

ITCs, using historical cohorts or other CAR-Ts, were submitted as supporting evidence for all SATs. All HTABs reported that ITC limitations caused uncertainties in the actual effect size (31 of 31 reports). HAS and G-BA rejected most ITCs because of substantial discrepancies in input data, absence of a bridge comparator, post-hoc ITCs, and the confounding factors leading to confusion bias. Although NICE and SMC adopted ITC results, their use impacted the certainty, and raised concerns about the credibility, of economic analyses.

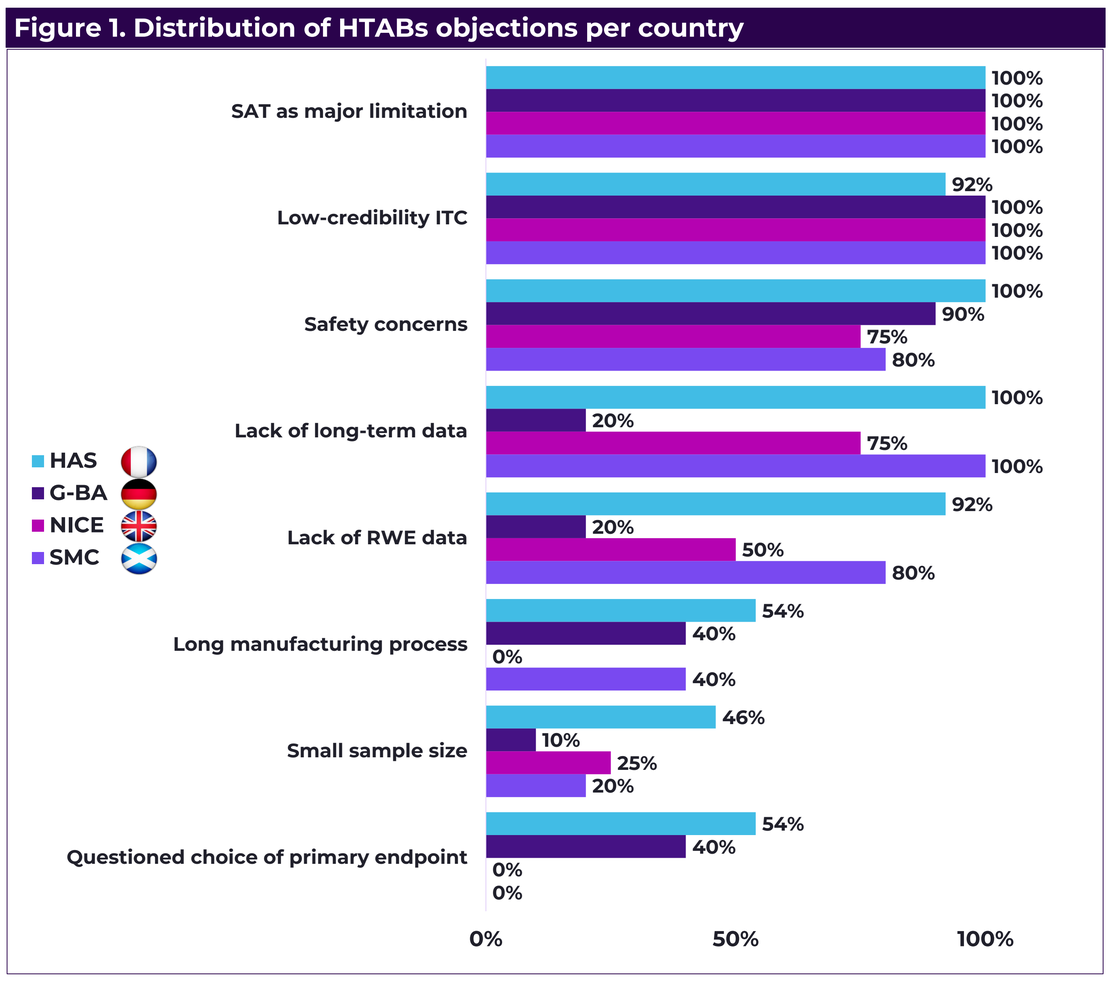
3 Safety concerns

The safety profile of CAR-T therapies was questioned in almost all assessments (90%; 29 of 32 reports). Key adverse events identified across all products included neurotoxicity, cytokine release syndrome, and other notable risks such as cytopenia and infections.

4 Lack of long-term data

Median follow-up periods ranging from 8.7 to 28.9 months were deemed insufficient for assessing response maintenance and long-term safety of CAR-T therapies. Long-term outcomes supported by registry data were crucial in all reports in France, Scotland, and England.

Figure 1. Distribution of HTABs objections per country



5 Lack of real-world evidence data

More than half of the reports (63%; 20 of 32 reports) noted the importance of RWE or included requests to establish a registry for CAR-Ts to document use in clinical practice. This was especially common in HAS (92%; 12 of 13) and SMC (80%; 4 of 5) reports.

6 Long manufacturing process

The manufacturing process duration—defined as the time from leukapheresis to drug infusion—ranged from 13 to 54 days across studies. The long manufacturing process was highlighted by all HTABs except NICE [54% of reports in France (7 of 13), 40% of reports in Germany (4 of 10) and 40% in Scotland (2 of 5)]. It led to selection bias; because of long waiting periods, not all patients were eligible for CAR-T treatment.

7 Small sample size

Sample sizes ranging from 71 to 111 patients were considered small in SATs and constituted a source of high uncertainty, particularly for HAS (33%; 4 of 12 reports). Small sample sizes were less frequently reported as a potential objection in NICE (25%; 1 of 4 reports) and SMC (20%; 1 of 5) reports.

Inadequate sample size led to uncertainty in subgroup analyses, especially in France and Germany.

8 Questioned choice of primary endpoint

The choice of primary endpoint was only criticised by HAS (54%; 7 of 13 reports) and G-BA (40%; 4 of 10).

Objective response rate was not deemed clinically relevant by HAS, and G-BA rejected it from the benefit assessment on the grounds that it was not patient-relevant.

The criticism of objective response rate primarily stems from its inclusion of partial responses along with complete responses; HTABs tend to view complete responses as more relevant.

Conclusions

- Despite the uncertainty related to the clinical data available at time of launch, CAR-T therapies have successfully reached the European onco-haematology market in the last 5 years through restrictions of indication and/or time-limited and outcome-based reassessment decisions
- The CAR-T landscape is rapidly evolving, with increasing experience and competition in the development of new-generation CAR-Ts (new targets, allogeneic CAR-Ts, and indication expansion). Hence, HTABs may strengthen their requirements, particularly under the joint clinical assessment planned for cell and gene therapies starting from 2025. This joint clinical assessment will be crucial for patient access. However, concerns have been raised regarding the proposed methodologies' ability to accurately reflect the unique characteristics of advanced therapy medicinal products and fully capture their benefits; studies lack long-term durability, lack an appropriate comparator, and are small in size (2,3)
- Manufacturers must emphasise the curative potential of CAR-Ts and deliver high-quality clinical data to demonstrate their long-term benefits. It is crucial for manufacturers to closely monitor changes in EU regulations and policies because they could have substantial implications for the future of CAR-Ts

Abbreviations: 2-3-4L (+), second-third-fourth line (and further); 3B, grade 3B disease; AB, added benefit; ASMR, Amélioration du Service Médical Rendu; ALL, acute lymphocytic leukaemia; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; DLBCL, diffuse large B-cell lymphoma; EoL, end-of-life criteria; EU, European Union; FL, follicular lymphoma; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HGBL, high-grade B-cell lymphoma; HR, hazard ratio; HTA, health technology assessment; HTAB, health technology assessment body; ITC, indirect treatment comparison; ITT, intent-to-treat; MAA, managed access agreement; MA, marketing authorisation; MCL, mantle cell lymphoma; MM, multiple myeloma; NICE, National Institute for Health and Care Excellence; OD, orphan drug; PAS, Patient Access Scheme; PMBCL, primary mediastinal large B-cell lymphoma; RCT, randomised controlled trial; RWE, real-world evidence; SAT, single-arm trial; SMC, Scottish Medicines Consortium; SMR, Service Médical Rendu; TBC, to be confirmed; tFL, transformed follicular lymphoma.

References

1. Lu, Jiang. Mol Cancer. 2022;21(1):194
2. Commission Regulation 2021/2282, 2021 O.J. (L 458/1)
3. Alliance for Regenerative Medicine. https://alliancerm.org/wp-content/uploads/2023/06/20230608-V5_HTA-Advocacy.pdf

Contact
Clément François
Clement.Francois@putassoc.com

Find out more at putassoc.com