CAR-T cell therapy pathway: Evolution of management and costing methodology in the French CEA landscape

R Sellami[1], M Sivignon[2], O Doghri[1], R Supiot[1]
[1]Putnam, Paris, France; [2]Putnam, Lyon, France

Acceptance code EE127

Introduction

The number of CAR-T cell therapies entering the market is increasing. Practices to identify and collect relevant cost inputs are evolving accordingly in the regulatory landscape.

Objectives

The objectives of this analysis are to review relevant literature sources, enumerate CAR-T cell therapy steps, and gather approaches used to estimate cost inputs of CAR-T cell therapies related CEA in the French health economics landscape.

Methods

Available French opinions on CAR-T cell therapies in oncology and recent French publications on CAR-T cell pathway management were reviewed. They included 7 cost-effectiveness opinions [YESCARTA in DLBCL (1); KYMRIAH in DLBCL (2), ALL (3), and FL (4); TECARTUS in Mantel cell lymphoma (5); and ABECMA and CARVIKTY in multiple myeloma (6,7)], three full papers [Huguet et al. (8), recommendations of the Société francophone de greffe de moelle et de thérapie cellulaire (9), and Beignon (10)], and 2 posters by Di Blasi et al. (11,12).

In each publication, costing approaches were reviewed, and the costs considered were identified. Methods of costing were compared. When the French HTA body made specific cost-related requests, the requests were also identified. Recent relevant items published in economic official updates were identified. Identified approaches included a collective perspective for efficiency opinions released before 2020 and a healthcare system perspective for those released afterward.

Results

Seven efficiency opinions, three full papers, and two posters were reviewed. CAR-T cell therapy pathway steps associated with costs included CAR-T cell therapy eligibility, leukapheresis, bridging and lymphodepletive chemotherapies' administration, CAR-T cell therapy infusion, hospital stay and post-infusion follow-up, hospital discharge either to patient hotel or to rehabilitation centre, and management of AESCs. A summarised overview of the CAR-T cell therapy pathway with a brief description of each step and the corresponding costing approach and estimated costs is presented in Figure 1 below.

1 CAR-T cell therapy eligibility

How is it assessed?

There were **35** CAR-T qualified centres in France in April 2023, according to the patients' association Ensemble Lymphome Espoir [Figure 2 (13)]. The choice of CAR-T cell treatment is made by the referring centre in a multidisciplinary meeting, using a screening form provided by the patient's haematologist. This form includes medical history, disease details, and relevant test results. Eligibility is confirmed in a consultation with the haematologist, and a consent form is signed for each product by the patient after being informed about the treatment, the procedure, and the main adverse events. The patient is registered in DESCAR-T. The coordination nurse is the main contact person for the patient during the whole treatment process (9).

How is it included in CEA?

Cost of CAR-T eligibility assessment was **only** considered in the KYMRIAH efficiency opinion for FL. It was assessed based on experts' opinion, and the cost assigned was €298 in 2021 (4).

2 Leukapheresis

What is it?

Leukapheresis is a technique of separation and extraction of patient's leukocytes. Once collected, the T lymphocytes are extracted. It is then possible to manipulate different subtypes of T lymphocytes; CD8+ lymphocytes are most often used in current therapies. After separation, the cells are usually cryopreserved for future use (10).

How is it included in CEA?

The cost of leukapheresis was usually determined using DRG 28Z16Z [blood apheresis (1-7)]. The French HTA mentioned in its opinion on KYMRIAH in FL that the use of this DRG is acceptable because the new CAR-T cell specific codes for leukapheresis were not associated to tariffs (4). A RWE study was conducted in the efficiency opinion of CARVIKTY to generate costs. In general, one leukapheresis treatment was considered at each CAR-T cell therapy infusion (6), and the cost ranged from €1279 to €1973 (1,3) with a cost of €1940 estimated via a RWE study that included transportation costs (7).

3 Bridging chemotherapy (if any)

What is it?

Bridging therapy is a systemic therapy meant to maintain patient health at its best state during CAR-T therapy manufacturing and shipping, maximising the chance that the patient would remain eligible for treatment, if the patient's health requires it (10).

How is it included in CEA?

Inpatient and outpatient administration were costed using DRG 28Z07Z (chemotherapy for tumour, in sessions) and 17M06 (chemotherapy for other tumour), respectively (1,2,3,6,7). Assumptions were based on the proportion of patients receiving treatment in inpatient versus outpatient settings; administration cost ranged from €2885 to €8445 (2,3).

Prophylaxis using immunoglobulins was requested to be added either in the context of bridging chemotherapy or as long-term management of the risk of hypogammaglobulinaemia (1).

4 Lymphodepletive therapy

What is it ?

Lymphodepletive therapy is conducted for all patients before CAR-T infusion. It comprises fludarabine and cyclophosphamide, the doses of which vary according to the type of CAR T-cell and the pathology (10).

How is it included in CEA?

Cost of administration was considered as either included in or on top of CAR-T infusion. In the second case, it was estimated using the same DRGs selected to calculate the cost of administration of bridging therapy, implying assumptions on the administration setting (inpatient versus outpatient). Follow-up during lymphodepletive therapy was also included in the total cost of this phase. The associated cost was provided in only one source of those reviewed and was of €2121 (6).

5a CAR-T cell therapy infusion

How is it included in CEA ?

Until 2020, the cost of CAR-T administration was valued using the DRGs 27Z03 and 27Z02 [autologous haematopoietic stem cell transplants and allogeneic hematopoietic stem cell transplants (1-3)]. Since 2021, the approach has evolved, and the cost of administration is now valued using DRG 17M15 (lymphomas and other malignant lymphoid disorders), taking severity into account, and DRG 17M163 (chronic myeloid leukaemia, level 3) (5-8). Two other DRGs for valuing CAR-T administration costs were also mentioned: DRG 17M08 (acute leukaemia, age under 18) and 17M09 (acute leukaemia, age over 17) (8). A new act, FGLF671, specific to CAR-T infusion, was introduced in 2022 (14).

Complementary technical fee

A complementary technical fee of €15,000, which includes additional costs that may arise from CAR-T treatment, was introduced in 2021 and updated to €9940 in 2023 (15).

Figure 1. Summary of costing approaches and of estimated costs in CEA for CAR-T therapies in France

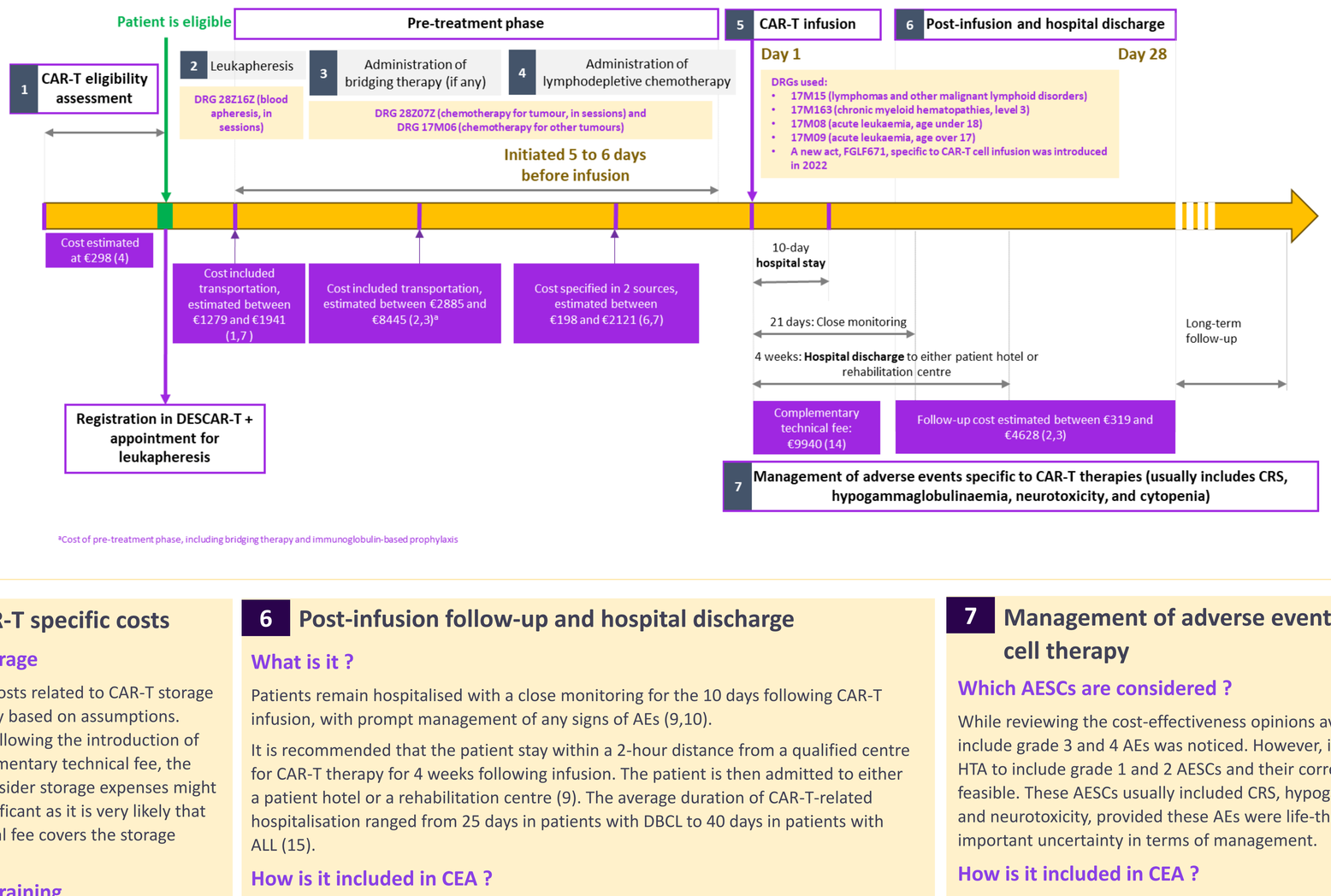
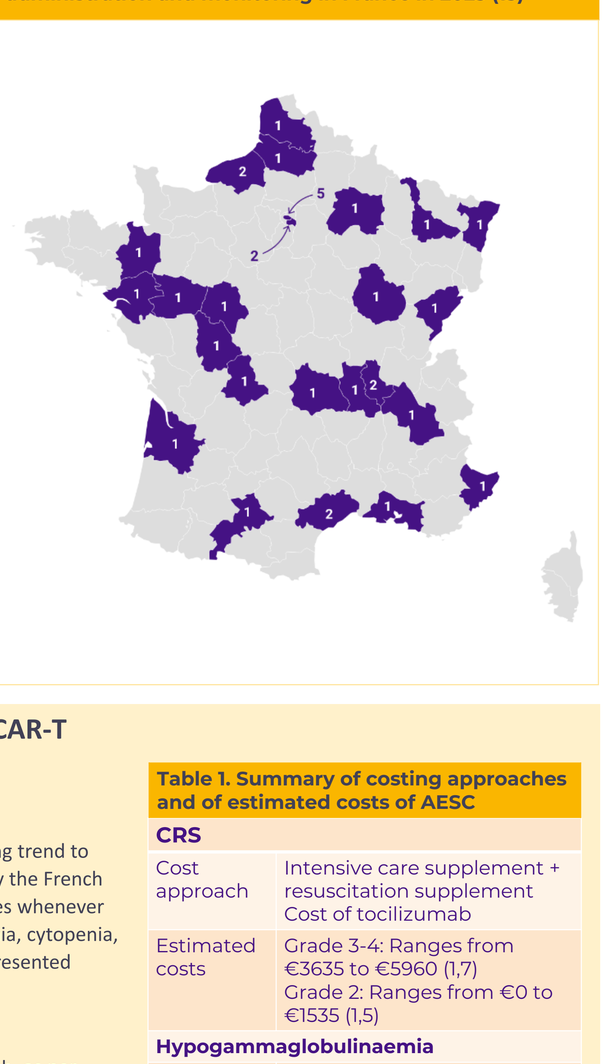


Figure 2. Distribution of qualified centres for CAR-T administration and monitoring in France in 2023 (13)



5b CAR-T specific costs

CAR-T storage

Estimated costs related to CAR-T storage were usually based on assumptions. However, following the introduction of the complementary technical fee, the need to consider storage expenses might be less significant as it is very likely that the technical fee covers the storage expenses.

Hospital training

The costs related to hospitals' training were dependent on the manufacturer, the centre itself, and the CAR-T therapy. Therefore, these costs were usually provided by the manufacturer as input data, based on internal studies.

6 Post-infusion follow-up and hospital discharge

What is it ?

Patients remain hospitalised with a close monitoring for the 10 days following CAR-T infusion, with prompt management of any signs of AEs (9,10).

It is recommended that the patient stay within a 2-hour distance from a qualified centre for CAR-T therapy for 4 weeks following infusion. The patient is then admitted to either a patient hotel or a rehabilitation centre (9). The average duration of CAR-T-related hospitalisation ranged from 25 days in patients with DBCL to 40 days in patients with ALL (15).

How is it included in CEA ?

The cost of the stay has been valued using either the cost documented in the 2015 agreement released by the Gustave Roussy Institute and referenced in the 2015 HAS report, which involves agreements with nearby commercial hotels (average of €85 per night from a collective perspective, and average of €80, updated in 2022), or by considering the average cost of a standard room in French hotels. This follow-up cost ranged between €319 and €4628 (3,4).

7 Management of adverse events specific to CAR-T cell therapy

Which AESCs are considered ?

While reviewing the cost-effectiveness opinions available, a prevailing trend to include grade 3 and 4 AEs was noticed. However, it was requested by the French HTA to include grade 1 and 2 AESCs and their corresponding expenses whenever feasible. These AESCs usually included CRS, hypogammaglobulinaemia, cytopenia, and neurotoxicity, provided these AEs were life-threatening and represented important uncertainty in terms of management.

How is it included in CEA ?

Costs of management of CRS mainly hinged on the cost of tocilizumab, as per recommendations. As for hypogammaglobulinaemia, the principal treatment was IVIG, implying assumptions about the doses administered and treatment duration. Costing approaches and estimated cost ranges are summarised in Table 1 (1-7).

The French HTA requested sensitivity analyses on the duration of these AEs until resolution.

Table 1. Summary of costing approaches and of estimated costs of AESC

CRS	
Cost approach	Intensive care supplement + resuscitation supplement Cost of tocilizumab
Estimated costs	Grade 3-4: Ranges from €3635 to €5960 (1,7) Grade 2: Ranges from €0 to €1535 (1,5)
Hypogammaglobulinaemia	
Cost approach	IVIG + administration cost + transportation cost
Estimated costs	Ranges from €2564 to €3866 (1,5)

Conclusions

This review helped elaborate a costing approach for the management of CAR-T cell therapy in France, considering the relevant publications available and reflecting the evolution of costs over time.

Although costs estimated using DRGs seem to be commonly used in different CEAs, others like the management of AESCs or transportation costs are presented with great uncertainty, given the assumptions made to estimate them.

In general, with CAR-T therapy being individualised to fit each patient's condition, there will always remain a degree of uncertainty when it comes to conducting a CEA, incorporating an average profile of a patient receiving CAR-T therapy. It is also important to highlight that the CAR-T therapy market remains very dynamic and that healthcare regulations are evolving to adapt to the rising number of such therapies.

With the availability of a comprehensive national registry of patients receiving CAR-T agents in France, real-world studies are the most accurate sources to document the costs related to CAR-T therapy.

Abbreviations: AE, adverse event; AESC, adverse event specific to CAR-T; ALL, acute lymphoblastic leukaemia; CAR-T cell, chimeric antigen receptor T-cell; CEA, cost-effectiveness analysis; CRS, cytokine-releasing syndrome; DESCAR-T, French national database of CAR-T therapies; DLBCL, diffuse large B-cell lymphoma; DRG, diagnosis-related group; FL, follicular lymphoma; HAS, Haute Autorité de Santé; HTA, health technology assessment; IVIG, intravenous immunoglobulin; RWE, real-world evidence

References

1. Haute Autorité de Santé. Efficiency opinion of YESCARTA® (axicabtagene ciloleucel): refractory or relapsed diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMLBCL) after at least two lines of systemic therapy. Saint-Dénis (France): Haute Autorité de Santé; 2019.
2. Haute Autorité de Santé. Efficiency opinion of Kymriah® (tisagenlecleucel): diffuse large B-cell lymphoma (DLBCL). Saint-Dénis (France): Haute Autorité de Santé; 2019.
3. Haute Autorité de Santé. Efficiency opinion of Kymriah® (tisagenlecleucel): acute lymphoblastic leukemia. Saint-Dénis (France): Haute Autorité de Santé; 2019.
4. Haute Autorité de Santé. Efficiency opinion of Kymriah® (tisagenlecleucel): follicular lymphoma. Saint-Dénis (France): Haute Autorité de Santé; 2022.
5. Haute Autorité de Santé. Efficiency opinion of Tecartus® (autologous anti-CD19-transduced CD3+ cells): Mantel cell lymphoma. Saint-Dénis (France): Haute Autorité de Santé; 2021.
6. Haute Autorité de Santé. Efficiency opinion of Abecma® (idécabtagène vicleucel): multiple myeloma. Saint-Dénis (France): Haute Autorité de Santé; 2021.
7. Haute Autorité de Santé. Efficiency opinion of Carvikty® (ciltacabtagene autoleucel): multiple myeloma. Saint-Dénis (France): Haute Autorité de Santé; 2022.
8. Huguet M, Raimond V, Kaltenbach E, Augusto V, Perrier L. How much does the hospital stay for infusion of anti-CD19 CAR-T cells cost to the French National Health Insurance? Bull Cancer. 2021;108(12):1170-80.
9. Beauvais D, Andrianne C, Aubrun C, et al. Le parcours de soins du patient dans le cadre des CAR T cell: recommandations de la Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). Bull Cancer. 2020;107(12S):S170-7.
10. Beignon M. Les CAR T dans les hémopathies malignes: état des lieux, perspectives et mise en place dans la pratique clinique. Talence (France): Université de Bordeaux; 2020.
11. Di Blasi R, Thieblemont C, Haioun C. EE138 healthcare resource use and associated costs of patients with diffuse large B-cell lymphoma treated with CAR-T cells in France—a real-world study using data from PMSI. Value Health. 2022;25(12 suppl):S79-80.
12. Di Blasi R, Thieblement C, Haioun C. EPH145 treatment patterns among patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who are ineligible for transplantation—a real-world study using French PMSI. Value Health. 2022;25(12 suppl):S218.
13. Comment soigner les lymphomes/ LLC ? [Internet]. Paris: Ensemble Leucémie Lymphome Espoir; 7 April 2023 [cited 17 September 2023]. Available from: https://www.ellye.fr/comment-soigner-les-lymphomes-llc#Les_centres_agr%C3%A9%C3%A9s_en_France.
14. Campagne tarifaire et budgétaire 2022: Nouveautés PMSI: Champs MCO, HAD, SSR et psychiatrie. Lyon (France): Agence Technique de l'Information sur l'Hospitalisation; 21 December 2022. Available from: https://www.atih.sante.fr/sites/default/files/public/content/4196/notice_technique_atih-tous_champs-2022-hh.pdf.
15. Thieblemont C, et al. Coûts de la prise en charge hospitalière des patients adultes avec un lymphoma à grandes cellules B et des enfants et jeunes adultes atteints d'une leucémie aigue lymphoblastique B, traités par CAR T-cells en France: une analyse du PMSI. Poster presented at: 42nd Congress of the Société Française d'Hématologie; 2022 30 March-1 April; Paris.

Contact
Marine Sivignon
Marine.Sivignon@putassoc.com

Find out more at putassoc.com