



HAL
open science

How much does the hospital stay for infusion of anti-CD19 CAR-T cells cost to the French National Health Insurance?

Lionel Perrier, Marius Huguet, Véronique Raimond, Emmanuelle Kaltenbach,
Vincent Augusto

► To cite this version:

Lionel Perrier, Marius Huguet, Véronique Raimond, Emmanuelle Kaltenbach, Vincent Augusto. How much does the hospital stay for infusion of anti-CD19 CAR-T cells cost to the French National Health Insurance?. *Bulletin du Cancer*, 2021, 10.1016/j.bulcan.2021.06.005 . halshs-03428065

HAL Id: halshs-03428065

<https://shs.hal.science/halshs-03428065>

Submitted on 5 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

How much does the hospital stay for infusion of anti-CD19 CAR-T cells cost to the French National Health Insurance?

Coût du séjour hospitalier lié à l'injection de CAR-T anti-CD19 pour l'Assurance Maladie

Marius Huguet^a, Véronique Raimond^b, Emmanuelle Kaltenbach^b, Vincent Augusto^a, and Lionel Perrier^{c,d,e}

^a Mines Saint-Etienne, Univ Clermont Auvergne, CNRS, UMR 6158 LIMOS, Centre CIS,

F-42023 Saint-Etienne, France

^b Haute Autorité de santé, Department of Economic and Public Health Evaluation, F- 93200 Saint Denis, France

^c Univ Lyon, Centre Léon Bérard, GATE L-SE UMR 5824, F-69008 Lyon, France

^d Human and Social Science Department, Centre Léon Bérard, F-69008 Lyon, France

^e Haute Autorité de santé, Committee for Economic and Public Health Evaluation, F- 93200 Saint Denis, France

* Corresponding author: Lionel Perrier

Centre Léon Bérard, Direction of Clinical Research and Innovation (DRCI) - 28 rue Laënnec, 69008 Lyon, France

Email: lionel.perrier@lyon.unicancer.fr

Abstract

Chimeric antigen receptor T-cells (CAR-T cells) have the potential to be a major innovation as a new type of cancer treatment, but are associated with extremely high prices and a high level of uncertainty. This study aims to assess the cost of the hospital stay for the administration of anti-CD19 CAR-T cells in France. Data were collected from the French Medical Information Systems Program (PMSI) and all hospital stays associated with an administered drug encoded 9439938 (tisagenlecleucel, Kymriah®) or 9440456 (axicabtagene ciloleucel, Yescarta®) between January 2019 and December 2020 were included. 485 hospital stays associated with an injection of anti-CD19 CAR-T cells were identified, of which 44 (9%), 139 (28.7%), and 302 (62.3%) were for tisagenlecleucel in acute lymphoblastic leukaemia (ALL), tisagenlecleucel in diffuse large B-cell lymphoma (DLBCL), and axicabtagene ciloleucel respectively. The lengths of the stays were 37.9, 23.8, and 25.9 days for tisagenlecleucel in ALL, tisagenlecleucel in DLBCL, and axicabtagene ciloleucel, respectively. The mean costs per hospital stay were €372,400 for a tisagenlecleucel in ALL, €342,903 for tisagenlecleucel in DLBCL, and €366,562 for axicabtagene ciloleucel. CAR T-cells represented more than 80% of these costs. N = 13 hospitals performed CAR-T cell injections, with two hospitals accounting for more than 50% of the total number of injections. This study provides original data in a context of limited information regarding the costs of hospitalization for patients undergoing CAR-T cell treatments. In addition to the financial burden, distance may also be an important barrier for accessing CAR T-cell treatment.

Keywords: Cancer; CAR-T cell; Costs; Leukemia; Lymphoma; France

Résumé

Les cellules T à récepteur antigénique chimérique (CAR-T cells) ont le potentiel d'être une innovation majeure dans le traitement des cancers mais sont associées à des prix extrêmement élevés et à un fort niveau d'incertitude. Cette étude évalue le coût du séjour à l'hôpital pour l'administration de cellules CAR-T anti-CD19 en France. Les données du programme de médicalisation des systèmes d'information (PMSI) ont été mobilisées et tous les séjours hospitaliers associés à l'administration d'un médicament codé 9439938 (tisagenlecleucel, Kymriah®) ou 9440456 (axicabtagene ciloleucel, Yescarta®) entre janvier 2019 et décembre 2020 ont été inclus. 485 hospitalisations associées à une injection de cellules CAR-T anti-CD19 ont été identifiées, dont 44 (9 %), 139 (28,7 %) et 302 (62,3 %) concernaient respectivement le tisagenlecleucel dans la leucémie aigüe lymphoblastique (LAL), le tisagenlecleucel dans le lymphome diffus à grandes cellules B (DLBCL) et le axicabtagene ciloleucel. Les durées des séjours étaient de 37,9 jours pour le tisagenlecleucel dans la LAL, 23,8 jours pour le tisagenlecleucel dans le DLBCL et de 25,9 jours pour l'axicabtagene ciloleucel ; les coûts moyens du séjour hospitalier s'élevaient respectivement à 372 400€, 342 903€ et 366 562€. Les CAR-T cells représentaient plus de 80 % de ces coûts. Les injections de CAR-T cells ont été effectuées dans N=13 hôpitaux, deux hôpitaux représentant plus de 50 % du nombre total d'injections. Cette étude fournit des données originales dans un contexte d'informations limitées. Outre le coût, la distance peut également constituer un obstacle important à l'accès au traitement par CAR-T cells.

Mots Clés : Cancer ; CAR-T Cell ; Coûts ; Leucémie ; Lymphome ; France.

Introduction

Extensive in-depth research has led to the development of chimeric antigen receptor T cells (CAR-T cells), which are engineered human T cells with modified T-cell receptors for use in immunotherapy [1–4]. They have the potential to be a major therapeutic development, especially for the treatment of blood cancers [5,6]. However, management of the associated toxicities is essential to reduce the morbidity and mortality [7]. Indeed, cytokine release syndrome can occur in up to 100% of cases with some CD19-targeted CAR-T cells, whereas neurotoxicities have been reported to occur in up to 61 and 67 percent of patients with lymphoma and leukemia, respectively [8]. Although the toxicities remain very substantial, tisagenlecleucel (Kymriah[®], Novartis) and axicabtagene ciloleucel (Yescarta[®], Gilead) are the first CAR-T cells to obtain marketing authorization in the US in 2017, and one year later for European countries. In France, the early access program “temporary use authorization” has even made it possible to make tisagenlecleucel and axicabtagene ciloleucel available to patients prior to the European Medicines Agency’s marketing authorization [9,10]. The Transparency Committee from the French authority for health (HAS) rated (i) tisagenlecleucel as having a substantial medical benefit (SMR) and a moderate added medical benefit (ASMR III) in refractory B-cell acute lymphoblastic leukemia (ALL) that has relapsed after transplantation, or after the second or later relapses in young adult patients up to the age of 25 years; and a substantial medical benefit and a minor added medical benefit (ASMR IV) in third-line or later treatment of refractory or recurrent diffuse large B-cell lymphoma (DLBCL); (ii) axicabtagene ciloleucel as having a substantial medical benefit and a moderate added medical benefit (ASMR III) for diffuse large B-cell lymphoma and relapsed or refractory primary mediastinal large B-cell lymphoma in third-line or more [11–13]. Several published economic evaluations have been conducted in order to determine the costs and the efficiency of these innovations [14–25]. They mostly report that these treatments are cost-effective, even though the French Economic and Public Health Committee (CEESP, French Authority for Health), as well as the National Institute for Health and Care Excellence (NICE) in the United Kingdom, have expressed several reservations, especially a high degree of uncertainty due to the short period of follow-up [9,26–28]. Thus, there is a clear need for additional evidence based on observational data regarding the costs and consequences of CAR-T cell

treatments. Additionally, these products are expensive, even though the estimated research and development costs have been shared between public and private payers [29]. Moreover, as mentioned by J. Jørgensen, there is limited European data on the cost of hospitalization for patients treated with CAR-T cell therapies [9]. In this context, the aim of this study was to assess the costs of the hospital stay for infusion of anti-CD19 CAR-T cells and to explore the geographic distribution of patients and hospitals in France. Our contribution to the literature stems in part from the use of a nation-wide administrative dataset, which allows us to describe the costs associated with the administration of anti-CD19 CAR-T cells for the French National Health Insurance, and the geographical breakdown of patients and hospitals using real-world data.

Method

In this study, we identified three populations of interest (i.e., patients treated with tisagenlecleucel for ALL, tisagenlecleucel for DLBCL, or axicabtagene ciloleucel), by using hospital discharge data from the French Medical Information Systems Program (PMSI), managed by the government agency Agence Technique de l'Information sur l'Hospitalisation (ATIH).

The PMSI is an exhaustive nationwide database that records information about each hospital stay in France [30]. Each observation in the PMSI corresponds to a hospital stay, which is composed of one or more Medical Unit Summaries. Indeed, a Medical Unit Summary is produced at the end of each patient's stay in a medical unit providing medical, surgical, obstetrical, and dental care. These summaries contain administrative and medical information, coded according to standardized nomenclatures and classifications to allow automated processing. Thus, we also recorded the number of medical unit summaries for the hospital stay, as well as the number of medical procedures performed during the hospital stay. To identify our populations of interest, we first included all of the hospital stays associated with an administered drug (Unite Commune de Dispensation UCD) encoded 9439938 (tisagenlecleucel) or 9440456 (axicabtagene ciloleucel) between the 1st of January 2019 and the 18th of December 2020. In France, in 2019, each stay for which a patient is treated by injection of CAR-T cells is coded according to the applicable methodological guidelines and classified according to the grouping function, which in practice most frequently corresponds to diagnosis-

related groups (DRGs) 17M08 “Acute leukemia, under 18 years of age”, 17M09 “Acute leukemia, over 17 years of age”, or 17M15 “Lymphomas and other lymphoid malignancies” according to the pathology coded as the main diagnosis. Each stay is hence valued according to its level of severity [31,32]. The hospital stays associated with tisagenlecleucel were then subdivided into ALL and DLBCL groups based on the corresponding medical indication.

For each hospital stay, we extracted the FINESS code (a unique identifier for hospitals in France) for hospitals where CAR-T cell injections were performed, the exact location of the hospitals, the residential location of the patients (at the municipality level), the duration of the patients’ hospital stays, the patients’ age, the International Classification of Disease tenth revision (ICD-10 code), the Diagnosis Related Group (DRG), and information regarding the costs.

The costs were restricted to the perspective of the French National Health Insurance and valued from the national tariffs. The costs that were funded in addition to the DRG-based payment (e.g., medicines placed on the list of innovative high-cost medicines, use of intensive care units) were added. Only hospital stays related to anti-CD19 CAR-T cells infusion, which are likely the most expensive in terms of patient management, were taken into account in this study. Hence, the inpatient and outpatient costs for pre-treatment, rehospitalizations, patient-out-of-pocket costs, informal carer payments, and end-of-life costs were not included. Transportation costs were also not taken into account. Costs were not discounted due to the short time horizon.

We also computed the straight-line distances in kilometers between the patients’ residential municipalities and the exact locations of their hospitals. Information about the type of hospital (public, private for-profit, private not-for-profit) was included from the French Hospital Survey (Statistique annuelle des établissements - SAE) managed by the Directorate for Research Studies Evaluation and Statistics (DREES).

Descriptive statistics were performed. The continuous data are presented as mean values with the standard deviation (SD) and the categorical data as frequencies and percentages. Statistical Analysis Software (SAS Institute Inc. Cary, North Carolina, USA) was used for all of the analyses. One-way sensitivity analyses were conducted by varying cost parameters by plus or minus 20% (except for the costs associated with DRG where the lower vs. higher national tariffs were retained) and illustrated graphically in a Tornado diagram. 95% confidence intervals (CI) for the mean total costs were also computed.

This study was conducted in compliance with the reference methods (MRs) for data processing in health research (MR-005 access to the PMSI).

Results

We identified 485 hospital stays associated with an injection of either tisagenlecleucel or axicabtagene ciloleucel between 2019 and 2020. We observed a maximum of one injection per patient for tisagenlecleucel and for axicabtagene ciloleucel. These injections of CAR-T cells were performed in 13 hospitals in mainland France. Of these, 11 (84.6%) were university teaching hospitals and 2 (5.4%) were not-for-profit cancer centers. Figure 1 shows that the distribution of CAR-T cell injections among the 13 providers was rather centralized, with both hospital number 12 and number 13 accounting for more than 50% of the total market share.

[INSERT FIGURE 1]

As reported in Table 1, out of all of the injections of tisagenlecleucel and axicabtagene ciloleucel, 44 (9%) were tisagenlecleucel for ALL, 139 (28.7%) were tisagenlecleucel for DLBCL, and 302 (62.3%) axicabtagene ciloleucel. Even though all of the patients in the tisagenlecleucel ALL group had an ICD-10 code for acute lymphoblastic leukemia, we observed a degree of variation in the ICD-10 codes for the tisagenlecleucel DLBCL and the axicabtagene ciloleucel groups. Indeed, out of the 302 injections of axicabtagene ciloleucel, 290 (96%) were associated with diffuse DLBCL, while the diagnoses for the remaining 12 injections (4%)

comprised follicular lymphoma, peripheral T-cell lymphoma, mediastinal large B-cell lymphoma, non-Hodgkin lymphoma, septic shock, and antineoplastic chemotherapy or immunotherapy. Similarly, out of the 139 injections of tisagenlecleucel for DLBCL, 130 (94%) were for diffuse DLBCL, while the diagnoses for the remaining nine injections (6%) included follicular lymphoma, lymphoblastic lymphoma, non-follicular lymphoma, pneumonia due to pseudomonas, and antineoplastic chemotherapy or immunotherapy.

[INSERT TABLE 1]

Table 2 displays the patient characteristics and information about the hospital stays for the CAR-T cell injections. On average, the patients were 14.8 years of age for the tisagenlecleucel ALL group, 60.8 years of age for the tisagenlecleucel DLBCL group, and 59.1 years of age for the axicabtagene ciloleucel group. It should be noted that tisagenlecleucel for ALL is indicated for patients up to 25 years of age. The length of stay for the infusion of anti-CD19 CAR-T cells was broadly similar for the lymphoma patients (i.e., on average 23.8 nights for tisagenlecleucel and 25.9 nights for axicabtagene ciloleucel), and substantially higher for the tisagenlecleucel ALL patients, with on average of 37.9 nights spent in the hospital. A higher standard deviation, as well as a wider distribution, are shown in Figure 2, indicating a greater variation in the length of the stay for the tisagenlecleucel ALL patients compared with the tisagenlecleucel DLBCL patients and those treated with axicabtagene ciloleucel, with a maximum of 148 nights spent in the hospital for the leukemia patients. Regarding the composition of the hospital stays for the CAR-T cell injections, the average number of medical procedures during the hospital stay was 19.34 for the tisagenlecleucel ALL patients, 8.34 for the tisagenlecleucel DLBCL patients, and 12.81 for the patients treated with axicabtagene ciloleucel. Similarly, the number of medical unit summaries for the hospital stay, which relates to the variety of medical units involved, was on average 2.02 for the tisagenlecleucel ALL patients, 1.47 for the tisagenlecleucel DLBCL patients, and 1.39 for the patients treated with axicabtagene ciloleucel. As only 13 hospitals performed CAR-T cell injections in the period considered in mainland France, the travel distances from the patients' residential locations to the hospitals is an important factor to be taken into account. The average distances were indeed relatively long, with 200.6 kilometers for the tisagenlecleucel ALL patients, 112.2 kilometers for

the tisagenlecleucel DLBCL patients, and 98.6 kilometers for the patients treated with axicabtagene ciloleucel.

[INSERT TABLE 2]

[INSERT FIGURE 2]

Table 3 provides a description of the costs associated with the hospital stay for the CAR-T cell injections. On average, the cost per hospital stay for the infusion of anti-CD19 CAR-T cells was €372,400 (95% CI: [360,045; 384,754]) for the tisagenlecleucel ALL patients, €342,903 (95% CI: [339,188; 346,617]) for the tisagenlecleucel DLBCL patients, and €366,562 (95% CI: [364,457; 368,667]) for the patients treated with axicabtagene ciloleucel. These costs include the cost of the CAR-T cell products (€303,916.9 for tisagenlecleucel and €333,867 for axicabtagene ciloleucel), the cost associated with the stay itself, i.e. DRG (€27,423.96 for tisagenlecleucel ALL treatment, €14,090.9 for tisagenlecleucel DLBCL treatment, and €15,971.1 for axicabtagene ciloleucel), as well as extra charges including intensive care (€41,059.4 in case of tisagenlecleucel for ALL, €24,895.9 in case of tisagenlecleucel for DLBCL, and €16,724.2 in case of axicabtagene ciloleucel). Considering only the intensive care surcharge, it reached on average €13,934 for the tisagenlecleucel ALL patients, €8,716 for the tisagenlecleucel DLBCL patients, and €8,406 for the axicabtagene ciloleucel patients. Finally, CAR-T cell products represented 81.61%, 88.63%, and 91.08% of the total stay for tisagenlecleucel with ALL, tisagenlecleucel with DLBCL, and axicabtagene ciloleucel, respectively; the share of the cost associated with the DRG was 7.36%, 4.1%, and 4.36% for tisagenlecleucel with ALL, tisagenlecleucel with DLBCL, and axicabtagene ciloleucel, respectively; the intensive care units 3.74% %, 2.54%, and 2.29% for tisagenlecleucel with ALL, tisagenlecleucel with DLBCL, and axicabtagene ciloleucel, respectively; the other supplements 7.28%, 4.72%, and 2.26% for tisagenlecleucel with ALL, tisagenlecleucel with DLBCL, and axicabtagene ciloleucel, respectively.

The vast majority of hospital stays for tisagenlecleucel with ALL were associated with a DRG for acute leukemia (DRGs 17M08 and 17M09), and to a DRG for lymphomas and other lymphoid malignancies (DRG

17M15) for tisagenlecleucel with DLBCL and axicabtagene ciloleucel. Nevertheless, we also observed a high degree of variation in the cost of the hospital stay for the infusion of anti-CD19 CAR-T cells according to the associated DRG. For example, the total cost exceeded €400,000 for the DRGs for hematopoietic stem cell allografts and autografts (DRG 27Z02, 27Z03, and 27Z04Z). The costs were naturally higher for the DRGs with higher severity levels.

[INSERT TABLE 3]

Figure 3 shows Tornado diagrams that illustrated the impact of $\pm 20\%$ variation in the values of cost parameters (except for the costs associated with DRG where the lower vs. higher national tariffs were retained) on the cost of the hospital stay for the infusion of anti-CD19 CAR-T cells. The vertical lines represent the mean cost per patient when all parameters assume their base values. The most sensitive parameters were the costs of CAR-T cell products. Decreasing these costs by 20% decrease the cost from €372,400 to €311,616 for the tisagenlecleucel ALL patients, from €342,903 to €282,120 for the tisagenlecleucel DLBCL patients, and from €366,562 to €299,789 for the patients treated with axicabtagene ciloleucel.

[INSERT FIGURE 3]

In order to provide evidence regarding patient access to CAR-T cell injection, the two maps in Figure 4 illustrate the geographical repartition of the hospitals, the patient density, and the distance to a hospital per department in mainland France. It can be seen that the 13 hospitals performing CAR T-cell injections are relatively well spread over the French territory, except for the center of France and Corsica. Nevertheless, we observed a high degree of spatial variation in the patient-hospital distance, ranging from 0 – 50 kilometers on average in some departments to more than 200 kilometers in other departments. Central western France, as well as Corsica, were particularly affected by long travel distances. In terms of patient access to CAR-T cell injections, there was also a broad trend of a higher density of patients receiving CAR-T cell injections in departments where there is a hospital with a record of performing CAR-T cell injections.

[INSERT FIGURE 4]

Discussion

The use of CAR-T cells has the potential of becoming a major innovation in the treatments of leukemia and lymphomas that needs to be confirmed with longer-term data [5,6]. Indeed, the costs and the consequences of these innovations remain uncertain due to a lack of evidence based on real-world data [14,15,18–20].

In this study, we assessed the costs of the hospital stays for the infusion of anti-CD19 CAR-T cells for the French National Health Insurance using nation-wide administrative data from 2019 – 2020. From January 2019 to December 2020, 485 patients received a single CAR-T cell injection of either tisagenlecleucel or axicabtagene ciloleucel in France. Most of the injections of CAR-T cells were related to lymphoma treatments, while only 10% were related to leukemia (Table 1). The costs of the hospital stay for the infusion of anti-CD19 CAR-T cells, including the cost of the CAR-T cell product, were €372,400 on average for tisagenlecleucel ALL treatment, €342,903 for tisagenlecleucel DLBCL treatment, and €366,562 for axicabtagene ciloleucel (Table 3). In concordance with the literature, the leading component of these costs was the acquisition of the anti-CD19 CAR T-cell drug, at a cost of €303,916.9 for tisagenlecleucel and €333,867 for axicabtagene ciloleucel. G.H. Lyman, for example, reported a cost expressed in 2018 US dollars from lymphodepletion to 30 days after CAR-T cell infusion in patients with relapsed or refractory DLBCL of \$454,611 in academic hospitals. The CAR-T cell drug cost was \$373,000 (82.05%) and the hospitalizations and office visit costs \$53,360 (11.74%) [21]. In the economic analysis in pediatric patients with relapsed/refractory ALL performed by Thielen et al., the cost of the CAR-T cell product (€320,000) represented 78.13% of the total costs from a healthcare perspective (i.e., €409,563). The costs of the treatment, which included the drug and the procedure costs, and the costs for the inpatient and the outpatient visits reached €338,122 [33]. This cost, as well the cost input related to the administration of anti-CD19 CAR-T cells (i.e., €15,932), appears to be lower than the cost determined in our study. However, comparisons should be made very cautiously, as health systems vary and costs do not necessarily include the same items. In any case, real-life studies are needed to generate new results and to refine the

assumptions of future models in a context of limited data regarding the costs of the hospitalizations of patients undergoing CAR-T cell treatments.

As initial coverage decisions were based on preliminary data, our study shows that beyond the reevaluation of the clinical benefits, the costs and the cost-effectiveness analyses submitted to the CEESP also need an update. Indeed, the total cost estimated by the manufacturers over 10 and 20 years for tisagenlecleucel and axicabtagene ciloleucel, respectively, and our results, based only on the hospital stay for the administration of anti-CD19 CAR-T cells, appear to be similar despite measuring costs at different time horizons [26–28,34].

In regard to the geographical approach, our findings indicate an average distance between the patients' residential municipalities and the hospital locations of 200.6 kilometers for tisagenlecleucel ALL treatment, 112.2 kilometers for tisagenlecleucel DLBCL treatment, and 98.6 kilometers for treatments involving axicabtagene ciloleucel (Table 2). These relatively long distances can be explained by the fact that only 13 hospitals performed CAR-T cell injections in mainland France in 2019-2020. Moreover, the distribution of CAR-T cell injections among the 13 providers was rather centralized, with two of the providers accounting for more than 50% of the total market share (Figure 1). The longer travel distance for tisagenlecleucel ALL patients could be explained by the fact that among the 13 hospitals, only 7 hospitals (54%) performed injections of tisagenlecleucel for ALL, while all 13 of the hospitals performed injections of either tisagenlecleucel for DLBCL or axicabtagene ciloleucel or both. Thus, leukemia patients had fewer options to choose from when seeking a hospital for a CAR-T cell injection, which might in turn increase travel distances. We also observed a high degree of spatial variation in the distance between the patients' residential municipalities and the hospital locations, ranging from 0 – 50 kilometers on average in some departments to more than 200 kilometers in other departments, which could be due to a lack of hospitals in central western France, as well as in Corsica (Figure 3). In terms of patient access to CAR-T cell injections, it also appears that patients living in departments where there is an established hospital were more likely to be treated compared to patients living farther away from a provider, which is even more important considering

the low number of hospitals providing CAR-T cell treatment in mainland France (Figure 3). But population densities are also higher in the large cities where university hospitals and not-for-profit cancer centers are located. Further research, including incidence data, is, therefore, necessary. Distances may be an important barrier to access to CAR-T cell therapy. In the US, for example, fewer than one-hundred hospitals are certified to infuse Axicabtagene ciloleucel, while 46.6% of the population lives within thirty minutes of one of the 200 transplant centers. The longer travel distance for pediatric and young adult patients are also concordant with the literature [35,36].

The stakes for CAR-T cell therapy are major: (i) the scientific stakes related to the prospect that research that has broadly involved several generations of researchers, physicians, and many other personnel and that has required massive public and private investments can deliver very significant benefits for patients [3]; (ii) clinical issues because even though there have been clear successes with anti-CD19 CAR-T cell therapy, the CAR-T cells' persistence or antigen escape may be limited and there is still ample room for improvement of the safety and efficacy of the use of CAR-T cells to treat blood cancers [6,8,37]. Moreover, some facilities perform very few injections. It is not clear how many should be performed to ensure quality of care. Is there a cumulative effect? There needs to be a balance between proximity and the activity threshold. Indeed, there have been hundreds of studies investigating the volume-outcome relationship in healthcare, and they indeed tend to indicate that higher-volume hospitals tend to provide higher-quality care, especially for complex procedures such as surgeries in cancer care [38,39]; (iii) the economic stakes due to the extremely high prices of tisagenlecleucel and axicabtagene ciloleucel. The costs could be even higher when used in combination with other cancer therapeutics such as immunotherapies [18]. These very high costs raise the question of the sustainability of the health care systems to cope with expenses of this nature and the capacity of patients to cope with the remaining out-of-pocket costs. Fortunately, there appear to be options to improve and even ensure access to all patients requiring such treatments: the implementation of different production methods. T. Ran assessed the "on-site" CAR-T cell production costs in a non-profit setting in Germany including leukapheresis, cell production, cryopreservation, and additional contamination control

to being close to €60,000 at the maximum capacity of the machine. The cost could have even decreased to €45,000 if three machines would be installed as a result of the economies of scale [16,17,23]; the development of innovative pricing mechanisms [40]; and the generation of on-the-shelf universal T cells [6].

(iv) the ethics stakes, with key issues raised by the national ethics counselor for life sciences and health sciences: why are the prices of these innovative therapies so high? The necessity to rapidly bolster a regulatory system that allows joint preservation of public and industrial interests. The search for a "fair price" is part of a negotiation between private and public parties, whose interests are partly divergent (profit vs. public health) [41]. In France, an annual reassessment of clinical benefits includes adverse events based on long-term follow-up data from pivotal trials, and the collection of real-world data has been scheduled for the anti-CD19 CAR-T cell products tisagenlecleucel and axicabtagene ciloleucel.

This study has some limitations, in particular the fact that only the hospital stay related to the infusion of anti-CD19 CAR-T cells was taken into account. Hence, several cost items were not included, e.g., inpatient and outpatient hospitalizations/office visits pre- and post-infusion, patient-out-of-pocket costs, informal carer payments, the fixed-price supplement of €15,000 applies only to the tisagenlecleucel and axicabtagene ciloleucel specialties within the indications of the market access and within the limit of the target population of 400 patients, or the possible financial costs related to the delay between the date of payment by the hospitals for the treatment and the date of reimbursement by the health insurance. We also computed straight-line distance in kilometers between the patients' residential municipalities and the exact locations of the hospitals, which minimizes the actual distances travelled. Furthermore, although the PMSI is a tool of particular interest, the risk of coding errors in hospital discharge data cannot be ignored [42–44]. Indeed, variations were observed in the ICD-10 codes for the tisagenlecleucel DLBCL and the axicabtagene ciloleucel groups. Several worldwide studies have investigated the accuracy of routinely collected hospital episode data in order to determine to what extent overall rates of accuracy coding errors impact the quality of results. These studies measured the coding accuracy by comparison of routine discharge statistics for an episode of hospital care with the original medical record.

The overall levels of accuracy were generally found to be quite high [45–47]. Nevertheless, as shown by our study, it is important to follow the coding rules (the ATIH provides a yearly methodological coding guide), to use the correct ICD 10 codes, and to develop coding improvements using, for example, data mining techniques [48].

Acknowledgments

This work was supported by the SIRIC LYriCAN (INCa-DGOS-INSERM_12563) and the Institut Convergences Plascan (ANR-17-CON-002). The authors wish to thank the Agence Technique de l'Information sur l'Hospitalisation (ATIH) for the access to the PMSI database. The authors are grateful to Sophie Domingues-Montanari who helped with the final editing of the manuscript. The authors also thank the reviewers for their valuable comments.

Conflict of Interest

The authors declare that they have no competing interests.

Cet article fait partie du numéro supplément Nouvelles stratégies en immunothérapie : CAR-T et cellules bispécifiques réalisé avec le soutien institutionnel de Celgene – BMS et Gilead – Kite.

References

1. Anderson JK, Mehta A. A review of chimeric antigen receptor T-cells in lymphoma. *Expert Rev Hematol*. 2019;12(7):551-561. doi:10.1080/17474086.2019.1629901
2. Andrea AE, Chiron A, Bessoles S, Hacein-Bey-abina S. Engineering next-generation car-t cells for better toxicity management. *Int J Mol Sci*. 2020;21(22):1-25. doi:10.3390/ijms21228620
3. Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. *Science (80-)*. 2018;359(6372). doi:10.1126/science.aan4672
4. Mohty M, Dulery R, Gauthier J, et al. CAR T-cell therapy for the management of refractory/relapsed high-grade B-cell lymphoma: a practical overview. *Bone Marrow Transplant*. 2020;55(8):1525-1532. doi:10.1038/s41409-020-0892-7
5. Beyar-Katz O, Gill S. Advances in chimeric antigen receptor T cells. *Curr Opin Hematol*. 2020;27(6):368-377. doi:10.1097/MOH.0000000000000614
6. Chicaybam L, Bonamino MH, Invitti AL, Rozenchan PB, Vieira I de L, Strauss BE. Overhauling car t cells to improve efficacy, safety and cost. *Cancers (Basel)*. 2020;12(9):1-26. doi:10.3390/cancers12092360
7. Shpall EJ. Chimeric antigen receptor. *Nat Publ Gr*. 2017. doi:10.1038/nrclinonc.2017.148
8. Siegler EL, Kenderian SS. Neurotoxicity and Cytokine Release Syndrome After Chimeric Antigen Receptor T Cell Therapy: Insights Into Mechanisms and Novel Therapies. *Front Immunol*. 2020;11(August):1-11. doi:10.3389/fimmu.2020.01973
9. Jorgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. *J Mark Access*

Heal Policy. 2020;8(1715536).

10. Rémuzat C, Toumi M, Jørgensen J, Kefalas P. Market access pathways for cell therapies in France. *J Mark Access Heal Policy*. 2015;3(1):29094. doi:10.3402/jmahp.v3.29094
11. Haute Autorité de Santé. Kymriah® (Tisagenlecleucel) Lymphome diffus à grandes cellules B - Avis de la Commission de la Transparence. 2018:1-23.
12. Haute Autorité de Santé. Kymriah® (Tisagenlecleucel) Leucémie aigue lymphoblastique - Avis de la Commission de la Transparence. 2018:1-23.
13. Haute Autorité de Santé. YESCARTA® (Axicabtagene ciloleucel)- Avis de la Commission de la Transparence. 2018:1-23.
14. Sarkar R, Gloude N, Schiff D, Murphy J. Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-cell Acute Lymphoblastic Leukemia. *JNCI J Natl Cancer Inst*. 2019;111(7).
15. Thielen F, Dongen-Leunis A, Arons A, Ladestein J, Hoogerbrugge P, Uyl-de Groot C. Cost-Effectiveness of Anri-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *Eur J Haematol*. 2020;105.
16. Schmitt M, Schmitt A, Thalheimer M, Dreger P, Müller-Tidow C. Comments on “Cost of decentralized CAR T cell production in an academic non-profit setting.” *Int J Cancer*. 2021;148(2):514-515. doi:10.1002/ijc.33254
17. Ran T, Eichmüller SB, Schmidt P, Schlender M. Reply to: Comments on “Cost of decentralized CAR T cell production in an academic non-profit setting.” *Int J Cancer*. 2021;148(2):516-517. doi:10.1002/ijc.33253
18. Yadav R, Ali A, Kumar S, et al. CAR T cell therapy: newer approaches to counter resistance and cost. *Heliyon*. 2020;6.
19. Flowers CR, Ramsey SD. What can cost-effectiveness analysis tell us about chimeric antigen receptor T-cell therapy for relapsed acute lymphoblastic leukemia? *J Clin Oncol*. 2018;36(32):3183-3185. doi:10.1200/JCO.2018.79.3570
20. Lin JK, Muffly LS, Spinner MA, Barnes JI, Owens DK, Goldhaber-Fiebert JD. Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma. *J Clin Oncol*. 2019;37(24):2105-2119. doi:10.1200/JCO.18.02079
21. Lyman GH, Nguyen A, Snyder S, Gitlin M, Chung KC. Economic Evaluation of Chimeric Antigen Receptor T-Cell Therapy by Site of Care Among Patients With Relapsed or Refractory Large B-Cell Lymphoma. *JAMA Netw open*. 2020;3(4):e202072. doi:10.1001/jamanetworkopen.2020.2072
22. Harrison RP, Zylberberg E, Ellison S, Levine BL. Chimeric antigen receptor–T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. *Cytotherapy*. 2019;21(2):224-233. doi:10.1016/j.jcyt.2019.01.003
23. Ran T, Eichmüller SB, Schmidt P, Schlender M. Cost of decentralized CAR T-cell production in an academic nonprofit setting. *Int J Cancer*. 2020;147(12):3438-3445. doi:10.1002/ijc.33156
24. Hernandez I, Prasad V, Gellad W. Accounting for All Costs in the Total Cost of Chimeric Antigen Receptor T-Cell Immunotherapy-Reply. *JAMA Oncol*. 2018;4(12):1785-1786. doi:10.1001/jamaoncol.2018.4657
25. Roth JA, Sullivan SD, Lin VW, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. *J Med Econ*. 2018;21(12):1238-1245. doi:10.1080/13696998.2018.1529674
26. Haute Autorité de Santé. AVIS D’EFFICIENCE : Kymriah® (Tisagenlecleucel) Leucémie aigue lymphoblastique. *CEESP*. 2019.

27. Haute Autorité de Santé. AVIS D'EFFICIENCE : Kymriah® (Tisagenlecleucel) Lymphome diffus à grandes cellules B. *CEESP*. 2019.
28. Haute Autorité de Santé. AVIS D'EFFICIENCE : YESCARTA® (axicabtagene ciloleucel). *CEESP*. 2019.
29. Prasad V. Tisagenlecleucel - The first approved CAR-T-cell therapy: Implications for payers and policy makers. *Nat Rev Clin Oncol*. 2018;15(1):11-12. doi:10.1038/nrclinonc.2017.156
30. Boudemaghe T, Belhadj I. Data resource profile: The French national uniform hospital discharge data set database (PMSI). *Int J Epidemiol*. 2017;46(2):392-392D. doi:10.1093/ije/dyw359
31. Agence Technique de l'Information sur l'Hospitalisation. Campagne tarifaire et budgétaire 2019 Nouveautés « financement ». [Accessed January 19, 2021]. https://www.ameli.fr/sites/default/files/Documents/5229/document/facturation-medicaments-retrocedes_assurance-maladie.pdf. 2019.
32. Agence Technique de l'Information sur l'Hospitalisation. Campagne tarifaire et budgétaire 2020 Nouveautés « financement ». [Accessed January 19, 2021]. https://www.atih.sante.fr/sites/default/files/public/content/3936/notice_technique_n_cim-mf-579-7-2020_nouveautes_financement_2020.pdf. 2020:1-16.
33. Thielen FW, van Dongen-Leunis A, Arons AMM, Ladestein JR, Hoogerbrugge PM, Uyl-de Groot CA. Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *Eur J Haematol*. 2020;105(2):203-215. doi:10.1111/ejh.13427
34. Raimond V, Kaltenbach E, Adam C, et al. Challenges raised by the economic evaluation of CAR-T-cell therapies. The review by the French National Authority for Health. [Submitted]. *Bull Cancer*.
35. Delamater PL, Uberti JP. Geographic access to hematopoietic cell transplantation services in the United States. *Bone Marrow Transplant*. 2016;51(2):241-248. doi:10.1038/bmt.2015.246
36. Kansagra A, Farnia S, Majhail N. Expanding Access to Chimeric Antigen Receptor T-Cell Therapies: Challenges and Opportunities. *Am Soc Clin Oncol Educ B*. 2020;(40):e27-e34. doi:10.1200/edbk_279151
37. Grain A, Dourthe ME, Baruchel A. CAR-T cells in acute lymphoblastic leukemias: What's new? *Bull Cancer*. 2020;107(2):234-243. doi:10.1016/j.bulcan.2020.01.009
38. Cowan RA, O'Ceirbhail RE, Gardner GJ, et al. Is It Time to Centralize Ovarian Cancer Care in the United States? *Ann Surg Oncol*. 2016;23(3):989-993. doi:10.1245/s10434-015-4938-9
39. Friebel R, Hauck K, Aylin P. Centralisation of acute stroke services in London: Impact evaluation using two treatment groups. *Health Econ*. 2018;27(4):722-732. doi:10.1002/hec.3630
40. Barlow JF, Yang M, Teagarden JR. Are Payers Ready, Willing, and Able to Provide Access to New Durable Gene Therapies? *Value Heal*. 2019;22(6):642-647. doi:10.1016/j.jval.2018.12.004
41. Comité consultatif national d'éthique pour les sciences de la vie et de la santé. Avis 135 « Accès aux innovations thérapeutiques : Enjeux éthiques ». [Accessed January 19, 2021]. https://www.ccne-ethique.fr/sites/default/files/publications/avis_135_0.pdf. 2020.
42. Champeaux C, Weller J, Katsahian S. Epidemiology of meningiomas. A nationwide study of surgically treated tumours on French medico-administrative data. *Cancer Epidemiol*. 2019;58(May 2018):63-70. doi:10.1016/j.canep.2018.11.004
43. Scotte F, Martelli N, Vainchtock A, Borget I. The Cost of Thromboembolic Events in Hospitalized Patients with Breast or Prostate Cancer in France. *Adv Ther*. 2015;32(2):138-147. doi:10.1007/s12325-015-0187-3
44. Asfari H, Bousquet C, Paviot BT, et al. Chocs anaphylactiques d'origine médicamenteuse : sous-notification et PMSI. *Thérapie*. 2014;69(6):483-490. doi:10.2515/therapie/2014057

45. Gouverneur A, Dolatkhani D, Rouyer M, et al. Concordance entre les codes de diagnostic du PMSI et les données de dossiers médicaux pour identifier le cancer colorectal métastatique et les comorbidités associées chez des patients âgés. *Rev Epidemiol Sante Publique*. 2017;65(4):321-325. doi:10.1016/j.respe.2017.03.132
46. Campbell S, Campbell M, Grimshaw J, Walker A. Systematic review of discharge coding accuracy. *J Public Health Med*. 2001;23(3):205-211. doi:10.1093/pubmed/fdr054
47. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. *Health Serv Res*. 2005;40(5 II):1620-1639. doi:10.1111/j.1475-6773.2005.00444.x
48. Djennaoui M, Ficheur G, Beuscart R, Chazard E. Improvement of the quality of medical databases: Data-mining-based prediction of diagnostic codes from previous patient codes. *Stud Health Technol Inform*. 2015;210:419-423. doi:10.3233/978-1-61499-512-8-419

Figure 1 - Number of anti-CD19 CAR-T cell injections per hospital

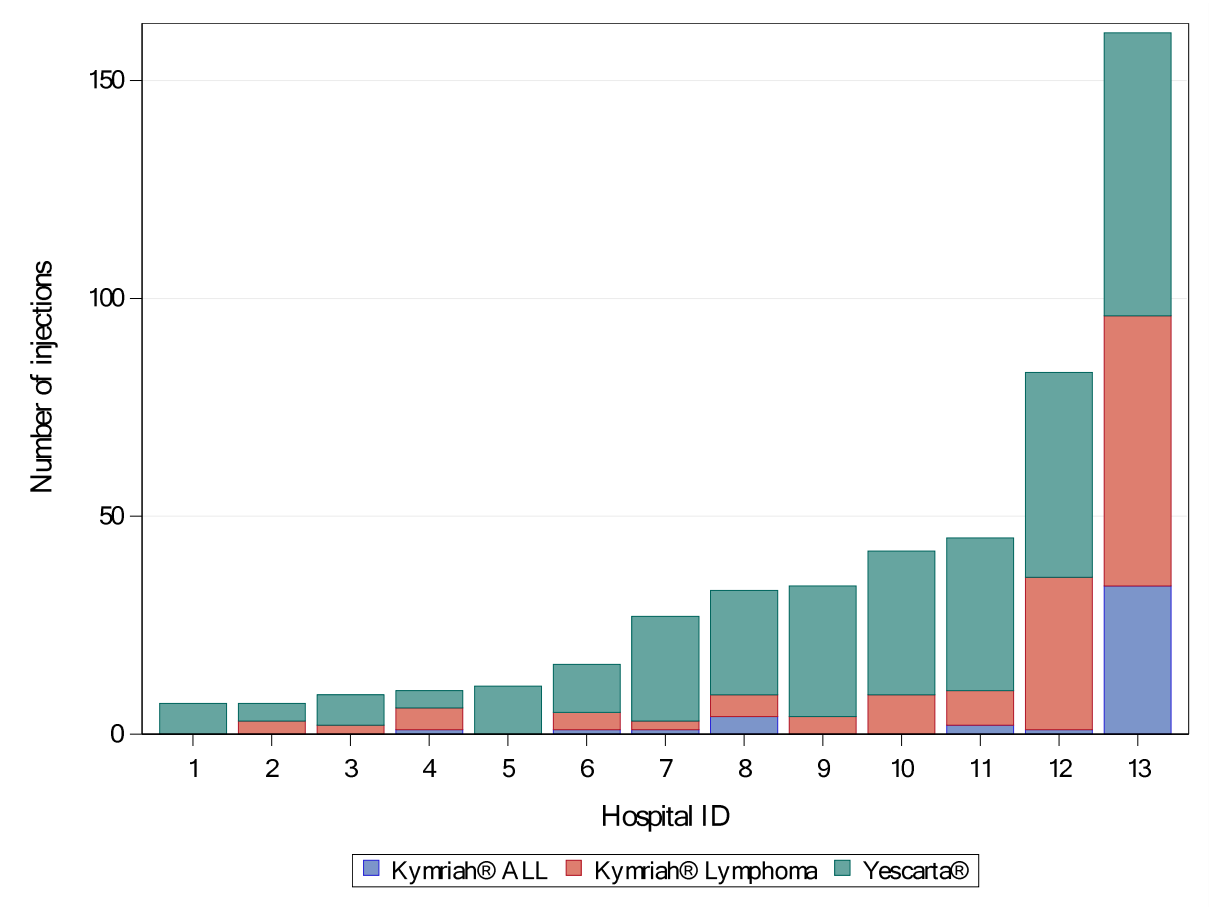


Figure 2 - Distribution of patient length of stay (in number of nights)

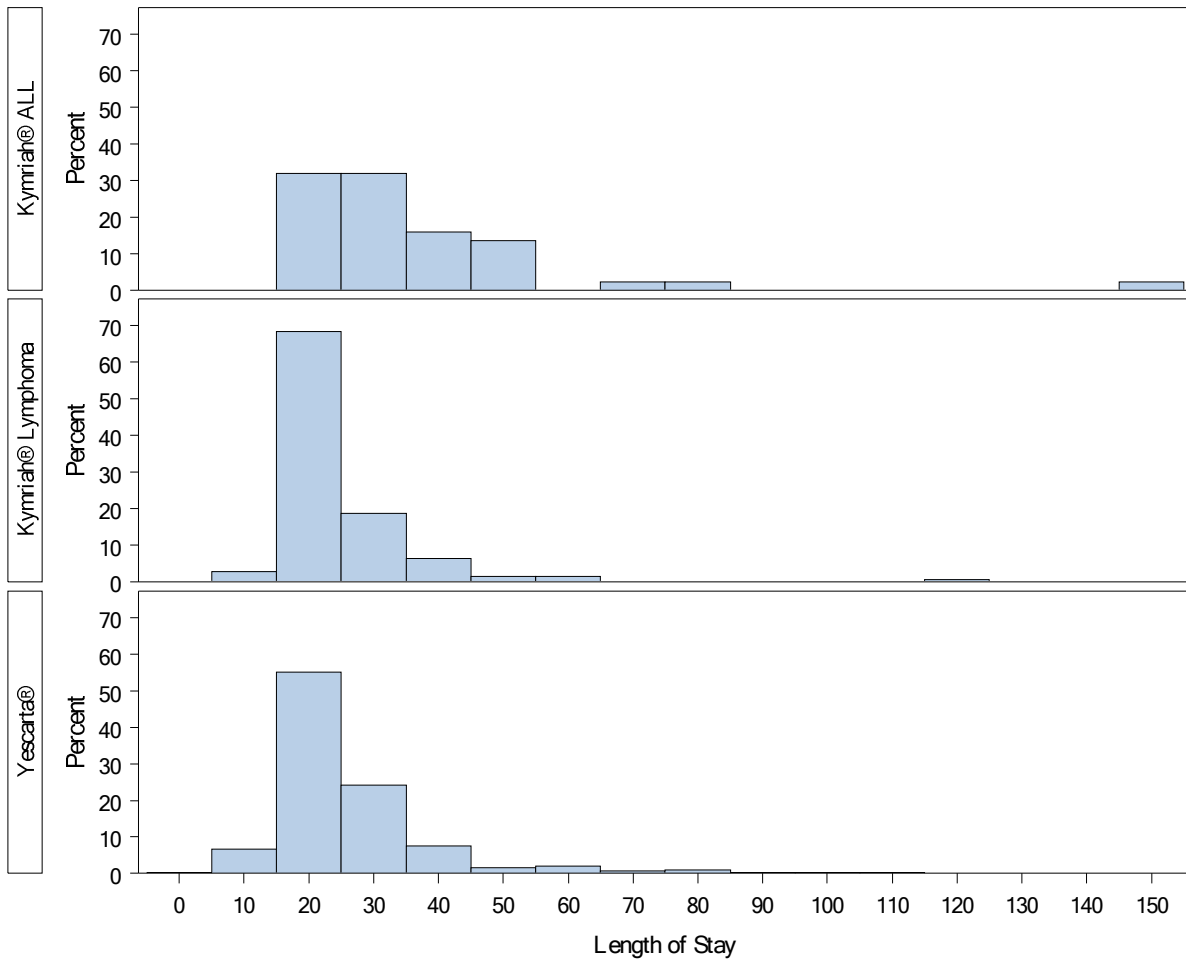
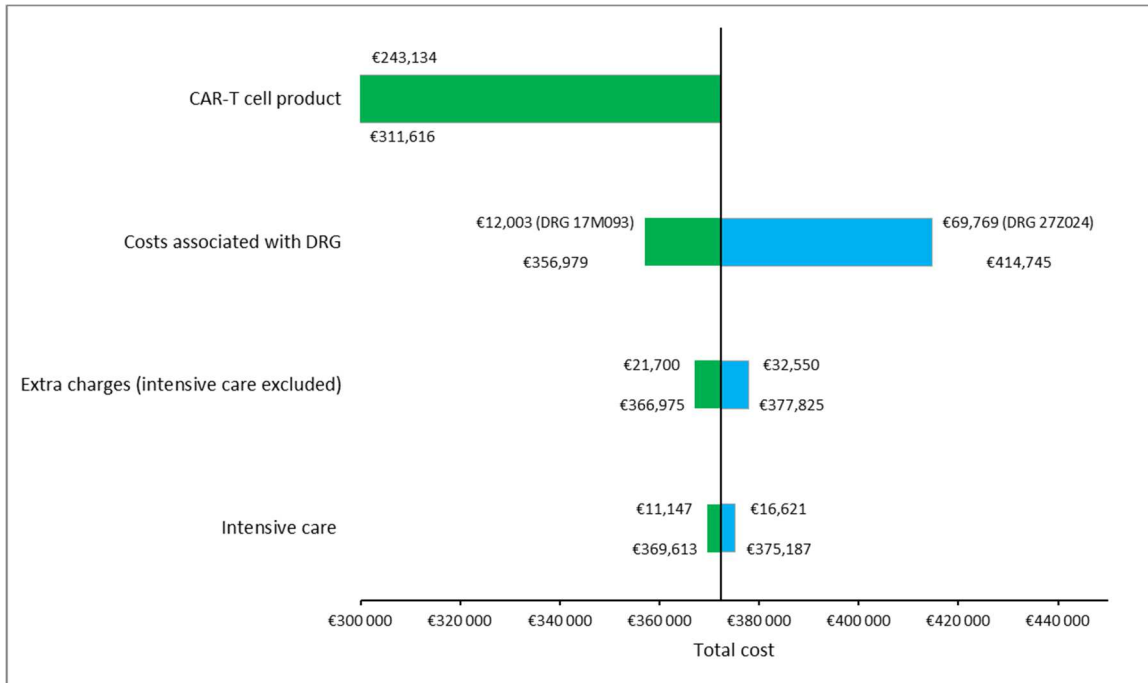
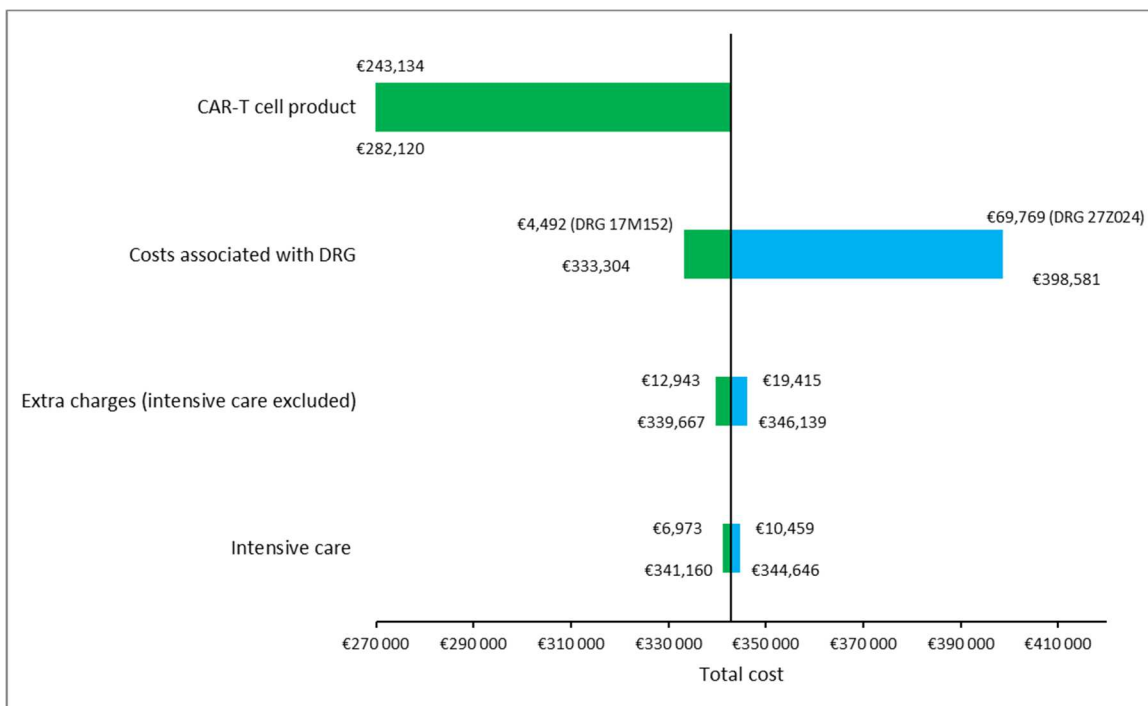


Figure 3 – One-way sensitivity analyses

tisagenlecleucel ALL patients



tisagenlecleucel DLBCL patients



axicabtagene ciloleucel patients

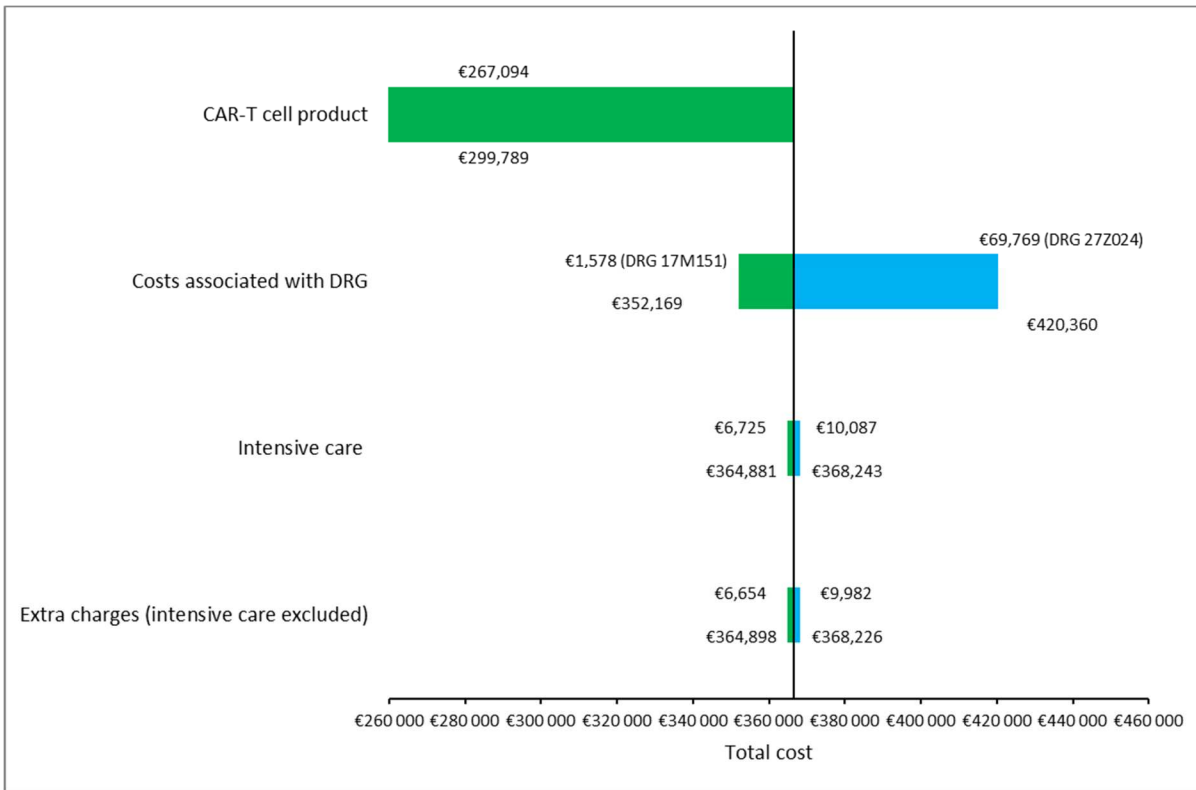


Figure 4 – Patient density per department (blue grid), average patient-hospital distance per department (orange grid), and geographic distribution of hospitals (dots) for anti-CD19 CAR-T cell injections in mainland France.

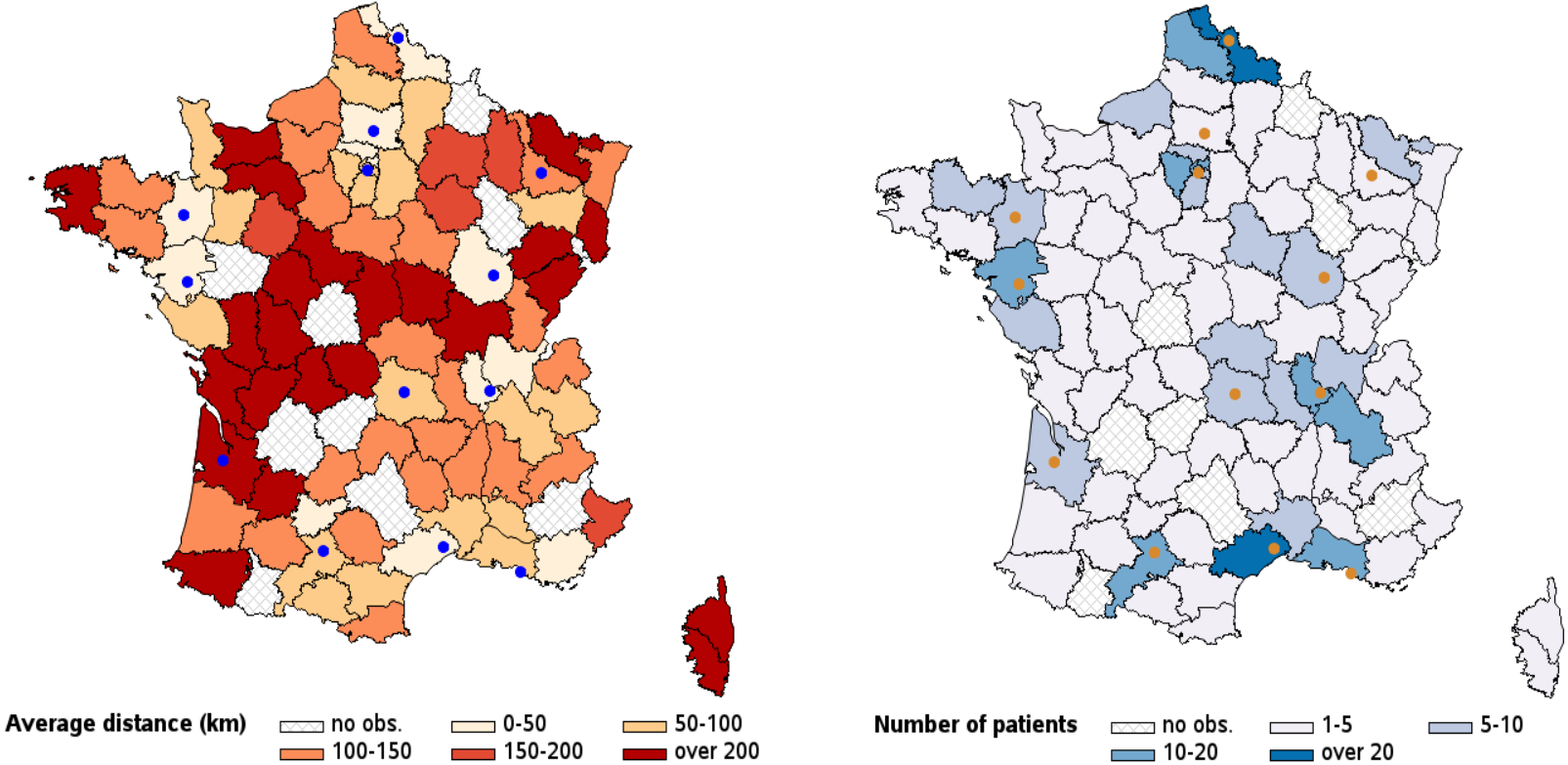


Table 1: Prescription of anti-CD19 CAR-T cells by diagnosis code (ICD-10)

ICD-10 Code	Label	Frequency of patients			
		tisagenlecleucel	tisagenlecleucel	axicabtagene	Total
		ALL	DLBCL	ciloleucel	
C829	Follicular lymphoma, unspecified	0	4	2	6
C833	Diffuse large B-cell lymphoma	0	130	290	420
C835	Lymphoblastic (diffuse) lymphoma	0	1	0	1
C839	Non-follicular (diffuse) lymphoma, unspecified	0	1	0	1
C844	Peripheral T-cell lymphoma, not classified	0	0	1	1
C852	Mediastinal (thymic) large B-cell lymphoma	0	0	5	5
C857	Other type of Non-Hodgkin lymphoma	0	0	1	1
C859	Non-Hodgkin lymphoma, unspecified	0	0	1	1
C910	Acute lymphoblastic leukemia [ALL]	44	0	0	44
J151	Pneumonia due to Pseudomonas	0	1	0	1
R572	Septic shock	0	0	1	1
Z511	Appointment for antineoplastic chemotherapy and immunotherapy	0	2	1	3
Total		44	139	302	485

Note: International Classification of Diseases (ICD-10)

Table 2: Patients and hospital stay characteristics for infusion of anti-CD19 CAR-T cells

	tisagenlecleucel ALL (n=44)			tisagenlecleucel DLBCL (n=139)			axicabtagene ciloleucel (n=302)		
	Mean	Std	[Min; Max]	Mean	Std	[Min; Max]	Mean	Std	[Min; Max]
Age	14.8	7.4	[0; 25]	60.8	11.6	[20; 77]	59.1	12.3	[18 ;78]
Length of stay	37.9	26.1	[19; 148]	23.8	11.7	[5; 117]	25.9	13.4	[2 ;109]
# medical procedures during hospital stay	19.34	57.73	[0; 373]	8.34	9.69	[0; 51]	12.81	23.92	[0; 284]
# medical unit summaries	2.02	1.65	[1; 7]	1.47	0.89	[1; 6]	1.88	1.39	[1; 8]
Distance patient – hospital	200.6	231.1	[2.9; 960.2]	112.2	120.4	[0.1; 683.5]	98.6	105.6	[2.3; 778.3]

Note: Number of (#); Standard deviation (Std); Minimum (Min); Maximum (Max); Frequency (n). The patient-hospital distance is in kilometers, the patients' age in years, and the length of stay in nights.

Table 3: Costs of the hospital stay associated with anti-CD19 CAR T-cell injections based on the national tariffs

DRG	DRG cost (€, V2020)	tisagenlecleucel ALL (Value RR 2020 = 303,916.9)			tisagenlecleucel DLBCL (Value RR 2020 = 303,916.9)			axicabtagene ciloleucel (Value RR 2020 = 333,867)		
		n	Extra. IC Mean (Std)	Total Mean (Std)	n	Extra. IC Mean (Std)	Total Mean (Std)	n	Extra. IC Mean (Std)	Total Mean (Std)
04M074	7,887.81	0			1	21,186.8 (.)	367,663.4 (.)	0		
17C084	21,855.71	0			0			2	18,548.9 (7,320.6)	398,336.2 (1,970.7)
17M064	8,197.67	0			2	11,890 (1,528.6)	324,785.1 (1,236.5)	1	10,197.3 (.)	349,110.5 (.)
17M083	18,119.42	5	13,644.8 (3,491.5)	349,072.3 (8,985.1)	0			0		
17M084	34,849.92	15	16,615.1 (6,202.9)	384,109.4 (29,330)	0			0		
17M093	12,002.84	5	9,041.9 (1,518.1)	339,390.4 (13,603.1)	0			0		
17M094	24,687.03	11	10,012.1 (4,398)	368,617.4 (21,165.8)	1	19,024.1 (.)	353,064.7 (.)	0		
17M151	1,578.14	0			0			1	808.2 (.)	336,636.4 (.)
17M152	4,492.29	0			1	0 (.)	316,038.9 (.)	0		
17M153	8,254.22	0			28	6,880.1 (4,212.2)	336,596.8 (27,496.8)	18	6,629.7 (3,885.6)	353,492.9 (7,070.2)
17M154	14,239.62	0			90	8,885.3 (50,605.9)	343,152.2 (15,672.6)	233	8,152.2 (5,596.2)	364,645.2 (12,857.5)
27Z023	50,670.13	0			0			5	10,496.9 (4,718.8)	407,112 (10,172.8)
27Z024	69,769.28	1	34,670.9 (.)	520,066.5 (.)	3	8,721 (232.4)	403,680.3 (1,248)	7	14,659.4 (5,275)	425,847.8 (10,286.7)
27Z03Z	18,622.81	0			0			1	24,995.3 (.)	414,579.1 (.)
Total		37	13,934.1 (6,697.1)	372,400.3 (37,183.9)	126	8,716.2 (4,992.2)	342,903.1 (21,274.4)	268	8,406.5 (5,745.9)	366,562.3 (17,581)

Note: Diagnosis Related Group (DRG); Value at 100% of the Responsibility Rate (Value RR); Extra charge for Intensive Care (Extra IC); Frequency (n); Standard deviation (Std); Missing standard deviation due to single observation (.); Total cost associated with the DRG, CAR-T cells, and all extra charges included except patient transportation (Total Cost). DRG 04M074 Respiratory infections and inflammations, age over 17, Level 4; DRG 17C084 Minor interventions of disease classification CMD17, Level 4; DRG 17M064 Chemotherapy for other tumors, Level 4; DRG 17M083 Acute leukemia, age less than 18 years, Level 3; DRG 17M084 Acute leukemia, age less than 18 years, Level 4; DRG 17M093 Acute leukemia, age over 17 years, Level 3; DRG 17M094 Acute leukemia, age over 17 years, Level 4; DRG 17M151 Lymphomas and other lymphoid malignancies, Level 1; DRG 17M152 Lymphomas and other lymphoid malignancies, Level 2; 17M153 Lymphomas and other lymphoid malignancies, Level 3; DRG 17M154 Lymphomas and other lymphoid malignancies, Level 4; DRG 27Z023 Hematopoietic stem cell allografts, Level 3; DRG 27Z024 Hematopoietic stem cell allografts, Level 4; DRG 27Z03Z Hematopoietic stem cell autografts. The costs do not take into account the 54 stays for which the CAR-T cell products were financed by the companies. Costs were expressed in Euros for 2019-2020.