



# CAR-T Therapy

## WHITE PAPER



European Cancer  
Patient Coalition

Cancer is a leading cause of death worldwide with increasing incidence and mortality. Over the years, several conventional treatments have been developed and for decades, therapy relied on the conventional surgery, chemotherapy, and radiotherapy. However, the effectiveness of such approaches remains limited, especially to patients with refractory or relapsed diseases. Hence, there is an ongoing search for therapies with improved outcomes, one of them is immunotherapy, such as Chimeric Antigen Receptor T-cells (CAR-T), which enhances the patient's immune response capacity. These are treatments used for severe diseases associated with considerable societal costs and can offer sustained disease remission and even cure for some patients with relapsed or refractory disease, which have otherwise limited options and poor prognosis <sup>1,2,3,4</sup>.

CAR-T cells are genetically modified T-cells which express a CAR corresponding to a specific tumour antigen, thus making it able to recognize and target tumour cells exclusively, unlike conventional treatments. The one-time infusion of CAR-T therapy has shown promising clinical outcomes, with rates of lasting survival benefits of 45 to 51% and with full-recovery of up to 92% of patients with haematological malignancies. This has led to a positive scientific recommendation from the European Medicines Agency (EMA), and approval of the European Commission and the U.S. Food and Drug Administration (FDA) <sup>5</sup>. In 2018, the European Commission approved Novartis' *Kymria*<sup>®</sup> (*Tisagenlecleucel*), and Kite/Gilead's *Yescarta*<sup>®</sup> (*Axicabtagene ciloleucel*) as the first two for treatments. In December 2020, Kite/Gilead's *Tecartus*<sup>®</sup> (*KTE-X10*) was also approved by the EC, followed by BMS' *Abecma*<sup>®</sup> (*Idecabtagene Vicleucel*) in August 2021, and BMS' *Breyanzi*<sup>®</sup> (*Ilisocabtagene maraleucel*) in April 2022 <sup>6,7,8,9,10</sup>. Additionally, in March 2022, the EC positively recommended the granting of a conditional marketing authorisation to *Carvykti*<sup>®</sup> (*ciltacabtagene autoleucel*), from Janssen-Cilag International NV <sup>11</sup>. Despite approvals, patients are still facing barriers to treatment. Indeed, CAR-T is one of the most expensive therapeutic options, which can impact healthcare budgets and patients<sup>12</sup>.

In view of the foregoing, this white paper aims to bring to light the information available on the current situation of CAR-T therapies in term of accessibility, delivery, pricing, reimbursement, as well as ethics.

1 Ronco, V., Dilecce, M., Lanati, E., Canonico, P. L., & Jommi, C. (2021). Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations? *Journal of Pharmaceutical Policy and Practice*, 14(1), 1-11.

2 Kozani, P., Rahbarizadeh, F., & Khoshtinat Nikkhou, S. (2021). Strategies for Dodging the Obstacles in CAR T Cell Therapy. *Frontiers In Oncology*, 11. doi: 10.3389/fonc.2021.627549

3 Hartmann, J., Schüßler-Lenz, M., Bondanza, A., & Buchholz, C. (2017). Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts. *EMBO Molecular Medicine*, 9(9), 1183-1197. doi: 10.15252/emmm.201607485

4 Snider, J. T., Brauer, M., Kee, R., Batt, K., Karaca-Mandic, P., Zhang, J., & Goldman, D. P. (2019). The potential impact of CAR T-cell treatment delays on society. *Am. J. Manag. Care*, 25, 379-386.

5 Thielen, F. W., van Dongen-Leunis, A., Arons, A. M., Ladestein, J. R., Hoogerbrugge, P. M., & Uyl-de Groot, C. A. (2020). Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. A societal view. *European journal of haematology*, 105(2), 203-215.

6 Subklewe, M., von Bergwelt-Baildon, M., & Humpe, A. (2019). Chimeric antigen receptor T cells: a race to revolutionize cancer therapy. *Transfusion Medicine and Hemotherapy*, 46(1), 15-24.

7 Miliotou, A., & Papadopoulou, L. (2018). CAR T-cell Therapy: A New Era in Cancer Immunotherapy. *Current Pharmaceutical Biotechnology*, 19(1), 5-18. doi: 10.2174/1389201019666180418095526

8 EMA. (2021a). *Tecartus* - European Medicines Agency. Retrieved from <https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus>

9 EMA. (2021b). *Abecma* - European Medicines Agency. Retrieved from <https://www.ema.europa.eu/en/medicines/human/EPAR/abecma>

10 BMS. (2022). Bristol Myers Squibb Receives European Commission Approval for CAR T Cell Therapy Breyanzi (Ilisocabtagene maraleucel) for Certain Forms of Relapsed or Refractory Large B-cell Lymphoma. Retrieved from: <https://news.bms.com/news/corporate-financial/2022/Bristol-Myers-Squibb-Receives-European-Commission-Approval-for-CAR-T-Cell-Therapy-Breyanzi-Ilisocabtagene-maraleucel-for-Certain-Forms-of-Relapsed-or-Refractory-Large-B-cell-Lymphoma/default.aspx>

11 EMA. (2022) *Carvykti* – European Medicines Agency. Retrieved from: [https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-carvykti\\_en.pdf](https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-carvykti_en.pdf)

12 Sarkar, R. R., Gloude, N. J., Schiff, D., & Murphy, J. D. (2019). Cost-effectiveness of chimeric antigen receptor T-cell therapy in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia. *JNCI: Journal of the National Cancer Institute*, 111(7), 719-726.

Patients' access to innovative therapies like CAR-T, is affected by various factors. In Europe, the EMA needs to provide a positive evaluation of the quality, safety, and clinical efficacy, for the therapy product to receive centralized market authorisation by the European Commission. This authorisation from the EC covers all EU Member States. However, obtaining market access is done at national level. To obtain national market access, the product needs to be evaluated by a national HTA body on basis of the criteria of medical need, cost-effectiveness, budget impact, and relative clinical effectiveness. As each country makes the decision individually, it leads to EU-wide disparities in criteria, processes, and decision, which may impact access as well. Once the product is positively evaluated by the HTA body, it receives reimbursement by the country and can be prescribed. Further, the accreditation for centres offering CAR-T therapies are regulated by policies established by National Authorities through the Joint Accreditation Committee ISCT-Europe and EBMT (JACIE) and multidisciplinary medical teams. However, the finalization of the administrative procedures and the integration into the health system vary from one country to the other. Additionally, there are barriers related to the awareness of the prescribers concerning available therapies. Thus, there is a lack of uptake with regards to the prescription, although therapies might be available and reimbursed <sup>13,14,1</sup>. Due to their expected high clinical benefits, CAR-T therapies such as Kymriah® and Yescarta®, have been granted approval and reimbursement in most EU countries. Yescarta has been granted approval in all the 27 EU countries, but reimbursement only in 7; whereas Kymriah had been granted approval and reimbursement equally in 13 countries <sup>15,1</sup>.

In France, access to new products is possible before Market Authorization through an Early Access Program (EAP). However, the EAP does not equal reimbursement, as is it does not require any prior HTA. This means EAP is not available for all therapies and patients, and the delay in formal reimbursement can also impact the access to the therapies <sup>12</sup>.

In Germany, after receiving the EC marketing authorization, therapies are immediately reimbursed. However, the innovative nature of the therapy can delay the uptake in prescription. CAR-T are integrated in a slow fashion into clinical practice, as both professionals and patients need time to become aware and familiar with the new therapy, or until the HTA process is completed <sup>1,16,17</sup>.

13 Rial-Sebbag, E., & Chabannon, C. (2018). Chapitre 6. Enjeux juridiques et pour le système de santé du développement d'une nouvelle classe de médicaments de thérapie innovante en onco-immunologie : les "Car-T Cells". *Journal international de bioéthique et d'éthique des sciences*, 29(2), 113-128.

14 Vintura, 2020. Everyday counts – Improving time to patient access to innovative oncology therapies in Europe. Retrieved from: <https://www.efpia.eu/publications/downloads/efpia/every-day-counts-improving-time-to-patient-access-to-innovative-oncology-therapies-in-europe/>

15 Ellis, L., & Masters, W. (2019). Accessing CAR-T Therapies. Retrieved from <https://invivo.pharmaintelligence.informa.com/IV124390/Accessing-CAR-T-Therapies>

16 Strategy&. (2020). CAR T-cell therapies in Germany: Overview of political fields of action for better patient access. Retrieved 1 October 2021, from [https://www.gilead-dialog.de/wp-content/uploads/2020/05/CAR-T-Studie\\_PWC\\_2020\\_09.pdf](https://www.gilead-dialog.de/wp-content/uploads/2020/05/CAR-T-Studie_PWC_2020_09.pdf)

17 Chomienne C, Sierra J, Einsele H, Jäger U. (2019). EHA Guidance. The process of CAR-T cell therapy in Europe. HemaSphere; 03:04. <http://dx.doi.org/10.1097/HS9.0000000000000280>



In Italy, the regional governments manage the accreditation process, alongside AIFA (Agenzia Italiana del Farmaco) and the Italian Medicine Agency regulating the criteria for centers' selection. There is also a possibility for the MAH to request the recognition of "Innovative status" for their product. These Innovative medicinal product benefit from direct access to regional lists, dedicated funds and are not subjected to temporary price reductions. However, innovativeness needs to be appraised based on three criteria: *"unmet medical need, added therapeutic value and quality of available evidence and lasts maximum 3 years"*<sup>1</sup>.

## CROSS-BORDER

There exist cross-border arrangements made to facilitate the access of care abroad, be it at National level or at EU level. Additionally, the Directive 2011/24/EU was adopted in 2011, providing patients the right to seek care in another EU MS, under certain circumstances. However, refusal may happen if the same therapy is available in the home MS and can be received within appropriate timing. This can hamper the uptake, since the benefit baskets patients are provided within their home MS may influence the quantity and quality of care they can receive abroad. Patients from richer countries will have more opportunities and benefits than those of poorer countries. Indeed, there is a lack of uptake also due to other factors, such a lack of proper knowledge from the patients about their rights, differences in administrative systems, and costing and reimbursement frameworks between the MS<sup>18,19</sup>. CAR-T therapy is not yet reimbursed in every MS, which is an added barrier to cross-border patient access. Thus, cross-border access, be it regional, national or between insurers, could be impaired due to the required cross-border reimbursement system which are not fully placed yet and still need further agreements between the various parties<sup>20,17</sup>. Furthermore, many patients from the lower income and Eastern countries lack access to these promising therapies due to their difficulties in reimbursement<sup>21</sup>.

## Pricing and Costs

Member states have sovereignty when it comes to pricing and reimbursement of pharmaceuticals. When it comes to high-cost medicines that have a substantial therapeutic value, such as CAR-T, in a majority of MS, a Health Technology Assessment, or economic evaluation is done to make pricing and reimbursement decisions<sup>22,23,24</sup>. However, only a few HTA

18 EPHA. (2015). Closing Gaps, Stimulating Health Equity: EPHA Report on the Implementation of the Cross-border Healthcare Directive. Retrieved from: <https://epha.org/wp-content/uploads/2015/10/EPHA-report-on-implementation-of-cross-border-health-directive.pdf>

19 Ostuni, E., Eschgaeller, B., Chou, W., Bilbao, I. A., Harrington-Smith, K., Jousseume, E., ... & Blumer, K. (2020). Commercialising CAR-T Therapies: The Evolution of a Revolution. In Second Generation Cell and Gene-based Therapies (pp. 747-775). Academic Press.

20 van Overbeeke, E., Michelsen, S., Toumi, M., Stevens, H., Trusheim, M., Huys, I., & Simoens, S. (2020). Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions. *Drug Discovery Today*.

21 Heine, R., Thielen, F. W., Koopmanschap, M., Kersten, M. J., Einsele, H., Jaeger, U., ... & Uyl-de Groot, C. A. (2021). Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future. *HemaSphere*, 5(2).

22 Ranson, P. (2020). Medicines pricing and reimbursement: EU | Practical Law. Retrieved 1 October 2021, from [https://uk.practicallaw.thomsonreuters.com/w-005-2025?contextData=\(sc.Default\)](https://uk.practicallaw.thomsonreuters.com/w-005-2025?contextData=(sc.Default))

23 Vogler, S., & Martikainen, J. (2014). Pharmaceutical Pricing in Europe. *Pharmaceutical Prices in the 21st Century*, 343-370. doi: 10.1007/978-3-319-12169-7\_19

24 WHO. (2018). Medicines reimbursement policies in Europe (2018). Retrieved from <https://www.euro.who.int/en/publications/abstracts/medicines-reimbursement-policies-in-europe>

bodies have appropriate long-term pathways for ATMPs. Additionally, there is a wide variation in HTA methods, criteria, and decision-making processes, which also impact the pricing of ATMPs <sup>25</sup>. In Europe, CAR-T therapies are priced approximatively at 320,000 EUR, making them the most expensive cancer treatment currently on the market <sup>19,6</sup>. The costs of these therapies are not limited to the acquisition costs only, but include hospitalization, intensive care unit stays, treatments for possible adverse events, laboratory work, alongside out-of-pocket spending from patients due to travel necessities and stays near the administration facilities. The utilization of CAR-T therapies can result in high overall opportunity costs and healthcare spending, thus changing the allocation of the healthcare budget <sup>19,18,26,27,28,17</sup>. Additionally, CAR-T are one-shot therapies with lifelong benefits, which may lead to long-term positive economic impact <sup>1,18</sup>.

Beyond the costs, the cost-effectiveness of these therapies is an important factor to consider, and adding other aspects such as informal care costs, productivity losses/gains, travel costs to conduct it from a societal perspective is more interesting. The results have shown that assessing the cost-effectiveness from a societal perspective increased estimates of total costs and ICERs. It made possible to capture the costs from a broader economic perspective, indicating significant benefits for both society and patients <sup>29</sup>.

Other studies also found that despite the high costs, CAR-T therapy may be cost-effective when compared to other standard cancer therapies, mainly due to the survival advantage which CAR-T offers to the patients and the increase in QALYs per life gained, which in the studies were under the threshold for both healthcare and societal perspective. These results were in line with the results from the National Institute for Health and Care Excellence (NICE) and Institute for Clinical and Economic Review (ICER) studies. Independent of their different approaches, the studies found CAR-T to be cost-effective and outperform 48 to 72% of other treatments, even more so for the paediatric indications <sup>10,30,31</sup>.

## Health Technology Assessment (HTA) and Reimbursement

In the European Union, decision-making on pricing and reimbursement of medicinal products is done at National level. Thus, the process can be variable depending on the MS and the stakeholders involved <sup>6,22,32</sup>. The criteria used for decision-making vary but some common ones

25 ARM. (2019). Getting Ready: Recommendations for Timely Access to Advanced Therapy Medicinal Products (ATMPs) in Europe. Retrieved 1 October 2021, from <http://alliancerm.org/wp-content/uploads/2019/07/ARM-Market-Access-Report-FINAL.pdf>

26 Ran, T., Eichmüller, S. B., Schmidt, P., & Schlander, M. (2020). Cost of decentralized CAR T-cell production in an academic nonprofit setting. *International Journal of Cancer*, 147(12), 3438-3445.

27 Jönsson, B., & Wilking, N. (2007). The burden and cost of cancer. *Annals Of Oncology*, 18, iii8-iii22. doi: 10.1093/annonc/mdm097

28 Jönsson, B., Hofmarcher, T., Lindgren, P., & Wilking, N. (2016). The cost and burden of cancer in the European Union 1995–2014. *European Journal Of Cancer*, 66, 162-170. doi: 10.1016/j.ejca.2016.06.022

29 Thielen, F. W., van Dongen-Leunis, A., Arons, A. M., Ladestein, J. R., Hoogerbrugge, P. M., & Uyl-de Groot, C. A. (2020). Cost-effectiveness of Anti-CD19 chimeric antigen receptor T-Cell therapy in pediatric relapsed/ refractory B-cell acute lymphoblastic leukemia. A societal view. *European journal of haematology*, 105(2), 203-215.

30 Lin, J. K., Muffly, L. S., Spinner, M. A., Barnes, J. I., Owens, D. K., & Goldhaber-Fiebert, J. D. (2019). Cost effectiveness of chimeric antigen receptor T-cell therapy in multiply relapsed or refractory adult large B-cell lymphoma. *Journal of Clinical Oncology*, 37(24), 2105-2119.

31 Baumgardner, J. R., Brauer, M. S., Zhang, J., Hao, Y., Liu, Z., & Lakdawalla, D. N. (2020). CAR-T therapy and historical trends in effectiveness and cost-effectiveness of oncology treatments. *Journal of comparative effectiveness research*, 9(5), 327-340.

32 Hagenbeek, A., Gribben, J., Jäger, U., Kapitein, P., Merlini, G., Piggin, M., ... & Doeswijk, R. (2020). Fair Pricing of Innovative Medicines: An EHA Position Paper. *HemaSphere*, 4(5).

are therapeutic benefit, medical necessity, safety, cost-effectiveness, and budget impact. Even though there have been efforts to harmonize and align these assessment methods across all EU Member states, the techniques and criteria used still vary greatly, along with payer's decision to use HTA for coverage decisions <sup>18,22</sup>.

Consequently, CAR-T has had a limited market uptake in Europe due to the difficulties in obtaining reimbursement in all countries <sup>33</sup>. Manufacturers are willing to cooperate with payers to reach reimbursement agreements, proposing options such as price-volume agreements, discounts, outcome-based agreements (OBs), value-based agreements, and price by indication. However, many countries can still not afford it <sup>19</sup>. Most studies are limited to France, Germany, Italy, Netherlands, Austria, and the United Kingdom, which are already reimbursing CAR-T therapies, but little is investigated on the other EU countries, especially Eastern countries, which might have greater difficulties in reimbursing these therapies <sup>19,31</sup>. These disparities can have a negative impact on the overall price levels, accessibility, value for money and sustainability of the health systems <sup>30</sup>.

Several EU countries have adopted diverse pricing and reimbursement schemes. France has adopted the coverage with evidence development schemes, Italy and Spain opted for outcome-based staged payments, Germany negotiated a pay-for-performance agreement, and Austria has various cost-sharing agreements in place. In the Netherlands, Kymriah® is reimbursed through the standard scheme as its budget impact was found to be relatively low, while Yescarta® was placed in a 421 day “lock” before being reimbursed <sup>19,34</sup>. France, Germany, Italy, and Spain have mainly single-payer healthcare systems, where public health insurance covers most of the population, whereas Italy and Spain have more decentralized systems, where healthcare services are under regional authority. Both Kymriah® and Yescarta® have obtained reimbursement in these countries, with similar list prices, as shown in Table 5 <sup>35,1</sup>.

Outcome-based reimbursement schemes have become more prominent over the last years, due to the uncertainty on the risk-benefit of the therapies <sup>1,33</sup>. Outcome-based spread payments may solve the immediate unaffordable budget impact due to high upfront prices while solving the short and long-term clinical uncertainties <sup>31</sup>. However, there is still some reluctance to the adoption of OBR schemes in Europe, as in single-payer countries the wish for a long-term scheme may be high. Furthermore, there is a need to consider the feasibility of patient follow-up, meaningful outcomes for payers, the availability of a data collection infrastructure and resources, such as professional staff, registries, etc <sup>33</sup>.

CAR-T are promising therapies for haematological affections. The current pricing might be an affordability barrier on the healthcare system, however, OBR and spread payments might be a

33 Michelsen, S., Nachi, S., Van Dyck, W., Simoons, S., & Huys, I. (2020). Barriers and Opportunities for Implementation of Outcome-Based Spread Payments for High-Cost, One-Shot Curative Therapies. *Frontiers in pharmacology*, 11.

34 Petrou, P. (2019). Is it a chimera? A systematic review of the economic evaluations of CAR-T cell therapy. *Expert review of pharmacoeconomics & outcomes research*, 19(5), 529-536.

35 Jørgensen, J., & Kefalas, P. (2021). The use of innovative payment mechanisms for gene therapies in Europe and the USA. *Regenerative Medicine*, 16(04), 405-422.

solution to solve this barrier. Further, there are differences in reimbursement schemes between the different MS, which hinders the uptake of Car-T therapy throughout the EU. Indeed, in some countries, the associated costs of pre- and post-care are not reimbursed sufficiently, in others, reimbursement of CAR-T therapy is not yet available. However, according to various studies and evidence, CAR-T treatments seem to be affordable and attainable, and payers are willing to negotiate <sup>19,24,29,32</sup>.

## Ethics

CAR-T therapies raise some bioethical issues, notably regarding their affordability <sup>36</sup>. Development costs are particularly high due to the volume, and quality of safety and efficacy data required by health agencies before they put any drug on the market <sup>11</sup>. The access to these novel therapies may be hindered as there is an unbalanced distribution of wealth in the population, and only people who can afford them can have access to it <sup>34</sup>. Another issue is prioritization and appropriate incentivisation in R&D. Indeed, there are various cancer therapies available which seem to have inferior value compared to CAR-T, yet they are approved by European Commission and FDA and are reimbursed and prescribed. It is important to assess whether we should continue to pay premiums for therapies that provide incremental benefits, whereas budget constraints are limiting access to more transformative therapies, such as CAR-T <sup>28</sup>.

## EQUITABILITY

The access and use of CAR-T therapy depends on various factors and their complex interrelationships, namely referring physicians, payers, manufacturers, and therapy administration centres. These factors may become barriers to access <sup>37</sup>. Referring physicians need appropriate education about CAR-T to assist the patients during the process and ensure timely referrals. This can have an immediate impact on treatment outcome and needs joint efforts from treatment centres, manufacturers, professional societies, and policy makers. Related to patient referral, appropriate patient selection for CAR-T could also be a challenge as selection criteria are in constant evolution <sup>35</sup>. Furthermore, waiting time during the CAR-T cells manufacturing can be long. According to past studies, the waiting time can range from 17 to 54 days, which can be a psychologically challenging and stressing time for the waiting patients. Additionally, some patient may need bridging therapy to control the disease in the meanwhile, or they can become ineligible for CAR-T and end up passing away due to the fast progression of the disease <sup>24,35</sup>.

Moreover, carers and patient out-of-pocket costs can also be impacted. During the CAR-T therapy, it is essential for patient to have a caregiver available to help them adhere to their care

<sup>36</sup> Carvalho, M., Sepodes, B., & Martins, A. P. (2017). Regulatory and scientific advancements in gene therapy: state-of-the-art of clinical applications and of the supporting European regulatory framework. *Frontiers in medicine*, 4, 182.

<sup>37</sup> Kansagra, A., Farnia, S., & Majhail, N. (2020). Expanding Access to Chimeric Antigen Receptor T-Cell Therapies: Challenges and Opportunities. *American Society of Clinical Oncology Educational Book*, 40, e27-e34.

plan, monitor the possible toxicities and be an emotional support during this intense process. Lack of caregiver can be a barrier to the therapy and influence the decision to proceed with it. Further, patients need to stay at proximity of the treatment centre and that for approximately four weeks, thus adding to the financial burden of both patient and caregivers. Consequently, another barrier to access would be the distance from the therapy centre <sup>35</sup>. Furthermore, even though the overall impact of CAR-T therapies on the budget might be like cheaper treatment for a larger population's impact, the emotional impact of high prices might be stronger, and thus undermine equity <sup>1</sup>.

Finding a balance between quality and access is another barrier. In the context of widening the access of CAR-T at the site of administration, the question of optimisation of patient access is central. There is a need for an appropriate infrastructure able to handle all logistics in the CAR-T therapy process, while still maintaining the quality in the chain of custody and identity for the products. It is important that CAR-T therapies are administered in experienced centres with established quality infrastructure and personnel, such as ones accredited by FACT <sup>35</sup>.

## Delivery

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The EBMT and JACIE recommend for CAR-T cells therapy to be delivered within a framework of an accredited HCT.

### CAR-T DELIVERY DURING COVID-19

Considering the disruptions caused by the ongoing COVID-19 pandemic, there are considerations to account for regarding the administration of CAR-T therapies during a pandemic. There is a need to harmonize opinions on the delivery of these therapies to counter the potential disruptions, such as staff shortage, lack of availability, reagent shortage, etc. Ensure dedicated, adequate, and sufficient staff throughout the whole process in order to prevent possible shortage. It is important to ensure the continuous availability of a cellular therapy team member with the capacity to respond to COVID-19 issues, establish a centre specific workflow for COVID-19-positive patients, and consider creating COVID-19-specific inpatient units with dedicated rounding teams. A triage algorithm should be established to delay and/or cancel as many CAR-T activities as possible. Preferentially select patients who are most likely to benefit, who have no effective alternative treatment options, and in whom the risk of CAR-T toxicities is lower <sup>38</sup>.

To organize appropriate adjustments and ensure the protection of professionals while delivering the best outcomes to patients, a multidisciplinary team is crucial. Delaying or dismissing the CAR-T therapies is not realistic as these therapies have a curative potential

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<sup>38</sup> Bachanova, V., Bishop, M. R., Dahi, P., Dholaria, B., Grupp, S. A., Hayes-Lattin, B., ... & CAR T-cell Consortium. (2020). Chimeric antigen receptor T cell therapy during the COVID-19 pandemic. *Biology of Blood and Marrow Transplantation*, 26(7), 1239-1246.



for patients with dismal prognosis, given the fast disease progression. It would be more reasonable to implement strict measures to mitigate the risk of COVID-19 pre-“CAR-T”, such as screening and preventive measures, as well as post-“CAR-T”, such as care delivery, education, supportive care infection prophylaxis, etc <sup>36</sup>.

## ELIGIBILITY

The estimated number of patients being eligible for CAR-T therapy for the period of 2019-2029 would be ranging from Eurostat forecast of 95954 patients to the Globocan forecast of 111545 patients, and that for paediatric Acute Lymphocytic Leukaemia (pALL), Diffuse Large B-Cell Lymphoma (DLBCL), Mantle Cell Lymphoma (MCL), Follicular Lymphoma (FL), Acute Myelogenous Leukaemia (AML), Chronic Lymphocytic Leukaemia (CLL), Multiple Myeloma (MM). Hence, it is important to establish the selection criteria for patients that could benefit from CAR-T therapy <sup>19,39</sup>. We can also infer that the selection criteria used for admission in the CAR-T trials could be similarly used for normal therapy selection. According to research, the eligible patients need to meet the criteria of relapsed/refractory diffuse large B-cell lymphoma or more systemic therapies, and their attending physician need to consider CAR-T as the right treatment. The presence of a multidisciplinary team is a necessity. Indeed, decisions to treat with a CAR-T therapy should be made collectively by a multidisciplinary team at an expert centre, with the patient's medical history and physical conditions being considered <sup>32,40,41</sup>.

## EU Regulations and Frameworks

In 2007, Regulation (EC) No.1394/2007 presenting a clear definition of ATMPs was adopted. This regulation, alongside the regulation 726/2004, outlines the marketing authorization (MA) procedures and requirements describe post-authorization obligations, such as risk management and efficacy<sup>34,15</sup>. Post-authorization requirements include educational programs for healthcare professionals and patients, execution of a Post-Authorisation Safety Study (PASS) and submission of Periodic safety update reports (PSURs) at specific intervals. Kymriah® and Yescarta® were required the same post-authorisation measures, apart from the need of a Post-Authorisation Efficacy Study (PAES) study for patients with refractory or relapsed DLBCL and for paediatric patients under the age of 3 years with ALL <sup>42,43,44</sup>.

39 Chabannon, C., & Larghero, J. (2018). "Considerations pertaining to cell collection and administration of industry-manufactured autologous CAR-T cells, in relation to French healthcare organization and regulations." *Current research in translational medicine* 66, no. 2, 59-61.

40 Greinix, H. T., Attarbaschi, A., Girschikofsky, M., Greil, R., Holter, W., Neumeister, P., ... & Jaeger, U. (2020). Ensuring centre quality, proper patient selection and fair access to chimeric antigen receptor T-cell therapy: position statement of the Austrian CAR-T Cell Network. *memo-Magazine of European Medical Oncology*, 13(1), 27-31.

41 Yakoub-Agha, I., Chabannon, C., Bader, P., Basak, G. W., Bonig, H., Ciceri, F., ... & Kröger, N. (2020). Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Haematologica*, 105(2), 297.

42 Detela, G., & Lodge, A. (2019). EU regulatory pathways for ATMPs: standard, accelerated, and adaptive pathways to marketing authorisation. *Molecular Therapy-Methods & Clinical Development*, 13, 205-232.

43 Directive 2001/83. Community code relating to medicinal products for human use. European Parliament, Council of the European Union. Retrieved from: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2001:311:FULL&from=EN>

44 Regulation 1394/2007. On advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. European Parliament, Council of the European Union. Retrieved from <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394&from=EN>

In EU, Kite/Gilead's Yescarta® and Novartis' Kymriah® are the first two ATMPs to have obtained Market Authorization, in 2018. Since then, two more therapies have been approved: Bristol Myers Squibb's Abecma® and Kite/Gilead's Tecartus®, and more are in the process of being assessed in clinical trials. Yescarta® and Kymriah® represent the first CAR-T cells to be marketed in the EU and brought to the market through the priority medicine scheme (PRIME)<sup>40,45,8,9</sup>.

The EMA has introduced PRIME in 2016, to accelerate clinical development and allow new medicines to reach the market and patient in an early fashion. This Prime scheme is the main mechanism by which support is provided, and the eligibility to this scheme was granted to Kymriah following the demonstration of initial clinical efficacy, in the CCTL019B2202 trial. The EMA included recommendations regarding comparability between processes and manufacturing sites, development of risk minimization plans and registry of long-term safety data, as well as guidance on the PIP<sup>40</sup>.

Additionally, prior to the Regulation (EC) No. 1394/2007 on ATMPs, there was the directive 2001/83/EC which established a community code on medicinal products for human use. The Regulation (EC) No. 1394/2007 modified and added a clause to the Directive 2001/83/EC which provides exclusion from the centralized procedure to certain drugs. This clause is also called the "Hospital Exemption", which means the product is prepared on a non-routine basis, within one MS and used at a specific hospital, for a specific/single patient. This clause enables the MS to provide provisory access to the ATMPs without a marketing authorization, hence, these products are not intended for marketing and are often manufactured by hospitals themselves. Indeed, HE is useful in a scenario where there are high unmet medical needs, yet no product is available on the market; it exceptionally gives patients access to new medicinal products, provided under controlled conditions. However, CAR-T product cannot be used by every hospital, as it requires advanced practical skills and expertise, as well as specific equipment and facilities for it to become a qualified treatment centre. Some of the eligibility criteria for qualified treatment centres are a high expertise in stem cell transplant, presence of an expert physician, ICU environment able to manage any eventual adverse events, patient support capabilities, etc. Hence, it's important for HE to be used in its true purpose, and not to circumvent the clinical trials and MA rules<sup>15,17,41,42,46</sup>.

## Recommendations

Conventional treatments have incremental costs with incremental benefits which affect the budget in the long-term. Single-administration therapies such a CAR-T have upfront costs which impact the budget in the short term, with possible long-term benefits. Additionally, the upfront high costs of CAR-T could be curbed in the long-term through many solutions, such as

45 Albinger, N., Hartmann, J. & Ullrich, E. Status and perspective of CAR-T and CAR-NK cell therapy trials in Germany. *Gene Ther* 28, 513–527 (2021). <https://doi.org/10.1038/s41434-021-00246-w>

46 ARM. (2020). Recommendations for the use of Hospital Exemption. Retrieved 1 October 2021, from [https://alliancerm.org/sites/default/files/ARM\\_position\\_on\\_HE\\_final.pdf](https://alliancerm.org/sites/default/files/ARM_position_on_HE_final.pdf)

alternative payment methods, namely OBR or managed entry agreement. OBRs address the data uncertainties coming from the long-term sustainability of treatments effects; hence, they can enable the adjustment of payments over time. This is particularly valid in the case of single-administration therapies, such as CAR-T, where profitability of cost-effectiveness can increase without the risk of decreasing the product value. Furthermore, according to many studies, even though the therapy is expensive, it can also be cost-effective. Beyond the costs, CAR-T has proved to be a curative innovation, which could offer a solution where there was none before, thus having a great impact on patients. Despite the prices, CAR-T offers a better value for money than standard therapies, and in the long run has potential to be more cost-effective to society and a valuable investment for patients likewise. Would it be ethical to continue to fund and provide treatments that would offer them lower value? According to the WHO, public resources should not be wasted on treatments that offer less than any other treatments<sup>33</sup>.

There was very little to no information on the possible cross-border access to CAR-T. The unavailability of information on the therapies in some EU member states enhances issues around access for patients, even more so for cross-border access. A better dissemination of the patients' cross-border rights can enhance the uptake. Further, a general repository of the centres offering or directing to CAR-T therapies could also help ease the access. The Cross-border Healthcare Directive is quite complex and would benefit from simplification. Further than that, seeing the wide differences between the MS, alignment between their frameworks is a need. Indeed, with the emergence of more novel therapies, such as CAR-T, it is important to harmonize the procedures and criteria and create sustainable long-term pathway. After 10 years of being in place, the cross-border directive is being evaluated by the commission, hence this is the perfect time to make some improvements for the future.

Coordination and collaboration between member states is important to ensure fair access to all citizens. However, emphasis should be put on the national economies to not apply a one-size-fits-all, which could greatly disadvantage lower-income countries. To be able to develop a 'fair pricing' approach, it is necessary for manufacturers to be transparent about their costs. However, there are diverging opinions between the various stakeholders, who agree to disagree on the subject. Furthermore, the whole process, from drug development to pricing and reimbursement should be patient-centric, and the new drugs should not only be safe and effective but also be accessible and affordable<sup>30</sup>. However, the causes of these high prices are complex and varied, hence no single model or measure will be enough to decrease prices and keep CAR-T accessible and affordable. A collaboration of all the centres involved in the administration of CAR-T therapy would help in ensuring fair access for all citizens, the selection of appropriate patients, the wise and proper use of the resources, EU or National registration, collection of RWEs ensuring retrospective analyses of predictive factors, the creation of a network for studies, and avoiding hospital tourism<sup>38</sup>.

It is important to encourage innovation and ensure equitable and affordable access to novel therapies, since the principle of the European laws governing innovative therapy drugs is to

support and promote the dissemination and equal access of these technologies to all the citizens residing in the European Territory. All patient residing in the European Union have a right to a fair chance to access these novel therapies and it is our ethical duty to provide them with the best chances of survival, and that is what CAR-T therapy is and will be for many people. CAR-T will provide people with a chance of survival, which is possible, available, and already proved to be feasible in the long term. Therefore, CAR-T therapies need to be more accessible and affordable for the patients.

Further, seeing as the therapy is a long and strenuous process, the patients-caregivers dyads need more support throughout the whole process. Providing support through all the steps of the therapy, and throughout their survivorship journey will be just as important, as CAR-T therapy will affect patient and caregivers in a lifelong fashion. Indeed, it is important for the therapy to be reimbursed to not put the patients in financial burden and give fair access to everyone, independently of their socio-economic classes. The associated costs need to be considered as well, as these out-of-pocket costs may be the ones to burden the patients and caregivers, be it financially or mentally. Beyond alleviating the financial burden incurred by the therapy and its associated costs, it is also very important to provide patients and caregivers with an easy access to ample and appropriate information about not only CAR-T but also their journey before, during, and after the treatment. In parallel, it is of high importance to also educate healthcare providers about CAR-T therapy and the patient journey as a whole, seeing as they will be the first point of contact for patients and caregivers, and will help in bridging the gap between specialists and the patient-caregiver dyad. Increasing the professionals' knowledge in CAR-T will also increase the access, as patient referral will be done more appropriately. Moreover, patients and caregivers need to be included in the decision-making process, as they can provide an incredible resource of information and improvement ideas.



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