



Celebrating the registration of 9.000 patients treated with CAR T cells in the EBMT registry: Collection of real-world data in the context of hematopoietic cellular therapies

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ABSTRACT

The European society for Blood and Marrow Transplantation (EBMT) has a long-standing interest in the evaluation of hematopoietic cell transplantation. More than three decades ago, its members established a continental registry. Today, more than 700,000 patients have been registered, and information has been gathered on more than 800,000 transplants. This huge amount of information has allowed conducting multiple retrospective studies, evaluating changes in practices over time and for different categories of diseases, benchmarking outcome across EBMT affiliated centers, and increasingly serves to build synthetic comparators to evaluate the introduction of therapeutic innovations in the field of hematology. CAR-T cells therapies draw on human and technical resources that are also used to deliver HCT; they elicit side effects that require the implementation of risk mitigation plans; they are living drugs that persist in the body of the recipient and thus deserve prolonged follow-up; the introduction of CAR-T cells in the pharmacopeia is likely to significantly impact on the practice of BMT; for all these reasons and even

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before the first approvals of CAR-T Cells in Europe, EBMT engaged in a project aiming at complementing the EBMT Registry with a Cellular Therapy Form, with the objective to register CAR-T cells treated patients and collect information on their short-, middle- and long-term outcome. The goal is to provide EBMT investigators with a tool for primary analyses of the collected information and to support secondary use of data transferred at the individual level to Marketing Authorization Holders and other interested parties, to fulfill their obligations to health authorities and further evaluate the actual medical values of CAR-T Cells in different contexts and indications. The EBMT Registry received a positive opinion from the European Medicines agency in 2019, and five years later contains information on more than 9.000 treated patients. This article describes the journey to start this new activity, lessons to be drawn in view of improving the collection of real-world data, and what existing information tells us in terms of patient access.

Abbreviations & glossary

ALL	Acute Lymphoblastic Leukemia
ATMP	Advanced Therapy Medicinal Product
CA	Competent Authority
CAR	Chimeric Antigen Receptor
CASTOR	database used to register the 1st EU patients treated with CAR-T cells, and collect follow-up data
CAT	Committee for Advanced Therapies
CIBMTR	Center for International Blood & Marrow Transplant Research
CIDR	Cellular Immunotherapy Data Resource
CRS	Cytokine Release Syndrome
CTF	Cellular Therapy Form (of the EBMT Registry)
DESCART	Dispositif d'Enregistrement et de Suivi des CAR-T (a nationwide registry for patients treated by CAR-T Cells in France)
DLBCL	Diffuse Large B Cell Lymphoma
EBMT	European society for Blood and Marrow Transplantation
EHA	the European Hematology Association
EMA	European Medicines Agency
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food & Drug Administration
FL	Follicular Lymphoma
(LT)FU	(Long-term) follow-up
GDPR	Global Data Protection Regulation
GMO	Genetically Modified Organism
GTMP	Gene Therapy Medicinal Product
HCP	Healthcare Professionals
HCT	Hematopoietic Cell Transplantation
HE	Hospital Exemption
HTA	Health Technology Assessment
ICANS	Immune effector Cells Associated Neurological Syndrome
IECs	Immune Effector Cells
ISCT	International Society for Cell & gene Therapy
IT	Information Technologies
JACIE	Joint Accreditation Committee of ISCT & EBMT
JCA	Joint Controller Agreement
MA	Marketing Approval
MAH	Marketing Approval Holder
MCL	Mantle Cell Lymphoma
OS	Overall Survival
PAES	Post-Authorization Efficacy Study
PASS	Post-Authorization Safety Study
PFS	Progression-Free Survival
PMBCL	Primary Mediastinal B Cell Lymphoma
r/r	relapsed/refractory
RWD	Real World Data
SCTMP	Somatic Cell Therapy Medicinal Product
SmPC	Summary of Product Characteristics

SOC	Standard of Care
SoHO	Substance(s) of Human Origin
TEP	Tissue Engineered Product

As we enter the third decade of the century, three generations of hematopoietic cellular therapies are available to clinicians.

Firstly, blood transfusion was made possible after the description of blood groups, and remains widely used to treat patients suffering important traumas, undergoing major surgery, affected with inherited or acquired diseases that decrease blood cell production, or receiving myelotoxic treatments such as cytotoxic agents combined in many chemotherapy regimen.

Secondly, Hematopoietic Cell Transplantation (HCT) with non- or minimally manipulated stem cell products was introduced, a lifesaving therapy for a variety of hematological malignancies, as well as inherited or acquired disorders that negatively affect hematopoiesis. It is interesting to note that in the first group of indications, allogeneic HCT acts through the allogeneic recognition of residual tumor cells, and thus represents the first generation of cellular immunotherapies (“version 1.0”), while for the second group of indications it can be seen as a form of “regenerative medicine”. Allogeneic HCT was made possible after the description of Human Leukocyte Antigens (HLA, the products of the Major Histocompatibility Complex or MHC in humans), a better understanding of HLA matching and mismatching criteria between donor and recipient, and continuous improvements in the design of immune-suppressive regimen administered to recipients in order to efficiently mitigate the risk of Graft-versus-Host Disease (GVHD), a feared complication where donor-derived alloreactive T-cells attack normal donor tissues; it also provided a biological, technological and conceptual basis that helped develop the next generation of cellular therapies [1]. After 6 decades of medical practices and continuous improvements in outcome of HCT recipients, HCT remains a popular therapeutic option mostly in the field of hematology, while it brings benefit only to small subsets of patients with solid tumors and struggles to enter the field of autoimmune or chronic inflammatory disorders [2–6]. Similar to blood transfusions, the autologous or allogeneic graft that supports therapeutic intervention was never approved as a medicinal product. Its procurement and administration are covered by another set of regulations that in Europe derive from the Cell and Tissue Directives approved by the European Parliament in 2004, that underwent revision over a several year period of time and will be soon replaced along with the Blood Directive by a new EC regulation on Substances of Human Origin (SoHO).

Thirdly, and more recently, manufacturing of hematopoietic cellular therapies through substantial – including genetic – manipulations have produced compelling clinical results, generally obtained through a collaborative effort between academia and pharma, in some cases leading to FDA and EMA approval; these advanced therapies that qualify as medicinal products are now entering the market in growing numbers for increasing numbers of indications and patients, and CAR-T Cells may represent one of the first commercial success as well as widely accessible treatment in this emerging field (Table 1). In contrast to transfusion products and hematopoietic grafts, the manufacturing and administration of these advanced therapy medicinal products (ATMPs) fall under different regulations in Europe, as defined in Regulation EC 1394/2007, and face stricter regulatory requirements for their development and production, but also more obligations to monitor patients after infusion. The most publicized of these advanced therapies are CAR-T cells, autologous or allogeneic T-cells that are genetically modified to express a synthetic sequence coding for a “Chimeric Antigen Receptor” (CAR); the extracellular domain of CARs comprises a fragment of an immunoglobulin and allows for the recognition of the target antigen expressed at the surface of the cells independently of HLA restriction, while the intracellular domain variously integrates several elements of the T-cell activation machinery (TCR and co-stimulation chains and domains); upon binding of the CAR to its cognate ligand, genetically modified T-cells exert cytotoxicity towards the cancer cell. So far in Europe, 6 industry-manufactured autologous CAR-T cells targeting CD19 (four out of 6) [7–10] or BCMA (two out of 6) [11,12] have received marketing approval from EMA, and for a variety of relapsed or refractory (r/r) lymphoid malignancies [7–12] (Table 1). Many autologous and allogeneic CAR-T cells and other Immune Effector Cells based therapies are in development: of special interest is an additional autologous CAR-T cells targeting CD19: ARI-0001 [13] that has been granted PRIME designation by EMA in December 2021, and is seeking conditional marketing approval; ARI-0001 is developed by an academic institution, taking advantage of the Hospital Exemption (HE) embedded in Regulation EC 1394/2007 [14,15].

The time elapsed since the first approvals of CAR-T Cells is relatively short, but the field is making fast progress; in 2022, the results of three randomized trials that compared autologous CAR-T Cells targeting CD19 with the Standard of Care (SOC) - i.e. salvage chemotherapy followed in responding patients by high-dose consolidation therapy supported with autologous hematopoietic cell transplantation - in patients with refractory or 1st relapse of DLBCL, were published [16–18]; both the ZUMA-7 trial [18] and the TRANSFORM trial [17] showed better PFS than SOC, while the BELINDA trial turned out to be negative [16]. Initial results of the ZUMA-7 trials were further confirmed with the recent demonstration that axicel improves OS in this trial, when compared with SOC. Both axicel and lisocel received extended MA for use in 2nd line, based on data from the ZUMA-7 and TRANSFORM studies respectively. It is important to note that international randomized multicenter trials remain relatively rare in the field of ATMPs, and that beyond any lessons learned from the results of the studies, their conduct is itself a remarkable achievement.

The increased obligation by authorities to monitor patients after CAR T infusion is a consequence of the fact that CAR-T cells belong to the subcategory of “Gene Therapy Medicinal Products” (GTMP), since their biological and clinical activity derives from the synthetic sequence encoding the CAR. In addition, CAR-T cells also qualify as “Genetically Modified Organisms” (GMO). Currently approved and commercialized CAR-T cells are manufactured through the use of clinical grade replication defective and integration competent retroviral or lentiviral vectors; use of these tools theoretically carries the risk of insertional mutagenesis, whereby the viral vector integrates near and activates a proto-oncogene; such events have been observed when Hematopoietic Stem Cells have been retrovirally transduced [19]; recently reports of T-cell lymphomas in patients who were treated with CAR-T cells raised alarms in the field [20,21], leading the Food & Drug Administration (FDA) to request reinforced warnings and extended follow-up of CAR-T Cells treated

individuals. Earlier, a clonal proliferation of lentiviral-transduced CAR-T cells has been reported in a single case of a patient carrying a homologous inactivating mutation in one of the tet-2 alleles, whereby the CAR sequence inserted in the normal allele [22]. For these and other reasons, some CAR-T cells in development use non-viral technologies [23], although recent evidence suggest that genetic accidents may happen [24]; more recently gene editing was used in the manufacturing process of investigational CAR-T Cells currently being tested in clinical trials [25]; if approved, these medicinal products will most likely also require longer post-marketing surveillance.

The potentially increased risk for transformation of engineered immune cells once infused into patients resulted in the obligation of

Table 1

A non-exhaustive list of ATMPs approved by EMA since the publication of Directive EC 1394/2007. Adapted from Ref. [29] and from SmPC of each medicinal product. For abbreviations, see glossary. ATMPs that have been withdrawn or are no longer available on the European market appear in italics. CAR-T Cells are shown in bold characters.

International non-proprietary name (INN) or common name	Commercial name	MAH	Regulatory status	Composition and active principles	Date of approval
	<i>Chondrocelect™</i>	<i>TiGenix N.V.</i>	<i>TEP</i>	<i>viable autologous cartilage cells expanded ex vivo</i>	<i>October 2009</i>
<i>alipogene tiparvovec</i>	<i>Glybera™</i>		<i>GTMP</i>		<i>October 2012</i>
	<i>MACI™</i>	<i>Vericel Corporation</i>	<i>TEP, combined ATPM</i>	<i>matrix applied characterised autologous cultured chondrocytes</i>	
<i>sipuleucel-T</i>	<i>Provenge™</i>	<i>Dendreon</i>	<i>SCTMP</i>	<i>autologous peripheral-blood mononuclear cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (sipuleucel-T)</i>	<i>September 2013</i>
	<i>Holoclar™</i>	<i>Chiesi SA/Holostem Therapie Avanzate s.r.l.</i>	<i>TEP</i>	<i>Autologous human corneal epithelial cells</i>	<i>February 2015</i>
<i>talimogene laherparepvec</i>	<i>Imlygic™</i>	<i>BioVex Inc. (Amgen)</i>	<i>GTMP</i>	<i>Oncolytic HSV-1 – GM-CSF</i>	<i>December 2015</i>
	<i>Strimvelis™</i>	<i>Fondazione Telethon ETS/ AGC Biologics S.p.A. [Orchard Therapeutics]</i>	<i>GTMP</i>	<i>Autologous human CD34⁺ cells retrovirally transduced with the human ADA gene</i>	<i>May 2016</i>
	<i>Zalmoxis™</i>	<i>Molmed S.p.A</i>	<i>SCTMP</i>	<i>Allogeneic human T cells retrovirally transduced with HSV-TK</i>	<i>August 2016</i>
	<i>Spherox™</i>	<i>CO.DON AG</i>	<i>TEP</i>	<i>Spheroids of autologous matrix-associated chondrocytes</i>	<i>July 2017</i>
<i>darvadstrocel</i>	<i>Alofisel™</i>	<i>Takeda</i>	<i>SCTMP</i>	<i>Allogeneic expanded adipose stem cells</i>	<i>December 2017</i>
tisagenlecleucel	Kymriah™	Novartis	GTMP	Autologous CAR-T Cells targeting human CD19	August 2018
axicabtagene ciloleucel	Yescarta™	Kite/Gilead	GTMP	Autologous CAR-T Cells targeting human CD19	August 2018
<i>voretigene néparvovec</i>	<i>Luxturna™</i>	<i>Novartis</i>	<i>GTMP</i>	<i>Vector genomes for subretinal use</i>	<i>September 2018</i>
<i>betibeglogene autotemcel</i>	<i>Zynteglo™</i>	<i>BlueBirdBio</i>	<i>GTMP</i>	<i>Autologous human CD34⁺ cells lentivirally transduced with the lentiglobin gene</i>	<i>May 2019</i>
<i>onasemnogene abeparvovec</i>	<i>Zolgensma™</i>	<i>Novartis</i>	<i>GTMP</i>	<i>Contains a functional copy of the gene known as SMN1</i>	<i>March 2020</i>
brexucabtagene autoleucel	Tecartus™	Kite/Gilead	GTMP	Autologous CAR-T Cells targeting human CD19	December 2020
<i>atidarsagène autotemcel</i>	<i>Libmeldy™</i>	<i>Orchard Therapeutics</i>	<i>GTMP</i>	<i>Autologous human CD34⁺ cells lentivirally transduced with the human arylsulfatase A gene</i>	<i>December 2020</i>
<i>elivaldogene autotemcel</i>	<i>Skysona</i>	<i>BlueBirdBio</i>	<i>GTMP</i>		<i>July 2021</i>
idecabtagene vicleucel	Abecma	BMS	GTMP	Autologous CAR-T Cells targeting BCMA	August 2021
lisocabtagene maraleucel	Breyanzi	BMS	GTMP	Autologous CAR-T Cells targeting human CD19	April 2022
ciltacabtagene autoleucel	Carvykti	Janssen Pharmaceuticals	GTMP	Autologous CAR-T Cells targeting human BCMA	May 2022
<i>eeladocageene exuparvovec</i>	<i>Upstaza</i>	<i>PTC GTherapeutics Limited International</i>	<i>GTMP</i>		<i>July 2022</i>
<i>valoctocogene roxaparvovec</i>	<i>Roctavian</i>	<i>BioMarin Pharmaceutical</i>	<i>GTMP</i>		<i>August 2022</i>
<i>tabelecleucel</i>	<i>Ebvallo</i>	<i>Pierre Fabre Laboratories</i>	<i>SCTMP</i>	<i>EBV specific human allogeneic T-Cells</i>	<i>December 2022</i>
<i>Etranacogene dezaparvovec</i>	<i>Hemgenix</i>	<i>CSL Behring</i>	<i>GTMP</i>		
varnimbtagene autoleucel	ARI-0001	Hospital Clinic, Barcelona, Spain	GTMP	Autologous CAR-T Cells targeting human CD19	

Marketing Approval Holders (MAH) to provide post-Authorization and long-term follow-up of pre-defined numbers of patients treated with each of their products. Both the FDA in the USA and the EMA in Europe justified this step not only because of the potential increased risk of genetically modified products but also the fact that first-in class CAR-T cells were approved based on Phase I/II non-randomized clinical trials that included relatively low numbers of patients [7–12] with an unbalanced representation of patients from different ethnic origins, and inclusion/exclusion criteria that typically limit accrual of patients of older age or with comorbidities. The follow-up was relatively short, and data about long-term follow-up did not exist at time of submission. Head-to-head comparisons of products that target the same tumor antigens have not been carried out and are unlikely to be carried out in the future. Obligations imposed by the FDA and EMA have led MAH to launch Post-Authorization Safety Studies (PASS). Since new and expensive drugs increasingly target molecularly defined diseases and reach the market after evaluation in small patient samples sizes, we expect that Post-Authorization Safety Studies (PASS) and Post-Authorization Efficacy Studies (PAES) might become an important part of ongoing evaluations for many categories of innovative treatments, not only advanced therapies.

To establish a framework for PASS studies and explore how such studies can be embedded in a broader infrastructure in Europe, EMA started in 2017 the Patient Registry Initiative [26], which aimed to coordinate national and international registry initiatives, harmonize protocols, scientific methods and data structure as well as establish methods of data sharing and transparency [27]. This resulted in a multistakeholder meeting to define needs of registries that can be used for such purposes and resulted in the definition of “must-have” and “nice-to-have” data sets for CAR-T. As registries do not have the same quality of data collected for clinical studies, and taking advantage of its historical experience in the field of HCT, EBMT proposed a quality control of its registry and the to be implemented data set, which resulted in a draft and later qualified opinion highlighting strengths and weaknesses of the EBMT registry (Table 2).

MAH formed part of the multi stakeholder consultation at EMA to explore their own registry needs and also gain detailed insight into the design of the EBMT registry. The outcome of the EBMT registry evaluation was also made public with its strength and areas for improvement after the EBMT registry received a positive qualification opinion from EMA in early 2019 [28]. Based on these insights MAH commercializing approved products in 2019 decided to sign agreements with EBMT; predefined numbers of registered patients treated with tisacel on one hand, and axicel on the other hand have now been met, and data can be used for an array of studies.

During the establishment of PASS studies for similar and other products, further harmonization was needed as knowledge in the field was rapidly progressing, and final protocols for PASS partially differed from initially agreed data sets. This highlights the constant need to dynamically harmonize data sets in registries during product adoption. Multi-stakeholder meetings have now been set up to allow periodic changes in the registry on defined data sets, balancing ambitions of authorities and investigators with current and future capacities of academia to report. These include PASS analyses. These are some of the incentives that led to such initiatives such as the GoCART Coalition (<https://thegocartcoalition.com>). The GoCART coalition provides a forum to multiple stakeholders in the field, including patient advocates and representatives, competent authorities, HTAs, pharmaceutical companies, healthcare representatives including professional associations and cooperative groups. The GoCART coalition is jointly supported by the EBMT and the EHA [29]. The goal is to jointly tackle some of the major issues that the field faces, including practice harmonization [30], education of the various categories of healthcare professionals, facilitation and harmonization of center qualification, policy and advocacy. EBMT is also constantly coordinating its efforts with CIBMTR and CIDR in order to harmonize the format in which data are reported, with a view to conducting joint studies in the future, as has been done on many occasions in the field of HCT. Thus, beside a global definition of registry data that are collected is an even more important asset of registries and the possibility to adopt uniform data sets for collection.

EBMT faced a number a hurdles, while deploying its organization to register patients and collect follow-up data with the CTF but also develop new areas and a unique network which is very valuable for all future studies that will run via the EBMT registry. One was the implementation at country levels of the new set of legal dispositions for data collection, transfer and use defined in the EU Global Data Protection Regulation (GDPR); this led to redefine conditions for firstly, cross-border transfer of pseudonymized primary data from treating and reporting centers mostly but not exclusively operating in European member states to the EBMT, that is established in the Netherlands as a not-for-profit association, and secondly: transfer in view of secondary use of individual-level pseudonymized data from EBMT to a third-party that can be established in or outside of Europe, i.e. MAH that had contracted with EBMT for PASS. This has led to establishing Joint Controllorship Agreements (JCA) between reporting centers and EBMT. Deploying an updated and GDPR compliant Informed Consent Form took almost 1,5 year to be rolled out and to be implemented within European countries. Due to commercial approval in August 2018, but the late contracting between EBMT and the first CAR-T MAHs in early 2020, a major part of the patients needed to be collected retrospectively. The re-consenting process took more time than originally anticipated.

Internally, EBMT faced at the same time the workload and complexity associated with the transfer of its database from PROMISE to a new IT system; this has led to the establishment of a transient solution to register CAR-T cells treated patients and collect follow-up data: CASTOR was a data management platform used by various institutes to perform clinical studies, and conforms to all international regulations regarding data safety (ISO 27001, GDPR); CASTOR has been in use up to the end of July 2023. The new EBMT registry finally went live on Aug 24th, 2023, and has been in operation since then. Despite these hurdles, data collection for PASS studies is now considered to be a success and the first PASS studies have been completed in 2023 (Table 3).

While EBMT was pushing forward to establish a continental CAR T registry not restricted to a defined hematological malignancy, with well-defined and evolving data sets and to overcome the legal hurdles produced through the heterogeneity of European regulations, several national parallel competing initiatives led by cooperative groups in several member states have been initiated, focusing on defined diseases and products; the most advanced of these initiatives is the French DESCART registry [31]. Some of these national registries received support from their Health Technology Assessment (HTA) agencies, that are involved in reimbursement decisions taken at national levels, after the central MA has been issued by EMA, and that are focused on Post-Authorization Efficacy Studies

Table 2

A timeline of major achievements in building an EU registry for short-, middle- and long-term follow-up of patients treated with CAR-T Cells.

Date	Achievement
1974	Collection of data on Hematopoietic Cell Transplant by EBMT starts. At the time of writing, the EBMT Registry holds data on more than 700,000 patients and 800,000 Transplants
September 2015	Interactions between EBMT and EMA start in the context of the Registry Initiative
March 2017	EBMT launches a MED/A form designed for Cellular Therapy
August 2018	EMA approves tisacel for the treatment of r/r B-cell ALL in children and adults below the age of 25, based on results of the ELIANA trial, as well as for r/r DLBCL in 3rd line, based on results from the JULIET trial.
	EMA approves axicel for the treatment of r/r DLBCL and PMBCL in 3rd line, based on results of the ZUMA-1 trial
February 2019	The CHMP at EMA publishes a Qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry
July 2019	EBMT starts publishing numbers of registered patients who have received therapy with commercial or investigational CAR-T Cells at EU
February 2020	The GoCART Coalition is officially launched during the official opening of the 2nd joint EBMT-EHA EU CAR-T Cells meeting, taking place in Sietges, Spain
July 2020	EBMT starts establishing Joint Controllorship Agreements (JCA) with reporting centers. Implementation of the new ICF to share data with the MAHs/EMA
October 2020	1000 EU patients treated with either commercial or investigational CAR-T Cells are registered in the EBMT Registry
April 2021	1st call launched by the Scientific Excellence WG of the GoCART Coalition is launched. 3 out of 9 projects are selected
August 2022	2nd call launched by the Scientific Excellence WG of the GoCART Coalition is launched. 3 out of 16 projects are selected
May 2023	5000 EU patients treated with either commercial or investigational CAR-T Cells are registered in the EBMT Registry
May 2023	3rd call launched by the Scientific Excellence WG of the GoCART Coalition is launched. Ongoing process.
July 2023	CAR-T Cells treated patient registration and collection of follow-up data in CASTOR stops. PROMISE and CASTOR are no longer collecting data, although already collected data remain accessible
August 2023	The new EBMT Registry goes live, allowing EBMT Affiliated centers and programs to register new patients, and enter follow-up
February 2024	At the 6th edition of the EBMT-EHA European CAR-T Cells meeting that takes place in Valencia, Spain, the EBMT and the GoCART Coalition celebrate the registration of 7.000 CAR-T Cells treated patients in the EBMT Registry https://www.ebmt.org/registry/ebmt-car-t-data-collection-initiative

Table 3

High-level PASS status overview.

	Aug 2021	January 2022	May 2022	January 2023
# sites activated	26	46	63	79
# patients eligible for safety reports	568	706	842	1004
# CAR-T Cells treated patients registered	>1500	>2500	>3000	>4600

(PAES) to measure the actual medical value of innovative and costly therapies through collection of Real-World Data (RWD). This occurred in spite of the fact that EUnetHTA, the EU initiative to harmonize HTA within the EU, had already investigated the value of the EBMT registry within the context of reimbursement and released its report in 2021 [32], following the qualified opinion by EMA. This situation has led to duplication of efforts in many countries, as well as non-exhaustive reporting to competing registries with data sets for even the same item not comparable as data are differently collected in terms of timing as well as data value.

Despite all these difficulties, RWD has started to yield interesting observations, originally in the USA, later on in Europe. The efficacy and safety profile of tisacel and axicel for the first approved indications (r/rALL and 3rd line r/r DLBCL and PMBCL) are quite similar in real-world conditions [33–35] as compared to data produced in the registration trials ELIANA [9], JULIET [8] and ZUMA-1 [7]. Importantly, and while as already mentioned there is no head-to-head comparison of similar CAR-T Cells, the analysis of approximately one thousand patients registered with the DESCART registry has yielded important information on significant differences in the safety and efficacy profiles of tisacel and axicel for 3rd line r/r DLBCL, an observation that has significant impact on medical practices and commercial adoption of competing medicinal products [35].

As more indications are covered and more investigational products – including allogeneic CAR-T cells – are evaluated, additional questions arise, including the optimal sequencing of CAR-T cells with other forms of immunotherapies such as bispecific antibodies, or the management of relapse after CAR-T cells treatment. Navigating the evolving landscape of modern treatments for the ultimate benefit of patients requires the production of robust evidence-based medicine; this can be provided by well-designed and iterative analyses of higher-quality RWD, whose value improve through repeated cycles of “access and play” (“collect once and use often” is one of the principles promoted through the GoCART Coalition).

In conclusion, beyond new hopes and clinical benefits brought by the rapid emergence of Immune Effector Cells based therapies, in particular of CAR-T cells, the field has provided a paradigmatic example of the challenges faced by initiatives aiming at the collection of high-quality RWD on a large (continental) scale. Despite recent alerts on the risk of secondary malignancies after CAR-T Cells treatments, data are so far reassuring in terms of safety profiles, and the uses for this class of advanced therapies are growing. However, and beyond considerations of medical toxicities [36], the “financial toxicity” [37] and complexity in early and late developments warrant further investigations that will take advantage of advanced and high-quality data repositories such as the EBMT registry.

CRediT authorship contribution statement

Christian Chabannon: Conceptualization, Investigation, Project administration, Supervision, Writing – original draft. **Annalisa Ruggeri:** Writing – review & editing. **Silvia Montoto:** Writing – review & editing. **Anja van Biezen:** Conceptualization, Data curation, Project administration, Writing – review & editing. **Steffie van der Werf:** Data curation, Writing – review & editing. **Annemiek Markslag:** Conceptualization, Data curation, Project administration, Writing – review & editing. **Isabel Sanchez-Ortega:** Writing – review & editing. **Rafael de la Camara:** Writing – review & editing. **Per Ljungman:** Project administration, Writing – review & editing, Conceptualization, Resources, Supervision. **Mohamad Mohty:** Resources, Writing – review & editing, Project administration, Funding acquisition. **Nicolaus Kröger:** Resources, Writing – review & editing, Project administration, Funding acquisition. **Ana Sureda:** Project administration, Resources, Writing – review & editing, Funding acquisition. **Eoin McGrath:** Conceptualization, Project administration, Resources, Supervision, Writing – review & editing. **Chiara Bonini:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Jurgen Kuball:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

AvB, SvdW, AM, ISO, EMG are or have been permanent and paid employees with EBMT. CC, AR, SM, RdIC, PL, MM, NK, AS, CB & JK volunteer part of their professional time to contribute to EBMT missions and tasks, in different and temporary positions. In their different capacities, all co-authors have interacted with Pharma companies (including Novartis, Kite/Gilead, BMS, Janssen) that develop and commercialize CAR-T Cells and other advanced therapies to establish the European CAR-T Cells Registry described in this manuscript, and launch PASS and PAES. Interactions with Pharma companies as well as with other public or private, not-for profit or for-profit organizations is ongoing in the context of the GoCART Coalition. JK received funding from Novartis, Miltenyi Biotech, is a cofounder of Gadeta as well as shareholder of flow-up companies of Gadeta such as Century Therapeutics and Adeta.

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