iPAAC
INNOVATIVE PARTNERSHIP
FOR ACTION AGAINST CANCER

Co-funded by
the Health Programme
of the European Union

Real-life monitoring of innovative immunotherapies

Focus on patients treated with CAR-T cells

Author(s):	Lead author: French National Cancer Institute (INCa) – Hélène Denis (until October 2020), Lucie Sagot (since September 2020), Sophie Negellen (until december 2020), Marianne Duperray
Version:	3.0
Date:	01.06.2021

Contents

This report arises from the Innovative Partnership for Action Against Cancer Joint Action, which has received funding from the European Union through the Consumers, Health, Agriculture and Food Executive Agency of the European Commission, in the framework of the Health Programme 2014-2020.

Abbreviations & Concepts

CAR-T	Chimeric Antigen Receptor-T
CHMP	Committee for Medicinal Products for Human Use
CIBMTR	Center for International Blood and Marrow Transplant Research
EBMT	European Society for Blood and Marrow Transplantation
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicine Agency
ESMO	European Society for Medical Oncology
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
HAS	Haute Autorité de santé (French HTA agency)
HOPE	European Hospital and Healthcare Federation
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
INCa	French National Cancer Institute
iPAAC	Innovative Partnership for Action Against Cancer
KCE	Belgian Health Care Knowledge Center
LEEM	Les Entreprises du Médicament (French pharmaceutical industry network)
MA	Marketing Authorization
MCBS	Magnitude of Clinical Benefit Scale
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
PASS	Post-authorization safety study
PAES	Post-authorization efficacy study
SIOPE	The European Society for Paediatric Oncology
WP	Work Package

Advanced therapy medicinal products (ATMP)	New medical products for human use based on genes (gene therapy), cells (cell therapy), or tissues (tissue engineering).
Biobanks	A biobank is a large, organised collection of samples, usually human, used for research. Biobanks catalogue and store samples using genetic, clinical, and other characteristics such as age, gender, blood type, and ethnicity.
Cell therapies	Cell therapies contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases.
Clinician-reported outcome	A type of outcome assessment determined by a trained health-care professional after observation of a patient's health condition.
Chimeric Antigen Receptor (CAR) T-cells	CAR-T cells are a type of immunotherapy and more specifically a type of gene and cell therapy. They are thus part of ATMPs. CAR-T cells are T cells that have been genetically engineered ex-vivo to express a specific receptor at their surface. This so-called chimeric antigen receptor will then enable the T cell to recognize antigen present on the surface of tumor cells and thus activate the immune response to destruct tumor cells.
Clinical study	A clinical study is a scientific investigation in which participants receive a health-

	related intervention, such as a medicine, in order to learn about (discover or verify) how it works and interacts with the body (clinical, pharmacological, pharmacodynamics, and pharmacokinetic effects), or to identify any adverse reaction in order to understand the safety of and/or how well the medicine works (efficacy).
Cohort	Set of subjects, groups of people who are selected on the basis of certain characteristics and monitored over time. Cohorts monitoring is organized to identify one or more given events, such as the occurrence of an illness or death.
Cohort studies	Cohort studies are used to study how common diseases are, their causes, and their prognoses. They can be prospective (cohorts are identified before any signs of disease and are followed up over time) or retrospective (data is used that has already been collected, possibly over a long period of time). Cohort studies are a kind of observational study, in which the researcher does not perform any intervention (such as administering a medicine).
Gene therapies	Gene therapies contain genes that lead to a therapeutic, prophylactic or diagnostic effect. They work by inserting 'recombinant' genes into the body, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.
Interventional study	An interventional study is one in which the participants receive some kind of intervention, such as a new medicine, in order to evaluate it. In the medicines development process, medicines are evaluated through interventional studies known as clinical trials.
Managed entry agreement (MEA)	Contracts that can be used for mitigating the uncertainty regarding a medicine's relative effectiveness, cost-effectiveness, or budget impact. There are arrangements between a manufacturer and payer/provider that enables access to a health technology subject to certain conditions. Managed entry agreements (MEAs) are arrangements between firms and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance.
Marketing Authorization	Marketing authorisation (MA) refers to the approval for a medicine to be marketed. Marketing authorisations are granted only when a competent authority (or 'regulatory authority') has conducted a scientific evaluation, and is satisfied that a medicine is sufficiently safe and effective, and of high enough quality.
(Non-interventional) observational study	Observational study draws conclusions about the possible effect of a treatment on participants, where the assignment of participants into a treatment group versus a control group is outside the control of the investigator. In a non-interventional observational study, no additional diagnostic or monitoring procedures are applied to the patients, and epidemiological methods are used for the analysis of collected data.
Patient reported outcome	A patient-reported outcome (PRO) is a measure of the experience or view of a participant in a clinical study. It is not a clinical measure, or an assessment made by anyone else involved in the study. PROs are commonly collected by asking patients to fill in questionnaires, or by interviewing patients.
Pay for performance model in healthcare	Reimbursement model in which payment is dependent on achievement of targeted performance measures assessed against one or more predefined measures.
Post-authorization	Post-authorisation efficacy studies take place after marketing authorisation is granted

efficacy study (PAES)	and the medicine is in general use. They are Phase IV studies, intended to complement efficacy data that are available at the time of the initial authorisation, and gather long-term data about how well the medicine works when used widely. A post-authorisation efficacy study (PAES) may be voluntary or imposed by regulatory authorities.
Post-authorization safety study (PASS)	A post authorisation safety study is a study carried out after a medicine has been given a marketing authorisation. Its purpose is to obtain further safety information or to assess how well risk-management measures are working. A post authorisation safety study might be a clinical trial or a non-interventional study, and can be created voluntarily by the MAH, or can be required by the regulator.
Phase IV clinical trial	Several phases of clinical trial exist from I to IV. Phase IV clinical trials take place after country approval and there is a need for further testing in a wide population over a longer timeframe. Phase IV studies usually collect additional information about side-effects and safety, long-term risks and benefits, and/or how well the medicine works when used widely.
Prospective Cohort Study	In a prospective cohort study, groups of people are identified before they show any signs of disease and are followed up over time. Alternatively, in retrospective cohort studies, data is used that has already been collected (possibly over a long period of time) for other purposes. Cohort studies are one type of observational study, in which the researcher does not perform any intervention (such as administering a medicine).
Registry	Permanent and exhaustive investigation. This term is usually reserved for investigations concerning a well-specified pathology in a given geographical area.
Patient registry	A patient registry is a collection of information about individuals, usually those with a specific diagnosis or with specific risk factors for a disease. Registries can be funded and/or managed by government agencies, non-profit organisations, clinics, or commercial organisations. Patient registries have multiple uses. For example, registries for rare diseases can be used to establish the basic characteristics of the disease, how it is managed in clinics, and what outcomes people experience. Other uses include helping to measure clinical effectiveness of treatments in 'real world' settings, and investigating quality of patient care.

Executive summary

Introduction and objectives

The field of anticancer drugs has strongly evolved over the past years and the clinical development remains very large. The recent arrival of immunotherapies in cancer treatment strategies was associated with strong hopes among cancer care communities. However, despite their arrival on the market, uncertainties can remain regarding the benefit-risk ratio or regarding their position in therapeutic strategies notably due to the nature of data from clinical trials (immaturity, non-comparativeness). Innovative therapies are also most of the time linked with high prices which can lead to major impacts on healthcare financing systems.

CAR-T cells, recently approved in Europe, particularly illustrate these challenges related to innovative immunotherapies. Indeed, the assessment of the benefit-risk ratio of these therapies was based on early data from non-comparative clinical trials. These gene and cell therapies have been associated with strong toxicities requiring in some cases the administration of expensive treatments for their management. Their place in the therapeutic strategies is yet to be defined, for instance compared to stem cell transplantations. CAR-T cells are also associated with a complex therapeutic course and manufacturing process as well as with high prices.

The collection of efficacy and safety data in real-life settings appears thus essential to make sure that the benefit-risk of the new therapy remains positive and to implement efficient pay for performance contracts. In this context, the WP9 task 4 has taken the CAR-T cells as an example to identify what kind of programs and initiatives were implemented in European countries to monitor the use of these innovative therapies in real-life. The WP9 aimed to provide a state of play of existing initiatives for the real life monitoring of CAR-T cells and to highlight the most innovative ones. The WP9 also aimed to identify potential fields with remaining challenges and notably, which would need further European coordinated approach.

Method

Firstly, the WP9 performed a literature review to identify existing initiatives for the monitoring of patients treated with CAR-T cells in real-life settings as well as relevant experts on this domain. A dedicated meeting was organized with experts and partners in Ljubljana in February 2020 to collect additional information on existing initiatives and to discuss potential gaps, challenges and needs on this topic. Finally, a questionnaire was more broadly spread in Europe during the summer 2020 to complete the inventory of existing initiatives and gaps identified.

Results

Access to CAR-T cells in European countries

The WP9 was able to collect 17 replies from 12 countries for the questionnaire. The results showed that the access to CAR-T cells is very variable across European countries for the two approved indications at the time of the questionnaire dissemination. About half of the countries answering to the questionnaire are now reimbursing CAR-T cells in Europe. However, several European countries have implemented some specific conditions to obtain the reimbursement, such as the necessity to collect specific real-life data, a limited timeframe for shipping the treatment, or time-limited access program with reinforced collection of safety and efficacy data. In most countries, only few centers are authorized to provide CAR-T cells,

mainly due to the specific competencies and facilities required for these products. In addition to the large number of ongoing clinical trials involving CAR-T cells sponsored by the pharmaceutical industries, several academic trials are also ongoing with CAR-T cells produced in hospitals.

State of play of existing initiatives for the real-life monitoring of patients treated with CAR-T cells

A total of 14 initiatives for the real-life monitoring of patients treated with CAR-T cells in Europe have been identified, including 5 financing or access programs, 5 registries and 4 research studies. Most of them (N=10) are national initiatives. It is interesting to note that all countries where an access is possible to CAR-T cells outside clinical trials are collecting real-life data for patients treated with these therapies. Among the 14 initiatives, 6 are specific to CAR-T cells, and 6 can be applied to other innovative, expensive or anticancer medicines but do also present some particularities for CAR-T cells such as specific data to collect. Furthermore, 2 described initiatives are not specific to CAR-T cells.

These initiatives can answer several goals such as economic, research, medico-administrative purposes, but also aiming to meet regulatory requirements or to inform commissioning decision. About half of the initiatives can answer several purposes. Half of these initiatives are under the umbrella of public institutions.

Some data are recurrently collected for the real-life monitoring of patients treated with CAR-T cells throughout the different initiatives. For instance, for the assessment of long-term efficacy, it appears important to collect the disease progression and patient status after treatment. Regarding the evaluation of the safety profile, the occurrence of adverse events is often observed with a strong focus on cytokine release syndrome, neurotoxicity, persistent hematological toxicity and insertional mutagenesis.

Other broader international collaborations on the topic have been identified such as the ACCELERATE platform which aims to implement a structured long-term follow-up of children and adolescents treated with innovative therapies.

Discussion and remaining challenges

Considering the various stakeholders interested by real-life data on patients treated with CAR-T cells and various goals and possible uses of these data, it appears difficult to have one unique model answering to all stakeholders' expectations. However, it remains very important to reinforce collaboration on this sector to create synergies rather than duplication. An important point raised several times by the experts consulted was the need to have interoperable systems to facilitate future collaboration and pooling of data. Harmonised education and communication from central bodies like EMA and the EU Commission could help ensure consistency between and within countries in facilitating access and subsequent data collection.

Data on quality of life and patient reported outcomes appears very important to be integrated in long-term follow-up, but are one of the hardest parameters to integrate.

Furthermore, the clinical development of CAR-T cells remains currently very broad. Systems and initiatives implemented will have to be adjustable/ adaptable to enable potential link for new indications.

Acknowledgment

The iPAAC WP9 acknowledges all its partners including the following organizations: Sciensano, the Catalonia institute of oncology (ICO), the clinical center of Kragujevac, the Aviano Oncological reference center, the Vilnius university hospital Santaros Klinikos, the biomedical research center of Slovak academy of sciences, the Italian Istituto Superiore di Sanita (ISS), the National Public Health Institute from Slovenia (NIJZ), the National Cancer Institute of Luxembourg (INC), the European society for pediatric oncology (SIOPE), the European hospital and healthcare federation (HOPE), the association of European Cancer Leagues (ECL), the European Cancer Patient Coalition (ECPC), the biomedical research center network CIBERONC and the Biomedical Research Institute INCLIVA/University of Valencia.

The WP9 also thanks the strong involvement from experts of the following organization for taking part to the WP9 meetings and/or for providing feedback to the questionnaire: the European Medicine Agency (EMA); the French HTA Agency (Haute Autorité de santé) representing the EUnetHTA WP5B, the Lymphoma Study association and other cooperating groups involved in the DESCAR-T registry, The Belgian sickness and invalidity insurance institution (INAMI), the European Society for Blood and Marrow Transplantation (EBMT), the Portuguese Institute of Oncology from Lisbon, the National Institute for Health and Care Excellence (NICE), the Catalan Cancer Strategy team, the Lithuanian State Medicines Control Agency, the Bambino Gesù Hospital, the Azienda Ospedaliera di Bologna, the Veneto Institute of Oncology (IOV-IRCCS), Amgros I/S from Denmark, the National Cancer Control Programme from the Health Service Executive in Ireland.

1 Introduction and objectives

Cancer continues to present one of the key public health challenges in the European Union. Over the last 8 years, we have seen an intensification of the activities at the level of the European Union in order to tackle cancer from different aspects. Still, a number of important outstanding issues in cancer control remain unaddressed. The Innovative Partnership for Action Against Cancer (iPAAC), which has been selected for funding under the Third Health Programme 2014–2020, aims to build upon the outcomes of previous EPAAC and CANCON Joint Actions.

The general objective of the iPAAC Joint Action (JA) is to develop innovative approaches to advances in cancer control. The innovation that will be covered within the JA consists of further development of cancer prevention, comprehensive approaches to the use of genomics in cancer control, cancer information and registries, improvements and challenges in cancer care, mapping of innovative cancer treatments and governance of integrated cancer control, including a new analysis of National Cancer Control Plans. The key focus of the Joint Action will be on implementation, reflected in the key deliverable: the *Roadmap on Implementation and Sustainability of Cancer Control Actions*, which will support Member States in implementation of iPAAC and CANCON recommendations.

In this joint action, the Work Package (WP) 9 is dedicated to innovative therapies in cancer. Indeed, the panel of anticancer drugs available has strongly evolved over the past few years. Some innovative therapies, such as specific immunotherapies have disrupted the landscape of therapies available, and the development in this field remains very large. The recent arrival of innovative therapies such as specific immunotherapies in cancer treatment strategies was associated with strong hopes among cancer care communities. However, despite their arrival on the market, uncertainties can remain regarding the benefit-risk ratio or regarding their position in therapeutic strategies notably due to the nature of data from clinical trials (immaturity, non-comparative). Innovative therapies are also most of the time linked with high prices which can lead to major impacts on healthcare financing systems.

CAR-T cells, recently approved in Europe, particularly illustrate these challenges. Indeed, the assessment of the benefit-risk ratio of these therapies was based on early data from non-comparative clinical trials. These gene and cell therapies have been associated with strong toxicities requiring in some cases the administration of expensive treatments for their management. Their place in the therapeutic strategies is yet to be defined, for instance compared to stem cell transplantations. These therapies are also associated with a complex therapeutic course and manufacturing process as well as with high prices.

The collection of efficacy and safety data in real-life settings appears thus essential to continue gathering clinical evidence to confirm the positive benefit-risk of new therapies. Gathering and analyzing real-life data on innovative products enables to get results complementary to clinical trials. They enable a longer term follow-up and an increased number of patients observed. Monitoring patients treated with innovative therapies can be done in various ways such as exploiting data already collected in existing registries or databases, creating or adapting specific registries, especially when additional data are needed compared to existing systems. Some programs such as access or financing programs can also required the collection of additional clinical data.

In this context, the WP9 had chosen to take CAR-T cells as an example in this task to see what kind of programs and initiatives were implemented in European countries to monitor the use of innovative therapies.

The aims of the WP9 task 4 were:

- to provide a state of play of existing initiatives in terms of real-life monitoring of CAR-T cells;
- to identify the most innovative ones;
- to identify potential fields with remaining challenges and notably, which would need further European coordinated approach.

2 Methodology

The discussion on the detailed methodology started with the WP9 partners on 02-03 July 2018 during the WP9 kick-off meeting organized by the French National Cancer Institute (INCa) in Paris.

The first step of the WP9 methodology was to identify existing initiatives via a literature review. Feedback from relevant experts and stakeholders was then collected by emails and with the conduct of a dedicated meeting. Finally, a questionnaire aimed to complete the WP9 task 4 work was sent out to partners and identified experts/agencies.

2.1 Literature review

The WP9 performed a literature review on 3 main steps to identify existing programs enabling the real-life monitoring of patients treated with CAR-T cells:

- research on PubMed and Google;
- review of the websites of national health authorities and organizations involved in health policy such as the European members of the International Network of Agencies for Health Technology Assessment (INAHTA);
- search on the main existing registries of clinical studies.

Several equations of search were tested on PubMed Q1 2020 with the following key words:

- chimeric antigen; CAR-T; CAR T; CAR; tisagenlecleucel; Kymriah; CTL019; axicabtagene ciloleucel; Yescarta; chimeric; cell immunotherapy; gene therapy; cellular therapy;
- real-life monitoring, pay-for-performance, managed entry agreement(s), risk-sharing agreement(s), patient access scheme(s), performance-based reimbursement, conditional reimbursement.

However, the research on PubMed did not enable the WP9 to perform an efficient benchmark of existing initiatives; probably due to the recent approval of CAR-T cells on the European market and thus limited experience in real-life settings. It could also be linked to the nature of the initiatives that the WP9 was looking for as it is less common to have publications presenting financing systems or registries. The same key words were thus tested on Google and on the websites of health authorities and organizations involved in health policy.

The scope of the review included:

- registries and cohorts collecting data for patients treated with CAR-T cells;
- financial agreements including managed entry agreements, pay for performance systems;
- long-term observational studies;
- other programs enabling long term evaluation of efficacy, safety or proper use.

For each initiative, the following information were collected when available:

- scope;
- organization in charge;
- purpose of the initiative;
- year of implementation / implementation steps;
- added value and lessons learned;

- specificities for CAR-T cells;
- possibility to inter-operate with other existing systems;
- challenges encountered.

The following registers of clinical studies were reviewed:

- EU PAS Register with INN (key words: tisagenlecleucel & axicabtagene ciloleucel and brand names (Kymriah, Yescarta));
- Clinicaltrial.gov (key words: chimeric antigen receptor OR CAR; filter on phase III and IV).

The focus was given to initiatives that have some specificities for CAR-T cells patients.

Case reports on individual patients were not taken into account.

2.2 Collection of feedback from WP9 partners and experts

Prior the first meeting dedicated to this task, the WP9 contacted by emails all partners and relevant known experts who could have information on this topic.

Then, partners and experts were gathered for a face to face meeting in Ljubljana on February 25th, 2020. The goal was to provide an overview of the existing initiatives and collaborations in Europe for the real-life monitoring of patients treated with CAR-T cells. It was also the opportunity to question the working group regarding the potential gaps and remaining challenges on this topic as well as possible needs for further collaboration. The agenda which was prepared for the meeting is presented in the Appendix 1.

2.3 Questionnaire

The questionnaire was built in February 2020 by the INCa team and the first version was collectively reviewed during the task 4 meeting in Ljubljana on February 25th 2020. Feedback and suggestions for improvement were collected.

The goal of the questionnaire was to complete the literature review and to have a more global and exhaustive approach to benchmarck existing initiatives for the real-life monitoring of patients treated with CAR-T cells in Europe.

2.3.1 Structure and content

The questionnaire was structured in 2 main parts:

1) Availability of CAR-T cells in Europe

Few questions were added to enable the WP9 to have a good idea of CAR-T cells availability in the country of the responder for each indication approved in Europe.

It was also suggested at the Ljubljana meeting to address the accreditation of centers eligible to provide CAR-T cells in the questionnaire. A question was thus added on this topic.

2) Existing programs for the monitoring of patients treated with CAR-T cells in real-life settings

The final version of the questionnaire is available in the appendices (Appendix 2).

2.3.2 Dissemination of the questionnaire

The questionnaire was addressed during summer 2020 to persons involved in the implementation of programs and initiatives enabling the monitoring of patients treated with CAR-T cells in real-life settings.

It was decided to have an online version of the questionnaire to enable better dissemination.

It was suggested at the Ljubljana meeting to also disseminate the questionnaire to clinicians through national and European learned societies. The European Hospital and Healthcare Federation (HOPE) and the European Society for Blood and Marrow Transplantation (EBMT) offered their contribution to facilitate the dissemination of the questionnaire among their members.

3 Results

This section gathers the results from the literature review, from the meeting with experts which took place in Ljubljana in February 2020 and from the questionnaire results disseminated during the summer 2020. The full minutes of the Ljubljana meeting is available in Appendix 3: WP9 Task 4 Ljubljana Meeting minutes and the questionnaire is available in Appendix 2: WP9 task 4 Questionnaire

Five initiatives have been identified via the literature review results only.

Regarding the questionnaire, a total of 17 replies were collected from 12 countries (France (2), Portugal (1), England (1), Spain (2), Malta (1), Lithuania (1), Italy (2), Serbia (1), Denmark (1), Luxembourg (1), Ireland (1), Belgium (1)), plus two from European networks: one from the European Society for Blood and Marrow transplant (EBMT) and one from the European Hospital and Healthcare Federation (HOPE).

The profile of questionnaire responders is presented on the graph below.

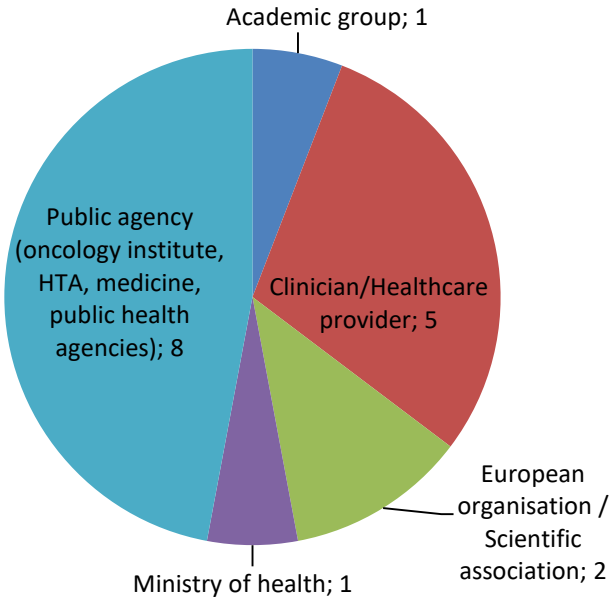

Figure 1: Profile of iPAAC task 4 questionnaire responders

3.1 Access to CAR-T cells in European countries

Of note, this part concerns CART-T cells therapies which were available in Europe during the diffusion of the questionnaire, which is before the end of August 2020. On 15 October 2020, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a conditional marketing authorisation for the medicinal product Tecartus® (brexucabtagene autoleucel), intended for the treatment of relapsed or refractory mantle cell lymphoma (MCL). These new CAR-T cells are not included in this report.

3.1.1 Overview of access in Europe to commercialized CAR-T cell therapies per indications

3.1.1.1 Acute lymphoblastic leukemia

Kymriah® (tisagenlecleucel) is indicated for paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. This indication has been approved in Europe since August 2018. The figure 2 below presents the access to CAR-T cells for acute lymphoblastic leukemia observed in European countries who participated to our task 4 questionnaire (N=12 countries).

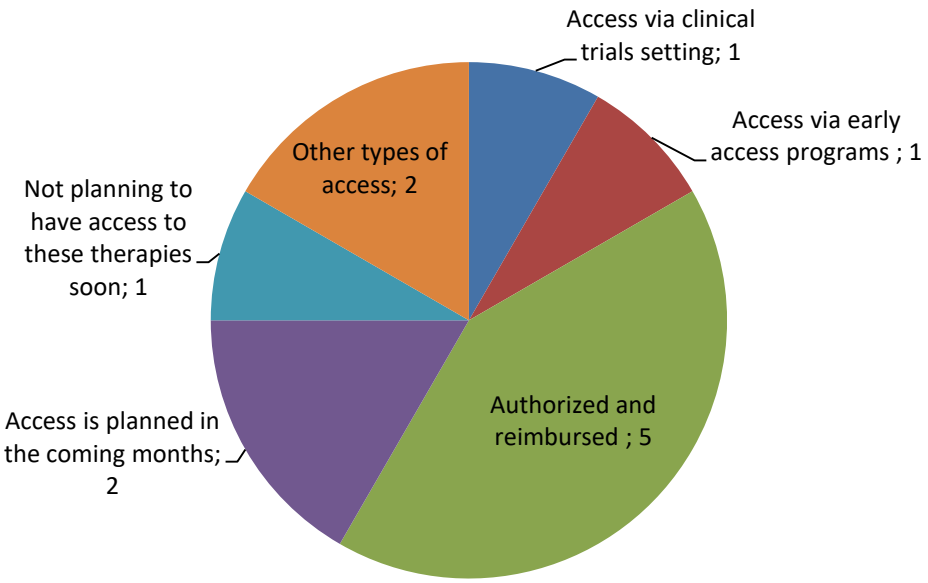

Figure 2: Access to CAR-T cells observed in European countries for acute lymphoblastic leukemia (N=13 countries)

Two countries mentioned that they had another type of access:

- in England, access and reimbursement are possible via a time limited Managed Access Agreement with ongoing data collection;
- in Luxembourg, patients that might benefit from this treatment are sent abroad, as Luxembourg does not have a centre of reference for the treatment with CAR T-cells.

There was no reported restriction of use compared to the European approved indication for Kymriah®, except in Belgium for which the restrictions are described in a pay for performance financial convention.

3.1.1.2 Large B-cell lymphoma

Two CAR-T cells have been approved for large B-cell lymphoma in Europe:

- Kymriah® (tisagenlecleucel) is indicated for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy;

- Yescarta® (axicabtagene ciloleucel) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy).

The figure 3 below presents the different access to CAR-T cells that can be found in Europe for diffuse large B-cell lymphoma and for primary mediastinal large B-cell lymphoma (similar data for these two indications).

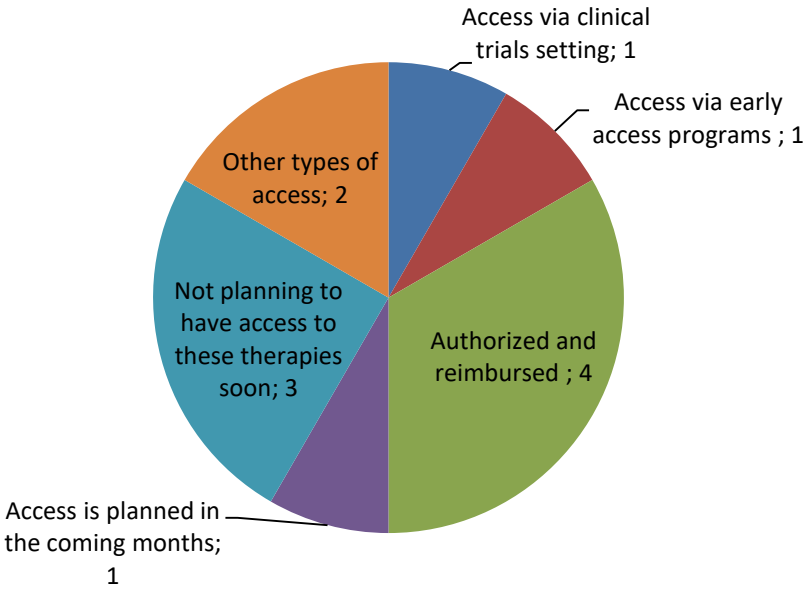

Figure 3: Access to CAR-T cells observed in European countries for large B cell lymphomas (N=12 countries)

The two countries where a different type of access was reported were the same as for the indication ALL.

There was no reported restrictions of use compared to the European approved indication neither for Kymriah®, nor for Yescarta® for these 2 indications, except in Belgium for which the restrictions are described in a pay for performance financial convention.

3.1.2 Specific reimbursement conditions

Several countries have implemented specific conditions for the reimbursement of CAR-T cells.

- In Spain, a specific authorization process was established for eligible patients to CAR-T cells. This authorization process involves regional and national authorities to assess the suitability of the patient. A managed entry agreement was established at national level with pharmaceutical companies under which indications of the drug can be dispensed.
  Centres authorised for CAR-T are selected by the national authorities and autonomous communities make a proposal for optimal centres within its region.
  Reimbursement is split in two parts, once after the infusion and the other conditioned to the response of the therapy, following the latter a pay for performance model. Economic

incentives were introduced; if the cell therapy is not ready in less than 31 days, once the leucopheresis is performed, the therapy will not be reimbursed.

- In Belgium, the reimbursement is made in two times, the first part at the beginning of the therapy, and the last amount is provided only if requested criteria are filled in.

- In Italy, the payment of CAR-T therapy is made in three times: first at administration, second after 6 months and third after one year, only if the therapy is shown to be effective. National registries enable the tracking and paying for patients outcomes (https://www.efpia.eu/media/554543/novel-pricing-and-payment-models-new-solutions-to-improve-patient-access-300630.pdf).

- In France, Kymriah® and Yescarta® are reimbursed on the condition that a CAR-T-specific registry be established to collect further data from French patients to assess the effectiveness and tolerance observed in the real world. In addition, the French Health Authority (HAS) will undertake annual reassessment of the improvement in clinical benefit (ASMR) using the data collected in the registry, as well as any new data available from the follow-up of the pivotal trials.

- In England, both Kymriah® and Yescarta® are reimbursed in their EMA approved indications through the Cancer Drugs Fund (CDF) which is a cancer-specific funding source that enables access to drugs for which there is plausible potential that they would satisfy the criteria for routine commissioning, but where there is significant clinical uncertainty.

3.1.3 Centers authorized to provide CAR-T cells

In most countries, the prescription and administration of CAR-T cells have been limited to few healthcare centers, mainly due to the specific competencies and facilities required for these products. Several methods for selection of centers eligible to provide CAR-T cells are applied in European countries and are presented on the graph below.

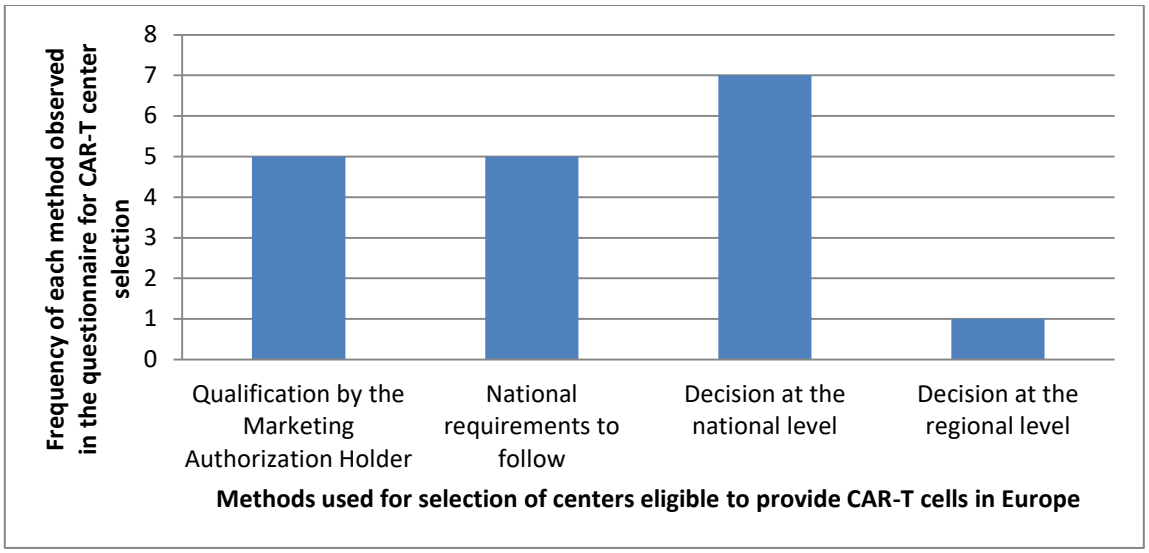

Figure 4: Frequency of methods used for the selection of centers eligible to provide CAR-T cells in Europe (as per questionnaire results; N = 12 countries)

Four out of the 12 countries for which a reply was provided, reported two or more methods.

3.1.4 Academic clinical trials with CAR-T cells

Many clinical trials are currently ongoing with CAR-T cells, mainly sponsored and produced by the pharmaceutical industry. It is however interesting to note that there are also some ongoing academic clinical trials ongoing in Europe, with “home-made“ CAR-T cells. Even though Italy and Catalonia already have access to commercial CAR-T cells and have implemented programs for the monitoring of these products in real-life settings, there are also ongoing academic clinical trials with CAR-T cells in these 2 countries/regions.

In Italy, the Bambino Gesù Hospital conducts several trials involving CAR-T cells, notably the two following:

- NCT03373097: Anti-GD2 CAR-T Cells in Pediatric Patients Affected by High Risk and/or Relapsed/Refractory Neuroblastoma or Other GD2-positive Solid Tumors. (Anti-GD2 CAR T Cells in Pediatric Patients Affected by High Risk and/or Relapsed/Refractory Neuroblastoma or Other GD2-positive Solid Tumors - Full Text View - ClinicalTrials.gov).
- NCT03373071: Anti-CD19 CAR T Cells in Pediatric Patients Affected by Relapsed/Refractory CD19+ ALL and NHL. (Anti-CD19 CAR T Cells in Pediatric Patients Affected by Relapsed/Refractory CD19+ ALL and NHL - Full Text View - ClinicalTrials.gov).

In Spain, a trial in which CAR-T cells are produced using the CliniMACS Prodigy system, was conducted in two hospital in Barcelona:

- NCT03144583: Pilot Study on the Infusion of ARI-0001 Cells in Patients With CD19+ Leukemia or Lymphoma Refractory to Therapy (CART19-BE-01) (Pilot Study on the Infusion of ARI-0001 Cells in Patients With CD19+ Leukemia or Lymphoma Refractory to Therapy - Full Text View - ClinicalTrials.gov). ARI-0001 has already got the marketing authorization.

3.2 State of play of existing initiatives for the real-life monitoring of patients treated with CAR-T cells

3.2.1 Presentation of existing initiatives for the real-life monitoring of patients treated with CAR-T cells in Europe

A total of 14 initiatives for the real-life monitoring of patients treated with CAR-T cells were identified and are presented in table 1.

Table 1: Existing initiatives for the real-life monitoring of patient treated with CAR-T cells in Europe

Country/ Region	Name of the program	Organizations in charge	Brief description	Link for additional information
Europe	EBMT registry	The European Society for Blood and Marrow Transplantation (EBMT)	The EBMT registry was established in 1974 initially to gather data on patients receiving haematopoietic stem cell transplant. A specific form to collect data on cellular therapy was more recently developed to capture data on patients receiving cellular therapies, including CAR-T cells.	https://www.ebmt.org/
England	Cancer Drugs Fund (CDF)	National Institute for Health and Care Excellence (NICE) / National Health Service England and National Health Service Improvement (NHSE&I)	Cancer Drugs Fund: Launched in 2010 as an additional funding source for cancer drugs, reformed in 2016 as a partnership between NHSE&I and NICE. Managed access agreement defines eligible population and the data that must be collected to resolve the uncertainty identified by the NICE appraisal committee for each specific indication. The treatment is covered for a time limited period by the payer for all treatment eligible patients while futher data is collected to inform a future guidance review by NICE. At the end of the data collection period, the company submits a new evidence dossier to NICE for a guidance review, of which the outcome can be positive, negative or optimised recommendation for route NHS commissioning.	https://www.england.nhs.uk/cancer/cdf/ https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund

Spain	Valtermed	Spanish ministry of health (MSCBS)	The Registry VALTERMED has recently been implemented in order to determine the real therapeutic value of pharmaceuticals used in clinical practice within the National Health System. The main objective is to dispose of suitable information for decision making on the pharmaceutical management.	https://www.mscbs.gob.es/profesionales/farmacia/valtermed/home.htm
Catalonia (Spain)	Pharmaco-therapeutic harmonization program (PHF-MHDA)	Catalan Health Service	In Catalonia, high cost drugs (such as CAR-T cell) are reimbursed through the pharmacotherapeutic harmonization program. Under this program, the clinician in charge must fulfil an application form with information related to the patient and the hospital, and more specifically on the drug to be prescribed and its indication in a registry of clinical data of patients and treatments (RPT-MHDA). Economic incentives are in place in the catalan context in order to control and assure appropriate use of drugs;	https://catsalut.gencat.cat/ca/proveidors-professionals/farmacia-medicaments/programa-harmonitzacio-farmacoterapeutica/
Belgium	CAR-T temporary reimbursement convention	The National Institute for Health and Disability Insurance (NIHDI/RIZIV/INAMI)	By negotiations with pharmaceutical company a contract can be concluded between NIDHI and a pharmaceutical company in order to implement a temporary reimbursement based on conditions set out in a contract (confidential). Agreements try to link the price of a medicinal product to its specific added value. It is conditioned by the gathering of clinical evidence on utilization and outcomes.	https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/fr/Public/ProductSearch

France	ATIH (Technical Agency for Information on Hospital Care) French national initiative DESCAR-T	The Lymphoma Academic Research Organisation (LYSARC)	A French decree subjects that the financial coverage of CAR-T cells by health insurance requires the collection and transmission of certain information relating to its prescription. This data collection is performed through the ATIH database and is mandatory for reimbursement. Following a request for additionnal evidence by HAS (French HTA agency) addressed to pharmaceuticals companies, an additionnal initiative, named DESCAR-T, was set up. This initiative is piloted by the academic group LYSARC and funded by industrial companies. The goal of the initiative DESCAR-T is to create a unique national registry that would be useful for several stakeholders including payers, pharmaceutical companies, academy. DESCART and ATIH databases are now interconnected to facilitate the data collection, however the databases are not completely similar (DESCART is broader).	https://experts-recherche-lymphome.org/lysa/parcourir-les-etudes-cliniques-en-cours/descar-t/ ATIH: data to collect: https://www.atih.sante.fr/sites/default/files/public/content/3595/notice_technique_atih-371-6-2019_car-t-cells.pdf)
France	Oral presentation at European Hematology Association	French healthcare centers	Real-world results on CD19 CART-T-cell for 60 french patients with relapsed/refractory diffuse large B-cell lymphoma included in a temporary authorization for use (ATU) program: Retrospective analysis of the patients treated with Axicabtagene or Tisagenlecleucel between April 2018 and Feb 2019 in the 5 authorized centres (APHP, Hôpital Saint-Louis-Paris, CHU Montpellier, CHU Nantes, CHU Lyon, CHU Lille), under the ATU program.	https://library.ehaweb.org/eha/2019/24th/267354/catherine.thieblemont.real-world.results.on.cd19.car.t-cell.for.60.french.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D2%2Amedia%3D3%2Atopic%3D1574

Italy	CAR-T monitoring registries	The Italian Drug Agency (AIFA)	AIFA Monitoring registries are administrative tools to improve early access of innovative therapies and guarantee sustainability, and collecting epidemiological data to monitor safety and appropriate usage. Monitored drugs are in general high cost medicines, many of which biotech products, often registered through a European centralised authorization procedure. The common characteristics is the high level of uncertainty with regard to safety, appropriate use in real world, cost-efficacy, budget impact issues. Each registry usually covers one drug & one indication only. The agreement provides for a payment method conditional on the result (payment at results).	https://www.prpchannel.com/en/aifa-approves-the-reimbursement-of-a-new-car-therapy/
Austria	LKF financing for CAR-T including agreement with the MAH	GmbH	Following agreement has been reached with the company that distributes the drug: the costs for the drug is covered by the company in case of death of the patient during the stay and in case of therapy interruption during the stay. CAR-T is only coded and financed if the therapy is successful (patient leaves the hospital).	https://www.sozialministerium.at/Themen/Gesundheit/Gesundheitssystem/Krankenanstalten/Leistungsorientierte-Krankenanstaltenfinanzierung-(LKF).html.
International	PASS sudy	Novartis	Study required by the EMA within the Risk Management Plan (RMP), as condition of the marketing authorization. This registry study aims to assess the long-term safety of patients with B lymphocyte malignancies treated with tisagenlecleucel. Patient data will be retrieved from established Registries conducted by the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR).	http://www.encepp.eu/encepp/viewResource.htm?id=32498

International	PASS sudy	Gilead	Study required by the EMA within the Risk Management Plan (RMP), as condition of the marketing authorization. It is a long-term, Non-interventional Study of Recipients of Yescarta® for Treatment of Relapsed or Refractory Diffuse Large B-Cell Lymphoma and Primary Mediastinal B-Cell Lymphoma. Patients' data might be entered into the European Society for Blood and Marrow Transplantation (EBMT) Registry up to 1 week prior or anytime following Yescarta infusion and patients will be followed for 15 years in the EBMT registry.	http://www.encepp.eu/encepp/viewResource.htm?id=34323
Germany	Outcome-based deal for reimbursement	Novartis & GWK	Agreement between Novartis and the group of German health insurance providers GWQ. Outcome data has to be collected to enable the reimbursement.	https://mapbiopharma.com/home/2019/03/kymriah-secures-novel-outcomes-based-deal-in-germany/ https://www.apmhealtheurope.com/freestory/0/64434/major-german-payers-sign-pay-for-performance-agreements-on-car-ts https://pink.pharmaintelligence.informa.com/PS124927/Novartis-Strikes-Kymriah-OutcomeBased-Deal-With-German-Insurers

Germany	Scientific publication	Healthcare centers	Real life experience in the treatment of pediatric, adolescent and young adult ALL patients using commercially available CAR-T cells | P. Bader: report the first results using commercially available CAR-T-cell product Tisagenlecleucel (Kymriah®) in patients with ALL treated by the University Hospital for Children and Adolescents Frankfurt am Main, the Department of Medicine III, University Hospital LMU Munich, and the von Hauner Kinderspital, LMU Munich, Germany.	https://www.ebmt.org/ebmt/news/reports-1st-european-car-t-cell-meeting-14-16-february-2019-paris-france https://www.oncoletter.ch/ebmt/oral-session-Late-breaking-abstracts-Peter-Bader.html https://library.ehaweb.org/eha/2019/cart/261151
Portugal	National Cancer Registry	National health services	The Portuguese national cancer registry is under the umbrella of the National health servicies. There are no specificities fo CAR-T cells.	https://www.sns.gov.pt/noticias/2017/07/14/registo-oncologico-nacional-em-2018/

3.2.2 Thematic focuses regarding the initiatives identified

3.2.2.1 Description of the typology of the initiatives

As represented on the graph below, three main types of initiatives for the real-life monitoring of patients treated with CAR-T cells were identified: 4 research studies, 5 registries and 5 financing/access programs.

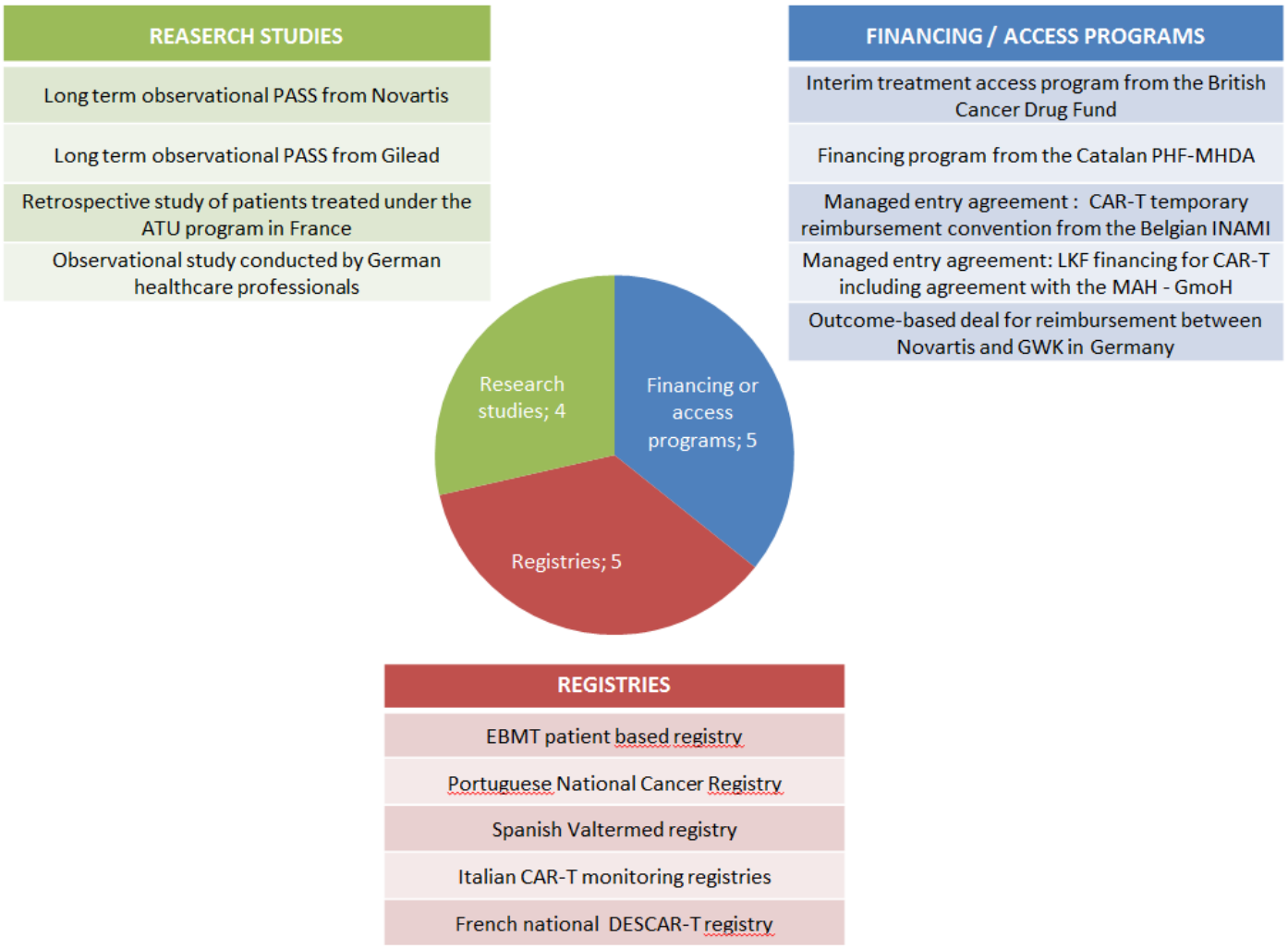

Figure 5: Repartition of initiatives according to their typologies (N = 14 initiatives)

It was observed that the typology can sometimes overlap. For instance, some of the registries have been implemented as part of a financing or access program, and vice-versa, some access programs are based on registries.

Initiatives can also be linked one to another. For instance, the two Post Authorization Safety Studies (PASS) conducted by Novartis and Gilead are using data collected in the EBMT registry.

To be noted that the definition of the terms such as registries, research studies can be found on the glossary pages 4 to 6.

3.2.2.2 *Scope of the initiatives*

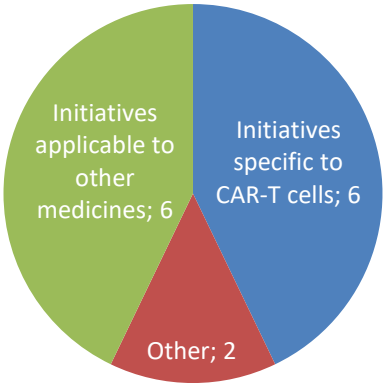

Figure 6: Scope of the initiatives (N = 14 initiatives)

Among the 14 initiatives identified, 6 were specific to CAR-T cells including:

- Four research studies with a goal of analysing real-life data on commercialized CAR-T cells:
  - three focused on B-cell malignancies:
    - one for patients treated with axicabtagene ciloleucel or tisagenlecleucel for relapsed/refractory diffuse large B-cell lymphoma (included in a temporary authorization for use access program);
    - one for patients treated with tisagenleuclecel for B lymphocyte malignancies;
    - one for patients treated with axicabtagene ciloleucel for relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma.
  - the fourth one aimed to report real-life experience with tisagenlecleucel for the treatment of paediatric, adolescent and young adult for acute lymphoblastic leukaemia.
- The French DESCAR-T registry has been initiated specifically to follow in real-life settings patients in intention of CAR-T cells treatment, extending collection of data to patients without CAR-T cell infusion.
- The financing agreement between Novartis and GWK was implemented specifically for tisagenlecleucel in Germany.

Then, 6 out of the 14 initiatives identified can be applied to other medicines, such as innovative, expensive, and/or anticancer medicines. However, these 6 initiatives do present some specificities for CAR-T cells. For instance in Belgium, the national system was already in place prior arrival of CAR-T cells on the market, but has been adapted to be able to collect more detailed information and time specific check points on efficacy for CAR-T cells. In England, the Cancer Drug Fund has been implemented for a few years now, but they do have specific data collection arrangement individualized for each product / indication.

Finally, 2 out the 14 initiatives are not specific to CAR-T cells:

- the EBMT registry was initially built to gather data from patients receiving haematopoietic stem cell transplantation and recently evolved to enable the collection of additional relevant data for patient treated with cellular therapies;
- the Portuguese national cancer registry, for which a reply was obtained for the questionnaire, does not collect any particular additional data for patient treated with CAR-T cells.

3.2.2.3 Organizations in charge

Different organizations in charge of initiatives for the real-life monitoring of patients treated with CAR-T cells have been observed. The graph below shows the repartition of the identified initiatives according to the type of organizations in charge.

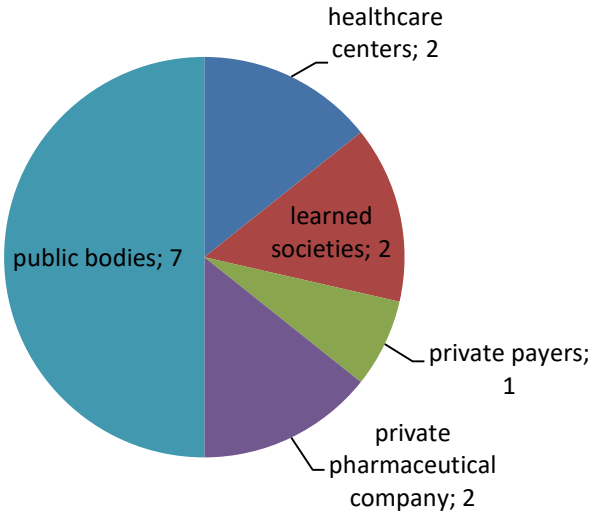

Figure 7: Repartition of the organizations in charge of initiatives for the real-life monitoring of patients treated with CAR-T cells (N = 14 initiatives)

3.2.2.4 Geographical repartition of initiatives

The figure 8 presents the distribution of initiatives depending on their geographical localization.

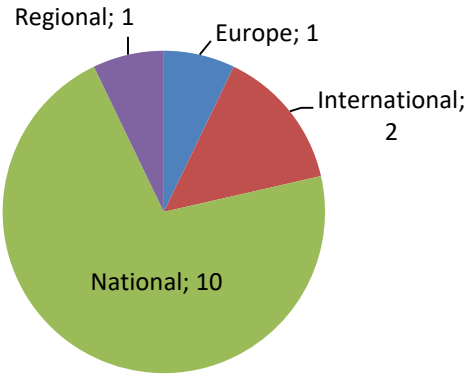

Figure 8: Repartition of initiatives depending on their geographical scope (N= 14 initiatives)

It is interesting to note that, in the 5 countries where CAR-T cells are available outside clinical trials, data related to the use of CAR-T cells in real-life settings are collected.

3.2.2.5 Main goals and uses of data

The goals of the 14 initiatives enabling the collection of real-life data for patients treated with CAR-T cells are quite various. Four main purposes have been identified and are represented on the graph below according to their frequency observed. About half of the initiatives have more than one main purpose.

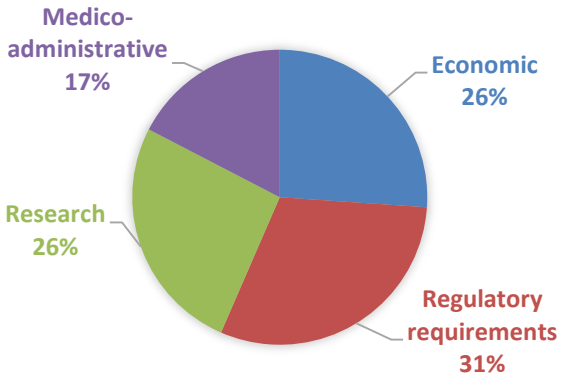

Figure 9: Purposes and their frequency of the initiatives for the real-life monitoring of patients treated with CAR-T cells (N= 14 initiatives)

<u>Initiatives with an economic purpose</u>

Six initiatives have a clear economic purpose such as the implementation of reimbursement systems conditioned by the collection of additional data or the verification of performance criteria linked with the payment system.

<u>Initiatives aiming to collect clinical data for regulatory requirement</u>

Seven initiatives aim to enable the collection of clinical data for regulatory requirements such as the reevaluation of the benefit/risk ratio or long term follow-up of the drug marketed.

Some of them, such as the 2 post-authorisation studies sponsored by the marketing authorization holders of Kymriah and Yescarta, have been implemented to respond to regulatory requirements imposed by the European health authorities (part of the risk management plan).

The European EBMT, French DESCAR-T and Spanish VALTERMED registries also enable the conduct of studies for this purpose.

In addition, the main purpose of the British Cancer Drug Fund was described in the questionnaire as the "collection of data to inform a long term commissioning decision".

Initiatives with a research purpose

Six initiatives have been implemented to further improve the overall knowledge on CAR-T cells such as place in the therapeutic strategies, better define responsive and non-responsive patients. This includes for instance the two non-mandatory studies presented by the two healthcare centers in France and Germany.

The European EBMT, the French DESCAR-T, the Spanish VALTERMED and the Italian registries also enable the conduct of studies for this purpose.

Initiatives with a medico-administrative purpose

Some of the initiatives have medico-administrative purposes such as checking the proper use of CAR-T, checking patient's eligibility.

There was no initiative identified for which the only purpose was medico-administrative. It is always combined with another purpose, such as financial or research.

The graph below shows the main uses of real-life data collected through the initiatives and their frequency.

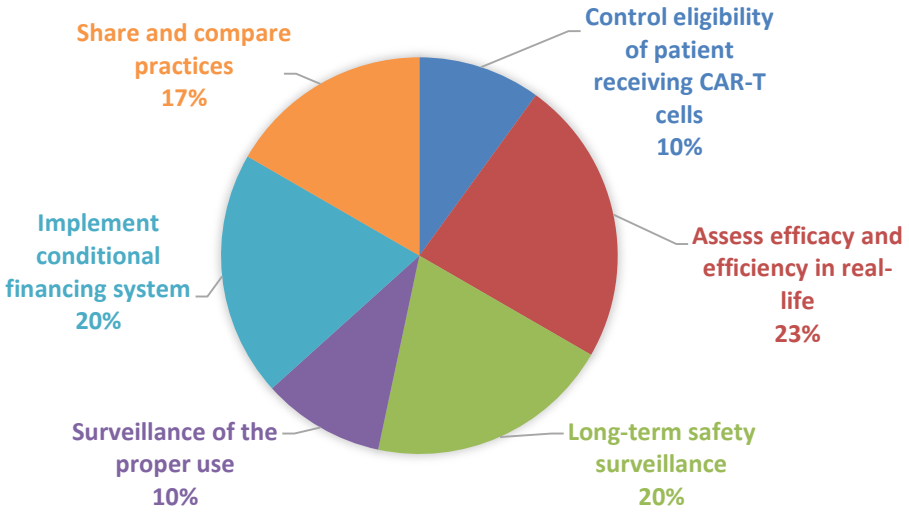

Figure 10: main uses of data collected through the initiatives for the real-life monitoring of patients treated with CAR-T cells

Other uses of real-life data on patients treated with CAR-T cells reported in the questionnaire were:

- to provide data to answer the clinical uncertainties identified by the HTA appraisal committee;

- real world validation of clinical trial outcomes.

3.2.2.6 Nature of data collected

Several published documents provide details on the specific data that are or should be collected for the real-life monitoring of patients treated with CAR-T cell therapies. The table in Appendix 4 provides the link towards the available detailed information for each document identified. It concerns 5 out of the 14 initiatives identified and it includes also a guidance from EMA which is not linked with any of the 14 identified initiatives but proposed data elements relating to efficacy and to safety that should be collected for CAR-T cell therapy registries.

Some data are recurrently collected throughout the different initiatives. For instance, for the assessment of long term efficacy, it appears important to collect the disease progression and patient status after treatment (at defined interval). These parameters can be important to collect for initiatives with different objectives such as the re-evaluation of the benefit-risk ratio, but also for the implementation of a financing depending on efficacy outcomes.

The diagnosis and the CAR-T indication appear also as one of the most frequently collected information, regardless of the initiatives' purposes.

Regarding the evaluation of the safety profile, the occurrence of adverse events is often observed with a strong focus on:

- cytokine release syndrome;
- neurotoxicity;
- persistent hematological toxicity;
- insertional mutagenesis.

Data regarding the dose, length and treatment received for the management of adverse events appear also essential to collect to better understand how adverse event can be managed the best as possible.

Furthermore, in order to better define responder profile, data on performance status, prior therapy received are important.

In the questionnaire, participants were asked to indicate if some criteria were collected in their initiative. The table in Appendix 5 summarizes the replies received.

3.2.2.7 Data linkage

Out of the 6 initiatives for which details were provided through the questionnaire, 3 reported the possibility to link data collected on CAR-T cells use with other existing databases and registries, and 1 reported that there was a plan for collaboration or linkage with other systems in the near future.

Several initiatives used more than one source of data, especially several national initiatives that also use data collected within the EBMT registry.

3.2.3 Other international collaboration on the topic

3.2.3.1 Center for International Blood and Marrow Transplant Research

In the USA, the FDA has required marketing authorization holders of CAR-T cells to follow-up patients treated with these therapies for 15 years. The Center for International Blood and Marrow transplant research (CIBMTR) is an outcomes database to follow patients who have received hematopoietic cell transplantation (HCT). They have recently expanded their infrastructure to capture data on cellular immunotherapies. The aim is comprehensive data collection through a standardized approach that can be used for both regulatory requirements and research. Several real-life studies are being conducted with data available from this registry.

3.2.3.2 Collaboration EMA and EBMT

The EMA organized a workshop dedicated to CAR-T cells therapy registries in February 2018 with all relevant stakeholders. The objective of this workshop was to facilitate the long-term follow up of CAR-T cell products in a real world setting and enable the generation of meaningful efficacy and safety data using haemato-oncological registries. The goal was to agree on implementable recommendations on core data elements to collect and other matters including patient consent, governance, quality assurance and registry interoperability as well as recommendations to optimise collaboration among registry holders, marketing authorisation holders and regulators (https://www.ema.europa.eu/en/events/chimeric-antigen-receptor-car-t-cell-therapy-registries-workshop).

The CHMP considered that the status of the cellular therapy module of the EBMT registry may allow its use as a data source for regulatory purposes in the context of specific studies concerning CAR-T cell therapies authorized for haematological malignancies. The EBMT has thus been qualified as a suitable platform for the collection of data for post-authorization safety study (PASS) and for the conduct of pharmaco-epidemiological studies for regulatory purposes concerning CAR-T cells. Details are provided in the qualification opinion on cellular therapy module of the European Society for Blood and Marrow Transplantation (EBMT) registry which was published in February 2019 on the EMA website (https://www.ema.europa.eu/en/documents/scientific-guideline/qualification-opinion-cellular-therapy-module-european-society-blood-marrow-transplantation-ebmt_en.pdf).

EBMT also collaborates with the CIBMTR from the United States regarding the form to collect data on cellular therapy. Indeed, standardization of data elements collected between several registries facilitates data sharing and pooling for analysis.

3.2.3.3 European Network for Health Technology Assessment

The European Network for Health Technology Assessment (EUnetHTA) Joint Action 3 (2016 – 2020), and more especially the WP5 stand B focuses on post-launch evidence generation and registries. A tool entitled REQueST (Registry Evaluation and Quality Standards Tool) was developed through this consortium. The REQueST tool aims to support HTA organizations in guiding and evaluating registries for effective usage in HTA.

EUnetHTA presented at the Ljubljana meeting on February 25th their current collaboration with EBMT in order to certify the EBMT registry for HTA purposes. The goal of this

collaboration is to provide HTA advice on the quality and usability of the EBMT registry for post-launch follow-up of CAR T therapies. Two tasks have been set up:

1) agree on the common data set for CAR-T cells real-world follow-up, and check the suitability of the EBMT data set for that purpose;
2) check the EBMT quality against REQueST.

3.2.3.4 Innovative Medicines Initiative

The Innovative Medicines Initiative (IMI) has launched two calls in 2019 to support the development of ATMPs, and more specifically CAR-T cells.

- "Accelerating research & innovation for advanced therapy medicinal products" (https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/imi2-2019-18-05);
- "Supporting the development of engineered T cells" (https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/imi2-2019-18-06).

These two initiatives could help contributing to the improvement of the real-life monitoring initiatives implemented for CAR-T cells.

3.2.3.5 ACCELERATE international platform

The ongoing international initiative entitled the ACCELERATE international platform aims to accelerate innovation in drug development for children and adolescents with cancer. ACCELERATE was jointly created in 2015 by the European Society for Paediatric Oncology (SIOP Europe), the European consortium for Innovative Therapies for Children with Cancer (ITCC), and the Cancer Drug Development Forum (CDDF) within the ENCCA project (European Network for Cancer research in children and adolescents). This platform involves multiple stakeholders including clinicians, researchers, patient advocates, industry representatives and regulatory bodies. One of the objectives, under the umbrella of the working group 7, is to set up long-term follow-up of children and adolescents exposed to new drugs. The goal would be to create an international, open, harmonized, and sustainable data registry with ACCELERATE to collect long term side effects of new anti-cancer therapies in children (https://www.accelerate-platform.org/work-programme/; https://www.ejcancer.com/article/S0959-8049%2814%2901065-X/fulltext).

3.3 Remaining challenges identified through the WP9 work

Various stakeholders and expectations for the real-life monitoring of patients treated with CAR-T cells

As seen throughout the WP9 task 4 activities, various stakeholders can be interested in real-life data of patients treated with CAR-T cells for different purposes. Thus, having one model, one system for all appears very difficult considering the **different goals and expectations from each stakeholder**.

Having a centralized European registry in place for the monitoring of patients treated with CAR-T cells, such as the EBMT registry, is a very interesting approach. However, there can be additional expectations at the national or regional level linked for instance to specific localized access or financing programs leading to the need to have additional national initiatives.

Initiatives that have been implemented for the real-life monitoring of patients treated with CAR-T cells in Europe are quite various, but the **risk for overlapping exists**. This shows the necessity to strengthen collaboration to find synergies and complementarities within existing initiatives in order to avoid duplication of initiatives and double data entry.

Many databases and registries aiming to collect health data, including data on patients treated with innovative therapies already exist. **The difficulty is to know if the data available in an existing system is sufficient to answer the expected goals or if additional data are needed**. Indeed, it is easier to conduct real-life studies based on an existing database, rather than creating or adapting a specific registry.

Challenges regarding data collection, analysis and interpretation of data

The standardization of data elements collected between several registries **facilitates data sharing and pooling for analysis**. This might for instance be very helpful for international pharmaceutical industries that would like to pool and analysis data with their products from several regions in the world. This can be done only if similar and comparable data are available in the different regions. EBMT and their equivalent database, CIBMTR, in the United States, have for instance collaborated regarding the data collection form on cellular therapy.

Interoperability should be ensured accross systems and initiatives implemented as much as possible in order to facilitate collaboration and pooling of data. “Collect data once, use it often” was raised as a strong wish, but can be difficult to implement.

It can be very interesting, especially for research purposes, to have registries collecting large amount of data. However, a balance should be found to **avoid an increased workload for the persons collecting the data**. Future integration with healthcare data systems in hospitals could significantly help to collect data automatically.

Data on **quality of life** and **patient reported outcomes** appears very important to be integrated in long-term follow-up, but are one of the hardest parameters to integrate in long terms follow-up.

The quality and reliability of data collected is of priordial importance. As there is currently no standardization regarding source verification, it can be challenging to define the best scenario of data validation.

One of the main goals of real-life studies is to compensate the uncertainties remaining after clinical studies to further investigate long-term safety and efficacy of the products. However, the **level of evidence and acceptability of the data and algorithms used for health decisions** has not clearly been defined so far. The development of further methodological guidance and standards would be helpful on these aspects.

For CAR-T cells, the need to better collect and understand the reasons why patients who receive leukapheresis did not go on to receive CAR-T infusion was raised.

Challenges regarding data sharing and governance

Registry maintenance costs can be considerable. Financial supports and governance are thus important to consider prior to implementation of a registry in order to ensure sustainability.

Processes for data sharing are very important to address as early as possible. Some experts reported challenges that have been encountered for data sharing notably due to the consent model and due to the time taken to set up national data sharing and funding agreements.

Experts present at the Ljubljana meeting mentioned that the owner of the data should ultimately be the patient; but that in practice, this can be hard to manage especially with the General Data Protection Regulation (GDPR) framework. Clinical decisions must come from experts but patient's perspective and preferences should be included into the final decision.

The very novel nature of these therapies and the need to adapt regulatory frameworks to include them presents a challenge. Stakeholders such a data protection agencies, regulators and ethics committee, particularly at national or local levels, require time to understand how these therapies differ from more traditional pharmaceutical products. Harmonised education and communication from central bodies like EMA and the EU Commission could help ensure consistency between and within countries in facilitating access and subsequent data collection. Intiatives by EMA in 2020 around secondary use of healthcare data for regulatory purposes and guidance on registry-based studies are welcome.

Furthermore, the **clinical development of CAR-T cells remains currently very broad.** Clinical trials are ongoing in many cancer localizations, including hematologic cancers, but also solid tumors. **Systems and initiatives implemented will have to be adjustable/adaptable to enable potential link for new indications.** Initiatives implemented for the real-life monitoring of patients treated with current commercialized CAR-T cells might have to adapt and evolve to make sure that they track potential additional data relevant for new indications of CAR-T cells.

4 Conclusion

Considering all the challenges associated with innovative therapies and more especially with CAR-T cells, it appears very important to ensure a proper monitoring of patients treated with these therapies in real-life settings.

Access to CAR-T cells is very variable across European countries for the two approved indications. It is however interesting to see that all countries where CAR-T cells are available outside clinical trials are collecting data related to the use of CAR-T cells in real-life settings. Indeed, several European countries have implemented some specific conditions to obtain the reimbursement, such as the necessity to collect specific real-life data, a limited timeframe for shipping the treatment, or time-limited access program with reinforced collection of safety and efficacy data.

In some European countries, where initiatives already exist to gather data in real-life settings for innovative, expensive or anticancer therapies for instance, some specificities were implemented for CAR-T cells. However, in other countries, the need to reinforce existing systems was seen and thus initiatives were developed especially for these therapies.

Having a centralized European registry in place for the monitoring of patients treated with CAR-T cells, such as the EBMT registry, is a very interesting approach. However, there can be additional expectations at the national or regional level linked for instance to specific localized access or financing programs leading to the need to have additional national initiatives.

Furthermore, the clinical development of CAR-T cells remains currently very broad. Systems and initiatives implemented will have to be adjustable/adaptable to enable potential link for new indications.

Interoperability of systems appears essential as well as continuing collaboration. Harmonised education and communication from central bodies like EMA and the EU Commission could help ensure consistency between and within countries in facilitating access and subsequent data collection.

References

Constances Cohort website glossay, available at https://www.constances.fr/glossaire.php

European Patients' Academy glossary, available at https://www.eupati.eu/glossary/

WHO International Clinical Trials Registry Platform Glossary, available at https://www.who.int/ictrp/glossary/en/

The Belgian national sickness and invalidity insurance institution (INAMI) website glossary, available at https://www.inami.fgov.be/fr/Pages/dictionnaire.aspx

European Observatory on health systems and policies series. Paying for performance in health care. Implications for health system performance and accountability, available at http://www.euro.who.int/__data/assets/pdf_file/0020/271073/Paying-for-Performance-in-Health-Care.pdf.

European Medicine Agency webpage on ATMPs, available at https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

Payment for performance in health care. Mannion R, Davies HT. Payment for performance in health care. BMJ. 2008;336(7639):306-308. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2234517/

Managed Entry Agreements for Pharmaceuticals in the Context of Adaptive Pathways in Europe. Bouvy JC, Sapede C, Garner S. Front Pharmacol. 2018;9:280. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5881456/

OECD. Performance-based managed entry agreements for new medicines in OECD countries and EU member states. Wenzl M, Chapman S, 2019. Available at https://www.oecd.org/health/health-systems/HWP-115-MEAs.pdf

EHA Guidance Document: The process of CAR-T cell therapy in Europe. HemaSphere, Chomienne C, Sierra J, Einsele H, Jäger U. 2019;00:00. Available at: https://journals.lww.com/hemasphere/Documents/EHA%20Guidance%20Document%20CAR-T%20Cell%20Therapy.pdf

Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. Jørgensen J, Hanna E, Kefalas P. J Mark Access Health Policy. 2020 Jan 15;8(1):1715536. doi: 10.1080/20016689.2020.1715536.

Legifrance. Arrêté du 30 avril 2019 subordonnant la prise en charge d'un médicament par l'assurance maladie au recueil et à la transmission de certaines informations relatives à sa prescription, en application de l'article L. 162-17-1-2 du code de la sécurité sociale. 2019 cited 2019 Nov 11. Available from: https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000038438805&dateTexte=&categorieLien=id

Kymriah Summary of product characteristics: https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf

Yescarta summary of product characteristics: https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf

Appendix 1: Agenda of the task 4 meeting

WP9 – Innovative therapies in cancer
Real-life monitoring of CAR-T cells in Europe

25 February 2020
National Institute of Public Health, Slovenia
(Trubarjeva 2, SI-1000 Ljubljana)

Agenda

	Real-life monitoring of CAR-T cells in Europe: current initiatives and beyond
08.45	*Welcome around a coffee*
09.00	Opening of the meeting + roundtable *Sophie Negellen*
9:10	WP9 Task 4 work : objectives and methodology *Sophie Negellen*
09:30	Challenges associated with the clinical development of CAR-T *Julio Delgado*
10.00	Review of the current existing national initiatives for the real-life monitoring of CAR-T cells in Europe *Presentation of literature search + presentation of the survey to conduct (questionaire)* *Hélène Denis*
10.15	*Break*
10.30	National initiatives • France : LYSARC CAR-T cells registry - *Florence Broussais* • Catalonia: data utilization in immunotherapy – *Cristina Coll* • Belgium: INAMI temporary reimbursement system – *Susana Da Silva Sanchez* • Italy: AIFA monitoring system for CAR-T – *Roberta De Angelis*
12:00	*Lunch Break*
13:00	European initiatives • EUnetHTA - *Iréna Guzina (by phone)* • European EBMT CAR-T cell Registry - *Eoin McGrath*
14:00	Discussion
15:00	*End of meeting*

Appendix 2: WP9 task 4 Questionnaire

Existing initiatives and programs for the monitoring of patients treated with CAR-T cells in real-life settings in Europe

Dear all,

This survey had been developed in the context of the European joint action iPAAC (*Innovative Partnership for Action Against Cancer*), which is funded under the Third Health Programme of the European Commission. The iPAAC joint action aims to develop innovative approaches to advances in cancer control. More information can be found on the iPAAC website: https://www.ipaac.eu/.

Within iPAAC, the Work Package (WP) 9 is dedicated to innovative therapies in cancer. Thanks to this survey, the WP9 intends to **map existing programs for the real-life monitoring of innovative therapies in Europe**. The focus had been given on the real-life monitoring of patients treated with **CAR-T cells**, more especially for indications already approved in Europe as of March 2020: acute lymphoblastic leukemia (ALL) and B-cell lymphomas.

This benchmark is an opportunity to get a **current state of play of the existing initiatives in Europe for the monitoring of patients treated with CAR-T cells,** such as registries, long-term follow-up studies or conditional financing systems. The WP9 also plans to highlight remaining gaps and challenges related to the real-life monitoring of innovative therapies for which further collaboration would be needed. The most innovative initiatives could be highlighted in iPAAC final deliverable called the roadmap.

Thank you very much for your active participation.

The WP9 team

Data protection statement: As part of its public service missions, the French National Cancer Institute has developed this survey in the context of the iPAAC joint action, and more especially for the WP9, which is dedicated to innovative therapies in cancer. Within this questionnaire, the Institute will collect personal data about your identity and your professional life in order to elaborate statistics on the aforementioned points. The Institute is the controller of the processing of your personal data and will retain it until the end of the iPAAC joint action and six month beyond. In accordance with the General Data Protection Regulation 2016/679, you have the right to access, to rectification, to erasure and to portability of your data, the right to restriction and to object to the processing. To exercise these rights, please submit your request to the following e-mail address: servicejuridique@institutcancer.fr. The Institute, the Institute's representative and the Institute's Data Protection Officer contact information can be found on e-cancer.fr. You also have the right to submit a request to the "Commission nationale de l'informatique et des libertés", the French supervisory authority.

I declare that I have acquainted myself with the above data protection statement and that I have understood the terms of the processing and my related rights.

❍

Identification of the responder

Please indicate your country / region: _____

Please indicate which of the following option best describes your professional role to answer to this questionnaire:

□ Clinician/Healthcare provider
□ Ministry of health
□ Healthcare payer organism
□ Public agency (oncology institute, HTA, medicine, public health agencies)
□ Other, please specify: _____

Name of the organizations where the responder works: _____

Do you agree to be contacted by the WP9 team if we have further questions?

□ Yes □ No

If yes, please provide contact email address: _____

Availability of CAR-T cells in your country

Acute Lymphoblastic leukemia

Can patients in your country be treated with CAR-T cells for the acute lymphoblastic leukemia?
Several answers can be chosen

□ Yes, in clinical trials setting
□ Yes, through early access programs
□ Yes, CAR-T cells are authorized and reimbursed for this indication in my country
□ No yet, but access is planned in the coming months
□ No, my country is not planning to have access to these therapies soon
□ Other: _____

The following question will appear only if the 2nd or the 3rd box of the above question is checked:

Is there any restriction of use compared to the European approved indication?
Kymriah® is indicated in Europe for paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse

□ No restriction compared to the European indication
□ Restriction regarding the age of the targeted population
□ Restriction depending on previous treatment received
□ Other restriction, please specify:

_____

B-cell lymphoma

Can patients in your country be treated with CAR-T cells for diffuse large B-cell lymphoma?

□ Yes, in clinical trials setting
□ Yes, through early access programs
□ Yes, CAR-T cells are authorized and reimbursed for this indication in my country
□ No yet, but access is planned in the coming months
□ No, my country is not planning to have access to these therapies soon
□ Other: _____

Can patients in your country be treated with CAR-T cells for primary mediastinal large B-cell lymphoma?

□ Yes, in clinical trials setting
□ Yes, through early access programs
□ Yes, CAR-T cells are authorized and reimbursed for this indication in my country
□ No yet, but access is planned in the coming months
□ No, my country is not planning to have access to these therapies soon
□ Other: _____

The following question will appear only if the 2nd or the 3rd box of one the two above questions is checked:

Is there any restriction of use compared to the European approved indication for Kymriah®?
Kymriah® is indicated in Europe for adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

□ No restriction compared to the European indication
□ Restriction regarding the age of the targeted population
□ Restriction depending on previous treatment received
□ Not applicable
□ Other, please specify: _____

Is there any restriction of use compared to the European approved indication for For Yescarta®?
Yescarta® is indicated in Europe for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

□ No restriction compared to the European indication
□ Restriction regarding the age of the targeted population
□ Restriction depending on previous treatment received
□ Not applicable
□ Other, please specify: _____

How are selected the centers in your country which are eligible to provide CAR-T cells?
Several answers can be chosen

□ Qualification by the Marketing Authorization Holder
□ National requirements to follow
□ Decision at the national level
□ Decision at the regional level
□ Other: _____
□ Not applicable

Existing initiatives for the monitoring of patients treated with CAR-T cells in real-life settings

1) Are data related to the use of CAR-T cells in real-life settings collected in your country?
   □ Yes □ No □ I don't know

The following questions 2 to 12 will be displayed in the online version only if "yes" is ticked in the above question.

2) What is/are the main use(s) of the real-life data collected? (several choices possible)
   □ Control eligibility of patient receiving the treatment with CAR-T cells
   □ Assess efficacy and efficiency in real-life
   □ Long-term safety surveillance
   □ Surveillance of the proper use
   □ Implement conditional financing including pay-for-performance system
   □ Share and compare practices to improve quality of care and optimize treatment strategies

3) How are data collected?
   Several answer can be chosen
   □ EBMT registry
   □ national program which was already in place prior arrival of CAR-T cells on the market
   □ Local program which was already in place prior arrival of CAR-T cells on the market
   □ New program implemented specifically to follow-up patients treated with CAR-T cells
   □ Other, please specify: _____

4) What is the name of the program enabling the collection of real-life data for CAR-T cells?
   If several programs exist, please report one first and you will be able to present the other ones at the end of the questionnaire.
   _____
   _____

5) Who is in charge of this program?
   □ Public agencies/Ministry of health
   □ Hospitals / Healthcare centers
   □ Healthcare professional network/Learned societies
   □ Association of patients
   □ Other, please specify: _____

6) When did the program start?
   □ Prior 2018
   □ Between 2018 and 2020
   □ Not yet started

7) How is the program financially supported?

□ Government public fund
□ Private fund from pharmaceutical industries
□ Mix of private and public fund
□ Other, please specify: _____

8) Could you please provide the main purpose of this program?

□ Economic (e.g. reimbursement conditioned by the collection of additional data, verification of performance criteria linked with the payment system)
□ Collection of clinical data for regulatory requirement (e.g. enabling the reevaluation of the benefit/risk ratio or long term follow-up of the drug marketed indication)
□ Research purpose (e.g. improving overall knowledge on CAR-T cells such as place in the therapeutic strategies, better define responsive and non-responsive patients)
□ Medico-administrative (e.g. check the proper use of CAR-T, check patient's eligibility)
□ Other: _____

9) Which of the following terms would best characterize/define the program?

□ Registry
□ Research study
□ Financing system
□ Other: _____

10) What are the criteria collected in this program for patients treated with CAR-T cells in real-life settings?

□ Patient medical history
□ Previous line(s) of treatment
□ Diagnosis and CAR-T indication
□ Response to treatment
□ Patient status after treatment
□ Biological parameters
□ Adverse events
□ Treatment administered to manage CAR-T cells related adverse events
□ Other, please specify: _____

11) Who is responsible to enter additional data?

□ treating physicians
□ pharmacists
□ nurse
□ data manager
□ other, please specify: _____

12) Is there already a possible linkage of data collected on CAR-T cells use with other existing national or regional databases/registries?

□ Yes
□ No

If yes, please specify: _____

If no, is there a plan for collaboration or linkage with other systems?

□ Yes. Please specify: _____
□ No

13) Do you have any comment, or would you like to share any difficulty/challenge that you might have encountered for the monitoring of patients treated with CAR-T cells?

_____
_____

14) Is there another program for the monitoring of patients treated with CAR-T cells in real-life settings that you would like to present?

□ Yes
□ No

Thank you for your participation

Appendix 3: WP9 Task 4 Ljubljana Meeting minutes

Meeting minutes

Title:	WP9 task 4 meeting : Real-life monitoring of patients treated with CAR-T cells in Europe
Purpose:	Discussion on the monitoring of patients treated with CAR-T cells in real-life settings: existing initiatives and remaining gaps and challenges
Date and time:	25 February 2020
Location:	NIJZ, Ljubljana, Slovenia

Attendees

Name	Organisation (department, division)
Albreht Tit	NIJZ - SLOVENIA
BROUSSAIS Florence	LYSARC - FRANCE
DA SILVA SANCHEZ Susana	INAMI - BELGIUM
COLL Cristina	Catalonia Institute of Oncology (ICO) - SPAIN
DE ANGELIS Roberta	Instituto Superiore di Sanità (ISS) - ITALY
DENIS Helene	French National Cancer Institute (INCa) - FRANCE
JELENC Marjetka	NIJZ - SLOVENIA
LIPUSCEK Tina	NIJZ - SLOVENIA
McGrath Eoin	European Society for Blood and Marrow Transplantation (EBMT)
NEGELLEN Sophie	French National Cancer Institute (INCa) - FRANCE
VAN DEN BULCKE Marc	Sciensano - BELGIUM
WEHENKEL Sophie	National Cancer Institute (INC) - LUXEMBOURG
GUZINA Irena	EUnetHTA
VOJE Natasa	NIJZ - SLOVENIA

Attachments

1_iPAAC WP9 task 4 introduction	2_CAR-T cells, literature review and	3_French National Initiative DESCAR-T
4_INAMI_Belgium	5_AIFA_Italy	6_EBMT

Decisions made

What and why was decided, what impacts are expected

1. Questionnaire

A first version of a questionnaire aiming to identify existing initiatives enabling the monitoring of patients treated with CAR-T cells in real-life settings was presented. INCa will review the questionnaire with suggestions made during the meeting. A new version will be circulated for review. The final version will be disseminated with an electronic format.
Post-meeting note: Due to the COVID-19 epidemic, the dissemination of the questionnaire will be postponed until the epidemic settles.

2. iPAAC WP9 task 4 deliverables

Existing initiatives enabling the monitoring of patients treated with CAR-T cells as well as results of the questionnaire will be presented in a specific deliverable focusing on task 4. Remaining gaps and challenges in Europe on this thematic will be discussed in this deliverable. Partners and experts involved in WP9 meetings will be asked to contribute and to review this deliverable.
In addition, some One-pagers will be suggested by the WP9 partners and experts to be included in the iPAAC roadmap.

Discussion

Items or knowledge to be shared

<u>Introduction</u>

Tit Albreht, scientific coordinator of the iPAAC joint action, welcomed participants in the NIJZ premises. The iPAAC WP1 (coordination) and WP4 (roadmap) should be able to meet the commissioner Stella Kyriakides the week following this WP9 meeting.

Neda Milosavljevic (Serbian WP9 partner) and Julio Delgado (CIBERONC) informed that could not attend the meeting.

<u>WP9 Task 4 work : objectives and methodology</u>

For details, see presentation 1, from Sophie Negellen, INCa, France

Sophie Negellen, WP9 leader, gave an overview of the content of the WP9, which is

dedicated to innovative therapies in cancer. She then detailed the main purposes of the WP9 task 4:

- Establish a state of play of existing European initiatives enabling the real-life monitoring of patient treated with CAR-T cells;
- Define potential fields with remaining challenges which would need further European coordinated approach;
- Highlight the most innovative initiatives through the roadmap.

Methodology, timelines, milestones and expected deliverable content were presented.

<u>Review of the current existing national initiatives for the real-life monitoring of CAR-T cells in Europe: presentation of literature search + questionnaire</u>

For details, see presentation 2, from Hélène Denis, INCa, France

To start, the main key facts and challenges related to CAR-T cells products were highlighted to show the importance to monitor patients treated with CAR-T cells in real-life settings.

Then, the first results of the literature review aiming to identify existing initiatives for the real-life monitoring of patients treated with CAR-T cells were presented.

Finally, the questionnaire goal, content and dissemination strategy were displayed.

<u>Presentation of Catalonia: feasibility of real world data analysis and CAR-T use</u>

The first part of the presentation showed the feasibility of a real world data analysis with a case study on the pharmaceutical treatment of non-small cell lung cancer in Catalonia.
The Catalan Registry of morbidity and healthcare resources (MUSSCAT), collects clinical and administrative information by the Catalan Health Service (CatSalut) and for high cost drugs, the Pharmacotherapeutic Harmonization Program (PHF-MHDA) was introduced to avoid differences on the introduction of drugs at hospital level. The case study showed that database linkage for cancer treatment is feasible using real-world data techniques and that it is feasible to link administrative and clinical data with reimbursement models. Some difficulties were highlighted, notably the difficulty to collect the stage of illness and some uncertainties regarding the incidence data.

The second part of the presentation presented the use of CAR-T cell therapy in Catalonia including the authorization process, number of requests, authorizations and infusions performed.
The VALTERMED national registry was introduced in 2019 and it is going to be developed in 2020: this is an information system to determine the therapeutic value in real clinical practice of medicines of high health and economic impact within the NHS. VALTERMED is

also going to be integrated into the information systems of the autonomous communities (i.e., within the PHF-MHDA in Catalonia).

Considering the different committees involved in the decision process (at the regional level (CatSalut) + at the national level (ministry of health: MSCBS), a comment was raised regarding the length of the authorization process, which should not be too long to avoid loss of chances for the patient. Moreover, if the regional committee (CatSalut) refuse the authorization, the process stops and the request would not reach the national re-evaluation by the ministry of health.

Presentation of the French national initiative DESCAR-T

For details, see presentation 3, from Florence Broussais, LYSARC, France

The French national initiative DESCAR-T involves several cooperating groups in oncology: the lymphoma study association (LYSA), the cooperating group on acute lymphoblastic leukemia (GRAAL) and the French cooperating group on childhood cancers (SFCE).
The registry will not limit enrolment to patients who have received CAR-T; it will also include patients who are not eligible for CAR-T during tumor board or who did not receive the CAR-T injection after being eligible.
The goal is to implement a single national and independent tool for monitoring patients treated with CAR-T cells in France, which would be interoperable with existing registries.
The main goals of this registry are to better understand:

- characteristics of eligible patients
- efficiency in real-life
- CAR-T secondary and subsequent treatments
- Long term safety profile
- Manufacturing times and availability

Primary objective: To evaluate for each CAR-T product the efficacy in real-life of CAR-T on overall survival from the date of eligibility for eligible patients (as decided by expert tumor board) and included in the registry.

The registry will not respond to quality of life or to organizational impact.
Potential off-label use won't be collected (e.g. follicular lymphoma).
Further details regarding the planning, data collection, data monitoring and registry governance are available in the related presentation.
The difficulty to follow-up patients who don't have social insurance in France was raised.

Presentation of the Belgian experience with CAR-T temporary reimbursement convention

For details, see presentation 4, from Susana Da Silva, RIZIV/INAMI, Belgium
First, the Belgian healthcare system was presented with a focus on the reimbursement

system for medicines.
Types of uncertainties leading to possible managed entry agreements were developed. In Belgium, more than 70 managed-entry agreements are in place for ATC code L (*Antineoplastic And Immunomodulating Agents*).
Performance based schemes: the reimbursement rate is related to the actual future performance with a pre-specified definition of response.

Then, an example with Kymriah was given. The homepage of the RIZIV/INAMI program web was presented to show data that are publicly available on this website (including the price).
Specific data to collect via the system eHealth for the 2 Kymriah® indications (in acute lymphoblastic leukemia (ALL) and in diffuse large B-cell lymphoma (DLBCL)) were then specified.

To be noted that in Belgium, 4 centers are authorized to provide CAR-T cells.
For CAR-T cells: the first main payment is made up-front, but additional payments are made only if additional data requested are completed and eligible for reimbursement.

<u>Presentation of AIFA monitoring registries – post-marketing data collection and evidence evaluation (Italy)</u>

For details, see presentation 5, from Roberta De Angelis, ISS, Italy

AIFA Monitoring registries are administrative tools, introduced in 2005, to improve early access of innovative therapies and guarantee sustainability, and collecting epidemiological data to monitor safety and appropriate usage.
Cancer drugs were monitored first, now the scopes are extended to several therapeutic areas. Monitored drugs are in general high cost medicines, many of which biotech products, often registered through a European centralised authorization procedure
The common characteristics are the high level of uncertainty with regard to safety, appropriate use in real world, cost-efficacy, and budget impact issues.

Each registry is specific to one drug and one indication.

The AIFA monitoring registries system was presented with a focus on:
- Actors of the network
- Workflow and data entry forms
- Analysis of managed-entry agreement and evaluation

There are currently 69 managed entry agreements in Italy for 57 drugs, mainly payment by results models.

Regarding CAR-T cells, AIFA approved their reimbursement in 07 August 2019.

Prescribing centers of CAR-T cells therapies are subject to the qualification by the Marketing Authorization Holder. The selection of clinical centers is under the responsibility of the 21 regions. AIFA set minimum criteria for prescribing centers (see PowerPoint for details).
The AIFA registry workflow for CAR-T cells is quite similar to other regular drugs. Payment is split at different time points from the infusion date and according to predefined outcome (payment by result model).

EUnetHTA collaboration on RWD generation:
Current achievements of JA3 WP5B and the example of the CAR-T pilot with EBMT

An overview of the EUnetHTA joint action was provided including history, governance and activities.
Then, the focus was given to the WP5B, which the main objective is to confirm possible levels of cross-border collaboration on Post-Launch Evidence Generation (PLEG), develop/complement standards and procedures.

The main outputs were presented:

- Registry evaluation and Quality Standards Tool (REQueST®): this is a tool aiming to assess registries. The final version was published in Oct 2019.
- PLEG pilots
    - Product specific pilots (to check variables which should be collected)
        - ex: Spinraza®, Ibrance®
    - Registry specific pilots (to check the quality of the registry)
        - ex: CAR-T pilot in collaboration with EBMT: the objective of this pilot is to provide HTA advice on the quality and usability of the EBMT registry for post-launch follow-up of CAR T therapies. It includes 2 main tasks:
            1. Agree on the common data set for CAR-T real-world follow-up, and check the suitability of the EBMT data set for that purpose;
            2. Check the EBMT quality against REQueST®.

The EBMT Registry and facilitating real-life follow-up of patients treated with CAR-T cells

For details, see presentation 6, from Eoin McGrath, EBMT

To start, an overview of the European Society for Blood and Marrow Transplantation (EBMT) was given. Then, the EBMT registry was presented.

EMA has registry requirements for post-authorization follow-up of CAR-T cell therapies.
The EMA qualification process for the EBMT registry was explained.
Main points raised by EMA:

- Data quality control including completeness, source data verification and periodic auditing
- Robust patient consent procedures to include data sharing
- Data access facilitation to different stakeholders

The EBMT registry is now suitable for collecting CAR-T cell therapy data and performing pharmacoepidemiological studies.
The newsletter released publicly every month displays:

- The number of CAR-T-cell treated patients registered in the EBMT registry
- A map of countries reporting CAR-T cell treated patients to the EBMT registry

EBMT had recently (Feb 2020) come to a collaboration agreement with Novartis to be in charge to track long-term outcome data for Kymriah®. EBMT is committed to further share data.

<u>Discussion regarding the questionnaire</u>

- Dissemination should be also done at clinicians level. Suggestion: go through national and European learned societies to help dissemination among clinicians.
- Online version preferred
- Avoid open question, and provide boxes to tick: easier to answer and to analyse
- Regarding the interoperability: question should make the distinction: what is possible now and what is plan in the future
- It should also address the accreditation of centers eligible to provide CAR-T cells

<u>Challenges raised over the presentations and the discussion time:</u>

- Registry maintenance costs can be considerable. Financial supports and governance to ensure sustainability of registries are important to consider.
- “Collect data once, use it often”: is what we all want, but can be difficult to implement.
- Different stakeholders, different wishes
- Owner of the data: should be the patient; but hard to manage
- Interoperability: very important
- Systems and initiatives implemented will have to be adjustable/ adaptable to enable potential link for new indications.
- Integration of patient reported outcome / Quality of life aspects: important but harder to implement

Appendix 4: Specific data that are or could be collected for the real-life monitoring of patients treated with CAR-T cell therapies

Country	Organisation	Type of document	CAR-T and indication involved	Link for details
UK	NICE	Cancer Drugs Fund managed access agreement data collection arrangement	Kymriah® ALL	https://www.nice.org.uk/guidance/ta554/resources/managed-access-agreement-december-2018-pdf-6651288397
			Kymriah® B-cell lymphomas	https://www.nice.org.uk/guidance/ta567/resources/managed-access-agreement-march-2019-pdf-6718513213
			Yescarta®	https://www.nice.org.uk/guidance/ta559/resources/managed-access-agreement-january-2019-pdf-6660053245
France	ATIH	Technical note aiming to provide instructions and format for data to collect for CAR-T cells	All CAR-T cells	https://www.atih.sante.fr/sites/default/files/public/content/3595/notice_technique_atih-371-6-2019_car-t-cells.pdf
Belgium	INAMI	Legal text accompanying reimbursement modalities	Kymriah®	https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/fr/Public/ProductSearch
Spain (Catalonia)	Ministry of health	Protocol of use in the national health system – information system to determine the therapeutic value in real practice of medicines with high health and economic impact (VALTERMED)	Kymriah® ALL	https://www.mscbs.gob.es/en/profesionales/farmacia/pdf/20190508_Protocolo_farmacoclinico_tisagenlecleucel_LLA.pdf
			Kymriah® B-cell lymphoma	https://www.mscbs.gob.es/en/profesionales/farmacia/pdf/20191128_Protocolo_farmacoclinico_tisagenlecleucel_axicel_LBDCG.pdf
Europe	EMA	Proposed data elements relating to efficacy and safety – CAR-T cell therapy	All CAR-T cells	https://www.ema.europa.eu/en/documents/report/appendix-1-proposed-data-elements-relating-

		registries workshop		efficacy-safety-car-t-cell-therapy-registries-workshop_en.pdf
Europe	EBMT	Data collection forms for cellular therapy	All cellular therapies	https://www.ebmt.org/registry/data-collection

Appendix 5: Data collected for patients treated with CART-T cells in real-life settings in 6 out of the 14 initiatives identified

	Data collected	**Registries**				**Financing / access program**	
		DESCAR-T registry	Portuguese cancer registry	VALTERMED - Spain	Italian CAR-T registry	Cancer Drug Fund - UK	INAMI - Belgium
Suggested in the questionnaire	Patient medical history	X	X		X		
	Previous line(s) of treatment	X			X	X	
	Diagnosis and CAR-T indication	X	X	X	X	X	X
	Response to treatment	X	X	X	X		X
	Patient status after treatment	X	X	X	X		X
	Biological parameters	X		X	X		
	Adverse events	X	X	X	X		
	Treatment administered to manage CAR-T cells related AEs	X		X		X	
Additional suggestio	Patients in intention for CAR-T, finally not treated	X					
	Overall survival, performance status, rate and time to SCT					X	

Administrative data			X			
Data related to quality of life			X			