AVANTYO
INSTITUTE OF CLINICAL RESEARCH

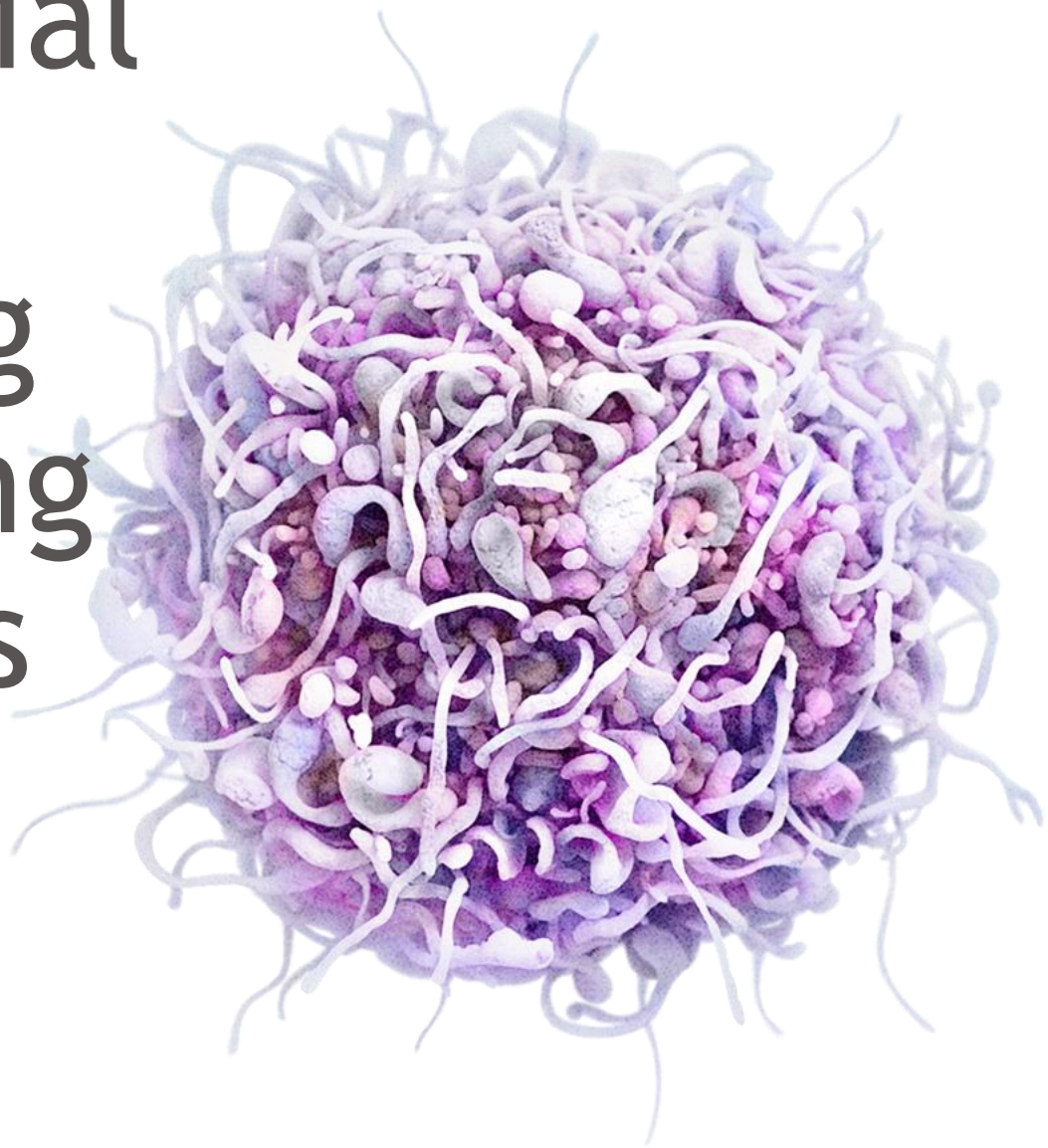
INNOVATION IN EDUCATION

"Stay Ahead of the Game:
Transformation in Clinical Trials
in the Age of Artificial Intelligence."

ANNUAL CLINICAL TRIALS SYMPOSIUM

November 8th, 2024

Unlocking the Potential of CART Trials in Romania: Overcoming Challenges and Seizing Growth Opportunities



8th November 2024, Avantyo Symposium

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Bristol Myers Squibb®

Romania

EU member country, *6th largest*

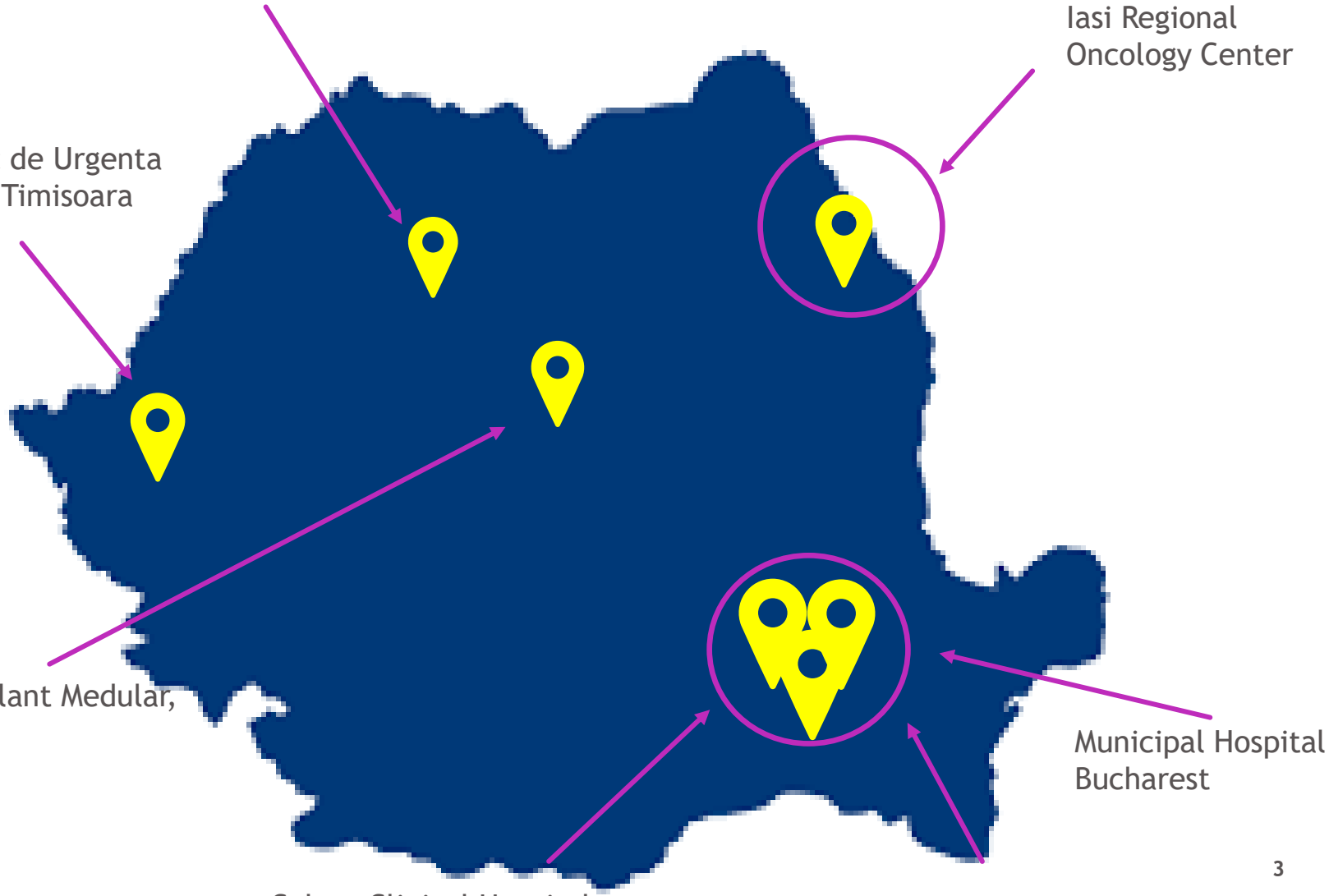
Total population

19,31 mio*

#Of sites: 7, of which 2 have CAR-T experience

 # CAR-T CTs experienced sites in Romania: 1 of 7

#Apheresis sites experienced in CTs in Romania: 1 of 7



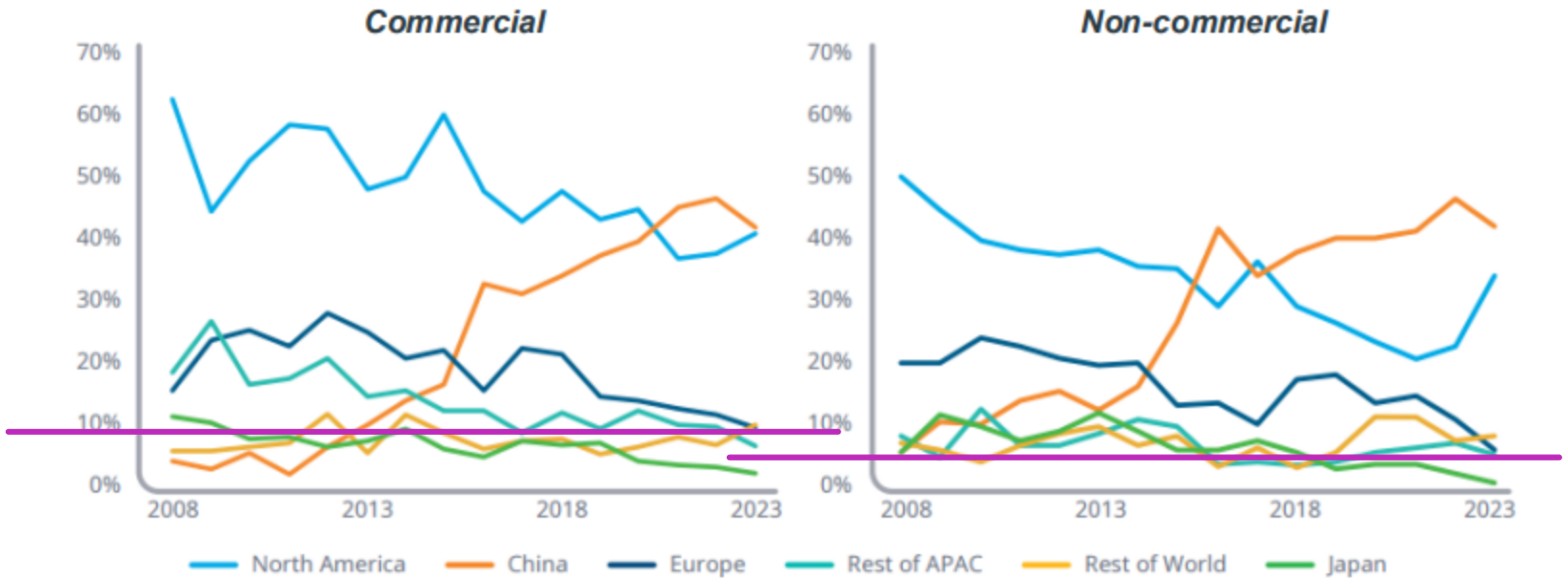
Indications: oncology (solid tumors & hematology), CV, CNS (including psychiatry), CARTs, Immuno-science

*https://ec.europa.eu/romania/news/20210211_previziuni_economice_iarna_ro

Europe's share of Cell and Gene Therapy trials has decreased since 2013, whilst China has experienced rapid growth in the last decade

Cell and Gene Therapy (CaGT) spotlight

Share of cell and gene therapy trial starts by geography (2013-2023)



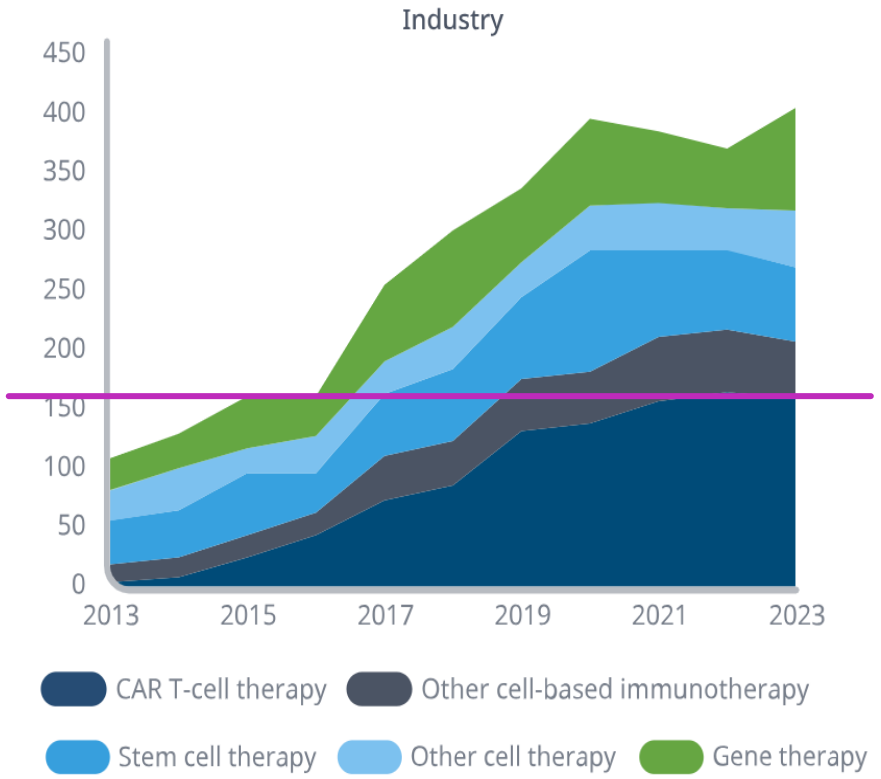
Europe's participation in global cell and gene therapy trials has steadily decreased since 2013.

During this period, China has seen a dramatic rise in CaGT trials since 2013, to become the leading region. This trend may be attributed to a favourable regulatory environment, funding streams, and strategic focus on these technologies

Between 2014-2022, The US share of CaGT trials declined, though the US remains the second-largest region for commercial and non-commercial trials. Since 2021, there has been a notable increase in non-commercial CaGT trials in the US, suggesting the US is increasing its focus in this area

Source: Strengthening Pathways for Cell and Gene Therapies, IQVIA Institute

Cell therapy clinical trial start 2013-2023



Source: Citeline Trialtrove, Dec 2023; IQVIA Institute, Jan 2024.

Source: Strengthening Pathways for Cell and Gene Therapies: Current State and Future Scenarios - IQVIA

CAR-T Clinical Trials Local level Romania

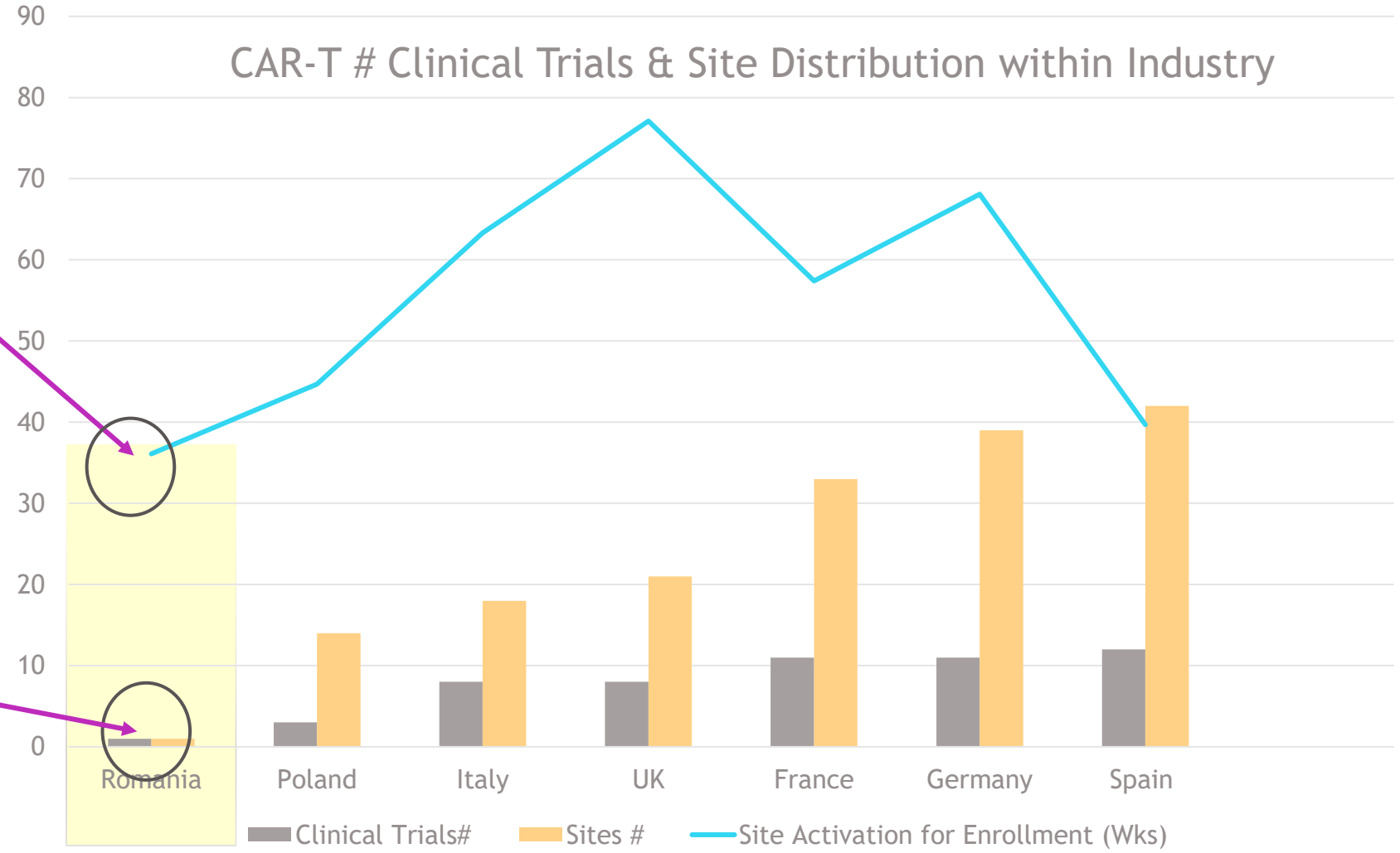
ID	Phase	Primary Indication
2023-503452-27-00 (Registry Identifier) (REGISTRY: EU CT Number)	III	r/r Follicular Lymphoma – 1 site Recruiting in Bucharest
2022-501346-30 (EudraCT Number)	III	Multiple Myeloma – active not Recruiting 1 site in Bucharest
N/A	III	Relapsed or refractory Multiple Myeloma- not yet recruiting 1 site in Bucharest, 1 site in Iasi

Source: Data based on public information ClinicalTrials.gov

Cellular Therapy Local centers distribution vs. Study Start-up Cycle times (Weeks)

Romania is low saturated and has fast start-up cycle times from selection to activation across select Countries Western and Eastern Europe

Currently 2 Ongoing CAR-T Clinical Trials**



*Data based on **DQS Industry Data - List of Cell Therapy Trials with Data Available**
**Data based on public information ClinicalTrials.Gov

What Do We Need From CAR T Study Sites?

Access to patient population with disease indication	Cell therapy standards: facilities, equipment, and systems logistics accreditation of apheresis unit and cell processing lab (e.g. The Foundation for the Accreditation of Cellular Therapy (FACT), the Joint Accreditation Committee ISCT- Europe & EBMT (JACIE)- (FACT/JACIE)
Start-up cycle time	Apheresis Unit & Cell Processing Lab (on/off-site, process, type of contract agreement & timing, etc.)
Competing Trials (internal/external; similar patient population, and CAR T trials)	Apheresis Machine Utilized (Example models: TerumoBCT Spectra Optia, TerumoBCT COBE Spectra, Fresenius Amicus)
Staff/Site resources (e.g. sufficient resourcing for study coordinator/research nurse)	Departmental Interdependencies (ICU proximity and bed availability for clinical trial patients, ensure site formulary has tocilizumab and siltuximah)
CAR T trained personnel Physicians, neurologist, nurses, ICU staff and other hospital personnel available to care for CAR T subjects, before, during, and after CAR T cell therapy.	Shipment/Receiving (e.g. proximity to major airport, able to receive/store drug product in liquid nitrogen container/freezer)
Familiarity with Investigational Product (IP) Preparation Utilization of lymphodepleting chemotherapy agents (protocol defined) Administration and availability of tocilizumab for Cytokine Release Syndrome (CRS) for possible toxicity management	

- CAR T-cell therapies require infrastructure, processes, and workflows different from those in a general oncology practice e.g., Institutional Biosafety Committee (IBC) approval- GMO Application in addition to IRB/EC & MOH approval;
- Safe administration and management of these therapies requires appropriate education, competencies, standard operating procedures, processes, and stringent Sponsor, Investigator and Institutional oversight

Source: JACIE Accreditation | EBMT

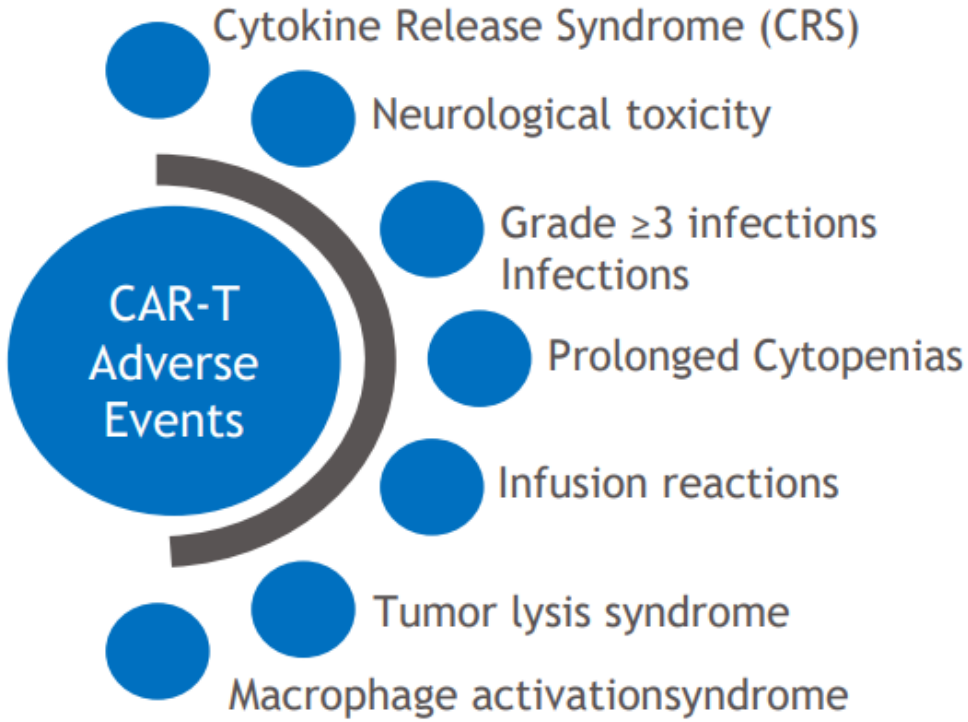
Patient Journey

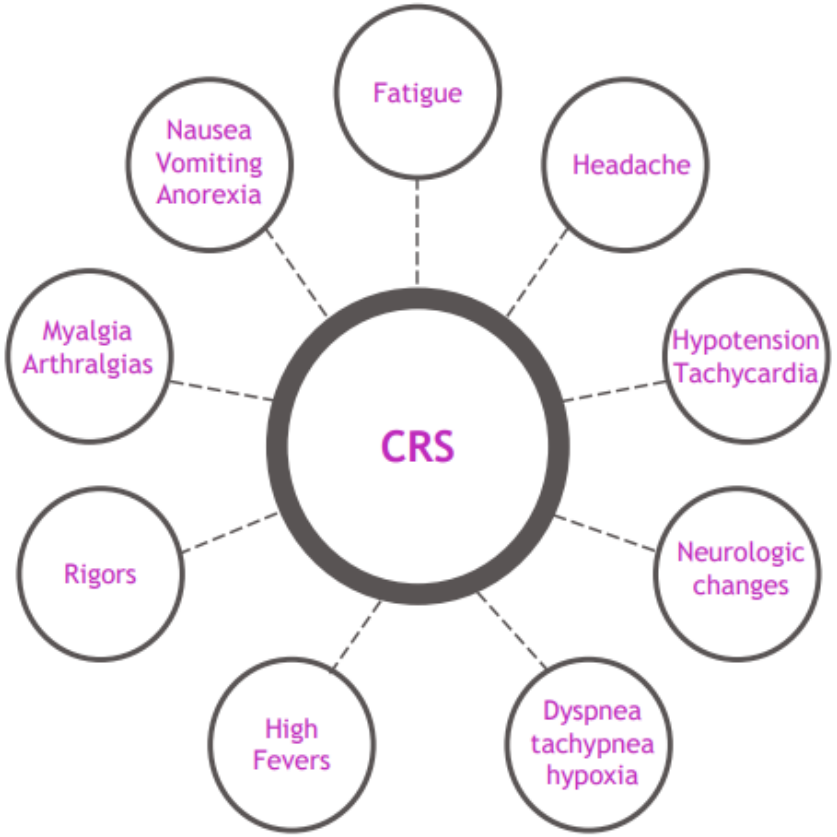
CAR T Patient Journey: A Multi-Step Process Over Several Weeks

Patient referral and entry	Patient eligibility	Leuka-pheresis	Conditioning therapy	CAR T creation and expansion	CAR T infusion	Monitoring
Patient qualifies and is referred to a CAR T physician	Patient undergoes pretreatment eligibility assessment	Peripheral blood mononuclear cells undergo apheresis and are shipped to a manufac-turing facility	Patient undergoes conditioning chemo-therapy during cell processing	CAR T-encoding genetic material is transferred via viral vector—CAR T cells are then expanded	CAR T cells are administered to patient following lympho-depletion	Patient is closely monitored with a long-term follow-up plan

Source: Beaupierre A et al. Clin J Oncol Nurs. 2019

CAR-T Therapy Toxicity Requires Careful Clinical Management





Diagnosis is based on clinical symptoms

Source: Chieh Yang, John Nguyen & Yun Yen, Complete spectrum of adverse events associated with chimeric antigen receptor (CAR)-T cell therapies, Journal of Biomedical Science, 2023

What Do We Need From CAR-T Study Sites?
Pain Points

1. Accredited Apheresis center and Cell Therapy Laboratory on site ***or*** willingness for inter-institutional collaboration with a CAR-T center nearby

2. Qualification and Validation

Personnel Requirements (physicians and nurses):

Apheresis Collection Facility holds training in cell collection and/or transplantation

3. Cell Processing Lab Capabilities

3.1 Implementing a quality management system: Management of the apheresis schedule and/or procedure oversight; process to secure an apheresis slot

3.2 Written policies and procedures for handling investigational products which include specific requirements for gene therapy/Cell Therapy Lab (CTL), as for Internal Audit and Record management system, Labeling, others, per local legislation

4. Process in place to allow LTFU - Mandated 15 year follow up from the time of the subjects last CAR T infusion required by regulatory agencies to monitor for recurrence of the autoimmune disease and/or any complications of the cell therapy.

Source: JACIE Accreditation | EBMT

Unlocking potential in CAR-T CTs:

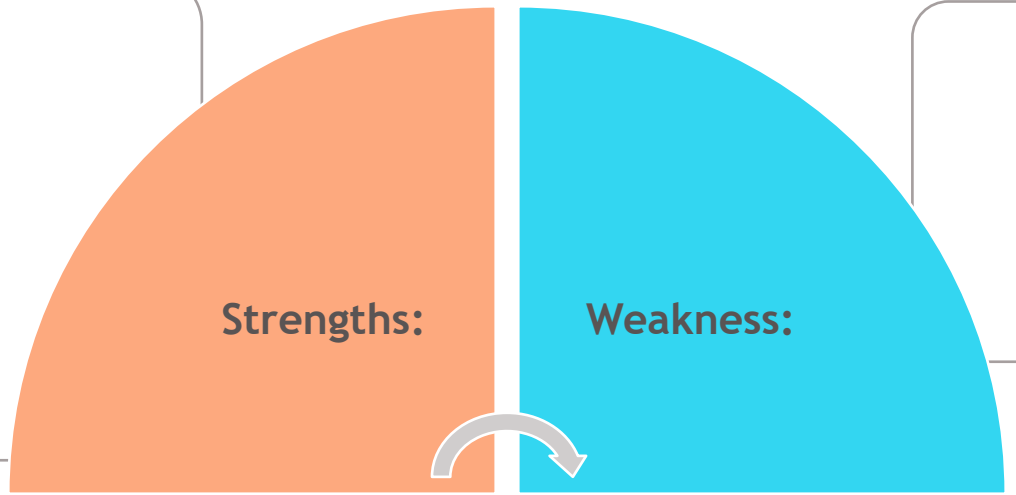
Factors Which may contribute to attracting Investments in Romania may include:

- ✓ Increase Quality of healthcare system (infrastructure with Apheresis centers)
- ✓ Foster communication channel between the site and Apheresis and or Cell Therapy Unit
- ✓ Inter-institutional contracts and infrastructure between Apheresis Collection Centers and Cellular Therapy Sites
- ✓ Aligned process for commercial/ Clinical trial collaboration model
- ✓ Development of Local Non-industry trials /Academia trials (Globally represented 36% of trial starts in 2023)
- ✓ There are already **key research centers in major cities** to be explored for future CAR-T Trials

- ✓ Successfully implementation of New European Legislation EU-CTR > Significant improvement in Regulatory Clinical Trial Environment **up to 106 Days** Clinical Trials Approval per EU-CTR
- ✓ GMO Authorization Smooth process submission same time with the Clinical Trials Application
- ✓ Trial approval time comparable with EEA Countries
- ✓ Site Start-up time lower than other EEA timeliness
- ✓ Romania is very attractive country due to low access to innovative medicine (Towards the end in Europe as speed of access to medicines) > expected continuous increase in R&D Investments

Triggers for attracting new CAR-T Clinical Trials various indications

SWOT Analysis



Strengths:

- Already Experienced centers with CAR-T (via Commercial process and CTs)
- Trained personnel in different CAR-T Centers in EU ready to share and apply knowledge, well trained and equipped ATI staff in management of AE CAR-T infusion
- Qualified Apheresis centers, from which 1 in the process of obtaining JACIE Accreditation
- Industry, Regulatory bodies, academia, patient association & clinical sites initiatives to accelerate and increase #of CTs in the country – HUB Innovation

Weakness:

- Low number of apheresis centers Country level
- Low relevant experience in CAR-T Clinical Trials
- Sites/Institution resources: human & administrative
- Limited Hospital capacity and hospital infrastructure in treating multiple patients (leukapheresis and CAR-T infusion)

Opportunities:

- To foster Communication/Collaboration paths between Institutions country level
- Satellite sites to cover CAR-T Infusion
- To set up Patient referral process country level
- To explore future upcoming therapeutical areas
- Absorb external funds in developing new apheresis centers
- The increase of CAR-T CTs will trigger future CAR-nK future innovative medicine opportunities

Threats:

- Clinical Trial Site Allocation
- Competitive landscape & low number of HCPs with expertise in cell therapy*
- High geographical uncovered area to allow patient access to cell therapy
- Limited awareness on local approved CAR-T Clinical trials (for local territory HCP)
- Lack of post study drug access local regulation

Open Question for Audience:

1. How can pharma sponsors/Industry help foster communication channels/learning paths between institutions with CAR-T experience and those without?

Open Question for Audience:

2. How can pharma sponsors/Industry enhance the competitive landscape despite sites limited experience

(e.g. CAR-T Trials conduct, AE Management/post-infusion monitoring)?