CAR-T cell product
Cell & Gene Therapy

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Barcelona
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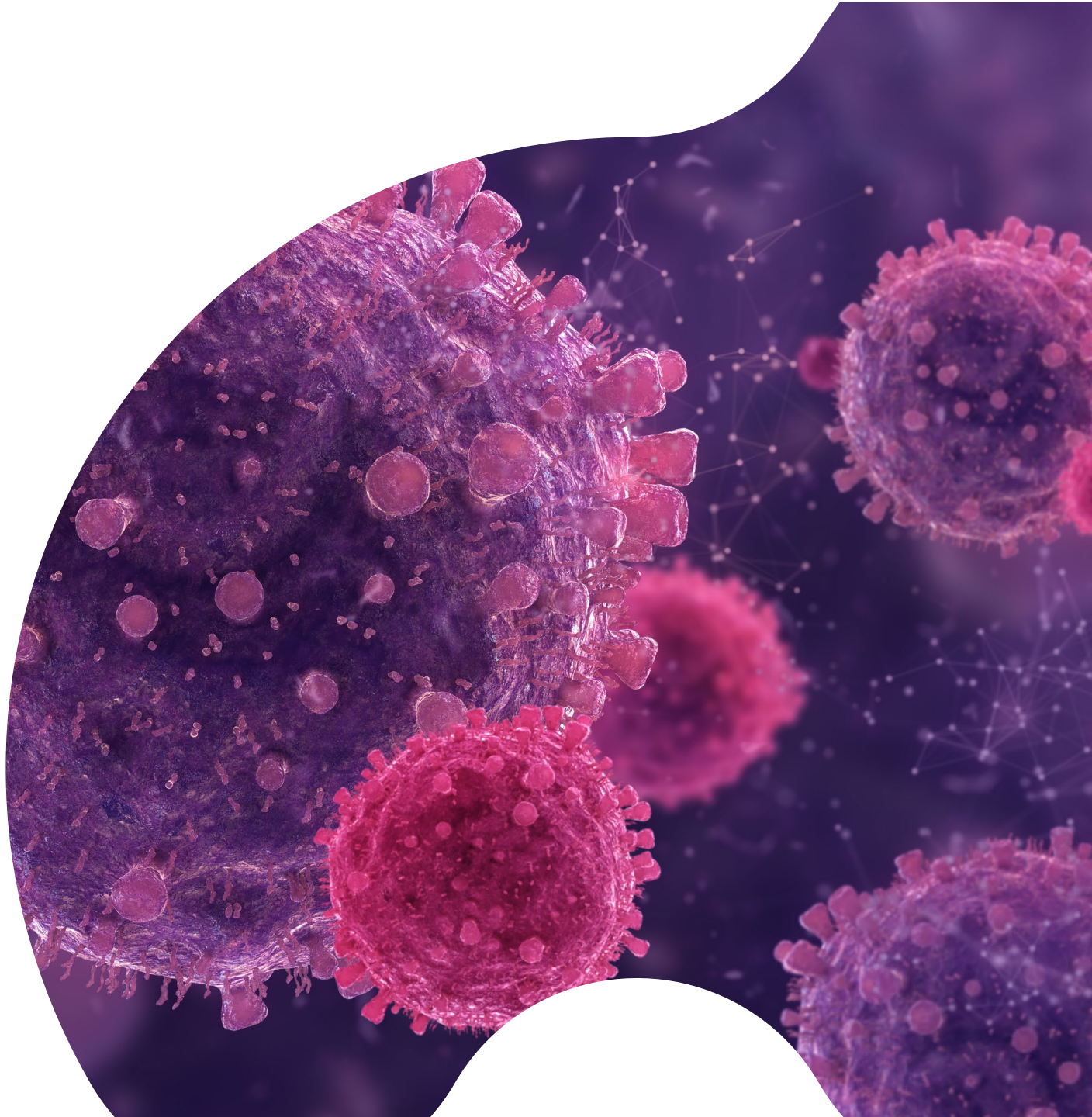
NOVARTIS | Reimagining Medicine



Agenda

"Given the exclusively educational and eminently illustrative nature and purpose of the class explanations of this presentation, the author invokes article 32 of the current Intellectual Property Law with respect to the partial use of other people's works such as images, graphics or other materials contained in the different slides."

Introduction

- What is a CAR-T cell product
- Mechanism of action
- Examples of CAR-T cell products

Relationship with the Hospital

- A new paradigm
- Hospital & Industry stakeholders involved in the patient's treatment

Regulatory requirements

- Regulations to be followed
- The path for CAR-T cell treatment to reach patients in Spain
- List of centers designated by the Ministry of Health

Center qualification

- Overview/Qualification steps
- Apheresis Collection Unit
- Cell Processing Unit
- Maintenance & Oversight

High level process overview

- Tisagenlecleucel manufacturing process
- Chain of Identity
- Transport & Temperature monitoring
- Finished Product & Infusion
- CAR-T Therapy: Possible toxicities & Clinical Signs and Symptoms

Future of Cell Therapy

Q&A

Introduction

- What is a CAR-T cell product
- Mechanism of action
- Examples of CAR-T cell products

What is a CAR-T cell product

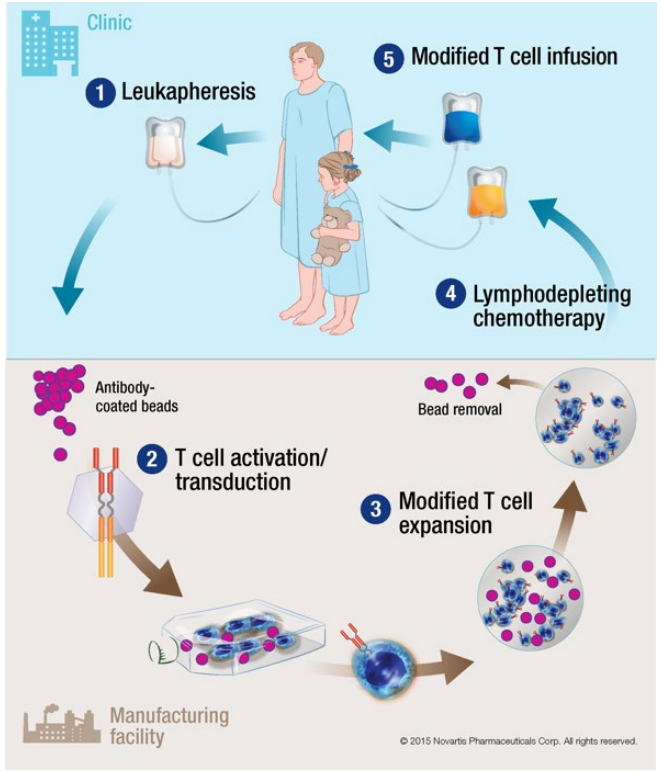
CAR-T cell therapy is a type of immunotherapy that uses the body's own immune cells, called T cells, to fight cancer.

CAR-T stands for chimeric antigen receptor T cell.

The therapy involves extracting a patient's T cells, genetically modifying them to produce chimeric antigen receptors (CARs) on their surface, and then infusing them back into the patient.

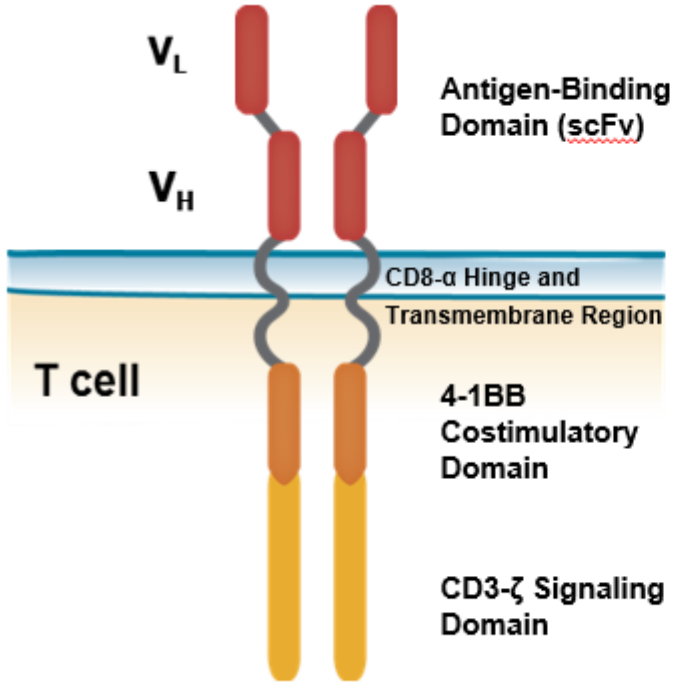
These CARs allow the T cells to recognize and target specific cancer cells by binding to antigens present on their surface.

CAR-T cell products refer to the modified T cells that are infused into patients as part of this therapy.



Example of CAR: CTL019 (tisagenlecleucel)

The CTL019 chimeric antigen receptor (CAR) consists of intracellular domains that signal T cell activation, proliferation, antitumor activity and persistence of CAR-T cells coupled to an anti-CD19 single-chain variable fragment[1-3]



Antigen-binding domain
- Recognizes CD19 on B cells

4-1BB (CD137) costimulatory domain
- Augments antitumor activity
- Enhances proliferation and persistence of CAR-T cells

CD3-ζ chain signaling domain
- Initiates T cell activation
- Mediates antitumor activity

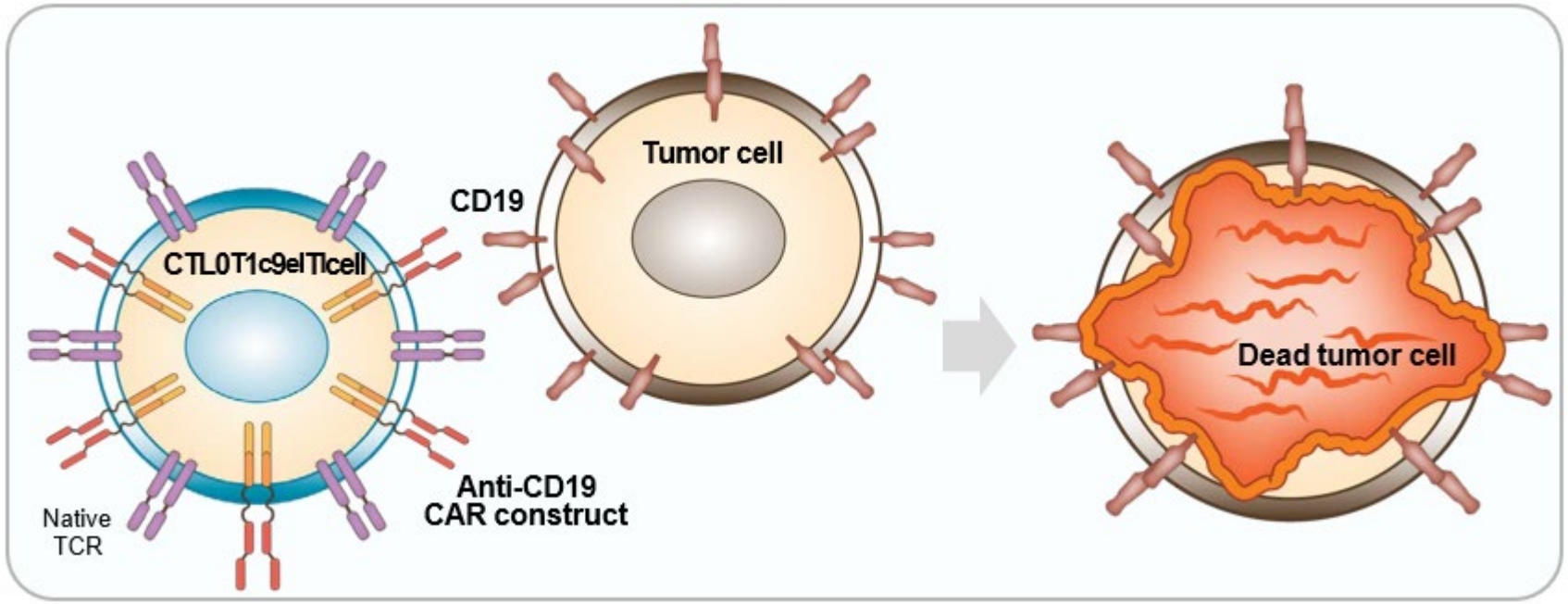
References: 1. Milone MC, et al. *Mol Ther*. 2009;17:1453-1464; 2. Zhang H, et al. *J Immunol*. 2007;179:4910-4918; 3. Kalos M, et al. *Sci Transl Med*. 2011;3:95ra73.

Mechanism of action - Tisagenlecleucel

Gene-transfer technology is used to stably express CARs on T cells, in order to provide the T cell with novel antigen specificity for the cancer cell[1,2]

CTL019 cells have affinity for any cell that expresses the CD19 surface antigen

CTL019 has demonstrated cytolytic activity against CD19-expressing cells in an antigen-dependent manner[1,3]



TCR, T cell receptor.

References: 1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Hollyman D, et al. *J Immunother.* 2009;32:169-180; 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

Examples of CAR-T cell products

There are several CAR-T products that have been approved by the FDA and EMA or are currently under investigation.

These are just a few examples of CAR-T products that have been approved /commercialized.

Ongoing research and clinical trials continue to explore the potential of CAR-T therapy in treating various types of cancers.

BRAND NAME	GENERIC NAME	TARGETED DISEASE
Kymriah™	tisagenlecleucel	Follicular Lymphoma, Diffuse Large B-cell Lymphoma, or Lymphoblastic Leukemia
Yescarta™	axicabtagene ciloleucel	Follicular Lymphoma or Diffuse Large B-cell Lymphoma
Tecartus™	brexucabtagene autoleucel	Mantle Cell Lymphoma or Acute Lymphoblastic Leukemia
Breyanzi®	lisocabtagene maraleucel	Large B-cell Lymphoma
Abecma®	idecabtagene vicleucel	Relapsed or Refractory Multiple Myeloma
Carvykti™	ciltacabtagene autoleucel	Relapsed or Refractory Multiple Myeloma

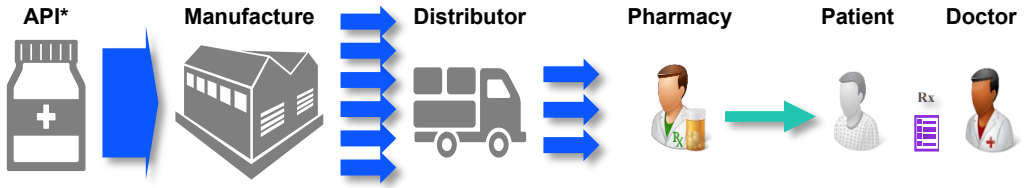
Relationship with the Hospital

- A new paradigm
- Hospital & Industry stakeholders involved in the patient's treatment

A new paradigm in the Pharmaceutical Industry Hospital relationship

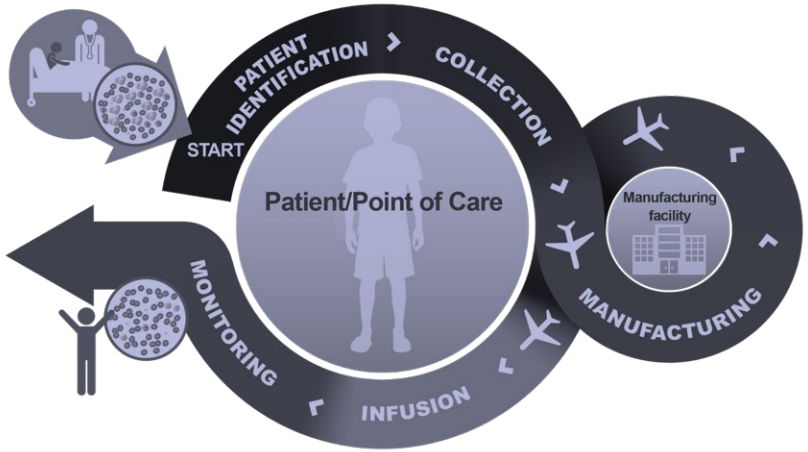
Traditional Pharmaceuticals

Pill **– one-way supply chain**

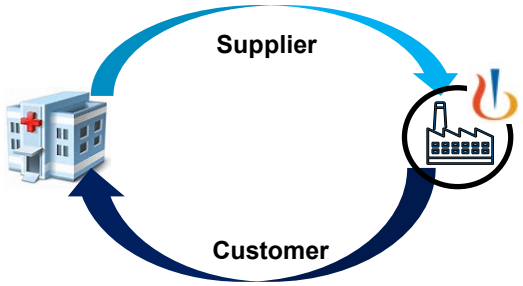


One Treatment	**Simple Process**	Many Prescribers	Many Patients

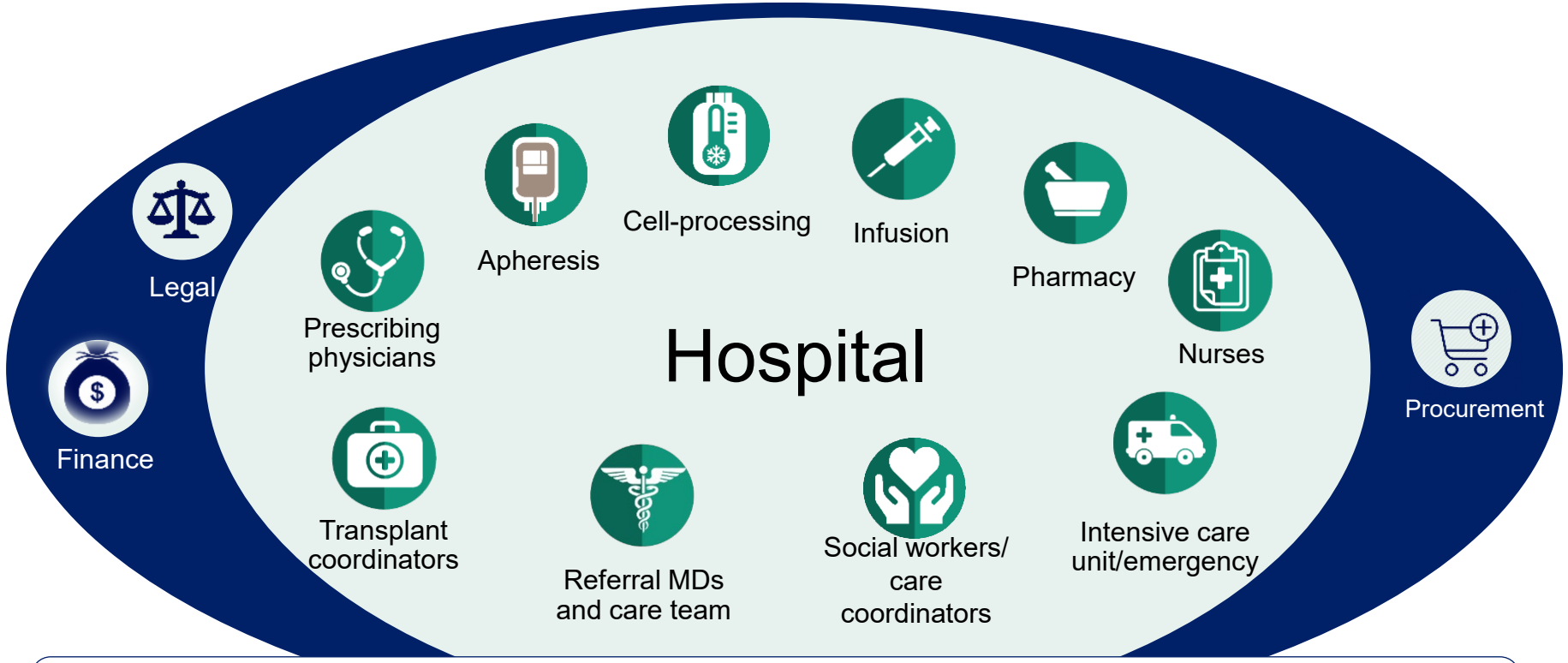
CAR-T Individualized Treatment



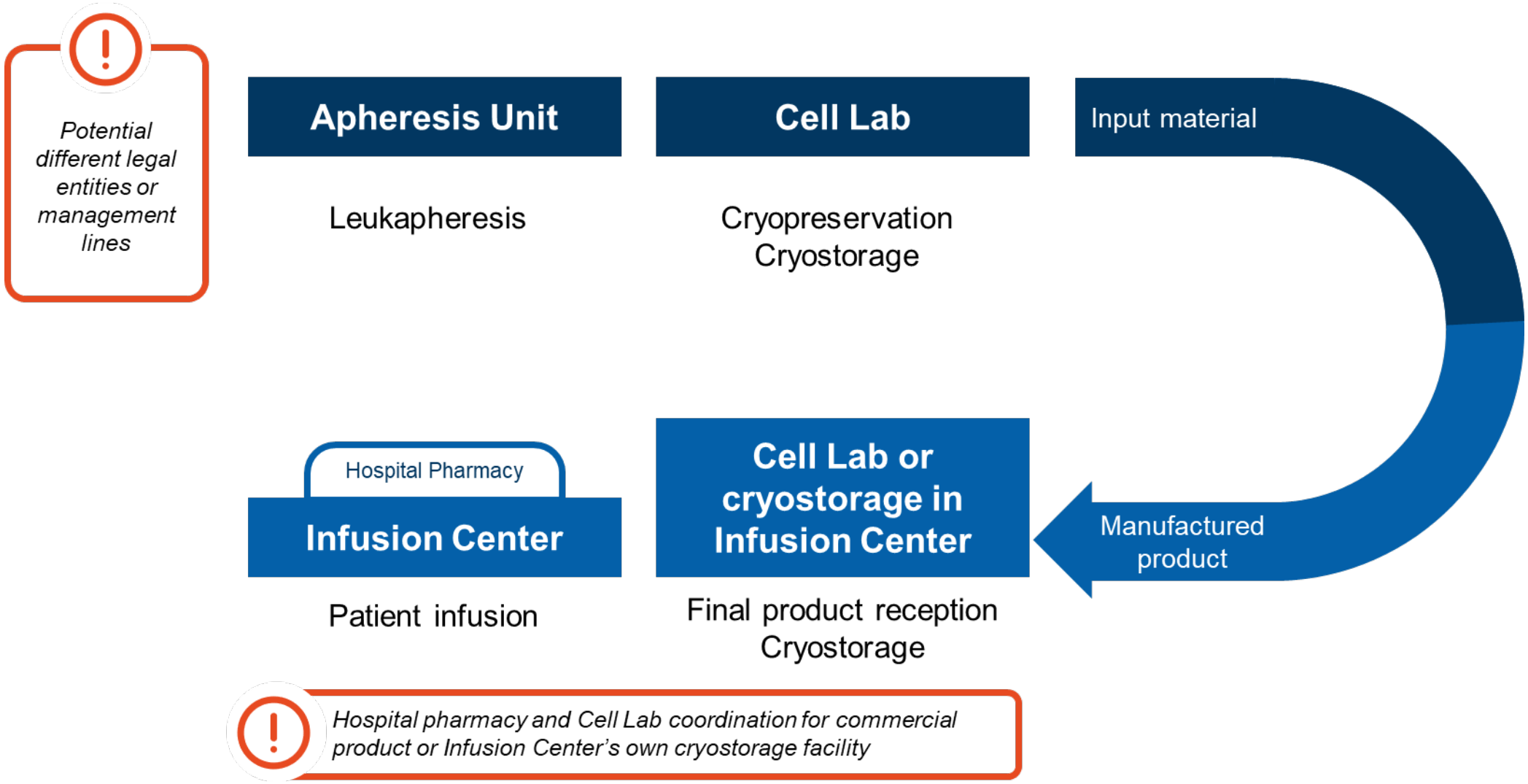
One Treatment	**Complex Process**	Limited HCPs & many Stakeholders	One Patient



Hospital & Industry stakeholders involved in the patient's treatment



Potential complexity with several different legal entities and departments / units in the institution



Regulatory requirements

- Regulations to be followed
- The path for CAR-T treatment to reach patients in Spain
- List of centers designated by the Ministry of Health

Regulations to be followed

European Union

Hospitals/Centers have to follow the Tissue or Blood EU Directives and respective local laws:

- ✓ Directive **2002/98/EC** setting standards of quality and safety for the collection, testing, processing, storage and distribution of **human blood and blood components** and amending Directive 2001/83/EC.
- ✓ Directive 2004/33/EC implementing Directive 2002/98/EC as regards certain technical requirements for blood and blood components (Text with EEA relevance).
- ✓ Directive 2005/61/EC implementing Directive 2002/98/EC as regards traceability requirements and notification of serious adverse reactions and events (Text with EEA relevance).
- ✓ Directive 2005/62/EC implementing Directive 2002/98/EC as regards Community standards and specifications relating to a quality system for blood establishments (Text with EEA relevance).
- ✓ Directive **2004/23/EC** on setting standards of quality and safety fort he donation, procurement, testing, processing, preservation, storage and distribution **of human tissues and cells.**
- ✓ Directive 2006/17/EC implementing Directive 2004/23/EC as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.
- ✓ Directive 2006/86/EC implementing Directive 2004/23/EC as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. (Includes zoning requirements)
- ✓ Directive 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells.

JACIE Joint Accreditation Committee ISCT | EBMT

Shall maintain accreditation by the Joint Accreditation Committee for the European Society for Blood and Marrow Transplantation and International Society for Cellular Therapy ("**JACIE**") or **equivalent accreditation awarded by a relevant local authority**.

EBMT International Society ISCT Cell & Gene Therapy

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The center qualification process is a regulatory requirement from EMA:

- ✓ The EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines, Part IV - GMP requirements for Advanced Therapy Medicinal Products
- ✓ The Regulatory dossier approved by Local Health Authority (EMA, FDA, ...)

Regulations to be followed

The most representative legal framework in Spain

- ✓ Reglamento (CE) Nº 1394/2007 del Parlamento Europeo y del Consejo de 13 de noviembre de 2007 sobre medicamentos de terapia avanzada.
- ✓ Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios (artículo 47), que traspone la Directiva 2001/83/CE del Parlamento Europeo y del Consejo de 6 de Noviembre de 2001, por la que se establece un código comunitario sobre medicamentos para uso humano
- ✓ Real Decreto 1345/2007, de 11 de octubre, por el que se regula el procedimiento de autorización, registro y condiciones de dispensación de los medicamentos de uso humano fabricados industrialmente.
- ✓ Orden SAS/1144/2010, de 3 de mayo, por la que se modifica el anexo I del Real Decreto 1345/2007, de 11 de octubre, por el que se regula el procedimiento de autorización, registro y condiciones de dispensación de los medicamentos de uso humano fabricados industrialmente, en lo que se refiere a los medicamentos de terapia avanzada
- ✓ Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial.
- ✓ Real Decreto Ley 9/2014, de 4 de julio, por el que se establecen las normas de calidad y seguridad para la donación, la obtención, la evaluación, el procesamiento, la preservación, el almacenamiento y la distribución de células y tejidos humanos y se aprueban las normas de coordinación y funcionamiento para su uso en humanos.

The path for CAR-T cell treatment to reach patients in Spain

"Novartis is at the forefront of the science and development of immunocellular therapy as a potential new innovative approach to treating certain cancers where there are limited options."

Vasant (Vas) Narasimhan, MD,
Chief Executive Officer of Novartis

Aug 2012
Novartis enters collaboration with **The University of Pennsylvania**

Dec 2012
Novartis purchases **cell manufacturing facility in Morris Plains, New Jersey (USA)**

July 2014
US FDA designates CTL019 as a **Breakthrough Therapy** in (r/r) pediatric and adult acute lymphoblastic leukemia (ALL)

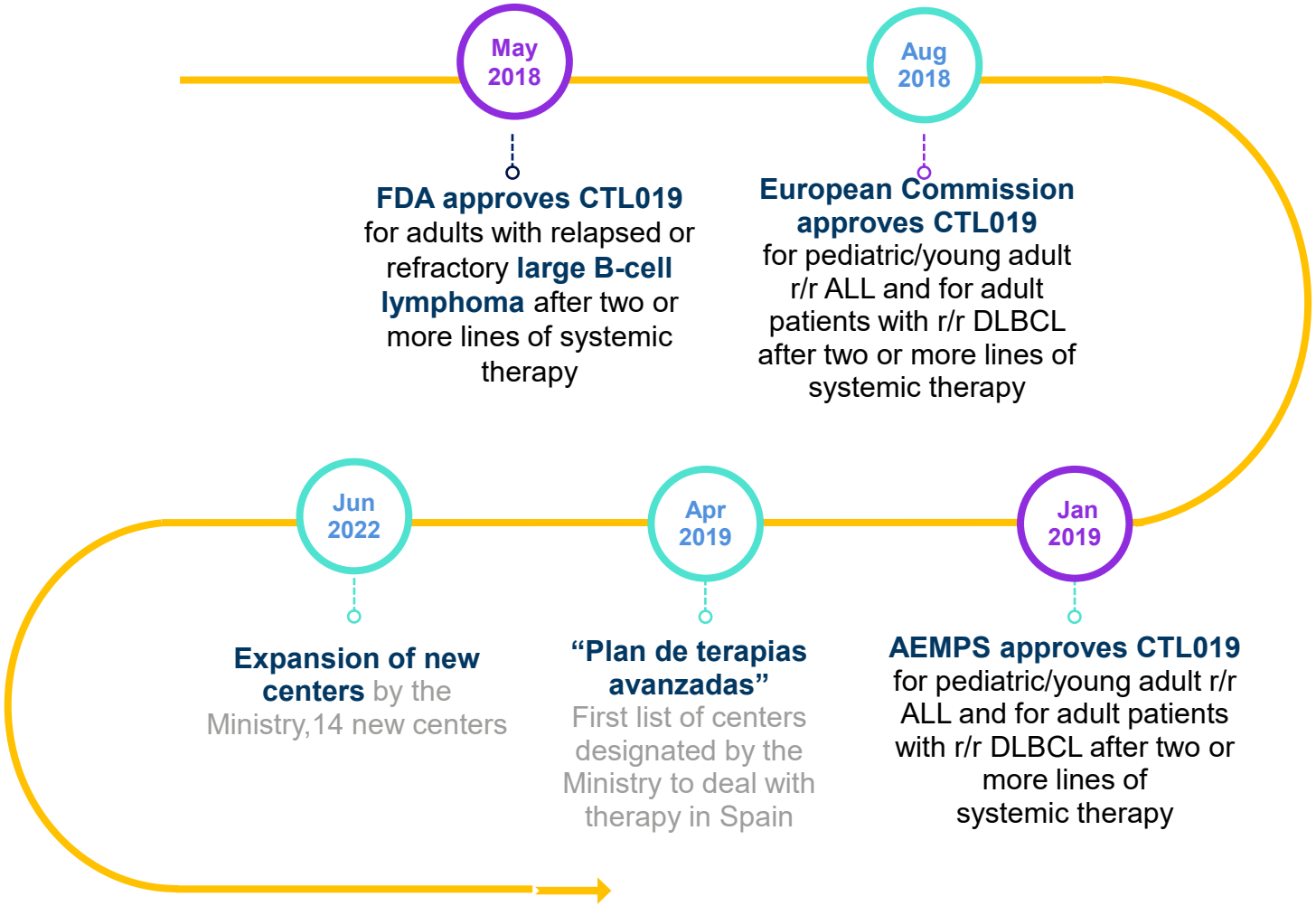
Feb 2017
Novartis submits **Biologics Licensing Application** (BLA) to **FDA** for CTL019 for pediatric / young adult r/r ALL

April 2017
FDA grants CTL019 **Breakthrough Therapy** designation in r/r diffuse large b-cell lymphoma (DLBCL)

July 2017
US FDA Advisory Committee votes unanimously in favor of CTL019 approval

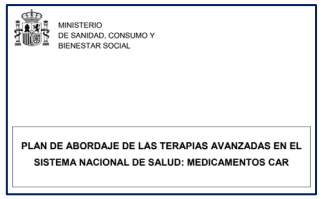
Aug 2017
FDA approves CTL019 (tisagenlecleucel) for patients up to 25 years of age with B cell precursor ALL that is refractory or in second or later relapse

The path for CAR-T cell treatment to reach patients in Spain



List of centers designated by the Ministry of Health

[Ministerio de Sanidad - Áreas - Terapias Avanzadas]


MINISTERIO
DE SANIDAD, CONSUMO Y
BIENESTAR SOCIAL

PLAN DE ABORDAJE DE LAS TERAPIAS AVANZADAS EN EL SISTEMA NACIONAL DE SALUD: MEDICAMENTOS CAR

MINISTERIO DE SANIDAD

Castellano | Buscar

Ministerio | Áreas | Prensa y comunicación | Sanidad en datos | Servicios a la Ciudadanía | Participación Pública

Webs temáticas | Sede Electrónic@

Traducir | Está usted en: > Áreas > Farmacia > Información de medicamentos > Terapias avanzadas

- Quiénes somos
- **Información de medicamentos**
- Comisión interministerial de precios
- Consumo de medicamentos
- Información dirigida a la industria
- Trámites y Sede Electrónica
- Comités adscritos
- Legislación
- Publicaciones

Terapias avanzadas

PLAN DE ABORDAJE DE LAS TERAPIAS AVANZADAS EN EL SISTEMA NACIONAL DE SALUD: MEDICAMENTOS CAR

1. Criterios y estándares para la designación de centros para la administración de las CAR-T
2. Red de centros designados para el uso de medicamentos CAR-T en el SNS. Actualización 2022
3. Procedimiento para la valoración de solicitudes por el grupo de expertos del SNS
4. Procedimiento para la derivación de pacientes a los centros designados para la utilización de medicamentos CAR en el SNS
5. Procedimientos técnicos para la obtención de la muestra para la fabricación de medicamentos que contienen células T CAR anti-CD19 y para su utilización
6. Protocolo clínico para el manejo de efectos adversos graves en pacientes tratados con medicamentos que contienen células T CAR anti-CD19
7. Protocolos farmacoclínicos de uso de terapias avanzadas en el SNS
8. Medicamentos de terapia avanzada de fabricación no industrial en el SNS
9. Informes de seguimiento de la Dirección General de Cartera Común de Servicios del SNS y Farmacia sobre el Plan para el Abordaje de las Terapias Avanzadas en el SNS
10. Jornadas

1. Criterios y estándares para la designación de centros para la administración de las CAR-T

- Criterios y estándares designación de centros CAR-T
- Lista comprobación cumplimiento criterios centros CAR-T
- Manual Instrucciones Autoevaluación CAR-T
  - **Actualización de criterios (Diciembre de 2021)**
    - Criterios y estándares designación de centros CAR-T
    - Lista comprobación cumplimiento criterios centros CAR-T
    - Manual Instrucciones Autoevaluación CAR-T

2. Red de centros designados para el uso de medicamentos CAR-T en el SNS. Actualización 2022.

3. Procedimiento para la valoración de solicitudes por el grupo de expertos del SNS

4. Procedimiento para la derivación de pacientes a los centros designados para la utilización de medicamentos CAR en el SNS

- Procedimiento para la derivación de pacientes a los centros designados para la utilización de medicamentos CAR en el SNS

5. Procedimientos técnicos para la obtención de la muestra para la fabricación de medicamentos que contienen células T CAR anti-CD19 y para su utilización

- Procedimientos técnicos para la obtención de la muestra para la fabricación de medicamentos que contienen células T CAR anti-CD19 y para su utilización.

6. Protocolo clínico para el manejo de efectos adversos graves en pacientes tratados con medicamentos que contienen células T CAR anti-CD19

- Protocolo clínico para el manejo de efectos adversos graves en pacientes tratados con medicamentos que contienen células T CAR anti-CD19

7. Protocolos farmacoclínicos de uso de terapias avanzadas en el SNS

8. Medicamentos de terapia avanzada de fabricación no industrial en el SNS

- Acuerdo CISNS sobre condiciones de MTA de fabricación no industrial en el SNS
- Propuesta precio MTA no industrial SNS-CISNS

9. Informes de seguimiento de la Dirección General de Cartera Común de Servicios del SNS y Farmacia sobre el Plan para el Abordaje de las Terapias Avanzadas en el SNS

- Informe de Seguimiento sobre el Plan para el Abordaje de las Terapias Avanzadas (26 de mayo de 2020)
- Informe de Seguimiento sobre el Plan para el Abordaje de las Terapias Avanzadas (1 de diciembre de 2020)
- Informe de Seguimiento sobre el Plan para el Abordaje de las Terapias Avanzadas (1 de junio de 2021)
- Informe de Seguimiento sobre el Plan para el Abordaje de las Terapias Avanzadas (15 de julio de 2022)

10. Jornadas

- I Jornada. 2 años tras la aprobación del Plan para el abordaje de las Terapias Avanzadas en el SNS: pasado presente y futuro
  - Esta jornada se retransmitió a través del canal del Ministerio: https://www.sanidad.gob.es/retransmision/terapiasAvanzadas/home.htm

Center qualification

- Overview/Qualification steps
- Apheresis Collection Unit
- Cell Processing Unit
- Maintenance

Overview/Qualification steps

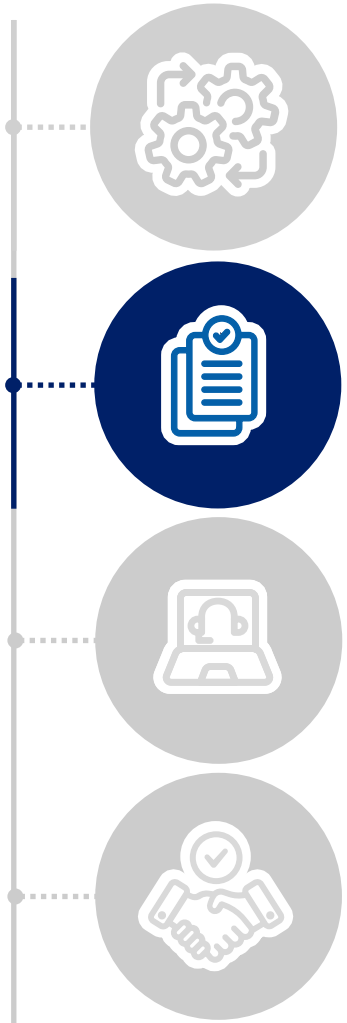
Initial engagement/commitment
Confidential Agreement

Assessments (Documentation Review, Site evaluation (e.g. Third party request/ Survey/ SQRA)
Audits (if required)

Technical & online portal training
Mock shipment

Technical/Quality Agreements & other contracts

Overview/Qualification steps



Initial engagement/commitment
Confidential Agreement

Assessments & Audits

Technical & online portal training
Mock shipment

Technical/Quality Agreements & other contracts

Apheresis Collection Unit

Cell Processing Laboratory

Organization & Management
Quality System
Personnel
Facilities
Equipment & Materials
Documentation & Records

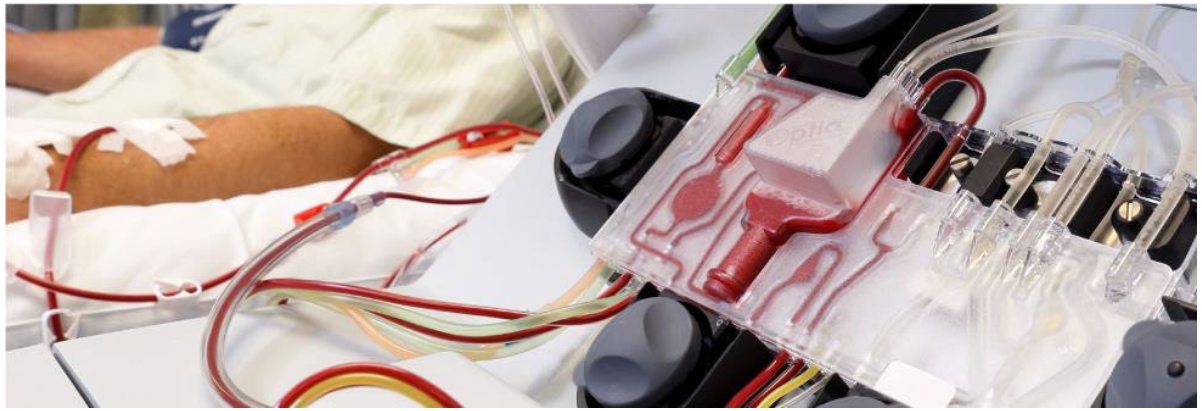
Blood collection

Cell Processing Storage and Distribution

Leukapheresis Collection and Cell Processing are critical steps, as they provide with the starting material required to manufacture product.

Apheresis Collection Unit

Spectra Optia™



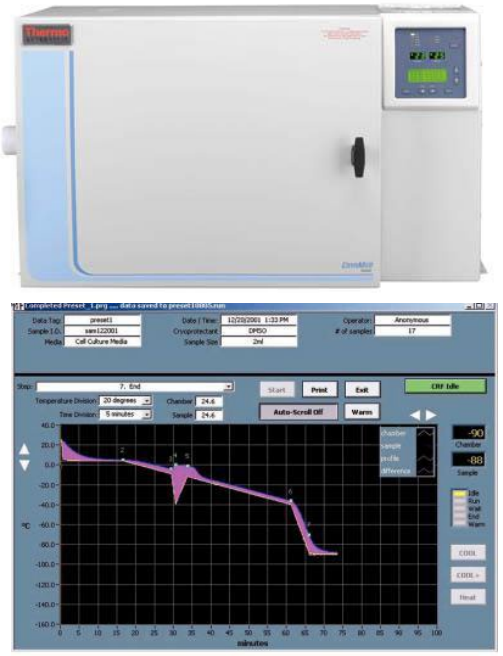
- **Temperature and Humidity monitored in the room & storage areas**

Amicus™

Cell Processing Unit

Biosafety Cabinet Type II,
Class A / ISO 5

Flow Cytometer

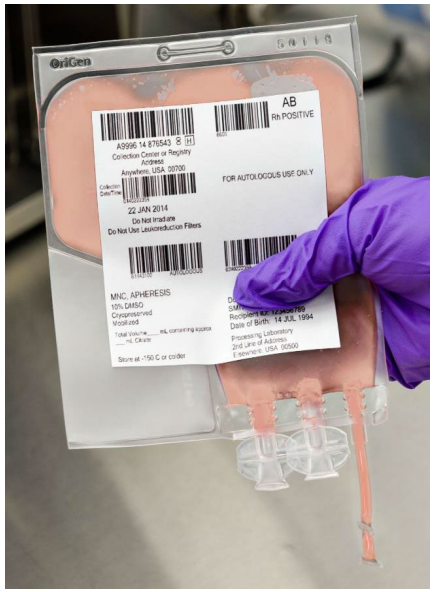


Controlled Rate Freezer
& Freeze Curve

LN2 storage tanks
Vapor phase

- **Air in the room where the Biosafety Cabinet is located, minimum Class D**
- **Temperature and Humidity monitored in the room & storage areas**
- **LN2 located in a secure, limited access area**

Cell Processing Unit – packing & transport



Cryopreserved bag
ISBT label

Examples of a Cryoport dry vapor shipper

Example of an evo® DV10 dry vapor shipper

Example of Standard Cryoport Packing Procedure

COI, Chain of Identity.

Sentinel vials

Maintenance – oversight & monitoring

Elements	Description
Technical Survey	*Ensure technical aspects are up to dated*
Contract Management	*Ensure Technical/Quality Agreements are maintained.*
Site Quality Risk Assessment Review	*Review and update periodically and as needed.*
Accreditation Status	*Manage understanding of ongoing accreditation and HA authorization status of sites*
(Audits)	*(Routine or for-cause audits and CAPA follow-up)*
Training	*Refresher training and as-needed training of sites.*
Change Controls, Deviations, Investigations	Manage internal quality-system actions and ensure external site processes are operating.
Person in Plant	*Novartis visits to sites to complete reviews or execute oversight/monitoring.*
Key Performance Indicator (KPI) monitoring	*Establishment and tracking of KPI.*

Following Novartis SOPs

- **Deviations** from Apheresis:

Handling/approval of deviation investigation, initial assessment, actions, CAPAs, and «Track and Trend» investigations.

- **Change control** management with the Apheresis site:

-Documentation of major/critical changes

-Assessment of potential actions (audit, on-site visit, others)

- **OOS/Terminations:**

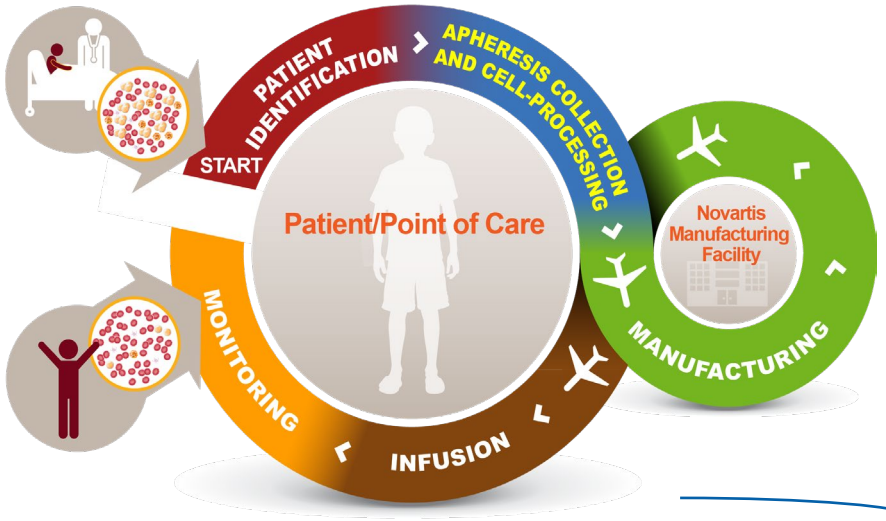
Discussions

Meetings and collaboration with site if needed

High level process overview

- Tisagenlecleucel manufacturing process
- Chain of Identity
- Finished Product & Infusion
- CAR-T Therapy: Possible toxicities & Clinical Signs and Symptoms

High level process overview



Pre-collection: determination patient readiness for leukapheresis

-Initial health assessment + infectious Disease Testing

-Current and previous therapy timing (Drug Washout periods)

-Peripheral blood counts

Leukapheresis material specifications

-Requirements for Patient Infectious Disease Testing

-Minimum cellular requirements

Leukapheresis collection

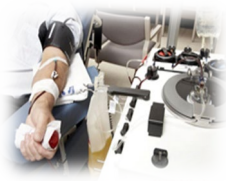
-Process an appropriate TBV* to meet the required specification. Multiple days of collection are permitted to meet cell specifications

Cell processing & Packing**

Patient Identified

Patient enrolled / accepted by Novartis

Scheduling
Apheresis – Transport (to/from)
Manufacturing - Treatment



Apheresis
In certified centers

On line portal

Transport
By certified / validated transporter
Within 24h @
Cryo preserved

Manufacturing & Release
Work Center assigned
Raw materials available: Beads, Virus, Plasmids, ...Transduction & cell expansion
Qualify control & release

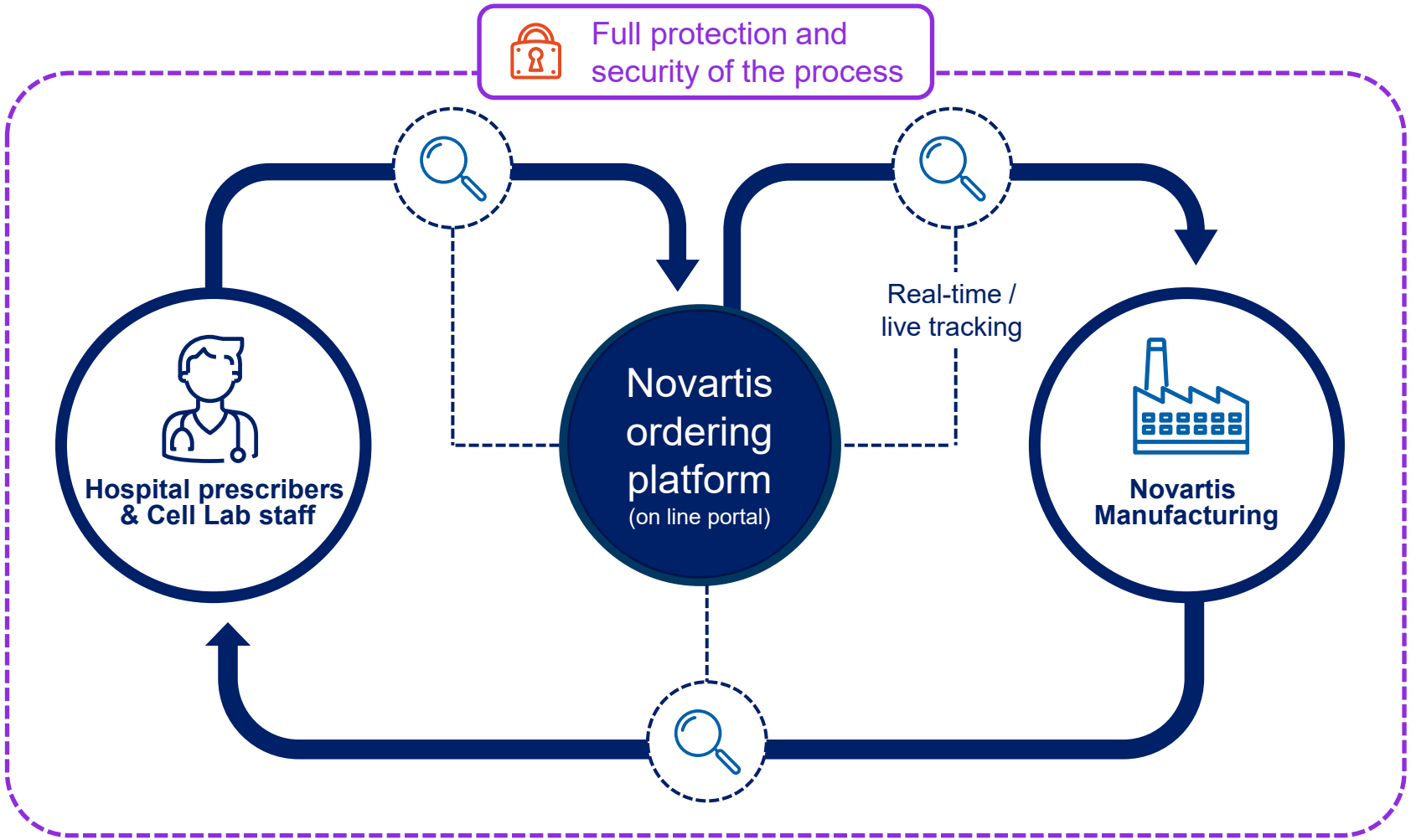
Transport
By certified / validated transporter
Cryo preserved

Treatment
Patient prepared
Intensive care unit available

*Total blood volume
**Cell processing may not be required depending on the type of CAR-T product

A web-based platform connects the hospital to Novartis manufacturing

Ensuring protection of the patient's chain of identity & continuous access to cell status throughout manufacturing

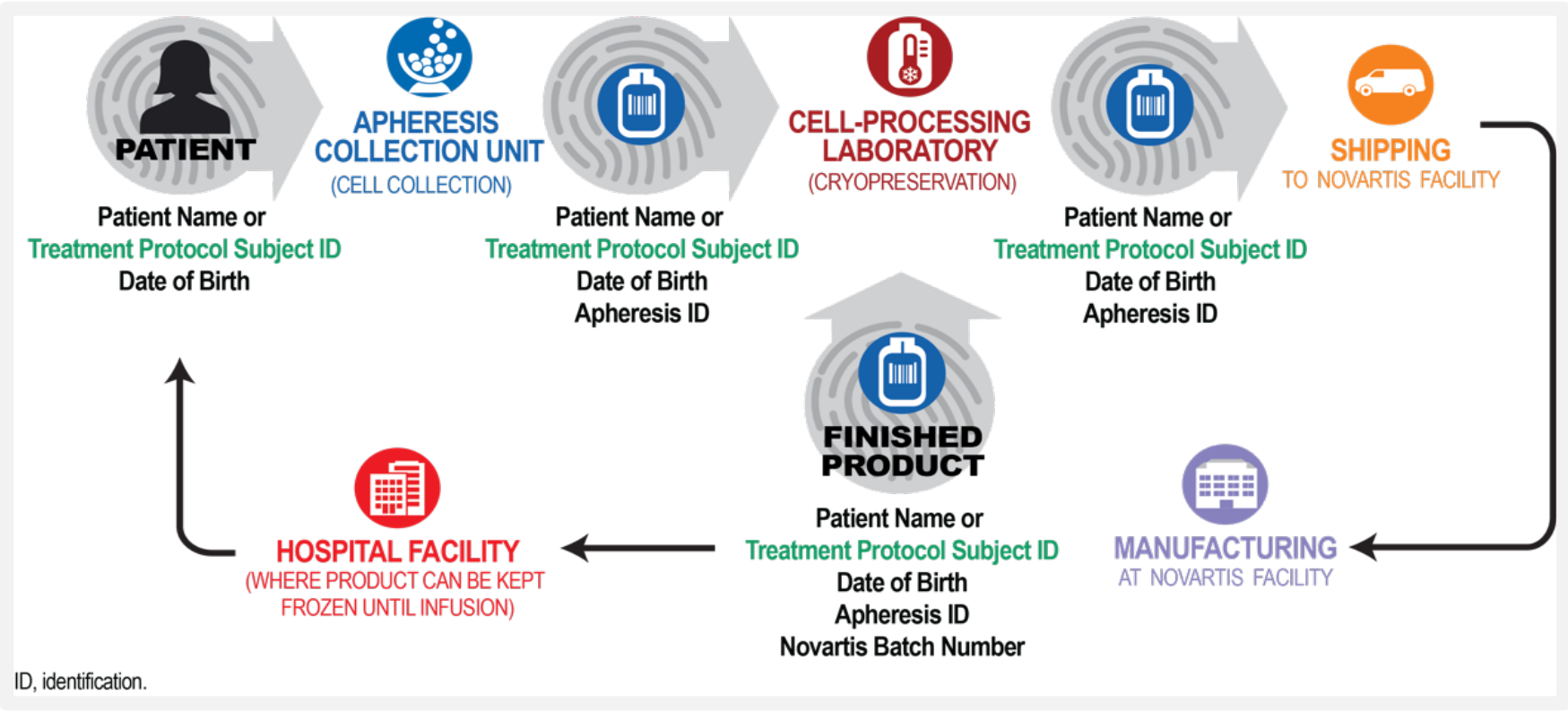


Chain of Identity

- Autologous product requires that cells collected from a patient must be infused into the same patient after product manufacturing
- The detailed tracking and verification of all patient materials and data throughout each step of the process to ensure Chain of Identity (COI) is critical

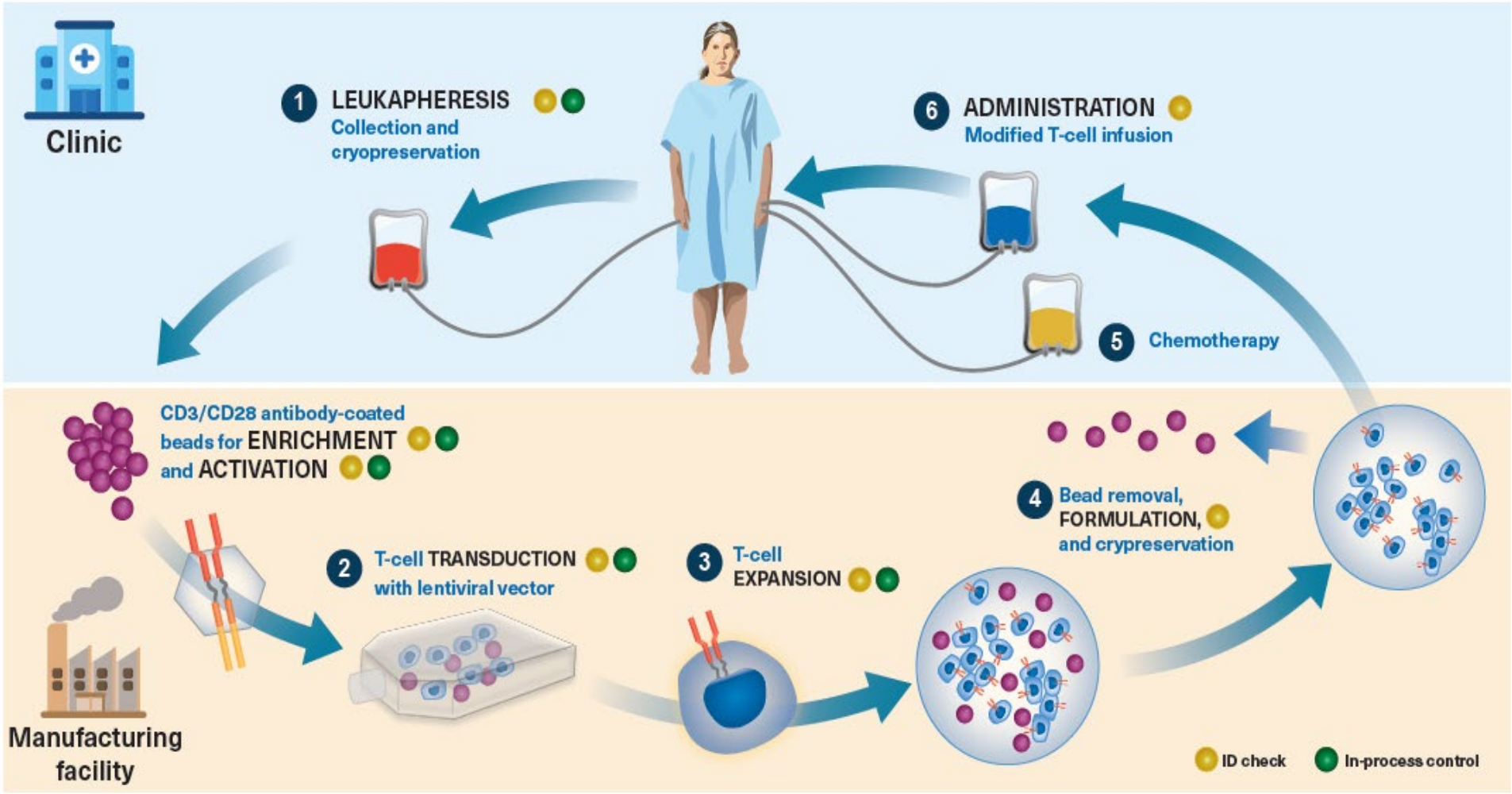
On line portal

Labels



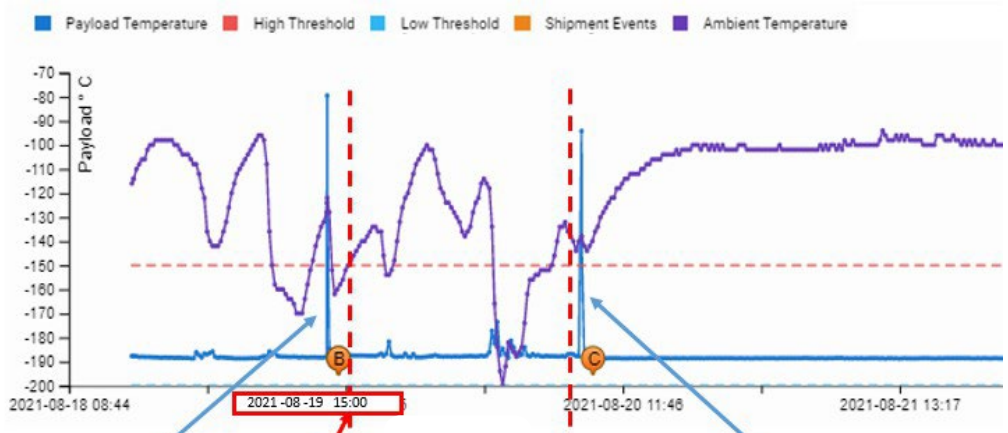
Tisagenlecleucel manufacturing process

Tisa-cel is an autologous immunocellular therapy



Transport & Temperature monitoring

Example of Temperature Log and verification of the temperature during the Transit Period



Packing of the CAR-T cell product into the dewar at the manufacturing plant or distribution depot

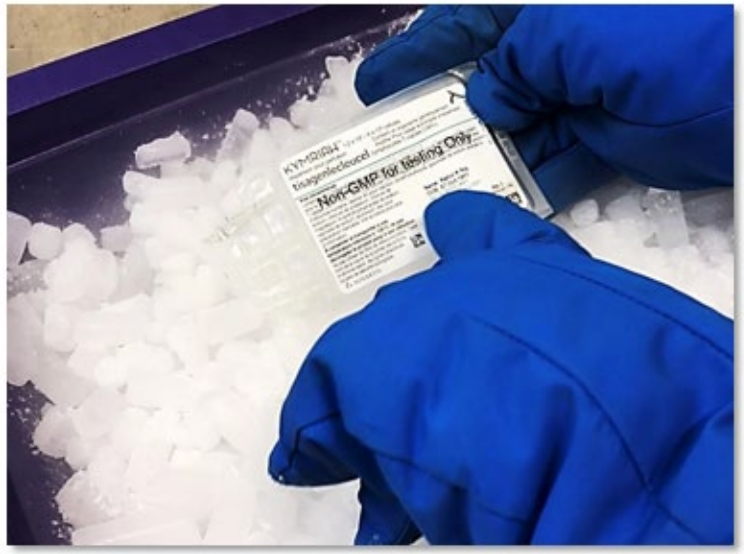
Pickup date and time of the dry vapor shipper by the courier at the manufacturing plant or distribution depot

Transit period of the CAR-T cell product to be checked by the end user

Opening of the dewar before transferring the CAR-T cell product to the on-site storage

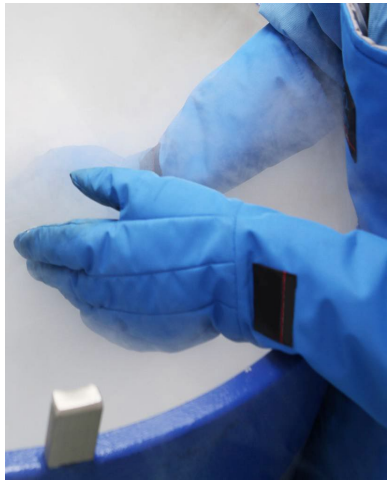
Finished Product: cheking at center/hospital

Checking the CAR-T Cell Product Bag(s) and Label Information



Example of tools

- 1 patient = 1 batch
  - ✓ CoA
  - ✓ Certificate of Compliance (QP released)



Infusion

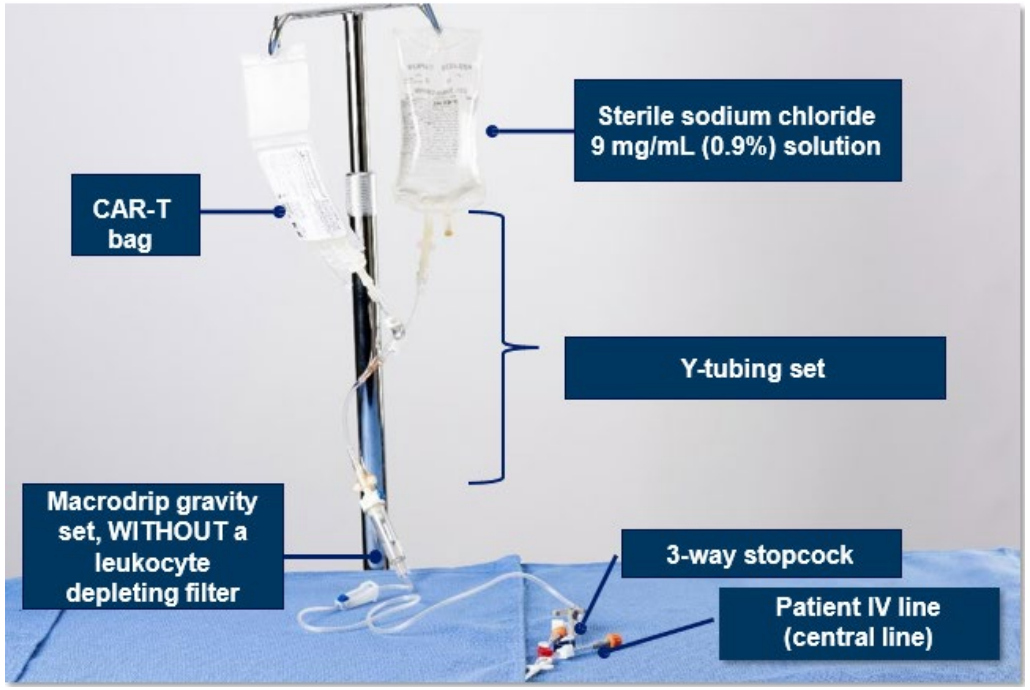
Precautions

- **Health care professionals should employ appropriate precautions** (eg, wearing gloves and glasses) when handling CAR-T cell product to avoid potential transmission of infectious diseases when handling the producto.
- CAR-T cell product should be transported within the facility in closed, break-proof, leak-proof containers. **Do not irradiate.**
- All material that has been in contact with CAR-T cell product (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of biological waste.

Preparation for Infusion

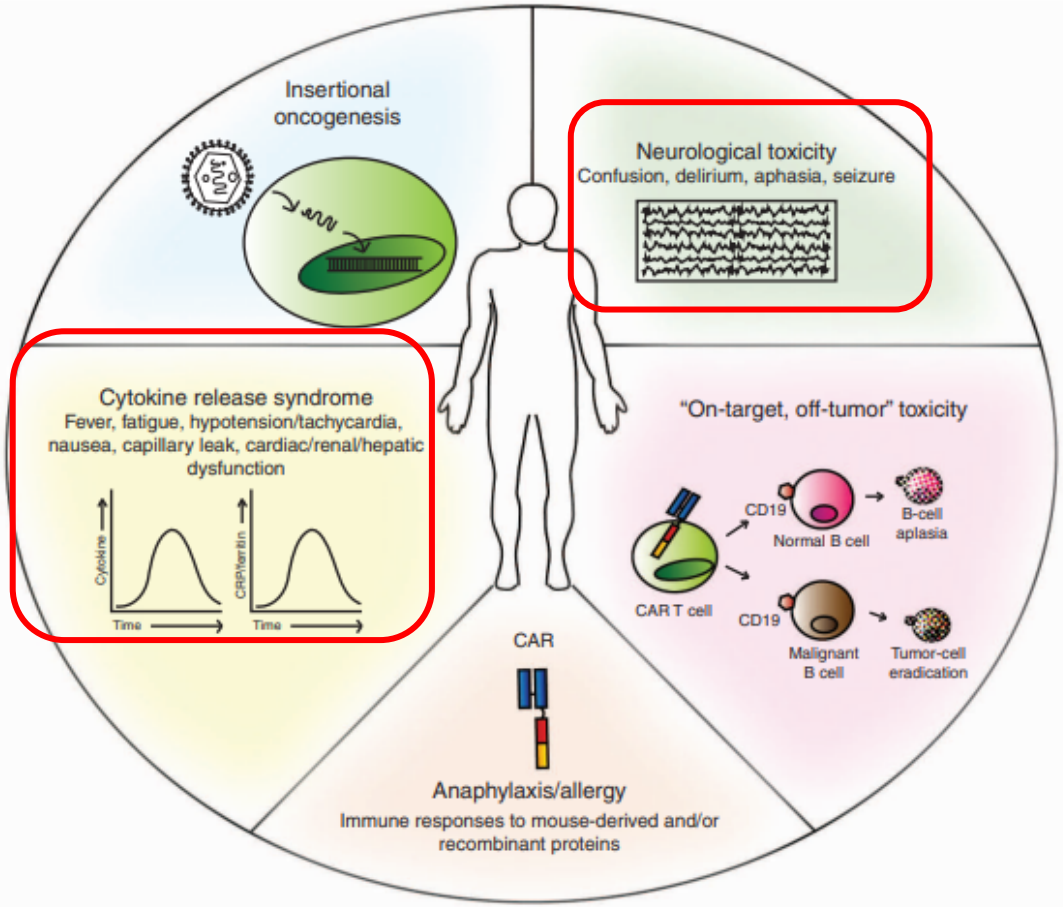
- Confirm patient identity
- It is **recommended** that patients be **premedicated** with acetaminophen/ paracetamol and diphenhydramine or another H1 antihistamine within approximately 30 to 60 minutes prior to CAR-T cell product infusion.
- **The timing of thaw of CAR-T cell product and infusion should be coordinated.** The infusion start time should be confirmed in advance and adjusted based on the time of thawing, so that CAR-T cell product is available for infusion when the recipient is ready.
- One dose of **tocilizumab** and emergency equipment must be available per patient prior to infusion and during the recovery period.
- The treatment center must have access to additional doses of tocilizumab within 8 hours to manage CRS according to the CRS management algorithm per local prescribing information.

Example of CAR-T infusion setup



Dry thaw method or water bath

CAR-T Therapy: Possible Toxicities & Clinical Signs and Symptoms[1-6]



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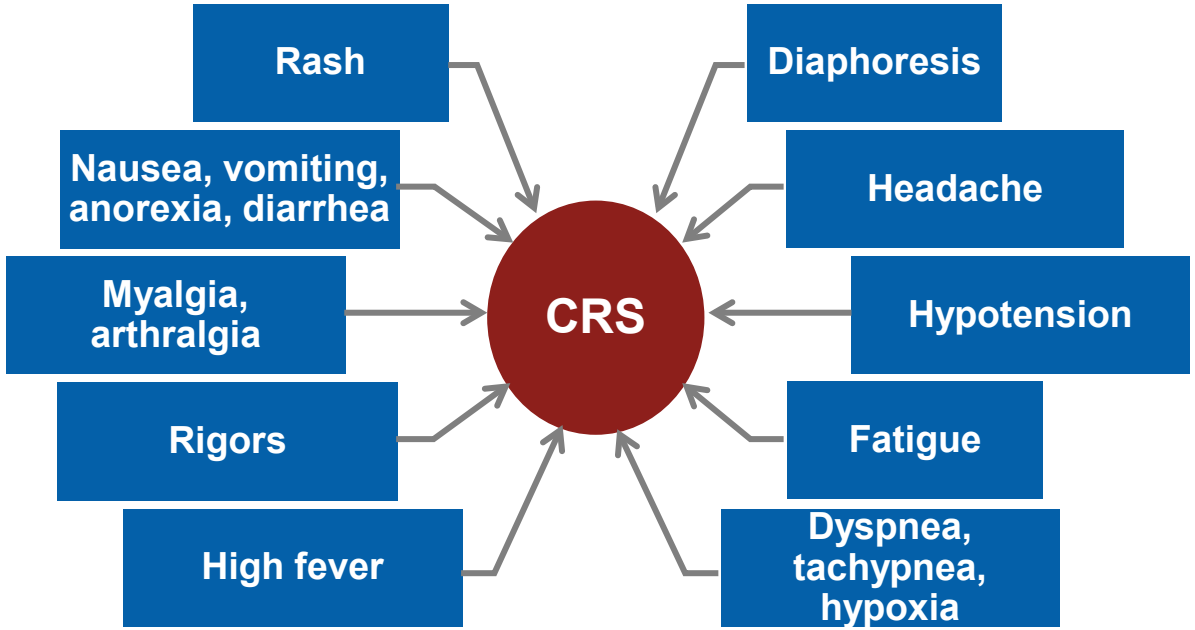


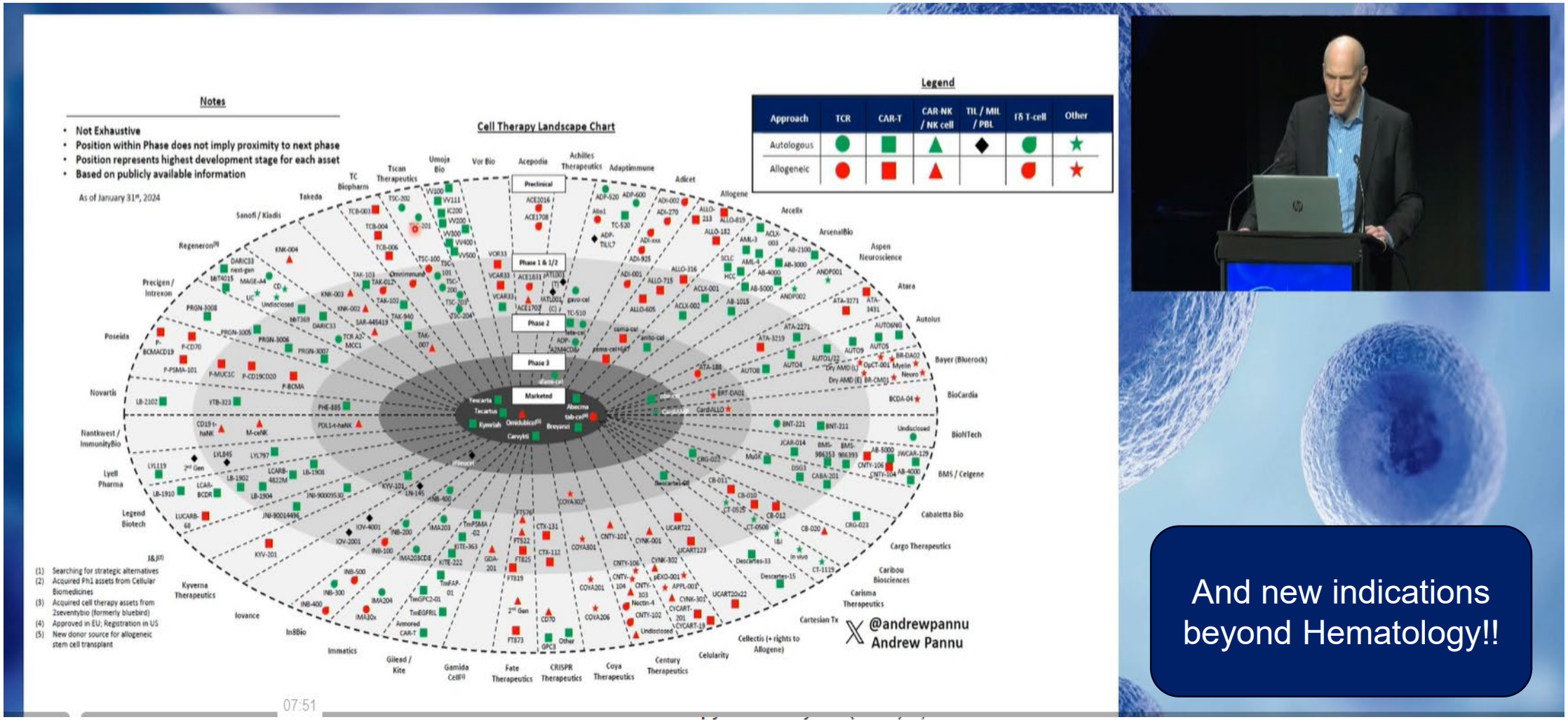
Note: Adapted REMS slide.
CRS, cytokine release syndrome; REMS, Risk Evaluation and Mitigation Strategy.
References: 1. Lee DW, et al. *Blood*. 2014;124(2):188-195; 2. Grupp SA, et al. *N Engl J Med*. 2013;368(16):1509-1518; 3. Kalos M, et al. *Sci Transl Med*. 2011;3(95):95ra73; 4. Porter DL, et al. *Blood*. 2013;122(21): Abstract 873; 5. Grupp SA, et al. *Blood*. 2014;124(21): Abstract 67; 6. Lee DW, et al. *Biol Blood Marrow Trans*. 2019;25(4):625-638.

Future of Cell Therapy

- Cell Therapy Landscape
- Some of the most important Congresses

Cell Therapy Landscape as of Jan 31st 2024

- CAR-T success leads to massive investment in Cell Therapy of all kinds - many therapies are on the way: autologous and allogenic



Carl June, MD, CAR-T Cell Therapy pioneer – University of Pennsylvania

Some of the most important Congresses

ASH Annual Meeting:
The American Society of Hematology (ASH) holds an annual meeting that is considered one of the most important Congresses for CAR-T cell therapy. The ASH Annual Meeting discusses the latest advancements, clinical trials, and outcomes related to CAR-T cell therapy for hematological malignancies.

EHA Congress:
The European Hematology Association (EHA) Congress focuses on advancements in hematology and highlights breakthroughs in CAR-T cell therapy. This Congress provides a comprehensive overview of clinical trials, patient outcomes, and emerging treatments for hematological malignancies using CAR-T cell therapy.

ASCO Annual Meeting:
The American Society of Clinical Oncology (ASCO) Annual Meeting is another significant Congress for CAR-T cell therapy. It provides a platform to present and discuss clinical trial results, safety and efficacy data, and new advancements in CAR-T cell therapy for various solid tumors.

European CAR-T Cell Meeting
The European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT) jointly organize the European CAR-T cell Meeting. This meeting covers a wide range of topics, including deep science, translational research, clinical advancements, and commercial development in the field of CAR-T.

These Congresses serve as crucial platforms for the scientific community to share knowledge, present research findings, and foster collaborations in the field of CAR-T cell therapy. They play a pivotal role in advancing the understanding, clinical application, and patient outcomes of this revolutionary treatment approach.

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Q&A

Thank you!