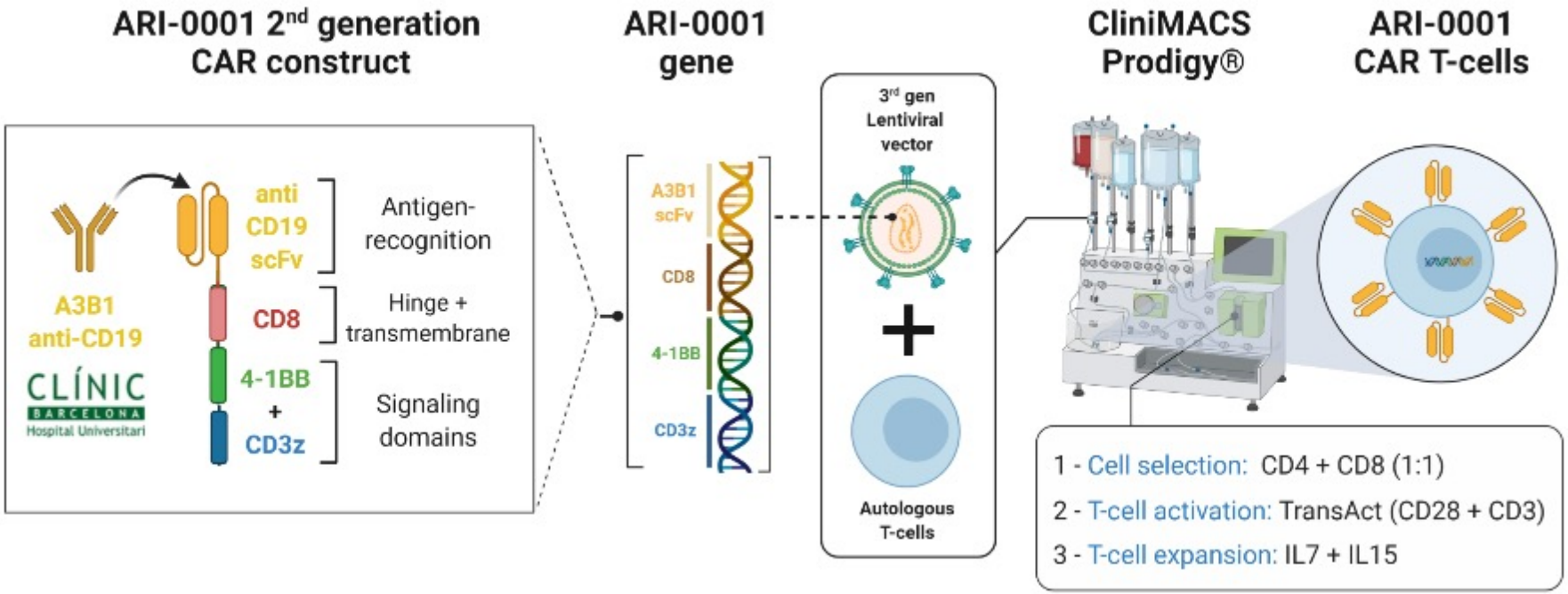
ATMPs: from bench to bedside (through the regulator's desk)

Dr. Julio Delgado
Oncoimmunotherapy Unit
Department of Haematology
Hospital Clinic de Barcelona - IDIBAPS

Conflicts of interest

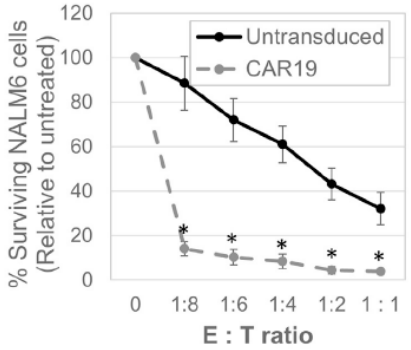
	Type of Financial Interest	Name of Commercial Interest
☐	Grants/Research Funding	
☐	Stock Shareholder	
☐	Consulting Fees	
☐	Employee	
X	Principal investigator	Clinical trials involving varnimcabtagene autoleucel
☐	Other (Receipt of Intellectual Property Rights, Speaker's Bureau)	

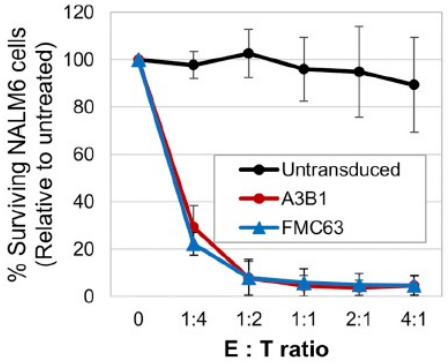
ARI-0001 cells *(varnimcabtagene autoleucel [var-cel])*

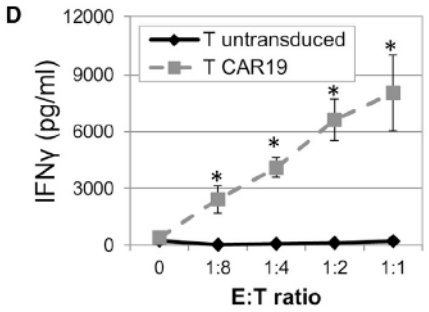


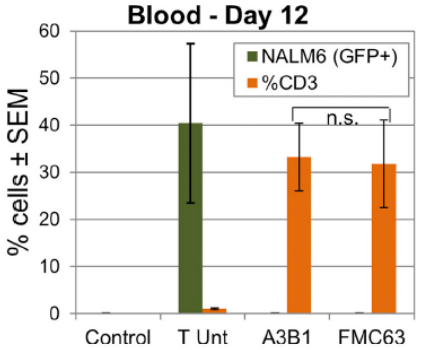
Castella M, et al. *Mol Ther Methods Clin Devel* 2019

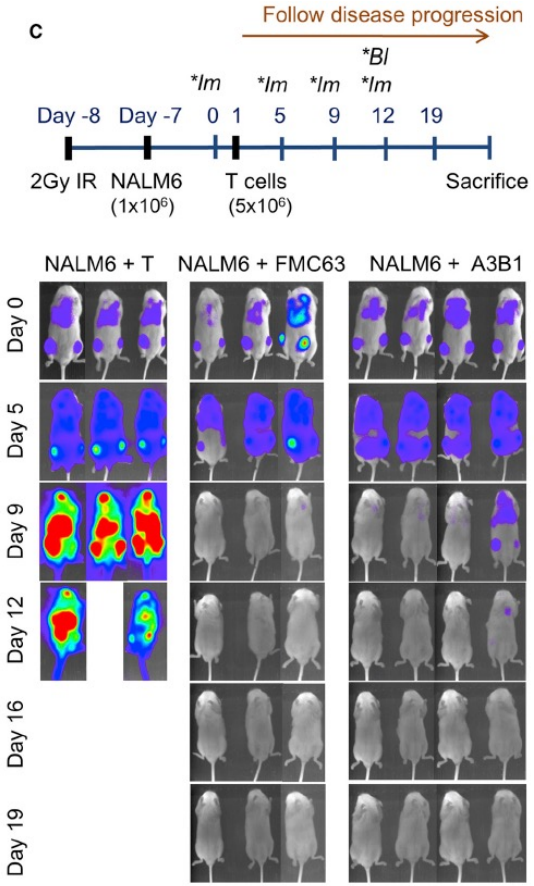
Nonclinical evaluation











Early contact with regulators → scientific advice!

Toxicology? Genotoxicity?

Good laboratory practice (GLP)

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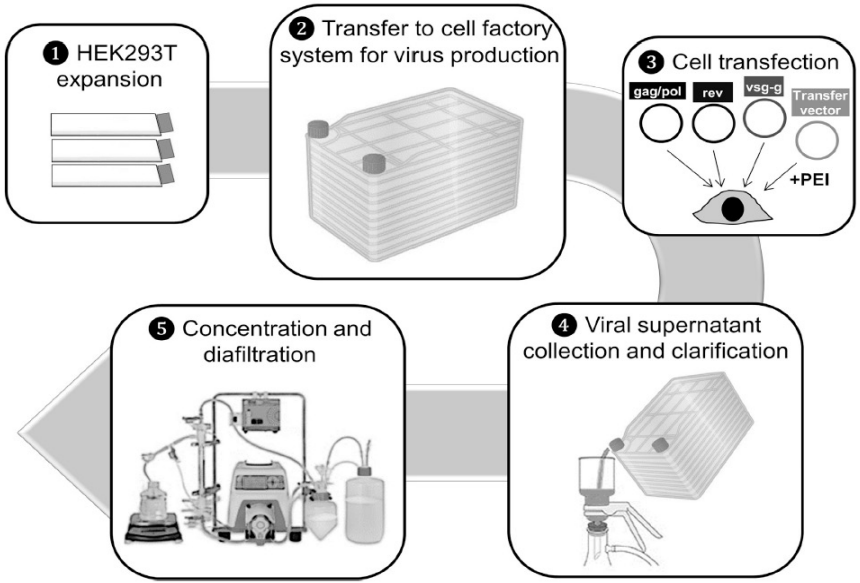
Lentiviral production



Creatio | Production and validation center of advanced therapies UNIVERSITAT DE BARCELONA

- Early contact with regulators
- Very manual manufacturing process
- Importance of master cell bank of HEK293T cells (annual fee payment to Rockefeller University)
- Beware of the limitations of HEK293T cells

Cell Banking of HEK293T cell line for clinical-grade lentiviral particles manufacturing

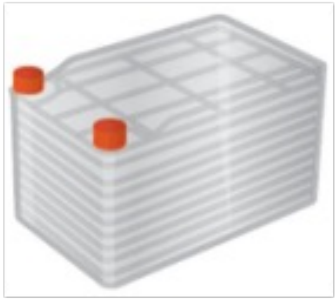
Unai Perpiñá[1,2,3,4], Cristina Herranz[1,2,3,4], Raquel Martín-Ibáñez[1,2,3,4,5], Anna Boronat[4,6], Felipe Chiappe[1,2,3,4], Verónica Monforte[1,2,3,4], Gemma Orpella-Aceret[1,2,3,4], Ester González[1,2,3,4], Myriam Olivé[1,2,3,4], María Castella[4,7,8], Guillermo Suñé[4,7], Álvaro Urbano-Ispizua[4,7,9,10], Julio Delgado[4,7,9,11], Manel Juan[4,6,9,12] and Josep M. Canals[1,2,3,4]*

Castella M, et al. *Mol Ther Methods Clin Devel* 2019

Scaling up of lentiviral production

GENEVECTOR
The Future of Health, Today

Current production system → **New production system**



Cell growth area: 2.4 m^2

Cell growth area: 10 m^2 or 30 m^2

Current purification system → **New purification**

Clarification by:
- Centrifugation
- Microfiltration

Concentration/diafiltration by TFF
Fill & finish

- Functional LV titer
- HCD quantity and fragment size
- HCP
- BSA
- Residual plasmid
- Residual DNAse

Clarification by:
- Deep filtration (1-2 filters)
- DNAse treatment

Concentration/diafiltration by TFF (x2)
Purification by IEX **chromatography**
Fill & finish

Quality control (lentivirus)

Quality control tests for lentiviral batches used to manufacture var-cel

Parameter	**Acceptance criteria**	**Method**
Appearance	Yellowish aqueous solution	Visual observation
Identity	Covered sequence ≥95% Sequence identity ≥ 95%	PCR / sequencing
Infectious particles	≥3.75x10^{7} IP / mL	Limiting dilution
Endotoxin	≤ 4 EU / mL	Ph. E. 2.6.7
Mycoplasma	Absent	Ph. E. 2.6.14
Sterility	No growth	Ph. E. 2.6.1
pH	6.9 - 7.8	Ph. E 2.2.3

Cell production

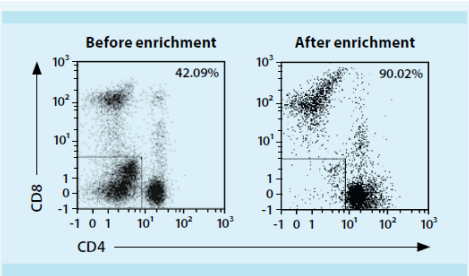
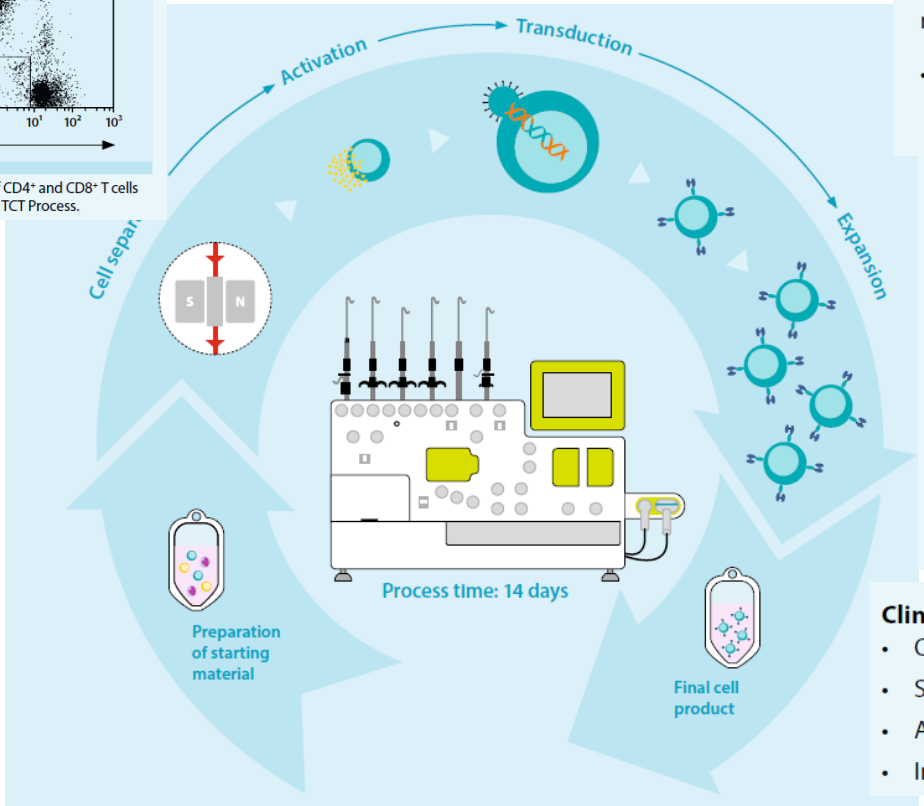


Figure 1: Flow cytometric analysis shows purity of CD4+ and CD8+ T cells automatically enriched by the CliniMACS Prodigy® TCT Process.



MACS® GMP T Cell TransAct™, with its unique features, enables biologically appropriate activation for your T cell manufacturing.

- **Unique format:** A colloidal polymeric nanomatrix conjugated to humanized, recombinant CD3 and CD28 agonists.

TexMACS™ GMP Medium

- Specifically developed for T cell cultivation
- Serum- and xeno-component free
- Pharmaceutical-grade human serum albumin
- QC functionality test on every batch

MACS® GMP Cytokines

- Lot-to-lot consistency and lot-specific certificates of analysis
- Designed according to the recommendations of <USP 1043> on ancillary materials
- Manufactured and tested under a certified ISO 13485 quality system

CliniMACS Prodigy® TS 520

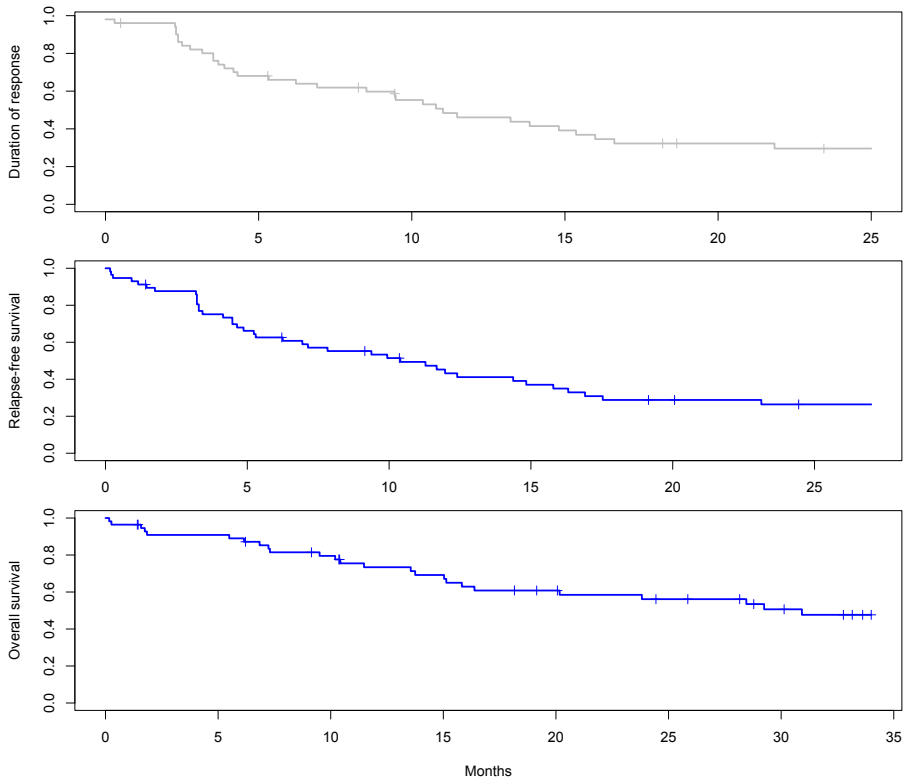
- One single-use tubing set for the entire workflow
- Sterile filters at access ports
- A truly closed system
- Integrated sampling pouches allowing IPC/QC anytime

Quality control (cells)

Parameter	Method	Acceptance criteria
Appearance	Visual inspection (in house)	Translucent substance without lumps
Cell count	Neubauer chamber (in house)	≥0.5 x10^6 CAR+ cells/kg
Identity (% CART+ cells)	Flow cytometry (in house)	≥20%
Purity (% CD3+ cells)	Flow cytometry (in house)	≥70%
Viability	Neubauer chamber using Trypan blue (in house)	≥70%
Sterility	Bacterial culture (Ph Eur 2.6.1)	Sterile
Endotoxin	Chromogenic kinetic method (Ph Eur 2.6.14-D)	≤0.5 EU/mL
Adventitious agents	External qPCR	Absence of virus in the media
Mycoplasma	External PCR	Absence
VCN (vector copy number)	qPCR (in house)	≤10
RCL (replication competent lentivirus)	qPCR (in house)	Absence of RCL
Potency	Flow cytometry (in house)	Surviving fraction of NALM6 <70% at 1:1 tumour:CART ratio; and/or difference of surviving fraction of NALM6 >50% for CART vs UT cells at a 4:1 tumour:CART ratio

Efficacy of var-cel for the treatment of R/R ALL

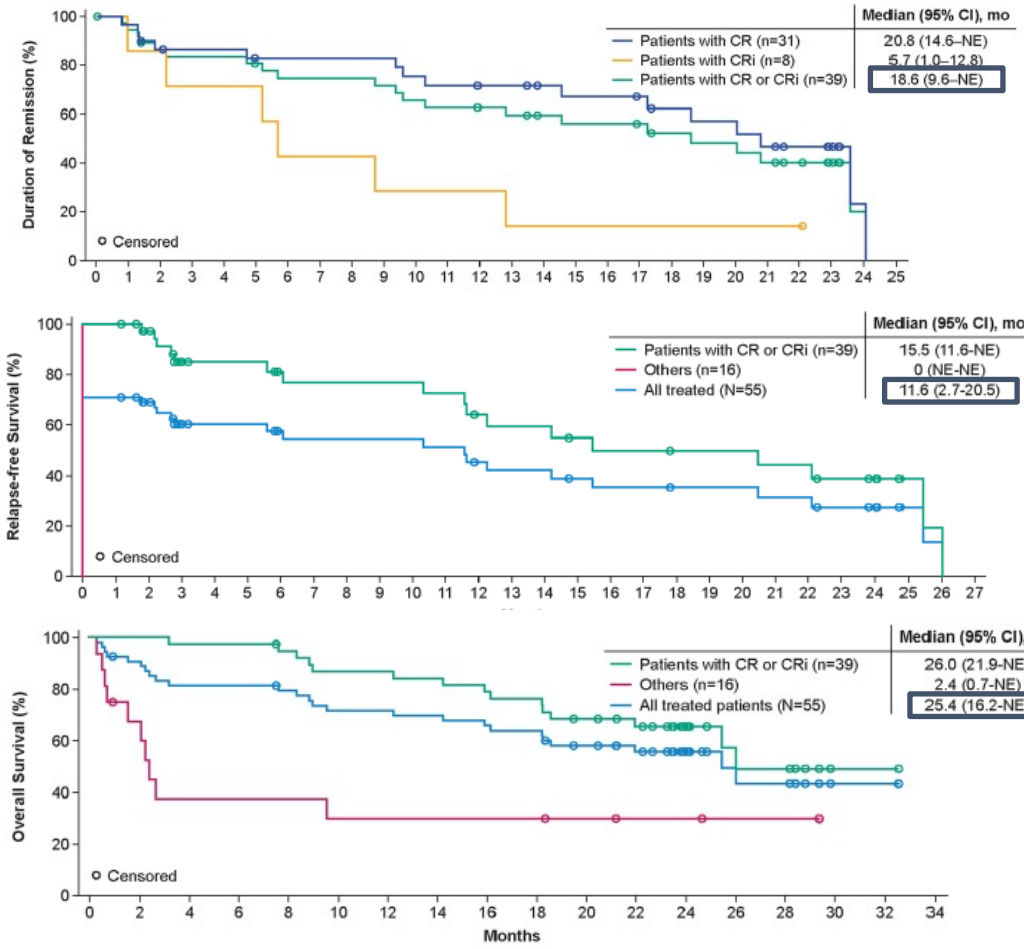
	Pts	MRD- CRR at day +28 (CI 95%)	Median DOR from day +28 (CI 95%)	Median PFS (CI 95%)	Median OS (CI 95%)
Adult patients (>18 yr)	57	89% (79-95%)	11 mo (6.9-16.6)	10.4 mo (6.2-16.3)	30.9 mo (16.4-NA)



	All grades	Grade ≥3
CRS	52% (40-65%)	7% (3-17%)
ICANS	7% (3-17%)	0% (0-6%)

Unpublished. May 2023

Efficacy of brexu-cel in adult patients with R/R ALL



CRR	71% (57-82%)

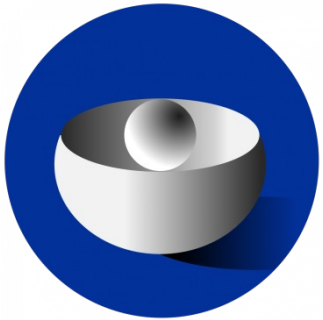
	All grades	Grade ≥3
CRS	89% (78-94%)	24% (14-36%)
ICANS	60% (47-72%)	25% (16-38%)

Shah et al. JHO 2022

What do we do next?

Can we carry on running clinical trials forever? National grants? International grants?

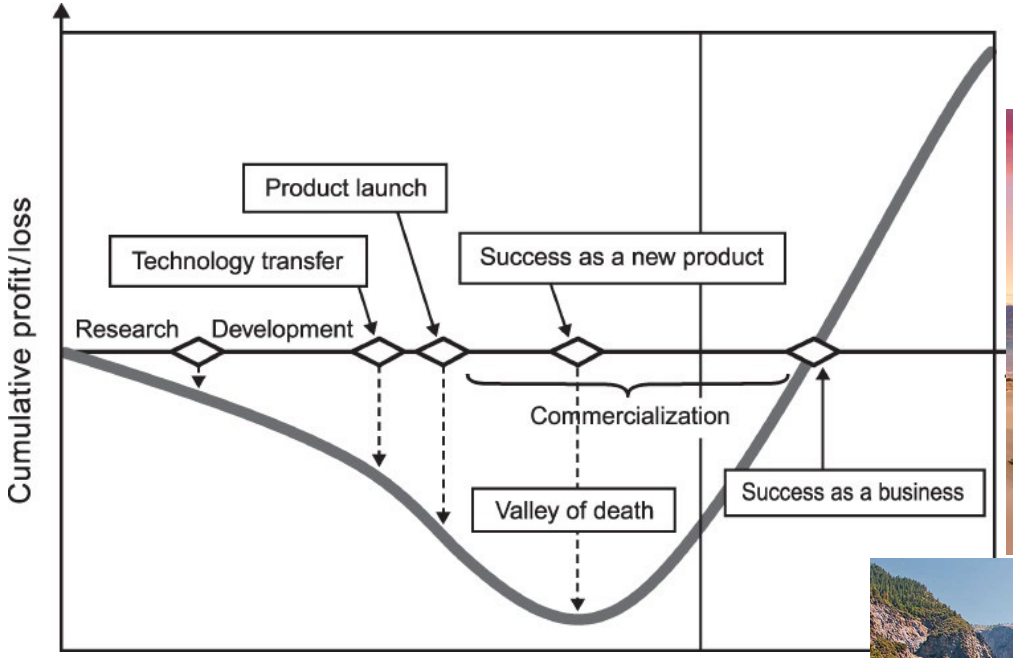
Is it possible to register your CAR T-cell?

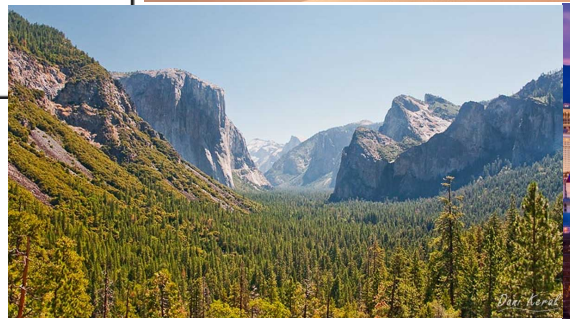


The centralised procedure is **compulsory** for:

- human medicines containing a new active substance to treat:
    - human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS);
    - **cancer**;
    - diabetes;
    - neurodegenerative diseases;
    - auto-immune and other immune dysfunctions;
    - viral diseases.
- medicines derived from **biotechnology** processes, such as **genetic engineering**;
- **advanced-therapy medicines**, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
- orphan medicines (medicines for rare diseases);
- veterinary medicines for use as growth or yield enhancers.

Can we really cross the “valley of death”?





What does it entail (going to the EMA)?

1. Intellectual property → needed for an INN
2. Non-similarity → check other drugs with orphan designation
3. Paediatric investigation plan (or a waiver)
4. Scientific advice (fee!)
5. Type of approval → full vs. conditional → check for fully approved drugs (“major therapeutic advantage”)
6. Documentation preparation (and software needed)
7. Marketing authorisation application (MAA) fee

How can you ease the pain?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1. Start thinking as a drug developer (what is your aim?)
2. Early contact with regulators:
    1. Nonclinical tests
    2. Quality control
    3. Design of your clinical trial
3. Surround yourself with experts in regulatory science
4. Secondment as national expert
5. PRIME designation → new mechanism of action, unmet medical need (game changers!!) → relatively easy (no committee involved) → BENEFIT: scientific advice for FREE
6. Orphan designation → it must be a rare disease (most haematological malignancies are) and “significant benefit” must be demonstrated → BENEFIT: market exclusivity + reduced submission fees
7. Pilot programme of enhanced support to academic and non-profit developers of ATMPs → contact the Advanced Therapies Office

05 January 2019
EMA/CHMP/205/95 Rev.6
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the clinical evaluation of anticancer medicinal products

Parliamentary question - E-000739/2021
European Parliament

Availability of CAR-T cell therapy in the

5.2.2021

Question for written answer E-000739/2021
to the Commission
Rule 138
Liudas Mažylis (PPE)

Chimeric antigen receptor (CAR) T-cell therapy is a well-established breakthrough treatment in oncology that is personalised for each patient. Unfortunately, its price is particularly high and can reach up to EUR 500 000 per person. Lithuania is one of the countries in which Novartis and Thermo Fisher Scientific are involved in this therapy, but this modern treatment method is inaccessible not only in Lithuania, but also in some other Member States.

1. What approach to funding should be followed in order to expand cell therapy (CAR-T) to the largest possible number of cancer patients?
2. What should the Commission do – and what assurances can it make – to ensure that modern but expensive treatments are equally accessible to citizens of all Member States and become common practice in all Member States? Will the new Europe's Beating Cancer Plan address the issue of access to modern cancer treatments?
3. With regard to the new EU approach to health policy (European Health Union), are there any plans to address existing inequalities in treatment (between Member States, different age groups, etc.)? How will the EU4Health programme ensure the transparency of data and processes in the development and/or sale of medicines and medical devices?

High Cost of Chimeric Antigen Receptor T-Cells: Challenges and Solutions

Edward R. Scheffer Cliff, MBBS, MPH[1,2]; Amar H. Kelkar, MD[2,3]; David A. Russler-Germain, MD, PhD[4]; Frazer A. Tessema, BA[1,2]; Adam J.N. Raymakers, PhD[1,2]; William B. Feldman, MD, DPhil, MPH[1,2,5]; and Aaron S. Kesselheim, MD, JD, MPH[1,2]

Features | April 29, 2022

Access to CAR-T therapies in Central and Eastern Europe in "catch-up" mode compared to the West

Although some countries are moving ahead, the use of CAR-T therapies in the region remains uneven.

Comment | November 21, 2022

Manufacturing challenges set back development progress of cell therapies in oncology

GlobalData Healthcare

Availability & reimbursement

Country	Kymriah	Yescarta	Tecartus	First use	Centres	Pts treated*	NHL	p ALL
Bulgaria				--	--	--	--	--
Croatia				2020	1	28	24	4
Czech R.				2019	7	128	118	10
Estonia				--	--	--	--	--
Hungary				2023	2	1	0	1
Latvia				--	--	--	--	--
Lithuania				--	--	--	--	--
Poland				2021	6	82	57	25
Romania				2022	1	15	10	5
Slovakia				2023	3	0	0	0
Slovenia				2021	1	9	7	2

*By December 2022

Hajek. Presented at EHA-EBMT CART-cell meeting. Rotterdam. February 2023

What about Hospital Exemption?

Allows for the use of an ATMP without a marketing authorisation under certain circumstances:

- Only applies to a hospital setting
- Non-routine basis
- For an individual patient
- No centrally authorised treatment or clinical trial is available

Principles of long-term follow-up should apply to commercial and non-commercial manufacturers

Need for publicly available information about HE product at EU and/or national levels (use and safety/efficacy profile)

Need for further harmonization of HE requirements/licenses and eligibility criteria across all Member States

Stem Cell Reports
ISSCR
Perspective
OPEN ACCESS

Unproven cell interventions in Poland and the exploitation of European Union law on advanced therapy medicinal products

What did we do?

Compassionate use program approved by the AEMPS and Ministry of Health (patients outside currently approved indications)

Registration dossier submitted to the AEMPS in February 2020 (Hospital Exemption) → ARI-0001 cells (var-cel) approved for patients older than 25 years of age with R/R ALL (February 2021)

Price & reimbursement agreed with Ministry of Health in June 2021 → €89,270

Creation of our pharmacovigilance programme

Phase 2 trial (registration?) trial currently ongoing in 12 Spanish centres, specifically intended for adult patients with R/R ALL

What was our experience with Hospital Exemption?

Strict (and lengthy!) evaluation by the Spanish Medicines Agency:

- Nonclinical
- Quality
- Clinical

Approval limited to patients with R/R ALL **older than 25 years**

No need for:

- Prior scientific advice procedure
- Paediatric investigation plan
- Non-similarity evaluation
- Fees

What are we doing now?

PRIME designation granted by EMA in December 2021 for patients older than 25 years of age with R/R ALL → kick-off meeting held in April 2022

Paediatric Investigation Plan submitted in July 2022 (based on the CART19-BE-03Ped trial) → first response in October/2022 → revised in Jan/2023 → agreed in May/2023

Scientific Advice submitted in July 2022 → first response in November/2022 → final letter received in late December 2022 → preparing 2 more SAs (validation of QC tests and comparability studies)

Matched-indirect comparison of our phase 2 results designed → external statistician identified + external database (PETHEMA)

Plan to apply for conditional marketing authorisation (CMA) → need to demonstrate “major therapeutic advantage” over fully approved products (Blincyto, Besponsa).

A third EU-based trial will be needed in case of CMA

What are the main difficulties?

Clinical trial costs:

- CART19-BE-02: €1.2M (€1.44M in cell production only)
- CART19-BE-03Ped: €1.4M (€1.35M in cell production) → PDCO asking for 70 pts (30% from other EU countries) → will need around €3M (IT, NL, FR interested)
- CART19-EU-04: seeking €9.8M (trial in ES, FR, NL, BE, AT)

Consolidate point-of-care manufacturing → network of academic centres across the EU

Creation of a company for lentiviral manufacturing (MIA) → Gene Vector Ltd.

Document preparation → software required (€100,000)

Fees!!!

Fees for ATMPs (EMA)

	Current			Future
	Big Pharma	**Micro + SME**	**Academia**	**Big Pharma**
MAA (full dossier)	€313,200	Conditional fee exemption + deferral	?	€684,900
Extension for paediatric use	€94,000	€0 if micro; €56,400 if SME	?	€99,800
Type II variations*	€94,000	€0 if micro; €56,400 if SME	?	€99,800
Inspection (GMP)	€23,700	€2,370	?	€24,800
Scientific advice (Q, S and C)	€94,000 €32,900 for ATMPs	€0 if PRIME or OD; €9,400 if not	0€ if PRIME	€55,200

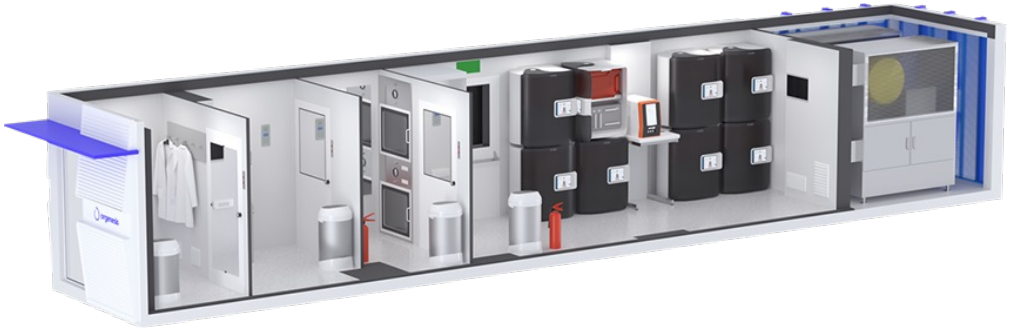
*New indication, changes in SmPC (pharmacovigilance, etc), changes to the manufacturing process, addition of new manufacturing site

What if var-cel is approved in the EU?

We need a network of academic institutions willing to manufacture var-cel

Experience with HO161 trial → quality control criteria for releasing the cells were not completely harmonised with us → the dose administered is too low

What about countries where no institution is willing to make the investment of building a clean room?

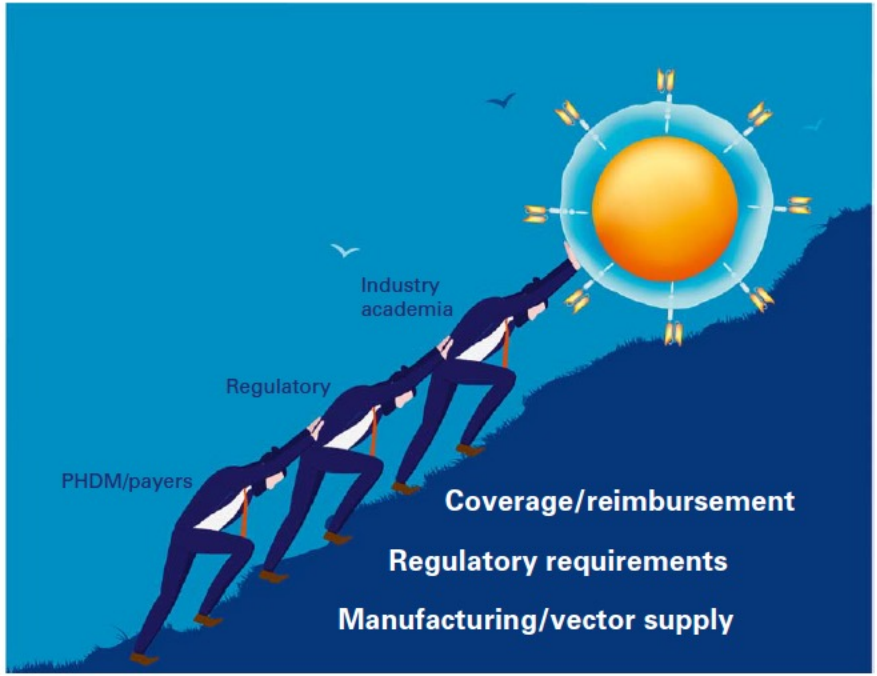


Conclusions

- Academic CART-cell development is possible
- Requires a change of mentality
- Requires help from experts in regulation
- Requires generosity

If you want to go fast, go alone;
If you want to go far, go together

- Requires stamina



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Núria Martínez
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G024 – G063
Lymphoma/Myeloma
Transplant

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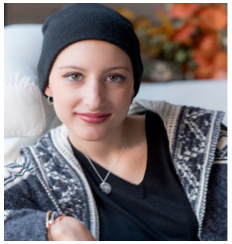
IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer



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Institut de Recerca contra la Leucèmia Josep Carreras

LEITAT managing technologies

GeneVector The Future of Health, Today

Fundació Glòria Soler

"la Caixa"

agencia española de medicamentos y productos sanitarios

Instituto de Salud Carlos III