How did the field of ATMPs evolve over time: the perspectives from the former CAT chairs

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Gene therapy on the move

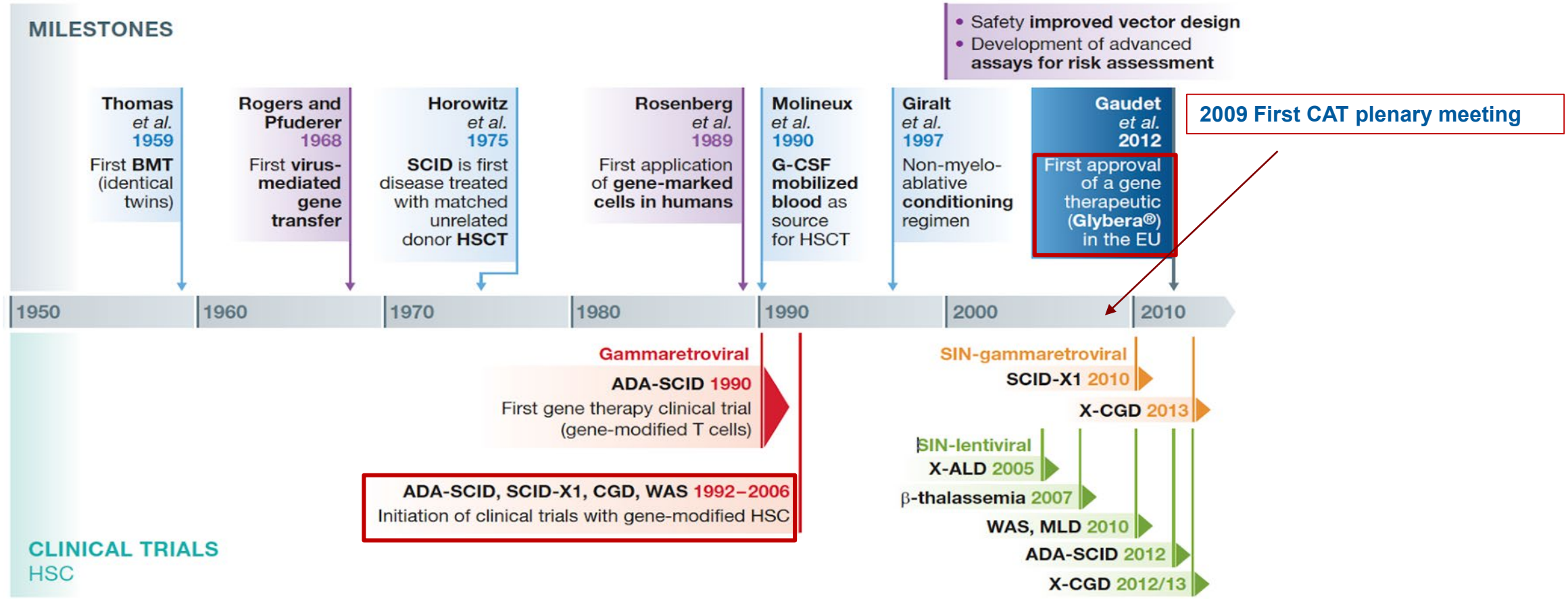
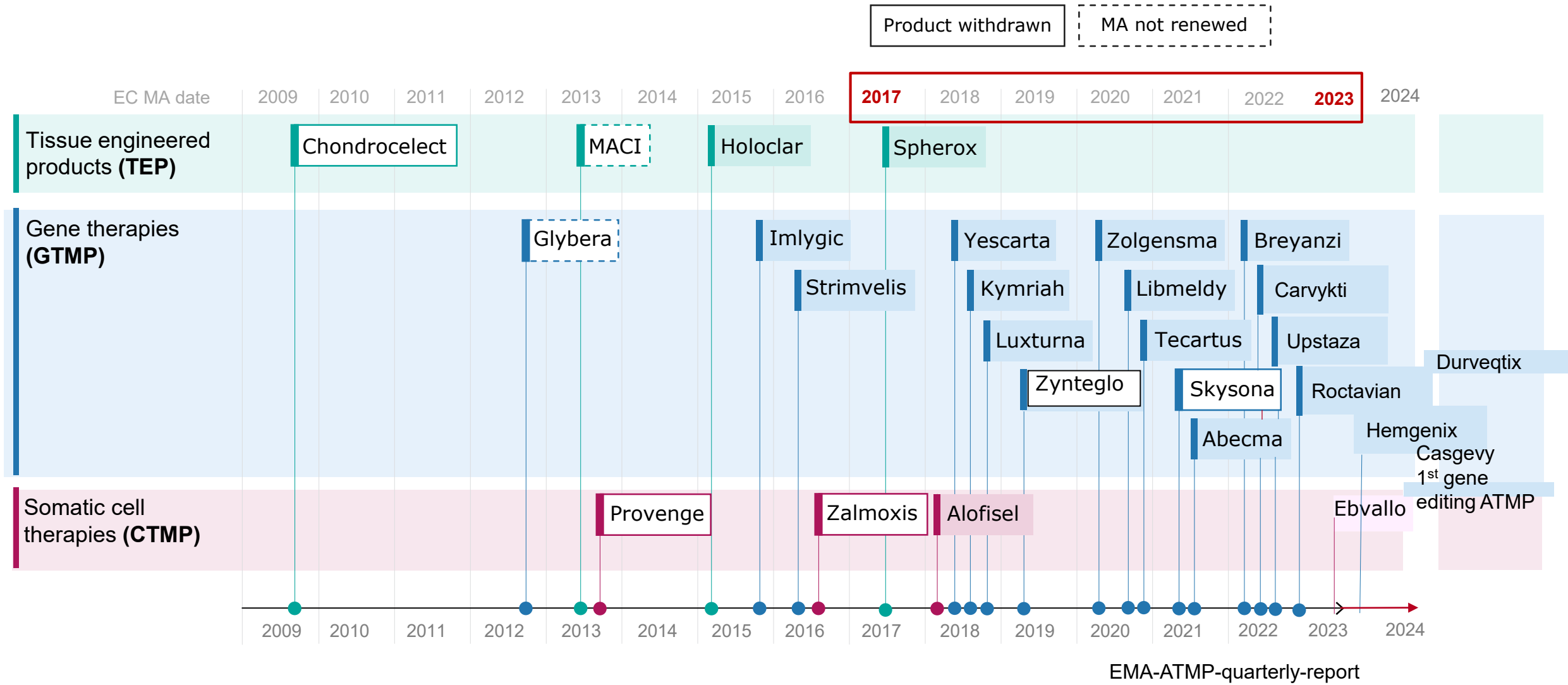


Image: Kaufmann et al. EMBO Mol Med 2013

Approved ATMPs 2009 – 2024



EMA-ATMP-quarterly-report

CAT`s highly innovative products
EU gene therapy marketing authorisations since 2017

Ex vivo genetically modified cells

T-cells	(Shortened) Indication	Approval	OD
Kymriah®	B-ALL, NHL subtype	MA	✓
Yescarta®	NHL subtype	MA	✓
Tecartus®	B-ALL, NHL subtype	cMA	✓
Abecma®	NHL multiple myeloma	cMA	✓
Breyanzi®	NHL subtypes	MA	✓
Carvykti®	NHL multiple myeloma	cMA	✓
CD34+ cells			
Zynteglo®	β-thalassaemia	cMA	✓
Skysona®	Adrenoleukodystrophy	MA	✓
Libmeldy®	Metachromatic LD	MA	✓
Casgevy®	Sickle cell disease, β-thalassaemia	cMA	✓

In vivo gene therapies

rAAV vector	(Shortened) Indication	Approval	OD
Luxturna®	Retinal dystrophy	MA	✓
Zolgensma®	Spinal muscular atrophy	cMA	✓
Upstaza®	AADC deficiency	Exceptional	✓
Roctavian®	Haemophilia A	cMA	✓
Hemgenix®	Haemophilia B	cMA	✓
Durveqtix®	Haemophilia B	cMA	✓

Marketing authorisations (MA)	16
Orphan designations	16
Conditional MA (cMA)	9
Full MA	6
Exceptional circumstance	1

OD-Orphan Disease

ATMPs - Differences to other medicines

- Represent technological and scientific breakthroughs
- Repair disease-causing mutations with potential for cure with single administration
- Complex products to develop, manufacture, characterise, test
- Non-standard non-clinical development programmes
- Concomitant therapies, e.g. conditioning therapy
- Novel toxicities, unknown risk for insertional mutagenesis events
- Specific post-authorization obligations to address remaining uncertainties and build knowledge
- No precedent cases for regulatory decision making

The ATMP life cycle

ATMP DEVELOPMENT

MARKETING AUTHORISATION
COORDINATED BY EMA

POST-APPROVAL LIFE CYCLE MANAGEMENT, PHARMACOVIGILANCE

Discovery

Pre-clinical → Clinical Evaluation → Clinical Trial Authorisation

CAT* → CHMP* → PRAC* COMP*

Benefit-risk assessment / opinion

European Commission (conditional) **approval**

Post approval obligations
Indication extension →

Medicine is reimbursed and available/patient access

National Scientific Advice

Simultaneous NSA

EMA scientific advice

National HTA advice

EMA/HTA parallel advice

Scientific assessments and authorisations by experts from NCAs throughout life cycle

*Committee for Advanced Therapies
*Committee for Medicinal Products for Human use
*Pharmacovigilance Risk Assessment Committee
•Committee for Orphan Medicinal Products

CAT – decision making in the ATMP life cycle

A selection of pivotal discussion and action points 2017 – 2023

- Information flow and exchange across committees
- Consistency in decision making
- Benefit-risk assessment and limited clinical evidence
- Analysis population and inication wording
- Post-authorisation knowledge building and real world data collection

Information flow and exchange across committees

CAT`s contribution to a complex EMA assessment and approval process

- Ensure flow of information across committees
- Avoid differences and gaps in knowledge base
- Appreciate scientific background, specificities of ATMPs
- Avoid surprises and controversial outcomes in CAT and CHMP

Tools

- ➢ Invite CHMP and PRAC members to CAT milestone discussions
- ➢ Regular exchange between committee chairs
- ➢ CAT members and chair in CHMP discussions
- ➢ Company oral explanations in front of CAT

Consistency in decision making

CAT-CHMP working group on „Comprehensiveness“ in marketing authorisations 11.2020 – 5.2022

- Standard vs non-comprehensive clinical data package
- Standard vs conditional marketing authorisation
- Consistent decisions across products and indications
- Comprehensiveness criteria in D80 Overview template

CAT working group on Guideline on Core product information for genetically modified cells 1.2020 – 5.2022

1. NAME OF THE MEDICINAL PRODUCT

[The strength should be expressed on the basis of the general term ‘cells’, which in this section is considered to define cells which contribute to the therapeutic effect.

e.g. CAR-T cells = total number of viable transduced cells
e.g. total number of $CD34^+$ cells including the transduced cells: in addition to the therapeutic effect of the progeny of genetically modified stem/progenitor cells, the hematopoietic and immune reconstitution of the whole population is clinically relevant.

The specific cell type contributing to the therapeutic effect should be specified in section 2 of the SmPC, and in section 1 of Annex IIIA and IIIB in brackets beside the INN.

EMA/CAT/CHMP/158266/2021

Robust clinical evidence at marketing authorisation
Randomized controlled studies and ITT principle

- Clinical evidence: the totality of clinical data about the use, benefits and risks of a medicinal product across the development program.
  - Clinical trial data, data from hospital exemption, early access programs, real world data
- Randomized controlled trials (RCTs) as standard for providing robust and confirmatory evidence.
- Statistically compelling, clinically relevant data
- Same principles for ATMPs
  - randomized controlled design
  - also in late stage refractory disease
  - randomize to best supportive care, investigator`s choice
  - Adhere to intention-to-treat (ITT) principle,
  - EMA/CAT/GTWP/671639/2008 Rev. 1 – corr, CAT guideline with Annex CART-cells


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 November 2020
EMA/CAT/GTWP/671639/2008 Rev. 1 - corr
Committee for Advanced Therapies (CAT)

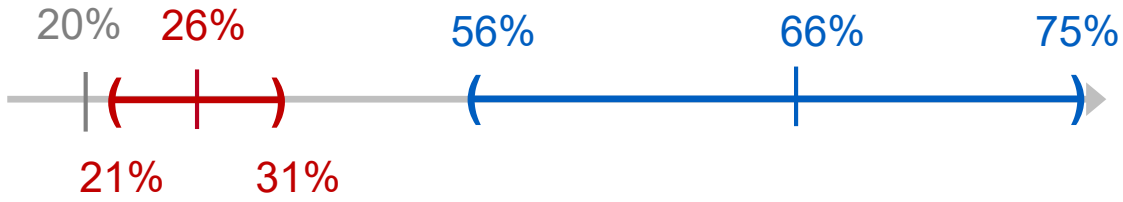
Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

Sources:
ICH E8,9,10. EMA PtC single pivotal study CPMP/EWP/2330/99, FDA substantial evidence one well-controlled clinical investigation 44625092draft

Clinical evidence based on single arm trials (SAT)
Definition of outstanding effect

- The threshold of efficacy to show that treatment is working?
- The role (and issue) of Real World Data (RWD)
  - To contextualize the SAT data
  - To derive a threshold
  - To interpret clinically relevant effects

Yescarta MAA for DLBCL



ORR with CI (SCHOLAR-1)

ORR in ITT set (ZUMA-1)

Axicabtagen ciloleucel, Yescarta

- single arm trial ZUMA-1
- 111 patients enrolled (ITT), 101 treated (mITT)
- Primary endpoint overall remission rate
- RWD from retrospective patient-level outcomes in refractory NHL, Scholar-1

CAT decision based on
- “Worst case” re- analysis of Scholar-1
- Raw data analysis of ZUMA-1 **
- 35% difference in ORR, CR makes chance finding unlikely

[1] Papadouli et al. (2020), EMA Review of Axicabtagene Ciloleucel (Yescarta) The Oncologist, https://doi.org/10.1634/theoncologist.2019-0646

EMA RF on establishing efficacy based on single arm trials 2023

Analysis population and indication wording in (ultra-) rare disease

Options

- Positive benefit-risk for studied patient population
- Positive benefit-risk for subset of studied patient population
- Positive benefit-risk for broader than studied patient population -> extrapolation to more or less severely affected, older or younger patients
- Regulatory or legal provisions that „dictate“ indication wording

Analysis population and indication wording in (ultra-) rare disease
Libmeldy, atidarsagen autotemcel, metachromatic leukodystrophy

- *Ex vivo* genetically modified CD34+ cells encoding the human arylsulfatase A (ARSA) gene
- Analysis population
  - n=20 subjects, bi-allelic mutations, single arm trial
  - Longitudinal observational study
- Clinically relevant effects
  - late infantile and early juvenile, pre-symptomatic subjects -> normal motor and cognitive development 3-5 years post treatment
  - early juvenile, early symptomatic subjects -> magnitude of effect less evident, symptom worsening, but slower deterioration compared to untreated subjects (external control)
- Additional considerations
  - Identification of pre-symtomatic patients in absence of EU-wide newborn screening
  - Exclusion of children with chance for clinical improvement over time

Analysis population and indication wording in (ultra-) rare disease
Libmeldy, atidarsagen autotemcel, metachromatic leukodystrophy

CAT decision for indication wording

- Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD) characterized by biallelic mutations in the arylsulfatase A (ARSA) gene leading to a reduction of the ARSA enzymatic activity:
- - in children with late infantile or early juvenile forms, without clinical manifestations of the disease,
- - in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline

HTA decision on extent of additional benefit and significance of evidence

→ Hint of major additional benefit

→ Hint for a non-quantifiable additional benefit, since the scientific data does not allow a quantification

EMA CHMP assessment report Libmeldy
Schüßler-Lenz, Hofner: Marketing authorisation for rare diseases, ZEFQ 2024
G-BA_2021_AM-RL-XII Aditarsagen-autotemcel

Analysis population and indication wording in (ultra-) rare disease
Tecartus (brexucabtagene autoleucel), B cell acute lymphocytic leukemia

- CD19 targeting CART cell
  - conditional marketing authorisation mantle cell lymphoma in 2020
- Analysis population, indication extension
  - ZUMA-3: SAT in adults 18 years and older with r/r B-ALL
- Clinically relevant effects
- Scientific Advisory Group Oncology
  - Broad indication recommended
- Additional considerations: regulatory/legal
  - In case of conditional marketing authorisation mandated to show „major therapeutic advantage (MTA)“ over authorised treatment (full marketing authorisation)
    - MTA over certain anti-B-ALL medicinal products
    - No MTA over other CART cell product, paediatric and young adult patients up to 25 years of age

Analysis population and indication wording in (ultra-) rare disease
Tecartus (brexucabtagene autoleucel)

Decision for indication wording

- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.
- Adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).
- Conditional marketing authorisation

US FDA indication, package insert

- Adult patients with relapsed or refractory mantle cell lymphoma (MCL). Accelerated approval
- Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

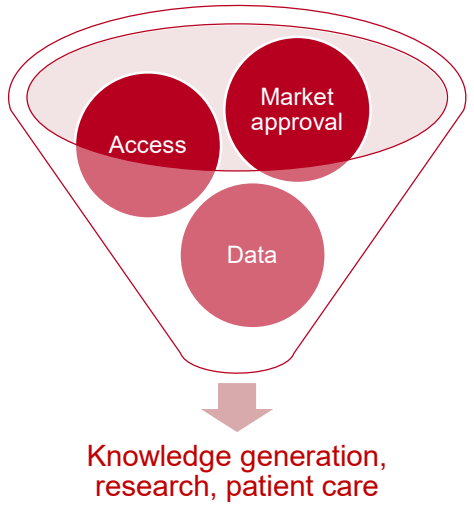
Post-authorisation knowledge building and real world data collection
Link to patient access and incremental knowledge gain

Post-authorisation safety and efficacy studies

- Complement and expand evidence generated in clinical trials

Tools

- Prospective observational data collection acc to CAT/PRAC agreed protocol
- Embedded in disease registries



CAT`s experience

- Delays and gaps in RW evidence reporting, Issues with data quality
- Suitability of national registries - CART cells, up to 45 treatment centers/member state
- Suitability of EU wide, global registries - 12 patients treated with commercial ATMP since 2022, Upstaza

CAT`s action items

- CAT working group on RWD in 2021 -> EMA funded study on SMA registries
- Recommendations for ATMP developers, implementation of milestones in Priority Medicines scheme

The CAT
Major contributions to safe and efficacious innovative medicines

A committee

- with multidisciplinary expertise
- with time and expertise to discuss innovative ATMPs
- with EU member state representation to foster transparancy of decisions, mutual learning, flow of information
- highly engaged patient and physician representatives
- ensures consistency in decision making
- for cutting edge innovative medicines of which there are many more to come

Thank you all!