EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

"CAR T cells – regulatory aspects from the EMA Committee for Advanced Therapies."

CDDF Spring Conference
10-12 February 2020

Presented by Martina Schüssler-Lenz
Chair, EMA Committee for Advanced Therapies (CAT)
Paul-Ehrlich-Institut

Disclaimer

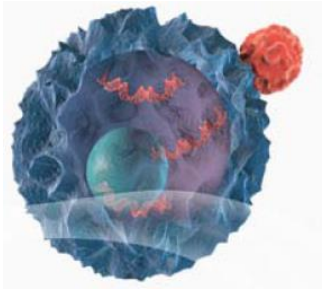
The views expressed in this presentation are the personal views of the author and may not be understood or quoted as being made on behalf of the European Medicines Agency or the Paul-Ehrlich-Institut

Legal Framework

Advanced Therapy Medicinal Products (ATMPs) Regulation (EC) No1394/2007

- ATMPs are medicinal products
- Are authorized in EU via the centralized procedure
- Are assessed by the Committee for Advanced Therapies

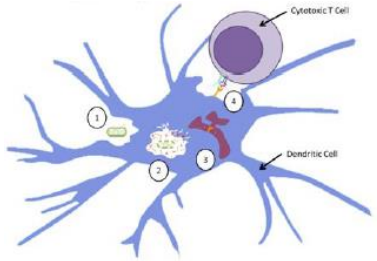
Gene therapy
e.g.CAR T cells



Dt. Ärzteblatt 11.2018

➔ **Recombinant nucleic acid**

Somatic cell therapy



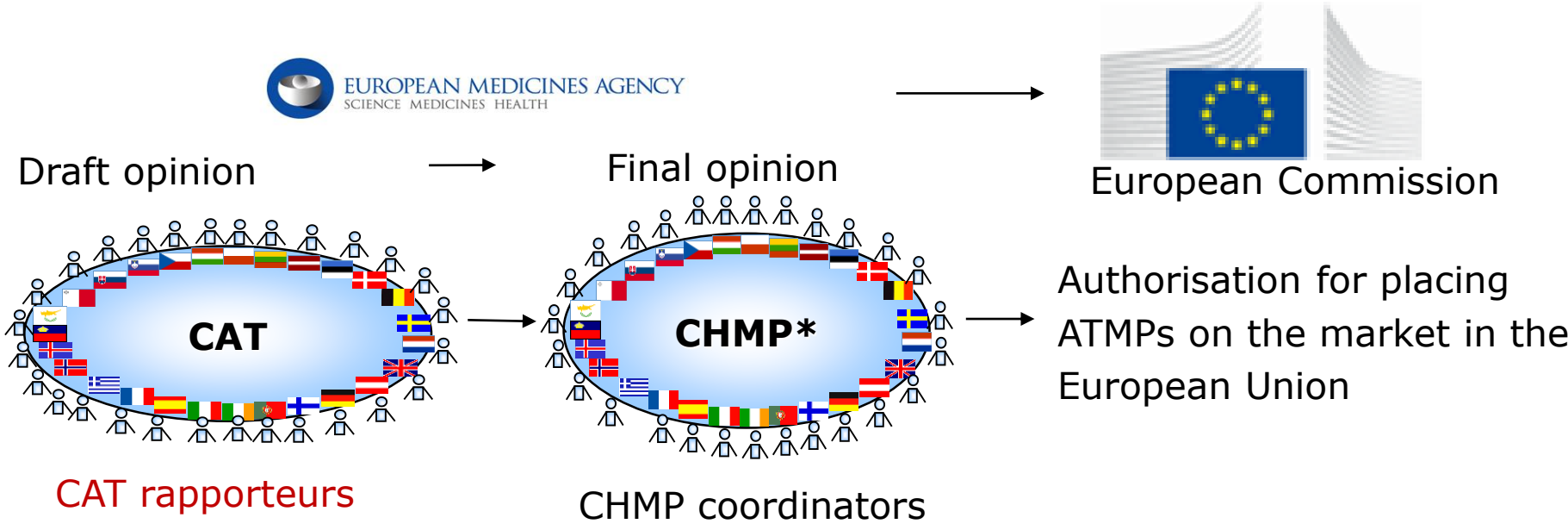
➔ **Pharmaco-immunological…**

Tissue engineered product

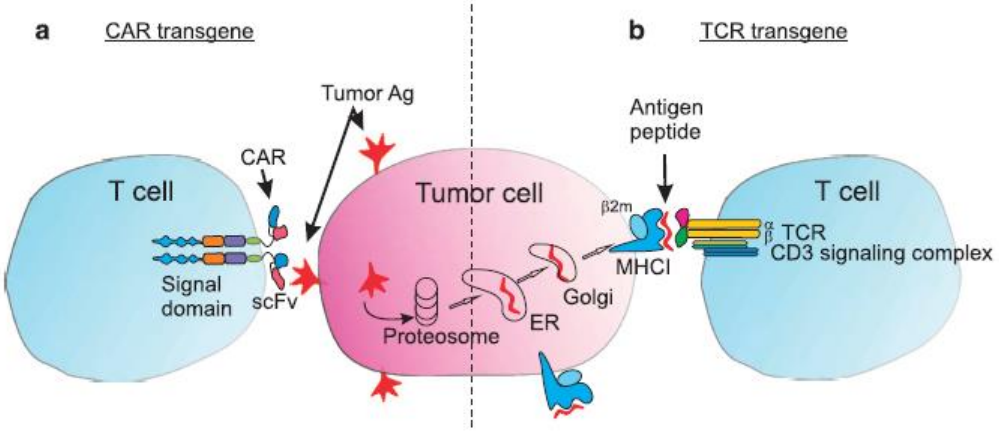
➔ **Regeneration, repair….**

EMA Committee for Advanced Therapies (CAT)

Responsible for assessing quality, safety, efficacy of ATMPs



*Committee for Medicinal Products for Human Use



Kershaw MH et al: Clin. & transl. Immunology 2014

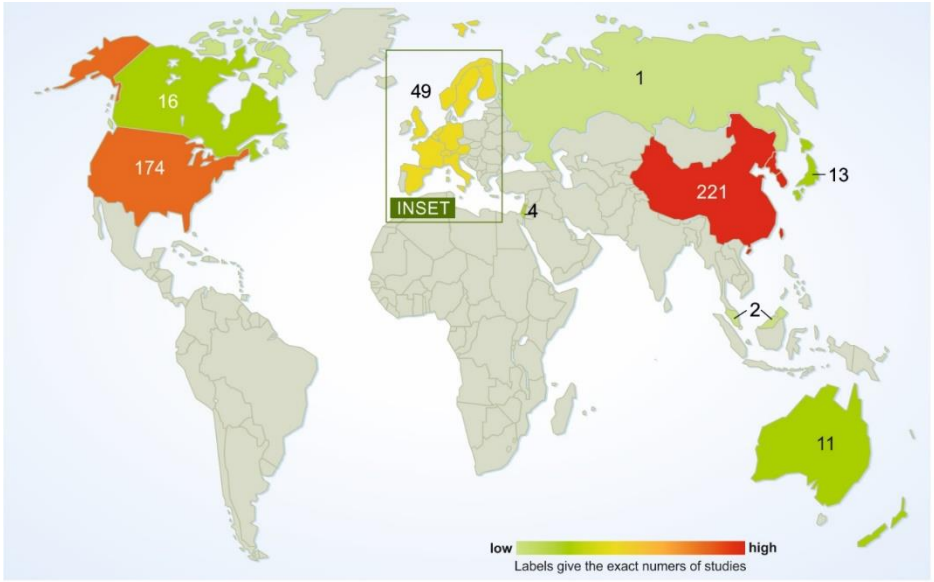
CAR-T cells

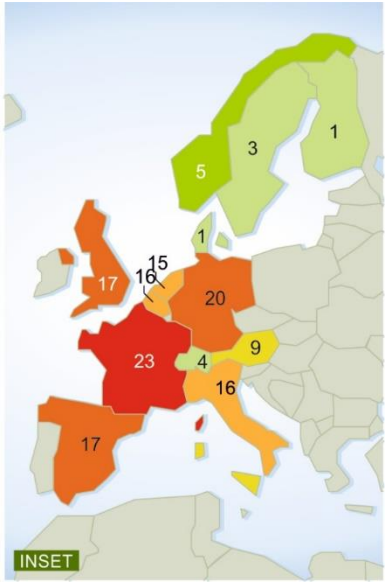
- Recognize antigen via extracellular single-chain antibody domain (scFv)
- Only antigen on cell surface

TCR modified T-cell

- Recognize peptide fragment/MHC complex
- HLA restriction
- Antigen can be intracellular or surface

Geographical Distribution of CAR T cell trials





436 ongoing trials world wide ←w/o LFU→

- including 31 multi-national trials (≥2 countries)
- Europe is counted as one country
- for some trials no information on trial sites exist

49 registered trials in Europe

- including 25 multi-national trials (≥2 countries)

Updated from as of 30.10.2019 :

Hartmann J, Schüßler-Lenz M, Bondanza A, Buchholz CJ, *EMBO Mol Med* , 8 2017.

LFU = long-term follow-up

EMA/CAT forecast for CAR T cell marketing authorisations

Two CAR T cell products authorised in 8/2018

- Axicabtagene ciloleucel, Yescarta®
- Tisagenlecleucel, Kymriah®

Seven CAR T cell products receive enhanced development support in the PRIME (Priority Medicines) Scheme

- Application for marketing authorisation 2020-2022 expected
- Cluster around CD19 and BCMA targets, one bi-specific CAR T
- More information at https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines

One T cell receptor modified T-cell in PRIME-> targets NY-ESO, sarcoma

CAR T Cells

EU authorised (8/2018)

Axicabtagene ciloleucel , Yescarta®

Anti-CD19, CD28/CD3-zeta

co-stimulatory domains

Treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy

Tisagenlecleucel, Kymriah®

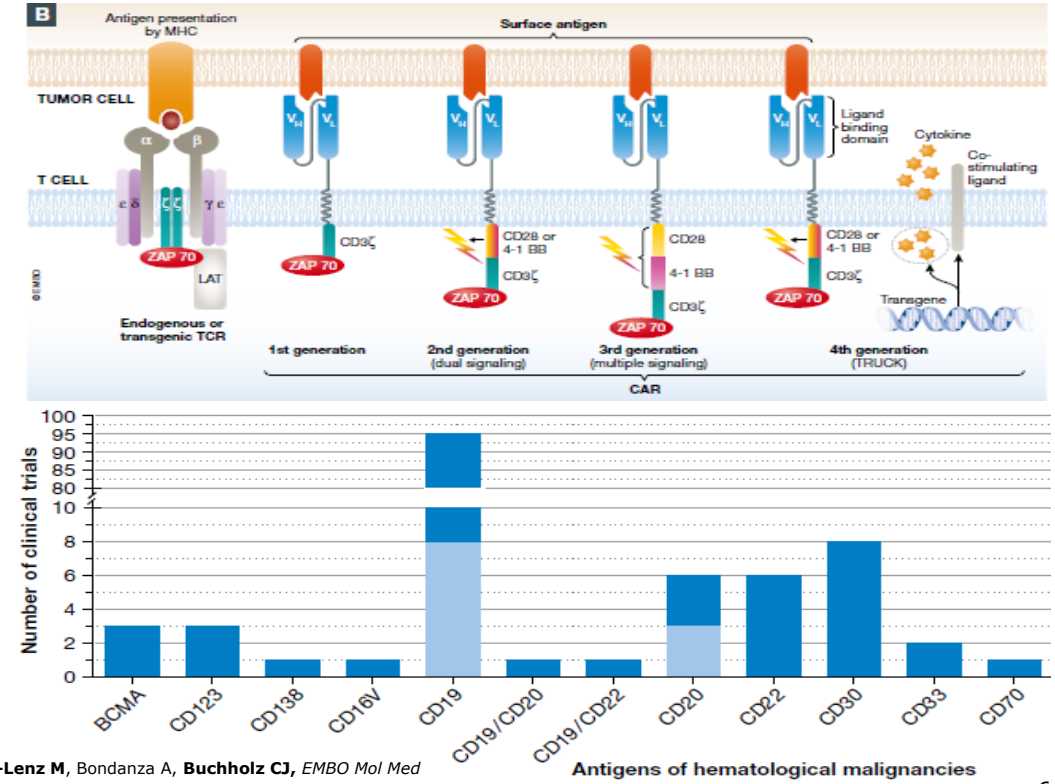
Anti-CD19, 4-1BB/CD3-zeta co-stimulatory domain

Treatment of paediatric and young adult patients (up to 25 years of age) with B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

CAR T cells

- Chimeric antigen receptor modified T cells (CAR T cells)
- have complex and variable structural features
  - different co-stimulatory signaling domains
  - different extracellular antigen/ligand binding domains



Hartmann J, **Schüßler-Lenz M**, Bondanza A, **Buchholz CJ,** *EMBO Mol Med* , 8 2017.

CAR T cells - from apheresis to infusion

EU hospital/trial site → EU preselection site → US manufacturing site / EU manufacturing site → EU hospital/trial site

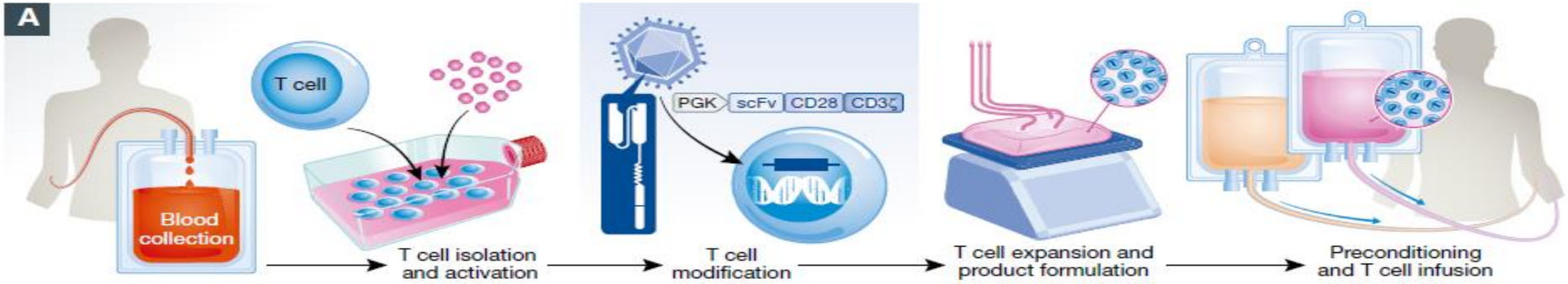
Freeze -> thaw

Freeze -> thaw

Apheresis PBL

Lymphodepletion/ Conditioning

Infusion



Hartmann J, **Schüßler-Lenz M**, Bondanza A, **Buchholz CJ,** *EMBO Mol Med* , 8 2017.

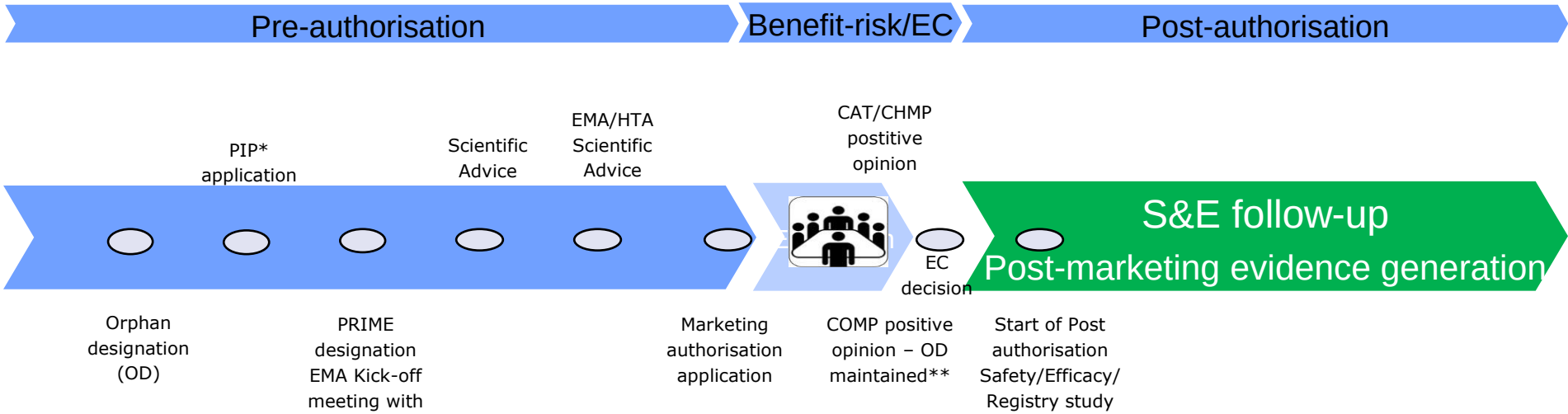
Translational aspects/challenges towards First-in-man trials

- Manufacturing process changes towards first-in-man trials
  - Impact on interpretation of non-clinical data if performed with non-comparable CAR T product
- Non-clinical aspects
  - Relevance of animal models when human CAR T cells are used
  - Dose-limiting toxicities, e.g cytokine release syndrome, neurotoxicity -> prediction based on animal models
- Clinical aspects
  - Relevance of classical 3+3 dose escalation scheme -> DLT and MTD: CAR T cells are „living drugs“

Challenges towards Marketing Authorisation

- Manufacturing process changes during clinical development
  - Comparability of pre-versus post-authorisation CAR T cell product
- CAR T cell production issues and supply chain management
  - Vein-to-vein time EU-vs-US patients (25-35 days)
  - ITT patient population vs infused population
    - Disease progression
    - Manufacturing failures
- Clinical aspects
  - Clinical trials with seamless design, single arm, external control
  - Limited patient numbers, limited follow-up time
- Strategy for post-authorisation data generation incl. HTA aspects

CAR T cells – key regulatory milestones



*PIP Pediatric development plan (Pediatric committee)
**Committee for Orphan Medicinal Products

EMA Priority Medicines scheme for CAR T cells (1)

Potential to address to significant extent the unmet medical need

Discussion platform applicant – rapporteur – other experts

- Overview of development programme and milestones
  - Quality, non-clinical, clinical aspects
  - Changes to commercial manufacturing process and comparability analysis
  - Clinical data package at marketing authorisation, full versus conditional approval
  - Interaction with Health Technology Assessment bodies (HTAs)
  - Availability of disease registries and strategy for post-authorisation studies

EMA Priority Medicines scheme for CAR T cells (2)

Potential to address to significant extent the unmet medical need

Discussion platform applicant – rapporteur – other experts

- Pediatric investigation plan PIP
  - Initiation of pediatric development, adolescent population and age subsets
- Orphan designation

➢ Gap analysis and next steps

  ➢ scientific advice on key decision points -> marketing authorisation -> accelerated (shortened) CAT/CHMP review time

Post-authorisation evidence generation

Background

- All patients receiving commercial CAR T cells are to be followed up for safety and efficacy > post-licensing evidence generation (legal obligation)
- Concise strategy regarding CAR T cell post-authorisation measures
  - Positive impact on benefit-risk evaluation at marketing authorisation
  - Positive impact on patient access <-> HTAs, reimbursement bodies

Post-authorisation evidence generation

Present your strategy at Scientific Advice

Key elements of a post-authorisation safety/efficacy study (PASS/PAES)

- Overall approach to generate real-world clinical evidence post-approval
- Main data source: existing disease registry or product registry
- Design
  - Objectives related to long-term safety and efficacy assessment
  - Patient numbers
  - CAR T cell specific data elements and variables
  - Details/frequency of adverse event reporting
- Duration of follow-up
- Comparative analysis to other treatments-> contextualize results

Authorised CAR T cells - Post-aurhorisation measures and conditions

Conditions or restrictions regarding supply and use

Subject to restricted medical prescription: administered in a qualified treatment centre: hemato-oncology, 4 doses of Tocilizumab available for use in CRS

Conditions and restriction regarding safe and effective use

- Site qualification

- Educational programme

Obligation to conduct post-authorisation measures

- Non-interventional PASS: disease registry (EBMT)

- PAES: disease registry (EMBT), manufacturing turn around time (Kymriah), results from ongoing RCT (Kymriah)….

EU Orphan legislation

Implications for market access of CAR T cells targeting same antigen

Once a marketing authorisation for a BCMA targeting, orphan CAR T cell is granted

- The EU shall not, for 10 years, accept another marketing authorisation application, or grant authorisation
- For the same indication
- With respect of a similar CAR T cell-> protection against products with similar active substance

➢ Need for second BCMA targeting CAR T cell developer to address non-similarity

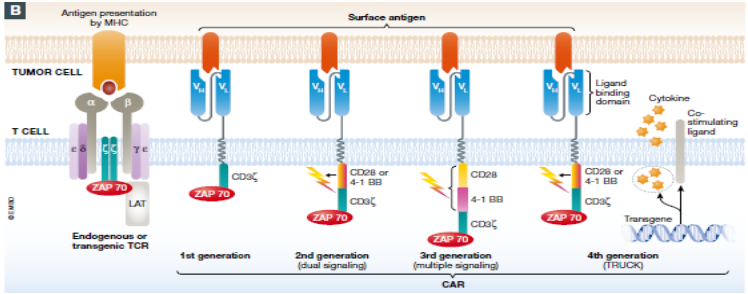
➢ Committee for Advanced Therapies opinion on (non-)similarity of a BCMA targeting CAR T cell product vis-a-vis authorised orphan CAR T cell or other products.

EU Orphan legislation

Question and answer document – similarity for ATMPs/orphans

Two CAR T cells shall not be considered similar in case of differences in

- therapeutic sequence
- viral vector, transfer system
- regulatory sequences
- manufacturing technology



Hartmann J, **Schüßler-Lenz M**, Bondanza A, **Buchholz CJ,** *EMBO Mol Med* , 8 2017.

AND

Differences shall have impact on biological activity/therapeutic effect

https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/2018_qa_atmps_en.pdf.

EU Orphan legislation

Present your strategy at Scientific Advice

STEP 1: demonstrate that your CAR T cell is non-similar to authorized CAR T cell

- What makes your CAR T cell different?
- Which differences affect biological activity?

Step 2: demonstrate „Significant benefit" against all authorised products

- At time of orphan designation (non-clinical or early stage clinical data)
- At time of marketing authorisation (clinical data)

- ➢ „Orphan similarity" (CAT) and „Significant Benefit" (COMP) are assessed at marketing authorisation
- ➢ Present your strategies in advance at EMA Scientific Advice

Marketing authorization of CAR T cells - The EMA perspective

Conclusion

- CAR-Tcells have the potential to address to significant extent unmet medical need
- Seven CAR T cell products are currently provided enhanced regulatory support in Prime Scheme
- Scientific and regulatory topics deserve specific attention

- Post-authorisation evidence generation
- The EU orphan legislation for CAR T cells targeting the same antigen
  - Orphan (non-)similarity
  - Significant benefit

- Discuss your strategy in due time before submitting your marketing authorisation application

Last but not least….

The Committee for Advanced Therapie`s recent support to developers

Visit EMA homepage
https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products

Guidelines and other documents related to CAR-Tcells

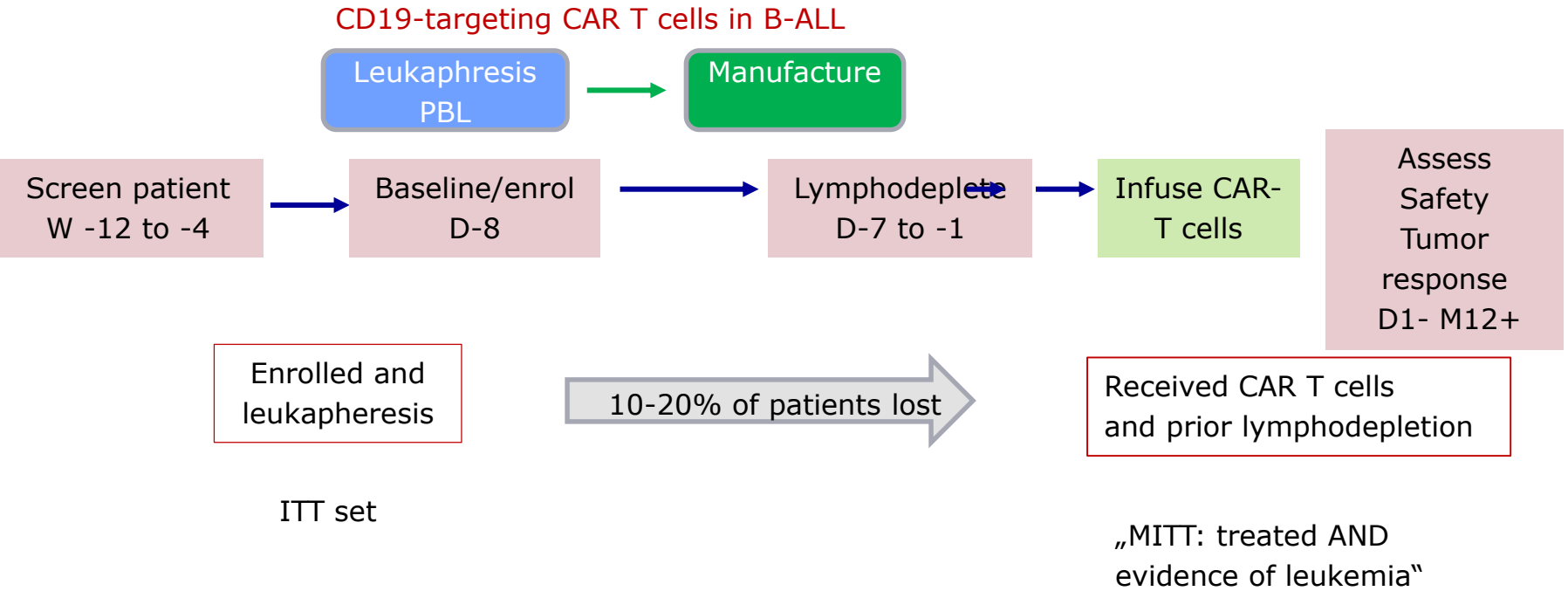
- New: *Guideline on requirements for investigational ATMPs*
- New: *Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP)*
- New: *Questions and answers on use of out-of-specification batches of authorized cell/tissue-based ATMPs*
- New: Common application form for GMO related aspects CAR T cells in clinical trials
- Revision: *Guideline on safety and efficacy FU and risk management for ATMPs*
- Revision: Guideline for genetically modified cells incl. Special considerations CAR T cells

Thank you for your attention

Martina.schuessler-lenz@pei.de

Back-up

Clinical Trial Features
Primary Efficacy Analysis



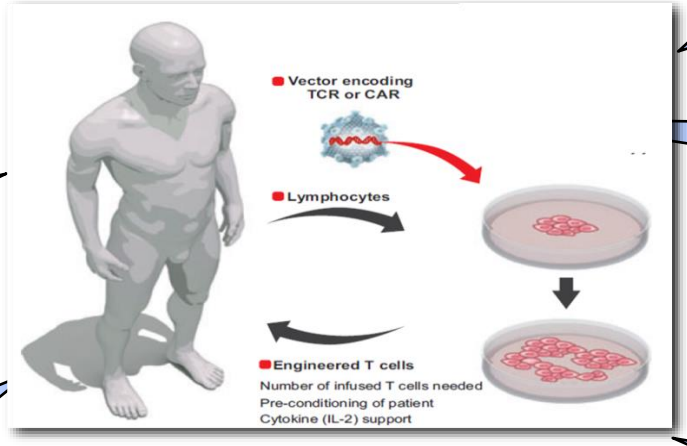
CAR T Cells – Toxicities

Impact on Trial Design/Risk Management

Neurological events

Risk of leukapheresis

Risk of 2ndary malignancy?



Risks related to conditioning regimen

Risk of infections

Hypersensitivity

Risks related to the mechanism of action (e.g. Cytokine release syndrome)

Prolonged cytopenias

Hypogammaglobulinemia

EU Orphan legislation

Implications for market access of CAR T cells targeting same antigen

Promote development of medicines for rare diseases

Incentives

- Reduced EMA fees
- National incentives
- 10 year market exclusivity
  - Orphan status, maintenance at marketing authorisation
  - Rarity, seriousness
  - Significant benefit over existing treatment

BCMA targeting CAR-Tcell

- Demonstrate significant benefit over existing therapies in multiple myeloma
- Defined as
  - Clinically relevant advantage
  - Improved efficacy, improved safety
  - Major contribution to patient care
  - Decision taken by COMP (Committee for Orphan Medicinal Products)