Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

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From Clinical Trials to Marketing Authorization of Advanced Therapies

CDDF - Gene and Cell Therapies in Oncology, 29.11.2021

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No conflicts of interest declared

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EMA Committee for Advanced Therapies

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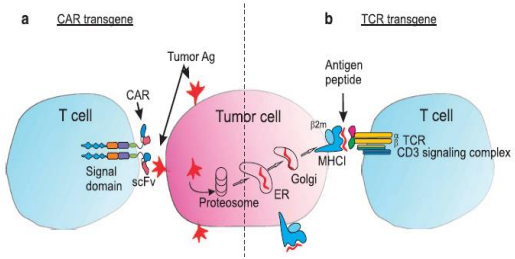
Gene and Cell Therapies in Oncology
The EU Regulatory Frame (EC) No 1394/2007

- Defines Advanced Therapy Medicinal Products (ATMPs)
- They are authorized via the centralized procedure (EMA)
- Principles of existing legislation apply: Quality, Safety, Efficacy
- They are assessed by a specialized Committee for Advanced Therapies (CAT)

Gene therapy

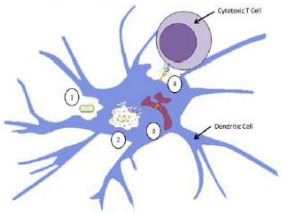
➔ Recombinant adeno-associated viral vectors (off-the-shelf)

Genetically modified or genome edited cells



➔ CAR T cells, TCR modified cells

Somatic cell therapy

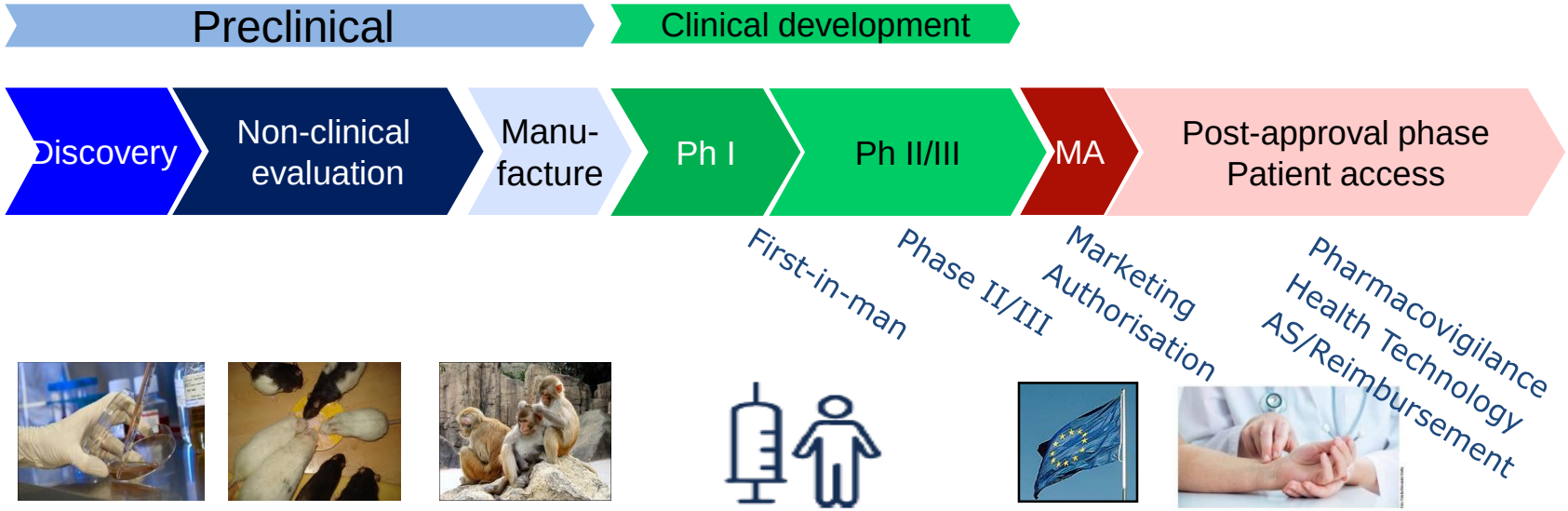


➔ Dendritic cells loaded ex vivo with tumor-specific antigen

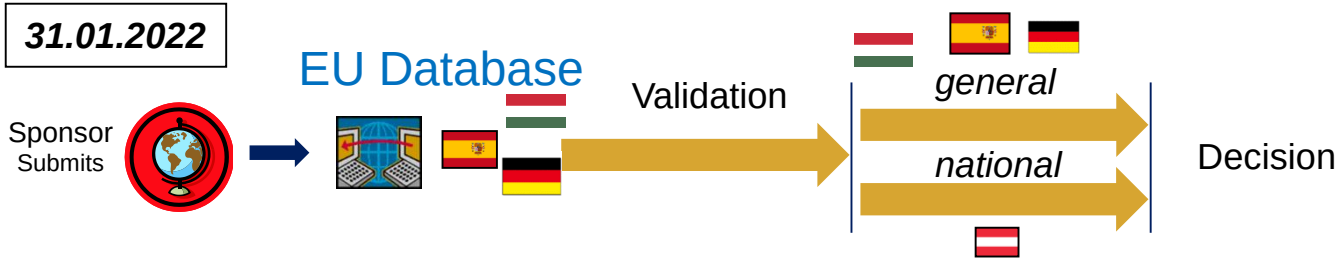
Tissue engineered product

➔ Cultured chondrocytes

The Life Cycle of Medicines
Research & Development - Authorisation – Post-Authorisation



Clinical Trial Application
Regulation 536/2014



Harmonized
- Single application and procedure
- Clinical Trials Information System CTIS: EU Portal and database
- Co-ordinated multinational assessment (rapporteur)

Member states retain authorisation and oversight

Clinical Trials Regulation: 31.01.2022

Online training modules on EMA homepage

Selected major changes

- All clinical trial applications/communications via the EU portal
- Sponsors propose a Reporting Member State in multinational CT
- Single decision by member state: competent authority and Ethics Committee*.
- Shortened time lines for sponsors to address questions (12 days)
- Transition period of 1 year, if sponsor opts for „old“ system

https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-training-support

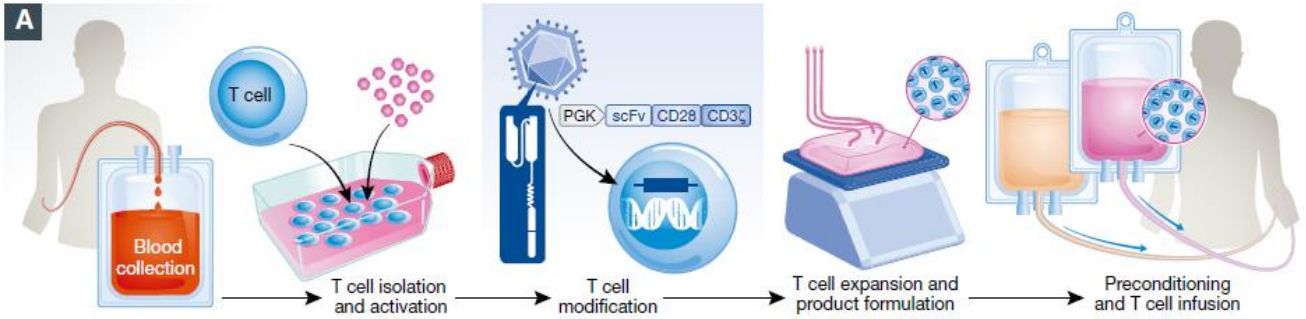
CAR T cell development – a combination of challenges

- Patient derived starting material, small scale vs large scale vs decentralized manufacturing, supply chain logistics, importation from third countries
- Patient related variables, T cell fitness, bridging therapy during manufacturing
- Single administration, re-treatment (?), duration of efficacy, specific (high grade) toxicities, insertional mutagenesis long-term?
- Specific trial design considerations
- Specialized centres, high expenditure medicines, patient access

Apheresis PBL

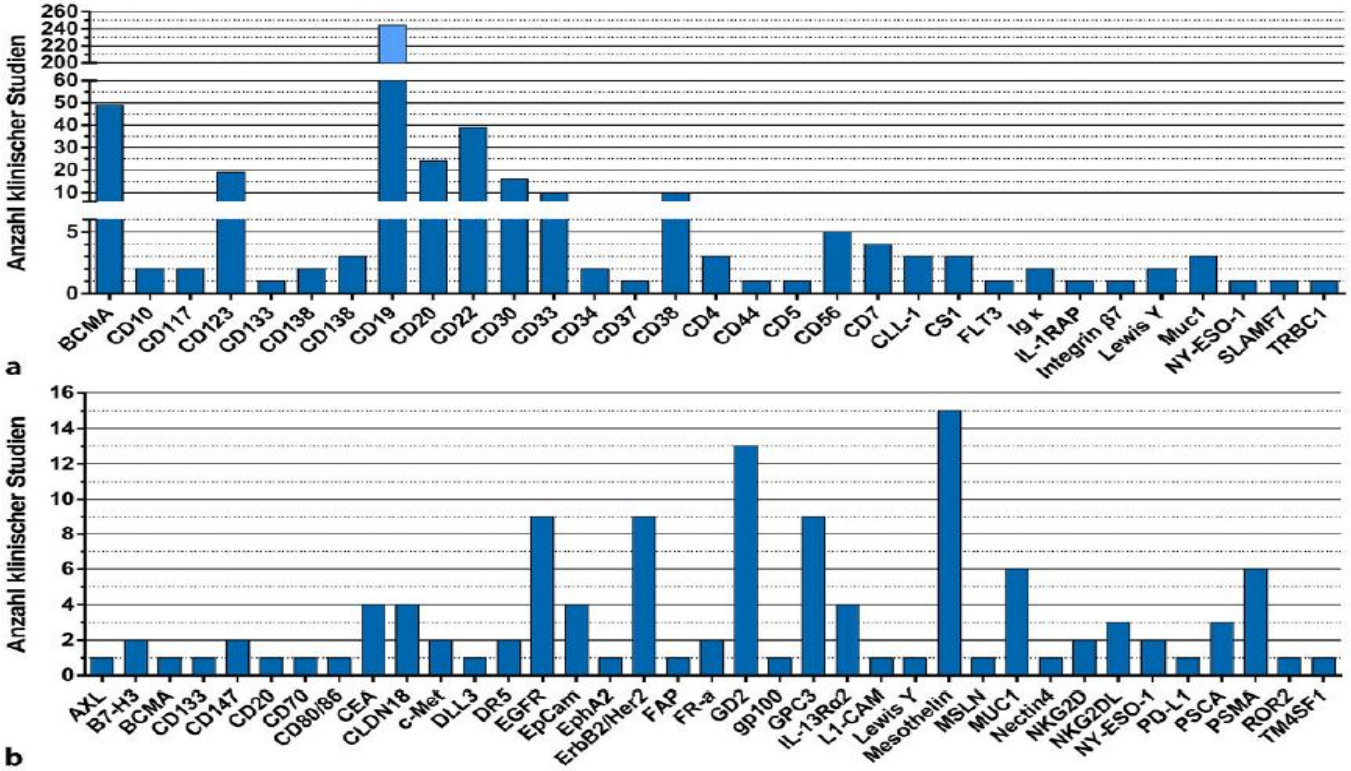
Lymphodepletion/ Conditioning

Single administration



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

Antigen targets of CAR T cells and T cell receptor modified cells in clinical development (clinicaltrials.gov)

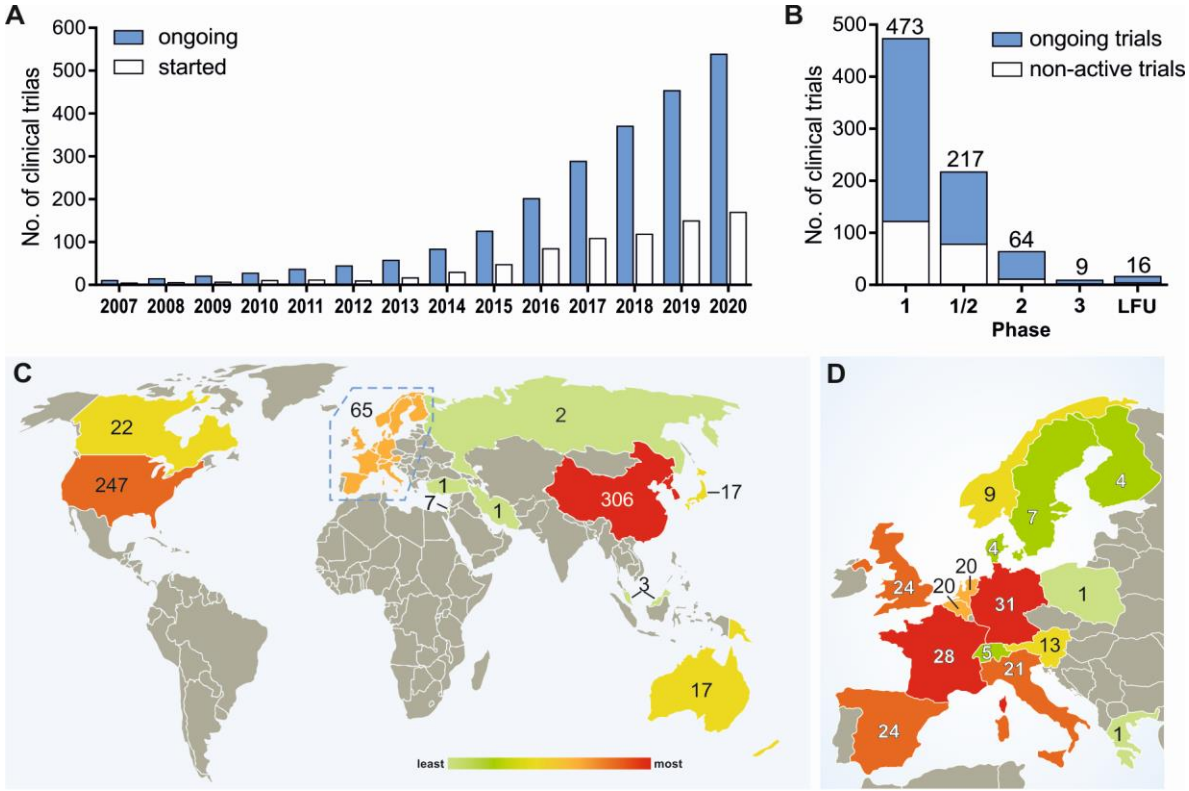


a) Target antigens of haematological malignancies

b) Target antigens of solid tumors

Source: J. Hartmann, PEI

CAR T cell clinical trials 2007 – 2021
Overview based on clinicaltrials.gov



A) Ongoing/started
B) per trial phase
C) Worldwide
D) EU

Jan. 2021
510 – China
362 – US
91 - EU

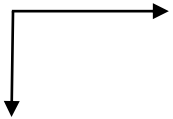
Source: J. Hartmann, PEI

The ATMP life cycle – road to patient access

Pre-authorisation | Marketing A. | Post-authorisation

- Primary evidence generation
- Single arm trials, orphan, unmet need
- Limited patient numbers
- Limited follow-up time
- Compelling efficacy data
- RW data to contextualize results
- Wait for more data and delay MA?

Benefit-risk Uncertainties



Conditions/ Obligations

- Post-authorisation evidence generation
  - Adress uncertainties
  - Follow-up safety and efficacy (ATMP regulation)
  - Comply with pharmacovigilance
  - Satisfy HTA and payers needs, outcomes-based reimbursement
- Timely patient access to ATMPs

The EU Marketing Authorisation Process
Quality, safety, efficacy -> benefit-risk assessment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Draft opinion →

→ Final opinion

→ European Commission

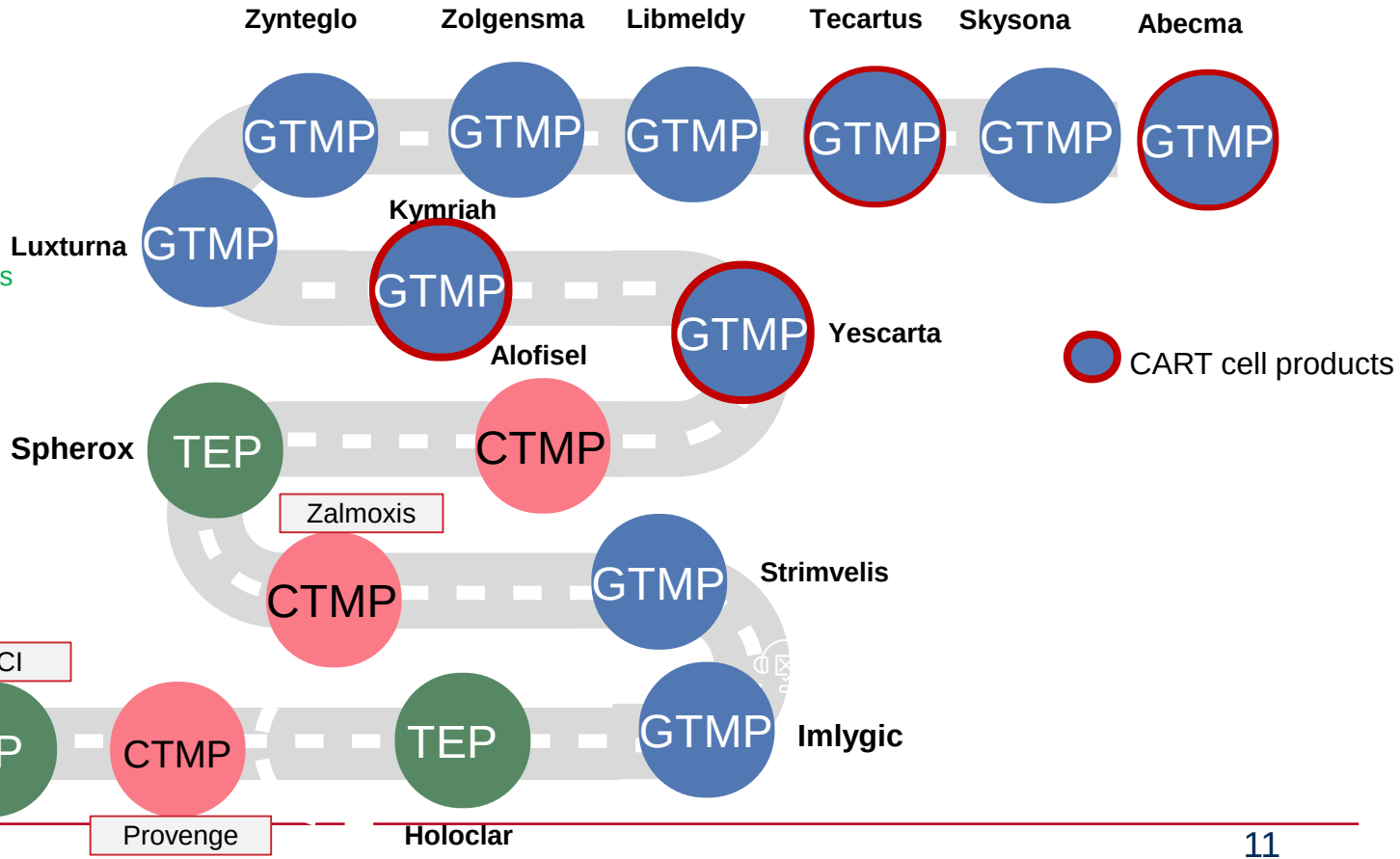
Authorisation for placing the product on the market in the European Union

* Committee for Medicinal Products for Human Use

Approved ATMPs 2009 - 2021

- Gene therapies
- Somatic cell therapies
- Tissue Engineered products

Products withdrawn



Chimeric antigen receptor (CAR) modified T cells
EU Marketing Authorisations

CART cell product	Target antigen	Indication
Idecabtagen vicleucel (Ide-cel; Abecma)	B-cell maturation antigen (BCMA)	Adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
Brexucabtagene autoleucel (Tecartus)	CD19	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.
Axicabtagene ciloleucel (Yescarta)	CD19	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.
Tisagenleucel (Kymriah)	CD19	- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy - Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

Approved ATMPs
Common characteristics and considerations

- Issues related to immature manufacturing process -> clinical data relate to representative process
- Orphan diseases, small clinical evidence base
- Administered as single administration -> patient follow-up for safety and efficacy
- Treatment in specialized hospitals –> treatment center „qualification“
- Requirement for post-authorisation safety and efficacy follow-up
  - -> patients followed-up under real world conditions
  - Supplement available data, pharmacovigilance, life cycle management, convert conditional to full marketing authorisation
- European peculiarities of reimbursement

What about patient access to CART cells?

- The average time to reimbursement of innovative treatments across EU/EEA countries differs by factor of 7 (127 – 823 days, average 504 days*)

- The CAT perspective
  - EU patients should have equal and timely access to CART cells

- The downstream decision makers perspective (Health technology assessment (HTA), pricing and reimbursement bodies)
  - CART cells are approved with too limited data
    - Small, uncontrolled single arm trials, uncertainty regarding duration of efficacy
    - Conditional Marketing authorisation – non-comprehensive data

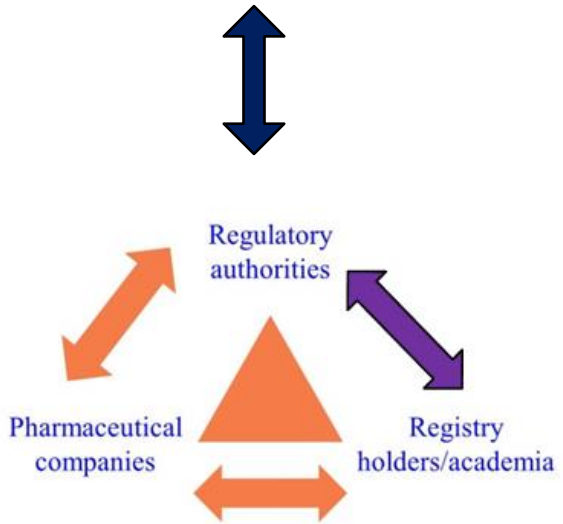
- The industry perspective
  - Centralized marketing authorisation vs disharmonized requirements by downstream decision makers

*Root cause unavailability innovative medicines EU (EFPIA), 7.2020

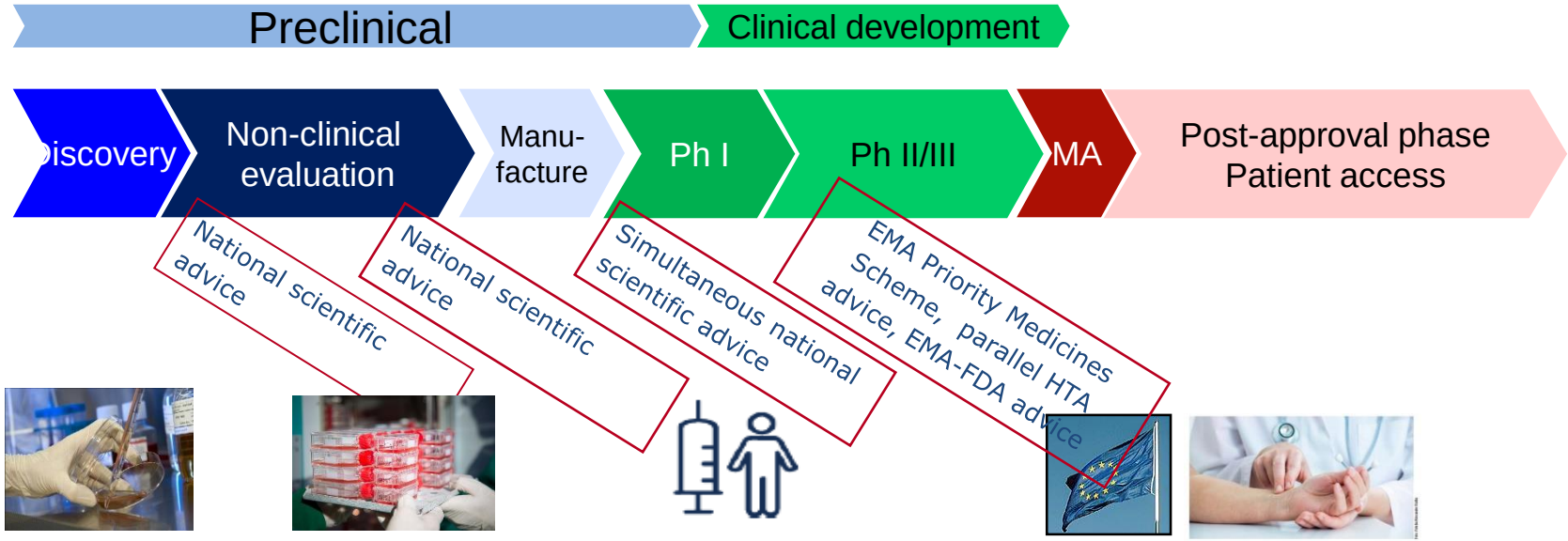
Timely and sustainable patient access to ATMPs
CAT/EMA led initiative

- Improve post-authorisation real world registry based data collection and reporting
  - Evaluate EU landscape of ATMP relevant disease registries
  - Encourage ATMP developers for early landscaping of EU disease registries
  - Advocate for acceptance of RW data collection and reporting by patients, physicians, national decision makers
- Increase exchange and collaboration with HTAs
  - EMA/HTA joint scientific advice for ATMPs (HTA regulation)
    - Pre-authorisation pivotal trial data
    - Post-authorisation RWD

HTAs and payer communities



Interaction and advice in a complex EU legal medicines frame



Summary

- Clinical trials are assessed and authorized by national competent authorities now and in the future harmonized process (EU-portal).
- The combination of different challenges in the development of gene and cell therapies for haemato-oncological malignancies calls for intense interaction with regulators on national and EMA level.
- The Committee for Advanced Therapies and the EU network have taken initiatives to close gaps and delays in post-authorization RWE generation of ATMPs.
- While the different roles and responsibilities are acknowledged the integration of regulatory, HTA and payers needs is essential to foster patient access to ATMPs
- The legal/regulatory framework needs to adapt to innovation → Pharmaceutical Strategy discussions are ongoing, update expected end of 2022.

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Thank you for your attention

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Photo: Rob Acket

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