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# Clinical and regulatory challenges in the development of CAR-modified and TCR- modified T cells in EU

EMA/CAT Workshop  
16.11.2016

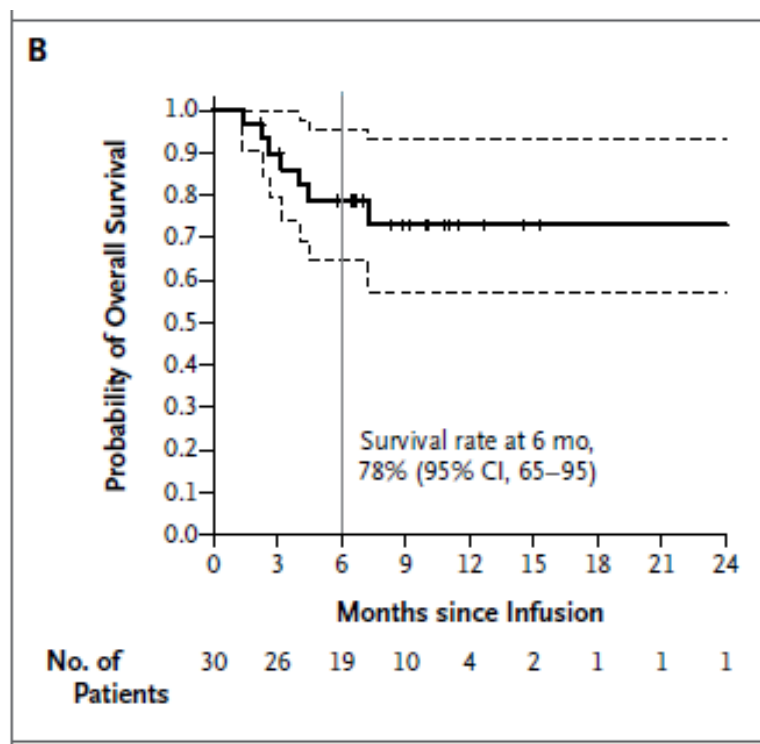
Vice Chair  
Committee for Advanced Therapies  
European Medicines Agency  
  
Paul-Ehrlich Institute, Langen

Martina Schüssler-Lenz



# CD19 CAR-T cells

## Sustained remissions in refractory leukemia



Maude SL et al. N Engl J Med 2014; 371:1507-17



# CD19 CAR-T cells

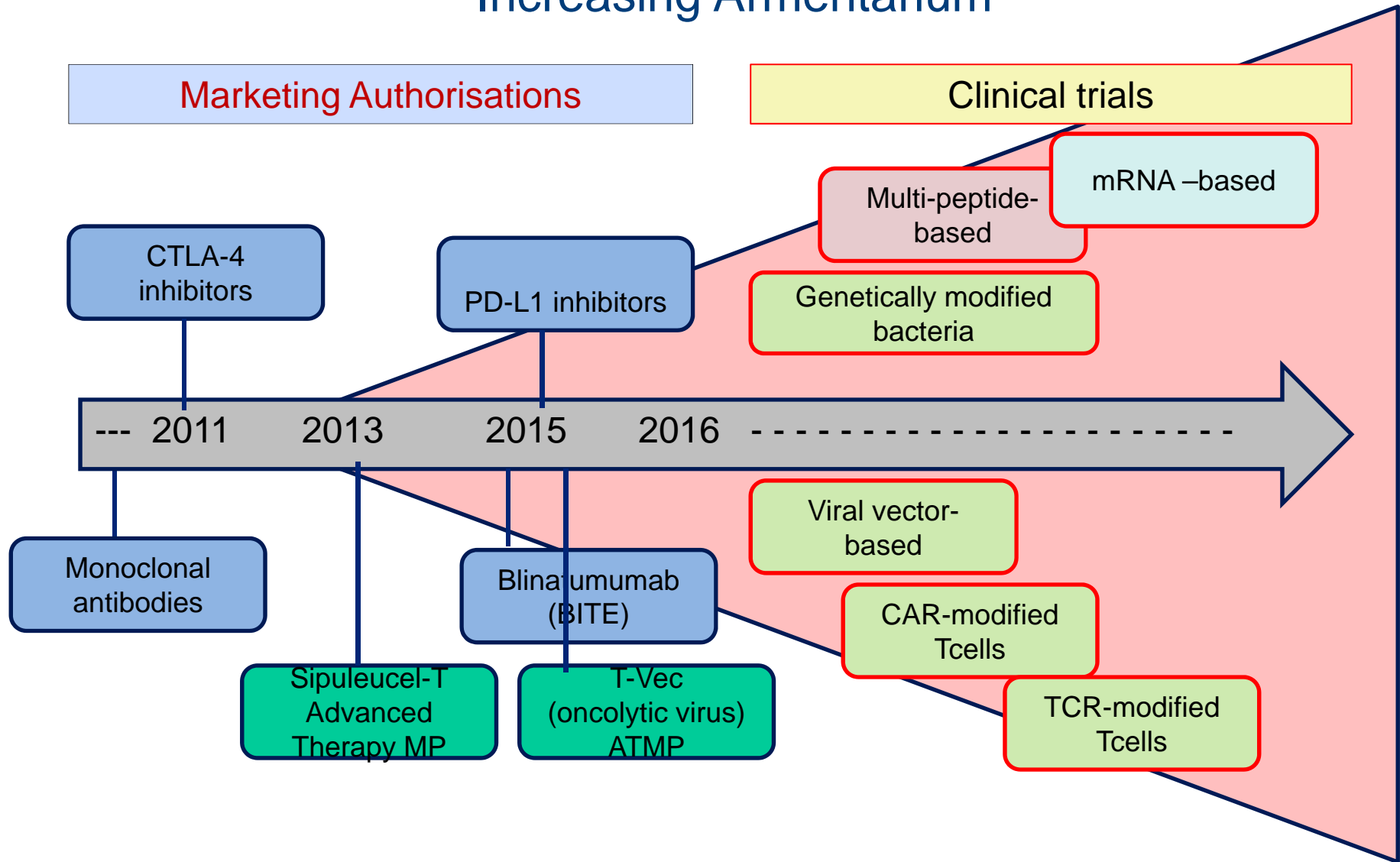
## Fatal events



<http://labiotech.eu/car-t-cd19-trial-death-jcar015/>

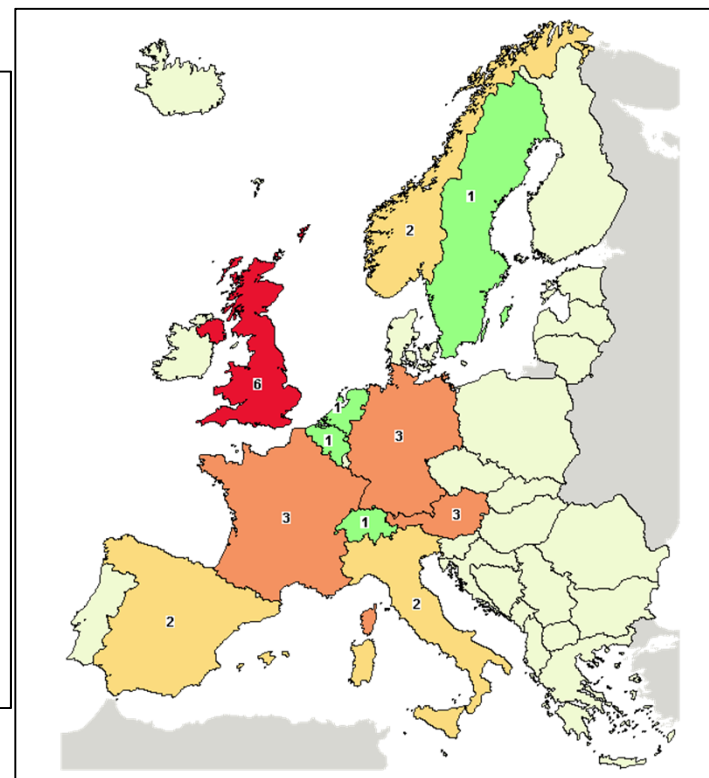
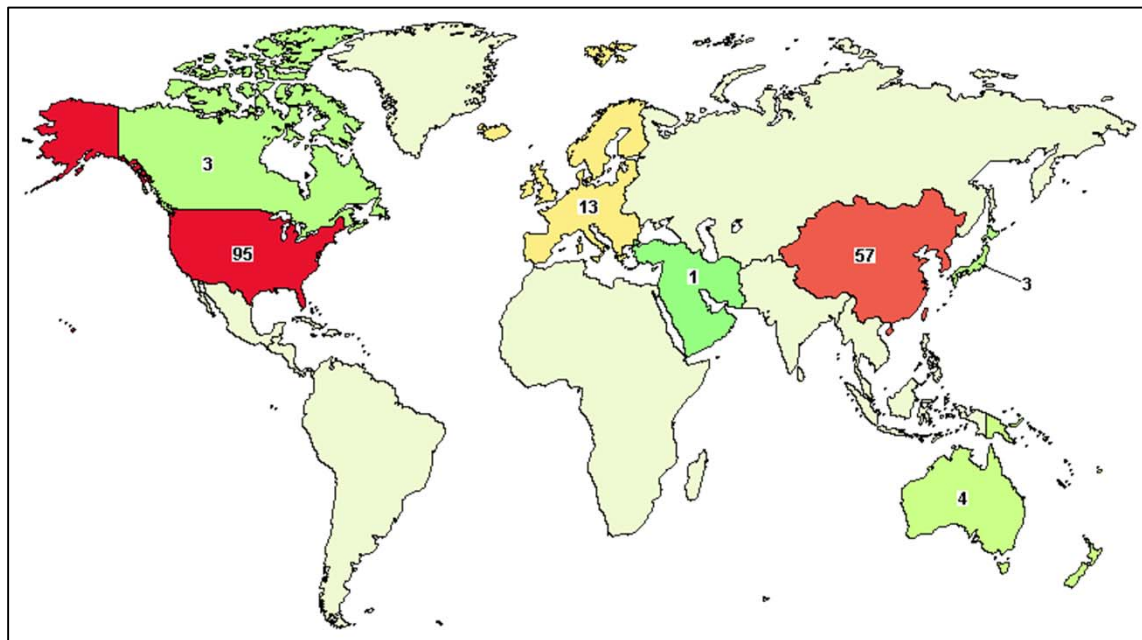


# Cancer Immunotherapies Increasing Armentarium





## Clinical Trials with CAR-T cells



188 ongoing trials world wide (10/2016)

121 for lymphoma, leukemia

60 for solid tumors

9 Long-term follow-up studies

13 trials in Europe

Courtesy of Jessica Hartmann



# CAR/TCR-modified T cells

## Activities in European Union - Examples

Targets	Indications	Pre-marketing Procedures	Developers
<ul style="list-style-type: none"><li>■ CAR-T<ul style="list-style-type: none"><li>■ CD19</li><li>■ CD20</li><li>■ CD123</li><li>■ ErbB2/HER2</li></ul></li><li>■ TCR-T<ul style="list-style-type: none"><li>■ Ny-ESO-1</li><li>■ Mage-A-10</li><li>■ Mage-A-1</li><li>■ WT1</li></ul></li></ul>	<ul style="list-style-type: none"><li>Leukemia</li><li>Lymphoma</li><li>Solid tumors</li></ul>	<ul style="list-style-type: none"><li>National Scientific Advice</li><li>Clinical Trial Authorisation</li><li>EMA Scientific Advice (O. Tenhunen)</li><li>PRIME Scheme</li></ul>	<ul style="list-style-type: none"><li>Biotech Companies US-based (S. Frankel)</li><li>Pharmaceutical Companies</li><li>Academic Developers EU-based (G. Willimsky)</li></ul>



# Regulatory Guidance Clinical

- Adoptive immunotherapy
- CAR/TCR –modified T-cells **not covered**
- EMA/CAT Guidance for Advanced Therapies
- EMA/CHMP Anticancer Guideline 205/95/Rev5 (2016)
  - Rev 4: section 6.3.2. Immune modulating compounds
- Clinical Practice Guidelines
  - Member States (national), ESMO, ASCO etc



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### Multidisciplinary: Cell therapy and tissue engineering

This page lists the scientific guidance documents on **cell therapy and tissue engineering**.

If you have comments on a document which is open for consultation, please use the form for submission of comments on scientific guidelines.

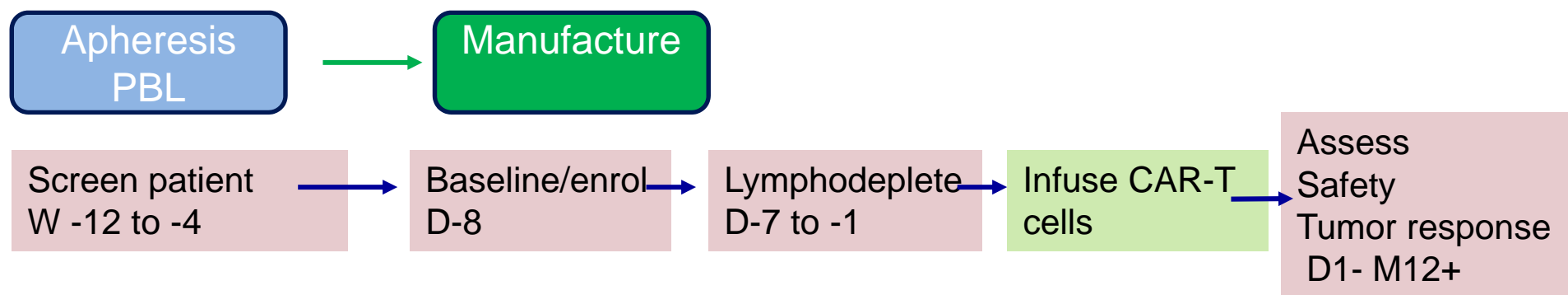
Topic	Documents	Reference number	Publication date	Effective date	Remarks
Clinical aspects related to tissue engineered products	Draft reflection paper	CAT/CPWP/573420/2009	Released for consultation Apr 2012	Deadline for comments 31 Jul 2012	
Risk-based approach according to Annex L part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products	Draft guideline Concept paper	CAT/CPWP/066637/2011	Released for consultation Jan 2012	Deadline for comments 30 Jun 2012	
CHMP/CAT position statement on Creutzfeldt-Jakob disease and advanced therapy	Adopted guideline Overview of comments Draft guideline	CHMP/CAT/0697/09/2010	June 2011	June 2011	
Reflection paper on stem cell-based medicinal products	Overview of comments Adopted reflection paper	CAT/7114/09	February 2011	January 2011	
Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee	Overview of comments Draft reflection paper Adopted reflection paper	CAT/CPWP/56618/2009	May 2010	April 2010	

<http://www.ema.europa.eu/ema/index>



# Clinical Trial Features Commonalities

## CD19-targeting CAR T cells in B-ALL





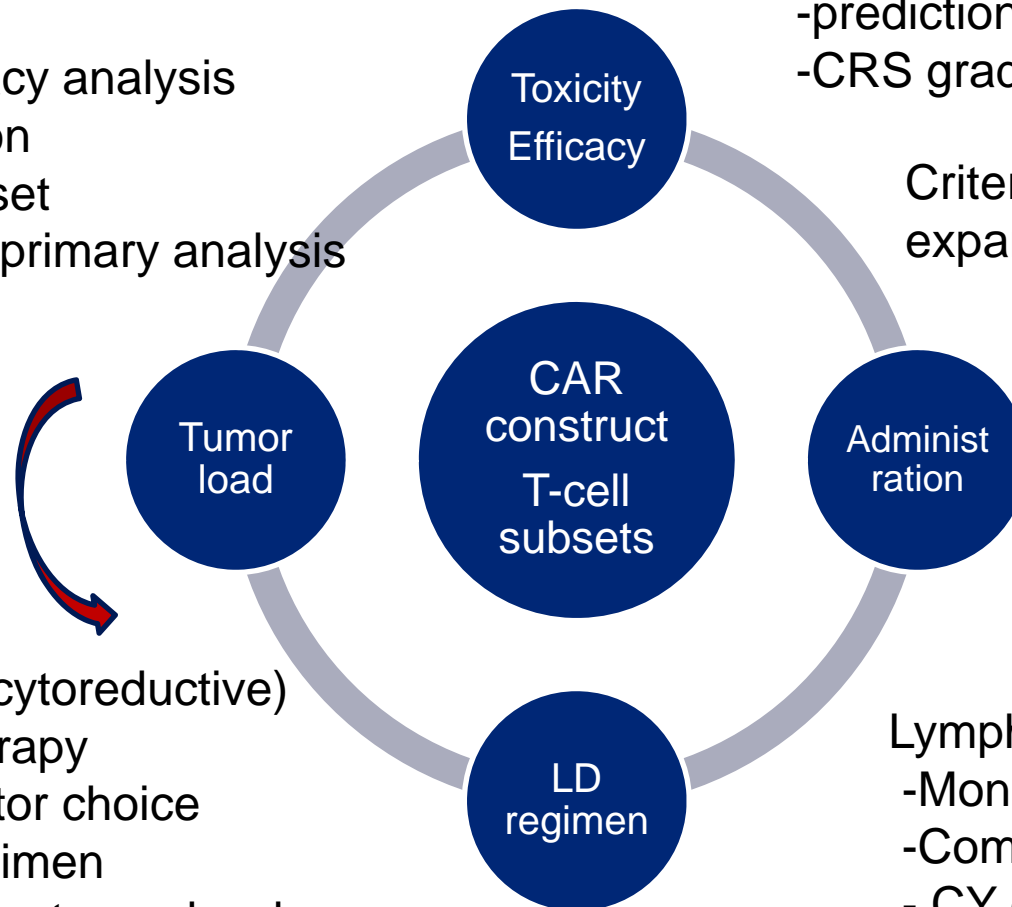


# Clinical Trial Features Variations

## CD19-targeting CAR T cells in B-ALL

### Primary efficacy analysis

- ITT population
- full analysis set
- time point of primary analysis



### Toxicity management

- prediction
- CRS grading, tx algorithm

Criteria driving in vivo expansion and persistence

### Dosing and schedule

- per kg vs flat
- single vs repeat
- based on tumor load

### Bridging (cytoreductive) chemotherapy

- Investigator choice
- Fixed regimen
- high vs low tumor burden

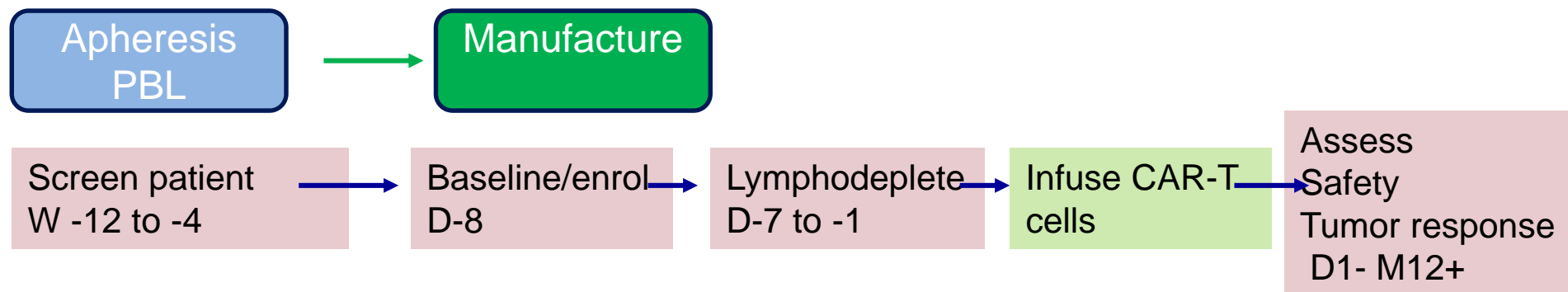
### Lymphodepleting chemoth.

- Monotherapy CY
- Combination CY/F3
- CY dosing range 2-8 gram

# Clinical Trial Features Variations Primary Efficacy Analysis



## CD19-targeting CAR T cells in B-ALL



Enrolled and leukapheresis

10-20% of patients lost

Received CAR T cells and prior lymphodepletion

„Enrolled set“

„Full analysis set FAS“

„MITT: treated AND evidence of leukemia“

„MITT: treated with >50% of dose“

„FAS: treated“

„Per-protocol set: treated and compliant“



# PRIME Scheme Rapporteur`s Experience

Kick-off meeting - starting point to discuss regulatory strategy

## Regulatory

- Milestones leading to accelerated review of marketing authorisation application
- Interaction with Pediatric Committee, status of pediatric investigation plan (PIP)
- Interaction with Orphan Committee, [orphan similarity](#)

Quality, non-clinical, clinical issues

## Postmarketing

- Risk management plan
- Registries



## Orphan Similarity

- Article 8 of Regulation (EC) No. 141/2000, where a marketing authorisation in respect of an orphan medicinal product is granted in all Member States, “the Community and the Member States **shall not, for a period of 10 years, accept another application for a marketing authorisation**, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, **for the same therapeutic indication, in respect of a similar medicinal product**”.
- Same Mechanism-of -Action and same indication
  - claim for non-similarity based on ‘principle molecular structural features (PMSF) “
- **Relevant for CD19 targeting CAR T cells in indication B-ALL**



# Challenges

## View of a Developer/applicant

- Understanding the EU regulatory system
- Transferring manufacturing to EU facilities – comparability
- Dealing with different players/authorities in regulatory system
  - GMP certificate
  - Clinical trial authorisation
  - Marketing authorisation



# Challenges

## Clinical Trial Authorisation – Benefit-Risk Assessment

- Variability
  - product, patients, trial features
- Low predictability of toxicity
  - Onset
  - Severity
  - Course – duration of patient hospitalisation
  - Link to efficacy (double edged sword)
- Qualification of EU trial centres
  - Transplant centres
  - Training of involved personnel

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## Conclusion

- Differences between products require case-by-case decisions
- Iterative discussions and exchange of information is needed between scientists, physicians, developers, regulators
- Unmet medical need - regulatory path requires tailored approach
- Best way forward in the EU regulatory system to enable and foster patient access?



Thank you

