Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

www.pei.de

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

EMA/CAT Workshop

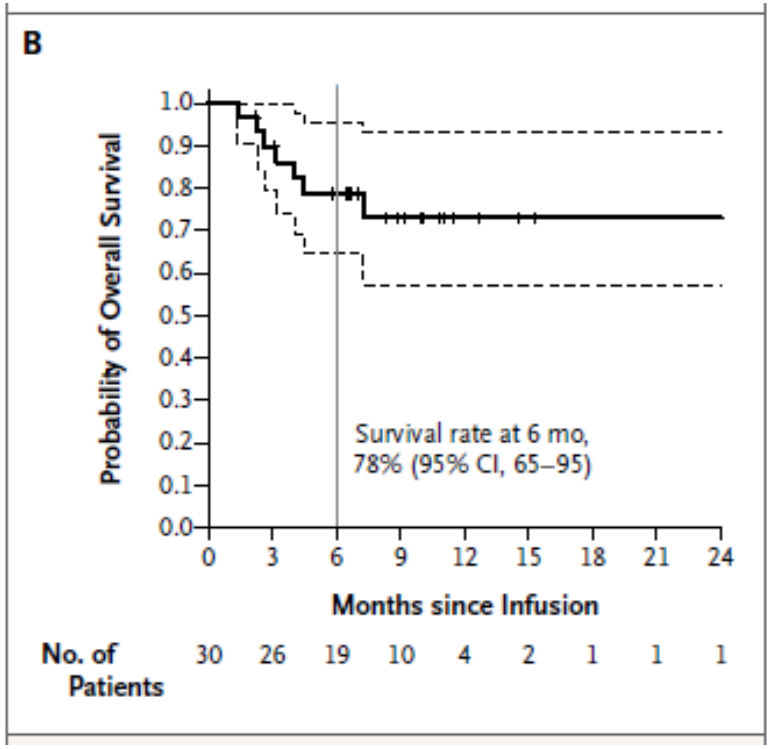
16.11.2016

Martina Schüssler-Lenz

Vice Chair
Committee for Advanced Therapies
European Medicines Agency

Paul-Ehrlich Institute, Langen

CD19 CAR-T cells
Sustained remissions in refractory leukemia

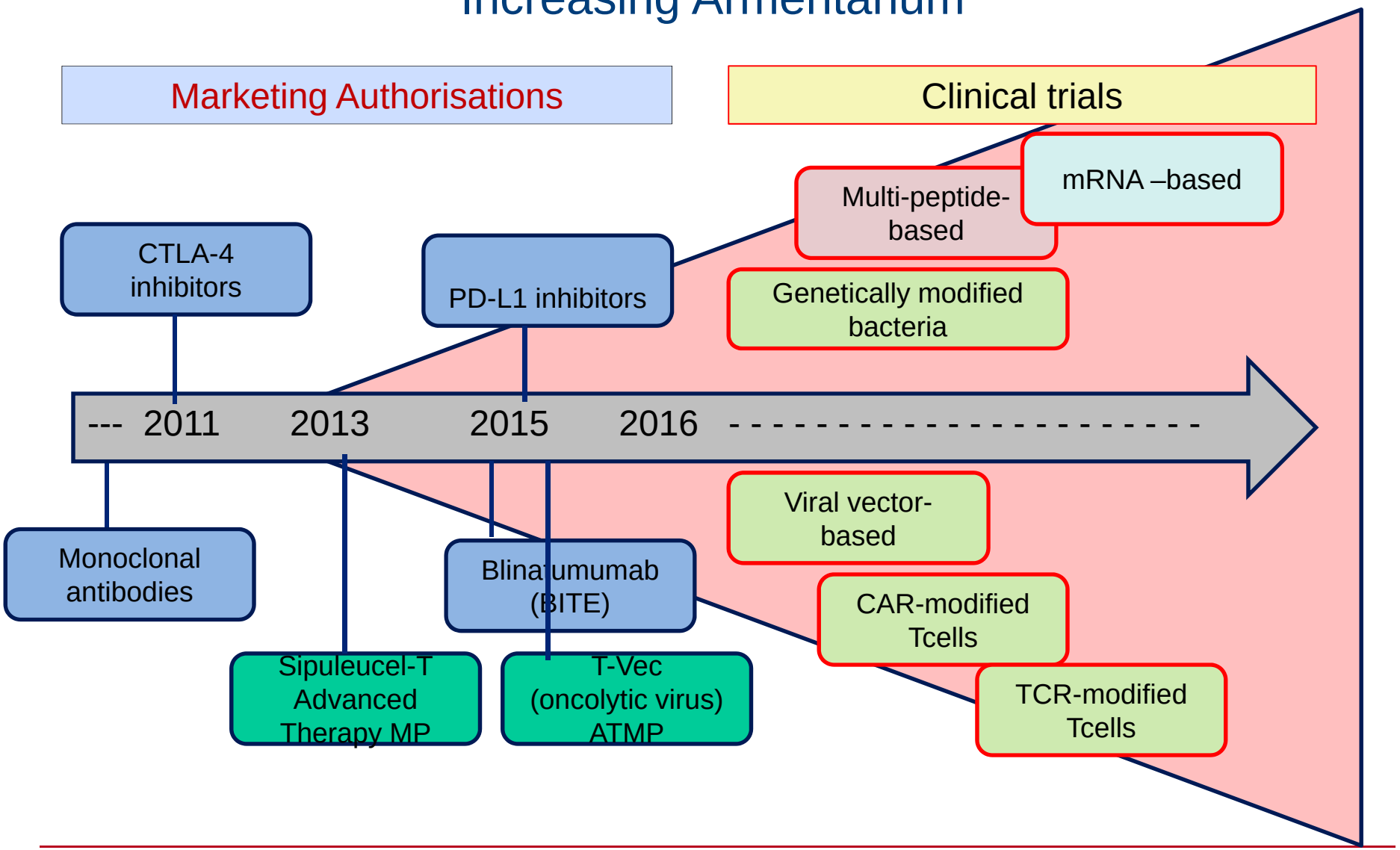


Maude SL et al. N Engl J Med 2014; 371:1507-17

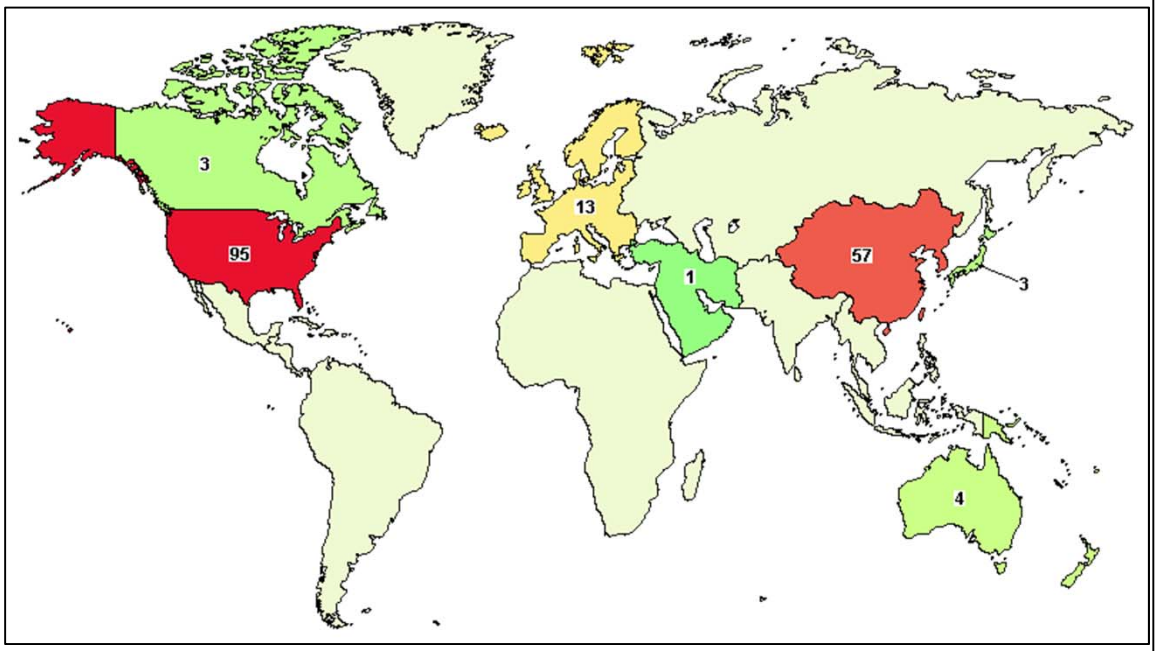
CD19 CAR-T cells
Fatal events

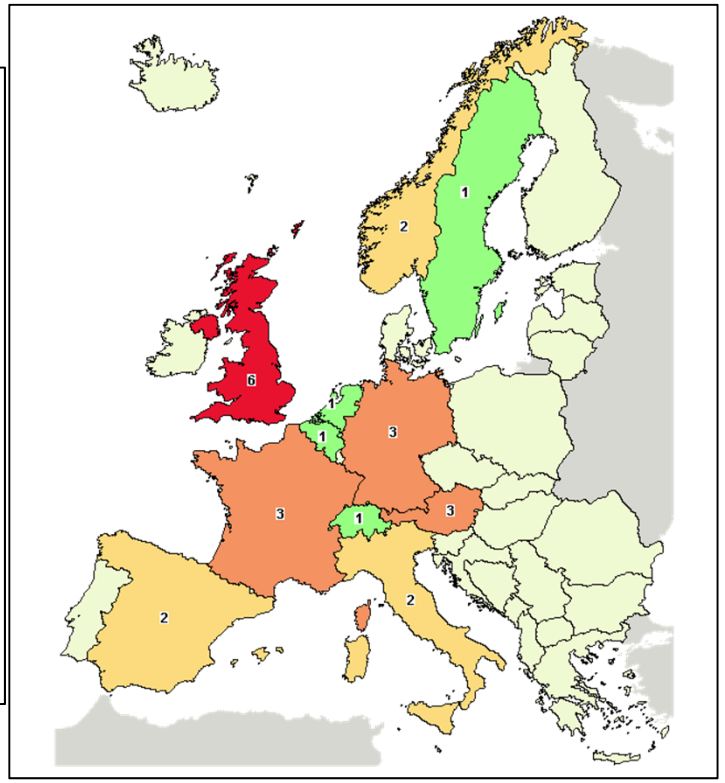
http://labiotech.eu/car-t-cd19-trial-death-jcar015/

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
▪ CAR-T ▪ CD19 ▪ CD20 ▪ CD123 ▪ ErbB2/HER2 ▪ TCR-T ▪ Ny-ESO-1 ▪ Mage-A-10 ▪ Mage-A-1 ▪ WT1	Leukemia Lymphoma Solid tumors	National Scientific Advice Clinical Trial Authorisation EMA Scientific Advice (O. Tenhunen) PRIME Scheme	Biotech Companies US-based (S. Frankel) Pharmaceutical Companies Academic Developers EU-based (G. Willimsky)

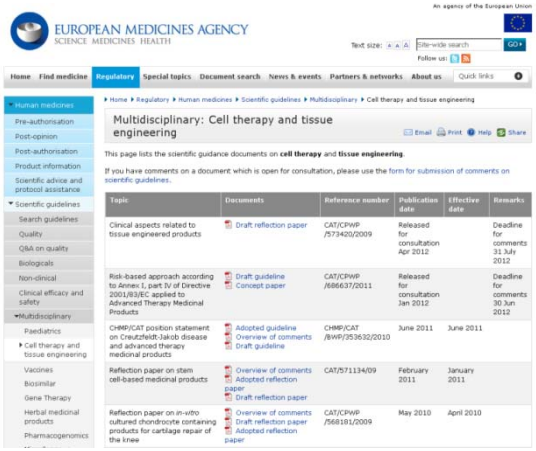
Regulatory Guidance
Clinical

- 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

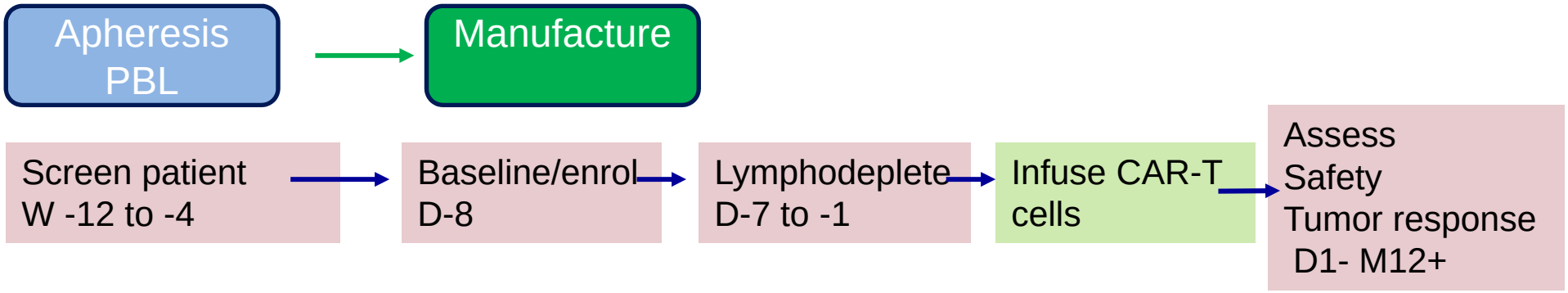
- Clinical Practice Guidelines
  - Member States (national), ESMO, ASCO etc



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

Clinical Trial Features
Commonalities

CD19-targeting CAR T cells in B-ALL



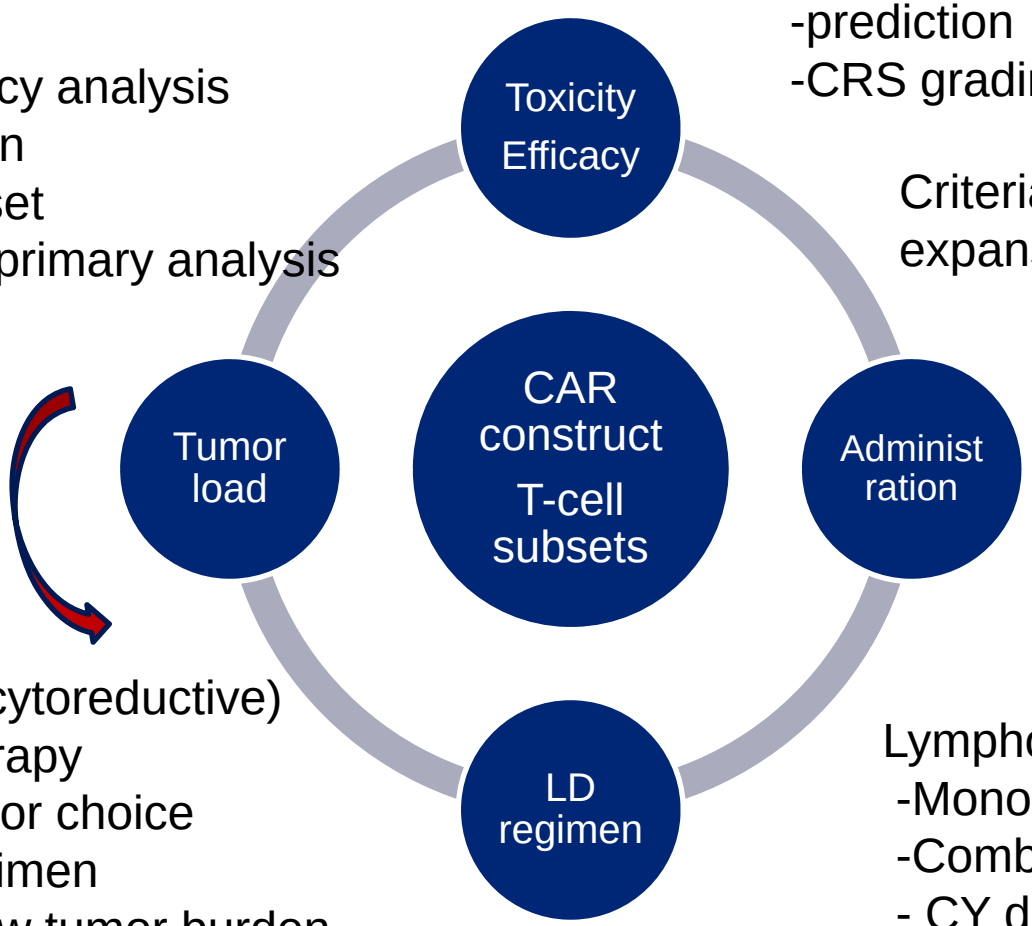
Clinical Trial Features
Variations

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



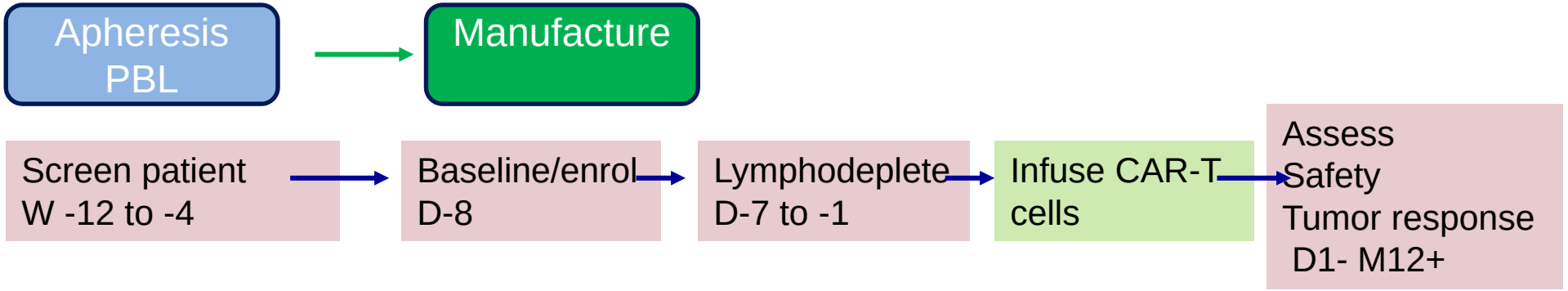
Dosing and schedule
-per kg vs flat
-single vs repeat
-based on tumor load

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 Members 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 personel

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

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