Challenges with CAR T Cells
A European Regulatory Perspective

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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 Paul-Ehrlich-Institut or the European Medicines Agency.
Innovative Approaches in Cell Therapies

Product-specific attributes
Source - Autologous vs Allogeneic
Genetic modification - viral vectors vs genome editing
Target antigens
Co-stimulatory domains

Kershaw et al. 2014
A European Regulatory Perspective

- Update – tasks and current activities at the Committee for Advanced Therapies/European Medicines Agency
- Challenges with CAR T cells
- Pre-marketing considerations
- Post-marketing considerations

Gene therapy medicinal product GTMP

Somatic cell therapy

Tissue engineered product

Genetically modified cells

Recombinant nucleic acid

Pharmaco-immunological...

Regeneration, repair....

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The ATMP Regulation (EC) No 1394/2007

Key elements

- no marketing without prior approval
- demonstration of quality, safety and efficacy
- mandatory centralised procedure
- scientific assessment by European Medicines Agency (EMA) and committees
- risk management & long term traceability
- creation of an expert committee at EMA: Committee for Advanced Therapies (CAT)
Committee for Advanced Therapies (CAT)

Standing WPs

- BWP
- SAWP
- PCWP
- QWP
- HCPWP
- SWP

Temporary WPs

- VWP
- BSWP
- BPWP

CHMP

CAT

2 Representatives of Clinicians + alternates

1 Nor + 1 Ice + alternates

Experts from national CA + alternates

5 „double members“ CHMP and CAT

2 Representatives of patient organisations + alternates

200 Representatives of Clinicians + alternates

1 Nor + 1 Ice + alternates

Experts from national CA + alternates

5 „double members“ CHMP and CAT

2 Representatives of patient organisations + alternates

200
Assessment of Marketing Authorisation (MA) Applications
Interaction CAT-CHMP-PRAC

Rapporteur from CAT
+ corresponding CHMP member (CHMP Coordinator)
+ PRAC Co-Rapporteur including Quality/Safety/Efficacy/PhV/ERA experts

Co-Rapporteur from CAT
+ corresponding CHMP member (CHMP Coordinator)
including Quality/Safety/Efficacy/PhV/ERA experts

PRAC: Pharmacovigilance Risk Assessment Committee

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Committee for Advanced Therapies (CAT) - Tasks

- Lead responsibility for assessment of (centralized) marketing authorisation applications of ATMPs
  - CAT prepares draft opinion on each ATMP, CHMP adopts final opinion

- Scientific recommendation of classification of ATMP
  - Is a product an ATMP?
  - → Scientific recommendation from CAT

- „Certification procedure“
  - Quality/Non-Clinical review (for ATMP only, for Small and medium sized enterprises (SME) only)

- Scientific assistance
  - Development of guidelines
    - Scientific Advice of ATMP (via SAWP)
    - Pediatric investigation plan (PIP) of ATMPs (via PDCO)
Advanced Therapies - Marketing Authorisations in Oncology

- Autologous peripheral blood mononuclear cells, activated, metastatic prostate cancer
  - Provenge®
- HSV1 vector for oncolytic immunotherapy, injectable melanoma.
  - Imlygic®

Marketing authorisations under evaluation

- CD19-targeting CAR T cells – lymphoma, leukemia - two products
- Genetically modified bacteria – solid tumors
are gene therapy medicinal products (Advanced Therapies)

have complex and variable structural features

- different co-stimulatory signaling domains

- different extracellular antigen/ligand binding domains
CAR T Cells – Specificities

- Represent a specific form of „adoptive immunotherapy“

1. Apheresis
   PBL

2. Lymphodepletion/Conditioning

3. Infusion

CAR T Cells – Specificities

- are characterised by a
  - specific mode of action
  - specific kinetics (living drug)
  - specific remission kinetics
  - specific toxicity

Maude SL et al, 2014
CAR T Cells – Specificities
Impact on Trial Design

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

Lymphodepleting chemoth.
-Monotherapy CY
-Combination CY/F3
-CY dosing range 2-8 gram

Bridging (cytoreductive) chemotherapy
-Investigator choice
-Fixed regimen
-high vs low tumor burden

Toxicity Efficacy
CAR construct T-cell subsets
Tumor load
Administ ration
LD regimen
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CAR T Cells – Specificities
Impact on Trial Design/Risk Management

- Neurological events
- Risk of leukapheresis
- Risk of secondary malignancy?
- Risks related to conditioning regimen
- Risk of infections
- Risks related to the mechanism of action (e.g. Cytokine release syndrome)
- Hypersensitivity
- Prolonged cytopenias
- Hypogammaglobulinemia

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Towards Marketing Authorisation

- Generating Quality, Safety, Efficacy data - defining the safety and efficacy of the product
- A MA is granted based on a positive Benefit-Risk balance

Product development → Marketing Authorisation (MA)
Towards Marketing Authorisation
Perspectives

- CAR T cell developer
  - Manufacturing, comparability (US versus EU manufacturing)
  - Non-clinical aspects
  - Clinical aspects
    - Appropriate EU study centers
    - Study population - variety of CD19+ B cell malignancies, refractory versus early stage disease
    - Dose and schedule
    - Trial design: Single arm vs controlled trial, trial endpoints, duration of follow-up, comparator (authorised CAR T cell product ?)

- Regulator
  - Benefit-risk assessment - limited patients numbers, single arm trials, substantial toxicities, limited follow-up
  - Resulting uncertainties
CAR T cells - Long-term follow-up in B-ALL

B  Event-free and Overall Survival

Event-free survival

Overall survival

No. of Patients  | No. of Events  | Median Survival | Rate at 6 Mo % (95% CI)
---|---|---|---
Overall Survival  | 75  | 19  | 19.1 | 90 (81–95)
Event-free Survival  | 75  | 27  | not reached | 73 (60–82)

No. at Risk

UPenn
Maude SL et al.


MSKCC
Park JH et al.

A  Event-free Survival, According to Disease Burden

Probability of Event-free Survival

No. at Risk
Low burden  | 75  | 19  | 19.1 | 90 (81–95)
High burden  | 75  | 27  | not reached | 73 (60–82)

No. at Risk
Low burden  | 20  | 10  | 7  | 5  | 4  | 2  | 1
High burden  | 21  | 13  | 10  | 5  | 4  | 2  | 1

Probability of Survival
Marketing Authorisations - Tools

Full MAA

- Annex II:
  - PAES delegated act:
    - (a) surrogate endpoints
    - (b) combination
    - (c) sub populations
    - (d) long term efficacy
    - (e) real –life conditions (vaccines)
    - (f) change of standard of care
    - (g) new scientific factors

PASS

Exceptional circumstances

- Specific obligations
  - Comprehensive data cannot be provided based on rarity
  - Based on scientific grounds
  - Ethics
  - B/R positive
  - Comprehensive data will never be provided

Annual reassessment

Conditional MA

- Specific Obligations:
  - Seriously debilitating / life threatening diseases
  - Emergency
  - Orphans
  - B/R positive;
  - Comprehensive data will be provided;
  - Unmet medical need
  - Public health benefit outweighs the risks

Need for annual renewal

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Beyond Marketing Authorisation

- A Marketing Authorisation (MA) is granted based on a positive Benefit-Risk balance.

- Risks identified during the evaluation of a MA should be minimised and/or further characterised (Post-Authorisation Safety Study (PASS)).

- Efficacy should be followed-up.

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Efficacy and safety follow-up studies - specific framework according to Art 14 of ATMP Regulation

Methodology to follow when designing post-authorisation studies:

- Define precisely the study objective(s)
- Consider the appropriate study design and the data source:
  - Extension phase of pre-authorisation trials
  - Clinical trial (randomised controlled trial?)
  - Observational studies (cohort study, case control study, use of external controls, using health care database…)
  - Registry
Registry – Benefits versus Obstacles

- An organised system that uses observational methods to collect uniform data ….
- Represents one out of several options

Potential benefits
- Up and running
- EU coverage
- Data on course of disease
- Source for Real World Evidence
- Not restricted to one product
- Comparative analysis
- (might be linked to reimbursement decisions)

Potential obstacles
- Suitability for new product class
- Adaptation/implemention of core data elements
- Quality and monitoring
- Cost
- Collaboration between MAH/MAA
- Patient consent, confidentiality
- Data access and use
- Patient-reported outcome / interventional study (?)
What else is keeping us busy in the CAT

- Guideline for safety and efficacy follow-up, risk management of ATMPs, revised draft published on 1.2.2018 (EMEA/149995/2008rev.1) for 3 months public consultation

- Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. Includes CAR T cell specific aspects – currently updated

- Genome editing derived ATMPs – scientific and regulatory aspects

- Genetically modified organisms (GMO) regulation – towards EU harmonisation

- Substantial number of advanced therapies in the PRIME scheme
  - Addressing unmet medical need
  - Therapeutic innovation
  - Aiming for accelerated assessment of marketing authorisation