OVERVIEW ON CAR T DEVELOPMENT AND REGULATORY ASPECTS

Maria Cristina Galli

REGULATORY WORKSHOP ON THE DEVELOPMENT OF CAR-T CELLS
Jointly organized by the H2020 projects
EURE-CART (European Endeavour for Chimeric Antigen Receptor Therapies) **&**
CARAMBA (SLAMF7-CAR T for Immunotherapy of Multiple Myeloma)
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CAR T SUCCESSFUL DEVELOPMENT

Efficient translation from research to medicinal product
Efficient transition through clinical development
Both essential for giving effective treatment options to patients

clinical development under EU Dir 2001/20

→ approval at national level

(centralised approval: EU Reg 536/2014 ???)

marketing authorization

→ at EMA level

CHALLENGES FOR TRANSLATION

Common to both developers and regulators:

how to determine if data available are sufficient to allow progression from non clinical studies to clinical trial

a potential risk-potential benefit assessment should be done

REGULATORY TOOLS

Regulatory requirements are being adapted to new landscape
→early and continuous interaction with the regulatory bodies welcomed and expected

Interaction mechanisms offered to developers:

- Scientific advice (EMA and national)
- EMA PRIME scheme →not eligible for first in human studies

Clinical trial approval step:

- Voluntary Harmonisation Procedure at CTFG

→not eligible for GMO-based ATMP (i.e. CAR T)

TO REDUCE RISK OF FAILURE: KNOW YOUR PRODUCT!

From the very beginning of development have clear in mind ***what the clinical product will be***

→design, develop and validate an appropriate production process

During development, any change in vector and /or production process may impact on the comparability of product across studies

→carefully plan changes

TRANSGENE CHANGE →NEW PRODUCT

TO REDUCE RISK OF FAILURE: KNOW YOUR DISEASE!

Need to have

- well designed clinical endpoints
- validated appropriate biomarkers
- appropriate analysis of clinical data

in order to obtain robust clinical data

MAIN RISKS FOR GTMP

Germ line transduction: **unacceptable** (dir. 2001/20-EU Reg.536/2014) → germ line manipulation e.g. by means of CRISPR technology is not acceptable in EU

Insertional mutagenesis→ oncogenesis

Replicating viral vector →target cell lysis / dissemination / shedding (ERA)

Oncolytic viruses→ ectopic replication

Transgene and/or vector immunogenicity→ impairment of clinical efficacy/immune-toxicity

Transgene ectopic/disregulated expression→ toxicity/impairment of clinical efficacy

GERM LINE TRANSDUCTION

EU REG. 536/2014 on clinical trials, art. 90

EU Directive 2001/20 on clinical trials, art 9 point 6

No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity.

MAIN RISKS FOR CTMP/TEP

Infections (viruses, TSE)
Tumorigenicity
Failure to differentiate in vivo as expected for therapeutic effect
Distribution to unwanted sites
Unwanted/ectopic proliferation
Unwanted cell elimination e.g. because of immune/inflammatory reactions

CAR T QUALITY

It depends also **on production process**

►quality/safety of starting/ raw materials is critical (plasmids, viruses, packaging cell line, bacterial cells, reagents, etc.)

► control of the production process: validation, ipc, stability

Characterisation and QC: appropriate mixture of molecular and biological testing methods

EUROPEAN PHARMACOPEA TEXTS RELEVANT FOR CART CELLS PRODUCTS

5.14 5.14 Gene transfer medicinal products for human use

►currently under revision

5.2.12. Raw materials for the production of cell-based and gene therapy medicinal products

QC FOR CAR T CELLS

Minimum program for first-in-human use:

Viability

Identity: immune-phenotype

Purity/safety: microbiological control, endotoxins, replication competent vector (RCV); process derived impurities

Activity: CART (and other transgenes, e.g. suicide genes) expression and biological activity; percentage of transduced cells; vector copy number

Quantity: cell concentration; percentage of transduced cells

Stability studies:

to include trasportation of starting material and final product

BIOACTIVITY/POTENCY

at least gene expression
quantitative potency assay reflective of bioactivity *in vivo*

ICH Q6B Specifications

Biological activity:

- product specific ability or capacity to achieve a defined biological effect.

Potency:

- biological activity measure using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product, which is linked to the relevant biological properties

REGULATORY EXPECTATIONS

1) An appropriately validated potency assay should be based on a defined biological effect **as close as possible to the mechanism(s) of action/clinical response**. Surrogates for potency may be developed to demonstrate biological activity

2) In principle, the results of potency assay should provide assurance that the active ingredient amount is sufficient to induce a meaningful response and that it is consistent from batch to batch. As such, **the potency assay should be able to detect clinically meaningful changes in the amount** of active ingredient in a human dose of a product.

►**potency is also important to prove stability and consistency during process changes**

CAR T POTENCY ISSUES

Cytotoxic activity against patient's tumour cells

- ❖ linked to MoA, practically very difficult to carry out

Cytotoxic activity against tumour cell lines

- ❖ still a direct measure, but not easily adapted to GMP conditions

Expression of cytokines produced as a consequence of CAR engagement to target cell

- ❖ indirect measure

Expression of CAR

- ❖ gene expression

NON CLINICAL DATA FOR GTMP

Proof of concept
Gene expression persistence versus clinical regimen and doses
Expression restricted to target cells or ectopical
Biological activity on target/off target
Dose- response
Bio-distribution (including gonads)
Risk of vertical transmission (to germline)
Toxicology (single and/or repeated doses)
Insertional mutagenesis, carcinogenicity, immuno-toxicology

NON CLINICAL DATA FOR CTMP/TE

Proof of concept
Persistence
Dose- response
Bio-distribution and microenvironment (*niche*)
In vivo differentiation and tissue formation
In vivo proliferation
Tumorigenicity
Immune rejection
Potential inflammatory/immune response

ISSUES FOR CART PRECLINICAL STUDIES

Animal model selection

►no real recommendation in guidelines on what species to choose

Homologous models: low/no relevance to clinical situation (product/disease)

→immune-deficient mice

CAR T-RELATED TOXICITIES

Cross-reactivity (on target off tumor)

- (animal) model

Cytokine release syndrome ►clinical level

Neurotoxicity ►clinical level

TAKE HOME MESSAGE

Improve product characterisation

→in order to design appropriate/meaningful testing methods, in particular for potency, to be correlated to clinical endpoints

Improve knowledge of disease clinical and biological features

→in order to choose relevant transgenes

→in order to design/validate appropriate/meaningful endpoints, appropriate/informative monitoring methods

Make systemic delivery more efficient

→ in order to reach the right cell target