Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

Experience from Scientific Advices for CARs/TCRs

Scientific and Regulatory Challenges of Genetically Modified Cell-Based Cancer Immunotherapy Products

2016-11-16

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Contents

- Overview of EMA Scientific Advice procedures
- Existing (non-existing) regulatory guidance of anti-cancer immunotherapies
- Clinical **efficacy** aspects/issues arising from SAs
- Clinical safety issues raised in SAs

→General challenges/problem statements in the clinical development of cell-based immunotherapy development in solid tumours and hematological malignancies

- Scientific = regulatory challenges or scientific ≠ regulatory challenges?

Disclaimer/CoI

- Member of the Scientific Advice Working Party
- Member of the Oncology Working Party
- Alternate Member of CAT

- No interests in pharmaceutical industry
- Views expressed in this presentation personal

Principles of EMA Scientific Advice

- Strategic preauthorisation advice on drug development, including quality, non-clinical and clinical issues
- Article 57-1 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004: one of the tasks of the Agency is "advising undertakings on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products"
- Protocol Assistance in the context of orphan medicinal products
- Not legally binding nor a preassessment of data, but on a general level following the Agency’s increases probability of regulatory approval

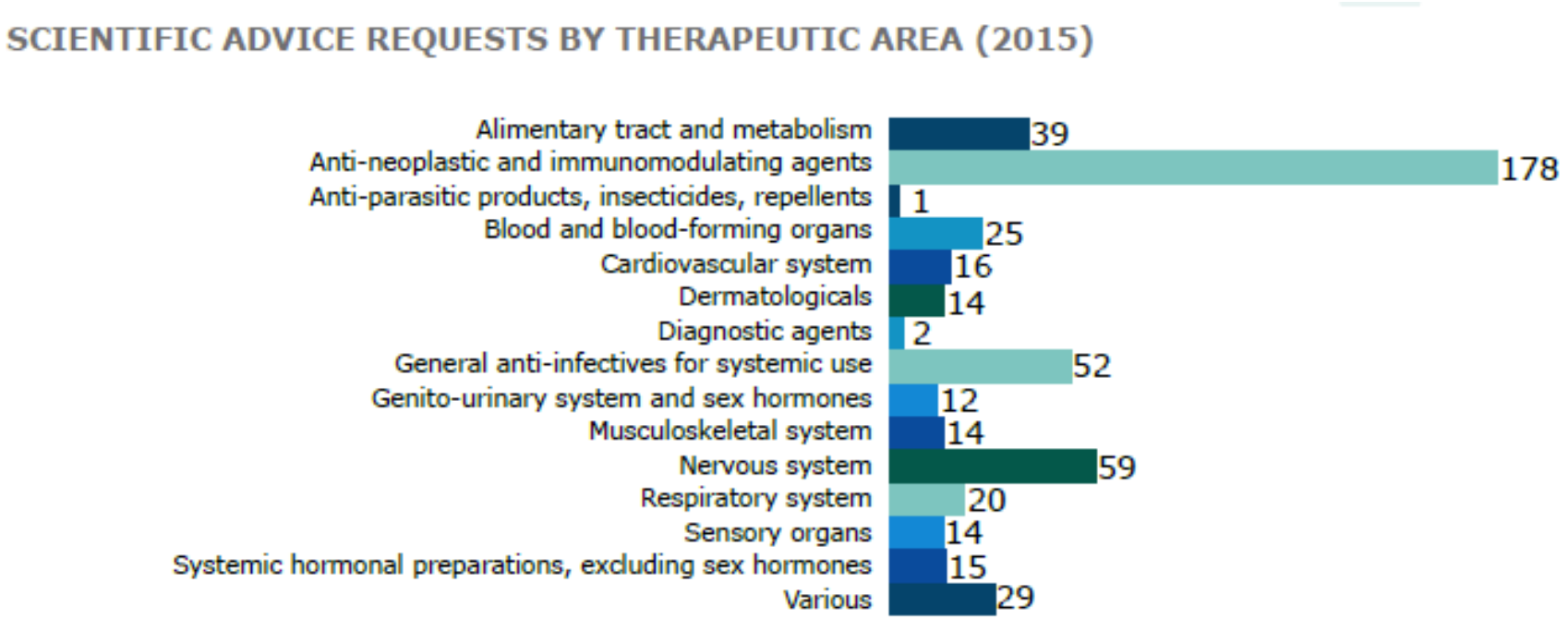
Principles of EMA Scientific Advice

- Given by the Scientific Advice Party, adopted by the CHMP
- CAT rapporteurs and CAT involvement during procedure in all ATMPs
- Answers to specific questions (included in the Company's briefing package) by the Companies addressed in an advice letter:

"The response given by the CHMP is based on the questions and supporting documentation submitted by the Applicant, considered in the light of the current state of the art in the relevant scientific fields"

- Timetable: a planning phase with/without a presubmission meeting, and an evaluation phase without discussion meeting (40 day) OR with a discussion meeting (70 day)
- Can be provided in parallel with FDA and HTA bodies

EMA Scientific Advices 2015



Regulatory Guidance

- EMA/CHMP/205/95/Rev.4: Evaluation of anti-cancer medicinal products in man

6.3.2. Immune modulating compounds including tumour vaccines

Immune therapies including therapeutic cancer vaccines are aimed to induce specific anti-tumour immunity toward existing malignant disease. Such immune therapies are normally aimed to induce adaptive T and B cell as well as innate immune responses in cancer patients. The nature of the drug substances used is highly variable, including synthetic peptides, recombinant proteins, virus-like particles, immune-modulating antibodies, gene therapy, and cell-based products. As it is difficult to break tolerance towards tumour antigens which are normally derived from self-antigens, cancer vaccines are often combined with pharmacologically active adjuvants such as cytokines or toll-like receptor agonists. One other approach to break immune tolerance is to block T cell inhibitory signals, e.g. with monoclonal antibodies. The resulting T-cell activation and proliferation leads to wanted and unwanted immune stimulatory effects: the desired anti-tumour effect as well as the appearance of immune related toxicities like colitis and endocrine insufficiency.

Non-clinical in vitro and in vivo proof-of-concept studies should be presented to justify the planned starting dose and schedule in phase I studies. Furthermore, and on a case-by-case basis, the rationale

Regulatory Guidance

The aim of early clinical trials is to determine the safety and the dose and schedule that induced a desired immune response. Dose-finding studies are generally required to establish the recommended phase II dose. Monitoring the immune response, i.e. the induction of antigen-specific T cells or the presence of a humoral response are of interest to determine appropriate dose and schedule. To

who have responded to chemotherapy. The design of clinical studies using clearly experimental therapies in patients with limited and measurable disease, not heavily pretreated with cytotoxic regimens has to be carefully justified. As for other agents, evidence of anti-tumour activity is essential prior to the initiation of confirmatory studies.

under investigation. Revised criteria defining progression is accepted if properly justified, in confirmatory studies, however, OS is the recommended outcome measure.

Possible toxicities like induction of autoimmune reactivity (cellular and humoral) and induction of tolerance should be carefully monitored during the clinical development.

→ *A need for a scientific dialogue between regulators, developers and academia*

Challenges in clinical efficacy

- Existing guidelines do not give specific clinical guidance to cell-based anti-cancer immunotherapies

- A key clinical question: are genetically modified cell-based immunotherapies ultimately different from other anti-cancer products in terms of efficacy/measures of benefit?
  - is the meaning of end points the same?
  - is the meaning of cure or palliative therapy the same?
  - how do they differ from each other (in terms of vectors etc.)?
  - what is the relevance of non-clinical data and how are quality and clinical aspects connected?

Challenges in clinical efficacy: study designs

- Is a randomised trial always more valuable than a single-arm study?
- Target condition? Rare or less rare? Available treatment options?
- How are biomarkers and toxicity linked to the study design?
- How are primary end point and study design linked to each other?
- Is the aim full or conditional approval, and what are the conditions – is a randomised trial feasible in the post-authorisation setting?

Challenges in clinical efficacy: single arm studies – pros and cons

- (Conditional) regulatory approval based on a single-arm design not excluded
- The majority of cell-based immunotherapies target conditions that at present have few, if any therapeutic options
- The mechanism of action and target populations are well-defined
- Lack of comparative efficacy data
- Lack of comparative safety data – long term safety?
- Biases in patient selection

Challenges in clinical efficacy: conditional approval

- the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive
- it is likely that the applicant will be in a position to provide the comprehensive clinical data
- unmet medical needs will be fulfilled
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required

Challenges in clinical efficacy: end points

7.1.5. Endpoints

Confirmatory trials should demonstrate that the investigational product provides clinical benefit. There should thus be sufficient evidence available demonstrating that the chosen primary endpoint can provide a valid and reliable measure of clinical benefit in the patient population described by the inclusion criteria. In the following, superiority trials are the focus of the discussion.

Acceptable primary endpoints include cure rate, OS and PFS/DFS. Convincingly demonstrated favourable effects on survival are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial. Prolonged PFS/DFS as such, however, is considered to be of benefit to the patient. The choice of primary endpoint should be guided by the relative toxicity of the

7.2. Treatment administered with curative intent

The ultimate aim of developing new therapies, e.g., in patients with high grade lymphoma, germ cell tumours or in the adjuvant setting, is to improve cure rate and survival or to relevantly decrease toxicity without loss of efficacy. Nevertheless, in some cases and due to the complexity of administered therapies, e.g. in AML, the impact of a relevantly active experimental compound on these endpoints may be hard to demonstrate.

Challenges in clinical efficacy: end points

- The primary end point and study design are linked
- Limited value of time-to-event end points in a single arm design
- Available historical data variable – more data in hematology registries than in the context of solid tumours
- On the other hand, **survival data feasible** in most of the target indications

Challenges in clinical efficacy: ORR

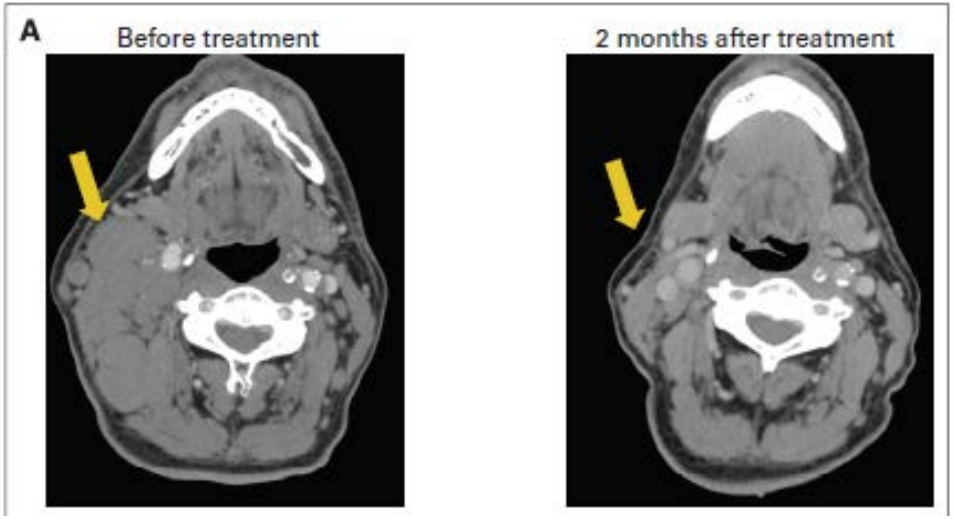
- In general, ORR may be informative in single-arm designs
- Key question in terms of benefit/risk: what is the meaning/value of response in genetically modified cell-based immunotherapies?
- When should the response be assessed, and what is a relevant duration of response?
- Feasibility of other treatments (HSCT?) or retreatment with/after cell-based immune therapies?

Challenges in clinical efficacy: ORR

- The value of response (and duration) is highly dependent on the clinical context: overall remission rate vs. overall response rate – hematological vs. ORR in solid tumours vs. ORR in lymphomas

- Leukemias > aggressive lymphomas > indolent lymphomas and solid tumours?

- Supportive end points!



Kochenderfer et al. J Clin Oncol. 2015 Feb 20;33(6):540-9

Challenges in clinical safety

- From a regulatory point of view, the more advanced/detailed safety management algorithms are, the better
- Long-term safety issues and conditions – are we expecting what we should expect, and what is based on assumptions?
- **Mechanistic** data of importance
- Safety should be seen also in the context of the target condition

Challenges in benefit/risk: evolving field

- The uncertainties we have now may be different from those we have in the future
- Lessons from RWE and long-term follow-up of efficacy and safety
- What are the differences between individual products – and how are they reflected in real-world safety and efficacy?
- How does the landscape change if/when first products are authorised –> how is it reflected in future approvals, MA conditions and feasibility of confirmatory trials?
- Regulatory context should not be separated from the real world (→ parallel HTA views important)

Conclusions

- Clinical development of genetically modified cell-based immune therapies raises fundamental questions in terms of efficacy: what is the very meaning of conventional end points?
- Novel safety aspects need novel strategies to address them
- Scientific = regulatory challenges
- Different from other anti-cancer products – yes and no
- The field is rapidly evolving, and it is difficult to foresee also the regulatory context after approval of the first products