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# Briefing meeting report

## Actively Personalized Vaccines (APVACs)

Association of Cancer Immunotherapy (CIMT)
Regulatory Research Group (RRG)

## Briefing meeting held at the European Medicines Agency (EMA) on 06 January 2012

| **Proposed product name:** | **Actively Personalized Vaccines (APVACs)** |
|---|---|
| Applicant: | Association for Cancer Immunotherapy (CIMT)<br>[Legal entity : Immunologische Krebs-Therapie e.V.]<br>Address :<br>c/o TRON<br>Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz gGmbH<br><br>Langenbeckstr. 1, Building 708<br>55131 Mainz, Germany |
| Proposed active substance: | n/a |
| Proposed finished product: | n/a |
| Proposed indication: | All cancer indications |
| Attachment: | Presentation held at meeting (pdf file) |

## Participants

CIMT participants:

Cedrik Britten (CIMT Executive Director; TRON gGmbH; Ribological GmbH)
Christoph Huber (CIMT Chairman of Board; TRON gGmbH)
Ulrich Kalinke (CIMT RRG Chair; Twincore)
Harpreet Singh (CIMT RRG Co-Chair; Immatics Biotechnologies GmbH)

EMA participants:

Falk Ehmann, ITF secretariat, ITF coordinator
Marisa Papaluca-Amati, ITF secretariat
Milton Bonelli, Scientific Support and Projects
Spiros Vamvakas, Scientific Advice
Jorge Martinalbo, Scientific Advice
Kristina Larsson, Scientific Advice
Patrick Celis, CAT secretariat
Lucia D'Apote, CAT secretariat
Marie-Helene Pinheiro, Regulatory affairs
Stefanie Prilla, Pharmacovigilance
Ralf Herold, Paediatric
Stefan Vieths, PEI
Eric Abadie, PGWP (per TC)
Jean-Hugues Trouvin, BWP (per TC)
Micha Nuebling, PGWP (per TC)
Walter Janssen, SAWP (per TC)
Martina Schuessler-Lenz, CAT/PEI (per TC)
Anke Zobywalski, PEI (per TC)

## Disclaimer presented at beginning of meeting

The views expressed in this document are the opinion of the members of the Innovation Task Force and of the experts who contributed, and may not reflect the opinion of the EMA scientific committees. Therefore, the answers provided should not be interpreted as regulatory guidance or review recommendations for an application, but as a preliminary set of scientific considerations of the information presented.

Should aspects of the subject matter discussed herein become part of a formal data submission, application, or supplement, it is at the full discretion of the appropriate working party, evaluation team or scientific committee to completely and independently assess the product(s) in question.

## 1. Background

In the last years, advances in tumor immunology, biomarker research, mass spectrometry and particularly – with the introduction of full-genome (next generation) sequencing – genomics have opened dramatically new options to approach cancer immunotherapy. This newly gathered knowledge presumably will result in a personalisation of cancer medicines and could potentially achieve improved efficacy for the treatment of cancer patients.

The Association for Cancer Immunotherapy (CIMT) – a non-profit organisation dedicated to the advancement of cancer immunotherapy – and particularly its Regulatory Research Group (RRG) propose a classification of personalized medicine on the basis of shared principles of regulation. The group has identified cancer therapy concepts that reach a high level of personalization by actively incorporating results from biomarker assays in the design and composition of the resulting drug product. The group described regulatory principles that might apply for **actively personalized vaccines (APVACs)** that are composed of molecularly defined antigens selected on the basis of molecular biomarker analysis of tumor and host (patient) factors and manufactured and administered for one individual patient only. This may particularly also include antigens derived from mutations found uniquely only in the tumor of one or very few patients.

The CIMT RRG is seeking advice from experts with scientific, clinical and regulatory background to bring the still theoretical concept of APVACs to clinical practice.

## 2. Objectives of the meeting

1. Introduce to experts at EMA the concept of actively personalized vaccines (APVACs) in cancer, the differentiation from other personalised cancer medicine and the lack of regulation for APVACs.
2. Present first preclinical proof-of-principle data for the APVAC concept.
3. Discuss with experts at EMA initial considerations with regard to preclinical, pharmaceutical and clinical aspects and challenges of a regulatory approach to APVACs.

## 3. Issues raised

### 1. Introduction to APVACs and three distinct levels of personalized cancer immunotherapy

In the field of cancer immunotherapeutics CIMT proposed distinction of three different levels of personalization. These include (A) biomarker-based **stratification** of patients for treatment with an invariant drug product (e.g. trastuzumab), (B) **passive personalization** based on treatment with unique drug products that bear intrinsic variability which are obtained by a standardized manufacturing process leading to variant drug products (typically autologous products, e.g. sipuleucel-T) and (C) **active personalization** by biomarker-based manufacturing of variant drug products to treat one individual patient. Some first examples for level C personalised products that were introduced to clinical testing in US and Japan were presented (see attached presentation file for details). While level A and B are covered by existing guidance, there is uncertainty on how level C products should be dealt with.

Among actively personalised products, two approaches can be envisioned: 1. the "**warehouse approach"**, where the drug product is individually composed of a selection of a pool or shelf of predefined components (antigens and possibly even immunomodulators) and 2. ***de novo* synthesis**, where the immunotherapeutic components are manufactured based on unique features specific for the tumor of one individual patient, typically mutations identified by differential next-generation sequencing of tumor vs. healthy tissue (e.g. PBMC).

There was general understanding between CIMT and EMA experts that actively personalised products are not fully covered by existing regulatory guidance and that regulatory challenges could potentially be identified especially with the *de novo* synthesis approach, where typically only few weeks or months are available to manufacture the drug product due to ongoing progress of the disease in the patient. In such a time-constrained setting, not all of the generally accepted principles of current drug development can be applied. However, prior validation of the concept in non clinical models, and independent validation of some elements of the whole process, should be envisaged unless otherwise justified. It is indeed acknowledged that the "final product" would be too patient specific to allow an extensive validation, but some part of the approach are common to all final products and could thus be subject to some validation and proof of concept approach.

## 2. Preclinical APVAC proof-of-principle data

CIMT presented first preclinical proof-of-principle data on the feasibility to identify and validate mutations in the cancer genome by differential next-generation sequencing of tumor and healthy animal tissue. From the presented data it appeared that peptide immunotherapy products - derived from such mutations - can be immunogenic, are endogenously presented and can have antitumor efficacy in an animal model. The observations are meanwhile published (Castle J. et al. Cancer Research, 2012).

There approach of the CIMT and the EMA experts was that such data may potentially constitute a first proof-of-principle for the approach. Several EMA experts also pointed out that in addition to a Proof of Concept in a melanoma model similar experiments in at least one additional non-related animal tumor model should be performed. CIMT highlighted that several studies with different tumor models are expected to be published by different research groups within the next 1-2 years.

## 3. Discussion of principle considerations with regard to

### a) Preclinical aspects

Mechanism of action

CIMT proposed, when using actual human antigens (intended for clinical development), to focus on *in vitro* studies with human cells. This is due to strictly species-specific binding of epitopes to HLA receptors and that HLA-transgenic mice are also not suitable due to the lack of a larger number of human components of antigen processing and presentation. According to the CIMT, while the proposed *in vitro* immunogenicity studies are feasible for the warehouse approach they can not be done routinely for the *de novo* synthesis approach for every antigen but should be rather performed on selected antigens.

Experts at EMA indicated that the *in vitro* approach seems to be principally valid and suitable for this purpose but requested that such human *in vitro* data should be substantiated by more *in vivo* data using exemplary animal antigens in animal models (also see above, point 2.).

Animal toxicology

CIMT proposed-due to the known limited predictive value of animal models for testing of human antigens and moreover and due to the fact that extended animal toxicology studies, will not be feasible for the *de novo* synthesis approach-that animal studies should be substituted by well designed *in vitro* experiments for selected epitopes. Such *in vitro* data could address issues such as of cross-reactivity of mutated antigens.

Experts at EMA principally agreed that the application of human antigens in animal models may have limited predictive value. Although *in vitro* studies seem to be appropriate such studies should be accompanied by safety studies in animal models challenged with animal antigens. More detailed discussion is required in the context of scientific advice so that the approach chosen for either the warehouse or the de novo synthesis manufacturing strategy is duly designed and justified.

It was preliminarily concluded that in light of feasibility considerations (restricted time frame in APVAC setting) and generally good tolerability of antigen-specific cancer immunotherapeutics, proceeding into the clinical setting could be considered for the de-novo synthesis APVAC products if adequate scientific background data were available and appropriate risk mitigation measures are in place in the respective clinical study (see below).

## b) Pharmaceutical/CMC aspects

Content, purity, identity

CIMT proposed that also for APVACs content, purity and identity have to be prospectively defined and captured by appropriate release testing. As APVACs are molecularly defined drug products manufactured via established synthetic or recombinant use, they are well defined.

Stability and shelf life

For highly variant, actively personalised drug products used typically in one individual patient only, mid-/long-term stability data and shelf life cannot be established for every batch due to the “on-demand” production and short time until administration of the immunotherapy product..CIMT proposed to apply the approach also followed for autologous (level B) personalised products, where stability data are generated for a defined number of patients whereas shelf life of drug products subsequently manufactured by the same standardised process is extrapolated.

Experts at EMA pointed out that CMC aspects have to be discussed specifically in a product-specific scientific advice meeting. However, there was general understanding that typical approaches for non-variant drug products were not easily applicable and that a pragmatic approach for appropriately selected APVACs may be an acceptable way to proceed.

Potency

CIMT suggested defining surrogate potency assays for APVACs if potency testing is required for the drug class. For synthetic drug products such as peptides or RNA this would be the proof of the correct molecular structure. For cellular therapies, specific potency assays may have to be developed (e.g. CD54 expression in sipuleucel-T).

Experts at EMA pointed out that this question needs to be specifically discussed for the relevant product but that a pragmatic and feasible approach should be followed.

## c) Clinical aspects

Efficacy

CIMT pointed out that to determine efficacy of APVACs, criteria were not different from other drug products. I.e. established clinical endpoints (preferably overall survival) and appropriately controlled and randomized trials should be performed, though there is a promise that due to expected higher efficacy of APVACs patient numbers to demonstrate efficacy may be lower than for conventional drug products. Furthermore, as should be the case for marketing authorization of all cancer immunotherapies, in particular for APVACs the regulatory pathway should be accompanied by a comprehensive biomarker program which in this case might even play a more dominant role than for conventional products.

Safety

CIMT proposed that adequate risk mitigation measures should be followed in early clinical development including staggered (step-wise) enrolment of the first patients, the use of a limited number of mutations per immunotherapy product in the first patients (with increasing numbers of mutated antigens for subsequent patients), a restricted number of experienced centres and physicians specialised in early diagnosis and treatment of potential autoimmunity and pre-defined rules how to control autoimmunity including stopping rules.

Experts at EMA principally agreed that an appropriate risk mitigation approach should be in place for early clinical development. Particularly, (i) step-wise recruitment of patients and (ii) the restriction to few mutations for the first patients in order to observe safety of such mutated antigens was pointed out to be an appropriate measure. Moreover, immunogenicity analyses should be included into the trial concept as one measure of mode of action.

It was also discussed that the patient's disease stage, inclusion criteria and life expectancy of the cancer patient should be considered and that it might not be necessary to wait for cancer patients to move into the pre-final setting for first-in-man application of APVACs. For fast-progressing tumors, the APVAC could be manufactured before entering the pre-final stage of disease. The product would then be available when needed, provided that the stability profile in frozen conditions, followed by a thawing step, has been studied, demonstrated and evaluated to be satisfactory. With accumulation of knowledge APVAC administration in earlier disease stages should be considered.

## Concluding comments

Several experts at EMA pointed out that on the basis of the preliminary presented data, the proposed approach to manufacture and administer actively personalised immunotherapy products could be scientifically appealing subject to further development into the clinical setting. Experts at EMA encouraged further development of this approach. They also suggested, that a separate discussion with the Agency of specific aspects of a final developed product could take place at a later stage, in the context of scientific advice,