



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

December 30, 2010

Submission of comments on 'Concept paper on the need to revise the guideline on the evaluation of anticancer medicinal products in man' (EMA/EMA/CHMP/EWP/433478/2010) from 22 July 2010

## Comments from:

Name of organisation or individual

***Cancer Immunotherapy Consortium  
of the Cancer Research Institute (CIC-CRI),  
New York, NY, USA  
and  
Association for Cancer Immunotherapy (CIMT),  
Mainz, Germany***

### Information on the authors:

#### **Cancer Research Institute**

The Cancer Research Institute (CRI), established in 1953, is the world's only nonprofit organization that is dedicated exclusively to transforming cancer patient care by advancing scientific efforts that are leading to new and effective immune system-based strategies to treat, control, and prevent cancer. Guided by a world-renowned Scientific Advisory Council that includes four Nobel laureates and twenty-nine members of the National Academy of Sciences, CRI has invested nearly \$200 million in support of research conducted by immunologists and tumor immunologists at the world's leading medical centers and universities, and has contributed to many of the key scientific advances that have led to the recent explosion of interest in the potential for immunotherapy to change the face of cancer treatment. To accelerate the pace of progress in the field, CRI convenes and coordinates global collaborations among academics, industry scientists and decision makers, regulatory representatives, and health research associations focused on discovery, development, and refinement of new cancer immunotherapies. A founding visionary and scientific leader in tumor immunology, CRI is helping to shape the emerging field of immuno-oncology, and is ushering in a new era of medical progress to bring more treatment options to cancer patients sooner.

#### **CRI Cancer Immunotherapy Consortium**

The Cancer Immunotherapy Consortium, a program of the Cancer Research Institute, is an international association of more than 70 academic institutions, pharmaceutical and biotech companies, who share a common goal of improving patient care by making cancer vaccines part of the standard-of-care in oncology. Member scientists, clinicians, and industry leaders



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exchange information with one another to analyze and establish solutions to common challenges in cancer immunotherapy use, development, and commercialization. For more information, visit <http://www.cancerresearch.org/consortium>

**CIMT Association for Cancer Immunotherapy**

The Association for Cancer Immunotherapy (CIMT) is a non-profit organization and was founded in fall 2002 as an information and education platform for immunological cancer therapy. CIMT organizes annual scientific meetings located in Mainz, Germany. The CIMT Regulatory Research Party (RRP) was founded in 2008. It incorporates members from academia, biotech industry and regulatory authorities such as the Paul-Ehrlich-Institute (PEI). The group is aiming to facilitate the translation of scientific knowledge from bench to bedside. RRP's main goals are: (1) identification of regulatory challenges posed by emerging immunotherapies, (2) development of new regulatory concepts to facilitate clinical testing of innovative immunotherapies and (3) to facilitate discussion between all groups relevant for the translation of scientific knowledge into the hospital. (<http://cimt.eu>).

Submitted by Axel Hoos, MD, PhD and Harpreet Singh, PhD on behalf of CIC-CRI and CIMT.

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

## 1. General comments

Stakeholder number <i>(To be completed by the Agency)</i>	General comment (if any)	Outcome (if applicable) <i>(To be completed by the Agency)</i>
	<p>CIC-CRI and CIMT are both community-based non-profit organizations with broad expertise in the area of cancer immunotherapy and are partnering on many different levels. Both organizations acknowledge and highly welcome the planned revision of the guideline on the evaluation of anticancer medicinal products in man in order to address specific characteristics of cancer immunotherapy development. Taking into account that (i) several anticancer immunotherapeutics are currently in late stage clinical development and (ii) the first cancer vaccine has recently been licensed in the US, more specific guidance appears to be required for such products. Both CRI-CIC and CIMT suggest that particular focus should be placed on the definition and measurement of clinical endpoints in the context of development of novel biologics such as cancer immunotherapeutics with distinct biology compared to conventional chemotherapy agents. Further, specific considerations about the development of anti-tumour vaccines should be included.</p> <p>Over the last 6 or more years CIC-CRI and CIMT have facilitated the knowledge generation and scientific exchange in this area of biologics research on a community-wide basis in Europe and the USA and contributed to the creation of a new paradigm for cancer immunotherapy evaluation. At the core of these considerations is the fact that chemotherapies treat the tumour directly, while immunotherapies treat the immune system, which in turn builds a response against the tumour. The kinetics of both mechanisms are distinct and should be acknowledged in the methods used for clinical evaluation. The following methodological considerations are viewed as important and are derived from our experience in evaluating immune therapies in humans:</p>	

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	<p>1. <i>The definition of the disease setting for immunotherapy investigations:</i> Cancer immunotherapies may be best studied in patients with no clinical evidence of disease, minimal burden of disease, or slowly progressing metastatic disease. Patients without rapidly progressing end-stage-disease, may have a better opportunity to mount an effective immune response that can lead to clinical activity. Measures to inform patients about potential harm of cancer immunotherapy and to monitor e.g. immune tolerance induction wherever possible should be considered in parallel.</p> <p>2. <i>Clinical kinetics of cancer immunotherapies:</i></p> <p>a) <i>Consideration of a delayed onset of clinical activity:</i> Immune therapies do not act directly on the tumour but on the immune system. The immune system builds an immune response against tumour cells, which may take weeks to months until it translates into measurable clinical activity. During this time, some patient's tumours may either progress, or increase their volume/develop new lesions (some possibly due to inflammation), which may be followed by a delayed response (1, 2, 3). The definition of progression may therefore be adjusted to account for such delayed clinical effects. Further, in some patients the immune response may create equilibrium with the tumour (4) and lead to long-term disease stabilization, which should be considered as clinical activity (2, 3). Similarly, clinical protocols may allow for continued treatment post progression to avoid premature discontinuation of an active immunotherapy (1, 2, 3). Continued treatment beyond progression under certain conditions should be monitored closely by independent experts (typically a data safety monitoring board</p>	

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	<p>– DSMB) that frequently reviews decisions to continue treatment of such patients according to a number of pre-specified parameters. Treatment should be stopped in light of clinical deterioration (e.g. change in performance status). Long-term effects of immune therapies may need to be considered, which may influence results of subsequent therapies.</p> <p>b) <i>Immunotherapy endpoints (adjustment of conventional endpoints):</i> As described, immunotherapy may induce novel patterns of antitumor response not captured by Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria. Clinical protocols for investigation of cancer immunotherapies may utilize adjusted response criteria for endpoints such as response rate or PFS, which more comprehensively capture all response patterns (2, 3). Such criteria must be prospectively defined. Similarly, Kaplan-Meier survival curves may show a delayed separation of curves in randomized immunotherapy trials (separation months after randomization), which can affect results. Altered statistical models describing hazard ratios as a function of time and recognizing differences before and after separation of curves may be prospectively employed for designing Phase 3 trials (3, 5, 6).</p> <p>3. <i>Endpoints for licensure:</i> If clinically validated and based on sufficient clinical data, adjusted endpoints as described above may be acceptable as efficacy endpoints for licensure. All endpoints must be prospectively defined, included in the statistical analysis plan and agreed to with EMA.</p>	

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4. *Early human testing in the absence of adequate animal models:*  
Animal models used for investigation of cancer immunotherapies may not be predictive of the human situation. In particular, for some antigen-specific cancer vaccines the target antigen may not have a close homolog in animals. In situations where reliable predictive animal models to assess immunological toxicity and activity are not available, in vitro data using human cells/cancer tissues and careful Phase I human testing may be more appropriate (1) than performing classical animal toxicology.
5. *Toxicity screening for cancer vaccines:*  
Cancer vaccines have historically shown minimal toxicity. In first-in-human trials the following steps may be employed to create a balance between controlling safety risk and managing toxicity screening: a) conduct a standard safety panel of examinations/tests to cover major organ systems as used in general oncology drug development; b) address vaccine-specific toxicities unique for the investigated product based on toxicity expectations from preclinical models, including autoimmunity as applicable; c) allow for investigation of unexpected toxicities through collection of serum and other samples from patients at predefined time points, and ad-hoc when toxicity occurs. These samples may be used for further laboratory testing in case unexpected toxicity is being observed throughout the study (1).
6. *Immune response assay use in clinical trials:*
  - a) *The definition for immune response:*  
The characteristics (cut off values) of an immune response should be prospectively identified to define the change necessary for a response and to define the proportion of study patients needed for a positive study outcome (1). Requirements regarding the number

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	<p>of assays, level of qualification/validation of assays and pre-specification of assays are dependent on the stage of development and the endpoints of the trials.</p> <p>b) <i>Consistency of immunological assays:</i> Cellular immune response assays can generate variable results. The use of such assays in clinical trials should follow quality assurance measures (e.g. harmonization of assays) to minimize data variability. Assays with reproducible outcomes should be used to investigate the relationship between immune response and clinical outcomes (1, 7, 8, 9). To base developmental decisions on immune response data, the use of more than one immunological assay may be considered. Monitoring of the immune response in the actual tumor material may be considered to assess the functionality of the immune response. Strategies to obtain tumor material without significantly affecting patient quality of life or well being (i.e. neoadjuvant) may be considered.</p> <p>7. <i>Conditions for Combination therapies:</i> Some immunotherapies may only be effective or may be more potent if developed in combination with another immunotherapy to synchronously address synergistic immunologic mechanisms (e.g. an antigen-specific cancer vaccine to target disease and an immune checkpoint modulator to enhance the immunologic effect). Such agents may both be investigational and provisions should be made for their co-development.</p>	

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**References:**

- (1) Hoos A, Parmiani G, Hege K, et al: A clinical development paradigm for cancer vaccines and related biologics. *J Immunother* 2007; 30:1–15.
- (2) Wolchok JD, Hoos A, O’Day S, et al: Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: immune-related Response Criteria. *Clin Cancer Res* 2009; 15:7412-7420.
- (3) Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. *J Natl Cancer Inst.* 2010; 102:1388-1397.
- (4) Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol.* 2004;22:329-60.
- (5) Fine GD: Consequences of Delayed Treatment Effects on Analysis of Time-to-Event Endpoints. *Drug Information Journal* 2007; 41:535-539.
- (6) Finke LH, Wentworth K, Blumenstein B, et al: Lessons from randomized phase III studies with active cancer immunotherapies—outcomes from the 2006 meeting of the Cancer Vaccine Consortium (CVC). *Vaccine* 2007; 25:B97-B109 (suppl 2).
- (7) Janetzki S, Panageas KS, Ben-Porat L, et al., for the Elispot Proficiency Panel of the CVC Immune Assay Working Group 2007: Results and Harmonization Guidelines from two large-scale international Elispot proficiency panels conducted by the Cancer Vaccine Consortium (CVC/SVI). *Cancer Immunol Immunother* 2008; 57:303-315.
- (8) Britten CM, Gouttefangeas C, Schoenmaekers-Welters MJP, et al: The CIMT-Monitoring panel: A two-step approach to harmonize the enumeration of antigen-specific CD8+ T lymphocytes by structural

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	<p>and functional assays. Cancer Immunol Immunother 2008; 57:303-315.</p> <p>(9) Britten CM, Janetzki S, Ben-Porat L, et al, for the HLA-peptide Multimer Proficiency Panel of the CVC-CRI Immune Assay Working Group: Harmonization guidelines for HLA-peptide multimer assays derived from results of a large scale international proficiency panel of the Cancer Vaccine Consortium (CVC). Cancer Immunol Immunother 2009; 58:1701-1713.</p>	

## 2. Specific comments on text

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Stakeholder number <i>(To be completed by the Agency)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>	Outcome <i>(To be completed by the Agency)</i>
		Comment:  Proposed change (if any):	
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