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CIMT Regulatory
Research Group

CIP
CIMT Immunoguiding
Program

CIMT – Regulatory Research Group RRG
CIMT – Immunoguiding Program CIP

Immunomonitoring Regulation User's Perspective

CIMT 2013
Mainz, May 16, 2013

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immatics biotechnologies GmbH, Tuebingen, Germany

immatics

Agenda

1. Regulatory Landscape for Immunomonitoring
2. EMA reflection paper (draft)
3. Context-specific regulation
4. EMA reflection paper (final)
5. Example: T-cell immunomonitoring

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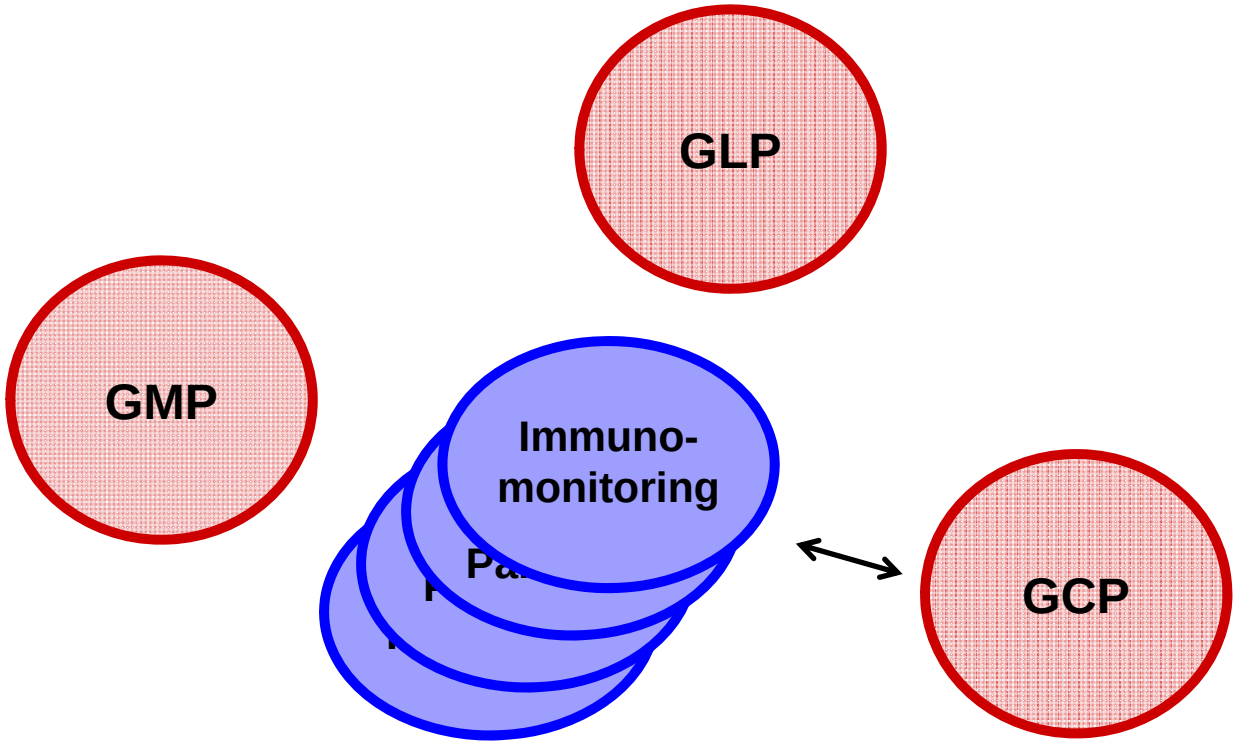
1. Regulatory Landscape for Immunomonitoring



1. Regulatory Landscape for Immunomonitoring

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GCP

EU-Directive 2001/20/EC

EU-Directive 2005/28/EG

European Medicines Agency

July 2002
CPMP/ICH/135/95

ICH Topic E 6 (R1)
Guideline for Good Clinical Practice

Step 5

NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE
(CPMP/ICH/135/95)

1. Regulatory Landscape for Immunomonitoring

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

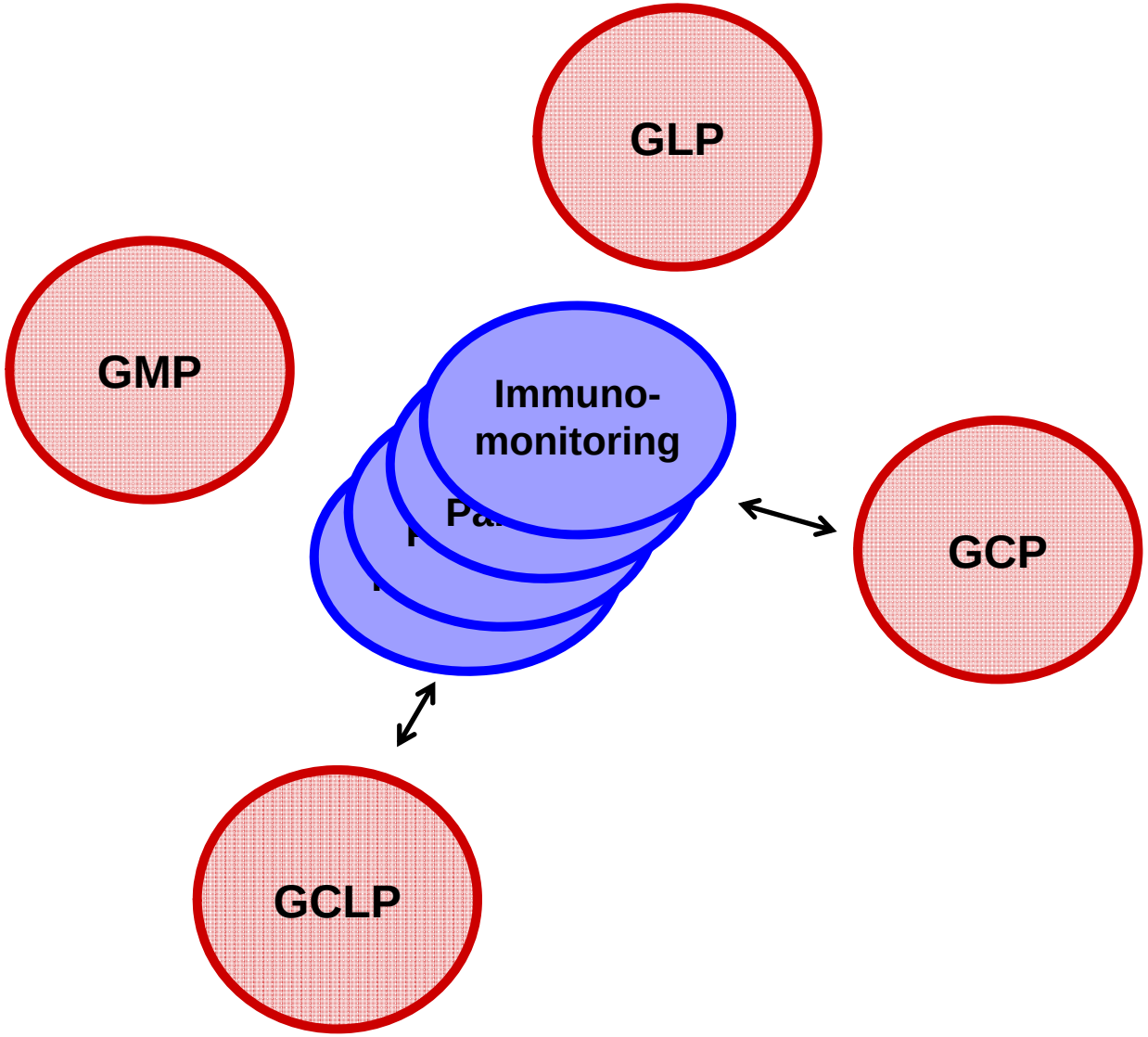
2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

1. Regulatory Landscape for Immunomonitoring



1. Regulatory Landscape for Immunomonitoring

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GCLP

BARQA Guideline 2003

"A Quality System for Laboratories that undertake the Analysis of Samples from Clinical Trials"

WHO TDR 2006

"Good Clinical Laboratory Practice (GCLP)"

MHRA Guidance 2009

"Guidance on the maintenance of regulatory compliance in laboratories that perform the analysis or evaluation of clinical trial samples."

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5. Example: T-cell immunomonitoring

2. EMA reflection paper (draft)

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28 February 2012
EMA/INS/GCP/532137/2010
GCP Inspectors Working Group

6.2 Reflection Paper

A reflection paper may be developed to communicate the current status of discussions or to invite comment on a selected area of medicinal product development or a specific topic. It can provide a framework for discussion or clarification particularly in areas where scientific knowledge is fast evolving or experience is limited. A reflection paper does not provide scientific, technical or regulatory guidance, but may contribute to future development of such guidelines, or related documents.

Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

Draft agreed by GCP Inspectors Working Group	10 June 2010
Adopted by GCP Inspectors Working Group for release for consultation	10 June 2010
Start of public consultation	23 September 2010
End of consultation (deadline for comments)	28 February 2011
Adopted by GCP Inspectors Working Group	28 February 2012

3. Scope

This reflection paper is designed to provide guidance to laboratories and other facilities that perform the analysis or evaluation of samples collected as part of a clinical trial. The guidance is designed to complement existing quality systems where they exist. Inspectors are encouraged to consider the scope and focus of existing quality systems before performing GCP laboratory inspections in order to avoid duplication of effort.

The guidance does not apply to non-interventional trials.

= <u>All</u> kinds of lab analyses within clinical trials

2. EMA reflection paper (draft)

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6.1 Organisation of a laboratory including documented roles and responsibilities

6.2 Documented training

6.3 Setup of written contracts and agreements between different parties

6.4 Accordance with the protocol

6.5 Prohibition of work not specified in the clinical study protocol

6.6 Agreements with subcontractors

6.7 Arrangements to ensure timely assessment and reporting of safety results

6.8 Mechanisms to ensure that patient' informed consent covers actual analyses

6.9 Control of shipment conditions, labelling, documented sample booking, monitoring of samples storage, backup facilites

6.10 Validation of all analysis methods

In all but exceptional circumstances, analysis should be performed using appropriately validated methods with defined acceptance criteria where appropriate.*

** Where the validation of a method is one of the clinical trial objectives.*

2. EMA reflection paper (draft)

6.11 Rules for repeat analyses
6.12 Rules for data recording and handling
6.13 Rules for data reporting
6.14 Appropriateness of facilites
6.15 Acceptance testing and continuous maintenance of all equipment
6.16 Development, validation, and maintenance of computerized systems
6.17 Setup of local Quality Assurance processes, including regular audits
6.18 QC checks for processes and kits
6.19 Activities covered by SOPs
6.20 Blinding / unblinding of clinical trials
6.21 Archiving of trial data
6.22 Preparation and distribution of clinical kits

Prior to use, all computerised systems should be subject to an appropriate level of validation. […] Validation should be performed in accordance with a documented plan. […] For each computerised system, the components (e.g. hardware and software) which constitute the system should be clearly defined. This information should be documented with the associated validation package. […] If additional functionality is utilised which is beyond the scope of the original validation the need to perform additional validation must be considered and, in most cases, will be required. […]Following changes to computer software such as a system upgrade, or the installation of "patches", the need to re-validate the computerised system should be determined. It may be appropriate to perform a documented risk assessment which will determine what level of re-validation is required.
Etc.

Issues

- We acknowldedge that patients‘ rights and well-being are paramount. If these are affected by lab analyses, appropriate regulation should be in place.
- Many novel lab assays are introduced in clinical trials to generate hypotheses and to study mechanism of action.
- It is not yet known which of these assays will be developed to surrogate endpoints or to market.
- **Applying equal levels of regulation to all lab analyses within clinical trials will prevent the entry of innovation to translational research.**
- **Context-specific regulation is required.**

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3. Context-specific regulation

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Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

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3. Context-specific regulation

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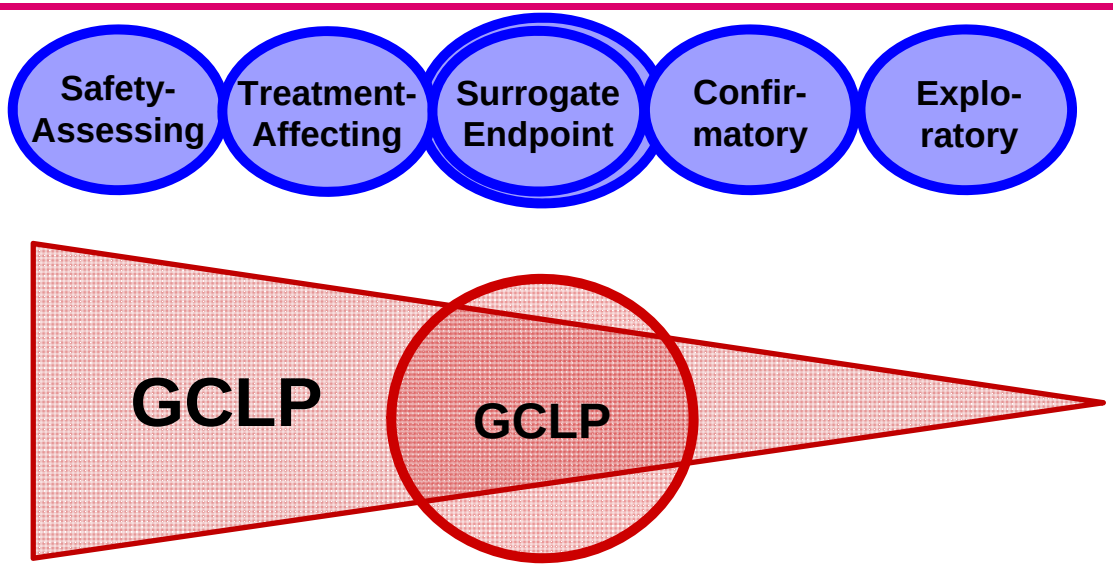
27 February 2011

Submission of comments on '**Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples**'
(EMA/INS/GCP/532137/2010)

Comments from: Association for Cancer Immunotherapy (CIMT) and CRI Cancer Immunotherapy Consortium (CIC-CRI)

3. Context-specific regulation



Safety-Assessing

- Determination of drug safety
- E.g. neutrophil blood counts

Treatment-Affecting

- Immediate treatment decision in late-stage trials
- E.g. HLA typing in study screening

Surrogate Endpoint

- Efficacy surrogate in late-stage trials
- E.g. antibody titer for prophylactic vaccine in Ph. III

Confirmatory

- Hypothesis validation as 2nd endpoint or in early phases
- E.g. immune response comparison in multi-arm Ph. IIa

Exploratory

- Hypothesis generation
- E.g. analysis of Treg levels to gain insight in MoA

3. Context-specific regulation

	Safety-Assessing	Treatment-Affecting	Surrogate Endpoint	Confir-matory	Explo-ratory
6.1 Organisation of a laboratory including documented roles and responsibilities	☑	☑	☑	☐	☐
6.2 Documented training	☑	☑	☑	☑	CV only
6.3 Setup of written contracts and agreements between different parties	☑	☑	☑	CSP only	CSP only
6.4 Accordance with the protocol	☑	☑	☑	☑	☑
6.5 Prohibition of work not specified in the clinical study protocol	☑	☑	☑	☑	☑
6.6 Agreements with subcontractors	☑	☑	☑	CSP only	CSP only
6.7 Arrangements to ensure timely assessment and reporting of safety results	☑	n/a	n/a	n/a	n/a
6.8 Mechanisms to ensure that patient' informed consent covers actual analyses	☑	☑	☑	☑	☑
6.9 Control of shipment conditions, labelling, documented sample booking, monitoring of samples storage, backup facilites	☑	☑	☑	☑	Descrip-tive only
6.10 Validation of all analysis methods	☑	☑	☑	Descrip-tive only	Descrip-tive only

3. Context-specific regulation

	Safety-Assessing	Treatment-Affecting	Surrogate Endpoint	Confir-matory	Explo-ratory
6.11 Rules for repeat analyses	☑	☑	☑	☑	Document repeats
6.12 Rules for data recording and handling	☑	☑	☑	☑	☑
6.13 Rules for data reporting	☑	☑	☑	☑	☑
6.14 Appropriateness of facilites	☑	☑	☑	☑	☑
6.15 Acceptance testing and continuous maintenance of all equipment	☑	☑	☑	☑	Descrip-tive only
6.16 Development, validation, and maintenance of computerized systems	☑	☑	☑	Descrip-tive only	Descrip-tive only
6.17 Setup of local Quality Assurance processes, including regular audits	☑	☑	☑	☑	☐
6.18 QC checks for processes and kits	☑	☑	☑	☑	☐
6.19 Activities covered by SOPs	☑	☑	☑	☑	☐
6.20 Blinding / unblinding of clinical trials	☑	☑	☑	☑	☑
6.21 Archiving of trial data	☑	☑	☑	☑	☑
6.22 Preparation and distribution of clinical kits	☑	☑	☑	☑	☑

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4. **EMA reflection paper (final)**
5. Example: T-cell immunomonitoring

4. EMA reflection paper (final)

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Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

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4. EMA reflection paper (final)

3. Scope

The nature and purpose of laboratory work conducted as part of a clinical trial is extremely broad. Laboratories perform a wide range of activities which provide data that is used to monitor trial subject safety, assess pharmacokinetic parameters and to measure end points. Consequently, because of the diverse nature of laboratory work associated with clinical trials, it is very difficult to provide guidance which is wholly applicable in all situations. It is acknowledged that the recommendations set out in the paper may not be applicable in their entirety to some laboratories. The paper is primarily aimed at contract research organisations, sponsors laboratories and non commercial laboratories that are involved in the production of data that is used to assess end points of safety and efficacy. The paper is not specifically designed for laboratories that perform routine clinical chemistry or gather data which will be used for purposes not directly linked to the primary objectives of the trial. However, it should be noted that there is a requirement for all laboratories that perform work in support of clinical trials to implement appropriate measures to assure the quality and integrity of the data they produce and to exercise due diligence to ensure that the trial subjects rights are not compromised.

This reflection paper is designed to complement existing quality systems where they exist. Inspectors are encouraged to consider the scope and focus of existing quality systems before performing a laboratory inspection in order to avoid duplication of effort.

The information detailed in this reflection paper is applicable to all laboratories that generate data which will be used in dossiers submitted to EU/EEA regulatory authorities as part of a clinical trials application or marketing authorisation. The reflection paper is also applicable to investigator initiated trials.

This paper does not apply to non-interventional trials.

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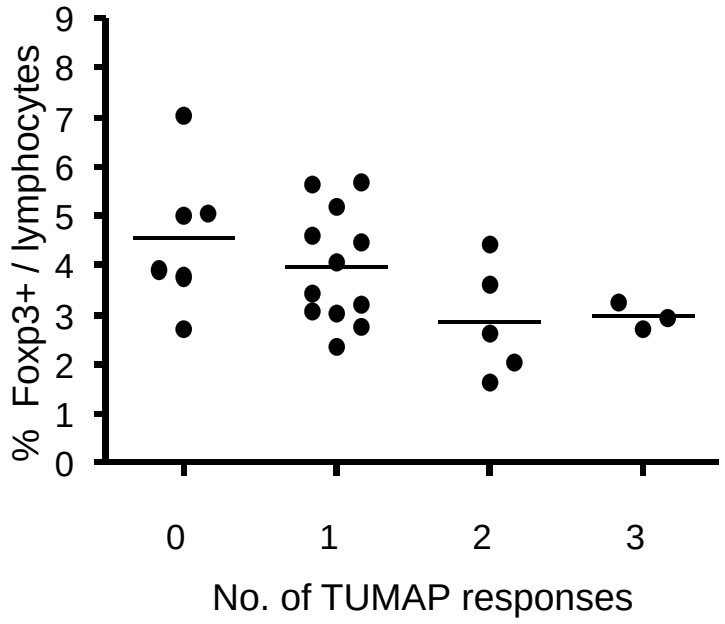
5. Example: T-cell immunomonitoring

Phase I trial of IMA901 vaccination in N=28 HLA-A*02 RCC patients:

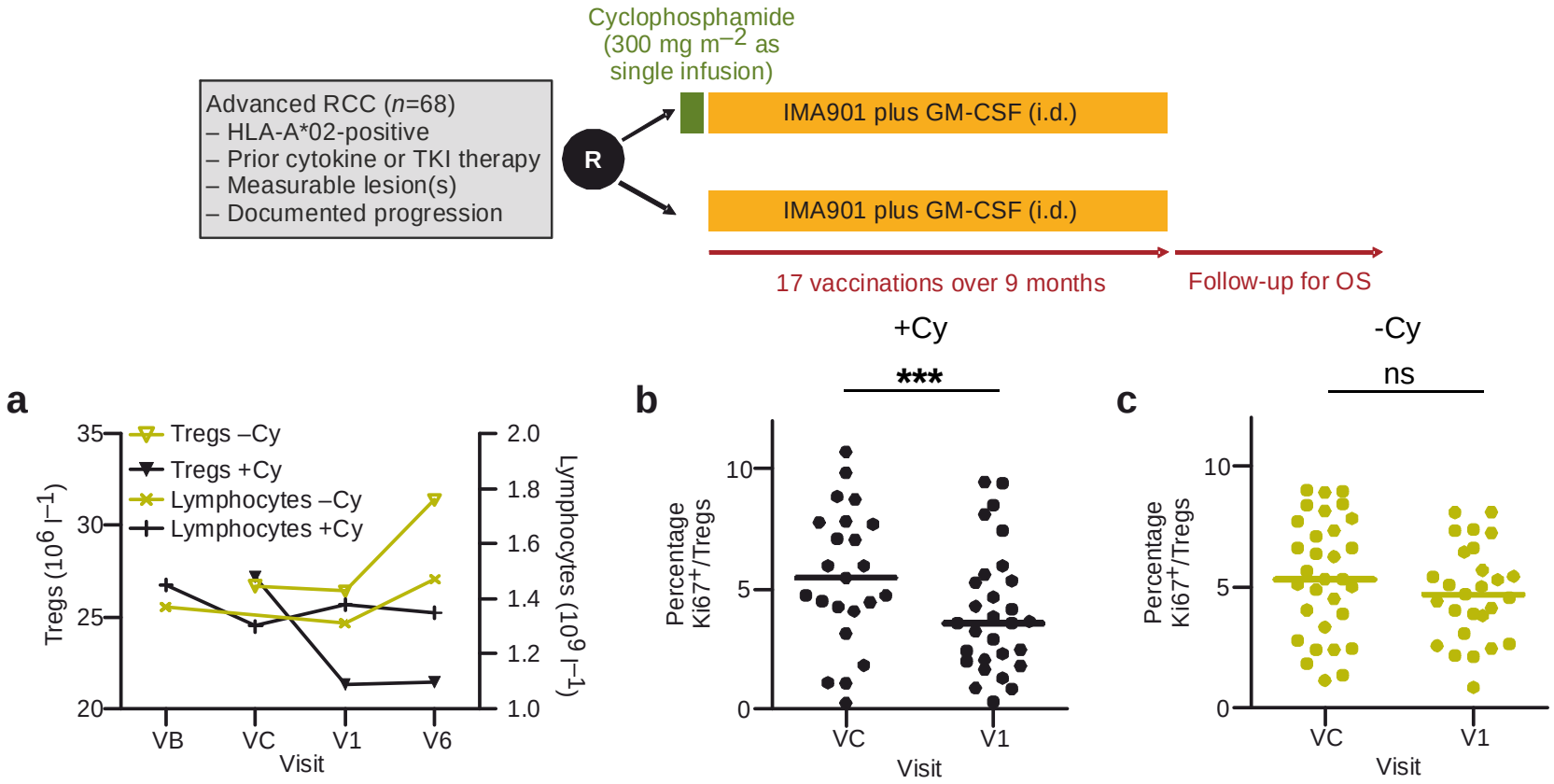
Significant correlation between pre-vaccine levels of Foxp3^{+} regulatory T-cells and multi-TUMAP responses (p = 0.02)



Treg assay was introduced late as number of available PBMCs was not precisely known during study design.

Walter, Weinschenk et al. (2012), Nature Medicine

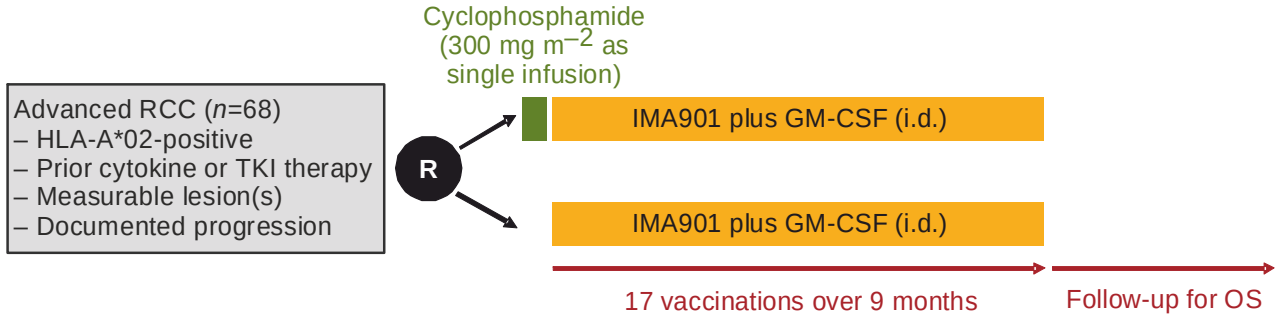
5. Example: T-cell immunomonitoring

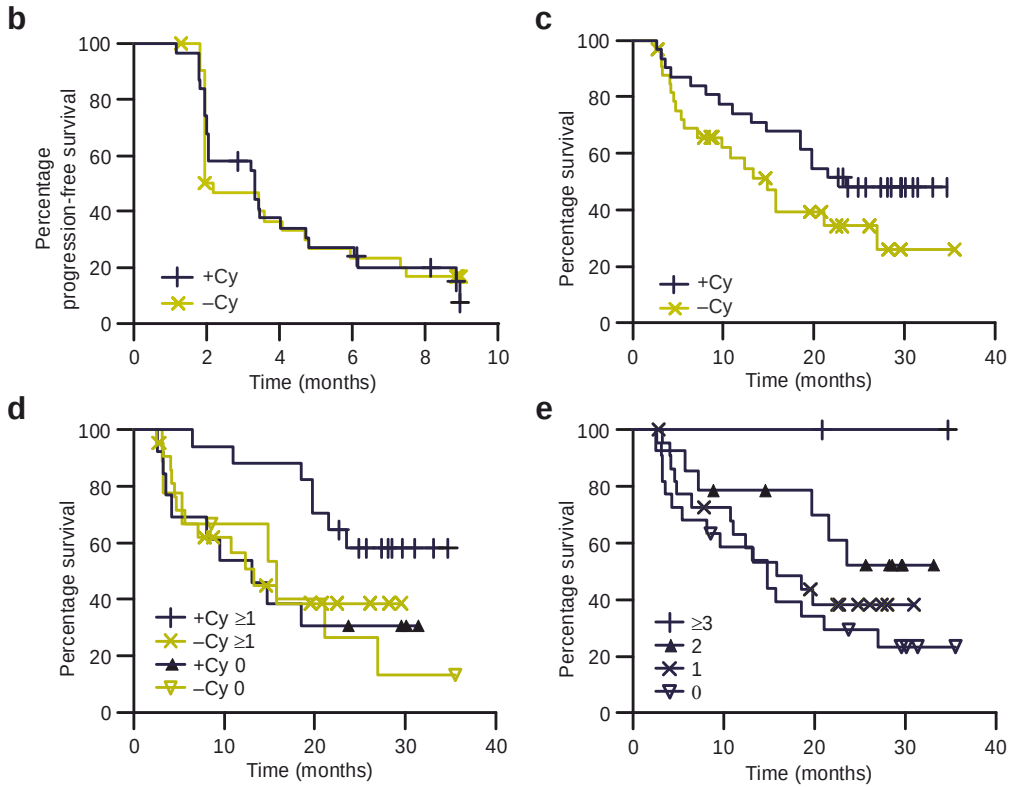


- **Reduction in absolute Treg levels induced by single-dose CY pre-treatment**
  - Significant decrease in absolute Treg levels from pre CY VC to post CY V1 (**p=0.013**) in the +CY arm

Walter, Weinschenk et al. (2012), Nature Medicine

5. Example: T-cell immunomonitoring





- **Single-dose CY pre-treatment associated with survival benefit**
  - Only in patients with vaccine-induced immune responses (HR=0.38, p=0.040)
  - Not in patients without immune responses, arguing against single agent effect of CY (HR=0.92, p=0.870)
- **Number of immune responses associated with survival**
  - (p=0.023)

Walter, Weinschenk et al. (2012), Nature Medicine

Summary

- The „one-fits-all“ approach of regulation does not take into account the different functions of laboratory analyses in clinical trials
- We have to determine first in hypothesis-generating analyses which parameter are interesting enough to be fully validated
- If this reflection paper finds its way into a EMA guideline, innovative analyses in clinical trials may be sharply stifled in the EU
- **Context-specific regulation provides a possible solution to protect both patient rights and to enable innovation**

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CONTRIBUTORS

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Panel Participants

- 55 participating labs
- 12 European countries
- 5 USA-based labs via CIC

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CIP Members Member

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