

Thema der Masterarbeit:

Thema auf Deutsch:

Die Einbindung von Biomarkern in der klinischen Forschung: Eine Übersicht unter besonderer Berücksichtigung operativer Aspekte bei der Planung onkologischer Entwicklungsprojekte.

Thema in Englisch:

The inclusion of biomarkers in clinical research: An overview with focus on operational aspects in the planning of oncological development projects.

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Kurzfassung

1 Introduction

Advances in biotechnology and the science of molecular biology, especially the development of new methods to better characterize the structure of molecular targets on cells, e.g. receptors, have enabled pharmaceutical research to develop new therapeutic strategies that influence more specifically as in the past important molecular targets of the pathophysiological mechanisms of a disease. Such targeted therapies are highly specific in their mode of action for a certain disease or for a certain patient population. They aim on the one hand side at reducing the influence of a therapeutic agent on healthy cells or normal physiological processes, thereby reducing potential side effects. On the other hand side, they are intended to maximize the patients' benefit from the treatment by increasing the likelihood of a therapeutic response.

Reliable biological (physiological, molecular, or genetic) indicators, so-called biomarkers, are new important tools in the pharmaceutical development process. It is by now widely accepted that the implementation of biomarker research into drug development has the potential to not only accelerate the drug development process, but at the same time to increase the likelihood of success by allowing a company to identify and to focus on the most promising drug candidates, resulting in a reduced attrition rate in the development pipeline. However, the implications of an integrated biomarker strategy in clinical development program for operational activities in clinical research, i.e. the organization and coordination of clinical trials, are often underestimated.

The aim of this thesis is to give an introduction to the topic of biomarkers, their role and development within clinical research and to present operational aspects that need to be considered for the planning and conduct of clinical trials, in which biosamples for molecular biomarker research are to be collected. In this context, important operational issues will be discussed, based on case examples from current clinical research and solutions will be presented.

Due to the complexity and continuously proceeding environment of this topic, the aim is not to provide an exhaustive summary of detailed aspects but to present an overview in order to increase the level of awareness for this topic and the related operational aspects, focusing on the therapeutic area of oncology, in which biomarker research is nowadays already considered as state-of-the-art. The main focus with respect to the current view by the health authorities will be laid on the two major pharmaceutical markets: being the US as well the EU. Also the third major pharmaceutical market Japan, which has a quite complex and different regulatory framework in place, will be briefly mentioned.

2 General aspects of biomarker research and the implementation in drug development projects

Biomarkers are used in various aspects. They can e.g. provide an early signal for activity and tolerability during the drug development process. In addition they can assist in the diagnosis as well as in initial and constant prognosis of a disease. In case a biomarker is shown to have a predictive value, it can potentially be used to select the appropriate patient population for a clinical study, discriminating between patients in which the investigational treatment is likely to have a favorable risk-benefit ratio from those with a presumably unfavorable ratio. Furthermore, a validated biomarker can also play an important role as a surrogate endpoint, i.e. as a substitute for a clinical endpoint, if it is influenced by the disease or related pathophysiological processes. (see figure 1).

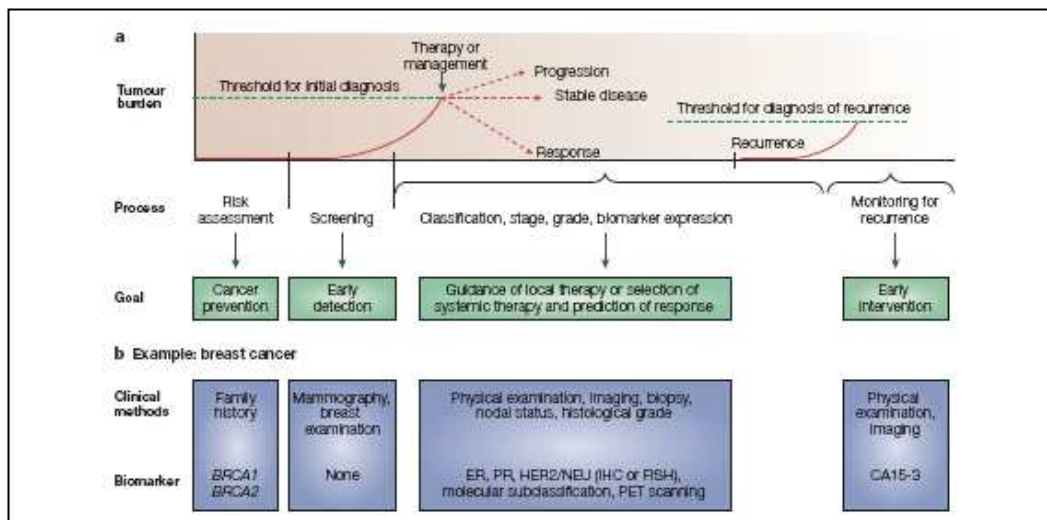


Figure 1: Schematic representation of the uses of biomarkers at different stages in the clinical evolution of cancer, with breast cancer biomarkers as an example. (Ludwig and Weinstein 2005i).

In order to promote the use of new innovative approaches such as biomarkers in drug development, leading health authorities (FDA, EMEA, PMDA) have started various initiatives (“Critical Path Initiative” by the FDA, “Road Map 2010” by the EMEA) and encouraged collaborations to address open questions with the industry and academia. These initiatives and activities resulted so far in some guidance documents, that are partly still drafts and focus mainly on the topics of pharmacogenetics and pharmacogenomics with respect to e.g. the terminology, analytical method validation. However, some key problems for industry, such as the validation of a biomarker itself, in order to be usable as a surrogate endpoint in clinical trials, still remain to be addressed and are urgently awaited.

There is a common understanding between industry and leading authorities that the inclusion of biomarker research in the drug development process has advantages for both the pharmaceutical company and the patients. On the patient's side, biomarkers are a crucial prerequisite for the ultimate goal of bringing the right drug to the right patient, thereby reducing the risk of treatment failures and adverse effects. On the side of the industry, biomarkers can facilitate internal decision making, e.g. regarding the most promising development candidate and can accelerate the drug development process.

The development of a biomarker, however, is a lengthy procedure that needs to be closely linked to the overall drug development process and should be undertaken in close cooperation with the regulatory authorities. After discovery, selection of the ideal marker and the validation of the assay methods the clinical validation of a new biomarker is the greatest challenge. This content validation, that is based on established scientific framework or body of evidence, is unlikely to be undertaken by a single company especially if clear guidance is missing. (see figure 2).

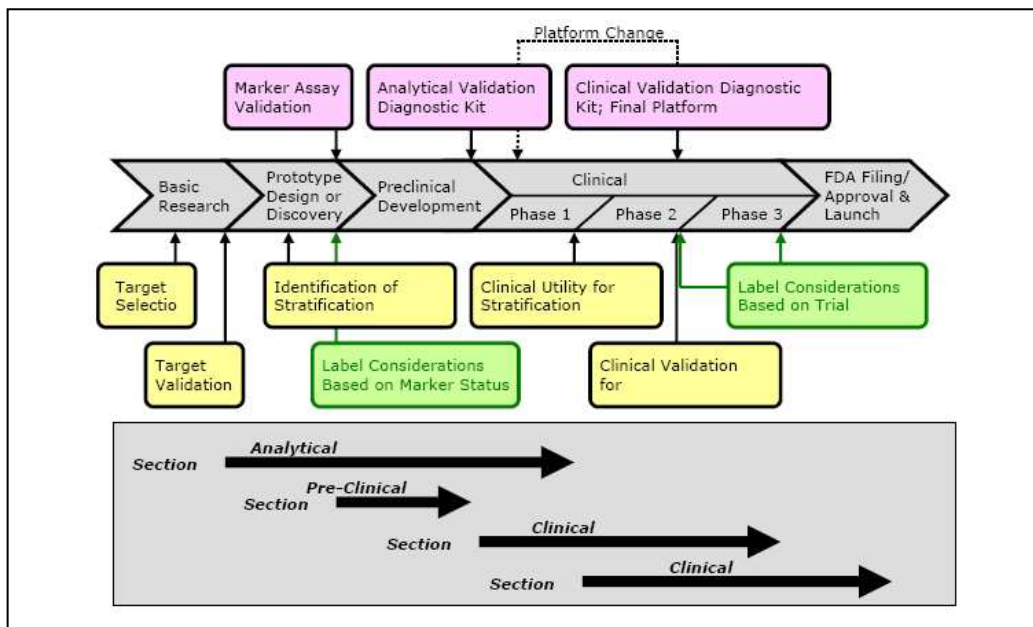


Figure 2: The so-called Drug-Device Co-Development Process as presented by the FDA with the device being e.g. biomarker assay for mandatory use in decision making about drug selection for patients in clinical practice. The diagnostic tests being considered in this context may be used to identify patients most likely to respond to a drug, patients most likely to fail to respond to a drug, and/or patients most likely to exhibit adverse events that might contraindicate drug administration. (FDA 2005ⁱⁱ).

The benefits and risks of the implementation need to be evaluated in each case individually, taking also into account operational aspects as well as budget and resource implications. Besides the obvious benefit, i.e. the acceleration of the drug development process due to the ability to take earlier and profound internal decisions and a likely earlier marketing approval e.g. based on surrogate endpoints, there are also risks. These includes the significant increase in operational activities and the risk of a label restriction thus resulting in a smaller market.

3 Operational aspects of the implementation of biomarker research in drug development projects: general considerations and case examples

Case example 1: A global Phase III trial, in which biomarker analysis was included as a mandatory part in the clinical study protocol.

The implementation of the biomarker research in this clinical trial involved a tremendous amount of operational considerations (e.g. legal and regulatory framework and considerations, third provider selection for sample preparation, analysis, transport, storage, planning of sample logistics including the logistics at the clinical sites, adequate information of patients) and interdisciplinary activities during the set-up phase in order to organize the very complex logistics that were required for a successful conduct. The process was very time consuming and required significant budget and personnel resources. Companies should take this into account in cases where inclusion of biomarker analysis in a clinical trial is optional and not requested by the scientific circumstances or by the authorities.

Case example 2: A global Phase III trial, in which biomarker analysis was initially not planned for in the protocol

At a late point in this trial a regulatory authority requested to retrospectively analyze the biomarker samples thus creating a lot of ad hoc activities (similar to the ones discussed for case example 1), that involved significant additional time, resources and budget on the sponsor's side. In contrast to case example (1) this request came up unexpectedly and in a situation of time pressure. The critical point in this case example was the availability of samples, that were no longer accessible since most patients could no longer be contacted; since 85% of samples were therefore not available for retrospective analysis, the analysis was due to caused lack of statistical significance not analyzed.

Case example 3: A global Phase II trial, in which biomarker analysis was taken into consideration for a later point in time

In this clinical trial biomarker research was implemented into the CSP but was not specified yet. Appropriate provisions for the case that the samples are eventually going to be collected for future research, were already implemented in the operational planning, and only limited resources were required to do this. Some ECs had objections as the future research to which the patient was asked to consent to was not specified yet, however, this did not pose any insurmountable challenges. Thus this compromise bears an operational risk that seemed until today to be both calculable and manageable. However, it still remains to be seen, whether in due time indeed all samples can be collected within a short time and whether all samples will still have the appropriate quality to be analyzed.

The three case examples presented show different approaches for the implementation of biomarker research in clinical studies. As a general rule, the employed biomarker strategy should correspond to the objectives and timelines of the respective clinical trial and should be in line with the overall biomarker strategy of the respective drug development program. Each operational approach has its advantages and disadvantages that need to be carefully balanced by the sponsor, when setting up a clinical study protocol. (see figure 3).

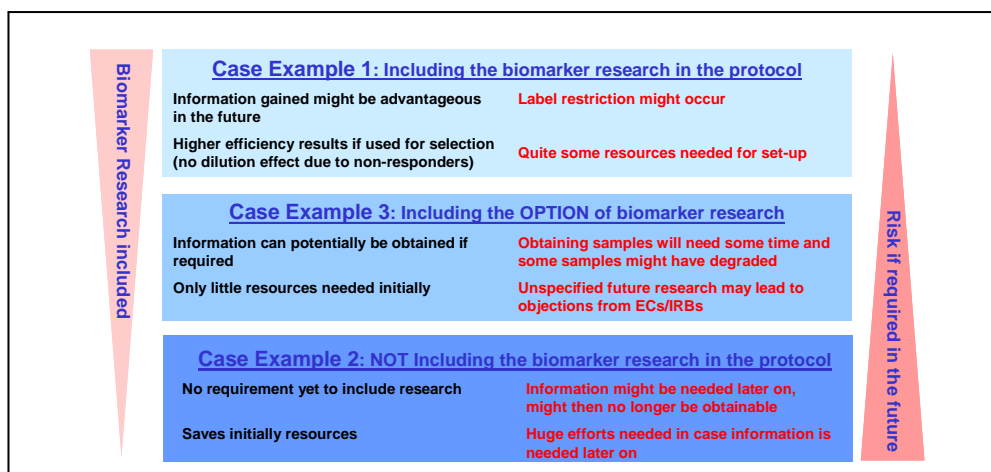


Figure 3: The advantages as well as the risks of different implementations of the biomarker research into the clinical study protocol (CSP).

There is a common understanding that molecular biomarkers will play an important role in the development of future drugs therapies. For the operational clinical team of a pharmaceutical company, this can represent a formidable challenge.

In case example (2), the consequences of a late decision or requirement to include biomarker research in a clinical trial were presented. This example shows the sudden peak in the required resources needed from various disciplines and more importantly, the unsuccessful outcome of the operational exercise of case example (2) may serve as a warning for neglecting biomarker research in clinical trials. Case example (1) presents several issues that need to be considered beforehand when a biomarker assay is included in a trial can be regarded as general practical guidance for the implementation of biomarker analyses in a clinical trial. Finally, the scenario presented in case example (3) lies in the middle between case examples (1) and (2) by taking all possible precautions for future biomarker research at a later stage. This strategy is also associated with a certain amount risk, and whether this model will be successful in this particular case example remains to be seen in the future. Nevertheless, it represents an alternative that can be considered in the planning of a study.

To date, companies are largely free in their decision to integrate biomarker research in their development process. However, it needs to be mentioned that the regulatory landscape is changing. Health authorities have become increasingly interested in the submission of respective data and it is not unlikely that the submission of biomarker data will become a standard request in the future. This momentum is sustained by authorities and institutions that are dealing with reimbursement-questions for approved drugs. Treating a patient with the drug that is most suitable for his individual case individually, in terms of safety and efficacy, appears very close to the ideal scenario in a health care system.

It was said that within 10 years, biomarkers will become a standard aspect for the drug development of any investigational drug. However, during the last 2-3 years it appeared as if the regulatory progress despite the interest from the regulatory authorities in this new tools had slowed-down. Many regulatory aspects that were already discussed earlier are still not clarified to date e.g. the validation of a biomarker, and (maybe as a consequence) only a limited number of 'known valid biomarkers' are presently available. In the light of the unmet medical needs of patients suffering from serious or life threatening diseases, the hope remains that the full potential of biomarkers will be exploited in the end and that ultimately the right dose of the right drug can be delivered to the right patient.

ⁱ **LUDWIG, J. A; WEINSTEIN, J. N.. (2005).** Biomarkers in Cancer Staging, Prognosis and Treatment Selection. *Nature Reviews Cancer* 5: 845-856.

ⁱⁱ **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) FOOD AND DRUG ADMINISTRATION. (2005).** Draft: Drug-Diagnostic Co-Development Preliminary Concept Paper.