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Review

Moving molecular targeted drug therapy towards personalized medicine: Issues related to clinical trial design

Jaap Verweij, Maja de Jonge, Ferry Eskens, Stefan Sleijfer*

Erasmus University Medical Center, Daniel den Hoed Cancer Center, s' Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

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ABSTRACT

With the event of new Molecular targets, clinical trial design requirements to perform these trials are changing. This paper discusses some of the considerations that need to be taken into account when designing a trial, including those trials that assess combinations of targets.

1. Introduction

The rapidly increasing knowledge in tumor biology has changed drug development importantly and has brought personalized medicine closer to reality. Better than before are we able to identify patient populations with tumors that harbour specific molecular alterations. If these molecular alterations are truly tumor growth driving factors, then their inhibition should lead to inhibition of tumor growth. That means that establishing the functionality of an assumed growth factor is crucial before even starting clinical research on a molecularly targeted therapy that aims to inhibit this factor. It also means that without evidence of inhibition of the target following administration of the drug of interest, we may consider to halt development of that drug.

A problem in oncology is the lack of short-term endpoints of treatment. For this reason usually only progression-free survival or overall survival benefit are sufficient to enable registration of the drug. This is completely different from other fields of healthcare where drugs can be registered upon short-term endpoint benefit. Downsides of the latter approach are the possibility that the effect on the short-term endpoint may not lead to relevant ultimate health benefits and the risk of withdrawal from registration based upon late occurring side effects, a withdrawal that hardly ever occurs in oncology.

For early decision making it is thus important to try and rely on surrogate or intermediate endpoints. In order to ensure we are all on the same page concerning the terminology used, we would like to use the term *"proof of mechanism"* for any evidence that shows that a new drug inhibits its assumed molecular target. If that target is truly functional for tumor growth, the inhibition should affect cell kinetics. This could be termed *"proof of principle"*. If the effects on cell kinetics are sufficient, inhibition of a truly functional growth factor should

* *Corresponding author.*
E-mail address: j.verweij@erasmusmc.nl (J. Verweij).
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lead to inhibition of tumor growth, which could be evidenced by anatomic size changes or validated functional imaging. This could be termed *"proof of concept"*. Each of these proofs could have a related biomarker, the pharmacodynamic, predictive (that can be used for patient selection), and the biomarker of cancer growth, respectively (Tables 1 and 2).

Given the costs involved in drug development, the abundance of new chemical entities in development, the increasing discussion in society on drug cost-effectiveness, and the limitations of affordability, we need to find all types of "proof of" as early as possible, and try to predict Drug-Registration already in the earliest clinical studies (Fuchs, 2011; Sleijfer and Verweij, 2009). This will be possible by designing smart, selective and specific clinical trials. This chapter will put current issues in designing clinical trials of molecularly targeted drugs eventually leading to approval, into perspective.

2. The preclinical information required prior to start of an early clinical trial: functionality of the target

The information we used to require prior to exposing human beings to a new chemical entity has not been changed with the emergence of molecularly targeted drugs. Here we will not discuss the obvious requirements of activity in models, safety in animals etc. But it is important to stress that since the early clinical trial will gain importance, and will be seeking selection of a better defined populations of individuals based upon detailed tumor characteristics, we will need even more specific information prior to clinical trial start.

Since we are targeting specific molecular alterations, we will first have to convince ourselves of their functional relevance in driving tumor growth (Verweij, 2008). Unfortunately as far as tumor cell related targets are concerned, the currently available preclinical models do require optimization given their lack of resemblance with the human situation. They are even more limited in predictability for targets located outside tumor cells, in the tumor environment. Yet, only this type of information will enable us to take Go/No–Go decisions on further development at the end of the first clinical studies, and will enable us to develop all of the biomarkers required for rapid drug development.

Table 1 – Biomarkers in drug development.

Pharmacodynamic biomarkers (Proof of *Mechanism*):
- To prove a drug inhibits its putative target
  - In surrogate tissues (with major limitations)
  - In tumor tissues
- To help assign an optimal dose/schedule for efficacy evaluations

Predictive biomarkers (Proof of *Principle*):
- To select patients most (or least) likely to benefit

Biomarkers of *cancer growth* (Proof of *Concept*):
- To reflect changes in tumor's anatomical and biological growth

Table 2 – Expected problems and consequences for trial design.

Chronic dosing required	→adjust DLT period and DLT criteria
PK interaction	→Include formal drug interaction assessment in the phase I study
PD interaction	→3+3+3 design →Implementation of control group

3. Trial design and flow–rapid movement to registration trials

In case of development of a drug with a well-defined functional molecular target, proven to be inhibited in the preclinical studies, the clinical studies can be focused by rigorously selecting patients whose tumors harbour the essential molecular change. Developing and assessing the so-called "selection biomarker" or "proof of principle" biomarker is thus crucial for this purpose. Nice examples can be found in the use of *c-KIT* mutations for GIST and *EML4-ALK* mutations for non-small cell lung cancer (Verweij et al., 2004; Kwak et al., 2010). Since it starts to become evident that molecular changes in tumors evolve over time, and that thus the characteristics of primary tumors may be different from those of metastases, it will become increasingly important to use actual tumor materials, i.e. a biopsy of either the primary tumor or the metastases depending on the disease stage treated, or circulating tumor cells in which characterization in great detail is nowadays also possible (Sleijfer et al., 2007; Sieuwerts et al., 2011). The latter use would avoid the practical hurdles that some have reported in performing repeat biopsies. While there are some examples of concordance of biomarker expression between primary and metastatic sites, in the majority of cases of metastatic disease, working with primary tumor tissue will likely no longer be adequate.

The evolving personalized treatment trial design for this scenario will be selection of patients based on tumor characteristics and only patients with the requested tumor characteristic will be entered on study. If the preclinical data are adequate, this means that the dose seeking part of development can even be combined with the screening for activity part. In older terms: the phase I and II study parts can be combined. If such a combined study then fails to show sufficient evidence of antitumor activity, clinical development should be halted and the drug could be brought back to the preclinical stage of research.

While previously the so-called "expanded cohort" mainly served the purpose of better defining pharmacokinetics and ensuring safety at the dose recommended for phase II studies, this cohort can also serve to screen for antitumor activity. The development and subsequent results of Imatinib for CML and GIST, Vismodegib for metastatic basal cell carcinoma of the skin and crizotinib for EML4-ALK fusion protein harbouring non-small-cell lung cancer, respectively, may serve as examples (Verweij et al., 2004; van Oosterom et al., 2001; Von Hoff et al., 2009).

In case the evidence of assumed functionality of the molecular target cannot convincingly be provided, and thus a higher level of uncertainty concerning the target may be considered,