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Review

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

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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

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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,

early use of pharmacodynamic biomarkers can be taken into account to confirm that a first-in-class drug inhibits its putative biological target, particularly when a new mechanism of action (or resistance) is revealed. If the evidence of clinical efficacy is unclear, evidence of target engagement in tumor tissues (or lack thereof) can be informative, and be mainly used for a No–Go decision should the target be inhibited insufficiently as compared to preclinical information on required inhibition in relation to tumor size effects.

One of the best validated pharmacodynamic markers remains the use of size measurement of existing tumor deposits (Verweij et al., 2009). Certainly if there is tumor regression as classified by RECIST, this can be taken as evidence of target inhibition (Eisenhauer et al., 2009). True stable disease (so no real change in tumor size) is less easy to assess, since it can also reflect the natural history of disease, certainly in case of slowly growing tumors. However, if the study aims to include proof of tumor growth in the individual prior to study entry, evidenced by making radiology studies available for the 4–6 months prior to study entry, a change in tumor growth dynamics can in theory be assessed and taken as evidence of target inhibition. This can either be by calculating the ratio of the time to tumor progression on study to the time to tumor progression on the treatment given prior to study entry, or alternatively by using the patient as its own control (Mick et al., 2000; Sonpavde et al., 2009).

Just like in case of well-defined molecular target functionality, also in this scenario combination of phase I and phase II elements can be pursued early on. Yet some kind of limited formal phase II development may be required. It is conceivable that in this scenario we need to pursue randomization early; either as a randomized discontinuation design or alternatively as a formal randomized phase II study, to decrease the financial risks related to a failed phase III study (Stadler and Ratain, 2000).

This brings us to the general cost issue. In drug development we can no longer ignore the consequences of our previous designs on the resulting costs of our treatments. The smaller the benefit we are looking for, the larger the trials will have to be, and thus the more costly drug development will be (Stewart and Kurzrock, 2009; Sobrero and Bruzzi, 2009). We may therefore be forced to limit our studies in aiming for a large magnitude of effect, which can be proven in a relatively robust way by a trial with a relatively small sample size.

4. Pharmacological aspects

From a pharmacology perspective it is also important to stress specific aspects of the early clinical trial. In essence proper pharmacologic information will be the basis of proper development decisions. Correlating drug exposure to other outcome parameters can lead to individual treatment decisions. So in performing early clinical trials the use of real time pharmacokinetics is crucial to help guide Go/No–Go decisions (Soepenberg et al., 2004; de Jonge et al., 2010; LoRusso et al., 2011).

For oral drugs the relevance of food effect and bioavailability information early on in development has been published before, where we have advocated the design of a multipurpose study (Verweij, 2008). Without early food effect studies it is highly likely that major marketing strategies will go wrong. For instance the marketing approval for lapatinib and abiraterone involves a dose that can possibly and largely be lowered without loosing activity, by taking the drug at appropriate times relative to food intake (Ratain and Cohen, 2007). Assessment of drug scheduling is impractical during the clinical phase and should be performed in models.

5. Issues of multiple simultaneous targets

In the (patho)physiology of cancer cells, a complex network of transmembrane receptors and receptor driven and mutually interactive intracellular signal transduction pathways is responsible for the malignant and/or invasive phenotype. For the majority of cancer cells, and hence human tumors, it is virtually impossible to point at one single receptor, intracellular pathway or signal protein whose abnormal functioning is solely and exclusively driving this phenotype. In the cases where, however, this seems possible, it is conceivable that due to genetic instability alternative receptors or pathways may become sequentially responsible for the malignant phenotype at various times during the course of the disease. It is conceivable that these changes might be responsible for emerging drug resistance during treatment.

Most target inhibitory anticancer agents exert biological activity ('proof of mechanism') at a specific place within the cellular signal transduction network. While monoclonal antibodies are usually highly target selective, small molecule target inhibitory agents can be more or less selective in their target affinity.

Considering the complexity and interactivity of the intracellular signal transduction network, it is difficult to envision that single target inhibitors would be able to durably and consistently inhibit overall signal transduction activity and thus show convincing proof of concept. Still, and maybe somewhat counterintuitive, clinical evidence exists that some target-specific inhibitors, be it monoclonal antibodies or small molecule inhibitors, have shown proof of concept in such malignancies as GIST, CML, HER2 positive breast cancer, renal cell carcinoma, BRAF mutated melanoma, and non-small cell lung cancer harbouring either mutated Epidermal Growth Factor receptors or oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) (Verweij et al., 2004; Kwak et al., 2010; O'Brien et al., 2003; Slamon et al., 2001; Motzer et al., 2008, 2009; Hudes et al., 2007; Robert et al., 2011; Chapman et al., 2011; Jonker et al., 2007; Mok et al., 2009). While single target inhibition in these circumstances has shown meaningful clinical efficacy, for the majority of human tumors such an approach has not (yet) proven to be very effective.

Given the described complexity and interactivity of the signal transduction network, it may be more rational to try to inhibit more than one target or pathway at a time. As nowadays a large number of biologically active single target inhibitory compounds are available, a great variety of concomitant combined approaches can be considered. For this reason, and here only given as examples of this approach, combined inhibition

of the EGFR and HER2 pathway, the Ras-Raf MAPK-ERK and PI3K-AKT-mTOR pathway, as well as combined inhibition of the C-Met and EGFR pathway are currently being explored. Even though large randomized phase III trials with well-defined endpoints such as progression-free and overall survival have started to enrol patients, a large number of these drug combination studies are focussing on short-term endpoints such as demonstration of proofs of mechanism and proof of principle. If the outcomes of these studies are convincing, the pivotal randomized phase III studies will subsequently have to be performed in order to prove these effects on overall survival. As, especially in well-selected patient populations, it can be anticipated that prolonged periods of treatment will probably have to be given in order to demonstrate and sustain effect, issues of optimal drug tolerance and treatment adherence deserve great attention. In the following we will provide additional considerations on some important aspects of target inhibitory drug development and study design.

When considering simultaneous multitarget or multipathway inhibition, the question is whether the application of a combination of single target or small spectrum inhibitory agents should be favoured, allowing for flexibility of administration of each compound, or whether one broad target inhibiting agent should be preferred. The latter would probably increase patient convenience and treatment adherence and avoid drug–drug interactions with their chance of negative alteration of drug activity or increased likelihood of side effects. Here parallels with prolonged treatment approaches in some non-malignant chronic diseases could be drawn (Ratain et al., 2008).

Decades of experience how to control actual signs and symptoms of the underlying diseases, and knowledge which targets or receptors could best be blocked in their activity, have enabled successful development of multitarget inhibition or combinational approaches of hypertension and diabetes. With treatments that most often have to be given forever, adherence is a major challenge, and ease and simplicity of drug administration is thus key.

Projecting the single agent "multi-hit" treatment paradigm to cancer would lead to favour the use of single agent therapy with broad spectrum target inhibition. However, one will have to take into account that the genetically instable nature of malignant disease differs from the more stable nature of most if not all of the mentioned non-malignant diseases, where second and subsequent lines of treatment can accomplish effectivity that is comparable to first line treatment.

With an eye on resistance development one could hypothesize that combined inhibition of multiple targets at the same time is a negative. This is currently unknown. However, if this would be the case it is conceivable that a stepwise target inhibition (subsequent, rather than multiple at the same time) might be useful. With regard to the pro's and cons of concomitant or sequential treatment, some considerations come into play.

First of all it is important to realize in the concept of growth inhibition, the aim becomes to turn cancer into a chronic disease with disease control while maintaining quality of life, throughout long periods of treatment. Thus pursuing measurable tumor shrinkage becomes less an endpoint, whereas decreasing tumor viability and stabilizing its anatomical size becomes the new endpoint. This means that disease- or progression-free survival will become very important endpoints in clinical oncology trials. In patients with hormone receptor positive metastatic breast cancer, the paradigm of sequentially treating that patient with different target inhibitory agents in order to prolong disease-free survival is already routine daily practice, but also for cytotoxic treatment these aims seem to hold in diseases as colorectal carcinoma, non-small cell lung cancer and (albeit maybe less convincing) breast cancer (Koopman et al., 2007; Marsland et al., 2005; Felip et al., 1998; Carrick et al., 2009; de Bono and Ashworth, 2010).

Second, given the fact that within the currently unravelled signal transduction network system a very large number of receptors and intracellular proteins are considered to be potential targets for specific inhibitory agents, a tremendous number of compounds and combinations become conceivable. Choices will therefore have to be made, as resources will hamper full testing of all theoretical possible combinations.

A final issue that could be considered when exploring the role of all these individual pathways and receptors is whether there chronological relationship between them in the cell-cycle order of events. For many routinely used cytotoxic agents, combination regimens are indeed based upon such considerations. If membrane bound and cytoplasmatic target processes were just as chronologically dependent on each other, it may be that certain administration sequences are most effective. Even though currently there is no indication of such 'sequence driven' target inhibition interplay, studies assessing this have recently.

In the current highly competitive field, target affinity has been suggested to provide distinction. Currently, however, there is no clinical evidence that higher target affinities predict superior clinical activity. That is, the actual pharmacokinetic behaviour and absence or pharmacokinetic interactions might possibly be more predictive for biological and clinical activity, and pharmacokinetic–pharmacodynamic correlations should be determined as much and as early as possible throughout clinical development for any target inhibitory agent irrespective its inhibitory profile.

The optimal target inhibitory strategy for a given patient should no longer solely depend on the availability of agents, but should preferentially be guided by a thorough and repeated analysis of the role and activity of the various targets that are inducing the malignant phenotype of the tumor. The optimal design for studies that are exploring the added value of these target inhibitory strategies in populations of patients should take into consideration the selection of patients based upon (repeated) molecular analyses, and should consider the assessment of repeated periods of progression-free survival rather than focussing on a single period of overall survival following the first line of treatment.

6. Rational drug combinations

As mentioned before, although several tumor growth driving mutations have been identified for which inhibition of the target results in tumor shrinkage, in most tumors the genetic

changes are complex and inhibition of a single target or pathway will not lead to sustained tumor growth inhibition. Therefore combined interference with different but related tumor targets is pursued. As already stated, the large number of new agents registered and still in development could result in a vast amount of two-drug combinations. Not to mention the possibility to combine targeted agents with classical chemotherapy and 3 or 4 drug combinations. Due to our restrictions both in budget and time, choices will continuously have to be made to prioritize the combinations to study. In former days choices for combining cytotoxic agents were based on single agent activity in a certain tumor types and non-overlapping toxicities. In addition preclinical evidence of additive or synergistic activity for the combination provided the rationale for performing clinical studies. Also for the combination of small molecularly targeted agents preclinical evidence should demonstrate at least additive effects of both agents. However, presently our preclinical models do not adequately predict efficacy of combinations of targeted agents in the clinic. Cancer cell lines have been adapted to grow in the laboratory and may not be indicative of the actual tumor they are meant to represent; they are frequently genetically very ill-defined, there is a potential mismatch between human tumor cells and mouse stroma, a severely compromised immune system in the host animal, while the endpoints used in these preclinical experiments are often ill-defined (de Bono and Ashworth, 2010). In order to improve our preclinical screening tools the NCI initiated an *in vitro* combination drug screen that accommodates testing of rationally designed choices but also allows for serendipity (Kummar et al., 2010).

From a theoretical point of view the combination of agents targeting a single crucial target in the cancer cell aiming to optimize target inhibition, the same pathway or intersecting pathways are compelling (Hamberg and Verweij, 2009).

This approach would imply that we have full understanding of the mechanism of action, resistance and interaction of the administered agents already prior to the phase I studies also enabling selection of patients based on their specific tumor characteristics to enrich the study population. Unfortunately this is not always the case as exemplified by the requirement of EGFR expression in the early studies for the presumed efficacy of cetuximab and erlotinib, and the development of BRAF inhibitors (Ratain and Glassman, 2007). Despite the limitations, and as discussed above, in specific circumstances the implementation of biomarkers may help in phase I studies to establish target inhibition in a given dose range.

Actually, most likely targeting different pathways simultaneously may be most optimal for improving the outcome for the patient.

The design of combination phase I studies is also crucial. Given the fact the most targeted agents are administered orally on a chronic basis, the classical phase I design is no longer appropriate. For the combination of targeted agents chronic dosing and therefore cumulative toxicity is as important as the toxicities observed in the acute phase, often the first 3 to 4 weeks of treatment. Also due to the aimed chronic administration of these drugs the definition of dose limiting toxicities (DLTs) should be adjusted. Patients will tolerate short periods of i.e. grade 2 non-haematological toxicities. However, for prolonged periods of time, chronic grade 2 non-haematological toxicities might be intolerable. In case of a combination of drugs an intermittent schedule may be most optimal to maximize target inhibition in balance with acceptable toxicities (Kummar et al., 2010).

For several combinations involving targeted agents (for instance the combination of VEGF-based multi-tyrosine kinase inhibitors with all kinds of cytotoxics) unexpectedly enhanced toxicity was observed allowing only dosing at doses that are quite lower than each of the respective single agent doses. Especially agents targeting the same pathway tend to induce increased toxicity preventing full dosing of either agent. Combinations with monoclonal antibodies seem better tolerated. Unfortunately data on mechanism of toxicity are limited, thereby preventing our abilities to predict the safety of a given combination of drugs (Kummar et al., 2010). In case dose reductions are necessary to enable combination treatment of targeted agents, it becomes extremely important to incorporate measurements of biomarkers in the phase I studies in order to assess adequately maintained target inhibition.

Phase I trial design will also be dictated by the anticipated interaction between the administered agents. In case a pharmacokinetic (PK) interaction is expected, which we observe more often with the combination of orally administered agents, extensive PK sampling should be incorporated during the phase I study. In order to compare the PK data for the combination with single agent data also PK for the single agents will have to be assessed (Hamberg et al., 2010). If a pharmacodynamics interaction is anticipated these should be optimally monitored.

For combination therapies different Maximum Tolerated Doses (MTDs) can be established dependent on the schedule of administration used, choices made to dose one of the agents at single agent dose and escalation steps used allowing optimal dosing of one of the agents in the combination (Hamberg et al., 2010). One must be aware of the consequences of the choices made in the study design used on the determined MTDs.

Another challenge that has to be tackled in combination phase I studies is to discern the real toxicity of the combination from the background toxicity attributable to each of the components in that combination, which by chance can be higher than is expected based on historical data. There are several options to define the toxicity attributed to the combination more precisely (Hamberg and Verweij, 2009; Hamberg et al., 2010). By using the classical 3+3 design the chance of halting the dose escalation falsely due to the effect of chance will increase with a higher incidence of unknown but true severe toxicity. This might especially impose a problem when cytotoxics are combined with targeted agents. By expanding the dosing cohorts from 6 to 9 patients the chance of halting the dose escalation falsely can be largely reduced. Another option to reduce the influence of chance on the outcome of the phase I combination study is the introduction of a control population. Patients can either be used as their own control, by administering the first cycle with a single agent only and compare the toxicity observed with the toxicity in the second cycle with the combination therapy. Another option would be to introduce a randomization in the phase I study between single agent and combination therapy. Both options might also be

combined in which the patient assigned to single agent therapy in the first cycle will be treated with the combination from the second cycle onwards. As stated these adaptations in trial design are most applicable for combinations with an expected high incidence of severe toxicity and when overlapping toxicity of the combining agents is expected.

As stated already, for combination therapy randomized phase II studies are essential in order to evaluate antitumor efficacy. Since several MTDs for a combination may be identified these should be studied in randomised phase II studies also allowing for a dose range with biological activity. It is essential to perform these studies in patient populations selected on the basis of tumor characteristics in order to increase the possible benefit of treatment. Due to our financial restrictions we will have to focus on more robust treatment effects allowing studies with smaller sample size both in phase II and III developments.

7. Regulatory issues

Regulatory decision making is a very delicate process. On the one hand, novel treatments yielding superior clinical benefit over available therapies should be made available to patients as early as possible. On the other hand, however, inactive treatments must be prevented to come on the market as this will expose patients to toxicity from inactive therapies, may block evaluation of other novel, potentially active treatments, and will lead to increased health care costs.

The highest level of certainty whether or not a novel therapy improves outcome in cancer patients can be obtained from a randomized phase III trial with overall survival (OS) as primary study endpoint. Accordingly, such trials preferably form the basis for decision making by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, since OS as a study endpoint may take long to establish and a potential OS difference between two treatment approaches can be severely obscured by active post-study treatments, surrogate endpoints for clinical benefit are increasingly used and accepted by regulatory agencies for approval. Examples of these endpoints include disease-free survival (DFS) for adjuvant therapies, progression-free survival (PFS) for the metastatic setting, and quality of life parameters, the latter in terms of pain relief or prevention/attenuation of toxicity from treatment. Taken as an example of the latter, dexrazoxane was approved for anthracycline-induced cardiomyopathy. However, such surrogate endpoints for clinical benefit are difficult to interpret. With exception of DFS in breast and colon cancer, it is unknown whether a prolongation in DFS or PFS translates into a true clinical benefit, and if so, what the magnitude of difference between two treatments should be. This uncertainty accounts largely for the frequent differences in approved indications between the FDA and EMA. A recent study revealed that for 42 anticancer drugs approved for 100 different indications by the EMA, there were differences in FDA registration for 47 of the 100 indications. Out of these, 19 indications were only approved by one agency (Trotta et al., 2011).

The successes obtained with molecular targeted drugs in selected cancer populations have added another level of complexity. Based on the identification of tumor-driving factors in an increasing number of tumor types, the availability of drugs effectively inhibiting the function of these factors, and tools enabling the identification of patients with tumors harbouring the target of interest, we nowadays sometimes see impressively and unprecedentedly improved antitumor activity in terms of response rate, PFS, and OS already in single-arm, early clinical trials. Recent examples include the studies on vemurafenib (PLX4032) in patients with metastatic melanoma harbouring a *B-RAF V600E* mutation and crizotinib in non-small lung cancer patients with an *EML-ALK* transfusion gene (Kwak et al., 2010; Flaherty et al., 2010). Logically, the question has been raised whether also such promising drugs should undergo the full traditional process of clinical testing comprising phase I, phase II and phase III studies, a process that on average takes 7 years to complete. And in case of the absence of an appropriate standard therapy the ethics of randomization may be questionable.

The fastest way to get approval for new treatments is through the accelerated approval process. For agents that are highly likely to benefit patients with life-threatening diseases compared to available treatments, accelerated approval can be obtained on the basis of surrogate endpoints for clinical benefit such as response rate, DFS or (while considered the most difficult to interpret by FDA) PFS, even in the context of single-arm studies. Importantly, post-approval trials to confirm that the drug indeed yields clinical benefit are required. In a recent review, FDA's experiences with accelerated approval for new cancer drugs were described (Johnson et al., 2011). From the initiation in December 1992 till July 2010, 35 new cancer drugs were approved for 47 different indications. For 26 of these 47 indications regular approval were obtained as clinical benefit could be confirmed in post-approval trials. Clinical benefit could not be confirmed for three indications leading to withdrawal of approval, while for the remaining 18 indications, post-approval trials were not completed (14 indications) or under review at the time of writing the article (four indications of which one, bevacizumab in metastatic breast cancer, recently lost approval). The success of this program is clear for agents for which activity could be subsequently confirmed and regular approval was obtained. However, some major problems, that in particular may apply to molecular targeted agents in selected populations, are less obvious.

After accelerated approval, confirmatory trials should be done in a timely-fashion. But because patients can get access to the drug for their life-threatening disease, accrual for such trials will be challenging and maybe even ethically questionable. Additionally, molecular targeted agents are frequently only active in very selected and thus rare tumors. Large trials in the 5% of NSCLC patients with an *EML-ALK* translocation will be still feasible because of the high incidence of NSCLC, but impossible in other more rare tumor types. For example, sunitinib and cediranib yield impressive outcomes in case series of patients with metastatic alveolar soft part sarcomas (ASPS) (Gardner et al., 2009; Stacchiotti et al., 2009). However, randomized trials will be hardly feasible in this tumor type, even when these trials are aiming for a big improvement

over another therapy and thus requiring relatively small numbers of patients. ASPS are extremely rare with in the USA an annual incidence of approximately 90 new cases of which the minority will get metastatic disease.

In addition to the problems on how to get regulatory approval swiftly, another topic that should be taken into account when allowing a drug to the market are the costs. Molecular targeted drugs are extremely expensive. Furthermore, large numbers of patients need to be screened to identify the appropriate population using expensive molecular assays. To end up with 82 evaluable NSCLC patients with *EML-ALK* translocations, 1500 NSCLC patients needed to be screened (Kwak et al., 2010). As a consequence, the costs are bearable for society when it concerns only a few drugs and indications, but with the rapidly increasing number of agents and indications, this will clearly become a major problem (Sleijfer and Verweij, 2009).

To overcome the problems mentioned above, Chabner recently made an appeal for more flexible rules for accelerated approval for molecular targeted cancer drugs without the necessity of randomized trials with minimally effective comparators (Chabner, 2011). On the basis of his proposals with some additions and alterations, novel criteria for approval for cancer drugs could be: drugs that target a specific factor, in a patient population for whom no effective treatments exists, which can be properly identified by a well-validated biomarker assay yielding high response rates (i.e. >50%), high non-progression rates (i.e. >40%) at 6 months in patients with objective tumor progression within 6 months before trial entry, with an acceptable toxicity profile tested in a series of 75–100 patients. Additionally, the drug should be cost-effective (i.e. maximum of 80,000 euros per 1 year PFS gained compared to the PFS of the tested population before trial entry). Costs should also include the screening costs identify the population of interest. After approval, subsequent trials should focus on the most appropriate schedule, further refinement to identify the population to treat, and combination studies.

8. Conclusion

With the emergence of the molecularly targeted agents and the impressive antitumor activity that is nowadays seen in early clinical trials, it is time to adapt our rules of trials design, approval and registration. Hopefully, this will lead to faster evaluation and approval of novel treatments and eventually, improved cost-effectiveness of cancer treatment and better outcomes for patients with cancer.

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