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'No risk, no fun': Challenges for the oncology phase I clinical trial time-performance ☆

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ABSTRACT

Drug development in oncology is faced with the challenge of making active new compounds available for standard of care in the shortest possible time frame. While rules and regulations create an accepted factor in delaying trial execution, protocol issues and procedures are more often a delay factor than needed, particularly in industry-sponsored studies. This provides an option to decrease trial time, without affecting patient safety.
Among the possible rooms for improvement are a balanced use of in- and exclusion criteria, justified by animal toxicology, and flexible dose escalation steps still defined *a priori*. It is also of crucial importance to make sure in the phase I programme that the pharmacology of the agent involved is appropriately understood. Including real-time pharmacokinetics, food-effect studies and, if possible, bioavailability studies in the phase I programme would decrease the risk of taking the wrong decisions for follow-on development.
The concept of increasing the number of study sites to speed up accrual has a negative effect on trial execution and is actually a delay factor that in addition has the intrinsic risk of putting patient safety at stake.

1. Introduction

Drug development in oncology, just like in any other field of medicine, is faced with the challenge of making active new compounds available for standard of care in the shortest possible time frame, with minimum possible physical risk for patients, and involving the smallest possible number of patients that enables provision of the most convincing dataset.

During a discussion on dinner choice, the late cancer drug developer, Michel Clavel, once justified his meal choice in an exquisite French restaurant with the statement: 'No risk, no fun'. What Michel wanted to say is that without some very balanced risk, one would never optimally enjoy the pleasures of life. In other words, 'Take your chances' and don't be too defensive. To some extent Michel's motto also applies to the methodologies of drug development, although this should never involve a safety risk for our patients.

To streamline the process of study performance and safeguard patient safety it is evident the rules and regulations, as issued by relevant authorities, are inevitable. The GCP guidelines and the recent EU directive for clinical trials exemplify this. Our task is to balance a minor calculated risk in phase I clinical trial performance against a potential major benefit that an earlier market release could have for a large number of patients.

Rules and regulations are an accepted fact, albeit that they create an unavoidable factor in delaying trial execution. Yet the current rules and regulations are certainly not the only administrative delaying factor. Among the worst delaying factors are the defensive internal procedures in the pharmaceu-

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tical industry, and to a lesser extent, those in cooperative group structures. While for the latter their delay does not result in pressure on the study sites to catch up with time lost, for industry related studies the time-pressures and -demands forced upon investigators sometimes become totally unrealistic. It would be great if one was able to simplify internal industry procedures and thus not worry about having to catch up for time lost.

As long as patient safety is appropriately taken into account, a balanced 'risk' in trial methodology and performance, and development strategy, could ultimately lead to an earlier achievement of GO/NO-GO decisions. A large gain in development speed could probably be achieved by carefully considering the clinical trial protocol. Clinical trials take up a considerable part of the development of new agents. Even though major changes in clinical trial design, and also in phase I trial design,[1,2] have been implemented in recent years, there is still a lot of cut and paste in protocols that should be avoided. Proper consideration in protocol writing could avoid unnecessary protocol amendments that are always a major source of time lost. Not only could time be gained in trial design and protocol details, but also in trial performance. In the following text, I will discuss several topics where time-saving may be possible in phase I clinical trials in oncology.

2. Centre selection and drug formulation

In phase I studies the safety of patients is an even greater concern than in later stage development, because of the as yet unknown toxicity profile in human beings at the start of the programme. Given this uncertainty, and in view of the need to collect optimal information, it is of utmost importance to perform these studies in investigator sites that have a specific interest in these studies and that are equipped to enable very frequent toxicity monitoring and immediate reporting of observed side effects, and not only the severe ones. Centre selection is therefore a key issue.

Likewise, much time could be saved by careful consideration of protocol content on practical issues, prior to protocol execution. In addition, it is recommended that, certainly in the case of oral drugs, multiple tablet or capsule strengths be made available prior to the start of the study. Without this availability it may be impossible to appropriately adapt dosing safely, certainly if dose limiting toxicity (DLT) is found early in the study.[3] Since formulation can take considerable time, the resulting delay in trial execution could also be very de-motivating and ultimately affect accrual.

3. The study protocol

3.1. *In- and exclusion criteria*

Rapid patient accrual and execution of phase I studies, apart from requiring appropriate numbers of eligible patients and committed investigator sites, would also profit from common-sense flexibility concerning in- and exclusion criteria. Far too often, particularly in protocols written by non-physician industry representatives, in- and exclusion criteria are unrealistically conservative, without justification from animal toxicology. This leads to a situation where the eligible patient is the odd, hardly existing patient. Obviously, this should be balanced against a non-justified relaxation on patient related criteria for which there is evidence that safety could become an issue.

There are currently some examples in the literature of institutions that have tried to create prognostic scores as a guideline to decide on accruing an individual patient into a phase I study. It turns out that some of the key factors currently used, such as an estimated survival of at least 3 months beyond entry, are very difficult to appropriately assess. Even in extremely experienced teams, the misinterpretation rate can be over 50%, albeit that the introduction of a prognostic score could decrease this to 15%. Still, it would mean that 15% of patients would in retrospect have to be considered ineligible to the trials. This offers room for further improvement.[4] The published data also suggest that prognostic selection scores enable a better prediction of potential clinical benefit,[5,6] or survival,[7–9] of patients entered into phase I studies. Most of the information comes from institutional analyses, which inevitably suffer from selection biases based on centre and health care culture related referral patterns. Therefore, a multi-institutional multi-national approach in a large sample of patients seems warranted for prognostic score development. This could lead to a much more focused selection of patients for phase I studies.

Interestingly, the currently available data seem to suggest that the number of prior therapies is not a factor to take into account for any of the above parameters. This may be different for toxicities. However, an appropriate assessment on this aspect is currently lacking. Yet, it is conceivable that drug-tolerance is dependant on remaining organ function. It is, for instance, possible that residual bone marrow capacity is not a common prognostic indicator, but could be a strong prognosticator for an individual agent when bone marrow toxicity is the anticipated DLT.

In this consideration, the specificities related to the drug target are also important. These drug characteristics on mechanism of action should also be given appropriate consideration in the possibilities to enrich the population. On the other hand, population enrichment in phase I studies should only be included if there is absolute certainty on the functionality of the assumed target. The recent development of farnesyl transferase inhibitors, for instance, and the activity of these agents in breast cancer and acute myeloid leukaemia, would never have been discovered if the phase I study population had been enriched for presence of RAS as the assumed target.

3.2. *Starting dose*

The time required to perform phase I studies is obviously related to the number of escalation steps required. Therefore, one has considered whether starting at a higher dose would be possible without increasing the safety risk for patients. In an analysis of 100 phase I studies[10] it turned out that only in two studies did the starting dose exceed the MTD, which apparently was not predicted in the extensive animal testing preceding the clinical studies. In the vast majority of cases

the MTD was > 5 times the starting dose, indicating on one hand an important safety margin, and on the other hand possibly suggesting that a somewhat higher starting dose can also be considered. This would save at most one or two escalation steps, and would thus only marginally shorten trial time by some 4–8 weeks. Whether this is worth the potential marginal increase of patient risk is still an open question. More time is likely to be gained in other aspects of phase I trial design and performance.

3.3. *Dose escalation steps*

A major and most frequently underestimated delaying factor in phase I studies is the use of pre-described dose levels, calculated from the starting dose. The use of pre-defined dose levels, almost without exception, necessitates submission of amendments to the IRBs, to either speed up the conduct of the study in the lower-dose range, or to study intermediate dose-levels once serious toxicities have been observed. The mandatory submission of these amendments and the involved review processes, particularly within industry, lead to tremendous delays in trial performance.

A flexible dose-escalation schedule (Table 1), where decisions are based on observed side effects and pharmacokinetics in the previous cohort, balanced against the animal pharmacology data with regard to anti-tumour activity, enables sponsors and investigators to jointly take appropriate decisions, without the requirement of amendments.

Another important question is the need to dose-escalate to dose-limiting toxicity (DLT). This should be carefully balanced against the toxico-kinetics observed in animals and relates to the question to be discussed hereunder on toxicity endpoint definition.

3.4. *Toxicity endpoint definition*

The definition of dose limiting toxicity is not a simple cut and paste procedure. The acceptable maximal toxicity will heavily depend on the type of agent, the type of side effect, and the route and length of drug administration. For instance, for an oral drug given every day without interruption, even daily grade 1 nausea could conceivably be considered unacceptable, while for an intravenous drug given once every 3 weeks, grade 3 nausea for 1 day may not even be considered unacceptable. Similar balancing should be considered for side effects such as mucositis and diarrhoea.

Toxicity endpoints are not frequently a time delay factor in trial performance. However, certainly with the newer agents involved, it has become questionable if one should still pursue the aim of the maximal tolerated dose (MTD), or should one rather aim for something like the optimal biological dose (OBD). The immediate first problem to the latter is to find an appropriate definition of OBD. Since this assumes adequate information on treatment related anti-tumour outcome, it is difficult to define OBD prior to outcome studies, unless a certain threshold of target inhibition is almost certainly going to lead into adequate clinical anti-tumour activity. Obviously, if definable, an OBD could be reached earlier than an MTD (although the opposite is also conceivable and would lead to discontinuation of development of the compound involved). In a recent assessment across studies, studies aiming at OBD had a significantly shorter accrual time and accrued smaller numbers of patients.[11]

Possibly, an easier definable endpoint could be the biological effective dose (BED), which would be the dose with evidence of activity below the MTD. Still, this would require dosing until the MTD, as it would require measures to assess effectivity. For the latter purpose, biomarkers are frequently used, the definitions and limitations of which will be discussed in the next paragraph.

In any case, for a proper assessment of these endpoints, highly specialised laboratory facilities are often needed, which urges for a very close cooperation and optimal communication between clinical and preclinical scientists, which in turn limits the setting in which this can be achieved and thus, again, focuses the attention on the relevance of centre selection.

3.5. *Using biomarkers for response: The dual waterfall*

A frequently used definition of a 'biomarker' is that it is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. The biomarker pursued in phase I clinical trials, in essence, can be a pharmacodynamic marker either for toxicity or efficacy, which is measured after dosing. However, most biomarkers, as currently reported in phase I studies, would be considered pharmacodynamic markers for efficacy.

It is highly questionable if the current extensive efforts to use biomarkers in phase I studies do not represent an overshoot. Only if these markers had already been validated previously in phase III studies might they help in early detection of possible activity during a phase I study. Therefore, the phase I study would very likely not provide data to support or refute the hypothesis that a biomarker predictive

Table 1 – Flexible dose-escalation steps

Dose level	Escalation or de-escalation compared to previous dose
−1	−25–100%
0	Starting dose selected based upon animal toxicology
1 and onward	Dose double until any grade 2 toxicity is observed
From Grade 2 toxicity onward	+25–100% based upon observed toxicity in previous cohorts and taking into account human pharamacokinetics, balanced against animal pharmacokinetics and aimed exposure

for efficacy exists. In this respect, assays performed on pre-treatment samples are unlikely to be of greater value than those performed on samples obtained from any other source.

This is just as unlikely as a new predictive biomarker being identified in a phase I study, which could guide patient selection in subsequent studies. For agents such as the EGFR inhibitors, for instance, the appropriate predictive biomarkers were only identified during phase III development.

We should avoid limiting the eligibility in phase I studies based on a hypothetical biomarker, and also similarly avoid the use of invasive biomarkers and the ignorance of the potential of germline DNA to predict efficacy.

Also, if a biomarker is used for pharmacodynamics, we should make every effort to try to include it in GO/NO-GO decisions. An important anatomical biomarker is the suggestion of absence of tumour growth while the patient is on treatment. This is frequently presented graphically as a so-called waterfall-plot. The waterfall-plot in itself is not always very informative, but should on the other hand not be ignored if the shift from positive to negative is too far right on the graph (Fig. 1). Adding duration of observed absence of progression could increase the relevance of the waterfall-plot in decision-making. Also, trying to incorporate biological biomarkers of pharmacodynamic activity into the anatomical size derived waterfall-plot might, in theory, with an appropriate reference matrix that should yet be developed, enable NO-GO decisions at the end of phase I studies, for reasons of absence of desired biomarker activity. At the recent ASCO conference a few examples were presented where the pharmacodynamic biomarker was extensively inhibited, while at the same time tumour growth, as measured by tumour size, was hardly arrested.[12–15] Such combined observations should give rise to concerns. If we were able to create the required reference guideline (similar to the guidelines already available for scoring anatomical tumour response and toxicity), a balanced assessment in the dual-waterfall of the point where the tumour size crosses the 0 line and where the biomarker crosses the 0 line (Fig. 2) could make us decide to stop devel-

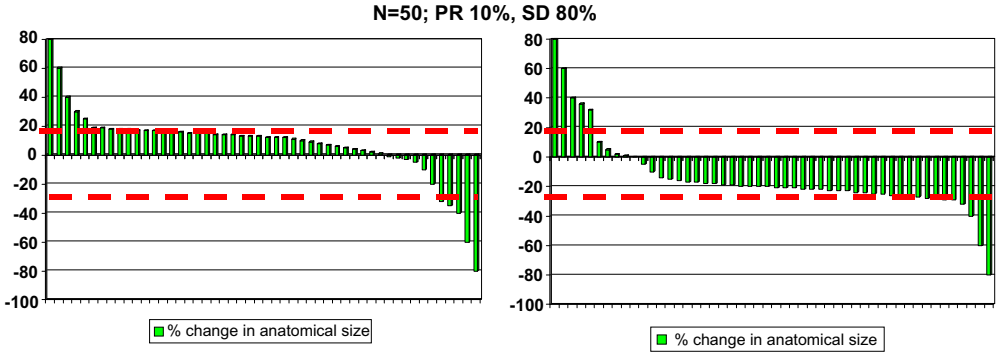

Fig. 1 – The waterfall plot. The graph shows a hypothetical study with 50 patients, yielding a 10% partial remission according to RECIST and 80% stable disease. The red dotted lines indicate the 20% size increase (progressive disease) and 30% size decrease (partial remission). The point where the bars cross 0 is important in assessing the activity of the agent. It should be as far left as possible.

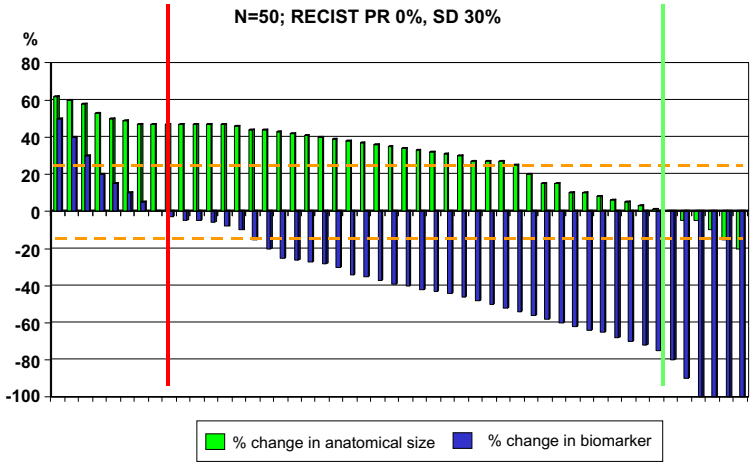

Fig. 2 – The dual waterfall plot. The green bars represent the change in size of the tumour lesions, the blue bars the percentage inhibition of the biomarker. A balanced assessment of the point where the tumour size crosses the 0 line (vertical green line) versus where the biomarker crosses the 0 line (vertical red line) could be referenced against a matrix. Preferably, both the green and the red lines should be as far left as possible.

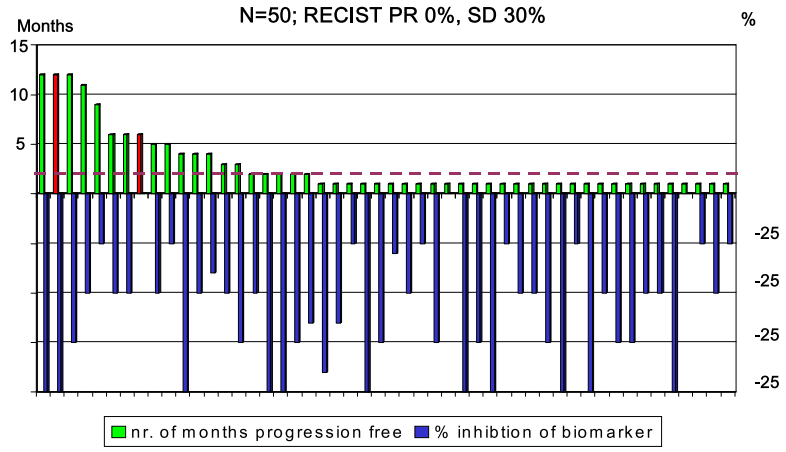

Fig. 3 – The dual waterfall time-plot. The purple dotted line represents the time of first assessment of disease after institution of the treatment under study. This is usually after 6 or 8 weeks. All bars with a height at or under this dotted line represent inactivity of the agent. The two red bars represent formal PRs according to RECIST. One could also present CRs by different colour.

opment of an agent already at this stage. Preferably, both the green and the red lines should be as far left as possible.

The problem, however, of the waterfall plot presented this way, is that it does not take into account the most important parameter of anti-tumour effect, i.e. time. Absence of progression is the ultimate aim of our treatments. For that reason it matters less if this is coincided by anatomical size regression or not. Size regression is important of course, in case of downsizing prior to surgery, or in case it coincides with symptom regression.

A possible way of graphic representation that includes the time parameter is presented in Fig. 3. This presentation would be better fitted particularly for the more modern types of agents. Giving a different colour to the complete and partial remissions and the stable diseases according to RECIST could still include the size change. In the ideal scenario the number of bars with a height higher than the dotted line should be as large as possible, and mirrored by the change in biomarker. If the size changes are mainly stable diseases, then the biomarker would be a helpful tool to decide on development continuation.

4. The importance of pharmacokinetics

One of the essential elements of any phase I study is the inclusion of the assessment of the drug's pharmacokinetics. The resulting data should be part of decision making while the studies are ongoing, but their interpretation is also important in the crucial decision on continuation of development. Getting the pharmacology right early on in development saves a lot of time at later stages. The phase I trial in this respect can be considered the key in drug development. In the development of vatalanib (PTK787/ZK 222584) it was suggested that a dose of at least a 1000 mg would achieve the exposure required for drug activity, and thus result in an enhancement of non-progressive disease. However, this assumption was based on the outcome of the day 1 pharmacokinetic data. The phase I pharmacokinetic data could also be correlated with day 1 assessment of dynamic contrast-enhancer magnetic resonance imaging.[16] Also in the same phase I trials, subsequent assessment of pharmacokinetics was done at later time points, for instance after 4 weeks of drug administration. Apart from the fact that the drug exposure was non-dose proportional, the exposure after 4 weeks was significantly less than after 1 week.[16] There are no data beyond this time point, but it is not inconceivable that there may be a further exposure reduction. Thus, starting phase III studies without further pharmacologically guided studies seems to be a major risk and provides a possible explanation for the negative outcome observed in those phase III studies.[17]

Similarly, in the recent development of the multi-tyrosine kinase inhibitor AMG706, it was decided to drop the b.i.d. dosing part of the phase I study,[18] and study this regimen at a later stage. This seems somewhat in conflict with data presented on the obtained pharmacokinetics. The dose of the agent selected for phase II and III studies with the single daily administration was chosen by the fact that the achieved exposure would provide continuous coverage above the concentration that inhibits 50% (IC50) of proliferation in human umbilical vein endothelial cells *in vitro*, realising that it is not inconceivable that an even better exposure could be achieved by b.i.d. dosing. This sounds like an argument to first fully explore this schedule before starting a phase II and III programme, rather than starting a programme with the possibility of a suboptimal single dose per day.[19]

The early pharmacokinetic data on lapatinib suggested less variability in plasma drug exposure with twice-daily dosing as compared to once daily dosing.[20] Yet the once daily dosing was pursued[21,22] and is currently registered for use. In the only published phase I study of single-agent lapatinib, objective responses or stable disease lasting > 6 months were observed at daily doses ranging from 500–1600 mg in patients with tumours expressing HER-1 and/or overexpressing HER-2, without a clear dose-response relationship. While one of the most important aims of a phase I study is to recommend a dose for further testing, this paper did not recommend one. A more recent study comparing a 500-mg twice-daily to a

1500-mg once-daily regimen[23] in a randomised phase II trial in metastatic breast cancer, did not suggest significant differences between the treatment arms. Surprisingly, the pharmacokinetic analyses were still not available at the moment of publication, which is a major limitation given the results of this study. Yet there is a possibility that the lower daily dose given b.i.d. is equivalent to the higher daily dose given once daily.

In the case of lapatinib we can conclude that the decision to use a possibly suboptimal dose did not have detrimental consequences for drug registration.

4.1. *Real-time pharmacokinetics*

As indicated, the absence of pharmacokinetic data was a limitation in the aforementioned lapatinib study, even while that study was a phase II study.

Assessing the pharmacokinetic behaviour is certainly an integral and crucial part of phase I studies. The pharmacokinetic profile could be reason for adaptations in dose or schedule of administration and is part of the recommendation of the dose for further studies. It is crucial that the pharmacokinetic data become available very rapidly, so that they can be taken into account at dose escalation decisions. For instance, should there be suggestions of non-linear pharmacokinetics this would lead to different decisions than with linear pharmacokinetics. Without pharmacokinetic information one is taking an extra and unnecessary risk when escalating to the next dose. Since dose-escalations as defined by protocol usually have an interval of at least 4 weeks, this means that real-time pharmacokinetic data need to be available within this time frame. In other words, the turnaround time should be no more than the interval of dose-escalation decisions. Not only are the pharmacokinetics a crucial element in dose-escalation decisions, they can also be a reason for definitive closure of a study. For instance, in the development of LEP, a liposomal taxol derivative, the whole blood clearance of total paclitaxel was similar for LEP (15.3+/−8.98 l/h/m(2)) and taxol (17.5+/−3.43 l/h/m(2)), and the extra-liposomal to total drug ratio increased rapidly to unity at later sampling time points.[24] Assessment of the pharmacokinetics and clinical data suggested that LEP was unlikely to have any advantages over Taxol, and in the absence of the desired pharmacokinetic profile further development was already abandoned during the phase I study.[24] More recently, further fruitless dose escalations of GDC0449 were halted when it became evident that the pharmacokinetics were saturable. This decision, that was taken while the study was running, also enabled the investigators to drop further time points for pharmacokinetic and pharmacodynamic sampling.[25] It is important that investigators and sponsors ensure availability of real-time pharmacokinetics data, but unfortunately this crucial element is far too often ignored. One could even argue that without real-time pharmacokinetic data a first-in-man single agent phase I study should not be performed.

4.2. *Food effect and bioavailability assessment*

Certainly with the development of oral compounds, the earliest possible assessment of bioavailability and the effect of food on drug absorption seems important. Unfortunately, for some reason, these aspects are frequently only studied in later stages of drug development, and as separate studies.[26] This is less efficient and creates the risk of selecting the wrong method of administration.

If an i.v. formulation of an oral compound is also available it is not inconceivable to give a single i.v. dose followed, after an appropriate washout period estimated based on the expected drug elimination half life, by the oral formulation either only once first, or immediately on a daily basis, again based on the expected half life (Fig. 4). This can be incorporated into the phase I study and would provide information on the bioavailability at all of the dose levels studied, albeit in small numbers.

It is even possible to also do a food effect study in this design, by asking the patients to first take the oral formulation, either fed or fasted, and the day thereafter the other way.

Thus, bioavailability and food-effect can be studied in the very first phase I study. The obtained data would ensure that subsequent development is performed under the adequate fed or fasted conditions during drug intake and with appropriate assessment of the consequences of bioavailability. It is evident that the information on food effect should be available prior to registration, but it is even strongly recommendable it is available prior to phase II studies. Without such information, interesting confusing situations could occur. A nice example can again be seen with lapatinib, as discussed by Ratain and Cohen.[27] They argue that by taking the drug with food, and swallowing it while drinking grapefruit juice, based upon the known consequences of this way of drug administration and the resulting pharmacokinetics it would be conceivable that a much lower dose than registered by

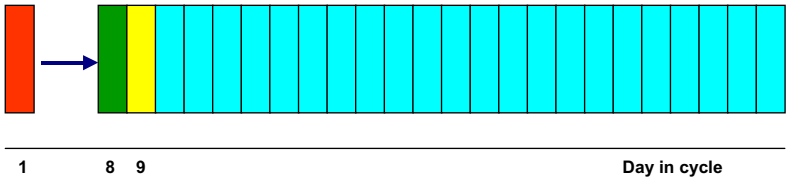

Fig. 4 – Bioavailability and food effect assessment in a single study. The bars represent drug administrations. The red bar represents an i.v. administration, the others are oral administrations. The dark green bar represents intake in a fasted state, the yellow bar intake after a standardised fatty meal. The dark blue arrow represents a 'wash-out' period. Depending on the estimated drug half-life, another wash-out could be scheduled between the green and yellow bars. The light blue bars simply represent further drug administrations as scheduled for the toxicity assessment of the phase I study.

label could be used, achieving the same drug exposure as compared to the registered dose taken without these measures. This, added to the study presented by Gomez,[23] sheds a whole new light on the required dose of lapatinib. While the derived financial savings would be fantastic for health care consumers at first sight, the detrimental consequences for subsequent drug development would create concern.

4.3. *The expanded cohort*

The classical phase I study ended when an MTD or recommended dose for further testing was defined in six patients. To enable a more precise assessment of pharmacokinetics with inter-patient variation and provide more extensive information on safety prior to the start of phase II studies this cohort was more recently expanded and is therefore now also called the expanded cohort. There is no international consensus on the size of this expanded cohort but most commonly it has been limited to 10–12 patients. However, over the last few years, particularly in industry-sponsored studies, this cohort has been increased in size with the intention to obtain anti-tumour data. Cohorts up to 50 patients have already been suggested. However, it should be realised that the expanded cohort cannot replace the appropriately sized phase II study, for which there are other issues.[1,2,28] It can only serve to provide a few hints that could help to estimate the required size of the phase II study or, in case of combinations of agents, to size the randomised phase II study or randomised phase III study. There has not been any proof yet that the expanded cohort actually serves this purpose, or has enabled the total skipping of phase II studies. While in certain circumstances it is conceivable that a phase I study is followed by a phase III study, this means taking a huge leap of faith, also in view of the fact that phase II information (and thus also phase I activity information) is known to overestimate the actual anti-tumour activity.[29] It thus seems appropriate to work with the smallest possible expanded cohort that enables the best possible assessment of inter-patient pharmacokinetic variation and inter-patient safety.

4.4. *The involved number of study sites*

As indicated, phase I studies, just like other clinical studies, should be performed in the shortest possible time-frame. Over the last decade a frequently pursued way to speed up accrual in phase I studies has been to simply add study sites. In a recent analysis of the literature, Dowlahti et al.[11] actually indicated that by expanding the number of sites, the accrual time increased and thus the opposite of what was intended was achieved. There are many possible explanations for this observation,[30] but what is most important is to realise that the increased level of complexity in a phase I study related to increasing the number of investigator sites does not at all balance against any advantage in accrual time, and thus should be avoided. Issues such as site selection, based on track record and investigator incentives, and the already mentioned topics in trial design may therefore be far more important for accrual time than just expanding the number of participating sites. The more sites, the more difficult the communication in effective exchange on safety information, thereby potentially affecting patient risk unnecessarily. The more sites, the more limited the experience per investigator site will be, leading to a decreased recognition of side effects.[31]

In preference, and with the possible exception of studies with rare molecular targets, disease-oriented phase I studies, and studies of major technical complexity, such as in the case of gene-therapy, phase I studies should involve one or at most two clinical sites.

5. Conclusion

Early clinical studies are of utmost importance in setting the stage for further development. It is critical that in industry-sponsored trials, the sponsor and the investigators are considered a true partnership, where the investigator site is a very important source of knowledge and information. Cutting and pasting in protocols should be avoided and every page of the protocol should be carefully considered. This will take time to start with, but will save time in trial execution. Patient safety should remain key in all of the considerations. We will obviously have to validate several of the suggestions put forward in the above, but in appropriate partnership a rapid trial performance is absolutely possible.

Conflict of interest statement

None declared.

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