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Position Paper

Phase 0 clinical trials: Recommendations from the task force on methodology for the development of innovative cancer therapies

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ABSTRACT

The Methodology for the Development of Innovative Cancer Therapies (MDICT) task force has been established as an expert forum to develop practical guidance on the development of innovative anticancer agents, in particular targeted agents. The task force recently addressed the utility, design and application of Phase 0 clinical trials in anticancer drug development. It was concluded that the role of non-therapeutic Phase 0 trials is controversial for several reasons, including the lack of clinical benefit for participating patients. However, it was recognised that Phase 0 trials provide an opportunity to generate essential human pharmacokinetic and pharmacodynamic data earlier in the drug development process, which could be a major advantage in the design and decision making concerning further clinical development of an agent. Construction of a 'decision chart' was highly recommended to assist investigators and sponsors in determining whether an agent is suitable for evaluation in a Phase 0 trial.

1. Background

The Methodology for the Development of Innovative Cancer Therapies (MDICT) task force is an independent international task force comprising a core group of academic drug development experts assembled to provide clinical oncologists with practical guidance on the development of targeted anticancer agents (Table 1).[1,2] The third annual meeting of the MDICT task force was held on 19th March, 2008, in conjunction with the 6th International Symposium on Targeted Anticancer Therapies, in Bethesda, Maryland. Participants were invited to discuss clinical trial methodology, focusing on the potential benefits and drawbacks of Phase 0 trials. Dr. James Doroshow, National Cancer Institute (NCI), presented an overview of

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Table 1 – MDICT task force participants.

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Phase 0 clinical trials, and MDICT Chairs Drs. Hilary Calvert and Giuseppe Giaccone led the plenary discussion. This paper provides the main considerations and recommendations ensuing from task force discussions.

2. Phase 0 clinical trial paradigm

The current Phase I/II/III model for chemotherapeutic development can be traced back to the mid 1960s.[3] However, the complexities of optimally assessing molecularly targeted agents, associated costs and clinical failure rates of over 90% have resulted in a re-evaluation of this paradigm.[4] Addressing these challenges, the United States Food and Drug Administration (FDA) established an Interagency Oncology Task Force with the NCI, and held multiple discussions with the pharmaceutical industry as part of its Critical Path Initiative.[5,6] One outcome of these discussions was the publication of the Exploratory IND Guidance document in January 2006 to expedite the identification and development of promising candidate drugs.[7] The exploratory IND supports Phase 0 studies which are defined as first-in-human trials with no therapeutic or diagnostic intent, a limited number of patients (less than 15) and with limited drug exposure (i.e. low doses administered for a limited period). Phase 0 trials can provide human data very early in clinical development.[8,9] Such trials can potentially establish whether the investigational drug affects its alleged target in the desired manner; provide human pharmacokinetic (PK) and pharmacodynamic (PD) data to inform further agent development; validate biomarker assays for target modulation effects; allow selection of the most promising candidate from a set of analogues and evaluate human biodistribution, binding and target effects using highly sensitive imaging technologies (Box 1). Dose escalation is permitted provided the objective is to modulate the target and not to establish the maximum tolerated dose (MTD). The latter would be determined later under a traditional IND Phase I/II trial; the required IND-directed toxicology studies for Phase 0 trials are limited to demonstrating the safety of the intended dosing regimen.

Box 1 Three examples of Phase 0 studies supported by the Exploratory IND Studies Guidance document.[7]

1. Pharmacokinetics or imaging: Evaluate human biodistribution and target binding characteristics using sensitive imaging techniques or microdoses (1/100th of the pharmacologically active dose [up to a maximum of 100 μg] or 30 nmol for protein products). Preclinical toxicology studies should demonstrate that a dose 100 times the proposed human dose does not induce adverse effects.
2. Pharmacologically relevant doses: Evaluate human PD and/or PK (e.g. bioavailability) of two or more analogues to select a lead agent. Preclinical toxicology studies must establish the no observed adverse effect level (NOAEL) in a rodent 2 week toxicology study; the clinical starting dose is generally 1/50th of this dose.
3. Pharmacodynamic end-point studies: Evaluate whether the new molecular entity modulates its intended target. Supporting preclinical toxicology studies are generally short-term, modified-toxicity or safety studies in two species.

The NCI has a focused drug development effort that evaluates molecularly targeted agents by assessing the proposed mechanism of action (MoA) and by correlating PK of the drug with PD effects on a specific target in both the preclinical and clinical settings.[8,9] Characteristics of agents suitable for consideration in a PD-driven Phase 0 studies include a wide preclinical therapeutic index allowing assessment of target modulation at low doses and short durations of exposure with minimal risk of toxicity. For example, a Phase 0 trial can evaluate whether an agent inhibits the intended target (PD) or if adequate drug levels are achieved following oral administration (PK). Agents that have a narrow therapeutic index, are cytotoxic, or lack a defined MoA or PD assay can be evaluated in a Phase 0 PK (i.e. pharmacologically relevant doses), biodistribution, or imaging study or in a traditional

Phase I study. Therefore, the decision to conduct a Phase 0 trial and the design of such a trial are dependent on the type of agent and the questions being asked.

Phase 0 trials with PD end-points require reliable, validated assays to measure target modulation. Only when the PD end-point has undergone intensive evaluation prior to trial initiation can questions about MoA and correlation of PK and PD effects be answered with reasonable confidence. Assay methodology determining target modulation should therefore be optimised in preclinical models using clinical procedures and tissue handling, processing and storage procedures standardised prior to clinical trial initiation. These will establish, for example, whether the amount of tissue obtained from an 18-gauge percutaneous needle biopsy is sufficient to reliably measure target modulation, or confirm that the sample handling procedures followed in an interventional radiology suite will not impair evaluation of target effects. Validation requires extensive resources and an integrated multidisciplinary team, limiting the feasibility of performing Phase 0 trials at some institutions.

Phase 0 trials that utilise PK end-points also require sophisticated and sensitive tools. PK analysis of microdoses (<100 μg) of drug requires accelerator mass spectrometry (AMS) or positron emission tomography (PET) techniques, and for drugs with nonlinear PK, extrapolation to the PK profile at therapeutic doses may be challenging.[10–12] However, accurate assessment of the PK of such drugs can be achieved by administering pharmacologically active, but subtherapeutic doses.

3. Role of Phase 0 studies in drug development

The Phase 0 concept is a new strategy with potential value for drug evaluation, especially in oncology. However, the FDA review process for exploratory INDs is relatively untested, and there is limited published experience with Phase 0 trials to date. Many questions remain about drug suitability for Phase 0 evaluation, choosing an appropriate starting dose, the extent of preclinical toxicology studies required, as well as incentives for conducting a Phase 0 trial.[13] Phase 0 study designs are therefore worthy of discussion to clarify what these trials can and cannot achieve, as well as to explain different regulatory requirements for exploratory and traditional INDs. MDICT task force members discussed the following specific questions pertaining to Phase 0 trials.

4. How can Phase 0 trials improve the efficiency and success of subsequent trials?

Phase 0 trials can provide critical human PK and PD data rather than just animal data to support the design and development of subsequent trials and can provide a close approximation to a safe, potentially pharmacodynamically active starting dose for Phase I studies. Based on these data, better informed decisions can be made to proceed directly to Phase I/II trials or conduct a combination Phase I trial with a non-investigational agent, thus expediting development of agents or combinations of agents likely to demonstrate clinical activity. Validated assay methodology and standard operating procedures (SOPs) for tissue handling, processing and storage can be incorporated into larger, definitive trials. Results from Phase 0 trials can also highlight any undesirable PK or PD properties, such as poor bioavailability or the lack of target modulation, supporting the decision to eliminate an agent from the clinical development pipeline and saving resources in the process. Thus, Phase 0 trials offer a mechanism that allows for the early assessment and expeditious development of promising agents as well as deprioritisation of agents unlikely to provide clinical benefit. Phase 0 trials with PD end-points require allocation of extensive resources early in the drug development process, but could potentially compress the overall development timeline by allowing earlier informed go/no go development decisions, improve the success rate (defined as number of agents that are approved for standard clinical use), and save valuable patient resources.[5,13]

5. Will patients participate in a clinical trial that lacks therapeutic intent?

Of importance to the MDICT task force is whether patients with cancer are willing to participate in Phase 0 trials and to donate tumour biopsy samples for research purposes, as well as the implications of obtaining informed consent from patients with advanced cancers. It was felt that such trials would be difficult to explain to most patients in general oncology clinics, and accrual would be a major hurdle for successful implementation of Phase 0 trials. In the absence of therapeutic benefit, the acceptance rate for participation and the need to undergo invasive biopsies will depend on patient willingness to support oncology research and help future patients with cancer. Most members agreed that they could imagine presenting Phase 0 trials to patients who had participated in other research trials, as they were more likely to understand the research component.[14] A desire for altruism in this patient population is indicated by the successful accrual of patients to the first Phase 0 trial conducted by the NCI.[15] However, whether this could be replicated in other institutions remains a concern.

Another consideration is whether participation in a Phase 0 trial would delay or exclude patients from participating in other trials that might confer the possibility of benefit. Given the low doses and short duration of exposure, patients from a Phase 0 study should have a shorter washout period. For instance, the NCI's Phase 0 trial, which determined the dose range and time course over which ABT-888 inhibits PARP activity, had a washout period of 2 weeks.[16] Patients who participated went on to safely participate in other trials without significant delay. MDICT members felt that for each patient there should be a defined plan of how to integrate participation in a Phase 0 trial with the overall plan for clinical care. All options, including other clinical trials, should be clearly discussed during the consent process.

MDICT agreed with the NCI's approach for their first Phase 0 trial of not excluding the patients who received the investigational agent from participating in later-phase trials of that

agent or class of agents. Acceptance of this concept will require consistency across the oncology community and changing protocol eligibility requirements to allow Phase 0 participants to enroll in the clinical trial of their choice at any institution.

6. Why not just include pharmacodynamic end-points in Phase I trials?

Including PD end-points in Phase I trials was the subject of a previous MDICT discussion,[2] which recommended including validated assays wherever appropriate to inform selection of indication in Phase II testing. However, the majority of Phase I trials conducted to date do not have PD (e.g. biologic markers) as a primary end-point, instead establishing the MTD and toxicity profile remain primary objectives.[17–19] It will require incorporation of validated PD assays into Phase I trials to obtain reliable data, which can then form a basis for agent development decisions. Thus, the amount of preclinical resources required for assay validation would be similar between Phase 0 and Phase I trials with PD end-points. However, because the toxicology data required to support a Phase 0 trial are less than that for a Phase I trial, Phase 0 trials can be initiated earlier. This does not mean that a Phase 0 trial will inherently be less safe than a Phase I trial. Sufficient safety data are generated in both cases and the drug exposure in a Phase 0 trial is significantly less than in a Phase I trial. In addition, only 10–15 patients will be required to undergo invasive tumour biopsies as opposed to 20–25 patients for a Phase I trial or more for a Phase II trial. Unlike Phase I trials, where PK and PD analyses are frequently batched at the end of a trial, real-time analyses of samples during a Phase 0 trial allows procedures to be optimised within the scope of a single trial and permit modification of the trial to explore alternate sampling times. Thus, optimal, feasible procedures are already developed for assay methodology and sample handling prior to initiation of a definitive Phase I trial. However, considerable resources are required to develop and validate such assays and to perform real-time analyses, raising concern about the wider applicability of Phase 0 trials.

MDICT task force members felt that the ability to make earlier go/no go development decisions could be of great benefit for cancer research. It will be challenging to integrate Phase 0 studies with PD end-points into pharmaceutical industries' go/no go decision making given the resources required to develop validated PD assays.[20,21] However, the industry has already adopted Phase 0 trials to select the best drug from several analogues based on PK data.[22] MDICT task force members noted that only when Phase 0 trials with PD assays and end-points show their value, i.e. a reduced development time and/or increased success rate of agents, will industry show greater enthusiasm for these studies. MDICT members noted that a decision chart to aid in the decision making process of choosing Phase 0 over Phase I development would clarify the process and promote adoption of the concept outside of the NCI. An example of such a flowchart is shown in Fig. 1.

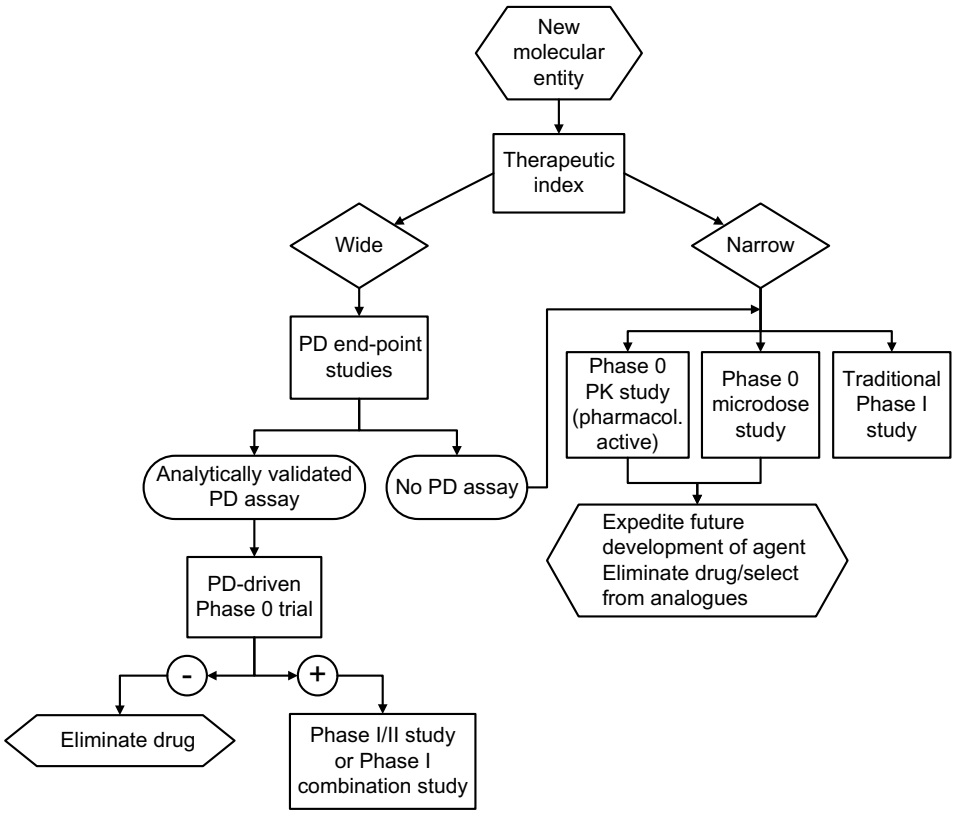

Fig. 1 – Phase 0/Phase I decision chart for clinical evaluation of a new molecular entity. The decision to proceed with a Phase I or Phase 0 study design depends on the characteristics of the agent as well as on development objectives.

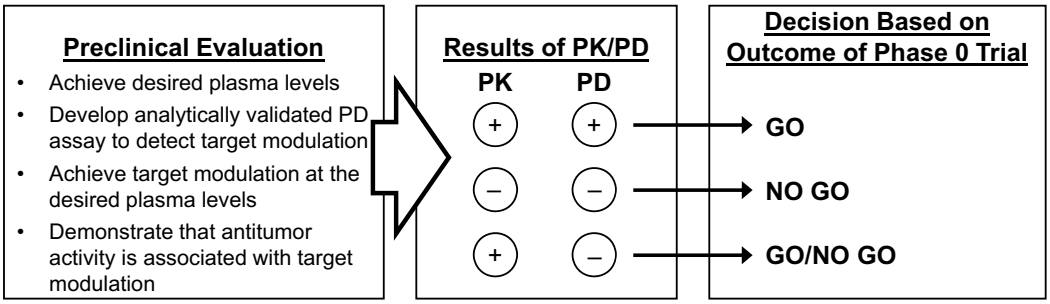

Fig. 2 – Go/No Go clinical development decisions based on PK and PD assessments in Phase 0 trials.

7. What if the drug does not modulate the intended target in a Phase 0 trial?

There is no certainty that a drug will behave in patients as it did during preclinical evaluation.[23] While Phase 0 trials provide an early opportunity to assess the PK and PD of a drug in humans, the primary end-point of target modulation may not be observed. There are several possible explanations for this: the drug may not be absorbed and sufficient plasma levels not be achieved; the target may not be modulated by the drug in some or all of the patients included in the trial or the PD assay may not be sufficiently sensitive or robust for use in human samples in contrast to what was anticipated from preclinical validation studies. Sorafenib was mentioned as an example of a targeted agent that has clinical efficacy without the presumed target, Raf, being modulated.[24] It was further noted that sorafenib did not undergo the level of preclinical evaluation that is being proposed for Phase 0 trials. For instance, the demonstration that inhibition of the presumed target was associated with an antitumour effect in animal models was not obtained before clinical testing of the drug began. Ideally, if sorafenib were going to be evaluated in a Phase 0 trial, multiple targets would have been evaluated; if one or more targets were found to be associated with the antitumour effect, those would have served as trial end-points. The decision to proceed with a Phase 0 trial is based on the preclinical data, resources available and the precise question needing to be answered about further clinical development.

The opportunity to make clinical development decisions based on observed target modulation, or lack thereof, depends on the extent of the preclinical evaluation (Fig. 2). It requires development of validated PK and PD assays and the demonstration of an association between desired target modulation at achievable plasma levels of the drug and antitumour activity in preclinical models. Accordingly, there can be three types of Phase 0 trial outcomes (Fig. 2). (1) If target plasma levels are achieved and target modulation is observed (PK+, PD+), further agent development is warranted. (2) If target plasma levels are not achieved and the expected PD effect is not observed (PK–, PD–), further development is not warranted. (3) If target plasma levels are achieved but target modulation is not observed (PK+, PD–), continued development will depend on the strength of the preclinical evaluation and type of assay used. For example, if the agent were an enzyme inhibitor, did the PD assay measure activity of the target enzyme or a downstream event of enzyme inhibition such as apoptosis? If the PD assay evaluated direct enzyme inhibition and no inhibition was observed, the agent may not be worth further development. When downstream events such as apoptosis are being evaluated, the target enzyme may have been inhibited, but cell death may require additional events that are not a direct consequence of target enzyme inhibition. In such a case, one decision could be to incorporate more than one measure of PD effect to adequately assess the agent.

As with Phase I trials, there is always a potential for false-negative results, especially in a small and highly heterogeneous patient population.[25] Choices then include continuing to pursue the agent in larger trials, administering higher doses of study drug and examining other possible biologic markers downstream of the intended PD target for evidence of activity or utilising the resources to evaluate another agent.

8. Can the costs of non-therapeutic clinical trials be defrayed?

Given the non-therapeutic nature of Phase 0 trials, costs will probably not be covered by national health systems or by insurance and therefore will have to be covered by research funds or drug sponsors. This may make conducting a Phase 0 trial more feasible for a pharmaceutical company with assay development resources and a broad pipeline than for a small biotech company.

9. Conclusions

The mechanism of clinically testing new oncology drugs has not changed substantially in 40 years. The failure rate for new oncology drugs is currently over 90%.[4] Phase 0 trials provide an alternative early drug development paradigm that addresses some of the current pitfalls. This new paradigm incorporates validated assays for assessing PD and PK early in clinical development to potentially expedite rational drug development. Through this mechanism, drugs unlikely to have a therapeutic effect may be deprioritised early in the interest of furthering the expeditious development of more promising and potentially efficacious agents. An aspect of Phase 0 trials that have already demonstrated value to industry is informing selection of true clinical development candidates among analogues based on PK parameters.[22] However, only once Phase 0 trials are more widely adopted will it be

possible to answer the most critical and commonly asked questions about the concept: do Phase 0 trials actually shorten the drug development timeline; what percent of drugs would qualify for Phase 0 testing; would patients in centres outside of the NCI volunteer for trials of such nature; and would early go/no go decisions offset the costs of validating a PD assay so early in development? One suggestion from the MDICT task force to explore the Phase 0 concept more thoroughly is to consider running traditional Phase I and PD-driven Phase 0 studies in parallel to evaluate the impact of the Phase 0 trial on the subsequent development of an agent. Throughout these discussions, the MDICT task force recognised that although the PD-driven Phase 0 trials are complex and require intense resource utilisation earlier than traditional Phase I studies (prior to initiating the clinical trial), they have potential value in oncologic drug development by informing the path of new agents early in the clinical evaluation process.

Conflict of interest statement

None declared.

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