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Position Paper

Targeted agents: How to select the winners in preclinical and early clinical studies? ☆

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ABSTRACT

There has been a significant shift within oncology drug development away from empiric screening of cytotoxic compounds to the era of genomics and molecularly targeted agents. The drug development process is evolving with greater emphasis on proof-of-mechanism studies in both preclinical and early clinical development. The Methodology for the Development of Innovative Cancer Therapies (MDICT) Task Force, established as a forum for academic and pharmaceutical leaders to discuss methodological issues in targeted anticancer therapy development, met in March 2010 to review what were the minimal data required to make appropriate decisions about moving new targeted cancer agents from late preclinical development into phase I and from phase I into phase II trials. A number of specific questions were posed, and responses to each developed through survey, literature review and discussion at the face to face meeting of the MDICT Task Force. Consensus emerged around the necessity to demonstrate proof-of-mechanism and obtain information on key pharmacokinetic aspects of drug behaviour in late preclinical and early clinical trials. However, controversy remains on the extent of *in vivo* anti-tumour efficacy required to support clinical development of targeted agents. A systematic review of the data in this area would be informative. Further, while objective response in phase I trials may be a favourable signal about the potential activity of a new agent, debate exists around the weight that should be placed on the observation of stable disease or functional imaging changes in driving drug development decisions in the absence of observing either responses or convincing pharmacodynamic data in phase I. MDICT made a number of recommendations that may aid in future development of targeted agents.

1. Introduction

Preclinical drug development involves a series of steps including *in vitro* assays followed by *in vivo*, pharmacological and toxicological studies. There has been a paradigm shift in antineoplastic drug development over the past few decades. Until the last 10–15 years, cancer drug development focused mainly on cytotoxic compounds often with unknown modes of

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action. This was driven by an empiric screening process of compounds for potential activity as the starting place of drug discovery. Contemporary anticancer drug development in the era of biology-driven medicine has shifted with the molecular target now being the focus of drug discovery and development. It has been proposed that preclinical development steps may need to vary depending on whether the compound has an unknown or specific target.[1] Further, it has been suggested by Workman and colleagues that the concept of a 'Pharmacologic Audit Trail' can aid in cancer drug development decisions.[2,3] In this construct, a hierarchical framework of decision points around target validation, pharmacological and pharmacodynamic measures as well as selection biomarkers are intended to optimise design and decision making in early cancer trials.

While there are standard expectations with respect to toxicology data in the preclinical arena, there is no formal consensus available on the body of preclinical and early clinical trial pharmacologic, pharmacodynamic and efficacy data required to advance new agents along the drug development pathway. As well, there remains debate about the performance and predictive value of commonly used *in vivo* xenograft models in predicting clinical efficacy of molecularly targeted drugs. Beyond the nature of the *in vivo* model, questions remain unanswered regarding the number of models to test and whether they should be molecularly characterised. Finally, the role of non-toxicity end-points such as pharmacokinetic, pharmacodynamics (molecular markers) and functional imaging in decision making at the end of phase I remains a topic of continued discussion. All the aforementioned factors have yet to be studied in depth in the context of combining two or more molecular targeted drugs, a therapeutic strategy that is currently being deployed in many Phase I/II clinical trials.

Therefore, in an effort to develop consensus and highlight where data are needed to resolve controversy, the Methodology for the Development of Innovative Cancer Therapies (MDICT) Task Force discussed this topic at its meeting in March 2010: '*Targeted agents: How to select the winner in preclinical and early clinical studies*'.

The 'Methodology for the Development of Innovative Cancer Therapies' (MDICT) Task Force was established by the NDDO Research Foundation as a forum for the discussion of methodological issues in contemporary oncology drug development. The mission of this independent international task force is to develop practical guidance on the optimal development of anticancer targeted agents as highlighted in Table 1. Membership in the MDICT task force is by invitation and includes a core group of academic drug development experts. Representatives from industry and regulatory agencies are invited to participate in the scientific session as observers.

The fourth meeting of the MDICT Task Force occurred on 3 March 2010 in conjunction with the 8th International Symposium on Targeted Anti-Cancer Therapies in Bethesda, MD, United States of America (USA). Participants included 16 experts from academic centres in nine countries, together with nine participants from industry and regulatory agencies (listed in Appendix I). The goal of this MDICT meeting was to discuss and make recommendations regarding targeted agents and how to select the 'winners' in preclinical and early clinical trials. The Task Force interpreted this to mean *how to make go/no go decisions at the preclinical/phase I and at the phase I/II interface*. In preparation for the meeting, a survey of the Task Force members was undertaken asking key questions about this topic to garner opinions and identify areas of controversy (Appendix II). At the meeting, the results of the survey were discussed with the aim of developing consensus for each question posed, if possible. If consensus was not reached then a summary of the discussion was documented.

This report provides a brief scientific background summary on preclinical efficacy models and pharmacodynamic end-points to guide the decision to move agents into phase I, followed by a summary of the literature regarding end of phase I decision making. Thereafter, the report summarises the discussion held at the MDICT meeting around the questions posed and the 2010 MDICT recommendations.

2. Literature review

2.1. *Preclinical efficacy and pharmacodynamic data prior to first in human trials*

In vivo testing is a critical part of preclinical development because it offers the first evidence that the new agent has a favourable anti-tumour effect in a whole animal, thus accounting for other mechanisms impacting on cancer growth such as the stromal environment. As well, it provides valuable animal pharmacokinetic and pharmacodynamic information that can be used to plan the starting dose and schedule of subsequent phase I studies. The focus of this section is review of the data requirements generated from *in vivo* studies. What information is required to move an agent from pre-clinical to clinical phase I testing? In order to address this topic, we assumed the compound has shown convincing *in vitro* activity against a panel of cancer cell lines, as well the formulation and toxicology data supporting its study in human.

Table 1 – Mission and goals of the MDICT Task Force.

The mission of MDICT is to develop practical guidance on the optimal development of innovative anticancer agents.

1. Methodological guidance developed by MDICT should improve the efficiency of the future development of oncology drugs, in particular the early clinical phase.
2. Output generated by MDICT should be generalisable to all targeted agents and not just confined to one drug class.
3. Methodological output generated by MDICT should be made publicly available without restrictions on its use.
4. Organisational aspects of early-phase clinical development of anticancer agents will be addressed to promote the smooth flow of the most interesting agents thought the clinical development pipeline worldwide.

2.2. Preclinical efficacy and pharmacodynamic data requirements

While there are specific requirements for toxicological studies of new agents before they can be studied in first in human trials, only general considerations exist, for example from the European Medicines Agency (EMEA), regarding the preclinical efficacy data set needed prior to clinical testing of a new cancer agent. Furthermore, there is no specific consensus in the research community on the minimal data required. In general, according to Hirschfield,[4] preclinical studies should support the *biologic plausibility* of the agent and its target being relevant in cancer and that there is a 'reasonable' expectation that *benefit may be achieved at safe doses* in humans. As outlined by Eisenhauer et al.[5] preclinical studies should provide data on (i) *the agent and its effect on target*, (ii) *in vivo* and *in vitro efficacy*, as well as (iii) *pharmacokinetics*.

In the era of molecular targeted agents, the target is not only usually known but the agent has been selected to inhibit or modulate it. The preclinical data set must include information supporting the validity of the target in preclinical models, and experimental results showing that the drug is affecting its target *in vitro* (for example downstream changes in protein phosphorylation).

Beyond these data, prior to initiating clinical studies there should be a reasonable expectation of benefit in humans based on results of *in vivo* efficacy experiments. The importance of this is to demonstrate the agent has activity in a living organism mediated through target inhibition/modulation. In the ideal situation the following data from *in vivo* models would be available: dose related effects on drug plasma levels, on target inhibition in implanted tumours, and dose-related anti-tumour efficacy. These data would create a body of evidence supporting that there was a direct relationship between drug levels achieved, target inhibition/modulation and tumour shrinkage. Ideally as well they would assess target inhibition using an assay that was intended for extrapolation to clinical studies.[5]

Animal pharmacokinetic data including absorption, distribution, and metabolism are used to plan further drug testing. Half life of the drug aids in determining dosing intervals. Correlations between plasma drug levels and toxicity and efficacy in animal models are used to plan dose escalations in subsequent phase I studies. Knowledge of metabolism and organs involved will help to predict and avoid adverse drug interactions.

2.3. Choice of in vivo models

As outlined by Suggit[6] and Damia,[1] a variety of *in vivo* models are used to screen compounds for possible clinical activity. These include murine tumour models, *in vivo* hollow fibre assay, subcutaneous implanted human tumour xenografts, orthotopic and metastatic tumour models, and genetically engineered cancer models. It is beyond the scope of this paper to explore these techniques in detail, however a brief description of each and their strengths and limitations will follow.

Beginning in the 1950s, *murine tumour models* were deployed to screen new drugs for anti-tumour activity and initially focussed on leukaemic cell lines. After a few decades, this approach was modified given it tended to preferentially select for compounds active against fast growing tumours. Solid tumour models such as B16 melanoma and Lewis lung carcinomas were introduced.[6] Although these models did select for some active drugs to move to phase I testing, the correlations with clinical efficacy were low.[7] Thus murine solid tumour models were eventually largely replaced by xenograft approaches.

The *in vivo hollow fibre assay* was developed by NCI as an intermediary assay between *in vitro* and *in vivo* testing.[1] The aim was to better predict which active agents in the NCI expanded 60-cell line panel also show activity in xenograft testing. Tumour cells are grown in hollow fibres followed by *in vivo* implantation at intraperitoneal and subcutaneous sites of nude mice. The unique aspect of this assay is the ability of anti-neoplastic agents to enter into the hollow fibre pores, while at the same time, the pores are too small to allow cancer cells to exit. Xenograft activity was found to correlate with intraperitoneal hollow fibre response.[8] The hollow fibre method also has been described as having low rates of false negatives minimising the rejection of potentially active drugs.[1]

The assay details of *subcutaneously implanted human tumour xenografts* can vary, however the basic principle involves inoculating human tumour cells subcutaneously into nude mice. The inoculum can be either tumour cells grown as *in vitro* cell lines or fragments of fresh patient tumour biopsies. A pioneer of the subcutaneous xenograft model was Fiebig at the University of Freiburg in Germany.[9] Fiebig and colleagues developed more than 300 xenografts representative of all major tumour types by transplanting tumours s.c. into nude mice and compared the response of human tumour xenografts to the tumour clonogenic assay and found correlations of 90% (19/21) for drug sensitivity and 97% (57/59) for drug resistance.[9] Studies such as these increased enthusiasm for use of xenograft models for drug discovery and preclinical screening.

NCI conducted a retrospective study of the value of xenograft data from preclinical new drug screening in predicting phase II activity of cytotoxic drugs. Johnson et al.[8] studied 39 cytotoxic compounds for which both xenograft data and phase II trial results were available and found, except for non-small cell lung cancer, *in vivo* activity in a particular histology did not correlate well with phase II activity in the same human cancer histology.

Whether the s.c. xenograft model predicts for drug activity in the clinic is still a matter of debate. As outlined by Kelland,[10] the advantages of the s.c. xenograft model in the era of cytotoxics include: growth of tumours can be monitored using simple caliper measurements, it is useful for assessing pharmacokinetics and pharmacodynamics, and attempts have been made towards validation. Major disadvantages include poor transplant uptake when using patient samples, methods are time-consuming and expensive, and there are animal ethics issues. The s.c. xenograft model often does not metastasise, so it is a poor model for assessing metastasis. Furthermore, the data from targeted agents have not been systematically reviewed.

Orthotopic xenograft tumour models involve the transplantation of human tumour material to a matched anatomical site of origin in the mouse. For example, human colon cancer cells

are transplanted to the mouse colon. Advantages of orthotopic tumour models are that they more often metastasise to similar sites as in humans and they allow studies to target processes of local invasion and spread.[11] Disadvantages include the more challenging technical aspects of tumour implantation and the fact these models are more time-consuming. As well, determining the efficacy of therapy may be more difficult and require imaging assessments.[11] Whether orthotopic tumour systems improve the preclinical to clinical correlation still remains to be shown.

Improvements in genetic techniques have allowed for *genetically engineered cancer models (GEM)*. Mice are engineered to have either overexpression of oncogenes or mutated tumour suppressor genes (TSG) by gene knockout or expression of a dominant-negative TSG. These changes lead to development of spontaneous cancers.[1] A major advantage of GEM is that tumours grow in an intact immune system. Thus it more precisely mimics the human situation. Incorporation of GEM into drug development has been limited to date because of numerous issues including expense, patent and technical expertise issues, and the ability to breed animals and run experiments at the same stage of tumour growth. This is an actively growing field but its impact on preclinical drug development is limited to date.

Debate also surrounds the issue of the *number of xenograft models to evaluate* as part of new drug development. In general, activity in multiple tumour models or panels of models (rather than a single model system) is more predictive of clinical activity. In a study by Johnson et al.[8] it was found that compounds showing activity in at least 1/3 of xenografts were active in clinical study (defined as responses in at least two tumour types). As well, Voskoglou-Nomikos et al.[12] found that activity in a panel of ovarian xenografts (defined as two or more xenografts of the same tissue origin) also predict for activity in phase II clinical trials.

In vivo models also have utility in helping determine the most promising schedule or route of administration, may offer insights into genetic factors predicting for activity (since many models are now characterised genetically) and provide tissue that can be queried for drug target effects at the same time anti-tumour activity is being captured.

In summary, *in vivo* techniques are numerous and vary in their strengths and limitations. No single model system is considered the gold standard for predicting clinical activity. In general, studies of the predictive value of model types have been conducted on cytotoxic agents only.

3. Literature review

3.1. *Transition decisions from phase I to II trials of anticancer agents*

Similar to the preclinical to clinical transition, consensus guidelines are lacking outlining the nature of findings required in phase I studies to warrant progression to phase II testing. The International Conference on Harmonisation states that 'studies conducted in phase I typically involve one or more of the following: estimation of initial safety and tolerability, pharmacokinetics, assessment of pharmacodynamics and early measurement of drug activity.' While unacceptable toxicity at doses far below those likely to be required for efficacy is an example of data that may halt drug development, the nature of minimal 'positive' findings that encourage (or are necessary) for subsequent drug evaluation are left to the opinion of the clinical investigators and sponsors to determine.

The primary goal of oncology phase I (first-in-man) studies is to define the recommended dose of the new drug in the schedule(s) tested in cancer patients. Secondary goals generally also include: (i) description of toxic effects, (ii) determination of pharmacokinetic behaviour, (iii) documentation of evidence of anti-tumour anti-tumour response, (iv) description of relationships between dose (or pharmacokinetic (PK) measures). and effects on toxicity and measures of molecular drug effect on target (pharmacodynamic effects).[5]

Historically, the end-point used to determine the recommended phase II dose was toxicity. More recently, measures of drug exposure or pharmacodynamic effects have been incorporated into determination of phase II doses. Despite these newer techniques, Parulekar found that toxicity was still used to define the recommended phase II dose in a majority of cases when 60 phase I studies of targeted, non-cytotoxic agents were reviewed.[13] The 2007 MDICT position paper on design of phase I studies of targeted agents underscored this: generally it was agreed that toxicity remains a useful measurement to establish dose range and if no dose limiting toxic effects are seen, then PK measurements (e.g. area under the curve (AUC), time above threshold, or steady state concentration) and in some cases biomarker measurements (defined as tissue or imaging) were suggested as measures useful in recommending a phase II dose.[14] In addition, it was suggested that proof-of-mechanism at the recommended dose was highly desirable. However, the 'must have requirements' to make go/no go decisions were not addressed during that task force review, hence the topic for this position paper.

Others such as Yap et al.[3] have also emphasised the importance of going beyond toxicity as the single end-point in phase I trials of targeted drugs to document proof of molecular effect and wherever possible to investigate the molecular genetic characteristics of the tumour in patients who show evidence of tumour shrinkage during first-in-human trials. However, debate remains on whether stable disease or functional imaging changes in phase I trials of targeted agents are associated with eventual drug success in phase II or phase III trials. Thus, despite the invocation to add more measures in phase I to maximise what can be learnt at this early stage of drug development, it remains uncertain what *specific* observations are required to proceed to phase II – or by corollary-what, if seen or not seen, would result in a decision to stop drug development? It was this topic that was the focus of the MDICT Task Force discussion.

4. MDICT Task Force discussion: *preclinical/clinical transition*

Part one of the Task Force discussion focused on questions regarding the decision to move a targeted agent from preclinical to clinical testing. The four questions discussed are outlined in Appendix II. In addressing the questions, it was

assumed that the *target* of a new drug appeared relevant to malignancy having been 'validated' by the standard *in vitro* and *in vivo* approaches. As well, Task Force members were asked to assume that the drug which was developed to inhibit the target had formulation and toxicology data that supported its study in humans. Thus the focus of the discussion was on the ideal PK and pharmacodynamic (PD) 'credentialing' of the agent prior to first-in-human trials

4.1. *Are in vivo PK/PD data important to make go/no go decision?*

There was consensus among the Task Force members that data from *in vivo* PK/PD studies are important to the decision to bring a drug into clinical evaluation. The Task Force focused on two questions during this discussion: (i) what type(s) of *in vivo* data are necessary to *support* clinical investigation?; and (ii) what, in considering this, would be *insufficient* data to proceed to clinical trials?

Several types of *in vivo* data that would be necessary were discussed. Evidence of target inhibition in relevant models was universally agreed to be necessary. Additionally, preclinical data should include information on the minimum drug concentration and time above this level or area under the curve associated with maximal target effects. Suggestions were made that *in vivo* data should move beyond simply showing the drug interacted with its target to providing evidence of real biologic changes in the target pathway associated with anti-tumour effects. Ideally, associations such as those between drug exposure, level of target effect and reduction of tumour growth should be demonstrated.

Some Task Force members argued the inhibition of target and anti-tumour effects should be shown in multiple *in vivo* models. However, all agreed that without *in vivo* data of the type described above (PK and proof of target inhibition), clinical investigation should not proceed. At a minimum, displaying drug target effect would be required, and if there is no evidence of *in vivo* target inhibition then drug development should be stopped.

4.2. *What in vivo anti-tumour efficacy data should be seen to support clinical studies?*

The Task Force considered two questions: (i) the types and, in particular, the number of anti-tumour models required; and (ii) whether models need to be molecularly characterised with respect to the target or pathway relevant to the agent being tested. These topics gave rise to considerable debate with no consensus reached.

It was the opinion of several participants that current *in vivo* models do not consistently predict success so their value was limited. It was acknowledged, however, that there is no overview available on the performance of *in vivo* efficacy models in predicting activity of *targeted drugs* (most reviews have focused on cytotoxic agents). Such data could prove useful if patterns emerged regarding the predictive value of particular models.

On the other hand, most did agree that demonstration that a new agent has activity in a whole tumour-bearing animal was important. As noted, however, there was no consensus reached on the nature and number of models showing anti-tumour activity to support clinical testing. Those arguing in favour of multiple *in vivo* models suggested this was more representative of the complexity of human tumour genetics where the target is active/mutated/relevant, and could provide evidence to aid in future patient selection. As well, data from cytotoxic agents suggest that the more models showing preclinical activity, the more likely the compound will show clinical activity. Another point of view highlighted was that the number of models required depends on the type of drug being studied. For molecular targeted agents, activity in a tumour model where the target is present and believed relevant should be seen – lack of efficacy in an uncharacterised tumour model would not exclude the possibility that the target (or drug) has potential value in the clinic.

4.3. *What PD or PK efficacy data should be in place to support clinical trials?*

There was consensus that three key pieces of information are needed before proceeding to phase I:

(i) The minimum drug exposure required to affect the target
(ii) The Cmax or time above a threshold that is required for efficacy. The impact of the aforementioned measure on the target should be described.
(iii) Finally, information related to schedule dependency should be available.

The Task Force recognised that the relationship between PK/PD and efficacy data may not be linear, but nonetheless it is important to have these data prior to designing phase I trials. All agreed that drug development should be halted if preclinical data did not show evidence that the drug could affect its target at plausibly achievable doses.

4.4. *What other data are to be considered to make the preclinical/clinical go/no go decision?*

This open ended question generated a variety of comments. Factors such as the novelty of the drug and its target, and the clinical need the agent was foreseen to address were mentioned. Furthermore, there was general agreement that the more biomarker development done prior to clinical testing the better (this applies not only to assays used to show proof of mechanism in clinical trials but also to possible selection or predictive markers). If the agent being developed is not first in class, then factors influencing its future development were the pharmaceutical properties of the agent compared to other in-class agents, whether it was foreseen to overcome limitations of other agents affecting the same target, and its ability to be combined with other drugs.

5. MDICT Task Force discussion: phase I/II transition

In the second half of the meeting the Task Force members were asked to reflect on making go/no go decisions at the

phase I/II interface. This discussion presumed that the new drug had acceptable phase I toxicity (that a maximal tolerated dose was identified) and the discussion focused on proof-of-mechanism and efficacy data.

5.1. *Are pharmacodynamic (PD) results relevant to the decision to continue to phase II? If so, in normal or tumour tissue?*

In the context of this question, PD referred to molecular and clinical measures of target inhibition (including downstream effects). There was consensus that demonstration of target effect in tissue in clinical trial(s) is an important prerequisite for continued development of a targeted agent. This underscores the need for availability of robust and validated assays to assess this end-point in clinical tissue as part of early drug development. Most Task Force members agreed that normal tissue data only may suffice to demonstrate proof-of-mechanism, and this could be acceptable if there were clear preclinical data showing a relationship between normal and tumour tissue measures of the same PD end-point. However, showing effects in normal tissue only would not be relevant for those agents targeting tumour-*specific* proteins (e.g. mutated braf). Overall it was agreed that evidence of drug effect on its target is important and that ideally this should be demonstrated in tumour tissue and, at a minimum, at the recommended dose level.

The Task Force members acknowledged that, for some agents, there are insufficient preclinical data to be able to set criteria on the minimal degree and duration of effect on target required for anti-tumour activity. However, if data on minimal target effect for response are known, efforts to document that this effect is achieved in tumour during phase I are advocated. That being said, there are constraints around tumour biopsies (how many can be obtained and what timing post treatment) that may make this challenging.

5.2. *Are pharmacokinetic results relevant to the decision to continue to phase II?*

There was consensus concerning this question. At a minimum, Task Force members agreed PK should show that minimum drug levels/exposure required to inhibit the target in preclinical experiments can be safely achieved. Furthermore, PK results should show the drug behaviour is predictable and consistent. It is also important to look for unexpected results in PK data such as long half-life of a drug, low bioavailability, or evidence of saturable absorption for oral agents. A drug with very poor pharmacokinetic behaviour should likely be dropped from development and, if warranted, returned to the lab for more work in formulation or chemistry.

5.3. *Are objective response results relevant to the decision to continue to phase II?*

Task Force members had difficultly coming to consensus on whether the observation of objective response or prolonged stable disease was of critical importance in progressing new agents from phase I to II. Certainly, signals of clinical anti-tumour effects can be used to assist future trial planning and perhaps also provide important information on which tumour subtypes may be most likely to benefit. Some participants felt that if objective responses were observed, this observation might even trump poor PD or PK data. Whether the observation of 'stable disease' was as useful was a topic of debate. This being said, it was felt on the one hand that the goal of phase I trials are not to assess efficacy on clinical end-points, so failure to observe evidence of anti-tumour effects is not a reason to stop development. Therefore, in most cases if the compound has acceptable PK and PD data then development should move to phase II. However, an important exception to this would be when the compound being studied is evaluated in a molecular defined phase I population in which activity is expected to occur (e.g. dasatinib phase I in imatinib resistant CML). If in this scenario, no activity is seen at the recommended dose, a decision to stop development would be reasonable.

5.4. *Are the answers to Sections 4.1–4.3 the same if drug is not first in class?*

To put this question in context, Task Force members were asked to consider a situation where the drug in question is not first-in-class while the first in class drug affecting the same target did have desirable PD data and clinical response. An example was also given: 'would you be interested in a new EGFR inhibitor if it produced no skin rash or responses in mutated NSCLC?'

EGFR = Epidermal Growth Factor Receptor
NSCLC = Non-Small Cell Lung Cancer
CML = Chronic Myeloid Leukemia
AKT = does not stand for anything, it is name of a serine threonine kinase

There was some debate around this topic since the answer to the question would depend upon whether (i) the first-in-class compound *failed* in clinical trials, or (ii) the first in class was *successful* in clinical trials. If the first-in-class agent failed in clinical trials, then a failure analysis should have provided some explanation for why it failed and why the new compound would, in contrast, overcome the problem and be successful. At a minimum in this case, demonstration of target inhibition in the clinic by the new agent is required. If the first-in-class was successful in previous trials, then the advantage of the new agent over the first-in-class should be clearly demonstrated preclinically and the clinical trial should be designed to evaluate whether those observations can extend into the clinic.

5.5. *What other data are to be considered before making a go/no go decision?*

This open ended question elicited a variety of comments. Clinical safety of a new drug is always a key point of consideration. As well, the development plans for the drug must be understood. For example, one must consider if the agent is affecting a target already known to be relevant in human cancer or is first-in-class. The Task Force members recognise

drug development is very competitive and one needs to be aware of who the competitors are and their future study plans. When specific tumour types will be targeted in clinical development, appropriately designed phase I (and II) combination studies with agents relevant to that tumour type will be important, provided preclinical information suggests this is a safe and effective next step.

6. MDICT Task Force recommendations

Based on the presentations and discussion, the MDICT task force prepared a series of recommendations for the topic: *Targeted agents: How to select the 'winners' in preclinical and early clinical studies?*

6.1. Preclinical/clinical transition

1. Preclinical *in vivo* studies should provide information about PK and PD including:
   (a) Evidence of molecular target inhibition/modulation.
   (b) Drug concentrations required for target inhibition/modulation.
2. *In vivo* data, in addition to showing target effect, should demonstrate efficacy with reduction of tumour growth, including, if possible, data linking anti-tumour efficacy and the minimal level and duration of target inhibition required to achieve this.
3. Additional studies are needed to clarify areas of controversy including:
   (a) A review of the value of commonly used xenograft models in predicting the anti-tumour activity of targeted agents in later clinical studies.
   (b) Increased utilisation of tumour models representing the complexity and diversity of human disease for *in vivo* testing
   (c) Better preclinical qualification of new agents with respect to understanding of degree and duration of target inhibition/modulation required for anti-tumour efficacy. Without these data, it is not possible to understand if the target inhibition seen in phase I clinical studies is likely to be sufficient for anti-tumour effects.
4. Agents should not go into clinical development if preclinical evaluation shows:
   (a) No evidence of *in vivo* anti-tumour activity.
   (b) No evidence of effect on the drug target in in vivo tumour models at doses that are plausibly achievable in humans.

6.2. Phase I/II transition

5. Pharmacokinetic studies in phase I trials should provide information showing the drug
   (a) Meets or exceeds minimum levels (steady state, AUC or other measure) required for efficacy as extrapolated from preclinical data.
   (b) Has predictable pharmacokinetic behaviour.
6. Phase I studies should provide PD (proof-of-mechanism) results including: evidence of target inhibition or downstream pathway effects using robust and validated assays developed as part of preclinical development of the compound. Occasionally toxic effects mediated by target inhibition in normal tissue may qualify for this criterion.
7. Ideally proof-of-mechanism (PD) should be shown in tumour tissue. While normal tissue may be a suitable surrogate surrogate in most situations, it may not be if preclinical data do not support a clear relationship between normal tissue and tumour PD. Proof-of-mechanism in tumour tissue will also be important to show if the agent is:
   (a) First-in-class.
   (b) Is developed to affect a tumour-specific target (e.g. mutated braf).
8. While observation of objective responses in phase I trials is encouraging and may shape the future development path, the observation of response(s) is not a necessary requirement for a drug to continue development provided PK and PD criteria are met. In the absence of achievement of PK or PD criteria, the observation of objective response may salvage a drug for further study and, if tissues from such patients can be analysed, may also provide important information on potential molecular markers for activity. The value of stable disease (non-progression) or other measures of tumour perturbation (e.g. functional imaging changes) in predicting future drug success is unclear and merits further study.

7. Summary

There has been a significant shift within oncology drug development away from empiric screening of cytotoxic compounds to the era of genomics and molecularly targeted agents. The drug development process is evolving with greater emphasis on proof-of-mechanism studies in both preclinical and early clinical development. The MDICT Task Force, established as a forum for academic and pharmaceutical leaders to discuss methodological issues in targeted anticancer therapy development, reviewed questions regarding the minimum data required to inform decision making in late preclinical/early clinical drug development for which no regulatory guidance exists. Consensus emerged around the necessity to demonstrate proof-of-mechanism and obtain information on key pharmacokinetic aspects of drug behaviour in making decisions around the fate of drugs in late preclinical and early clinical trials. However, controversy remains on the extent of *in vivo* anti-tumour efficacy required to support clinical development of new agents. A systematic review of the data in this area would be informative. While objective response in phase I trials may be a favourable signal about the potential activity of a new agent, debate remains on the importance of observing durable stable disease or functional imaging changes in driving drug development decisions, particularly in the absence of objective response or proof of mechanism within phase I. Resolution of this debate may be possible

Appendix I. MDICT: members participating in March 2010 Task Force meeting

Academic				
Aamdal	S	The Norwegian Radium Hospital	Oslo	Norway
Awada	A	Institut Jules Bordet	Brussels	Belgium
Calvert	AH	UCL Cancer Center	London	United Kingdom
Clark	JW	Massachusetts General Hospital	Boston, MA	USA
De Braud	F	Istituto Europeo di Oncologia	Milan	Italy
Delord	JP	Institut Claudius Regaud	Toulouse	France
Eisenhauer	EA	NCIC Clinical Trials Group	Kingston, ON	Canada
Fojo	A	National Cancer Institute	Bethesda, MD	USA
Giaccone	G	National Cancer Institute	Bethesda. MD	USA
Kummar	S	National Cancer Institute	Bethesda, MD	USA
O'Dwyer	PJ	Abramson Cancer Center, University of Pennsylvania	Philadelphia, PA	USA
Sessa	C	Ospedale San Giovanni	Bellinzona	Switzerland
Soria	JC	Institut Gustave Roussy	Villejuif	France
Tolcher	AH	START (South Texas Accelerated Research Therapeutics)	San Antonio. TX	USA
Tomaszewski	J	National Cancer Institute	Bethesda, MD	USA
Industry				
Fowst	C	Pfizer	Milano	Italy
Kirsch	I	Amgen	Seattle, WA	USA
Tahkhurta	AG	AstraZeneca	Wilmington, DE	USA
Teicher	BA	Genzyme Corporation	Framingham, MA	USA
Westin	EH	Eli Lilly	Indianapolis, IN	USA
Thibault	A	Regeneron	Tarrytown, NY	USA
Winkler	J	Array BioPharma	Boulder, CO	USA
Graf Finckenstein	F	Bristol-Myers Squibb	Princeton, NJ	USA
Buck	E	OSI Pharmaceuticals	Farmingdale, NY	USA
NDDO Education Foundation				
Lobbezoo	MW	NDDO Education Foundation	Amsterdam	The Netherlands

Appendix II. Survey questionnaire for MCICT Task Force meeting 2010: Targeted agents: How to select the winners in preclinical and early clinical studies?

Part I: Making go/no go decisions at preclinical/clinical interface. This presumes that
(a) the new drug has a *target* of relevance to malignancy which is inhibited by the new drug in *in vitro* systems.
(b) the drug has *formulation* and *toxicology data* that support its study in humans.

If you wish, you may complete this section using a hypothetical agent designed to inhibit AKT.

1. Are *in vivo PK/PD data* important to make go/no go decision? If so, what type(s) of data are necessary to *support* clinical investigation?

What, in considering this, would be *insufficient* data to proceed to clinical trials?

2. What *in vivo anti-tumour efficacy data* should be seen to support clinical studies? (e.g. types/numbers of models, do models need to be molecularly characterised).
What, in considering this, would be *insufficient* data to proceed to clinical trials?
3. What *PD or PK/efficacy data* should be in place to support clinical trials? e.g. demonstration of target inhibition dose-effect in tumour models that parallels anti-tumour efficacy dose effect? Minimum PK or PD level for efficacy?
What, in considering this, would be *insufficient* data to proceed to clinical trials?
4. What other data do you look for to make the go/no go decision? Please also feel free to recommend literature addressing this topic.

Part II: making go/no go decisions at phase I/II interface. This presumes that:
(a) the new drug has acceptable type(s) of toxicity (e.g. no irreversible major organ effects) and that the upper range of dosing was established using a toxicity end-point (MTD established)

Appendix II (*continued*)

If you wish, you may complete this section using a hypothetical agent designed to inhibit AKT.

1. Are *PD results* (such as measure of target inhibition or downstream effects or even target-related toxicities) relevant to decision to continue to phase II? If yes,
   (a) is PD in *normal tissue* (e.g. skin) sufficient? Would that depend on animal PD information in normal/tumour tissue?
   (b) is PD in *tumour tissue* needed?
   (c) if PD must show target effects to continue to phase II, *what is minimum desired outcome to continue to develop agent* (e.g. consistent inhibition at what level at recommended dose?)
2. Are *PK results* relevant to the decision to continue to phase II? If yes, how?
3. Are *objective response or SD results* relevant to continue to phase II? If yes, how?
4. Are your answers to 1, 2, 3 the same if this drug is *not* the first in class affecting that target and the first in class agent has PD effects and responses seen? (e.g. would you be interested in a new EGFR inhibitor if it produced no skin rash or responses in mutated NSCLC???)
5. What other data do you look for to make the go/no go decision? Please also feel free to recommend literature addressing this topic.

through a systematic review of the results of phase I trials of targeted agents to determine if such changes are associated with eventual drug success in phase II or III trials.

8. Conflict of interest statement

None declared.

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