

Methodology for the Development of Innovative Cancer Therapies Task Force addresses methodological issues in the clinical development of innovative cancer therapies

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The Task Force on Methodology for the Development of Innovative Cancer Therapies is an expert forum established to discuss methodological issues in the early clinical development of new molecular-targeted cancer therapeutics. This paper describes the mission, structure and organization of the Task Force and its achievements thus far. Experts from academia, industry and regulatory agencies participate in Task Force meetings and discussions. Since it was established in 2006, the Task Force has met annually and has published recommendations on various design aspects of early-phase cancer clinical trials as well as on decision criteria to continue development from preclinical to Phase I and from Phase I to Phase II studies.

Keywords: anticancer agents • drug development • early-phase clinical development • guidance in drug development • molecular targets • targeted cancer therapeutics

The face of oncology drug development has changed profoundly over the last 15 years. Large numbers of anticancer agents with defined molecular target(s) have entered clinical development. Furthermore, many potential new targets have been identified and are being pursued in preclinical studies. Characteristics that differentiate targeted anticancer agents from cytotoxic agents include their usually modest toxicity profile and the fact that many may produce efficacy through slowing tumor progression, rather than causing a substantial proportion of patients to experience tumor regression. Their toxicity profile may allow daily administration and many are administered orally, whereas conventional chemotherapy is often given intravenously and in courses incorporating drug-free periods to allow recovery from toxicity.

Given the different modes of actions and types of toxicities of targeted agents compared with conventional cytotoxic agents, many believe that the methodology of their drug development requires novel approaches. In particular, optimal early-phase clinical development of targeted agents has been and continues to be debated frequently [1–3]. To promote discussion between stakeholders in drug development and the formulation of recommendations on a number of pressing drug development issues, the NDDO Education Foundation (formerly NDDO Research Foundation) took the initiative to create the Task Force on Methodology for the Development of Innovative Cancer Therapies (MDICT).

Mission

At its inauguration in 2006, the mission of the MDICT Task Force was defined as:

- To develop practical guidance on the optimal development of innovative anticancer agents, in particular targeted agents;

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- To generate methodological recommendations to improve efficiency and success rate of the development of oncology drugs, in particular in the early clinical phases (Phase I and II), including organizational aspects of early-phase clinical development;
- To promote the smooth flow of interesting new agents through the clinical development pipeline worldwide;
- Recommendations developed should be applicable to groups or classes of drugs, such as agents with a similar mode of action, not a specific agent, or to certain types of studies, not a specific study in particular;
- Output generated should be made publicly available without restrictions.

Structure & participants

The MDICT Task Force is comprised of a semi-permanent group of experts, invited to be members and administratively supported by the NDDO Education Foundation, a not-for-profit entity registered in The Netherlands. The foundation is the single sponsor of the Task Force.

Participation in Task Force meetings is by invitation and attendance may vary from meeting to meeting. Contributors to the discussions are actively engaged in early-phase clinical development of anticancer agents in a senior position at an academic or governmental research institute or at a pharmaceutical or biotechnology company. The Task Force is led by a steering committee composed of three academic experts (Calvert, Eisenhauer and Giaccone) who chair the annual Task Force meetings. An NDDO Education Foundation representative (Lobbezoo) serves the Task Force as administrator and scientific secretary.

Initially, industry and regulatory agencies were invited to send representatives to the scientific sessions as observers to comment on draft recommendations developed by the academic core membership. Currently, the Task Force operates as a group of peers, each delegate bringing his or her expertise and experience from a different working environment. In general, no more than one representative per institute or company is invited. This mode of operation ensures that the Task Force's output will be discussed between the primary stakeholders in the drug development process before it is released and published.

Task Force chairpersons and participants do not receive remuneration for their contributions to the activities of the Task Force.

Organization of meetings & output

Task Force meetings are held annually in association with the International Congress on Targeted Anticancer Therapies (TAT congress), usually the day before the opening of the congress [101]. The topic for discussion at each meeting is identified well ahead of the scheduled date by the steering committee. An expert on the subject matter is then invited to prepare an introduction to the topic for presentation at the meeting. A verbal report summarizing the Task Force meeting is always presented in one of the plenary sessions of the TAT congress, usually by one of the Task Force co-chairs. A manuscript detailing the considerations, discussions and recommendations is then usually prepared, circulated among the writing committee and submitted to an oncology journal for peer review and publication. The publication lists those present at the Task Force meeting in an Appendix.

Achievements to date

On average, 20–30 experts have participated in each meeting with fairly consistent core attendees. Approximately ten industry observers attend each meeting and individuals employed by the US FDA or European Medicines Agency have occasionally also joined the discussions.

The topics that have been discussed so far are listed in Table 1. Discussions have covered various aspects of Phase 0, I and II studies of targeted anticancer agents. Reports of the meetings held in 2006–2008 and 2010 have been published [4–7]; a paper reporting on the 2011 meeting that reviewed the topic ‘identification of patients in Phase II likely to benefit from a targeted agent’ is under preparation.

■ Phase 0 studies

The utility, design and application of Phase 0 clinical trials in anticancer drug development were discussed. It was concluded that the role of nontherapeutic Phase 0 trials in the field of cancer therapeutics is controversial for several reasons, one being the lack of clinical benefit for participating patients [4]. However, it was recognized that Phase 0 trials could provide an opportunity to generate essential pharmacokinetic (PK) and pharmacodynamic data in humans early on in clinical development, which might be an advantage in the design and execution of the drug's further development. A ‘decision chart’ was developed and included in the full paper to assist investigators and sponsors in determining whether an agent is suitable for evaluation in a Phase 0 setting.

■ Phase I studies

This first Task Force meeting addressed various aspects of Phase I studies of new targeted anticancer

Table 1. Task Force on Methodology for the Development of Innovative Cancer Therapies topics and reporting status.

Year	Topic	Report
2006	End points and other considerations in Phase I studies of targeted anticancer therapy	Published [5]
2007	Design and conduct of Phase II studies of targeted anticancer therapy	Published [6]
2008	Phase 0 clinical trials	Published [4]
2009	Combinations of targeted agents	Verbal report [†]
2010	Targeted agents: how to select the winners in preclinical and early clinical studies?	Published [7]
2011	Identification of patients in Phase II likely to benefit from a targeted agent	In preparation

[†]Presented by Hilary Calvert, during the International Congress on Targeted Anticancer Therapies 2009 congress in Amsterdam, March 2009.

therapeutics [5]. Defining appropriate end points for Phase I trials was the focus of this meeting. A review of current practice suggested that toxicity remained the most commonly used information used when making decisions on the recommended Phase II dose of targeted agents. Although a strong rationale for the use of toxic effects was recognized, the Task Force recommended investigators and sponsors also consider other end points, including biomarker effects, PK end points and antitumor activity in determining the recommended dose of a new targeted agent.

■ Phase II studies

The Task Force recommended that multinomial end points and designs should be considered for Phase II studies for molecular-targeted agents, that single-arm as well as randomized designs remain appropriate in certain settings, and that further assessment of novel end points (tumor growth kinetic assessment, biomarker or functional imaging) and designs (randomized discontinuation or Bayesian adaptive design) should be encouraged. The Task Force cautioned on the use of small randomized trials and strongly encouraged complete reporting in the literature of all Phase II trials, including negative trials [6].

■ Combinations of targeted agents

Several questions and issues regarding the study of combinations of targeted agents were addressed: how do we select (biologically) meaningful combinations of targeted agents; how do we design a Phase I study for such combinations; how do we convince drug sponsors to allow combining their targeted agents with those of other sponsors? Deliberations were based upon 42 Phase I combination studies reported in the literature and at ASCO meetings between 2005 and March 2009, investigating 33 different drug combinations. A number of (partial) solutions to the issues mentioned were identified and reported verbally during the TAT 2009 congress. A paper on this session has not yet been

published.

■ How to select the winners in preclinical & early clinical studies?

The Task Force reviewed what minimal data should be known in order to make appropriate decisions about moving a new targeted cancer agent from late preclinical development into Phase I and from Phase I into Phase II trials [7]. Consensus existed around the necessity to demonstrate proof-of-mechanism and obtain information on key PK aspects in late preclinical and early clinical studies. Controversy remained on the extent of *in vivo* antitumor efficacy required to support clinical development. Furthermore, while objective responses in Phase I trials may be a signal indicating potential clinical activity of a new agent, debate existed around the weight to be placed on the observation of stable disease or functional imaging changes in driving drug development decisions in the absence of responses or convincing pharmacodynamic data in Phase I.

Conclusion

The MDICT Task Force has proven to be a useful forum for discussion of a range of methodological issues in the early phases of development of targeted cancer therapeutics between stakeholders in academia and industry. Useful recommendations in the fields of Phase 0, I and II studies have emerged from the Task Force meetings held thus far. In view of the paucity of methodological and strategic issues in drug development of innovative cancer therapeutics, the Task Force is planning to continue its efforts.

Future perspective

As of the late 1990s, a range of innovative anticancer agents have been developed successfully. Several of these agents have changed systemic treatment strategies in solid tumors and hematological malignancies, such as advanced renal cell cancer (various

anti-antigenic agents and mTOR inhibitors), gastrointestinal stromal tumor (imatinib, sunitinib), non-Hodgkin lymphoma (rituximab) and chronic myelogenous leukemia (imatinib, dasatinib and nilotinib). Despite these successes, the unmet medical need in advanced cancer remains high. Many companies and research institutes have joined the search for new targets and drug molecules. Currently, hundreds of potential targets and experimental anticancer agents are being investigated in preclinical and clinical studies. In this context, a number of major drug development methodology challenges are foreseen, two of which will be discussed briefly.

One of the new challenges is codevelopment of new targeted agents and companion diagnostics, which serve to test for a biomarker that predicts which patients are most likely to respond to the new agent. This problem has been tackled retrospectively for epidermal growth factor receptor inhibitors with some degree of success. EGFR (activating mutations) and KRAS (wild type) mutational status have been identified and implemented in drug labeling as predictive biomarkers for EGFR-targeted agents (receptor tyrosine kinase inhibitors and monoclonal antibodies) in non-small-cell lung cancer (NSCLC) and colorectal cancer, respectively [8–10].

More recently, the ALK inhibitor crizotinib and the BRAF inhibitor vemurafenib have been evaluated prospectively in patient populations selected on the basis of a specific molecular abnormality in tumor tissue. Crizotinib has been evaluated in NSCLC having a specific EML4-ALK rearrangement and vemurafenib in advanced melanoma with the V600E BRAF mutation. Both drugs showed remarkable clinical activity in these molecularly selected patient populations and have recently received regulatory approval in advanced NSCLC and advanced melanoma, respectively [11,12]. Both approvals were for the drug in combination with a diagnostic tool testing for the ALK rearrangements in the case of crizotinib, and the V600E BRAF mutation in the case of vemurafenib. Methodological issues encountered in the combined development of a targeted agent and its companion diagnostic include the selection of an appropriate (i.e., truly predictive) biomarker for which a diagnostic kit should be developed, validation of the selected biomarker in the clinical setting, optimal phasing of diagnostic development relative to the development of the new agent itself and the feasibility of pivotal trials in molecularly fragmented patient populations.

In addition to companion diagnostic development

for new agents, the lack of predictive biomarkers for a number of approved targeted agents, such as VEGF(R)-targeting angiogenesis inhibitors, remains a challenge.

Another major challenge is the development of combinations of targeted agents from the start of the clinical development program, which is increasingly occurring. The complexity of signal transduction in tumor cells predicts that a single targeted agent may not provide sufficient signal transduction inhibition to affect tumor cells to the extent that they will stop proliferating. Parallel signal transduction pathways may be activated, bypassing the initial blockade and crosstalk between different pathways may also result in a bypassing growth signal. It is hoped that this problem may be overcome by rational combinations of targeted agents, affecting various signal transduction targets. There are multiple methodological challenges in the development of combinations of targeted agents; for instance, the rationale for the choice of individual agents or classes of agents to be combined, dose schedule and dose escalation strategy in Phase I, the optimal sequence in which drugs are to be administered, dissection of observed toxicities, and how to convince drug companies to allow combined development of their targeted agents. Whether or not combinations of targeted agents will yield viable therapeutic options remains to be seen in the years to come. Some of the initial attempts to combine different targeted agents have shown enhanced toxicity of the combination compared with the single agents, as illustrated by the combination of sorafenib and bevacizumab in patients with advanced solid tumors [13].

The examples of predictive biomarkers/companion diagnostics and combined development of targeted agents clearly illustrate the continued usefulness of a forum such as the MDICT Task Force, where major stakeholders in oncology drug development (i.e., clinical investigators and corporate drug development experts) may discuss issues of common interest and generate recommendations on the basis of accumulating evidence and experience.

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Financial & competing interests disclosure

Executive summary**Mission**

- To develop practical guidance on the optimal development of innovative anticancer agents.
- To generate methodological recommendations to improve efficiency and success rate, in particular regarding the early clinical development phases.
- To promote the smooth flow of interesting new agents through the clinical development pipeline worldwide.
- Recommendations applicable to groups or classes of drugs or to certain types of studies.
- Output publicly available without restrictions.

Structure & participation

- Semi-permanent group of experts in senior positions at academia or industry.
- Administrative support by NDDO Education Foundation (not-for-profit).
- Participation in meetings is by invitation; attendance may vary from meeting to meeting.
- Task Force is led by steering committee composed of three academic experts who also chair annual meetings.
- Regulatory agencies are invited to send representatives to annual meetings as observers.

Organization of meetings & output

- Task Force meetings are held annually in association with International Congress on Targeted Anticancer Therapies.
- Topics for discussion are identified by the steering committee.
- An expert introduces the topic at the Task Force meeting.
- A verbal report of the Task Force meeting outcome is presented during the Targeted Anticancer Therapies congress.
- A manuscript detailing considerations, discussions and recommendations is prepared and submitted to an oncology journal.

Achievements to date

- On average, 20–30 experts have participated in each meeting.
- Discussions and manuscripts thus far have covered Phase 0, I and II studies:
 - Utility, design and application of Phase 0 clinical trials in anticancer drug development (2008);
 - Various aspects of Phase I studies of new targeted anticancer therapeutics (2006);
 - End point and design issues in Phase II studies of molecular-targeted agents (2007);
 - Questions and issues regarding early-phase clinical studies of combinations of targeted agents (2009; no full report available);
 - How to select the winners in preclinical and early clinical studies? (2010);
 - Identification of patients in Phase II likely to benefit from a targeted agent (2011).

Future perspective

- Several major challenges in drug development of innovative anticancer agents are foreseen for the coming years.
- Methodology for the Development of Innovative Cancer Therapies Task Force plans to continue serving as a forum for discussion between major stakeholders in oncology drug development on the basis of accumulating evidence and experience.

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- **Describes the utility, design and application of Phase 0 clinical trials in anticancer drug development. It provides a decision chart to assist investigators and sponsors in determining whether an agent is suitable for evaluation in a Phase 0 setting.**

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Lobbezoo MW, Seymour LK, Eisenhauer EA. End points and other considerations in Phase I studies of targeted anticancer therapy: recommendations from the Task Force on Methodology for the Development of Innovative Cancer Therapies (MDICT). *Eur. J. Cancer* 44, 19–24 (2008).

- **Recommends investigators and sponsors to consider, in addition to toxicity, other end points in Phase I studies of new targeted agents, including biomarker effects, pharmacokinetic end points and antitumor activity.**

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- Provides recommendations on end points and designs for Phase II studies of molecular-targeted agents. Further assessment of novel end points (tumor growth kinetic assessment, biomarker or functional imaging) and designs (randomized discontinuation or Bayesian adaptive design) is encouraged.
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