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Design and conduct of early clinical studies of two or more targeted anticancer therapies: 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 considered aspects of the design and conduct of early (phase I and II) studies of combinations of molecular targeted agents during their 2012 meeting. The task force defined necessary non-clinical data, such as evidence of additive or synergistic effects in multiple molecularly credentialed and validated models, and appropriate pharmacodynamic marker development. A robust hypothesis was considered critical while non-clinical pharmacokinetic studies were also considered valuable.

Clinical trials should include clear objectives that will prove or disprove the hypothesis. Predictive biomarkers/classifiers should be explored in phase I studies, rather than used to select patients. Trial design should be efficient and flexible rather than based on a strict progression from phase I to II to III; researchers could consider phase I studies with an expansion cohort, Phase I/II designs or phase II studies with a safety run in. Pharmacokinetics are recommended when interactions or overlapping toxicity is expected. Pharmacodynamic evaluations should be considered especially in a subset of patients closest to the recommended dose; an attempt should be made to validate surrogate tissues to enable inclusion for all patients. Schedule and or dose should be formally explored for e.g. with a randomised or an adaptive design.

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Data and knowledge sharing was strongly recommended, including the creation of formal or informal consortia of laboratories with individual expertise in pathway or target based models, collaboration between companies to ensure that agents which are 'best in class' are combined, and the development of databases which will be able to inform the development of future recommendations/guidelines.

1. Background

Virtually all early clinical trials conducted or planned in the last decade have included at least one molecularly targeted agent, used either as a single agent, or more commonly, in combination with standard therapies (usually cytotoxic chemotherapy).[1] More recently, new targeted agents are being combined with each other, in the hopes of maximising anticancer effect by using two or more drugs active on the same target (e.g. epidermal growth factor receptor (EGFR) pathway tyrosine kinase inhibitors (TKI) plus monoclonal antibodies (MA) against EGFR[2]), or on different targets within an aberrant pathway (e.g. phosphoinositide 3-kinase (PI3K) inhibitors plus mammalian target of rapamycin (mTOR) inhibitors[3]). In some instances therapeutics that effect overlapping or complementary pathways,[4] or, may overcome resistance, (inherent or secondary,[5,6] e.g. Met or Insulin Like Growth Factor Receptor-1 (IFGR-1). inhibitors in combination with EGFR TKI) have been combined. The selection of agents to combine, and the design and conduct of early clinical trials of combinations of molecularly targeted agents has been largely empiric and based on experience with cytotoxic agents. Not surprisingly, investigators have reported numerous concerns regarding these combinations, ranging from 'supra-additive' toxicity to inferior anticancer activity.[7–10]

Despite the keen interest in exploring combinations, there is generally a paucity of data driven recommendations to guide the researcher. Available resources include the draft Federal Drug Administration (FDA) guidance[f] as well as various publications,[8,9,11,12] but these often address the rationale for combining agents based on a hypothesis, rather than specific guidance on design and conduct, and are not generally based on reviews of studies conducted.

The 'Methodology for the Development of Innovative Cancer Therapies' (MDICT) task force was established by the New Drug Development Office (NDDO) Research Foundation in 2006 to provide practical guidance on the development of anticancer targeted agents. The task force mission, membership and activities have been described in other publications.[13–15] The seventh annual meeting of the MDICT task force was held on March 6, 2012, in conjunction with the 10th International Symposium on Targeted Anticancer Therapies in Amsterdam. Participants included experts from academic centres as well as from industry. The mandate of the meeting was to review current knowledge and discuss and make recommendations regarding the design and conduct of early clinical studies of combinations of targeted anticancer agents. We report here on the meeting as well as the task force recommendations.

2. Scientific review and discussion

2.1. Review of experience to date

A review of published literature and abstracts, as well as clinical trial registries reveal literally hundreds of phase I studies on combinations of targeted agents completed, being conducted or planned. The stated rationales for exploring combinations such as these are summarised in Table 1. Although many of the combinations are in early phase development, a number have reported results in late phase II or phase III studies, in some instances being associated with significant incremental toxicity and failure to demonstrate superior efficacy compared to one agent alone.[16–18] A number of publications, as well as reviews by groups such as the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI, United States of America (USA))[8,9] have highlighted the difficulty of combining novel agents, not only with regard to trial design and endpoints, but also to successfully select agents which can be administered together in doses sufficient to result in incremental efficacy.[19]

The MDICT task force then explored issues in the design of phase I studies of combinations of targeted anticancer therapy, addressing a series of structured questions shown in Table 2.

2.2. Discussion

2.2.1. General discussion

The participants felt strongly that while combinations of novel agents were of great interest, many combinations had been tested without necessarily having all required or pertinent information available. With the increasing understanding of the multiplicity of mechanisms of cancer development and progression, it has become apparent that for most tumours, there are multi-

[f] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf.