Investigator-initiated trials of targeted oncology agents: why independent research is at risk?

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Received 18 December 2009; accepted 30 December 2009

Background: Drug development traditionally has relied upon the complementary contributions of clinicians and scientists at academic institutions and at pharmaceutical companies. Greater regulatory burdens, increased bureaucratic requirements, restricted reimbursement, and spiralling research and development costs are exerting pressure on the drug development pipeline. The result is a de-emphasis of exploratory research, particularly independent academic research, despite its proven value in identifying new drug targets and developing innovative cancer therapies.

Design: An expert panel assembled by the Biotherapy Development Association—a nonprofit international forum for academic and industry researchers, patients, and government regulatory and postregulatory agencies—examined the growing schism between academia and industry and identified several causes of declining academic research.

Results: The authors propose solutions to sustain investigator-initiated research and provide a new model whereby expert organisations provide a forum for academia and industry to plan studies within a regulatory framework to support licensure/authorisation and reimbursement for new molecularly targeted agents and biomarkers.

Conclusions: Investigator-initiated trials have led to the discovery and development of innovative, safe, and effective cancer treatments. To ensure that such research continues, action will be required on the parts of legislative and regulatory bodies, industry, universities, patient advocacy organisations, and preclinical and clinical academic scientists.

Key words: academic research, Clinical Trials Directive, drug development, investigator-initiated trials, oncology, targeted therapies

Introduction

Do independent academic researchers no longer have a role in the clinical development of anticancer drugs? What are the barriers to academic research? How can academic investigators continue to contribute value in developing and testing new targeted therapies? Such provocative issues were discussed by an expert panel convened in Innsbruck, Austria, by the Biotherapy Development Association (BDA). This paper outlines barriers to independent academic research and proposes solutions that will require action by academic investigators, pharmaceutical companies, regulatory agencies, universities, and reimbursement authorities to increase the availability of independent clinical research in oncology.

Investigator-initiated academic clinical research—conceived and developed by physician–scientists—has contributed substantially to modern oncology [1, 2]. Academic investigators have played critical roles in discovering targeted biotherapies [3] and driving innovation in design and execution of company-sponsored pivotal trials. Examples include Dennis Slamon’s development of trastuzumab at the University of California, Los Angeles [4]; V. Craig Jordan’s work at Leeds University, UK, on tamoxifen [5]; and Brian Druker’s work at Oregon Health & Science University Portland, OR, USA on kinase inhibitors [6].

Academic investigators participate in company-sponsored pivotal trials for developing prospective databases for tumour profiling and patient selection, for recruiting and monitoring...
subjects, for collecting safety and efficacy data to be used in support of product licensure and reimbursement, and also in testing novel applications of existing drugs. A key example is the study published by Smith et al. [7] in 2002 on the use of docetaxel in the neoadjuvant setting.

In recent years, regulatory and bureaucratic hurdles have increased significantly while government funding for biomedical research has declined or remained flat [8], leaving pharmaceutical companies to fill the gap, especially in late-phase clinical research [9–11]. In addition, cancer treatment is evolving from a disease-specific orientation to a targeted individualised approach, a shift that offers many new challenges, such as predicting which patients are most likely to respond to a particular therapy.

The departure from a disease-specific orientation is also changing business models, which have generally relied on new drugs with large markets to offset huge development costs. Molecularly targeted anticancer therapies are designed for use in selected patient populations, but this transition requires new thinking from both regulators and companies to ensure that investment in new drugs continues to make sense financially. And even if a new drug is licensed, pharmaceutical companies have no assurance that they will be reimbursed [12, 13].

Today, although they were once partners in drug development, industry and academia seem to be growing apart, and increasingly, the academic investigator engaged in translational and clinical research is left out, leading to a ‘lost generation’ of biomedical researchers [8, 14–16]. Patients may bear the greatest cost if independent academic research is not revived.

searching for new anticancer therapies

Independent academic clinical research in drugs has often focussed on new uses of agents with no or limited commercial potential. With the introduction of many new compounds into clinical development, independent trials using these compounds have received greater focus, often through an investigator-initiated (noncommercial) trial (IIT). These studies are usually conducted in an academic setting and most often with a drug under full patent protection. From the perspective of the pharmaceutical company, the central aim of supporting IITs is collecting additional safety data and data that could be used to support new indications or be included as part of the dossier for licensure. Academia’s interest in translational science, in many cases, dovetails with industry’s desire to bring new products to market [14].

Table 1 highlights some key differences between IITs (noncommercial) and company-sponsored (commercial) trials. Pharmaceutical companies may provide support to academic investigators through various mechanisms, while the academic researcher, as the sponsor, assumes responsibility for designing the study; writing the protocol; monitoring the study; managing, analysing, and reporting the data; indemnifying investigators and trial subjects; and selecting study personnel.

Figure 1 depicts the general process for initiating, conducting, and completing an IIT.

A survey of 28 pharmaceutical and biotechnology companies found that 88% had developed processes for soliciting and accepting proposals from academic investigators [17], but companies must be able to justify the financial support for research both internally and to regulatory bodies to ensure that the investment is legitimate and not covert promotion. By establishing standard procedures for collecting proposals, companies reduce external confusion between investigators and company representatives and minimise redundancies of clinical trials [17]. Publicising the company’s goals for IITs helps ensure that incoming proposals are strategically aligned with organisational interests [17].

Successful proposals demonstrate scientific merit, address an unmet medical need, and include a study budget and clinical supply requirements. Medical science liaisons can serve as pharmaceutical companies’ main points of contact with academia-based physicians and researchers and can monitor progress according to agreed milestones.

barriers to IITs and possible solutions

companies have limited control over IITs

IITs can often be carried out at lower cost than company-sponsored research, but companies must have a hands-off relationship with investigators to avoid appearing to influence the results. The academic investigator must adhere to good scientific practice and comply with good clinical practice monitoring and quality assurance requirements. In addition, changes in Europe require independent academic research to comply with the same governmental regulations as industry-sponsored research with licensing intention.

growing bureaucratic hurdles hamper clinical development

Around the globe, fewer IITs are being undertaken. In 2004, the European Union Clinical Trials Directive (CTD) was introduced, with the objective of harmonising the regulatory environment in Europe and setting pan-European standards of protection for participants in clinical trials [18]. It strengthens the responsibilities of trial sponsors, who must assume full responsibility and liability, including covering the costs of all drugs or devices used in a study [19]. Unfortunately, albeit unintentionally, the CTD has severely hampered clinical research in Europe. For example, the European Organisation for Research and Treatment of Cancer reported that the number of new cancer trials under its aegis fell from 19 in 2004 to just 7 in 2005. At the same time, trial costs increased 85% and insurance costs more than doubled [20]. The number of clinical trials in the UK has declined by two-thirds since 2004 [21], and similar reductions have been reported elsewhere [20, 22, 23].

Moreover, key components of CTD have been interpreted differently in different countries. A striking example is research using biologicals, such as those requiring ex vivo expansion. Dendritic cell-based vaccines [e.g. Sipuleucel-T (Provenge; APC8015)], the first active immunotherapy to demonstrate improved overall survival in advanced prostate cancer [24], and expanded T-cell therapies have both been shown to convey clinical benefit to subsets of patients. Under the CTD, such research can no longer be considered routine academic investigation; instead, pharmaceutical-standard laboratories are needed, along with layers of paperwork and a sophisticated
quality control setup. Often, such trials do not herald any immediate commercial application, making commercial funding very unlikely.

International collaboration in cancer clinical trials is essential to make progress in cancer treatment and screening. Greater transparency and harmonisation of regulatory and logistical requirements will be needed to support effective international collaboration in academic cancer treatment trials [25].

As of 2006, nearly 2000 molecules were in various stages of development, 400 of them anticancer agents. Half of those in late-stage development were targeted therapies [26]. Academic investigators can help focus drug development and distinguish efficacy signals and, by designing and conducting phase 0 strategies, facilitate proof-of-concept demonstrations for target modulation, improve patient selection for pivotal trials, and allow the early termination of less-than-promising lead compounds on the basis of pharmacokinetics [27–29]. Phase 0 studies may be useful in guiding later stages of drug development [27]; such studies entail microdosing, which requires a simplified safety/toxicity package. Human pharmacokinetic data, therefore, can be obtained at a very early stage of drug development [28].

The microdosing strategy is most powerful when in vitro techniques or animal models are unreliable or show ambiguous results. A review of published phase 0 studies has shown that the pharmacokinetics of microdoses predicted therapeutic doses for 18 of 25 drugs with a wide range of physicochemical and pharmacokinetic characteristics [30]. The technique has been used successfully with small molecules, but further study is needed to learn if it is valid for biologics.

The cost of research and development is unsustainable

The average out-of-pocket cost to develop a new chemical entity has been estimated at $400 million (£243 million; €286 million (all exchange rates are current as of 12 June 2009)] [31]. If the opportunity cost of failed development efforts is included, the figure exceeds $800 million (£487 million, €572

Table 1. A comparison of typical IITs and company-sponsored trials.

<table>
<thead>
<tr>
<th>IIT</th>
<th>Company-sponsored trial</th>
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<tr>
<td>Primary purpose</td>
<td>The main interest is scientific investigation culminating in publication or procurement of additional research funding</td>
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<tr>
<td>Conclusions may be considered hypothesis generating</td>
<td>The overarching goal generally is to develop a product intended for large markets to ensure financial success</td>
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<td>Academic researchers tend to have greater interest in niche indications</td>
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<td>Comparing efficacy of drugs from different manufacturers is often a chief aim of academic investigations although such studies can be very difficult with unlicensed oncology agents</td>
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<tr>
<td>Funding mechanism</td>
<td>IITs are supported by different sections of a pharmaceutical company, sometimes marketing departments</td>
</tr>
<tr>
<td>Study conduct</td>
<td>Investigators follow certain guidelines, e.g. the CTD and GCP, as well as SOPs of their institutions. The company providing the study agent must oversee safety aspects of the study and review any publications</td>
</tr>
<tr>
<td>IIT progress is outside the company’s control with regard to recruitment, number of study sites, resolution of operational issues, and so forth</td>
<td>Sponsor responsibilities insofar as GCP compliance and suitability of company capabilities, facilities, and procedures are verifiable from technical and scientific standpoints, SOP review, staff, and facilities assessment</td>
</tr>
<tr>
<td>Data collection and analysis</td>
<td>Development of action plan and definition of critical time points are required in advance</td>
</tr>
<tr>
<td>Database structure likely differs from that of the company; therefore, data cannot be imported into company systems</td>
<td>Quality of output is ensured</td>
</tr>
<tr>
<td></td>
<td>Complete safety database is available</td>
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</tbody>
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IIT, investigator-initiated trial; CTD, Clinical Trials Directive; GCP, good clinical practice; SOP, standard operating procedure

Figure 1. The general process for initiating, conducting, and completing investigator-initiated trials.
Further, the trend towards individualised medicine is affecting not only the costs of research and development for innovative biological products but might also be limiting the potential markets for such agents [32]. However, the new understanding of the molecular principles of cancer is also increasing the probability of success [13]. Rational development of molecularly targeted agents, which has relied heavily upon translational research largely carried out by academic investigators, has led to improved success rates compared with conventional cancer cytotoxic compounds [33].

Although regulatory standards and procedures in Europe improved following the establishment of the European Medicines Agency in 1995, the number of major issues with marketing authorisation applications for biotechnological products remains high [34]. Increased use of scientific advice and an improvement in the advisory process in the European Union (EU) with the participation of academic experts would go some way towards improving this situation.

Companies have substantially reduced their support for IITs in an attempt to further focus drug development programmes despite the substantial impact on independent academic research. Therefore, to ensure balance in the generation of new knowledge, academia must contribute its part to translational research programmes using academic research grants and...
institutional infrastructure. The USA National Cancer Institute, for example, is endeavouring to provide investigators with wider access to several agents with known substantial immunologic or physiologic activity that have not been tested or have been inadequately tested in cancer patients. At a 2007 workshop, 20 promising agents were ranked on the basis of a broad consensus of the immunology and immunotherapy community with the aim of making the agents available for IITs [35, 36] A different model has been adopted by the Italian Medicines Agency, which set up a programme in 2005 to support clinical research on drugs in areas of interest to the country’s National Health Service, where commercial support is normally insufficient [37].

**drug sales are less certain with health technology assessment-negative or -conditional reports**

We are currently witnessing the increasing use of health technology assessment, a process that aims to inform patient-focused, safe and effective health policies that seek to achieve best value [38]. After a manufacturer has shown evidence of a product’s quality, safety, and efficacy to achieve registration, the product will face the ‘fourth hurdle’ of cost-effectiveness to be approved for reimbursement by postregulatory authorities [39] Academicians and senior physicians can design additional studies to collect data that will help a new drug surmount the cost-effectiveness hurdle by demonstrating patient benefit. For example, postregulatory agencies such as National Institute for Health and Clinical Excellence (NICE, UK) and the Scottish Medicines Consortium are increasingly considering health-related quality-of-life data in reimbursement decisions [13]. IITs may include the collection of patient-related outcomes using suitably validated instruments.

**action is needed to dismantle barriers to clinical development**

Action is ongoing in several areas to overcome the challenges imposed on academic researchers. The ICREL (Impact on Clinical Research of European Legislation) project is collecting data from various stakeholders (e.g. industry, academia, small biotech companies) and arguing for the need to adapt the current legislation with the objective of making clinical research more competitive in the EU while providing fair and equivalent protection to participants in every category of clinical research [40]. In parallel, universities must provide infrastructure to help researchers deal with regulatory demands and they should consider acting as study sponsors.

**conclusions**

Declining support for independent academic research and IITs in oncology is multifactorial and potentially damaging to the clinical research foundations in this global therapeutic area. It is incumbent on academia, industry, and regulatory bodies to recognise the nature and dimensions of the problem. The complementary contributions of clinicians and scientists from academia and industry can expedite drug discovery and development while also reducing the costs of research and development, thus increasing the chance that new biologics will be perceived as both clinically safe and effective and cost-effective.

Drug development must be sharply focused to further decrease attrition rates. The negative consequences for independent research must be compensated by increased availability of academic funding and support for clinical researchers. The regulatory framework needs to be revised to be in alignment with the resources available within academic institutions for compliance with regulatory requirements for clinical research. A new model or paradigm is proposed in Figure 2 to encourage more groundbreaking academic research.

Global expert organisations can provide forums for academia and industry to plan studies within a set regulatory framework to support licensure/authorisation and reimbursement for new molecularly targeted agents and biomarkers. The model outlines the responsibilities of academic institutions to help sustain independent noncommercial research, and it provides channels to garner input from charities, patients, and advocacy groups. Also proposed is a role for expert organisations in advising policy and decision makers about possible revisions to the CTD and other regulatory barriers to academic research. Such changes will have to occur to achieve the ultimate goal of improving patient and market access to innovative cancer therapies.

**acknowledgements**

The BDA thanks the authors of this manuscript and Karen M. Eddleman of Palladian Partners, Silver Spring, MD, USA, who helped to draft and refine this paper.

**disclosure**

The following authors of this paper declare that there is no conflict of interest involved in this paper: LB, AGD, TTH, SR, SP, JS, SE-A, and HZ. The following authors declare a conflict of interest on the basis that they are full-time employees of commercial companies concerned with the research, development, marketing, and selling of pharmaceutical products and services: BB (Ortho Biotech Oncology), MvE (Roche), and GLL (Xceleron, Inc.). All the authors of this paper declare that there is no disclosure.

**references**


