FROM THE ANALYST'S COUCH

Oncology's trials

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Degas couch, 'Rehearsal', by Heather Sussman © 2002

The oncology market has witnessed remarkable growth during the past five years and is poised for even greater growth during the next three years. The total oncology market is expected to reach more than US $32 billion in size by 2005, driven by factors including a continued trend towards aggressive chemotherapy, active patient populations that demand access to the latest therapies, and continued favourable pricing due to high unmet need. Moreover, nearly all of the major pharmaceutical companies have active oncology development programmes, and for biotech firms, oncology projects dwarf all other R&D programmes.

Challenges from attrition

In spite of all this positive momentum for the oncology market, pharmaceutical and biotech companies who play in this area face the crucial issue of late-stage clinical attrition. Even with more than 500 oncology compounds in development, only a few achieve regulatory approval each year and there are only ~90 approved oncology drugs in the US today. A number of high-profile clinical and regulatory setbacks, such as the cases of gefitinib (Iressa; AstraZeneca) and cetuximab (Erbitux; Imclone), highlight the challenges that oncology drug candidates are facing. The dramatic unpredictability of single-arm, uncontrolled Phase II trials in cancer helps explain why anti-cancer drug development is so challenging. Although oncology projects have higher average success rates than other therapeutic areas in early-stage trials (that is, Phase I and II), these projects have a lower average success rate than other therapeutic areas at Phase III. Oncology projects are riskier than those in other therapeutic areas, precisely at the stage of clinical development in which costs are highest. Moreover, early development trials do not seem to be very predictive of success rates for later development, which could mean that the industry might soon face a big series of disappointments in the form of failed drug candidates.

Causes of high attrition

Several key factors drive the high rate of attrition we are seeing with oncology compounds: market pressures, challenges with the underlying science and changes in the regulatory environment. On the market side, companies are under significant pressure to reach for the broadest possible label on first regulatory approval to capture a broad market. As such, many initial label applications target one or more of the 'big four' tumour types: breast, prostate, lung and colon cancer. The challenge in doing this is that the standard clinical practice for these tumours often involves multiple drug cocktails of cytotoxic chemotherapy agents. So, for new therapies, clinical trials need to show incremental improvement over these multiple existing chemotherapy regimens, which can be difficult to demonstrate, especially with smaller size trials.

Scientific and regulatory challenges

The nature of the basic science of oncology also leads to high attrition rates for anticancer compounds. With the rapid accumulation of new knowledge, there are more and more novel approaches to anti-cancer drug development. Indeed, more than 40% of the compounds in development for cancer are directed against novel or 'unprecedented' mechanisms, and almost 70% of the drug targets that are being investigated in discovery are unprecedented. In earlier research, we had shown that novel approaches had significantly higher risks than tried-and-tested approaches, and, notably, some of the more high-profile recent setbacks in oncology have involved novel mechanisms, such as drugs targeting signal transduction (for example, RAS farnesylation). For every major success such as bevacizumab (Avastin; Genentech) in colorectal cancer, there have been many more failures.

The last factor for high attrition rates in oncology has been a growing conservatism within the US FDA and other regulatory approval bodies. In the past, when there were fewer available cancer therapies, the FDA often accepted surrogate endpoints (such as tumour reduction). Today, with better available treatments, the FDA has moved more aggressively towards clinical endpoints such as survival, which are exceedingly tough to prove in populations with refractory, progressive tumours — the types that are often the focus of clinical trials today. Not surprisingly, these higher regulatory hurdles increase the likelihood of clinical attrition. Given recent public pressure, however, the FDA could be easing its stance. For example, it recently approved gefitinib with only clinical response and no survival benefit in lung cancer.

Future of oncology drug development

Given the market, science and regulatory drivers behind attrition in oncology drugs, how can oncology drug development move forward? First of all, biotech and pharmaceutical companies should consider pursuing initial indications in well-defined, potentially niche tumours that will allow for a potentially lower-risk path to get regulatory approval. Once the drug has received initial regulatory approval, there are many other opportunities to expand indications through additional post-marketing trials. About 70% of cancer drugs are used off label — for example, thalidomide, which although not even approved as a cancer therapeutic is a dominant drug in myeloma and melanoma and is being tested in renal and prostate cancer.

There is a significant opportunity for concurrent research into biomarkers at the same time that the target mechanism is being explored. Tissue imaging, in particular, could be a fruitful source of biomarkers given the advances in magnetic resonance imaging and positron emission tomography imaging. As a caveat, however, biochemical and molecular markers have not yet proven to be predictive of clinical response; for example, vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) expression do not correlate with response to the appropriate antagonists.

Finally, companies should consider other Phase II trial designs that are more predictive of Phase III success. Examples include randomized Phase II studies, Bayesian approaches, studies in tough, defined populations such as the truly refractory, and uses of 'easier' endpoints such as time to progression[1]. A key challenge for both industry and the regulatory agencies in the development and approval of combinations of multiple novel cytotoxics and cytostatics in patients with minimal residual disease, the exact scenario in which beneficial outcomes are most likely, but where proving these benefits can be complex. ▶

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Market indicators

Phase II trials in oncology do not show significant predictability for Phase III outcomes (TABLE 1). A comparison of trial success rates across different therapeutic areas again shows the poor correlation between Phase II and Phase III success rates for oncology trials (FIG. 1). One of the key drivers for the high clinical attrition rates for oncology compounds is the high proportion of unprecedented targets that these compounds are directed against (FIG. 2). Historically, compounds directed against unprecedented targets have a higher level of clinical attrition than compounds against targets with a precedent. The total oncology market is expected to reach more than US $32 billion by 2005 (FIG. 3).

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doi:10.1038/nrd1158

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2. Stadtmauer, E. *et al.* Conventional dose chemotherapy compared with high dose chemotherapy plusautologous hematopoietic stem cell transplantation for metastatic breast cancer. *N. Engl. J. Med.* **342**, 1069–1076 (2000).

Online links

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EGFR | VEGF
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Table 1 | **Oncology trial examples**

Promising Phase II studies	Negative Phase III studies
Multiple second- and third-generation lymphoma regimens showed doubling of responses and survival compared with first generation CHOP regimen.	SWOG randomized study comparing CHOP with second generation ProMACE-CytaBOM or MACOP-B showed no difference in CR, time to treatment failure, or OS.
Phase II studies of angiogenesis inhibitor SU5416 showed better responses and survival compared with historic controls in advanced colorectal cancer.	A large phase III study of standard chemotherapy with or without the angiogenesis inhibitor SU5416 in the treatment of patients with advanced stage colorectal cancer did not achieve its endpoints.
Several Phase II studies from late 1980s showed higher response rates (73–100%) and 7–18% DFS post-five-years for high-dose chemotherapy and stem cell transplantation for metastatic breast cancer.	ECOG study[2] reported no differences in survival or time to disease progression between autologous stem cell transplant with high dose chemotherapy and conventional chemotherapy.

CR, complete response; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; SWOG, South Western Oncology Group

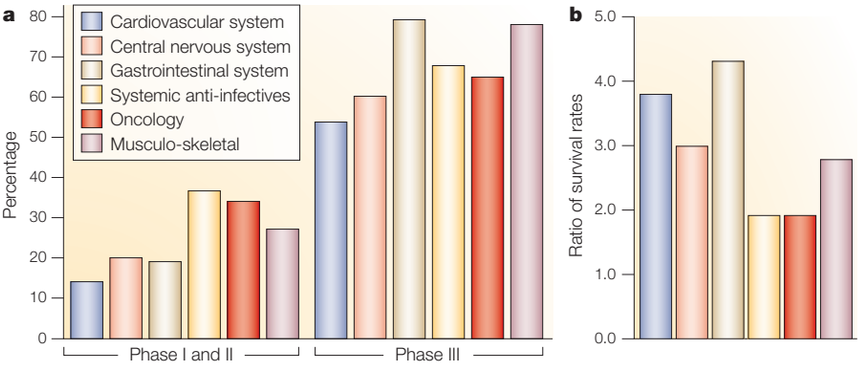

Figure 1 | **Project survival rates. a** | Comparison of rates through Phases I/II and Phase III/registration between 1991 and 2000 at fifteen top pharmaceutical companies. Projects without updated data after five years were considered failures. **b** | The low ratio of Phase II/registration to Phase I/II success rates for both systemic anti-infectives and oncology projects, is indicative of the low predictive power of early stage trials in these two areas. Source: PBJ Publications Pharmaprojects; US FDA/Center for Drug Evaluation Research; McKinsey analysis.

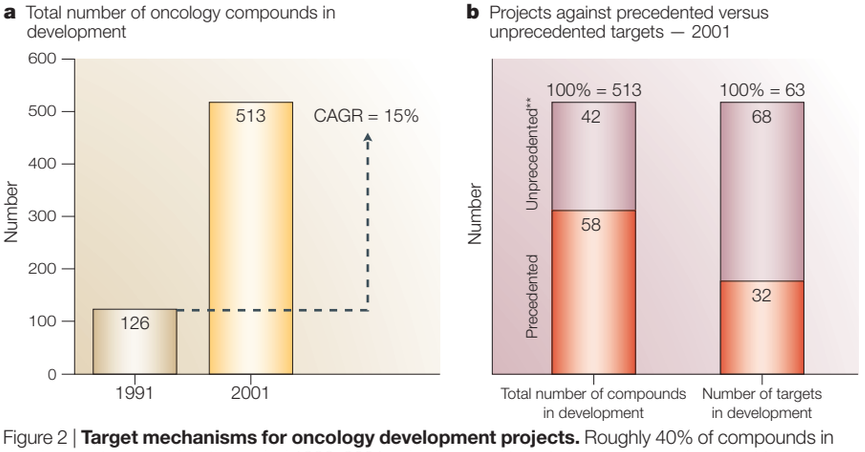

Figure 2 | **Target mechanisms for oncology development projects.** Roughly 40% of compounds in development are novel. In the period 1996–2001 only nine novel targets had compounds against them approved, whereas today 15 novel targets are being tested in Phase III trials. CAGR, compound annual growth rate. Source: PBJ Publications Pharmaprojects; US FDA/Center for Drug Evaluation Research; McKinsey analysis.

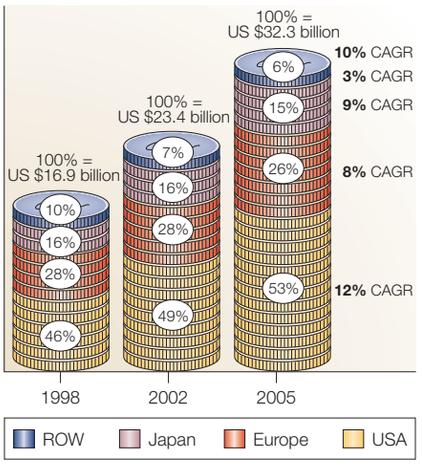

Figure 3 | **Expected growth of global oncology market.** CAGR, compound annual growth rate.