Imatinib and the long tail of targeted drug development

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New molecular insights occasionally lead to the rapid development of therapeutic agents that improve the outcomes of patients with cancer; however, these breakthroughs can be followed by extensive, empirically driven and often unsuccessful efforts at extending the drug to other indications or combinations. Herein, we describe the clinical development of imatinib, a paradigm of rapid molecularly driven drug development, and advocate for a balanced portrayal of the potential of molecularly targeted therapies for cancer.

> The optimism with which imatinib was advanced and the successes it achieved are not unique

Advances in oncology occasionally come in quantum leaps. New molecular paradigms emerge that speed novel therapies through clinical development and dramatically improve patient outcomes, making drug development look incredibly efficient. Less widely appreciated, however, is the fact that such bursts of innovation are often followed by extensive and generally unproductive research efforts that seem to be driven less by molecular insights than by empiricism. As a result, a research programme that was very efficient initially can become much less so when viewed across its whole life cycle.

Consider imatinib, which by any measure was a quantum advance in oncology[1]. Imatinib entered clinical testing in 1998 and was approved by the FDA in 2001 (REF.[2]). Imatinib was developed based on an understanding of the genetic abnormality that underlies chronic myeloid leukaemia (CML), known as the 'Philadelphia chromosome'. The use of imatinib was rapidly extended to gastrointestinal stromal tumours, Philadelphia chromosome-positive acute lymphoblastic leukaemia, three other cancer indications and one non-cancer indication[3] (FIG. 1). These rapid and impactful advances were, however, followed by prolonged and seemingly empirically driven efforts to apply imatinib to new indications and/or drug combinations. Indeed, a phase II trial with results published in December 2018 marks yet another unsuccessful effort at extending imatinib to a new indication[4]. That such later efforts were, for the most part, unsuccessful has important ethical and policy implications.

We searched the literature for trials of imatinib in indications and combinations that were not approved by the FDA at the time of trial launch (see Methods in Supplementary information). In the 10 years following the first clinical trial of imatinib, 128 trials with published results were launched in at least 42 different disease indications, featuring 41 discrete drug combinations and involving 7,911 patients (FIG. 1; Supplementary Fig. 1). A statistically significant improvement in the primary end point was attained in 24% of these trials. FDA approval was granted for 14% of all drug–indication pairings (6 of 42) involving imatinib monotherapy; no combination therapies were approved. Of 7,911 patients enrolled, 21% participated in trials that led to either an FDA approval, a labelling revision or a subsequent randomized controlled trial (RCT) with positive results in the same indication within 8 years of the launch of the first trial in that indication.

Drug developers were remarkably successful at discovering effective uses of imatinib before FDA approval, when molecular insights were fresh. Imatinib was approved for 67% of cancer indications (4 of 6) in which it was tested clinically before the first approval. Nine of 15 clinical trials (60%) launched before the first approval involved indications that achieved FDA approval or a positive RCT result within 8 years. Among trials launched before the first approval, 45% (20 of 44) had a positive result for their primary end point. The success of this subset of trials contrasts with those launched after imatinib received its first FDA approval, of which 6% (2 of 36) would result in an FDA approval or a positive RCT within 8 years. A positive result for the primary end point was significantly less common in trials launched after the first approval than in those launched before the first approval (13% versus 45%; $P < 0.001$).

Imatinib was initially put into development as a precision medicine drug. Among the trials launched before the first approval, 80% (12 of 15) enrolled patients with tumours positive for a biomarker such as *BCR–ABL1*; 67% of these trials (8 of 12) tested indications with a subsequent FDA approval or RCT with positive results. Among trials launched after the first approval, 46% (41 of 90) restricted enrolment to patients with biomarker-positive tumours. The difference in the proportion of trials enriched for patients

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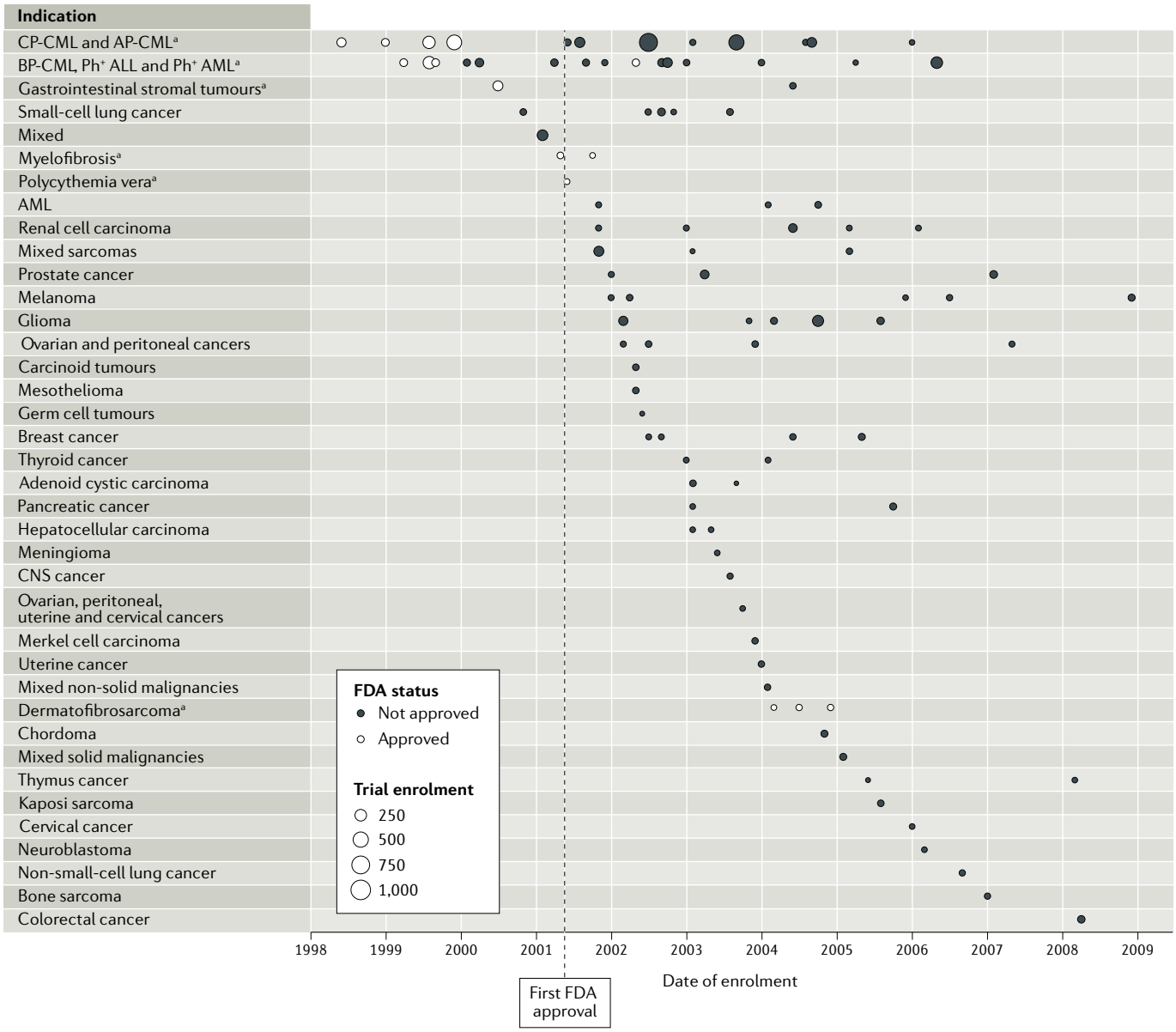

Fig. 1 | **Accumulating evidence and research organization (AERO)[8] diagram of published clinical trials of imatinib.** ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; AP, accelerated phase; BP, blastic phase; CML, chronic myeloid leukaemia; CNS, central nervous system; CP, chronic phase; Ph+, Philadelphia chromosome-positive. [a]Indications approved by the FDA.

with biomarker-positive tumours is statistically significant ($P < 0.001$). None of the trials without biomarker enrichment led to an FDA approval or a positive RCT within 8 years.

While rapid and efficient early development of imatinib led to major advances in cancer care, after these initial achievements, research seems to have been driven less by molecular insights than by empirical testing. Thus, a broader view of the development of imatinib reveals a process not substantially different from conventional anticancer drug development. To put the above figures in perspective, we compared them with those for trials of the cytotoxic drug ixabepilone[5]. The proportion of trials in indications that received FDA approval is similar for imatinib and ixabepilone: 14% (18 of 128) and 10% (6 of 62), respectively. The percentage of indications for which imatinib was approved by the FDA after the first approval is the same as the overall percentage of indications for which ixabepilone was approved within 8 years: 6% (2 of 36 and 1 of 17, respectively)[5].

A simple explanation for the patterns described above is that researchers and companies are good at prioritizing the most promising hypotheses, postponing the clinical testing of more risky indications or drug combinations until after an agent is first approved. If found to be common in other drug-development efforts, this behaviour has important implications for policy and human protections. First, ethics review committees should be aware that the evidentiary basis (and hence

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the risk:benefit ratio) for drug testing could diminish for indications and combinations tested after a new drug is approved. These committees should either demand stronger evidence for research efforts after approval or modify informed consent to highlight the potentially worse risk:benefit ratio. Second, the patterns we describe should chasten some of the optimism surrounding molecularly targeted approaches in drug development. Molecular insights are and will continue to be at the vanguard of major advances in cancer. However, across the entire life cycle of a therapeutic agent, a large proportion of the research with molecularly targeted treatments might be empirically driven.

The optimism with which imatinib was advanced and the successes it achieved are not unique. Immune-checkpoint inhibitors (ICIs) occupy this privileged position in the current drug development landscape. The ICI pembrolizumab, for example, is the first cancer drug to be approved by the FDA for a tissue-agnostic indication[6]; the time between its first clinical trial and FDA approval was 4 years. Many applications of cancer immunotherapy have already been integrated into routine clinical practice.

It is too early to say whether the dynamics we describe for imatinib apply for the current reigning quantum advances, such as ICIs. In their heyday, kinase inhibitors (such as imatinib) were also believed to mark a break from previous empirical drug development paradigms in oncology[7]. Soon we will learn whether the rapid progress made in the development of ICIs will be offset by a programme of trials that attempts to extend these drugs to new uses — often on the basis of weak molecular evidence — reducing the efficiency of the research programme as a whole.

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Competing interests
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