In December last year, a breast-cancer trial for the experimental drug neratinib captured industry attention — but the buzz was not just about the drug.

What was unusual was the trial itself. Known as I-SPY 2, it assesses multiple drug candidates in parallel, instead of the usual practice of one at a time. The approach is part of a wave of efforts to reform the costly and time-consuming process of drug approval that often fails to take into account the complex realities of cancer biology.

In I-SPY 2, each drug is screened in patients whose tumours have specific molecular profiles. The trial ‘learns’ as it accumulates data, so rather than randomly assigning new patients to just treatment or control, it uses early results to adjust recruitment. Made by Puma Biotechnology in Los Angeles, California, neratinib was just one of five targeted compounds being tested, and all were designed to selectively block signalling pathways involved in tumour growth.

The standard road to drug approval involves demonstrating safety in phase I, clinical effect in phase II and then a phase III randomized controlled trial (RCT) to confirm whether the experimental treatment provides a statistically meaningful improvement over the current standard of care. RCTs have enabled the discovery of valuable treatments that bolster both survival time and quality of life. “We actually had some outstanding successes early on — like childhood leukaemia, where we saw small improvements from various drugs stack up until the disease turned into something that is usually cured,” says Richard Kaplan, a medical oncologist at the UK Medical Research Council’s Clinical Trials Unit in London.

Progress against cancer has since slowed down, but many oncologists are hopeful that it is poised to accelerate once more. Thanks to a deeper knowledge of genetics and cell biology, the blunt instrument of cytotoxic chemotherapy — which indiscriminately targets all rapidly dividing cells — is now being supplemented by drugs created for tumours with specific molecular features, or biomarkers. But clinical-study design has not kept pace. Many RCTs still tend to take a broad view, making relatively simple comparisons of drug performance in two roughly identical patient groups. But their failure to account for individual genetics means that they can give rise to misleading results.

Witness the tale of gefitinib, a targeted drug developed by AstraZeneca in London and marketed as Iressa. After showing early promise in some patients with non-small-cell lung cancer (NSCLC), the drug failed in a phase III trial in 2005 (ref. 1). The trial’s nearly 1,700 patients had not been selected on the basis of their tumour mutational profile. “The company took the tack of trying to get all of NSCLC,” says Donald Berry, a biostatistician at the MD Anderson Cancer Center in Houston, Texas. “It hoped that the benefit in this small subset would drive things.” The poor results of the trial led the US Food and Drug Administration (FDA) to put

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With standard treatments being replaced by more personalized ones, trial design needs to change, too.

CLINICAL TRIALS

More trials, fewer tribulations

Clinical studies that group patients according to their molecular profile can make for better and faster drug approval decisions.

BY MICHAEL EISENSTEIN

severe restrictions on who could be prescribed the drug. Later analyses², however, revealed that the drug was effective in a specific subset of patients, and gefitinib is now available in Europe to patients with the appropriate mutations.

Critics point to the gefitinib story as a collision between new drugs and old trial design. They assert that conventional randomized trials are too costly, delay the identification of good therapies and mask the benefits of good drugs that work in only a subset of patients.

OPEN ARMS

In one way, however, gefitinib is an example of progress in getting drugs to patients more quickly. It is one of a number of oncology drugs to be approved for use by the FDA through its accelerated approval programme. The programme allows drugs to be marketed if they show strong evidence of clinical effect in a phase II study as long as a subsequent phase III trial is done to confirm the effect. (This is where gefitinib fell down and gained its tight restrictions).

With numerous candidates in their pipelines, pharmaceutical companies must make difficult decisions about how to invest their resources. When many separate trials are done in parallel, they compete for a limited pool of patients. One study³ showed that filling all pancreatic-cancer trials in the United States in 2011 would have required the participation of 83% of patients with surgically treatable tumours. Yet only about 5% of patients volunteer for trials, according to the American Cancer Society.

Multi-armed adaptive trials such as I-SPY 2 and FOCUS4 — a colorectal cancer trial that started recruitment in January — offer a way to tackle limits on both company resources and the number of available patients. These phase II

trials study several markers and drug candidates at once, responding to results by expanding studies for promising treatments and discontinuing them for those that are not showing any effect (see ‘Adaptive design’).

I-SPY 2 divides patients with breast cancer into ten subgroups on the basis of their tumour’s molecular profile. Each subgroup is then divided among the treatment and control groups. Responses to each drug are compared against a single control arm. Future recruitment is not strictly randomized, but rather is informed by incoming trial data. This way, drug–biomarker combinations with early promise are allocated more patients with the same biomarker profile.

“We will need to test a new strategy of customization.”

“This is about updating knowledge as you go and modifying your actions on the basis of that knowledge,” says Berry, who co-organized the trial with breast-cancer specialist Laura Esserman from the University of California, San Francisco. I-SPY 2 has a second graduate moving on to phase III trials — the drug veliparib from AbbVie in North Chicago, Illinois. Five other compounds are still being tested.

FOCUS4 is recruiting patients to four treatment arms. Unlike in I-SPY 2, patients are assigned to the treatment for which their biomarker profile is thought to be a match. Each treatment arm has its own control group, made up of patients with the same biomarkers. Drugs that perform well in their biomarker-matched group will also be given to individuals whose tumours lack that marker to test for broader effects. A separate chemotherapy-only arm will treat patients who, for whatever reason, cannot participate in the other groups, as well

as those who have not responded to the treatment on trial but might benefit from future drugs that target their tumour subtype.

In another shift from business as usual, I-SPY 2 is focusing on initial treatment, rather than limiting itself to patients facing poor prognoses from advanced, metastatic or drug-resistant disease. “Looking at metastatic disease is always first in cancer, and if nothing happens you don’t continue,” says Berry. “We have to look earlier.” Women in I-SPY 2 receive ‘neoadjuvant’ treatment that is intended to shrink their tumours before they are removed. Trial designers have tended to shy away from early-stage patients who might already be curable with standard treatments, but early-stage tumours often have fewer mutations and are more homogeneous, so could be easier to target.

Such early-stage testing has led to improved outcomes in chronic myelogenous leukaemia (CML), says Razelle Kurzrock, director of the Center for Personalized Cancer Therapy at the University of California, San Diego. There is already an effective targeted drug for CML: imatinib, which Novartis markets as Gleevec or Glivec. When physicians were using this drug only as a last resort, imatinib offered limited returns. But Kurzrock says that when doctors started giving it to patients upon diagnosis, the improvement in performance was dramatic. “The response rate is no longer just 10%,” she says. “It’s close to 100%.”

Encouragingly, the FDA declared in mid-2012 that it would consider accelerated approval for breast-cancer drugs that can eliminate detectable tumour tissue without surgery⁴, based in part on data from trials such as I-SPY 2. In September 2013, the agency issued its first such approval for the neoadjuvant use of pertuzumab, which Roche markets as Perjeta.

These trial designs offer greater opportunities for patient participation by creating treatment groups for almost all comers, rather than simply rejecting patients who do not match a single-biomarker criterion. Furthermore, I-SPY 2’s sole control arm yields considerable savings relative to the expense of having a control group for each treatment. Both FOCUS4 and I-SPY 2 also offer the potential for even greater cost-cutting by seeking stronger gains from the drugs than those generally sought in clinical trials — typically, a doubling of survival without tumour progression on the treatment drug than on the control. This reduces the number of patients needed to obtain robust phase III data and ensures that only high-performance candidates move forward. “If a drug doesn’t meet its prespecified outcome during interim analysis, we’re going to close that arm,” says Kaplan.

Successful graduation from I-SPY 2 requires a projection that a drug has an 85% chance of succeeding in a 300-patient phase III trial, and treatment arms in FOCUS4 can move seamlessly into phase III if participating companies opt to continue. This is also a feature of the

Lung Cancer Master Protocol, an adaptive trial for squamous-cell lung cancer developed with support from the advocacy group Friends of Cancer Research in Washington DC. The trial is expected to start recruiting soon.

DISEASE REDEFINED

As genomic studies start to provide further information about the mutation profiles of different cancers and as more biomarkers emerge, researchers are re-evaluating cancer classification (see 'Second chance'). A colorectal cancer that shares a mutation with a breast carcinoma may have more in common than two breast carcinomas with different mutations, for example. If this proves to be the case, then these should be the similarities that inform drug testing.

Kurzrock is among many who favour molecular profiling over tissue-based definitions. "If you have a drug that targets a specific abnormality, you would want to look at that abnormality — not whether you're dealing with breast cancer," she says. Evidence to support this model is mounting. For example, although the FDA has approved crizotinib (marketed by Pfizer as Xalkori) for NSCLC, clinical studies suggest that the drug could also be effective for children with aggressive brain tumours that have the same mutation⁵.

Such approvals must now be won gradually through trials on different diseases. To speed things up, several companies are pursuing 'basket' trials that test treatments on multiple cancers with common genetic disruptions. GlaxoSmithKline is testing two melanoma drugs, dabrafenib and trametinib, in nine cancers — including brain, thyroid and intestine — that share mutations in the gene *BRAF* that could render them susceptible to these drugs. Rafael Amado, senior vice-president for oncology research and development at the firm, argues that this approach offers hope to patients with rare cancers who might otherwise slip through the cracks. By performing analyses that take data from across tumour groups, even small sets of positive outcomes can become statistically meaningful. As a result, says Amado, "we don't have to run very large randomized trials in these ultra-rare populations".

The US National Cancer Institute is exploring this approach through its Molecular Analysis for Therapy Choice programme, using targeted gene sequencing to match various drugs to people with solid tumours or lymphomas whose disease has progressed on existing treatments. "We'll have about 20 arms to start with, targeting the usual suspect mutations that you might find in cancer," says Barbara Conley, associate director of the institute's cancer-diagnosis programme. "If we can get 35% or more patients across tumour types to survive six months or more, that's an interesting signal." These are essentially phase II trials looking for indications that could justify a move to

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SECOND CHANCE

A new perspective for past drug decisions

A drug's journey to the clinic doesn't necessarily end with a regulator's decision. As clinical oncologists learn more about the interplay between a patient's response to a drug and his or her genetics, it is becoming clear that some failed drugs might be rehabilitated by looking at instances in which a small subgroup of participants showed significant benefit.

Take everolimus, developed by Novartis. This drug failed a phase II trial for metastatic bladder cancer — but one patient's cancer went away and stayed away for more than two years. Researchers at the Memorial Sloan-Kettering Cancer Center in New York subsequently found that about 8% of people with bladder cancer carry a mutation that makes their tumour susceptible to the drug⁶. The US National Cancer Institute is now examining other reports of rare but significant drug responses through its Exceptional Responders programme, which might see some failed drugs put back into development. "We've looked at some of the phase II trials that didn't get approval over the past few years, and in lots of them as many as 10% of the people had exceptional responses," says Barbara Conley, associate director of the institute's cancer-diagnosis programme.

Conversely, even when a drug is approved, its success can only really

be assessed in the real world. "Trial subjects don't have cardiac or renal disease," says Ian Tannock, an oncology researcher at Princess Margaret Cancer Centre in Toronto, Canada. "But then that result is taken out into a community of unselected patients where there is a lot of comorbidity." As a result, small benefits may disappear and rare toxicities may become apparent. Tannock advocates large-scale research to track the performance of drugs after they have been approved. But such observational studies require close collaboration across clinical centres — a process made difficult in the United States, at least, by the lack of a central national cancer registry.

The American Society for Clinical Oncology hopes to rectify this problem with CancerLinQ, which integrates patient treatment and outcome data. "This would allow us to query data for a group of patients with a particular set of molecular characteristics, look at what treatments those patients received and identify the treatment that seemed to work the best in that subset of patients," says Neal Meropol, a medical oncologist at Case Western Reserve University in Cleveland, Ohio, and a member of society's board of directors. "We can now ask questions that simply could not be answered in a standard clinical trial." **M.E.**

phase III, but regulators say that they are willing to formally recognize robust evidence of cross-tumour efficacy. "The FDA could approve a drug based on a molecularly defined population rather than a disease-site-specific indication," says Richard Pazdur, director of the agency's Office of Oncology and Hematology Products.

Additional complexity could confound this broad biomarker-informed research, however. For instance, *BRAF* inhibitors that work in some melanomas are ineffective in colorectal tumours with the same mutations. But Kurzrock maintains that universal effectiveness is an unrealistic expectation. "If you look at drugs that were approved for lung cancer, the response rates were usually in the range of 15–20% of patients," she says. "We cannot expect 100% of patients treated on the basis of a genomic classification to respond."

Indeed, tumours often contain multiple mutations that might drive drug resistance — a common roadblock for targeted agents suggesting that each patient's cancer may require a specialized cocktail of agents. "We will need to test a new strategy of customization per patient and patient-centric care," says Kurzrock, "rather

than just the old way of testing a drug or combination of drugs."

This complexity will mean a steep learning curve for researchers and oncologists. Berry believes that oncology will ultimately undergo a broad transformation — approaching drug testing as an opportunity to gain insight into the disease rather than merely validate existing hypotheses. "The future really is combining clinical practice and clinical trials, and having a notion of both learning and confirming in the trial," he says. "It will mean a completely different regulatory perspective and an entirely different business model for companies." ■

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