RUSSELL COBB

PERSONALIZED MEDICINE

Special treatment

Therapies targeted at the specific genetics of a patient's lung cancer have proved harder to realize than expected.

BY MICHAEL EISENSTEIN

Ramaswamy Govindan vividly remembers the first time he treated his patients with the cancer drug gefitinib. It was the start of the millennium, and the outlook for patients with metastatic non-small-cell lung cancer (NSCLC) was dire: less than 40% survived a year after diagnosis.

"The second patient I treated was about to go into hospice care," recalls Govindan, a medical oncologist at Washington University School of Medicine in St Louis, Missouri. "But she went on to live three years before dying of a heart attack."

Gefitinib was approved by the US Food and Drug Administration (FDA) in 2003. Marketed as Iressa by AstraZeneca, its arrival was a watershed moment in the treatment of NSCLC, the most common type of lung cancer. The drug blocks a protein called epidermal growth factor receptor (EGFR), which transmits signals that help to control the division and migration of cancer cells.

However, although some patients responded well to the treatment, many others did not. The same was true for another drug that targets EGFR: erlotinib (Tarceva), developed by Genentech and OSI Pharmaceuticals and approved by the FDA in 2004. The only apparent trend was that non-smokers were more likely than smokers to respond to erlotinib. "Back in the day, you would give Tarceva to somebody because they didn't smoke, but in the vast majority of those people it didn't help," says Mark Kris, a thoracic oncologist at Memorial Sloan Kettering Cancer Center in New York City.

In 2004, two research teams — one of which included Kris — discovered the secret[1,2]. Both gefitinib and erlotinib were selectively active against lung cancers with hyperactive, mutated versions of the *EGFR* gene, but ineffective against tumours in which the gene was not mutated. Mutated *EGFR* is predominantly found in a type of NSCLC called adenocarcinoma, which accounts for 40% of lung cancers and is the most common form of the disease in people who have never smoked.

The realization that specific genetic variants might help researchers to develop personalized lung-cancer treatments has launched a generation of targeted drugs that can deliver years of additional life to certain subgroups of patients. But some patients are still waiting to reap the medical benefits of the post-genomic era, and many doctors and clinical researchers fear that the low-hanging fruits of lung-cancer genetics may already have been picked.

FOLLOW THAT DRIVER

The cancer genome is a battered and scarred landscape of DNA-sequence changes as well as swapped, duplicated and deleted regions. The therapeutic focus is on the subset of these mutated genes — 'drivers' — that are essential for aggressive cell growth. The most useful drivers from a therapeutic perspective are oncogenes, which encode proteins that promote uncontrolled cell division and have the potential to convert a normally functioning cell into a cancer cell. Drugs that target mutant oncogenes might halt or reverse tumour growth.

One major lung-cancer oncogene is *EGFR*. Mutations to the *EGFR* oncogene are detected in more than 40% of adenocarcinomas. Three drugs are commercially available for *EGFR*-mutant cancers, and more are in trials. In 2007, researchers uncovered a second driver oncogene that is present in 5–7% of adenocarcinomas. Called *ALK*, this gene encodes a poorly understood signalling protein and occasionally undergoes a genomic rearrangement that leaves the resulting protein permanently turned on. In 2011, the FDA approved crizotinib (marketed by Pfizer as Xalkori) for NSCLC patients whose tumours exhibit such rearrangements. Phase III trial data presented by Pfizer at the 2014 annual meeting of the American Society for Clinical Oncology (ASCO) indicate that crizotinib can extend the life of patients whose tumours have mutations in *ALK*.

However, the benefits of these targeted drugs are only temporary — after about a year of remission, most tumours acquire resistance.

For example, more than half of the tumours treated with *EGFR* inhibitors acquire a mutation called T790M in the *EGFR* gene[3]. This blocks the drug without interfering with the mutant protein's signalling.

Tumours often contain genetically distinct cell populations, and many researchers believe that cancer recurrence may represent the evolutionary victory of an already-resistant minority. "Once we start to kill off cells that have the sensitizing mutation, the intrinsically resistant cells start to grow," says Tony Mok, a clinical oncologist at the Chinese University of Hong Kong.

Presentations at this year's ASCO meeting revealed promising clinical-trial data on drugs being developed by Clovis Oncology and AstraZeneca that inhibit the T790M mutant receptor. One molecule induced tumour shrinkage in almost two-thirds of patients.

Patients with crizotinib-resistant tumours also received hopeful news this year. Such resistance often arises in the absence of a detectable mutation, which suggests that other mechanisms increase *ALK* activity to overwhelm crizotinib's modest capacity for inhibition. In April 2014, the FDA moved with unprecedented speed to approve the drug ceritinib (marketed by Novartis as Zykadia) based purely on a phase I trial[4] showing a strong clinical response in resistant patients. Subsequent data suggest that ceritinib works equally well in both previously untreated and crizotinib-resistant patients.

Ceritinib is 5 to 20 times more potent than crizotinib as an *ALK* inhibitor, and it is also more selective, says Alice Shaw, an oncologist at Massachusetts General Hospital in Boston, whose team led the phase I trial. At least nine other *ALK* drugs are in development.

A FACE IN THE CROWD

Targeted treatments benefit only a minority of lung-cancer patients. For the rest, the hunt continues for drivers that might prove vulnerable to therapy. Most progress has been seen in people diagnosed with adenocarcinoma and who do not smoke, many of whom have cancers that have arisen through one primary driver mutation (see page S12). By contrast, the mutational load in a smoker's tumour can be overwhelming, making it a challenge to separate the signals of likely driver mutations from the noise generated by large numbers of 'passenger' mutations that make a minimal contribution to tumour growth.

But even targeting the genetic culprit in a single driver mutation can be tricky. Take the example of the oncogene *KRAS*, which encodes a signalling protein involved in cell proliferation. *KRAS* mutations appear in as many as one-quarter of adenocarcinomas, but attempts at targeted therapy have so far failed. A study reported at the 2014 ASCO meeting suggests that a subset of patients with *KRAS*-mutant NSCLC may benefit from a combination of drugs that target several proteins in the same biological pathway as *KRAS*. So far, only 10–15% of *KRAS*-mutant tumours respond to combination treatment, says Vassiliki Papadimitrakopoulou, a medical oncologist at the MD Anderson Cancer Center in Houston, Texas, who helped to coordinate the study. "We would like to see more than that."

For patients with non-adenocarcinoma lung cancers, targeted options are limited. Very few patients with squamous cell carcinoma (SCC) — the second most common form of lung cancer — have *EGFR* or *ALK* driver mutations. Most SCC tumours occur in smokers, and are plagued by the same extensive genomic mutation that is confounding efforts to apply targeted treatment to smokers' adenocarcinomas.

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This may be about to change, thanks to the work of Govindan and his colleagues at the Cancer Genome Atlas (TCGA), which in 2012 published a detailed assessment of the SCC genomic landscape derived from tissue samples from 178 SCC tumours[5]. The results suggested a number of avenues for potential intervention. A mutation in the gene *CDKN2A*, for example, is found in 70% of SCC tumours and could be a target.

JOINT FORCES

The urgent need for progress in lung-cancer treatment has inspired Papadimitrakopoulou, who is collaborating with other US investigators on the Lung Cancer Master Protocol. Launched in June, this multi-arm, multi-institutional clinical trial will use sequencing to match SCC patients with targeted drug candidates. It will also accumulate a lot of cancer genomic data. "We will be characterizing the largest set of SCCs across the United States," says Papadimitrakopoulou.

Govindan and his colleagues are also working on large-scale genomic analysis. After a genomic survey of mutations in 230 adenocarcinoma tumours[6], published in July 2014, he and fellow TCGA coordinators Louis Staudt and Matthew Meyerson are working on plans to study a larger number of tumour samples in the hope of detecting additional targetable drivers.

The robust performance of drugs that target *ALK* and *EGFR* has made testing for mutations in these genes routine. But as the cost of sequencing plummets, some clinicians believe that it makes more sense to survey hundreds of cancer-related genes rather than just those two to provide a larger set of potential targets. Kris is among the evangelists for extensive clinical sequencing. "If you have lung cancer in 2014, the first thing we do is a biopsy that includes a comprehensive genetic test for all potential drivers," he says. Companies are also providing the tools to do this. Foundation Medicine, a company in Cambridge, Massachusetts, co-founded by TCGA scientists, generates oncology diagnostic reports for clinicians based on sequencing data from 236 cancer-associated genes. The company expects to do 25,000 tests in 2014, up from 9,000 in 2013. In June, the Memorial Sloan Kettering Cancer Center forged a partnership with Quest Diagnostics of Madison, New Jersey, to broaden clinician access to the centre's in-house genetic test, which also surveys numerous oncogenes in parallel.

Genetic analyses could help to identify patients with mutations that are rare in lung cancer but are common in other tumour types. For example, a subset of adenocarcinoma patients with mutations affecting the *RET* gene might benefit from cabozantinib, a drug that targets this alteration in thyroid cancer[7]. And with much of the pharmaceutical industry's oncology efforts focused on developing targeted drugs, data from sequencing the genes of lung-cancer patients can also help to direct those patients to clinical trials. To assess the impact of sequencing on lung-cancer care, Kris and other scientists — who formed a group called the Lung Cancer Mutation Consortium — sequenced as many as 10 known oncogenes in more than 1,000 patients. Kris reports that 28% of the people tested were matched to clinical trials they might not otherwise have known about[8].

As with *KRAS*, many oncogenes are informative scientifically but are not medically useful, leading some researchers to question the short-term benefits of routine, large-scale tumour sequencing in patients — a practice Mok says is unlikely to improve lung-cancer care significantly until the next *EGFR* comes along. Still, he believes that genetic analysis must be embedded into the diagnostic process so that drugs can be matched to a patient as quickly as possible — he holds out hope that new drivers will soon join *ALK* and *EGFR*.

As would everyone struggling to find new weapons against this lethal disease. With such resources at hand, more doctors might look forward to experiencing the sweet satisfaction Govindan encountered on providing his patient with just the treatment she needed to buy years of additional life. ■

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