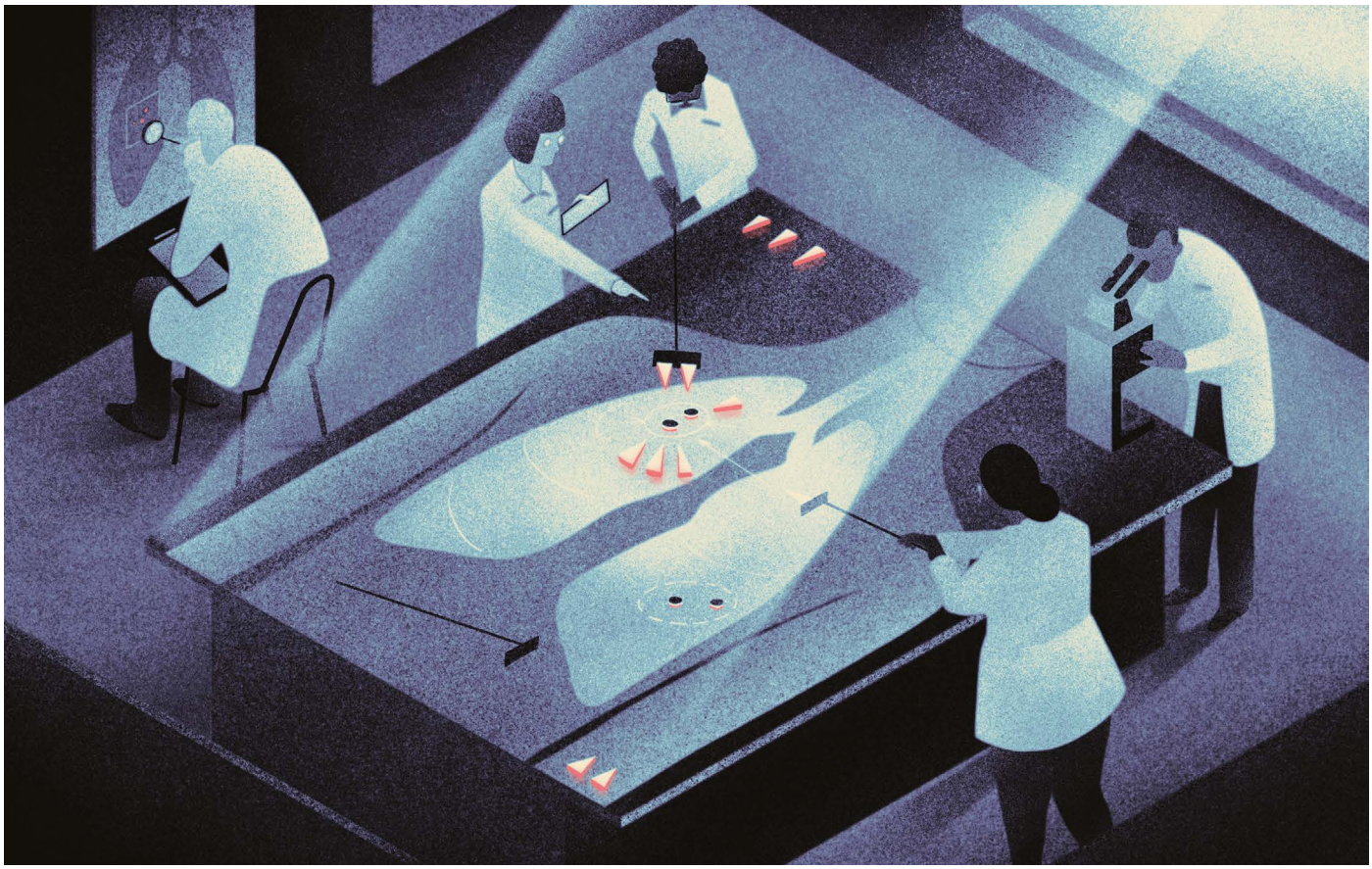


DANIEL STOLLE

More options for treating lung cancer

A growing arsenal of drugs is extending people's survival times despite tumours becoming resistant to existing therapies. **By Michael Eisenstein**

Rather than using numbers, Tony Mok prefers a more anecdotal indicator to describe the shift in treatment for advanced lung cancer. "I receive more wine at Christmas than I did 20 years ago, because more patients are alive year after year," says Mok, a medical oncologist at the Chinese University of Hong Kong.

This change has been rapid and dramatic, powered by remarkable progress in the development of mutation-specific targeted therapies and drugs known as checkpoint inhibitors, which put tumours back in the crosshairs of the immune system.

"Fifteen years ago, we had some chemotherapy regimens and everybody got essentially the same treatment," says Alex Adjei, a medical oncologist at the Mayo Clinic in Rochester, Minnesota. Fewer than 20% of people would survive for five years after diagnosis, and those with advanced disease typically had only a few months left. But today, nearly everyone with non-small-cell lung cancer (NSCLC), which accounts for the vast majority of lung cancer cases, has a choice of therapeutic options.

People with advanced and metastatic NSCLC that responds to targeted therapies or checkpoint inhibitors now routinely survive for three or four years after diagnosis, Mok says, and a lucky few live substantially longer. Even people diagnosed with small-cell lung cancer (SCLC), which represents 10–15% of lung cancer cases and has been stubbornly difficult to treat, are seeing glimmers of hope from immunotherapy.

But sizeable subsets of tumours become resistant or fail to respond meaningfully, even when treated with a well-matched therapy. And with many new drugs now available, clinicians are still waiting to find out which patients each treatment is most likely to help and how long their benefits will last.

Eyes on the target

In the beginning, there was gefitinib. First identified in 2001, this molecule proved to be a potent inhibitor of a signalling protein called epidermal growth factor receptor (EGFR). Certain mutations in EGFR promote the aggressive proliferation of tumour cells, and these alterations are particularly common in NSCLC tumours — especially when the cancer is not caused by tobacco use. It accounts for about 40% of lung cancers in people in the United States who have never smoked, says Pasi Jänne, a medical oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts. "For Asian never-smokers, it could be up to 50–60% of lung cancers." This makes EGFR mutations one of the most common causes of NSCLC.

When gefitinib was approved in Japan in 2002 and in the United States a year later, clinicians finally had a weapon to target those mutations. Mok, who coordinated one of the trials of gefitinib, describes a sea change in care for people with NSCLC who had run out of options. "You can imagine patients coming in with symptoms," he says. "Then I give them one pill a day, and within two weeks they can walk and talk normally."

Scientists have since identified many targeted drugs that hit other driver mutations, but they have also made considerable headway in going after EGFR more effectively. Gefitinib and other first-generation EGFR inhibitors established a therapeutic proof of principle while also improving patient survival. A second generation of inhibitors, including afatinib and dacomitinib, bolstered performance by irreversibly inhibiting EGFR.

But even these drugs ultimately lost their potency as tumours developed resistance. "About 60% of patients develop a specific mutation called T790M," explains Tejas Patil, an oncologist at the University of Colorado Cancer Center in Aurora. "It's a mutation that evolves in the binding pocket where the drug would go." For most people, Mok says, resistance arising from T790M or other mutations allows the cancer to come back.

A third-generation EGFR inhibitor has now emerged that is effective against many of those resistant tumours. Osimertinib, which was developed by pharmaceutical company AstraZeneca, based in Cambridge, UK, gained US approval in 2017. It differs from previously developed agents because it was designed to bind the tumour-promoting forms of EGFR — including the drug-resistant T790M mutant — but not the normal protein. This selectivity, says Jänne, leads to longer survival times for people with advanced disease.

Phase III trials showed that people receiving this drug survived on average for more than three years. As an initial treatment, osimertinib extended survival in one trial by seven months relative to first-generation EGFR drugs[1], and doubled the time before onset of recurrence in those who developed resistance to older therapies[2].

A similar story has played out for another prominent class of NSCLC mutations: those affecting the anaplastic lymphoma kinase (ALK) gene, which occur in 2–7% of NSCLC cases. The first drug to target these mutations was crizotinib in 2011, developed by New York City-based pharmaceutical company Pfizer, but this was followed by more potent and selective inhibitors. For example, the second-generation ALK inhibitor alectinib, developed by the biotechnology company Genentech, based in South San Francisco, California, and Tokyo-based Chugai Pharmaceuticals, dramatically outperformed crizotinib in the ALEX clinical trial[3], which reported in 2018. "The difference between the first and second generation is huge," says Mok, who coordinated the ALEX study. "The median progression-free survival increased from 10 months to over 30 months." Third-generation inhibitors are in development, including Pfizer's lorlatinib, which can overcome resistance mutations that stymie other ALK inhibitors.

Drugs such as osimertinib and alectinib offer more durable benefit and less toxicity than their predecessors. They also have the ability to cross the blood–brain barrier, preventing deadly brain metastases from taking hold (see page S14). Accordingly, many clinicians reach straight for the latest and greatest when planning treatment. "We want to, in general, use our best drugs first," says Jänne. But the older drugs can still deliver survival benefits and their prices have fallen considerably.

"I give them one pill a day, and within two weeks they can walk and talk normally."

People who experience resistance to the newer treatments might also benefit from the older drugs. According to Adjei, some tumours that become resistant to alectinib exhibit abnormal activity in a parallel signalling pathway that fortuitously responds well to crizotinib. A similar situation occurs in individuals with resistance to osimertinib. "In about 15% of those patients, prior-generation EGFR inhibitors actually work against those mutants," says Jänne. Trials are now underway to examine the advantages of applying osimertinib and gefitinib in combination.

There has also been considerable progress in developing targeted therapies for other, less-common NSCLC mutations. With access to approved agents and experimental drugs, Patil estimates that about one-half of people with NSCLC have a mutation that could, in principle, be targeted.

Perhaps the greatest excitement surrounds the recent breakthrough in targeting the protein KRAS. This is among the most commonly mutated proteins in NSCLC, particularly among people with smoking-related disease, but it has been a difficult target to hit. KRAS is roughly spherical, Mok says, and so offers little purchase for drugs to bind. But in 2013, researchers identified[4] a distinctive pocket that forms in an especially common mutant known as G12C, which occurs in roughly 11% of NSCLC tumours. There are at least four KRAS-G12C inhibitor drugs in development that exploit this vulnerability, and initial data suggest that previously untreatable tumours are responding.

Charging through the checkpoint

For now, however, the range of approved targeted therapies leaves most people with lung cancer out in the cold. "It's probably around 30% of patients who benefit from approved drugs," says Adjei. Fortunately, immunotherapies have rapidly evolved to fill that void.

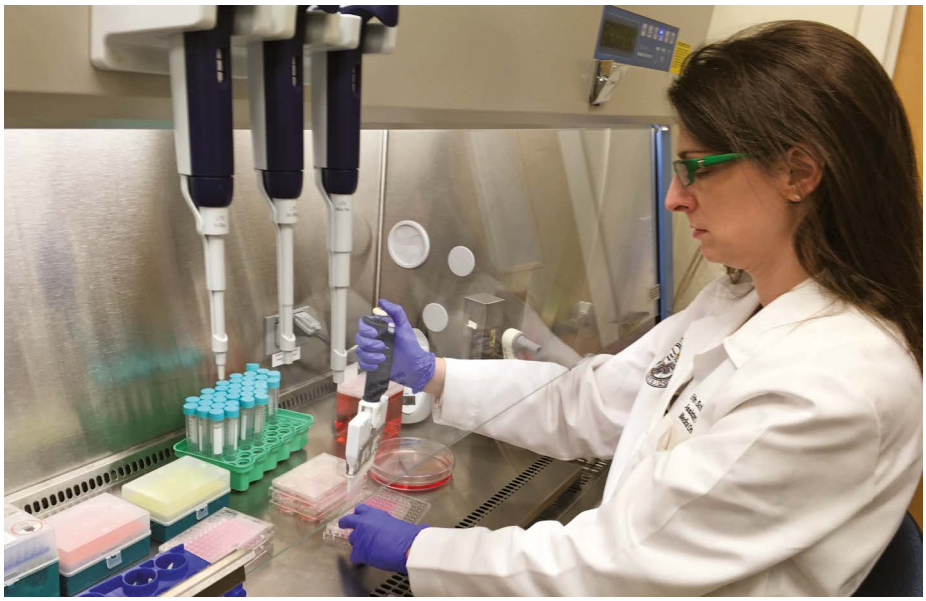
Many tumours protect themselves by exploiting the immune system's natural safeguards, such as checkpoint proteins, which normally help to prevent uncontrolled inflammation or autoimmunity. For example, by activating the checkpoint protein PD-1, tumour cells can lull T cells into a dormant state and protect themselves from destruction. Drugs that block PD-1 or its partner protein PD-L1 can wake T cells back up and give patients a fighting chance against advanced disease.

"I cannot overstate how important the immunotherapy revolution has been for giving new hope to my patients," says Erin Schenk, a medical oncologist at the University of Colorado Cancer Center. When treatment is successful, the turnaround in disease can be striking, doubling overall survival in advanced NSCLC relative to chemotherapy in clinical trials, with some patients achieving long-term remission. "For those patients that have a response, about 10% to 30% of patients maintain that response for years," says Julie Brahmer, director of thoracic oncology at the Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland. "I have some folks that are going beyond five years without having to restart therapy."

There are now six approved drugs that target PD-1 or PD-L1. They can be used alone or in combination with other therapies, the most widely used standalone drug being the PD-1 inhibitor pembrolizumab.

Predicting who will benefit from immunotherapy remains something of a guessing game. Pembrolizumab is commonly given as a monotherapy to patients with tumours in which at least half the cells in a biopsy express PD-L1. "If PD-L1 levels are high, then the chance of benefit is about 40–45%," says Brahmer.

Still, clinicians recognize the limitations of this biomarker. "It increases your likelihood of benefit but it doesn't tell you that you can't benefit if you have a low level of PD-L1," says Jänne. For unselected patients, the likelihood of responding to treatment with a checkpoint inhibitor is considerably lower — one study estimated that in 2018, only about 7% of people



Erin Schenk treats people with lung cancer by using checkpoint-inhibitor immunotherapy.

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with NSCLC in the United States were likely to benefit. Accordingly, the hunt is still on for molecular or histological indicators that might guide more effective treatment.

The good news is that immunotherapy is generally safe, with a well-documented profile of side effects that can be effectively managed at cancer centres. Schenk says that at her practice, the only patients who are consistently deemed ineligible for such treatment are organ-transplant recipients, because of the risk of transplant rejection. Nearly everyone else who is ineligible for targeted therapy — typically 70–75% of individuals with metastatic NSCLC — is a candidate for checkpoint-inhibitor treatment. People with EGFR or ALK mutations that respond to targeted therapy, however, rarely benefit from the added punch of a checkpoint inhibitor. Indeed, Mok points out that studies of such combinations have produced concerning side effects, including lung and liver disease.

Other immunotherapy combinations are proving fruitful. For example, a two-drug strategy that combines PD-1 inhibition with an agent that targets another immunomodulatory protein known as CTLA-4 recently won approval for treating advanced NSCLC. It is not yet clear whether this is more effective than simply treating patients with pembrolizumab alone, says Schenk, but she sees a mechanistic argument for why that might be the case. "PD-1 inhibition augments the immune response that is already there, while CTLA-4 inhibition helps to augment the immune response that's coming up," she explains. "So in theory, putting the two together would help to bolster a more long-lasting immune response."

Chemotherapy can also get a boost from immunotherapy. Indeed, that pairing is now recommended for people with NSCLC who have relatively low PD-L1 levels in their tumour tissue. This dual-therapy strategy is also gaining momentum for treating SCLC, which has been far harder to treat than the much more common NSCLC, with no real success in the development of targeted therapies. Two trials have shown that chemotherapy plus checkpoint inhibition can extend survival in people with SCLC relative to chemotherapy alone. "The overall survival increased from about 10 months to about 12 months, and there was a slight improvement in progression-free survival," says Mok, who was involved in one of the trials. Even if the difference is only a few months, these findings are still a success story in the face of a malignancy that has seen no new treatment options for decades. "There's clearly a signal that there are patients that could benefit — the goal is to increase that," says Jänne.

"We've seen amazing responses that we hope will equate to long-term survival."

An earlier start

The front line of drug development is advanced disease, where surgery is no longer feasible and clinicians have run out of other options. This is an especially tough proving ground for therapies, and success against a tumour that has spread to far-flung metastatic nodes is a powerful demonstration of a treatment's mettle.

But these same treatments could have an even more profound effect if delivered earlier in the process. Several trials are exploring whether targeted agents and immunotherapy have greater benefits if applied to early-stage cancers. At this year's meeting of the American Society of Clinical Oncology, researchers presented results from the ADAURA clinical trial showing that when osimertinib was given to people with stage 2 EGFR-mutated tumours after surgery, the number of patients who remained disease-free after two years doubled. "This will likely result in a change in clinical practice in the US," says Jänne.

Brahmer is involved with several trials in which checkpoint inhibitors are applied before surgery to shrink the tumour and increase the likelihood of completely removing the malignancy. "We've seen amazing responses that we hope will equate to long-term survival," she says. These trials are still ongoing, however, and it will be difficult to evaluate such early-stage interventions because it can take many years to assess the impact on survival, and people with early-stage lung cancer often respond well to conventional treatment.

Various other treatments are also being explored. For example, Adjei is enthusiastic about antibody–drug conjugates, in which powerful chemotherapy agents are linked to an antibody that binds selectively to a protein target found only on tumour cells. "You are delivering highly toxic agents you couldn't simply administer into the bloodstream directly to that tumour," he says. "A number of companies have figured out a way of putting a lot of toxins onto one antibody." Such drugs have already won regulatory approval for breast and haematological cancers, and several early-stage trials are now underway to assess their safety and efficacy in lung cancer.

A cure for lung cancer might still be some time coming. But more tolerable treatment regimens and a better understanding of how and when to use them could offer the next-best thing: a return to relative normality.

"I mention to my patients that HIV is still not curable but it is very controllable," says Patil. "And that has sort of been the design of some of these targeted therapies. How do we reduce their cancer burden so that they live a normal life with minimal symptoms?"

Michael Eisenstein is a science writer in Philadelphia, Pennsylvania.

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