PETER BAKER

Robert Carlson enjoys his new lease of life.

LUNG CANCER

Breathe easier

Scientists hope to improve checkpoint-inhibitor treatments to aid more than a few people with lung cancer.

BY KAREN WEINTRAUB

For Robert Carlson, a former slot-machine attendant from Hebron, Connecticut, 18 months of chemotherapy was harsh enough to make death seem inviting. Then the drug stopped working.

His doctor tried him on another treatment for his non-small-cell lung cancer (NSCLC), but it didn't last long. "It was supposed to knock the hell out of the cancer, but it knocked the hell out of me, too," says Carlson, now 74, who had hoped that his long-distance running would counteract his half-century of smoking. His doctor told him he was out of treatment options, so "I said all my goodbyes and made all my amends," Carlson says.

Then a doctor at nearby Yale New Haven Hospital got him into a clinical trial for an experimental immunotherapy drug. Carlson had no serious side effects, his tumours shrank and he kept on living.

The drug he took, the antibody atezolizumab, belongs to a new class of medicines called immune checkpoint inhibitors. The basic idea is to release a brake that cancer applies to the immune system. If immune cells are poised to attack a tumour and are being held back solely by this brake, then releasing it can yield a long-term win against the disease.

A phase III trial comparing the checkpoint inhibitor nivolumab and the chemotherapy drug docetaxel reported that nivolumab had enabled 51% of people with advanced non-squamous NSCLC to survive for at least one year — compared with 39% for chemotherapy alone (see 'Boosting survival in lung cancer') (H. Borghaei *et al. N. Engl. J. Med.* **373,** 1627–1639; 2015). In about 18% of the participants, according to an update from the trial sponsor Bristol-Myers Squibb in New York City, the immune system fought off tumour cells for at least three years and might do so indefinitely — similar to the way a body, once trained to fight measles, retains that memory for a lifetime. "The durability of immunotherapy has been what's so transcendent," says Matthew Hellmann, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York City.

Since March 2015, three checkpoint inhibitors have won approval from the US Food and Drug Administration (FDA) to treat NSCLC. They are all antibodies: pembrolizumab (marketed as Keytruda by Merck in Kenilworth, New Jersey); nivolumab (marketed as Opdivo by Bristol-Myers Squibb); and atezolizumab (marketed as Tecentriq by Genentech in South San Francisco, California). The drugs have already changed the practice of medicine. "The landscape in lung cancer has completely flipped in the last couple of years," says Justin Gainor, a thoracic oncologist at the Massachusetts General Hospital Cancer Center in Boston.

The brake that these inhibitors work on comes in two parts. One piece — called programmed cell death protein 1 or PD-1 — sits on the T cell; its mate, the ligand PD-L1, sits on the tumour cell. When the two are coupled, the brake is on and the T cell cannot attack the tumour. Checkpoint inhibitors decouple the pairing and allow the T cell to act against the malignancy. Nivolumab and pembrolizumab work on the PD-1 side of the brake, whereas atezolizumab acts on PD-L1.

The compounds were initially approved as second-line therapy (following chemotherapy) in people with NSCLC. But last year, researchers found that pembrolizumab was better than chemotherapy at extending median survival time. As a result, many people are now getting a checkpoint inhibitor as their first treatment. "That is really exciting and completely changed how we've approached these patients," Gainor says. His colleague Mark Awad at the Dana-Farber Cancer Institute in Boston adds that, "practically speaking, almost every patient with NSCLC will receive an immune checkpoint inhibitor".

BROADENING THE BENEFITS

However, only a small fraction of people with advanced lung cancers get long-term benefits from checkpoint inhibitors. Researchers are trying to understand why this is so. One theory is that the tumours could have more than one brake that needs releasing. Another is that the T-cell foot soldiers of a patient's immune system aren't ready to storm past the checkpoint when it opens. The task of the coming decades will be to work out how better to treat those people — mainly by combining checkpoint inhibitors with other therapies (see page S67) — and how not to waste people's time, money and hopes on treatments that won't help.

With the cost of checkpoint-inhibitor therapy approaching US$150,000 per year in the United States, and with almost 2 million new cases of lung cancer worldwide each year, the answers are important both to patients — who struggle with the stress of treatment and (in many countries) expensive co-payments — and to the entire health-care system.

"I wish we knew how to personalize it better," says Julie Brahmer, a thoracic oncologist at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland. "It's great that we have many more options for treatment. But trying to tailor the treatment for a patient and manage expectations is an art."

Part of the art is working out how long the treatment needs to last. Most patients stay on checkpoint inhibitors for two years, but some may need longer and others less, Brahmer says. It is widely thought that to reach more patients, checkpoint inhibitors will need to be combined with other, complementary, treatments — but no one knows which.

There are more possible treatment combinations than there are patients, and a large number of trials are under way. Merck has 67 combination trials in progress in lung cancer alone, says Roy Herbst, chief of medical oncology at the Yale Cancer Center in New Haven, Connecticut. "There are possibly too many trials," says Herbst.

Researchers and companies say they are taking a rational approach to working out the most effective combinations, and sorting out crucial details such as dosing and the optimal sequence. But they also admit to a certain amount of guesswork and finger-crossing — at least by others. "Too many of the combinations we see in the clinic are being conducted with noses held or eyes closed," says Ira Mellman, vice-president of cancer immunology at Genentech. "We just don't know enough about the basic mechanisms."

Another challenge is side effects: checkpoint inhibitors can unleash T cells not only to fight lung tumours but also in other parts of the body, leading to symptoms typical of autoimmune diseases. (These side effects are generally manageable with steroids, which fortunately do not seem to counteract the work of the checkpoint inhibitors.)

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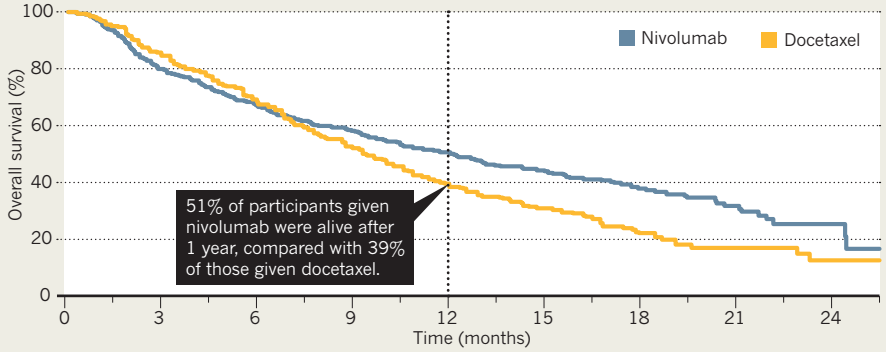
Combining checkpoint inhibitors with other therapies can compound these potentially deadly effects. "It really does take an army to manage the various different types of toxicities," Gainor says, adding that his team includes pulmonologists, hepatologists and a dedicated rheumatologist. This depth of expertise is generally found only at major teaching hospitals.

Researchers are learning and re-learning one hard lesson: not all cancer types respond in the same way to immune-system manipulations.

BOOSTING SURVIVAL IN LUNG CANCER

In a phase III trial in 582 people with advanced non-squamous non-small-cell lung cancer, those who received the checkpoint inhibitor nivolumab showed significant improvements in survival compared with those who received standard treatment with the chemotherapy docetaxel.



SOURCE: H. BORGHAEI *ET AL. N. ENGL. J. MED.* **373**, 1627–1639 (2015)

The combination of two checkpoint-inhibitor drugs with different targets, ipilimumab (which targets a protein called CTLA-4 on cytotoxic T cells) plus nivolumab, seems to work well in melanoma, but has been a failure so far in lung cancer.

In January, Bristol-Myers Squibb, which makes both drugs, decided not to pursue fast-track FDA approval for the combination as an early treatment for NSCLC. And in July, AstraZeneca, based in Cambridge, UK, and its subsidiary MedImmune in Gaithersburg, Maryland, announced disappointing results from a collaborative phase III trial that combined two types of checkpoint inhibitor for the treatment of NSCLC: the combination failed to extend progression-free survival compared with standard chemotherapy. Undeterred, Merck announced in October that it plans to launch a large phase III trial combining its own PD-L1 drug with Bristol-Myers Squibb's ipilimumab (marketed under the name Yervoy).

CHECKING THE COMBOS

The combination with the most supporting evidence so far is chemotherapy plus checkpoint inhibitors. This approach has been validated in early-stage clinical trials, and phase III trial results are expected soon. In May, for example, the FDA approved the use of Merck's pembrolizumab as a first-line therapy in combination with two chemotherapies — pemetrexed and carboplatin — on the basis of the results of a phase II trial funded by the company.

Several researchers are also enthusiastic about combining checkpoint inhibitors with therapies that target specific gene mutations in lung cancer — especially for treating non-smokers, who haven't seen as much benefit as smokers from the checkpoint-inhibitor drugs. Theoretically, such targeted therapies could increase the effectiveness of checkpoint inhibitors in two ways: by making some cancer cells more vulnerable, and by driving T cells into the tumour.

So far, there's no reliable way of predicting who will respond to which drugs or to which combinations. Several companies have tried to use PD-L1 as a biomarker to predict success with checkpoint drugs, because the level of PD-L1 seems to correlate with the number of T cells in the tumour. The connection is far from universal, though. Some people with low PD-L1 fare well on checkpoint inhibitors, and many with high levels get no response at all (S72).

Checkpoint inhibitors seem to work best against tumour types and cancers with lots of genetic mutations. Because it is unusual in the body, this heavy mutational load seems to be easier for the immune system to identify as not belonging to 'self'. Lung cancers triggered by smoking are generally loaded with mutations, and smokers respond to the checkpoint-inhibition therapies better than those who have never smoked. One strategy is to use combination therapies — such as chemotherapy plus a checkpoint inhibitor — to trigger mutations that will make it easier for the immune system to recognize tumour cells.

While scientists and clinicians struggle to increase and improve the immunotherapy stockpile, all Carlson knows is that the day he spends at Yale every three weeks has kept death at bay for four years and counting. Unlike the torment of his previous treatments, he hasn't endured any side effects with the checkpoint inhibitor, although Herbst, his doctor, says Carlson needed to have one adrenal gland removed to stop a localized cancer spread.

Without this therapy, Carlson's chances of survival would have been 10% or less at one year and essentially zero at three to four years, Herbst says.

Carlson is making the most of his extra time, spending it with his wife of 20 years, his cat Ziva and on his favourite pastime: heading out into the woods with his camera. "When you think your milk carton is stamped with an expiration date and you've exceeded your expiration date by four years," he says, "it's kind of amazing". ■

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