PAUL BLOW

THERAPEUTICS

Spoilt for choice

People with metastatic bladder cancer once faced meagre treatment options and a grim prognosis. But immunotherapy has started to yield results.

BY MICHAEL EISENSTEIN

With a typical prognosis of just a few months to live, many people with advanced bladder cancer come to terms with their condition and make arrangements for their final days. But some are now finding their plans unexpectedly altered. "I've got patients who have sold their house or given it to their kids, and a patient who planned a world tour and spent his life savings," says Thomas Powles, an oncologist at Barts Cancer Institute in London. "They've made their plans and spent their money — and now they're kicking around in long-term durable remission."

The reason for these welcome but surprising reprieves is the recent availability of a range of immune-modulating drugs known as checkpoint inhibitors, which have already sparked a revolution in other types of cancer. The first on the market was atezolizumab from drug company Roche, based in Basle, Switzerland, which won accelerated approval for the treatment of metastatic bladder cancer from the US Food and Drug Administration (FDA) in May 2016. The FDA has since approved four more checkpoint inhibitors for bladder cancer, all of which unleash the full force of a patient's immune system on tumour cells. The European Medicines Agency has so far approved only one of these agents for bladder cancer — nivolumab from New York-based drug company Bristol-Myers Squibb — but others are likely to follow.

The approval of atezolizumab was a watershed moment — it was the first drug to be approved to treat bladder cancer since platinum-based chemotherapy three decades earlier. Although such chemotherapy can be effective, many people with bladder cancer ultimately develop resistance and are left without good treatment options, says Daniel Petrylak, a urologic oncologist at the Yale Cancer Center in New Haven, Connecticut. Additional 'second-line' chemotherapy drugs are available but are less effective. "When patients failed primary treatment, they would typically relapse and die within six to nine months," he says.

Checkpoint inhibitors can add years of life with minimal side effects for around 20% of these people. But there is little to help the remaining patients, and the hunt is on for additional therapies and treatment combinations that can benefit them.

NOWHERE TO HIDE

Many tumours produce abnormal proteins known as neoantigens that trigger the immune system to send T cells to hunt and kill the cancer. However, T cells also have fail-safe mechanisms, known as a checkpoints, that keep them from over-reacting and causing a damaging autoimmune response. For example, T cells have a checkpoint protein called PD-1 that causes them to call off their attack when it recognizes another protein called PD-L1, which is found on host cells. But cancer is highly effective at self-preservation, and tumours often evolve strategies to evade the system. If a tumour expresses PD-L1, it can activate the T cells' immune checkpoint and stop them attacking, allowing the tumour to grow unmolested.

Checkpoint inhibitors are antibodies that block this immune suppression by acting on either PD-1 (in the case of nivolumab) or PD-L1 (atezolizumab). These drugs have a strong track record against certain lung and skin cancers that share one of the key features of bladder cancer — a heavily mutated genomic landscape.

"Tumours harbouring more mutations tend to respond better to immunotherapy, and it's postulated that this is because they produce more neoantigen proteins," says Matthew Galsky, who specializes in treating genitourinary cancers at the Icahn School of Medicine at Mount Sinai in New York City. More neoantigens means that there are more potential targets for T cells — if the T cells are not being suppressed.

Numerous clinical trials have shown that checkpoint inhibitors are highly effective against bladder cancer. "I've used all five drugs

and treated over 200 patients," says Powles, "and we see somewhere between one in five and one in four patients having an unexpected impressive response." By 'impressive', he means that metastatic disease is greatly diminished and in some cases eradicated — an outcome that oncologists refer to as a complete response.

This response can last for a remarkable amount of time. "I have several patients who are over three years on treatment with durable partial and even complete remissions," says Arlene Siefker-Radtke, an oncologist at the MD Anderson Cancer Center in Houston, Texas. By contrast, those who receive conventional treatment for metastatic disease often have a life expectancy of much less than a year.

Checkpoint inhibitors are also generally safe, unlike older, platinum-based drugs such as cisplatin. Elizabeth Plimack, an oncologist at the Fox Chase Cancer Center in Philadelphia, Pennsylvania, says that cisplatin produces a meaningful tumour response for 70% of people, achieving a durable effect for 10–15% of them. But chemotherapy treatments can also be quite toxic. Checkpoint inhibitors cause fewer problems. A subset of people in trials of checkpoint inhibitors experience severe side effects, such as inflammation of the skin and organs, but these can generally be addressed by steroid treatment. In most cases, however, the drugs are well tolerated and patients experience only minor issues associated with intravenous infusion. For instance, in a recent trial of pembrolizumab, developed by Merck, based in Kenilworth, New Jersey, twice as many people dropped out because of side effects in the chemotherapy arm as in the treatment arm (J. Bellmunt *et al. N. Engl. J. Med.* **376,** 1015–1026; 2017). "We see many patients who feel fine," says Plimack. "They come in for their treatments, and they can't tell they're on treatment."

Checkpoint inhibitors have so far been approved only for the more aggressive, muscle-invasive form of bladder cancer (see page S34). For those with the more common localized form, the treatment is rather different (see 'Revisiting an old idea'). But even here, some form of immunotherapy is still the important element.

PICKING WINNERS

Having five almost identical drugs to treat metastatic bladder cancer could potentially leave oncologists confused as to which is best for their patients. Trial data suggest that all five have similar performance, with some minor differences. Pembrolizumab is the only one with a published randomized phase III comparison with chemotherapy. In the KEYNOTE-045 study (J. Bellmunt *et al. N. Engl. J. Med.* **376,** 1015–1026; 2017), 44% of participants receiving the drug were still alive after a year, compared with 31% of those given the existing standard of care. "Pembrolizumab currently has the most robust data," says Powles. But clinical evidence for the checkpoint inhibitors strongly suggests that there are no 'wrong' choices. "Comparing across the published studies, on average, we get around a 20% response rate, so it's pretty hard to argue that one is better than another," says Plimack.

Unfortunately, there are no good strategies for predicting who will be in that lucky 20%. These drugs act on immune checkpoint pathways mediated by PD-L1, so several clinical trials have tried to assess whether elevated PD-L1 expression can predict drug efficacy. In some studies, this strategy flagged people with higher response rates, but not consistently — and some researchers believe it may be the wrong sort of indicator. Petrylak says there is evidence that people with PD-L1-positive tumours may, for some unknown reason, have a better baseline prognosis than most people with bladder cancer, so any apparent survival benefit from selecting PD-L1-positive people could be innate, rather than a result of the drug.

A procedure for selecting people based on a combination of genetic, proteomic and immunological indicators is more likely to yield stronger predictive performance. But Plimack says that only a highly accurate diagnostic test will offer much value, because there are so few obvious downsides to taking a checkpoint inhibitor anyway — and there are no good alternatives. "This is a lethal disease," she says. Before a clinician would withhold a drug, "you would have to have a biomarker that guarantees the patient in front of you is not going to benefit".

The priority now is to build on the success of the checkpoint inhibitors. The FDA has approved all five drugs for advanced metastatic disease as follow-up treatments when chemotherapy fails. But it has also given the nod to atezolizumab and pembrolizumab for first-line use in people who are ineligible for cisplatin. Using checkpoint inhibitors at an earlier stage may prevent the spread of cancer and the severe treatment that entails. "The majority of late-stage patients I see have had their bladder removed and the cancer has come back, and they're dead in a year," says Powles. "This is a bad story, and we need to change it."

A multipronged immunological attack could be the answer, and several trials of drug combinations are under way. Drug companies have developed a variety of molecules that target immune regulatory proteins other than PD-1 and PD-L1. For example, Bristol-Myers Squibb has shown that the effects of nivolumab in people with metastatic bladder cancer can be bolstered by pairing it with ipilimumab, which inhibits the CTLA-4 protein from another checkpoint pathway. "That was a nice trial with very interesting results," says Gary Steinberg, director of urologic oncology at the University of Chicago Medicine. "There was a dose that appeared to have less toxicity and a response rate that increased from around 20% to the 30–40% range."

"I have several patients who are over three years on treatment with durable partial and even complete remissions."

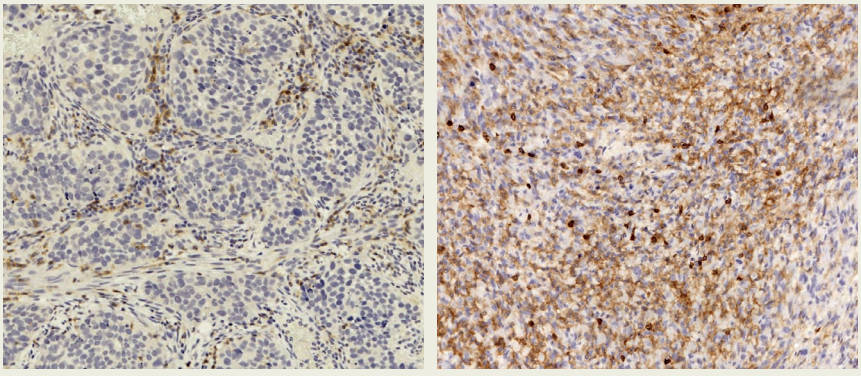
Researchers are seeing a similar boost in therapeutic response in a small ongoing trial combining pembrolizumab with a drug called epacadostat from Incyte, based in Wilmington, Delaware. Epacadostat inhibits an enzyme that would otherwise make the tumour environment inhospitable for immune cells.

TARGET PRACTICE

Immunotherapy may have grabbed all the headlines, but it is not the only treatment available. Researchers are developing other targeted therapies to interfere with specific molecules that, as the result of genetic mutations, drive cancerous growth. Such mutations are common in bladder cancer (see page S44), but the development of targeted therapies for bladder cancer has lagged behind that for other tumour types and has a history of disappointing setbacks.

SPACE INVADERS

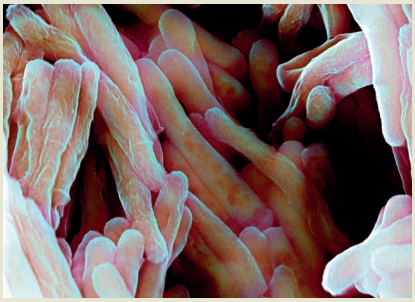
T cells (brown) initially ignore bladder-cancer cells (left panel), but one week after treatment with a checkpoint inhibitor they are infiltrating and destroying the tumour (right).



MD ANDERSON CANCER CENTER

REVISITING AN OLD IDEA

Immunotherapy for localized cancer.



SPL

The bacillus Calmette–Guérin (BCG) vaccine uses attenuated *Mycobacterium bovis* bacteria.

Doctors have been using a primitive form of immunotherapy to treat non-muscle-invasive bladder cancer for more than 40 years. The bacillus Calmette–Guérin (BCG) vaccine, which was initially used to prevent tuberculosis, elicits an immune reaction when injected into the bladder. People receiving this treatment are 70% less likely to experience recurrence of their cancer one year after surgery.

"The BCG story is complex," says Gary Steinberg, director of urologic oncology at the University of Chicago Medicine in Illinois. "It's effective and sets a high bar, but it's unclear as to exactly why it works." Despite this, it ultimately fails for many patients, and others do not respond at all.

Steinberg hopes the efficacy of BCG might be augmented by checkpoint inhibitors in localized, aggressive forms of the disease. He is collaborating with drug company Roche on a clinical trial that combines the vaccine with atezolizumab. "The concept is that BCG helps direct the immune response to the bladder, and that some of the patients are not responding because of checkpoint inhibition that you can block," says Steinberg. Similar trials are under way to test pembrolizumab and durvalumab with combinations of BCG and radiation, but these studies are still at an early stage.

Several companies are also exploring virus-based therapies that, like BCG, can be injected directly into the bladder. For example, CG0070 from Cold Genesys, based in Santa Ana, California, selectively reproduces in tumours with a mutation in the retinoblastoma gene, which is a relatively common driver of tumorigenesis. Steinberg believes that as many as 60–70% of tumours that are unresponsive or become resistant to BCG may harbour such mutations. Once in the tumour, the virus replicates until the tumour cells rupture, while also producing a signalling protein that draws a strong antitumour response from the immune system.

Steinberg is the lead investigator on the BOND2 clinical trial, which has released preliminary data showing that CG0070 performed particularly well with carcinoma *in situ*, the highest-risk form of non-muscle-invasive disease. "We saw a very significant 50–58% complete response rate at six months," he says. "But we clearly need to take this out to 12 and 18 months." M.E.

One of the biggest disappointments concerns a protein called vascular endothelial growth factor (VEGF), which stimulates the growth of the blood vessels needed to feed a fast-growing tumour. Several groups have tried to develop anti-VEGF treatments for bladder cancer. Powles and colleagues even had to halt one trial early, for a drug called pazopanib. "It did significantly worse than second-line chemotherapy, which everyone thought was hard to do," he says.

However, this therapeutic strategy may have found redemption with a newer agent called ramucirumab, which blocks the VEGF receptor, rather than the protein itself. In a phase II trial, people receiving ramucirumab plus chemotherapy avoided disease progression for almost twice as long as those receiving only chemotherapy. A larger, phase III trial is under way, and the early data are promising, says Petrylak, who led both studies.

Petrylak is also excited about antibody drugs that target specific proteins on tumours and deliver chemotherapy agents directly to the cancer cells. He was involved with a phase I trial to test the safety and efficacy of enfortumab vedotin, which was developed jointly by Tokyo-based drug company Astellas and Seattle Genetics in Washington. The drug binds to Nectin-4, a protein commonly found on the surface of tumours. "We saw about a 45% response rate in second-line therapy, and about a 35% response rate in patients who had failed on checkpoint inhibitors," says Petrylak. A phase II trial is planned that, if successful, could give clinicians a follow-up option for people who are not helped by immunotherapy.

Targeted therapies of this sort can help people with bladder cancer, but the benefits are often small compared with the dramatic gains seen with checkpoint inhibitors. Powles thinks that they might buy patients a few progression-free months, but without any significant effect on survival. "This is not what we're looking for," says Powles.

When immunotherapy and targeted therapy are used in combination, however, their effects could be greater than the sum of their parts. Several companies are testing agents that target fibroblast growth-factor receptor 3 (FGFR3), which is frequently mutated in bladder cancer. Inhibiting FGFR3 does not profoundly affect tumour progression on its own, but it may offer a way to boost the power of checkpoint inhibitors. "In the patients that I've treated with immunotherapy who have an FGFR3 mutation, I've seen very limited efficacy," says Siefker-Radtke. "Inhibiting the FGFR3 pathway could enhance the ability of the immune system to infiltrate these immunologically 'cold' cancers."

Several multi-arm trials are under way that could accelerate the discovery of effective drug pairings. Powles is coordinating one such study known as BISCAY, which will test durvalumab, an FDA-approved checkpoint inhibitor developed by AstraZeneca, based in Cambridge, UK, in combination with a host of early-stage targeted therapies from the company's drug pipeline. "The trial has an adaptive design, so when AstraZeneca buys a new drug or we find something new and interesting, we can just stick that in," explains Powles. BISCAY already has five treatment arms, and Powles is confident that this approach will help them home in on drug pairs and even trios that will amplify the benefits of checkpoint inhibition. "We're trying to generate response rates in the range of 50% for groups of biomarker-selected patients," he says.

CHANGING PLANS

For clinicians who have toiled in this field for years, the surge of interest in bladder cancer has been something to behold. "Ten years ago there were probably around 200 patients on randomized front-line trials in bladder cancer around the world," says Powles. "Today, just the ones I'm involved in have 3,500 patients."

Clinical researchers, who once had to beg and plead for pharmaceutical investment, now have partners queueing up at their door. "You can do a study in mice, and six months later 'big pharma' is going to be looking for investigator-initiated small trials," says Steinberg.

Motivated by dramatic tales of surprising survival, people with bladder cancer are clamouring to get into the latest trials, even if the odds of meaningful benefit are something of a lottery. In the meantime, oncologists are hoping that the growing arsenal of drugs will allow more people with late-stage cancer to reconsider their 'final' plans.

"Could this be a potential cure for previously incurable tumours? We don't know that yet," says Siefker-Radtke. "But having several patients on treatment for over three years is really quite exciting, and it's something for us to build on." ■

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