Herceptin binds to a receptor called HER2 that is produced in excess by some breast cancer cells (pink).

MEDICINE

Eyes on the target

A push to expand the success of a pair of antibody-based drugs is buying some women years of freedom from breast cancer.

BY MICHAEL EISENSTEIN

Descriptions of a drug as revolutionary, transformative or a home run are usually reserved for press releases or presentations to investors. But oncologists are embracing such language to describe two drugs that allow them to offer some people with breast cancer a cure rather than a consolation.

The drugs are trastuzumab (Herceptin) and pertuzumab (Perjeta). Both are antibody-based agents that target the signalling protein HER2, which is produced in abundance in 20–25% of breast tumours. The high levels result in poorly controlled cell growth and proliferation. For decades, the

protein has been regarded as the hallmark of a dire prognosis, says oncologist Luca Gianni, at the San Raffaele Hospital Scientific Institute in Milan, Italy.

Today, many patients with HER2-positive tumours are essentially having their cancer eradicated by receiving a double-hit of targeted therapy before surgery. Even patients diagnosed with late-stage, metastatic disease — once seen as an imminent death sentence — are living much longer than ever before. In a few exceptional cases, the duration of these benefits can be remarkable. “We never use the ‘c-word’ with metastatic disease, but

I have one patient in my practice who has been in complete remission for 13 years,” says Shanu Modi, a medical oncologist at New York’s Memorial Sloan Kettering Cancer Center. “I think of her as a cured person who just comes by my clinic to visit every three months.”

These two agents exemplify the modern model of targeted therapy in oncology — give patients personalized treatments that selectively hit tumours based on their specific set of mutations, rather than conventional chemotherapy, which is broadly toxic to healthy as well as dangerous cells. Nevertheless, cancers will return in many people who receive prompt treatment. “I still don’t think we’re curing the vast majority of patients,” says Modi. New agents in the clinical pipeline could improve the effectiveness of these targeted agents and help doctors and patients to achieve more and longer-lasting victories, although some worry that soaring costs (see ‘Crippling costs’) will limit the reach of these next-generation therapeutics.

A DYNAMIC DUO

Trastuzumab was the first HER2-targeting drug to reach the market, following a phase 3 clinical trial that showed that the drug improved the odds of survival by 20% in women with metastatic HER2-positive breast cancer¹. Subsequent data showed that giving people the drug after the surgical removal of early-stage tumours cut the risk of the cancer returning in half². “That’s an absolute home run,” says Elizabeth Mittendorf, a surgical oncologist at Houston’s MD Anderson Cancer Center. “We don’t see numbers like that often in oncology.”

In 2012, data from the CLEOPATRA clinical trial showed that oncologists could expect an even better return by pairing trastuzumab with pertuzumab³. Both drugs are antibodies that specifically bind HER2, but each recognizes a different site on the protein, and their combined effects (along with conventional chemotherapy) resulted in even greater tumour shrinkage and further improvements in prognosis for people with metastatic breast cancer. The combination prolonged median survival by well over a year relative to trastuzumab alone. “We give that combination to all of our metastatic patients as first-line treatment if we can,” says Modi, “and they’re being treated for three or four years on average.” In two further trials^{4,5}, by using the trastuzumab-pertuzumab combination to shrink tumours before surgery — an approach known as neoadjuvant therapy — clinicians discovered that they could eradicate all traces of cancer from the breast and lymph nodes (known as a pathological complete response) in roughly half of patients.

That is not the same as a cure, however, and these trials are too recent to confirm

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how durable the benefits are. Still, physicians are already seeing clear benefits in other domains. Mittendorf says she can now perform less-invasive operations that leave the breast largely intact, and neoadjuvant treatment can eliminate lymph node growths that previously required surgical removal. Oncologists are now eagerly awaiting the results from the recently concluded APHINITY trial, which measured survival and recurrence in patients given the combined therapy after surgery.

Other HER2-targeted therapies have reached the clinic, but without offering such a clear patient benefit. Lapatinib, for example, delays tumour progression by interfering with HER2 signalling, but also exhibits more toxicity and is generally less effective as a first line of treatment than its antibody-based counterparts. As a result, lapatinib is generally reserved for late-stage treatment of patients whose tumours acquire resistance to trastuzumab or pertuzumab. Importantly, this treatment may also be effective at limiting metastatic growth in the brain — a particular threat to patients who are HER2-positive (see 'Staving off a deadly invasion').

Another HER2-targeted drug called T-DM1 (Kadcyla) mitigates the severe toxicity associated with conventional chemotherapy agents by physically tethering the chemotherapeutic agent DM1 to trastuzumab. This restricts the toxic effect to HER2-expressing cells. "There's no hair loss and very little neuropathy," says Modi. "I think patients are enjoying a much better quality of life on T-DM1." As one of the first antibody-drug conjugates to reach the clinic, T-DM1 extends median survival by more than five months in patients with recurrent HER2-positive breast cancer relative to lapatinib.

A recently concluded trial called MARIANNE examined whether T-DM1 could replace trastuzumab and chemotherapy as the first line of treatment. Although less toxic than the standard drug combination, T-DM1 proved no more effective at delaying disease progression, and so will probably remain a second-line option. Gianni hopes that these results will not prevent clinicians from finding smart ways to incorporate this safe and generally effective drug into their regimens.

"T-DM1 was presented as the solution to all of our problems, and now it's being demonized as an expensive failure — but this is not so," he says. "It is simply a drug that requires some better thinking and a different approach."

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TARGETED THERAPY

Crippling costs

The life-extending advances in targeted therapy that are causing so much excitement for clinicians and patients with breast cancer are not cheap. In the United Kingdom, a course of T-DM1, for example, costs £90,000 (US\$138,000). The country's National Institute for Health and Care Excellence rejected routine coverage of the drug through the National Health Service (NHS) because of the high cost. For now, this drug is available through a special fund that provides access to medications that are not generally available through the NHS, although this fund is due to end next spring.

As costs soar, even the best drugs risk becoming bogged down in protracted negotiations. Consider the antibody-based agent pertuzumab. It was approved for presurgical, or 'neoadjuvant' use, by the European Medicines Agency in June, but cannot be used in this way until the various national health systems agree on a price. "Until recently, everything that had clear

benefits was approved and reimbursed," says oncologist Thomas Bachelot at the Centre Léon Bérard in Lyon, France. "But costs are really getting very high very rapidly, and there will be some tough decisions to make."

In the United States, private insurance generally covers these pricey treatments, but policies don't always cover the full costs, leaving many patients with crippling bills. In August, more than 100 clinicians signed a letter in *Mayo Clinic Proceedings*⁹ to support a patient petition for vigorous pricing reforms, noting that every oncology drug approved by the Food and Drug Administration in 2014 cost upward of US\$120,000 per year — and that patients routinely shoulder up to a quarter of that cost. "We are negating therapeutic opportunities," says oncologist Luca Gianni at the San Raffaele Hospital Scientific Institute in Milan, Italy, "and this should not happen."

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CUTTING OFF THE EXITS

The ability to target HER2 has been a life saver for many patients, but it is far from a complete victory. Many people who receive neoadjuvant treatment will not have their cancer eradicated. And although oncologists can keep cancer in people with metastatic disease at bay for years, this requires multiple rounds of therapeutic attack with a shifting arsenal of drugs. "The chance of having a durable response is much higher, and we're seeing patients with metastatic disease go through five, six or seven lines of treatment," says Nancy Lin, an oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts. "But the disease is generally not curable."

The mechanisms by which HER2-positive tumours acquire resistance to the drugs that once laid them low are poorly understood. Gianni sees the tumour environment, which contains a diverse mixture of cells with distinct mutational profiles, as part of the problem. "If 30% of the cells in a tumour overexpress HER2, that's a HER2-positive tumour," he says, "but many cells still do not express that target." Thus, killing off trastuzumab-vulnerable cells will still leave a large cancerous community. This highlights the value of generalized chemotherapy, and Francisco Esteva at New York University's Langone Medical Center suggests that this phenomenon may also be to blame for T-DM1's modest performance in MARIANNE. "If you target too much, the other

clones can escape," he says.

However, Thomas Bachelot, a medical oncologist at the Centre Léon Bérard, in Lyon, France, does not believe that this is the only mechanism by which tumours can recur after an initial therapeutic victory. "I do a lot of biopsies, and they always remain HER2-positive — they don't lose it," he says, adding that even if the tumour rebounds while patients are taking trastuzumab or pertuzumab, they still draw some benefit from those drugs. If HER2-targeted therapies are halted, he says, patients tend to fare even worse than if they had stayed the course. This outcome hints at other cellular pathways and processes that amplify or mitigate the effects of HER2-targeted treatment. These pathways might therefore serve as useful biomarkers to guide therapy. The trial data point to sub-populations with strong responses in both directions — one neoadjuvant trial⁴ found that nearly 17% of patients had a pathological complete response from targeted drugs without any chemotherapy, a result that suggests that some patients could skip the most toxic components of treatment. Other tumours remain stubbornly unresponsive. "About 10% of our HER2-positive patients do not respond at all to trastuzumab and pertuzumab," says Bachelot. "There is this huge primary resistance, and we don't know why."

Another apparent pathway to resistance arises from hyperactivation of a signalling cascade known as the phosphoinositide

3-kinase (PI3K) pathway. Preliminary clinical studies suggested that everolimus, a drug that interferes with PI3K signalling, might increase the effectiveness of trastuzumab against metastatic breast cancer. Although results from two phase 3 trials proved disappointing, subsequent examination of the data revealed that everolimus may delay progression in patients with mutations that affect PI3K activity⁶. However, Modi believes that future studies should hit this pathway through alternate means. “You can get a few weeks improvement from everolimus, but with a lot of toxicity,” she says. “There have got to be better drugs for targeting PI3K.”

Her team is evaluating one such drug, BYL719, and has also seen promising results from another approach to bolstering HER2-targeted treatment. Tumour cells rely on a molecule called heat-shock protein 90 (HSP90) to manage the production of HER2, and Modi and colleagues have found that chemical inhibition of HSP90 can stall HER2-dependent tumour growth⁷. “In our first phase 2 trial, we combined an HSP90 inhibitor with Herceptin and saw a nearly 25% response rate from just these two agents, without any chemo,” she says. Her team is working with two different HSP90 inhibitors, including a compound that can be isotopically labelled so that the extent to which tumours are taking up the drug can be directly monitored.

Most breast tumours also show excessive activity by the receptors that respond to the reproductive hormones oestrogen and progesterone, and numerous studies suggest that these hormone receptors influence the response to HER2-targeted drugs. Data from dual-therapy neoadjuvant trials indicate that the pathological complete response rate jumps from around 50% to more than 80% in patients with hormone receptor-negative tumours⁵.

A growing body of data demonstrate that these two signalling pathways collaborate to promote growth⁸, suggesting that multiple hits may be necessary to limit the tumour's escape routes.

Ultimately, combinations of highly targeted treatments with more broadly active therapy regimens may hold the key to ensuring that no patient with cancer gets left behind, Gianni says. “We now have plenty of drugs that exploit different mechanisms of action,” he says. “The challenge is to use them in the optimal way.” For now, these targeted therapies are giving some patients the opportunity to live cancer-free, and giving many others the prospect of additional years of life — and a chance to think differently

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METASTATIC TUMOURS

Staving off a deadly invasion

HER2-positive breast cancer can spread to the brain (green cross in left image); some patients have been shown to respond to targeted therapy to reduce the metastasis (right).

Doctors and patients who wage a successful first-round bout with an HER2-positive breast tumour may subsequently find themselves grappling with a more fearsome opponent. “About half of those patients who have HER2-positive metastatic tumours develop cancer in the brain,” says oncologist Nancy Lin of the Dana-Farber Cancer Institute in Boston, Massachusetts. Part of the cause is biological, and Lin believes “there is probably some inherent predilection for these tumours to go to the brain”. However, the remarkable success of targeted treatments is itself a factor. The prolonged life of patients with metastatic breast cancer simply creates more opportunities for brain growths to form.

It remains unclear whether trastuzumab and pertuzumab are effective at hitting these metastases. Some researchers believe that the capillaries within the brain have too tight a seal for these relatively large drugs to penetrate. However, oncologist Thomas Bachelot of the Centre Léon Bérard in Lyon, France, thinks that this barrier is sufficiently leaky within tumours to grant these drugs access, and points to trial data suggesting that patients with stable brain metastases¹⁰

respond well to targeted treatment. Bachelot and colleagues have also found¹¹ that the small-molecule drug lapatinib, in combination with chemotherapy, controls brain metastases well. “You get very good results in terms of time to progression that are equivalent to what you see with disease outside the brain,” he says.

Radiotherapy approaches have also become more sophisticated; rather than subjecting patients to highly damaging whole-brain irradiation, clinicians can now selectively hit lesions while sparing healthy nervous tissue. People who once faced six-month life expectancies can survive five years or longer.

For years, the presence of disease in the brain automatically disqualified patients from being involved in trials. “It was often just part of the boilerplate language for eligibility,” says Lin, resulting in missed opportunities to identify regimens that might control or kill such growths. These restrictions are now being removed. Some companies are considering opening up trials to patients with untreated or progressive brain metastases, she says, a move that could quickly widen the battle against invasive breast cancer. **M.E.**

about their futures. “It’s completely changed the conversation in my office,” Mittendorf says. ■

Michael Eisenstein is a freelance science writer living in Philadelphia.

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