Table 1 Selected trials in HER2-positive breast cancer

Company	Regimen	Comparator	Indication	Stage
Roche/ Genentech	Pertuzumab + Herceptin + chemotherapy	Herceptin + chemotherapy	Untreated metastatic breast cancer	Phase 3
			Operable HER2-positive breast cancer (adjuvant setting)	Phase 3
	Pertuzumab + T-DM1	Herceptin + chemotherapy	Untreated metastatic HER2-positive breast cancer	Phase 3
	T-DM1	Tykerb + chemotherapy	HER2-positive locally advanced or metastatic breast cancer	Phase 3
GlaxoSmithKline	Tykerb + Herceptin + chemotherapy (concomitantly or sequentially)	Tykerb + chemotherapy or Herceptin + chemotherapy	HER2-positive early breast cancer after surgery	Phase 3[a]
Pfizer (New York)	Neratinib (an irreversible small-molecule inhibitor of Erbb1, ErbB2 and ErbB4 tyrosine kinases) after adjuvant Herceptin	Adjuvant Herceptin	HER2-positive early-stage breast cancer	Phase 3

[a]Trial protocol recently amended to discontinue Tykerb as monotherapy, after an assessment indicating that it was unlikely to meet noninferiority with respect to Herceptin as monotherapy.

scientist Mark Sliwkowski, who has been part of Genentech's effort in developing HER2-targeting therapies for some 20 years.

The anti-HER2 mAb Herceptin is thought to exert its therapeutic effects through multiple mechanisms. These include the promotion of antibody-dependent cellular cytotoxicity and the disruption of HER2-associated signaling, leading ultimately to cancer cell cycle arrest (*Cancer Res.* **70**, 4481–4489, 2010). The drug initially gained approval in 1998 as a front-line treatment, in combination with chemotherapy, for HER2-positive metastatic breast cancer. In 2006, it was approved as an adjuvant therapy for women with early-stage, HER2-positive cancer, who had undergone surgery or another primary therapy. In this setting, survival rates have improved from around 65% to >85%, says Sliwkowski.

"It has a big impact, but it's not a curative therapy," says Larry Norton, deputy physician-in-chief for breast cancer programs at Memorial Sloan-Kettering Cancer Center in New York, who was senior author on the paper that reported the first pivotal trial of the drug (*N. Engl. J. Med.* **344**, 783–792, 2001). Resistance to Herceptin develops within a year in a majority of patients who respond initially, and ~15% of women who receive adjuvant therapy still progress to metastatic disease (*Breast Cancer Res.* **8**, 215–222, 2006).

Pertuzumab, a humanized mAb that Genentech describes as a "HER2 dimerization inhibitor," binds a different epitope on the HER2 receptor and blocks its activation. The first study combining pertuzamab, Herceptin and chemotherapy that got the company "jazzed," Sliwkowski says, was a phase 2 trial in 66 HER2-positive metastatic breast cancer patients whose disease had progressed, despite having previously undergone treatment with Herceptin plus chemotherapy. The objective response rate—which includes patients who achieved either a complete or a partial response—was 24%. Another 26% had stable disease for at least six months (*J. Clin. Oncol.* **28**, 1138–1144, 2010). "In that disease setting, that's a big signal," Sliwkowski says.

A second phase 2 trial, called NeoSphere, took a completely different tack, by examining the combination in the so-called neoadjuvant setting (**Table 1**). It recruited 417 patients with early-stage HER2-positive breast cancer who had not undergone surgery or any other therapy. Here, too, the pertuzumab/Herceptin/chemotherapy combination was clearly differentiated from the Herceptin/chemotherapy treatment, with a complete response of 46% and 29%, respectively. "Basically you've looked at the ceiling, you've looked at the floor—you've looked at both ends of the spectrum," Sliwkowski says. The so-called NeoALLTO phase 3 study, which looked at a combination of chemotherapy, Herceptin and Tykerb (lapatinib), a dual EGFR/HER2 tyrosine kinase inhibitor marketed by London-based GlaxoSmithKline, obtained a similar outcome in the neoadjuvant setting as well.

"The NeoSphere and NeoALLTO data presented at San Antonio [last year] were very impressive in that they indicated that pathological complete response rates in the upper twenties for [Herceptin] trastuzumab and paclitaxel were increased by 20%, through dual blockade of the HER2 pathway. If this translates into the metastatic setting, the Cleopatra results to be presented at San Antonio could be extremely exciting," says

IN brief

Gilead donates patents for generics

Gilead Sciences and the Geneva-based Medicines Patent Pool (MPP) have entered into an agreement allowing manufacturers to produce low-cost versions of the biotech firm's HIV drugs. Gilead's Viread (tenofovir), Emtriva (emtricitabine), cobicistat and elvitegravir, along with a combination of all four called the Quad, will be produced by generics manufacturers in India in return for modest royalties. "This should become a win-win for much of the global HIV-infected community and Gilead," says John Erickson, CEO of Sequoia Pharmaceuticals of Gaithersburg, Maryland. Cobicistat and elvitegravir are in phase 3, meaning low-cost versions could be available in developing countries immediately after approval. The MPP hopes the deal struck with Gilead, of Foster City, California, will bring other companies on board, and is focused on negotiations with a drawn-up list of pharma companies. For biotechs with phase 1 and 2 products, such as Sangamo BioSciences of Richmond, California, Tobira Therapeutics of S. San Francisco, and Chimerix of Durham, North Carolina, it appears too early to consider the patent-pool scheme; they are more likely to wait until their products are closer to market. According to Erickson, inducing early-stage deals will require a different licensing rationale to avoid devaluing companies' drug intellectual property through limiting its options prematurely. For instance, the MPP or one of its generic partners could become a fully fledged development partner that shares the risks. "Otherwise, aside from optics [public relations], it is difficult to see any benefit to MPP or biotechs for entering into licenses for early-stage drugs," says Erickson. *Simon Frantz*

South Korea's stem cell approval

On July 1, the Korea Food and Drug Administration approved a stem cell treatment for acute myocardial infarction developed by FCB-Pharmicell of Seongnam. Locals view the regulatory go-ahead as a world first and also a vote of confidence for the nation's scientific expertise following the cloning scandal that found stem cell scientist Woo Suk Hwang guilty of fraud (*Nat. Biotechnol.* **24**, 745–747, 2006). The treatment, Hearticellgram-AMI, is an autologous stem cell transplant of mesenchymal stem cells, cultured from a patient's own bone marrow, injected into the coronary arteries. The approval comes after six years of clinical trials; as yet, the company has not published results in a peer-reviewed journal. Another major caveat is clinical efficacy: patients showed a 6% improvement in the left ventricular ejection fraction used as measure of heart function six months after one dose of Hearticellgram-AMI. "6% is not terrible. You're getting a modest improvement, and that might be the best they ever do" says University of Michigan cardiologist Mark Russell. For Hearticellgram-AMI, a price tag of 20-million Won ($19,000) may be overly optimistic," says Russell. *Heiko Yang*