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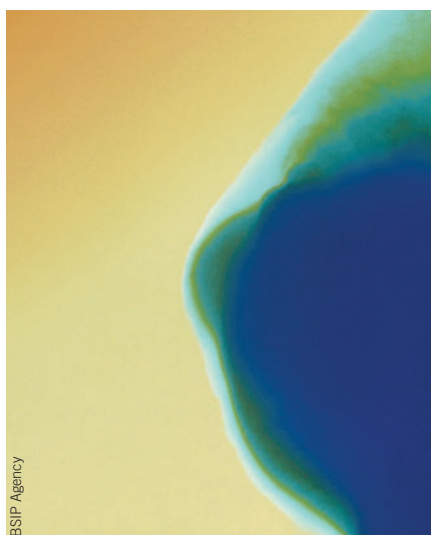
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GlaxoSmithKline cancer drug threatens Herceptin market

The first targeted therapy for breast cancer, Genentech's Herceptin (trastuzumab), approved in 1998 in the US, could soon face direct competition. GlaxoSmithKline (GSK) has been ramping up efforts to bring small-molecule GW 572016 (lapatinib), the only dual-action tyrosine kinase inhibitor in phase 3 trials, to the market by 2007. Meanwhile, large pharma and biotech companies are testing other multitargeted therapies, forcing GSK to prepare for a potentially crowded market.

Herceptin, an injectable humanized IgG1κ monoclonal antibody, targets the extracellular domain of HER2, a protein in the epidermal growth factor family. Herceptin is designed to counter the overexpression of HER2, which is involved in the growth and spread of tumor cells in 25–30% of all metastatic breast cancer patients. But because Herceptin only targets one protein, it is limited in the range of patients it can reach. "With targeted therapies, there are so many signal pathways for mutation, to cover one just doesn't cut it," says Fil Manuguid, an oncology consultant for IMS Health Global Consulting in London.

Instead, "you need to use two or more targeted therapies and a cytotoxic to clear away those mutations," Manuguid adds (*Nat. Biotechnol.* 23, 639, 2005). That's where lapatinib, used in combination with traditional



chemotherapy and as a monotherapy, could supplant Herceptin. It targets the intracellular domain of HER2, plus that of a close relative, HER1. GSK researchers believe lapatinib prevents tumor growth by inhibiting intracellular

tyrosine kinase activity. GSK's latest results showed a 35% response rate in 40 first-line metastatic breast cancer patients, according to results reported in November at the European Cancer Conference (ECCO) in Paris.

Edith Perez, an oncology physician at the Mayo Clinic in Jacksonville, Florida, and a researcher who participated in clinical studies of Herceptin, says lapatinib could garner a place in the market if phase 3 trials demonstrate it either works in combination with Herceptin in what is called a 'total blockade' of HER1 and HER2 signal transduction pathways, or shrinks tumors in refractory patients.

Although side effects, including rash and sometimes diarrhea, affect patients receiving both therapies, lapatinib edges out Herceptin in a couple of areas already. Because lapatinib targets more than one protein, GSK researchers hope fewer people will develop resistance. More importantly to patients, lapatinib comes in a tablet taken orally once a day, cutting down on trips to the hospital. But Herceptin touts two sizeable advantages over lapatinib. It has already been tested and shown to be effective—a substantial hurdle in itself. And because Herceptin is an antibody, its immune effects may spur the immune effector cells to kill the tumor cells—something small-molecule lapatinib cannot do.

Table 1 Next generation breast cancer drugs in phase 2 and 3

Drug	Company	Mechanism of action	Phase
Avastin (bevacizumab)	Roche (Basel), Protein Design Labs (Fremont, California), Genentech (S. San Francisco, California)	Anti-VEGF mAb	3
GW-572016 (lapatinib)	GlaxoSmithKline	Erb-B1 & Erb-B2 dual kinase inhibitor	3
Tarceva (erlotinib)	Genentech, Roche, OSI Pharmaceuticals (Melville, New York)	EGFR antagonist	2
Nexavar (sorafenib)	Bayer / Onyx Pharmaceuticals (Emeryville, California)	RAF kinase, VEGFR-2, VEGFR-3, PDGFR-, KIT, FLT-3 & RET inhibitor	2
Sutent (sunitib malate)	Pfizer (New York)	VEGFR, PDGFR, KIT, RET, & FLT-3 inhibitor	2
AG-13736	Pfizer	VEGFR, PDGFR & KIT inhibitor	2
PTK/ZK (vatalanib)	Schering / Novartis (Basel)	VEGFR kinase inhibitor	2
Iressa (gefitinib)	AstraZeneca (London)	EGFR antagonist	2
ZD6474 (Zactima)	AstraZeneca	EGFR & VEGFR inhibitor	2
Erbix (cetuximab)	ImClone Systems (New York)	EGFR antagonist mAb	2

VEGFR, vascular endothelial growth factor/receptor; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; FLT-3, fms-like tyrosine kinase-3.

Source: Evaluate Pharma (<http://www.evaluatepharma.com/>) and company web sites.

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Box 1 Targeted therapy delayed by inadequate FDA approval process

Citing poor results in a recent trial, IMS Health's Manuguid is leery of projecting lapatinib as a blockbuster drug. The results were part of a phase 2 trial presented earlier this year that tested lapatinib's efficacy in 41 patients who did not respond to Herceptin. Only four patients responded to the treatment. Paoli Paoletti, a senior vice president of oncology development at GSK, says results were poor because the FDA trials force targeted therapies to develop their drug the old way—like a cytotoxic; they test populations of people who haven't responded to other treatments.

Targeted drugs, however, are tailored to specific sets of patients who overexpress certain targets, he says. Other experts agree. "Targeted therapies aren't suited for FDA trials," says Van Etten, who published a paper on the topic in July 2005 in the *New England Journal of Medicine* (353, 172–187). "It is common for the FDA to take all comers of failed therapies. But if you have some idea which patients are expressing the target, you ought to be selecting those patients."

Paoletti says the formula for FDA trials stalled the development of multitargeted drugs for about five years. Despite the setback, he hopes sequential use of targeted agents will someday eliminate the need for cytotoxic chemotherapy. "I just hope I'm alive long enough to see it," he says.

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Manufacturing, hospital and travel costs of administering an intravenous drug, such as Herceptin, surely dwarf the cost of producing a pill. But experts such as Richard Van Etten, a professor of medicine at Tufts University in Boston say GSK may charge just as much for lapatinib as Genentech charges for Herceptin. "GSK will price it as high as they think the market will bear" to cover their R&D costs, Van Etten says.

Herceptin costs about \$60,000 per patient per year, according to Perez at the Mayo Clinic. Most US government and private insurers cover Herceptin for all indications. Most European governments, however, only cover patients who take Herceptin in late stages of the disease or after all other treatments fail.

If GSK adopts a similar pricing structure for lapatinib, it could follow in the steps of Herceptin, which is due to generate \$1.5 billion revenue in 2005 worldwide, according to estimates by business intelligence firm Evaluate Pharma of London. The figure is forecasted to grow to \$3.7 billion by 2007. But to become the next generation breast cancer treatment, lapatinib must either replace Herceptin or prove efficacious in combination with the drug.

Other large companies such as Roche, Pfizer and AstraZeneca are currently testing their own targeted cancer drugs in combination with each other and with more traditional treatments such as hormones and chemotherapies. They know some patients will require a cocktail of targeted drugs to kill

their tumors, but analysts say direct competition between the targeted therapies is inevitable (Table 1).

In fact, if lapatinib reaches the market as scheduled, it could face several newcomers shortly after (Box 1). Genentech/Roche's Avastin, a single-targeted therapy approved in the US for colorectal cancer, is in phase 3 trials for breast cancer. Several multitargeted therapies follow close behind in phase 2 trials: Pfizer's Sutent (sunitinib malate), Bayer's Nexavar (sorafenib) and AstraZeneca's ZD6474 (Zactima). IMS Health's Manuguid questions whether healthcare systems can actually afford all of these therapies.

"Lapatinib is part of a new class of targeted therapies and it will do quite well,"

"GSK will price it as high as they think the market will bear" to cover their R&D costs, Van Etten says.

says Fleur Pijpers, an oncology analyst for Datamonitor in London. "By the time Sutent and sorafenib are approved, it is likely that GSK will have initiated line extension

[for other indications] within breast cancer for lapatinib. But the only way to say one is better than the other is by looking at clinical trial results, and it is too early to say."

If GSK wants lapatinib to succeed in the face of such competition, experts say the company can't settle for conservative marketing strategies. "GSK must break through their reputation," says IMS Health's Manuguid. "You have to have strength to market a targeted therapy. So far, they've been somewhat lackluster in oncology. Their biggest obstacle is how much money they're willing to invest in it."

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