uation at Heidelberg Innovation, where all funding applicants are unrestricted in their choice of venture capital, other finance supplier, or legal services. For people like Thomas Werner, who have had their applications for seed finance turned down by BioM, the prospects for interesting other venture capital companies are low. "When a young entrepreneur does the rounds in Munich in order to raise money, he knocks at the door of at least five various institutions. But the same person

is always sitting behind the desk," says Werner. He says that it is impossible to present a business plan to a venture capitalist in Munich without members from BioM's advisory or seed financing boards, for example, knowing about it. Two of Munich's biggest venture companies, TVM and Atlas, both have representatives on the seed finance board.

Horst Domdey concedes that "the one thing you can reproach Munich with" is that a limited group has all the decision-making abil-

ity over who is funded. That group may be even smaller than just the six members of the BioM board and the five members of the BioM seed financing arm. According to Helmut Schühlsler, at least as far as seed finance is concerned, the decisions may come down to one man. "On the basis of my expert opinions, Domdey decides who gets the money," he says. That sort of concentration of control does not make for healthy competition.

Ingeborg Fürst

Genentech's anticancer Mab expected by November

Herceptin, Genentech's (S. San Francisco, CA) humanized monoclonal antibody that targets the HER2/neu receptor, and a HER2 diagnostic kit could both be marketed for breast cancer in the United States by November. Results from two phase III trials of Herceptin for the treatment of aggressive metastatic breast cancer (released May 18, 1998 at the American Society of Clinical Oncology meeting in Los Angeles) indicated not only that the HER 2 receptor is an important target for cancer therapies but also that Herceptin, with or without chemotherapy, can be an effective treatment.

The first of two phase III trials compared the effect of a combination of Herceptin and chemotherapy—either taxol or anthracyclines—with chemotherapy alone in 469 women with breast tumors that overproduced the cancer-associated HER2/neu antigen and who had not previously had chemotherapy. Solid breast tumors were eliminated or halved in size in 49% (114/235) of the patients treated with Herceptin and chemotherapy compared with 32% (74/234) of patients treated with chemotherapy alone.

The increase in the number of patients showing a complete or partial response in the group receiving the combination therapy is primarily due to the tremendous difference in the clinical activity of taxol when administered with Herceptin. Forty-two percent of the patients treated with taxol and Herceptin showed a positive response as compared with the 16% responding in the taxol-only patient group.

The effectiveness of anthracyclines was boosted from 43% in the anthracycline-only group to 52%. On average, of the women responding to any treatment, those receiving a combination therapy showed a 65% increase in delay of disease progression, delaying the cancer growth by 7.6 months compared with 4.6 months in patients receiving no Herceptin. In addition, 28% of the women receiving the drug combination showed no tumor progres-

sion after a year (14% in the chemotherapy only group), and there was a 53% increase in the rate of tumor shrinkage compared with patients treated with chemotherapy alone.

The second phase III trial tested Herceptin alone as a first-line treatment without chemotherapy on women who had previously relapsed from other cancer therapies, including chemotherapy. Sixteen percent of the 222 women responded to the monoclonal antibody with greater than 50% tumor shrinkage for nine months, and experienced none of the side effects, such as nausea and hair loss, common with more toxic drugs. Melody Cobleigh, a research physician at Rush-Presbyterian-St. Luke's Medical Center (Chicago, IL) and principal investigator studying Herceptin believes that the 16% response rate and nine-month duration of response are "particularly interesting given the seriousness and aggressive nature of metastatic cancer." Most current treatments for end-stage breast cancer are primarily palliative, she says.

Genentech clinical researchers say that the 16% success rate underestimates the effectiveness of the drug. "The criterion for success was very strict in this study, with a positive response being measured when the tumor decreases 50% in size after treatment with Herceptin," says Steven Shak, lead clinical scientist at Genentech. Thus, "lack of response" in this study means that tumors did not shrink more than 50%. "Several patients showed a minor response (less than 50%) or stable disease where the tumor did not grow," Shak says.

Tumors overproducing the HER2 protein are a particularly aggressive form of breast cancer; patients typically live 10–18 months after the cancer has become metastatic compared with six to seven years for those who express HER2 at normal levels. Gene amplification within transformed tissue causes overexpression of HER2 transmembrane protein in 25–30% of breast tumors. "Herceptin is the first successful cancer treatment that targets specific genetic alteration as opposed to using a shotgun approach that kills both diseased and healthy cells," says Dennis Slamon, director of

the Revlon/UCLA Woman's cancer research program (Los Angeles, CA) and lead scientist in the trials.

When Herceptin binds to the extracellular domain of the HER2 transmembrane protein, cell division and tumor growth are inhibited. However, the mechanism of this inhibition is unclear. Genentech's Shak says that Herceptin binding to the receptor does not interfere with the growth factor's natural ligand binding. Instead, the drug may work through one of several mechanisms including downregulation of the receptor on the cell surface due to binding of the antibody, interference with growth factor receptor signaling, or possibly an induction of an antibody-dependent cellular response."

Genentech granted a worldwide license to its patents on HER2 gene in May to DAKO, the in vitro diagnostic company based in Copenhagen, Denmark. DAKO will develop an immunohistochemical diagnostic test to be used to screen breast cancer patients for overexpression of HER2. "Because HER2 is a known marker for faster growing, more serious disease," says Slamon, "it will be critical that effective HER2 testing be integrated into diagnostic and treatment guidelines."

Herceptin has been designated a fast track product under the US Food and Drug Administration (FDA; Rockville, MD) Modernization Act of 1997, and a US marketing approval decision is expected at the beginning of November, six months after its filing in May. DAKO planned to file its regulatory documents with the FDA last quarter so that both the drug and the diagnostic kit can be introduced in November 1998. There are concerns that, even after approval, the demand for the drug by 40,000 eligible women will seriously outweigh the supply. Genentech has promised to increase the availability of the drug by streamlining its processes in time for the drug's approval. Genentech is currently providing limited supplies through the FDA's "compassionate use" program, which selects 100 women per month through a computerized lottery.

Debra Robertson

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