EGFR inhibitors square off at ASCO

Competition in the nascent targeted-cancer therapeutic market is expected to heat up at the annual meeting of the American Society of Clinical Oncologists (ASCO) held on June 5–8, where clinical researchers will reveal data from dozens of studies of five epidermal growth factor receptor (EGFR) inhibitors. How these drugs split up the market will depend on what indications they are ultimately approved for, their relative successes in patients with and without relevant biomarkers, and their synergies with each other and other cancer therapies.

By establishing themselves against different cancer types, the first two EGFR inhibitors to the market staked out different patients. Iressa (gefitinib), a small molecule from AstraZeneca (London), treats non-small cell lung cancer (NSCLC); Erbitux (cetuximab), a monoclonal antibody from ImClone (New York), is for colorectal cancer. Both struggled to get past the Food and Drug Administration (Rockville, MD, USA), and they may soon struggle for market share.

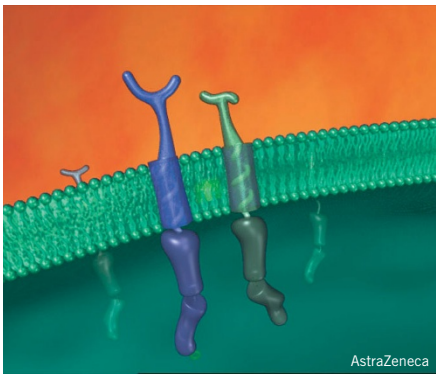
On April 25, Genentech (S. San Francisco, CA, USA) and OSI Pharmaceuticals (Melville, NY, USA) announced that another small-molecule EGFR inhibitor, Tarceva (erlotinib), extended survival in a phase 3 trial, the first EGFR inhibitor to do so. (Iressa and Erbitux were approved on the basis of surrogate endpoints, such as tumor shrinkage.) Meanwhile, a handful of other small molecules and at least two more monoclonal antibodies against EGFR are winding their way through clinical trials: ABX-EGF (panitumumab; AbGenix, Fremont, CA, USA) is in phase 3 trials for colorectal cancer; and TheraCIM (h-R3; YM Biosciences, Mississauga, Canada) is in phase 2 trials for head-and-neck cancer. And both the marketed and clinical EGFR inhibitors are under study for a variety of other cancers including brain, breast and pancreatic.

If these therapies eventually receive approval in multiple cancers, then will they all survive the competition or will there be a darwinian shakeout to rid the market of the least-fit drugs? Many oncology firms and investors are watching this space closely not only because EGFR inhibitors represent a huge market in themselves, but also because they represent the first real market competition for targeted therapies and should provide a case study for predicting what might happen to other targeted therapy markets in future.

Some insight was provided the same week that the Tarceva results were announced, when two publications tied Iressa's ability to shrink tumors to a set of mutations occurring in about 10% of lung cancer tumors. Should the mutations turn out to be sufficiently reliable to determine which patients should get the drug, several scenarios are possible. If Iressa prescriptions become restricted to only 10% of NSCLC patients, then its market could shrink, says Richard Wagner, a consultant with DaVinci Healthcare Partners (Hayward, CA, USA), a consulting company specializing in the oncology market. Alternatively, he says, the drug's market might expand if the biomarker could be used in clinical trials to enroll only the patients who are most likely to respond to the drug, which would increase the odds (and lower the costs) of demonstrating efficacy and winning regulatory approval in other cancers.

EGFR inhibitors represent the first real market competition for targeted therapies and should provide a case study for predicting what might happen to other targeted therapy markets in future.

Results for Iressa could well apply to Tarceva, though the studies have not yet been done; both drugs are small molecules in the quinazoline family that bind to the intracellular tyrosine kinase domain of EGFR, where the published mutations occur. The results are less likely to apply to the antibody therapeutics, which block EGFR's activity by binding to the receptor on the cell's surface. Nonetheless, different biomarkers may be relevant for the antibodies. "The extracellular domain of the receptor also has some mutations, resulting in several variants," explains Normando Iznaga, head of business and development at the Centro de Inmunología Molecular (Havana, Cuba), which is jointly developing TheraCIM with YM. For example, an antibody that targets a variant that is overexpressed in multiple cancers' tumors could garner a larger market than an antibody that targets a variant overexpressed in a single cancer's tumors.



Antibody EGFR inhibitors target the extracellular (orange) portion of the receptor, whereas small molecule drugs tend to inhibit the intracellular tyrosine kinase domain.

Cost will certainly be a factor in determining market share if two products' effects on survival and symptom relief are comparable, in which case the cheaper, orally available small molecules would have an advantage over costly antibodies. However, Lee Blansett, a partner at DaVinci, thinks drug companies will do their best to make sure that doesn't happen. He predicts that combinations of EGFR inhibitors, particularly of small molecules and antibodies, are a likely strategy to improve efficacy and avoid tumor resistance to cancer drugs. Combinations with other targeted therapies are likely, too; studies of Tarceva with Genentech's Avastin (bevacizumab), an antibody that blocks angiogenesis by binding VEGF, are already underway. So drugs with synergistic effects against cancer could also have synergistic effects on market share.

How the market plays out will depend on which cancers are most responsive to EGFR inhibitors, and which patient subpopulations respond to which drugs. The upcoming ASCO meeting will reveal more clinical data on ABX-EGF, Erbitux, Iressa and Tarceva in NSCLC, but there will be no direct comparisons between therapies. Answering more straightforward questions, such as why Tarceva did not synergize with conventional chemotherapy, will not be easy; rating drugs against each other is even harder. For definitive answers on what drug to use for a particular patient, the ASCO meeting of 2009 will likely be more forthcoming than the one in 2004.

Monya Baker, San Francisco