Lapatinib Moves Forward in Inflammatory and Early HER2-Positive Breast Cancer Trials

By Rabiya S. Tuma

Following on the heels of trastuzumab’s success in HER2-positive breast cancer, lapatinib is moving rapidly through clinical development and already heading into trials in early breast cancer patients.

In its first major test, lapatinib, which also targets the HER2 receptor protein, improved disease-free survival in advanced breast cancer patients. More recent analyses show that the drug may have less cardiac toxic effects than trastuzumab and that it may work in disease settings where trastuzumab doesn’t. The next big hurdle, however, will be whether lapatinib can improve clinical outcomes for patients with early-stage breast cancer.

“Lapatinib is certainly an active drug,” said David Cameron, M.D., of the Western General Hospital in Edinburgh, Scotland, who has led some of the advanced breast cancer trials with lapatinib. “There are details that need working out about the drug, but basically we have proof of activity, hints that it may prevent [central nervous system] metastases in one or two studies. The next step is really in the earlier [disease] setting, and then we’ll see really just how good it is.

“It has the potential to be as good as, better than, or something that needs to be given in addition to or in sequence with trastuzumab.”

Previously treated with trastuzumab had a median progression-free survival time of 36.7 weeks on the combination therapy compared with 17.9 weeks for those patients taking capecitabine alone.

Preliminary biomarker data from that trial suggest that lapatinib’s inhibition of HER2 is more important than its blockade of EGFR in stopping tumor growth. All the patients had HER2-positive disease and there was no correlation between the likelihood of response and the level of HER2 overexpression, suggesting that all HER2-positive disease has a chance of responding. Meanwhile, when researchers compared EGFR expression level in the tumor samples with progression-free survival, they found that the expression level did not correlate with response in either arm of the trial, said Cameron, who reported the data at the San Antonio Breast Cancer Symposium in December. Similarly, patients with high levels of EGFR protein fragments in their blood at the beginning of the trial were no more likely to respond to therapy than those with low levels. This finding suggests “that EGFR is overall not very important in lapatinib efficacy” in this patient population, Cameron said.

So why does lapatinib work in patients who have already become resistant to trastuzumab therapy? “The bottom line is that we don’t know,” Cameron said. “However, one hypothesis is that when proteases cleave [off the outside of HER2 they leave] this truncated form, which is much more active and, obviously, trastuzumab cannot bind to it. But other small-molecule drugs, like lapatinib, can still inhibit the activity of the receptor.” The biomarker data are consistent with that hypothesis but do not prove it.

Lapatinib has also shown remarkable activity in inflammatory breast cancer in two phase II trials, and again the drug’s activity appears to be based primarily on HER2 inhibition. In a trial testing lapatinib alone in women with inflammatory breast cancer, researchers divided the women into two groups based on the expression profile of HER2 and EGFR. Women whose tumors overexpressed HER2 were included in one group, regardless of their EGFR expression status. Of 32 patients, 16 had an objective response to the drug, said Maureen Trudeau, M.D., director of the division of medical oncology and hematology at the Toronto Sunnybrook Regional Cancer Centre, who presented the data at the European Society of Medical Oncology (ESMO) meeting last fall. The 15 women whose tumors did not overexpress HER2 but did overexpress EGFR constituted the second group. Of those, only one patient showed an objective response.

Biomarker analysis of the responders showed that 98% had high levels of HER2
overexpression and 80% had activated EGFR. Trudeau indicated that HER2 activation may be triggering EGFR activation in these tumors, and thus lapatinib’s inhibition of both targets may in fact be important.

The objective response rate was even higher in a second phase II trial testing lapatinib plus paclitaxel in a similar group of patients, according to data presented at the San Antonio Breast Cancer Symposium by Massimo Cristofanilli, M.D., an associate professor at the University of Texas M.D. Anderson Cancer Center in Houston. Of 30 women whose tumors overexpressed HER2, 23 (77%) had an objective response. Of 30 women whose tumors overexpressed HER2, 23 (77%) had an objective response. Of 30 women whose tumors overexpressed HER2, 23 (77%) had an objective response. Of 30 women whose tumors overexpressed HER2, 23 (77%) had an objective response. Only five women with HER2-negative, EGFR-positive tumors were enrolled in the trial, and none of those patients responded to the therapy.

Safety data from all the lapatinib trials, including those in inflammatory breast cancer, indicate that in addition to having activity different from that of trastuzumab, lapatinib may come with a considerably different safety profile. Common grade 3/4 toxic effects in the trial of lapatinib alone included diarrhea, anorexia, headache, anemia, and a low platelet count. Lower-grade skin and gastrointestinal side effects were common.

However, lapatinib may not have the same level of cardiac toxic effects as trastuzumab. Historic data indicate that trastuzumab causes cardiac toxicity in 5% of women who have been previously treated for metastatic breast cancer, with 4% experiencing symptoms. Also, 27% of metastatic breast cancer patients who received anthracycline and trastuzumab at the same time developed cardiac problems, with 16% showing symptoms. Given these high rates, only individuals with healthy cardiac function have been enrolled in lapatinib trials and cardiac function has been carefully monitored regularly while they were on the drug, said Edith Perez, M.D., director of the breast cancer program at the Mayo Clinic in Jacksonville, Fla.

In an analysis of the first 3,558 patients and healthy volunteers exposed to lapatinib, Perez reported at the ESMO meeting that only 58 (1.6%) patients had a drop in left ventricular ejection fraction, which serves as a measure for cardiac toxicity. Only seven (0.2%) individuals showed symptoms of a decline in cardiac functioning. Of 598 patients previously treated with anthracyclines, seven (1.2%) had a decreased left ventricular ejection fraction while on lapatinib, as did 13 (1.7%) of the 759 patients who had prior exposure to both trastuzumab and anthracycline chemotherapy.

Perez says that whether lapatinib’s cardiac toxicity is lower than that of trastuzumab is not yet clear—that won’t be known until head-to-head trial results are available from the adjuvant setting—but “the data look really good.”

Given the drug’s effectiveness in advanced breast cancer and the possibility that it is associated with a lower incidence of cardiac problems, researchers and drug developers are excited to test lapatinib in early-stage breast cancer patients. Two such adjuvant trials are in the works.

The first trial, which is called TEACH (Tykerb Evaluation After Chemotherapy), is already enrolling patients. Under trastuzumab’s current regulatory approval, the drug must be started while a woman is undergoing chemotherapy. Paul Goss, M.D., Ph.D., director of breast cancer research at the Massachusetts General Hospital Cancer Center in Boston, estimates that there are as many as 160,000 women in the United States who might benefit from anti-HER2 therapy but are not eligible for trastuzumab because they completed their chemotherapy before its approval. “In this country, if you’ve had your chemo and you haven’t had [trastuzumab], that is it,” said Goss, who is leading the trial.

TEACH is designed to test the drug’s efficacy in patients with HER2-positive early breast cancer who have already completed chemotherapy. “The trial is designed to address [existing] cases of HER2-positive breast cancer,” he said, whether they completed the adjuvant therapy 5 months or 15 years ago. The randomized controlled trial is designed to enroll 3,000 women in 32 countries. Women will be randomly assigned to 1 year of lapatinib or 1 year of a placebo. If the trial results show that lapatinib decreases the rate of disease recurrence, all patients initially assigned to the placebo arm will be offered a full year of lapatinib free of charge.

A second and larger early breast cancer trial is called ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization). Researchers are currently finalizing the design, which will include an unusual two independent primary end-points. As currently organized, the trial will enroll 8,000 women who will be randomly assigned to one of four treatments arms: trastuzumab alone, lapatinib alone, trastuzumab and lapatinib in sequence, or a combination of the two drugs. The trial is jointly sponsored by the Breast International Group, the National Cancer Institute, and lapatinib maker GlaxoSmithKline.

ALTTO is powered to detect a 22% reduction in relapse rate in one of the lapatinib arms, relative to trastuzumab alone, said Richard Gelber, Ph.D., a professor of pediatrics and biostatistics at Harvard Medical School and the School of Public Health. Also, the investigators have prospectively designed the trial to compare the two drugs alone. This unusual design could benefit both the patients and GlaxoSmithKline. The design protects GlaxoSmithKline’s ability to apply for regulatory approval in the adjuvant setting even if the drug is no better than, but as effective as, trastuzumab.

Gelber, though, says that his goal is improving patient care. “We are doing it to protect the patients,” he said when asked about the unusual design. “Lapatinib is oral and it may have a better toxicity profile, though we don’t know that.”

The ALTTO trial won’t answer all the questions about how best to use lapatinib and trastuzumab in early breast cancer patients, Perez said. But it will answer the most pressing ones, including whether one agent is better than the other, whether one is safer, and whether the drugs should be used separately, concurrently, or in tandem.

Putting together such a large trial, with so many interested parties, has not been easy, “but it will be worth it,” said Perez. “It allows us to answer the questions without duplicating our efforts.”