



Emerging promise of a novel targeted agent for breast cancer patients in Hong Kong

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The tyrosine kinase receptor inhibitor (TKI), lapatinib (Tyverb[®]), has shown favourable results alone and in combination with traditional chemotherapy regimens in recent breast cancer studies and is currently in ongoing trials for various indications, with promising preliminary results.

Addressing the recent Medical Summit in Clinical Oncology 2008, Dr Ava Kwong, Chief of the Breast Surgery Division at the University of Hong Kong, Queen Mary Hospital, said over-expression of tyrosine kinase receptors ErbB-1 and/or ErbB-2 is associated with poor prognosis and advanced stage cancers.

An oral ErbB-1 and ErbB-2 inhibitor, lapatinib directly blocks kinase activity. In a randomized Phase III trial of capecitabine (Xeloda[®]) with or without lapatinib in patients with advanced or metastatic breast cancer (MBC) who had progressed on treatment with trastuzumab (Herceptin[®]), the combination was associated with a longer median time to disease progression and progression-free survival (PFS) versus capecitabine monotherapy. Side effects were mainly gastrointestinal (GI) and were manageable.

Two Phase II studies have investigated lapatinib monotherapy in MBC patients whose disease progressed on trastuzumab. Lapatinib improved the overall response rate (ORR), suggesting some degree of non-cross reactivity between lapatinib and trastuzumab.

In study EGF20009, oral lapatinib 1,500 mg/day or 500 mg b.i.d. doses were safe and effective as first-line treatment in 130 chemotherapy-naïve patients with fluorescence *in situ* hybridization- (FISH) positive MBC, eliciting significantly increased ORRs and acceptable partial responses. While cardiotoxicity is a potential concern with TKIs, no serious decreases were seen in left

ventricular ejection fractions (LVEF).

In study EGF30001, 570 therapy-naïve patients with advanced or MBC not over-expressing ErbB-2 were randomized to lapatinib plus i.v. paclitaxel or paclitaxel plus placebo. The combination was associated with a significant increase in time to disease progression (TTP) in ErbB-2-positive but not ErbB-2-negative subjects.

While addition of lapatinib to paclitaxel resulted in a higher frequency of GI and severe adverse event-related mortality, this was probably due to lack of experience in managing diarrhoea and possible pharmacokinetic interaction between the agents.

Two Phase III trials are underway of lapatinib combinations in chemotherapy-naïve patients with FISH-documented ErbB-2-positive MBC. Study EGF104535 compares i.v. paclitaxel plus oral lapatinib versus paclitaxel plus placebo in 424 patients, while EGF104383 compares paclitaxel/lapatinib regimen plus i.v. trastuzumab with trastuzumab/paclitaxel in 700 patients, to investigate the effect of trastuzumab addition on survival.

When ErbB-2-positive MBC patients are treated with an anti-oestrogen such as letrozole, the decreased oestrogen level leads to increased ErbB receptor expression, which in turn can cause a type of vicious circle, with over-expression of ErbB-2 receptors increasing the tumour's resistance to oestrogen receptor (ER) inhibitors.

This resistance can be overcome by the use of appropriate combinations, since ErbB-2 blockade may reverse resistance to anti-oestrogen therapies. This provided the rationale for study EGF30008, an ongoing Phase III comparison of oral letrozole with or without lapatinib in 1,280 (ER)/progesterone receptor- (PgR)

positive MBC to determine whether the anti-oestrogen will improve survival.

The Tyverb Evaluation After Chemotherapy (TEACH; EGF105485) trial is currently recruiting trastuzumab-naïve women with early-stage invasive ErbB-2-positive breast cancer. Patients are stratified according to disease severity and hormone receptor status, then allocated to oral lapatinib or placebo, with treatment continued until disease recurrence or a second primary cancer, with long-term follow-up.

After surgery and complete neoadjuvant anthracycline-based chemotherapy, patients in the ongoing Adjuvant Lapatinib and/or Trastuzumab Treatments Optimization (ALTTO) with centrally-determined ErbB-2-, ER- and PgR-positive invasive breast cancer with LVEF $\geq 50\%$ will be allocated to 52 weeks of targeted endocrine therapy with trastuzumab or lapatinib alone or in combination, according to menopausal status, with radiotherapy if indicated.

In a second ALTTO design, patients will be treated with paclitaxel concurrent with targeted endocrine therapy with trastuzumab or lapatinib alone or in combination after any anthracycline-based chemotherapy over 52 weeks. The primary end-point is disease-free survival, with secondary end-points including overall survival, time to disease recurrence, incidence of the central nervous system (CNS) as first site of tumour recurrence, safety and tolerability, and investigation of biological markers of disease status.

ErbB-1 and ErbB-2 receptor over-expression have been observed in patients with inflammatory breast cancer (IBC), who generally have a poor prognosis, said Dr Kwong, noting that such patients should benefit from lapatinib.

Two studies of lapatinib alone or with paclitaxel began in early 2005. Study EGF102580 evaluated the pathological complete response (pCR) rate with neoadjuvant lapatinib combined with paclitaxel in treatment-naïve IBC. Secondary end-points included clinical response to lapatinib monotherapy followed by combined weekly paclitaxel, and identification of an IBC tumour profile predictive for increased likelihood of lapatinib response. Patients were divided into those over-expressing ErbB-2, or ErbB-1-positive subjects not over-expressing ErbB-2.

Lapatinib was clinically active as neoadjuvant

treatment for ErbB-2-positive IBC, with a 30% clinical response to lapatinib alone within 14 days, a 77% response to combined lapatinib and paclitaxel, and a 17% pCR rate at surgery. The most frequent Grade \geq III toxicities with the combination included GI symptoms, asthenia and fatigue. Preliminary analysis of biomarkers predictive of a response to lapatinib is underway.

Study EGF103009 is an ongoing Phase II trial of lapatinib in patients with relapsed or refractory IBC, who are divided according to ErbB-2 over-expression or ErbB-2 non over-expression and treated with oral lapatinib, with tumour biopsies performed pre-dose and 21 days post-dose, with lapatinib monotherapy continued thereafter. The primary end-point will be ORR, with secondary end-points including clinical benefit and PFS.

Preliminary results show a 62% partial response in ErbB-2-positive patients versus 8.3% among ErbB-2-negative subjects, with the latter having a higher progressive disease rate. Grade III/IV adverse events included diarrhoea, anorexia and headache, while minor events were GI- or skin-related.

Incidence of CNS metastases ranges from 30% to $>50\%$ in breast cancer patients treated with trastuzumab, probably due to improved patients survival rather than the treatment *per se*. Study EGF105084 was a Phase II trial of lapatinib 750 mg b.i.d in 220 patients with Stage IV ErbB-2-positive breast cancer who had developed brain metastases after trastuzumab therapy.

Preliminary data suggest a good response to lapatinib, with a 15% partial CNS response and stable disease in 42% after 8 weeks. Lapatinib elicited a $\geq 50\%$ reduction in brain tumour volume in 7% and a 20% reduction in 19% of patients. There was also increased PFS in lapatinib responders versus non-responders and relatively low toxicity.

In an extension of EGF105084, the lapatinib dose was increased to 1,250 mg/day in combination with capecitabine 2,000 mg/day in these partial lapatinib responders, with an increased partial response seen in a further 20% of those receiving the combination.

Concluding, Dr Kwong said that although lapatinib alone and in combination has shown promising results in treatment of breast cancer in different settings, further research is needed to evaluate other combinations and schedules.