



## EVIDENCE WATCH

### A review and assessment of recent clinical trial data

*Oncology Exchange* continues overviews of important clinical trial data presented at the 29<sup>th</sup> San Antonio Breast Cancer Symposium (SABCS), held December 14–17, 2006 and at the 48<sup>th</sup> Annual Meeting of the American Society of Hematology (ASH), held December 8–11, 2006 in Atlanta, Georgia. Leading Canadian experts offer commentary and clinical interpretations.

## Presentations from the 29<sup>th</sup> Annual San Antonio Breast Cancer Symposium

### Inflammatory breast cancer

#### **A PHASE II COMBINATION STUDY OF LAPATINIB AND PACLITAXEL AS A NEOADJUVANT THERAPY IN PATIENTS WITH NEWLY DIAGNOSED INFLAMMATORY BREAST CANCER (IBC). SABCS 2006, ABSTRACT 1.**

*Investigators: M. Cristofanilli et al.*

**TRIAL SUMMARY:** Inflammatory breast cancer (IBC) often overexpresses ErbB2 and/or expresses ErbB1 receptors. Lapatinib is a small-molecule dual-inhibitor of ErbB1 and ErbB2 that demonstrated antitumour activity in preclinical studies and in a clinical trial of IBC patients unresponsive to or who relapsed following anthracycline chemotherapy.<sup>1</sup> Patients in this Phase II study presented at the December SABCS received 1500 mg lapatinib orally once daily as monotherapy for 14 days, followed by an additional 12 weeks in combination with weekly paclitaxel 80 mg/m<sup>2</sup>. An independent reference laboratory determined the IBC tumour type of 49 enrolled subjects: 42 had ErbB1-positive (any staining) and/or ErbB2-overexpressing (2+ or 3+ by immunohistochemistry [IHC]) tumours, with 79% expressing an activated phospho-ErbB2. A second cohort of

subjects (n = 7) had tumours that were ErbB1-positive but ErbB2-negative.

In the ErbB1- and/or ErbB2-positive group, 77% of subjects had a clinical response. Interestingly, in approximately one-third of these patients, a response was seen following the 2 weeks of lapatinib monotherapy alone. The overall pathological complete response (pCR) rate in the breast and axillary lymph nodes was 17% following the entire 12-week course of lapatinib and weekly paclitaxel. Most of the adverse events noted were Grade 1–2 gastrointestinal and skin toxicity, although a significant proportion of patients experienced Grade 3 diarrhea. One patient had Grade 3 cardiotoxicity necessitating withdrawal from the trial. The authors concluded that further investigation of this pretreatment regimen is warranted.

**COMMENTARY: Stephen Chia, MD, ABIM, FRCPC, Medical Oncologist, British Columbia Cancer Agency, Vancouver, BC.**

Inflammatory breast cancer is felt to represent a distinct entity from locally advanced breast cancer by both clinical and molecular parameters. It is characterized clinically by

skin erythema and edema, and molecularly by higher expression of ErbB2, increased microvessel density and angiogenic factors (VEGF), as well as stromal interaction

factors such as E-cadherin and RhoC. The overexpression or amplification of specific genes and/or proteins not frequently expressed in non-inflammatory breast cancer may allow for targeted therapy to be rationally studied in this highly aggressive subset of locally advanced breast cancer.

**FIRST COMBINATION RESULTS FOR LAPATINIB**

This combination study of lapatinib + weekly paclitaxel is built upon the data of EGF103009, a trial of monotherapy with lapatinib at 1500 mg orally once per day in relapsed/refractory IBC presented by Neil Spector et al at the ASCO 2006 meeting.<sup>1</sup> This trial showed an impressive 72% response rate (8/11) in the cohort with ErbB2-overexpression. The EGF103009 trial also provided interesting biological data in that all responding patients had increased p-ErbB2, p-ErbB3, and coexpressed IGF-IR. PTEN status did not alter response to lapatinib.

The study presented by Massimo Cristofanilli et al at this year's San Antonio meeting was the first to combine lapatinib with conventional chemotherapy in IBC. The results, however, were less impressive than expected. Although cross-study comparisons are plagued with differences in patient selection and methods of assessment of pCR, and are by no means conclusive, the pCR rate in this study of 17% is within the range seen with non-taxane-containing chemotherapy alone. A previous study by Buzdar et al in primary operable breast cancer showed that adding trastuzumab to paclitaxel (225 mg/m<sup>2</sup> x 4 cycles) and FEC75 (fluorouracil 500 mg/m<sup>2</sup>, epirubicin 75 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> x 4 cycles) for 24 weeks, increased the pCR (in breast and axilla) from 25% to 67% (p = 0.02) compared to the identical chemotherapy regimen without trastuzumab.<sup>2</sup> It is important to stress that these 2 studies had different patient populations:

those in Cristofanilli's had only IBC, whereas those in Buzdar's had primary operable breast cancer. In addition, patients receiving lapatinib + weekly paclitaxel appeared to have a higher rate of Grade 3 diarrhea than that expected with either agent alone.

In conclusion, much work remains ahead to develop the optimal regimen to deliver combinations with lapatinib (and also with trastuzumab) as neoadjuvant therapy in both primary operable and locally advanced breast cancer. The low pCR rate may in part be due to the absence of anthracyclines in the regimen — it appears quite clear now that both ErbB2<sup>3</sup> and topoisomerase II (topo2)<sup>4,5</sup> overexpressing tumours are highly sensitive to anthracyclines. It will be important to monitor and follow toxicities over time, both cardiac and others. Translational trials with neoadjuvant therapies will hopefully further our knowledge of the biology of breast cancer, and produce predictive factors that clinicians can use to better tailor treatment to the individual patient and to select the most appropriate candidates for the different treatments available.

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**Metastatic breast cancer**

**LAPATINIB PLUS CAPECITABINE SHOWS SUPERIOR EFFICACY COMPARED TO CAPECITABINE ALONE IN PATIENTS WITH ERBB2 POSITIVE ADVANCED OR METASTATIC BREAST CANCER INITIAL BIOMARKER DATA. SABCS 2006, ABSTRACT 2.**

*Investigators: D. Cameron et al.*

**TRIAL SUMMARY:** This report is an update of the NSABP lapatinib trial presented at the 2006 ASCO Annual Meeting by Geyer et al and published in the *New England Journal of Medicine* in December, 2006.<sup>1</sup> Participants in this Phase III study had ErbB2-positive advanced breast cancer and had received prior therapy with anthracyclines, taxanes and trastuzumab. They were randomized to receive lapatinib 1250 mg once daily + capecitabine 2000 mg/m<sup>2</sup>/day for 14 days, every 21 days, or capecitabine alone at a higher dose of 2500 mg/m<sup>2</sup>/day for 14 days, every 21 days. The primary endpoint was median time to progression, evaluated by blinded independent review. In 321 patients with data available, median time to progression was 36.9 weeks in patients

receiving lapatinib + capecitabine vs 19.7 weeks for those receiving capecitabine alone (HR 0.51, 95% CI 0.35–0.74, log rank p = 0.00016). Median progression-free survival was 36.9 weeks vs 17.9 weeks (HR 0.48, 95% CI 0.33–0.70, log rank p = 0.000045). Adverse events were generally similar, but diarrhea occurred in 58% of those in the lapatinib + capecitabine group vs 39% of those in the capecitabine monotherapy group, the difference being mainly due to Grade 1 diarrhea. Hand-foot syndrome occurred in 43% vs 34%, and rash in 30% vs 18% of patients, respectively, resulting in a numerically high rate of toxicity in the combination arm. An asymptomatic 20% relative decrease in left ventricular ejection fraction occurred in 2.5% vs < 1% of subjects in the 2 arms.

**COMMENTARY: Stephen Chia, MD, ABIM, FRCPC, Medical Oncologist, British Columbia Cancer Agency, Vancouver, BC.**

The focus of the update presented by David Cameron at last December's San Antonio meeting was to assess the EGF100151 trial's biomarker data with respect to benefit of therapy. Treatment after disease progression in ErbB2-overexpressing advanced breast cancer is one of the most important and common clinical dilemmas encountered today. Patients usually request that trastuzumab be continued with the successive chemotherapeutic regimens, but there is no randomized clinical data to support this practice. The standard is, and should be, to discontinue trastuzumab at the time of documented progression following the first chemotherapeutic regimen and subsequent maintenance trastuzumab.

Although lapatinib is a different molecule and targets the HER2 receptor differently (in addition to ErbB1), the EGF100151 trial does support the concept that continued inhibition of ErbB2 in combination with capecitabine improves the clinical parameters of response rate and progression-free survival in women with ErbB2-positive advanced breast cancer previously exposed to trastuzumab. Of note, preclinical data demonstrated in vitro that ErbB2-positive breast cancer cell lines resistant to trastuzumab were sensitive to lapatinib.<sup>2</sup> It is unclear whether capecitabine is additive or synergistic to lapatinib, and in fact whether capecitabine is required at all. The trial so far shows no difference in overall survival (HR 0.93,  $p = 0.80$ ), although as of the ASCO 2006 presentation the overall death rate was only 18% so it is still too early to draw conclusions.

## BETTER BIOMARKER STUDIES NEEDED

The translational component of EGF100151 was assessment for markers predictive of benefit or lack of benefit for

the combination of lapatinib + capecitabine. When the investigators looked at ErbB2-overexpression by fluorescent in situ hybridization (FISH), the FISH+ cohort had better progression-free survival (HR 0.371) than the FISH- cohort (HR 0.476,  $p = 0.005$ ), but both groups still benefited a great deal. Importantly, the FISH- cohort did show HER2-overexpression by IHC. The investigators also looked at whether serum levels of HER2 extracellular domain (HER2 ECD, a component of the HER2 protein), as determined by enzyme-linked immunosorbent assay (ELISA), were predictive of benefit to either study arm. The highest quartile of HER2 ECD was associated with a shortened progression-free survival in the capecitabine-alone arm but not in the combination arm of lapatinib + capecitabine ( $p = 0.14$ ). This component of the study was not prospectively powered, however, and at this time higher levels of HER2 ECD should not be used to deny patients lapatinib or capecitabine therapy.

Future studies of lapatinib or trastuzumab as first- or second-line therapy in ErbB2-positive metastatic breast cancer need to be adequately powered to prospectively assess these markers for predictive significance. Validated predictive factors will allow clinicians to better tailor treatment to the individual patient, in particular when very expensive agents are being used for palliative treatment of a common disease.

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## Presentations from the 48<sup>th</sup> Annual Meeting of the American Society of Hematology

### Diffuse large B cell lymphoma

#### ADDITION OF RITUXIMAB (R) TO CHOP IMPROVES SURVIVAL IN THE NON-GCB SUBTYPE OF DIFFUSE LARGE B CELL LYMPHOMA (DLBCL). ASH 2006, ABSTRACT 816.

*Investigators: P. Farinha et al.*

**TRIAL SUMMARY:** This group of researchers tested the hypothesis that rituximab added to chemotherapy using cyclophosphamide + doxorubicin + vincristine + prednisone (CHOP) would be of most benefit in patients with non-germinal centre B cell (GCB) lymphomas compared to those with GCB lymphomas. Study subjects were 163 dif-

fuse large B cell lymphoma (DLBCL) patients who had been treated with either CHOP or CHOP + rituximab and for whom tissue paraffin blocks and interpretable immunostaining were available to allow determination of cell of origin status (GCB vs non-GCB) using the method of Hans et al.<sup>1</sup> Because the 2 treatment cohorts represent consecutive eras

of therapy,<sup>2</sup> the median followup of patients still alive was 5.1 years for those taking CHOP and 4.0 years for those on CHOP + rituximab. In 157 interpretable cases (74 GCB and 83 non-GCB), Bcl2 protein was expressed in 70% of the GCB cases and in 73% of the non-GCB cases ( $p = 0.72$ ). Bcl6 was expressed in 96% of GCB cases and in 63% of non-GCB cases ( $p < 0.0001$ ).

Univariate analysis showed an association of better prognosis with addition of rituximab in non-GCB cases ( $p = 0.02$ ),

but not in the GCB cases ( $p = 0.3$ ). Independent predictors of overall survival in non-GCB DLBCL were addition of rituximab to CHOP chemotherapy ( $p = 0.02$ ) and International Prognostic Index (IPI) ( $p = 0.016$ ). The addition of rituximab was also of prognostic importance in the lymphomas that overexpressed Bcl2 ( $p = 0.0081$ ). The authors concluded that the improved survival seen with immunochemotherapy using CHOP + rituximab is due largely to its effect on the non-GCB cases.

## **STRONG P53 EXPRESSION IS AN INDEPENDENT PREDICTOR OF OUTCOME IN DE NOVO DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) TREATED WITH EITHER CHOP OR CHOP-R. ASH 2006, ABSTRACT 812.**

*Investigators: P. Farinha et al.*

**TRIAL SUMMARY:** When CHOP alone was the standard of care for DLBCL, p53 mutations in DLBCL were associated with an aggressive clinical course and shortened survival. In the present study, the researchers measured nuclear expression of the p53 antibody to determine p53 gene mutational status in 155 patients (77 treated with CHOP and 78 treated with CHOP + rituximab) from the study described above.<sup>2</sup> Nineteen cases (12.3%) were strongly p53-positive: 10/75 GCB cases and 9/80 non-GCB cases. All the strongly p53-positive cases were negative for p21

expression and 16/17 analyzable cases had p53 mutations. Univariate analysis showed both IPI and p53 expression to be of prognostic importance ( $p < 0.0001$ ). Independent predictors of overall survival by multivariate analysis were strong p53 expression ( $p = 0.005$ ) and IPI ( $p < 0.0001$ ). Strong p53 expression was significant in both CHOP ( $p = 0.015$ ) and CHOP + rituximab treatment groups ( $p = 0.012$ ). The authors concluded that p53 continues to be an important prognostic indicator for DLBCL in the era of rituximab treatment.

**COMMENTARY: Douglas A. Stewart, MD, FRCPC, Associate Professor, Departments of Oncology and Medicine, University of Calgary and Tom Baker Cancer Centre, Calgary, AB.**

### **DETERMINING TREATMENT OPTIONS IN DLBCL**

Clinical and molecular predictive factors are useful in oncology to help estimate prognosis with standard treatments, stratify patients into different treatment strategies, facilitate interpretation of clinical trial results, help understand tumour biology and guide development of new targeted therapies. Four general treatment categories have improved survival rates for DLBCL, including:

- orthovoltage radiotherapy for non-bulky Stage I–IIA disease
- CHOP-like conventional-dose chemotherapy
- high-dose alkylating agent-based chemotherapy and autologous stem cell transplantation
- (most recently) anti-CD20 monoclonal antibody therapy with rituximab.<sup>3–6</sup>

It is often difficult to determine the need for each of these treatments, or at least the optimal sequence of their use, or whether the option to pursue experimental treatment approaches is better for an individual patient. Reliable predictive factors would be a tremendous help in guiding these therapeutic decisions.

The clinical IPI and the use of molecular markers of GCB and non-GCB subtypes have been the 2 most widely adopted predictive tools for CHOP-like chemotherapy. High-risk IPI is defined as having 4–5 of the following criteria: age > 60 years, Stage III–IV disease, elevated lactose dehydrogenase (LDH), > 1 extranodal site, Eastern Cooperative Oncology Group (ECOG)

**TABLE 1. Selected biomarkers reported to predict outcome of DLBCL<sup>12</sup>**

type	markers
cell differentiation	Bcl6, HGAL, CD10, FOXP1, MUM1, CD5
cell cycle regulation	p53, Ki67, cyclin D2, cyclin D3
anti-apoptosis	Bcl2, survivin, Caspase 8 or 9 inhibition
tissue invasion	serum ICAM1, CD44
angiogenesis	serum VEGF and endostatin, MMP9
immune response regulation and/or growth signalling	sIL10, nm23H1

performance status 2–4. Non-GCB status is suggested by disease that is Bcl6-negative, CD10-negative, MUM1-positive and Bcl2-positive. High-risk IPI and non-GCB status are associated with lower survival rates following CHOP.<sup>1,7,8</sup> These predictive markers now need to be re-evaluated in the era of immunochemotherapy with CHOP + rituximab (RCHOP).

Three studies by the Lymphoma Group at the British Columbia Cancer Agency (BCCA) reported at the 2006 ASH


meeting have significantly added to this ongoing re-evaluation. Sehn and colleagues reported the results of a revised IPI for a series of 523 DLBCL patients treated in British Columbia with RCHOP.<sup>9</sup> Using this revised IPI, 4-year progression-free survival rates were approximately 95% for patients with 0 IPI risk factors, 80% for those with 1–2 factors, and 55% for those with 3–5 factors. They also found a similar stratification by simply evaluating Stage 3–4 and elevated LDH with 4-year progression-free survival rates of 92%, 78% and 56%, respectively, for patients with 0, 1 or both of these factors. The 4-year progression-free survival rate estimates should be interpreted with some caution, however, because at the time of reporting the median followup was only 2 years.

In a separate report, summarized above, Farinha and colleagues at the BCCA suggest that the improvement in outcome with the addition of rituximab to CHOP is relatively greater for Bcl2-positive DLBCL, and for the non-GCB subtype relative to the GCB subtype. This improvement in outcome for non-GCB patients is perhaps of such a degree that the division of DLBCL into GCB and non-GCB subtypes may no longer be of clinical importance in the era of RCHOP. A previous report by Mounier and colleagues supports this relatively greater benefit of RCHOP over CHOP for Bcl2-positive compared to Bcl2-negative DLBCL.<sup>10</sup> As opposed to the decreased predictive value of GCB vs non-GCB phenotypes, Farinha and colleagues at the BCCA suggest in a third study, also summarized above, that mutated p53 continues to be associated with decreased survival despite RCHOP. This observation was supported by other studies presented at the 2006 ASH meeting, although methodology for measuring and interpreting p53, including threshold cutoffs, is not consistent between studies.<sup>11</sup>

## INTERPRETING MOLECULAR MARKER STUDIES

The difficulty in attaching clinical significance to such studies is that numerous biomarkers have been reported to predict outcome of DLBCL, many of them shown in **Table 1**, page 19.<sup>12</sup> Although research in this area is advancing, it is currently not possible to use any of these markers to reliably predict prognosis or guide therapy. Reasons for this include the lack of standardized or uniformly available methodology, lack of consistent, reproducible results from separate large studies that demonstrate predictive ability independent from other clinical and molecular prognostic markers, and lack of a

proven superior alternative treatment for poor-prognosis subgroups identified by the molecular markers.

Before their routine measurement should become part of standard lymphoma management, further work needs to be done to validate and standardize measurement of p53 and other biomarkers, as well as to develop effective alternative treatments for DLBCL patients who have these adverse markers. Nevertheless, we can now conclude that biomarkers that predict outcome of cytotoxic chemotherapy may not predict outcome of other therapeutic approaches such as immunotherapy with monoclonal antibodies. We can also remain very optimistic that biomarker research will refine our ability to predict outcome of cancer treatment, and lead to new targeted therapies for poor-prognosis subgroups of patients. 

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