



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 49th Annual Meeting of the American Society of Hematology (ASH), held December 8–11, 2007 in Atlanta, Georgia, and at the 30th San Antonio Breast Cancer Symposium (SABCS), held December 13–16, 2007. Leading Canadian experts offer commentary and clinical interpretations.

Contributors were selected by Laurie H. Sehn, MD, MPH, FRCPC, British Columbia Cancer Agency and Joseph Ragaz, MD, FRCPC, McGill University, Montreal, QC.

Follicular non-Hodgkin lymphoma

Laurie Sehn, MD, MPH, FRCPC

90Y-IBRITUMOMAB TIUXETAN (ZEVALIN) CONSOLIDATION OF FIRST REMISSION IN ADVANCED STAGE FOLLICULAR NON-HODGKINS LYMPHOMA: FIRST RESULTS OF THE INTERNATIONAL RANDOMIZED PHASE 3 FIRST-LINE INDOLENT TRIAL (FIT) IN 414 PATIENTS. ASH 2007, ABSTRACT 643.

Investigators: A. Hagenbeek et al.

TRIAL SUMMARY: This study examined whether a single infusion of yttrium-90 (90Y) ibritumomab tiuxetan following induction chemotherapy would prolong progression-free survival (PFS) in patients with previously untreated follicular non-Hodgkin lymphoma. Participants were 414 patients \geq 18 years with CD20-positive Grade 1 or 2 follicular lymphoma who had Stage III–IV disease at diagnosis, normal peripheral blood counts, less than 25% bone marrow involvement and achievement of a complete or partial response after first-line chemotherapy. Following various standard regimens of induction chemotherapy (mostly without rituximab), enrolled patients were randomized to receive either 90Y ibritumomab tiuxetan (250 mg/m² rituximab on Day -7 and Day 0 + 90Y ibritumomab tiuxetan 0.4 mCi/kg on Day 0 [maximal dose 32 mCi], n = 208) or no further treatment (n = 206). As shown in **Table 1**, at median followup of 2.9 years, median PFS, the primary endpoint, was 37 months in the 90Y ibritumomab tiuxetan group vs 13.5 months in the control group (p < 0.0001, hazard ratio [HR] 0.463). **Table 1** also shows median PFS for patient subgroups with partial and complete response to

TABLE 1. Median PFS at median followup of 2.9 years in patients receiving 90Y-ibritumomab tiuxetan consolidation therapy vs controls

response to induction chemotherapy	median PFS, months		p-value	hazard ratio
	90Y-ibritumomab tiuxetan consolidation	controls		
complete response	54.6	29.9	p = 0.01	0.609
partial response	29.7	6.3	p < 0.0001	0.304
combined complete and partial response	37	13.5	p < 0.0001	0.463

induction chemotherapy. Notably, 77% of patients with post-induction partial response achieved a complete response following 90Y ibritumomab tiuxetan therapy, such that 87% of patients were in complete response (CR) following

consolidation (76% confirmed CR and 11% unconfirmed CR). The mainly hematologic toxicities included a median nadir platelet count of $45 \times 10^9/L$ (range 8–404 $\times 10^9/L$) at 5 weeks post-consolidation therapy and a median nadir neutrophil count of $1.0 \times 10^9/L$ (range 0.02–6.6 $\times 10^9/L$) at 6

weeks post-consolidation therapy. Grade 3–4 infections occurred in 16 (8%) of 90Y ibritumomab tiuxetan patients vs 5 (2%) of controls. The authors concluded that treatment with 90Y ibritumomab tiuxetan is highly effective with manageable toxicity in this population.

COMMENTARY: Laurie H. Sehn, MD, MPH, FRCPC, medical oncologist at the British Columbia Cancer Agency; Clinical Assistant Professor at the University of British Columbia.

Follicular lymphoma remains a treatment challenge for clinicians. Most patients require multiple courses of therapy in their lifetime, achieving successive remissions followed by inevitable relapse. Recently, several randomized controlled trials have demonstrated improved PFS and overall survival (OS) with the addition of rituximab to chemotherapy in previously untreated patients, making immunochemotherapy the new standard of care.^{1,2} These trials have been among the first to suggest that choice of initial therapy in indolent lymphoma can have an impact on OS. In addition, the use of maintenance rituximab following induction therapy has been shown to prolong the duration of remission and perhaps to improve OS in patients with relapsed disease.³ While randomized trials investigating the use of maintenance rituximab following immunochemotherapy in the upfront setting have yet to be reported, it has become standard practice in many provinces to treat newly diagnosed patients with 2 years of maintenance rituximab following successful induction therapy.

WELCOME PROGRESS

However, as follicular lymphoma remains incurable with conventional therapy, alternative treatment strategies must be explored. Two radioimmunoconjugates, 90Y ibritumomab tiuxetan and 131I tositumomab, have been approved for the treatment of relapsed or refractory low-grade lymphoma. These agents combine the specificity of an anti-CD20 monoclonal antibody with a radioactive moiety that allows the targeted delivery of systemic radiation therapy. Both agents have demonstrated moderate activity in patients whose disease has relapsed, yielding overall response rates in the range of 65% to 80% and a 20% to 30% complete remission rate.^{4,5} More impressively, prolonged remissions of greater than 5 years' duration have been observed in approximately 20% of treated individuals.⁶ Limited data from Phase II trials in patients with previously untreated follicular lymphoma suggest that radioimmunotherapy may be even more effective in this setting.⁷

At the December 2007 ASH 49th annual meeting, Hagenbeek et al presented preliminary results of the First-line Indolent Trial (FIT), the first Phase III randomized controlled trial investigating the utility of 90Y ibritumomab tiuxetan consolidation in patients with advanced-stage follicular lymphoma who had responded to first-line induction therapy. This international trial randomized 414 patients to receive a single infusion of 90Y ibritumomab tiuxetan vs no further therapy. Various induction chemotherapy regimens were used but only 59 patients (14%) received a rituximab

combination. With median followup of 2.9 years, patients who received of 90Y ibritumomab tiuxetan achieved a higher rate of complete remission (87% vs 53%) and had significantly longer PFS of 37 months vs 13.5 months ($p < 0.0001$). 90Y ibritumomab tiuxetan therapy was well tolerated with the primary toxicities being hematologic. Thus far, no difference in OS has been noted.

FIT is noteworthy in that it demonstrates that a single dose of 90Y ibritumomab tiuxetan administered during 1 week following induction therapy can result in a very high rate of complete remission and can prolong PFS by approximately 2 years for patients with previously untreated advanced-stage follicular lymphoma. However, this trial was initiated prior to the routine use of immunochemotherapy and maintenance rituximab, making the relevance of these findings unclear. It is unknown whether 90Y ibritumomab tiuxetan administration following immunochemotherapy will confer the same degree of benefit, due to the potential for molecular target saturation. While 90Y ibritumomab tiuxetan consolidation can be administered in a shorter time frame than can maintenance rituximab, long-term toxicity is unknown and a survival advantage has not yet been demonstrated. The high rate of complete remission is intriguing, although longer followup will be required to see whether this translates into a survival plateau. The utility of 90Y ibritumomab tiuxetan consolidation following induction immunochemotherapy and prior to maintenance rituximab will serve as the next question for a planned international Phase III trial.

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Trastuzumab in early breast cancer

Debjani Grenier, MD, FRCPC

TRASTUZUMAB FOLLOWING ADJUVANT CHEMOTHERAPY IN NODE-POSITIVE, HER2-POSITIVE BREAST CANCER PATIENTS: 4-YEAR FOLLOW-UP RESULTS OF THE PACS-04 TRIAL. SABCS 2007, ABSTRACT 72.

Investigators: M. Spielmann et al.

TRIAL SUMMARY: This multicentre, Phase III trial initially randomized 3010 women aged ≤ 65 years with node-positive early breast cancer to receive 6 cycles every 3 weeks of either adjuvant fluorouracil 500 mg/m² + epirubicin 100 mg/m² + cyclophosphamide 500 mg/m² (FEC100) or concomitant epirubicin 75 mg/m² + docetaxel 75 mg/m² (ED). Patients had radiotherapy after surgery and those with hormone receptor-positive tumours received hormonal therapy. In addition, patients with human epidermal growth factor receptor 2 (HER2)-positive tumours (n = 528) underwent a second randomization to receive 1 year of trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks) following chemotherapy, provided they had normal cardiac function, or to observation alone. Trastuzumab was initiated after the completion of both chemotherapy and radiation. The results presented at the 2007 SABCS were from this second randomization.

Baseline characteristics were well balanced between arms. After median followup of 48 months, disease-free survival (DFS)

was equivalent, at 72.7% in the trastuzumab-treated patients and 73.2% in the observation-only patients (HR 0.86, 95% CI 0.61 to 1.22). Similarly, OS was the same in both groups (HR 1.27, 95% CI 0.68 to 2.38). An exploratory analysis suggested that trastuzumab was more effective at reducing the risk of a first event during the first 18 months of therapy, but not thereafter, although statistical significance was not obtained: the HR for a first event during months 0–18 was 0.57 (95% CI 0.3 to 1.09) and during months 18–48 it was 1.04. Sixteen percent of patients discontinued trastuzumab in accordance with the trial’s cardiac stopping rules, but there were no trastuzumab-associated cardiac deaths, and 75% of patients received the majority of planned treatments, 16–18 doses. The incidence of heart failure was 1.7% in the trastuzumab-treated group and 0.4% in the observation group. Approximately 2% of women randomized to trastuzumab did not receive study treatment due to development of cardiotoxicity during chemotherapy.

COMMENTARY: Debjani Grenier, MD, FRCPC, Medical Oncologist, CancerCare Manitoba, St. Boniface General Hospital; Assistant Professor, University of Manitoba, Winnipeg MB.

The PACS-04 trial is the sixth reported randomized study of adjuvant trastuzumab in combination with chemotherapy in women with HER2-overexpressing early breast cancer. After median followup of 4 years, trastuzumab after adjuvant anthracycline or taxane-based chemotherapy produced no difference in DFS or OS compared with observation alone. This is the first time a trial has shown no benefit of adjuvant trastuzumab. As summarized in **Table 2**, overwhelming evidence from clinical trials that included more than 10,000 early-stage, HER2-positive breast cancer patients supports the use of adjuvant trastuzumab, with significant improvements in DFS and OS.¹⁻⁴

Two potentially interactive yet independent factors lend perspective on the equivocal results of the PACS-04 trial: a lower benefit due to small patient sample size, with resulting inability to detect small differences, and use of the sequential chemotherapy–trastuzumab approach rather than a concomi-

tant approach. The PACS-04 trial is relatively small, with 528 patients compared to > 3000 patients per trial in the large studies, so it may be underpowered to show a difference.

The Finland Herceptin (FinHer) trial also included a small number of patients (n = 231), and yet with only 9 weeks of trastuzumab combined with non-anthracycline chemotherapy,

TABLE 2. Trial results of trastuzumab given as adjuvant therapy in early breast cancer

study	timing of trastuzumab	years of followup	number of patients	hazard ratio for DFS
HERA ¹	sequential	2	3401	0.64
NSABP B-31/NCCTG 9831 ²	concurrent	2	3351	0.48
NCCTG 9831 ²	sequential	1.5	1964	0.87 (NS)
BCIRG 006 ³		3	3222	0.61
FinHer ⁴	concurrent	3	232	0.42
PACS-04	sequential	4	528	0.86 (NS)

NS = not significant

the hazard ratio for DFS significantly favoured trastuzumab.⁴ Thus, the sequencing of chemotherapy with trastuzumab may also be of importance. The North Central Cancer Treatment Group (NCCTG) 9831 trial randomized patients to trastuzumab concurrently with a taxane vs trastuzumab given after chemotherapy completion. An unplanned interim analysis suggested superior outcomes if trastuzumab was given concurrently with chemotherapy compared to sequentially.² In the PACS-04 trial, trastuzumab was started after completion of chemotherapy and radiotherapy.

Exploratory analysis of PACS-04 suggested a trastuzumab benefit during the first 18 months of therapy but not thereafter, highlighting the uncertainty of the optimal duration of therapy, so results of 1 vs 2 years of trastuzumab in the Herceptin Adjuvant (HERA) trial are eagerly

awaited. The PACS-04 results are reassuring in terms of cardiac safety, with severe symptomatic cardiac toxicity being rare despite prior anthracycline exposure. Of all the adjuvant trastuzumab trials, PACS-04 has the longest median followup. Thus, further analyses of the other trastuzumab studies are essential.

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Targeted therapies in metastatic breast cancer

Joseph Ragaz, MD, FRCPC

SAFETY OF PERTUZUMAB PLUS TRASTUZUMAB IN A PHASE II TRIAL OF PATIENTS WITH HER2-OVEREXPRESSING METASTATIC BREAST CANCER WHICH HAD PROGRESSED DURING TRASTUZUMAB THERAPY. SABCS 2007, ABSTRACT 73.

Investigators: P. Fumoleau et al.

TRIAL SUMMARY: The humanized monoclonal antibody pertuzumab targets many HER pathways by binding to HER2 and blocking both HER2 homodimerization and heterodimerization between HER2 and other HER receptors. Trastuzumab operates by a different mechanism: preventing HER2 signal transduction (e.g. conversion of an external signal to a functional change within the cell) and shedding of the extracellular domain of the HER2 receptor. To examine the efficacy and safety of combining these 2 agents, this single-arm, 2-stage trial enrolled patients with HER2-overexpressing metastatic breast cancer who had received up to 3 lines of treatment including trastuzumab, but whose disease was progressing despite trastuzumab. To be eligible, a patient's baseline cardiac left ventricular ejection fraction (LVEF) had to be at least 55%, with no decline to less than 50% during prior trastuzumab treatment. Trial participants received trastuzumab 2 mg/kg every week (following a 4-mg/kg loading dose) or 6 mg/kg every 3 weeks (following

a 8-mg/kg loading dose), plus pertuzumab 420 mg every 3 weeks (following a 840-mg loading dose). By the end of April, 2007, in the 33 patients who had had at least 1 tumour evaluation after at least 1 treatment, complete response was seen in 1 (33%), partial response in 5 (15%), stable disease for < 6 months in 10 (30%), stable disease for ≥ 6 months in 7 (21%) and disease progression in 10 (30%). In 42 patients evaluable for safety, 34 had 1 or more adverse events. Adverse events occurring in > 10% of patients included diarrhea (57%), nausea and/or vomiting (33%), fatigue (31%), rash (28%), muscle spasms (17%), cough (14%), headache (12%), dyspnea (12%) and nasopharyngitis (12%). More than 80% of the frequent adverse events were of Grade 1 or 2 severity. With 64.3% of patients having received prior anthracyclines, only 1 experienced a decline in LVEF to < 50%, and this patient remained asymptomatic. As this combination appears to be safe and to have some efficacy, further studies in women with metastatic and early breast cancer are planned.

COMMENTARY: Joseph Ragaz, MD, FRCPC, Medical Oncologist and Senior Oncology Researcher, McGill University, Montreal, QC.

This study, one of the largest Phase I–II studies of pertuzumab + trastuzumab combination therapy in breast cancer, shows early safety and response data for pertuzumab (formerly rhuMab 2C4), a humanized monoclonal antibody and the first of a new class of HER dimerization inhibitors.

HER BIOCHEMISTRY

Pertuzumab and trastuzumab act against different segments (epitopes) of the extracellular domain of the HER2 receptor: trastuzumab blocks the HER2 heterodimer signalling pathway, while pertuzumab blocks the HER2–HER3 heterodimer

signalling pathway — an active pathway not blocked by trastuzumab that may be implicated in acquired resistance to trastuzumab monotherapy.

To understand the mechanism of the HER receptor block by trastuzumab and pertuzumab, it is important to appreciate the dynamics of cellular and biochemical responses of the HER receptors in response to ligand binding. The HER ligands are biochemical molecules floating in the serum that have a particular attraction for all tyrosine kinase receptors. Ligand-receptor binding triggers the heterodimerization of HER receptors — a process in which the HER receptors couple or “dimerize” with each other on the cell membrane surface.¹ This structural process of HER dimerization is followed by substantial genetic and biochemical signalling and activation of molecular cascades, leading to cancer cell proliferation. Importantly, these molecular signals precede and promote metastatic spread. HER2 is the preferred partner for dimerization with the HER1, HER3 and HER4 receptors. The HER2–HER3 dimers are exceptionally active in breast cancer signalling: their formation is followed by more substantial downstream detection of activated protein kinases such as MAPK, AKT, Src and other important pathways related to breast cancer biology.¹ Pertuzumab — but not trastuzumab — blocks this dimerization by inactivating the HER2 dimerization-related epitope.

In animal studies, a combination of trastuzumab and pertuzumab antibodies inhibited formation and size of experimental tumours more effectively than either alone.² Other experimental evidence showed that treatment with the HER-inactivating triple-drug combination of trastuzumab + pertuzumab + gefitinib was more effective than any of these agents alone, both in inhibiting MAPK and AKT activation and in the related suppression of tumour clone proliferation with associated increase of apoptosis.³ These results support the hypothesis that acquired resistance to individual HER-related antibodies may result from incomplete blockade of the complex HER receptor-signalling network, and that this resistance might be overcome by a combined modality approach using different biologics simultaneously or sequentially.

ENCOURAGING SAFETY AND EFFICACY RESULTS


Fumoleau et al’s study was designed to evaluate the early response rates and safety of pertuzumab added to trastuzumab in women with HER2-positive Stage IV breast cancer whose disease had progressed on a trastuzumab + chemotherapy combination. Sixty-four percent of enrollees had received prior anthracyclines; 78% had visceral lesions and 51% were estrogen receptor-positive. The pertuzumab + trastuzumab combination was initiated within 9 weeks of the last trastuzumab therapy, and a median of 4 pertuzumab cycles were given. Data from 61 patients were available for safety analysis, and from 33 for efficacy analysis. The objective response rate in the 33 efficacy-evaluable patients was 18.2% (CR + PR), with clinical benefit (defined as CR + PR + subjective response) seen in 39.4%. The main symptoms indicating toxicity were mild diarrhea, skin rash, gastrointestinal upset including nausea and/or vomiting, and fatigue. All symptoms were self-limited, with Grade 3–4

diarrhea, skin rash and deep vein thrombosis each seen in 1 patient (2%). Cardiotoxicity was acceptable. LVEF remained unchanged from the median baseline value of 60%, even after 6 cycles of pertuzumab, with 23 patients experiencing a change of 2%. Even after 12 cycles, 10 patients had < 2% change in LVEF. Only 2 patients had LVEF reductions of 6.4% and 6.6% from baseline; 1 had no cardiac symptoms and 1 was withdrawn from the study because of disease progression. The authors concluded that adding pertuzumab to treat women whose disease had progressed on a trastuzumab and chemotherapy combination was shown to be safe, with some efficacy.

FURTHER RESEARCH

Fumoleau et al’s trial is ongoing, with the next report planned for the 2008 Annual Meeting of the American Society of Clinical Oncology. Further, a pertuzumab monotherapy arm has been added.

A Phase III randomized double-blind trial (CLEOPATRA, NCT00567190) will randomly assign women with HER2-positive Stage IV breast cancer to receive docetaxel + trastuzumab + pertuzumab vs docetaxel + trastuzumab + placebo as first-line therapy for metastatic disease. As well, planning is underway for a 4-arm trial of neoadjuvant pertuzumab + docetaxel vs trastuzumab + docetaxel vs pertuzumab + trastuzumab + docetaxel vs pertuzumab + trastuzumab without docetaxel, all patients receiving both preoperative and postoperative chemotherapy. These trials have the potential to clarify the interaction of the 2 principal HER2-related antibodies.

The data presented thus far show effectiveness of pertuzumab in patients with HER2-positive disease that has progressed on trastuzumab, with relatively good tolerance. The absence of additional cardiotoxicity despite ongoing delivery of trastuzumab is reassuring. Pertuzumab is emerging as a promising agent for breast cancer, with a new mechanism of action involving the dimers of HER2–HER3 receptors. More trials are required to confirm the full extent of its effectiveness and optimal sequencing with established breast cancer therapies. 

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Disclosure

Dr. Grenier reports being on advisory boards of AstraZeneca and GlaxoSmithKline. Dr. Ragaz reports serving on advisory boards of GlaxoSmithKline, Novartis, Roche and Sanofi-Aventis. Dr. Sehn reports receiving research support from Roche, serving as a consultant to Roche and Biogen Idec, serving on the advisory board of Roche, and on the speaker’s bureau for Genentech.