

EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 28th San Antonio Breast Cancer Symposium, held December 8–11 in San Antonio, Texas, and at the 47th Annual Meeting of the American Society of Hematology, held December 10–13 in Atlanta, Georgia. Leading Canadian experts offer commentary and clinical interpretations. Reporting on both conferences will continue in the next issue of *Oncology Exchange*.

Presentations from the 27th Annual San Antonio Breast Cancer Symposium

Contributors were selected by Dr. Joseph Ragaz, MD, FRCPC, Director, Oncology Program, McGill University Health Centre, Montréal, QC

Adjuvant and neoadjuvant chemotherapy

PHASE III STUDY OF DOXORUBICIN-CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL OR DOCETAXEL GIVEN EVERY 3 WEEKS OR WEEKLY IN PATIENTS WITH AXILLARY NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE BREAST CANCER: RESULTS OF NORTH AMERICAN BREAST CANCER INTERGROUP TRIAL E1199. ABSTRACT 48.

Investigators: J.A. Sparano et al.

The Breast Cancer Intergroup of North America (TBCI) Trial E1199 aims to compare the efficacy and toxicity of the taxanes docetaxel vs paclitaxel (2 regimens each) after doxorubicin + cyclophosphamide chemotherapy in women with node-positive or high-risk (tumour ≤ 2 cm), node-negative, operable Stage II or IIIA breast cancer. A total of 4988 eligible participants were randomized to 4 treatment arms, receiving 4 cycles of doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² every 3 weeks (AC) followed by one of 4 regimens:

- P3: 4 cycles of paclitaxel 175 mg/m² every 3 weeks (standard treatment)
- P1: 12 cycles of weekly paclitaxel 80 mg/m²
- D3: 4 cycles of docetaxel 100 mg/m² every 3 weeks
- D1: 12 cycles of weekly docetaxel 35 mg/m²

TABLE 1. Outcomes at 46.5 months in trial E1199

	hazard ratio for DFS events (95% CI)*	p-value	Grade 3 toxicity	Grade 4 toxicity
P3: paclitaxel 175 mg/m² q 3 weeks x 4 (standard treatment, control)	1.0	—	24%	6%
P1: weekly paclitaxel 80 mg/m² x 12	1.20 (0.99–1.46)	p = 0.06	24%	4%
D3: docetaxel 100 mg/m² q 3 weeks x 4	1.13 (0.94–1.30)	p = 0.20	21%	50%
D1: weekly docetaxel 35 mg/m² x 12	1.03 (0.85–1.23)	p = 0.78	39%	6%

* HR = P3 vs others (> 1 signifies inferior to P3)

Women with hormone receptor-positive tumours received 5 or more years of adjuvant hormonal therapy with tamoxifen and/or an aromatase inhibitor. The primary endpoint was disease-free survival (DFS), defined as absence of local, regional and/or distant relapse, a second primary breast cancer or death without recurrence.

At median followup of 46.5 months and 856 events — the fourth planned interim analysis — no significant differences were seen in DFS, although there was a trend in favour of weekly paclitaxel compared to the standard 3-weekly schedule. Toxicity was most significant in the 3-weekly docetaxel arm with predominantly neutropenic

and infectious complications followed by stomatitis and fatigue. Weekly paclitaxel had the most favourable toxicity profile but had an 8% rate of Grade 3–4 neuropathy. **Table 1** shows hazard ratios (HRs) for DFS events comparing experimental to standard treatments and occurrence of Grade 3 and 4 toxicities.

COMMENTARY: Hagen Kennecke, MD, MHA, FRCPC, Medical Oncologist, British Columbia Cancer Agency, Vancouver, BC

This well designed 2 by 2 factorial design trial set out to independently compare taxane type and schedule of delivery. The head-to-head comparison is particularly relevant given the widespread use of both taxanes in the adjuvant setting and the current uncertainty regarding the optimal adjuvant regimen for women with high-risk breast cancer. In this final analysis of the trial, with just under 4 years of followup, no significant differences were found between the groups. DFS was better than expected in all groups at P3 = 80.3%, P1 = 83.5%, D3 = 83.1% and D1 = 80.5%. HRs were very close to 1 both for the comparisons of paclitaxel vs docetaxel and for the 3-weekly vs 1-weekly schedules, and it is unlikely that greater statistical power would have detected a difference in the primary comparisons. In the exploratory secondary comparisons the P3 arm was compared to the remaining 3 arms. **Table 1** shows a trend for superiority of the P1 and D3 arms compared to P3, with 20% more events in P3 than in P1 (HR 1.2, $p = 0.06$) and 13% more events in P3 than in D3 arms (HR 1.13, $p = 0.20$).

Since the publication of the results of the US Intergroup/CALGB trial C9344 in 2003,¹ AC followed by paclitaxel has become one of the more favoured treatment regimens for high-risk breast cancer. While the lack of a difference among the primary comparisons in E1199 does not compellingly call for a change in practice, the secondary comparisons point to the possibility of better outcomes with weekly paclitaxel or 3-weekly docetaxel. In particular, in the estrogen receptor-negative (ER-) subgroup, the HR for P3 vs P1 was 1.3 ($p = 0.07$) in favour of P1. This likely results from an augmentation of benefit from a moderately superior regimen in a subgroup that is inherently more chemosensitive, and mirrors the trend seen in the initial C9344 trial where the ER- subgroup, but not the ER+ subgroup, benefited from the addition of paclitaxel to AC. This differs from the subgroup analysis of TAC (docetaxel, doxorubicin and cyclophosphamide) vs FAC (5-fluorouracil, doxorubicin, and cyclophosphamide)² in which a statistically significant benefit in favour TAC over FAC was seen for both ER+ and ER- subgroups, with no difference of docetaxel impact according to ER status. Docetaxel given every 3 weeks also demonstrated a trend towards a reduced event rate compared to the standard 3-weekly paclitaxel, but at a price of increased toxicity — primarily related to bone

marrow effects (neutropenia and infections) — demonstrating that docetaxel is perhaps best used with prophylactic granulocyte colony-stimulating factor (G-CSF). On the other hand, fewer patients in the D3 arm receiving 3-weekly docetaxel (4%) than in the P1 arm receiving weekly paclitaxel (8%) had Grade 3–4 neurotoxicity, an important concern especially in the adjuvant setting.

In contrast to the metastatic setting, where docetaxel was found to be superior to paclitaxel,³ the results of E1199 did not demonstrate a difference between efficacy of the taxanes in the adjuvant setting although it did highlight differences in toxicity. Nevertheless, adjuvant taxanes are actively used or under consideration for funding in a number of Canadian provinces. Use of taxanes, particularly docetaxel, is likely to increase in Canada, as 2 mature adjuvant trials of docetaxel over anthracycline-containing regimens have demonstrated significant improvement in both disease-free and overall survival.^{2,4}

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FIVE YEAR FOLLOW-UP OF INT C9741: DOSE-DENSE (DD) CHEMOTHERAPY (CRX) IS SAFE AND EFFECTIVE. ABSTRACT 41.

Investigators: C. Hudis et al.

The INT C9741 study compared efficacy and safety of 4 cycles of 2-weekly dose-dense chemotherapy with doxorubicin 60 mg/m² + paclitaxel 175 mg/m² + cyclophosphamide 600 mg/m² to standard 3-weekly therapy (same doses and number of cycles) and also compared concurrent to sequential doxorubicin + cyclophosphamide (same doses and number of cycles). A previous 36-month

analysis¹ found that dose-dense was superior to 3-weekly chemotherapy in terms of both DFS (HR 0.74) and overall survival (OS) (HR 0.69). In the current 69-month analysis, significantly better DFS and a trend towards better OS was observed in the patients receiving dose-dense therapy. In an unplanned subgroup analysis according to ER status, only patients with ER- disease benefited:

the HR for DFS was 0.75 (p = 0.031) and for OS it was 0.77 (p = 0.073), with no significant benefit seen in the ER+ subgroup. Long-term toxicity was similar to that of earlier analyses with a less than 1% incidence of acute myeloid leukemia and/or myelodysplastic syndrome in all 4 treatment groups and a 1% to 3% rate of delayed cardiac toxicity overall which did not differ between treatment groups.

COMMENTARY: Hagen Kennecke, MD, MHA, FRCPC, Medical Oncologist, British Columbia Cancer Agency, Vancouver, BC

Dose-dense AC followed by paclitaxel has been a popular choice among oncologists and patients alike as it is generally well tolerated, with a low rate of complications and significantly reduced duration of therapy. With the loss of a statistically significant survival benefit, however — particularly evident among ER+ patients — oncologists will question whether dose-dense chemotherapy is still a viable option. With a followup of over 5 years, this trial may be considered mature — future analysis is unlikely to demonstrate a different result as chemotherapy affects the rates of recurrence primarily in the first 1–3 years after diagnosis and has a much smaller impact on rate of late recurrence after 5 years, even in ER+ disease.² The subgroup analysis according to ER status highlights a trend also seen in trial E1199 (page 10–11), wherein patients with ER- tumours differentially benefit more than do those with ER+ disease. This is likely due to ER- breast cancer being inherently more chemosensitive, thereby augmenting the benefits of a regimen that is moderately superior.

Two issues dominate current questions in the adjuvant chemotherapy of early breast cancer. First is dose density. The C9741 trial shows that for some patient subsets, e.g. those with high-risk ER- tumours, dose density is preferable. The other issue is the role of taxanes in conjunction with anthracyclines. Presentations from this and last year's American Society of Clinical Oncology (ASCO) Annual Meeting and San Antonio Symposium brought evidence from at least 2 European trials (the French PACS 01 trial³ and the Spanish GEICAM 9906 trial⁴) confirming observations from prior North American studies that adding taxanes to anthracyclines in the adjuvant setting significantly improves event-free survival of women with early breast cancer. In the French PACS 01, docetaxel 100 mg/m² q 3 weeks was added to treatment after 3 months of FEC 100 (5-fluorouracil 500 mg/m² + epirubicin 100 mg/m² + cyclophosphamide 500 mg/m²).³ In the recent Spanish GEICAM 9906 trial, 2 months of paclitaxel 100 mg/m² weekly followed after 3 months of FE90C (600 mg/m² + epirubicin 90 mg/m² +

cyclophosphamide 600 mg/m²).⁴ In both trials, taxanes significantly improved outcomes compared to FEC given without taxanes.

In the 15-year update of the Oxford Overviews,⁵ which compared approximately 6 months of anthracycline-based chemotherapy to cyclophosphamide, methotrexate and 5-fluorouracil (CMF), the former reduced the risk of breast cancer mortality by 38% in women less than 50 years old and 20% in those aged 50 to 69, and this benefit was seen in both ER+ and ER- subgroups.

The question of how well dose-dense anthracyclines followed by 3-weekly paclitaxel chemotherapy compares to approximately 6 months of “standard” anthracycline therapy remains open. This important issue will be addressed by the MA21 trial, which completed enrollment in spring of 2005 with early analyses expected at the end of 2006. Until then, clinicians have several viable options as discussed in this overview.

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Presentations from the 47TH Annual Meeting of the American Society of Hematology

Contributors were selected by Isabelle Bence-Bruckler, MD, FRCPC, Hematologist and Associate Professor of Medicine, The Ottawa Hospital, Ottawa, ON.

Follicular lymphoma

CHIMERIC ANTI-CD20 MONOCLONAL ANTIBODY (RITUXIMAB; MABTHERA) IN REMISSION INDUCTION AND MAINTENANCE TREATMENT OF RELAPSED / RESISTANT FOLLICULAR NON-HODGKIN'S LYMPHOMA: FINAL ANALYSIS OF A PHASE III RANDOMIZED INTERGROUP CLINICAL TRIAL. ABSTRACT 353.

Investigators: M.H.J. van Oers et al.

The EORTC 20981 trial randomized patients with advanced-stage refractory and/or relapsed follicular non-Hodgkin's lymphoma (NHL) Grades I-III to 6 cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) vs the same chemotherapy plus rituximab 375 mg/m² on Day 1 of each cycle of CHOP (R-CHOP). Study participants had received a maximum of 2 prior non-anthracycline-containing regimens. After 6 cycles, patients achieving partial or complete response — the primary endpoint of the first randomization — underwent a second randomization to maintenance therapy of rituximab 375 mg/m² every 3 months for up to 2 years, or to observation alone.

Of 461 patients in the R-CHOP arm, 29% achieved complete response and 56% partial response, with an overall response rate (ORR) of 85%. Among patients in the CHOP arm 16% achieved complete response and 57% partial response, with an ORR of 73%. The difference in complete response rates was statistically significant ($p = 0.0004$); the partial response rates were the same in both arms. Progression-free survival (PFS) based on induction therapy was 33 months for patients receiving R-CHOP and 20 months for those receiving CHOP, but the interpretation of these results was complicated by the fact that both arms underwent a second randomization. PFS after the first randomization was 33 vs 20 months ($p = 0.0003$) (Table 2). OS based on induction

TABLE 2. Results in the EORTC 20981 trial

Analysis by induction therapy (n = 461)			
	R-CHOP	CHOP	p-value
Complete response	29%	16%	$p = 0.0004$
Partial response	56%	57%	$p = NS$
Progression-free survival	33 months	20 months	$p = 0.0002$
Overall survival from 1 st randomization	83 months	72 months	$p = 0.096 (NS)$
Analysis by maintenance vs observation (n = 319) at a median of 33 months' followup from time of maintenance randomization			
	maintenance rituximab	observation	p-value
Progression-free survival	52%	15%	$p < 0.0001$
3-year overall survival	85%	77%	$p = 0.011$

therapy did not differ significantly between the 2 groups, at 83 months for patients receiving R-CHOP vs 72 months for those receiving CHOP ($p = 0.096$).

For the analysis of progression-free survival (PFS) and overall survival (OS) following the maintenance randomization, 319 patients were evaluable from a total of 334. Median followup after the second randomization was 33 months. PFS from the time of the second randomization was 52 months in the maintenance group compared to 15 months for those in the observation group ($p < 0.0001$). Three-year OS, calculated from the time of the second randomization, was 85% in the rituximab-maintenance arm compared to 77% for those without maintenance rituximab,

and this difference was statistically significant ($p = 0.011$).

Analysis according to both induction and maintenance treatments showed that in the R-CHOP induction arm, PFS for patients subsequently randomized to maintenance rituximab was 52 months vs 23 months for those with observation alone ($p = 0.004$), and in the CHOP-alone induction arm, PFS was 42 months with maintenance vs 12 months without ($p < 0.0001$ by log rank test).

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MAINTENANCE RITUXIMAB AFTER CVP RESULTS IN SUPERIOR CLINICAL OUTCOME IN ADVANCED FOLLICULAR LYMPHOMA (FL): RESULTS OF THE E1496 PHASE III TRIAL FROM THE EASTERN COOPERATIVE ONCOLOGY GROUP AND THE CANCER AND LEUKEMIA GROUP B. ABSTRACT 349.

Investigators: H.S. Hoehster et al.

In this report of the E1496 Phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG) and the Cancer and Leukemia Group B (CALGB), patients with previously untreated follicular Grades I and II lymphoma received 6–8 cycles of cyclophosphamide, vincristine and prednisone (CVP). Patients with complete response (CR), partial response (PR) or stable disease were randomized to maintenance rituximab 375 mg/m² weekly for 4 weeks, repeated every 6 months for 2 years, vs no maintenance. At a median followup of 3 years after randomization, in 237 evaluable patients the primary endpoint of PFS was 61 months with maintenance rituximab vs 15 months without main-

TABLE 3. PFS and OS in ECOG/CALGB trial E1496

	maintenance rituximab	observation only	p-value
PFS: all patients (n = 237)	61 months	15 months	p < 0.0001
PFS: high-risk disease	59 months	28 months	p < .00001
PFS: low-risk disease	65 months	51 months	p = 0.025
OS at 42 months	91%	75%	p = 0.03

tenance therapy (p < 0.0001) (Table 3). Among the one-third of patients with follicular lymphoma international prognostic index (FLIPI) high-risk disease, those receiving maintenance achieved PFS of 59 months vs 28 months without

(p < 0.0001), while in low-risk patients PFS was 65 vs 51 months (p = 0.025). Differences in OS became evident after 2 years. At 42 months, OS was 91% for patients on maintenance therapy vs 75% for those without (p = 0.03).

COMMENTARY: Isabelle Bence-Bruckler, MD, FRCPC, Hematologist and Associate Professor of Medicine, The Ottawa Hospital, Ottawa, ON

For patients with advanced-stage follicular NHL, rituximab combined with chemotherapy is the established optimal first-line therapy, resulting in superior response rates and PFS¹⁻⁴ and, in some studies, OS, compared to chemotherapy alone.^{2,3,5} Despite these improvements, patients continue to relapse with a shortening duration of each subsequent remission. Strategies to prolong remission duration, specifically with the use of maintenance rituximab, have been evaluated.^{6,7} Two oral presentations at the 2005 ASH meeting addressed this question.

EORTC 20981

Marinus van Oers presented final results of the Phase III randomized intergroup trial EORTC 20981, in which the National Cancer Institute of Canada (NCIC) and the Australasian Lymphoma Groups also participated. The trial had a double-randomization design: patients with advanced-stage refractory and/or relapsed follicular Grades I–III NHL were randomized to remission induction with CHOP with or without rituximab, followed by maintenance rituximab vs observation. Response rate was the primary endpoint after the first randomization. An interim analysis, presented at the 9th International Conference on Malignant Lymphoma in Lugano in June 2005, demonstrated a superior CR rate with R-CHOP compared to CHOP alone and an improvement in PFS with rituximab maintenance compared to observation. The trial was halted based on these results.

The median age of patients was 55 years and the study arms were well balanced with respect to prior therapies and response rates. One-third had intermediate-risk FLIPI scores (retrospectively determined) and one-third had high-risk disease. As shown in Table 2, page 13, PFS improved both with the

addition of rituximab to induction therapy and with maintenance rituximab following completion of chemotherapy. Of note, the analysis of PFS based on induction therapy was confounded by the use of subsequent maintenance rituximab. Results indicate a benefit to maintenance even when rituximab was included in the induction regimen. The effect of initial response rate after induction was also examined: patients achieving CR as opposed to PR had a larger benefit from maintenance therapy, with PFS of 52 months vs 45 months.

In conclusion, R-CHOP induction resulted in a superior CR rate compared to CHOP alone in patients with refractory and/or relapsed follicular NHL. Maintenance rituximab administered every 3 months for 2 years or until progression resulted in significant prolongation of PFS in patients who achieved a response to first-line CHOP or R-CHOP, and was associated with a survival benefit.

ECOG/CALGB E1496

This trial presented by Sandra Horning enrolled patients with follicular Grades I–II lymphoma and small lymphocytic lymphoma (SLL), but data was only presented on the follicular lymphoma patients. The study initially had 2 induction arms: cyclophosphamide + fludarabine (CF) vs CVP. The CF arm was terminated due to toxicity. Median age was lower in the observation arm (35 years) vs the maintenance arm (43 years). One-third of enrolled patients were FLIPI high-risk and two-thirds had high tumour burden. All patients benefited from rituximab maintenance with an improvement in PFS. At 42 months, an OS advantage was also apparent of 91% vs 75% (p = 0.03).

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LANDMARKS

Bence-Bruckler, continued from page 15

RITUXIMAB MAINTENANCE

While both trials addressed the role of maintenance rituximab, they differed in terms of patient population, induction regimen and maintenance schedule.

Patients in the EORTC 20981 trial had refractory and/or relapsed disease, while those in E1496 were all newly diagnosed. E1496 patients did not receive rituximab with their induction CVP regimen, but did receive up to 20 maintenance doses. Would giving rituximab during induction have abrogated the effect of maintenance? Results of EORTC 20981 imply that the benefit of maintenance rituximab does extend to patients already receiving rituximab (i.e. R-CHOP) during induction.

Despite their differences, both trials demonstrated improvement in both PFS and OS in patients receiving some form of maintenance rituximab. These data are consistent with the growing body of evidence demonstrating improved outcomes in patients with follicular lymphoma in recent times. Improved response rates correlate with improved PFS, which in turn may translate into improved survival of these patients. The optimal dosing and duration of rituximab maintenance therapy vs retreatment strategies remains to be determined. 

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