



## EVIDENCE WATCH

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

*Oncology Exchange* provides overviews of important clinical trial data presented at the 42<sup>ND</sup> Annual Meeting of the American Society of Clinical Oncology (ASCO), held June 2–6, 2006 in Atlanta, Georgia. Leading Canadian experts offer commentary and clinical interpretations.

Contributors were selected by Joseph Ragaz, MD, FRCPC, Director, Oncology Program, McGill University Health Centre, Montréal, QC; Dr. Fred Saad, MD, FRCSC, Director of Urologic Oncology, Centre Hospitalier de l'Université de Montréal; and Amil Shah, MDCM, FRCPC, FACP, Medical Oncologist, Vancouver Cancer Centre. ASCO reporting will continue in the October issue of *Oncology Exchange*.

## Renal cancer

### PHASE III RANDOMIZED TRIAL OF SUNITINIB MALATE (SU11248) VERSUS INTERFERON-ALFA (IFN- $\alpha$ ) AS FIRST-LINE SYSTEMIC THERAPY FOR PATIENTS WITH METASTATIC RENAL CELL CARCINOMA (MRCC). ASCO 2006, ABSTRACT LBA3.

Investigators: R.J. Motzer et al.

**TRIAL SUMMARY:** This international Phase III trial randomized 750 treatment-naïve patients with clear-cell metastatic renal cell carcinoma (mRCC) to receive 6 cycles of either sunitinib 50 mg orally once daily for 4 weeks, followed by 2 weeks off, or of interferon-alfa (IFN- $\alpha$ ) subcutaneous injection 9 MU given 3 times per week for 6 weeks. Median progression-free survival (PFS), the primary endpoint, was 47.3 weeks (95% CI 40.9–not yet reached) for sunitinib vs 24.9 weeks (95% CI 21.9–37.1) for IFN- $\alpha$ , with a hazard ratio (HR) of 0.394 (95% CI 0.297–0.521,  $p < 0.000001$ ) (Table 1). The rate of objective response by third-party independent review was 24.8% (95% CI 19.7–30.5) for sunitinib vs 4.9% (95% CI 2.7–8.1) for IFN- $\alpha$  ( $p < 0.000001$ ). For sunitinib vs IFN- $\alpha$ , respectively,

there were 49 vs 65 deaths and 8% vs 13% of patients withdrew due to adverse events.

**TABLE 1. Sunitinib vs IFN- $\alpha$  in 750 patients with metastatic renal cell cancer**

Endpoint	sunitinib n = 375	IFN- $\alpha$ n = 375	hazard ratio	p-value
Progression-free survival	47.3 weeks	24.9 weeks	0.394	$p < 0.000001$
Objective response rate*	24.8%	4.9%	not given	$p < 0.000001$

### TEMSIROLIMUS (TEMSR) OR INTERFERON-ALPHA (IFN) OR THE COMBINATION OF TEMSR + IFN IN THE TREATMENT OF FIRST-LINE, POOR-RISK PATIENTS WITH ADVANCED RENAL CELL CARCINOMA (ADV RCC). ASCO 2006, ABSTRACT LBA4.

Investigators: G. Hudes et al.

**TRIAL SUMMARY:** This Phase III open-label study randomized 626 previously-untreated patients with poor-risk, advanced renal cell carcinoma to 3 treatment arms: temsirolimus 25 mg intravenous once per week, IFN- $\alpha$  up to 18 MU subcutaneous 3 times per week, or temsirolimus 15 mg intravenous once per week + IFN- $\alpha$  6 MU

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# LANDMARKS

subcutaneous 3 times per week. Enrolled patients had at least 3 of 6 risk factors (the 5 Motzer criteria and metastatic disease). At the time of this interim analysis, 442 patients had died. Median overall survival (OS), the primary endpoint, was greater in the patients treated with temsirolimus (10.9 months, 95% CI 8.6–12.7) compared to those treated with IFN- $\alpha$  (7.3 months, 95% CI 6.1–8.9) and temsirolimus + IFN (8.4 months, 95% CI 6.6–10.2) (Table 2). Grade 3 or higher adverse events were asthenia (occurring respectively in 27%, 30% and 12% of patients), anemia (24%, 39% and 21%) and dyspnea (8%, 11% and 9%). The authors concluded that first-line temsirolimus monotherapy significantly increases overall survival with acceptable toxicity in poor-risk patients with advanced disease.

**TABLE 2. Temsirolimus vs IFN- $\alpha$  vs temsirolimus + IFN- $\alpha$  in poor-risk patients with advanced renal cell cancer**

	temsirolimus	IFN- $\alpha$	temsirolimus + IFN- $\alpha$
median overall survival	10.9 months (95% CI 8.6–12.7)	7.3 months (95% CI 6.1–8.9)	8.4 months (95% CI 6.6–10.2)
deaths	141 (32%)	149 (34%)	152 (34%)

**COMMENTARY: Eric Winquist, MD, MSc, FRCPC, Medical Director, Genitourinary Disease Site Team, London Health Sciences Centre; Associate Professor, University of Western Ontario, London, ON.**

Historically, patients with metastatic renal carcinoma have had few effective treatment options. Conventional chemo- and hormonal therapies are inactive. Although IFN- $\alpha$  with or without cytoreductive nephrectomy has become established as a standard over the past few years, low objective response rates and dose-limiting constitutional symptoms have limited the appeal of this approach. High-dose interleukin-2 therapy has been available in the U.S. and some European countries, but only for patients with excellent performance status who are willing to accept the limited evidence of benefit, toxicities and expense. So it remains justifiable in 2006 to offer renal cell carcinoma patients investigational drugs as first-line treatment.

This makes the clinical developments of the past year all the more startling. Initial hints of the activity of new molecularly-targeted agents were observed in cytokine-refractory patients. In 2003, a randomized Phase II trial reported improved progression-free survival (PFS) with the anti-VEGF monoclonal antibody bevacizumab. In 2004, Phase II trials reported tumour responses and hints of improved PFS with both sorafenib (formerly BAY 43-9006), an orally bioavailable small-molecule Raf kinase and VEGFR-2 tyrosine kinase inhibitor, and temsirolimus (formerly CCI-779), an intravenous inhibitor of mTOR in the PI3K-Akt signalling pathway. Sorafenib was reported to be stunningly superior to placebo in cytokine-refractory patients at ASCO 2005, and was approved for this indication by the U.S. FDA in December 2005. Sunitinib malate (formerly SU011248) is an orally bioavailable multikinase inhibitor of the VEGFR1–3, PDGFR, c-KIT, RET, and FLT3 tyrosine kinases. Phase II trials in 2005 reported unprecedented objective response rates in the range of 40% in cytokine-refractory patients. Although quite dissimilar drugs, all of these agents appear to disturb VEGF-mediated angiogenesis stimulated through HIF- $\alpha$  upregulation.

## RANDOMIZED TRIALS

With this background the obvious and logical next step was to study these agents in comparison to standard therapy in treatment-naïve patients. The 2006 ASCO annual meeting plenary sessions featured presentations from 2 of these trials. Motzer

et al reported the positive results of their trial randomizing 750 patients with untreated good- or intermediate-prognosis metastatic clear-cell renal carcinoma to either sunitinib malate or IFN- $\alpha$ . The primary endpoint of PFS strongly favoured sunitinib (11 vs 5 months; HR 0.42,  $p < 10^{-6}$ ). Objective response was superior with sunitinib (31% vs 6%,  $p < 10^{-6}$ ). Although median survival had not been reached in either arm, treatment with sunitinib was associated with better OS (HR 0.65,  $p = 0.0219$ ). Adverse effects of sunitinib (diarrhea, hypertension and hand-foot reaction) were different from those with IFN- $\alpha$ , but occurred with similar frequency and severity. Importantly, overall health-related quality of life measured using Functional Assessment of Cancer Therapy-General (FACT-G) also favoured sunitinib ( $p < 0.0001$ ).

Hudes et al reported the positive results of their trial randomizing 626 poor-prognosis metastatic renal cell carcinoma patients to temsirolimus, IFN- $\alpha$  or temsirolimus combined with IFN- $\alpha$ . Patients had at least 3 poor-prognosis factors including elevated lactate dehydrogenase, anemia, hypercalcemia, a time from diagnosis of less than 1 year, Karnofsky performance status 60–70 and multiple organ sites of metastases. OS favoured single-agent temsirolimus over IFN- $\alpha$  (median OS 10.9 vs 7.3 months, HR 0.73,  $p = 0.0069$ ). PFS was better in the 2 temsirolimus arms (median 3.7 vs 1.9 months,  $p = 0.001$ ). Clinical benefit was greater with temsirolimus compared with IFN- $\alpha$  (46% vs 29%,  $p = 0.0019$ ). There was less asthenia with temsirolimus, but more rash and edema.

## CLINICAL APPLICATION

Based on these data, sunitinib must be considered the most effective therapy for good-to-intermediate-prognosis patients and temsirolimus for those with poor prognosis. Neither drug is currently approved in Canada for these indications, although sunitinib has been approved for the treatment of imatinib-refractory gastrointestinal stromal tumours. The value of temsirolimus for good-to-intermediate-prognosis patients, and of sunitinib for poor-prognosis ones, remains uncertain. Certainly sunitinib needs to be used with care, particularly in the first cycle of therapy, as some patients

experience unexpectedly severe idiosyncratic reactions — perhaps related to the drug's P450 cytochrome metabolism and multiple enzyme targets. Results of trials comparing IFN- $\alpha$  with sorafenib, and of bevacizumab combined with IFN- $\alpha$ , are pending and awaited with interest.

Renal cancer now joins other solid tumours in an emerging age of molecular therapeutics. Questions remain about

the optimal sequencing and combinations of molecular and conventional therapies, whether there is a role for the post-operative adjuvant use of these drugs, and how to use emerging, still unproven new drugs. Undoubtedly sunitinib and temsirolimus will be expensive, and current enthusiasm about their efficacy is likely to be tempered in future by questions about their availability, funding and accessibility.

## Colorectal cancer — intermittent chemotherapy

### **OPTIMOX2, A LARGE RANDOMIZED PHASE II STUDY OF MAINTENANCE THERAPY OR CHEMOTHERAPY-FREE INTERVALS (CFI) AFTER FOLFOX IN PATIENTS WITH METASTATIC COLORECTAL CANCER (MRC). A GERCOR STUDY. ASCO 2006, ABSTRACT 3504.**

**Investigators:** F. Maindrault-Goebel et al.

**TRIAL SUMMARY:** The OPTIMOX2 trial randomized 187 patients to either a “maintenance” arm or a “stopping” arm. The maintenance arm (Arm 1) received 6 cycles of modified FOLFOX7 (mFOLFOX7) (oxaliplatin 100 mg/m<sup>2</sup> + leucovorin 400 mg/m<sup>2</sup> over 2 hours, then a 46-hour continuous infusion of fluorouracil 3000 mg/m<sup>2</sup>) every 2 weeks, followed by maintenance therapy with the simplified LV5FU2 (sLV5FU2) (leucovorin 400 mg/m<sup>2</sup>, then a 46-hour continuous infusion of fluorouracil 3000 mg/m<sup>2</sup>) every 2 weeks until disease progression, at which time mFOLFOX7 was reintroduced. The stopping arm (Arm 2) received 6 cycles of mFOLFOX7 followed by a complete stop of chemotherapy, with reintroduction of mFOLFOX7 before tumour progression reached the patient's baseline measurements. The primary objective was to determine the duration of disease control (DDC) in each arm, defined as the sum of the first PFS interval and the second PFS interval in patients who achieved response or stable disease to initial and reintroduced mFOLFOX7. There were no formal hypotheses for comparison between arms.

At median followup of 70 weeks, OS data was not avail-

able. Complete response was 3% in both arms; partial response was 58% in both arms; stable disease was 27% in Arm 1 and 32% in Arm 2; and progression was 11% vs 6%. Patients in Arm 2 received 21% more oxaliplatin but had 36% fewer cycles of chemotherapy. There were no complete responses to reintroduction of mFOLFOX7, partial response was 13% in Arm 1 and 31% in Arm 2, stable disease was 43% vs 24% and progression was 40% in both arms. Median PFS was 38 weeks in Arm 1 vs 30 weeks in Arm 2 ( $p = 0.009$ ). Median PFS with reintroduction of mFOLFOX7 was 16 vs 18 weeks. Median DDC was 56 vs 51 weeks ( $p = 0.41$ ). The median chemotherapy-free interval for Arm 2 was 20 weeks, and up to 35 weeks in patients without adverse prognostic factors (performance status 2, elevated LDH, alkaline phosphates  $\geq 3$  and  $> 1$  metastatic site). The authors concluded that maintenance therapy with fluorouracil and leucovorin increases PFS but not DDC, that it was too early to know the impact on OS, and that a break in treatment can be considered for patients who respond to first-line FOLFOX, especially those without adverse prognostic factors.

### **ALTERNATING VERSUS CONTINUOUS “FOLFIRI” IN ADVANCED COLORECTAL CANCER (ACC): A RANDOMIZED “GISCAD” TRIAL. ASCO 2006, ABSTRACT 3505.**

**Investigators:** R. Labianca et al.

**TRIAL SUMMARY:** This randomized study aimed to evaluate intermittent vs continuous FOLFIRI (irinotecan 180 mg/m<sup>2</sup> Day 1 + leucovorin 100 mg/m<sup>2</sup> + fluorouracil 400 mg/m<sup>2</sup> bolus + fluorouracil 600 mg/m<sup>2</sup> 22-hour infusion, Day 1 and 2 every 2 weeks). A total of 337 patients were randomized to receive either this regimen intermittently, 2 months on then 2 months off (Arm A), or continuously (Arm B), until disease progression. The study was designed as a non-inferiority trial. The primary objective was to compare OS, with secondary endpoints of PFS and toxicity.

At a median followup of 30 months, OS was 16.9 months in Arm A vs 17.6 months in Arm B (HR 1.03, 95% CI 0.78–1.35). The complete response rate was 4.2% in Arm A vs 3.0% in Arm B, partial response was 29.4% vs 33.5%, stable disease was 31.4% vs 35.1% and progression was 35% vs 28.4%. PFS was 6.2 months in Arm A vs 6.5 months in Arm B (HR 1.01, 95% CI 0.78–1.27). Toxicities reported were similar in both groups. The authors concluded that pending the final analysis, intermittent FOLFIRI is possibly not inferior to continuous treatment in terms of OS and PFS, with similar toxicity.

**COMMENTARY: Lyly H. Lê, MD CM, FRCPC, Medical Oncologist, BC Cancer Agency, Fraser Valley Centre.**

Significant advances in the treatment of metastatic colorectal cancer (mCRC) have been made over the last decade. Median survival has increased from 11 months, when fluorouracil and leucovorin were the only available active agents, to more than 20 months with combination chemotherapy using fluorouracil, irinotecan, oxaliplatin, and more recently, biologic agents such as bevacizumab. Some loss of quality of life generally accompanies the increase in quantity of life. The combination regimens require placement of indwelling vascular access devices, frequent visits to the clinic for treatment and blood work, and significant, sometimes debilitating, toxicity.

The rationale for intermittent chemotherapy in patients with mCRC undergoing first-line treatment includes pre-clinical evidence, cited by the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente) group, that intermittent exposure of cell cultures to fluorouracil resulted in a doubling of the time to developing resistance compared to continuous exposure.<sup>1</sup> An earlier study done by Hejna et al found that patients who responded to an initial 6 months of first-line fluorouracil and leucovorin could be given a break from treatment and rechallenged successfully with the same regimen 3 or more months later.<sup>2</sup> A study done by the Medical Research Council in the United Kingdom showed that continuing treatment indefinitely until documented disease progression gave no overall survival advantage compared to interrupted treatment.<sup>3</sup> The 2 trials summarized here investigate this issue with current chemotherapy regimens, FOLFOX and FOLFIRI, both generally more toxic than fluorouracil alone.

The GERCOR (Groupe Cooperateur Multidisciplinaire en Oncologie) trial was originally designed as a Phase III study but had to be downsized to a large Phase II trial when bevacizumab became available and enrolment was likely to be affected by the new standard of care. The primary endpoint was duration of disease control (DDC), introduced in the original OPTIMOX1 study. That study showed similar efficacy and better tolerance of FOLFOX when administered with a “stop and go” approach: mFOLFOX7 was given for 6 cycles, maintenance with infusional fluorouracil continued for 12 cycles, and oxaliplatin was then reintroduced — as compared to treatment with FOLFOX4 until progression. In the current OPTIMOX2 study, the maintenance regimen from OPTIMOX1 was compared to a true intermittent strategy: patients were given mFOLFOX7 for 6 cycles and then no further chemotherapy until they progressed back to baseline tumour measurements. It was not clear from the presentation how new sites of disease were incorporated into the determination of “baseline progression”. Nonetheless, there was no significant difference in DDC despite a statistically significant difference in PFS after initial chemotherapy. The maintenance fluorouracil likely delayed initial progression, but in the end this was probably balanced by a lower partial response rate to reintroduction of mFOLFOX7 in the maintenance arm (Arm 1).

Unfortunately, no formal assessment of quality of life was done. Patients had a median break from chemotherapy of

4.6 months, and almost 8 months if they had no poor prognostic factors. Most of us have seen patients rejoice at the thought of time away from the chemotherapy room. Because of the shorter interval between exposures to oxaliplatin, however, the rates of Grade 3 peripheral neuropathy with reintroduction of mFOLFOX7 vs maintenance were 13.5% vs 8.7%, respectively. Second-line treatment will have a major impact on OS in these patients, and further information about what second-line therapies were given in each group will be needed before the OS data can be used to validate DDC as an endpoint.

The GISCAD study was a straightforward comparison of continuous vs intermittent first-line FOLFIRI. It was designed as a non-inferiority trial with a generous margin of 4 months' difference being considered acceptable. There was no difference in efficacy and, surprisingly, in toxicity. The trial recommended that an oxaliplatin-containing regimen be used for second-line treatment, and since roughly equal numbers of patients in both arms chose this option, subsequent therapy should not adversely affect the usefulness of OS data. At the time of presentation the required number of events had not yet occurred, but the authors concluded that the 2 methods of delivery were likely to be similar in terms of PFS, OS and toxicity.

## INTERIM CLINICAL IMPLICATIONS

Firm conclusions will be possible only when final OS data becomes available. These studies do imply, however, that for patients who respond to first-line therapy — especially those without poor prognostic factors as outlined in the GISCAD trial — treatment until progression is not necessarily required, and that appropriate patients can be treated intermittently. A 3–4 month trial of first-line chemotherapy to assess individual response and tolerance should allow proper patient selection and reassure those who worry that stopping treatment may allow the cancer to grow back. This strategy can delay the onset of severe peripheral neuropathy related to oxaliplatin. Further, providing the same outcome with fewer doses of chemotherapy is economically advantageous. Upcoming trials will incorporate targeted agents: the GERCOR group outlined their pending DREAM trial, which proposes using bevacizumab and erlotinib during the maintenance phase. Final results of both trials are eagerly awaited.

## References

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## Breast cancer: neoadjuvant chemotherapy

**SWOG 0012, A RANDOMIZED PHASE III COMPARISON OF STANDARD DOXORUBICIN (A) AND CYCLOPHOSPHAMIDE (C) FOLLOWED BY WEEKLY PACLITAXEL (T) VERSUS WEEKLY DOXORUBICIN AND DAILY ORAL CYCLOPHOSPHAMIDE PLUS G-CSF (G) FOLLOWED BY WEEKLY PACLITAXEL AS NEOADJUVANT THERAPY FOR INFLAMMATORY AND LOCALLY ADVANCED BREAST CANCER. ASCO 2006, ABSTRACT LBA537.**

**Investigators:** G.K. Ellis et al.

**TRIAL SUMMARY:** SWOG 0012 randomized 372 women with locally advanced breast cancer (LABC) or inflammatory breast cancer (IBC, an aggressive form of LABC), prior to surgery, to receive either 5 cycles of doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide chemotherapy 600 mg/m<sup>2</sup> given intravenously every 3 weeks (standard AC), or weekly doxorubicin (24 mg/m<sup>2</sup>) for 15 weeks + oral cyclophosphamide 60 mg/m<sup>2</sup> for 15 weeks with granulocyte colony stimulating factor support (continuous or “metronomic” AC). Both groups then received weekly paclitaxel (80 mg/m<sup>2</sup>) for 12 weeks prior to surgery. In this report on 265 evaluable patients, including those who did not have surgery, 27% of the women receiving continuous AC vs 17% of those receiving standard AC had complete pathologic response (by NSABP criteria) at the primary site (p = 0.06).

Forty-one percent of patients receiving continuous AC vs 49% of those receiving standard AC had negative estrogen and progesterone status. Rates of complete pathologic response in the ER-negative/PR-negative patients receiving continuous vs standard AC were 43% vs 26%, compared to 14% vs 9% in those with positive estrogen and/or progesterone status (Table 3). When adjusted for hormone status (49% of patients were ER-negative) and disease type (locally advanced vs inflammatory), the odds ratio for the standard vs continuous AC regimen was 1.98 (95% CI 1.05–3.74, p = 0.034) — thus significantly inferior for the standard regimen. Patients with inflammatory breast cancer showed higher pathologic complete response (pCR) rates with con-

**TABLE 3. Pathologic complete response to continuous vs standard preoperative AC chemotherapy in women with locally advanced and inflammatory breast cancer**

Patient group	continuous AC	standard AC	p-value
All	27%	17%	p = 0.06 (NS)
Hormone receptor-positive	14%	9%	Not reported
Hormone receptor-negative	43%	26%	Not reported
Inflammatory disease	33%	12%	p = 0.033

tinuous vs standard AC (33% vs 12%, p = 0.33). HER2 status (29% were positive) did not predict response or interact with treatment. Regarding Grade 3-4 toxicities, 13% vs 0% of patients receiving continuous vs standard AC experienced hand-foot syndrome, and 11% vs 2% had stomatitis. Incidence of Grade 3-4 neutropenia was 16% vs 47%, of neutropenic infection 0.6% vs 1.8%, and nausea and/or vomiting 5% vs 11%. The authors concluded that continuous (metronomic) chemotherapy with AC is superior to standard AC therapy, noting the exceptionally high rate of response for this patient population, with significantly lower rates of Grade 3-4 neutropenia.

**COMMENTARY:** Susan Dent, MD, FRCPC, Medical Oncologist, The Ottawa Hospital Regional Cancer Centre and Assistant Professor of Medicine, University of Ottawa.

The treatment of IBC and LABC has been hampered by the limited number of clinical trials, particularly ones using modern day chemotherapeutic regimens. The Aberdeen trial<sup>1</sup> treated women with LABC with an anthracycline-containing regimen (CVAP: 4 cycles of cyclophosphamide + vincristine + doxorubicin + prednisone), and randomized those who responded to a further 4 cycles of CVAP or 4 cycles of docetaxel. This study clearly showed a benefit for adding taxanes in women who had experienced a response to anthracyclines (pCR 34% vs 16%). Lack of response to treatment with upfront anthracyclines was a predictor of poor outcome despite further treatment with docetaxel (pCR 2%). Current treatment of LABC has evolved to include anthracycline regimens such as AC (doxorubicin +

cyclophosphamide) followed by taxanes (docetaxel or paclitaxel) with pCR rates reported in the range of 20% to 25%. A number of questions remain: What is the best combination of drugs? how many cycles and in which order? Which is better: continuous upfront systemic treatment or a split course of chemotherapy, pre- and post-surgery? How best to treat residual disease following surgery? Is dose-intense or standard chemotherapy best, and for which subsets?

### METRONOMIC VS STANDARD AC

SWOG 0012 was a Phase III trial comparing the use of continuous or metronomic AC (with growth factor support) to standard AC, followed by conventional paclitaxel chemotherapy, in women with IBC or LABC. The study

reported significantly higher pCR rates in women who received metronomic AC (31% vs 19%,  $p = 0.02$ ) vs standard AC. Striking differences were seen in the response rates based on hormone receptor status and type of LABC: women with ER-negative/PR-negative tumours experienced significantly higher pCR rates compared to those with ER-positive/PR-positive tumours, and within these groups those receiving metronomic AC experienced higher response rates than the women receiving standard AC, although the significance levels were not reported. Metronomic AC had a significant advantage in women with IBC (pCR 33% vs 12%,  $p = 0.033$ ).

This study suggests that metronomic-type AC chemotherapy may offer an advantage to women with LABC, particularly in those with ER-negative/PR-negative tumours. Different systemic approaches may be necessary for those with hormone-sensitive disease, given the overall low pCR rate of 9% to 14%. Based on these results, SWOG has initiated a Phase III trial (SWOG 0221) of metronomic AC vs standard AC followed by paclitaxel in the adjuvant setting. Further studies are needed to determine the optimal timing and dosing of systemic therapy in women with LABC. The NCIC Clinical Trials Group is conducting a Phase I–II study (MA.22) of escalating doses of epirubicin and docetaxel given in a dose-dense (every 2 weeks) fashion, with growth factor support, in women with LABC or IBC.

The role of neoadjuvant trastuzumab in those women who overexpress HER2 needs to be explored. Lybaert et al reported, at the 5<sup>th</sup> European Breast Cancer Conference (2006), preliminary results of neoadjuvant capecitabine + docetaxel +/- trastuzumab in women with inoperable Stage III breast cancer.<sup>2</sup> This regimen showed promising clinical response rates (90%) with acceptable toxicity. The treatment of women with gross residual disease following surgery remains a challenge. Further studies such as SWOG 0012 will lead to a better understanding of how to manage this unique population of women.

### RISK ASSESSMENT IN IBC AND LABC

Two additional studies presented at this year's ASCO assist with predicting risk and response to treatment in these difficult breast cancers. Fernandez et al (Abstract 626) reported a study that determined the pCR rate in patients treated

with neoadjuvant chemotherapy (doxorubicin and docetaxel) according to ER, PR and HER2 status. Both negative hormone receptor status (ER-negative/PR-negative) and positive HER2 status predicted with significance for high pCR. Out of 100 patients, 18 achieved pCR, 9 of whom were ER-negative/PR-negative/HER2-negative and 5 were ER-negative/PR-negative/HER2-positive. Very few who were ER-positive/PR-positive/HER2-positive responded to therapy. These results are consistent with other prospective studies showing higher pCR rates in women receiving neoadjuvant chemotherapy for ER-negative/PR-negative tumours and much less benefit in those with hormone receptor-positive disease.

Symmans et al (Abstract 536) considered residual tumour burden following surgery as a potential predictor of survival after neoadjuvant chemotherapy. They reviewed pathological slides from 432 patients in 2 neoadjuvant trials: 189 received FAC (fluorouracil + doxorubicin + cyclophosphamide) and 243 received paclitaxel + FAC. Residual Cancer Burden (RCB) was calculated as an index that combined size and cellularity measurements of the primary tumour, and number and size of nodal metastases. The pCR rates were higher with paclitaxel + FAC vs FAC alone (24% vs 16%,  $p < 0.05$ ) and after weekly vs q 3-weekly paclitaxel (30% vs 16%,  $p = 0.01$ ). In patients with residual disease, RCB measurements were lower in those who had received paclitaxel + FAC vs FAC alone ( $p < 0.0001$ ). RCB score was a continuous predictor of distant relapse-free survival after paclitaxel + FAC (HR 1.86, 95% CI 1.51–2.30) or FAC (HR 1.67, 95% CI 1.38–2.01) with a median followup of 5 and 8 years. RCB score of -3 (representing chemoresistance) was a stronger predictor of relapse compared to TNM stage and identified a larger group of high-risk patients. This is one of the first retrospective studies to look at how to assess the risk of women with residual disease following systemic therapy, and RCB is a tool that warrants further exploration and validation in prospective studies.

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## Breast cancer: chemotherapy-related cardiotoxicity

### CONGESTIVE HEART FAILURE (CHF) IN OLDER WOMEN TREATED WITH ANTHRACYCLINE (A) CHEMOTHERAPY (C). ASCO 2006, ABSTRACT 521.

Investigators: S.H. Giordano et al.

**TRIAL SUMMARY:** This was an observational, retrospective examination of long-term cardiotoxicity in 34,621 women with breast cancer between the ages of 66 and 90 years, comparing 3 groups: Group 1 patients treated with anthracycline chemotherapy ( $n = 2728$ ), Group 2 received non-anthracy-

cline chemotherapy ( $n = 3253$ ) and Group 3 had no chemotherapy ( $n = 28,640$ ). Five- and 10-year cumulative rates of congestive heart failure (CHF) and factors predictive of CHF were estimated using multivariate Cox regression analysis. As a group, the women who received anthracycline chemotherapy

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were younger and had fewer comorbidities but more advanced disease than those treated with non-anthracycline chemotherapy ( $p < 0.001$ ) or who received no chemotherapy ( $p < 0.001$ ). **Table 4** shows the occurrence of CHF in the younger women, aged 66–70 years. The adjusted HR for anthracycline chemotherapy vs other chemotherapy was 1.45 (95% CI 1.19–1.76), and for no chemotherapy vs other chemotherapy it was 0.97 (95% CI 0.82–1.14). In the women older than age 70, differences in rates of CHF were not statistically significant, however, the authors note that selection biases were likely stronger in this group. Other significant predictors of CHF included black race, increasing comorbidity, preexisting hypertension and peripheral vascular disease. Thus, women aged 66–70 treated with anthracycline chemotherapy had signifi-

**TABLE 4. Rates of CHF in women aged 66–70 with breast cancer**

followup	anthracycline chemotherapy	other chemotherapy	no chemotherapy
5 years	19%	14%	12%
10 years	47%	33%	28%

cantly higher rates of CHF, increasing over the 10 years of followup, despite better general health.

## LONG TERM CARDIAC TOLERABILITY OF TRASTUZUMAB IN HER-2-OVEREXPRESSING METASTATIC BREAST CANCER (MBC). ASCO 2006, ABSTRACT 629.

**Investigators:** V. Guarneri et al.

**TRIAL SUMMARY:** This study looked at cardiac toxicity in 173 evaluable patients out of 218 women with metastatic breast cancer who received trastuzumab for at least a year. Cardiotoxicity grading was by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. Median age was 50 years (range 26–79) when trastuzumab therapy began, median cumulative time on trastuzumab was 21.3 months (11.6–77.6) and median followup was 32.2 months (9.7–79.0). The majority of women (85%) had received prior anthracycline chemotherapy with a median cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin.

Short-term cardiac events occurred in 49 (28%) of patients: 3 (1.7%) had an asymptomatic 20% decrease in left ventricular ejection fraction (LVEF), 27 (15.6%) had Grade 2 cardiac toxicity, 18 (10.4%) had Grade 3 cardiac toxicity

and 1 died (0.5%). Cardiac event-free survival was 87.3% at 1 year. After stopping trastuzumab and/or receiving appropriate therapy, all but 4 had improved LVEF or CHF symptoms. Following recovery, 26 patients resumed trastuzumab therapy, and 16 of these had no further cardiac events. The only factor significantly associated with cardiac events was concomitant taxane chemotherapy (HR 4.37, 95% CI 1.06–17.98,  $p = 0.04$ ). Women who were on prior anthracycline chemotherapy did not experience significantly more cardiac events. The authors concluded that long-term trastuzumab-based therapy confers an acceptable and usually reversible risk of cardiac toxicity, that resumption of trastuzumab can be considered after recovery of cardiac function and that further study is needed regarding the risk of cardiotoxicity associated with taxane administration.

**COMMENTARY:** Susan Dent, MD, FRCPC, Medical Oncologist, The Ottawa Hospital Regional Cancer Centre and Assistant Professor of Medicine, University of Ottawa.

### CONCERN OVER LONG-TERM CARDIAC EFFECTS OF ANTHRACYCLINES

Modern systemic therapies have led to gains in both disease-free (DFS) and overall survival (OS) in women with early-stage breast cancer. The anthracyclines remain one of the most active classes of agents in the treatment of early and advanced breast cancer. The potential short-term cardiotoxic effects of anthracyclines have been extensively reported in the literature; however there is little data on long-term cardiac morbidities and/or events. Giordano et al reported a population-based observational study from SEER (Surveillance, Epidemiology, and End Results, a program of the U.S. National Cancer Institute) on the 5- and 10-year cumulative rates of CHF in women over the age of 65, diagnosed with early-stage breast cancer between 1992 and 1999, who received anthracycline vs non-anthracycline chemotherapy vs no chemotherapy. Women aged 66–70 who had been treated with anthracycline-based chemother-

apy were more likely to be diagnosed with CHF at 5 years (19% vs 14%) and 10 years (47% vs 33%) compared to those receiving non-anthracycline-based chemotherapy (12%) or no chemotherapy (28%). No statistically significant difference in CHF rates in women over the age of 70 was seen; however it is likely that fewer women in this group received systemic chemotherapy. This observational study clearly highlights the potential long-term detrimental cardiac morbidity associated with anthracyclines, thus supporting the exploration of effective non-anthracycline regimens in this setting as well as the use of less cardiotoxic anthracyclines (e.g. liposomal doxorubicin), particularly in the elderly.

Shepherd et al (Abstract 522) presented a study highlighting the potential long-term cardiac risks of anthracyclines. Between 1989 and 1993, 710 perimenopausal women with node-positive breast cancer were randomized in the NCIC-CTG

*continued on page 24*

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MA.5 study to receive CEF (oral cyclophosphamide 75 mg/m<sup>2</sup> Days 1–14 + epirubicin 60 mg/m<sup>2</sup> Days 1 and 8 + fluorouracil 500 mg/m<sup>2</sup> Days 1 and 8) or CMF (oral cyclophosphamide 100 mg/m<sup>2</sup> Days 1–14 + methotrexate 40 mg/m<sup>2</sup> Days 1 and 8 + fluorouracil 500 mg/m<sup>2</sup> Days 1 and 8). Baseline LVEF was captured in 100% of women at baseline and in 64% by 60 months, at which time decreases of greater than 10% were seen in up to 25% of patients receiving CEF (cumulative epirubicin dose of 720 mg/m<sup>2</sup>) therapy and in 9% of those receiving CMF. In the CEF group, 4/8 patients with LVEF declines of greater than 20% developed CHF, while no CHF was reported in the CMF group.

## TRASTUZUMAB CARDIAC EFFECTS APPEAR MANAGEABLE

The addition of trastuzumab to systemic chemotherapy in women with HER2-overexpressing tumours represents a significant advance in the treatment of women with breast cancer, however there are significant concerns with regards to the potential short- and long-term cardiac toxicities of this treatment. Guarneri et al examined the rate of cardiac events in women with metastatic breast cancer receiving trastuzumab for at least 1 year. Of 173 evaluable patients, 49 (28%) experienced a cardiac event. Most were not life threatening and resolved upon discontinuation of trastuzumab, with or without other medical management. Twenty-six patients were able to resume trastuzumab therapy, the majority experiencing no further cardiac events. Prior anthracycline use was not associated with increased risk. Patients receiving concomitant taxanes were more likely to experience a cardiac event, something not observed in adjuvant studies and thus requiring further investigation.

In the adjuvant setting, the NSABP B-31 study compared AC + paclitaxel with or without trastuzumab. The 3-year cumulative incidence of cardiac events (Class III–IV CHF or death) was 4.1% with trastuzumab vs 0.8% without.<sup>1</sup>

Four-year cumulative cardiac toxicity rates, presented by Geyer et al at this meeting (Abstract 581), have remained stable for both arms: 3.9% with trastuzumab vs 0.8% without, thus alleviating the concern that the incidence of trastuzumab-related cardiotoxicity may increase over time.

Dose-dense chemotherapy is now a common systemic approach for the treatment of women with early-stage breast cancer, however there is little data on the cardiotoxicity of trastuzumab administered with this schedule. Dang et al (abstract 582) examined dose-dense AC followed by paclitaxel and trastuzumab. Seventy HER2-positive patients were treated with 4 cycles of adjuvant dose-dense (q 2-weekly) AC followed by paclitaxel, and 1 year of trastuzumab. Patients were monitored by Multi-Acquisition Gated (MUGA) scan at baseline and months 2, 6, 9 and 18. The median LVEF at baseline was 68% and to date the median LVEF is 66% (n = 39) at 6 months and 64% (n = 23) at 9 months. One patient had clinical CHF at 4 months (LVEF 45%) and improved significantly after receiving appropriate cardiac medication. Based on this preliminary data there appears to be no significant cardiac toxicity from the addition of trastuzumab to dose-dense chemotherapy, however further followup will be needed.

In summary, trastuzumab has led to significant gains in DFS and OS in women with HER2-overexpressing early-stage breast cancer. The additional cardiotoxicity seen in women receiving adjuvant trastuzumab appears to be manageable and in many instances reversible. The approach to diagnosis and management of cardiac events and/or morbidity (e.g. declines in LVEF) needs to be standardized in order to maximize the potential benefit of trastuzumab in these women without compromising their cardiac health.

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## Breast cancer: switching hormonal therapies

### MORTALITY BENEFIT OF SWITCHING TO AN AROMATASE INHIBITOR IN EARLY BREAST CARCINOMA: POOLED ANALYSIS OF TWO CONSECUTIVE TRIALS. ASCO 2006, ABSTRACT 548.

Investigators: F.M. Boccardo et al.

**TRIAL SUMMARY:** This was an update and pooled analysis of mortality in 2 similar trials: GROCTA 4 (Italian cooperative group for chemohormonal therapy of early breast cancer) and ITA (Italian tamoxifen Arimidex) trials. Women who had already received 2–3 years of tamoxifen were randomized to 1 of 3 treatments: continue tamoxifen, switch to aminoglutethimide or switch to anastrozole for another 3–2 years, for a total 5 years of hormonal therapy. The analysis included 828 postmenopausal women with ER-positive tumours, most of them also node-positive, who had been followed up for a median time of 68 months (range 1–141 months).

**TABLE 5. Mortality benefit of switching to an aromatase inhibitor after 2–3 years of tamoxifen vs 5 years tamoxifen**

	hazard ratio	95% confidence interval	p value
All-cause mortality	0.60	0.41–0.87	p = 0.007
Breast cancer-specific mortality	0.62	0.39–0.97	p = 0.03

Switching significantly improved all-cause mortality (HR 0.60, 95% CI 0.41–0.87,  $p = 0.007$ ) and breast cancer-specific mortality (HR 0.62, 0.39–0.97,  $p = 0.03$ ) (Table 5). The difference in deaths not related to breast cancer was not significant. Age, tumour size, treatment allocation and nodal status all independently predicted mortality. The

same factors, with the exception of age, independently predicted breast cancer-related mortality. The authors concluded that switching to an aromatase inhibitor after 2–3 years of tamoxifen significantly improves survival, as compared to 5 years of tamoxifen.

**SURVIVAL BENEFIT OF SWITCHING TO ANASTROZOLE AFTER 2 YEARS’ TREATMENT WITH TAMOXIFEN VERSUS CONTINUED TAMOXIFEN THERAPY: THE ARNO 95 STUDY. ASCO 2006, ABSTRACT 547.**

**Investigators:** M. Kaufmann et al.

**TRIAL SUMMARY:** This was an interim analysis of the ARNO 95 study, a prospective, open-label comparison of women with early breast cancer randomized to either switch to anastrozole for 3 more years after 2 years of tamoxifen or continue tamoxifen therapy for 3 more years, for a total of 5 years of hormonal therapy in both arms. Study participants were 979 postmenopausal hormone receptor-positive breast cancer patients, without recurrence after 2 years on tamoxifen, who received no adjuvant chemotherapy. Their mean age was 60 years, 74% had node-negative tumours and 97% had hormone receptor-positive disease. At median followup of 30.1 months, DFS, the primary endpoint, and OS improved significantly in the switching group compared to those who remained on tamoxifen (Table 6). As well, the patients who switched to anastrozole had fewer serious adverse events (22.7%) compared with those who remained on tamoxifen (30.8%).

**TABLE 6. Survival benefit of switching to anastrozole after 2 years of tamoxifen vs 5 years of tamoxifen**

	estimated hazard ratio 95% confidence interval p value	
	by log-rank test	by Cox proportional hazard model
Disease-free survival	0.66 0.44–1.00 $p = 0.049$	0.61 0.40–0.93 $p = 0.023$
Overall survival	0.53 0.28–0.99 $p = 0.045$	0.48 0.25–0.91 $p = 0.025$

**FIRST MATURE ANALYSIS OF THE INTERGROUP EXEMESTANE STUDY. ASCO 2006, ABSTRACT LBA527.**

**Investigators:** R.C. Coombes et al.

**TRIAL SUMMARY:** The Intergroup Exemestane Study (IES) randomized 4724 postmenopausal women with ER-positive or ER-unknown tumours who had no recurrence after 2–3 years on tamoxifen to either switch to exemestane or remain on tamoxifen, for a total of 5 years of adjuvant hormonal therapy. At this report, 95% of patients had  $\geq 3$  years followup (median 56 months), and 22 women originally considered to be ER-unknown had been reclassified as ER-negative. In women with positive or unknown ER status, after adjusting for nodal status, use of chemotherapy and hormonal therapy,

the HR for DFS was 0.74 (95% CI 0.64–0.85,  $p < 0.0001$ ) and for OS it was 0.83 (95% CI 0.69–0.99,  $p = 0.04$ ). Non-breast cancer-related deaths included 14 cardiac deaths of patients on exemestane vs 13 on tamoxifen, 17 vs 11 vascular deaths and 20 vs 35 deaths from other cancers, including uterine. Differences in rates of myocardial infarctions, angina and cerebrovascular accidents were not statistically significant. More patients on tamoxifen had thromboembolic and serious gynecologic events. Patients on exemestane experienced more fractures (7% vs 4.8%,  $p = 0.003$ ).

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

Aromatase inhibitors (AIs) are integral drugs for adjuvant therapy of postmenopausal breast cancer, and are indicated either as upfront therapy or after some years of tamoxifen — the optimal strategy remains unknown. The incorporation of an AI as adjuvant treatment has improved DFS compared to tamoxifen treatment alone and now there is

evidence for a survival benefit to switching to an AI for 2–3 years after 2–3 years of tamoxifen.

**THE LATEST EVIDENCE**

The first analysis, presented by F. Boccardo, is a pooled analysis of 2 Italian trials using 2 different aromatase inhibi-

tors, the first-generation AI aminoglutethimide, and the third-generation anastrozole. With a median followup of almost 7 years, switching to an AI after 2–3 years of tamoxifen improved OS with a 40% relative reduction in the risk of death, compared to 5 years of tamoxifen alone. A similar study by Kaufmann et al in a lower-risk population and for a shorter median followup of 2½ years also showed statistically significant improvement in survival with the switching strategy (> 40% reduction in death). In the IES, the largest of the switching trials (n = 4724), with a median followup of 56 months, 2.4% of women had ER-negative breast cancers. DFS improved significantly in the ITT population and in the ER-positive or ER-unknown populations, with a 25% relative improvement in women switching to exemestane. Although OS was not statistically different in the ITT population, the women with ER-positive or ER-unknown cancers had a 17% relative reduction in the risk of death if they switched to the AI (HR 0.83, 95% CI 0.69–1.00, p = 0.04). Safety information was updated and, reassuringly, no differences were seen in ischemic cardiac events between the 2 groups.

These updated results illustrate the emerging, albeit modest, survival benefit of the tamoxifen-to-AI switch strategy and the continued reduction in the risk of breast cancer recurrence. The overall side effect profile also favours this strategy. The biologic reason for the benefit is unknown, but it may be that tamoxifen sensitizes breast cancers to estrogen deprivation. Despite this wealth of information, unanswered questions still remain: which strategy is best for incorporating AIs; what is the optimal duration of AI treatment; and, are the 3 commonly used AIs equivalent?

## HOW TO HANDLE REMAINING QUESTIONS

### Best strategy

How to best incorporate AIs into therapy remains unclear. Two large Phase III trials have compared upfront AI use for 5 years to 5 years of tamoxifen alone, and although AI use improves DFS, an overall survival benefit has yet to emerge.<sup>1,2</sup> By comparison, the switching strategy appears superior as several large Phase III trials have now reported OS benefit. Importantly, however, trials of switching cannot be directly compared to trials of upfront AI use because the study populations are different: the switching trials include patients with more endocrine-sensitive disease as none of them relapsed in the first 2–3 years of endocrine therapy with tamoxifen. Unfortunately, no patient or tumour characteristic can currently guide the choice of strategy. The BIG I-98 trial may give us the answer but not until 2008, at the earliest. This trial compares outcomes of 4 different treatments: 5 years of letrozole, 5 years of tamoxifen, 2–3 years of tamoxifen followed by 2–3 years of letrozole, and 2–3 years of letrozole followed by 2–3 years of tamoxifen.

Current practice suggests the use of an AI upfront in patients at high risk of early relapse. The natural history of hormone receptor-positive breast cancer is very long, however, and at least in patients treated with 5 years of tamoxifen, more than half of breast cancer recurrences are in years

6 to 15.<sup>3</sup> Therefore, the switch strategy appears a very reasonable option in women with endocrine-sensitive breast cancers.

### Duration

The optimal duration of AI use is also unknown. Currently there is no evidence for more than 2–3 years of AI use after 2–3 years of tamoxifen. The NSABP is addressing this question of extended AI use after initial AI exposure in the NSABP B42 trial that is just starting. As previously noted, an ongoing lifetime risk of recurrence likely remains after completion of 5 years of endocrine therapy, especially in those women with higher-risk disease at diagnosis. The NCIC MA.17 trial<sup>4</sup> addressed the issue of extended endocrine therapy with letrozole after completion of 5 years of tamoxifen in postmenopausal women. This trial showed the incremental benefits of extended therapy with the AI in terms of DFS and, in lymph node-positive patients, improved OS. The updated analysis of this trial prior to unblinding, recently presented by Ingle et al,<sup>5</sup> showed continued benefit of the AI with extended duration of use. Obviously one cannot use the MA.17 trial results to decide the appropriate duration of endocrine therapy after AI exposure in the first 5 years, as this trial did not address this question. It is reasonable, nonetheless, to discuss continuing use of aromatase inhibitors after the first 5 years of endocrine therapy, especially in those women who remain at high risk of relapse, while balancing expected benefits with the potential toxicities.

### Which AI?

Finally, are the commonly used AIs, namely anastrozole, exemestane and letrozole equivalent? All suppress the aromatase enzyme but have different potencies, with letrozole being the most potent AI of the 3 in vitro. At the 2006 ASCO, Dixon et al (Abstract 552) reported that letrozole suppressed estradiol (E<sub>2</sub>) levels more than anastrozole in 54 postmenopausal women with ER-positive breast cancers. These women were randomized to 12 weeks of letrozole followed by 12 weeks of anastrozole or 12 weeks of anastrozole followed by 12 weeks of letrozole. E<sub>2</sub> levels were determined before and after 12 weeks of each drug. The mean E<sub>2</sub> level after anastrozole was 2.91 pmol/L and after letrozole it was 1.76 pmol/L. The clinical implications of this biochemical observation remain unknown. In the metastatic setting, anastrozole was compared to letrozole in women whose tumours progressed on tamoxifen.<sup>6</sup> No differences were seen in terms of time to tumour progression although response rates were higher with letrozole. The ongoing NCIC MA.27 adjuvant trial comparing the efficacy of anastrozole to exemestane is still accruing patients, so results will not be available for many years.

## CLINICAL IMPLICATIONS

In clinical practice, it is reasonable to recommend the AI that was most studied in that particular setting and that demonstrated efficacy in randomized trials. For example, there is data for the upfront use of anastrozole and letrozole but the data on anastrozole is more mature for efficacy

and, importantly, for safety. Similarly, after 2–3 years of tamoxifen, there is data for the use of exemestane and anastrozole for 2–3 years with fairly mature followup data for both drugs. However, the IES trial using exemestane included the largest numbers of women. For extended AI use after 5 years of tamoxifen, there is evidence for benefit with letrozole and to a smaller extent with anastrozole.

In summary, AIs should be incorporated into adjuvant therapy in postmenopausal women with endocrine-sensitive breast cancers. The optimal strategy is unknown but switching to an AI after 2–3 years of tamoxifen has shown survival benefits and an overall favourable safety profile. The optimal duration of AI use similarly remains unknown, but in the absence of a clinical trial it is reasonable to discuss extended AI use, especially in women who remain at higher risk of relapse after 5 years of initial endocrine therapy.

py. With this plethora of treatment options, the outlook for women with early-stage breast cancer continues to flourish.

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## Breast cancer: hormonal therapies and bone health

### ANALYSIS OF FRACTURE RISK FACTORS FROM THE 'ARIMIDEX', TAMOXIFEN, ALONE OR IN COMBINATION (ATAC) TRIAL: 5-YEAR DATA. ASCO 2006, ABSTRACT 563.

**Investigators:** A. Howell et al.

**TRIAL SUMMARY:** This study analyzed the impact of many known factors for skeletal fracture risk on actual fracture rates in the ATAC (Arimidex, tamoxifen alone or in combination) trial, which was 8.8% overall (548 out of 6186). Using the Cox proportional hazards model, statistically significant predictors of fracture were older age, higher-risk geographic region and treatment with anastrozole (as opposed to tamoxifen) (Table 7). Statin use was associated with significantly lowered fracture risk. Non-significant predictive factors included body mass index, previous hormone replacement therapy, smoking status and other medications (including calcium, Vitamin D, corticosteroids, thyroid hormones and bisphosphonates). The researchers concluded that identification of individuals at high risk of fracture at diagnosis before starting AIs is essential to ensure appropriate evaluation of this side effect and its treatment.

**TABLE 7. Predictors of fracture risk in the ATAC trial**

Risk factor	number of patients	hazard ratio	95% confidence interval
Treatment			
tamoxifen	3094	-	-
anastrozole	3092	1.54	1.30-1.84
Age			
< 60 years	2195	-	-
60-70 years	2329	1.41	1.13-1.76
> 70 years	1662	2.17	1.74-2.70
Region			
low or moderate risk	628	-	-
high risk	3904	1.15	0.82-1.60
very high risk	1654	2.25	1.60-3.16
Statin use			
no	5398	-	-
yes	788	0.62	0.47-0.81

### EFFECT OF ANASTROZOLE ON BONE MINERAL DENSITY: 5-YEAR RESULTS FROM THE 'ARIMIDEX', TAMOXIFEN, ALONE OR IN COMBINATION (ATAC) TRIAL. ASCO 2006, ABSTRACT 511.

**Investigators:** R.E. Coleman et al.

**TRIAL SUMMARY:** This was a 5-year report of bone mineral density (BMD) results in the women in the ATAC trial who took anastrozole only (n = 81) or tamoxifen only (n = 86). Assessments of lumbar spine and total hip BMD were made at baseline and after 1, 2, and 5 years, using

dual-energy X-ray absorptiometry (DEXA) (Table 8, page 28). The treatment effect of anastrozole relative to tamoxifen was -8.1 (95% CI -10.1 to -6.1, p < 0.0001) for lumbar spine and -7.4 (95% CI -9.6 to -5.3, p < 0.0001) for total hip. The rate of BMD loss in the lumbar spine declined from

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years 2 to 5 ( $p = 0.0002$ ) compared to the first 2 years but no slowing of loss of hip BMD was noted. Among women who were osteopenic at baseline, 15% of those on anastrozole became osteoporotic vs 4% of those on tamoxifen. None of the women with normal baseline BMD were osteoporotic at 5 years.

**TABLE 8. BMD changes in ATAC trial participants**

	lumbar spine median BMD (range)		total hip median BMD (range)	
	anastrozole	tamoxifen	anastrozole	tamoxifen
2 years from baseline	-4.0 (-13.3 to 2.4)	+2.1 (-7.6 to 11.1)	-3.9 (-12.7 to 8.1)	1.2 (-8.9 to 11.5)
5 years from baseline	-6.1 (-17.7 to 2.6)	+2.8 (-12.7 to 17.7)	-7.2 (-20.4 to 3.8)	+0.7 (-1.4 to 9.2)

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

The toxicities of AIs must be balanced with their efficacy, and of most concern is the increased likelihood of osteoporosis and subsequent fracture risk. Although ischemic cardiac events have numerically been more prevalent in women receiving an AI compared to those taking tamoxifen, their incidence may be similar to that with placebo, as tamoxifen may in fact confer a protective cardiac effect. These 2 abstracts by Howell and Coleman both explore the issue of bone health as analyzed in the ATAC trial.<sup>1</sup>

At a median followup of 68 months, anastrozole increased the risk of osteoporosis and fractures compared to the risk with tamoxifen: 11% of women on anastrozole experienced a fracture vs 7.7% of those on tamoxifen (HR 1.54). Not surprisingly, treatment with anastrozole and older age were strong predictors of fracture. Of interest, statin use was associated with decreased fracture risk but this may be due to related factors, not specifically to the drug. Coleman describes BMD changes in a subgroup of 167 ATAC trial participants. Bone turnover markers, urine N-telopeptide and bone alkaline phosphatase were also measured. Anastrozole decreased L-spine BMD by 2% per year in years 1 and 2 and 1% per year in years 2–5. Conversely, tamoxifen increased BMD, especially in the first 2 years. A similar pattern emerged for hip BMD. Importantly, no patient with normal BMD at baseline became osteoporotic after 5 years of anastrozole therapy. Also, if women were osteopenic at baseline, very few became osteoporotic after 5 years of therapy, although more did so in the anastrozole-treated group (15%) compared to the tamoxifen group (4%). Anastrozole increased bone turnover markers and tamoxifen suppressed them. Increased levels of these markers appeared to be associated with greater BMD loss. Although fracture rates were increased on anastrozole, there was a suggestion that these rates declined once anastrozole was finished, but the numbers were too small to be definitive.

## RECOMMENDATIONS FOR MONITORING

Based on these presentations, one can conclude that women on AIs have an increased risk of fractures and that certain women may be at higher risk and should be closely monitored. Although bone turnover markers may predict changes in BMD, they are not ready for practical clinical use. Reassuringly, women with baseline normal BMD

exams did not become osteoporotic after 5 years of anastrozole therapy. Although these results specifically examined fracture risks from anastrozole, all trials of AIs demonstrate increased fracture risk.

Physicians can refer to the American Society of Clinical Oncology Guidelines<sup>2</sup> for screening and treatment of osteoporosis. Postmenopausal women on AIs are considered to be high-risk and annual BMD is recommended, although this may need to be revised in light of the data from the ATAC bone subprotocol, especially in women with normal baseline BMD. Of note, the most reliable indicator of fracture risk is the T score on the BMD exam, defined as the number of standard deviations above or below the mean BMD for normal young adults. Studies exploring the best strategy for incorporating a bisphosphonate into therapy are underway. All women should be advised regarding exercise, smoking cessation and supplemental therapy with calcium and vitamin D — and use of bisphosphonates if bone density is decreasing on AIs.

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## Breast cancer: biological therapies and EGFR

### SERUM HER-2/NEU CHANGE PREDICTS CLINICAL OUTCOME TO TRASTUZUMAB-BASED THERAPY. ASCO 2006, ABSTRACT 500.

Investigators: S.M. Ali et al.

**TRIAL SUMMARY:** In this pooled analysis of 7 trials of first-line trastuzumab therapy given with or without chemotherapy for metastatic breast cancer, HER2 levels were measured by ELISA before and 16–120 days after treatment in 307 women, with survival data available on 236. Overall, serum HER2 levels decreased a median 31% (range: 98% decrease to 239% increase). The women with more than a 20% decrease in HER2 levels had significantly higher objective response rate (ORR, complete + partial response), longer duration of response, time to progression, and overall survival (Table 9). Timing of the second HER2 measurement did not affect these results. The authors concluded that patients with less than a 20% decrease in serum HER2 levels derive decreased benefit from trastuzumab therapy and should be considered for alternative HER2-targeted therapies.

**TABLE 9. Outcomes associated with HER2 level decrease from baseline in metastatic breast cancer patients treated with trastuzumab**

	> 20% decrease	< 20% decrease	p value
Overall response	56.5%	28.4%	p < 0.001
Median duration of response	369 days	330 days	p = 0.008
Median time to progression	320 days	182 days	p < 0.001
Median overall survival	898 days	593 days	p = 0.018

### EGFR EXPRESSION IN BREAST CANCER: ASSOCIATION WITH BIOLOGIC PHENOTYPE, PROGNOSIS, AND RESISTANCE TO ADJUVANT THERAPY. ASCO 2006, ABSTRACT 513.

Investigators: M.F. Rimawi et al.

**TRIAL SUMMARY:** To examine whether epidermal growth factor receptor (EGFR) expression is associated with more aggressive and treatment-resistant breast cancer, this group evaluated the tumours of 2567 cases for which the EGFR levels were known from a database of 54,865 patients with breast cancer. A central lab performed ligand binding assay on frozen tissue. A total of 475 tumours (18.5%) were positive based on a prospectively-determined cutoff value of > 10 fmol/mg of cytosol protein.

The rate of EGFR-expressing tumours was higher in patients who were < 50 years old (40% vs 24%, p < 0.0001), premenopausal (20% vs 10%, p < 0.0001) and of African-American origin (10% vs 6%, p = 0.005) (Table 10). Tumours were more likely to be positive if larger (64% vs 46%, p < 0.0001), aneuploid (68% vs 46%, p < 0.0001), with high S-phase fraction (53% vs 22%, p < 0.0001) and with nodal involvement (43% vs 37%, p = 0.009). EGFR-expressing tumours were more likely to be HER2-positive (26% vs 16%, p < 0.0001), less likely to be estrogen receptor positive (60% vs 88%, p < 0.0001), and less likely to be progesterone receptor positive (26% vs 65%, p < 0.0001). Multivariate analysis showed independent correlation of EGFR expression with worse disease-free survival (DFS) (HR 1.6, 95% CI 1.2–2.2, p = 0.001) and overall survival (OS) (HR 1.7, 95% CI 1.2–2.4, p = 0.001) in treated

**TABLE 10. Association of high-risk breast cancer phenotype with EGFR expression**

	EGFR-negative
Age < 50	40%
African American	10%
Caucasian	87%
Tumour > 2 cm	64%
Aneuploidy	68%
High S-phase fraction	53%
Positive nodes	43%
HER2 expression	26%
ER-/PR-	37%

patients (n = 1256), but not in untreated patients (n = 1068). The authors concluded that blocking EGFR may help overcome the resistance of EGFR-expressing tumours to chemotherapy.

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## LANDMARKS

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### PHASE II TRIAL OF LAPATINIB FOR BRAIN METASTASES IN PATIENTS WITH HER2+ BREAST CANCER. ASCO 2006, ABSTRACT 503.

**Investigators:** N.U. Lin et al.

**TRIAL SUMMARY:** This was an open-label Phase II evaluation of lapatinib (750 mg po bid), an oral inhibitor of EGFR and HER2, in 39 patients with HER2-positive breast cancer who had brain metastases and at least one low-density brain lesion > 1.0 cm in diameter. The primary endpoint was objective response of the brain lesions: complete and partial, measured by MRI every 8 weeks and by FDG-PET scans at baseline, week 1 and week 8, using

Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Two patients achieved a partial response by RECIST, and 5 achieved stable disease after more than 16 weeks. Median time to treatment failure was 3.2 months (95% CI 2.3–3.8). The most common adverse events were Grade 3 diarrhea (21%), fatigue (16%) and rash (5%). The authors concluded that lapatinib appears to penetrate the CNS and is well tolerated, warranting further studies.

**COMMENTARY:** Joseph Ragaz, MD, FRCPC, Director, Oncology Program, McGill University Health Centre, Montréal, QC.

As in recent years, biological therapies continued to dominate breast cancer advances reported at this year's ASCO. Trastuzumab is rapidly becoming guideline-recommended therapy for adjuvant treatment of HER2-expressing breast cancers, while new data is emerging on therapies effective in trastuzumab-resistant tumours, notably lapatinib.

#### NEW TRASTUZUMAB DATA

At a special scientific session Ian Smith provided an update of the European HERA (HERceptin® Adjuvant) trial, now with 2 years' median followup.<sup>1</sup> For the first time in this study, trastuzumab shows a significant OS advantage compared to observation only (97.4% vs 89.7%; HR 0.66,  $p = 0.015$ ), in addition to the significant DFS improvement seen in previous reports.<sup>2</sup> This confirms that DFS is a good surrogate for OS — as previously seen with adjuvant chemo-hormonal therapy<sup>3</sup> and radiotherapy.<sup>4,5</sup> It is an issue of particular importance because in the HERA and other trastuzumab trials many patients in the control, non-trastuzumab arm crossed over to trastuzumab. In HERA, the analysis included both intention-to-treat (ITT) as well as the censored analyses at the time of crossover. Both show a significant avoidance of relapses ( $p < 0.001$ ), with HRs of 0.60 (ITT) and 0.63 (censored). For OS, there was a 36% reduction of deaths (HR 0.66,  $p = 0.015$ ) in the ITT analysis, and a similar survival benefit for the censored analysis (HR 0.63,  $p = 0.005$ ). These data therefore confirm that giving trastuzumab after completion of chemotherapy provides mortality reduction similar to that when it is given concurrently with chemotherapy, as reported in the NSABP & NCCTG 2005 joint trial analysis which showed a 33% reduction in the risk of death ( $p = 0.015$ )<sup>6</sup> and in the FinHer trial (HR for recurrence or death 0.42, 95% CI 0.21–0.83;  $p = 0.01$ ).<sup>7</sup>

#### TRASTUZUMAB RESISTANCE

The issues dominating trastuzumab therapy include resistance, optimal duration of treatment and the predictive worth of biomarkers. G. Sledge summarized trastuzumab resistance in a special scientific session, outlining the main factors: a truncated HER2 receptor, target proteins such as PTEN, cMYC and topo2a, and alternative signaling markers such as IGF-IR, Ras, Raf, mTOR and VEGF.<sup>8</sup>

#### Truncated HER2 receptors

Studies confirm the inability of trastuzumab to bind to truncated HER2 receptors. Baselga and colleagues, Sledge reported, have transfected breast cancer cell lines with a truncated form of HER2 (p95HER-2), documenting no response to trastuzumab, while transfection with a full HER2 receptor (p185HER-2) scored a high degree of trastuzumab response. It appears very likely that trastuzumab is unable to bind to a damaged receptor — a limitation not seen with lapatinib.

#### Target proteins

Nagata et al previously identified significantly different response rates to trastuzumab of 65% vs < 10%, according to PTEN expression.<sup>9</sup> S. Paik's group recently reanalyzed the data from the NSABP trastuzumab trial according to cMYC expression, documenting significantly higher DFS among cMYC-positive cases than in those without coexpression of cMYC and HER2.<sup>10</sup> Lastly, Slamon et al recently reported a significant interaction between topo2a and stronger response to trastuzumab among anthracycline-treated patients.<sup>11</sup> These data indicate an urgent need to reanalyze all adjuvant trastuzumab trials according to PTEN, cMYC and topo2a expression.

#### Alternative signaling by pathways

Alternative signaling by pathways such as IGF-IR, or Ras-Farnesyl transferase inhibitors, AKT and Raf, mTOR and (importantly) VEGF, are increasingly implicated in the mechanism of HER2-mediated responses of trastuzumab, and can each potentially be inhibited, bringing issues of combined, multitargeted therapy — a cocktail of biologicals — into the forefront of research endeavors.

#### EFFECT OF TRASTUZUMAB ON SERUM HER2 PREDICTS RESPONSE

At this year's ASCO, Ali et al reported that women whose HER2 expression level decreased after treatment with trastuzumab by more than 20% had double the response rate (56.5%) compared to those with a decrease of less than 20% (28.4%,  $p < 0.001$ ). Time to progression and OS also significantly improved (Table 9, page 29).

Several studies have shown a growing importance of HER1 in breast cancer, particularly if coexpressed with HER2. Thus, studies of dual HER1 and HER2 inhibition showing benefit confirm the need to suppress both pathways. Rimawi et al reported on the association of expressed EGFR-1 (HER1) in one of the largest studies on the subject. In over 54,860 patients in the database of Baylor College in Houston, TX, among whom EGFR status was known in 2567 cases, 82% were EGFR-negative and 18% (475 patients) were EGFR-positive. Stronger EGFR expression was significantly associated with a high-risk breast cancer phenotype, which was in turn associated with young age (< 50 years), African American racial origin, large tumour size, high S-phase fraction, HER2-expression and ER-negative/PR-negative tumour phenotype (Table 10, page 29). EGFR expression had no impact on outcome among cases not receiving therapy, but among patients treated with chemohormonal therapy, EGFR expression was associated with a significantly higher rate of relapse (HR 1.6,  $p = 0.001$ ) and of death (HR 1.7,  $p = 0.001$ ). These data indicate that the association of EGFR with high-risk breast cancer phenotype is of interest not only regarding disease biology and epidemiology, but also because it may predict the effect of chemohormonal therapy. The EGFR data are especially relevant to understanding lapatinib's mode of action.

## LAPATINIB

Studies correlating inhibition of the EGFR's tyrosine kinase receptor by the dual HER2 and HER1 inhibitor lapatinib seem to confirm EGFR's major role in breast cancer. Several Phase I–II studies have noted good response to this agent in Stage IV breast cancer. At this year's ASCO, Lin et al from the Dana-Farber Cancer Institute (Boston, MA) reported on 39 advanced breast cancer cases with CNS metastases. Two patients (5%) achieved partial response of 158 and 347 days duration, respectively, 1 achieved > 30% reduction of disease measurement, and 5 had stable disease for more than 16 weeks. The main dose-limiting toxicities were diarrhea, fatigue and headaches. Skin rash, anorexia and nausea occurred in a small proportion of patients, with no toxicity reaching Grade 4. Cardiac effects were recorded, but to a lesser degree than with trastuzumab. Four of 39 patients had decreases of < 10% in LVEF (i.e. Grade 2), with 1 case of >10% LVEF decrease (Grade 3). All were asymptomatic, with no signs of clinical left ventricular dysfunction. The study is important in documenting that lapatinib appears to penetrate the CNS and is well tolerated, even in women exposed in the past to trastuzumab.

Spector et al (Abstract 502) reported on 22 patients with inflammatory breast cancer who had relapsed on prior chemotherapy using anthracyclines (98%) and/or anthracyclines and taxanes (78%). A response to lapatinib was seen in 8/11 HER2-positive cases (82%) but in none of 6 HER2-negative cases, showing that, similar to trastuzumab, activity of lapatinib is also restricted to patients with positive HER2 status.

The strongest case for lapatinib's effect among trastuzumab failures was presented by the NSABP's Geyer et al at a special session.<sup>9</sup> In the EGF 100151 study, 321 HER2-

positive breast cancer patients, all having failed past chemotherapy and trastuzumab for metastatic or Stage III disease, were randomized to capecitabine 2000 mg/m<sup>2</sup> po per day + lapatinib 1250 mg po per day in combination, vs capecitabine 2500 mg/m<sup>2</sup> po per day alone. The overall response rate for the combination was 22.5% vs 14.3% for capecitabine alone. Importantly, lapatinib significantly prolonged the time to progression (median 36.9 weeks for lapatinib + capecitabine vs 19.7 weeks for capecitabine alone (HR 0.51, 95% CI 0.35–0.74,  $p = 0.00016$ ), as was PFS ( $p = 0.000045$ ). Presently, several North American and European randomized trials of lapatinib are underway or in the planning stages. Three of first-line treatment in women with Stage IV disease are EGF 30008 (letrozole + lapatinib vs letrozole + placebo), EGF 104383 (paclitaxel + trastuzumab + lapatinib vs paclitaxel + trastuzumab + placebo) and EGF 10061 (docetaxel + trastuzumab + lapatinib vs docetaxel + trastuzumab + placebo). Two studies of lapatinib as adjuvant therapy are also in preparation. The US NCCTG is preparing a 3-arm trial (doxorubicin + cyclophosphamide [AC] + trastuzumab + lapatinib vs AC + trastuzumab vs AC + lapatinib). The European Afrodite trial, a joint effort of the Breast International Group and the National Cancer Institute of Canada, will have 4 arms: any chemotherapy + trastuzumab vs any chemotherapy + lapatinib vs any chemotherapy + trastuzumab + lapatinib vs any chemotherapy + lapatinib, followed by lapatinib.

Availability of lapatinib in Canada is presently restricted to patients participating in randomized trials. However, GlaxoSmithKline has filed in Canada for a special accelerated access program for women with Stage IV, HER2-positive disease who failed trastuzumab, hopefully to be granted in the autumn of 2006.

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## Breast cancer: biomarkers predicting chemotherapy effect

### HER2 PREDICTS BENEFIT FROM ADJUVANT PACLITAXEL AFTER AC IN NODE-POSITIVE BREAST CANCER: CALGB 9344. ASCO 2006, ABSTRACT 510.

Investigators: D.F. Hayes et al.

**TRIAL SUMMARY:** In this analysis of node-positive patients in the CALGB 9344 trial (n = 3121), 2 sets of 750 patients each were randomly selected from about 2800 subjects in whom tissue blocks were collected. Patients in CALGB 9344 received 4 q 3-weekly cycles of doxorubicin (60, 75, or 90 mg/m<sup>2</sup>) + cyclophosphamide followed by either 4 cycles of paclitaxel (175 mg/m<sup>2</sup> q 3 weeks) or no paclitaxel. HER2 expression was evaluated by FISH and 2 types of IHC. The study showed a significant correlation between HER2 and paclitaxel (p = 0.013) (Table 11). The authors concluded that the benefit of adding paclitaxel to doxorubicin + cyclophosphamide is greater for HER2-positive tumours, even if ER-positive, but provides no benefit for ER-positive/HER2-negative cases.

**TABLE 11. Impact on overall survival (percent benefit) of adding paclitaxel to doxorubicin + cyclophosphamide, according to ER and HER2 expression**

	All	ER-positive	ER-negative
All	7%	16%	0%
HER2-negative	2%	8%	-1%
HER2-positive	22%	31%	9%

### TOP2A ABERRATIONS AS PREDICTIVE AND PROGNOSTIC MARKER IN HIGH-RISK BREAST CANCER PATIENTS. A RANDOMIZED DBCG TRIAL (DBCG89D). ASCO 2006, ABSTRACT 532.

Investigators: A. Knoop et al.

**TRIAL SUMMARY:** In this followup of previously-published data, 962 women with high-risk breast cancer were randomized to receive 9 cycles of either CMF (cyclophosphamide, methotrexate, fluorouracil) (n = 495) or CEF (cyclophosphamide, epirubicin, fluorouracil) (n = 467) every 3 weeks. The tumour tissue available from 806 patients (84%) was analyzed for number of topoisomerase (topo2a) copy changes. Topo2a-amplified tumours were found in 92 (12.0%) of patients, and topo2a-deleted tumours in an additional 86 (11.1%). Topo2a gene amplification predicted recurrence-free survival (RFS), the primary endpoint (HR 0.39, 95% CI 0.22–0.70, p = 0.0017) (Table 12). Topo2a deletions showed a non-statistically significant similar trend (HR 0.61, 95% CI: 0.35–1.07, p = 0.082). The Topo2a aberration (i.e. combined amplification and deletion, 23.1% of all cases), had independent prognostic value and was associated with worse RFS (p = 0.036) and OS (p = 0.012).

**TABLE 12. Impact of topo2a on recurrence-free survival of CEF (dose more intense) vs CMF (dose less intense) adjuvant chemotherapy for breast cancer**

	hazard ratio (95% CI)	p value
topo2a amplification	0.39 (0.22–0.70)	0.0017
topo2a deletion	0.61 (0.35–1.07)	0.082
normal topo2a	0.94	Ns

**COMMENTARY: Joseph Ragaz, MD, FRCPC, Director, Oncology Program, McGill University Health Centre, Montréal, QC.**

The presentations at this year's ASCO covered a wide range of exciting news on use of blood monitoring as an effective tool, including circulating cells, serum HER2 and insulin or its surrogate, C-peptide (Abstract 524). As predicted more than 20 years ago,<sup>1</sup> progress with in-vivo monitoring of neoadjuvant systemic therapy effects, both hormonal and chemotherapeutic, continues. Not only does exposing tumour to systemic therapy immediately after diagnosis contain growth more effectively, but regular tumour sampling to assess changes in biological markers offers the most

definitive insight into response to systemic therapy. Such an approach allows measurement of pathologic complete response, distinguishing responders from non-responders very early in the treatment course. This enhances breast conservation and should render neoadjuvant therapy a routine, cost-effective treatment modality.

#### TUMOUR HER2 PREDICTS RESPONSE TO TAXANES

The study presented by Hayes et al analyzed the CALGB trial 9344 of 3121 node-positive breast cancer cases treated

# LANDMARKS

with doxorubicin + cyclophosphamide every 3 weeks x 4 (all patients) and randomized to receive additional paclitaxel every 3 weeks x 4 or placebo. While paclitaxel was of benefit overall, a prior analysis<sup>2</sup> had shown a trend for much greater benefit among ER-negative than for ER-positive cases.


The present analysis confirmed the significant ER interaction, with paclitaxel providing improvement in OS of 16% in ER-negative tumours vs 0% in ER-positive cases. However, HER2 expression predicted paclitaxel's effect with greater refinement than ER status alone, with 22% OS improvement in patients with HER2-positive tumours but only 2% in the HER2-negative group. Further, paclitaxel provided a 9% survival advantage in HER2-positive/ER-positive cases — benefit that would have been foregone had the assessment relied on ER status alone. For ER-negative/HER2-negative cases, the 8% survival advantage is more marginal, while HER2-positive/ER-negative tumours derived the largest magnitude of benefit, 31%. These data are in concordance with a recent *NEJM* publication of Pritchard et al showing that patients with amplified HER2 derive more benefit from CEF compared to CMF, while cases without expression of HER2 have similar outcome whether treated by CMF or CEF.<sup>3</sup>

## TOPO2A

Knoop et al reported on the Danish trial, which examined topo2a in women with high-risk breast cancer randomized to receive either CMF or CEF chemotherapy. While topo2a aberration (either amplification or deletion) was associated with worse prognosis both for DFS ( $p = 0.036$ ) and OS ( $p = 0.012$ ), it predicted a significantly better impact of CEF over CMF for amplification (HR 0.39, 95% CI 0.22–0.70),

with a similar trend for deletion (HR 0.61, 95% CI 0.35–1.07) (Table 12, page 47). For the majority of patients with normal topo2a (i.e. 67%), the outcomes of CEF and CMF were identical (HR 0.94,  $p = ns$ ).

O'Malley et al reported similar outcomes (Abstract 533) in the Canadian MA.5 trial, of similar design: 710 premenopausal women with node-positive breast cancer received either CMF or a substantially more dose-intensive regimen of CEF, both with oral cyclophosphamide. While all patients allocated to CMF had significantly higher rates of relapse and mortality, those with normal topo2a (81.2%) had similar outcomes on both regimens, (DFS: HR 1.09,  $p = 0.6$ ; OS: HR 0.89,  $p = 0.5$ ). Topo2a deletion, found in 6.9% of tumours, was significantly associated with higher rates of relapse and mortality with CMF treatment compared to CEF (DFS: HR 6.42,  $p = 0.008$ ; OS 10.02,  $p = 0.005$ ). Topo2a amplification had a similar trend (DFS: HR 1.69; OS: HR 2.11).

These data corroborate the new paradigm that biomarkers can select for agents and dose intensity, restricting the use of costly and toxic therapies for those patients most likely to benefit. This development is emerging as one of the most important parameters affecting clinical practice, comparable to how estrogen receptor status is now used to predict response to hormonal therapy. 

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