



EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 44th Annual Meeting of the American Society of Clinical Oncology (ASCO), held May 30–June 3, 2008. Leading Canadian experts offer commentary and clinical interpretations.

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Colorectal cancer

Lylly H. Lê, MDCM, FRCPC

RANDOMIZED PHASE III STUDY OF CAPECITABINE, OXALIPLATIN, AND BEVACIZUMAB WITH OR WITHOUT CETUXIMAB IN ADVANCED COLORECTAL CANCER (ACC), THE CAIRO2 STUDY OF THE DUTCH COLORECTAL CANCER GROUP (DCCG). ASCO 2008, ABSTRACT LBA4011.

Investigators: C.J. Punt et al.

TRIAL SUMMARY: The CAIRO2 study was undertaken to evaluate the benefits and risks of targeting both vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) by adding cetuximab to first-line capecitabine + oxaliplatin (CapOx) + bevacizumab in patients with advanced colorectal cancer. A total of 755 patients with inoperable and/or metastatic colorectal cancer who had not received adjuvant chemotherapy for at least 6 months prior were randomized. Of these, 731 received at least 1 treatment cycle of either capecitabine 1000 mg/m² orally twice per day on Days 1–14 + oxaliplatin 130 mg/m² intravenously (IV) on Day 1 + bevacizumab 7.5 mg/kg IV on Day 1, every 3 weeks (n = 368), or the same regimen + cetuximab 250 mg/m² IV, weekly following a loading dose the first week of 400 mg/m² (n = 368). Oxaliplatin was stopped after Cycle 6 and could be reintroduced upon disease progression. Response was assessed every 3 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST). Patients received a median of 10 treatment cycles (range 1–39) in the no-cetuximab group and 9 cycles (range 1–40) in the cetuximab group. At median followup of 18.7 months, median progression-free survival (PFS), the primary endpoint, was 10.7 months in the no-cetuximab group and 9.6 months in

the cetuximab group (p = 0.018; hazard ratio [HR] = 1.21; 95% CI 1.03–1.45). Results for other endpoints differed very little between the 2 treatment arms, including disease control rate (i.e. complete response + partial response + stable disease) of 83% vs 81% (p = 0.39) and median overall survival (OS) of 20.4 vs 20.3 months (p = 0.21). Grade 3–4 toxicities occurred in 72% of patients not receiving cetuximab vs 82% of those receiving it (p = 0.0013), but with skin effects of cetuximab excluded, the overall toxicity rates were similar in both groups at 72% vs 75% (p = 0.37). The only Grade 3–4 toxicity that differed was diarrhea (19% in the no-cetuximab vs 26% in the cetuximab group, p = 0.026). Reasons for treatment discontinuation did not differ between the 2 groups. While PFS in KRAS wild-type vs mutated tumours (61% vs 39% of the 501 patients tested) did not differ significantly, PFS in patients with mutated KRAS was 12.5 in the no cetuximab group vs 8.6 in those receiving cetuximab (p = 0.043). No correlation was seen between KRAS genotype and cetuximab-related skin effects. The authors concluded that adding both antibodies (cetuximab and bevacizumab) to CapOx resulted in a significantly decreased PFS compared to CapOx with bevacizumab alone, no effect on overall survival and an increased but tolerable level of toxicity.

COMMENTARY: Lyly H. Lê, MDCM, FRCPC, Medical Oncologist, British Columbia Cancer Agency; Clinical Assistant Professor, University of British Columbia.

This late-breaking abstract was one of a number of presentations given at this year's ASCO Annual Meeting dealing with colorectal cancer and agents targeting EGFR, such as the chimeric monoclonal antibody cetuximab and the humanized monoclonal antibody panitumumab. The trial used capecitabine combined with oxaliplatin (CapOx) and bevacizumab as the standard treatment arm. While not widely used as a first-line regimen in Canada, there is some local experience with the combination as many centres took part in a recently published trial comparing CapOx to fluorouracil + folinic acid + oxaliplatin (FOLFOX4) +/- bevacizumab, which demonstrated that CapOx was not inferior to FOLFOX4.¹ The CAIRO2 study was done to examine the effect of adding cetuximab to CapOx + bevacizumab.

The results of CAIRO2 were much anticipated in light of the concerns raised by the Phase III Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial, where patients receiving first-line treatment with either FOLFOX + bevacizumab or fluorouracil + folinic acid + irinotecan (FOLFIRI) + bevacizumab (based on investigator's choice) were randomized to additional panitumumab or not. At the first pre-planned interim analysis, patients who received panitumumab were found to have significantly worse PFS.² Additional unplanned analyses showed increased toxicity and lower overall survival in the panitumumab group, leading to early closure of the study. This was in contrast to the previously reported Phase II Bowel Oncology With Cetuximab Antibody (BOND)-2 trial, which studied a population of heavily pretreated patients with irinotecan-refractory colorectal cancer who were randomized to cetuximab + bevacizumab +/- irinotecan.³ In this small, randomized Phase II study, the combination of bevacizumab and cetuximab was well tolerated both with and without irinotecan.

The results of the CAIRO2 trial do not demonstrate any added benefit of combining biologics targeting EGFR and angiogenic factors such as VEGF with chemotherapy in first-line treatment of metastatic colorectal cancer. In fact, there appears to be a negative effect on the primary endpoint of PFS (9.6 months with cetuximab vs 10.7 months without, HR = 1.21) similar to PFS in the PACCE trial (9.5 months with panitumumab vs 11.0 months without, HR = 1.29). No difference was seen in median overall survival in the CAIRO2 study; the most recent update of PACCE results suggested inferior overall survival (although a pre-specified statistical significance boundary was lacking).⁴

The increased toxicity seen with cetuximab in CAIRO2 was related to skin toxicity and diarrhea, whereas the PACCE study reported more non-skin Grade 4 toxicity, specifically diarrhea, infections, dehydration, hypokalemia, hypomagnesemia and pulmonary emboli. It is not clear if this is an effect of the different types of anti-EGFR antibodies, the different chemotherapy protocols used, or both. The no-cetuximab arm in CAIRO2 did receive a slightly higher median number of cycles than the cetuximab arm (10 vs 9, $p = 0.02$), however, the reasons for discontinuing therapy were the same in both. The protocol called for discontinuing oxaliplatin after 6 cycles to prevent neuropathy, with the option of reintroducing it

upon disease progression. No data were presented describing how many patients were re-treated with oxaliplatin or how many received second-line therapy. Any imbalance of these factors could account for the lack of difference in overall survival despite the difference in PFS.

As in many of the other studies looking at anti-EGFR therapy, skin toxicity and KRAS mutational status were examined in CAIRO2. Subjects who had only Grade 0-1 skin toxicity with cetuximab had significantly worse PFS compared to those with Grade 2-3 skin toxicity with cetuximab or who did not receive cetuximab, but there was no significant difference in PFS between those who had Grade 2-3 skin toxicity with cetuximab and those who did not receive it. With respect to KRAS mutation status, the results presented are based upon only the 66% of patients enrolled who were tested (501/755). The presenter did comment, however, that the KRAS mutational and wild-type groups were similar except for a higher serum lactate dehydrogenase (LDH) in the wild-type group. PFS was the same in patients with wild-type KRAS (10.5 months with cetuximab vs 10.7 months without, $p = 0.10$), but those with mutant KRAS had worse PFS with cetuximab (8.6 months with cetuximab vs 12.5 months without, $p = 0.043$). No correlation was found between KRAS status and cetuximab skin toxicity.

COMBINATIONS REMAIN INVESTIGATIONAL

The results of this study do not encourage combination use of anti-EGFR and anti-VEGF agents. This goes to show that despite preclinical models suggesting additive effects of VEGF and EGFR inhibition,⁵ translation to clinical practice is not always straightforward. A discussant raised the possibility of a negative interaction between the 2 types of agents; further evaluations are needed to confirm this. Emerging data about KRAS mutational status suggest that much remains to be understood about the mechanisms of action of these agents, and by extension, their interactions with each other and with other targeted agents. Studies of various combinations of anti-EGFR and anti-angiogenesis agents are in development and should be reconsidered or amended as a consequence of the results of this trial and the PACCE study. Importantly, any combined use of anti-EGFR and anti-angiogenesis agents should remain investigational at this time.

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Pancreatic cancer

Howard J. Lim, MD, PhD, FRCPC and Hagen Kennecke, MD, MPH, FRCPC

CONKO-001: FINAL RESULTS OF THE RANDOMIZED, PROSPECTIVE, MULTICENTER PHASE III TRIAL OF ADJUVANT CHEMOTHERAPY WITH GEMCITABINE VERSUS OBSERVATION IN PATIENTS WITH RESECTED PANCREATIC CANCER (PC). ASCO 2008, ABSTRACT LBA4504.

Investigators: P. Neuhaus et al.

TRIAL SUMMARY: To examine the efficacy and toxicity of using adjuvant gemcitabine chemotherapy to treat patients with completely resected pancreatic cancer, this Phase III trial randomized 354 patients to receive either gemcitabine 1 g/m² on Days 1, 8 and 15 every 4 weeks for 6 months, or observation only. A previous publication reported that the treatment was well tolerated.¹ The patients receiving gemcitabine had significantly longer median disease-free survival (DFS) of 13.4 months com-

pared to 6.9 months for those on observation ($p < 0.001$), and longer DFS was observed in all subgroups stratified by resection (RO or R1), tumour stage and number of positive lymph nodes. Median OS was also longer in the patients receiving gemcitabine compared to those without, at 22.8 months vs 20.2 months ($p = 0.005$). Estimated 3-year OS was 35.5% for patients receiving gemcitabine vs 19.5% for those on observation only, and 5-year estimated OS rates were 21% vs 9%, respectively.

COMMENTARY: Howard J. Lim, MD, PhD, FRCPC, Gastrointestinal Oncology Fellow and Hagen Kennecke, MD, MPH, FRCPC, Medical Oncologist, British Columbia Cancer Agency.

Of approximately 3000 Canadians diagnosed with pancreatic cancer in 2008, 2900 will die of the disease. Currently only 20% of cases of pancreatic cancer are resectable. With surgery alone providing only a 25% 5-year OS rate, better therapy is clearly required. Based on data from the European Study Group for Pancreatic Cancer 1 (ESPAC-1) trial,² the current standard of care is to provide bolus fluorouracil for 6 months post-surgery for resected pancreatic adenocarcinomas.

Gemcitabine has proved superior to fluorouracil in the metastatic setting, and is currently approved for this indication.³ When *JAMA* published initial results in 2007 of the randomized Phase III Charité Onkologie 001 (CONKO)-001 trial comparing adjuvant gemcitabine to placebo,¹ the primary endpoint of DFS was met: 13.4 months vs 6.9 months ($p < 0.001$), but no OS benefit was seen. The final OS results released at this year's ASCO, summarized above, demonstrated an improved 22.8 months with gemcitabine vs 20.2 months without ($p = 0.005$). Estimated survival rates at 3 years were 36.5% for gemcitabine vs 21% for observation, and 5-year survival rates were 19.5% vs 9.0% years, again favouring gemcitabine.

There are some data from the randomized Radiation Therapy Oncology Group (RTOG) 9704 trial⁴ comparing chemotherapy with fluorouracil (continuous infusion of 250 mg/m² per day) vs gemcitabine (30-minute infusion of 1000 mg/m² once per week), for 3 weeks prior to chemoradiation therapy and for 12 weeks after chemoradiation therapy. Chemoradiation was a continuous infusion of 250 mg/m² fluorouracil per day with radiation of 50.4 Gy. A further 3 months of chemotherapy was given of continuous fluorouracil 4 weeks with 2 weeks off for 2 cycles or gemcitabine 3 weeks on with 1 week off for 3 cycles. Patients taking gemcitabine

TABLE 1. Summary of adjuvant chemotherapy trials for resected pancreatic cancer

patient population	GITSG	EORTC	ESPAC-1	RTOG 9704	CONKO-001
T3-T4	n/a	0	n/a	70-81	86
node-positive	30	47	50	65-68	71
R1 disease	0	19	28	33-35	19
mean survival in best arm	21 months	17.1 months	20.1 months	20.6 months	22.1 months
3-year survival	24%	30%	30%	31%	34%
5-year survival	19%	20%	21%	n/a	22%

GITSG = Gastrointestinal Tumor Study Group⁵

EORTC = European Organisation for Research and Treatment of Cancer⁶

ESPAC-1 = European Study Group for Pancreatic Cancer 1²

RTOG 9704 = Radiation Therapy Oncology Group³

CONKO-001 = Charité Onkologie 001¹

COMPARATIVE ADJUVANT DATA NEEDED

Given this OS benefit, a trial comparing gemcitabine to fluorouracil, the current standard for adjuvant treatment of resectable pancreatic cancer, is needed.

had improved OS of 20.5 months vs 16.9 months, but the difference missed statistical significance (HR = 0.82; p = 0.09).

Chemoradiation is more commonly used in the U.S. than in Canada, but this trial currently serves as the only direct comparison of gemcitabine to fluorouracil. If we look at OS across trials, the benefit of gemcitabine appears to be consistent, at approximately 20–22 months. The survival benefit of fluorouracil chemotherapy seen in both ESPAC-1² and RTOG 9704³ was approximately 17 months. Another trial, ESPAC-3, randomized patients with pancreatic and ampullary cancers to receive fluorouracil or gemcitabine; preliminary results are expected within the next 12 months.

CURRENT IMPLICATIONS

Table 1 summarizes advances in adjuvant therapy for pancreatic cancer over the past 20 years, showing only modest survival gains over the time from early trials with adjuvant radiotherapy to ESPAC-1 with chemoradiotherapy. The longest reported OS was the 22.8 months reported by CONKO-001. The benefits seen in both DFS and OS support the use of gemcitabine as a standard adjuvant therapy until better therapies with longer survival duration are found.

Patient selection may become a key factor in determining who will truly benefit from treatment. The survival curves reveal a population of patients who have a chance of cure, with 5-year OS improving from 9% to 19.5%. Outside of performance status and standard staging techniques, no biomarkers have yet been defined that predict who will derive benefit from gemcitabine. In the absence of predictive markers, gemcitabine may be used as standard adjuvant therapy for resected pancreatic cancer.

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Early-stage breast cancer

Caroline Lohrisch, MD, FRCPC

STANDARD CHEMOTHERAPY (CMF OR AC) VERSUS CAPECITABINE IN EARLY-STAGE BREAST CANCER (BC) PATIENTS AGED 65 AND OLDER: RESULTS OF CALGB/CTSU 49907. ASO 2008, ABSTRACT 507.

Investigators: H.B. Muss et al.

TRIAL SUMMARY: The Cancer and Leukemia Group B (CALGB) / Cancer Support Trials Unit (CTSU) 49907 trial was undertaken to examine the efficacy of standard chemotherapy vs oral capecitabine in older women with early-stage breast cancer. Eligible patients were 65 years or older, less than 84 days post-surgery, and had Stage 1–4 tumours, 0–3 positive lymph nodes, no metastases, performance status of 0–2 and adequate organ function. They were randomized to receive capecitabine (2000 mg/m² on Days 1–14, every 3 weeks for 6 cycles) (capecitabine group) or either standard CMF (oral cyclophosphamide 100 mg/m² on Days 1–14, methotrexate 40 mg/m² on Days 1 and 8 and fluorouracil 600 mg/m² on Days 1 and 8) or AC (doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² every 3 weeks for 4 cycles) (standard chemotherapy group). Patients with hormone receptor-positive tumours were advised to take endocrine

therapy. In 633 women, at 2.4 years of followup, Bayesian prediction calculations showed that patients receiving capecitabine were 2.09 times more likely to have locoregional or distant relapse or death (95% CI 1.4–3.2; adjusted p = 0.0006), and 1.85 times more likely to die (95% CI 1.1–3.1; p = 0.019). Reported toxicities were mild, with more myelosuppression in women on standard chemotherapy and more hand-foot syndrome in those taking capecitabine. Two women in the capecitabine group died due to drug-related events. Unplanned subset analysis showed that standard therapy was particularly advantageous in women with hormone receptor-negative tumours (HR = 4.39; 95% CI 2.9–6.7; p < 0.0001). The authors concluded that capecitabine provides results inferior to standard therapy in older women with early breast cancer, especially in those with hormone receptor-negative tumours.

COMMENTARY: Caroline Lohrisch, MD, FRCPC, Medical Oncologist, British Columbia Cancer Agency.

The majority of women presenting with breast cancer are older than 50 years. Data about the benefit, if any, of chemotherapy in older women following curative-intent surgery for breast

cancer is insufficient. Few trials have focused exclusively on the postmenopausal population, and many adjuvant chemotherapy trials excluded women older than 65. The general

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perception is that chemotherapy adds little value for most older women: while there might be a small improvement in avoiding breast cancer recurrence, comorbidities and age largely prevent these from translating into meaningful overall survival gains. Further, accentuated side effects of chemotherapy with advancing age may make short-term harm prohibitive.

DATA ON OLDER WOMEN

Limited data exist from the Intergroup 0100,¹ Programme Adjuvant cancer du Sein (PACS) 01² and Breast Cancer International Research Group (BCIRG) 001³ trials, all of which included older women. At 9 years' followup, the Intergroup 0100 trial, which compared tamoxifen alone vs tamoxifen with CAF (cyclophosphamide + doxorubicin + fluorouracil) chemotherapy in estrogen receptor (ER)-positive postmenopausal women with node-positive disease, demonstrated an absolute survival advantage for chemotherapy in the order of 5%. Forty-five percent of the 1477 trial participants were 65 years or older. Subset analysis suggested that no benefit accrued to women whose tumours had any of the following characteristics: strongly ER-positive (with Allred score ≥ 7), Grade 1 or 2, accompanied by 1–3 positive nodes, and HER2-negative status.¹ The PACS 01 and BCIRG 001 trials, both of which demonstrated that adding docetaxel to anthracycline-based chemotherapy provided superior DFS and OS, enrolled women up to the ages of 65 and 70 years, respectively. Notably, 76% of women in each of these trials had hormone receptor-positive disease for which they received standard hormone therapy. On subset analysis, the PACS 01 trial demonstrated a considerable and statistically significant disease-free survival benefit for women over 50, who represented roughly half the study population.² BCIRG 001 did not analyze results by age, but again, half the study population was ≥ 50 years old.³ All these results raise the possibility that if one regimen is better than another, some regimens must be better than no chemotherapy at all in the appropriate circumstances.

NEW FINDINGS FROM CALGB 49907

This randomized trial of women 65 years and older with early breast cancer, presented at the 2008 ASCO and summarized above, goes a long way to enhance our understanding of the role of chemotherapy in the elderly. The design is laudable for addressing the value of chemotherapy in a previously understudied population, and for evaluating both standard polychemotherapy and a less toxic monotherapy. The trial population was women ≥ 65 years old with Stages I–III breast cancer who underwent curative-intent surgery and had at least a 5-year life expectancy based on other comorbidities. The randomization was to either standard-dose polychemotherapy (4 cycles of AC or 6 cycles of CMF) or 6 cycles of capecitabine 1000 mg/m² twice per day for 14 days, every 21 days. To the investigators' credit, the design employed a lower dose of capecitabine than the reference standard, recognizing that delivery of the higher dose in this age group is challenging, and that in the metastatic setting, where capecitabine is frequently used in the elderly, it is virtually always started at a dose of 1000 mg/m² twice per day or lower.

Sixty percent of the study population were between 70 and 79 years old, and only 4% were ≥ 80 years old. Roughly 70% were node-positive, a similar proportion were ER-positive and a minority (about 11%) were HER2-positive. The toxicity data presented from this trial demonstrated several important findings. One was that even over the first 4 cycles, AC appeared easier to deliver than CMF, based on the percentage receiving each cycle — this was also observed in the National Surgical Adjuvant Breast and Bowel Project (NSABP) 15 study, which compared 6 cycles of CMF to 4 cycles of AC.⁴ It is generally held that older women have less chemotherapy-induced nausea, a chronic symptom with the oral cyclophosphamide schedule of CMF, and that the mucosal toxicity of AC may be worse in older women. Both factors might be expected to make CMF more tolerable in this population rather than less. An explanation for the opposite finding may be that investigators selected CMF for women they considered slightly more frail, reserving AC for the more robust. Another surprising finding was that while monotherapy might have been anticipated to be better tolerated than combination therapy, the dropout rates at each cycle in 2 treatment groups were very similar, despite fewer Grade 3 and 4 toxicities observed for capecitabine (34%) than for AC (59%) and CMF (69%). Hypotheses to explain this are that Grade 2 toxicities (not reported) in this age group have a meaningful impact on quality of life, and that older patients will accept less toxicity for a given relapse-free survival (RFS) gain. Not provided was whether the majority of dropouts at each cycle were due to subject or investigator decisions. In addition, the quality of life data collected during the trial, which may shed additional light on these findings, were not presented.

The most informative findings pertained to the primary endpoint, RFS. Because of the possibility that the monotherapy might result in an inferior outcome, the first interim analysis was planned after the first 600 subjects out of a maximum of 1800 had been randomized. The trial's Data Safety Monitoring Board recommended closing the study at this first interim analysis because the capecitabine-treated group had significantly worse RFS, with a hazard ratio of 0.53. Statistical calculations predicted that even with full accrual, there was a 90% probability that this difference would remain at least 20% — an unacceptably high risk to expose additional study subjects to.

RFS events were defined as local recurrence, distant recurrence (with or without local recurrence) and death without breast cancer recurrence. At the time of reporting, median followup was 2.4 years, during which 60 events (affecting 20% of patients) occurred in the capecitabine arm vs 35 (11%) in the AC/CMF arm. Exclusion of non-breast cancer deaths left 43 (14%) RFS events in the capecitabine group vs 20 (6.5%) in the AC/CMF group. The 9% difference in RFS was highly significant, with a p-value of 0.0009, and although few of the women had died, OS was significantly better for the polychemotherapy group (88% vs 93%; p = 0.019). While more women on capecitabine than AC/CMF died of breast cancer (18 [5.8%] vs 8 [2.5%]), non-breast cancer etiologies were the dominant cause of death in both groups. On an unplanned subset analysis, the largest disparity in both RFS and OS was seen for women with

hormone receptor-negative disease, such that women with receptor-negative cancers receiving capecitabine had a 4.4-fold higher likelihood of relapse than those with any other hormone receptor and treatment combination ($p < 0.0001$).

These data strengthen the observations seen in the Intergroup 100, PACS 01, and BCIRG 001 trials: older women may benefit from chemotherapy. Furthermore, those with the greatest risk, such as those with hormone receptor-negative cancers, can be expected to derive the most benefit. While no other contemporary monotherapy vs polychemotherapy trials have been completed in the adjuvant setting, these results are congruent with several (although not all) trials of first-line therapy in metastatic breast cancer that have demonstrated improved survival for combinations compared with single agents (e.g. capecitabine + docetaxel vs docetaxel⁵ and gemcitabine + paclitaxel vs paclitaxel⁶).

CAVEATS AND IMPLICATIONS

We must remember that very little information is available about women 80 years and older, and that the women enrolled in this study were relatively fit — given that they were excluded if they had comorbidities (including age itself, presumably) that might result in less than 5 years of additional life. Important take-home messages include that recurrences can occur within the first few years following high-risk breast cancer; that given the inferiority of capecitabine monotherapy, polychemotherapy is better than no chemotherapy at all in the appropriate, fit, high-risk older

woman; and that, if the woman’s cardiac health is intact, AC appears to be better tolerated than CMF. Escalating therapy to regimens beyond AC necessarily enhances toxicity. However, with the hematopoietic growth factor and other supportive medications currently available, the older woman can be safely navigated through chemotherapy such that she will realize its benefit in protecting her from breast cancer recurrence. The study presenter’s comment that predictive knowledge is critical in designing future therapy trials for women with breast cancer, including the elderly, is absolutely on the money.

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INTERIM RESULTS OF INTERGROUP EC-DOC TRIAL: A RANDOMIZED MULTICENTER PHASE III TRIAL COMPARING ADJUVANT CEF/CMF TO EC- DOCETAXEL IN PATIENTS WITH 1-3 POSITIVE LYMPH NODES. ASCO 2008, ABSTRACT 515.

Investigators: U. Nitz et al.

TRIAL SUMMARY: This Phase III trial was done to clarify whether taxane-based adjuvant chemotherapy provides optimal efficacy compared to non-taxane-containing chemotherapy when treating early breast cancer patients with 1–3 positive lymph nodes. A total of 2011 women were randomized to receive either (Arm A) 4 cycles of epirubicin 90 mg/m² + cyclophosphamide 600 mg/m² every 3 weeks, followed by 4 cycles of docetaxel 100 mg/m² every 3 weeks (n = 1008); or (Arm B) 6 cycles of either epirubicin 100 mg/m² + fluo-

rouracil 500 mg/m² + cyclophosphamide 500 mg/m² every 3 weeks (n = 828), or cyclophosphamide 600 mg/m² + methotrexate 40 mg/m² + fluorouracil 600 mg/m² on Days 1 and 8, every 4 weeks (n = 175). At median followup of 3 years, 34 primary events had occurred in the patients receiving docetaxel vs 64 in those not receiving the taxane, and there were 17 vs 36 deaths, respectively, prompting this interim analysis. The authors concluded that the docetaxel-containing regimen shows strong superiority.

RANDOMIZED PHASE III TRIAL COMPARING THE SEQUENTIAL ADMINISTRATION OF DOCETAXEL FOLLOWED BY EPIRUBICIN PLUS CYCLOPHOSPHAMIDE VERSUS FE75C AS ADJUVANT CHEMOTHERAPY IN AXILLARY LYMPH NODE-POSITIVE BREAST CANCER. ASCO 2008, ABSTRACT 521.

Investigators: D. Mavroudis et al.

TRIAL SUMMARY: This multicentre, prospective, stratified Phase III study examined the benefit of adding docetaxel to anthracycline-based adjuvant chemotherapy when treating women with axillary node-positive, operable early breast cancer, WHO performance status of 0–2 and good organ function. A total of 756 women were randomized to receive either

docetaxel 100 mg/m² every 21 days for 4 cycles, followed by epirubicin 75 mg/m² + cyclophosphamide 700 mg/m² on Day 1, every 21 days for 4 cycles (docetaxel group, n = 378), or fluorouracil 700 mg/m² + epirubicin 75 mg/m² + cyclophosphamide 700 mg/m² every 21 days for 6 cycles (non-docetaxel group, n = 378). At median followup of 62.5

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months (range 3.4–132.7 months) in the docetaxel group and 52.7 months (range 2.8–136.2) in the non-docetaxel group, rates of 5-year RFS, the primary endpoint, were 74.8% vs 68.9% ($p = 0.029$) in the docetaxel vs non-docetaxel groups, respectively. There were 94 (24.9%) vs 115 (30.4%) relapses ($p = 0.08$) and 69 (18%) vs 64 (17%) deaths ($p = 0.6$). Grade 3–4 toxicities included neutropenia in 72% vs 42% of

patients ($p = 0.0001$), febrile neutropenia in 8% vs 3% ($p = 0.003$) and diarrhea in 3.7% vs 0% ($p = 0.0001$); 342 (90.5%) patients receiving docetaxel used secondary granulocyte colony-stimulating factor support vs 281 (74.3%) of the non-docetaxel patients. The authors concluded that the regimen containing docetaxel resulted in both greater efficacy and more toxicity in this population.

COMMENTARY: Caroline Lohrisch, MD, FRCPC, Medical Oncologist, British Columbia Cancer Agency.

These 2 randomized controlled trials (RCTs) reported at ASCO 2008 confirm the 5% to 6% RFS advantage from adding docetaxel to anthracycline-based adjuvant chemotherapy for node-positive early breast cancer previously observed in the PACS 01¹ and BCIRG 001 trials.² The Nitz et al trial focused specifically on women with 1 to 3 positive nodes, while Mavroudis et al enrolled women with up to 9 involved nodes. Despite the consistent RFS advantage observed, these 2 trials have some design limitations. In both, the non-docetaxel “standard” regimen was shorter by about 40 days than the docetaxel regimen, an average of about 2 cycles. While the CMF option in the Nitz trial was the same duration as the experimental arm, there was no anthracycline, and the debate about the absolute need for anthracyclines has not yet been definitively settled. However, the National Cancer Institute of Canada Clinical Trials Group (NCIC–CTG) MA5 trial showed a 7% OS gain for CEF (cyclophosphamide + epirubicin + fluorouracil) compared with CMF.³ This raises the possibility that the CMF used in the Nitz trial’s control arm was an inferior standard regimen and that this contributes to the observed difference favouring the experimental arm, although retrospective analysis of available tumour blocks found that the advantage of CEF in the MA5 trial was only in women with HER2-positive cancers. The chief limitation of the Mavroudis trial was the sample size, which may have limited its statistical power to demonstrate OS differences. Both trials reported relatively few events, and neither has robust survival data to date. Nevertheless, their results are in line with the earlier trials testing the same question.

While RCT data have consistently supported a benefit for incorporating taxanes into adjuvant breast cancer chemotherapy, the effect has been more consistent for docetaxel than paclitaxel. The NSABP B28⁴ and Intergroup 9344 trials⁵ both reported small RFS and OS gains from adding 4 cycles of paclitaxel to standard-dose AC. Subset analysis, however, suggested that the benefit was largely confined to the ER-negative breast cancers, at least in the 9344 study. Moreover, Hayes et al published a retrospective examination of this dataset⁶ in which they found essentially no benefit for paclitaxel among women with ER-positive and HER2-negative cancers. Both trials were confounded by a design flaw in that the paclitaxel-containing arms delivered 12 weeks more chemotherapy than the standard therapy arms, which may explain some or all of the additional benefit observed for paclitaxel. In the MA21 trial,⁷ the AC + paclitaxel regimen was inferior to an anthracycline-only regimen given for the same duration.

FURTHER REFINING THE VALUE OF PACLITAXEL

The Intergroup 9741⁸ and E1199⁹ trial results both suggest that the activity of paclitaxel is schedule-dependent. Intergroup 9741 demonstrated the superiority of delivering AC–paclitaxel every 2 weeks, with growth factor support, instead of every 3 weeks.⁸ As recently published in the *New England Journal of Medicine*,⁹ E1199 used 3-weekly AC–paclitaxel as a reference standard against which 3 other taxane schedules were compared following 4 cycles of AC: weekly paclitaxel for 12 weeks, weekly docetaxel for 12 weeks and 3-weekly docetaxel for 4 cycles. Weekly paclitaxel and 3-weekly docetaxel provided the best RFS results, both about one-third better than the reference regimen. However, perhaps surprisingly, only weekly paclitaxel demonstrated OS superiority ($p = 0.019$), while 3-weekly docetaxel demonstrated merely a trend ($p = 0.25$). In E1199, 89% of the study population was node-negative. Not surprisingly, toxicity, especially hematologic (Grade 3–4 neutropenia, febrile neutropenia and infections), was greatest in the 3-weekly docetaxel arm. Weekly paclitaxel was well tolerated, with modest hematologic toxicity, but a high incidence of close to 30% Grade 2–4 peripheral sensory neuropathy was observed.

CONCLUSIONS FROM ADJUVANT TAXANE TRIALS TO DATE

First, few data exist for the node-negative population, with most of the trials enrolling exclusively node-positive breast cancer patients. Second, the benefit of paclitaxel appears to be schedule-dependent, with weekly or bi-weekly dosing being better than 3-weekly. Third, the benefit of adding docetaxel to anthracyclines has been demonstrated consistently across at least 4 adjuvant trials. The E1199 trial did not statistically compare 3-weekly docetaxel to weekly paclitaxel (comparisons were all against the standard arm, 3-weekly paclitaxel), so while it may be tempting, it is not possible to determine if one has superior efficacy over the other. Whether to choose more frequent paclitaxel and accept the higher incidence of peripheral sensory neuropathy (which can be long-lasting), or 3-weekly docetaxel with the option of mitigating the associated marrow suppression with primary growth factor support, is an individual decision. Patient convenience, chemotherapy unit resources, third-party drug coverage for growth factor support, age, comorbidity, individual preference and physician experience with paclitaxel and docetaxel will all influence the choice. Eventually, adjuvant data for nanoparticle albumin-bound paclitaxel (nab-paclitaxel), which is associated with less long-term peripheral sensory neuropathy and shorter infusion times, may facilitate decision-

making. Although the importance of these factors cannot be overlooked, it remains clear that tailoring a treatment plan not only to prognostic factors, but also (and especially) to predictive factors, needs to be part of daily adjuvant treatment decision-making if we expect to refine the balance between toxicity and benefit for the individual patient and overall breast cancer population.

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Premenopausal breast cancer

Debjani Grenier, MD, FRCPC

ADJUVANT OVARIAN SUPPRESSION COMBINED WITH TAMOXIFEN OR ANASTROZOLE, ALONE OR IN COMBINATION WITH ZOLEDRONIC ACID, IN PREMENOPAUSAL WOMEN WITH HORMONE-RESPONSIVE, STAGE I AND II BREAST CANCER: FIRST EFFICACY RESULTS FROM ABCSG-12. ASCO 2008, ABSTRACT LBA4.

Investigators: M. Gnant et al.

TRIAL SUMMARY: The Austrian Breast and Colorectal Cancer Study Group Trial (ABCSG)-12 randomized 1803 premenopausal women with endocrine-responsive breast cancer to receive 1 of 4 regimens for 3 years: (1 and 2) goserelin 3.6 mg subcutaneous every 28 days + tamoxifen, with or without zoledronic acid 4 mg IV every 6 months, or (3 and 4) the same dose of goserelin + anastrozole 1 mg orally per day, again with or without zoledronic acid. At median followup of 60 months, DFS was 94% and OS was 98.2%. DFS, the primary endpoint, did not differ significantly between the patients receiving tamoxifen vs anastrozole (HR = 1.10; 95% CI 0.79–1.54; p = 0.59), but the patients

receiving either of the endocrine therapies plus zoledronic acid had a 36% relative improvement in DFS compared to those receiving only endocrine therapy (HR = 0.64; 95% CI 0.46–0.91; p = 0.01). A nonsignificant trend favoured zoledronic acid for overall survival (HR = 0.60; 95% CI 0.32–1.11; p = 0.10). Toxicities were similar to those reported in previous studies, with no renal toxicity or confirmed cases of osteonecrosis of the jaw. The authors concluded that this large trial demonstrates that zoledronic acid’s antitumour activity improves treatment outcomes in the premenopausal, hormone-responsive breast cancer population, and that use of this agent should be considered in these women.

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

Postmenopausal women with early, endocrine-responsive breast cancer have several established choices of hormonal therapy, namely tamoxifen and aromatase inhibitors. For premenopausal women, however, the choice is more limited, with tamoxifen being the standard of care and the precise role of ovarian function suppression undefined as of yet.

Gnant and co-investigators explored the role of aromatase inhibitors in premenopausal women with early, hormone receptor-positive breast cancers. These drugs alone are contraindicated in this population due to a feedback loop on the hypothalamic–pituitary system that leads to ovarian stimulation and increased estrogen production. However, this loop can be inhibited by the addition of luteinizing-hormone

releasing hormone (LHRH) agonists such as goserelin. The questions asked in this trial were: can anastrozole, used after ovarian suppression using goserelin, improve clinical outcome of premenopausal breast cancer patients, compared to tamoxifen and goserelin? And, can bisphosphonates added to endocrine therapy further improve outcomes?

ANASTROZOLE INSTEAD OF TAMOXIFEN

After median followup of 5 years, there was no significant difference in outcome between tamoxifen and anastrozole. However, this trial is likely underpowered to answer the endocrine question. There were 137 events in the 1803 patients randomized — a low event rate. If one compares

this trial to the parallel one in postmenopausal women, namely the Arimidex, Tamoxifen, Alone, or in Combination (ATAC) trial of adjuvant anastrozole vs tamoxifen, after a similar median followup,¹ 1226 events occurred in 6241 women, leading to a significant improvement in DFS in the anastrozole arm with an HR of 0.87. Similarly, in the Breast International Group (BIG) 1-98 trial of adjuvant letrozole vs tamoxifen,² there were 770 events in the 4922 women randomized, with an HR of 0.82 for DFS significantly favouring the letrozole-treated women. In addition to insufficient power, the treatment duration of endocrine therapy was 3 years in Gnant's study and this may not be adequate to show treatment differences; further, treatments were not double-blinded. Of concern is that this trial not only did not rule out a benefit, but also did not rule out potential harm: 23 distant recurrences occurred in women treated with tamoxifen compared to 41 in those on anastrozole, although OS remains the same between the 2 groups at this time.

Therefore, the study results were inconclusive in answering the endocrine question, and results of other ongoing adjuvant endocrine trials in premenopausal women are awaited. The Gnant study did not include a standard control arm, namely tamoxifen alone. The ongoing Suppression of Ovarian Function Trial (SOFT) trial (BIG 2-02, NCIC-MAC4, NCT00066690) is better designed to answer the question of whether the addition of an LHRH agonist to standard endocrine treatment in premenopausal women confers incremental benefit. This trial also explores the use of an aromatase inhibitor, namely exemestane, together with an LHRH agonist. The Tamoxifen and Exemestane Trial (TEXT) study (BIG 3-02, NCIC-MAC5, NCT00066703) randomizes premenopausal women to an LHRH agonist + tamoxifen vs an LHRH agonist + exemestane. In conclusion, until further results are available, tamoxifen remains the standard adjuvant treatment for premenopausal women with hormone receptor-positive breast cancers.

ADDITION OF BISPHOSPHONATES TO ENDOCRINE THERAPY

Preclinical experiments suggest that bisphosphonates have direct antitumour activity in addition to their effects on osteoclasts. Antitumour effects include antiangiogenic properties, induction of apoptosis and inhibition of tumour cell invasion. Since 1998, several adjuvant bisphosphonate trials have reported conflicting results. In a recent meta-analysis of 3 of these trials, including more than 1600 patients, no significant differences were seen in OS, bone metastasis-free survival or non-skeletal metastasis-free survival in patients with early breast cancer receiving adjuvant clodronate compared to those receiving standard adjuvant therapy alone.³ Now in 2008, Gnant and colleagues report significantly improved DFS in women who received the bisphosphonate zoledronic acid intravenously twice a year for 3 years vs the control arm with no bisphosphonate, with an HR of 0.64 ($p = 0.04$) and no safety issues identified. There was no difference in OS between the 2 groups, although a trend for improved OS was noted in the zoledronic acid-treated women.

Clinical implications

The bisphosphonate results of this trial are encouraging but likely not yet practice-changing, and certain points need to be considered. Although the HR for DFS favours the use of adjuvant zoledronic acid, the actual absolute difference in DFS between the 2 groups is 3% (94% in the zoledronic acid arm vs 91% in controls) and almost all of the observed benefit appeared to be in the anastrozole cohort. The tamoxifen-treated cohort did not benefit from the addition of the bisphosphonate: perhaps zoledronic acid benefit is more notable in women with reduced bone mineral density or in the setting of increased bone turnover. Also, because the majority of patients did not receive adjuvant chemotherapy, the trial population may not represent the women in daily practice. Thus a question remains open whether the differences in outcomes between the zoledronic acid-treated vs the no zoledronic acid group may be much smaller in women treated with adjuvant chemotherapy. However, it is reassuring that the trial population had excellent outcomes overall with very few cancer events, despite a third of the women having lymph node-positive disease.

It is meanwhile important to await results from other large adjuvant bisphosphonate trials. One is the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE, NCT00072020) trial of more than 3000 women with Stage II breast cancer randomized to 5 years of zoledronic acid vs no further treatment; an interim analysis of this trial is anticipated later this year. Other adjuvant trials are the NSABP B-34 (NCT00009945) study of clodronate, the German Adjuvant Intergroup Node-positive (GAIN, NCT00196872) study of oral ibandronate, and the Postoperative Use of Zoledronic Acid in Breast Cancer Patients After Neoadjuvant Chemotherapy (NaTan, NCT00512993) trial of zoledronic acid. Together, these trials will include more than 10,000 women and presumably will answer the adjuvant bisphosphonate question.

For now, women should be aware of the emerging data and encouraged to participate in adjuvant bisphosphonate trials. Patients at risk for osteoporosis and fractures — including those taking aromatase inhibitors or with treatment-related premature menopause — should be identified and managed appropriately with lifestyle modifications, calcium and vitamin D supplementation, and monitored with bone mineral density examinations. Whether upfront bisphosphonate prophylaxis ultimately reduces skeletal events in these groups is unknown as of yet, but trials are underway and appear to show protection of bone mineral density at least.⁴

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Vitamin D and breast cancer

Joseph Ragaz, MD, FRCPC

FREQUENCY OF VITAMIN D (VIT D) DEFICIENCY AT BREAST CANCER (BC) DIAGNOSIS AND ASSOCIATION WITH RISK OF DISTANT RECURRENCE AND DEATH IN A PROSPECTIVE COHORT STUDY OF T1-3, N0-1, M0 BC. ASCO 2008, ABSTRACT 511.

Investigators: P.J. Goodwin et al.

TRIAL SUMMARY: This study enrolled 512 consecutive newly diagnosed breast cancer patients between 1989 and 1995, and followed them prospectively until 2007. Data including risk factors and dietary intake were collected. Blood samples were drawn and frozen within 8 weeks after surgery, and serum levels of 25-hydroxy Vitamin D (25-OH Vitamin D) were measured in 2007 by radioimmunoassay immunohistochemistry (IHC). Levels were considered deficient if < 50 nmol/L, insufficient if 50–72 nmol/L, adequate if 72–372 nmol/L and toxic if > 373 nmol/L.

The mean level was 58.1 ± 23.4 nmol/L (range 8–177 nmol/L) with 192 women (37.5%) deficient, 197 (38.5%) insufficient, 123 (24.0%) adequate and none (0%) toxic. There were positive associations between lower levels of Vitamin D and premenopausal status at diagnosis, high body mass index (BMI), high insulin levels and high tumour grade (all p < 0.03), and between low levels of Vitamin D and low dietary intake of retinol, Vitamin E, grains and alcohol (all p < 0.02). As shown in **Table 2**, at median followup of 11.6 years, distant disease-free survival (DDFS) and OS

were significantly lower in women with deficient vs adequate initial measurements of Vitamin D. This association was independent of age, BMI, insulin levels, disease stage, nodal status and tumour grade. Estrogen receptor status, adjuvant chemotherapy and tamoxifen did not significantly modify the DDFS associations, although OS was modified by tumour grade. There was no association between Vitamin D level and OS in ER-negative disease. The authors concluded that Vitamin D deficiency is common in women at the time of breast cancer diagnosis and is associated with poor prognosis.

TABLE 2. Association of baseline Vitamin D levels and 10-year distant disease-free survival (DDFS) and overall survival (OS)

	deficient Vitamin D (< 50 nmol/L)	insufficient Vitamin D (50-72 nmol/L)	adequate Vitamin D (72-372 nmol/L)	hazard ratio (HR)*
10-year DDFS	69%	79%	83%	1.94 (p = 0.02)
10-year OS	74%	85%	85%	1.73 (p = 0.02)

*HR between deficient vs adequate

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

The well-known association between Vitamin D levels, Vitamin D intake and cancer in humans became more relevant after 2 recent publications relating increased Vitamin D levels with reduced risk of cancer, particularly for colorectal, lung and breast cancers.^{1,2} Further evidence implies a possible link between Vitamin D levels and reduced all-cause mortality.³ A recent study correlated non-melanoma skin cancer incidence — a surrogate for increased sun exposure — with decreased colorectal and breast cancer incidence rates.⁴ Thus, recent literature shows an overall benefit of sun exposure on human health, despite the proven association of sun exposure with increased incidence rates of melanoma, and calls into question the long-held dogma forbidding sun exposure. The ASCO 2008 presentation of Goodwin et al is therefore very timely.

VITAMIN D BACKGROUND

Vitamin D in the human body originates either in the gut

(via dietary intake or supplements) or from the skin, via activation through sun exposure. Epidemiologic observations link levels of Vitamin D and geographic latitude, indirectly reflecting the exposure of populations to sunlight. Both dietary and skin-derived Vitamin D are metabolized first in the liver to the inactive 25-OH Vitamin D, then in the kidneys to the active form, 1-25 dihydroxy Vitamin D.

There is now evidence that breast tissues also convert inactive 25-OH Vitamin D into active 1-25 dihydroxy Vitamin D, through a poorly understood pathway.⁵ As well, evidence from tissue cultures links the Vitamin D effect with biologic signals for proliferation and angiogenesis.⁴ The final Vitamin D pathway has recently been shown to involve increased rates of apoptosis and differentiation, both essential factors linked with reductions in carcinogenesis and in the aggressiveness of human cancer.⁴ While consensus is lacking, Dr. Goodwin noted that several studies have docu-

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mented an inverse relationship between Vitamin D intake and the risk of breast cancer, particularly for premenopausal women. Few studies have explored the association of Vitamin D levels with breast cancer mortality.

VITAMIN D BLOOD LEVELS AND BREAST CANCER OUTCOME

Goodwin et al's study analyzed Vitamin D levels in blood samples of 512 Stage T 1–3, N0–1 breast cancer patients. Importantly, less than a quarter (24%) of these women had adequate Vitamin D levels. Positive associations were seen between low levels of Vitamin D and several features of high-risk breast cancer, namely premenopausal status, BMI, high insulin levels and high tumour grade (all $p < 0.03$). Low Vitamin D levels were also associated with low dietary intake of retinol, Vitamin E and grains, and alcohol (all $p < 0.02$). The alcohol–Vitamin D level correlation was non-linear, with the highest levels associated with intake of 5–10 drinks per week. These associations were reported as significant but not strong. Patients designated for adjuvant chemotherapy had significantly lower Vitamin D levels, a probable association with younger age, higher grade, positive nodal status and overall higher-risk tumour — constituting indications for adjuvant chemotherapy. As shown in **Table 2**, page 21, at median followup of 11.6 years, women in the deficient vs adequate groups were 1.94 times more likely to develop distant recurrence, as expressed by the 10-year distant DDFS (HR = 1.94; 95% CI 1.16–3.25). The inverse association between Vitamin D and outcome was independent of age, BMI, insulin, disease stage, nodal status and tumour grade. The significant inverse relationship remained after adjusting for tumour size, ER status and nodal status. Distant DFS — a good surrogate for OS — predicted OS at 10 years, with cases in the deficient group compared to the adequate group having a 1.7-fold higher likelihood of dying from any cause (HR = 1.73; 95% CI 1.05–2.86). Adjustment for tumour and nodal stages and for ER status again confirmed Vitamin D levels as an independent factor.


Because of the lack of difference in outcomes between the insufficient and adequate groups, the authors modeled the interaction of hazard ratio of death with Vitamin D levels using a smooth log-hazard model, which showed the lowest hazard to be in the Vitamin D level range of 80–110 nmol/L, with increased hazard at higher blood levels. Dr. Goodwin noted that the data from this study do not explain this finding. She mentioned reports of increased cardiac risk and lower overall health with very high Vitamin D levels, suggesting that a fairly narrow range may be optimal.

IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

This study provides evidence for a statistically significant inverse relationship between serum Vitamin D level at diagnosis and breast cancer outcome. The authors proposed a reanalysis of Vitamin D levels and outcomes in the large, completed, randomized NCIC–CTG MA21 trial, which compared 3 dose-intense chemotherapy arms vs standard CEF chemotherapy, and a new randomized trial

of Vitamin D vs placebo for the cases found deficient. They also recommended that Vitamin D levels be monitored in breast cancer patients or, where not feasible, that women take 400–800 mg per day of Vitamin D supplements.

These are reasonable recommendations. However, with rising amounts of data confirming associations of Vitamin D deficiency with poor health outcomes, Canadian practitioners are in need of more specific guidelines with regards to when vitamin D levels should be monitored and whether supplements should be recommended in cases of deficiency. While the therapeutic benefit of intervention has not been confirmed, a lot of data including the present study indicate that monitoring and possibly supplementation are sensible approaches. A growing number of newly diagnosed breast cancer patients know about the results of this and other recent studies on Vitamin D, and are likely to consider implementing supplementation on their own, especially considering that Vitamin D taken within recommended doses represents one of the least toxic agents available.

The conclusions of this well-conducted study are provocative. If the oncology community is to be perceived as representing the interests of their patients, the onus is now on cancer care providers to either monitor Vitamin D levels and launch trials on the therapeutic benefits of supplementation, or to articulate the rationale for why these measures are not being taken. 

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Disclosure

Drs. Kennecke, Lim and Ragaz report having no relevant conflicts of interest. Dr. Grenier reports being on advisory boards of AstraZeneca and GlaxoSmithKline. Dr. Lê reports serving on advisory boards and speakers bureau of Roche. Dr. Lohrisch reports receiving research support from AstraZeneca, being on advisory boards of Amgen, AstraZeneca and Roche, and being on the speakers bureau of Roche.

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