

LANDMARKS **Reports of recent clinical trial data**



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Prostate cancer

BONE HEALTH IN MEN RECEIVING ANDROGEN DEPRIVATION THERAPY

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TRIAL SUMMARY: Denosumab for prevention of fractures

Smith MR, Saad F, Egerdie B et al. Effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. *J Urol* 2009;182(6):2670-5.

A previously reported Phase III trial¹ examined the effects of denosumab, a fully human monoclonal antibody against receptor activator of NFK β Ligand (RANKL), on bone mineral density (BMD) and fractures in men receiving androgen deprivation therapy (ADT) for non-metastatic prostate cancer. Study participants included men \geq 70 years old or $<$ 70 with either a low BMD or a history of osteoporotic fracture. They were randomized to receive either denosumab 60 mg by subcutaneous injection every 6 months ($n = 734$) or placebo ($n = 734$), and received daily calcium and vitamin D supplements for three years. This update of results including prespecified subgroup analysis showed that at the end of three years, denosumab had significantly increased BMD compared to placebo by 7.9% in the lumbar

spine, 5.7% in the total hip and 6.9% in the distal third of the radius ($p < 0.0001$ for all three sites). Similar benefit was seen in all patient subgroups as defined by age, presence of prevalent (pre-existing) vertebral fractures, type of ADT, baseline BMD and levels of the bone turnover markers C-telopeptide (sCTx, a bone collagen breakdown product due to osteoclast action) and tartrate-resistant alkaline phosphatase 5b (TRAP-5b, an osteoclast-specific enzyme). Greater mean increases in lumbar spine BMD were seen in men with the highest levels of bone turnover markers, lower body-mass index (BMI), lower BMD T-scores and longer duration of ADT. Greater mean increases in total hip BMD were seen in those with lower BMD T-scores and higher levels of bone turnover markers. Greater BMD increases at the distal third of the radius (evaluated in 309 patients) were seen in younger men and in those with higher levels of bone turnover markers. The authors concluded that denosumab consistently showed significantly increased BMD at all skeletal sites and in every subgroup, including in men at greatest risk for bone loss and fractures.

COMMENTARY: Osteoporosis is prevalent in both women and men. Osteoporosis in men can lead to significant morbidity, as men account for a third of all hip fractures. As well, men have a higher rate of death compared to women after hip fracture.² More than 50% of all cases of osteoporosis in men are associated with alcohol abuse, long-term glucocorticoid therapy or hypogonadism. Gonadotropin-releasing hormone (GnRH) agonists are the mainstay of ADT for patients with locally advanced, recurrent, or metastatic prostate cancer; however, they increase bone turnover, decrease BMD and lead to increased risk of fracture. Studies have reported 2% to 3% decreases per year in BMD of the hip and spine during initial therapy despite concurrent administration of supplemental calcium and vitamin D.

BMD seems to decline steadily during long-term ADT, which is important as some patients may receive treatment for a number of years. However, the mechanism leading to adverse skeletal effects of GnRH agonists is more related to estrogen deficiency than to testosterone deficiency. Osteoblasts and osteoclasts, which are important in bone regulation, express estrogen receptors. Therefore, in addition to bisphosphonates, selective estrogen receptor modulators and, as described below, disruptors of the RANK signaling pathway, may play a role in management and prevention of osteoporosis in this patient population.

Dr. Smith et al's new article provides an update of previously reported data regarding Phase III studies of denosumab in prostate cancer patients without bone metastases on ADT.¹

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Denosumab is a human monoclonal antibody that binds to the RANKL. RANK signaling is important in activation, differentiation, proliferation and apoptosis of osteoclasts. The earlier data reported increased lumbar spine BMD at 24 months of 5.6% for men receiving denosumab vs loss of 1.0% with placebo ($p < 0.001$; absolute change +6.7%), fewer new vertebral fractures at 12, 24 and 36 months and statistically significant differences in BMD at the hip and distal third of the radius. Data presented at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) by Fred Saad³ demonstrated positive effects on fractures at multiple sites. The new data summarized above show that denosumab prevented fractures of the lumbar spine, hip and distal third of the radius by a statistically significant margin in all patient subgroups.

Another agent under investigation is toremifene, a selective estrogen receptor modulator that simulates the beneficial effects of estrogens in the bone. A presentation at the 2009 ASCO Annual Meeting by Karen A. Veverka reported

IN BRIEF

Already known

- Among men with prostate cancer receiving androgen deprivation therapy (ADT), increased bone mineral density (BMD) of the lumbar spine and non-vertebral sites, and decreased incidence of new vertebral fractures, had been reported in those receiving denosumab, a human antibody against RANKL, compared to those receiving placebo.
- Toremifene, a selective estrogen receptor modulator under investigation, has shown improved hip and lumbar BMD and reduction in new vertebral fractures in this population.
- Both denosumab and toremifene simulate the benefits of estrogen in the bone.

What this study showed

- This update reported further increases in BMD with denosumab in the lumbar spine, hip and distal third of the radius, as well as further decrease of vertebral fractures and of fractures in the hip and distal third of the radius, in this population.
- Benefits were seen in all patient subgroups including those at greatest risk for fractures.

Next steps

- Once available in Canada, new agents that can prevent skeletal fractures will be a valuable additional tool to preserve quality of life in men receiving ADT for prostate cancer.

TABLE 1. Results at 24 months with denosumab (60 mg subcutaneously every 6 months) and toremifene (80 mg oral daily) in men receiving ADT for prostate cancer

	denosumab	toremifene
change in lumbar spine BMD	+6.7%	+2%
relative risk reduction in vertebral fracture (vs placebo)	-70%	-54.8%

results of a Phase III trial of oral toremifene 80 mg daily vs placebo.⁴ Study participants were men ($n = 1382$) aged 50 years or older with histologically confirmed prostate cancer, with no bone metastases, who had received ADT either continuously for at least six months or intermittently for at least 12 months prior to enrollment. All patients received continuous ADT during the study. After two years, new vertebral fractures occurred in 1.6% of patients receiving toremifene vs 3.5% of those on placebo (relative risk reduction 54.8%; $p = 0.023$). With toremifene, hip and lumbar spine BMD had increased 1.6% and 2% respectively. BMD increases were seen in patient subgroups including those with differences in age, fracture prevalence, baseline BMD, exposure to ADT and use of calcium and vitamin D supplements. Limited toxicity data were presented, but toremifene has been associated with possible cardiovascular effects (prolonged QT interval and deep vein thrombosis) while improving hot flushes and lipid profiles. **Table 1** compares 24-month results for denosumab and toremifene on lumbar spine BMD and rate of vertebral fractures.

ROLE OF PHYSICIANS

Physicians need to have a high level of suspicion for osteoporosis in this patient population — bone density scans are generally recommended for monitoring. However, with the emergence of agents that can maintain and even increase BMD, prevention of bone loss is increasingly important in men receiving ADT. Patients also need to understand that healthy diet and exercise help combat other potential side effects of ADT such as muscle loss and cognitive dysfunction. Currently neither toremifene nor denosumab are available in Canada, but denosumab is under review by Health Canada.

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3. Saad F, Smith MR, Egerdie B et al. Denosumab for prevention of fractures in men receiving androgen deprivation therapy (ADT) for prostate cancer (PC). ASCO 2009, Abstract 5056.
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Non-small cell lung cancer

TREATMENT OF ADVANCED DISEASE

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STUDY SUMMARY: Gefitinib monotherapy

Shepherd FA, Douillard J-Y, Fukuoka M et al. Gefitinib versus Docetaxel in Patients with Pretreated Advanced Non-Small-Cell Lung Cancer (NSCLC): Meta-Analysis from Four Randomized Clinical Trials. IASLC 2009, Abstract A2.4.

This meta-analysis presented at IASLC 2009 analyzed patient data from four open-label, randomized Phase II–III trials evaluating gefitinib (250 mg orally once per day) vs docetaxel (75 mg/m² intravenously every three weeks [60 mg/m² in one trial]) in a broad range of patients who had received prior treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC). The four trials were:

- the multinational Iressa NSCLC Trial Evaluating REsponse and Survival against Taxotere; multinational (INTEREST; n = 1466; 972 patients of Asian origin)¹
- the Japanese V-15-32 trial (n = 489; all patients of Asian origin)²
- the multinational Second-line Indication of Gefitinib in NSCLC trial (SIGN; n = 141; none of Asian origin)³
- the IRESSA as Second-line Therapy in Advanced NSCLC–Korea trial (ISTANA; n = 161; 160 of Asian origin)⁴

As shown in **Table 2**, both unadjusted analyses and analyses adjusted for covariates showed similar overall survival (OS) and progression-free survival (PFS), and superior overall response rate (ORR) of gefitinib compared to docetaxel. In patients of Asian origin, PFS was superior with gefitinib compared to docetaxel. The authors concluded that given the similar efficacy and superior tolerability, quality of

TABLE 2. Hazard or odds* ratios (HR or OR) for efficacy endpoints in four trials of gefitinib vs docetaxel

All patients			
variable	number of patients and events	unadjusted analysis HR or OR 95% CI p-value	adjusted† analysis HR or OR 95% CI p-value
overall survival	n = 2224 1608 events	HR = 1.03 95% CI = 0.93–1.113 p = 0.5773	HR = 1.00 95% CI = 0.91–1.10 p = 0.9912
progression-free survival	n = 2005 1710 events	HR = 0.97 95% CI = 0.88–1.07 p = 0.536	HR = 0.96 95% CI = 0.87–1.07 p = 0.536
overall response rate	n = 2005	OR = 1.58 95% CI = 1.19–2.10 p = 0.002	OR = 1.65 95% CI = 1.24–2.21 p = 0.001
Patients of Asian origin			
variable	number of patients and events	unadjusted analysis HR or OR 95% CI p-value	adjusted† analysis HR or OR 95% CI p-value
overall survival	n = 2224 1608 events	HR = 1.04 95% CI = 0.88–1.22 p = 0.651	HR = 0.99 5% CI = 0.84–1.17 p = 0.894
progression-free survival	n = 2005 1710 events	HR = 0.83 95% CI = 0.71–0.96 p = 0.013	HR = 0.81 95% CI = 0.69–0.94 p = 0.006
overall response rate	n = 2005	OR = 2.52 95% CI = 1.71–3.72 p < 0.001	OR = 2.63 95% CI = 1.76–3.93 p < 0.001

* HR < 1 indicates a lower risk of event with gefitinib; OR > 1 indicates a higher chance of response on gefitinib

† adjusted for randomized treatment, study, smoking history, number of primary chemotherapy regimens, performance status, sex, age and best response to prior chemotherapy

life benefits and ease of administration of gefitinib, this agent shows a superior risk-benefit ratio compared to docetaxel.

COMMENTARY: This meta-analysis provides support for the use of gefitinib in metastatic NSCLC. Gefitinib has a checkered past in the treatment of this malignancy. It initially received accelerated approval by the Food and Drug Administration (FDA) in May of 2003, based on two Phase II trials: Iressa Dose Evaluation in Advanced Lung cancer (IDEAL) 1⁵ and IDEAL 2.⁶ These trials, conducted in Asia and the US respectively, enrolled a total of over 400 patients who had failed first- or second-line chemotherapy. Response rates ranging from 9% to 19% were observed. The FDA-approved indication was as monotherapy in patients with locally advanced or metastatic NSCLC after failure of both platinum- and docetaxel-based chemotherapies. This approval

was contingent on post-marketing study commitments to complete several trials including the Iressa Survival Evaluation in Lung cancer trial (ISEL),⁷ a randomized Phase III study comparing gefitinib vs placebo in subjects with advanced NSCLC who had received one or two prior regimens and had refractory disease (defined as progression within three months of first-line therapy) or were intolerant to their most recent regimen. ISEL's results were surprisingly negative, with no improvement in survival (5.6 months vs 5.1 months, not statistically significant). However, issues have been raised regarding the dose of gefitinib used, as the researchers elected to proceed with the optimum biologic dose (250 mg) instead of the typical maximum tolerated dose

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(500 mg), and the refractory patient population selected, which may have negatively affected the study outcome.

In 2005 the FDA reviewed the results of the Phase III trials involving gefitinib. In addition to the negative ISEL trial, they assessed the Phase III Southwestern Oncology Group (SWOG) 0023 trial,⁸ which compared cisplatin + etoposide given concurrently with radiotherapy and consolidation docetaxel, followed by maintenance therapy with gefitinib vs placebo, in patients with inoperable locally advanced Stage III NSCLC. This study was closed early based on an unplanned interim analysis that suggested a possible detrimental effect of the maintenance gefitinib on survival. The data from these trials prompted a revision of the FDA indication, to allow treatment only of patients who were currently receiving and benefiting from the drug; Health Canada followed suit. This was a serious setback in the development of gefitinib, a drug that clearly had activity in NSCLC. An uphill battle ensued, and now the results of this meta-analysis by Frances Shepherd et al and the recent Iressa Pan Asian Study (IPASS)⁹ provide evidence to support the reapproval of this agent in North America.

RECONSIDERING GEFITINIB

Dr. Shepherd et al's meta-analysis evaluated the data from four trials comparing gefitinib to docetaxel in previously treated advanced NSCLC: INTEREST,¹ V-15-32,² SIGN³ and the ISTANA trial.⁴ Docetaxel has demonstrated an improvement in survival of 7.5 months vs 4.6 months compared to best supportive care in the second-line setting,¹⁰ and as one of the standard care options for previously

treated advanced NSCLC patients it is an appropriate comparator arm for gefitinib. This meta-analysis of over 2000 patients, also reported at ASCO 2009,¹¹ indicates that gefitinib has similar efficacy to docetaxel with respect to OS, PFS and improved response rate, with better tolerability.

The trials on which this conclusion is based vary significantly with respect to patient characteristics. INTEREST and SIGN were multinational efforts, while V-15-32 and ISTANA were conducted in Japan and Korea, respectively. The latter two studies enrolled only Asian patients and had a higher proportion of never-smokers (32% and 41%) and adenocarcinoma (78% and 68%). INTEREST, however, as the largest study (n = 1466), dilutes the effects such that in the overall meta-analysis the composition included 41% Asians, 36% females, 25% never-smokers and 62% adenocarcinomas. Nonetheless, it is clear that the meta-analysis included an enhanced population of patients with clinical predictors of benefit for epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), namely female, Asian, non-smoking status and adenocarcinoma. While ORR and PFS were superior in the Asian subgroup, the survival benefit with gefitinib was seen across all ethnic groups. When adjusted for randomized treatment given, study, smoking history, number of prior chemotherapy regimens, performance status, sex, age and best response to prior chemotherapy, the analysis continued to support positive outcomes with gefitinib. Based on this, the authors concluded: "gefitinib has a favourable benefit-risk profile compared to docetaxel in a broad pretreated advanced NSCLC patient population." While only two of the four trials met their primary endpoint — INTEREST (non-inferior OS) and ISTANA (superior PFS) — the data clearly suggest that gefitinib is an effective therapy in NSCLC.

OTHER SUPPORT FOR GEFITINIB

The results of the Iressa Pan-Asia Study (IPASS) trial also provide compelling evidence for use of this agent.⁹ IPASS was a Phase III study of gefitinib vs carboplatin + paclitaxel in first-line advanced NSCLC, conducted in Asia. The unique feature of this trial was the criteria for patient selection: light or never-smoking status and adenocarcinoma. Thus, selection was for patients most likely to have tumours with activating EGFR mutations, known to be exquisitely sensitive to EGFR-TKIs. EGFR mutations typically occur in exon 19 and 21 in the tyrosine kinase domain, resulting in a receptor that is constitutively "on" and consequently a prime target for inhibition. The biomarker studies confirmed this with 59% of tested samples having EGFR mutations. Designed to demonstrate non-inferior PFS, IPASS results surpassed expectations: gefitinib was superior to carboplatin + paclitaxel with a hazard ratio of 0.741 (p < 0.0001). Not only did this study support the use of gefitinib, it suggested that EGFR mutation-positive patients should receive first line-treatment with gefitinib.

Gefitinib has regained approval in Europe: the Committee for Medicinal Products for Human Use has recommended the approval of gefitinib for adults with locally advanced or metastatic NSCLC with activating mutations of EGFR tyrosine kinase in all lines of therapy. It was recently approved

IN BRIEF

Already known

- Results from earlier studies of gefitinib monotherapy and maintenance therapy in advanced NSCLC were inconsistent, and initial marketing approvals were subsequently withdrawn except for continuing treatment of patients who were already receiving and benefiting from the drug.

What this study showed

- This meta-analysis of four trials of gefitinib vs docetaxel showed that gefitinib provides similar progression-free and overall survival, a greater response rate and better tolerability.
- Results of the IPASS study showed superior PFS for gefitinib compared to carboplatin + paclitaxel in a population of never-smoking patients in Asia with adenocarcinoma.

Next steps

- Health Canada's recent approval of gefitinib for patients with advanced NSCLC who have activating mutations of EGFR tyrosine kinase provides a new therapeutic option for these patients.

by Health Canada for first-line treatment of patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC who have activating mutations of EGFR tyrosine kinase.

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MOLECULAR-BASED TREATMENT

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STUDY SUMMARY: Predictive value of KRAS status in NSCLC

Gatzemeier U, Paz-Ares L, Rodrigues Pereira J et al. Molecular and clinical biomarkers of cetuximab efficacy: Data from the phase III FLEX study in non-small cell lung cancer (NSCLC). IASLC 2009, Abstract B2.3.

The multinational, randomized, Phase III First-Line Erbitux in Lung Cancer (FLEX) study demonstrated improved OS, regardless of tumour histology, with the addition of cetuximab to cisplatin + vinorelbine chemotherapy in first-line treatment of patients with advanced epidermal growth factor receptor (EGFR)-expressing NSCLC. This post-hoc analysis examined whether KRAS mutation predicted for efficacy of cetuximab in NSCLC, as has been shown in colorectal cancer, and also the prognostic value of acne-like rash developing within 21 days of starting treatment with cetuximab.

KRAS mutational status was analyzable from formalin-fixed paraffin-embedded tumour samples of 395 of the 1125 patients (35%) participating in the FLEX trial. Mutation was found in 75 (19%) of these in both cetuximab and non-

cetuximab-treated patients, using an assay that detected oncogenic mutations at codons 12 and 13. Kaplan-Meier estimates of OS showed no significant differences between patients with normal (wild) vs mutated KRAS. However, in an analysis of the 518 patients overall receiving cetuximab who were alive on Day 21 of the first treatment cycle, the 290 (56%) who had a rash of any grade survived longer than the 228 with no early rash (median OS 15.0 months [95% CI 12.8 to 16.4] vs 8.8 months [95% CI 7.6 to 11.1]; HR 0.63; 95% CI 0.52 to 0.77; p < 0.001). Patients not receiving cetuximab rarely had rash. Only 25% of tissue samples were evaluable for EGFR gene copy number, detected by fluorescent in situ hybridization (FISH). Of these, 37% were FISH-positive by the Colorado scoring system, and neither OS, PFS nor response rate differed significantly according to treatment. The authors concluded that KRAS status does not predict for the efficacy of adding cetuximab to platinum-based first-line chemotherapy in patients with NSCLC, and that early-onset skin rash correlates with longer survival in patients receiving cetuximab.

COMMENTARY: The dream of a thoroughly molecular-based treatment algorithm in NSCLC has been elusive. In leukemia and lymphoma, the molecular and genetic characteristics of malignancies have determined treatment approaches for decades, a paradigm that is also well established in breast cancer. Even in colorectal cancer, several recent studies

have shown that KRAS mutations preclude benefit from anti-EGFR monoclonal antibody (mAb) therapy in metastatic colorectal cancer (CRC), an observation seen in several settings and with more than one anti-EGFR mAb.^{1,2} This is very satisfying for two reasons: it implies that we can direct expensive “targeted” therapies to those patients most likely

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to benefit, while also validating the impression that we know what is happening at the molecular level in these cancer cells. So it was somewhat disappointing that what was expected to be a useful predictive marker for benefit in NSCLC turns out not to be. This finding fuels the nihilistic impression that lung cancer really is different and much more difficult to understand than other cancers. Why then is KRAS mutational status not predictive for benefit of anti-EGFR mAb treatment in NSCLC?

SOME CLUES

In attempting to answer this, the first point to highlight is the difference in proportion of enrolled patients whose tumour samples are analyzable at the molecular level. In CRC studies virtually all patients have interrogable biopsies or good quality resected tissue available for analysis, but of the patients enrolled in the FLEX study, KRAS mutational analysis was possible on only about a third. This is not unusual in lung cancer: a low proportion of analyzable samples is a conspicuous feature of all NSCLC trials that include molecular correlative studies in their design — highlighting one of the challenges inherent in any translational work in this disease. The recent tendency to overinterpret the significance of predictive molecular markers in NSCLC is at least partly attributable to small sample sizes and subgroup analysis of retrospective data.^{3,4} Changing this pattern will require some creative thinking. Traditionally there has been no drive to sample more or better quality material when biopsying lung lesions beyond the need to confirm malignancy and exclude small cell lung cancer. Better biopsying practices and new

immunohistochemical rather than mutation-based analyses may help, and a blood sample-based analysis of circulating tumour cells or cell-free nucleic acid would bypass the problem altogether. Until then, NSCLC molecular research will be handicapped by the small proportion of patients whose diagnostic samples can be utilized.

A second factor may be the relative magnitude of the immune-modulatory effect of anti-EGFR mAbs in NSCLC vs in CRC. It was assumed that this would be similar regardless of the cancer at which the mAb is directed, however that may not necessarily be the case. In vivo studies that track and quantify mAb-mediated immunomodulatory effects have not been carried out and will be challenging to design and implement. A clearer impression of the importance of this effect is beginning to emerge. For example, it has been shown that the in vitro extent of cetuximab-mediated lysis of squamous cell carcinoma of the head and neck cells is influenced not only by EGFR expression and cetuximab concentration, but also by polymorphisms of the FcγR receptors for IgG, which can affect NK cells and macrophages' cytotoxicity. Effector cells expressing the FcγR IIIa-158 valine V/V allele are more effective than those expressing FcγR IIIa-158 V/phenylalanine (F) in mediating cell lysis.⁵ Clinical studies seem to corroborate this effect in CRC patients. In a study of 69 patients whose FcγR was genotyped in detail, those with FcγR IIa-131 histidine H/H and/or FcγR IIIa-158 V/V genotypes had a 1.5-month longer PFS than FcγR IIa-131 arginine (R) and FcγR IIIa-158 F carriers, a difference that remained significant for patients with mutated KRAS.^{6,7} Such studies clearly imply that immune factors play a role in determining response to anti-EGFR mAbs, irrespective of KRAS status. Prospective studies to quantify this effect in NSCLC need to be carried out and compared to the magnitude seen in CRC.

A third issue may be the very role and nature of KRAS mutations in NSCLC compared to CRC. Intriguing research dating from the 1990s has suggested that the impact of activating KRAS mutations on outcome in NSCLC is not uniform. Two reports in particular, albeit on relatively small samples sizes, demonstrated that activated KRAS mutations may not all be harmful. Mutations resulting in the substitution of a hydrophobic amino acid, and even some smoking-associated transversions, seem to confer an improved outcome compared to others.^{8,9} More recent analysis by a team from the University of California, Davis¹⁰ has expanded on this theme, confirming that the nature of KRAS mutation differs in NSCLC compared to CRC in several ways, being less common (21% vs 39% for CRC), virtually absent in squamous cell tumours, more likely to be smoking-associated (69% vs 38%) and more likely to be a transversion rather than a transition (ratios 3.08 vs 0.80 in NSCLC vs CRC). Given this, it is not surprising that KRAS mutational analysis of NSCLC assumes a different significance from that in CRC.

GLIMPING A MOLECULAR-BASED ALGORITHM

The emergence of EGFR-activating mutations as a strong predictor of benefit from EGFR-TKIs is promising. Meanwhile, the predictive role of KRAS in NSCLC must be prospectively studied in several separate clinical settings: the

IN BRIEF

Already known

- It was known from the FLEX study that adding cetuximab to cisplatin + vinorelbine chemotherapy improved overall survival regardless of tumour histology, in first-line treatment of patients with advanced epidermal growth factor receptor (EGFR)-expressing non-small cell lung cancer (NSCLC).

What this study showed

- In this post-hoc analysis of FLEX data, KRAS status did not predict for efficacy — contrary to expectations, since it does predict for efficacy in colorectal cancer — while early-onset skin rash did correlate with longer survival in patients receiving cetuximab.

Next steps

- The predictive role of KRAS in NSCLC should be prospectively studied in other clinical settings of NSCLC: in adjuvant chemotherapy, metastatic chemotherapy and metastatic disease treated with targeted agents including the EGFR-TKIs and the anti-EGFR mAbs.

adjuvant chemotherapeutic setting, the metastatic chemotherapeutic setting and the metastatic setting with targeted agents including the EGFR-TKIs and the anti-EGFR mAbs. Ideally such studies will address not only the molecular makeup of NSCLC cells but also the stromal influences driving NSCLC and the immunologic factors determining response to new targeted agents. Undoubtedly, knowledge gained in such an exercise will propel the dream of molecular-targeted treatment forward, making the next few years an exciting time in this disease.

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Breast cancer

COMBINING TARGETED THERAPIES IN WOMEN WITH METASTATIC BREAST CANCER

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TRIAL SUMMARY: Lapatinib + trastuzumab in women with MBC

Blackwell KL, Burstein HJ, Sledge GW et al. Updated Survival Analysis of a Randomized Study of Lapatinib Alone or in Combination with Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer Progressing on Trastuzumab Therapy. *SABCs 2009*, Abstract 61.

This report presented updated survival data from the EGF104900 (NCT00320385) trial, which compared lapatinib + trastuzumab to lapatinib alone in women with HER2-positive metastatic breast cancer (MBC) who had experienced disease progression after prior palliative chemotherapy and trastuzumab regimens (median 3 cycles of trastuzumab-containing regimens). The 296 women enrolled were randomized to receive lapatinib 1000 mg once daily in combination with trastuzumab 2 mg/kg, after a 4-mg/kg loading dose, (n = 148) or lapatinib alone, at 1500 mg (n = 148) once daily.

Although median followup was not provided, data were mature at the time of this analysis, given that 218 (74%) of patients had died and a further 8.9% were lost to followup. Seventy-seven (52%) subjects on lapatinib monotherapy crossed over to the combination at progression, as allowed by protocol. Median OS was 60.7 weeks for lapatinib + trastuzumab and 41.4 weeks for lapatinib. The unadjusted hazard ratio (HR) for OS was 0.74 (95% CI 0.57 to 0.97; p = 0.026) equivalent to a 26% reduction in risk of death (p = 0.080). After adjusting for crossover, the HR was 0.71 (95% CI 0.54 to 0.93; p = 0.012). Survival benefit was also seen after adjusting for baseline prognostic factors. The authors concluded that the OS benefit of the combination treatment with lapatinib plus trastuzumab was improved by a statistically significant margin compared to lapatinib alone in heavily pretreated women with HER2-positive MBC, and that crossover likely caused underrepresentation of the survival benefit.

COMMENTARY: While it may be regular practice in many places to treat HER2-positive MBC with repeated sequential lines of trastuzumab-containing anticancer therapy after disease progression on first-line trastuzumab, proven benefit for this approach has been lacking until now. Several previous trials that tried to address this question had design limitations. Bartsch et al¹ reported a 24-month OS and 8-month PFS for the combination of trastuzumab and capecitabine following prior treatment with anthracyclines, taxane or vinorelbine, and trastuzumab among 40 patients, however there was no

comparison arm without trastuzumab. The von Minckwitz trial,² which did randomly compare capecitabine to capecitabine + trastuzumab, is underpowered due to premature closure after the Geyer trial³ reported superior time to progression (TTP) for capecitabine + lapatinib (8.4 months) over capecitabine alone (4.4 months) after trastuzumab. The present study, presented by Blackwell from Indiana University on behalf of colleagues from Barcelona and Baylor, compares lapatinib to lapatinib + trastuzumab in patients heavily pretreated with chemotherapy and trastuzumab for

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metastatic disease. Both drugs target different areas of tyrosine kinase receptors, and lapatinib is known to be active after trastuzumab resistance develops. It is therefore reasonable to hypothesize that the combination may result in longer disease control than when one agent is given singly. A Phase I trial among 54 patients reported a 15% response rate and established the dose for the combination, which was used in this trial.⁴

In this update, we learn of a 20-week improvement in median OS (from 9.5 to 14 months), equivalent to a 26% reduction in the hazard of death, from adding trastuzumab to lapatinib. How do these results compare to other treatments following trastuzumab? Novel drugs targeting the HER2 and Erb family, such as pertuzumab (alone or with trastuzumab), trastuzumab-DM1, and neratinib have or are being studied in patients with two or more prior therapies for metastatic disease, but there are no mature TTP or survival data. The other cited trials, including the Geyer trial (lapatinib + capecitabine),³ which had no improvement in survival, the Bartsch series, which reported 24-month median survival,¹ and the von Minckwitz trial (capecitabine + trastuzumab), which reported 25-month median survival,² were all second-line trials, therefore not directly comparable.

QUESTIONS ABOUT HER2 DISEASE

Two broad questions come to mind in trying to place this

data in today's HER2 breast cancer population. First, what is the activity of trastuzumab or any other anti-HER2 therapy after adjuvant trastuzumab? Disease that recurs after adjuvant trastuzumab is likely more resistant than disease that relapses without adjuvant trastuzumab. In the trials cited above, a minority of patients had adjuvant trastuzumab (5% in the Geyer trial, 2.5% in the Bartsch series; 2% in the von Minckwitz study) and the percentage has not yet been reported in this study. Thus it is difficult to generalize the results of any of these studies to that patient group.

Second, what are the implications of these results for the adjuvant management of HER2-positive disease? In terms of efficacy and toxicity, it may be very difficult to unseat adjuvant trastuzumab. Despite a 15% to 20% four-year event rate in the trastuzumab arms of adjuvant trials,⁵ the relapse rates in standard practice to date seem exceptionally low. While lapatinib reports less cardiotoxicity, it has only been examined in trastuzumab-pretreated patients, likely preselecting individuals less vulnerable to this side effect. Experience with lapatinib suggests that diarrhea and gastrointestinal toxicity are more clinically significant than appreciated from published studies. Thus there is a risk that the currently enrolling adjuvant trials BETH (NCT00625898) and ALTTO (NCT00490139) will show increased toxicity from adding to or replacing trastuzumab, with little added relapse-free or survival gain.

In conclusion, this study does not suffer the design flaws of prior trials exploring trastuzumab beyond progression. The finding of a considerable survival improvement in spite of 52% crossover at progression strengthens the conclusion that combining lapatinib and trastuzumab enhances disease control and should be strongly considered in clinical practice. One might interpret this data, together with the von Minckwitz trial, to recommend that for patients with progression on prior trastuzumab in the metastatic setting, continuing trastuzumab and adding one of several other anticancer therapies provides superior disease control than stopping trastuzumab. However, further data are needed to determine the value, if any, of this approach in breast cancer that relapses after adjuvant trastuzumab.

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5. Update of the HERA trial presented by Martine Piccart at the St. Gallen Oncology Conference 2009: Primary Therapy of Early Breast Cancer.

IN BRIEF

Already known

- Previous studies of sequential lines of chemotherapy including trastuzumab showed probable benefits in women with metastatic breast cancer (MBC) but had methodologic shortcomings.

What this study showed

- The combination of trastuzumab + lapatinib vs lapatinib alone in women with MBC who had received multiple lines of chemotherapy including trastuzumab offered a statistically significant survival benefit for the combined therapy, despite many of the patients who were randomized to lapatinib alone crossing over to the combination upon disease progression.

Next steps

- The combination of lapatinib and trastuzumab should be strongly considered in clinical treatment of women with MBC following progression after prior trastuzumab-containing therapy.
- Further research is needed to ascertain the activity of trastuzumab in recurrent disease when adjuvant therapy included adjuvant trastuzumab.
- The role of lapatinib in early disease has not been established, and will require closer evaluation of the side effects of both drugs.

PREVENTION

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TRIAL SUMMARY: Oral Bisphosphonates and Breast Cancer Prevention.

Chlebowski RT, Chen Z, Cauley JA et al. Oral Bisphosphonate and Breast Cancer: Prospective Results from the Women’s Health Initiative (WHI). SABCS 2009, Abstract 21.

This trial retrospectively analyzed data on breast cancer risk factors and oral bisphosphonate use of 154,768 postmenopausal women participating in the Women’s Health Initiative (WHI). At the time of enrollment, 2816 of the women were taking oral bisphosphonates (90% alendronate, 10% etidronate). Among 10,693 women with both measures at the time of enrollment, a significant correlation was found between hip fracture risk scores calculated by BMD and by a model that does not incorporate BMD.¹ Breast cancers were evaluated by a central review of pathology reports. **Table 4** shows the hazard ratios (HRs, by Cox proportional hazards regression) for invasive breast cancer according to bisphosphonate use after followup of 7.8 years (standard deviation 1.7). The authors concluded that women receiving an oral bisphosphonate at the start of the WHI study had fewer estrogen receptor (ER)-positive breast cancers by a statistically significant margin, with a non-significant trend

toward fewer ER-negative breast cancers, and that this suggests a possible direct inhibiting action of oral bisphosphonates on breast cancer.

TABLE 4. Incidence of invasive breast cancer among postmenopausal women in the Women’s Health Initiative study according to use of oral bisphosphonates at study entry

	incidence of invasive breast cancer* (95% CI)		bisphosphonate use			
			yes		no	
	hazard ratio (95% CI)	p-value	n	rate†	n	rate*
all	0.68 (0.52–0.89)	p < 0.01	64	3.29	5092	4.38
ER-positive	0.70 (0.52–0.95)	p = 0.02	50	2.56	3829	3.28
ER-negative	0.66 (0.31–1.39)	p = 0.27	8	0.41	717	0.61

* multivariate adjusted hazard ratios
† per 1000 woman-years of followup

COMMENTARY: The bisphosphonates have been known for over two decades to affect bone structure and prevent bone loss. With recent data showing significant reduction of skeletal and non-skeletal lesions, a new paradigm is now emerging: in the process of ameliorating the bone milieu, bisphosphonates may also interfere with the process of metastasis.

Studies by Powles et al² and Patterson et al³ piloted the use of clodronate in breast cancer. Diel et al⁴ first showed that in breast cancer patients whose bone marrow was positive for metastasis at diagnosis, clodronate significantly reduced both bone and visceral metastases, providing longer overall survival.

PRECLINICAL STUDIES

Recent studies imply that the significant benefit of bisphosphonates with respect to breast cancer disease-free survival may be explained by several antitumour mechanisms. Preclinical studies showed that zoledronic acid inhibited tumour-to-stromal cell adhesion, reducing invasion and proliferation of malignant cells. Induction of apoptosis in a variety of human tumour cell lines was also documented.^{5,6} Other data suggested that zoledronic acid can stimulate antitumour immune reactions^{7,8} and exert antiangiogenic effects.⁹ Of great interest, a recent study from China¹⁰ documented significant reduction of vascular endothelial

growth factor (VEGF) and N-telopeptide, a marker of bone resorption, within the first four weeks of weekly 1-mg zoledronic acid (a low-dose, metronomic regimen). These reports suggest that bisphosphonates act through secondary molecular mediators affecting both bone resorption (i.e. via markers such as N-telopeptide or cytokines such as VEGF) and malignant cancer clones.

CLINICAL STUDIES

A growing number of studies have shown that in patients receiving adjuvant aromatase inhibitor therapy, zoledronic acid at a dose of 4 mg every six months prevents the bone loss caused by aromatase inhibitors. Moreover, several studies have shown reduced incidence of micrometastases in the bone marrow of breast cancer patients who have received zoledronic acid.¹¹

The most recent and largest work on the impact of bisphosphonates on skeletal events in breast cancer is Gnant et al’s Austrian study,¹² which randomized 1803 premenopausal patients receiving tamoxifen + goserelin vs aromatase inhibitors + goserelin, with or without zoledronic acid, given at 4 mg intravenously every six months for three years. While no difference was seen in outcome between tamoxifen and aromatase inhibitors, zoledronic acid provided a significant 36% reduction in the risk of disease progression (HR 0.64; 95% CI 0.46 to 0.91; p = 0.001).

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Finally, in the integrated analysis of the Zometa–Femara Adjuvant Synergy Trial,¹³ zoledronic acid significantly reduced breast cancer recurrence among postmenopausal women in the adjuvant setting, raising the question of whether it should be used routinely to prevent metastases. This would require guideline changes extending use of zoledronic acid beyond the current restriction (in most centres) to preventing and improving bone loss.

WHAT ABOUT BREAST CANCER PREVENTION?

Chlebowski et al, representing the Women’s Health Initiative, take the work one step further into the arena of prevention. Data were presented at the 32nd San Antonio Breast Cancer Symposium from an observational cohort study of 154,768 postmenopausal women (none of whom had breast cancer at enrollment) in the WHI study, which evaluated the impact of oral bisphosphonates on bone health and breast cancer incidence.

A logistic problem of the analysis was that in general women with low BMD have a lower risk of breast cancer. To correct for this possible bias, an algorithm for bone (hip) fracture risk was used to adjust for potential differences between women who used bisphosphonates and those who did not. A separate Cox proportional hazards model that

accounted for factors known to affect breast cancer risk was used to compute the hazards for breast cancer.

The final analysis showed a significant reduction in breast cancer incidence in bisphosphonate users vs nonusers (HR 0.68; $p < 0.01$). There was no difference by age; however, a difference according to ER status was shown: significant event reduction of ER-positive tumours and a non-significant trend towards reduction of ER-negative tumours (HR 0.66; 95% CI 0.31 to 1.39). Importantly, the incidence of ductal carcinoma in situ (DCIS) was higher in bisphosphonate users than in nonusers (HR 1.59; $p = 0.002$), suggesting that the DCIS increase may represent an arrest in progression into invasive disease — while increasing the rate of DCIS (as seen in the STAR Trial with raloxifene).¹⁴

A confirmatory prevention case-control study of 4575 women was conducted in Israel,¹⁵ showing a 29% reduction in breast cancer incidence in those who reported using bisphosphonates for five years or more (adjusted HR 0.71, 95% CI 0.57 to 0.90). Reduced risks were evident only in year two and beyond; bisphosphonates used for less than a year were not associated with a change in breast cancer risk.

ARE MONOCLONAL ANTIBODIES AN ALTERNATIVE TO BISPHOSPHONATES?

A study by Stopeck et al from the University of Arizona¹⁶ illustrates the most recent development in bone health, reporting a benefit of denosumab over zoledronic acid (to date the most potent bisphosphonate) in breast cancer patients. Denosumab is a human monoclonal antibody that binds and inhibits RANKL, the primary mediator of osteoclast formation involved with cancer-induced bone resorption. The researchers postulated that suppression of RANKL would interfere with bone resorption. Women with Stage IV breast cancer and bone metastases were randomized to denosumab ($n = 1026$ available for analysis) vs zoledronic acid ($n = 1020$). By week 34 of the study, the patients taking denosumab had an 18% reduction in time to first on-study skeletal event and a 23% reduction of overall skeletal events (HR 0.77; $p = 0.01$). However, as yet, no effect on OS has been seen.

A TSUNAMI OF DATA

The newly emerging benefit of better breast cancer outcome through ameliorating bone health presents an important new option of routinely using these agents (both the bisphosphonates and newer agents such as denosumab) in adjuvant treatment as they may directly influence disease outcome. Chlebowski et al’s study pushes the rationale for bisphosphonate use into the arena of breast cancer prevention. Undoubtedly, these results need further refinement from randomized trials, particularly as to the agents used, subsets of women selected for this approach, and the cost-benefit profile. However, the already well-documented improvement of bone health (evidence level I), and the growing data showing a significant reduction of metastatic events in breast cancer make a strong case for the guideline-recommended use of agents affecting bone health for the majority of newly diagnosed breast cancer patients, as well as for women at high risk for breast cancer.

IN BRIEF

Already known

- It has long been known that bisphosphonates affect bone structure and prevent bone loss, especially in women receiving aromatase inhibitors as adjuvant therapy for breast cancer.
- Studies have also shown improvement in disease-free survival for women with breast cancer receiving bisphosphonates — first clodronate and more recently zoledronic acid.

What these studies show

- An analysis of the Women’s Health Initiative study has shown that women who took bisphosphonates had a lower risk of developing breast cancer.
- Another study comparing the monoclonal antibody denosumab to zoledronic acid reported greater reduction in skeletal events with the use of denosumab — the first indication of “proof of principle” for effectiveness of biological agents that target bone metabolism pathways.

Next steps

- The evidence for a significant effect of bisphosphonates in reducing metastatic events in breast cancer makes a strong case for the use of agents affecting bone health for the majority of women newly diagnosed with breast cancer, and perhaps as well as for routine use in women at high risk for breast cancer.

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HORMONAL THERAPY IN POSTMENOPAUSAL EARLY BREAST CANCER

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TRIAL SUMMARY: Exemestane vs tamoxifen followed by exemestane

Rea D, Hasenbaur A, Seynaeve C et al. Five Years of Exemestane as Initial Therapy Compared to 5 Years of Tamoxifen Followed by Exemestane: The TEAM Trial, a Prospective, Randomized, Phase III Trial in Postmenopausal Women with Hormone-Sensitive Early Breast Cancer. *SABCS 2009*, Abstract 11.

This was a report at five and a half years median followup of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study, which enrolled 9775 postmenopausal women with hormone receptor-positive early breast cancer.

Initially, in 2001, the women were randomized to receive exemestane 25 mg per day or tamoxifen 20 mg per day, after surgery and chemotherapy, as indicated. In 2004 the trial was modified to switch patients initially receiving tamoxifen to exemestane after two and a half to three years. No significant differences were found between the women switching to exemestane vs those staying on exemestane in terms of five-year DFS (85.7% vs 85.4%, respectively), five-year OS (90.5% vs 90.6%) or five-year rate of recurrence (10.2% vs 10.9%). Reported adverse events were as expected. The authors concluded that both treatment options are potentially appropriate.

TRIAL SUMMARY: Tamoxifen followed by exemestane vs tamoxifen

Bliss JM, Kilburn LS, Coleman RE et al. Disease Related Outcome with Long Term Follow-Up: An Updated Analysis of the Intergroup Exemestane Study (IES). *SABCS 2009*, Abstract 12.

In the Intergroup Exemestane Study (IES), 4724 postmenopausal women with early breast cancer whose disease had not recurred after two to three years of adjuvant tamoxifen were randomized to either continued tamoxifen or exemestane 25 mg per day, for a total of five years of hormonal therapy. This planned analysis at 91 months median followup of 4599 women (with 91% of women

having ≥ 6 years followup) excluded the 135 known to have estrogen receptor (ER)-negative disease. The unadjusted hazard ratio (HR) for breast cancer-free survival (i.e. excluding deaths from other causes) was 0.81 (95% CI 0.71 to 0.92; p = 0.001), favouring the patients receiving exemestane after two to three years of tamoxifen, and was similar in the 4052 women with ER-positive disease (HR 0.80; 95% CI 0.70 to 0.92; p = 0.002) and in the 547 whose ER status was unknown (HR 0.85; 95% CI 0.60 to 1.20; p = 0.36). Other analyses showed benefit of exemestane over tamoxifen in other prognostic subgroups, and also that the benefit continued posttreatment (HR 0.94; 95% CI 0.80 to 1.10; p = 0.46).

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COMMENTARY: The emergence of the aromatase inhibitors (AIs) has been hailed as a major advance in the adjuvant therapy of hormone-sensitive breast cancer. Guidelines from numerous jurisdictions now include AIs as part of the recommended options whether used instead of, sequenced with, or after five years of tamoxifen. With the commercial availability of three major AIs from three competing pharmaceutical houses, each having been studied in very large clinical trials, it has been confusing — to say the least —

IN BRIEF

Already known

- Aromatase inhibitors (AIs) offer better relapse-free survival (RFS) than tamoxifen, but with different side effect profiles.
- All three commercially available AIs (anastrozole, exemestane and letrozole) provide similar RFS benefits when used for five years in sequence (two to three years of tamoxifen followed by two to three years of AI).
- Letrozole has shown a significant RFS benefit when used for an additional five years; the other AIs have not been studied in the setting of hormonal therapy lasting for 10 years.
- No distinct survival benefit has been shown to using initial AI over tamoxifen, although subgroup analyses have suggested a possible benefit.

What these studies showed

- The TEAM results presented at SABCS 2009, at five and a half years median followup, showed equivalence between adjuvant exemestane for five years vs sequential tamoxifen (for two and a half to three years) followed by exemestane for a total of five years.
- The IES results presented at SABCS 2009, at 91 months median followup, showed continuing disease-free and overall survival results in women whose tumours were estrogen receptor (ER)-positive who received exemestane after two to three years of tamoxifen, but in the ER-unknown patients results were similar between the two groups (women with ER-negative disease were excluded from the analysis).

Next steps

- These results support the practice of switching to an AI after two and a half to three years of tamoxifen, for a total of five years of hormonal therapy.
- Until further research examines the question of duration of therapy when the initial five years includes sequential tamoxifen followed by an AI, these results provide support for the practice of stopping AI-containing adjuvant therapy after five years.

for oncologists to select the “best” strategy or drug for their patients. Indeed, understanding the theory of relativity, the space-time continuum or small-particle physics seems to pale in comparison!

There is no question that the AIs offer advantages over tamoxifen with regards to relapse-free survival (RFS), whether one uses the nonsteroidal (letrozole or anastrozole) or the steroidal (exemestane) variety. In the absence of direct comparisons of these drugs, it is also fair to state that when used instead of tamoxifen, both letrozole and anastrozole offer RFS advantages as per the results of the BIG 1-98¹ and ATAC² trials; all three drugs confer similar benefits when used in sequence — after two to three years of tamoxifen (for a combined duration of five years) as per results of the BIG 1-98,¹ ARNO,³ ITA⁴ and IES⁵ studies. Only letrozole has been meaningfully studied in the extended setting (following five years of tamoxifen) with significant RFS observed in all subgroups and a survival advantage in the node-positive subset.⁶ All three drugs essentially produce similar side effects, some representing improvements over tamoxifen (hot flushes, gynecologic symptoms and thromboembolism) and some unique to the class and increasingly challenging to deal with (arthralgia, myalgia and osteoporosis). Choices of modality (upfront, sequenced or extended) or drug aside, there are also legitimate concerns over cost, adherence to therapy and appropriate patient selection — an issue that none of the studies addressed prospectively. It has been asserted from subgroup analyses that an AI might be preferentially chosen over tamoxifen alone in women at a higher risk of early relapse (variably described as node-positive, progesterone receptor-negative, HER2 overexpressing, high-grade, increased Ki-67, etc) but it is critical to note that this is speculative.

NEW INFORMATION FROM SABCS 2009


Compared to ATAC, BIG 1-98 or even IES, which compared five years of tamoxifen with an AI, the TEAM study presents us with two new questions: is adjuvant exemestane for five years superior to sequential tamoxifen (for two and a half to three years) followed by exemestane (for two and a half to three years) and are there any differences between upfront exemestane and tamoxifen after the initial two and a half years of therapy? Conducted in almost 10,000 postmenopausal women, the study was powered to answer both questions with a primary endpoint of DFS and secondary endpoints that included OS, RFS and tolerability. Almost 50% of cases were node-positive, and 100% were ER-positive. Interestingly, given the node-positive rate, only 36% patients in each arm received adjuvant chemotherapy, reflecting the age of patients entered on this trial and perhaps the importance that oncologists increasingly place on hormone therapy alone in ER-positive disease.

The therapies were absolutely equivalent and the expected drug-specific toxicities were observed. In an era of event-driven studies and interim analyses, the researchers are to be applauded for their patience in the release of these results — at a median followup of 5.1 years 60% of patients had completed five years of therapy, lending credence and

confidence to the observations. It is obviously not possible to state whether exemestane is better than other AIs upfront and whether metabolism of tamoxifen plays a role — as might be determined through prospective CYP2D6 analysis. But it is reasonable to conclude that exemestane alone could be added to the therapeutic options for women in whom an AI is being considered. It is even more attractive to consider the sequence so that women might not be exposed to a particular drug's side effects or risks for the entire duration of therapy.

The second exemestane study from SABCs 2009, presented by Bliss et al on behalf of the Intergroup Exemestane Group, provides even more food for thought. The IES results are well known: a superior outcome in the tamoxifen followed by exemestane arm, with an absolute difference in DFS at five years median survival of 3% (95% CI 1.3 to 4.6), and an absolute difference in OS of 1.4% (95% CI 0.1 to 2.5) in the ER-positive or ER-unknown group. This therapeutic approach clearly has merit, in part for the reasons outlined above. The long-term results presented at SABCs 2009 were conducted at 91 months median followup and represent an impressive 32,296 women-years. In the ER-positive or ER-unknown subset, absolute DFS and OS advantages continued to be observed for the sequenced arm, with a DFS difference of 4.4% (95% CI 1.8 to 7.2) and an OS difference of 2.4% (95% CI 0.1 to 4.8). In the sequenced arm, the annual event rate was significantly lower in both the node-positive and node-negative subgroups, and the breast cancer-specific event rates (including distant and local relapses and new primary tumours) were lower in the sequenced arm. As well, a smaller number of recurrences involving bone and lower incidence of non-breast cancer primaries were seen — an interesting hypothesis-generating observation.

FOR CLINICAL PRACTICE

In light of the widely adopted results of the NCIC MA17 trial⁶ of extended therapy with letrozole following approximately five years of adjuvant tamoxifen, Rea et al's report provides reassuring data to oncologists and patients wondering if five years of sequenced therapy (tamoxifen for two to three years followed by an AI until five years of hormonal therapy has been completed) is sufficient. While this study may provide some impetus to stopping hormonal therapy after five years, the ongoing question of extended therapy after up to five years or less of an adjuvant has not been answered and requires additional prospective randomized studies. These should test five years of the sequenced regimen — presently the best adjuvant hormonal combination — against 10 years of adjuvant hormone therapy (i.e. five additional years of AIs). Such a design is needed to fully address the issues of side effects, hazards and costs of extended adjuvant therapy. 

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Disclosure

Dr. Bebb reports being on advisory boards of AstraZeneca, Bristol-Myers Squibb, Novartis and Roche. Dr. Canil reports being on advisory boards of Novartis and Pfizer, and receiving educational grants from Pfizer and Wyeth. Dr. Ho reports being on an advisory board of Roche. Dr. Lohrisch reports receiving research support from AstraZeneca, being on advisory boards of AstraZeneca, Glaxo-Smith Kline, Novartis and Roche, and being on the speakers bureau of Roche and sanofi-aventis. Dr. Ragaz and Dr. Verma report no conflicts of interest pertaining to this article.

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