



# EVIDENCE WATCH

## A review and assessment of recent clinical trial data

*Oncology Exchange* provides overviews of important clinical trial data presented at the 43<sup>rd</sup> Annual Meeting of the American Society of Clinical Oncology (ASCO), held June 1–5, 2007. Leading Canadian experts offer commentary and clinical interpretations.

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### Hepatocellular cancer

Jennifer Knox, MSc, MD, FRCPC

#### **SORAFENIB IMPROVES SURVIVAL IN ADVANCED HEPATOCELLULAR CARCINOMA (HCC): RESULTS OF A PHASE III RANDOMIZED PLACEBO-CONTROLLED TRIAL (SHARP TRIAL). ASCO 2007, ABSTRACT LBA 1.**

Investigators: J. Llovet et al.

**TRIAL SUMMARY:** The Sorafenib HCC Assessment Randomized Protocol (SHARP) trial was a large, multi-centre, placebo-controlled Phase III study that randomized 602 patients with advanced, measurable hepatocellular carcinoma (HCC) and no prior systemic therapy to treatment with either sorafenib 400 mg twice per day (n = 299) or placebo (n = 303). To be eligible, patients needed Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better, and Child-Pugh status (an assessment scale for prognosis in liver disease) A.

The trial was stopped early, in accordance with predetermined criteria, when 143 deaths had occurred in patients receiving sorafenib and 178 in those on placebo, a total of 321 deaths. Median overall survival, a primary endpoint, was 10.7 months with sorafenib vs 7.9 months with placebo. The hazard ratio (HR) for overall survival was 0.69 (95% CI 0.55–0.88, p = 0.00058), a 44% improvement favouring sorafenib. The difference between treatment arms in time to symptomatic progression, the other primary endpoint, was not statistically significant, with median time to disease progression (assessed by independent review) of 5.5 months for sorafenib vs 2.8 months for placebo. The HR for time to progression was 0.58 (95% confidence interval [CI] 0.45–0.74, p = 0.000007). The disease-control rate

**TABLE 1. Serious adverse events in patients with hepatocellular cancer receiving sorafenib vs placebo**

	sorafenib 400 mg bid	placebo
overall serious adverse events	52%	54%
Grade 3–4 diarrhea	11%	2%
Grade 3–4 hand-foot skin reaction	8%	1%
Grade 3–4 fatigue	10%	15%
Grade 3–4 bleeding	6%	9%

was 43% with sorafenib vs 32% with placebo. As shown in **Table 1**, patients in both treatment arms experienced similar rates of serious adverse events.

**COMMENTARY: Jennifer Knox, MSc, MD, FRCPC, Medical Oncologist, Princess Margaret Hospital; Assistant Professor, Department of Medicine, University of Toronto, Toronto, ON.**

The SHARP trial marks the first time a drug has convincingly demonstrated benefit in patients with hepatocellular cancer (HCC). Sorafenib targets vascular endothelial growth factor (VEGF) receptor-2 tyrosine kinase and affects several targets, notably the Ras/Raf/MEK pathway. With established clinical activity in advanced renal cell carcinoma, it has been licensed internationally. HCC is known to overexpress VEGF, and increased expression correlates with poorer stage and prognosis. It is also one of the most vascular cancers known. Sorafenib showed promising activity in HCC in Phase I and II trials. The fact that as a single agent it has demonstrated significant impact on survival in this end-stage population provides proof of principle that tumour vasculature is an appropriate target in HCC therapeutic development.

HCC is a disease of multiple etiologies including hepatitis B virus, hepatitis C virus and chronic liver diseases. Management challenges include late presentation, concomitant liver disease and difficulties with radiologic evaluation of response. There is no approved treatment for advanced disease and recent trials show median survivals in the range of 5–8 months. Doxorubicin is widely used based on objective response rates, but without evidence of meaningful impact on survival or patient benefit. Prior to the SHARP trial, the largest recent drug trial compared nolatrexed (a novel thymidylate synthase inhibitor) to doxorubicin in a similar HCC patient population ( $n = 455$ ). Overall survival was about 8 months vs 5 months favouring doxorubicin, but time to progression was only 8–9 weeks in both arms and Grade 3–4 treatment-related toxicities were significant.<sup>1</sup>

### IMPORTANCE OF PATIENT SELECTION

The SHARP trial was rigorously conducted and reported. The magnitude of impact on overall survival of about 3 months was both statistically and clinically relevant (10.7 vs 7.9 months, HR 0.69), and consistent with recognized indicators of progress in the treatment of advanced, treatment-resistant solid tumours. Survival with sorafenib was better than previously reported with doxorubicin. Adverse events were very similar between the 2 arms, implying that most are caused by patients' disease. Serious drug-related toxicities of diarrhea or rash were surprisingly low, at approximately 10% each, and no increase in serious bleeding caused by sorafenib was seen.

The patients enrolled in the trial were highly selected with respect to their underlying liver function (Child-Pugh status A) and performance status, as compared to many people with HCC who have a marked decline in these measures at the end of their lives. However, there is

The authors concluded that treatment with sorafenib provided statistically significant improvement in survival — for the first time in this type of cancer — with manageable side effects.

no shortage of similar patients who fit these “SHARP criteria,” especially in multidisciplinary centres where HCC patients are seen and followed throughout their disease course. Many of the patients enrolled in this trial would not have met the laboratory criteria cutoffs mandated for inclusion in most gastrointestinal oncology drug trials. The selection made to evaluate this new agent was appropriate and remains very important when it comes to integrating this therapy into our practices. Expanding its use to other HCC patient populations, while tempting, should wait for results from ongoing clinical trials.

The fact that the trial did not meet its second primary endpoint of time to symptomatic progression does not undermine the significance of the overall survival endpoint. The tool used to assess symptoms was probably inadequate. Few objective responses that could have translated into symptomatic improvement were seen, with an overall response rate of 2.3%. This result argues convincingly that new trials in HCC cannot rely on response data: Phase II trials need to evaluate progression-free survival as a primary endpoint and Phase III trials, overall survival.

### EXCITING IMPLICATIONS

Overall, the results of the SHARP trial are likely to spur more research into HCC, and this potential for greater progress is most exciting. Growing preliminary data suggest a class effect for targeting VEGF in treatment of HCC and a potential for additive benefit when combined with epidermal growth factor receptor (EGFR)-targeting agents. Reports of the effect of adding sorafenib to doxorubicin are expected at the European Cancer Conference in late September, 2007.

Sorafenib should be positioned as the new reference standard in HCC. Ways to obtain this important drug for our patients are needed. We must learn how to best select the patients most likely to benefit, an increasingly important question given the current high price tag on this drug. Trial designs to evaluate outcomes earlier in a patient's disease course, including the adjuvant setting, are currently in development and will likely translate this breakthrough into even greater benefit. We have definitely entered a new era in treating HCC patients, one that is welcome and long overdue.

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## Resectable liver metastases in colorectal cancer

Hagen Kennecke, MD, MHA, FRCPC

### FINAL RESULTS OF THE EORTC INTERGROUP RANDOMIZED PHASE III STUDY 40983 [EPOC] EVALUATING THE BENEFIT OF PERI-OPERATIVE FOLFOX4 CHEMOTHERAPY FOR PATIENTS WITH POTENTIALLY RESECTABLE COLORECTAL CANCER LIVER METASTASES. ASCO 2007, ABSTRACT LBA 5.

Investigators: B. Nordlinger et al.

**TRIAL SUMMARY:** European Organisation for Research and Treatment of Cancer (EORTC) study 40983 (also called EPOC, Eloxatin for Peri-Operative Use) enrolled 364 colorectal cancer patients who had 1–4 liver metastases that were initially evaluated as resectable, and randomized them to receive either perioperative FOLFOX4, for 6 cycles both before and after surgery, or surgery alone. The FOLFOX4 regimen was 2-week cycles of oxaliplatin 85 mg/m<sup>2</sup> and LV5FU2 (leucovorin 200 mg/m<sup>2</sup> as a 2-hour infusion, fluorouracil 400 mg/m<sup>2</sup> bolus and 600 mg/m<sup>2</sup> 22-hour continuous infusion, on Days 1–2). Patients in the FOLFOX4 arm received a median of 6 cycles of preoperative chemotherapy over 3 months, with relative dose intensity above 90%; 151 actually had surgical resections and 115 (63%) had a median of 6 cycles of postoperative chemotherapy, again for 3 months, with relative dose intensity of about 80%. Of the patients randomized to surgery alone, 162 had resections. Three patients died after surgery, 1 in the FOLFOX4 arm and 2 in the surgery-alone arm. The relative reduction in size of liver metastases after preoperative chemotherapy was 29.5%, with an overall response rate of 44%. Reversible postoperative complications occurred in 25% of chemotherapy patients vs 16% of those receiving surgery alone. At median followup of 48 months, among both patients whose liver metastases were eligible for resection and those who actually had the resections, those in the peri-

operative FOLFOX4 group had improved progression-free survival (PFS) (Table 2). As previously reported at the ASCO 2005 annual meeting,<sup>1</sup> the most common side effects due to preoperative FOLFOX4 were Grade 3–4 neutropenia in 18.1% of patients, Grade 3 diarrhea in 8.2% and Grade 3 sensory neuropathy in 3.2%; postoperatively 34.8% of patients experienced Grade 3–4 neutropenia and 9.6% experienced Grade 3 sensory neuropathy. The authors concluded that this treatment, delivered by a multidisciplinary team, should be the standard of care in this group of patients, noting that improved imaging techniques can reduce the number of patients found to be unresectable at surgery.

**TABLE 2. Three-year progression-free survival (PFS) in the EPOC trial of FOLFOX4 + surgery vs surgery alone in patients with potentially resectable liver metastases secondary to colorectal cancer**

	3-year PFS (absolute difference)	hazard ratio (95% CI)	p-value
all patients randomized (182 vs 182)	28.1% vs 35.4% (7.2%)	0.79 (0.62–1.02)	p = 0.058
patients eligible for surgery post-CT evaluation (171 vs 171)	28.1% vs 35.4% (8.1%)	0.77 (0.60–1.00)	p = 0.041
patients actually resected (151 vs 152)	33.2% vs 42.4% (9.2%)	0.73 (0.55–0.97)	p = 0.025

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

The EPOC investigators sought to determine the value of perioperative chemotherapy for the relatively small group of patients with metastatic colorectal cancer (mCRC) confined to the liver and presenting with resectable disease. While the liver represents the most common site of metastasis in colorectal cancer, two-thirds of mCRC patients have extrahepatic

metastatic disease, and only 20% have resectable liver lesions. Most patients are not surgical candidates because of tumour burden, tumour location or inadequate hepatic reserve. Nevertheless, surgical resection represents an important therapy and impressive 5-year survival rates of 25% to 60% have been reported among patients with resected mCRC.

Although some patients with initially unresectable disease may be rendered resectable after induction chemotherapy, this study only included patients with tumours initially considered resectable or potentially resectable.

Portier et al previously reported improved disease-free survival for adjuvant 5FU + leucovorin administered after resection of liver metastasis.<sup>2</sup> In the current trial, investigators sought to evaluate the value of oxaliplatin added to 5FU + leucovorin (FOLFOX4) for resectable liver metastases, administered both pre- and postoperatively. Chemotherapy did not result in a difference in the proportion of subjects who achieved resection of liver metastases — which was high (83%) in both groups. Postoperative toxicity was significantly higher in the chemotherapy arm (25%) than with surgery alone (16%); however, this did not translate into an increase in postoperative mortality. At median followup of 48 months, the proportion of subjects alive and free from progression was relatively low in both groups, indicating that the majority of patients who proceed to resection of liver metastases are destined to relapse, irrespective of perioperative chemotherapy.

#### EVIDENCE SUPPORTS STATUS QUO

Although the hazard ratio for perioperative FOLFOX4 reported in this trial was similar to that of adjuvant 5FU + leucovorin reported by Portier et al, the current trial failed to meet its primary endpoint of progression-free survival in

the first, intention-to-treat analysis ( $p = 0.058$ ). Two other analyses presented (Table 2), one of only eligible patients ( $p = 0.041$ ) and another of patients actually resected ( $p = 0.025$ ), should be interpreted with caution until a more complete description of these subgroups is available.

Clinicians may choose to continue to offer 4 to 6 months of postresection chemotherapy according to NCCN (National Comprehensive Cancer Network) guidelines, a practice supported by the Portier trial. The current evidence supports an intravenous 5FU + leucovorin regimen, and some clinicians may offer other regimens, particularly those with proven efficacy in the adjuvant setting; however, the value of these in the post-resection setting remains unproven. The role of preoperative chemotherapy for resectable liver metastasis remains unclear and, if offered, should be limited to 3 months to avoid undue hepatotoxicity. Further studies of perioperative chemotherapy are ongoing or planned, including evaluation of hepatic infusional chemotherapy by the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial C-09.

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## Small cell lung cancer

by Cheryl Ho, MD, FRCPC

### A RANDOMIZED TRIAL OF PROPHYLACTIC CRANIAL IRRADIATION (PCI) VERSUS NO PCI IN EXTENSIVE DISEASE SMALL CELL LUNG CANCER AFTER A RESPONSE TO CHEMOTHERAPY (EORTC 08993-22993). ASCO 2007, ABSTRACT 4.

Investigators: B. Slotman et al.

**TRIAL SUMMARY:** The EORTC 08993-22993 trial randomized 286 patients with confirmed extensive-disease small cell lung cancer (SCLC) to receive prophylactic cranial irradiation (PCI) — which is standard treatment in patients with limited-disease SCLC in complete remission — or no PCI. Eligibility requirements included World Health Organization (WHO) performance status 0–2, no brain metastases and response to 4–6 cycles of chemotherapy. Doses ranged from 20–30 Grays (Gy) in 5–12 daily fractions; 6% of the patients in the PCI arm were not treated and 3% did not complete treatment. At followup of 1 year, PCI significantly lowered the risk of developing symptomatic brain metastases, the primary endpoint, with an incidence of 14.6% for patients receiving PCI (95% CI 8.3–20.9) vs 40.4% in

controls (95% CI 32.1–48.6); the hazard ratio (HR) was 0.27 (95% CI 0.16–0.44,  $p < 0.001$ ). PCI significantly improved progression-free survival (rate at 6 months, 23.4% vs 15.5%; HR 0.76, 95% CI 0.59–0.96,  $p = 0.02$ ) and overall survival (rate at 1 year 27.1% vs 13.3%; HR 0.68, 95% CI 0.52–0.88,  $p = 0.003$ ). PCI did not significantly affect the rate of extracranial disease progression. Side effects of PCI included acute and late headache, acute nausea and/or vomiting (mostly < Grade 3). Quality of life was evaluated as similar in both groups. The authors concluded that PCI reduces symptomatic brain metastases and improves both disease-free and overall survival, and should be offered to all SCLC patients with extensive disease that responds to initial chemotherapy.

**COMMENTARY: Cheryl Ho, MD, FRCPC, Medical Oncologist, British Columbia Cancer Agency; Clinical Assistant Professor of Medicine, University of British Columbia, Vancouver, BC.**

## PROPHYLACTIC CRANIAL IRRADIATION IN SCLC

PCI is the standard of care in limited-stage disease small cell lung cancer (LD-SCLC) patients with a complete response to initial treatment. Auperin et al confirmed the benefit of PCI in patients with treated SCLC in complete remission in a meta-analysis that reviewed individual data on over 980 patients from 7 trials (86% with limited and 14% with extensive disease).<sup>1</sup> The incidence of brain metastasis in patients who did not receive PCI was 58.6% at 3 years in contrast to 33.3% in the treated group ( $p < 0.001$ ). This therapy also improved disease-free survival (relative risk 0.75,  $p < 0.001$ ) and overall survival (relative risk 0.84,  $p = 0.01$ ). Three-year survival in the control group was 15.3% vs 20.7% in the PCI-treated group, an improvement of 5.4%. PCI not only delayed brain metastases, but prevented them, and resulted in a small but significant improvement in survival. While the benefits of PCI were recognized, concerns were raised regarding the possibility of late neuropsychologic effects. Two studies evaluated untreated and treated PCI patients, finding no difference in changes in neuropsychiatric function or in frequency of CT scan abnormalities.<sup>2,3</sup> In any case, developing brain metastases has an undeniably significant negative impact on cognitive function and quality of life.

## THE ROLE OF PCI IN EXTENSIVE-DISEASE SCLC

The current study, EORTC 08993-22993, was a European-based randomized trial that examined the role of PCI in patients with extensive-disease small cell lung cancer (ED-SCLC). Patients with any positive response after 4–6 cycles of chemotherapy were eligible to participate provided they did not have evidence of brain metastasis or leptomeningeal disease. The required degree of response to chemotherapy was not strictly outlined: unlike the studies included in the Auperin meta-analysis, completely asymptomatic patients were allowed to enroll without radiographic documentation of brain disease-free status. CT or MRI was required if they had one or more symptoms suggestive of disease, including signs of increased intracranial pressure, nausea, vomiting, cognitive or affective changes, seizures or focal symptoms. The study's primary objective was to demonstrate a reduction in the risk of symptomatic brain metastases.

The 286 patients enrolled (143 in each arm) were randomized within 5 weeks after chemotherapy and began PCI within 4–6 weeks. The radiotherapy prescription in the PCI arm ranged from 20 to 30 Gy in 5–12 fractions, with 20 Gy in 5 fractions being the most common treatment regimen. Over 75% of patients enrolled had persistence of either primary or metastatic disease at the time of study entry. The treatment was well tolerated with only a small proportion of patients having Grade 3 toxicity, primarily headache.

Patients receiving PCI had an impressive reduction in symptomatic brain metastases, with a hazard ratio (HR) of 0.27 ( $p < 0.001$ ) and 1-year event rates of 14.6% vs 40.4%. Failure-free survival (HR 0.76,  $p = 0.02$ ) and overall survival (HR 0.68,  $p = 0.003$ ) with PCI were also improved, with 1-year survival of 27.1% in the treated group and 13.3% in the untreated group. The survival curves suggested that fewer than 10% of patients survive to 2 years, so long-term neurologic sequelae may not be as significant a consideration as in LD-SCLC.

This study indicates that, in addition to those who achieve complete remission with treatment for SCLC, patients with good performance status and positive treatment response should be considered for PCI. Even in patients with residual disease postchemotherapy, PCI confers a significant survival advantage and symptomatic benefit.

## MORE QUESTIONS

This study confirms the role of PCI in ED-SCLC patients who have a response to chemotherapy, even if they have persistent disease. The evidence indicates that all SCLC patients who respond to chemotherapy should be considered for cranial irradiation to prevent morbidity and mortality. As the central nervous system (CNS) relapse rate is 50% to 60%, the majority of patients will benefit from this low-toxicity maneuver.

While the advantages of treatment are not disputed, questions regarding dose and schedule remain. The Radiation Therapy Oncology Group (RTOG) and EORTC have collaborated on a Phase II–III trial comparing 2 different doses and 2 different schedules of PCI in LD-SCLC (RTOG 0212, PCI 01-EULINT1).<sup>4</sup> Patients were stratified by age and interval from induction therapy to randomization. The 3 arms were daily irradiation in 10 fractions to 25 Gy, daily irradiation in 18 fractions to 36 Gy and twice-daily irradiation in 24 fractions to 36 Gy. Closed to accrual in December 2005, the trial is currently compiling long-term data on neurocognitive function and quality of life. Results, anticipated in the near future, will provide further guidance with respect to dose, timing and technique.

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# Non-squamous non-small cell lung cancer

Janessa Laskin, MD, FRCPC

## **RANDOMISED, DOUBLE-BLIND MULTICENTRE PHASE III STUDY OF BEVACIZUMAB IN COMBINATION WITH CISPLATIN AND GEMCITABINE IN CHEMOTHERAPY-NAÏVE PATIENTS WITH ADVANCED OR RECURRENT NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC): BO17704. ASCO 2007, ABSTRACT LBA7514.**

Investigators: C. Manegold et al.

**TRIAL SUMMARY:** The AVAiL (Avastin in Lung Cancer) placebo-controlled Phase III study randomized 1043 chemotherapy-naïve patients with previously untreated advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) to receive intravenous cisplatin + gemcitabine, with 1 of 3 choices: bevacizumab 7.5 mg/kg (n = 345), bevacizumab 15 mg/kg (n = 351) or placebo (n = 347). Eligible patients had ECOG Performance Status of 0–1 and no brain metastases. All patients received cisplatin 80 mg/m<sup>2</sup> on Day 1 and gemcitabine 1250 mg/m<sup>2</sup> on Days 1 and 8 every 3 weeks for up to 6 cycles, and continued the bevacizumab or placebo until disease progression. As shown in **Table 3**, patients receiving either dose of bevacizumab had significantly longer progression-free survival (PFS), the primary endpoint, both in primary analysis and in a prespecified analysis with censoring of patients who

**TABLE 3. The AVAiL trial: Selected results for 2 doses of bevacizumab or placebo following cisplatin + gemcitabine chemotherapy in patients with non-squamous NSCLC**

	bevacizumab 7.5 mg/kg (n = 345)	bevacizumab 15 mg/kg (n = 351)	placebo (n = 347)
uncensored PFS	6.7 months	6.5 months	6.1 months
PFS (favouring bevacizumab)	0.75 (p = 0.0026)	0.82 (p = 0.03)	
censored PFS (favouring bevacizumab)	0.68 (p = 0.0001)	0.74 (p = 0.0021)	
response rate	34%	30%	20%
response duration	6.1 months	6.1 months	4.7 months
Grade 3–5 adverse events	76%	81%	75%
Grade 3–5 hypertension	6%	9%	2%
Grade 3–5 bleeding	4%	4%	2%
Grade 3–5 proteinuria	0.3%	1%	–

received non-protocol antineoplastic therapy. Response rate and duration of response also increased with bevacizumab;

followup is currently too short for overall survival results. Side effects were as expected, and manageable.

**COMMENTARY: Janessa Laskin, MD, FRCPC, Medical Oncologist, British Columbia Cancer Agency; Assistant Professor of Medicine, University of British Columbia, Vancouver, BC.**

It is often said that efficacy of the currently available chemotherapies for advanced NSCLC has plateaued. Advances in our knowledge of tumour biology and the influx of molecularly targeted agents have had little impact on first-line therapy for this malignancy. This is certainly not for lack of trying: in the last 5 years at least a dozen well-designed, well-orchestrated Phase III clinical trials have been conducted, but all failed to demonstrate an advantage to adding a novel targeted agent to standard platinum-based doublet chemotherapy.<sup>1-5</sup> Sadly, this has only increased the therapeutic nihilism that already surrounded the treatment of NSCLC.

With this backdrop, the positive results of the ECOG 4599 (E4599) trial, first presented in 2005, rejuvenated interest in this type of combination study.<sup>6</sup> E4599 was a

large, randomized Phase III trial in patients with advanced non-squamous NSCLC of standard carboplatin + paclitaxel with or without bevacizumab — a monoclonal antibody to VEGF. E4599 demonstrated an impressive 2-month survival benefit (10.3 vs 12.3 months) associated with the addition of bevacizumab to standard chemotherapy. The higher dose of bevacizumab (15 mg/kg) in E4599 was based on efficacy results of the Phase II study upon which it was designed.<sup>7</sup> The results of E4599 prompted some institutions to make the triple regimen a standard of care; however, many felt that a confirmatory trial was needed before taking this step. Since the AVAiL trial was already underway, the results presented at ASCO 2007 were anxiously awaited.

# LANDMARKS

The AVAiL study was a large, multicentre, placebo-controlled, randomized Phase III study looking at the addition of bevacizumab to standard cisplatin + gemcitabine chemotherapy for first-line treatment of selected patients with NSCLC. Importantly, the study population was carefully chosen, with inclusion and exclusion criteria based on risk of bleeding events noted in the Phase II clinical trial.<sup>7</sup> That trial included all histologies of NSCLC, and found that the risk of bleeding seemed to be associated with squamous cell histology and tumours near large blood vessels. Enrollment in both the E4599 and AVAiL trials was therefore restricted to try to prevent hemorrhages in high-risk areas such as the lung or the brain. Other trials currently underway will specifically address the use of bevacizumab in central and squamous tumours.

## POSITIVE RESULTS SO FAR

The toxicity of the regimen in the AVAiL study was acceptable and similar to the data from E4599. Response rates and the duration of response in the control arm were consistent with predictions from randomized trials of standard platinum-based doublet regimens. Originally the primary endpoint of AVAiL was to be overall survival, but it was changed to PFS partway through the study, presumably because of the excitement surrounding the results of E4599. The recent presentation at ASCO 2007 did not include any overall survival information, data that is not expected to be released for at least 18 months. However, PFS is a valid and clinically relevant endpoint for trials in metastatic disease and the AVAiL results shown in **Table 3**, page 21, do demonstrate a small but statistically significant difference between the placebo arm and each of the bevacizumab arms. While the study design does not allow for direct comparison between the different doses of bevacizumab, the results appear to be quite similar. This raises the question of the optimal biologic dose for bevacizumab in NSCLC, much as it has been raised in all of the other targeted therapies in clinical development.

There have been comments about the PFS differences, particularly in the control arms, between the E4599 and the AVAiL studies. In E4599, PFS was 6.2 months for the bevacizumab-containing arm and 4.5 months in the control arm. In AVAiL, PFS was 6.5 and 6.7 months for the bevacizumab-containing arms and 6.1 months for the control arm. However, it should be noted that the regular imaging was done every 3 months in the AVAiL study compared to every 2 months in E4599, perhaps making it more likely that progression would be noted sooner in E4599. This might help to explain why the control arm of AVAiL appeared to do so “well” compared to the control arm of E4599 — of course, this is speculative.

This era of biologically targeted therapy has been unpredictable at best, with unprecedented breakthroughs and crushing disappointments. The E4599 and AVAiL studies have rekindled some hope for combination trials in advanced NSCLC. Although it is difficult to make a definitive statement about the overall efficacy of this combination, with one positive trial (E4599) and the PFS survival results of AVAiL, it is certainly something to consider and watch for in the future.

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## Non-small cell lung cancer

Nevin Murray, MD, FRCPC

### PHASE III TRIAL OF CISPLATIN (P) PLUS ETOPOSIDE (E) PLUS CONCURRENT CHEST RADIATION (XRT) WITH OR WITHOUT CONSOLIDATION DOCETAXEL (D) IN PATIENTS (PTS) WITH INOPERABLE STAGE III NON-SMALL CELL LUNG CANCER (NSCLC): HOG LUN 01-24/USO-023. ASCO 2007, ABSTRACT 7512.

Investigators: N.H. Hanna et al.

**TRIAL SUMMARY:** This prospective Phase III trial randomized 243 patients with inoperable Stage III A–B NSCLC who had received concurrent chemoradiation (the current treatment standard) to either docetaxel 75 mg/m<sup>2</sup> (n = 73) every 21 days for 3 cycles or observation (n = 74). Eligibility criteria were ECOG Performance Status 0–1, forced expiratory volume in 1 second (FEV1) > 1, and unintended weight loss < 5%. All patients received chemoradiation consisting of cisplatin 50 mg/m<sup>2</sup> intravenously on Days 1, 8, 29 and 36 plus etoposide 50 mg/m<sup>2</sup> intravenously on Days 1–5, with radiation therapy of 59.4 Gy. The 147 patients whose disease had not progressed (72.4%) and who remained eligible were randomized to the 2 study arms. The trial was stopped early according to predetermined criteria, due to

evidence of no survival benefit upon analysis of the first 203 patients (p = 0.9). With median followup of 25.6 months, median overall survival was 21.5 months in the docetaxel group vs 24 months in the observation group, and 3-year survival rates were 27% in both groups. Progression-free survival with docetaxel was 12.3 months vs 12.9 months with observation only. Among patients receiving docetaxel, 10.9% experienced Grade 3–4 febrile neutropenia. Pneumonitis occurred in 9.6% vs 1.4% of those on observation, 28.8% vs 8.1% were hospitalized and 5.5% vs 1.5% died of docetaxel-related causes. The authors concluded that consolidation therapy with docetaxel fails to further improve survival following concurrent chemoradiation, while increasing toxicity, hospitalization and premature death.

**COMMENTARY:** Nevin Murray, MD, FRCPC, Clinical Professor of Medicine, University of British Columbia; Medical Oncologist, BC Cancer Agency, Vancouver, BC.

About 35% of patients with NSCLC have unresectable Stage III disease, mainly because of mediastinal lymph node involvement. Most are treated palliatively but a subgroup (20% to 25%) are selected for radical treatment with curative intent. The selection criteria include simple clinical parameters of good performance status (ECOG 1 and 2), minimal weight loss (ideally < 5%) and absence of serious comorbidity. Patients are also selected for a favourable distribution of disease (mainly in the upper lobes) whereby the primary tumour and involved mediastinum can be treated within a radical radiotherapy volume. Radical radiotherapy generally means > 60 Gy, and the volume of lung receiving > 20 Gy should be less than 35%.

#### CURRENT RADICAL TREATMENT IN STAGE III NSCLC

Standards of care for this population have evolved from radiotherapy alone, granting 5-year survival of 5% to 6%, to sequential chemotherapy followed by radiotherapy, with 5-year survival of 8% to 10%,<sup>1,2</sup> to initial concurrent chemoradiation, with 5-year survival of 15% to 20%.<sup>3,4</sup>

A number of chemotherapy regimens have been given concurrently with the thoracic irradiation. Commonly used protocols have included cisplatin + vinorelbine, carboplatin + paclitaxel and cisplatin + etoposide (PE). The taxanes do not mix well with concurrent chemoradiation because increased

toxicity to the normal tissues of the lungs and esophagus requires manipulation of the schedule to a low-dose weekly regimen. Even vinorelbine requires dose attenuation to 60% to 75% of standard chemotherapy protocols. The extent that such changes in chemotherapy dosing decreases systemic control has never been evaluated in a controlled trial.

Concurrent PE with thoracic irradiation was first reported in protocols for limited-stage small cell lung cancer.<sup>5</sup> This regimen has acceptable toxicity when given with thoracic irradiation, without requiring changes in the dose of chemotherapy or radiotherapy. The Southwest Oncology Group (SWOG) applied the PE regimen to Stage III NSCLC with results that compare favourably to anything published.<sup>6</sup> In a further body of work, SWOG added consolidation docetaxel (75 mg/m<sup>2</sup> for 3 cycles at 3-week intervals) to the PE chemoradiation model and generated provocative Phase II results in Stage III disease (median survival 26 months, 3-year survival 37%).<sup>7</sup> SWOG wished to test consolidation docetaxel in a Phase III study but this concept was not approved by the Cancer Treatment and Evaluation Program. Consolidation docetaxel became widely used in the United States based on the Phase II results and Canadian oncologists wondered if this protocol was necessary for our patients. Fortunately, a Phase III trial by the Hoosier Oncology Group (HOG), reported at ASCO 2007 and summarized above, resolves the issue.

## THE CURRENT STANDARD HOLDS FOR NOW

HOG LUN 01-24 randomized unresectable Stage III NSCLC patients to 2 cycles of PE concurrent with thoracic irradiation vs the same treatment plus 3 additional chemotherapy treatments with docetaxel. Although not a huge trial (203 patients received chemoradiation and 147 were randomized to receive or not receive docetaxel consolidation), the principal conclusion — that consolidation docetaxel is not a good thing to do — will stand for a number of reasons. First, consolidation docetaxel is toxic compared to PE alone (pneumonitis 9.6% vs 1.4%, hospitalization 28.8% vs 8.1%, fatal toxicity 5.5% vs 0%). Second, the survival outcomes show no trend in favour of docetaxel consolidation. Third, the overall survival in the study is quite good: median survival for all patients was 21.1 months, with 5-year survival of 27.8%. In the docetaxel and observation groups, respectively, median survival was 21.5 vs 24.4 months and 5-year survival 27.2% vs 27.6%. Had the overall survival outcomes been poor, it could have been said that the HOG study included mainly unfavourable cases whose outcome is difficult to change. Fourth, the fact that 2 cycles of chemotherapy performed as well as 5 cycles indicates that neither the addition of docetaxel itself or 3 further chemotherapy cycles adds value. Fifth, a factor important for the Canadian healthcare system is that PE is cheap. The drug acquisition cost for PE in a 1.75 m<sup>2</sup> patient at the British Columbia Cancer Agency is about C\$ 75 — about as much as a tank of gas for a compact vehicle.

The HOG study has delivered a knockout punch to consolidation docetaxel in Stage III NSCLC. Although not a move forward, it is a crucial clarification of standards of care: it clears the air. Compared with radical radiotherapy alone, the addition of concurrent PE adds about a year to the

median survival of 11–12 months from radiotherapy alone, and quadruples the proportion of long-term survivors from about 5% to 20%. This is accomplished with drug costs of roughly \$150! Contrast this with the addition of targeted agents that add about 2 months of median survival for palliative cases with no promise of long-term results, at a cost to our healthcare system that is 400-fold greater. PE for lung cancer is one of the greatest bargains in oncology.

## THE VALUE OF PHASE III DATA

Another important take-home message is that the purpose of a Phase II study is to determine whether a Phase III study should be performed. Always be skeptical of a promising Phase II result: standards of care should be determined by a Phase II study only in exceptional situations.

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## Melanoma

Teresa Petrella, BSc, MD, MSc, FRCPC

### EORTC 18991: LONG-TERM ADJUVANT PEGYLATED INTERFERON-ALPHA2B (PEG-IFN) COMPARED TO OBSERVATION IN RESECTED STAGE III MELANOMA, FINAL RESULTS OF A RANDOMIZED PHASE III TRIAL.

Investigators: A.M. Eggermont et al.

**TRIAL SUMMARY:** The EORTC 18991 trial randomized 1256 patients with Stage III melanoma to treatment with pegylated interferon alpha-2b (peg-IFN alfa-2b) (n = 627) vs observation (n = 629). The peg-IFN alfa-2b regimen was 6 µg/kg/week subcutaneous for 8 weeks followed by self-administered maintenance therapy of 3 µg/kg/week subcutaneous for total treatment duration of 5 years. At randomization, patients were stratified according to whether nodal involvement was microscopic (N1) or palpable (N2), number of nodes, Breslow measurement of thickness, pres-

ence of ulcerated primary tumour, sex and treatment centre.

At median followup of 3.8 yrs, peg-IFN alfa-2b appeared to provide more benefit in the 543 patients with N1 disease than in the 713 N2 patients, as shown in **Table 4**. Results were also better in patients with ulceration of the primary lesion. Toxicity resulted in 251 patients (40%) leaving the study; in those that remained, the ratio of actual dose received was a median of 88% in the induction phase and 83% in the maintenance phase. Importantly, toxicity did not increase with duration of therapy. Of patients receiving

**TABLE 4. Survival endpoints for patients receiving peg-IFN alfa-2b vs observation in patients with Stage II melanoma (EORTC 18991)**

	microscopic (N1) nodal involvement		palpable (N2) nodal involvement	
	hazard ratio	p-value	hazard ratio	p-value
relapse-free survival	0.73	p = 0.02	0.86	p = 0.12
distant metastasis-free survival	0.75	p = 0.03	0.94	p = 0.53
overall survival	0.88	p = 0.43	1.01	p = 0.91

peg-IFN alfa-2b, 47% reported Grade 3–4 toxicities (mainly Grade 3) vs 17% of those on observation, notably fatigue in 15%, hepatotoxicity in 10% and depression in 6%. During maintenance, 83% of the peg-IFN alfa-2b group had ECOG performance status of 0–1. The authors concluded

that long-term therapy with peg-IFN alfa-2b provided benefit in patients with Stage III melanoma in terms of relapse-free survival but not distant metastasis-free or overall survival, and that the benefit was greater in those with only microscopic nodal involvement.

**COMMENTARY: Teresa Petrella, BSc, MD, MSc, FRCPC, Medical Oncologist, Odette Cancer Centre, Sunnybrook Health Sciences Centre; Assistant Professor, Department of Medicine, University of Toronto, Toronto, ON.**

Melanoma is the most serious form of skin cancer, accounting for only 5% of all skin cancer cases but 80% of skin cancer deaths. The incidence and mortality rates of cutaneous malignant melanoma have risen dramatically over the past several decades, faster than those of any other malignancy. Although educational efforts may have resulted in earlier detection of melanoma, patients with Stage IIB and Stage III disease remain at high risk of recurrence after definitive surgery.

Data on adjuvant interferon therapy in melanoma have become muddled with inconsistent results over the past decade. Clinical studies evaluating adjuvant interferon following surgery generally show that interferon therapy decreases cancer recurrences compared to surgery alone, but with no consistent benefit in terms of survival or distant metastases. Considerable debate continues over the degree of utility of adjuvant interferon alfa administered in tolerable doses and over the optimal dose and treatment duration in Stage II–III melanoma.

**SUPPORTS PRIOR INTERFERON RESULTS**

This is a very important study because it adds consistency to the current body of literature. The authors have reported the largest adjuvant study so far conducted in Stage III melanoma. The 1256 patients enrolled were randomized to either observation or 5 years of peg-IFN alfa-2b. In intent-to-treat analysis, median recurrence-free survival at 4 years was 34.8 months in the peg-IFN alfa-2b arm vs 25.5 months in the observation arm (p = 0.01), giving a significant difference of 9.3 months. Distant metastasis-free survival and overall survival, however, were not significantly different. These results are consistent with those of the 4 ECOG adjuvant interferon alpha-2b (IFN alfa-2b) trials

conducted by Dr. Kirkwood’s group. In a pooled analysis of these studies, which included 1916 patients at median followup periods varying from 2.1 to 12.6 years, recurrence-free survival remained statistically significantly different (p = 0.006) but not overall survival.<sup>1</sup>

Response to therapy appeared to be most pronounced in a subgroup of patients with only microscopic nodal disease (those with positive sentinel lymph nodes). This group accounted for 43% of the study population and experienced both increased recurrence-free survival (p = 0.02) and distant metastasis-free survival (p = 0.03) with no benefit in overall survival. These findings are consistent with results from a subgroup analysis in microscopic nodal disease from another large randomized study conducted by Eggermont’s group using intermediate doses of IFN alfa-2b.<sup>2</sup> Sentinel node biopsy was not standard of care during the ECOG studies; hence this subgroup was not assessed. The ECOG 1694 trial included only 56 patients who had undergone a sentinel node biopsy. Other studies have shown that patients with lower disease burden are more likely to respond to immunotherapy treatments. Another important finding is that this study showed a sustained effect in the decreased hazard of recurrence over the 5 years, an effect not previously demonstrated in other trials that may aid in development of further trials assessing length of therapy.

The side effects of peg-IFN alfa-2b are similar to those observed with IFN alfa-2b, with fatigue, liver enzyme abnormalities and depression accounting for the majority of Grade 3–4 toxicities. Forty percent of the patients in this study discontinued treatment, mostly due to toxicity (31%), similar to the discontinuation rates seen in ECOG 1684<sup>3</sup> and 1694.<sup>4</sup> Only 23% of patients remained on treat-

# LANDMARKS

ment during Years 4 and 5 — emphasizing that patient tolerance is one of the greatest impediments to more widespread use of interferon and reinforcing the need for new agents with more acceptable toxicity.

Adding to the confusion, Gogas et al presented another seminal study assessing length of therapy.<sup>5</sup> This study compared 1 year vs 1 month of high-dose IFN alfa-2b, and showed no difference in disease-free or overall survival between the 2 groups; however, it has been criticized for its small sample size.

## FUTURE RESEARCH DIRECTIONS

This trial confirms the benefit of peg-IFN alfa-2b for recurrence-free survival in Stage IIB–III melanoma and adds consistency to the current available data. Key issues will be tolerability, compliance for 5 years and cost of therapy. The benefit in the microscopic-only subgroup is a very important finding that previous trials have not addressed. With increased use of sentinel lymph node mapping, this group comprises the majority of patients currently diagnosed with Stage III disease. However, despite this new data, no adjuvant treatment in melanoma unequivocally improves overall survival — further clinical trials testing agents with higher therapeutic ratios are desperately needed.

Several studies currently ongoing will aid in clarifying the most responsive population of patients for interferon and the length of therapy required. The Sunbelt Melanoma Trial is addressing, in a randomized fashion, the issue of sentinel node-positive patients and whether or not they benefit from IFN alfa-2b. Other trials such as NCIC-ME.10/ECOG 1697 and the European Association of Dermato-Oncology (EADO) 2001/CMII trial are addressing the most effective duration of therapy. Followup of patients from the EORTC 18991 trial will continue to assess long-term toxicity of peg-IFN alfa-2b and overall survival.

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## Trastuzumab in breast cancer

Joseph Ragaz, MD, FRCPC

### UPDATED RESULTS OF THE COMBINED ANALYSIS OF NCCTG N9831 AND NSABP B-31 ADJUVANT CHEMOTHERAPY WITH/WITHOUT TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE BREAST CANCER. ASCO 2007, ABSTRACT 512.

Investigators: E.A. Perez et al.

**TRIAL SUMMARY:** This was an updated report of the combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 trials of adjuvant chemotherapy (doxorubicin + cyclophosphamide [AC] followed by weekly or 3-weekly paclitaxel) with or without 52 weeks of trastuzumab. The 2 trials enrolled 3969 women with human epidermal growth factor receptor 2 (HER2)-positive resected early breast cancer, and this analysis included data from 413 women of the 1979 initially randomized to the no-trastuzumab group who switched to trastuzumab treatment following the initial results presented in 2005. As shown in

**TABLE 5. Updated joint analysis of NCCTG N9831 and NSABP B-31: selected 4-year DFS and OS results**

	trastuzumab arm	control arm	hazard ratio	95% CI
DFS, all patients	85.9%	73.1%	0.48	0.41–0.57
DFS, hormone receptor-positive	89.4%	76.9%	0.49	0.39–0.63
DFS, hormone receptor-negative	81.7%	68.2%	0.52	0.42–0.65
DFS, tumour size ≤ 2 cm	90.6%	81.4%	0.45	0.33–0.63
DFS, tumour size > 2 cm	76.7%	51.5%	0.42	0.28–0.64
overall survival	92.6%	89.4%	0.65	0.51–0.84

**Table 5**, with median followup among the 3711 women still alive of 2.9 years (maximum 6.4 years), 4-year disease-free survival (DFS) rates were 85.9% in the trastuzumab group vs 67.1% in the non-trastuzumab group (HR favouring trastuzumab 0.48, 95% CI 0.41–0.57,  $p < 0.00001$ ), and 4-year overall survival rates (OS) were 92.6% vs 89.4% (HR 0.65, 95% CI 0.51–0.84,  $p = 0.0007$ ). Benefit persisted among all subgroups studied including those determined by age, nodal involvement, hormone receptor status, tumour size and tumour grade. Peak disease recurrences occurred between years 2 and 3, with some occurring subsequently. At 3 years of followup, the cumulative rate of cardiac events in the N9831 trial was 2.5% in the patients receiving trastuzumab vs 0.2% in the no-trastuzumab

group, and no increase in rate of cardiac events was noted after longer followup. Data on central analysis for HER2 status of tumour samples in the N9831 trial was also presented. In the small group of patients (104 out of 1842) whose tumours were found on central testing to be HER2-negative by fluorescence in situ hybridization (FISH) and  $< 3+$  (i.e. negative) on immunohistochemistry (IHC), the HR for DFS favouring trastuzumab was 0.51 (95% CI 0.21–1.2,  $p = 0.13$ ). The authors concluded that the substantially improved outcomes previously observed in women who received trastuzumab in addition to chemotherapy continue, despite crossover to treatment with trastuzumab among women initially randomized to no trastuzumab.

**BENEFIT FROM ADJUVANT TRASTUZUMAB MAY NOT BE CONFINED TO PATIENTS WITH IHC 3+ AND/OR FISH-POSITIVE TUMORS: CENTRAL TESTING RESULTS FROM NSABP B-31. ASCO 2007, ABSTRACT 511.**

Investigators: S. Paik et al.

**TRIAL SUMMARY:** This analysis from the NSABP study B-31 examined whether the tests currently used to assess the sensitivity of breast cancer to treatment with trastuzumab — tests developed for treatment of metastatic disease — accurately predict benefit from adjuvant treatment in early-stage breast cancer. In NSABP B-31, patients were initially enrolled on the basis of IHC or FISH testing by any lab, and subsequent central testing showed a high rate of false positives. In the current analysis, the researchers correlated clinical results with central testing results on all available B-31 tissue blocks. Out of 1662 cases, 255 (15.3%) showed overexpression as determined by IHC, 207/1795 (11.5%) cases showed gene amplification by FISH and 161/1662 (9.7%) had no overexpression or gene amplification on either test.

As expected, trastuzumab showed benefit in all subsets considered positive for HER2 by either test. Surprisingly, however, DFS benefit from trastuzumab was also seen in cases with HER2-negative status, and did not correlate with HER2 overexpression as determined by IHC ( $p = 0.26$ ) or with HER2 gene copy number as determined by FISH ( $p = 0.60$ ). Thus, all subsets as defined by the 2 tests benefited from trastuzumab treatment — including women with tumours that tested negative on FISH and had  $< 3+$  IHC staining (relative risk 0.34, 95% CI 0.14–0.80,  $p = 0.014$ ) (Table 6). The authors concluded that definitions of HER2 overexpression and gene amplification may need to be modified for use of trastuzumab in early breast cancer, and recommended a randomized clinical trial to determine what modifications are needed.

**TABLE 6. Progression-free survival benefit in subsets defined by central testing of HER2 overexpression (IHC) and gene amplification (FISH) in NSABP-B31**

	number without vs with trastuzumab	PFS events	relative risk (95% CI) favouring trastuzumab	p-value
FISH+	789 vs 799	160 vs 85	0.47 (0.36–0.61)	$p < 0.0001$
FISH-	114 vs 93	23 vs 8	0.40 (0.18–0.89)	$p = 0.026$
IHC 3+	740 vs 748	151 vs 82	0.48 (0.37 vs 0.63)	$p = 0.0001$
IHC 0–2+	161 vs 138	32 vs 10	0.32 (0.16–0.65)	$p = 0.0017$
FISH, IHC 0–2+	92 vs 82	20 vs 7	0.34 (0.14–0.80)	$p = 0.014$

**COMMENTARY: Joseph Ragaz, MD, FRCPC, Director, Clinical Research, McGill University Health Centre, Royal Victoria Hospital; Clinical Professor, Medicine & Oncology, McGill University, Montreal, QC.**

Treatment targeting the HER2 protein with trastuzumab in women with both metastatic and adjuvant breast cancer produced unexpectedly encouraging results in the early 2000s. The 2001 reports showed that trastuzumab significantly increased response rates and survival in Stage IV disease.<sup>1</sup> The results presented at the 2005 ASCO annual meeting stunned the cancer care establishment by showing a very significant avoidance of metastases in the adjuvant setting, with an over 50% reduction in breast cancer events seen at 2 years' followup (median 1 year).<sup>2,3</sup>

Seldom before in the history of breast cancer research was so much improvement observed so soon after the introduction of just one agent, or breast cancer guidelines altered as rapidly. The NSABP B-31 trial reported significant DFS improvement with trastuzumab in May, 2005, and by September, before the October publication of these results in the *New England Journal of Medicine*, most North American centres had introduced this agent into routine therapy, with Europe following in about a year.

By 2007, most experts were asking the key question: was the trastuzumab-associated improvement seen in adjuvant treatment just a delay of metastases, or would there be a real impact on curability? Many critics argued that the early improvement of DFS, without significant improvement of OS, did not justify the cost and potential cardiac toxicity of trastuzumab. The updated joint analysis of the NSABP B-31 and NCCTG N9831 adjuvant trastuzumab trials presented at the 2007 ASCO annual meeting provided some answers.

## OS BENEFITS NOW ADDED TO DFS

The median followup of this update was 2.9 years, with a total of 619 events and 258 deaths reported (increased from 2.0 years, 395 events and 154 deaths in 2005). Results show steadily growing benefit from trastuzumab, with the same highly significant hazard ratios seen in the first analysis (HR 0.48, 95% CI 0.41–0.57,  $p < 0.00001$ ), indicating a persistent 52% avoidance of events. In terms of absolute benefits, the difference in DFS between the 2 arms at 2 years was 5.9% (92.3% with trastuzumab vs 86.4% in the control arm), and at 4 years the difference is 12.8% (85.9% vs 73.1%, respectively), as shown in **Table 5**, page 24.

This time, trastuzumab also significantly improved OS, with 35% of deaths avoided by trastuzumab overall (HR 0.65, 95% CI 0.51–0.84,  $p = 0.0007$ ), and an absolute difference of 3%. The survival benefit was seen despite the fact that 21% of all control patients crossed over to trastuzumab, after the May 2005 NSABP alert indicating significant benefit, and all patients with recurrences were also treated with trastuzumab. These crossovers are important factors that potentially decrease the statistical power for OS. The true “non-trastuzumab” OS outcome is likely much worse than this trial shows.

## Is DFS a surrogate of OS?

The significance of the OS data is increasing with duration of followup, in keeping with the increasing benefit in avoid-

ing metastases indicated by the DFS hazard ratios. The earlier avoidance of metastases at 2 years of followup, when OS had not reached significance, implies that DFS may be a valid surrogate of overall survival in breast cancer trials, particularly in the earlier years when patients with relapses are still alive and hence contribute to DFS events but not to OS events. The same pattern was seen in trials of other adjuvant breast cancer therapies, including tamoxifen and aromatase inhibitors.

## Subset analysis

With adequate numbers — more than 300 cases per group — all subsets analyzed showed similar magnitude of benefit for trastuzumab, with statistically significant HRs ranging from 0.42 to 0.54. These figures translate to a 46% to 58% reduction of events, indicating that while the outcomes are not the same, the benefit of trastuzumab is similar. For example, in estrogen and progesterone receptor-positive vs negative tumours, 4-year DFS was 89.4% and 81.7% for patients receiving trastuzumab vs 76.9% and 68.2% in those without trastuzumab, respectively, and in small tumours < 2 cm compared to those > 5 cm, DFS was 90.6% and 76.7% vs 81.4% and 51.5%.

## CARDIAC EVENTS

Reassuringly, the cumulative incidence of congestive heart failure at 3 years in the trastuzumab-treated group (2.5%) is not greater than that seen at 1 year (also 2.5%), and is only marginally more than that seen at 6 months (1.8%). Other data showed that most if not all women with trastuzumab-associated congestive heart failure responded adequately to appropriate cardiac medications, suggesting reversibility of clinically evident trastuzumab-related congestive heart failure. While caution is recommended, as early data showed a more substantial reduction of left ventricular ejection fraction and longer followup may show more clinically relevant cardiac morbidity and or mortality, it seems unlikely that delayed cardiac morbidity would offset the avoidance of breast cancer metastases and mortality.

## RETHINKING TRASTUZUMAB ELIGIBILITY


Surprising results from the NSABP B-31 and NCCTG N9831 trials were seen in the analysis of outcomes according to HER2 status by central testing. The 2 groups reported separate analyses. In her 2007 ASCO presentation, E. Perez related that in NCCTG N9831, patients with HER2-positive status (IHC 3+ or FISH HER2/CEP17 ratio  $\geq 2.0$ ) derived a magnitude of benefit similar to those with IHC3+ but FISH ratio < 2.0, with hazard rates of 0.47 and 0.61 respectively. Quite unexpectedly, the small group of 104 cases with truly negative HER2 status (IHC < 3+ and FISH ratio < 2.0) also achieved a 49% reduction of events (HR 0.51).

S. Paik presented identical results from NSABP B-31 central testing, with even more significance for trastuzumab benefit among HER2-negative cases. He reviewed the

cases with negative HER2 status — either FISH-negative (ratio < 2) but any IHC (207 cases), who had HR 0.40 (95% CI 0.18–0.89,  $p = 0.026$ ); or IHC-negative (< 3+) with any FISH (460 cases), who had HR 0.32 (95% CI 0.16–0.65,  $p = 0.0017$ ). Remarkably, the 174 cases that were HER2-negative by both IHC and FISH also showed significant trastuzumab benefit, with HR 0.34 (95% CI 0.14–0.80,  $p = 0.014$ ) (Table 6, page 25). The magnitude of benefit among HER2-negative cases was identical to the benefit seen among HER2-positive cases.

Data expressed according to FISH copy number, which is a quantitative expression of gene positivity, confirmed that the reduction of events by trastuzumab was similar among true FISH-negative cases (HER2 gene copy number < 2, HR 0.5) and those with medium-positive FISH (2–4 copies, HR 0.28) and those with high FISH positivity (4–9 copies, HR 0.65 or 10 copies, HR 0.40). Paik documented a high proportion of false negatives in cases not initially centrally reviewed (over 8% for FISH and 16% for IHC), supporting central review for HER2 status determination. He also discussed a possible explanation for the phenomenon of trastuzumab response among the HER2-negative subsets: in the adjuvant setting, in contrast to Stage IV disease, seemingly HER2-negative tumours may contain some cells (clones) with HER2 amplification, but not enough to provide an initial positive HER2 signal with conventional FISH or IHC measurement. The number of such cells can grow as disease progresses, possibly due to selection for HER2-amplified cells,<sup>4</sup> and inhibition of these clones is likely responsible for the trastuzumab benefit.

## HER2 TESTING RESULTS NEED CONFIRMATION

These data as presented by the joint analysis offer Level I evidence that the trastuzumab benefit in adjuvant breast cancer has increased over time — now including a significant survival benefit — despite cardiac morbidity. Unexpectedly, results documented benefit of trastuzumab among HER2-negative cases. Before clinical steps can be taken to consider trastuzumab therapy independently of HER2 status, however, this important observation will need confirmation from other Intergroup trials. If future therapy for high-risk breast cancer is to include trastuzumab regardless of HER2 status, the fiscal and logistic consequences could be staggering. Should future research confirm the preliminary data presented by Perez and Paik, this change in policy may have to be considered despite the cost — as in the long term, the cost of each avoided metastasis would substantially offset the upfront cost of trastuzumab.<sup>5</sup> 

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## Disclosure

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