

## EVIDENCE WATCH

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



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

Contributors were selected by Gwyn Bebb, BMBCh, PhD, FRCPC, Sebastien J. Hotte, MD, MSc, FRCPC, Joseph Ragaz, MD, FRCPC and Amil Shah, MD, FRCP

## KRAS as a predictive marker in metastatic colorectal cancer

Howard J. Lim, MD, PhD, FRCPC and Sharlene Gill, MD, MPH, FACP, FRCPC

KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. ASCO 2008, Abstract 2.

**Investigators:** E. Van Cutsem et al.

**STUDY SUMMARY:** This retrospective analysis was undertaken to determine the effect of KRAS mutation status in metastatic colorectal cancer (mCRC) patients who received first-line FOLFIRI chemotherapy with or without cetuximab in the Phase III prospective, randomized CRYSTAL trial.<sup>1</sup> The FOLFIRI regimen was irinotecan 180 mg/m<sup>2</sup> + fluorouracil 400 mg/m<sup>2</sup> bolus followed by a 2400 mg/m<sup>2</sup> continuous infusion + folinic acid every 2 weeks, and the cetuximab initial dose was 400 mg/m<sup>2</sup> on Day 1 followed by 250 mg/m<sup>2</sup> weekly. Chemotherapy was continued until disease progression. KRAS status was evaluable for 540 patients out of 1198

in the original trial, showing mutations in 192 (35.6%). Median progression-free survival (PFS) rates favoured cetuximab in patients with wild-type (non-mutated) KRAS (hazard ratio [HR] 0.68; 95% CI 0.051–0.934;  $p = 0.0167$ ), as did rates of complete + partial response (59% in patients receiving FOLFIRI + cetuximab vs 43.2% in those receiving only FOLFIRI;  $p = 0.0025$ ). Grade 3–4 adverse events did not differ significantly according to KRAS status. The authors concluded that patients with wild-type KRAS benefit significantly from addition of cetuximab to treatment while those with KRAS mutations do not.

KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: the OPUS experience. ASCO 2008, Abstract 4000.

**Investigators:** C. Bokemeyer et al.

**STUDY SUMMARY:** This retrospective analysis of tumour material archived for the randomized Phase II OPUS trial<sup>2</sup> assessed the effect of KRAS mutation status on outcomes achieved by FOLFOX with or without cetuximab in first-line treatment of patients with mCRC. The FOLFOX regi-

men was oxaliplatin 85 mg/m<sup>2</sup> + fluorouracil + folinic acid, and the cetuximab regimen was 400 mg/m<sup>2</sup> for the first dose followed by 250 mg/m<sup>2</sup> weekly. Out of the OPUS trial's 337 patients, 233 had evaluable tissue samples and 99 (42%) had KRAS mutations. Median PFS was significantly

# LANDMARKS

improved in patients with wild-type KRAS tumours who received cetuximab compared to those who did not (HR 0.57;  $p = 0.016$ ), as was complete + partial response rate (61% vs 37%;  $p = 0.011$ ). In patients with KRAS-mutant tumours, adding cetuximab to FOLFOX provided

no benefit — in fact, median PFS was worse (HR 1.83;  $p = 0.0182$ ). Toxicities for both regimens were consistent with earlier findings, with no important differences according to KRAS mutation status.

Relationship of efficacy with KRAS status (wild type versus mutant) in patients with irinotecan-refractory metastatic colorectal cancer (mCRC), treated with irinotecan (q2w) and escalating doses of cetuximab (q1w): the EVEREST experience (preliminary data). ASCO 2008, Abstract 4001.

**Investigators:** S. Tejpar et al.

**TRIAL SUMMARY:** The EVEREST trial<sup>3</sup> randomized patients who had Stage 0–1 skin reactions after 22 days of receiving a combination of cetuximab 250 mg/m<sup>2</sup> + irinotecan 180 mg/m<sup>2</sup> every 2 weeks, to continue receiving the same regimen vs a combination treatment using a higher dose of cetuximab, increased by 50 mg per week up to 500 mg/m<sup>2</sup>. Patients with Grades 2–3 skin toxicity were considered to have had a good response on cetuximab 250 mg/m<sup>2</sup>, and were not randomized to the assessment of dose escalation. KRAS mutation status was evaluated in 148 patients (94% of those originally randomized), and deter-

mined in 144. Overall PFS in patients with wild-type KRAS was 173 days (95% CI 141.3–204.7) vs 83 days in the KRAS mutant types (95% CI 75.9–90.2 days). Patients with KRAS mutations did not benefit from irinotecan + cetuximab treatment, nor did cetuximab dose escalation increase responses in these patients. Skin responses to cetuximab did not vary by KRAS mutation status. The authors concluded that patients with wild-type KRAS derived substantial benefit and that skin reactions to cetuximab and KRAS status are independent of each other.

**COMMENTARY:** Howard J. Lim MD, PhD, FRCPC, Gastrointestinal Oncology Fellow, British Columbia Cancer Agency (BCCA) and Sharlene Gill, MD, MPH, FACP, FRCPC, Assistant Professor of Medicine, University of British Columbia and Medical Oncologist, BCCA.

Because the efficacy of chemotherapeutic drugs overlaps with toxicity, the therapeutic index of cytotoxic chemotherapy is narrow. As molecular discoveries and techniques help refine treatment and define who will respond to treatment, oncologists will be able to spare patients therapies that are likely to cause significant toxicity while providing little benefit. At ASCO 2008, the predictive utility of KRAS mutation status in patients with mCRC treated with epidermal growth factor receptor (EGFR) monoclonal antibody therapies was a hot topic of discussion, as manifested by the plenary presentation by Dr. Van Cutsem in first-line treatment and the podium presentations by Dr. Bokemeyer and Dr. Tejpar of treatment in the second- and third-line settings, all summarized above.

## PREDICTIVE ROLE OF KRAS STATUS

The BOND-1 trial randomized Phase II trial demonstrated the efficacy of cetuximab with and without irinotecan in irinotecan-refractory patients<sup>4</sup> and led to its regulatory approval in Canada in 2004. However, outside of clinical trials, the use of anti-EGFR therapy in Canadian patients has largely been limited to user-pay or out-of-country administration in the third-line setting. Given the high financial costs and potential toxicity of treatment, the need to identify which patients are more likely (or less likely) to benefit is essential.

EGFR is a member of the epidermal growth factor superfamily that includes epidermal growth factor receptor 2 (HER2).

Receptor dimerization activates a series of tyrosine kinase-mediated signaling pathways with downstream effects of cell proliferation, survival, invasion and metastasis. Blockade of this pathway in combination with chemotherapy is thought to inhibit further cancer growth and proliferation. The role of KRAS status has been retrospectively analyzed in several randomized and non-randomized studies (see Table 1). It is now evident that mutated KRAS is a negative predictor of response to anti-EGFR therapy. The abstracts from this year's ASCO further validate the growing body of evidence that KRAS is a predictive test. A noteworthy post-ASCO presentation at the 10<sup>th</sup> World Congress on Gastrointestinal Cancer was the findings from the KRAS analysis of NCIC.CO17, a randomized trial of cetuximab vs best supportive care (BSC) in pretreated mCRC.<sup>5</sup> Mutant KRAS was detected in 42% of 394 evaluable tumour samples. Median survival of patients with wild-type KRAS tumours who were treated with cetuximab was 4.7 months longer than BSC alone (9.5 vs 4.8 months;  $p < 0.0001$ ). No improvement was observed in patients with mutant KRAS tumours. Likewise, the survival of patients with either wild-type or mutant KRAS was similar in the BSC arm, suggesting that KRAS status is not prognostic.

The repeated confirmation and robustness of the evidence to date has been accepted as unequivocal support for KRAS status as a predictor of response to anti-EGFR therapy. In the interim, the anti-EGFR monoclonal antibody panitumumab has received European and Health Canada

approval for third-line therapy in advanced colorectal cancers with a wild-type KRAS phenotype.

Beyond lack of benefit in mutated KRAS, data from ASCO 2008 also suggested a detrimental impact on PFS of EGFR antibody therapy when administered in combination with chemotherapy. In both OPUS (as summarized above, Bokemeyer et al) and the CAIRO2 study,<sup>13</sup> where patients were treated with cetuximab added to capecitabine + oxaliplatin + bevacizumab chemotherapy, PFS was observed to be inferior in those with KRAS-mutant tumours than in those with wild-type. A similar interaction has been reported in lung cancer, where the tyrosine kinase EGFR inhibitor erlotinib, in combination with carboplatin and paclitaxel, also decreased PFS in relapsed patients with mutant KRAS tumours.<sup>6</sup> The mechanism of this negative interaction is unclear and warrants further investigation.

It has been demonstrated that patients who develop skin toxicity associated with EGFR inhibitors derive a greater therapeutic benefit (BOND-1<sup>4</sup> and EVEREST<sup>3</sup>). However, this is a crude assessment of patient response and requires a trial of therapy. The EVEREST trial was initially designed to evaluate the impact of cetuximab dose escalation to  $\geq$  Grade 2 rash. The subsequent analysis presented by Tejpar et al, summarized above, demonstrated that skin rash on cetuximab did not vary by KRAS status and appeared to be independent of response. The cumulative impact of additional potential predictors that have been identified, including expression of the ligands epiregulin and amphiregulin, requires further investigation.<sup>12</sup>

**CHANGES UNDERWAY IN RESEARCH AND PRACTICE**

Ongoing studies evaluating the role of cetuximab in the adjuvant and metastatic treatment settings have been amended to restrict eligibility to patients with wild-type KRAS tumours. **Table 2** (page 12) outlines the Canadian cooperative group studies affected. In addition, the need to address alternative investigational strategies for the 35% to 40% of patients with advanced colorectal cancers harbouring mutated KRAS has now been propelled to the forefront.

The predictive role of KRAS status on anti-EGFR thera-

py has sparked an exciting paradigm shift in the treatment of advanced colorectal cancer. Mutated KRAS status is a negative predictor for patients undergoing EGFR antibody therapy. Determination of KRAS status should be the standard of care when considering patients for cetuximab or panitumumab therapy. As availability of clinical KRAS testing is presently limited in Canada, efforts to ensure timely and affordable KRAS testing in centralized, quality-assured laboratory settings should be vigorously supported and pursued.

**TABLE 1. Analyses supporting the correlation between KRAS mutations and lack of response to EGFR inhibitors in mCRC**

study	treatment arms	number of patients	percent mutant	objective response, number of patients (%)	
				wild-type	mutant
<b>first-line randomized studies</b>					
CRYSTAL <sup>1</sup>	FOLFIRI ± cetuximab	540	35.6	102 (59%)	38 (36%)
OPUS <sup>2</sup>	FOLFOX ± cetuximab	233	42	37 (61%)	37 (31%)
<b>chemorefractory randomized studies</b>					
C017 <sup>5</sup>	cetuximab vs BSC	394	42	13 (13%)	1 (1%)
Amado et al <sup>14</sup>	panitumumab vs BSC	208	40	21 (17%)	0 (0%)
<b>non-randomized studies</b>					
Tejpar et al <sup>3</sup>	irinotecan + cetuximab	148	39	20 (37%)	0 (0%)
Lièvre et al <sup>9</sup>	chemotherapy ± cetuximab	89	32	65 (40%)	0 (0%)
Benvenuti et al <sup>10</sup>	chemotherapy + cetuximab or panitumumab	48	33	10 (31%)	1 (6%)
De Roock et al <sup>11</sup>	cetuximab ± irinotecan	113	41	27 (41%)	0 (0%)
Finocchiaro et al <sup>12</sup>	chemotherapy ± cetuximab	81	40	13 (26%)	2 (6%)
Di Fiore et al <sup>13</sup>	chemotherapy ± cetuximab	59	27	12 (28%)	0 (0%)
Khambata-Ford et al <sup>8</sup>	cetuximab	80	38	5 (10%)	0 (0%)

BSC: best supportive care

**TABLE 2. Current NCIC.CTG-endorsed or -led cetuximab colorectal cancer trials recently amended to restrict eligibility to patients with wild-type KRAS**

trial	study population	treatment arms
NCCTG-N0147/ NCIC.CRC2/ NCT00079274	adjuvant treatment of Stage III colon cancer	FOLFOX <sup>1</sup> + cetuximab vs FOLFOX
CALGB-C80405/ NCIC.CRC5/ NCT00265850	first-line treatment of mCRC	FOLFOX <sup>1</sup> or FOLFIRI <sup>2</sup> + bevacizumab vs FOLFOX <sup>1</sup> or FOLFIRI <sup>2</sup> + cetuximab vs FOLFOX <sup>1</sup> or FOLFIRI <sup>2</sup> + bevacizumab + cetuximab
NCIC-CO20/ NCIC.CRC5/	third-line treatment of mCRC	cetuximab + brivanib alaninate vs cetuximab

<sup>1</sup> oxaliplatin + fluorouracil + folinic acid

<sup>2</sup> irinotecan + fluorouracil + folinic acid

## References

1. E. Van Cutsem, M. Nowacki, I. Lang et al. Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial. *J Clin Oncol* 2007;25(18S). ASCO 2007, Abstract 4000.
2. Bokemeyer C, Staroslawska E, Makhson A et al. Cetuximab plus 5FU/FA/oxaliplatin (FOLFFOX4) in the first-line treatment of metastatic colorectal cancer (mCRC): a large-scale phase II study, OPUS. *European Journal of Cancer Supplements* 2007;5(4):236. ECCO 2007, Abstract 3004.
3. S. Tejpar, M. Peeters, Y. Humblet et al. Phase I/II study of cetuximab dose-escalation in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic (PK), Pharmacodynamic (PD) and efficacy data. ASCO 2007:4037.
4. Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *NEJM* 2004;351(4):337-45.
5. Karapetis C, Khamaba-Ford S, Jonker D, O'Callaghan C et al. KRAS mutation status is a predictive biomarker for cetuximab benefit in the treatment of advanced colorectal cancer – Results from NCIC CTG CO.17: *Ann Oncol* 2008 19 (suppl6), 10th World Congress on Gastrointestinal Cancer 25-28 June, 2008, Barcelona, Spain.
6. Punt CJ, Tol J, Rodenburg CJ et al. Randomized phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). *J Clin Oncol* 2008;26: (May 20 suppl). ASCO 2008, Abstract LBA4011.
7. Eberhard DA, Johnson BE, Amler LC et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23(25):5900-9.

## In brief

### Already known

- Mutated KRAS is a negative predictor of response to anti-EGFR therapy using cetuximab in pre-treated metastatic colorectal cancer (mCRC).

### What these studies showed

- Mutated KRAS is a negative predictor of response to cetuximab in combination with first-line chemotherapy in metastatic colorectal cancer.
- Skin rash with cetuximab appeared to be independent of both KRAS status and response.
- Cetuximab may have a detrimental impact on progression-free survival when administered in combination with oxaliplatin-based chemotherapy in patients with mutant KRAS tumours.

### Next steps

- Ongoing cooperative group Phase III trials evaluating cetuximab in adjuvant colon and metastatic colorectal cancer have been revised to restrict eligibility to patients with wild-type KRAS.
- Efforts to identify novel therapies for patients with mutant KRAS tumours are needed.

8. Khambata-Ford S, Garrett CR, Meropol NJ et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol* 2007;25(22):3230-7.
9. Lièvre A, Bachet JB, Boige V et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol* 2008;26(3):374-9.
10. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. *Cancer Res* 2007;67(6):2643-8.
11. De Roock W, Piessevaux H, De Schutter J et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. *Ann Oncol* 2008;19(3):508-15.
12. Finocchiaro G, Cappuzzo F, Jänne PA et al. EGFR, HER2 and Kras as predictive factors for cetuximab sensitivity in colorectal cancer. *J Clin Oncol* 2007;25(18S). ASCO 2007, Abstract 4021.
13. Di Fiore F, Blanchard F, Charbonnier F et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy. *Br J Cancer* 2007;96(8):1166-9.
14. Amado RG, Wolf M, Freeman D et al. Panitumumab (pmab) efficacy and patient-reported outcomes (PRO) in metastatic colorectal cancer (mCRC) patients (pts) with wild-type (WT) KRAS tumor status. ASCO 2008 Gastrointestinal Cancers Symposium, Abstract 278.

## Microsatellite instability and Stage II colon cancer

Sharlene Gill, MD, MPH, FACP, FRCPC

Confirmation of deficient mismatch repair (dMMR) as a predictive marker for lack of benefit from 5-FU based chemotherapy in Stage II and III colon cancer (CC): a pooled molecular reanalysis of randomized chemotherapy trials. ASCO 2008, Abstract 4008.

Investigators: D.J. Sargent et al.

**STUDY SUMMARY:** This study aimed to confirm the value of mismatch repair (MMR) status, determined by microsatellite instability molecular genotyping or by immunohistochemistry for loss of expression of MMR proteins, as a predictor of whether giving adjuvant fluorouracil chemotherapy to patients with Stage II and III colorectal cancer improves survival. Testing was done for deficient MMR status by immunohistochemistry on the tumours of 491 patients with Stage II or III colon cancer enrolled in 5 randomized controlled trials. The patients had received either fluorouracil-based chemotherapy or no adjuvant chemotherapy; 49% had Stage II disease and 15% were MMR-deficient. Five-year disease-free survival (DFS) did not differ by a statistically significant degree between treated vs untreated patients in those with MMR-deficient Stage II, MMR-proficient Stage II and MMR-deficient Stage III disease, but, as expected, among those with Stage III MMR-proficient tumours, more treated patients were alive with

no recurrence (61% treated vs 41% untreated,  $p = 0.003$ ). Multivariate adjustment for disease stage and age did not change these findings.

The above results in Stage II patients were pooled with a previous study by the same research group,<sup>1</sup> yielding 1027 patients of whom 16% were MMR-deficient. In the pooled data set, the rate of 5-year DFS was higher in the untreated vs treated Stage II MMR-deficient patients (87% vs 72%,  $p = 0.05$ ), and overall survival of untreated Stage II MMR-deficient patients was also higher than in treated patients (93% vs 75%,  $p = 0.03$ ). The authors concluded that stratifying patients according to MMR status provides a useful method for determining which Stage II patients will benefit from receiving adjuvant fluorouracil-based chemotherapy. They noted that these findings may not apply to whether Stage II patients should receive FOLFOX (oxaliplatin + leucovorin) and other regimens currently used to treat Stage III disease.

**COMMENTARY:** Sharlene Gill, MD, MPH, FACP, FRCPC, Assistant Professor of Medicine, University of British Columbia and Medical Oncologist, BCCA.

Microsatellite instability (MSI) is a consequence of the inability of the DNA nucleotide mismatch repair system to correct replication errors. It is characterized by alterations in the length of repetitive microsatellite nucleotide sequences, due to accumulation of single nucleotide mutations. This occurs as a manifestation of defects in mismatch repair through inactivation of 1 or more of the dominant mismatch repair genes: MLH1, MSH2, MSH6 and PMS2. Approximately 15% of sporadic colorectal cancers are characterized by MSI, mostly due to epigenetic hypermethylation of MLH1. The role of MSI as a prognostic and predictive marker in colorectal cancer has been a topic of intense interest over recent years. The pooled analysis presented by Dr. Daniel Sargent at the colorectal cancer podium session at ASCO 2008, summarized above, is a noteworthy advance in our understanding of the clinical impact of the MSI phenotype on adjuvant treatment.

Earlier studies had established the correlation between MSI and proximal colon cancers with a female predominance, earlier stage of presentation and better stage-stratified prognosis.<sup>2,3</sup> It was postulated that defects in DNA MMR may confer tolerance to acquired DNA damage. In in-vitro cell models of MSI, deficient MMR systems were insensitive to

fluorouracil while cells proficient in MMR were capable of recognizing fluorouracil incorporation into DNA, resulting in cell-cycle checkpoint arrest.<sup>1</sup> In 2003, Ribic et al reported an analysis of 570 tumour specimens from patients with Stage II or III colon cancer enrolled in randomized trials of adjuvant fluorouracil chemotherapy. Among the 16.7% with high-frequency microsatellite instability (MSI-H), adjuvant chemotherapy did not correlate with survival benefit.<sup>4</sup> A similar observation was recounted by Carethers et al in a smaller study using patient data and tumour samples from a US Veterans' hospital registry.<sup>5</sup> However, an analysis of patients from 4 randomized adjuvant therapy trials from the National Surgical Adjuvant Breast and Bowel Project (NSABP) failed to confirm the negative predictive value of MSI-H.<sup>6</sup>

The study by Sargent and colleagues was the largest analysis of its kind to date. With inclusion of the Ribic cohort, it validated the prognostic impact of deficient MMR in untreated patients. It further verified a lack of benefit from adjuvant fluorouracil treatment in patients with MSI-H colon cancers. In addition, a significant decrease in survival was observed in treated patients with Stage II node-negative disease.

What remains uncertain at this time is whether the strength of the results observed in the node-negative setting can be

extrapolated to Stage III node-positive colon cancer or to rectal cancer. The clinical impact of MSI status on benefit with irinotecan or oxaliplatin regimens is also not entirely clear at present. In vitro observations suggest that defects in MMR proteins do not seem to be associated with resistance to irinotecan<sup>7</sup> or oxaliplatin.<sup>8</sup> Further, in an analysis of 482 tumour samples from Stage III trial subjects randomized to receive adjuvant irinotecan, fluorouracil and leucovorin vs fluorouracil and leucovorin alone (CALGB 89803), the addition of irinotecan appeared to be associated with a more favorable DFS among patients with MSI-H tumours.<sup>9</sup>

## READY FOR PRIME TIME

In the ASCO 2006 recommendations for use of markers in gastrointestinal cancers, MSI was not endorsed for predicting the effectiveness of fluorouracil adjuvant chemotherapy.<sup>10</sup> However, in light of this new data, should mismatch repair status (either by MSI genotyping or by loss of immunohistochemical expression of MLH1 or MSH2) now be recommended prior to consideration of fluorouracil-based adjuvant therapy for patients with resected Stage II colon cancer? The answer is yes, and in the ongoing prospective Eastern Cooperative Oncology Group (ECOG) E5202 trial (NCIC.CRC3), patients with resected Stage II colon cancer are risk-stratified by MSI and 18q status (loss of 18q is a marker associated with colon cancer progression). Low-risk patients (MSI-H and retained 18q) are assigned to observation while high-risk patients (microsatellite stable or with loss of 18q) are randomized to adjuvant FOLFOX or FOLFOX + bevacizumab.

Within the Canadian context, these findings now necessitate a concerted effort to ensure standardized, timely, affordable and accessible testing of MSI status for resected node-negative colon cancers, either by immunohistochemistry (MLH1, MSH2) or by molecular genotyping. Currently, access to MSI testing is limited in most Canadian cancer centres, but the presented data provide a powerful argument for widespread availability of real-time MSI testing. The era of molecular stratification is upon us — the challenge is now to incorporate biomarkers with validated clinical relevance, as is the case with MSI status, into routine clinical use and rational treatment delivery.

## References

1. Ribic CM, Sargent DJ, Moore MJ et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *NEJM* 2003;349(3):247-57.
2. Gryfe R, Kim H, Hsieh ET et al. Tumor microsatellite instability and clinical outcome in young patients with colorectal cancer. *NEJM* 2000;342(2):69-77.
3. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 2005;23(3):609-18.
4. Carethers JM, Chauhan DP, Fink D et al. Mismatch repair proficiency and in vitro response to 5-fluorouracil. *Gastroenterology* 1999;117(1):123-31.

## In brief

### Already known

- Deficiency in the DNA mismatch repair system, which corrects replication errors and is manifested by a tumour phenotype of microsatellite instability, correlates with a more favourable stage-stratified prognosis of colorectal cancer.

### What this study showed

- Deficient mismatch repair (microsatellite instability) is associated with a lack of benefit of adjuvant fluorouracil chemotherapy in resected Stage III colon cancers.
- Deficient mismatch repair (microsatellite instability) and adjuvant fluorouracil chemotherapy is associated with inferior survival in resected Stage II colon cancer.

### Next steps

- Microsatellite instability testing is recommended in resected Stage II colon cancers being considered for adjuvant fluorouracil chemotherapy.
- The relevance of microsatellite instability with adjuvant fluorouracil + oxaliplatin regimens in resected high-risk colon and rectal cancers warrants further study.

5. Carethers JM, Smith EJ, Behling CA et al. Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. *Gastroenterology* 2004;126(2):394-401.
6. Kim GP, Colangelo LH, Wieand HS et al. Prognostic and predictive roles of high-degree microsatellite instability in colon cancer: a National Cancer Institute-National Surgical Adjuvant Breast and Bowel Project Collaborative Study. *J Clin Oncol* 2007;25(7):767-72.
7. Bras-Gonçalves RA, Rosty C, Laurent-Puig P et al. Sensitivity to CPT-11 of xenografted human colorectal cancers as a function of microsatellite instability and p53 status. *Br J Cancer* 2000;82(4):913-23.
8. Sargent C, Franco N, Chapusot C et al. Human colon cancer cells surviving high doses of cisplatin or oxaliplatin in vitro are not defective in DNA mismatch repair proteins. *Cancer Chemother Pharmacol* 2002;49(6):445-52.
9. Bertagnolli MM, Compton CC, Niedzwiecki D et al. Cancer And Leukemia Group B. Microsatellite instability predicts improved response to adjuvant therapy with irinotecan, 5-fluorouracil and leucovorin in stage III colon cancer. *J Clin Oncol* 2006;24(18S). ASCO 2006, Abstract 10003.
10. Locker GY, Hamilton S, Harris J et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006;24(33):5313-27.

## A prognostic test for early Stage IB–II NSCLC

Gwyn Bebb, BMBCh, PhD, FRCPC

A 15-gene expression signature prognostic for survival and predictive for adjuvant chemotherapy benefit in JBR.10 patients. ASCO 2008, Abstract 7510.

Investigators: M.S. Tsao et al.

**STUDY SUMMARY:** With the ultimate aim of identifying which early-stage non-small cell lung cancer (NSCLC) patients (Stage I and II) are most likely to benefit from chemotherapy, this study analyzed stored tumour tissue from patients in the JBR.10/BR.10 trial (CAN-NCIC-BR10, NCT00002583).<sup>1</sup> In that trial, a total of 482 patients with completely resected Stage IB–II NSCLC were randomized to receive either vinorelbine weekly for 16 weeks + cisplatin on Days 1 and 8, every 4 weeks for 4 cycles, or to observation only. At median followup of 5 years, patients receiving chemotherapy had improved overall survival (HR = 0.69;  $p = 0.04$ ). Subsequent analysis, however, has suggested that only patients with Stage II disease benefited. In this study, the researchers developed a 15-gene expression signature, using gene expression profiling by Affymetrix GeneChip Human Genome U133A Array. Testing on RNA from 133

patients (71 receiving chemotherapy and 62 on observation) yielded 2 subgroups in the observation arm: 31 with high risk of recurrence and 31 with low risk (HR = 15.02;  $p < 0.0001$ ). The 15-gene expression signature was valid in patients with both Stage IB (HR = 13.32;  $p < 0.0001$ ) and Stage II (HR = 13.47;  $p < 0.0001$ ) disease. This prognostic utility was lost when the high-risk group received chemotherapy, implying a promising predictive utility (HR = 0.33;  $p = 0.0005$ ). The researchers then set out to validate this gene signature in 3 independent public NSCLC gene expression data sets, limiting analysis to patients with Stage I–II disease. The signature demonstrated prognostic utility in 2 out of 3 of these. The authors concluded that if validated by further prospective testing, this 15-gene expression signature holds promise for improving decisions about which patients will benefit from receiving adjuvant chemotherapy.

**COMMENTARY:** Gwyn Bebb, BMBCh, PhD, FRCPC, Medical Oncologist, Tom Baker Cancer Centre and Assistant Professor University of Calgary, Calgary AB.

Pignon's presentation of the meta-analysis of 5 trials confirming the benefit of adjuvant therapy in resected NSCLC was both welcome and reassuring.<sup>2</sup> The ability to better select patients most likely to benefit from such treatment seems more elusive in NSCLC than in several other malignancies. Such an ability would allow those patients unlikely to derive benefit to avoid the unwelcome side effects of chemotherapy, while simultaneously conserving the healthcare system's valuable resources. This need is most acutely felt in individuals with Stage I disease, in whom the benefit of chemotherapy is at best marginal (Stage IB) and at worst downright harmful (Stage IA). Ming Tsao and colleagues' study, described above, attempts to address this matter by defining molecular markers that indicate benefit from adjuvant treatment.

Their well-conducted study utilized fresh-frozen samples obtained from the BR.10 adjuvant trial.<sup>1</sup> By examining tumours from the control arm and using a microarray approach to analyze gene expression in resected tissue, a signature associated with good vs bad outcome was identified. Intriguingly, the 15 genes comprising it are not commonly associated with NSCLC, yet the signature seemed able not only to separate good from poor outcome, but also to predict benefit from cisplatin + vinorelbine adjuvant treatment. The signature therefore demonstrated both prognostic and predictive utility when applied to BR.10 patients treated with chemotherapy and was valid for both Stage II and IB disease.

Further validation of these results in 3 other collections of resected NSCLC tissue adds considerably to the impact of this study. The same signature was prognostic for outcome

in 2 of these other sample sets, the Directors Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma study (169 cases, all adenocarcinoma; HR 2.9;  $p = 0.002$ )<sup>3</sup> and the University of Michigan study (106 cases; HR 2.3;  $p = 0.026$ ),<sup>4</sup> but not in the third, conducted at Duke University (85 cases; HR 1.5;  $p = 0.19$ ).<sup>5</sup> The fact that prognostic utility was maintained across both adenocarcinomas and squamous cell carcinomas bodes well for the robustness of this signature. On the other hand, the smaller hazard ratios and the less impressive  $p$ -values seen in this exercise does not, and points to continued uncertainty regarding the signature's general clinical applicability.

Should this test be incorporated into the standard workup of patients with resected NSCLC? The answer, despite our eagerness, still remains no. The lack of significance when the test was applied to one of the data sets clearly implies that further validation in well-designed prospective clinical trials is required. Further, fresh-frozen samples of NSCLC are not generally available as yet — an evolution of this test that could be performed on formalin-fixed paraffin-embedded samples would be attractive. Ultimately, a simpler but equally robust test, possibly utilizing a single gene or protein expression, would simplify and reduce the cost of implementation. It is still not clear what the optimal signature for outcome in NSCLC is, nor how many genes should make up that signature. This study nevertheless makes a very significant contribution to the field of predictive testing in lung cancer, and is the only proposed signature with evidence based on randomized clinical trial samples.

## TRIAL HIGHLIGHTS IMPORTANT ISSUES

This trial reinforces the importance of banking interrogatable tissue for future research. The vision of the BR.10 investigators in setting this up is commendable, and continues to allow additional research on these samples. On the other hand, it also reminds us that even in the BR.10 study, not all patients enrolled provided tumour samples of sufficient quality to allow for such detailed interrogation. It is in the interest of all that high-quality banking of resected and biopsied tissue remains a priority across all Canadian institutions. This study also confirms that predictive tests in NSCLC are not limited to the realms of science fiction, and counteracts the rather nihilistic attitude that has pervaded this field. Although not quite ready for clinical prime time, this is exciting stuff. In addition, the study uncovered a range of genetic markers whose role in lung cancer has not yet been defined, thereby opening up a series of new research avenues in this disease. Lastly, it must be emphasized that the metastatic potential of a cell is determined not only by its nature (i.e. genetic makeup) but also by its nurture: the specific conditions in lung, liver, bone and brain that attract and foster metastatic growth. Interrogating tumours, whether at the protein or nucleic acid level, will always look at only one side of this equation, the cancer cell itself (the seed) but not the metastatic sites (the soil).<sup>6</sup> Devising research strategies that address the soil side of the equation in some detail is an even more difficult challenge that will require ingenious banking and clinical trial strategies to address.

### References

1. Winton T, Livingston R, Johnson D et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *NEJM* 2005;352(25):2589-97.
2. Pignon JP, Tribodet H, Scagliotti GV et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the IACE Collaborative Group. *J Clin Oncol* 2008;26(21):3552-9.
3. Shedden K, Taylor JM, Enkemann SA et al. Director's Challenge Consortium for the Molecular Classification of Lung Adenocarcinoma. Gene expression-based survival prediction in lung adenocarcinoma: a multi-site, blinded validation study. *Nat Med* 2008;14(8):822-7.
4. Raponi M, Zhang Y, Yu J et al. Gene expression signatures for predicting prognosis of squamous cell and adenocarcinomas of the lung. *Cancer Res* 2006;66(15):7466-72.
5. Potti A, Mukherjee S, Petersen R et al. A genomic strategy to refine prognosis

## In brief

### Already known

- Many or most Stage II but few or Stage IB non-small cell lung cancer (NSCLC) patients appear to benefit from cisplatin-based adjuvant chemotherapy, a treatment which entails significant side effects.

### What this study shows

- This retrospective analysis of fresh-frozen tissue samples identified a 15-gene signature that predicted good vs bad outcome and also benefit from cisplatin + vinorelbine adjuvant chemotherapy, in patients with both Stage II and IB disease.
- Analyses of 2 out of 3 other tissue sample sets validated the prognostic value of the signature, including both adenocarcinomas and squamous cell carcinomas.

### Next steps

- Further validation is needed before recommending incorporation of this test into standard care of patients with resected NSCLC.
- Develop a test utilizing formalin-fixed paraffin-embedded samples, and/or a single gene or protein expression, to facilitate widespread implementation.
- Make high-quality banking of resected and biopsied tissue a priority across all Canadian cancer care institutions.

6. in early-stage non-small-cell lung cancer. *NEJM* 2006;355(6):570-80.
6. Paget S. The distribution of secondary growths in cancer of the breast. *Lancet* 1889;1:571-3.

## Cetuximab in advanced NSCLC

Natasha B. Leighl, MD, MMSc, FRCPC

FLEX: A randomized, multicenter, Phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC). ASCO 2008, Abstract 3.

Investigators: R. Pirker et al.

**TRIAL SUMMARY:** The Phase III FLEX trial randomized 1125 patients with Stage IIIB-IV epidermal growth factor receptor (EGFR)-positive NSCLC to receive either the EGFR-inhibitor cetuximab (400 mg/m<sup>2</sup> initial dose followed by 250 mg/m<sup>2</sup> weekly) plus chemotherapy with cisplatin

(80 mg/m<sup>2</sup> on Day 1) and vinorelbine (25 mg/m<sup>2</sup> on Days 1 and 8) every 3 weeks (n = 557), or to cisplatin + vinorelbine chemotherapy alone (n = 568). After 868 survival events had occurred, the patients receiving cetuximab had significantly longer overall survival (OS), the primary endpoint.

Median OS was 11.3 months for patients receiving cetuximab + chemotherapy vs 10.1 months for those receiving only chemotherapy, with 1-year survival of 47% vs 42% (HR = 0.871; 95 CI 0.762–0.996;  $p = 0.044$ ). Significantly different secondary endpoints included better response rate (36% with cetuximab vs 29% without;  $p = 0.012$ ), and time to treatment failure (4.2 months vs 3.7 months;  $p = 0.015$ ); however, time to treatment failure included patients who went on second-line treatment without documented disease progression. Progression-free survival (PFS) was 4.8 months in both arms. Adverse events were as expected, with acneiform skin rash and higher rates of diarrhea, infusion reactions and febrile neutropenia in patients receiving cetuximab.

**COMMENTARY:** **Natasha B. Leigh, MD, MMSc, FRCPC, Medical Oncologist, Princess Margaret Hospital – University Health Network; Assistant Professor, Department of Medicine, University of Toronto, Toronto, ON.**

This very interesting trial raises questions about the role of EGFR inhibitors in combination with first-line chemotherapy for advanced NSCLC. Three Phase II trials<sup>1-3</sup> and a preliminary Phase III trial<sup>4</sup> have suggested improved response rates and potential for better survival when cetuximab is administered concurrently with first-line platinum-based chemotherapy. The FLEX trial is the first Phase III study to confirm a survival benefit with the addition of cetuximab. This is promising but modest, with an absolute 1-month median survival benefit, or 5% at 1 year. In contrast to the combination of the EGFR TKI inhibitors-gefitinib and erlotinib with chemotherapy, where there has been concern about potential negative interactions in subgroups,<sup>5-7</sup> cetuximab added to chemotherapy appears to improve response rates, and in post-hoc analysis, time to treatment failure. Progression-free survival, however, a better measure of first-line treatment outcome that incorporates disease progression and deaths from any cause, was identical in both treatment arms.

It is important to recall that time to treatment failure is a composite endpoint that includes discontinuation of treatment for any reason (including progression, treatment toxicity or death), and has not traditionally been considered an acceptable endpoint for drug approval. Does it make sense that a drug would improve OS but not PFS? A key question is how first-line cetuximab influences subsequent therapy in patients, how that impacts on survival, and whether this treatment strategy has some long-term biologic impact. In subset analyses, Caucasian patients appeared to derive a survival benefit from cetuximab while Asian patients did not, although substantially more Asian patients in the control arm crossed over to EGFR TKI therapy — which may explain the lack of survival advantage from cetuximab in this group. Otherwise, subgroup analyses from this trial confirm our current understanding of prognosis in NSCLC, namely that histology, gender, smoking status and ethnicity are important factors regardless of EGFR status.

## NEEDED RESEARCH

Is cetuximab plus chemotherapy in advanced NSCLC a new standard of care? Based on the modest survival benefit without improvement in PFS, it is important to replicate

Analysis of prespecified subgroups showed that Caucasians ( $n = 946$ ) appeared to derive greater benefit than Asians ( $n = 121$ ) from cetuximab therapy, independent of histologic factors. Caucasians had better survival in the cetuximab arm (median 10.5 months) than in the control arm (median 9.1 months) (HR = 0.803; 95% CI 0.694–0.928;  $p = 0.003$ ). Asians in both arms had better overall survival than Caucasians, but did not appear to benefit from the addition of cetuximab (17.6 months median OS with cetuximab vs 20.4 months without), however the  $p$ -value was not significant. The authors concluded that cetuximab added to platinum-based chemotherapy was a new standard for first-line therapy of NSCLC.

## In brief

### Already known

- Earlier trials had suggested improved response rates and potential for better survival with addition of cetuximab to platinum-based chemotherapy in first-line treatment for advanced non-small cell lung cancer (NSCLC).

### What this study showed

- Results from the Phase III FLEX trial showed a modest overall survival benefit. Progression-free survival did not differ between treatment groups, however.
- Subset analyses implied that cetuximab did not improve survival in Asian patients, an observation potentially confounded by the fact that more of the Asian patients in the control arm crossed over to EGFR tyrosine kinase inhibitors.

### Next steps

- Before incorporating cetuximab into standard first-line treatment for advanced NSCLC, the survival benefit needs to be confirmed in other trials.
- The need for EGFR protein expression to derive benefit from cetuximab needs to be confirmed. As well, the potential of KRAS status to determine which patients should avoid the expense and toxicity of adding cetuximab to therapy needs to be evaluated.

these trial results to confirm improved survival before adding substantial expense and toxicity to current cytotoxic therapy for people with advanced NSCLC. Subsequent trials should reevaluate the need for EGFR positivity for treatment, as this has not been shown to be critical in colorectal

cancer, and subgroup analyses by KRAS mutation status and EGFR status are eagerly awaited<sup>8,9</sup> to see if we can define a molecular subgroup of patients that may benefit significantly from EGFR inhibitor therapy.

## References

- Rosell R, Robinet G, Szczesna A et al. Randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone as first-line therapy in EGFR-expressing advanced non-small-cell lung cancer. *Ann Oncol* 2008;19(2):362-9.
- Butts CA, Bodkin D, Middleman EL et al. Randomized phase II study of gemcitabine plus cisplatin or carboplatin [corrected], with or without cetuximab, as first-line therapy for patients with advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2007;25(36):5777-84.
- Herbst RS, Chansky, Kelly K et al. A phase II randomized selection trial evaluating concurrent chemotherapy plus cetuximab or chemotherapy followed by cetuximab in patients with advanced non-small cell lung cancer (NSCLC): Final report of SWOG 0342. *J Clin Oncol* 2007;25:18S. ASCO 2007, Abstract 7545.
- Lynch TJ, Patel T, Dreisbach et al. A randomized multicenter phase III study of cetuximab (Erbixim[R]) in combination with Taxane/Carboplatin versus Taxane/Carboplatin alone as first-line treatment for patients with advanced/metastatic Non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2007; 2:S340. 12th World Conference on Lung Cancer, Seoul, Korea, September 2-6, 2007, Abstract B3-03.
- Herbst RS, Prager D, Hermann R et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005;23(25):5892-9.
- Giaccone G, Herbst RS, Manegold C et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 1. *J Clin Oncol* 2004;22(5):777-84.
- Herbst RS, Giaccone G, Schiller JH et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial-INTACT 2. *J Clin Oncol* 2004;22(5):785-94.
- Van Cutsem E, Lang I, D'haens G et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. *J Clin Oncol* 2008;26(May 20 suppl) ASCO 2008, Abstract 2.
- Hirsch FR, Herbst RS, Olsen C et al. Increased EGFR gene copy number detected by fluorescent in situ hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy. *J Clin Oncol* 2008;26(20):3351-7.

## Targeted therapies in metastatic breast cancer

Sunil Verma, MD, MEd, FRCPC and Danny Robson, MD, FRCPC

Randomized, double-blind, placebo-controlled, Phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (MBC): AVADO. ASCO 2008, Abstract LBA1011.

Investigators: D. Miles et al.

**TRIAL SUMMARY:** The international, randomized, double-blind Phase III Avastin and Docetaxel (AVADO) study investigated the combination of bevacizumab and docetaxel as first-line therapy in 736 women with HER2-negative, inoperable, locally recurrent or metastatic breast cancer. To be eligible, patients needed Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, adequate left

ventricular ejection fraction (LVEF), and no central nervous system metastases. Enrolled patients received either docetaxel (100 mg/m<sup>2</sup> every 3 weeks for up to 9 cycles) + placebo, every 3 weeks until disease progression or unacceptable toxicity (n = 241), or docetaxel (same schedule) + either bevacizumab 7.5 mg/kg (n = 248) or bevacizumab 15 mg/kg (n = 247) every 3 weeks until

disease progression or unacceptable toxicity. Patients initially receiving placebo were allowed to take bevacizumab upon disease progression.

As shown in Table 3, at median followup of 10.2 months, progression-free survival (PFS), the primary endpoint, and overall response rate were statistically significantly superior for both groups receiving bevacizumab combinations compared to the group receiving docetaxel alone. As well, rates of increased toxicity due to the addition of bevacizumab were low and no unexpected toxicities were detected.

**TABLE 3. Outcomes at median followup of 10.2 months in women with locally recurring or metastatic breast cancer treated with docetaxel + placebo or 2 doses of bevacizumab, each given every 3 weeks**

	docetaxel + bevacizumab 7.5 mg/kg n = 248	docetaxel + bevacizumab 15 mg/kg n = 247	docetaxel + placebo n = 241
response rate (complete + partial response)	55.2 (p = 0.0295 vs placebo)	63.1 (p = 0.0001 vs placebo)	44.4%
progression free survival (PFS)	8.7 months	8.8 months	8 months
hazard ratio (HR) for PFS (unstratified) vs placebo	HR 0.79 (p = 0.0318)	HR 0.72 (p = 0.0099)	
HR for PFS (stratified) vs placebo	HR 0.69 (p = 0.0035)	HR 0.61 (p = 0.0001)	
Grade ≥ 3 adverse events	250	247	233

**COMMENTARY:** Sunil Verma, MD, MEd, FRCPC, Medical Oncologist, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON; and Danny Robson, MD, FRCPC, Breast Oncology Fellow, Odette Cancer Centre.

### ADDING VEGF INHIBITION TO TAXANE CHEMOTHERAPY

As an endothelial cell-specific mitogen and a regulator of angiogenesis, vascular endothelial growth factor (VEGF) is believed to play a major role in breast cancer tumorigenesis. Bevacizumab is a monoclonal antibody targeted against VEGF, thereby inhibiting angiogenesis and tumour growth. Key trials have already investigated bevacizumab in the treatment of advanced breast cancer. Miller et al, in the E2100 trial,<sup>1</sup> studied weekly paclitaxel either alone or in combination with bevacizumab 10 mg/kg given on Days 1 and 15, as first-line treatment in a HER2-negative advanced breast cancer population. PFS, the primary endpoint, was significantly prolonged in the bevacizumab arm, from 5.9 to 11.8 months (HR 0.60;  $p < 0.006$ ). These results provided the rationale for approval by the US Food and Drug Administration (FDA) of bevacizumab in February 2008 for use in metastatic, HER2-negative breast cancer.

The AVADO trial, presented by Dr. David Miles at ASCO 2008, was originally designed as a confirmatory trial for E2100. A similar patient population was enrolled and the treatment arms varied only in type of taxane used (docetaxel every 3 weeks instead of paclitaxel) and use of placebo vs bevacizumab 7.5 or 15 mg/kg every 3 weeks.

Although a significant improvement in PFS was seen with the addition of bevacizumab, from 8 to 8.7 months in the 7.5-mg/kg arm and 8 to 8.8 months in the 15-mg/kg arm, results were decidedly less robust than those of E2100.

In an accompanying discussion, Dr. Kathy Albain suggested 2 possibilities for the discrepant results of these 2 taxane + bevacizumab trials. First, median PFS may be a statistically inadequate marker of therapeutic benefit because the shape of the Kaplan-Meier curve is influenced by the time of assessment; hazard ratios may provide a more accurate view of PFS throughout the entire study. Such a statistical phenomenon is evident in the AVADO trial, where significant hazard ratios of 0.72 and 0.79 in the high-dose and low-dose arms, respectively, are more convincing than the absolute incremental benefits in median survival of 0.7 and 0.8 months in PFS. Nevertheless, the E2100 PFS hazard ratio of 0.51 (95% CI 0.43–0.62) remains more robust by comparison. Second, weekly administration of paclitaxel in the E2100 trial may have provided additional synergistic antiangiogenic effects, imparting a “dual hit” on the VEGF pathway. A closer look at the toxicity profiles in each trial perhaps furthers this hypothesis. The incident rates of serious adverse events associated with angiogenesis blockade — thrombosis, hypertension and bleeding — were much higher in the weekly paclitaxel E2100 arm than in the 3-weekly docetaxel arm of AVADO. However, we need to be cautious when interpreting these results, as E2100 did not contain a placebo randomization, and incremental toxicity may have been biased towards the treatment arm in the E2100 study. Nevertheless, the toxicity rates seen in the AVADO trial were quite manageable.

### WE AWAIT FURTHER RESULTS

Despite the recent endorsement of bevacizumab for metastatic breast cancer in the US, Health Canada has not approved this indication and Canadian funding agencies do not cover it. A conservative approach may ultimately prove wise: followup data will reveal whether there is any overall survival benefit, and long-term toxicity data will mature. Further, some key trials will soon be reported, including RIBBON 1 (NCT00262067, with results expected at the San Antonio Breast Cancer Symposium [SABCS] 2008). This and the overall survival from AVADO (expected at ASCO 2009) may provide more conclusive results for the use of bevacizumab in HER2-negative advanced breast cancer.

## In brief

### Already known

- The randomized Phase III E2100 trial showed that adding the vascular endothelial growth factor (VEGF) inhibitor bevacizumab to the taxane paclitaxel significantly prolonged progression-free survival.
- The FDA has already approved the use of bevacizumab in patients with metastatic breast cancer, while Health Canada has not, nor do Canadian funding bodies cover it.

### What this study showed

- Results of the Phase III AVADO trial, similar to E2100, randomly comparing 2 doses of bevacizumab to no bevacizumab in patients receiving the taxane docetaxel, showed a statistically significant improvement in PFS with addition of either dose of bevacizumab, although less than that seen in E2100.

### Next steps

- Await overall survival results from AVADO and other trials, and more long-term toxicity data on bevacizumab.

# LANDMARKS

Randomized study comparing efficacy/toxicity of monotherapy trastuzumab followed by monotherapy docetaxel at progression, and combination trastuzumab/docetaxel as first-line chemotherapy in HER2-neu positive, metastatic breast cancer (MBC) (HERTAX study). ASCO 2008, Abstract 1014.

**Investigators:** M. Bontenbal et al.

**TRIAL SUMMARY:** This Phase II trial of Stage IV breast cancer patients evaluated the outcome and toxicity of 2 trastuzumab + chemotherapy delivery schedules: trastuzumab monotherapy followed by chemotherapy at progression vs combination chemotherapy + trastuzumab given simultaneously, in 99 women receiving first-line treatment for HER2-positive metastatic breast cancer. Eligible patients were randomized to receive either docetaxel 100 mg/m<sup>2</sup> every 3 weeks + trastuzumab (loading dose of 4 mg/kg followed by weekly 2 mg/kg) — the combination group, or the same dose of trastuzumab alone, followed by docetaxel (at a similar dosage) upon progression — the sequential group. The women were allowed to have received previous hormonal and adjuvant non-taxane chemotherapy, but not previous trastuzumab. Treatment arms were balanced in terms of age, tumour hormonal receptor status and other adjuvant therapies received.

At 36 months median followup, PFS, the primary endpoint, was 3.9 months with initial trastuzumab monotherapy vs 9.4 months with combination treatment (HR 2.47; 95% CI 1.56–3.52; p = 0.0001). With sequential addition of docetaxel in the group receiving initial trastuzumab mono-

therapy, PFS was 10.8 months — thus the difference vs 9.4 months with combination treatment was not statistically significant (HR 1.21; 95% CI 0.76–1.94; p = 0.42). Objective response rates, a secondary endpoint, were seen in 38 (73%) and stable disease in 6 (12%) women in the combination group, vs 22 (50%) and 15 (34%), respectively, in the sequential group (p = 0.02 for objective response rate). Overall survival was 30.5 months in the combination vs 20.2 in the sequential group (HR 1.45; 95% CI 0.87–2.41; p = 0.15). In the combination group, 8% of patients had Grade 3–4 neurosensory toxicity vs 0% in the sequential group. Other Grade 3–4 toxicities did not differ by statistically significant amounts, and included 23% vs 15% for neutropenic fever and 4% vs 11.1% for pulmonary complaints. A decline of > 20% in LVEF was seen in 24.4% vs 15% of patients. The authors concluded that trastuzumab given as monotherapy followed by docetaxel upon progression provides PFS similar to that with combined simultaneous docetaxel + trastuzumab, and is associated with less Grade 3–4 toxicity. They propose that delaying cytotoxic therapy by giving initial trastuzumab monotherapy may be a treatment option for selected patients.

A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. ASCO 2008, Abstract 1015.

**Investigators:** J. O’Shaughnessy et al.

**TRIAL SUMMARY:** This Phase III study (EGF104900) compared outcomes with lapatinib alone vs lapatinib + trastuzumab in 296 women with HER2-positive metastatic breast cancer whose disease had progressed on trastuzumab. Enrolled patients had received an average of 6 prior chemotherapy regimens including anthracycline-, taxane- and trastuzumab-containing treatments. After stratification by hormone receptor status and presence or absence of visceral disease, 296 women were randomized to receive either lapatinib 1500 mg every day or lapatinib 1000 mg every day + trastuzumab 2 mg/kg weekly, following a 4 mg/kg loading dose. Those in the lapatinib-only arm with disease progression were offered the option of receiving the combination.

As shown in **Table 4**, the women receiving combination therapy (intention-to-treat analysis) had significantly improved PFS (the primary endpoint, by investigator assessment) and clinical benefit rate, a secondary endpoint

composed of confirmed complete response + partial response + stable disease. Response rate and overall survival, the 2 other secondary endpoints, were similar in both treatment groups. Both regimens were generally well tolerated, with Grade 1–2 diarrhea higher in the combination arm (60% vs 40%). Acneiform rash occurred more in the

**TABLE 4. Efficacy outcomes in 296 women randomized to receive either lapatinib + trastuzumab or lapatinib monotherapy**

endpoint	lapatinib + trastuzumab	lapatinib monotherapy	hazard ratio (HR) or odds ratio (OR) (95% CI)	p-value
median progression-free survival	12 weeks	8.1 weeks	HR = 0.73 (0.57–0.93)	0.008
overall survival	51.6 weeks	39 weeks	HR = 0.75 (0.53–1.07)	0.106
clinical benefit rate*	24.7%	12.4%	OR = 2.2 (1.2–4.5)	0.01

\* confirmed complete response + partial response + stable disease

lapatinib-only group, as expected because of the higher lapatinib dose. Asymptomatic decline in LVEF > 20% and/or below the lower limit of normal occurred in 5% of patients in the combined treatment arm and in 2% of those receiving lapatinib only. The authors concluded that this large

Phase III study is the first to show synergy of combined therapy with the targeted agents lapatinib and trastuzumab in women with HER2-positive metastatic breast cancer, with improved clinical outcome and no substantial difference in toxicity.

**COMMENTARY:** Sunil Verma, MD, MEd, FRCPC, Medical Oncologist, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON; and Danny Robson, MD, FRCPC, Breast Oncology Fellow, Odette Cancer Centre.

**TWO NEW ANTI-HER REGIMENS**

These two abstracts evaluated new ways of utilizing existing anti-HER therapy to treat metastatic breast cancer. HERTAX, a randomized Phase II trial, attempted to delay exposure to chemotherapy and its associated toxicities in patients with HER2-positive metastatic breast cancer by assigning 1 arm to trastuzumab monotherapy with no chemotherapy until disease progression. The sequential administration of systemic agents mandated a unique PFS calculation defined as time from trastuzumab start to trastuzumab failure plus time from docetaxel start until docetaxel failure. This unconventional PFS time measure may be biased in favor of the sequential arm, due to the summation of 2 time periods in which disease relapse occurred twice. While the authors concluded that outcomes in the sequential vs combination arms did not differ significantly, their data actually show that all 3 outcomes — conventional PFS, response rates and OS — were superior in the combination arm, with little additional toxicity other than an 8% increased incidence of Grade 3–4 neurotoxicity. Further, based on these results and past studies, Dr. Francisco Esteva concluded in a subsequent discussion session that while single-agent trastuzumab may be an option for some patients,<sup>2,3</sup> the combination of trastuzumab plus a taxane or vinorelbine remains the standard of care for most patients with HER2-positive metastatic breast cancer.

Dr. O’Shaughnessy, in Abstract 1015, also attempted to limit chemotherapy in favour of biologics for women with HER2-positive metastatic breast cancer, albeit in a cohort of patients with heavily treated, advanced disease. Surprisingly, women randomized to the combination of lapatinib and trastuzumab had a significant improvement in response rates and PFS with little incremental toxicity compared to lapatinib alone.

**BENEFIT OF SUSTAINED HER BLOCKADE**

Two previous trials have clearly shown the importance of continued blockade of the HER2 and HER1 pathways in addition to chemotherapy. The first, reported by Geyer et al,<sup>4</sup> showed a 4-month improvement in time to progression with a capecitabine + lapatinib combination over capecitabine alone. In addition, Gunter Von Minckwitz’s data, presented at ASCO 2008, supports the use of trastuzumab beyond progression.<sup>5</sup> Women with advanced breast cancer whose disease had already progressed on first-line trastuzumab derived a further 2.6-month benefit in time to progression with the reintroduction of trastuzumab in combination with capecitabine (p = 0.034). The O’Shaughnessy

trial discussed here further supports the benefit of continued HER pathway blockade upon progression after trastuzumab. The combined effect of lapatinib in combination with trastuzumab is substantial.

**OUTSTANDING QUESTIONS**

Two questions remain unanswered, however. First, will we see the same magnitude of benefit with dual biologic blockade (trastuzumab + lapatinib) as was evident with the previous

**In brief**

**Already known**

- Trastuzumab administered concurrently with chemotherapy has provided significant improvement in outcomes of metastatic breast cancer.
- Previous trials have showed importance of continued blockade of the HER2 and HER1 pathways in addition to chemotherapy.

**What these studies showed**

- Administering trastuzumab sequentially instead of concurrently in the Phase II HERTAX trial did not improve survival endpoints, and in fact showed weaker overall response rates and a non-significant trend towards lower overall survival.
- Administering a combination of lapatinib + trastuzumab in women with advanced HER2-positive, heavily treated metastatic disease provided improved response rates and progression-free survival compared to trastuzumab alone, with little additional toxicity, compared to lapatinib alone.

**Next steps**

- These results confirm the benefit of continuous HER pathway blockade, even after disease progression on trastuzumab.
- Ongoing studies will answer questions about the magnitude of benefit with dual biologic blockade in various treatment settings.

chemotherapy + biologic combinations (capecitabine + lapatinib)? Cross-trial comparisons can be misleading and only a randomized trial will appropriately address this question. Second, what additional benefits of dual biologic blockade will be evident in first-line therapy of HER2-positive advanced disease, and earlier in the adjuvant treatment setting? While ongoing trials will address both of these scenarios in more detail, the above studies lend support for benefit of anti-HER2 + HER1 therapy even after progression on trastuzumab.

## References

1. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *NEJM* 2007;357(26):2666-76.
2. Vogel C, Cobleigh M, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20(3):719-26.
3. Mackey JR, Kaufman B, Clemens M et al. Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2006;100(suppl 1). SABCS 2006, Abstract 3.
4. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *NEJM* 2006;355(26):2733-43.
5. Von Minckwitz G, Zielinski C, Maarteense E et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). ASCO 2008, Abstract 1025.

## Hormonal therapy and targeted agents in metastatic breast cancer

Debjani Grenier, MD, FRCPC

A Phase II multicenter, double-blind, randomized trial to compare anastrozole plus gefitinib with anastrozole plus placebo in postmenopausal women with hormone receptor-positive (HR+) metastatic breast cancer (MBC). ASCO 2008, Abstract 1012.

**Investigators:** M. Cristofanilli et al.

**TRIAL SUMMARY:** This Phase II trial was designed to examine whether inhibiting both epidermal growth factor receptor (EGFR) and estrogen receptor signaling has an effect in overcoming resistance to hormonal therapy. Ninety-four newly diagnosed women with metastatic, hormone receptor-positive breast cancer (reviewed at a central laboratory) were randomized to receive anastrozole 1 mg/day and either gefitinib 250 mg/day (n = 43) or placebo (n = 50). Because of slow enrollment, the trial was stopped early, limiting statistical analysis. Women receiving gefitinib

+ anastrozole had superior PFS, the primary endpoint, compared to those receiving placebo + anastrozole, with median PFS of 14.5 vs 8.2 months (HR 0.55; 95% CI 0.32–0.94). No unexpected toxicities were reported; treatment-related adverse events (mostly mild) were seen in 79% of gefitinib + anastrozole patients vs 38% of placebo + anastrozole patients. The authors concluded that adding gefitinib to anastrozole increases PFS in women with newly diagnosed, hormone receptor-positive breast cancer, and that this combination warrants further investigation.

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

Novel approaches to endocrine treatment for hormone receptor-positive breast cancer include the addition of targeted therapies. For example, in patients with ER-positive, HER2-overexpressing metastatic breast cancers, the Trastuzumab in Dual HER2 ER-positive metastatic breast cancer (TANDEM) trial explored the addition of trastuzumab to anastrozole vs anastrozole alone.<sup>1</sup> The combination led to improved time to tumour progression of 4.8 months vs 2.4 months (p = 0.0007) and higher tumour responses of 20.3% vs 6.8% (p = 0.018). Another trial reported at ASCO 2008 used everolimus (formerly RAD001), a mammalian target of rapamycin (mTOR) inhibitor, in combination with letrozole, both neoadjuvantly; this trial showed benefits with the addition of neoadjuvant everolimus in terms of clinical tumour response rates, albeit not statistically significant.<sup>2</sup>

Because increased EGFR expression may promote breast cancer resistance to endocrine therapy, the combination of

EGFR-targeted agents with endocrine therapy is a rational strategy.<sup>3</sup> In the Phase II study by Cristofanilli and colleagues, summarized above, anastrozole was combined with the oral EGFR tyrosine kinase inhibitor gefitinib to treat postmenopausal women with estrogen receptor-positive metastatic breast cancer, given as first-line therapy. Unfortunately, the trial closed early due to poor recruitment and only 94 of the planned 174 patients were accrued. Therefore, the study was underpowered and the results were summarized without formal statistical testing, i.e. no p-values were determined. Yet, PFS was prolonged in the combination arm (14.5 months vs 8.2 months) with HR 0.55 (95% CI 0.32–0.94). Also, there was an improved clinical benefit ratio but no improved tumour response rate. The OS data were too immature to report.

## FURTHER STUDY WARRANTED

Despite the fact that this study was underpowered, the

combination of gefitinib with endocrine therapy warrants further study. Gefitinib as a single agent has shown little activity in metastatic breast cancer, but patients in the trials were heavily pre-treated. Osborne and colleagues reported results from a randomized, placebo-controlled Phase II study of combination tamoxifen + gefitinib vs tamoxifen + placebo in women with metastatic breast cancer.<sup>4</sup> A modest improvement in PFS was seen in the tamoxifen + gefitinib group, particularly among patients with hormonal treatment-naïve disease or who had completed adjuvant tamoxifen more than 1 year previously (10.9 vs 8.8 months; HR 0.84;  $p = 0.31$ ) — this was the first signal for possible benefit to the addition of an EGFR inhibitor.

The current data confirm a benefit of adding gefitinib to tamoxifen. Due to small sample size and short duration of followup, further Phase III trials of combined endocrine therapy and EGFR-targeted therapies in breast cancer are warranted. Of uppermost importance is identification of those women most likely to benefit from the combination. Trials of EGFR inhibition in patients with non-small cell carcinoma of the lung have suggested clinical benefit in certain subgroups of patients.<sup>5</sup> As in lung cancer, prospective validation of biologic markers in correlative studies from ongoing trials in breast cancer is needed to best select the appropriate study population.

**References**

1. Mackey JR, Kaufman B, Clemens M et al. Trastuzumab prolongs progression-free survival in hormone-dependent and Her-2 positive metastatic breast cancer. *SABCS 2006*, Abstract 3.
2. Baselga J, van Dam PA, Greil R et al. Improved clinical and cell cycle response with an mTOR inhibitor, daily oral RAD001 (everolimus) plus letrozole versus placebo plus letrozole in a randomized phase II neoadjuvant trial in ER+ breast cancer. *ASCO 2008*, Abstract 530.
3. Massarweh S, Osborne CK, Creighton CJ et al. Tamoxifen resistance in breast tumors is driven by growth factor receptor signaling with repression of classic estrogen receptor genomic function. *Cancer Res*. 2008. 68(3):826-33.
4. Osborne K, Neven P, Dirix L et al. Randomized phase II study of gefitinib or placebo in combination with tamoxifen in patients with hormone receptor posi-

**In brief**

**Already known**

- Several trials have shown that adding targeted therapies to endocrine treatment in hormone-positive breast cancer can improve tumour response rates and time to tumour progression.

**What this study showed**

- This Phase II trial combining anastrozole with the oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib as first-line adjuvant treatment of postmenopausal women with estrogen receptor-positive metastatic breast cancer showed prolonged progression-free survival and improved clinical benefit ratio. The trial closed early due to poor recruitment and therefore lacked the planned statistical power.

**Next steps**

- Phase III studies of gefitinib and other EGFR inhibitors combined with endocrine therapy in this population are warranted.
- Determination of molecular markers to identify women most likely to benefit is of utmost importance.

5. Reck M, Crino L. Advances in anti-VEGF and anti-EGFR therapy for advanced non-small cell lung cancer. *Lung Cancer* 2008, Jun 24 [Epub ahead of print].

**Trastuzumab in advanced breast cancer**

Joseph Ragaz, MD, FRCPC

Prognosis of women with Stage IV breast cancer by HER2 status and trastuzumab treatment: an institutional based review. *ASCO 2008*, Abstract 1018.

Investigators: S.S. Dawood et al.

**STUDY SUMMARY:** This retrospective study examined the effects of trastuzumab on women with Stage IV, HER2-positive breast cancer. The researchers identified patients from the M.D. Anderson Cancer Center database who had newly-diagnosed Stage IV or recurrent breast cancer, diagnosed between 1991 and 2007, and with known HER2 status. Of a total of 2091 cases, 1782 (85.3%) were HER2-negative

and had not been treated with trastuzumab; 118 (5.6%) were HER2-positive and also not treated with trastuzumab; and 191 were HER2-positive and were treated with trastuzumab, as recommended in Stage IV breast cancer therapy protocols of most North American institutions since 2001. Overall survival (OS) was defined as the time from the first known distant metastasis to the date of death or last followup.

**Table 5** shows the final analysis of 2091 women at median followup of 16.9 months. Overall survival at 1 year was 86.6% for HER2-positive cases treated with trastuzumab vs 70.2% in HER2-positive patients with no trastuzumab. Survival in HER2-positive cases treated with trastuzumab was also significantly improved compared to HER2-negative cases (i.e. without trastuzumab), with OS of 86.6% vs 75.1% (HR 0.56; 95% CI 0.45–0.69;  $p < 0.0001$ ). The authors concluded that substantial survival improvement has occurred with the addition of trastuzumab to treatment of women with HER2-positive breast cancer.

**TABLE 5. Survival of 2091 women with metastatic breast cancer according to HER2 status and receipt of adjuvant first-line treatment with trastuzumab, at median followup of 16.9 months**

	n (%)	estrogen receptor-positive	years diagnosed	1-year survival (95% CI)	5-year survival
HER2-negative	1782 (85.3%)	64%	1991–2007	75.1% (72.9%–77.2%)	24.5% (21.7%–27.6%)
HER2-positive without trastuzumab	118 (5.6%)	70%	1992–2006	70.2% (60.3%–78.1%)	13.2% (6.7%–25.9%)
HER2-positive with trastuzumab	191 (9.1%)	48%	1998–2006	86.6% (80.8%–90.8%)	23.4% (16.2%–33.9%)

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

Long-term breast cancer mortality in the western world has declined sharply over the past few decades. A main question related to the research of biologics is their potential to further reduce population breast cancer mortality beyond the achievements resulting from earlier diagnosis and conventional systemic and locoregional therapies.

The presentation by Dr. Shaheenah Dawood, summarized above, provides the first evidence that trastuzumab could make a difference on a population scale, outside the setting of randomized clinical trials. The authors reviewed 2091 Stage IV breast cancer cases diagnosed between 1991 and 2007 with known HER2 status and no prior trastuzumab treatment, of which 85% were HER2-negative. Of the 309 HER2-positive cases, 191 received trastuzumab as the first-line therapy and 118 did not. As expected, the time span of diagnosis of HER2-positive cases not treated with trastuzumab included the earlier years, from 1992 to 2006, compared to those who did receive trastuzumab, diagnosed in 1998 to 2006, as shown in **Table 5**.

Comparison of OS at 1 year after the first known distant metastasis showed that the HER2-positive cases had significantly better survival at 1 year if treated with trastuzumab vs not (86.6% vs 70.2%). There was also a significant survival benefit ( $p < 0.0001$ ) compared to those with HER2-negative disease. At 3 and 5 years, however, there was no difference between survival of those with HER2-positive tumours treated with trastuzumab vs those with HER2-negative tumours. Patients with HER2-positive disease without trastuzumab had the worst survival (**Table 5**).

The evidence from this study, while less strong than that from randomized, controlled trials, indicates that manipulating a molecular pathway indeed has the potential to reverse a malignancy's aggressiveness, such that the outcome of the population with "aggressive" (HER2-positive) disease may approximate that of the "non-aggressive"

## In brief

### Already known

- Before the era of trastuzumab, HER2-overexpression in breast cancer was a marker for poorer survival outcomes.
- Evidence from individual randomized trials had shown improved survival of women with HER2-positive Stage IV metastatic breast cancer treated with trastuzumab.

### What this study showed

- This retrospective study provides the first evidence from population-based research outside the setting of clinical randomized trials that trastuzumab improves 5-year survival in women with HER2-positive disease to a similar level as in those with HER2-negative disease.

### Next steps

- Confirm and quantify the survival benefits of trastuzumab therapy in a large meta-analysis of randomized controlled trials.

(HER2-negative) cases. It shows that adding trastuzumab to treatment improves the 5-year survival rate of women with HER2-positive, Stage IV metastatic breast cancer. Maturation of the overall age-adjusted population mortality trends before and after the era of trastuzumab, in followup

of this and other studies, will likely confirm whether trastuzumab therapy is changing the natural history of HER2-positive breast cancer.

**References**

1. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a mono-

clonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *NEJM* 2001;344(11):783-92.

2. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *NEJM* 2005;353(16):1673-84.

3. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *NEJM* 2005;353(16):1659-72.

## First-line treatment of metastatic renal cell cancer

Sebastien J. Hotte, MD, MSc, FRCPC

Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC). ASCO 2008, Abstract 5024.

Investigators: R.A. Figlin et al.

**TRIAL SUMMARY:** This was an updated report of a Phase III trial that randomized 750 patients with metastatic clear cell renal cell cancer to receive either sunitinib (50 mg orally once per day in 6-week cycles of 4 weeks on treatment, 2 weeks off, n = 375) or interferon-alfa (9 million units subcutaneously 3 times per week, n = 375). Median overall survival (OS), a secondary endpoint, had not been reached at the time of the second interim analysis and report.<sup>1</sup> In the present analysis (median followup not reported), median treatment durations were 11 months (range < 1–41 months) for sunitinib and 4 months (range < 1–40 months) for interferon-alfa; 52 patients originally randomized to sunitinib were still taking it, 6 were still taking interferon-alfa, and 25 had crossed over from the interferon arm upon disease progression, as permitted after the primary endpoint of PFS had been met. Overall response rates by independent review were 47% (95% CI 34% to 44%) for sunitinib vs 8% (95% CI 6% to 12%) for interferon-alfa (p < 0.000001). Median PFS remained at 11 months vs 5 months (p < 0.000001), as at the earlier analysis. No new unexpected Grade 3–4 adverse events were reported, with the most common being hypertension (12%), fatigue (11%), diarrhea (8%) and hand-foot syndrome (8%) in the sunitinib group and fatigue (13%) and anorexia (2%) in the interferon group.

As shown in **Table 6**, median OS including the crossover

patients was 26.4 months in the sunitinib group (95% CI 23.0–32.9) and 21.8 months in the interferon group (95% CI 17.9–26.9 months), with HR of 0.821 (95% CI 0.673–1.001; p = 0.051 by log-rank test and p = 0.0018 by Wilcoxon test). A total of 190 patients died in the sunitinib group compared to 200 in the interferon group. **Table 6** also shows OS with the 25 patients who crossed over to sunitinib censored from the analysis. An exploratory analysis that included only patients who received no other therapy was performed. In the sunitinib arm, 193 received no further treatment and experienced median survival of 28.1 months. In the interferon arm, 162 patients received no further treatment and had median survival of 14.1 months (HR 0.647; p = 0.0033).

**TABLE 6. Median overall survival of patients with metastatic renal cell cancer randomized to receive first-line treatment with sunitinib vs interferon-alfa**

	sunitinib (95% CI)	interferon-alfa	hazard ratio (95% CI)	p-value log rank test	p-value, Wilcoxon test
intention-to-treat	26.4 months (23.0–32.9)	21.8 months (17.9–26.9)	HR 0.821 (0.673–1.001)	p = 0.051	p = 0.0128
crossover patients censored	26.4 (23.0–32.8)	20.0 (17.8–26.9)	HR 0.808 (0.661–0.987)	p = 0.0362	p = 0.0081
no further treatment	28.1 months (19.5–not reached)	14.1 months	HR 0.647	p = 0.0033	

**COMMENTARY:** Sebastien J. Hotte, MD, MSc (HRM), FRCPC, Medical Oncologist, Juravinski Cancer Centre and Associate Professor, Department of Oncology, McMaster University, Hamilton, ON.

The survival update presented by Dr. Robert Figlin at the May 2008 ASCO reaffirms the role of sunitinib as the standard of care in patients with low- and intermediate-risk metastatic clear cell renal cell carcinomas. This randomized, multicentre, international Phase III trial was first presented

as a Plenary Session at the 2006 ASCO Annual Meeting and later published in the *New England Journal of Medicine*.<sup>1</sup> Patients who had received no prior systemic therapy for metastatic and/or locally advanced disease were randomized to receive interferon or sunitinib. Early reports showed

clinically and statistically significant improvement in the primary outcome measure of PFS from 5 months to 11 months in patients receiving sunitinib. A non-statistically significant trend for improvement in OS was noted. At the time, there were concerns regarding the true significance of the reported difference in OS because many patients on the interferon arm went on to receive sunitinib after progression of their disease.

## CONFIRMS AN OS ADVANTAGE FOR SUNITINIB

This final OS analysis was performed after 290 events were observed. In the non-stratified, intention-to-treat analysis, median OS was 26.4 months in the sunitinib arm and 21.8 in the interferon arm, with a hazard ratio of 0.821. P-values were calculated using both the log-rank and the Wilcoxon methods, yielding values of 0.051 and 0.0128, respectively. Although the log-rank method was chosen a priori, it tends to be more suitable when the ratio of death rates between 2 treatment groups is constant over time.<sup>2</sup> The Wilcoxon method is a more appropriate test when the ratio of death rates is not constant over time and/or in the situations where survival data may be confounded by crossover or post-study treatment, because it puts more emphasis on earlier events and time points.<sup>2</sup> Given that 33% of patients in the interferon group had second-line treatment with sunitinib compared to 11% on the sunitinib arm, this confounding potential is real — hence, the Wilcoxon p-value may be a better representation of the true statistical significance of the OS findings. A pre-specified OS analysis taking into consideration the stratification factors of ECOG performance status, LDH level and the presence or absence of prior nephrectomy was undertaken and showed identical median OS findings with a slightly lower HR of 0.818 and p-values of 0.0491 (log-rank) and 0.0132 (Wilcoxon). In any case, there is little doubt that treatment with sunitinib results in a 20% improvement in the risk of death when compared to placebo.

A few interesting, hypothesis-generating exploratory OS analyses were performed. When the 25 patients in the interferon arm who crossed over to sunitinib during the study period were censored, median OS differences improved to 26.4 months in the sunitinib arm and 20.0 months in the interferon arm. Although exploratory in nature, this may nonetheless represent a better estimate of the true magnitude of benefit that sunitinib has over interferon. Lastly, when only patients who did not receive any post-study treatment were included, the hazard ratio improved to 0.647 and the survival benefits improved significantly, with median OS of 28.1 months for patients receiving only sunitinib and 14.1 months in those receiving only interferon. Although very much exploratory, this offers a laudable best-case scenario.

It is important to note that only patients with clear cell tumours (roughly 75% of renal cell cancers) were eligible for this study, and the results cannot be generalized to other subtypes, such as papillary or sarcomatoid tumours. Further, only 7% of patients had high-risk disease, and this subset was not sufficiently large to provide the power to warrant treatment of all patients with high-risk disease with sunitinib. A recently published study of temsirolimus in this population resulted in improved survival and PFS parameters and is the de facto standard of care in patients with high-risk disease.<sup>3</sup>

## In brief

### Already known

- An earlier report of this trial comparing sunitinib to interferon in first-line treatment of patients with metastatic clear cell renal cancer (7% of whom had high-risk disease) had shown improved progression-free survival and a non-significant trend for overall survival (OS) favouring sunitinib.
- Many patients on the interferon arm had received sunitinib after disease progression, affecting the validity of the OS results.

### What this study showed

- This final OS analysis showed a significant difference between treatment arms when the p-value was calculated by the Wilcoxon method, likely more appropriate than the log-rank method because of the large crossover to sunitinib from the interferon arm. OS calculated by the log-rank method narrowly missed statistical significance.

### Next steps

- This study confirms the role of sunitinib for first-line treatment of patients with low- and intermediate-risk metastatic clear cell renal cancer.
- Ongoing trials will show whether the adjuvant use of multikinase inhibitors (e.g. sunitinib and sorafenib) will improve recurrence and survival rates in patients with fully resected clear cell renal cell cancer who are at high risk of recurrence.

In summary, sunitinib remains the reference standard of care for most patients with advanced clear cell renal carcinomas. Because of its potential for significant toxicity, such as hypertension, fatigue, diarrhea, skin rash and others, sunitinib should be prescribed only by physicians who have an interest and experience in administering tyrosine kinase inhibitors. Despite these significant advances, advanced renal cancer remains a largely fatal disease. Hopefully, multi-tyrosine kinase inhibitors such as sunitinib and sorafenib will soon be shown to improve the cure rate of patients at high risk of recurrence, e.g. in the Phase III Randomized Study of Adjuvant Sunitinib Malate Versus Sorafenib in Patients With Resected Renal Cell Carcinoma (ECOG-E2805, CAN-NCIC-E2805, NCT00326898).

### References

1. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *NEJM* 2007;356(2):115-24.
2. Collett D. *Modelling Survival Data in Medical Research*. London; Chapman & Hall, 1994.
3. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *NEJM* 2007;356(22):2271-81.

## Second-line treatment of metastatic renal cell cancer

Anil Kapoor, MD, FRCSC

A Phase II study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic renal cell carcinoma which has progressed on tyrosine kinase inhibition therapy. ASCO 2008, Abstract 5113.

**Investigators:** J. Jac et al.

**TRIAL SUMMARY:** This Phase II trial randomly assigned 410 patients with metastatic clear-cell renal cell carcinoma in a 2:1 ratio to receive everolimus (10 mg orally) + best supportive care (BSC, n = 272) or placebo + BSC (n = 138). Enrolled patients had experienced disease progression while being administered vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) therapy (sunitinib, 71%, sorafenib, 55% or both, 26%). More than 90% had > 1 site of metastatic disease, and 96% of patients in the everolimus arm and 95% in the placebo arm had prior nephrectomy. Prior bevacizumab and cytokine treatment was permitted. Treatment was continued until disease progression or intolerance of the treatment. Patients who showed signs of progression were unblinded and, if in the placebo arm, were given the opportunity to receive everolimus.

Following early termination of the study due to favourable results in the everolimus arm, analysis of data showed median PFS of 4.0 months in patients who received everoli-

mus compared with 1.9 months in those who received placebo ( $p < 0.001$ ; 95% CI 0.22–0.40). Twenty-six percent of patients in the everolimus group had experienced PFS of 6 months compared with 2% of patients in the placebo group. Frequent side effects including stomatitis (36% with everolimus vs 7% with placebo), asthenia and/or fatigue (28% vs 20%), rash (25% vs 4%), diarrhea (17% vs 3%), anorexia (16% vs 6%), nausea (15% vs 8%), vomiting (12% vs 4%), cough (12% vs 4%), peripheral edema (10% vs 3%), pneumonitis (8% vs 0%) and dyspnea (8% vs 2%). The main laboratory abnormalities included anemia (91% vs 76%), lymphopenia (42% vs 29%), thrombocytopenia (20% vs 2%) and neutropenia (11% vs 3%). As well, hypercholesterolemia, hypertriglyceridemia and hyperglycemia were higher in the everolimus arm compared to the placebo arm. Median overall survival (OS) was 8.8 months in the placebo group, and in the everolimus group OS was confounded by the built-in crossover and has not yet been reached.

**COMMENTARY:** Anil Kapoor, MD, FRCSC, Chair, Genito-Urinary Disease Site, Juravinski Cancer Centre, Hamilton, ON.

Treatment for metastatic renal cell cancer (mRCC) has undergone a paradigm shift in the last few years from the long-time mainstay of cytokine therapy with interferon-alpha 2A (IFN- $\alpha$ 2a) and interleukin-2 to new, targeted therapies including vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors. The new VEGF inhibitors include sunitinib and sorafenib, with sunitinib demonstrating efficacy as first-line therapy for mRCC in good- to intermediate-prognosis patients.<sup>2</sup> The mTOR inhibitor temsirolimus has been shown to prolong OS compared to interferon-alpha 2a in poor-prognosis patients.<sup>3</sup>

In current practice sunitinib is the generally accepted first-line therapy for new cases of mRCC, with temsirolimus an acceptable option for first-line therapy in poor-prognosis patients. There is no current standard for second-line therapy after failure of sunitinib or temsirolimus, although sorafenib has been shown to be effective in patients who have progressed on cytokine therapy.<sup>4</sup> Thus, oncologists are currently faced with the dilemma of what agent to administer to patients who progress on first-line sunitinib therapy: specifically, data on second-line therapy for those progressing on VEGF-targeted therapy has been lacking. The everolimus study described above provides new data on second-line therapy after VEGF-failure.

### MTOR INHIBITORS

The mTOR pathway has become a central target for cancer therapy, as mTOR is a central regulator signaling pathways associated with the abnormal growth, proliferation and survival of cancer cell growth and proliferation, via involvement in regulation of translation initiation. Two emerging drugs that target this pathway, temsirolimus (formerly known as CCI-779) and everolimus (formerly RAD001), are emerging as important therapeutic agents in mRCC.

Temsirolimus, a soluble ester analog of rapamycin (sirolimus), was evaluated in a Phase III open-label study<sup>3</sup> in poor-risk, advanced RCC patients with no prior systemic therapy that randomized patients to temsirolimus vs IFN- $\alpha$ 2a vs temsirolimus + IFN- $\alpha$ 2a. Single-agent temsirolimus significantly improved OS compared to IFN- $\alpha$ 2a (10.9 vs 7.3 months;  $p = 0.0069$ ), with acceptable safety. To date, no large, randomized controlled trial has evaluated temsirolimus in second-line treatment.

Everolimus is also a derivative of sirolimus and has both immunosuppressant and antiangiogenic properties, targeting mTOR. Phase I and Phase II data in patients with advanced renal cell cancer identified significant efficacy, leading to the current ongoing randomized Phase II second-line trial, described above. At ASCO 2006, a Phase II trial in 25 mRCC patients treated with everolimus after failure

# LANDMARKS

of cytokine or cytotoxic therapy (at a dose of 10 mg/day) showed a median PFS greater than 9 months in 25 patients.<sup>1</sup>

The data from the ASCO 2008 trial establishes the clinical benefit of everolimus as second-line therapy in mRCC patients who have progressed on first-line targeted therapy including sunitinib and sorafenib, with improvement in overall PFS vs placebo. Everolimus can be proposed as the new standard of care in the second-line setting for patients progressing on VEGF-inhibitor therapy. Everolimus has not yet been approved by Health Canada and is not marketed in Canada; however, based on this study, metastatic kidney cancer patients whose disease has progressed on sunitinib or sorafenib are offered everolimus as a second-line option, via an industry-sponsored trial.

## References

1. Amato RJ, Misellati A, Khan M, Chiang S. A phase II trial of RAD001 in patients (Pts) with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2006;24(18S), ASCO 2006, Abstract 4530.
2. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *NEJM* 2007;356(2):115-24.
3. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *NEJM* 2007;31;356(22):2271-81.
4. Escudier B, Eisen T, Stadler VM et al. Sorafenib in advanced clear-cell renal cell carcinoma. *NEJM* 2007;11;356(2):125-34.

## In brief

### Already known

- Data on second-line therapy after failure of the VEGF-inhibitor sunitinib in patients with metastatic renal cell cancer (mRCC) was lacking.

### What this study showed

- This randomized Phase II trial showed significantly improved progression-free survival in patients receiving everolimus compared to those receiving best supportive care alone.

### Next steps

- Everolimus appears to be the new standard of care for second-line treatment of patients with mRCC whose disease has progressed on VEGF-inhibitor therapy.

## Stage I testicular seminoma

Christian Kollmansberger, MD, FRCPC and Pdraig Warde MB, CHB, BAO, BA, FRCPC

Radiotherapy versus carboplatin for Stage I seminoma: updated analysis of the MRC/EORTC randomized trial (ISRCTN27163214). ASCO 2008, Abstract 1.

Investigators: R.T. Oliver et al.

**TRIAL SUMMARY:** This was an updated analysis of the UK Medical Research Council (MRC) TE19 / European Organization for Research on Treatment of Cancer (EORTC) 30982 trial,<sup>1</sup> in which 1447 patients with testicular seminoma were randomized in a 3:5 ratio to receive either a single injection of carboplatin (n = 573) or radiotherapy (n = 904). The current analysis at 6.5 years median followup, with 1148 (78%) of patients having ≥ 5 years of followup, showed 5-year relapse-free rates (RFRs) of 94.7% (95% CI 92.5% to 96.3%) in the carboplatin group vs 96% (95% CI 94.5% to 97.1%) in the radiotherapy group. Only 1 death from seminoma has been reported, and this occurred in the radiotherapy arm. In an exploratory subgroup analysis, the

occurrence of new, contralateral testicular germ cell tumours was significantly different, with only 2 cases in the carboplatin arm vs 15 in the radiotherapy arm (HR 0.22; 95% CI 0.05–0.95; p = 0.03). Because of a protocol error, a subgroup analysis on the effect of carboplatin dosage was possible, and showed that men who had received at least 99% of the AUC 7 dose (n = 347) had 5-year RFR of 96.1% as compared to 92.6% in those receiving lower doses (n = 212) (HR 0.51; 95% CI 0.24–1.07; p = 0.08). Also, tumours > 4 cm had poorer RFR (HR 3.68; 95% CI 1.49–9.13). The authors concluded that extended followup of this trial confirms non-inferiority of single-dose carboplatin compared to radiotherapy.

**COMMENTARY:** Christian Kollmansberger MD, Medical Oncologist, British Columbia Cancer Agency – Vancouver Cancer Centre; Clinical Associate Professor of Medicine, University of British Columbia; Pdraig Warde MB, CHB, BAO, BA, FRCPC, Department of Radiation Oncology, Princess Margaret Hospital; Professor of Medicine, University of Toronto.

Cure rates for Stage I seminoma approach 100%. Orchiectomy alone cures approximately 80% of patients, with 20%

of patients relapsing after surgery only. Radiation of the para-aortic lymph nodes with or without the pelvic lymph

nodes has been the standard adjuvant treatment after orchiectomy for more than 40 years, resulting in a relapse rate of approximately 4%.<sup>2</sup> Due to the increasing recognition of the long-term toxicities of radiation, in particular secondary non-germ cell cancers, alternate treatment options for this highly curable malignancy have been explored in the past decade. Active surveillance has become increasingly popular as an option, with several series demonstrating safety and an excellent outcome achieved by careful followup after orchiectomy — reserving treatment for patients who relapse.<sup>3</sup> Based on the exceptional chemosensitivity of seminomas, several Phase II studies have investigated 1–2 cycles of carboplatin as adjuvant therapy. Both strategies resulted in a very low recurrence rate, suggesting that carboplatin chemotherapy may be as effective as radiation therapy and is potentially associated with reduced risk of long-term side effects.<sup>4</sup>

The current study is the largest ever conducted in seminoma patients. It aimed to confirm the non-inferiority of 1 cycle of carboplatin to radiation therapy. The primary endpoint was the relapse-free rate (RFR); the study was designed to exclude an absolute difference between radiation and carboplatin of > 3%. The current analysis reports results after median followup of 6.5 years.

Since it is very unlikely that relapse rates will change significantly with a longer observation period, this trial establishes carboplatin as an additional treatment option for patients with Stage I seminoma — keeping in mind some important issues. This trial was designed as non-inferiority study: it has not established that carboplatin gives equivalent results to radiation therapy. Given the upper RFR confidence interval boundary of 3.5%, the relapse rate after carboplatin could be as high as 7%. Adequate dosing of carboplatin appears critical, since a dose < AUC 7 resulted in a higher relapse rate of 7.4%. The pattern of relapse after carboplatin is similar to the pattern after surveillance, with most relapses occurring in the retroperitoneum — requiring frequent imaging of the retroperitoneum during followup.

### THREE MANAGEMENT OPTIONS

Which is best for patients with Stage I seminoma: radiation, carboplatin or surveillance? The ultimate goal of treating our patients is to achieve maximum cure with the least toxicity for the entire patient population. With both radiation and carboplatin, the majority of patients will be over-treated since most patients with Stage I seminoma are cured by orchiectomy alone. Until we are able to reliably and better characterize a high-risk group of patients, treating all those with Stage I seminoma should be avoided.

The size of the primary tumour and invasion of the rete testis (the network of tubules carrying sperm from the seminiferous tubules to the vasa efferentia), as described by Warde et al,<sup>5</sup> are widely used to classify patients into prognostic groups, with the worst group having a 32% risk of relapse. However, this proposed classification has never been validated and should not be used in routine practice. Even if this classification is correct, 68% of patients are still treated without benefit while being exposed to potential acute and late toxicity.

## In brief

### Already known

- Approximately 96% cure rates are achieved with post-surgical radiation in Stage I seminoma (testicular cancer), but only 20% of patients would relapse without radiation. Therefore, radiation exposes a significant proportion of patients to side effects including secondary tumours — without benefit.
- Phase II studies had shown that 1–2 cycles of carboplatin as adjuvant chemotherapy may be as effective as radiation therapy and is potentially associated with reduced risk of long-term side effects.
- Active surveillance with treatment upon relapse is another option.

### What this study showed

- Carboplatin given at adequate dosing is indeed an additional treatment option for patients with Stage I seminoma, although not proven to be equivalent to radiation.

### Next steps

- Until better ways of risk stratification are developed to determine which patients should receive adjuvant treatment, they should be offered the option of active surveillance with treatment only upon relapse.

In particular, due to the risk of secondary malignancies, the use of radiation has decreased significantly over the past decade.<sup>6</sup> Although expected to be low, the long-term toxicity rate of carboplatin is currently unknown. A dose-dependent risk for secondary leukemias has been demonstrated for carboplatin as well as for cisplatin.<sup>7</sup> Further, cardiovascular deaths have been observed after 2 cycles of carboplatin; although all these patients had a history of pre-existing heart disease, an impact of carboplatin cannot be entirely excluded.<sup>8</sup> Active surveillance including regular followup visits, serum tumour marker testing and chest x-ray and computed tomography (CT) scan imaging, at intervals determined by risk,<sup>9</sup> has proven an effective alternative to radiation or carboplatin, with excellent outcomes.<sup>3</sup> Although treatment of Stage I testicular patients who relapse is more intense, the overall impact is lower and the majority of patients are completely spared the burden of treatment.

Because each of the 3 options has pros and cons that the patient needs to understand, a thorough discussion with each individual patient is required. If applied with rigour and experience and according to standard protocols, active

*Continued on page 31*

surveillance is safe, associated with an excellent outcome and incurs the least toxicity for the entire population — and should therefore be available to patients. **EB**

## References

1. Oliver RT, Mason MD, Mead GM et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet* 2005 Jul 23-29;366(9482):293-300.
2. Krege S, Beyer J, Souchon R et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): part II. *Eur Urol* 2008;53(3):497-513.
3. Warde PR, Chung P, Sturgeon J et al. Should Surveillance should be considered the standard of care in stage I seminoma? *J Clin Oncol* 2005;23(16S), ASCO 2005, Abstract 4520.
4. Oliver T, Dieckmann K, Steiner H, Skoneczna I. Pooled analysis of Phase 2 reports of 2 v 1 course of Carboplatin as adjuvant for Stage I Seminoma. *J Clin Oncol* 2005;23(16S), ASCO 2005, Abstract 4572.
5. Warde P, Gospodarowicz MK, Banerjee D et al. Prognostic factors for relapse in stage I testicular seminoma treated with surveillance. *J Urol* 1997;157(5):1705-9.
6. Travis LB, Fosså SD, Schonfeld SJ et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst* 2005; 97(18):1354-65.
7. Travis LB, Holowaty EJ, Bergfeldt K et al. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *NEJM* 1999;340(5):351-7.
8. Reiter WJ, Brodowicz T, Alavi S et al. Twelve-year experience with two courses of adjuvant single-agent carboplatin therapy for clinical stage I seminoma. *J Clin Oncol* 2001;19(1):101-4.
9. Martin JM, Panzarella T, Zwahlen DR et al. Evidence-based guidelines for following stage I seminoma. *Cancer* 2007;109(11):2248-56.

## Disclosure

Drs. Lim, Kollmansberger, Ragaz, Robson and Warde report having no potential conflicts of interest related to this article. Dr. Bebb reports being on advisory boards of AstraZeneca, Bristol-Myers Squibb, Novartis and Roche. Dr. Gill reports serving on advisory board of Amgen, Bristol-Myers Squibb and Sanofi-Aventis. Dr. Grenier reports being on advisory boards of AstraZeneca and GlaxoSmithKline. Dr. Hotte reports receiving research support from Pfizer and being on an advisory board and speakers' bureau of Pfizer. Dr. Kapoor reports research support from Novartis, Pfizer and Wyeth, and being on advisory boards of Bayer, Novartis, Pfizer and Wyeth. Dr. Leigh reports previous research support from Roche, being on advisory boards of AstraZeneca, Bristol-Myers Squibb and Roche, and receiving honoraria for CME lectures from AstraZeneca and Roche. Dr. Verma reports receiving research support from, and being a consultant and on advisory boards and speakers' bureaus for Roche, GSK and Sanofi Aventis.