



LANDMARKS

EVIDENCE WATCH

A review and assessment of recent clinical trial data

Oncology Exchange provides overviews of important clinical trial data presented at the 45th Annual Meeting of the American Society of Clinical Oncologists (ASCO), held May 29 to June 1, 2009 in Orlando, Florida. Leading Canadian experts offer commentary and clinical interpretations.

Contributors were selected by Hagen Kennecke, MD, FRCPC and Joseph Ragaz, MD, FRCPC.

Bevacizumab in colon cancer

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Wolmark N, Yothers G, O'Connell MJ et al. **A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08.** ASCO 2009, Abstract LBA4.

TRIAL SUMMARY: The NSABP Protocol C-08 trial randomized 2672 patients with Stage II (24.9%) or III colon cancer to receive either mFOLFOX6 or mFOLFOX6 + bevacizumab 5 mg/kg intravenously every two weeks for a year. The mFOLFOX6 regimen was oxaliplatin 85 mg/m² intravenously on Day 1, leucovorin 400 mg/m² intravenously on Day 1, fluorouracil 400 mg/m² by intravenous bolus on Day 1, and fluorouracil 2400 mg/m² by continuous infusion over 46 hours, every 14 days for 12 cycles.

COMMENTARY: NSABP C-08 was a large, well-conducted randomized trial evaluating the efficacy of adding bevacizumab to standard chemotherapy (FOLFOX) in patients with Stage II–III colon cancer. Importantly, bevacizumab was continued for a total of one year in the experimental arm. The preliminary news that NSABP C-08 was a negative trial was communicated in a press release two months before the ASCO meeting. As Dr. Wolmark stated in his presentation, the question left to answer during this plenary presentation was whether the trial failed “abominably or with distinction.” Although we were all left to come to our own conclusions, the latter may be more appropriate. An impressive benefit was seen in the experimental arm at the one-year timepoint, suggesting that bevacizumab resulted in a significant reduction in the risk of early relapse. This benefit was not sustained after discontinuation of therapy. By three years, DFS for the experimental arm was 77.4%, as compared to 75.5% in the control arm. Neither the Stage

II nor Stage III subgroups demonstrated significant benefit with the addition of bevacizumab. During the first year of followup, the patients receiving bevacizumab had statistically significantly better disease-free survival (DFS, the primary endpoint) for added bevacizumab (1-year hazard ratio [HR] 0.60; $p = 0.0004$), but this benefit was not present with further followup (3-year HR 0.89; 95% CI 0.76 to 1.04; $p = 0.15$). The authors concluded that adding bevacizumab did not significantly prolong long-term, overall DFS.

II nor Stage III subgroups demonstrated significant benefit with the addition of bevacizumab.

The analysis of the hazard ratio for DFS over time was thought-provoking and controversial. Wolmark and colleagues suggested a highly significant transient benefit of adding bevacizumab during the first year of followup, coinciding with the duration of bevacizumab treatment. It was suggested, therefore, that the primary endpoint of a 25% increase in DFS at three years might have been reached if bevacizumab had been continued longer, even indefinitely. Although the hypothesis-generating concept of an “Avastin for Life” clinical trial might be considered in light of this data, the absolute benefit of additional long-term treatment with bevacizumab in the context of unknown safety must be kept in perspective. As pointed out by the discussant, Dr. Lee Ellis, such a trial is unlikely because of cost implications and the small absolute number of patients who stand to benefit from long-term bevacizumab, even with the most optimistic estimates.

In the end, although bevacizumab remains an effective agent in the treatment of metastatic colorectal cancer, it does not appear to add benefit in the adjuvant setting. Given the recent experience with failure of another effective agent in treatment of metastatic colorectal cancer, irinotecan, in the adjuvant studies PETACC-31 and CALGB 89803,² we are reminded that agents showing benefit in metastatic treatment are not necessarily effective in the adjuvant setting. Data collection for the second study to explore the efficacy of bevacizumab in the adjuvant setting, the Roche-sponsored AVANT study (NCT00112918), has been com-

pleted, and primary efficacy analysis is eagerly expected in early 2010. AVANT randomized over 3000 patients to one of three options: FOLFOX alone, FOLFOX + bevacizumab, or capecitabine + oxaliplatin (XELOX) + bevacizumab. Similar to the NSABP C-08 study, bevacizumab was given in the experimental arms during chemotherapy and in an additional six-month "maintenance" phase. Multiple centres across Canada enrolled patients into this study, which closed to accrual in 2007. It will be interesting to compare and contrast the results of this study with NSABP C-08, particularly with regards to whether improvement in DFS is restricted to the first year of followup.

In brief

Already known

- The antiangiogenic agent bevacizumab has been shown to improve survival in patients with metastatic colorectal cancer.

What this study showed

- In Stage II or III (non-metastatic) colon cancer, the addition of bevacizumab given for one year to standard chemotherapy (mFOLFOX6) improved disease-free survival at one year's followup, but the effect did not last at three years' followup.

Next steps

- Further research is needed to identify if a subgroup of colon cancer patients will benefit from bevacizumab and/or other antiangiogenic agents added to standard adjuvant chemotherapy.

Research implications

As it is unlikely that bevacizumab benefits all patients with colorectal cancer to the same degree, and as we move into an era of personalized medicine, future work with bevacizumab and other antiangiogenic agents in colorectal cancer will need to focus on identifying a subgroup that would benefit from the addition of this therapy. To date, no predictive biomarker has been established for bevacizumab comparable to the predictive power of KRAS mutational status for cetuximab and panitumumab in colorectal cancer. Hopefully, the analysis of correlative studies embedded into trials such as NSABP C-08, AVANT and studies of bevacizumab in the metastatic setting will shed light on this, enabling us to select subgroups of patients with colorectal cancer who stand to gain the most from antiangiogenic therapy.

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Trastuzumab in advanced gastric cancer

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Van Cutsem E, Y. Kang Y, H. Chung H et al. **Efficacy results from the ToGA trial: A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC).** ASCO 2009, LBA4509.

TRIAL SUMMARY: The ToGA trial randomized 594 patients with HER2-positive gastroesophageal and gastric adenocarcinoma (locally advanced, recurrent or metastatic disease) to receive trastuzumab (given until disease progression) + standard chemotherapy (either fluorouracil or capecitabine + cisplatin, every three weeks for six cycles) or chemotherapy alone. Data was released after the planned interim analysis when 75% of enrolled patients had died, because of positive findings that exceeded prespecified end-

points (median followup 17.1 months). Patients receiving trastuzumab had significantly improved overall survival (OS, the primary endpoint) of 13.5 months, compared to 11.1 months in those not receiving trastuzumab ($p = 0.0048$; HR 0.74; 95% CI 0.60 to 0.91). The overall response rate (ORR) was 47.3% with trastuzumab vs 34.5% without ($p = 0.0017$). Safety events, including symptomatic congestive heart failure, were similar in both arms and consistent with expectations; however, asymptomatic decreases in

left ventricular ejection fraction were reported in 4.6% of the trastuzumab group vs 1.1% in the no-trastuzumab group. Central testing in tumours of 3807 patients showed

that 22.1% were HER2-positive. The authors concluded that trastuzumab is effective and well tolerated for treating gastric cancer.

COMMENTARY: With 930,000 cases diagnosed in 2002, stomach cancer is the fourth most common cancer worldwide.¹ It is a disease with a high death rate — about 800,000 per year — making it the second most common cause of cancer death worldwide after lung cancer.² It is more common in men and in developing countries.^{1,3} In Canada, approximately 2900 new diagnoses will be made and 1850 individuals will die of the disease in 2009.⁴ Results for chemotherapy trials of advanced gastric cancer (AGC) treatment have historically been modest. In the 1980s, combinations of fluoropyrimidines, anthracyclines and mitomycin C were explored, showing significant toxicities with marginal benefits. In the late 1990s, treatment of AGC with docetaxel + cisplatin + fluorouracil provided median OS of 10.2 months but again, with significant toxicities.⁵

While there is no worldwide standard of care in the treatment of AGC, combinations of a platinum agent with fluorouracil, with or without an anthracycline, have always been the favoured regimens. Before now, the only trial that significantly impacted worldwide management of this horrible disease was the REAL-2 trial comparing modulation of fluorouracil (infusional vs oral capecitabine) vs two platinum agents (cisplatin or oxaliplatin), all in combination with the anthracycline epirubicin. In that trial 1002 patients were randomized in a 2 x 2 fashion to one of four arms. The results were similar to those seen in the control arm of the ToGA trial described above (OS for epirubicin + oxaliplatin + capecitabine [EOX] 11.2 months; ORR 47.9%).⁶ It was widely accepted that epirubicin + cisplatin + capecitabine (ECX) or epirubicin + cisplatin + fluorouracil (ECF) would take the pivotal role as the standard of care because their toxicity profiles were better and survival rates were clinically comparable to previous regimens. Then, in a series of 223 patients, Lee et al showed an ORR of 45.5% in the intention-to-treat population (95% CI 32.9% to 50.2%) using capecitabine + cisplatin. There were no differences in ORR among the groups of resected metastatic, recurrent and initially metastatic patients (66.7% vs 36.5% vs 50.8%, respectively; $p = 0.35$). After median followup of 11.9 months (range 2.1 to 51.9 months), the median time to progression (TTP) was 6.3 months (95% CI 5.2 to 7.4 months) and the median OS was 11.1 months (95% CI 9.4 to 12.9 months).⁷ These results mimic the control arm of the ToGA trial.

First successful biologic in AGC

It has been reported that the overexpression of HER2 in AGC ranges from 10% to 18%, with rates in gastroesophageal junction malignancies being higher, at 24% to 32%.⁸⁻¹⁰ This has opened a new avenue: to try biologics directed at the HER2 receptor as a potential way to control cell growth and proliferation. In the ToGA study, which includ-

ed both AGC and gastroesophageal junction primary tumours, the rate of HER2 overexpression was 22.1%. As described above, the therapeutic intervention of adding trastuzumab did not seem to increase toxicity, unlike earlier attempts to add more cytotoxic chemotherapeutic agents. As well, ToGA is the first trial to break the 11-month survival hurdle set by the EOX regimen in REAL-2, with a median OS rate of 13.8 months in the chemotherapy + trastuzumab arm. HER2 positivity with either immunohistochemistry (IHC) 3+ or fluorescence in situ hybridization (FISH) was an inclusion criterion, but patients were not stratified based on their level of IHC positivity. The breakdown of survival in an exploratory fact-finding analysis suggested that the stronger the HER2 overexpression, the better the survival (up to 16 months in IHC3+ patients). In breast cancer, however, IHC tests are known to give a false-positive HER2 reading in approximately 20% of cases.¹¹ The final publication of ToGA will clarify the definitions of HER2 positivity and the mechanism of testing, which will be a significant factor in determining the utility of trastuzumab to treat advanced, recurrent or metastatic AGC.

Given the significant positivity of these results, it will be difficult to run a confirmatory trial. Studies with other agents directed against the HER2 receptor, including lapatinib, are currently ongoing. The Lapatinib Optimization Study in ErbB2 (HER2) Positive Gastric Cancer (LOGiC, NCT00680901) looking at capecitabine + oxaliplatin with or without lapatinib is currently ongoing, with Canadian trial sites in Alberta and Ontario. The primary endpoint is progression-free survival (PFS), with median OS a secondary endpoint. This trial may offer more confirmatory information as to the benefits associated with manipulation of the receptor and overall survival rates. While the data from the large ToGA trial are impressive, whether the use of HER2-receptor antibodies will become the newest standard of care for the therapy of HER2-positive gastric cancers may be influenced by the results of the LOGiC trial — positive results will likely sway funding bodies toward approval of anti-HER2 agents in this setting. The institution of routine HER2 testing for unresectable and/or metastatic gastric cancer will initially present a logistic and financial barrier to widespread use of trastuzumab at some institutions.

Complete information from the ToGA and LOGiC trials will determine whether these agents should be examined in the adjuvant setting. However, the question of what the standard therapeutic intervention for the comparative arm remains, hopefully to be answered by forthcoming results of CALGB-80101, in which patients received radiotherapy + fluorouracil in the midst of several courses of either leucovorin + fluorouracil or ECF.

The treatment of metastatic gastrointestinal malignancies is changing at an exciting rate. In the last five years we have

In brief

Already known

- Various combinations of cytotoxic chemotherapies to treat patients with advanced gastric cancer have yielded poor outcomes with high levels of toxicity, and attempts to add further agents have increased toxicity.
- About 10% to 18% of gastric tumours and 24% to 32% of gastroesophageal junction tumours overexpress HER2.

What this study showed

- In 594 patients with HER2-positive gastroesophageal and gastric adenocarcinomas, those randomized to receive trastuzumab in addition to standard chemotherapy (fluorouracil or capecitabine + cisplatin) had longer overall survival and overall response rates, with no additional symptomatic toxicity.

Next steps

- While a confirmatory trial is unlikely given the positive results, future research will explore outcomes with other agents directed against the HER2 receptor.
- Meanwhile, adding trastuzumab to standard non-anthracycline based cytotoxic chemotherapy could be considered the new standard of care for advanced HER2-positive gastric and gastroesophageal adenocarcinomas.

had significant advances in the management of metastatic colorectal cancer, hepatocellular carcinomas and cholangio-carcinomas, and now, advances in the management of gastroesophageal malignancies. It's an exciting time to be a gastrointestinal oncologist as we see better management options, longer survivals, better quality of life and improvement in the overall treatments we can offer to patients.

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Treatment of triple-negative/BRCA1-associated breast cancer

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O'Shaughnessy J, Osborne C, Pippen J et al. **Efficacy of BSI-201, a poly (ADP-ribose) polymerase-1 (PARP1) inhibitor, in combination with gemcitabine/carboplatin (G/C) in patients with metastatic triple-negative breast cancer (TNBC): results of a randomized phase II trial.** ASCO 2009, Abstract 3.

TRIAL SUMMARY: This multicentre, randomized, open-label Phase II study evaluated the efficacy and tolerability of BSI-201, a small-molecule poly (ADP-ribose) polymerase-1 (PARP-1) inhibitor, given in combination with gemcitabine and carboplatin chemotherapy to 123 women with metastatic triple-negative breast cancer. Enrolled patients could have received up to two prior chemotherapy regimens for metastatic disease. They were randomized to 21-day cycles

of either gemcitabine (1000 mg/m²) plus carboplatin (AUC = 2), given intravenously on Days 1 and 8, plus BSI-201 (5.6 mg/kg intravenously) on Days 1, 4, 8, and 11, or the same doses of gemcitabine and carboplatin alone. Primary endpoints were clinical benefit rate (CBR, defined as complete response + partial response + stable disease for at least six months) and safety. Secondary endpoints were overall tumour response rate (ORR), progression-free sur-

vival (PFS) and overall survival (OS). Restaging investigations were performed after every two cycles of therapy and upon disease progression; patients in the gemcitabine + carboplatin-only arm were offered BSI-201 in addition to continued chemotherapy. Approximately 60% of patients received study therapy as first-line treatment for metastatic disease. Outcome results for the first 86 patients showed improved CBR, ORR, PFS and OS in the group receiving BSI-201 (Table 1). No additional toxicity was seen with BSI-201, Grade 3 adverse events were uncommon and there were no Grade 4 toxicities. At the time of this report, 40% of patients randomized to chemotherapy alone had crossed over to receive BSI-201 at disease progression.

TABLE 1. Efficacy results for BSI-201 added to gemcitabine + carboplatin chemotherapy in 86 women with triple-negative metastatic breast cancer

	BSI-201 + gemcitabine + carboplatin (n = 42)	gemcitabine + carboplatin (n = 44)	p-value	hazard ratio (95% confidence interval)
clinical benefit rate (%)	26 (62%)	9 (21%)	p = 0.0002	
overall response rate (%)	20 (48%)	7 (16%)	p = 0.002	
median progression-free survival	6.9 months	3.3 months	p < 0.0001	0.34 (0.20–0.58)
median overall survival	9.2 months	5.7 months	p = 0.0005	0.35 (0.19–0.65)

Gronwald J, Byrski T, Huzarski T et al. **Neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients.** ASCO 2009, Abstract 502.

TRIAL SUMMARY: This study aimed to determine complete pathologic tumour response rate (pCR) after neoadjuvant cisplatin chemotherapy in women with a BRCA1 mutation and Stage I, II or III breast cancer. The 25 enrolled women received cisplatin 75 mg/m² intravenously every three weeks for four cycles, followed by definitive surgery. Eighty percent of these women (n = 20) had triple-negative

cancers, 52% (n = 13) had tumours measuring > 2 cm and 28% (n = 7) had positive lymph nodes.

After neoadjuvant therapy and surgery, 18 patients (72%) achieved a pCR, defined as no residual invasive disease in the breast and axilla. The authors concluded that platinum-based chemotherapy is effective in this population.

COMMENTARY: The triple-negative breast cancer (TNBC) phenotype is a tumour that does not express estrogen (ER) or progesterone (PR) receptors and also lacks overexpression of the HER2 receptor. This subtype comprises 15% of all breast cancers and has aggressive clinical features, with 30% of patients developing metastases after adjuvant therapies. Metastatic TNBC is associated with median OS of one year.¹ The majority of TNBC tumours demonstrate a “basal-like” molecular profile on gene expression arrays, with ER, PR and HER2 negativity and HER1 (EGFR) positivity. They also express basal-like cytokeratins (CK), namely CK5, CK6 and/or CK14.² These tumours share clinical and pathologic features of hereditary BRCA1-related breast cancers, which are often triple-negative and express basal-like cytokeratins.³ In addition, TNBCs have impaired BRCA1 gene function, while hereditary BRCA1 cancers have mutational inactivation of BRCA1. Since this gene plays an essential role in the repair of double-stranded DNA breaks by the process of homologous recombination, targeting this pathway in triple-negative and BRCA1-associated breast cancers is an attractive strategy.⁴

At this year’s ASCO, two interesting studies targeting TNBC/BRCA-1 associated breast cancer were presented, one with a PARP-1 inhibitor added to gemcitabine/carboplatin chemotherapy in the metastatic treatment setting, and the other with cisplatin as neoadjuvant treatment for earlier-stage breast cancer.

PARP inhibition in metastatic breast cancer

The poly (ADP-ribose) polymerase enzyme (PARP) plays a key role in DNA repair by detecting and initiating baseline excision repair after DNA strand breaks.⁴ When PARP is inhibited, double-strand DNA breaks accumulate that would normally be repaired via the process of homologous recombination.¹ As BRCA1 is required for this pathway, cells deficient in BRCA1 are sensitive to PARP inhibition, leading to persistent DNA damage and eventual cell death.⁴ Several PARP inhibitors are currently in clinical development including BSI-201 and olaparib (AZD 2281).

As described in the first trial summary, above, O’Shaughnessy and colleagues presented results at the ASCO 2009 Annual Meeting of their open-label, random-

ized Phase II study evaluating the intravenous, small-molecule PARP-1 inhibitor BSI-201 in combination with platinum-based chemotherapy in 116 women with metastatic TNBC. PARP inhibitors augment the cytotoxicity of platinum chemotherapy by inhibiting the base excision repair that normally removes platinum DNA adducts.⁵ Adding the PARP-1 inhibitor to chemotherapy significantly improved CBR, ORR, median PFS and median OS, with no differences in safety between the two randomized groups. PARP expression level was available for 50 patients, and was upregulated in the majority of these. The authors concluded that PARP-1 inhibition in combination with chemotherapy showed significant activity in patients with triple-negative metastatic breast cancer.

These findings were supported by Tutt and investigators who reported results at ASCO 2009 of a Phase II trial of the oral PARP-1 inhibitor olaparib, given as a single agent in patients with BRCA1- or BRCA2-associated metastatic breast cancer.⁶ In a heavily pretreated population of 54 patients who had received a median of three prior lines of chemotherapy for metastases, overall tumour response rate in women receiving olaparib 400 mg twice a day was 41%, with a

median PFS of 5.7 months. The drug was well tolerated and there were no discontinuations due to adverse events.

So, what can we conclude about the use of PARP-1 inhibitors in triple-negative, BRCA-deficient breast cancers? These agents show promise, with significant tumour activity demonstrated in initial clinical trials, and they appear to be well tolerated with minimal side effects. However, these observations are based on limited data from a few Phase II clinical trials with short median followup and small numbers of patients. As well, the open-label design of the trials may have introduced bias in interpretation of outcomes. Phase III randomized clinical trials are therefore warranted. Indeed, based on the promising efficacy and safety results from the Phase II randomized study reported by O'Shaughnessy, one such trial is set to open in the summer of 2009. This Phase III study (information at www.bipar-sciences.com) will randomize patients with metastatic TNBC to receive gemcitabine + carboplatin with or without BSI-201, with OS and PFS as primary endpoints.

Several questions remain unanswered, such as the optimal agent to combine with PARP-1 inhibitors, whether these drugs have activity in other breast cancer subtypes and other tumours, and their long-term safety. Of the current PARP-1 inhibitors, BSI-201 is the furthest along in clinical development.

In brief

Already known

- Sporadic triple-negative breast cancers (TNBCs) share many molecular features with hereditary BRCA1-associated breast cancers.
- These tumours are particularly sensitive to agents that impair DNA repair mechanisms, such as PARP-1 inhibitors, or to agents that induce DNA damage, such as platinum cytotoxics.
- PARP-1 inhibitors are a new class of agents currently in clinical development

What these studies showed

- Two PARP-1 inhibitors administered to women with metastatic breast cancer (one added intravenously to chemotherapy in TNBC, and the other as a single oral agent in women with BRCA mutations) conferred significantly improved outcomes with no serious toxicities in Phase II studies reported at ASCO 2009.
- A Phase II study of neoadjuvant cisplatin chemotherapy in women with BRCA1-associated Stages I, II and III breast cancers, 80% of whom had triple-negative disease, showed a high rate of pathologic complete tumour response.

Next steps

- Phase III randomized clinical trials are needed to confirm the results for PARP-1 inhibitors in triple-negative and BRCA-associated breast cancers and to determine optimal treatment combinations and long-term safety.
- Confirmatory trials of platinum-based therapies are also needed for this breast cancer population.

Cisplatin in early breast cancer

TNBCs are responsive to traditional chemotherapeutic agents such as anthracyclines and taxanes,¹ but might other cytotoxics be more active in this breast cancer subtype? Given that the majority of BRCA1-associated breast cancers are triple-negative and unable to repair DNA strand breaks, these tumours may be particularly sensitive to agents such as cisplatin and carboplatin that induce DNA damage.⁷

As described in the Trial Summary, Gronwald and colleagues presented results at ASCO 2009 of a Phase II study of neoadjuvant cisplatin chemotherapy in women with Stages I, II and III breast cancers who carried the BRCA1 mutation. Of the 25 women enrolled, 80% had triple-negative breast cancers. With a 72% pathologic complete tumour response (pCR) in the breast and axilla, the investigators concluded that platinum-based chemotherapy is effective in patients with BRCA1-associated breast cancers and warrants further investigation.

Although the high pCR rate observed with neoadjuvant cisplatin in this trial is promising, other studies with platinum agents have not shown similar results. For example, Garber studied 28 women with triple-negative early breast cancers treated with neoadjuvant single-agent cisplatin at a dose of 75 mg/m²

every three weeks for four cycles, prior to definitive surgery,⁸ and reported only a 23% pCR. Ryan and colleagues also explored cisplatin neoadjuvant chemotherapy in triple-negative breast cancer, but in combination with the vascular endothelial growth factor antibody bevacizumab,⁹ and only 15% of patients in this trial achieved tumour pCR.

Comparing results from the various trials is problematic due to differing eligibility criteria, addition of other agents to platinum chemotherapy and differing definitions of a pathologic complete tumour response. Therefore, the role of platinum-based therapy in triple-negative and hereditary BRCA1-associated breast cancers is still emerging.

We await more research

In summary, sporadic triple-negative breast cancers share many molecular features with BRCA1-associated breast cancers. They may be particularly sensitive to agents that impair DNA repair mechanisms, such as PARP inhibitors, and to agents that induce DNA damage, like platinum cytotoxics. Preliminary data from several Phase II trials using these agents, particularly PARP-I inhibitors given in combination with chemotherapy, show promising activity in these breast cancer subtypes, and numerous Phase II and III clinical trials are underway or starting. However, out-

side of a trial setting, these therapies are not currently standard for this breast cancer population and results of confirmatory studies are eagerly awaited.

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Receptor crosstalk in metastatic breast cancer

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Carlson RW, O'Neill A, Vidaurre T et al. **Randomized phase II trial of gefitinib plus anastrozole or fulvestrant in postmenopausal, metastatic breast cancer.** ASCO 2009, Abstract 1013.

TRIAL SUMMARY This non-comparative, randomized Phase II study enrolled postmenopausal women who had estrogen receptor- and/or progesterone receptor-positive metastatic breast cancer, and who had not had prior endocrine therapy for metastatic disease, prior adjuvant aromatase inhibitor or fulvestrant, or more than two chemotherapy regimens for metastatic disease. The 142 patients were randomized to receive either anastrozole 1 mg daily plus the oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib 250 mg daily (n = 73), or fulvestrant 250 mg every four weeks by intramuscular injection plus gefitinib (n = 69).

At median followup of 35 months, with a median of six 4-week cycles (range 1–42 cycles) in both groups, the primary endpoint of clinical benefit rate (complete response + partial response + stable disease) was 42% (95% CI 30% to 53%) for patients receiving anastrozole + gefitinib vs 38% (95% CI 28% to 52%) for those receiving fulvestrant + gefitinib. In the anastrozole vs fulvestrant groups, respectively, reasons for discontinuing treatment were 74% vs 75% for disease progression, 7% vs 10% for toxicity, 1% vs 3% for death, 8% vs 1% for withdrawal and 3% vs 7% for other reasons. Median progression-free survival (PFS) was 5.7 vs 5.2

months and median overall survival (OS) was 30.2 vs 23.8 months, respectively.

Toxicities were similar and manageable in both groups, with Grade ≥ 3 adverse events occurring in 35% of the anastrozole group and 39% of the fulvestrant group. Diarrhea occurred in 5% vs 13%, SGOT elevation in 7% vs 8% and infection without neutropenia in 1% vs 6%, respectively. The authors concluded that adding gefitinib to established hormonal therapy provided superior outcomes, with similar activity and tolerability for both anastrozole and fulvestrant. They proposed further exploration of anastrozole + gefitinib in Phase III comparisons.

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Cristofanilli M, Schiff R, Valero V et al. **Exploratory subset analysis according to prior endocrine treatment of two randomized phase II trials comparing gefitinib (G) with placebo (P) in combination with tamoxifen (T) or anastrozole (A) in hormone receptor-positive (HR+) metastatic breast cancer (MBC).** ASCO 2009, Abstract 1014.

STUDY SUMMARY: This post-hoc subgroup analysis of two past trials^{1,2} was conducted in women with endocrine-responsive metastatic breast cancer. It explored whether starting gefitinib at the same time as endocrine therapy to minimize acquired resistance to endocrine therapy, due to “crosstalk” between estrogen receptor and EGFR/HER2 pathways, may be more effective than starting an EGFR inhibitor only at disease recurrence, after exposure to endocrine therapy.

Patients in Trial 1, Valero et al,¹ received gefitinib 250 mg/day orally + anastrozole 1 mg/day orally vs placebo + anastrozole; those in Trial 2, Osborne et al,² received gefi-

COMMENTARY: Further clinical information about the potential interaction between estrogen receptor (ER)- and EGFR-targeted therapy was provided by two studies presented at the metastatic breast cancer poster discussion session of the 2009 ASCO meeting.

In Abstract 1013, Carlson et al reported activity and safety of gefitinib with either anastrozole or fulvestrant as first-line endocrine therapy for metastatic breast cancer. The addition of gefitinib provided superior outcomes to either anastrozole or fulvestrant alone, with no significant differences between anastrozole or fulvestrant partnered with gefitinib. The primary endpoint was clinical benefit rate, with no planned statistical comparison between the two groups. Among 142 randomized and eligible subjects,

tinib 250 mg/day orally + tamoxifen 20 mg/day vs placebo + tamoxifen. Cox proportional hazards modeling with an interaction test for treatment by subset of 299 patients (91 from Trial 1 and 206 from Trial 2) showed longer PFS due to gefitinib in the endocrine-naïve patients, as shown in Table 2. The interaction test p-values were 0.28 in Trial 1 and 0.13 in Trial 2. The authors concluded that the endocrine-naïve patients of both trials had prolonged PFS when treated with gefitinib + endocrine therapy, and that a prospective trial evaluating EGFR suppression with gefitinib + endocrine therapy in women with hormone receptor-positive metastatic breast cancer would be worthwhile.

the clinical benefit rates were 42% for anastrozole + gefitinib (AG) and 38% for fulvestrant + gefitinib (FG), both groups having primary progression rates of 42%. Median PFS (5.7 months for AG and 5.2 months for FG) and median OS (30.2 months for AG and 23.8 months for FG) were similar in patients receiving both endocrine therapies. Slightly more patients withdrew from the fulvestrant (14.5%) than from the anastrozole (9.6%) arm due to toxicity, however the rates of Grade 3, 4 and 5 toxicities were similar (28%, 4%, and 3% respectively for AG; 27%, 7% and 4% for FG). Highlighted toxicities were the incidence of diarrhea (5% for AG and 13% for FG) and infection without neutropenia (1% for AG, 6% for FG), presumably Grade 3 or higher. The presentation concluded that these results

indicate activity and relative safety of both combinations, warranting further evaluation in a formal Phase III trial of anastrozole + gefitinib against anastrozole + placebo.

Unraveling receptor pathway interactions

Recent preclinical and clinical work suggests crosstalk between the EGFR- and ER-receptor pathways in breast and lung cancer. Gefitinib, an oral inhibitor of EGFR-tyrosine kinase, has activity in non-small cell lung cancer. Two previously reported randomized Phase II placebo-controlled studies have suggested enhanced activity of combining first-line hormone therapy with gefitinib in ER-positive breast cancer.^{1,2} While both showed numerical improvement for gefitinib over placebo, the results of these two trials were strikingly different. In overall results for all patients, the median PFS

TABLE 2. Median progression-free survival in patient subgroups according to prior endocrine therapy, in two trials of hormonal therapy given with or without gefitinib.

	median PFS		hazard ratio (95% CI)
	gefitinib + anastrozole	placebo + anastrozole	
Trial 1, Valero et al¹ (n = 91)			
patients with prior endocrine-therapy	11.2 months	7.1 months	0.65 (0.32–1.33)
endocrine-naïve patients	20.2 months	8.4 months	0.39 (0.16–0.97)
Trial 2, Osborne et al² (n = 206)			
patients with prior endocrine-therapy	9.4 months	10.9 months	1.22 (0.81–1.86)
endocrine-naïve patients	12.1 months	8.9 months	0.78 (0.52–1.15)

for anastrozole + gefitinib was 14.5 months in the Valero study and only 6.7 months for tamoxifen + gefitinib in the Osborne study. In the endocrine-naive subgroup 1 of the Osborne study, which included women without prior hormone therapy or who were > 1 year post adjuvant tamoxifen, the PFS for tamoxifen + gefitinib was 10.9 months. While these were Phase II studies, and therefore not powered for statistical comparison, the difference between the placebo and gefitinib arms in the Valero study was 6.3 months, while in the Osborne study it was only 1.1 months overall, and 2.1 months in the endocrine-naive cohort. The PFS of 5.7 months for anastrozole + gefitinib observed in the Carlson study presented at ASCO 2009 is similar to that reported in the Osborne study, and congruent with the time to progression seen in early randomized trials of single-agent anastrozole (vs megestrol acetate) after either adjuvant or first-line tamoxifen (median time to progression 4.8 months).³

Several possibilities could explain the discrepancy between the Valero results, suggesting a large additional benefit from adding gefitinib, and the Osborne and Carlson studies, suggesting a modest impact of this agent. One is that the Valero study may be the statistical outlier, the one out of 20 trials that erroneously shows a benefit where none exists. Another is that the Valero study enrolled subjects with particularly sensitive cancers while the Osborne and Carlson studies selected patients less precisely. However, Valero was not able to identify any particular biochemical determinants of sensitivity to gefitinib among a variety of examined pathway markers including ApKT, pERK, HER2 or EGFR expression, and the eligibility criteria for the Valero study and assignment to the endocrine-naive subgroup of the Osborne study were similar (prior adjuvant tamoxifen or not, and no prior hormone therapy for metastatic disease). The other Osborne study subgroup had prior aromatase inhibitor either in the adjuvant or first line metastatic setting.

In Abstract 1014, Cristofanilli et al explored absence of prior hormone therapy exposure as a possible predictor of enhanced response to combination ER- and EGFR-targeted therapy. This subset analysis of the Valero and Osborne studies tested the hypothesis that cancers without any prior (adjuvant) hormone therapy exposure will respond better to the addition of gefitinib than will cancers with prior hormone therapy exposure. The biologic rationale is that cancer cells with prior exposure may upregulate the EGFR pathway, leading

to relative insensitivity to attempted suppression of cell signaling via this pathway and via ER-EGFR pathway crosstalk.

The hypothesis was tested separately in the two trials. In the Valero trial (Trial 1), among the 93 eligible subjects randomized to anastrozole and gefitinib, 42 had no prior hormone therapy and 51 had received adjuvant hormones. In the Osborne study, 206 received tamoxifen with either placebo or gefitinib; 158 were hormone therapy-naive and 48 had had prior adjuvant tamoxifen.

In the Valero trial, the PFS difference was 4.1 months in those with prior hormone therapy, and 11.8 months in hormone therapy-naive subjects. Similarly, in the Osborne trial, the difference favouring gefitinib was greater for the group with no prior endocrine exposure (3.2 months vs 1.5 months difference). The discrepancy between the hormone therapy-naive vs exposed populations reminds us that ER-positive breast cancer is a heterogeneous disease.

While there is a plausible biologic hypothesis for why populations behave differently with the addition of an

In brief

Already known

- Recent preclinical and clinical work suggests crosstalk between the EGFR- and ER-receptor pathways in breast cancer.
- Two previously reported Phase II randomized, placebo-controlled studies suggested enhanced activity of combining anastrozole or tamoxifen with the oral EGFR inhibitor gefitinib in first-line treatment of ER-positive postmenopausal breast cancer, but with very different rates of progression-free survival.

What these studies showed

- Carlson et al reported activity and safety of gefitinib with both anastrozole and fulvestrant as first-line endocrine therapy for ER-positive metastatic disease.
- Cristofanilli et al's subset analysis of the two Phase II trials showed better response to dual ER- and EGFR-targeted treatment (with hormone therapy plus gefitinib) in cancers without prior hormone therapy exposure compared to those with cancers with prior hormone therapy exposure.

Next steps

- Further evaluation in a Phase III trial of anastrozole + gefitinib against anastrozole + placebo is warranted.
- It might be worthwhile to re-examine the Tandem trial (in postmenopausal women with metastatic ER- and HER2-positive breast cancer randomized to anastrozole alone vs with trastuzumab) for outcome by prior hormone exposure.
- Further selection refinement by a combination of prognostic and predictive markers may result in more benefit for selected patients whose tumours are susceptible to the combined approach of gefitinib plus hormone therapy. This will be of particular importance in the adjuvant setting where there is a need to balance cure rates for the breast cancer population against individual benefit from each added therapy.

EGFR pathway inhibitor, these observations can only be regarded as hypothesis-generating, as the authors point out. Perhaps the Tandem trial,⁴ in which women with metastatic breast cancer that was both ER- and HER2-positive were randomized to anastrozole alone or with trastuzumab, would be worth re-examining for a similar effect by prior hormone exposure. More comprehensive inhibitors of the HER family might result in greater improvement in time to progression than seen with gefitinib.

Toward better patient selection

While not practice-changing, the data do not exclude the possibility that with further selection refinement, tumours susceptible to the combined approach may be identified, leading to benefit for selected patients. If the hypothesis of concurrent dual pathway targeting is confirmed in additional prospective studies, the natural place for this combined therapy is the adjuvant setting, which is where most ER-positive breast cancers are first exposed to endocrine therapy. Because our adjuvant paradigm currently involves treating a great number of women with adjuvant therapies that benefit only a few, it is critical to carefully select patients whose risk of recurrence following current adjuvant therapy remains moderate to high (i.e. with the help of prognostic markers) and that may be particularly sensitive to a given therapeutic

strategy (i.e. with the help of predictive markers).

Adding yet another drug such as the EGFR-inhibitor gefitinib to the adjuvant treatment program entails additional financial costs, side effects and quality of life alteration for patients — burdens that can only be justified by careful patient selection. Therefore we need to accelerate the current trend of scrutinizing potential new therapies for predictors of response, rather than the “trial and error” approach to testing sequential therapies in the metastatic treatment setting. Knowledge of predictors will ultimately advance our chance of cure in the adjuvant treatment setting.

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Bevacizumab in metastatic breast cancer

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Robert NJ, Dieras V, J. Glaspy J et al. **RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC).** ASCO 2009, Abstract 1005.

TRIAL SUMMARY: The RIBBON-1 study randomized 1237 women receiving first-line treatment for metastatic breast cancer in a 2:1 fashion to receive either bevacizumab (15 mg/kg every three weeks) or placebo, concurrently with chemotherapy. Chemotherapy options, chosen before randomization, were capecitabine 1000 mg/m² twice per day for 14 days (n = 615), nab-paclitaxel 260 mg/m² every three weeks, docetaxel 75 or 100 mg/m² every three weeks (taxane results were pooled, n = 307) or anthracycline-based chemotherapy every three weeks (n = 315). Upon disease progression, all patients were offered bevacizumab in addition to standard second-line chemotherapy. Median followup was 15.6 months

in the capecitabine group and 19.2 months in the taxane and anthracycline groups (data were combined for these two options). Independent review committee assessment of hazard ratios (HRs) for PFS (the primary endpoint) when bevacizumab was added were 0.68 (95% CI 0.54 to 0.86; p = 0.0011) in the patients receiving capecitabine and 0.77 (95% CI 0.60 to 0.99; p = 0.040) in those receiving taxane or anthracycline-based chemotherapy. With about two-thirds of patients still alive, overall survival (OS) was not statistically significantly different between the two groups. The authors concluded that adding bevacizumab to these standard first-line chemotherapy regimens improves PFS with no unexpected toxicities.

COMMENTARY: We now have evidence from three randomized Phase III clinical trials that have examined the potential benefit of adding bevacizumab to chemotherapy in women with metastatic breast cancer: E2100,¹ AVADO² and RIBBON-1. The addition of bevacizumab to taxane-based chemotherapy compared to taxane chemotherapy


alone (paclitaxel in E2100, docetaxel in AVADO) resulted in a statistically significant improved PFS: 5.8 months vs 11.3 months in E2100 (p < 0.0001), and 8.0 vs 8.7 months for 7.5 mg/kg of bevacizumab vs 8.8 for 15 mg/kg of bevacizumab in AVADO (p = 0.0318). Interestingly, while PFS was doubled with the addition of bevacizumab in the

E2100 study, the incremental improvement was much smaller in AVADO. Despite these improvements in PFS, neither study showed a significant difference in OS. Nonetheless, based on the PFS advantage of adding bevacizumab to chemotherapy in these studies, the US Food and Drug Administration (FDA) approved the use of bevacizumab in March 2008 for patients with metastatic, HER2-negative breast cancer. Health Canada approved bevacizumab for use in this population in February 2009.

Initial results of RIBBON-1 were presented at ASCO 2009. Unlike the two preceding studies, investigators had a choice of chemotherapy regimen — capecitabine, anthracyclines or taxanes — after which patients were randomized to receive bevacizumab (15 mg/kg every three weeks) or placebo. The results of this study are consistent with the previous two, demonstrating a PFS advantage with the addition of bevacizumab: 5.7 vs 8.6 months for capecitabine ($p = 0.0002$) and 8.0 vs 9.2 months for taxane- or anthracycline-based regimens ($p < 0.0001$). Toxicities demonstrated in the patients receiving bevacizumab were similar to those in other studies, including more Grade 3–4 hypertension and proteinuria. Patients treated with bevacizumab and taxane in RIBBON-1 also were noted to have more Grade 3–4 febrile neutropenia (7.9% with bevacizumab vs 2.0% without) and bleeding (5.4% vs 0%).

Clinical implications

Three studies now demonstrate a significant PFS advantage with adding bevacizumab to chemotherapy in women with metastatic breast cancer, although the absolute PFS benefits demonstrated in AVADO (HR 0.69 and 0.61) and RIBBON-1 (HR 0.69 and 0.64) were substantially less than that seen with the E2100 study (HR 0.48). No OS benefit has been shown with the addition of bevacizumab to chemotherapy. Given the number of chemotherapy options available to women once they progress, and the option of treatment with bevacizumab in RIBBON-1 at the time of progression (over 50% crossed to bevacizumab at progression), it is unlikely that a survival advantage will be demonstrated.

In this context, PFS may be a valid clinical endpoint. Bevacizumab in combination with taxane- and non-taxane-containing chemotherapy partners is a reasonable treatment option for women with HER2-negative metastatic breast cancer in the first-line setting. In Canada, however, there are considerable pharmacoeconomic issues that will need to be addressed prior to the widespread adoption of this treatment option in women with HER2-negative metastatic disease. 

Disclosure

Dr. Dent has served on advisory boards for Abraxis and Roche. Dr. Dowden reports being on advisory Boards of AstraZeneca, Bristol-Myers Squibb, Roche and sanofi-aventis. Dr. Grenier reports no potential conflicts of interest related to this article. Dr. Lohrisch reports receiving research support from AstraZeneca, being on advisory boards of AstraZeneca, Glaxo-Smith Kline, Novartis and Roche, and being on the speakers bureau of Roche and sanofi-aventis. Dr. Welch reports being on the advisory board and receiving an educational grant from Roche.

In brief

Already known

- In women with metastatic breast cancer, two prior trials (E2100 and AVADO) have shown improved progression-free survival (PFS), but not overall survival (OS), when bevacizumab is added to chemotherapy in women with HER2 metastatic breast cancer. The degree of improved PFS differed between the two studies.
- Bevacizumab has been approved by Health Canada as a treatment for HER2-negative, metastatic breast cancer.

What this study showed

- In the randomized RIBBON-1 trial, adding bevacizumab to a choice of standard chemotherapies also improved PFS but again, not OS, with toxicities similar to the earlier studies.
- Given the multiple treatment options available to patients at the time of disease progression (including bevacizumab for patients randomized to the no-bevacizumab treatment arm), a difference in OS is unlikely, perhaps making PFS a valid clinical endpoint.

Next steps

- Bevacizumab added to chemotherapy shows improved PFS but not OS, and is now considered a standard first-line treatment option for women with HER2-negative metastatic breast cancer in the US.
- However, pharmacoeconomic considerations make it unlikely that bevacizumab in combination with chemotherapy will be widely available for Canadian women with HER2-negative* metastatic breast cancer.

* Corrected September 10, 2009.

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