



EVIDENCE WATCH

A review and assessment of recent clinical trial data

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

Contributors were selected by Jean A. Maroun, MD, FRCPC, FRCP (London), Joseph Ragaz, MD, FRCPC and M. Neil Reaume, BSc, MSc, MD, FRCPC.

Head and neck cancer

Samy El-Sayed, MD, FRCPC

CETUXIMAB EXTENDS SURVIVAL OF PATIENTS WITH RECURRENT OR METASTATIC SCCHN WHEN ADDED TO FIRST LINE PLATINUM BASED THERAPY – RESULTS OF A RANDOMIZED PHASE III (EXTREME) STUDY. ASCO 2007, ABSTRACT 6091.

Investigators: J. Vermorken et al.

TRIAL SUMMARY: The EXTREME trial (Erbix in the First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer) evaluated the results of adding the epidermal growth factor receptor (EGFR)-inhibitor cetuximab to platinum-based chemotherapy in 442 patients with Stage III–IV recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). Eligible patients were not suitable for further local therapy (i.e. surgery and/or radiation) and had Karnofsky performance status of at least 70, and patients with nasopharyngeal disease were excluded. All patients were treated with 3-weekly cycles of either cisplatin (100 mg/m² on Day 1) or carboplatin (AUC 5, Day 1) + fluorouracil (1000 mg/m²/day continuous infu-

sion for the first 4 days of each cycle), for a maximum of 6 cycles. Subsequent to chemotherapy, patients were randomized to receive either cetuximab (initially 400 mg/m², then 250 mg/m² each week) until occurrence of disease progression or unacceptable toxicity (n = 222), or no cetuximab (n = 220).

The patients receiving cetuximab had improved median (overall) survival (10.1 months vs 7.4 months, HR 0.797, p = 0.0362). The authors noted that 10.1 months is the longest median survival time yet to be reported in a Phase III trial of this patient group. Analysis of secondary endpoints related to toxicity, safety and quality of life showed no significant effects related to the test drug.

COMMENTARY: Samy El-Sayed, MD, FFR(Dublin), FRCR(London), FRCPC, ABR, Associate Professor of Radiology (Radiation Oncology), University of Ottawa. Chair, Head and Neck Disease Site Group, the Ottawa Hospital Integrated Cancer Program, Ottawa, ON.

EGFR is highly expressed in head and neck cancer (HNC), and the degree of overexpression seems to have prognostic and predictive value. Since EGFR has a large extracellular ligand binding domain as well as an intracellular tyrosine kinase

domain, anti-EGFR therapy may involve both anti-ligand binding domain antibody inhibitor and tyrosine kinase-inhibitor therapies.

Phase II–III studies confirmed the efficacy of anti-EGFR antibody therapy in cases of squamous cell HNC. In com-

LANDMARKS

bination with radiation therapy, anti-EGFR antibody therapy improved survival of locally advanced HNC patients without adding significant toxicity. In cases of recurrent or metastatic HNC, anti-EGFR antibody therapy given alone or in combination with chemotherapy significantly increased remission rates without increasing toxicity.

EGFR INHIBITORS ADDED TO CHEMOTHERAPY IMPROVE SURVIVAL

The EXTREME trial presented by J. Vermorken at last June's ASCO Annual Meeting and summarized above provides further evidence of the efficacy of EGFR inhibitors in previously treated patients with advanced, recurrent or metastatic HNC. Many Phase II results presented at the same meeting emphasized the role of EGFR inhibitors in the management of recurrent and metastatic head and neck cancer.¹⁻⁴ Vermorken et al's trial furnishes the most convincing data to date on the efficacy and safety of adding EGFR inhibitors to conventional chemotherapy in first-line palliative management of HNC. The sample size was large enough to illustrate a small but worthwhile difference in survival. However, this study also reinforces the notion that in palliative treatment of patients with HNC, the benefit from targeted therapy is rather modest.

This is the second randomized Phase III trial addressing the same scientific question. An earlier study presented at ASCO 2002 by Barbara Burtness compared cisplatin + placebo to cisplatin + cetuximab (then called C225).⁵ Unfortunately this study was insufficiently powered to detect a statistically significant difference in survival, so did not confirm a survival benefit.

OUTSTANDING QUESTIONS

The EXTREME study, however, leaves many questions unanswered. First, it remains unclear whether fluorouracil adds any benefit to the combination. Second, the optimal

sequence and duration of EGFR inhibitor therapy is unknown. Third, the benefit of EGFR inhibitor treatment might be obtained by simply administering it at the time of progression, rather than immediately following chemotherapy. Another study by Vermorken and colleagues, in heavily pretreated patients who received cetuximab as monotherapy when they relapsed, showed a further delay of disease progression with a median time to progression of 70 days.⁶

IMPACT ON CLINICAL PRACTICE

This study confirms the value of EGFR inhibitors, specifically cetuximab, in the palliative management of patients with unsalvageable recurrent or metastatic head and neck cancer. It provides a useful, although expensive, additional therapy for this desperate group of patients. Importantly, it is associated with low additional toxicity. This treatment should be made available to appropriate patients, perhaps after assembling the evidence into guidelines for clinical practice. Some questions remain unanswered, particularly as to the sequence of treatment and the best combination.

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Renal cancer

Mary MacKenzie, MD, FRCPC

A RANDOMIZED, CONTROLLED, DOUBLE-BLIND PHASE III STUDY (AVOREN) OF BEVACIZUMAB/INTERFERON- α 2A VS PLACEBO/INTERFERON- α 2A AS FIRST-LINE THERAPY IN METASTATIC RENAL CELL CARCINOMA. ASCO 2007, ABSTRACT 3.

Investigators: B. Escudier et al.

TRIAL SUMMARY: This multinational, double-blinded study evaluated the combination of bevacizumab and interferon alpha 2a (IFN- α 2a) as first-line treatment in nephrectomized patients with metastatic renal cancer (mRCC). Enrolled patients (649 randomized, 641 treated) were randomized to receive IFN- α 2a 3 times per week at a recommended dose of 9 million international units (IU) for up to 1 year, plus either bevacizumab 10 mg/kg every 2 weeks until disease progression or placebo. At the time of analysis, 111 patients

remained on treatment, 287 had discontinued treatment due to adverse events and 251 had died. Patients in the bevacizumab + IFN- α 2a combination arm had significantly better progression-free survival (PFS) of 10.2 months compared to 5.4 months in the placebo + IFN- α 2a arm (HR 0.63, confidence interval not presented, $p < 0.0001$), as well as a higher rate of objective tumour response (30.6% vs 12.4%, $p < 0.0001$). Overall survival (OS), the primary endpoint, showed a non-significant trend favouring the bevacizumab

+ IFN- α 2a combination ($p = 0.0670$). Median duration of treatment was 10 months in the bevacizumab combination group and 5 months in the placebo combination group. Side effects were significant, with 60% of patients on the combination treatment arm experiencing Grade 3 or worse toxicity and 29% of combination patients having serious adverse events. Side effects with bevacizumab were similar to those in previous studies,

including fatigue, proteinuria, hypertension, hemorrhage, venous thromboembolism, gastrointestinal perforation and arterial ischemia. Twelve percent of patients receiving IFN- α 2a + placebo vs 28% of those on IFN- α 2a + bevacizumab discontinued treatment due to adverse events. The authors concluded that adding bevacizumab to IFN- α 2a improves PFS, with a trend to longer OS and no unexpected safety issues.

SUNITINIB VERSUS INTERFERON-ALFA (IFN-A) AS FIRST-LINE TREATMENT OF METASTATIC RENAL CELL CARCINOMA (MRCC): UPDATED RESULTS AND ANALYSIS OF PROGNOSTIC FACTORS. ASCO 2007, ABSTRACT 5024.

Investigators: R.J. Motzer et al.

TRIAL SUMMARY: This study randomized 750 patients with clear cell mRCC to treatment with either sunitinib 50 mg/day orally for the first 4 weeks out of each 6 ($n = 375$), or interferon- α (IFN- α 2a) 9 million IU subcutaneously, 3 times per week ($n = 375$). At the time of this analysis, median duration of treatment was 11 months for sunitinib and 4 months for IFN- α 2a. Overall response rate by investigator assessment was 46% (95% CI 39%–49%) for sunitinib vs 12% (95% CI 8%–5%) for IFN- α 2a ($p < 0.000001$). By independent central review, overall response rates were 39% vs 8% ($p < 0.000001$). PFS by central assessment was significantly improved in the sunitinib group compared to the IFN- α 2a group (Table 1), with a median of 11 months vs 5.1 months, respectively, and a hazard ratio (HR) for benefit of 0.538 ($p = 0.000001$). The sunitinib PFS benefit extended across all Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk factor groups (poor, intermediate and good); the most important predictive factors of longer survival were ECOG performance status score of 0 ($p = 0.006$), time from diagnosis to treatment of ≥ 1 year ($p = 0.001$) and corrected serum calcium ≤ 10 mg/dL ($p = 0.001$). OS data is not yet available. The authors concluded that sunitinib has become the reference standard for first-line

TABLE 1. Median progression-free survival by independent central assessment for mRCC patients receiving sunitinib vs IFN- α 2a as first-line treatment

	sunitinib (95% CI)	IFN- α 2a (95% CI)
progression-free survival	11 months (10.7–13.4 months)	5.1 months (3.9–5.1 months)
good risk (0 factors)	14.5 months (11.3–16.8 months)	7.9 months (7.0–10.5 months)
intermediate risk (1–2 factors)	10.6 months (8.2–10.9 months)	3.8 months (3.6–4.0 months)
poor risk (≥ 3 factors)	3.7 months (2.0–9.8 months)	1.2 months (1.0–2.4 months)

treatment of mRCC, with significant improvement in PFS and overall response rate compared to IFN- α 2a, and called for further research into factors predictive of treatment benefit.

RANDOMIZED PHASE II TRIAL OF FIRST-LINE TREATMENT WITH SORAFENIB VERSUS INTERFERON IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA: FINAL RESULTS. ASCO 2007, ABSTRACT 5025.

Investigators: C. Szczylik et al.

TRIAL SUMMARY: This open-label trial randomized 189 previously untreated patients with mRCC to receive either sorafenib 400 mg twice per day or IFN- α 2a 9 million IU 3 times per week. Upon disease progression, patients on sorafenib had the option of increasing their dose to 600 mg twice per day, and those on IFN- α 2a could cross over to sorafenib 400 mg twice per day. In the first phase of treatment, the difference in PFS was not statistically significant, with a median of 5.7 months in the sorafenib group ($n = 97$) vs 5.6 months in the IFN- α 2a group ($n = 92$) (HR 1.14, $p = 0.504$). While waterfall plots of tumour regression showed more tumour shrinkage in the sorafenib arm (68%) than the interferon

group (39%), this did not translate into a gain in PFS. Patients in the sorafenib group reported fewer symptoms related to kidney cancer than those in the IFN- α 2a group, with a difference of 5.9 points on the Functional Assessment of Cancer Therapy–Kidney Symptom Index 15-item (FKSI-15) score ($p = 0.15$) and greater satisfaction related to perception of effectiveness, treatment side effects and convenience (overall $p = 0.019$). As in prior studies, the most common treatment-related side effects occurring with sorafenib included hand-foot syndrome, diarrhea, rash, hypertension and nausea and/or vomiting. The most common treatment-related side effects with IFN- α 2a were diarrhea, fatigue nausea and/or

LANDMARKS

vomiting and abdominal pain. There was a positive correlation between decrease in soluble vascular endothelial growth factor (VEGF) receptor-2 expression (which occurred more in sorafenib-treated patients) and PFS. In the 44 patients who switched to a higher dose of sorafenib upon progression, 44.1% experienced tumour shrinkage, with median PFS of

4.1 months. In the 50 patients who switched from IFN-a2a to sorafenib, 75% experienced tumour shrinkage, with median PFS of 5.7 months. The authors concluded that sorafenib provides better tumour shrinkage and clinical benefit with comparable PFS and much better quality of life, and that dose escalation after disease progression provides further clinical benefit.

COMMENTARY: Mary MacKenzie, MD, FRCPC, Medical Oncologist, London Regional Cancer Centre; Assistant Professor, Department of Oncology, University of Western Ontario, London, ON.

Prior to the advent of angiogenesis-directed therapy, immunotherapy was the mainstay of treatment for advanced renal cell carcinoma. With the recent publication of several randomized Phase III trials of agents that target angiogenesis pathways,¹⁻³ immunotherapy is rapidly being supplanted by “targeted” therapy as the treatment of choice for mRCC.

BEVACIZUMAB

The trial presented by Escudier at the ASCO 2007 plenary session built on the results of a previously published Phase II trial evaluating bevacizumab in the treatment of mRCC.⁴ Bevacizumab is an intravenously administered antibody directed at VEGF. To be eligible for this study, patients had to be treatment naive, have biopsy-proven renal cell carcinoma with predominately (> 50%) clear cell histology, a prior nephrectomy, Karnofsky performance status of at least 70%, measurable disease according RECIST criteria⁵ and no evidence of central nervous system metastasis.

The treatment arms were well balanced for known prognostic factors, including assessment of patient prognosis by the previously validated MSKCC criteria,⁴ which include prior nephrectomy, performance status, corrected calcium, lactate dehydrogenase and hemoglobin. The majority of patients (56%) were intermediate-risk according to this prognostic system, and 8% of patients were poor-risk. As summarized above, the investigator-assessed tumour response rate was 31% vs 13%; the 13% response rate in the control arm was similar to that seen in previous interferon trials in mRCC.^{6,7} PFS (10.2 months vs 5.4 months) favoured the combination arm, and OS did not meet the prespecified target. Future assessment of survival in this trial is likely to be contaminated by subsequent treatment. In subgroup analysis, the patients in MSKCC good- and intermediate-prognosis groups both appeared to benefit from bevacizumab in terms of PFS. By comparison, the few patients who were poor-risk according to MSKCC criteria did not show prolonged PFS with bevacizumab (2.2 months for bevacizumab + interferon vs 2.1 months for placebo + interferon).

These findings are unlikely to change practice in the management of Canadian patients with mRCC. The substantial toxicity seen in the combination treatment group is of concern. This toxicity, coupled with the fact that the PFS is similar to that seen with oral sunitinib (11.0 months) in another first-line trial in mRCC,¹ makes the use of an intravenous and subcutaneous combination treatment difficult to justify. Given the choice, few medical oncologists sub-

specialized in renal cancer would presently include interferon as part of their therapeutic armamentarium. Because the high financial cost of this treatment will be an issue for healthcare bodies making policy recommendations to provincial Health Ministries, only the minority of Canadian patients with private drug insurance are likely to have access to bevacizumab. The results do, however, give additional credence to the strategy of VEGF inhibition in this disease.

SUNITINIB

Motzer updated the results published in January 2007¹ of a large randomized Phase III trial in the first-line treatment of mRCC, adding an analysis of prognostic factors in patients treated with sunitinib. Among the inclusion criteria for this trial were biopsy-proven clear cell histology, no prior systemic therapy, measurable disease by RECIST criteria, ECOG performance status 0 or 1 and adequate biochemistry.

Patients were randomized in a 1:1 fashion to either the oral tyrosine kinase inhibitor sunitinib (which inhibits both VEGF receptor and platelet-derived growth factor receptor) or interferon. The primary endpoint was PFS, and secondary endpoints included OS, response rate, patient-reported outcomes and safety. Patients were well balanced at baseline for known prognostic factors. Approximately 90% of patients in both arms had previously undergone a nephrectomy. The majority of patients in both treatment arms had more than one site of metastases.

In addition to the results summarized above showing favourable response rate and PFS benefits for sunitinib, the authors presented an analysis of patient baseline characteristics predictive of PFS benefit with sunitinib treatment. Multivariate analysis confirmed that performance status, time from diagnosis to treatment (more or less than 1 year) and corrected serum calcium were prognostic of PFS. Patients with none of these adverse risk factors had a median PFS of 14.8 months. The authors also presented a nomogram that aids in estimating the probability that a given patient will be progression-free after 12 months of treatment with sunitinib.

This presentation again confirmed a PFS benefit for treatment-naïve mRCC patients treated with sunitinib rather than the previous standard of care, interferon. Overall survival analysis — not the primary outcome of this trial — is not yet available, and is likely to be contaminated by subsequent treatment. No new data on safety and toxicity were presented. The presentation on prognostic factors essential-

ly confirms that the prognostic factors previously identified in the “immunotherapy era” (including prior nephrectomy, performance status, corrected calcium, hemoglobin and lactate dehydrogenase) are still relevant for predicting clinical outcome in the “tyrosine kinase era.”

SORAFENIB

Sorafenib is an oral tyrosine kinase inhibitor of VEGF that was previously shown in a randomized Phase II discontinuation trial to have antitumour activity in mRCC.⁸ In the trial presented at the 2007 ASCO by Szczylik, eligible patients were treatment-naïve, had biopsy-proven clear cell histology, and ECOG performance status of 0 or 1. All MSKCC risk groups were permitted. The 2 initial treatment groups were grossly balanced for known prognostic factors. Over 95% of patients in both arms had prior nephrectomies. The vast majority of patients were either good or intermediate-risk according to MSKCC criteria. Primary endpoints included PFS for Period 1 (sorafenib vs interferon randomization) and Period 2 (crossover to sorafenib or sorafenib dose escalation). Secondary outcomes included quality of life studies. Disappointingly, for the first comparison (sorafenib vs interferon), the PFS times were virtually identical between groups. Quality of life studies indicated that patients experienced lower rates of kidney cancer-related symptoms in the sorafenib group. Sorafenib-treated patients also experienced a longer time to patient-reported health-status deterioration. Predictably, higher rates of skin toxicity, diarrhea and hypertension were reported in the sorafenib group, and higher rates of Grade 3 and 4 fatigue in the interferon group.

Correlative studies included serum levels of VEGF and serum-soluble VEGF receptors. Unexpectedly, sorafenib treatment was associated with an increase in serum VEGF. Unlike most other recent clinical trials in mRCC, a laboratory-based predictive factor for PFS was identified: a large decrease in serum-soluble VEGF receptor correlated positively with PFS. Thus, while results of this small trial do not support the use of sorafenib in the first-line treatment of patients with mRCC, it does present an interesting signal that dose escalation of sorafenib may prolong disease control after standard dosing has failed. Further, it hints that a molecular predictor (decrease of serum-soluble VEGF receptors) may help target future therapy to those patients who are likely to benefit most.

FUTURE CHALLENGES IN mRCC

The management of metastatic renal cell carcinoma has changed more in recent years than the medical management of any other malignancy. As RCC does not commonly respond to cytotoxic chemotherapy, treatment options had been very limited until the arrival of targeted agents such as sunitinib, sorafenib, bevacizumab and temsirolimus — the fruit of decades of basic, translational and clinical research. With these promising therapies come difficult decisions regarding drug choice, sequencing of various treatment options and funding challenges. Given that 3 large randomized trials have now demonstrated the superiority of newer therapies

over single-agent interferon, most oncologists agree that anti-angiogenesis-based therapies should replace the previous standard treatment, interferon, in the first-line setting.

Outstanding issues to be resolved include comparing the newer agents to high-dose interleukin-2, which has been linked with long-term complete remission in a very small minority of patients in Phase II clinical trials with over 14 years of followup.^{9,10} This long-term remission is generally observed in patients with good prognostic factors and limited sites of metastatic spread. Given that none of the newer agents have yet demonstrated similar durable complete responses, the question remains whether patients who fit the eligibility criteria for previous high-dose interleukin-2 trials should still be offered this remote chance of cure. Only direct comparison of the 2 treatment strategies and long-term followup will answer this question.

The trial presented by Szczylik, along with another Phase II trial presented at ASCO,¹¹ underscores that we have yet to determine the optimal dose and schedule of the targeted agents. Pharmacodynamic and pharmacokinetic studies indicate high interpatient variability in the metabolism of these new agents.¹²

Clinicians also face the task of selecting second-line therapy for patients with mRCC. While a welcome relief from the previous problem of having essentially no effective or tolerable agents to offer, there is presently little evidence to guide this decision. Small studies presented at ASCO 2007 hint that there may be some role for second-line treatment with a different VEGF receptor inhibitor when a previous one has failed.^{13,14} Ongoing clinical trials will address the efficacy of mTOR (mammalian target of rapamycin) inhibitors such as temsirolimus and everolimus after progression on VEGF-directed therapy.

It is also difficult to know whether the previous clinical trials demonstrating a survival benefit for cytoreductive nephrectomy in addition to interferon¹⁵ can be extrapolated to the tyrosine kinase era. While nephrectomy is clearly a present standard of therapy (as evidenced by the ≥ 90% nephrectomy rates in all recent Phase III mRCC trials), it is not known if a comparable benefit for nephrectomy will be seen when newer agents are substituted for interferon. Nephrectomy is likely to remain a standard, however, given the risk of hematuria with anti-angiogenesis therapy when the tumour-bearing kidney remains in situ, and the pain and other local symptoms that may occur with local progression of disease in the kidney.

As few of the recent clinical trials (with the exception of the temsirolimus and/or interferon trial³) included patients with non-clear cell carcinoma, clinicians have very little information to guide treatment choices for their patients with the less common subtypes of renal cell carcinoma (e.g. papillary, chromophobe). Likewise, the majority of clinical trials had a small number of poor-risk patients (according to MSKCC criteria) and treatment decisions in this subgroup are therefore more difficult. Future trials in mRCC will evaluate the safety and efficacy of treatment with combinations of newer agents, and evaluate the use of the targeted agents in the adjuvant setting.

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Locally advanced prostate cancer

Lori Wood, MD, MSc, FRCPC

CONCOMITANT AND ADJUVANT ANDROGEN DEPRIVATION (ADT) WITH EXTERNAL BEAM IRRADIATION (RT) FOR LOCALLY ADVANCED PROSTATE CANCER: 6 MONTHS VERSUS 3 YEARS ADT—RESULTS OF THE RANDOMIZED EORTC PHASE III TRIAL 22961. ASCO 2007, ABSTRACT 5014.

Investigators: M. Bolla et al.

TRIAL SUMMARY: The EORTC 22961 trial randomized 970 men who had either localized prostate cancer with lymph node involvement or locally advanced disease, and who received up to 70 Gy external beam radiation therapy (EBRT) + 6 months of combined androgen deprivation therapy (ADT), to either no further ADT or 2.5 years of luteinizing hormone-releasing hormone (LHRH) agonist monotherapy. The primary objective was to demonstrate

non-inferior OS with adjuvant short-term (6 months) ADT compared to adjuvant long-term (36 months) ADT. At median followup of 5.2 years, the data monitoring committee recommended early disclosure of results because of failure to show non-inferiority with short-term ADT, as shown in **Table 2**. Quality of life, measured by the EORTC QLQ30 scale, did not differ between the two treatment arms.

TABLE 2. Efficacy results of EORTC 22961 comparing short- vs long-term androgen-deprivation therapy (ADT) in men with locally advanced prostate cancer

	short-term ADT (n = 483)	long term ADT (n = 4 87)	hazard ratio (96.4% CI)	p-value
5-year overall survival	80.6%	85.3%	1.43 (1.04–1.98)	p = 0.0191
5-year biochemical progression-free survival	58.9%	78.3%	2.29 (1.81–2.90)	p < 0.0001
5-year clinical progression-free survival	68.9%	81.8%	1.93 (1.49–2.51)	p < 0.0001

COMMENTARY: Lori Wood, MD, MSc(Epi), FRCPC, Associate Professor, Dalhousie University Department of Medicine; Medical Oncologist at the Queen Elizabeth II Health Sciences Centre, Halifax, NS.

In the EORTC 22961 study, patients with localized prostate cancer with lymph node involvement or locally advanced prostate cancer were treated with combined androgen blockade for 6 months along with EBRT and then randomized to either no

further therapy (short-term ADT) or 30 additional months of LHRH agonist monotherapy (long-term ADT). The study was designed to show non-inferiority of short-term to long-term ADT, and was stopped at an interim analysis.

Five-year biochemical PFS (i.e. lack of prostate-specific antigen [PSA] elevation) was significantly increased in the group receiving long-term ADT (78.3%) vs those receiving short-term (58.9%), as were 5-year clinical PFS (81.8% vs 68.9%) and 5-year OS (85.3% vs 80.6%). These conclusions support the previous EORTC study published by Bolla et al showing clinical disease-free and overall survival benefits from 3 years of adjuvant ADT compared to no adjuvant ADT in patients with locally advanced prostate cancer who were treated with EBRT.^{1,2}

CORROBORATES PRIOR RESULTS

The RTOG 92-02 study also looked at a similar patient population.³ In this study, 1514 patients with locally advanced prostate cancer (T2c-T4) received 65–70 Gy EBRT + 4 months of combined ADT and then were randomized to either no further ADT (short-term) or 24 months of LHRH agonist monotherapy (long-term ADT). Long-term ADT showed an advantage in terms of disease-free survival, biochemical failure rates, distant metastases and cause-specific survival. It did not show an improvement in OS at a median followup time of 5.8 years, except in the subgroup of patients with Gleason scores of 8–10. One could argue

whether a full 36 months of therapy is needed or whether 28 months is satisfactory — but the main point is that long-term ADT is superior to no ADT or short-term ADT.

The data shown in this presentation confirm the advantage of long-term ADT. In the prostate cancer patient population with T1c-T2b, N1-2 or T2c-T4, N0-2, M0 disease treated with pelvic EBRT, 3 years of ADT should be a standard approach after a thorough discussion regarding acute and long-term side effects of this treatment. With growing recognition of both short-term and long-term toxicities of ADT in terms of not only sexual function, but osteopenia and osteoporosis, anemia, cognitive changes and increased risk of metabolic syndrome, patients must be counseled thoroughly with regards to the expected and possible toxicities of ADT, and preventative measures should be taken where appropriate.

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Hormone-resistant prostate cancer

Lori Wood, MD, MSc, FRCPC

SATRAPLATIN (S) DEMONSTRATES SIGNIFICANT CLINICAL BENEFITS FOR THE TREATMENT OF PATIENTS WITH HRPC: RESULTS OF A RANDOMIZED PHASE III TRIAL. ASCO 2007, ABSTRACT 5019.

Investigators: C.N. Sternberg et al.

TRIAL SUMMARY: The multinational, Phase III, double blinded SPARC (satraplatin and prednisone against refractory prostate cancer) trial enrolled 950 men with hormone-resistant prostate cancer who had failed 1 line of prior chemotherapy. Patients were randomized in a 2:1 ratio, to receive either oral satraplatin 80 mg/m²/day for 5 days every 5 weeks + 5 mg prednisone twice per day + oral antiemetics (n = 635) or placebo + prednisone + placebo antiemetics (n = 315). Enrolled patients received a median of 4 treatment cycles in the satraplatin arm (range 1–28 cycles) vs 2 cycles in the placebo arm (range 1–16). The primary endpoints were OS and PFS, defined by death, symptomatic progression, a skeletal event or tumour

TABLE 3. Selected efficacy endpoints in the SPARC trial of 950 men with hormone-resistant prostate cancer

	satraplatin (n = 635)	placebo (n = 315)	p-value
median progression-free survival	11.1 weeks	9.7 weeks	p = 0.0000003
median time to pain progression	66.1 weeks	22.3 weeks	p = 0.0002
Pain response	24.2%	13.8%	p = 0.005
duration of pain response	39.1 weeks	24.1 weeks	–
objective tumour response (RECIST)	6.5%	0.6%	p = 0.001
PSA	25.4%	12.4%	< 0.001

LANDMARKS

progression as measured by RECIST criteria. Tumour progression was assessed by independent, blinded radiologists and medical oncologists without access to PSA scores, blood counts or investigators' assessments. Pain response was self-reported in detailed diaries that were assessed by a blinded independent review committee (IRC). Patients in the satraplatin group had a 33% improvement in PFS (HR 0.67, 95% CI 0.57–0.77, $p < 0.0000003$) as assessed by the IRC, and improvements in pain, tumour response, duration of tumour response and PSA (Table 3). All patient subsets examined had more favourable

results with satraplatin, including the 51% who had received prior docetaxel and those who entered the trial with different performance statuses, amounts of pain and types of tumour progression. More Grade 3–4 hematologic toxicities occurred in the patients taking satraplatin, with significantly lower counts of white blood cells (including neutrophils), platelets and hemoglobin, but rates of febrile neutropenia were low at 0.6% in patients on satraplatin vs 0% in those on placebo. Statistically significant Grade 3–4 non-hematologic side effects were vomiting (1.6% vs 0%) and diarrhea (2.1% vs 0%).

COMMENTARY: Lori Wood, MD, MSc(Epi), FRCPC, Associate Professor, Dalhousie University Department of Medicine; Medical Oncologist at the Queen Elizabeth II Health Sciences Centre.

The SPARC trial was designed to determine if the oral platinum compound satraplatin plus prednisone improved PFS and OS compared to placebo plus prednisone in men with metastatic hormone-refractory prostate cancer (HRPC) who had failed prior therapy. Although it was a second-line treatment study, only 51% of patients had received prior docetaxel (in Canada this would be close to 100%). In terms of the patient population and generalizability, the patients in this study were a fairly fit cohort with 38% having only PSA progression at study entry, and 65% having pain scores of 0–1 on a linear analog scale and 35% having pain scores of 2–5.

The satraplatin + prednisone combination was shown to provide a modest improvement in PFS (11.1 vs 9.7 months) with a HR of 0.67 (0.57–0.77), and palliative benefit with improved pain response (24% vs 14%) and duration of pain response. OS data was not reported.

WHAT ABOUT MITOXANTRONE?

In Canada, the current default standard of care (outside of a clinical trial) for second-line chemotherapy in patients with metastatic HRPC is mitoxantrone + prednisone, based on Phase II data predominantly pertaining to PSA.^{1,2} Even though this study showed a modest improvement in PFS and a clinically meaningful palliative benefit, the important question for Canadian oncologists, not addressed by this

study, is whether satraplatin + prednisone is any better than mitoxantrone + prednisone. Based on this study alone, it is unlikely that satraplatin will become the new standard second-line therapy in HRPC in Canada.

Another important issue facing the Canadian oncology community — both patients and healthcare professionals — is access to new treatments that have shown varying degrees of activity. Pressures are increasing from every level including individual hospitals, provincial cancer agencies, provincial governments and the federal government, to ensure that our treatments are “cost effective”. The process may become more unified with the Joint Oncology Drug Review (JODR) pilot project, a collaboration of all provinces except Québec — but time will tell. The genitourinary oncology community certainly feels the effect of the previous Common Drug Review (CDR) process for oral cancer drugs, which denied funding for both sunitinib and sorafenib for metastatic renal cell cancer. Therefore, it will be interesting to see if a drug like satraplatin, which shows a predominantly palliative benefit, will receive funding approval in Canada.

References

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Adjuvant taxanes in high-risk breast cancer

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

PHASE III STUDY OF DOXORUBICIN-CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL OR DOCETAXEL GIVEN EVERY 3 WEEKS OR WEEKLY IN OPERABLE BREAST CANCER: RESULTS OF INTERGROUP TRIAL E1199. ASCO 2007, ABSTRACT 516.

Investigators: J.A. Sparano et al.

TRIAL SUMMARY: The Intergroup E1199 study Phase III open-label study randomized 4950 women with high-risk early breast cancer to 4 treatment arms following 4 cycles

of AC chemotherapy (doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m² every 3 weeks): 3-weekly paclitaxel (175 mg/m² every 3 weeks for 4 cycles), weekly paclitaxel

(80 mg/m² for 12 weeks), 3-weekly docetaxel (100 mg/m² every 3 weeks for 4 cycles) or weekly docetaxel (35 mg/m² for 12 weeks). Eligible patients had positive axillary lymph nodes and/or tumours ≥ 2 cm. If indicated, hormonal therapy was given sequentially. At median followup of 60.2 months, no statistically significant differences were seen in disease-free survival (DFS), the primary endpoint, between the primary comparisons of type of taxane (HR 1.032, p = 0.61) and weekly vs 3-weekly schedule (HR 1.062, p = 0.33). Secondary comparisons of 3-weekly paclitaxel (the standard of care when this trial was initiated) to the other regimens showed an approximately 5% absolute improvement in DFS for the weekly paclitaxel and 3-weekly docetaxel arms, and a 3% absolute

improvement in OS for the weekly paclitaxel arm (Table 4). In exploratory subset analysis of DFS by hormone receptor expression (not centrally confirmed), statistically significant interactions were seen between the 3-weekly paclitaxel and weekly paclitaxel arms for hormone-negative disease (HR 1.40, p = 0.02) and between the 3-weekly paclitaxel arm and the 3-weekly docetaxel arm for hormone-positive disease (HR = 1.28, p = 0.03). The incidence of Grade 3–4 toxicities was 30% in the 3-weekly paclitaxel arm, 27% for weekly paclitaxel, 71% for 3-weekly docetaxel and 44% for weekly docetaxel (Table 4). The authors concluded that these results support the use of AC chemotherapy followed by weekly paclitaxel in upcoming trials of targeted therapies.

TABLE 4. Selected outcomes in the Intergroup E1199 trial comparing 4 taxane regimens

	3-weekly paclitaxel	weekly paclitaxel	3-weekly docetaxel	weekly docetaxel
5-year disease-free survival	76.9%	81.5%	81.2%	77.6%
5-year overall survival	86.5%	89.7%	87.3%	86.2%
all doses received	95%	88%	87%	75%
Comparison of weekly paclitaxel vs other arms				
disease-free survival	–	1.27 (p = 0.006)	1.23 (p = 0.02)	1.09 (p = ns)
overall survival	–	1.32 (p = 0.01)	1.13 (p = ns)	1.02 (p = ns)
Grade 3–4 toxicities				
febrile neutropenia	< 0.5%	1%	16%	1%
fatigue	2%	3%	9%	11%
myalgia	7%	2%	6%	1%
neuropathy	5%	8%	4%	6%
treatment-related deaths	1	1	2	0

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

Over the last few years a number of adjuvant trials studying anthracycline + taxane combination therapies have been published, all consistently showing improved DFS and OS with the combination compared to anthracycline-only chemotherapy. Medical oncologists have not reached a consensus, however, on a “gold standard” regimen. Specifically, there is much discussion on dose-dense vs conventional, paclitaxel vs docetaxel and weekly vs 3-weekly chemotherapy options.

This Intergroup trial randomized patients to 1 of 4 treatment arms after 4 cycles of AC chemotherapy. No statistically significant differences were noted in the primary endpoints (i.e. docetaxel vs paclitaxel and 3-weekly vs weekly chemotherapy). Patients in the weekly paclitaxel arm did have significantly improved DFS and OS compared to those receiving 3-weekly

paclitaxel. As well, patients who received 3-weekly docetaxel had improved DFS compared to those receiving 3-weekly paclitaxel, but they also had increased rates of toxicity including febrile neutropenia.

IMPROVING ON STANDARD AC CHEMOTHERAPY

This is the third important study to highlight improved efficacy of a novel adjuvant regimen over standard AC followed by 3-weekly paclitaxel. Citron et al previously published results showing improved DFS and OS with dose-dense AC followed by paclitaxel as compared to conventional weekly AC followed by paclitaxel.¹ At the 2006 San Antonio Breast Cancer Symposium, the NCIC MA.21 study showed cyclophosphamide + epirubicin + fluorouracil (CEF) and dose-dense epirubicin

LANDMARKS

+ cyclophosphamide (EC) followed by paclitaxel to be superior to 3-weekly AC followed by paclitaxel. The E1199 study further demonstrates that AC followed by either weekly paclitaxel or 3-weekly docetaxel is superior to conventional AC followed by paclitaxel, although only on subgroup analysis. Based on these other randomized Phase III trials, however, the evidence is quite compelling that AC followed by 3-weekly paclitaxel should not be considered as a top-tier adjuvant breast cancer chemotherapy regimen in women with high-risk disease. In this regard, the more successful E1199 regimens (AC followed by weekly paclitaxel and AC followed by 3-weekly docetaxel) cannot easily be directly compared to other third-generation adjuvant regimens given their substandard activity as comparators.

Despite the promising results of weekly paclitaxel, however, clinical applicability may be limited as we are already struggling with busy chemotherapy suites across the country, and giving weekly chemotherapy is challenging both from system and patient perspectives.

FUTURE RESEARCH

Advances in adjuvant breast cancer chemotherapy have led to significant improvement in breast cancer mortality rates. A number of key ongoing breast cancer adjuvant trials are evaluating how the third-generation chemotherapy regimens compare to each other, as well as the effect of incorporating other chemotherapy agents such as gemcitabine and capecitabine, as in NSABP B-38.² Apart from integrating new agents, important questions that need to be addressed include:

- Do patients with estrogen receptor-positive tumours

benefit from chemotherapy? A number of trials are prospectively evaluating the clinical utility of gene signatures to help determine the answer.

- When are anthracyclines necessary and when can they be omitted from adjuvant regimens? The predictive utility of HER2 and topo2 need to be studied prospectively.
- What biologics should be evaluated in the adjuvant setting and for which patients? Bevacizumab in combination with paclitaxel has already shown promising results in first-line treatment of metastatic breast cancer, and is now being evaluated in the adjuvant setting. Specific tumour types — including triple receptor-negative (estrogen, progesterone and HER2 receptors) and HER2-positive tumours — are being targeted based on their underlying biologic properties.
- What can we do to address toxicity associated with adjuvant chemotherapy? In addition to preventing and proactively managing short-term side effects such as febrile neutropenia and anemia, long-term sequelae require more attention. We need to study how chemotherapy affects cognition, develop predictive models for cardiac toxicity, better understand the impact of chemotherapy on fertility and evaluate fertility-preservation techniques. We also need to ensure that our patients and their family physicians are educated on these toxicities such that they are addressed early and effectively.

References

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2. Information available at www.cancer.gov/clinicaltrials/NSABP-B-38

Chemotherapy in metastatic breast cancer

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

A RANDOMIZED TRIAL OF CAPECITABINE (C) GIVEN INTERMITTENTLY (IC) RATHER THAN CONTINUOUSLY (CC) COMPARED TO CLASSICAL CMF AS FIRST-LINE CHEMOTHERAPY FOR ADVANCED BREAST CANCER (ABC). ASCO 2007, ABSTRACT 1031.

Investigators: M. Stockler et al.

TRIAL SUMMARY: This trial randomized 325 women with metastatic breast cancer to 3 treatment arms, with treatment continuing until disease progression, unacceptable toxicity or intolerance:

- CMF chemotherapy: cyclophosphamide 100 mg/m²/day orally, on Days 1–14; methotrexate 40 mg/m² + fluorouracil 600 mg/m² intravenously, Days 1 and 8, every 28 days
- intermittent capecitabine: 2000 mg/m²/day orally for 14 of every 21 days
- continuous capecitabine: 1300 mg/m²/day orally every day

As the differences in efficacy and adverse events between intermittent vs continuous capecitabine were not statistically significant ($p > 0.4$), com-

TABLE 5. Efficacy endpoints for capecitabine vs CMF chemotherapy as first-line treatment in women with metastatic breast cancer

	hazard ratio	95% confidence interval	p-value
overall survival	0.72	0.55–0.94	p = 0.02
progression-free survival	0.86	0.67–1.1	p = 0.2
progression-free survival after 6 months	0.62	0.44–0.87	not reported

parisons were made between the 2 capecitabine arms combined and CMF. As shown in **Table 5**, women receiving both doses of capecitabine had longer OS than those receiving CMF (median 22 months vs 18 months). Rates of response (21% vs 18%, $p = 0.8$) and PFS (median 7 months) were similar, although PFS was longer with capecitabine for patients who had not had disease progression within 6 months (**Table 5**). More patients taking CMF experienced febrile neutropenia, infection and sore

mouth, and more on capecitabine reported hand-foot syndrome. More patients taking capecitabine (40%) continued therapy beyond 6 months compared to those taking CMF (21%). The authors concluded that women receiving capecitabine achieved longer OS compared to those receiving CMF, and that they tolerated treatment better, with less toxicity — indicating that for women with metastatic breast cancer in whom intensive treatment is not appropriate, capecitabine is a good first-line treatment option.

PHASE III TRIAL OF IXABEPILONE PLUS CAPECITABINE COMPARED TO CAPECITABINE ALONE IN PATIENTS WITH METASTATIC BREAST CANCER (MBC) PREVIOUSLY TREATED OR RESISTANT TO AN ANTHRACYCLINE AND RESISTANT TO TAXANES. ASCO 2007, ABSTRACT 1006.

Investigators: L.T. Vahdat et al.

TRIAL SUMMARY: This open-label Phase III trial randomized 752 heavily pretreated women with locally advanced or metastatic breast cancer to either ixabepilone + capecitabine ($n = 375$) or capecitabine alone ($n = 377$). Strict eligibility rules required that study participants could no longer be candidates for treatment with anthracyclines or taxanes due to resistance and/or total cumulative dose. Those in the ixabepilone + capecitabine arm received ixabepilone 40 mg/m² intravenously over 3 hours once every 3 weeks + capecitabine 1000 mg/m² orally twice a day for 14 days out of 21, and those in the capecitabine arm received a higher dose of 1250 mg/m² orally twice a day for 14 days out of 21. PFS, the primary endpoint, and response rate, a secondary endpoint, were assessed both by investigators and by an independent radiologic review (IRR) committee. As shown in **Table 6**, the women receiving ixabepilone + capecitabine had significant PFS improvement by IRR assessment, with a hazard ratio for benefit of 0.75 (95% CI 0.64–0.88, $p = 0.003$). Benefit persisted across predefined subgroups including those with triple-negative (HER2-negative, estrogen receptor-negative and progesterone-negative) tumours; HER2-positive tumours; visceral metastases; and poorer initial performance status. More treatment-related on-study deaths occurred in the ixabepilone + capecitabine arm (12 vs 2 patients), and as most of the deaths occurred

TABLE 6. Selected efficacy and safety results for ixabepilone + capecitabine vs capecitabine in heavily pretreated women with metastatic breast cancer

	ixabepilone + capecitabine (n = 375)	capecitabine (n = 377)	p-value
Efficacy endpoints			
progression-free survival, IRR assessment	5.8 months	4.2 months	$p = 0.0003$
overall response rate, IRR assessment	35%	14%	$p < 0.0001$
Safety endpoints			
on-study deaths	12 patients	2 patients	–
Grade 3–4 neutropenia	68%	11%	< 0.0001
Grade 3–4 neuropathy	23%	0%	–
Grade 3–4 hand-foot syndrome	18%	17%	–
Grade 3–4 fatigue	9%	3%	–

in patients with \geq Grade 2 liver dysfunction, the protocol was amended to exclude women with moderate liver dysfunction. Women receiving the combination regimen had more Grade 3–4 hematologic toxicities, fatigue and peripheral neuropathy, but equivalent rates of hand-foot syndrome (**Table 6**). The median time to resolution of peripheral neuropathy was 6 weeks. The authors concluded that ixabepilone + capecitabine offers a new potential option for patients with advanced breast cancer, with superior efficacy to capecitabine alone and a manageable toxicity profile.

LANDMARKS

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

The significant successes being made in the adjuvant treatment of breast cancer are having an impact on our options for treating metastatic recurrence. As more patients are receiving anthracyclines and taxanes in the adjuvant setting we are left to consider other chemotherapeutic agents when these patients develop metastatic breast cancer (MBC). In general, the treatment options available to patients who have had previous adjuvant treatment with anthracyclines and taxanes include rechallenge with anthracyclines or taxanes, capecitabine, gemcitabine and vinorelbine. Data have been limited, as most of the first-line MBC trials have lacked significant numbers of patients who had previously received taxanes in adjuvant treatment. Thus far, we have extrapolated the efficacy of these drugs based on trials evaluating patients who are considered taxane-refractory because their metastatic disease progressed on taxanes.

TWO PROMISING AGENTS

In the trial by Stockler et al (summarized above) patients were randomized to 1 of 3 arms: intermittent capecitabine, continuous capecitabine or CMF chemotherapy. This is just one of a few trials in MBC to show a survival benefit. The results indicate that despite a similar response rate and PFS, improvement in OS was statistically significant. The authors reviewed the post-progression treatment received by patients in all 3 arms and concluded that the difference in survival was not related to what patients received upon progression, but rather to benefits due to treatment with capecitabine as compared to CMF.


Despite the significant difference, this study has some limitations. About 20% of these patients had received previous adjuvant treatment with CMF chemotherapy, which might have affected the response to CMF when these patients developed MBC. Further, only about 5% of patients had previous adjuvant treatment with anthracyclines and 2% to 4% with taxanes, so the applicability of this trial may be limited to those patients not eligible for more intensive first-line regimens.

Disclosure

Drs. ElSayed, Hobson and Wood report having no potential conflicts of interest related to their commentaries. Dr. MacKenzie reports being on advisory boards for Bayer, Pfizer and Wyeth and receiving an unrestricted educational grant from Pfizer. Dr. Verma reports receiving research support from, and being a consultant and on advisory board and speakers' bureaus for Abraxis, BMS, Roche, Pfizer and Sanofi Aventis.

The other significant Phase III chemotherapy trial in MBC at this year's ASCO was presented by L. Vahdat. Ixabepilone is an epothilone B analog that stabilizes microtubules and has previously shown activity as a single agent in taxane-refractory MBC. In this trial, patients with anthracycline- and taxane-resistant MBC were randomized to receive capecitabine alone or capecitabine + ixabepilone. Patients randomized to the ixabepilone + capecitabine arm had a higher response rate (35% vs 14%) and longer PFS (5.8 vs 4.2 months) with a HR of 0.75 ($p = 0.0003$). The OS data were still premature and were not presented. The response rate seen with capecitabine alone was 14%, which is consistent with previous Phase III trials. The concern with the doublet therapy was increased rates of neuropathy (23% vs 0%). No additional increases in toxicity, such as hand-foot syndrome and diarrhea, were seen with capecitabine.

PROVIDES OPTIONS TO ANTHRACYCLINES AND TAXANES

Both these trials are significant as the landscape of MBC evolves. The first addresses an ever-increasing population of women who are unable, or unwilling, to accept the toxicities of standard anthracyclines or taxanes. Capecitabine was well tolerated and was shown to have a significant survival benefit as compared to CMF. The results might also extrapolate to women pretreated with anthracyclines or taxanes in either the adjuvant or metastatic settings. As the choice of active agents for MBC is limited, the second trial introduces us to a new active agent: ixabepilone. The combination of ixabepilone and capecitabine appears promising with an improved response rate of 35% — especially encouraging given that all these patients were considered anthracycline- and taxane-resistant. The concern with this doublet therapy is increased neuropathy. Before its routine use in clinical practice, further investigations are required that address who is at risk and how best to avoid this toxicity. 

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