

LANDMARKS Reports of recent clinical trial data



ANNUAL MEETING OF THE MULTINATIONAL ASSOCIATION FOR SUPPORTIVE CARE IN CANCER (MASCC) June 25–27, 2009, Rome, Italy

ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGISTS (ASCO) May 29 to June 1, 2009, Orlando, Florida.

Contributors were selected by Barry Bultz, PhD, RPsych; Hagen Kennecke, MD, MPH, FRCPC; Joseph Ragaz, MD, FRCPC; and Neil Reaume, BSc, MD, FRCPC, MSc.

Supportive care

SYMPTOM PATTERNS IN PATIENTS WITH ADVANCED CANCER

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STUDY SUMMARY: Age and gender differences

Dr. Winson Cheung’s oral presentation at the Multinational Association for Supportive Care in Cancer (MASCC) 2009 Annual Meeting, held June 25–27 in Rome, Italy, examined symptom patterns in patients with advanced cancers, with a view to identifying differences in intensity of symptom-related distress and incidence of symptom clusters related to age and gender. The researchers conducted principal component analysis (PCA) on Edmonton Symptom Assessment Scale (ESAS) questionnaires filled out by attendees of Princess Margaret Hospital’s Oncology Palliative Care Clinics, between 2005 and 2007 (audits show an approximate 90%

completion rate at initial assessment and subsequent visits to the clinic¹). The ESAS asks patients to rate the severity of nine symptoms (see **Tables 1** and **2**) on a scale from 0 to 10. In PCA, the degree to which a variable consistently associates with other results is termed its “factor loading score,” which predicts its assignment into an independent component or “cluster.” The analysis was done for all patients and for sub-groups determined by age and gender: men > and ≤ 60 years, and women > and ≤ 60 years. Of 1366 patients, there were 682 males (50%) and 684 females (50%), and 824 > 60 years (60%) and 542 ≤ 60 years, with a median age of 64 years (range 18 to 74). Gastrointestinal cancer was the most common disease site (27%), followed by lung (14%) and breast (11%) cancers.

For both men and women > 60 years old, fatigue, decreased appetite and poor general well-being were the symptoms reported as most distressing. As shown in **Table 1**, differences in factor loading scores related to age and gender were apparent. PCA identified two major symptom clusters: fatigue, nausea, drowsiness, decreased appetite and dyspnea (Cluster 1) and depression and anxiety (Cluster 2), and the incidence of these clusters varied by both age and gender (**Table 2**, page 12). The authors noted that pain and anxiety were worse in patients aged ≤ 60 years, that poor appetite and fatigue were worse in those > 60, and that nausea and anxiety were worse in females. They proposed that the ability to conduct research and offer palliative interventions designed to address prominent symptom clusters will likely offer greater benefit to patients, and perhaps better understanding of symptoms, than research and interventions directed to individual symptoms.

TABLE 1. Factor loading scores* in principle component analysis of symptoms reported on the ESAS by 1366 patients with advanced cancers, by age and gender subgroups

symptom	age ≤ 60 years		age > 60 years	
	male	female	male	female
pain	0.75	0.02	0.38	0.72
fatigue	0.63	0.32	0.60	0.69
nausea	0.22	0.63	0.19	0.51
depression	0.78	0.81	0.84	0.21
anxiety	0.70	0.71	0.87	0.14
drowsiness	0.19	0.67	0.71	0.52
appetite	0.75	0.38	0.06	0.85
well-being	0.76	0.36	0.33	0.56
dyspnea	0.16	0.12	0.11	0.04

* values > 0.60 (in bold) were prospectively considered to indicate greater likelihood of belonging to a symptom cluster

Cheung W, Le L, Zimmermann C et al. Age And Gender Differences In The Symptom Patterns Of Advanced Cancer Patients, MASCC 2009, Abstract 18-184.

COMMENTARY: Prevalence rates of distress have been a significant area of research in psychosocial oncology over the past several years.^{2,3} Of particular interest is the increasing awareness that symptoms of distress often present themselves not in a singular way but in clusters. This study by Cheung et al offers an interesting addition to the growing body of literature concerning symptom clusters.^{4,6} The large sample size and the focus on individuals with advanced disease are significant contributions. The objective of examining symptom clusters by age and gender in this population provides an important insight for supportive care treatment planning and for the design and testing of future symptom management interventions in patients with advanced disease. The descriptions of clusters within specific cancer disease sites are also useful, helping each member of the multi-disciplinary team to provide care based on the symptoms and concerns identified. Such descriptions enhance our capacity to comprehend the impact of the disease and plan timely, targeted treatment by the right professional.

The authors have pointed out important considerations for future work in this area. In particular, the issue of common criteria for inclusion of symptoms in a cluster is extremely important for comparisons across studies and populations. As well, the potential to understand symptom clusters over time across the entire disease trajectory — not just at the stage of advanced disease — offers another important area for future investigation and improvement of care. The notion of measuring distress and its specific associations with particular patient-identified problems or concerns has important implications for clinical application. Just because a symptom is present does not mean it is a source of significant distress for the patient or that the patient needs related assistance at a specific point in time.⁷

DISTRESS SCREENING AND INTEGRATED PERSON-CENTRED CARE

Besides the physical impacts, the psychosocial, emotional, spiritual and practical consequences of cancer and its treatment are important potential sources of distress throughout the cancer journey, and need to be taken into account to understand the patient experience and take steps to improve it.^{8,9} By integrating standardized structures and processes that facilitate the incorporation of psychosocial and practical domains together with the physical — for example, by using formalized Screening for Distress (the 6th Vital Sign)^{10,11} — we can begin to move toward integrated person-centred care. Efforts are underway in several cancer programs across Canada to implement Screening for Distress as a platform for achieving person-centred cancer care.¹² A national task group (the Screening for Distress Toolkit Working Group, under the auspices of the Cancer Journey Action Group of the Canadian Partnership Against Cancer) has agreed on items for a common minimum dataset related to Screening for Distress. The items are contained within the ESAS and the Canadian Problem Checklist.¹³ These screening instruments provide a basis for discussing and documenting concerns that focus on what is important to the patient at that time, and which may be sources of distress. Patients complete the instruments — either on paper or electronically — while waiting for a clinic appointment; the results are the starting point for the clinical encounter. The healthcare professional is able to engage in relevant assessment, intervention and/or referral beyond the core cancer care team, as necessary and appropriate. In the long term, documentation allows prospective longitudinal identification of symptom burden and relief across a range of physical, psychosocial and practical issues.

Implementing Screening for Distress thus has the potential to create practice change and influence the culture within the clinical environment, such that the intention is to start clinical interactions with what is important or of concern to the patient. Success will require interprofessional collaboration, effective partnerships and embracing an attitude that care must be person-centred and directed toward the whole person.¹⁴

TABLE 2. Factor loading scores* indicating symptom clusters in 1366 patients with advanced cancers, by age and gender

symptom	≤ 60 years n = 539		> 60 years n = 820	
	Cluster 1†	Cluster 2‡	Cluster 1†	Cluster 2‡
pain	0.68	0.17	0.27	0.64
fatigue	0.74	0.38	0.39	0.4
nausea	0.2	0.84	0.14	0.84
depression	0.6	0.52	0.85	0.23
anxiety	0.6	0.51	0.87	0.22
drowsiness	0.22	0.85	0.49	0.59
appetite	0.71	0.32	0.2	0.35
well-being	0.86	0.14	0.4	0.1
dyspnea	0.62	0.16	0.1	0.1
percent variance	53%	11%	46%	11%
	male n = 674		female n = 685	
pain	0.4	0.3	0.57	0.45
fatigue	0.59	0.33	0.55	0.47
nausea	0.17	0.08	0.62*	0.23
depression	0.85	0.31	0.79*	0.24
anxiety	0.87	0.19	0.82*	0.13
drowsiness	0.65	0.06	0.75*	0.14
appetite	0.09	0.79	0.17	0.86
well-being	0.35	0.83	0.26	0.77
dyspnea	0.11	0.21	0.17	0.17
percent variance	47%	12%	50%	11%

* values > 0.60 (in bold) were prospectively considered to indicate greater likelihood of belonging to a symptom cluster

† Cluster 1: fatigue, nausea, drowsiness, decreased appetite, and dyspnea

‡ Cluster 2: depression and anxiety

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IN BRIEF

Already known

- Previous research had demonstrated that in patients with advanced cancer, there tend to be two major symptom clusters: fatigue, nausea, drowsiness, decreased appetite and dyspnea (Cluster 1), and depression and anxiety (Cluster 2).

What this study showed

- The incidence of these two clusters and the severity of symptom-related distress varied by both age and gender, with pain and anxiety tending to be worse in patients aged ≤ 60 years, poor appetite and fatigue worse in those > 60 years and nausea and anxiety worse in females.

Next steps

- This work has important implications for making comparisons across studies and populations, for understanding symptom clusters over time across the entire disease trajectory and for organizing cancer care delivery towards integrated, person-centred care.

Colon cancer

BIOCHEMICAL MARKERS

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STUDY SUMMARY: Predictive value of MSI status in Stage II and III colon cancer

The Pan-European Trial in Adjuvant Colon Cancer 03 (PETACC-3) study enrolled 3278 patients with Stage II and Stage III colon cancer to receive postoperative fluorouracil + leucovorin with or without irinotecan; results showed no benefit for adding irinotecan to fluorouracil + leucovorin chemotherapy. The current analysis used the NCI extended panel of 10 markers to examine microsatellite instability (MSI) status of 1327 out of 1405 available tissue blocks. High MSI status (MSI-H) was defined as instability in three markers. At median followup of 68 months, 85 Stage II patients (22%) and 103 Stage III patients (12%) were identified as MSI-H, consistent with frequency in prior research, and the rest were deemed microsatellite stable (MSS). Age < 60, higher T stage, higher tumour grade, lower N stage and right-sided tumour location were significantly associated with MSI-H status. In Stage II disease, the hazard ratios (HR) for the prognostic impact of MSI-H on relapse-free survival (RFS) and overall survival (OS) were greater than in Stage III disease, as shown in Table 3. The authors concluded that, besides

confirming the strong prognostic value of MSI status for survival, MSI status may have stage-specific biologic effects. No evidence of benefit was seen from adding irinotecan in either Stage II or III subgroups.

Tejpar S, Bosman F, Delorenzi M et al. Microsatellite instability (MSI) in stage II and III colon cancer treated with 5FU-LV or 5FU-LV and irinotecan (PETACC 3-EORTC 40993-SAKK 60/00 trial). ASCO 2009, Abstract 4001.

TABLE 3. Hazard ratios (HR) in the PETACC-3 trial for survival outcomes in patients with microsatellite high (MSI-H) vs microsatellite stable (MSS) colon cancer

	recurrence-free survival	overall survival
Stage II	HR = 0.265 95% CI = 0.107–0.661 p = 0.0044	HR = 0.159 95% CI = 0.039–0.659 p = 0.011
Stage III	HR = 0.693 95% CI = 0.473–1.02 p = 0.06	HR = 0.699 95% CI = 0.446–1.09 p = 0.12

STUDY SUMMARY: Stage specificity of molecular markers

This analysis examined the incidence and prognostic value of a number of molecular markers in Stage II and III colon

cancer, including P53, SMAD4, thymidylate synthetase (TS) and human telomerase reverse transcriptase (hTERT), mutations of KRAS and BRAF, microsatellite instability (MSI) and 18q loss of heterozygosity (18q LOH). Tests were conducted on 1564 formalin-fixed paraffin-embedded tissue blocks collected prospectively from patients in the PETACC-3 trial, described above. The researchers found statistically significant differences in frequency per stage (n = 420 Stage II and 984 Stage III patients) for all markers except KRAS and BRAF. The only interaction of marker and stage besides that for MSI status, described above, was for 18q LOH (p = 0.04). A multivariate analysis of the prognostic impact of clinical, pathologic and biologic markers for RFS was done according to stage at presentation (Table 4). The authors concluded that the prognostic value of molecular markers in colon cancer are stage-specific, and suggested that the stages could represent different diseases.

TABLE 4. Multivariate analysis of clinical and pathologic variables and biomarkers and relapse-free survival in Stage II and III colon cancer

marker	Stage II		Stage III	
	hazard ratio	p-value	hazard ratio	p-value
T stage (T4 vs T3)	2.8	p = 0.0001	1.6	p = 0.0006
N stage (N2 vs N1)	N/A	N/A	2.2	p < 0.0001
histological grade (3-4 vs 1-2)	0.6	p = 0.55	1.4	p = 0.07
age (> 60 vs ≤ 60)	1.8	p = 0.026	1.1	p = 0.3
MSI (high vs stable)	0.3	p = 0.027	0.7	p = 0.12
P53 (high)	0.7	p = 0.27	1.3	p = 0.015
SMAD4 (any loss)	1.0	p = 0.9	1.6	p = 0.0002

Roth AD, P. Yan P et al. Stage-specific prognostic value of molecular markers in colon cancer: Results of the translational study on the PETACC 3-EORTC 40993-SAKK 60-00 trial. ASCO 2009, Abstract 4002.

COMMENTARY: In their well-conducted study, Drs. Tejpar et al have further contributed to our understanding of the prognostic and predictive impact of defects in mismatch repair in early-stage colon cancer.¹⁻⁵ Ribic et al⁴ demonstrated that patients with early-stage MSI-H tumours have a significantly superior prognosis (HR 0.3; 95% CI 0.14 to 0.72) compared to those whose tumours were MSS. There was a

trend for worse survival among MSI-H patients treated with adjuvant fluorouracil. Sargent et al⁵ confirmed the favourable prognostic impact of defective mismatch repair in Stage II but not Stage III colon cancer. Patients with MSI-H Stage II disease treated with adjuvant fluorouracil had significantly worse outcomes compared to those not treated adjuvantly (HR 3.15, CI 1.07 to 9.29). Tejpar et al's results documented a greater frequency of MSI-H in Stage II (22%) vs Stage III colon cancer (12%). In spite of all patients receiving adjuvant fluorouracil, MSI-H conferred a favourable prognosis for Stage II patients, similar to that seen in previous trials. A trend for superior outcomes was also seen among MSI-H Stage III patients. In contrast to a previous study,⁶ MSI-H did predict benefit of adjuvant irinotecan in Tejpar et al's study.

The biomarker study by Dr. Roth et al complemented the above results by providing an analysis of the prognostic impact of clinical, pathologic and molecular markers in Stage II vs Stage III colon cancer. While MSI status was strongly associated with improved outcome in Stage II tumours, improvement was not statistically significant in Stage III disease. High P53, loss of SMAD4 and more advanced T and N stage were associated with inferior survival among Stage III patients.

The combined results confirm the relevance of mismatch repair in Stage II colon cancer. Current consensus statements support the use of MSI to aid in decision-making for Stage II disease.⁷ MSI testing may be done by PCR-based analysis or by immunohistochemical staining for the gene products, most commonly MLH1 and MSH2. The evidence suggests that MSI-H Stage II colon cancer is associated with a favourable prognosis, so these patients generally do not require adjuvant chemotherapy. The question remains as to which prognostic and predictive markers should be used for the remaining approximately 80% of Stage II tumours, and what treatment to offer. In spite of recent negative results

IN BRIEF

Already known

- The predictive value of a number of molecular markers and patient and tumour characteristics, including microsatellite stability status (high: MSI-H or stable: MSS) in colon cancer has been previously shown.

What these studies showed

- MSI-H status predicted relapse-free survival in patients with Stage II more strongly than in Stage III colon cancer patients.
- The predictive impact of several factors varied according to disease stage (II vs III).
- It appears that most of the approximately 20% of Stage II colon cancer patients who are MSI-H do not require adjuvant chemotherapy, but it is not known which of the remaining 80% stand to benefit from adjuvant chemotherapy.

Next steps

- Results of future studies are expected to allow classification of patients into mutually exclusive prognostic and therapeutic subgroups

for use of adjuvant bevacizumab in NSABP trial C-08,⁸ the ECOG -5202 (NCT00217737) trial will continue and will prospectively describe outcomes of patients with low-risk Stage II colon cancer, while high-risk patients are randomized to leucovorin + fluorouracil + oxaliplatin (FOLFOX) with or without bevacizumab. Low- and high-risk groups are defined based on MSI status and chromosome 18q LOH, and the trial will represent one of the largest centrally validated prospective studies of the impact of mismatch repair and 18q LOH in Stage II colon cancer.

The current studies have improved our understanding of biomarkers in Stage II and III colon cancer. Further studies are needed to allow us to classify patients with early-stage colorectal cancer into mutually exclusive prognostic and therapeutic subgroups.

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Breast cancer

NAB-PACLITAXEL IN METASTATIC DISEASE

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TRIAL SUMMARY: Bevacizumab with three dosages of nab-paclitaxel

Abstract 1006 by AK Conlin et al described an open-label, randomized Phase II study comparing three dosing schedules of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) plus bevacizumab in women receiving first-line treatment for metastatic breast cancer. About two-thirds of the enrolled patients had previously had adjuvant or neo-adjuvant chemotherapy for early breast cancer. Those in Arm A (n = 74) received 260 mg/m² nab-paclitaxel + 15 mg/kg bevacizumab every three weeks, those in Arm B (n = 55) received 260 mg/m² nab-paclitaxel with filgrastim + 10 mg/kg bevacizumab every two weeks, and those in Arm C (n = 80) received 130 mg/m² nab-paclitaxel weekly + 10 mg/kg bevacizumab every two weeks. Dose reductions for specific signs and symptoms of toxicity were permitted. Overall response rate, the primary endpoint, was similar in all three arms (p = 0.575), with confirmed complete or partial response rates of 44%, 54% and 78% in Arms A, B and C, respectively (there was only one complete response in each arm). Overall Grade 3–5 toxicities, including sensory neuropathy, were statistically similar in all three arms, however

women in the every two-week (dose-dense, Arm B) group had more overall toxicities than those in the every three-week arm, and this arm (Arm B) was closed early to enrollment. In the absence of disease progression, women in arm B who were tolerating treatment continued with dose-dense nab-paclitaxel, with dose reductions permitted as necessary to nab-paclitaxel 220 mg/m² or 180 mg/m². Time to progression, a secondary endpoint, was longer in the patients receiving weekly nab-paclitaxel (Arm C, 9.0 months) compared to those in Arm B (6.3 months) and Arm A (7.7 months). Overall survival results are not yet available. The authors concluded that while all regimens showed antitumour activity, the combination of weekly nab-paclitaxel with 10 mg/kg bevacizumab every two weeks showed greater therapeutic efficacy but required more dose reductions and delays. A “three weeks on, one week off” schedule is being incorporated into future studies.

Conlin AK, Hudis CA, Bach A et al. *Randomized phase II trial of nanoparticle albumin-bound paclitaxel in three dosing schedules with bevacizumab as first-line therapy for HER2-negative metastatic breast cancer (MBC)*. ASCO 2009, Abstract 1006.

COMMENTARY: Nab-paclitaxel is clearly efficacious in the treatment of women with metastatic breast cancer. Gradishar conducted a randomized Phase III trial² comparing nab-paclitaxel (260 mg/m² every three weeks) to paclitaxel (175 mg/m² every three weeks), demonstrating a significantly longer median time to progression in patients receiving

nab-paclitaxel (23.0 vs 16.9 weeks; p = 0.006). Subsequently, Gradishar et al published a randomized Phase II study² demonstrating superior response rates (by independent review board) for patients receiving weekly nab-paclitaxel — 45% with 100 mg/m² and 47% with 150 mg/m² — compared to patients receiving docetaxel every three weeks

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(response rate 28%) or nab-paclitaxel every three weeks (response rate 35%).

Based on these studies, as well as the results from E2100³ and AVADO⁴ demonstrating the benefit of bevacizumab combined with a taxane in women with metastatic breast cancer, investigators from several US centres launched an open-label Phase II study of three different schedules of nab-paclitaxel combined with bevacizumab in women with metastatic breast cancer. The preliminary results — only 40% of patients have progressed — were presented at ASCO 2009. No statistically significant difference was seen in response rates between the three treatment arms. There were, however, considerable differences in the toxicities experienced by women receiving different schedules of nab-paclitaxel. Those receiving it every two weeks experienced significantly more fatigue, nausea, bone pain, arthralgias and myalgias, resulting in the premature closure of this study arm as per specified stopping rules in the protocol. The majority of women treated with uninterrupted weekly nab-paclitaxel required a dose reduction (64%) or at least one dose delay (86%). No statistically significant difference in sensory neuropathy was seen between treatment arms. Time to progression, a secondary endpoint, was longer with weekly nab-paclitaxel (9.0 months) compared to nab-paclitaxel every two weeks (6.3 months) and nab-paclitaxel every three weeks (7.7 months).

These preliminary results demonstrate that nab-paclitaxel is efficacious, but can be toxic when combined with bevacizumab in women with HER2-negative metastatic breast cancer. Of particular interest is the high rate of neurotoxicity (30% to 46% of patients across treatment arms reported Grade 3 neurotoxicity), raising concerns regarding the feasibility of the nab-paclitaxel + bevacizumab combination for community practice, regardless of reasonable responses. This concern was raised by the audience at ASCO and also mentioned by the session discussant, Dr. Kathy Miller.

IN BRIEF

Already known

- It has been shown that nab-paclitaxel is effective in producing a tumour response and delaying time to progression, with less toxicity than standard taxanes.

What this study showed

- This comparison of three different dosing schedules of nab-paclitaxel plus bevacizumab in first-line treatment of women with HER2-negative metastatic breast cancer showed similar efficacy but differing toxicity levels.

Next steps

- To find the optimal dosing schedule, a trial with nab-paclitaxel (100 mg/m² to 130 mg/m²) combined with bevacizumab in women with HER2-negative metastatic breast cancer may be conducted.
- Given limited funding for both agents, however, few Canadian women are expected to have access to this treatment combination.

The response rates seen in this study are comparable to those demonstrated in other taxane + bevacizumab metastatic breast cancer combination studies. The optimal schedule — yielding best efficacy and lowest toxicity — of nab-paclitaxel in combination with bevacizumab has yet to be determined. In view of the demonstrated toxicity, especially neurotoxicity, it seems reasonable to explore delivery of a modified weekly schedule of nab-paclitaxel in this patient population, e.g. 100 mg/m² to 130 mg/m² given weekly for three of four weeks in combination with bevacizumab.

In most Canadian provinces, funding for nab-paclitaxel is currently restricted to metastatic breast cancer patients who cannot tolerate paclitaxel or docetaxel therapy (mainly acute reactions to their associated solvents) or have intolerance to the corticosteroid premedication. Bevacizumab, despite the progression-free survival (PFS) advantage demonstrated in randomized Phase III trials, is not publicly funded for women with metastatic breast cancer. Given the costs associated with the administration of bevacizumab and nab-paclitaxel, it is unlikely that this treatment option will be widely available for our patients in the near future.

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Renal cancer

ADVANCED DISEASE

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TRIAL SUMMARY: Pazopanib vs placebo

This study presented at ASCO 2009 by Cora Sternberg randomized 432 patients with advanced renal cell cancer (RCC) in a 2:1 fashion to receive either the oral angiogenesis inhibitor pazopanib (800 mg once per day; n = 289) or placebo (n = 145); 202 patients had received one previous cytokine-based therapy and 233 were treatment-naive. Treatment

continued until unacceptable toxicity, disease progression or death, and placebo patients were offered the option of pazopanib treatment upon disease progression. As shown in **Table 5**, patients receiving pazopanib had significantly longer progression-free survival (PFS, the primary endpoint), both overall and in previously treated and untreated subgroups. Interim overall survival (OS) results showed a HR of 0.77 favouring pazopanib (95% CI 0.47 to 1.12; two-sided p-value = 0.02). Response rates were 30% with pazopanib vs 3% with placebo, and the median duration of response was 58.7 weeks. Adverse events were mainly Grade 1 or 2, most commonly diarrhea (52%; 4% Grade 3–4), hypertension (40%; 4% Grade 3–4), hair colour change (38%; < 1% Grade 3–4), nausea (26%; < 1% Grade 3–4), anorexia (22%; 2% Grade 3–4), and vomiting (21%; 2% Grade 3–4) in pazopanib-treated patients. 53% of patients (10% Grade 3; 2% Grade 4) had elevated liver enzyme alanine aminotransferase (ALT) elevation.

TABLE 5. Progression-free survival in advanced renal cancer patients receiving pazopanib 800 mg/day vs placebo

	pazopanib 800 mg/day (n = 289)	placebo (n = 145)	hazard ratio (HR) 95% CI p value
all patients	9.2 months	4.2 months	HR = 0.46 95% CI 0.34 to 0.62 p < 0.0000001
no prior treatment	11.1	2.8	HR = 0.40 95% CI 0.27 to 0.60 p < 0.0000001
prior treatment	7.4	4.2	HR 0.54 95% CI: 0.35 to 0.84 p < 0.001

Sternberg CN, Szczylik C, Lee E et al. A randomized, double-blind phase III study of pazopanib in treatment-naive and cytokine-pretreated patients with advanced renal cell carcinoma (RCC). ASCO 2009, Abstract 5021.

TRIAL SUMMARY: Updated prognostic factors

This study by Heng et al collected baseline characteristics of 645 patients with metastatic renal cell cancer from seven North American cancer care centres. Patients had not received prior anti-vascular endothelial growth factor (VEGF) agents, but 33% had received prior immunotherapy. During the study, patients received bevacizumab (n = 49), sorafenib (n = 200) or sunitinib (n = 396). At 25 months median followup, median OS was 22 months (95% CI 20.0 to 24.8).

Cox proportional hazards modelling showed that four of the five Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic factors (in use prior to the era of anti-VEGF therapies) continue to independently predict poor survival: hemoglobin below the lower limit of normal (p < 0.0001), corrected calcium above the upper limit of normal (p = 0.0006), Karnofsky performance status < 80% (p < 0.0001) and time

from initial diagnosis to initiation of therapy less than one year (p = 0.012); together with two other factors: neutrophil counts above the upper limit of normal (p < 0.0001) and platelet counts below the lower limit of normal (p = 0.0121). Assigning one point for each prognostic factor yielded three risk categories: favourable-risk (0 factors, n = 133) with median OS of 37.0 months, intermediate-risk (1–2 factors, n = 292) median OS 28.5 months and poor-risk (3–6 factors, n = 139) median OS 9.4 months (log rank p < 0.0001). The estimates were not affected by adjusting for prior use of immunotherapy or type of anti-VEGF agent used.

Heng DY, Xie W, Regan MM et al. Prognostic factors for overall survival (OS) in patients with metastatic renal cell carcinoma (RCC) treated with vascular endothelial growth factor (VEGF)-targeted agents: Results from a large multicenter study. ASCO 2009, Abstract 5041.

COMMENTARY: The presentation at the 2006 ASCO Annual Meeting of Phase III data demonstrating a large and significant improvement in PFS for kidney cancer patients treated with sunitinib compared to interferon was a game-changing event in kidney cancer research and management. Prior to this, there were very few effective treatments for patients with metastatic RCC and while there were tools such as the MSKCC criteria¹ to help prognosticate survival,

treatment did not impact survival much. The observation that VEGF-targeted therapy could significantly alter the natural history of this disease has resulted in two predictable outcomes: the proliferation of clinical trials assessing both “me too” therapies as well as those aimed at novel targets, and a natural tendency to reassess the variables that had previously defined our understanding of this disease and its outcomes. These two abstracts are prime examples of such outcomes.

LANDMARKS

ANOTHER ANTI-VEGF INHIBITOR FOR RCC

Pazopanib is a multi-targeted tyrosine kinase inhibitor (TKI) in the same class as sunitinib and sorafenib. Like sunitinib, pazopanib targets all three isoforms of the VEGF receptor, platelet-derived growth factor receptor (PDGFR) and c-kit, albeit with different affinities. This trial evaluating the efficacy of pazopanib in metastatic RCC was conceived and initiated prior to publication of the Phase III data for the other two TKIs, so a double-blind placebo-controlled design was appropriate. Once the efficacy of these agents had been demonstrated, the protocol was modified to allow enrollment of patients who had received no prior therapy. The patient population was well balanced for baseline variables and most patients fell into the intermediate or favourable risk groups by the MSKCC criteria.


Patients were allowed to cross over from the placebo arm after disease progression, and at this interim analysis, 48% of patients had crossed over (a number likely to increase over time). The highly statistically significant PFS benefit of five months is encouraging but is in line with that seen for similar agents. Indeed, the 11-month PFS seen for treatment-naïve patients is exactly what was observed in sunitinib's landmark Phase III trial.² It remains to be seen,

therefore, whether pazopanib represents a step forward in the management of RCC or is simply another agent in a rapidly expanding repertoire of TKIs. The COMPARZ study (NCT00720941), presently ongoing in many centres around the world including in Canada, will help answer this question, randomizing 876 patients to receive either pazopanib or sunitinib as first-line treatment.

UPDATING PROGNOSIS

The second presentation addressed two other important questions: Are the prognostic factors from the pre-targeted therapy era still valid? And, have newer therapies resulted in improved OS — as crossover designs have mostly confounded the ability of the registration trials to address this? The group led by Dr. Heng reviewed 645 consecutive patients treated with VEGF-targeted therapy (sunitinib, sorafenib or bevacizumab) in seven centres across North America — a major undertaking. Most other such analyses to date have been retrospective reviews of clinical trial patients or single-institution studies. Six prognostic factors were identified, of which four are in common with the MSKCC factors. Once verified externally, they will be used to assign patients into risk categories in clinical decision-making and research.

This work also allows for an indirect assessment of the impact of VEGF targeted therapy on the course of this disease. While direct comparison between prognostic groups in the eras of targeted therapies vs immunotherapy¹ is not valid, the observed median survivals of 37 vs. 29.6 months in the good-prognosis group, 27 vs. 13.8 months in the intermediate group, and 8.8 vs. 4.9 months in the poor-prognosis group probably do represent a true benefit of VEGF-targeted therapies. Because of the many lines of therapies now available, future RCC trials will likely depend on PFS or other surrogate endpoints.

We now have an embarrassment of riches in treatments available for RCC, and ongoing trials of TKIs, VEGF-targeted agents, mTOR inhibitors and other targeted therapies. The current need to identify which treatments are truly the best, and how to sequence them in our patient population, is a welcome challenge for most genitourinary oncologists. 

References

1. Motzer RJ, Bacik J, Murphy BA et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol* 2002;20(1):289-96.
2. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *NEJM* 2007;356(2):115-24.

Disclosure

Drs. Bultz, Fitch and Kennecke report no potential conflicts of interest relevant to this article. Dr. Dent reports being on advisory boards of Abraxis and Roche. Dr. Eigl reports receiving research funding from Pfizer.

Erratum

In *Oncology Exchange* Vol. 8, No. 3 an error appeared on page 21 in the last line of "In Brief": "HER2-positive" should be "HER2-negative". The online version at www.oncologyex.com has been corrected. *Oncology Exchange* apologizes for the error.

IN BRIEF

Already known

- Previous research has shown that anti-vascular endothelial growth factor (VEGF) agents prolong progression-free survival (PFS) in patients with metastatic renal cell cancer (RCC).
- Five Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic factors have been used to predict survival in these patients, but had not been tested specifically in patients receiving anti-VEGF therapies.

What these trials showed

- Interim results of a Phase III double-blind study of pazopanib vs placebo (initiated before the era of anti-VEGF agents in RCC) in patients with advanced RCC showed superior response rates, PFS and a trend to longer overall survival (with placebo patients allowed to cross over to pazopanib upon disease progression) for those receiving pazopanib, with acceptable toxicity.
- Another study identified six prognostic factors (including four of the MSKCC factors) for survival in RCC patients receiving anti-VEGF agents (sunitinib, sorafenib or bevacizumab) for the first time.

Next steps

- It is not known whether pazopanib provides superior PFS than sunitinib and/or sorafenib; a trial is underway comparing pazopanib to sunitinib.
- Once verified in other data, Heng et al's six prognostic factors will be useful for selecting patients most likely to benefit from anti-VEGF therapies.