

# Highlights from the 40th Annual Meeting of the American Society of Clinical Oncology

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Commentaries by:

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## Genitourinary Cancers

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“It’s a great day to be a GU oncologist” summed up the progress made over the last few years in the treatment and management of urologic malignancies. This statement by Bruce Roth, MD, of Vanderbilt University, concluded his review of the 2 large phase III studies of docetaxel (Taxotere, Aventis)-based therapy in hormone-refractory prostate cancer (HRPC) that were presented in the plenary session at this year’s annual meeting of the American Society of Clinical Oncology (ASCO). TAX 327 and Southwest Oncology Group (SWOG) trial 99-16 were randomized clinical trials in men with progressive metastatic HRPC.<sup>1,2</sup> TAX 327 enrolled 1,006 patients to 1 of 3 treatment arms, either docetaxel 75 mg/m<sup>2</sup> plus prednisone dosed every 3 weeks, docetaxel 30 mg/m<sup>2</sup> plus prednisone dosed weekly for 5 out of 6 weeks, or mitoxantrone (Novantrone, OSI) 12 mg/m<sup>2</sup> plus prednisone dosed every 3 weeks. SWOG 99-16 enrolled 770 men, of which 666 were fully evaluable, to 1 of 2 treatment arms, either docetaxel 60 mg/m<sup>2</sup> on day 2 and estramustine (Emcyt, Pfizer) 280 mg orally 3 times per day for days 1–5 of each 3-week cycle or mitoxantrone 12 mg/m<sup>2</sup> plus prednisone dosed every 3 weeks. Both studies demonstrated a survival benefit for docetaxel-based therapies over mitoxantrone and prednisone combination. In TAX 327, the every 3-week schedule of docetaxel/prednisone demonstrated a 2.4-month improvement in survival (18.9 months vs 16.5 months), or a 24% reduction in risk of death (hazard ratio [HR]=0.76, *P*=.009), as well as a significantly higher prostate-specific antigen response rate (45% vs 32%, *P*<.0005) and significantly higher reduction in pain (35% vs 22%, *P*=.01).

In SWOG 99-16, docetaxel/estramustine demonstrated a 2-month improvement in survival (18 months vs 16 months), or a 20% reduction in risk of death (HR=0.80, *P*=.01), a 3-month greater progression-free survival (6 months vs 3 months, HR=0.73, *P*<.0001), as well as a significantly higher prostate-specific antigen (PSA) response rate (50% vs 27%, *P*=.0001).

In both studies, higher rates of toxicity were seen with docetaxel-based therapies, yet there was no difference in toxic death rates or rates of study discontinuation. Based on the TAX 327 data and the large volume of data of docetaxel in HRPC, the US Food

and Drug Administration (FDA) granted approval to docetaxel in combination with prednisone for use in metastatic HRPC.

Also presented at this year’s ASCO meeting were the results of a large phase III randomized clinical trial of atrasentan and a pooled meta-analysis of the randomized clinical trials with atrasentan (Abbott) in metastatic HRPC.<sup>3</sup> Atrasentan is a potent, selective inhibitor of the endothelin A receptor. The clinical and biological effects of atrasentan on patients with asymptomatic metastatic HRPC have been studied in 2 large, randomized, placebo-controlled studies with time to progression as the primary endpoint. In total, 1,097 men have been randomized and treated, with 288 men participating in M96-594, and 809 men participating in the phase III study M00-211. Both studies demonstrated essentially the same result: atrasentan delays time to progression, but in the intent-to-treat analysis of both studies, the time to progression endpoint did not reach statistical significance. A pooled intent-to-treat meta-analysis, which included all 1,097 randomized patients, was performed. In the meta-analysis, the atrasentan-treated and placebo-treated groups showed no significant heterogeneity. Both studies included the same patient population and the same endpoint. The meta-analysis was conducted to more precisely estimate the treatment effect of atrasentan and to increase the power to detect a modest but potentially clinically meaningful effect. Results of the meta-analysis indicate that atrasentan significantly delays disease progression in this patient population. The log-rank statistical analysis shows a *P* value of .013, with an HR of 1.19, an approximately 20% reduction in the risk of disease progression while taking atrasentan. At the 3-month time point and beyond, the probability of patients receiving atrasentan not progressing was 25–35% greater than for those receiving placebo. Atrasentan significantly decreased both the incidence of bone pain and the time to the first onset of bone pain compared to placebo. Atrasentan-treated patients remained pain-free for a median of over 7 months, 97 days longer than placebo. Atrasentan was well tolerated, with primarily grade 1/2 rhinitis, peripheral edema, and mild headache as the most common adverse events. Abbott Laboratories announced that it will file a new drug application for atrasentan with the FDA later in 2004.

In the area of renal cell cancer (RCC) management, an Integrated Symposium summarized a number of new clinically active compounds that are in recently initiated phase III clinical trials. SU011248 (Pfizer), a multi-targeted tyrosine kinase inhibitor, demonstrated a 24% partial response rate and a

46% stable disease rate in metastatic RCC.<sup>4</sup> Data on BAY 43-0096 (Bayer), a multi-targeted tyrosine kinase inhibitor, was updated and again confirmed a 25% response rate and 15% stable disease rate in metastatic RCC.<sup>5</sup> The phase II study combination of erlotinib (Tarceva, OSI) and bevacizumab (Avastin, Genentech) was also presented, demonstrating a 40% response rate and 47% stable disease rate in metastatic RCC.<sup>6</sup> Follow-up data on CCI-779 (Wyeth), a mammalian target of rapamycin (mTOR) inhibitor, in combination with interferon- $\alpha$  for metastatic RCC demonstrated a 13% partial response rate with over 71% of patients having stable disease.<sup>7</sup> These response rates, including patients with stable disease, are clearly encouraging. Differences across the studies in terms of defining response or stable disease was quite variable, clearly supporting the need for well-conducted phase III trials of each of these agents.

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## Colorectal Cancer

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### Adjuvant Therapy of Colon Cancer

In Abstract 3500, Saltz et al<sup>1</sup> updated the results of the Cancer and Leukemia Group B (CALGB) intergroup trial C89803, which randomized patients to the bolus, weekly schedule of irinotecan (Camptosar, Pfizer), 5-fluorouracil

(5-FU)/leucovorin (LV) (IFL) versus the Roswell Park schedule of 5-FU/LV in patients with stage III colon cancer. IFL chemotherapy was associated with a significantly higher incidence of neutropenia, neutropenic fever, and death when compared to the control arm. Moreover, there was no clinical benefit observed with IFL in terms of disease-free survival or median survival. The conclusion from this study was that the bolus, weekly IFL regimen cannot be recommended for use in the adjuvant therapy of stage III colon cancer. Our European colleagues have investigated the use of infusional IFL in patients with high-risk stage II and stage III colon cancer and previously reported at the 2003 ASCO meeting that infusional IFL is relatively safe to administer. The clinical efficacy data have not yet matured but are expected to be presented at the 2005 ASCO meeting.

The results of the X-ACT study were presented by Cassidy et al<sup>2</sup> in Abstract 3509. In this study, patients with resected Duke's stage C colon cancer were randomized to receive oral capecitabine (Xeloda, Roche) (1,250 mg/m<sup>2</sup> twice daily on days 1–14 every 3 weeks) or to the standard Mayo Clinic regimen of 5-FU/LV. Both treatments were administered for a total of 6 months. A total of 1,987 patients were entered onto the study and the primary endpoint was to show at least equivalence in disease-free survival (DFS). There was a strong trend toward superior DFS for capecitabine versus 5-FU/LV (HR=0.87,  $P=.0528$ ) and a trend to superiority for overall survival (HR=0.84,  $P=.07$ ). Relapse-free survival was significantly superior for capecitabine when compared to 5-FU/LV (HR=0.86,  $P=.04$ ). Of note, the safety profile was significantly in favor of the capecitabine arm with a marked reduction in myelosuppression, neutropenic fever, mucositis, diarrhea, nausea/vomiting, and alopecia. This study showed that capecitabine is as effective as bolus 5-FU/LV and that this oral fluoropyrimidine should now be considered a reasonable treatment option for the adjuvant treatment of stage C colon cancer. However, this option needs to be weighed against recent data suggesting that oxaliplatin (Eloxatin, Sanofi-Synthelabo) plus 5-FU/LV (FOLFOX4) may be the standard approach for most of these patients.<sup>3</sup>

It is important to note that the National Surgical Adjuvant Breast and Bowel Project trial C-06 demonstrated comparable efficacy of UFT (tegafur plus uracil) to intravenous 5-FU (Abstract 3508).<sup>4</sup> However, UFT is not available in the United States at the current time.

### Chemotherapy of Metastatic CRC

At the 2004 ASCO meeting, deGramont and colleagues<sup>5</sup> updated the results of the phase III OPTIMOX study, which randomized patients with advanced CRC to receive either oxaliplatin plus 5-FU/LV (FOLFOX4) or FOLFOX7/LV5FU2. FOLFOX7 is a modification of FOLFOX4 where bolus 5-FU on days 1 and 2 is deleted and a 46-hour infusion is administered. In addition, a higher dose of oxaliplatin (130 mg/m<sup>2</sup> vs 85 mg/m<sup>2</sup> in FOLFOX4) is given. FOLFOX7 was associated with a reduced incidence of grade 3/4 neutropenia

(21.5% vs 31.7%) but did result in a greater thrombocytopenia (10.3% vs 2.7%). There was no difference in the overall development of peripheral neuropathy between FOLFOX4 and FOLFOX7. Moreover, oxaliplatin reintroduction did not increase the incidence of neurotoxicity in patients treated on the FOLFOX7/LV5FU2 arm. With respect to clinical efficacy, the response rate (58.8% vs 59.5%), time to tumor progression (9.2 months vs 9.0 months), time to disease control (9.9 months vs 11.3 months), and overall survival (20.7 months vs 21.4 months) were virtually identical between the 2 arms. The conclusion from this study was that FOLFOX7 has similar toxicity and clinical efficacy when compared to FOLFOX4 but is a much more convenient regimen to administer. As a result, FOLFOX7 should be considered a new treatment option in patients with metastatic CRC.

Equally important to the practice of oncology is the consideration of studies that would be characterized as “negative.” The CALGB study 89803 (Abstract 3503) presented by Miller and colleagues explored the concept that IFL chemotherapy would be superior to 5-FU/LV alone in stage III colon cancer patients.<sup>6</sup> When the study was designed, many practitioners had already adjusted their approach to these patients based on the evident superiority of IFL in patients with advanced disease.<sup>7</sup> However, the results of this study were negative. Not only did stage III colon cancer patients receiving IFL experience more toxicity and a greater risk of early death than patients receiving 5-FU/LV, there was no discernible difference in survival between the 2 arms.<sup>6</sup> This study underscores the need for prospective clinical trials, since the obvious is not always true.

### Epidermal Growth Factor Receptor (EGFR) Inhibitors and Other Antibody Therapy

Lenz and colleagues<sup>8</sup> reported the results of a large (n=347) phase II study of single-agent cetuximab (Erbix, ImClone/Bristol-Myers Squibb) in heavily pretreated patients who had previously failed both irinotecan and oxaliplatin (Abstract 3510). In this trial, the partial response rate of 12% and median overall survival of 6.7 months paralleled that previously reported in studies of irinotecan-refractory patients. Cetuximab monotherapy was well tolerated with fatigue/malaise being the most common grade 3/4 adverse event.

A similar phase II study was conducted by Hecht et al<sup>9</sup> (Abstract 3511) using the completely human immunoglobulin G2 monoclonal antibody panitumumab (Abgenix). A total of 148 patients were enrolled onto this trial, and panitumumab was administered at a dose of 2.5 mg/kg/week. The partial response rate was 10.1% and, as has been observed with cetuximab therapy, there did not appear to be a correlation between panitumumab clinical activity and EGFR expression. This therapy was well tolerated with the main grade 3/4 adverse event being fatigue. Acneiform skin rash was commonly observed in >90% of patients treated, but only 3.4% of patients experienced grade 3 toxicity.

Given the consistent clinical activity of these EGFR monoclonal antibodies in the refractory disease setting, there has been a significant interest in integrating EGFR inhibitors in standard combination regimens at earlier stages in their treatment course. At ASCO 2004, Taberero et al<sup>10</sup> reported on the preliminary results of a phase II study of cetuximab in combination with FOLFOX4 in Abstract 3512. A total of 43 patients with EGFR-expressing tumors were evaluable for response. The objective response rate, including 2 complete responses and 32 partial responses, was 81%, and the total disease control rate was 98%. This regimen which has been termed ERFLOX, has an acceptable profile. Except for grade 3/4 acneiform rash usually observed with cetuximab, there was no increase in the incidence of grade 3/4 adverse events generally associated with FOLFOX4. These results suggest a potential synergy between the FOLFOX regimen and cetuximab, and a randomized phase III trial is presently investigating the ERFLOX regimen versus FOLFOX in the second-line setting for patients with metastatic CRC.

Fisher et al<sup>11</sup> reported on a phase II trial in Abstract 3514 evaluating gefitinib in combination with FOLFOX4, in either the first-line setting of metastatic disease or in patients who had received prior therapy. The partial response rate to gefitinib/FOLFOX4 (IFOX) was 78% among 30 patients who had not had prior therapy for metastatic disease. In previously treated patients, the partial response rate was 36%. The median time to tumor progression was 9.3 months, and median OS had not been reached. Of some concern, however, is that patients experienced a significant degree of grade 3/4 toxicity in the form of myelosuppression (53%), diarrhea (49%), and nausea/vomiting (28%/21%) which is higher than what has previously been reported for FOLFOX4.

Monoclonal antibody 17-1A (GlaxoSmithKline) failed to meet expectations. In Abstract 3522, the CALGB reported no survival benefit in patients with stage II colon cancer treated with the antibody compared with patients who were observed.<sup>12</sup> While the preponderance of recent data suggested that this result might be expected, it is sobering to recall the original reports of this therapy, in which it appeared that this agent conferred the same benefit to these patients as combination therapy.

Finally, the limitations of one of the highlights of the 2003 ASCO meeting—bevacizumab—became apparent. Based on the interest generated by the advanced colon cancer presentation last year, and later published,<sup>14</sup> wide access to bevacizumab was arranged through an NCI-sponsored mechanism. This year, Chen et al reported the results of this expanded access experience (Abstract 3515).<sup>15</sup> According to their findings, the objective response rate in previously treated patients was 1%. While the results of this “study,” which included a very heterogeneous group of heavily pretreated patients, do not preclude the possible benefits of bevacizumab in similar populations, this report reminds us of the need to explore treatments widely before applying them in different settings.

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## Lung Cancer

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Two North American phase III, prospective, randomized adjuvant chemotherapy trials in patients with completely resected early stage non-small-cell lung cancer (NSCLC) were presented at the 2004 ASCO meeting. Both of these trials

showed statistically significant and clinically important prolongation of survival for patients receiving adjuvant chemotherapy versus those receiving no therapy.

Abstract 7018, an intergroup trial spearheaded by the National Cancer Institute of Canada, randomized 482 patients between 1994 and 2001 to the third-generation chemotherapy regimen vinorelbine (Navelbine, Glaxo-SmithKline)/cisplatin for 4 cycles (vinorelbine 25 mg/m<sup>2</sup> weekly for 16 weeks and cisplatin 50 mg/m<sup>2</sup> day 1 and 8 every 4 weeks for 4 courses) or to observation follow-up alone. Patients with completely resected stage IB or II (T<sub>2</sub>N<sub>1</sub>, T<sub>1</sub>N<sub>1</sub>) were included. Overall survival was significantly prolonged for the chemotherapy regimen (94 months vs 73 months; HR=0.69, P=.011) with a 5-year survival of 69% compared to 54% for patients on the control arm receiving no adjuvant chemotherapy.<sup>1</sup>

Abstract 7019, a CALGB study, was also presented and included only patients with completely resected stage IB NSCLC. They were randomly allocated to paclitaxel 200 mg/m<sup>2</sup> and carboplatin (AUC=6) every 3 weeks for 4 cycles versus observation follow-up alone. Three hundred forty-four patients entered between September 1996 and November 2003. Overall survival at 4 years was 71% in the chemotherapy group and 59% in the observation group. There were 34 deaths in the control group and 19 deaths in the chemotherapy group (HR=0.51; P=.018). This trial and the study described above show very similar improvements in overall survival compared to no further therapy after resection.<sup>2</sup> Both regimens were well tolerated.

These studies alone would be enough to change the standard of care, but there is little doubt when these data are combined with 2 previously reported studies from an International group and Japan also showing statistically significant and clinically important survival benefits for patients with completely resected stages IB-IIIa NSCLC.<sup>3,4</sup> The most compelling reason for the improved survival seen in the 2 North American studies is the enhanced effectiveness of the third-generation chemotherapy regimens compared to older second-generation cisplatin regimens. These studies are extremely important. As a result, patients with completely resected stage IB-IIIa NSCLC, who are otherwise relatively healthy, can now anticipate improved survival from post-operative chemotherapy, similar in many ways to the large groups of patients now routinely treated with breast and CRC in the adjuvant setting. All of us anxiously await refinements in adjuvant therapy or comparisons with neoadjuvant therapy, which will be forthcoming in the years ahead.

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## Lymphoma

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Several interesting abstracts concerning lymphoma were presented as oral and poster presentations at ASCO 2004. Abstract 6500 was a randomized trial of first-line treatment for patients  $\leq 60$  years of age with low-risk diffuse large B-cell non-Hodgkin lymphoma (DLBCL) with a CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone)-like regimen with or without the anti-CD20 antibody, rituximab (Rituxan, Genentech).<sup>1</sup> The results demonstrated that younger patients can benefit from rituximab added to chemotherapy just as older patients can. Michael Pfreundschuh, MD, the lead author of the study from the Mab Thera International Trial (MInT), reported on the large phase III clinical trial that was conducted in 18 countries. The study was halted early (December 2003) because it reached its prespecified primary efficacy endpoint early, which was improvement in time to treatment failure (TTF). Higher remission rates, reduced progression rates, prolonged TTF, and increased survival rates were also seen with no additional toxicity by the addition of rituximab. This is the first randomized phase III trial showing better outcomes for young, low-risk DLBCL patients using a CHOP-like regimen plus rituximab versus a CHOP-like

**Table 1.** E1496: CVP ± Rituximab Maintenance in Indolent Non-Hodgkin Lymphoma

	Maintenance (n=157)	Observation (n=148)
Age >60	43	36
Median age	56	58
Follicular histology, %	77	79
Stage IV, %	77	74
High tumor burden, %	62	68

CVP=cyclophosphamide, vincristine, and prednisone.

regimen alone. Eligibility criteria included untreated, low-risk DLBCL with an International Prognostic Index of 0, 1, stage II-IV or bulky I, and age 18–60. Patients in the 2 groups were fairly evenly matched for median age, histologic characteristics, bulky disease, B-symptoms, and extranodal involvement. There were 163 patients in the chemotherapy group (chemo) and 161 patients in the rituximab-chemotherapy group (R-chemo). The rate of complete response (CR)/CR-unconfirmed was 66% versus 85% ( $P=.0003$ ) in the chemo versus R-chemo group and with a median follow-up of 24 months. The TTF was 63% versus 84% ( $P<.000005$ ) in the chemo versus R-chemo group. It was this  $P$  value that reached critical value for early termination of the trial. The overall survival (OS) was 85% versus 95% ( $P=.0026$ ) in the chemotherapy versus the R-chemotherapy group. There was no significant difference in the grade 3/4 toxicity. The authors concluded that the addition of rituximab to a CHOP-like regimen significantly improves

**Table 2.** E1496: CVP ± Rituximab Maintenance in Indolent NHL: Response Data

	Maintenance (n=128)	Observation (n=119)	
CR after CVP, n (%)	22 (14)	24 (16)	$P=0.77$
PR after CVP, n (%)	101 (64)	95 (64)	
After second randomization, "further response"	28 (22)	9 (8)	$P=.002$
Final CR, %	30	22	
Final PR, %	51	58	
At median follow-up of 1.7 yr			$(P=.00003^*)$ $(HR=0.5^*)$ $P=.06$
PFS, yr	4.2	1.5	
2-year PFS, %	73%	43%	
2-year OS, %	96%	89%	

\* Reached early stopping endpoint. Study stopped November 2003.

CVP=cyclophosphamide, vincristine, and prednisone; NHL=non-Hodgkin lymphoma; CR=complete response; PR=partial response; PFS=progression-free survival; HR=hazard ratio; OS=overall survival.

**Table 3.** E1496: CVP ± Rituximab Maintenance in Indolent NHL: Benefit of Rituximab Maintenance

Parameter	Result
High tumor burden (n=198)	4.2 yr vs 1.4 yr, $P=.0001$
Minimal residual disease (n=171)	Median not reached vs 1.9 yr, $P=.0001$
Follicular histology (n=238)	Median not reached vs 1.5 yr, $P=.0002$
PFS	Not reached vs 1.5 yr
2-yr OS	96% vs 86%, $P=.02$
Death rate	No difference between arms

CVP=cyclophosphamide, vincristine, and prednisone; NHL=non-Hodgkin lymphoma; PFS=progression-free survival; OS=overall survival.

TTF in young patients with low-risk, untreated DLBCL and the CR rates and OS are also significantly longer in patients receiving rituximab.

In Abstract 6501, the effect of the addition of rituximab to front-line therapy with CHOP on the remission rate and TTF compared to CHOP alone in mantle cell lymphoma (MCL), was presented by the German Low Grade Lymphoma Study Group (GLGLSG).<sup>2</sup> One hundred twenty-two patients with untreated stage III/IV MCL were randomized to CHOP (n=60) or R-CHOP (n=62) × 6–8 cycles to a CR or partial response (PR). In the R-CHOP and CHOP arms, respectively, there was a higher rate of CR (34% vs 7%,  $P=.00024$ ), and overall response rate (CR plus PR) of 94% versus 75% ( $P=.005$ ). The TTF was significantly longer in R-CHOP ( $P=.0131$ ). Grades 3/4 granulocytopenia was more frequent after R-CHOP than with CHOP (63% vs 53%,  $P=.01$ ) but the rate of infection was similar in both arms. The senior author, Dr. Hiddemann, concluded that R-CHOP induces responses in almost all MCL patients (94%) and that R-CHOP increases TTF when compared with CHOP alone in untreated MCL (2 years vs 14 months).

Dr. Hochster presented the results of Eastern Cooperative Oncology Group trial E1496, a phase III trial of cyclophosphamide, vincristine and prednisone (CVP) with or without maintenance rituximab in advanced indolent non-Hodgkin lymphoma (NHL).<sup>3</sup> This study demonstrated that the use of rituximab maintenance therapy after induction chemotherapy with CVP significantly prolonged progression-free survival for patients with advanced indolent NHL. The study initially began in 1998 with a randomization between CVP versus cyclophosphamide plus fludarabine (CF) with a secondary randomization to maintenance therapy with rituximab

every 6 months for 4 weeks at a dose of 375 mg/m<sup>2</sup> for 2 years or no additional therapy. The CF arm was closed early because of excessive toxicity. Three hundred twenty-two patients were randomized to receive rituximab maintenance or no therapy and 303 patients were evaluable. Patients were stratified by histology, tumor burden, gender, B-symptoms, and marrow involvement. The majority of the patients had follicular histology, stage IV disease, and high tumor burden.

The authors conclude that maintenance rituximab is well tolerated with no increase in grade 3 or 4 toxicities and that maintenance improves response rate following CVP induction. It was found that maintenance rituximab prolongs median PFS by 2.7 year after CVP induction and that the greatest benefit from maintenance rituximab in PFS is seen in high tumor burden, follicular histology, and minimal residual disease. The study results are shown in Tables 2 and 3.

**References**

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