

# IMPRESSIONS FROM ASCO

Commentaries on Selected Abstracts Presented at the  
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## Lung Cancer

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Perhaps the most interesting abstract was that presented by Dr. Alan Sandler (Late-Breaking Abstract 4), reporting on a phase III trial (Eastern Cooperative Oncology Group [ECOG] trial E4599) of paclitaxel and carboplatin with or without bevacizumab in patients with advanced non–small-cell lung cancer (NSCLC). This study is the first to demonstrate that treatment with a targeted agent and concurrent chemotherapy increased the survival of patients with NSCLC compared to chemotherapy alone.

In this study, the overall response rate, median survival, and time to progression were all higher in the bevacizumab-containing arm ( $n=434$ ) compared with the chemotherapy-alone arm ( $n=444$ ). The overall response rate was 31.2% versus 10%, respectively ( $P<.001$ ). The median survival was 12.5 versus 10.2 months, which was also statistically significant, and the time to progression was 6.4 versus 4.5 months. The 1-year survival rate was 51.9% versus 43.7%, and the 2-year survival was 22.1% versus 16.9%. The usual 2-year survival rate among NSCLC patients is approximately 10–15%, so the finding in E4599 is very noteworthy.

Also of interest in this study was the finding that the overall survival benefit in the bevacizumab arm was more dramatic among men than women, a difference that was statistically significant. Toxicity was what might be expected with an antiangiogenesis agent: grade 3/4 hemorrhage was 5.0% in the bevacizumab-containing arm, compared with 0.9% for chemotherapy alone. There were 2 treatment-related deaths on the chemotherapy-alone arm, versus 9 on the bevacizumab arm.

The caveats to these positive findings include the fact that the study included only non–squamous cell histology. Patients with hemoptysis or brain metastases

were excluded. Also, bevacizumab was given at a higher dose—15 mg/kg/day every 3 weeks plus paclitaxel and carboplatin—than that used in the treatment of colorectal cancer. Although chemotherapy was given for 6 cycles, bevacizumab was continued until disease progression.

As Dr. Sandler noted, the experimental arm in this study will likely become the reference arm for future studies, and the findings provide oncologists who treat lung cancer patients with a therapeutic approach that may be more effective than chemotherapy alone.

The big question now is whether the US Food and Drug Administration (FDA) will limit the indication of bevacizumab for lung cancer to patients with adenocarcinoma, and whether the indication will be in combination with paclitaxel and carboplatin, as was used in E4599, or with all chemotherapeutic regimens. In colorectal cancer, bevacizumab appears to be effective in combination with several regimens, and the same might apply in the setting of lung cancer, except for the combination of gemcitabine/carboplatin, which has platelet count depression as one of its major toxicities.

Another important study was reported by Hanna et al on irinotecan plus cisplatin (IP) versus etoposide plus cisplatin (EP) for small-cell lung cancer (SCLC; abstract 7004). Previously, a Japanese study showed that IP was associated with improved overall survival versus EP, the standard treatment for extensive-stage SCLC. Using a modified regimen of IP versus EP, the current phase III trial was designed to confirm these results. Overall survival was not statistically significantly different between the 2 arms (9.3 months for IP vs 10.2 months for EP). The time to progression was 4.1 months for IP and 4.6 months for EP, and the 1- and 2-year survival rates were 35.4% and 8.0% versus 36.7% and 7.7% for IP and EP, respectively. Incidences of neutropenia, thrombocytopenia, and anemia were higher with the EP arm, and the incidence of diarrhea was higher with the IP arm (all statistically significant).

The results of another trial, this time using the same doses as were used in the Japanese study, are pending. It is hoped that those results will answer the question of which regimen is better. However, it may be that ethnic variation means that the Japanese findings cannot be fully extrapolated to US patients, and vice versa.

Gumerlock et al reported an important study (Abstract 7008) that evaluated a mutational analysis of K-RAS and epidermal growth factor receptor (EGFR) mutations for markers of resistance to EGFR inhibitor therapy among bronchio-alveolar carcinoma (BAC) patients enrolled in the Southwest Oncology Group trial S0126 and treated with gefitinib. Several abstracts looking at mutational analyses found that patients with an EGFR mutation were more likely to respond to a tyrosine kinase inhibitor. Gumerlock et al evaluated pretreatment tumor tissue from 66 of 137 patients in S0126. K-RAS was mutated 19 of 64 patients (all 12th codone point mutations). EGFR mutations were found in 12 of 64 patients (19%), and 4 patients (6%) had both K-RAS and EGFR mutations. The noteworthy finding of this study was that of the 19 patients with the K-RAS mutation, only 6% responded to treatment. Among the 12 EGFR-positive patients, 33% responded. Finally, among the 4 patients positive for both EGFR and K-RAS, none responded to treatment.

In this BAC cohort, K-RAS mutations were associated with smoking, and among patients with an EGFR mutation the absence of a K-RAS mutation was associated with response to gefitinib. Both of these findings were statistically significant. Thus, this study demonstrates that both mutations must be considered when trying to determine whether a patient might respond to gefitinib. Studies such as these are advancing our understanding about whether the factors involved in mutational analysis play a role in therapeutic response.

Blumenschein et al presented the findings of the SPIRIT-II study, a phase III trial evaluating paclitaxel plus carboplatin with or without bexarotene in patients with NSCLC (Late-Breaking Abstract 7001). This study found no difference between the 2 arms, save for an increase in hypertriglyceridemia in the bexarotene-containing arm. A subset analysis showed that patients with elevated triglycerides at the grade III/IV level experienced an improved median survival compared to those with normal triglycerides. A similar study evaluated vinorelbine plus cisplatin with or without bexarotene, with very similar results.

ANITA, a phase III study of adjuvant vinorelbine/cisplatin versus observation in completely resected stage I–III NSCLC confirmed the effectiveness of adjuvant therapy in stages II and III, but showed no benefit for stage IB patients, conflicting with some studies presented last year (Abstract 7013).

Finally, several studies evaluated the treatment of elderly patients. According to the findings, patients with good performance status, even if over the age of 70, tend to respond to therapy, while patients with poorer performance status, regardless of age, do not do as well. Thus performance status appears to be more important than age when considering whether a patient can tolerate therapy.

## Drug Development

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There were some very encouraging studies presented at this year's ASCO meeting. In particular, the studies evaluating adjuvant trastuzumab in breast cancer (Abstract 556) and lenalidomide in myelodysplastic syndrome (Abstract 5) were very impressive. In addition, studies in renal cell carcinoma (Abstracts 4540 and 4542) were also encouraging.

However, a notable aspect of this year's ASCO meeting was that many of the phase III clinical trials presented were either negative, or positive but cost-ineffective. One of the questions this raises is: when does cost outweigh the positive benefit of a treatment? As an example, the data on bevacizumab in the treatment of metastatic NSCLC showed this agent to be effective in prolonging survival, obviously an important and promising finding. However, the median survival increase was 2 months, prompting questions of whether the potential benefit balances the expense of the agent.

It may be that at some point the investigative community will need to decide whether or not to pursue trials examining regimens that, if beneficial, would be cost-ineffective. A drug such as imatinib is very cost-effective—significantly less than the standard of \$50,000 per quality-adjusted life-year. However, many other novel agents are much more expensive. One of the challenges is that there are so many different parties involved with this issue, from payers to drug developers to oncologists. It may be that in the future drug reimbursement will need to be regulated by the Centers for Medicare and Medicaid Services, which could set a limit on how much a drug would be reimbursed based on its benefit. The increasing number of effective but costly drugs raises the concern that as their use increases the healthcare system could become depleted.

Alongside this concern is the question of how studies are interpreted. In general, oncologists are trained not to think about cost—a reasonable approach considering the seriousness of malignant diseases. A small benefit is often considered a new standard of care even though the agent may be prohibitively expensive. Many studies presented at ASCO 2005 seem to indicate that it may be time for the oncology community to reapproach these difficult issues.

## Hematologic Malignancies

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Dr. Alan List presented a study evaluating lenalidomide in myelodysplastic syndrome (Abstract 5), which was an update of a paper published by Dr. List in the *New England Journal of Medicine*. This update included a larger number of patients and still showed an impressive response rate with regard to transfusion requirements in patients with interstitial deletion of chromosome 5q31 treated with lenalidomide. Some toxicity was observed, notably neutropenia and thrombocytopenia. The study findings are very encouraging.

Abstract 6515 was an update of the Spanish study using all-*trans*-retinoic acid and anthracyclines in the treatment of acute promyelocytic leukemia. The results were extraordinarily positive: the 5-year overall survival rate was 85% and the disease-free survival rate is 88%. This study is a good indication of how far the treatment of acute promyelocytic leukemia has come.

Abstracts 6519 and 6520 were particularly interesting. These studies evaluated a new SRC/ABL kinase inhibitor in patients with chronic myeloid leukemia, one study evaluating chronic phase and the other accelerated and blast phase. The agent, BMS-354825, appears to be active in imatinib-resistant patients. Among imatinib-resistant and -intolerant chronic-phase patients (n=36) treated with BMS-354825, the complete hematologic response rate was 86%, and almost half of these responses showed cytogenetic improvement, with a major cytogenetic response occurring in 31% of patients. The results were not quite as dramatic among accelerated- (n=8) and blast-phase (n=18) patients, but were still impressive. The hematologic response rate was 75% in accelerated-phase patients, and 76% among blast-phase patients. In addition, 2 out of 2 patients with Philadelphia chromosome-positive acute lymphoblastic leukemia responded to treatment. One concern expressed about these findings is that over time, resistance to this compound may emerge, as has been the case with imatinib.

Abstract 6530 presented a Cancer and Leukemia Group B (CALGB) study of EPOCH (infusional etoposide, vincristine, doxorubicin, bolus cyclophos-

phamide, prednisone) plus rituximab (R) in diffuse large B-cell lymphoma. This regimen was initially developed at the National Cancer Institute and the current study was an attempt to reproduce the initial findings in a multicenter cooperative group setting. Among 73 patients, 68% achieved a complete response and 32% experienced a partial response (many of which would likely have been considered complete responses if positron emission tomography had been used to evaluate response). At 18 months, the progression-free survival rate was 80%, and the overall survival rate was 88%. This study has now led to an international CALGB-led study of EPOCH-R versus CHOP (cyclophosphamide, vincristine, doxorubicin, prednisone)-R, in which all patients will also undergo biopsies for tissue microarray analyses.

An internationally conducted trial led by the MAB-THERA International Trial Group (Abstract 6529) updated a previous study conducted by these investigators. Last year, data were published suggested that the CHOEP-R (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone plus rituximab) regimen was superior to CHOP-R, the standard chemotherapy regimen for non-Hodgkin lymphoma. However, Abstract 6529 presented an analysis of patients who received CHOEP-R versus CHOP-R, and found no difference between the 2 arms. The investigators conclude that CHOP should continue to be the standard chemotherapy regimen to which rituximab is added because toxicity was more severe in the CHOEP arm.

A small but very interesting study evaluated imatinib in the treatment of polycythemia rubra vera (Abstract 6517). Among 16 patients there were 5 complete remissions with imatinib 400 mg/day. Since there are no good therapies available for polycythemia rubra vera, this study may provide a new direction for future research.

Finally, although not a hematologic malignancy-related study, long-term follow-up data on oblimersen sodium in patients with advanced malignant melanoma were also of interest (Abstract 7506). These data confirm that oblimersen sodium enhances the activity of chemotherapy and results in a durable remission in some patients, and with a survival advantage in a subset of patients. The patients will continue to be followed, but these findings are very encouraging. This agent was not approved by the FDA at its initial application because the study had initially failed to meet its primary endpoint of survival, although all secondary endpoints were met. Now, a predetermined subset of patients has experienced a survival advantage and, with longer follow-up, the study may meet its primary endpoint.

# Colorectal and Other Gastrointestinal Cancers

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One of the most intriguing studies in colorectal cancer was that presented by Giantonio et al of the ECOG E3200 trial (Abstract 2). The study showed that bevacizumab was beneficial when given with an oxaliplatin-based chemotherapy program in patients with colorectal cancer refractory to irinotecan-based therapy. The findings complemented the data from Hurwitz et al presented 2 years ago demonstrating the efficacy of bevacizumab in combination with irinotecan, 5-fluorouracil (5-FU) and leucovorin (LV), the regimen commonly known as IFL. Thus, ECOG E3200 was a proof-of-principle that chemotherapy and antiangiogenic therapy work well together, and that the benefit is a result of clinical synergy between these agents, rather than due to a specific drug effect. Initially, patients were randomized to 3 arms: FOLFOX (5-FU, LV, oxaliplatin) alone, FOLFOX plus bevacizumab, and bevacizumab alone. However, accrual to the bevacizumab-alone arm was stopped early because these patients were not faring as well. Based on these findings, it can be concluded that bevacizumab needs to be combined with chemotherapy in order to obtain optimal benefit, and it can be combined with a number of different regimens.

More sobering were the results of the randomized CONFIRM-1 study presented by Hecht and colleagues (Abstract 3) of FOLFOX plus or minus PTK787, which did not meet its prespecified primary endpoint. It is important to note that this endpoint was quite stringent: radiologist-confirmed progression-free survival (PFS). While the presentation noted that a related analysis based on investigator assessment of PFS revealed substantial activity, this notion of claiming significant results despite the lack of significance in the primary comparison did not appear to garner much support from the oncologists in the audience.

Having said that, PTK787 did show some activity. There was some suggestion that once-daily dosing is not the ideal way to administer this agent. It appears that with further investigation of how best to use this agent, PTK787 may have a role in the management of colorectal cancer in the future.

The data from the PETACC-3 trial were somewhat disappointing (Late-Breaking Abstract 8). In this study, 5-FU/LV was compared with 5-FU/LV plus irinotecan, given in a FOLFIRI-like regimen in patients with stage III colon cancer (there were some stage II patients enrolled, but this analysis was confined to stage III patients). According to the findings, the irinotecan-containing arm was not superior to the 5-FU/LV-alone arm. The data confirm those from the study by Saltz et al presented in 2004, and were consistent with the French ACCORD study, in which patients at high risk of recurrence due to multiple positive nodes and/or perforation or obstruction of their colon were treated with either a 5-FU/LV-based regimen or irinotecan plus 5-FU/LV-based regimen, with the latter again showing no benefit.

By contrast, longer-term follow-up data from the MOSAIC trial are showing an improvement in PFS for patients randomized to the FOLFOX arm of that study. The benefit is becoming more noticeable over time. There is still no difference in overall survival, but this is likely due in part to a longer time to relapse than has been previously observed, and a prolonged survival in those patients whose disease does recur. The endpoints of time to recurrence and survival are moving out further than what we were used to in the old days of using just 5-FU/LV alone. Data from the NSABP C-07 trial of 5-FU, LV, and oxaliplatin (FLOX) versus 5-FU/LV were also presented showing a similar benefit to that noted in the MOSAIC trial (Abstract 3500). Toxicity data were not presented in detail making it hard to determine if infusion- or bolus-based 5-FU is best.

The current studies comparing the various chemotherapeutic regimens for colorectal cancer give us a fairly firm answer that, for adjuvant therapy, oxaliplatin-containing regimens provide an advantage to patients, whereas the irinotecan-containing regimens employed thus far do not. Interestingly, the evidence has led to a change in the GI Intergroup adjuvant trial in the United States, in that the irinotecan-containing arms have been eliminated.

In the advanced disease setting, there is still hope for new agents beyond those currently approved, but there were no studies this year showing startlingly good outcomes for any new agents, which was disappointing.

An important advanced-disease study presented by a Spanish group looked at a combination of FOLFOX plus cetuximab (Abstract 3535). Like the bevacizumab data, the study suggested that cetuximab benefits patients when given in combination with chemotherapy, regardless of whether it is combined with an irinotecan- or oxaliplatin-based regimen.

Finally, the data from the BOND-2 trial, in which patients who had progressed on irinotecan were random-

ized to cetuximab/bevacizumab or cetuximab/bevacizumab/irinotecan, were also intriguing (Abstract 3508). The 2 monoclonal antibodies together had a significant response rate in the mid-20th percentile range, indicating that the combination is more effective than either as a single agent, raising the possibility of double monoclonal treatment without chemotherapy as a regimen for colorectal cancer.

In the noncolorectal areas, there were a couple of interesting studies presented. In the so-called MAGIC trial, presented by David Cunningham (Abstract 4001), patients with locally advanced but resectable gastric or gastroesophageal cancer were randomized to either chemotherapy and radiation followed by surgery or surgery alone. The findings showed an advantage to the multimodality therapy, with median survivals of 24 versus 20 months, which has important implications for the gastric adjuvant study being done in the United States that is comparing the ECF regimen (epirubicin/cisplatin/5-FU) to the Macdonald regimen of 5-FU/LV in patients who have already undergone surgery. The presentation on the MAGIC trial should spark interest in evaluating this multimodality approach in the postoperative setting as well.

In pancreatic cancer, the National Cancer Institute of Canada study, presented by Malcolm Moore, of gemcitabine plus or minus erlotinib, was interesting (Abstract 1). The study showed a modest advantage in survival for patients receiving the combination. Of note is that in looking at this study's results, advantage in median overall survival is a modest 2 weeks. However, this metric may underestimate the benefit of adding erlotinib to gemcitabine because the survival curves for both treatment arms were close together at this time point.

## Prostate Cancer

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A major theme at the prostate cancer sessions this year was prostate-specific antigen (PSA) as a surrogate tumor marker. A number of presentations by several groups evaluated the role of PSA in monitoring clinical response and outcome. Factors such as PSA velocity and absolute PSA were analyzed, as was how these factors correlate with other biologic markers.

Dr. Anthony D'Amico led a session discussing the various ways in which PSA might be used to select patients for trials and to predict outcome. Several studies were included in this session, including one evaluating docetaxel with the vitamin D analog calcitriol, which showed encouraging activity in prostate cancer (Abstract 4516).

The "take-home" message from this session was that PSA may be more informative than we thought. There are important insights to be gained from looking not only at absolute value, but also at velocity and a number of factors that can be developed into nomograms.

Historically, developing drugs for the treatment of prostate cancer has been difficult. However, there is now sufficient knowledge to create nomograms that can be used to determine in which patients cancer is likely to recur quickly, the likely location of recurrence, and other considerations, as well as patients' outcomes. Dr. D'Amico's work may set the stage for future studies.

This year's meeting was encouraging for prostate cancer, although there were no stand-out breakthroughs reported. There were no studies presented that are likely to change outcomes. Some pilot studies showed molecular activity with novel agents, but these findings are not practice-changing, at least not yet.

*Abstracts from the 2005 Annual Meeting of the American Society of Clinical Oncology  
are available on-line at [www.asco.org](http://www.asco.org).*