Breast Cancer

Presenter: Hope Rugo, MD, Clinical Professor and Director, Breast Oncology Clinical Trials Program, University of San Francisco, San Francisco, Calif.

The presence or absence of distant metastases is a more accurate predictor of overall survival than the more commonly employed disease-free survival endpoint, according to a finding from an analysis of nine key breast cancer adjuvant therapy studies by Dr. Rugo. The analysis included the following trials:

- National Surgical and Adjuvant Breast and Bowel Project (NSABP), studies B13, B14, B19, B20, and B31
- Arimidex or Tamoxifen Alone or in Combination (ATAC)
- Milan–cyclophosphamide, methotrexate, and fluorouracil (Milan–CMF)
- Breast International Group 1-98 (BIG 1-98)
- Intergroup Exemestane Study (IES)

Researchers typically rely on surrogate endpoints to assess chemotherapies, because using overall survival itself would require too many subjects and too lengthy a follow-up period. The most commonly used surrogate marker has been the disease-free interval, but Dr. Rugo claimed that it was inconsistent as a predictor; in addition, she said, it is defined in various ways.

Her analysis confirmed that distant metastases, the most common type of recurrence, were responsible for the initial peak of relapse observed two years after surgery. Metastases were also associated with the highest risk of death, compared with locoregional and contralateral events.

In the four studies (NSABP B14, ATAC, BIG 1-98, and IES) that evaluated the most commonly used adjuvant therapies—tamoxifen citrate (Nolvadex, AstraZeneca) and the aromatase inhibitors—improvements in survival without distant metastases (distant disease-free survival) seemed to correlate with later improvements in overall survival. NSABP B14, for example, showed that both distant disease-free survival at four years and overall survival at 10 years improved significantly.

The ATAC and BIG 1-98 trials were more difficult to interpret because of the short follow-up period. Women with visceral metastases fared worse than those with bone metastases. In IES, exemestane (Aromasin, Pfizer) reduced the risk of distant metastases. That reduction translated to a borderline significant overall survival advantage in women with estrogen receptor–positive or unknown primary tumors. Furthermore, in both IES and BIG 1-98, aromatase inhibitors were more effective than tamoxifen in reducing the risk of distant metastases.

“As reductions in distant metastases are likely to improve outcomes, distant disease-free survival may be a better short-term overall survival predictor,” Dr. Rugo concluded.

She added that use of that endpoint might be able to hasten the development of future adjuvant therapies for breast cancer.

Prostate Cancer

Presenter: Amado J. Zurita, MD, Assistant Professor, Division of Genitourinary Medical Oncology, MD Anderson Cancer Center, Houston, Texas

Metastatic castrate-resistant prostate cancers (i.e., those that do not respond to androgen-deprivation therapy) typically overexpress receptors for vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), two of the key cell-surface targets for sunitinib (Sutent, Pfizer). Oral sunitinib has emerged as a first-line therapy for renal cell carcinoma and as a treatment of gastrointestinal stromal cancer (GIST).

Dr. Zurita reported that adding sunitinib to docetaxel (Taxotere, Sanofi-Aventis) plus prednisone delayed disease progression and improved prostate-specific antigen (PSA) levels in some men with metastatic castrate-resistant prostate cancer in a clinical trial. The trial was planned on the basis of evidence from case reports that imatinib mesylate (Gleevec, Novartis), which targets only PDGF receptors, significantly reduced PSA levels in some patients.

The trial involved 25 men with metastatic and progressive prostate cancer despite pharmacological or surgical castration. During a six-week lead-in period, patients received sunitinib 50 mg once daily for four weeks, followed by a two-week rest. They were then randomly assigned to one of four treatment groups receiving different doses of intravenous docetaxel with sunitinib.
Meeting Highlights: ECCO and ACG

- docetaxel 60 mg/m² plus sunitinib 12.5 mg
- docetaxel 60 mg/m² plus sunitinib 37.5 mg
- docetaxel 60 mg/m² plus sunitinib 50 mg
- docetaxel 75 mg/m² plus sunitinib 37.5 mg

Docetaxel injections were given every three weeks. All of the men also took oral prednisone 5 mg twice daily.

During the lead-in period, sunitinib showed a curious tri-valent effect on PSA levels. Seven patients experienced a mean PSA decline of 40%; three among them showed a decrease greater than 50%. In contrast, 12 patients showed a steep rise of (mean) PSA of 273%, followed by a drop during the two-week rest period. Six others showed steady rises of (mean) PSA of 73% that were sustained during the rest period.

The docetaxel/sunitinib combination produced PSA reductions of greater than 50% below baseline levels in 10 of the 25 patients (i.e., in 40%). Four of the 20 patients (20%) with measurable disease at baseline had partial tumor responses, and 11 patients (55%) had stable disease. Tumors progressed in five patients during the one-year follow-up period.

Early-phase results led Dr. Zurita to administer a regimen of docetaxel 75 mg/m² plus sunitinib 37.5 mg in the ongoing phase 2 portion of the trial. At that dose, sunitinib was generally well tolerated and did not significantly add to the side-effect burden of docetaxel plus prednisone.

Which men were most likely to respond well to the combination therapy?

“Preliminary observations suggest that PSA reduction during the lead-in (sunitinib-only) phase likely predicted for later response to the combination,” Dr. Zurita said.

The predictive value of the lead-in PSA kinetics in determining later response is still to be clarified.

Renal Cancer

Presenter: Sylvie Negrier, MD, Cytokines and Cancer Research Unit, Centre Léon Bérard, Lyon, France

In a clinical trial of metastatic renal cancer, tumor responses and survival were better with sunitinib than with interferon. At the ECCO meeting, the higher cost of sunitinib was shown to be within accepted limits.

Dr. Negrier’s cost-effectiveness analysis was based on the international outcomes trial of Robert J. Motzer, MD, from Memorial Sloan-Kettering Cancer Center. In that trial, among 750 patients with metastatic renal cancer, median progression-free survival was 11 months for those receiving sunitinib and five months for those receiving interferon. Partial tumor responses were noted in 143 sunitinib-treated patients (39%) and in 29 interferon patients (8%). Within 33 months of follow-up, tumor progression was observed in 57 sunitinib patients (15%) and in 102 interferon patients (27%).

Sunitinib also produced fewer major adverse events. Side effects prompted 86 interferon patients (23%) and 59 sunitinib patients (16%) to discontinue treatment.

Projections showed that sunitinib treatment would give an advantage, compared with no treatment, of 0.92 progression-free years and of 2.09 total life-years. Interferon was anticipated to provide a progression-free survival advantage of 0.51 years and a total life-year advantage of 1.98 years. Dr. Negrier explained that the virtue of sunitinib, therefore, was in delaying inevitable progression.

In this analysis, the total discounted sunitinib cost ($224,970) was 4% higher than that of interferon ($214,436), including all ancillary treatments. Best supportive care costs were higher with interferon, whereas first-line drug costs and routine follow-up costs were higher for sunitinib, partly because of the longer-term treatment and survival.

The estimated cost per progression-free life-year gained with sunitinib was $18,611. Projecting costs and benefits over a 10-year span gave an incremental cost-effectiveness ratio for sunitinib, compared with interferon, of $67,215 per life-year gained and $32,595 per quality-adjusted life-year gained.

Dr. Negrier concluded, “This [amount] is well within the established threshold of $50,000 to $100,000 per life-year that society is willing to pay.”

Melanoma

Presenters:
- Alexander Eggermont, MD, PhD, Full Professor and Head, Department of Surgical Oncology, Erasmus University Medical Center, Rotterdam, The Netherlands
- Axel Hauschild, MD, Professor of Dermatological Oncology, University of Kiel, Germany
- Jesus Gomez-Nararro, MD, Research Assistant Professor, University of Alabama at Birmingham, Ala.

When early reports of increased mortality rates caused the premature discontinuation of the European Organisation for Research and Treatment of Cancer trial (EORTC 18961) of a postsurgical vaccine for patients with node-negative malignant melanoma, it cast a pall over the vaccine horizon, noted Dr. Eggermont. At a Pfizer-sponsored satellite symposium on cytotoxic T-lymphocyte antigen-4 (CTLA-4) agents, he described the situation for patients with advanced malignant melanoma, with three failed vaccine trials, as “quite disastrous.”

Immunology–oncology research continues, however, and the promising agents that are farthest along, stated Dr. Hauschild, are the CTLA-4 blockers, which enable greater T-cell activation. Two CTLA-4 inhibitors have emerged: Pfizer’s tremelimumab (formerly ticilimumab, or CP-675,206) and ipilimumab (Medarex/Bristol-Myers Squibb). Drs. Eggermont and Hauschild are principal investigators in trials of tremelimumab alone or in combination with other therapies.

Initial phase 1 and 2 data, reported by Dr. Gomez-Nararro, showed a marked improvement in overall survival in the tremelimumab-treated patients (17.6 months for all dose-groups combined), compared with the historical controls (seven months). Patients who did not show tumor responses have had improved survival, and some patients have had complete responses for more than two years. That result, Dr. Hauschild noted, is seldom seen with chemotherapy in melanoma trials.

The most common adverse reaction, attributed to T-cell activation, has been diarrhea (grade 1 and 2 in approximately 35% of patients) and autoimmunity colitis (severe in about 10% of patients). He commented that the gastrointestinal side effects are worth it if there is a complete tumor response. Furthermore, he suggested, there might be a correlation between clinical response and gastrointestinal symptoms.
Finally, Dr. Hauschild cautioned that although CTLA4 inhibitors look promising, because of the use of historical controls in existing research, prospective trials still need to be conducted.

**American College of Gastroenterology**

This year’s 72nd annual meeting in Philadelphia, Pennsylvania, attracted more than 4,000 attendees from October 12 to 17, 2007. In fulfilling its mission of serving the evolving needs of physicians treating gastroenterology patients, the meeting offered a wide array of clinical oral and poster sessions. Topics presented here include Crohn’s disease and ulcerative colitis.

**Crohn’s Disease with Fistula**

**Presenter:** William J. Sandborn, Head, Inflammatory Bowel Disease Research, MD, Mayo Clinic, Rochester, Minn.

Adalimumab (Humira, Abbott), a fully human monoclonal antibody that targets tumor necrosis factor (TNF), has been found efficacious for inducing and maintaining remission in patients with Crohn’s disease (CD). According to data presented at the meeting, adalimumab offers sustained responses for the 20% to 30% of patients whose course is complicated by fistulas, which often lead to the need for surgical resection.

The purpose of the CHARM study (Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance) was to determine the long-term efficacy and safety of adalimumab maintenance in fistula healing and patient responses beyond the 52-week blinded phase through a one-year, open-label extension study. In CHARM, about 800 patients with moderate to severely active CD, based on Crohn’s Disease Activity Index scores between 220 and 450, were randomly assigned to receive placebo or adalimumab 40 mg subcutaneously, either weekly or every other week. In the extension period, however, all patients received adalimumab weekly or every other week. A high percentage (about 50%) of patients received concomitant medications or had not previously responded to therapy while they were receiving an anti-TNF agent.

This analysis included 70 patients with fistulas who had received adalimumab in the blinded period. At two years, complete fistula healing was demonstrated in 60% of patients and a rate of 50% or more was shown in 71% of patients. At 12 months, the responses had been 50% (complete fistula healing) and 59% (50% or more healing), respectively.

Dr. Sandborn explained that of the patients with healed fistulas at the end of the CHARM study, more than 75% maintained healed status through the open-label extension year. Fistula responses (indicating a reduction of 50% or more) were observed in more than two-thirds of the open-label extension patients with fistulas at the baseline evaluation.

Rates of adverse events were low; serious infectious events were reported in 14.3% of the subjects.

Dr. Sandborn said, “There are rare serious events, but you have to consider them in the context of the benefits.”

Referring to a series of additional analyses presented at the ACG meeting, he noted that for patients receiving maintenance adalimumab therapy, the risk of hospitalization was reduced by about half.

He concluded, “Sustainable efficacy of adalimumab in fistula healing and response is evident after two years.”

**Ulcereative Colitis and Colectomy**

**Presenter:** Brian G. Feagan, MD, Professor of Medicine, Epidemiology, and Biostatistics, University of Western Ontario, Hamilton, Canada

In a study of ulcerative colitis, the proportion of patients needing a colectomy was significantly reduced by induction and maintenance treatment with the anti–TNF-alpha agent infliximab (Remicade, Centocor). The analysis was derived from the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2). The trials included 728 patients with active colitis and a Mayo score of 6 to 12 or moderate-to-severe colitis, with endoscopic subscores of 2 or higher.

For patients who received one or more of the following agents—corticosteroids, azathioprine, 6-mercaptopurine, or aminosalicylates—therapy failed or the patients had been unable to tolerate it. They had received infliximab 5 or 10 mg/kg or placebo at weeks zero, two, and six and every subsequent eight weeks through week 22 (in ACT 2) or through week 46 (in ACT 1). The patients were allowed to continue their conventional therapies.

The extension trial included 229 patients for whom additional treatment was considered worthwhile by their physicians. The primary endpoint was the time to colectomy during a 54-week follow-up evaluation period.

Dr. Feagan reported that among 82 patients undergoing colectomies, 28 patients had received infliximab 5 mg/kg, 18 patients had received 10 mg/kg, and 36 patients had received placebo; the colectomy rate for the combined infliximab groups was 9.5% versus 14.8% for placebo ($P = 0.035$). Compared with placebo, infliximab treatment also delayed the time to colectomy ($P = 0.015$).

In addition, the rate of hospitalizations for ulcerative colitis was reduced by 50% for the infliximab patients. Differences were significant even when the infliximab groups were evaluated separately or combined. In the group receiving the higher dose of infliximab, and for both infliximab groups combined, the number of colitis-related operations was approximately 40% lower than that for the placebo patients.

Dr. Feagan said that adverse events were generally similar in both infliximab groups and in the placebo group. There were no additional reports of tuberculosis or neurological or hematological events.

He concluded that induction and maintenance therapy with infliximab, when compared with placebo in patients with moderate-to-severe ulcerative colitis, significantly lowered the incidence of colectomy, decreased the proportion of patients with ulcerative colitis–related hospitalizations, and reduced the number of surgical procedures associated with this disease.