Exemestane Following Tamoxifen Extends Survival in Women with Breast Cancer

**Speaker:** Judith Bliss, MD, Professor of Medicine, and Director, Institute for Cancer Research, Clinical Trials and Statistics Unit, London, England

(Dr. Bliss spoke for the principal investigator, Raul C. Coombes, MD, PhD, Professor of Medical Oncology, and Head, Department of Oncology, Imperial College of London, London, England.)

A long-term analysis from a large-scale international clinical trial indicates that postmenopausal women with early breast cancer who were switched to exemestane (Aromasin, Pfizer) after two or three years of tamoxifen therapy (Nolvadex, AstraZeneca) experienced a significant improvement in survival and a marked reduction in the risk of breast cancer recurrence and metastasis compared with women who continued taking tamoxifen.

These findings were concluded from the first mature analysis of the Intergroup Exemestane Study, a randomized trial begun in 1998. The study enrolled 4,724 women from 37 countries. All of these patients had been treated for early breast cancer and had been disease-free after two to three years of tamoxifen treatment. Upon entry into the trial, the women were selected to switch to exemestane for an additional two or three years to complete five years of treatment or to continue with tamoxifen for a total of five years of treatment.

At a median follow-up of 4.8 years, an analysis was carried out in two groups of patients. An intent-to-treat (ITT) group included 122 patients with unknown estrogen receptor (ER) status; these patients were later found to be ER-negative, and the analysis was repeated to exclude the ER-negative patients. Overall, in the ITT population, there were 354 in the exemestane group and 454 in the tamoxifen group. Those using exemestane had a 24% lower risk of experiencing any first event, a 44% lower incidence of cancer in the contralateral breast, and a 17% reduction in the risk of metastasis, thus resulting in improved disease-free survival. In addition, women receiving exemestane had a 15% lower risk of dying of any cause than the women who continued using tamoxifen, thereby leading to improved overall survival.

Although there were no significant differences between the two treatment groups in terms of myocardial infarction, angina, or stroke, those continuing tamoxifen treatment tended to have more thromboembolic events (blood clots) and serious gynecologic events (uterine cancer, polyps, and vaginal bleeding). By contrast, patients receiving exemestane had a slightly higher number of bone fractures, a consequence that points to the need for bone density monitoring during exemestane therapy.

Modafinil Improves Quality of Life in Patients with Brain Tumors

**Speaker:** Thomas A. Kalita, PhD, Assistant Clinical Professor, Department of Psychiatry, David Geffen School of Medicine at University of California, Los Angeles, and Neuro-oncology Program, Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, California

Modafinil (Provigil, Cephalon), a drug used for a variety of sleep disorders, has been shown to enhance the quality of life in patients with malignant and nonmalignant cerebral tumors, improving cognitive function, mood, and fatigue levels with a low incidence of adverse drug effects (ADEs).
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Thirty patients, 21 to 65 years of age, were treated with neurosurgical resection, radiation, and/or chemotherapy. They were randomly assigned to receive modafinil 200 mg or 400 mg daily in divided doses for three weeks. This regimen was followed by a one-week washout period in which patients did not receive any drug at all. All of the patients were then entered into an eight-week, open-label extension phase during which they were given modafinil at doses determined to be optimal for each individual. The doses varied between 50 and 600 mg/day.

The researchers performed evaluations based on changes from baseline during scheduled visits at one, three, four, eight, and 12 weeks. Standardized tests were used to measure concentration, attention, fatigue, and mood evaluation and to identify specific symptoms of depression. These instruments included Parts A and B of the Trail Making Test, the Symbol Digit Modalities Test, the Verbal Fluency Test, the Hamilton Depression Scale, the Fatigue Severity Scale, the Visual Analogue Fatigue Scale, and the Modified Fatigue Impact Scale. Patients also received comprehensive neurological examinations at specific times and underwent brain magnetic resonance imaging before, during, and after the study.

In a comparison of various test scores at baseline and after eight weeks and 12 weeks of treatment, most patients showed statistically significant, as well as clinically meaningful, improvement in all tests. Test scores in cognitive abilities improved by an average of 21%; mood, by 35%; and fatigue, by 47%. The greatest improvements were observed at eight weeks.

Three patients did not respond to modafinil, possibly because of the tumor site or psychological factors.

**Cetuximab plus FOLFOX 6 Beneficial as First-Line Therapy in Metastatic Colorectal Cancer**

**Speaker:** Shaker Dakhil, MD, President, The Cancer Center of Kansas, Wichita, Kansas

Preliminary results from a phase 2 study suggest that the combination of cetuximab (Erbitux, Bristol-Myers Squibb/ImClone), an epidermal growth factor receptor (EGFR) targeting monoclonal antibody, with FOLFOX 6 (Oxaliplatin [Eloxatin, Sanofi-Aventis]), when added to simplified bi-monthly leucovorin (Leucovorin, Roxane) and a 5-fluorouracil (5-FU) regimen, was safe and effective as a first-line therapy in EGFR-positive patients with metastatic colorectal cancer.

Eighty-two patients who were 18 years of age or older with locally advanced or metastatic colorectal cancer and no prior therapy for advanced disease were treated with cetuximab 400 mg/m² as a two-hour infusion on day one and 250 mg/m² on day eight. For all subsequent cycles, the patients received a one-hour infusion.

A modified FOLFOX 6 infusion was administered, consisting of oxaliplatin 85 mg/m² given as a two-hour infusion on day one, leucovorin 400 mg/m² given as a two-hour infusion simultaneously with oxaliplatin, and a 5-FU bolus 400 mg/m² given on day one, followed by a 5-FU continuous infusion of 2,400 mg/m² over 46 hours. Cycles were repeated every 14 days.

The study’s objectives were response rate, progression-free survival, overall survival, and the overall safety profile.

Of the 82 patients, 66 were positive for EGFR expression; the median number of treatment cycles administered was 10. In the EGFR-positive group, the best outcomes were complete responses in three patients (6%), partial responses in 31 patients (57%), and stable disease in 16 patients (30%), for an overall response rate of 63%.

At the time of this report, 74 of the 82 patients (90%) were no longer in the study: five patients died during the study; 19 patients discontinued therapy because of toxicity; 34 patients discontinued therapy for disease progression; and four patients completed therapy.

**Vorinostat Shows Promise in Advanced Colorectal Cancer**

**Speaker:** Marwan Fakih, MD, Assistant Professor, Department of Medicine, University at Buffalo School of Medicine and Biomedical Sciences, and Staff Physician, Roswell Park Cancer Institute, Buffalo, New York

Vorinostat (Zolina, Merck), a novel histone deacetylase inhibitor, may have a role in the treatment of highly refractory advanced colorectal cancer.

In a phase 1 study, a group of patients with metastatic colorectal cancer received vorinostat twice daily orally at investigational dose levels of 100 mg, 200 mg, and 300 mg. None of these patients had responded to a previous combination of irinotecan (Camptosar, Pharmacia & Upjohn), cetuximab (Erbitux), FOLFOX (5-FU) leucovorin (Leucovorin), or oxaliplatin (Eloxatin).

Vorinostat was given three days prior to FOLFOX and was administered for one week, followed by a one-week break. FOLFOX was administered at a fixed dose every two weeks, and leucovorin 400 mg/m² and oxaliplatin 85 mg/m² were given over two hours. This regimen was followed by a bolus of 5-FU 400 mg/m² and a 50-FU infusion of 2,400 mg/m² over 46 hours.

The primary endpoint of the study was to determine the recommended dose of this combination of vorinostat and FOLFOX.

In the eight patients evaluable for safety, no dose-limiting toxicities were noted and no grade 3 toxicities were reported in the early cycles of treatment. Of the six patients evaluable for efficacy, four patients (one patient receiving vorinostat 100 mg and three patients receiving vorinostat 200 mg) experienced disease stabilization at more than five months and at two months, respectively. Two other patients receiving vorinostat 100 mg with biopsies showing liver metastases experienced a major decrease in thymidylate synthetase expression, the main target of 5-FU, after four days of vorinostat therapy.

**Sunitinib Superior to Interferon-α in Metastatic Kidney Cancer**

**Speaker:** Robert J. Motzer, MD, Attending Physician, Memorial-Sloan Kettering Cancer Center, New York, New York

Sunitinib maleate (Sutent, Pfizer), an oral tyrosine kinase inhibitor that targets a number of kinase enzymes (including vascular endothelial growth factor receptor [VEGFR]), demonstrated a statistically significant improvement in progression-
free survival and objective response rate when compared with interferon-α (Roferon, Roche) as first-line therapy in patients with metastatic renal cell cancer (MRCC).

Although the standard treatment for kidney cancer is either interferon-α or interleukin-2 (Proleukin, Chiron), both of which are immune therapies, the two treatment approaches are associated with a low response rate. On the basis of two recent phase 2 trials of sunitinib monotherapy, the Food and Drug Administration (FDA) approved the drug as a second-line treatment for advanced renal cell cancer, the most common type of kidney cancer.

With these findings in mind, a phase 3, international, randomized trial was conducted to compare sunitinib and interferon-α as a first-line systemic therapy for patients with MRCC. A total of 750 patients with advanced clear-cell MRCC and no previous chemotherapy were randomly assigned to receive either sunitinib 50 mg orally once daily for four weeks, followed by two weeks off, in six-week cycles, or interferon-α, given as a subcutaneous injection of 99 million international units (MU) three times weekly in six-week cycles.

The primary endpoint of the trial was progression-free survival. Secondary endpoints included objective response rate, overall survival, and ADEs. Median progression-free survival, as assessed by a third-party independent review, was 47.3 weeks with sunitinib and 24.9 weeks with interferon-α. The objective response rate was 35.7% with sunitinib and 8.8% with interferon-α.

The study was conducted from August 2004 to October 2005. As of June 2006, 632 patients (85%) were alive; 49 sunitinib patients (13%) and 65 patients in the interferon-α arm died (17.3%).

**HPV Vaccine Shows Benefits in Preventing Vaginal and Vulvar Cancers**

**Speaker:** Jorma Paavonen, MD, Professor and Chief Physician, Department of Obstetrics and Gynecology, University of Helsinki, Helsinki, Finland

Quadrivalent human papillomavirus (HPV) L1 virus-like particle (VLP) vaccine (Gardasil, Merck & Co.) prevented types HPV 16-related and HPV 18-related vaginal and vulvar high-grade precancerous lesions for at least two years after immunization. These findings support the prophylactic efficacy of the vaccine in preventing HPV 16-related and HPV 18-related vaginal and vulvar cancers.

Initially, the vaccine had been developed to target four strains of HPV: HPV 16 and 18 are linked to cervical cancer, and HPV 6 and 11 cause anogenital warts. For at least two years after immunization, the vaccine was 100% effective in preventing HPV 16-related and 18-related VIN grade 2 or 3.

The vaccine was 100% effective in preventing HPV related or 18-related VIN grade 2 or 3 or VaIN grade 2 or 3. No viral infections were observed for the women who had received at least one or more doses of HPV vaccine. Overall, protection with the HPV vaccine was 100%.

**High-Risk Cytogenetic Abnormalities Respond to Alemtuzumab in Patients with B-Cell Chronic Lymphocytic Leukemia**

**Presenter:** Anna Dmoszynska, MD, Professor, Department of Hematology, Medical University of Lublin, Lublin, Poland

A cytogenetic profile of the patients participating in a large-scale clinical trial comparing alemtuzumab (Campath, Berlex/Genzyme) with chlorambucil (Leukeran, GlaxoSmithKline) in previously untreated patients with progressive B-cell chronic lymphocytic leukemia (B-CLL) demonstrated statistically superior overall response rates and complete response rates to alemtuzumab in patients with certain poor prognostic cytogenetic abnormalities compared with patients treated with chlorambucil. This drug looks promising as a novel, more effective therapeutic option for patients with poor-risk B-CLL.

A total of 297 patients with previously untreated Rai stage I-V B-CLL were enrolled in a phase 3, open-label, randomized comparative trial. The patients were assigned to receive standard dosing regimens of alemtuzumab (n = 149) or chlorambucil (n = 148). Patients received intravenous (IV) alemtuzumab 30 mg three times weekly for a maximum of 12 weeks or oral chlorambucil 40 mg/m² once every 28 days for a maximum of 12 cycles.

As part of the overall study, a cytogenetic assessment was conducted before the start of the protocol-specified therapy. Chromosome aberrations were detected by fluorescence in situ hybridization (FISH) via specific DNA probes, including deletions (del) 6q21, 6q telomere, 11q 22-23, 13q 14-14.3, and 17p13, as well as trisomy bands of 8q24 and 12p11.1-q11.1. Statistically significant higher overall and complete response rates to alemtuzumab were observed in patients with a 13q...
Dasatinib Active in Patients with Resistant Chronic Myelogenous Leukemia

**Speaker:** Zeev Estoy, MD, Professor, Leukemia and Experimental Therapeutics, Leukemia/Bioimmunotherapy Center, University of Texas M.D. Anderson Cancer Center, Houston, Texas

Dasatinib (Sprycel, Bristol-Myers Squibb), a novel, oral dual Src-Abl kinase inhibitor, shows activity in patients with Philadelphia chromosome–positive chronic myelogenous leukemia (Ph + CML) whose condition is resistant to two Novartis therapies: imatinib (Gleevec) and the investigational agent AMN 107. Dasatinib proved to be 300-fold more potent than imatinib (the standard second-line treatment for refractory CML) and 20-fold more potent than AMN 107 (a potent oral tyrosine kinase inhibitor).

A study was conducted to report the experience with dasatinib in patients after treatment failure with AMN 107. Initially, all patients in the ongoing dasatinib studies at the M.D. Anderson Cancer Center were reviewed for previous therapy and their responses to AMN 107 and outcomes with imatinib. Sixteen patients with Ph + CML, all of whom had shown previous hematological resistance to imatinib, followed by treatment failure with AMN 107, received dasatinib 70 mg orally twice daily (10 patients), 140 mg orally in a single daily dose (five patients), or 120 mg orally twice daily (one patient).

In this group of patients, the CML phase was classified as “chronic” in two patients, “accelerated” in six patients, and “blastic” in six patients; a second, or repeated, CML phase was classified as “chronic/accelerated” in two patients. The median follow-up period for dasatinib was three months (range, from less than one month to nine months).

Responses were reported in five of seven patients with Abl mutations, including four of four patients with loop mutations and one of two patients with other mutations. Two patients with Abl mutations in gene T3151 had resistant disease.

For more information on Sprycel, see this month’s Pharmaceutical Approval Update: Oncology column on page 542.

**90Ibritumomab Tiuxetan plus High-Dose Chemotherapy Before Stem-Cell Transplantation Improves Outcomes in Non-Hodgkin’s Lymphoma**

**Speaker:** Avichai Shimoni, MD, Specialist in Internal Medicine, Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel Hashomer, Israel

**90Yttrium ibritumomab tiuxetan (90Y IT)** (Zevalin, Schering/Biogen Idec), when combined with high-dose chemotherapy in a conditioning regimen given before autologous stem-cell transplantation (SCT), may reduce the risk of relapse following the procedure and may improve the poor outcome of patients with refractory non-Hodgkin’s lymphoma (NHL) who undergo SCT with standard conditioning regimens.

Although high-dose chemotherapy and autologous SCT have an established therapeutic role in patients with a first chemosensitive relapse of aggressive NHL, autologous SCT has only limited success when administered in a refractory or progressive stage of the disease in heavily pretreated individuals or in patients who experienced multiple relapses.

Twenty patients with refractory NHL and active lymphoma, as shown on positron emission tomography and computed tomography (PET and CT) scans, were given a conditioning regimen of rituximab (Rituxan, Biogen Idec/Genentech). The patients then received 90Y IT 0.4 mCi/kg, which was administered on “day minus 14” prior to SCT (the 14th day before the procedure). A high-dose chemotherapy regimen of BEAM—carmustine (BiCNU), etoposide (Etoposide, Mylan), cytarabine (DepoCyt, Enzon), and melphalan (Alkeran, Celgene)—was started on “day minus 6.” Autologous SCT was performed on day zero (0).

Of the 20 patients enrolled in the study, 18 were evaluable for their responses. Of these 18 individuals, 10 achieved complete responses and eight had partial responses. Four of these eight patients later had complete responses with additional external irradiation to residual disease. Five patients relapsed after SCT, with a one-year cumulative incidence of relapse of 26%. This is a relatively low relapse rate in patients with refractory disease.

With a median follow-up period of 12 months, 13 patients were alive and seven died, and the estimated one-year overall survival rate was 59%. The projected one-year progression-free survival rate was 53%. This compared with an expected progression-free survival rate of less than 20% with standard transplantation in this high-risk population.

Concerning toxicity, no early infusion reactions occurred. Two patients died of multi-organ toxicities early after transplantation and before engraftment. The treatment-related non-relapse mortality at day 100, therefore, was 10%. Such rates of non-relapse mortality are expected in heavily pre-treated patients with refractory NHL. No additional toxicity was related to 90Y IT.