First-Line Combination Chemotherapy for Metastatic Breast Cancer (Docetaxel, Carboplatin, and Trastuzumab)

Speaker: Adam M. Brufsky, MD, PhD, Assistant Professor of Medicine, and Director of the Magee Breast Cancer Program, University of Pittsburgh Medical Center Cancer Centers, Pittsburgh, Pennsylvania.

The combination of docetaxel (Taxotere®, Aventis), carboplatin (Paraplatin®, Bristol-Myers Squibb), and trastuzumab (Herceptin®, Genentech) has been shown to be an extremely effective first-line treatment for Her2Neu-positive metastatic breast cancer.

Forty previously untreated women with metastatic breast cancer, 138 with Her2neu-positive disease, were enrolled into a phase II study. Carboplatin (area under the curve [AUC] = 5), docetaxel 75 mg/m², and trastuzumab 4 mg/kg on day one and then 2 mg/kg weekly were administered on day one every three weeks for up to nine cycles. Responses were evaluated after three and six cycles.

The overall response rate was 82%, with 14 patients (37%) having complete responses and 17 patients (45%) having partial responses. Five patients (14%) had stable disease after chemotherapy, and three of these women maintained stable disease for more than six months. Seventeen patients with complete responses, partial responses, or stable disease are still being observed without disease progression; four in the group have remained without progression for more than 30 months. The one-year overall survival rate in the total group was 93%.

EGFR-TK Inhibitor for Bronchoalveolar Cell Carcinoma (Erlotinib)

Speaker: Vincent A. Miller, MD, Oncologist, Memorial Sloan-Kettering Cancer Center, New York, New York.

The investigational drug erlotinib (Tarceva™, Genentech), an epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor, has shown promising activity in the treatment of bronchoalveolar cell carcinoma (BAC), a form of non-small cell lung cancer (NSCLC) that is usually resistant to chemotherapy.

Because anecdotal reports of the activity of erlotinib offered dramatic results in patients with BAC, a phase II trial was carried out to better define the activity of this novel agent. Initially, 64 patients with previous clinical pathology reports of BAC underwent diagnostic studies and BAC or a variant was confirmed in 42.

In 30 patients with BAC who had received erlotinib for one month or more, eight responded to the drug. All of these patients achieved partial responses, for a major objective response rate of 27%. Of the patients who responded to the drug, five had never smoked and two had smoked less than 10 pack-years. (A pack-year is defined as one pack of cigarettes a day for one year.) In contrast, only three cancers of 22 current smokers responded to treatment. These findings strongly suggest that tobacco-related genetic changes may predispose patients to resistance to erlotinib and emphasize the need for doctors to obtain detailed smoking histories of their patients.

Triple Chemotherapeutic Combo for Advanced Pancreatic Cancer (Folfirinox)

Speaker: Thierry Conroy, MD, Professor of Oncology, Nancy University, and Centre Alexis Vautrin, Vandoeuvre-Les Nancy, France.

A triple combination of 5-fluorouracil (5-FU)/leucovorin (LV), irinotecan (Camptosar®, Pharmacia), and oxaliplatin (Eloxatin™, Sanofi-Synthelabo), known as folfirinox, helps to provide outstanding long-term survival, a good safety profile, and promising response rates when administered as first-line therapy in patients with advanced pancreatic adenocarcinoma.

A total of 47 chemotherapy-naïve patients with histologically confirmed, unresectable, advanced pancreatic adenocarcinoma were enrolled into a multicenter, phase II clinical study. Of these, 46 patients received treatment with folfirinox: oxaliplatin 85 mg/m² on day one, plus irinotecan 180 mg/m²
on day one, plus LV 400 mg/m² on day one, followed by 5-FU 400 mg/m² in a bolus on day one and 2,400 mg/m² as a 46-hour continuous infusion biweekly. Quality of life was assessed before each course of treatment.

Overall, 297 cycles of folfirinox were administered, with a median of six cycles per patient. Forty-four patients were evaluable for therapeutic safety, with no deaths attributable to toxicity. Tolerance was excellent, with full doses given in 88% of the cycles. Neutropenia was common; 32% of patients had grade 3 and 12% had grade 4. Two patients had febrile neutropenia. Other relevant toxic effects included nausea and vomiting, diarrhea, and neuropathy, all grade 3 neutropenia or lower but none of them dose-limiting.

All 46 patients were evaluable for efficacy, with an overall objective response rate of 28%, including two complete responses and 10 partial responses. Another 10 patients had stable disease.

The median duration of response in responders was 10 months; the duration in patients with stable disease was nine months. In 33 patients with metastatic disease, the median overall survival was 9.5 months; in the 13 patients with locally advanced disease, the median overall survival has not yet been reached. In terms of quality of life, all scales improved, when measured at the end of treatment, except diarrhea.

**Anti-EGFR Monoclonal Antibody for Metastatic Colorectal Cancer (Cetuximab plus Irinotecan)**

**Speaker:** David Cunningham, MD, Professor of Medicine and Head of the Gastrointestinal and Lymphoma Units, Royal Marden Hospital, London and Surrey, United Kingdom.

The BOND (Bowel Oncology with Cetuximab Antibody) study demonstrates that cetuximab (Erbitux™, Merck KGaA/ImClone), an investigational immunoglobulin G (IgG1) monoclonal antibody that targets the epidermal growth factor receptor (EGFR), results in tumor growth inhibition and, when used in combination with irinotecan (Camptosar®, Pharmacia), represents a significant advance in the treatment of metastatic colorectal cancer, significantly slowing progression of the disease and shrinking tumors by 50% or more in almost 25% of the patients treated.

The BOND study, designed to compare cetuximab alone as monotherapy and in combination with irinotecan, enrolled 329 patients with metastatic colorectal cancer from 57 sites across 11 European countries.

In the combination-therapy arm, 218 patients received cetuximab 400 mg/m² at the first infusion, followed by 250 mg/m² weekly plus irinotecan at the same dose (125, 180, or 350 mg/m²) and schedule at which each patient stopped responding to irinotecan.

In the monotherapy arm, patients received cetuximab 400 mg/m² at the first infusion, followed by 250 mg/m² weekly, with the option to switch to combination therapy if monotherapy failed. The patients were randomly assigned in a 2:1 fashion.

The primary endpoint was the confirmed objective response rate of the cetuximab–irinotecan combination and of cetuximab monotherapy. Secondary endpoints included the time to disease progression, the overall survival time, and the safety and toxicity of both monotherapy and combination therapy.

When given alone, cetuximab showed an overall response rate of 11%; when given in combination with irinotecan, a statistically significant improvement was observed, with an overall response rate of 23%.

The disease control rate, encompassing complete responses, partial responses, and stabilization of disease, was 32.4% for cetuximab monotherapy and 55.5% for the combination therapy. The time to disease progression was 4.1 months with cetuximab plus irinotecan and 1.5 months with cetuximab alone, a significant benefit in favor of combination therapy. Overall survival was 8.6 months for patients taking combination therapy and 6.9 months for patients taking cetuximab monotherapy.

**Pox-Based Vaccine for Refractory Cancers**

**Speaker:** John Marshall, MD, Director of Developmental Therapeutics, and Associate Professor of Medicine at Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC.

A unique pox-based cancer vaccine (TRICOM, Therion Biologics), enhanced by molecules that activate the immune system, is safe and generates an antitumor response in patients with advanced cancer. The TRICOM vaccine consists of an anchor viral component, either fowlpox or vaccinia, that initiates an immune response against cancer cells expressing carcinoembryonic antigen (CEA). This response is enhanced by the addition of three co-stimulatory molecules designed to create an optimal immune response to the CEA-expressing cancer cells while leaving healthy cells alone.

In a phase I study, the TRICOM vaccine was evaluated in 58 patients with advanced CEA-expressing tumors. Most patients had heavily pre-treated colon tumors. Patients were divided into three therapy groups:

- fowlpox TRICOM, followed by monthly booster shots of the same vaccine
- vaccinia TRICOM, followed by monthly booster shots of fowlpox TRICOM
- vaccinia TRICOM, followed by monthly booster shots of fowlpox TRICOM plus granulocyte-macrophage colony-stimulating factor (GM-CSF), which acts as an additional immune system booster

The vaccines were administered intradermally and subcutaneously every month for six doses and then every three months.

One patient had a pathologic complete response; at the end of the study, the tumors of 25 patients were stable for more than four months. Another five patients showed decreased serum CEA levels, a positive indicator of effective immune response. Of the 25 patients treated for more than four months, seven received treatment for more than 12 months. Significant CEA-specific T-cell responses were observed in all patients tested, with a 2.5-fold to 7.3-fold increase in patients receiving GM-CSF.

Adverse effects mirrored those seen with other vaccine-related responses, including mild fever, skin reactions, and
lymph node swelling. On the basis of these findings, a phase II trial is under way in patients with colon and pancreatic cancers.

Novel Raf Kinase Inhibitor for Metastatic Melanoma (BAY 43-9006)

Speaker: Keith T. Flaherty, MD, Instructor of Medicine at the Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

A new investigational Raf kinase inhibitor, BAY 43-9006 (Bayer/Onyx), acts by blocking a key enzyme that triggers cell growth. Administered orally, together with paclitaxel (Taxol®, Bristol-Myers Squibb) and carboplatin (Paraplatin®, Bristol-Myers Squibb), the drug appears to produce promising anticancer activity in patients with metastatic melanoma.

Twenty patients with metastatic melanoma were enrolled in the first part of a phase I study designed to determine a safe dosage of the Raf kinase inhibitor for use in future studies. The patients were given BAY 43-9006 twice daily, in varying doses of 100, 200, or 400 mg from day two to day 19 of a 21-day cycle along with carboplatin (AUC = 6) and paclitaxel 225 mg/m², both administered on day one of the 21-day cycle.

The primary endpoints were safety and the maximum tolerated dose of BAY 43-9006 administered in combination with paclitaxel and carboplatin.

The safety profile of the combination therapy was determined to be favorable with minimal and reversible side effects, such as rash and diarrhea. To date, there have been no dose-limiting toxicities up to the high dose (400 mg) tested. Seven of 10 evaluable patients showed benefit, three with unconfirmed partial responses and four with stable disease lasting up to 10 months.

Bcl-2 Blocker for Aggressive Non-Hodgkin’s Lymphoma (Oblimerson Sodium)

Speaker: John Leonard, MD, Assistant Professor of Medicine at Weill Medical College of Cornell University and New York Presbyterian Medical Center, New York, New York.

Oblimerson sodium (Genasense™, Genta), a novel investigational anticancer agent that inhibits Bcl-2 production, a protein responsible for multidrug resistance in lymphoma, delays progression of disease in patients with relapsed or refractory mantle cell lymphoma (MCL), both alone and in combination with chemotherapy.

Thirty-seven patients with relapsed or refractory MCL or chemotherapy-naïve MCL were enrolled into a multicenter phase II trial. Both cohorts received oblimerson sodium, 3 mg/kg per day for seven days every 21 days, for up to six cycles or progression. Patients with relapsed or refractory MCL were allowed to receive six more cycles. Chemotherapy-naïve patients with progression of disease or without complete responses to six cycles of oblimerson sodium then received oblimerson sodium plus a standard regimen consisting of rituximab (Rituxan®, IDEC/Genentech), cyclophosphamide, doxorubicin, vincristine, and prednisone (known as R-CHOP), for up to six cycles. The R-CHOP regimen was given on day five of each combination cycle.

The primary endpoint was the overall response rate. Secondary endpoints were safety, complete response rate, time to progression, and survival.

To date, 25 patients have been evaluable for response to therapy and 14 of these patients are still receiving treatment. Across all treatment groups, 10 of 25 patients, or 40%, have remained stable without progression during all six treatment cycles of oblimerson sodium used alone. These include four of nine new patients (44%) and six of 16 previously treated patients (38%). Seven new patients have been switched to oblimerson sodium plus R-CHOP. In this latter group, there have been two complete responses, two partial responses, and three patients too recently enrolled to evaluate. Of the 16 previously treated patients, one patient achieved a complete response and six patients achieved stable disease with oblimerson sodium therapy alone.

Monoclonal Antibody plus Chemotherapy for Chronic Lymphocytic Leukemia (Fludarabine, Cyclophosphamide, and Rituximab)

Speaker: Michael J. Keating, MD, Professor of Medicine, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas.

Pairing chemotherapy with the monoclonal antibody rituximab (Rituxan®, IDEC/Genentech) has resulted in the most effective treatment yet for chronic lymphocytic leukemia (CLL). In the first trial to incorporate a chemoimmunotherapy protocol for CLL, 202 treatment-naïve patients received fludarabine (Fludara®, Berlex) 25 mg/m² per day for three days, cyclophosphamide (Cytoxan®, Norsar), and Endoxan® 250 mg/m² per day for three days, and rituximab 375–500 mg/m² on day one (FCR). The study has been accruing patients over a four-year period.

The use of FCR achieved a complete remission rate of 69%, the highest ever achieved for patients with CLL. The investigators also noted a nodal partial remission rate (a complete response except for residual lymphoid aggregates on bone marrow biopsy) of 18% and a partial remission rate of 14%. This approach appears to work in all age groups and in all stages of leukemia. Even patients older than 70 years of age had a response rate of more than 80%, with 40% to 45% achieving complete remissions, an uncommon finding in this age group. Although 15 responders have relapsed clinically and 13 patients have died, in almost half of the responders, the investigators found no evidence of disease, even when they used the most sensitive techniques available.

New Erythropoietic Agent for Chemotherapy-Induced Anemia (Darbepoetin alfa)

Speaker: Lee Schwartzberg, MD, Director of the West Clinic, Memphis, Tennessee.

A combined analysis of data from three studies suggests that front-loading with darbepoetin alfa (Aranesp®, Amgen) for...
four weeks, followed by maintenance dosing once every three weeks, is effective and provides an earlier and more robust response than conventional erythropoietic therapy with epoetin alfa (Procrit®, OrthoBiotech) in cancer patients with chemotherapy-induced anemia.

The authors performed the analysis to determine the consistency of hemoglobin endpoint results in multiple darbepoetin alfa front-loading studies, to compare maintenance approaches of therapy once every three weeks with once-a-week or other maintenance strategies, and to compare results of front-loading with darbepoetin alfa to standard therapy.

The three studies had similar designs: all were conducted in the U.S. and had similar eligibility criteria, identical hemoglobin thresholds for dose-withholding reductions, and comparable front-loading and maintenance regimens.

Seven hundred twenty-six patients with chemotherapy-induced anemia received either darbepoetin alfa 4.5 mcg/kg weekly for three months or front-loading darbepoetin alfa 4.5 mcg/kg weekly for four weeks, or front-loading darbepoetin alfa 4.5 mcg/kg or 325 mcg weekly, until hemoglobin levels were greater than 12 g/dl. All front-loading regimens were followed by a lower dose, a less frequent schedule of darbepoetin alfa, or both, primarily, once every three weeks. A total of 115 patients enrolled in the erythropoietin alfa control group in one of the studies.

Front-loading for four weeks with darbepoetin alfa was as effective as front-loading with 325 mcg weekly until hemoglobin concentrations were greater than 12 g/dl. Mean hemoglobin concentrations were higher with front-loaded darbepoetin alfa than with epoetin alfa. Maintenance dosing once every three weeks, either by weight dosing or by fixed dose, regardless of the front-loading regimen, was as effective in maintaining hemoglobin at target levels as 4.5 mcg/kg once weekly and standard epoetin alfa were. The time to hematopoietic response was faster in all the darbepoetin alfa front-loaded groups (median, 42 days) than in the epoetin alfa groups (median, 63 days).