MEETING HIGHLIGHTS

Chemotherapy Foundation Symposium XXVI
Innovative Cancer Therapy for Tomorrow

Marvin M. Goldenberg, PhD, RPh, MS

The mission of the 26th annual Chemotherapy Foundation Symposium, which took place in New York City from November 4 to 7, 2008, was to communicate the extensive scope and intensive coverage of emerging advances in the treatment of many neoplastic diseases. Almost 2,200 oncologists, hematologists, radiotherapists, immunologists, pharmacists, nurses, nurse-practitioners, physician assistants and other allied health care professionals, and representatives of the pharmaceutical industry attended. This article summarizes some of the important research and development in the various areas of oncology.

Voreloxin for Acute Myelogenous Leukemia
Gail J. Roboz, Cornell Medical School, New York, N.Y.

Voreloxin (formerly SNS-595, Sunesis Pharmaceuticals) is a novel first-in-class naphthyridine analogue, a subclass of quinolones not previously used in cancer treatment. It has a specific, saturable interaction with DNA, and it inhibits topo-isomerase II, resulting in replication-dependent, site-selective, double-stranded DNA damage; irreversible G2 arrest; and rapid apoptosis. Voreloxin is not a substrate for P-glycoprotein and is not p53 family member-dependent; it is thus able to evade common drug-resistance mechanisms. This may contribute to the agent’s activity observed in anthracycline-resistant patients. It also has a low potential for cytochrome P450-mediated drug–drug interactions.

Voreloxin is in phase 1 and 2 clinical trials of acute myeloid leukemia (AML) and ovarian cancer, with positive clinical responses being shown in these indications as well as in non–small-cell lung cancer (NSCLC) and small-cell lung cancer.

In a phase 1 dose-escalation study as a single agent in patients with relapsed or refractory acute leukemia, voreloxin was administered either weekly for three doses on days 1, 8, and 15 or twice weekly for four doses on days 1, 4, 8, and 11. At doses of 50 mg/m² or above weekly or at doses of 40 mg/m² twice weekly, clinical responses consisted of a reduction in bone marrow blasts or complete remission.

The maximum tolerated doses were 72 mg/m² weekly and 40 mg/m² twice weekly. The dose-limiting toxicity in both schedules was oral mucositis. Clinical responses to treatment (including complete remission, complete remission without platelet recovery, or complete remission with incomplete recovery of hematopoietic elements) were observed in patients with relapsed or refractory AML who were both older and younger than 60 years of age.

Complete remission and a reduction in bone marrow blasts to less than 5% correlated with the time above a threshold concentration of voreloxin of 1 of more for 20 hours or more per week. At the maximum tolerated dose, the weekly schedule allowed for more time above the threshold than the twice-weekly schedule allowed. Therefore, this schedule was chosen for additional development of voreloxin as a single agent. Voreloxin exhibited linear pharmacokinetics with an approximate half-life of 24 hours.

A dose-escalation study of voreloxin, in combination with continuous infusion of cytarabine liposome injection (Depo-Cyt, Enzon), is ongoing in patients with relapsed or refractory AML. Preclinical studies indicated enhanced activity of voreloxin and cytarabine in combination. Voreloxin was given via a short intravenous (IV) infusion (within 10 minutes) on the first and fourth days along with cytarabine 400 mg/m² per day by continuous IV infusion for five days. The dosing regimen was chosen to allow for adequate time above the threshold for voreloxin with cytarabine to maximize the potential for a synergistic interaction that had been observed in preclinical models.

Primary objectives were to determine the safety and pharmacokinetics of voreloxin. Secondary objectives were the preliminary assessment of anti-leukemic responses and pharmacodynamics markers. Voreloxin in doses of 10, 20, 34, 50, and 70 mg/m² was given as slow IV-pushes within 10 minutes. Complete remissions have been observed with 20, 34, and 50 mg/m², but it is too early to evaluate the 70-mg/m² dose. Thus, voreloxin pharmacokinetic parameters appear to be unaffected by cytarabine. Common adverse effects included febrile neutropenia and stomatitis.

Because voreloxin as a single agent produced clinically positive responses in older AML patients, a larger phase 2 study of newly diagnosed de novo or secondary AML in patients 60 years of age and older is in progress with the weekly schedule at a dose of 72 mg/m². The primary endpoints were clinical remission and partial clinical remission.

The author is President of Pharmaceutical and Scientific Services at Marvin M. Goldenberg, LLC, in Westfield, New Jersey. His e-mail address is marvinmgoldenberg@verizon.net.
Epigenetic Therapies for Myelodysplastic Syndromes and Leukemia: Azacitidine (Vidaza) And Decitabine (Dacogen)

Hagop M. Kantarjian, MD Anderson Cancer Center, Houston, Tex.

Epigenetic therapies modulate gene and protein expression. Global and site-specific DNA methylation induces suppression of regulatory genes, which promotes tumor progression and resistance. This mechanism is shared by many tumors, including hematological cancers. Protein or histone deacetylation also contributes to this process. Epigenetic therapy relies on two classes of agents that enhance hypomethylation or acetylation:

- hypomethylating agents:
  - azacitidine (Vidaza, Pharmion)
  - decitabine (Dacogen, MGI Pharma/SuperGen)
- histone deacetylase inhibitors:
  - valproic acid
  - depsipeptide (Romidespin, Gloucester; FK-228 [FR-901228, NSC-630176], Fujisawa)
  - vorinostat (Zolinza, Merck)
  - MGCD-0103 (Celgene)

Azacitidine. Azacitidine (AZA), an older cytotoxic drug, was synthesized in 1964 and approved by the FDA in 2004 for treating myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML).

In one European study, 358 patients with higher-risk MDS were randomly assigned to one of two groups; 179 patients received AZA and 179 received conventional or supportive care, low-dose cytarabine, or intensive chemotherapy. The study showed a significant survival benefit for AZA overall; median survival was 24.4 months versus 15 months with conventional care (P < 0.0001). The median number of AZA courses was nine. A survival benefit was noted not only in patients achieving complete responses but also in those achieving partial responses or showing hematological improvement.

In another study, different schedules of subcutaneous (SQ) AZA showed equivalent benefits in hematological responses. Schedules consisted of 50 mg/m² daily for five doses, although the five-day SQ schedule was also promising; decitabine in this low-dose schedule had significant anti-MDS activity in poorer-risk MDS patients. Adverse effects were acceptable, and timely and repeated courses of decitabine therapy were required for optimal response results. These findings were also confirmed in the Alternate Dosing for Outpatient Treatment (ADOPT) trial.

Summary. Hypomethylating agents (decitabine and AZA) might play a role in AML treatment, especially in elderly patients as well as in those receiving maintenance therapy after a complete response. An ongoing study is comparing decitabine with best standard therapy (supportive treatment with low-dose cytarabine) in older patients. Current studies include decitabine combinations with histone deacetylase inhibitors (valproic acid, vorinostat).

Decitabine. Decitabine is indicated for patients with MDS, including previously treated and untreated de novo and secondary MDS of all French–American–British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and CMML). This drug is also intended for patients in intermediate-1, intermediate-2, and high-risk MDS groups based on the International Prognostic Scoring System (IPSS).

Decitabine is thought to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation in vitro, which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are essential for controlling cellular differentiation and proliferation.

The complete response rate was highest with the five-day IV course, which also brought about the best degree of hypomethylation. The optimal dose of decitabine was 20 mg/m² IV daily for five doses, although the five-day SQ schedule was also promising; decitabine in this low-dose schedule had significant anti-MDS activity in poorer-risk MDS patients. Adverse effects were acceptable, and timely and repeated courses of decitabine therapy were required for optimal response results. These findings were also confirmed in the Alternate Dosing for Outpatient Treatment (ADOPT) trial.

Lenalidomide (Revlimid) in Relapsed or Refractory Aggressive Non-Hodgkin’s Lymphoma

Myron S. Czuczman, Roswell Park Cancer Institute, Buffalo, N.Y.

Lenalidomide (Revlimid, Celgene), a thalidomide analogue, belongs to a unique class of immunoregulatory drugs. It is approved as a single agent for transfusion-dependent patients with MDS who have a 5q-deletion (with or without additional cytogenetic injuries) and in combination with dexamethasone for patients with multiple myeloma who have received at least one prior therapy.

An earlier U.S.-based phase 2 study demonstrated activity of lenalidomide in relapsed or refractory aggressive NHL. To confirm the drug’s safety and efficacy, researchers undertook a larger international clinical trial using lenalidomide as a single agent in 200 patients. Patients received lenalidomide 25 mg orally once daily on days 1 to 21 every 28 days and continued treatment as tolerated or until disease progression.

The median patient age was 66 years (range, from 21 to 86 years), with 71% men. The median number of prior treatment regimens was three. Ninety-six percent of the patients had received rituximab (Rituxan, Genentech); 51% of NHL cases were refractory to rituximab, and 39% were refractory to the previous treatment.

The overall response rate to treatment for the first 83 patients was 24%; 5% had a complete response or an unconfirmed complete response, 19% had a partial response, and 19% had stable disease. Responses were observed for all NHL histological types treated (i.e., diffuse large B-cell lymphoma, mantle-cell lymphoma, grade 3 follicular lymphoma, and transformed NHL). It is too early to estimate a meaningful duration of...
response.

Overall, therapy was well tolerated; the most common grade 3 and 4 adverse events were hematological (i.e., cytopenia) and reversible in this heavily pretreated population. Patient compliance was excellent with the single-agent oral dosing regimen.

Dr. Czuczman concluded that salvage lenalidomide had significant activity in these patients with relapsed or refractory aggressive NHL, a poor prognostic group often having limited therapeutic options. Lenalidomide’s mechanism of action allowed significant anti-lymphoma therapy even in patients with rituximab-based combination immunochemotherapy-resistant disease. Further research is needed to establish the optimal dosing and schedule for lenalidomide alone and in combination with other active agents.

Chronic Myelogenous Leukemia: Is There Hope After Therapeutic Failure with Imatinib (Gleevec)?
• Jorge Cortes, MD Anderson Cancer Center, Houston, Tex.

Despite the success of imatinib (Gleevec, Novartis) among most patients with chronic myeloid leukemia (CML), some do not achieve the desired response, or eventually they might not respond adequately. The standard criteria that define treatment failure emphasize that it is not only important to achieve a complete cytogenetic response (cCR); the time needed to achieve such a response also determines the long-term outcome.

Patients meeting the criteria for failure have inferior outcomes. Those who are still in the chronic phase at the time of treatment failure have a median survival of five years, but survival is considerably shorter for patients with more advanced disease at the time of failure. In addition, a small percentage of patients are intolerant to imatinib, although the definition of “intolerance” has varied.

Second-generation tyrosine kinase inhibitors (TKIs) have been developed to overcome resistance and intolerance to imatinib.

Dasatinib and nilotinib. Dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis) have already been approved for use in this setting and few other agents are being developed. These drugs are significantly more potent inhibitors of Bcr-Abl kinase activity, compared with imatinib, and they retain activity in the presence of most of the common mutations identified in patients who have not responded to imatinib, one exception being the mutation T315I. All of these drugs have shown clinical activity in patients with resistance or intolerance to imatinib and have resulted in improved outcomes compared with previous treatments. However, there is significant variability in other properties, such as actual potency, the extent of other kinases inhibited, and their toxicity profile.

Dasatinib. Dasatinib is 300 times more potent than imatinib against Bcr-Abl. It is also a potent inhibitor of other kinases such as the Src family of kinases, platelet-derived growth factor receptor (PDGF-R), and c-kit. In an early study, dasatinib 70 mg twice daily showed significant activity in all stages of CML after imatinib failure, with complete cytogenetic response (CyllR) rates of 53% in the chronic phase, 33% in the accelerated phase, 27% in the myeloid blast phase and 46% in the lymphoid blast phase. The duration of response correlated with stage of the disease, with progression free-survival at 80% and 24% for those with chronic phase CML and at 46% for those with accelerated-phase CML.

Significant adverse events included myelosuppression (grade 3 and 4 neutropenia and thrombocytopenia in almost 50% each); pleural effusion; and gastrointestinal hemorrhage, particularly in advanced disease. Alternative schedules may improve the toxicity profile.

In a randomized study, dasatinib 100 mg once daily was associated with significantly less myelosuppression and pleural effusion when compared with 70 mg twice daily and with 50 mg twice daily or 140 mg once daily. The response to therapy was identical, with a trend for improved progression-free survival with 100 mg once daily. This regimen has now become standard for dasatinib in chronic-phase CML.

Nilotinib. Derived from the structure of imatinib, nilotinib has been modified to improve its binding affinity. It has increased selectivity for Bcr-Abl, with an increased potency of almost 30-fold while maintaining similar activity as imatinib against PDGF-R and c-kit. Significant activity has been documented in patients receiving imatinib after treatment failure with nilotinib 400 mg twice daily.

Toxic reactions include myelosuppression and biochemical abnormalities, such as elevated levels of bilirubin, lipase, and glucose; these have been usually transient and asymptomatic. There is also the potential for prolongation of the corrected QT (QTc) interval; however, fewer than 3% of patients have experienced significant QTc prolongation, which has frequently been asymptomatic.

Bosutinib. Bosutinib (SKI 6006) is an orally bioavailable inhibitor of Bcr-Abl and the Src kinase family, with little if any inhibitory effect over PDGF-R and kit. Phase 2 studies suggest that this is also an active compound, with major cytogenetic responses (MCyRs) reported in 41% of patients in chronic-phase CML for whom imatinib therapy failed despite a median follow-up of only three months. A potential advantage with bosutinib is the occurrence of fewer adverse events.

INNO-406. This potent Bcr-Abl inhibitor also inhibits Lyn, a member of the Src family, but not other members of this family. INNO-406 is under evaluation in an ongoing phase 1 study. Despite its very early stages of development and the fact that most patients treated with INNO-406 have not responded to imatinib or to at least one other tyrosine kinase inhibitor, responses have been observed in seven of 24 patients treated.

MK-0457. MK-0457 is a multi-kinase inhibitor with activity against Aurora, a family that plays a role in later stages of the cell cycle (from G2/M to the mitotic checkpoint and to late mitosis). Janus kinase-2 (JAK2), the most important tyrosine kinase inhibitor in erythropoietin signaling, is also involved in granulocyte–colony-stimulating factor (G-CSF), granulocyte–monocyte CSF, and interleukin-3 (IL-3). MK-0457 has activity against FLT3, a class III receptor tyrosine kinase structurally related to the receptors for PDGF, CSF-1, and the kit ligand (KL) in addition to Bcr-Abl. Early reports suggest that
MK-0457, unlike the other multi-kinase inhibitors, has activity in patients with T315I, an imatinib-resistant mutation of high importance.

Homoharringtonine. The anticancer agent Myelostat (Stragen) belongs to the plant alkaloid family of drugs. The elimination of the T315I clone and a cytogenetic response have been reported in some patients.

Summary. Studies of other inhibitors, such as PHA-739358, AP-24534, and DCC-2036, are expected to begin shortly. Each agent that was described in this section offers hope in cases of treatment failure with imatinib. The major challenges are to prevent the development of imatinib resistance and to find ways to eradicate all evidence of disease in all patients.

Trastuzumab–DM1 Conjugate for HER-2–Positive Breast Cancer

• Ian E. Krop, Dana-Farber Cancer Institute, Boston, Mass.

The introduction of trastuzumab (Herceptin, Genentech) and lapatinib (Tykerb, GlaxoSmithKline) into clinical practice has resulted in significant improvement in outcomes for women with HER-2–positive breast cancer. However, neither drug is perfect; de novo and acquired resistance to both agents remains an important clinical problem and new agents are needed to overcome therapeutic resistance.

Trastuzumab (T)-DM1 (T-DM1) is a first in its class HER-2 antibody–drug conjugate (ADC) in the development for HER-2–positive breast cancer. T-DM1 combines trastuzumab’s HER-2–blocking activity with a targeted delivery of a highly potent anti-microtubule agent (DM1) to HER-2–expressing cells. DM1 binds to tubulin competitively with vinca alkaloids but 20 to 100 times more potently than vincristine. DM1 is covalently attached to trastuzumab via a stable, non-reducible multiple-component condensation (MCC) linker molecule, which has been engineered to potentially enhance the therapeutic window of DM1 by minimizing systemic exposure to free DM1 and improving tumor exposure to T-DM1. A monoclonal antibody is linked with a cytotoxic agent to destroy tumor cells but minimize the impact on normal tissue. T-DM1 is the first antibody–drug conjugate with an MCC linker to be evaluated in clinical practice.

In a phase 1 study, T-DM1 was evaluated either weekly or every three weeks in 24 patients who had received previous therapy for metastasis. In the every-three-week cohort, the dose-limiting toxicity was grade 4 thrombocytopenia in two-thirds of patients at 4.8 mg/kg. In the weekly cohort, the dose-limiting toxicity was grade 2 or 3 thrombocytopenia, which prevented re-treatment at day 8 in two of three patients at 2.9 mg/kg.

The maximum tolerated dose was identified as 3.6 mg/kg every three weeks or 2.4 mg/kg per week. In both schedules, thrombocytopenia at the maximum tolerated dose was generally grade 1 or 2 and was reversible. Other common toxicities included transaminase elevations, fatigue, and headache, all of which were mild events of grade 1 or 2. There was no cardiac toxicity. The half-life of T-DM1 was two to four days, and concentrations of free DM1 were low (a peak concentration of below 10 ng/ml).

Overall, the initial clinical evaluation of T-DM1 has demonstrated that this agent was well tolerated at the maximum tolerated dose of 3.6 mg/kg every three weeks or at 2.4 mg/kg per week. T-DM1 is now in phase 2 studies in combination with other agents.

Oral Talactoferrin, an Immunomodulatory Agent for Non–Small-Cell Lung Cancer

• Giuseppe Giaccone, National Cancer Institute, Bethesda, Md.

Talactoferrin alfa (Agennix), an orally active immunomodulatory protein, acts at the gut and at gut-associated lymphoid tissue (GALT) through a novel mechanism of dendritic cell recruitment and activation. Following oral administration, this agent is transported by M cells into the small intestinal Peyer’s patches, where it recruits circulating immature dendritic cells to GALT and induces their maturation. Maturation of dendritic cells in the presence of tumor antigens and lymphoid effector cells induces a strong systemic innate and adaptive immune response mediated by anti-cancer natural killer (NK) cells. CD8+ lymphocytes and NK T cells result in the activation of tumor-draining lymph nodes, cellular infiltration of distant tumors, and tumor cell death.

A phase 2 double-blind, placebo-controlled study was conducted in 100 adults with locally advanced or metastatic (stage IIIB/IV) non–small-cell lung cancer (NSCLC) who had not responded to first-line platinum-based chemotherapy or second-line chemotherapy. The primary endpoint was overall survival. Talactoferrin alfa at a dose of 1.5 g twice daily or placebo was administered for up to three 14-week cycles (12 weeks on, two weeks off). All patients were included in the intent-to-treat (ITT) analysis. In another phase 2 study conducted in India, the primary endpoint was response rate in 110 chemotherapy-naïve patients with locally advanced stage IIIB or IV NSCLC.

The former trial met its primary endpoint with a 65% increase (2.4 months) in median overall survival from 3.7 months for the placebo arm to 6.1 months for the treated arm. The effect of talactoferrin alfa was also observed in prognostically relevant subsets. The six-month survival rate in the ITT population increased from 28% to 49% (P = 0.0272) with a trend toward improved progression-free survival. The treated patients experienced fewer adverse events than those receiving placebo, a difference that was statistically significant.

In another study of the previously untreated patients, talactoferrin alfa was administered for up to six six-week cycles (five weeks on, one week off) in combination with up to six three-week cycles of carboplatin/paclitaxel (C/P, or Taxol/Carbo). Patients showed improvement in response rates compared with those receiving placebo.

The addition of oral talactoferrin alfa to C/P improved response rates more than placebo plus C/P by 15% in the ITT population (27% vs. 42%, respectively) and by 18% in the evaluable patients (29% vs. 47%, respectively; P = 0.05, one-tailed test). Positive trends were observed in secondary efficacy endpoints, including progression-free survival and overall survival. Talactoferrin alfa was well tolerated, and no drug-related adverse effects were reported. Adding talactoferrin alfa to
C/P did not result in any overlapping toxicities.

Assessment of changes in circulating cytokines following the administration of talactoferrin alfa revealed a statistically significant increase in IL-8 concentrations in the single-agent studies. In the NSCLC combination study, baseline cytokine levels were similar in both groups. C/P administration was associated with a decrease in cytokine levels. Talactoferrin alfa administration resulted in a statistically significant protection from decreases in IL-8, IL-12, and GM-CSF concentrations, compared with the placebo plus C/P group.

Oral talactoferrin alfa is a promising, well-tolerated anticancer agent that significantly improved survival in patients with refractory NSCLC and improved response rates when it was added to C/P in previously untreated patients with NSCLC.

Phase 3 studies are being planned.

**Systemic ADH-1 (Exherin) and Melphalan (Alkeran) for Isolated Limb Infusion in Advanced Extremity In-transit Melanoma**

- Douglas S. Tyler, Duke University Medical School, Durham, N.C.

The use of melphalan (Alkeran, M-ILI, GlaxoSmithKline) in isolated limb infusion is a recently described and tolerated treatment for patients with in-transit melanoma (intralymphatic tumor dissemination) of the extremity. A 39% complete response rate in the cohort of treated patients was noted.

ADH-1 (Exherin, Adherex) is a cyclic pentapeptide that disrupts N-cadherin adhesion complexes. When given systemically in a preclinical model of regional melphalan therapy, tumor responses improved markedly.

A phase 1 dose-escalation study was performed to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of systemic ADH-1 with melphalan in patients with measurable in-transit melanoma of the extremity. The ADH-1 dose-escalation cohorts of three patients each received 1,000, 2,000, and 4,000 mg, administered systemically on days 1 and 8 in combination with standard-dose melphalan, corrected for ideal body weight, on day 1.

The 4,000-mg ADH-1 cohort was expanded to include a total of 10 patients. N-cadherin immunohistochemical staining and quantitative polymerase chain reaction analysis were performed on pre-treatment tumor tissue. At three months, the investigators used RECIST (response evaluation criteria in solid tumors) to define patient responses.

Sixteen patients, including six patients who had not responded to melphalan alone, were treated. No dose-limiting toxicities were observed. Common treatment-related grade 1/1 toxicities included dermatological events in 14 patients, pain in 13 patients, and nausea in five. Grade 3 toxicities included shortness of breath, hypertension, neutropenia, anemia, and elevated serum creatine phosphokinase (CPK) levels. Grade 4 toxicities included CPK elevation.

At three months, eight of the 16 patients had complete responses, two had partial responses, two had stable disease, and four had progressive disease. Pharmacokinetic analysis demonstrated increasing ADH-1 concentrations at each dose escalation and minimal variability in melphalan drug concentrations for all patients.

Systemic ADH-1 at a dose of 4,000 mg on days 1 and 8, in combination with melphalan on day 1, was well tolerated and represents a targeted therapy approach to regionally advanced melanoma. Tumor responses, especially complete responses, exceeded expectations in this group of heavily pretreated patients. Further study of this agent is warranted.

**Overcoming Immunosuppression in Head and Neck Cancer with Citoplurikin (IRX-2)**

- Jeffrey S. Moyer, IRX Study Group, IRX Therapeutics, Inc., Farmingdale, N.Y.

Significant suppression of the immune system is a consistent observation in patients with head and neck squamous cell carcinoma (HNSCC) and is associated with a poor prognosis. This finding supports the potential role for immunotherapy in this difficult-to-treat tumor type.

IRX-2 (citoplurikin) is a biologic response modifier derived from phytohemagglutinin (PHA)-stimulated mononuclear cells. It is composed of low-dose cytokines that are administered in combination with cyclophosphamide (Cytoxan, Bristol-Myers Squibb), indomethacin (Indocin, Merck), and zinc. IRX-2 stimulates and activates immature dendritic cells; increases expression of CD83, CCR7 and MHC-II markers; and protects from tumor-induced T-cell apoptosis.

A multicenter phase 2 trial was conducted to determine the feasibility, toxicity, and potential efficacy of a short-term, pre-operative IRX-2 regimen in 27 previously untreated patients with resectable, advanced HNSCC of the oral cavity (n = 15), oropharynx (n = 8), larynx (n = 3), or hypopharynx (n = 1). The Study Group assessed tumor response, cellular immune modulation, and toxicity and compared outcomes with those of 81 matched controls. Sixty percent of patients had stage IV cancer; 30% had stage III, and 10% had stage II.

The IRX-2 regimen consisted of cytoxan 300 mg/m² IV on the first day, followed by bilateral perilymphatic injections of IRX-2 (115 units of IL-2 equivalence bilateral daily for 10 doses) on days 4 and 5. Daily oral indomethacin, zinc, and omeprazole (Prilosec, AstraZeneca) were given on days 1 to 21. Planned definitive surgery was performed on or around day 22 (range, 22–47 days). The median follow-up period was 15 months.

The results showed that acute toxicity from the IRX-2 regimen was minimal (below grade 2). Serious adverse events (grade 3 and 4) occurring within 30 days of IRX-2 therapy included aspiration pneumonia in three patients, asthma in one patient, wound infection in one patient, alcohol withdrawal in one patient, and upper respiratory infection in one patient.

Objective tumor responses (less than a 12% decrease according to blinded reviews of computed tomography scans) were documented in 16% of patients. Overall, tumor size was either reduced or stable in 74% of patients. IRX-2 was associated with significant changes in tumor and lymph node lymphocytic infiltration. The estimated two-year overall survival rate was 72%, and disease-free survival was 67%.

The IRX regimen appears to be feasible and well tolerated. The findings of increased tumor lymphocyte infiltration, fibrosis, and objective tumor responses, together with excellent overall survival data, provide a rationale for initiating a pivotal phase 3 study (INSPIRE) in the fourth quarter of 2008.