A Phase 1 Safety Study of an IRX-2 Regimen in Patients With Squamous Cell Carcinoma of the Head and Neck

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Objectives: Head and neck squamous cell carcinoma (HNSCC) is associated with profound defects in cellular immunity. IRX-2, a primary cell-derived biologic containing multiple cytokines, has enhanced immune responses and induced tumor rejection in preclinical studies. This phase 1 open label study aimed to determine the clinical and laboratory safety of an IRX-2 regimen in patients with HNSCC.

Methods: Patients with HNSCC who had failed surgery and/or radiation therapy were enrolled. IRX-2 was injected subcutaneously at 115 units per dose, 2 doses/d over 10 days, starting on day 4. Patients received low-dose cyclophosphamide infusion on day 1 and took oral indomethacin and zinc daily from day 1 through day 21. Safety and laboratory assessments were undertaken throughout the treatment and 4 weeks after completion of the regimen.

Results: A total of 13 patients with advanced disease were enrolled in the safety/intent-to-treat population; all experienced treatment-emergent adverse events (AEs). The most frequent AEs were blood and lymphatic disorders, followed by gastrointestinal disorders. Most AEs were mild to moderate in severity. Three patients discontinued the study due to an AE, including 2 deaths. Two patients died after the study period due to tumor progression. No death or discontinuation was considered related to the study drugs. Antitumor responses were noted by radiographic assessment. In the 8 patients who had antitumor data at day 21, 1 patient had complete response, 5 had stable disease, and 2 had progressive disease.

Conclusions: The IRX-2 regimen was tolerated in patients with advanced HNSCC who failed surgery and/or radiation therapy. The safety and antitumor activity observed warrants further studies.

Key Words: cytokine, head and neck squamous cell carcinoma, immune response, IRX-2, phase 1

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Head and neck cancers of the oral cavity, pharynx and larynx regions are common, representing about 6% of all cancers, with an estimated 644,000 new cases and 352,000 cancer deaths worldwide each year.[1] In the United States, head and neck cancers will account for an estimated 3.3% (47,560) of all new cancers and 2% (11,260) of all cancer deaths in 2008.[2] More than 90% of head and neck cancers are of squamous cell histology.[3] Despite recent treatment advances, the overall 5-year relative survival rate has not changed much and remains at 50% to 59%.[4,5] Additionally, current tumor therapies often affect vital structures and functions of the anatomically complex region of the head and neck, and negatively impact patient quality of life (QOL).[6,7] For example, neck radiation therapy and neck dissection have been shown to be closely associated with lower head and neck symptom QOL scores.[6] Therefore, improvement of survival rate and preservation of organ function and patient QOL are important considerations in the treatment of head and neck cancer,[8] and immunotherapy provides an exciting option.

Patients with head and neck squamous cell carcinoma (HNSCC) are found to have profound immunosuppression and defects in cellular immunity that include both T cell anergy and apoptosis and dendritic cell dysfunctions.[9–12] In HNSCC patients, immunologic changes in lymph nodes have been reported to be related to survival.[13] Furthermore, systemic T cell counts are often low in HNSCC,[7,11] and are negatively associated with survival.[14] Current treatments, such as surgery, radiation therapy, and chemotherapy further exacerbate cellular immune deficiencies.[10,15] These observations make HNSCC a good candidate for immunotherapy.

IRX-2 is a primary cell-derived biologic containing multiple cytokines that has been shown in preclinical studies to enhance the body's cell-mediated immune responses. The primary active components in IRX-2 include interleukin 2 (IL-2), interleukin IL-1β, gamma interferon (γ-interferon), and tumor necrosis factor alpha (tumor necrosis factor-α).[16] Preclinical studies in immunodeficient animal models have found an increase in both $CD4^+$ and $CD8^+$ T cells following treatment with such human cytokine preparations.[17] To achieve higher efficacy of the immunotherapy, the design of the IRX-2 regimen also draws on several other findings. Low-dose cyclophosphamide has been shown to enhance cell-mediated immune response and to deplete and inhibit suppressive regulatory T cells.[10,18] The use of nonsteroidal anti-inflammatory drugs such as indomethacin has also been demonstrated to activate immune responses and increase tumor infiltration in cancer patients by reducing the immune-suppressing effect of prostaglandins.[19,20] It is well known that the trace metal zinc plays an important role in the development and function of cellular immunity.[21] Zinc deficiency, observed in 50% of HNSCC patients, is associated with increased tumor size and higher overall stage of the cancer, and negatively affects the disease-free interval.[22] Therefore, the IRX-2 regimen includes zinc, indomethacin, and low-dose cyclophosphamide, in addition to IRX-2 cytokines.

The goal of the phase 1 study was to determine the safety and antitumor responses of the IRX-2 regimen in HNSCC patients with advanced disease who have failed surgery and/or radiation therapy.

PATIENTS AND METHODS

Patients

Patients with histologic evidence of HNSCC who had failed surgery and/or radiation therapy were enrolled in the study. Eligible patients were 18 to 80 years of age, willing to adhere to the protocol, and with Karnofsky performance status $\geq$70%. Women of childbearing age had to have a negative pregnancy test, not be breast-

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feeding, and use medically acceptable contraceptive methods. Patients were excluded if they were currently under immunosuppressive therapy, used any investigational agent or had undergone surgery, radiotherapy, or chemotherapy within the previous 30 days. The exception is that patients who had been receiving weekly chemotherapy could enter 15 days after their last dose. Participants should not have had any known allergy or intolerance to 4-aminoquinolones, indomethacin, omeprazole, or nonsteroidal anti-inflammatory drugs. Patients with clinical instability, central nervous system involvement, positive assay for Hepatitis B or C or human immunodeficiency virus, or life-threatening local or metastatic diseases were also excluded. All patients gave informed consent. The study was approved by the Research Ethics Committees and the Institutional Review Boards at the University of Kentucky and the Mexico National Institute of Cancer (INCAN), and was conducted in conformity with the Declaration of Helsinki and in accordance with the United States Code of Federal Regulations.

IRX-2 Regimen and Treatment Schedule

IRX-2 was produced from healthy blood donors' leukocytes obtained from United States FDA licensed blood centers. Purified mononuclear cells were prepared and stimulated with phytohemagglutinin (PHA) to induce cytokine production. Steps were taken during manufacturing to ensure consistency, safety from bloodborne pathogens, and adherence to FDA guidelines for Good Manufacturing Practices (GMP) production of biologics under an approved United States Investigational New Drug application. Raw materials used for IRX-2 production are strictly controlled, batch records dictate each step of production, and all operations are controlled and reviewed by quality assurance personnel. Each lot of IRX-2 is tested for adherence to FDA-approved specifications: for content of IL-1β, IL-2, γ-interferon, tumor necrosis factor-α, and protein; for the absence of various viruses; and for sterility and low endotoxins. Each unit of IRX-2 contains 1 IU (approximately 48 pg) of IL-2.

In addition to the noted cytokines, IRX-2 also contains other cytokines, including IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage CSF (GM-CSF).[16]

IRX-2 was administered with 2 subcutaneous injections of 115 U each in the neck area just above and adjacent to the lymph nodes draining the head and neck. The injections were made at the insertion of the sternocleidomastoid muscle 2 cm below the mastoid tip ipsilateral to the tumor site and submandibularly in the midline.

The regimen also included a one-time low-dose infusion of cyclophosphamide (300 mg/m^2), oral indomethacin (25 mg Three Times Daily or three times a day [TID]) and zinc gluconate. In addition, although not part of the regimen, omeprazole (20 mg Every Day [QD]) was recommended as supportive care to decrease potential gastric symptoms related to the indomethacin.

The treatment lasted 21 days as diagrammed in Figure 1. On day 1, a noncytotoxic immunomodulatory dose of cyclophosphamide (300 mg/m^2) was administered intravenously. Oral indomethacin (25 mg TID) and zinc gluconate (65 mg QD) were taken daily from day 1 to day 21. IRX-2 was initiated on day 4 and administered subcutaneously in areas of draining lymph nodes as 2 injections of 115 U each on Mondays through Fridays over a 2-week period for 10 doses. All patients were to be followed up for 4 weeks after treatment until day 49.

Safety and Antitumor Assessment

Assessment of safety was based on adverse events (AEs), clinical laboratory measures, vital signs, and physical examinations. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0). Self-reported symptoms or investigator-identified signs and physical findings indicative of AEs were recorded each day during the treatment period through day 21, and weekly thereafter until study completion (day 49). The relationship between the administration of study drugs and the AE was recorded by the clinical investigator as "not related," "unlikely," "possibly related," or "probably related." An AE was classified as serious (SAE) if it was life-threatening or resulted in death, hospitalization, a persistent disability, a birth defect, or an immediate medical or surgical intervention to prevent one of the above outcomes. All SAEs were followed to resolution. Clinical laboratory assessments of hematology, chemistry, and urinalysis were conducted at baseline, day 17, day 21, and day 49.

The efficacy evaluation was the secondary objective in this study. Response data were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST). Tumors were assessed clinically and/or by computed tomography (CT) at baseline, day 21, and study completion. Tumor assessment was omitted in patients who underwent surgery or additional therapy after day 21. Clinical symptomatology related to tumor was also recorded.

Data analysis

In this phase 1 study, intent-to-treat (ITT) and per protocol (PP) analyses were performed. The ITT analysis was regarded as primary. The ITT population was defined as all patients who entered the study and received any amount of any component of the IRX-2 regimen. The PP population was defined as all patients who completed the study according to protocol and had no major protocol violations. Patients who were withdrawn from the study due to disease progression or an AE related to study medication were included in the PP population if they were otherwise valid. Data were summarized descriptively. Continuous variables were presented as summary statistics, such as number of patients, mean, standard deviation, minimum, median, and maximum. Categorical data were shown in absolute and relative frequencies or contingency tables. Statistical significance was defined as $P \leq 0.05$ in 2-sided t test. The 2-sided t test was to be used to compare whether the percentage change from Baseline differs significantly from zero. Analysis time points were as follows: baseline was defined as Screening (Day $-30-0$); Start of treatment = Day 1; and End of Study = Day 49. In the event of missing data, the last observation carried forward (LOCF) method was followed where appropriate. If a Screening (Day -30–0) value was missing, no percentage change

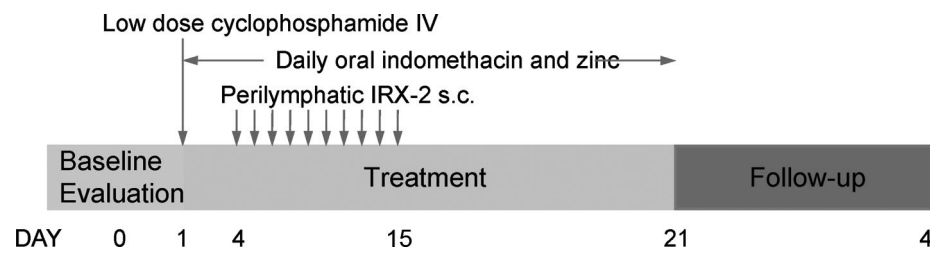

FIGURE 1. IRX-2 treatment scheme.

from Baseline was calculated. No imputation of incomplete or missing dates/data was done.

RESULTS

Patient Characteristics

Between January 2004 and June 2005, a total of 13 patients with HNSCC who had failed surgery and/or radiation therapy were enrolled in the study; their characteristics are listed in Table 1. All 13 patients were assessable for safety and efficacy. Nine patients were males and 4 females, with a median age of 58 years. Based on the Karnofsky Performance Status (KPS) at baseline, 5 patients (KPS, 90) were able to carry on normal activity with minor symptoms and 4 (KPS, 80) with some symptoms, while the other 4 patients (KPS, 70) were unable to carry on normal activities but could care for themselves. All patients had had treatment for HNSCC prior to the trial; most of them had had both surgical treatment and radiation therapy, and 5 patients had surgery, chemotherapy, and radiation therapy. The oral cavity was the primary disease site and the predominant site of recurrence in approximately half the patients. Patients' baseline nutritional status (mean and range) as defined by body mass index (derived from height and weight), serum albumin, and absolute lymphocyte count are depicted in Table 1.

TABLE 1. Patient Characteristics

Patients enrolled, N	13
Median age, yr (range)	58 (39–78)
Male:female	9:4
Race, n (%)	
White	4 (31)
Hispanic	9 (69)
Treatment history of HNSCC, n (%)	
Surgery	11 (85)
Chemotherapy	7 (54)
Radiation therapy	10 (77)
Karnofsky performance status, n (%)	
90	5 (38)
80	4 (31)
70	4 (31)
Site of primary disease, n (%)	
Oral cavity	6 (46)
Larynx	4 (31)
Pharynx	2 (15)
Oropharynx	1 (8)
Hypopharynx	1 (8)
Scalp*	1 (8)
Site of primary recurrence, n (%)	
Oral cavity	6 (46)
Anterior floor of mouth	2 (15)
Anterior tongue	2 (15)
Hard palate	1 (8)
Other	1 (8)
Larynx	3 (23)
Glottis	1 (8)
Other	2 (15)
Pharynx	2 (15)
Left piriform sinus	1 (8)
Soft palate	1 (8)
Nutritional status, mean (min–max)	
Body mass index	23.8 (17.6–32.6)
Albumin (g/dL)	3.4 (2.3–4.2)
Abs. lymphocyte count (10^3/mm^3)	1.34 (0.57–2.7)

*Site of disease recurrence at study entry was reported as a SCC scalp lesion and included in this manuscript for safety analysis only.

Safety

Safety was evaluated in all 13 treated patients, all of whom had at least one treatment-emergent adverse event (TEAE). All TEAEs observed in more than one patient are listed by MedDRA system organ class and preferred term in Table 2. An overview of AEs (safety population) is presented in Table 3. The most frequent TEAEs were observed in the blood and lymphatic system and the gastrointestinal system, with lymphopenia in 4 patients; and anemia, abdominal pain, and dysphagia in 3 patients each. Additionally, anorexia, headache, and dyspnea were each reported in 3 patients. There were 3 (23%) patients who discontinued from the study prematurely due to a TEAE. Of these, 2 patients (16%) died of causes not related to the study drug (1 patient died as a result of multiorgan failure and 1 died of a subarachnoid hemorrhage). One (8%) patient had mental status changes. Two more patients died

TABLE 2. TEAEs Occurring in >1 Patient by System Organ Class and Preferred Term

System Organ Class/Preferred Term	Patients, n (%)	Grade*
Blood and lymphatic system disorders	6 (46)	
Anemia	3 (23)	2, 1, 1
Lymphopenia	4 (31)	2, 2, 1, 1
Neutrophilia	2 (15)	1, 1
Gastrointestinal disorders	6 (46)	
Abdominal pain	3 (23)	2, 1, 1
Diarrhea	2 (15)	1, 1
Dysphagia	3 (23)	3, 3, 1
General disorders and administration site conditions	8 (61)	
Asthenia	2 (15)	2, 2
Injection-site reaction	2 (15)	1, 1
Pain	2 (15)	1, 1
Pyrexia	2 (15)	1, 1
Metabolism and nutrition disorders	5 (38)	
Anorexia	3 (23)	3, 2, 1
Dehydration	2 (15)	3, 3
Hypoalbuminemia	2 (15)	2, 1
Musculoskeletal and connective tissue disorders	3 (23)	
Arthralgia	2 (15)	1, 1
Myalgia	2 (15)	1, 1
Nervous system disorders	5 (38)	
Headache	3 (23)	3, 2, 1
Respiratory, thoracic, and mediastinal disorders	5 (38)	
Dyspnea	3 (23)	3, 2, 1
Rhinorrhea	2 (15)	1, 1
Vascular disorders	2 (15)	
Hypotension	2 (15)	3, 1

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 3.0).

TEAE indicates treatment-emergent adverse event.

after the study period due to tumor progression. None of the deaths or discontinuations was considered related to the IRX-2 regimen.

There were AEs that were considered related to one of the study drugs by the investigators. For IRX-2, AEs regarded as probably drug related included injection-site reaction in 2 patients and injection-site pain in 1 patient. Possibly related AEs were lymphopenia and pain in 2 patients each, followed by leukocytosis, neutrophilia, thrombocythemia, tinnitus, malaise, nasopharyngitis, and hypotension, each observed in 1 patient. For indomethacin, probably related AEs were abdominal pain in 2 patients, and nausea and anorexia, each observed in 1 patient. Dizziness in 1 patient was considered possibly related to cyclophosphamide, and constipation in 1 patient was reported as possibly related to zinc gluconate.

TABLE 3. Overview of AEs (Safety Population)

Characteristic	Patients, n (%)
No. patients in safety population	13 (100%)
No. patients with at least 1 AE	13 (100%)
No. patients with at least 1 TEAE	13 (100%
No. patients with at least 1 TEAE leading to premature discontinuation	3 (23%)
No. patients with at least 1 SAE	7 (54%)
No. patients with at least 1 drug-related TEAE	9 (69%)
No. patients with at least 1 TEAE resulting in death	4 (31%)
For TEAEs	
Severity (NCI CTC grade)	
1. Mild	11 (85%)
2. Moderate	9 (69%)
3. Severe	7 (54%)
5. Death related to AE	2 (15%)
Outcome	
Resolved	13 (100%)
Unresolved	11 (85%)
Death	4 (31%)
Other	1 (8%)
Relationship	
Not related	13 (100%)
Unlikely	2 (15%)
Possibly	6 (46%)
Probably	5 (39%)
If related, due to which study drug	
IRX-2	7 (54%)
Cyclophosphamide	1 (8%)
Indomethacin	4 (31%)
Zinc gluconate	1 (8%)

Note: TEAE was defined as any AE starting at or after the first administration of study drug and includes those AEs that started before the first administration but worsened after study drug intake.

Note: A related AE was defined as any TEAE judged by the investigator to have an "unlikely," "possible," or "probable" relationship to any study drug.

Note: Withdrawal due to AE: as reported on the "End of Study" CRF page as primary reason for discontinuation.

Note: Patient 002.B02: No severity was reported for AE "ulceration of left neck," as the patient discontinued the study before severity could be determined.

AE indicates adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event; NCI CTC, National Cancer Institute Common Terminology Criteria.

Most AEs were mild to moderate. The most frequent Grade 3 (severe) AEs were dysphagia in 2 patients (third patient had grade 1 dysphagia) and dehydration in 2 patients. There were no Grade 4 (life-threatening) AEs. Of the 2 patients with Grade 5 AE (death), one died of multiorgan failure and the other died of subarachnoid hemorrhage. Neither of these grade 5 AEs (death) was considered related to the study drugs. There were 7 patients with a total of 13 SAEs. Only one, hypotension, was considered by the investigator as possibly related to IRX-2, while an acute renal failure was defined as unlikely to be related to indomethacin.

Changes from baseline of some hematology, serum chemistry, and immunologic parameters reached statistical significance ($P < 0.05$) (Table 4). There were no statistically significant differences from baseline in urinalysis or physical examination results. Eight patients had 36 instances of clinically significant abnormal hematologic laboratory results. The most frequent were decreased lymphocytes (11 instances), increased neutrophils (8 instances), decreased hemoglobin (8 instances), and leukocytes (6 instances). A majority of these events were associated with infection at the tumor site, chronic bleeding, and the effects of advanced cancer. There were 6 patients with 31 incidents of clinically significant abnormal serum chemistry values, including those of albumin (8 instances), gamma-glutamyl-transferase (5 instances), and lactate dehydrogenase (4 instances). Most of these were associated with the metabolic effects of advanced cancer.

Antitumor Responses

Tumor responses were determined by radiographic assessment (Table 5). As indicated by radiographic assessment of the target lesions by RECIST in the 8 patients who had data at day 21, 1 patient (13%) had complete response, 5 (63%) had stable disease, and 2 (25%) had progressive disease.

Skin tests with IRX-2 and PHA were done at baseline with a subcutaneous injection on the forearm. An analysis of the skin test result and tumor response at day 21 is presented in Table 5. There were 5 patients with positive skin tests for IRX-2, defined as having erythema $\geq$3 mm. Of these, 3 patients also had positive skin test for PHA. Of the 5 IRX-2 skin-test positive patients, 1 had complete response, 1 had stable disease, 1 had progressive disease by radiographic assessment, and the others had incomplete data.

TABLE 4. Significant ($P < 0.05$) Mean Percentage Changes in Laboratory Values From Baseline

Variable	Mean Percentage Change	*P*
Laboratory values		
Hemoglobin	−6.5 at last IRX-2 injection	0.0091
Lymphocytes	−16.5 at last day of IRX-2 injection, and −23.5% at day 21	0.0038 and 0.0032
Albumin	−6.3 at day of last IRX-2 injection	0.0035
Blood urea nitrogen	34.8 at day of last IRX-2 injection	0.0221
Total protein	−5.6 at day of last IRX-2 injection	0.0046
B cells	−35.5 at day 21	0.0022

TABLE 5. Tumor Responses and Skin Test Results

	Response (at Day 21)	Skin Test	
Patient	Radiographic Assessment	IRX-2	PHA*
1	SD	Neg	Neg
2	NA	Neg	Neg
3	NI†	Neg	Neg
4	SD	Pos	Neg
5	SD	Neg	Neg
6	NA	Pos	Pos
7	NA	Pos	Pos
8	SD	Neg	Neg
9	NA	Neg	Neg
10	PD	Pos	Pos
11	CR	Pos	ND
12	SD	Neg	ND
13	PD	Neg	ND

*PHA was approved in the United States for in vitro use only and therefore was not administered to United States patients.

†Patient 3 site of disease recurrence at study entry was reported as a SCC scalp lesion and therefore not included in this efficacy analysis.

CR indicates complete response; SD, stable disease; PD, progressive disease; NA, not available; ND, not done; NI, not included.

DISCUSSION

The present phase 1 study was conducted to determine the safety of the IRX-2 regimen for patients with HNSCC who have failed surgery and/or radiation therapy. Overall, the regimen of 10 days of perilymphatic subcutaneous injection of IRX-2 in combination with a low-dose infusion of cyclophosphamide and daily oral indomethacin and zinc in a 21-day treatment cycle was tolerated. The most frequent TEAEs were blood and lymphatic disorders, followed by gastrointestinal disorders. Most AEs were mild to moderate in severity. Of the 13 patients who participated in the study, 3 discontinued from the study due to an AE, including 2 deaths. Two more patients died after the study period because of tumor progression. However, none of the deaths or discontinuations was considered related to the study drugs. There were 7 patients with a total of 13 SAEs. Only one SAE, hypotension, was considered by the investigator as possibly related to IRX-2. In general, the frequency of AEs, SAEs, and laboratory abnormalities would appear to be expected in this patient population. However, these are preliminary findings and further studies are warranted.

HNSCC has very high recurrence rates, with 50% of patients with locally advanced cancer developing locoregional or distant relapses and with second primary tumors developing at the rate of 3% to 5% each year.[7] Patients in the current study were those who failed previous treatments for HNSCC. Most of them had had both surgery and radiation therapy.

Traditional cytokine therapy in cancer treatment employs much higher doses, in the millions of units per administration.[23–26] However, AEs such as fever, hypotension, malaise, anemia, leukopenia, and hepatic and renal dysfunction have been reported, AEs which often lead to discontinuation of the treatment.[24,26] In our current study, low-dose ILs were used, which should limit systemic toxicity and improve tolerability. Three patients discontinued the study due to death or change of mental status, none of which was considered related to the study drugs.

Intravenous administration of ILs is frequently associated with an acute phase reaction characterized by rigors, fever, an increase in neutrophils, a decrease in lymphocytes, and changes in hormone levels.[27] On the other hand, locoregional administration can not only reduce systemic toxicity by lowering circulating concentration surrounding normal tissues, but also provide higher concentrations around the tumor. In our study, the ILs were delivered subcutaneously around the tumor-draining lymph nodes, which are believed to activate tumor-primed lymphocytes without direct mechanical manipulation of the tumor. A study of perilymphatically delivered low-dose recombinant IL-2 found no significant difference of complication and toxicity rates between the treatment group and controls.[28]

For patients with advanced recurrent and metastatic disease, the prognosis is poor, due to the residual disease that escapes conventional management.[28] Response rates with combinations of chemotherapy agents in this patient population range from 20% to 40%, and reach 26% with cetuximab and cisplatin combinations.[3] The antitumor responses of the IRX-2 regimen from our current study are encouraging for this patient group and will be further explored in a randomized controlled study. Based on radiographic assessment, 1 (13%) patient had complete response and 5 (63%) had stable disease at day 21.

In the present trial, only 5 patients had positive skin tests for IRX-2 and 3 of them were also positive for PHA. This probably reflects a depressed immune system in the patient group with advanced recurrent HNSCC. It has been reported that patients with cancer recurrence have greatly reduced T cell counts.[11] HNSCC patients with better immune response have a better chance of survival than those with poorer response. An earlier study of skin tests with dinitrochlorobenzene showed greater survival in patients who were dinitrochlorobenzene-positive. In this study, we used PHA and IRX-2 for the skin tests. PHA is a T-cell mitogen requiring accessory cells but not antigen presenting cells for its action, while the human cytokines in IRX-2 bypass the T cells and induce an accelerated monocyte/macrophage reaction.[15] Taken together, the presence and intensity of the skin test response to PHA and IRX-2 may reflect the cell-mediated immunity in patients with HNSCC. Of the 5 IRX-2 skin-test positive patients, 1 had complete response, 1 had stable disease, 1 had progressive disease, and no data were available on the other 2 patients. These patient numbers are too small to adequately evaluate the effects of skins tests as a predictor of responsiveness to IRX-2 and additional studies with larger number of patients are needed.

In conclusion, the results of the present study indicate that the IRX-2 regimen was tolerated in patients with HNSCC who had failed surgery and/or radiation therapy. The antitumor response including stable disease suggests larger studies are needed to determine the efficacy of this regimen.

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