

1. INTRODUCTION

1.1 BACKGROUND

The annual incidence of squamous cell carcinoma of the head and neck (SCCHN) is approximately 40,000 cases per year in the U.S. and 60,000 cases per year in Europe. It is estimated that in the U.S., 12,000 patients will die annually from their disease and that a similar number of deaths may occur in Europe. The key prognostic factor is the stage of disease at first diagnosis. If the patient presents with early disease, as in 25% of new cases, the standard treatment is surgery, radiation, or the combination of both. Long-term disease-free survival is approximately 70%. In this population, patients are more likely to die from a second primary malignancy (field cancerization) than from loco-regional recurrence or metastatic disease. On the contrary, for patients presenting with advanced disease (75% of new diagnoses), the failure rate following first-line therapy reaches 70% and the pattern of failure is primarily local and/or regional recurrence¹.

Regardless of the disease stage at initial presentation, patients having loco-regional recurrence invariably experience substantial tumor-related morbidity. The need for improved treatments to gain control of regional disease and preserve function in this patient population cannot be over-emphasized. To date the standard treatment for primary disease (surgery and/or radiation) is also used in the recurrent setting. For patients failing previous radiation and deemed unresectable, chemotherapy is accepted as a standard approach.

Several chemotherapy regimens have been used in SCCHN with disappointing success. Among single agents, weekly methotrexate has been considered the conventional palliative therapy with partial response rate < 21% (6 to 45%) lasting two to six months^{2,3,4}. Cisplatin (CDDP) monotherapy has a slightly better and more predictable response rate of 28% (14 to 41%), although toxicity is greater and survival is not affected^{3,4}. The taxanes are new compounds currently undergoing extensive study in head and neck cancer with response rates as single agent of 30-40% in recurrent disease^{5,6,7}. Docetaxel as a first line treatment in recurrent and metastatic head and neck cancer patients has shown to be active with 30% - 43% of response rate as a single agent²⁷.

Although many combination regimens have been studied, an analysis of the reported randomized trials between 1980 and 1992 concludes the combination of cisplatin plus 5-Fluorouracil administered every 21 days is more efficacious than single agent or other combination treatment, with an overall response rate of approximately 32% and complete response between 5 and 15%⁸. This combination has become the accepted chemotherapy standard for recurrent disease, however many patients are unable to tolerate the regimen for extended periods of time. Single agent taxanes are being used in patients who are ineligible for, or intolerable to, cisplatin. A treatment with limited toxicity that could be added to systemic treatments to improve loco-regional control and offer meaningful clinical benefit to patients with recurrent SCCHN is highly sought after.

Over the past decade investigation into the etiology of human cancer has identified two categories of genetic events leading to cancer: 1) the loss of a tumor suppressor gene and 2) the activation of a tumor promoter gene. The most prevalent identified tumor suppressor gene is p53⁹. It encodes a phosphoprotein that binds chromosomal DNA and regulates cell proliferation. In most instances when normal p53 function is lost, most often due to mutation or deletion, the cell's ability to undergo apoptosis is impaired. In the absence of physiological apoptosis, cancer can develop^{10,11,12,13}.

Mutation in or deletion of the p53 gene has been detected in greater than 50% of tumors in patients with SCCHN^{14,15}. Pre-clinical studies in cell cultures and animal models have shown that by introducing a normal p53 gene into head and neck cancer cells with gene transfer technologies, the cancer phenotype of cells derived from head and neck cancers can be reverted¹⁶.

1.1.1 RPR/INGN 201 (Ad5CMV-p53)

RPR/INGN 201 is a constructed adenoviral vector containing the normal p53 gene, driven by a CMV promoter. Pre-clinical studies have shown that cell lines derived from SCCHN could be transduced by RPR/INGN 201. In these cell lines, wild type p53 encoded by RPR/INGN 201 was expressed and apoptosis occurred. In rodent models, tumorigenesis of SCCHN was reduced when transduction with RPR/INGN 201 took place, regardless of the presence or absence of mutation in the p53 gene. Several studies suggested, however, that cells with mutated p53 were more sensitive to RPR/INGN 201 than those cells with wild type p53¹⁶.

In vitro studies in which RPR/INGN 201 has been combined with either CDDP or 5-FU have shown that the combination treatment leads to greater inhibition of tumor cell growth than either agent alone. These results have been confirmed *in vivo* in xenograph models of human cancer. Pre-clinical studies have also shown that the effects of RPR/INGN 201 in combination with CDDP or with 5-FU are schedule-dependent. The greatest inhibition of tumor cell growth resulted when cisplatin was administered at least one day prior to RPR/INGN 201 as indicated by both cell proliferation and apoptosis analyses. Results suggest also greater loss in tumor cell viability when pre-treatment with RPR/INGN 201 occurs 24 hours before 5-FU addition or with simultaneous treatment with the two agents.

The taxanes are new compounds that inhibit microtubule depolymerization, and have shown efficacy in a number of tumors. Three rodent (xenograft models of either NSCLC or pancreatic cancer) studies have been conducted in which RPR/INGN 201 was tested in combination with docetaxel (Taxotere®). Results have shown consistent findings of at least additive anti-tumor effects which appear to be dose related. Additionally, when RPR/INGN 201 was administered in 3 daily doses of up to 6×10^{10} vp/injection (100 times the maximum dose anticipated for use in human clinical trials) in combination with docetaxel at or near the highest non-toxic dose (HNTD), no apparent increase was observed in clinical toxicity. Animals receiving the highest doses of RPR/INGN 201 (167 times the maximum dose anticipated for use in human clinical trials) concurrently with docetaxel doses at or near the HNTD experienced increased toxicity, including death²⁸.

Phase I studies in patients with advanced SCCHN receiving RPR/INGN 201 via intra-tumoral injection on days 1, 3, 5, 8, 10 and 12 every four weeks have shown that related toxicities are minimal. Additionally, the toxicities reported are not those toxicities commonly associated with chemotherapy. Molecular analysis of tumor biopsies from SCCHN patients treated with RPR/INGN 201 have demonstrated expression of wild type p53 as a result of gene transfer [data on file]. These observations confirm the feasibility of transgene transfer and expression using RPR/INGN 201 in this patient population, as predicted by pre-clinical studies. More importantly, early phase II data (175 treated patients) confirm both partial and complete responses of lesions, as well as prolonged tumor growth control, in patients with recurrent SCCHN. The preliminary safety profile from these studies coincides with the low toxicity reported in Phase I studies. To date, intra-tumoral injection of RPR/INGN 201 has been combined with CDDP in a completed Phase I study of patients with advanced non-small cell lung cancer. In this study, the combination treatment related toxicity was no greater than that expected with each individual agent.

In summary, data from previous studies involving significant numbers of patients have demonstrated that RPR/INGN 201, when administered by intra-tumoral injection in patients with SCCHN, has anti-tumor activity and is well tolerated. Study patients have also reported clinical benefits including diminished tumor pain, improved tongue and neck mobility, and speech clarity. Further investigation of RPR/INGN 201 in recurrent SCCHN is clearly warranted, especially since few effective therapeutic options currently exist.

A detailed discussion of the pre-clinical and clinical data can be found in the Investigator Brochure¹⁶.