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A randomized, multicenter study to determine the safety and efficacy of the immunoconjugate SGN-15 plus docetaxel for the treatment of non-small cell lung carcinoma

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Summary
Purpose: Chemotherapy prolongs survival and improves quality of life (QOL) for good performance status (PS) patients with advanced non-small cell lung cancer (NSCLC). Targeted therapies may improve chemotherapy effectiveness without worsening toxicity. SGN-15 is an antibody—drug conjugate (ADC), consisting of a chimeric murine monoclonal antibody

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recognizing the Lewis Y (Le^y) antigen, conjugated to doxorubicin. Le^y is an attractive target since it is expressed by most NSCLC. SGN-15 was active against Le^y-positive tumors in early phase clinical trials and was synergistic with docetaxel in preclinical experiments. This Phase II, open-label study was conducted to confirm the activity of SGN-15 plus docetaxel in previously treated NSCLC patients.

Experimental design: Sixty-two patients with recurrent or metastatic NSCLC expressing Le^y, one or two prior chemotherapy regimens, and PS ≤ 2 were randomized 2:1 to receive SGN-15 200 mg/m^2/week with docetaxel 35 mg/m^2/week (Arm A) or docetaxel 35 mg/m^2/week alone (Arm B) for 6 of 8 weeks. Intrapatient dose-escalation of SGN-15 to 350 mg/m^2 was permitted in the second half of the study. Endpoints were survival, safety, efficacy, and quality of life.

Results: Forty patients on Arm A and 19 on Arm B received at least one treatment. Patients on Arms A and B had median survivals of 31.4 and 25.3 weeks, 12-month survivals of 29% and 24%, and 18-month survivals of 18% and 8%, respectively. Toxicity was mild in both arms. QOL analyses favored Arm A.

Conclusions: SGN-15 plus docetaxel is a well-tolerated and active second and third line treatment for NSCLC patients. Ongoing studies are exploring alternate schedules to maximize synergy between these agents.

1. Introduction

Lung cancer is the leading cause of cancer-related death with over one million deaths annually worldwide and over 160,000 deaths in the US in 2004 [1]. Non-small cell lung carcinoma (NSCLC) accounts for 80% of lung cancer diagnoses [2]. Most NSCLC patients are diagnosed with advanced stage disease not amenable to surgical cure [3]. Although some stage III patients can be cured with combined modality therapy, most advanced stage patients receive chemotherapy alone resulting in clinical response or disease stabilization in many cases, but with few long-term survivors [4—6]. Front line treatment with platinum doublet chemotherapy now produces median survivals of 8—11 months and provides clinically meaningful overall survival benefits, with 1 year survivals for stage IV NSCLC patients of 30—50% compared to 5—10% for patients receiving supportive care alone.

Taxanes are among the most active NSCLC chemotherapies acting on cells in the G2/M phase of the cell cycle by stabilizing microtubules, thus, disrupting normal mitosis and leading to activation of apoptotic pathways in sensitive cells. Both paclitaxel and docetaxel are approved in combination with cisplatin for first line therapy of NSCLC. Docetaxel is also approved as a single agent for patients who have failed first line chemotherapy and is associated with quality of life gains and survival benefits similar to those seen with first line therapy. Patients treated with second line docetaxel have about a 30% chance of living 1 year [7,8]. In the face of these modest gains, new approaches to systemic therapy of advanced NSCLC are needed.

Anthracyclines have low single agent activity against NSCLC, but doxorubicin was a component of CAP (cyclophosphamide, doxorubicin, and cisplatin), one of the first chemotherapy regimens to show a survival benefit in this disease [9]. Anthracyclines have been largely supplanted in recent combination chemotherapy regimens in favor of newer agents. However, if effective targeting can increase the specificity of drug delivery and if rational combinations successfully exploit synergistic cell cycle dependent interactions, they may hold greater promise than previously appreciated.

SGN-15 (cBR96-doxorubicin conjugate) is a novel antibody—drug conjugate that targets doxorubicin to tissues expressing the Le^y antigen. This carbohydrate antigen is abundantly expressed (>200,000 molecules/cell) by carcinoma cells [10]. Tissue binding studies show that cBR96 targets a wide variety of human carcinomas including lung, breast, colon, prostate, and ovary [10]. cBR96 also targets normal cells expressing Le^y, including differentiated epithelial cells of the GI tract and acinar cells of the pancreas. SGN-15 consists of doxorubicin conjugated to cBR96 at a molar ratio of 8:1 with 6 mg doxorubicin per 200 mg SGN-15. Phase I studies of SGN-15 showed evidence of activity in patients with Le^y expressing tumors [11]. Of 58 evaluable patients, 21 (36%) had stable disease after 6 weeks and there were two partial responses.

SGN-15 and docetaxel are synergistic in preclinical studies. Following exposure to doxorubicin, cells arrest in G2 [12] and are then sensitized to G2/M acting drugs such as taxanes. *In vitro* studies [13] and animal models [14] confirm that the combination of SGN-15 plus a taxane is more effective than either drug alone in several tumor types. Phases I and II studies in subjects with epithelial malignancies, including metastatic breast and colorectal carcinomas, confirm that the combination of SGN-15 and docetaxel is safe and clinically active [15—18] (unpublished data, Seattle Genetics, Inc.). In 29 evaluable patients with breast cancer, the disease control rate (i.e. stable disease or better) was 41% (seven stable disease [SD], two minimal response [MR], three partial response [PR]). Among 20 evaluable patients with colorectal carcinoma, the disease control rate was 20% (three SD, one MR). The toxicity profile was acceptable with gastrointestinal toxicities occurring most frequently. Other toxicities were mild and infrequent.

We now report the results of a randomized Phase II, multicenter study designed to determine the safety and efficacy of SGN-15 and docetaxel in patients with NSCLC.