BRIEF REPORT

Efficacy and Safety of Glembatumumab Vedotin in Patients With Advanced or Metastatic Squamous Cell Carcinoma of the Lung (PrECOG 0504)

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ABSTRACT

Introduction: Glycoprotein NMB is a transmembrane protein linked with poor prognosis and is expressed in most squamous lung cancer. Glembatumumab vedotin is an antibody-drug conjugate targeting glycoprotein NMB, administered intravenously every 3 weeks in this phase 1 study to determine the safety, tolerability, and maximum tolerated dose in patients who had progressed on any number of previous therapies.

Results: A total of 13 patients were enrolled; adverse events (of any grade) including dyspnea, neutropenia, respiratory failure, anemia, increased aspartate transaminase/alanine transaminase, diarrhea, and hypophosphatemia were seen in 15% of patients. Grade 5 events included two cases of respiratory failure, either completely or partially attributed to cancer progression. The only other grade 5 event was "disease progression." The most common adverse events (23%) were decreased appetite, fatigue, rash, and weight loss. The median overall and progression-free survivals were 5.7 months (90% confidence interval: 2.5–16.8) and 2.5 months (90% confidence interval: 1.6–5.8) respectively.

Conclusions: Glembatumumab vedotin exhibited no serious or unexpected toxicity in this heavily pretreated population, except those caused by disease progression. Modest anticancer activity was observed with a recommendation for a phase 2 dose of 1.9 mg/kg. This portion of the study was not undertaken owing to the company's decision to discontinue drug development.

Keywords: Squamous cell lung cancer; Targeted therapy; DC-HIL; gpNMB

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Introduction

The unique biology of squamous NSCLC exhibits a higher expression of cancer cell surface proteins. One such protein is glycoprotein NMB (gpNMB). The gpNMB is a type I transmembrane protein that is involved in mediating intercellular adhesion, promoting tissue repair, and regulating cell growth and differentiation.[1] In addition, it seems to have a negative prognostic association in glioblastoma and triple-negative breast cancer.[2,3] It is expressed on the surface and subcellular compartments of many different cells including osteoclasts, osteoblasts, macrophages, and dendritic cells.[1,4-6] Antibody-drug conjugates that target cancer-specific proteins or alter immune response like gpNMB may be effective because gpNMB is highly expressed in most squamous cell carcinoma. It can be measured using a nonquantitative scoring system using formalin-fixed, paraffin-embedded sections for immunohistochemical staining of samples from patients with squamous cell cancer.

Glembatumumab vedotin is an antibody-drug conjugate specifically targeting gpNMB. It consists of a fully human immunoglobulin G, subclass two monoclonal antibodies, CR 011, directed against gpNMB combined with the potent cytotoxic microtubule inhibitor monomethylauristan E using technology similar to that used in brentuximab vedotin. This compound is stable in the bloodstream but after internalization into the lysosomal compartment of gpNMB expressing cells the microtubule inhibitor monomethylauristan E is released by proteolytic cleavage. Earlier clinical trials administered glembatumumab vedotin to patients with melanoma and breast cancer,[7,8] including a mix of both gpNMB-expressing and not expressing. The activity was seen in both these cancer types at a dose of 1.88 mg/kg intravenously every 3 weeks. Responses were more robust in those cancers that had higher expression levels of gpNMB.

The goal of this open-label phase 1 study was to establish the maximum tolerated dose for every 3-week dosing of glembatumumab vedotin in squamous cell lung cancer, with this dose being used to determine the recommended dose for phase 2 trials.

Patients and Methods

Eligible patients were age 18 years and older with stage IIIB or IV squamous (or mixed adenosquamous) lung cancer measurable by Response Evaluation Criteria in Solid Tumors (RECIST 1.1).[9] Patients were required to have experienced progression or recurrence of disease during or subsequent to the most recent anticancer therapy. Any number of previous lines of systemic therapy was permitted. Immunohistochemistry gpNMB expression on greater than or equal to 5% of tumor epithelial cells was required. Patients with stable treated brain metastases were permitted. The study received institutional review board approval at all sites and was registered on ClinicalTrials.gov as NCT02713828.

Treatment and Study Safety End Points

Patients were given glembatumumab vedotin starting at a dose of 1.9 mg/kg as a 90-minute intravenous infusion for the escalation phase, on the basis of previous clinical trial results using glembatumumab vedotin[10] at 1.3 mg/kg one-dose level. The maximum tolerated dose for the dose escalation phase would be the highest dose level, at which none of three or only one of six patients of that cohort experienced dose-limiting toxicity (DLT). Further details about starting doses, additional dose modifications, DLT definitions, and safety evaluations using the National Cancer Institute common toxicity criteria for adverse events (AEs) are available on the publicly accessible study protocol at https://clinicaltrials.gov/ProvidedDocs/28/NCT02713828/Prot_000.pdf.

Statistical Methods

The two-sided 90% confidence interval (CI) of the RECIST best overall response rates (complete response + partial response) was calculated based on exact binomial distribution. Progression-free survival (PFS) was the time from study registration to the earliest of documented disease progression or death without previous progression. Patients not experiencing an event would be censored at their last adequate disease assessment date. Overall survival (OS) was defined as the time from study registration to the date of death from any cause. Patients not experiencing an event would be censored at the last follow-up date. PFS and OS were summarized descriptively using the Kaplan-Meier method and two-sided 90% CI for the median PFS and OS was provided on the basis of complementary log-log transformation.

Results

Between August 16, 2016 and April 5, 2018, a total of 13 patients were enrolled at six sites. Previous therapies, demographic details, and other patient characteristics of enrolled patients are listed in Table 1. No patients were found to be ineligible and all patients started treatment.

At dose level 1, a total of three patients were enrolled initially, with three more patients subsequently enrolled. One DLT was observed in the six patients. This was described as a grade 5 respiratory failure deemed as possibly related to study drug but complicated by progressive disease. To further characterize the safety of this drug, the protocol was modified and additional three patients were added to cohort 1 for a total of nine patients at 1.9 mg/kg dose. A second DLT was observed in cohort 1. The patient experienced grade 3 treatment-

Table 1. Demographic and Disease Details of All Patients Enrolled in the Clinical Trial

Variables	N = 13, n (%)
Age, median (range)	63 y (52-75)
Sex	
Female	6 (46)
Male	7 (54)
Race	
Asian	1 (8)
White	11 (85)
Not specified	1 (8)
Histologic diagnosis	
Adenosquamous	2 (17)
Squamous	10 (83)
Unknown	1 (8)
Stage	
IIIB	1 (8)
IV	11 (92)
ECOG PS	
0	2 (15)
1	11 (85)
Previous lines of trt	
1	5 (42)
2	4 (33)
≥3	3 (25)
Previous nonbrain XRT	
No	3 (25)
Yes	9 (75)
Previous brain XRT for NSCLC	
No	10 (83)
Yes	2 (17)
Previous surgery for NSCLC	
No	6 (50)
Yes	6 (50)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; trt, treatment; XRT, radiotherapy.

related pruritus requiring hospital admission. The dose was de-escalated to dose level 1. No DLT was observed at dose level 1 of 1.3 mg/kg. With these data, an additional patient was allowed on dose level 1, after which no other DLTs were noted. However, the study was terminated owing to the suspension of glembatumumab vedotin development and no further patients were enrolled.

The best objective response per RECIST 1.1 was of one patient who achieved a partial response (1 of 13 [7.7%], 90% CI: 0.4%–31.6%). This patient then discontinued the study agent and trial participation at sponsor discretion, before the progressive disease developed. Per protocol definition, the duration of response was 16 months while on glembatumumab vedotin. The patient subsequently progressed on ipilimumab and nivolumab 29 months after first responding to glembatumumab. Six patients experienced stable disease and four patients had progressive disease, and two patients were not assessable owing to death. After a median follow-up of 35.7 months, 11 patients were reported to have died, and all were

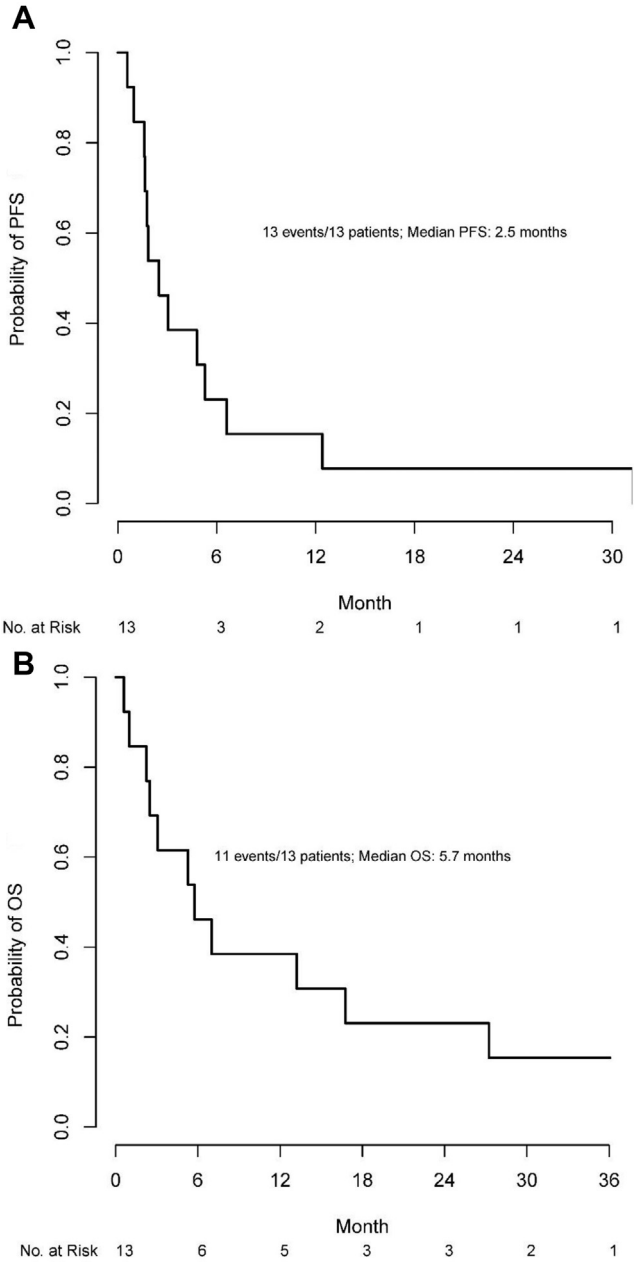

Figure 1. Kaplan-Meier curve of the PFS and OS. The *(A)* median PFS for patients was 2.5 months, and the *(B)* median OS was 5.7 months. OS, overall survival; PFS, progression-free survival.

because of disease deterioration or progressive disease. The median OS in this heavily pretreated population was 5.7 months (90% CI: 2.5–16.8) (Fig. 1*A*). All patients had disease progression or died. The median PFS was 2.5 months (90% CI: 1.6–5.3) (Fig. 1*B*).

Adverse Events

Table 2 describes all serious AEs regardless of attribution. All patients receiving treatment were assessed for AEs during the treatment period and during the

Table 2. Serious AE (Includes All Grades, Any Attribution)

Category	Toxicity Type	Grade 1/2	Grade 3	Grade 4	Grade 5	Total
Dose level 1 (n = 3)						
Gastrointestinal disorders	Abdominal pain	0	1	0	0	1
Dose level 1 (n = 10)						
General disorders and administration site conditions	Disease progression	0	0	0	1	1
Respiratory, thoracic, and mediastinal disorders	Dyspnea	0	0	2	0	2
Metabolism and nutrition disorders	Hypercalcemia	0	0	1	0	1
Metabolism and nutrition disorders	Hypokalemia	0	0	1	0	1
Blood and lymphatic system disorders	Neutropenia	0	1	1	0	2
Skin and subcutaneous tissue disorders	Pruritus	0	1	0	0	1
Respiratory, thoracic, and mediastinal disorders	Respiratory failure	0	0	0	2	2
Infections and infestations	Urinary tract infection	1	0	0	0	1

AE, adverse event.

DLT period. Common AEs of any grade seen in at least 15% of patients included dyspnea, neutropenia, new respiratory failure, anemia, elevated aspartate transaminase/alanine transaminase, diarrhea, and hypophosphatemia. The maximum frequency for any AE was 23%; these common AEs were decreased appetite, fatigue, rash, and weight loss.

A total of three grade 5 events were seen on the study and were either partially or wholly contributed by disease progression. Two grade 5 events included respiratory failure, of which one was completely attributed to cancer progression and the other partially so. The only other grade 5 event was described as "disease progression."

Discussion

The study PrECOG 0504 revealed that targeting the cancer-specific protein gpNMB with an antibody-drug conjugate is a viable treatment strategy in squamous cell cancer. Overall, the drug was well-tolerated in an especially heavily pretreated patient population. Even at a lower dose level, there was a considerable and sustained partial patient response seen. Though the study was not completed owing to the suspension of the development of this compound, our recommended phase 2 dose for glembatumumab vedotin in squamous cell lung cancer patients is 1.9 mg/kg.

The results from our study are consistent with a phase 2 study of the same drug in 62 patients with advanced melanoma.[8] In that single-arm study, the overall response rate was 11% and the most frequently seen AEs were alopecia, neuropathy, rash, fatigue, and neutropenia. Of note, the development of a treatment-related rash correlated with improved overall response rate and prolonged PFS in a previous clinical trial[7,11]; but in our analysis, there was no unequivocal correlation of rash with the response.

Future directions include developing new antibody-drug conjugates targeting gpNMB expressing cancers and exploiting the role of gpNMB in altering myeloid-derived suppressor cell (MDSC) function. Numerous studies reported that gpNMB targeting can result in effective cancer control and its strong tumor specificity suggest that newer agents may also exhibit activity. There is also an opportunity for gpNMB-targeting therapy in depleting MDSCs, which suppress T-cell function.[12] In this recently reported study, an in vitro analysis of blood from patients with cancer revealed significantly elevated blood levels of gpNMB positive MDSC's. This study found that using a different anti-gpNMB antibody to suppress MDSC helped to restore T-cell activity.

In summary, gpNMB represents a cancer-specific target that is highly expressed in squamous cell cancer cells. The investigational agent, glembatumumab vedotin, exhibited modest activity and safety in a heavily pretreated population, but it remains to be seen whether this is the ideal agent to be used in squamous cell lung cancer.

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