SYNOPSIS

Name of Sponsor: BioVex, Inc., a wholly owned subsidiary of Amgen Inc.

Name of Finished Product: Talimogene laherparepvec (formerly known as OncoVex^{GM-CSF})

Name of Active Ingredient: HSV-1 (strain JS1)/ICP34.5-/ICP47-/hGM-CSF

Title of Study: A Phase 3 Randomized Trial of Concurrent Cisplatin and Radiotherapy With or Without OncoVex^{GM-CSF} in Previously Untreated Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Investigator(s) and Study Center(s)

This study was conducted at 2 centers in the US:

[redacted]

Publication(s): None as of the date of this report

Study Period: The first subject received treatment on 08 February 2011. A decision to terminate Study 006/09 was made on 29 July 2011 (see Methodology). The last subject received treatment on 21 July and completed follow-up assessments on 11 October 2011.

Development Phase: 3

Objectives

In a previous phase 1/2 study (004-04) of subjects with locally advanced squamous cell carcinoma of the head and neck (SCCHN), the addition of talimogene laherparepvec to chemoradiotherapy was well tolerated and suggested clinical activity based on the high proportion of tumors that decreased in size and high rate of histopathological response at surgery.

The objective of the current phase 3 study was to evaluate the efficacy and safety of treatment with chemoradiation plus talimogene laherparepvec compared to chemoradiation alone in previously untreated patients with locally advanced SCCHN (stage T2 N2-3 M0, T3-4 N1-3 M0) for which surgical resection was not clinically indicated. The efficacy objective of this study was to demonstrate overall clinical benefit for patients treated with talimogene laherparepvec as compared to chemoradiation alone.

Primary Objective

- To demonstrate a statistically significant increase in 2-year event-free survival (ie, disease progression, recurrence, death from any cause) for patients treated with talimogene laherparepvec as compared to patients treated with chemoradiation alone

Secondary Objectives

- Clinical objective response (cOR) rate (partial response and complete response by clinical examination and computed tomography [CT]) by week 21 for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone

- Clinical complete response (cCR) rate (by clinical examination and CT) by week 21 for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Metabolic CR (mCR) rate (by fluorodeoxyglucose positron emission tomography [FDG PET]) at week 21 for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Pathologic CR (pCR) rate for those who went for surgery by week 22 for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Time to locoregional failure for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Time to distant tumor failure for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Time to any failure for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Overall survival (OS) for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Disease-specific survival for patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone
- Proportion of patients treated with talimogene laherparepvec as compared to those treated with chemoradiation alone for whom neck dissection was required, for those with N1-2 disease at baseline

[redacted]

Methodology

This was a phase 3, randomized, open-label study to compare the efficacy and safety of concurrent chemoradiation (radiation plus single-agent cisplatin) with and without talimogene laherparepvec as the primary nonsurgical therapy in subjects with advanced non-metastatic stage III or IV SCCHN (T2 N2-3 M0, T3-4 N1-3 M0). Subjects were randomized in a 1:1 ratio to chemoradiation with or without concurrent treatment with talimogene laherparepvec. The first dose of talimogene laherparepvec was up to 8 mL total volume (up to 4 mL per lesion) at 10^6 plaque-forming units (PFU)/mL, administered into all injectable affected nodes. Subsequent doses were up to 8 mL total volume (up to 4 mL per lesion) at 10^8 PFU/mL on days 21, 42, and 63. Subjects received cisplatin (100 mg/m^2) administered IV on days 0, 21, and 42 of the treatment course after radiation and talimogene laherparepvec (if applicable). Radiation (70 Gy; intensity modulated radiation therapy [IMRT] or 3-dimensional conformal radiation therapy) was administered concurrently with cisplatin in 35 fractions over a 7-week period. After completion of chemoradiation, all subjects were assessed for response between weeks 19 and 21. Subjects were to be followed every 3 months for 2 years after the completion of radiotherapy (for response), and every 6 months for an additional 3 years (for OS).

[redacted]

Number of Subjects Planned: Up to 580

Number of Subjects Enrolled: 5 (2 talimogene laherparepvec plus chemoradiation, 3 chemoradiation alone [control])

Diagnosis and Main Criteria for Eligibility

Eligible subjects were men and women 18 years of age or older with histological evidence (from the primary lesion and/or lymph nodes) of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx; stage III or IV disease, an Eastern Cooperative Oncology Group performance status of 0 or 1, and a life expectancy of ≥ 4 months. Subjects also were required to have no evidence of distant metastases, and adequate hematologic, liver, and renal function. Subjects were excluded if they had received prior treatment for locally advanced SCCHN, surgery ≤ 28 days before randomization, or radical radiotherapy to the head and neck region. Other exclusion criteria included T1-2 N1 or T1 N2-3 disease, pre-existing peripheral neuropathy ≥ grade 2, cancer of the nasopharynx, sinus, salivary gland, or skin, or any significant intercurrent illness that could have interfered with the chemoradiation regimen.

Complete inclusion and exclusion criteria are provided in the protocol (Appendix 1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Talimogene laherparepvec was provided as a sterile frozen liquid in single-use 2.0-mL vials containing talimogene laherparepvec at a nominal concentration of 10^6 PFU/mL or 10^8 PFU/mL in 1.15 mL solution for injection. The maximum dose per treatment day was 8 mL total volume (up to 4 mL per lesion). [redacted]

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Cisplatin was administered at a dose of 100 mg/m^2 administered IV, and was supplied according to country-specific guidelines.

Duration of Treatment: Talimogene laherparepvec was to be administered through day 63, cisplatin was to be administered through day 42, and radiotherapy was to be administered for 7 weeks.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was event-free survival at 2 years after randomization.

Secondary Efficacy Endpoints

Secondary efficacy endpoints are listed in the Objectives section.

Safety Endpoints

Safety was evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, based on adverse events, physical examinations, and clinical laboratory assessments.

Statistical Methods: Because this study was terminated with 5 subjects enrolled, data for selected endpoints were summarized in by-subject listings. No formal statistical analyses were conducted.

Summary of Results

Subject Disposition

Five subjects (2 talimogene laherparepvec, 3 control) were enrolled in this study. Four subjects (1 talimogene laherparepvec, 3 control) completed treatment, and 1 subject receiving talimogene laherparepvec discontinued treatment after the first dose due to disease progression.

Of the 4 subjects who completed treatment, all received 3 cycles of cisplatin without dose modifications. These 4 subjects also received 70 Gy of radiation; however, 2 subjects (in the control arm) had interruptions in radiotherapy, primarily due to scheduling issues.

Subject Demographics

Sex: 4 men, 1 woman

Median (Range) Age: 53 (48 to 67) years

Ethnicity (Race): 4 white, 1 black

Efficacy Results: At the end-of-treatment visit, 3 subjects (1 talimogene laherparepvec, 2 control) had a cCR. Two of these subjects (1 talimogene laherparepvec, 1 control) also had an mCR. One subject in the control arm had progressive disease (per clinical, metabolic, and pathologic evaluation), and 1 subject in the talimogene laherparepvec arm was unevaluable.

Safety Results

All subjects had adverse events during the study. Adverse events generally included gastrointestinal and constitutional symptoms consistent with those expected for subjects with head and neck cancer receiving chemoradiotherapy. Four subjects (2 talimogene laherparepvec, 2 control) had adverse events that were ≥ grade 3 or serious. Serious adverse events included mouth hemorrhage and dehydration (in the control arm), and acute renal failure, lung infection, urinary tract infection, hyperglycemia, pleural effusion, and malignant neoplasm progression (in the talimogene laherparepvec arm). All serious adverse events occurred in 1 subject each. One subject (in the talimogene laherparepvec arm) had a grade 3 prolonged QT on electrocardiogram 11 days after the first dose. The event was not serious, was not considered to be related to study treatment by the investigator, and resolved without treatment after 2 days. This subject discontinued treatment after the first dose (due to disease progression) and died of disease progression approximately 2 months later. No other deaths occurred during the study.

Individual out-of-range laboratory values were observed for all subjects; however, no trends suggested a safety issue with talimogene laherparepvec. Two subjects (in the talimogene laherparepvec arm) had elevated creatinine levels during the study: 1 had an elevated creatinine level before the first dose, and the other experienced grade 1 acute renal failure attributed to cisplatin. All subjects received concomitant medications, which were most commonly administered as prophylaxis for the effects of chemoradiation.

Conclusions: As this study was terminated early with 5 subjects enrolled, no conclusions can be drawn regarding the efficacy and safety of chemoradiation plus talimogene laherparepvec in previously untreated patients with locally advanced SCCHN.

Reference List

Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med.* 2010;363:24-35.

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29:4294–4301.

[redacted]