2. SYNOPSIS

Name of Sponsor: BioVex Ltd.

Name of Finished Product: OncoVEX^{GM-CSF} (INN name: Talimogene laherparepvec)

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

Title of Study:

An Exploratory Study of the Safety and Biological Activity of OncoVEX^{GM-CSF} in Combination with Radiotherapy and Cisplatin in the Treatment of Locally Advanced Epithelial Cancer of the Head and Neck

Investigator(s) and Study Center(s):

This study was conducted at 2 centers in the United Kingdom (UK):

Site 01: [redacted].

Site 02: [redacted].

Publication(s):

Harrington KJ, Hingorani M, Tanay MA, et al. Phase I/II Study of Oncolytic HSV^{GM-CSF} in Combination with Radiotherapy and Cisplatin in Untreated Stage III/IV Squamous Cell Carcinoma of the Head and Neck. Clin Cancer Res; 2010;16(15):4005-15.

The publication includes additional efficacy data from the investigative sites beyond the results included in this report.

Study Period:

The first subject was enrolled on 11 August 2005 and the last subject completed the study on 19 December 2007.

Development Phase: 1/2

Objectives:

Squamous cell cancer of the head and neck (SCCHN) is the sixth most common cancer worldwide. There are about 76,000 and 30,000 new cases diagnosed each year in Western Europe and the United States, respectively (Cooper et al, 2009; Parkin et al, 2005). Locally advanced disease usually requires a multidisciplinary approach which involves the use of radiotherapy (RT) with concomitant chemotherapy. In subjects with bulky tumor disease at presentation, chemoradiotherapy is often followed by radical neck dissection.

OncoVEX^{GM-CSF} is an oncolytic immunotherapy consisting of an immune-enhanced herpes simplex virus type-1 (HSV-1) that selectively replicates in solid tumors. In the OncoVEX^{GM-CSF} strain, the HSV-1 viral genes encoding ICP34.5 (a neurovirulence factor) and ICP47 (which blocks viral antigen presentation to major histocompatibility complex [MHC] class I and II molecules) have been functionally deleted. The coding sequence for human GM-CSF has been inserted in place of ICP34.5 and is intended to enhance the immune response to tumor antigens released after virus replication. Thus, the therapeutic strategy is to produce a direct oncolytic effect by replication of the virus in the tumor, and to induce a systemic anti-tumor immune response enhanced by the local expression of GM-CSF. The overall intent of this therapeutic strategy is to induce the destruction of injected tumors, the destruction of un-injected tumors, reduction in the development of new metastases, reduction in the rate of overall progression and relapse, and prolonged overall survival.

The primary objective of this study was to assess the safety of OncoVEX^{GM-CSF} combined with chemoradiotherapy in subjects with locally advanced cancer of the head and neck prior to radical neck dissection. The secondary objective was to assess the biological activity of the combination by computed tomography (CT) scanning, immunology testing, and the study of histopathology obtained at biopsy and at the time of surgery.

Methodology:

This was an open-label, dose-escalation study of 3 dose levels of OncoVEX^{GM-CSF} in combination with radiotherapy (RT) and concomitant cisplatin in the treatment of subjects with locally advanced stage III and IV head and neck cancer with 1 or more tumor metastases in the neck (N1-N3).

Subjects in each cohort received 4 doses of OncoVEX^{GM-CSF} once every 3 weeks (Q3W) as described below. The initial dose was 10^6 plaque-forming units (PFU)/mL, followed by 3 additional doses of the assigned dosing regimen. Chemoradiotherapy was administered to each subject over a 7-week period.

Four cohorts of 4 evaluable subjects each were treated with OncoVEX^{GM-CSF} Q3W as follows:

- Cohort 1: 4 doses of 10^6 PFU/mL
- Cohort 2: 1 dose of 10^6 PFU/mL followed by 3 doses of 10^7 PFU/mL
- Cohort 3: 1 dose of 10^6 PFU/mL followed by 3 doses of 10^8 PFU/mL
- Cohort 4: Administered the dose selected for further evaluation from cohorts 1 through 3

Where 2 or more metastases existed in a subject, at least 1 tumor was injected and at least 1 tumor remained uninjected.

Once the dose-escalation portion of the study was completed, a fourth cohort of up to 14 additional subjects was to be enrolled and treated [redacted]. The dosing regimen of OncoVEX selected for cohort 4 was 1 dose of 10 PFU/mL followed by 3 doses of 10^8 PFU/mL. [redacted].

Subject's tumors were evaluated for stage by CT scan prior to treatment and 1 week after the 4 doses of OncoVEX^{GM-CSF} had been administered. During treatment, biopsies of both injected and uninjected tumors were obtained for histopathological examination. Six to 8 weeks after chemoradiotherapy ended, and 3 to 5 weeks after the last OncoVEX^{GM-CSF} injection, subjects underwent neck dissection for removal of previously involved tumors. Histopathology of the tumors at the time of surgery was assessed, if possible.

A final follow-up visit was performed 1 month after the week 10 visit (if no surgery was performed) or 1 month after surgery. At this time, a physical examination was conducted and blood samples were obtained for hematology, clinical chemistry, HSV antibodies, and antinuclear antibody (autoantibody).

Number of Subjects Planned: A total of 35 subjects were planned in order to accrue up to 28 evaluable subjects.

Number of Subjects Enrolled: A total of 17 subjects were enrolled in the study; 4 subjects each in cohorts 1 through 3 and 5 subjects in cohort 4.

Diagnosis and Main Criteria for Eligibility:

Men or women ≥ 18 years of age who had histologically-confirmed squamous cell cancer of the head and neck of stage ≥ N1 in the ipsilateral or contralateral sides of the neck (with at least 1 tumor ≥ 1 cm in diameter), who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and who provided informed consent were eligible for the study if they met all of the inclusion criteria and none of the exclusion criteria.

Subjects who had undifferentiated carcinoma of nasopharyngeal type (UCNT) World Health Organization (WHO) type III, were pregnant or lactating, were receiving chemotherapy with agents other than cisplatin or carboplatin, had uncontrolled congestive cardiac failure, had active autoimmune disease, had active herpes simplex virus type 1, tested positive for human immunodeficiency virus (HIV), hepatitis B, hepatitis C or syphilis, or had a history of allergic reaction to platinum or platinum-containing compounds were excluded from the study.

A complete list of study inclusion and exclusion criteria is provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Each dose of OncoVEX^{GM-CSF} was administered by intratumoral injection. The initial dose was up to 4 mL of 10^6 PFU/mL (up to 2 mL per tumor). The remaining 3 doses of up to 4 mL at 10^6, 10^7, or 10^8 PFU/mL were administered Q3W. In cohort 4, up to 8 mL of an initial dose of 10^6 PFU/mL followed by 3 doses of up to 8 mL of 10^8 PFU/mL were administered.

[redacted]

Chemoradiotherapy consisted of radiotherapy (70 Gy in 35 fractions over 7 weeks) with intravenous (IV) infusions of cisplatin administered overnight on day 0 (week 0), day 21 (week 3) and day 42 (week 6). Cisplatin was administered at standard doses (100 mg/m^2 body surface area).

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

No reference therapy was administered in this study.

Duration of Treatment:

Subjects received 4 injections of OncoVEX^{GM-CSF} (at weeks 0, 3, 6, and 9) and chemoradiotherapy over 7 weeks. Three to 5 weeks after the last OncoVEX^{GM-CSF} injection, subjects were to undergo a neck dissection for removal of previously involved neck tumors. A final follow-up visit occurred 1 month after the week 10 visit (if no surgery was performed) or 1 month after surgery.

Study Endpoints:

The endpoints used to assess safety were study drug exposure, adverse events, deaths, injection site reactions, analysis of OncoVEX^{GM-CSF} in post-injection swabs, presence of herpes labialis, vital signs, laboratory parameters, HSV-1 antibodies, and physical examination.

The endpoints used to assess biological activity were clinical response as assessed by CT scan, histopathology and immunohistopathology of biopsies for the detection of residual viable tumor cells, and quantitative PCR for OncoVEX^{GM-CSF} in tumor tissue.

Statistical Methods:

All analyses of efficacy and safety were conducted in the intention-to-treat (ITT) population.

Analysis of Biological Activity:

For all clinical response variables, the number and percentage of subjects for each assessment were summarized by response (eg, decrease in tumor size, tumor viability, presence of OncoVEX^{GM-CSF} in tumor). All tumor measurements recorded on the CRF, including derived change and percentage change from screening, were listed by cohort and treatment. Histopathology of injected and, where possible, uninjected tumors, and T-cell proliferation data were evaluated separately.

Safety Evaluation:

Study drug exposure was summarized as the number of days from first to last dose as well as the total dose administered. Adverse events were listed by cohort and subject and provided time of onset relative to the last dose of study medication, duration of the adverse event in days, severity, relationship to treatment, and outcome. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. Adverse events were presented by system organ class (SOC) and preferred term. Injection site reactions were listed by visit.

For the swab analysis of post-injection viral shedding, data were listed by visit. All data on vital signs, hematology, chemistry and other laboratory values (including HSV-1 antibodies) at each time point were presented as absolute values and changes from baseline. Values above and below the normal range were flagged. HSV-1 antibody data were categorized as seropositive, seronegative, or equivocal (ie, inconclusive).

For analyses of biological activity and safety, missing data were treated as missing without imputation.

Summary of Results:

Subject Disposition:

A total of 17 subjects were enrolled in the study and treated at 2 study sites in the UK; 4 subjects each in cohorts 1 to 3, and 5 subjects in cohort 4. Based on the consistent and positive nature of the results obtained from the first 5 subjects in cohort 4, additional subjects were not recruited. All 17 subjects enrolled in the study were included in the ITT population and all analyses were performed on this population. No subjects withdrew from the study.

Baseline Demographics:

Sex: Fifteen (88%) subjects were men and 2 (12%) were women.

Age: The median age across cohorts 1 to 4 was 58 years (range: 41 to 74).

Ethnicity/Race: All 17 (100%) subjects were white.

Efficacy Results:

A total of 94.6% of measured tumors assessed by CT scan at screening had decreased in size at week 10. A greater mean decrease in size was observed in subjects administered a dose of 10^7 PFU/mL or higher of OncoVEX^{GM-CSF} compared with those administered 10^6 PFU/mL for 4 doses. In particular, none of the 5 injected tumors in the lowest dose cohort (10^6 PFU/mL) had resolved by week 10, whereas 37.5% (12/32) of measurable tumors resolved (ie, were no longer detectable) at the higher dose levels, suggestive of a dose-related effect. Assessment of objective response, as described in the protocol, was not carried out because histopathological response was felt to be more clinically meaningful.

Analyses of the tissue obtained during surgical neck dissection from 15 of the 17 subjects in the study provided further evidence of the clinical activity of OncoVEX^{GM-CSF} when added to chemoradiotherapy in the treatment of SCCHN. Two subjects did not undergo neck dissection after being assessed as clinical complete responders and refusing surgery. Histopathologic review of the surgical specimens established a pathologic complete response rate of 93% (14 of 15 subjects).

Needle biopsy tumor tissue samples were obtained for qPCR analysis from neighboring injected and uninjected neck nodes in 16 patients prior to neck dissection. Detection of virus in the injected tumors of 7 subjects and in the uninjected tumors of 1 subject suggested that virus replication had occurred. However, the frequency of virus detection in tumors may have been reduced since most tissue samples for the assay were obtained at the time of surgery, 3 to 5 weeks after the last administration of OncoVEX^{GM-CSF}.

Overall, the rate and extent of response, particularly complete histopathologic response, is suggestive of additional efficacy with OncoVEX^{GM-CSF} in combination with cisplatin and radiation.

Safety Results:

All subjects experienced at least 1 adverse event during the course of the study. The most common treatment-emergent adverse events observed across all 4 cohorts were weight decreased (16 subjects; 94%), constipation (15 subjects; 88%), mucosal inflammation and radiation skin injury (each 14 subjects; 82%), anemia and nausea (each 13 subjects; 76%), and dysphagia (12 subjects; 71%). The incidence of events was generally balanced across cohorts.

Most adverse events (86%) were CTCAE grade 1 or 2, and most (91.0%) were not considered related to OncoVEX^{GM-CSF} by the investigator. Thirteen (2.7%) adverse events considered related to OncoVEX^{GM-CSF} were grade 1, and 12 (2.3%) events were grade 2. There were no grade 3 or grade 4 treatment-emergent adverse events considered related to OncoVEX^{GM-CSF}. The most common grade 3 adverse events were mucosal inflammation (6 subjects; 35%); radiation skin injury (5 subjects; 29%); weight decreased and dysphagia (each 4 subjects; 24%); dehydration and leukopenia (each 3 subjects; 18%); febrile neutropenia, neutropenia, thrombocytopenia and

nausea (each 2 subjects; 12%). Only 3 grade 4 adverse events were reported (lymphopenia, dysphagia, and respiratory failure). There were no grade 5 treatment-emergent adverse events.

Sixteen of 17 subjects (94%) experienced treatment-emergent serious adverse events; however, none were considered related to OncoVEX^{GM-CSF} by the investigator, and all but 6 events resolved by end of study. No deaths or withdrawals due to adverse events occurred during the study.

Three of 17 subjects (18%) had virus detected on post-injection tumor swabs. Swabs obtained from the dressings covering the injection site(s) were negative for the presence of virus for all subjects at all timepoints.

Conclusions:

OncoVEX^{GM-CSF} in combination with chemoradiotherapy was well tolerated when administered intratumorally to subjects with squamous cell cancer of the head and neck in repeated doses of up to 10^8 PFU/mL. The high proportion of tumors that decreased in size as assessed by CT scan, and the high rate of histopathological response detected at surgery, suggest that the combination of OncoVEX^{GM-CSF} and chemoradiotherapy should be evaluated further in a randomized study.