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MONOGRAPH

ONCOVEX$^{GM\text{-}CSF}$

Armed Oncolytic Virus

ICP34.5- and ICP47-deleted oncolytic herpes simplex virus 1 (HSV-1) carrying the human *GMCSF* gene

EN: 304699

SUMMARY

The promise of cancer vaccines remains as yet unrealized as a reliable and effective therapeutic modality. There is now compelling evidence that collateral induction of antitumor immune responses contributes substantially to viral antitumor activities. In addition to the expected antiviral immune clearance, the "danger" signal created by virus-infected cells can generate immune costimulation known to override immune suppression and reverse tolerance within the tumor microenvironment. OncoVEX$^{GM\text{-}CSF}$ (JS1/34.5^{-}/47^{-}/GM-CSF) is a gene-modified, immune-enhanced oncolytic herpes simplex virus type 1 (HSV-1) with preclinical confirmation of mode of action and phase I and II evidence of safety when administered as an intratumoral in situ vaccination. A phase II study in 50 patients with stage IIIC and IV melanoma showed a 28% response rate, including 10 complete responses, with demonstrable durability of effect. This included patients who continued on a compassionate dosing extension study. Immune response analyses of tumor-infiltrating lymphocytes and peripheral blood mononuclear cells confirmed that in situ vaccination elicits both local and systemic antitumor-specific immune responses, establishing proof of principle for this therapeutic approach in the clinical setting. A pivotal randomized phase III study of OncoVEX$^{GM\text{-}CSF}$ in melanoma has been initiated and will provide additional data.

BACKGROUND

There is a compelling rationale for the development and therapeutic use of cancer vaccines, including enhanced target specificity (against tumor-associated antigens, TAAs), thereby widening the therapeutic window, a broadened TAA spectrum to mitigate the limitations imposed by inherent tumor heterogeneity, and durability of effectiveness consequent to development of immune memory (1). Unfortunately, the promise of this approach has not been kept. With melanoma as the index cancer and using a variety of effectors, elicited objective immune-mediated response rates to date have been approximately 3.3%, and 7.1% with dendritic cell therapeutics (2). However, accruing recent preclinical and clinical data support the concept of oncolytic immunotherapy, and specifically herpes simplex type 1 (HSV-1) immunotherapy, as a viable antitumor modality (3-11).

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OncoVEX$^{GM\text{-}CSF}$ (JS1/34.5^{-}/47^{-}/GM-CSF) is an immune-enhanced oncolytic HSV-1. It is deleted for ICP34.5 (*RL1* gene), providing tumor-selective replication, and ICP47 (*US12* gene), which otherwise blocks antigen presentation (5). In addition, ICP47 deletion allows for juxtaposition of the US11 coding domain to the α47 promoter, shifting the former from γ_2 to α region kinetics. This results in an increase in the early expression of US11, thereby enhancing virus growth and replication in tumor cells compromised in part by the double deletion of *RL1* (5, 12). The coding sequence for human granulocyte–macrophage colony-stimulating factor (GM-CSF) is inserted, replacing ICP34.5, to enhance the immune response to tumor antigens released following virus replication (Fig. 1).

Safety and antitumor activity, including the clearance of injected and uninjected tumors, have been demonstrated with OncoVEX$^{GM\text{-}CSF}$ in animal studies (5). Furthermore, a phase I investigation has established the safety and clinical activity of OncoVEX$^{GM\text{-}CSF}$ in patients with various tumor types, including melanoma (9), and the efficacy demonstrated in a recent phase II study in patients with unresectable metastatic melanoma (11) has provided the basis for the ongoing FDA-approved pivotal, randomized phase III study in the same population.

Constructing an oncolytic HSV-1 viral immunotherapeutic

Wild-type HSV-1 is an α herpesvirus capable of infecting a wide variety of human and nonhuman cells and tissues, and like all herpesviruses, it consists of a large double-stranded linear DNA genome containing 152 kb of linear double-stranded DNA arranged as covalently linked long and short components that is packaged into an icosahedral nucleocapsid approximately 100 nm in diameter. Herpesviruses are enveloped viruses with an amorphous structure between the nucleocapsid and envelope, known as the tegument, that contains virus proteins important in the early stages of the infection process. During lytic replication, packaged nucleocapsids bud through the host cell's Golgi network and plasma membrane. The size of the complete virion is approximately 120 nm. HSV-1-binding ligands are comprised of the envelope glycoproteins gB and gC targeting the cell-surface receptor heparin sulfate and gD targeting HVEM (herpesvirus entry mediator), and nectins-1 and -2 (13). Cell entry can be either endocytic or fusogenic, depending on cell type, and the same receptor can mediate both mechanisms (14). Following infection, the intracellular replication cycle is usually completed within 20 h. In order to allow for safe, differentially effective antitumor oncolysis, ICP34.5, the neurovirulence factor, is deleted. Early in the course of infection the presence of viral dsRNA activates the cel-

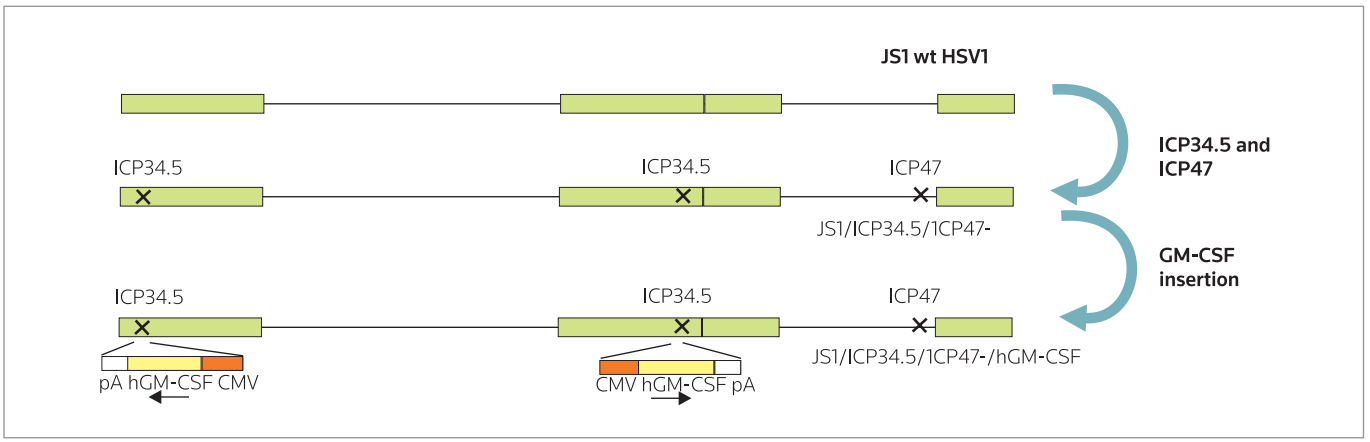

Figure 1. OncoVEX^{GM-CSF} deletion of ICP34.5 and ICP47; insertion of hGM-CSF at the site of ICP34.5 deletion. Reprinted by permission from Macmillan Publishers Ltd.: Liu, B.L., Robinson, M., Han, Z.-Q., Branston, R.H., English, C. et al. *ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumor properties. Gene Ther* 2003, 10(4): 292-303, © 2003.

lular kinase PKR, resulting in the phosphorylation and inactivation of eukaryotic translation initiation factor eIF-2α, thereby blocking cellular protein synthesis (15). Although the entire gene is required for replication in the nervous system, the carboxyl terminus of ICP34.5, which is homologous to GADD34 (growth arrest and DNA damage-inducible protein), functions as a regulatory subunit for protein phosphatase 1α (PP1α), resulting in the dephosphorylation of eIF-2α (16). Following deletion of *RL1*, phosphorylated eIF-2α accumulates, compromising continued viral replication. The US11 protein, which can interact with PKR to prevent PKR-mediated phosphorylation of eIF-2α, is produced late in the viral life cycle and, being dependent on viral DNA replication, is compromised by *RL1* deletion. Deleting the *α47* gene and placing the US11 coding domain under the control of the immediate–early (IE) α47 promoter shifts the former from γ_2 to α region kinetics. This results in an increase in the early expression of US11, thereby enhancing virus growth and replication compromised, in part, by the double deletion of *RL1* (5, 12) in tumor cells. This, in large part, selective effect in tumor cells is mediated by a variety of mechanisms. TANK-binding kinase TBK1 is inhibited by ICP34.5 (17). TBK1 activates interferon regulatory factor 3 (IRF3) and cytokine expression, and therefore its inhibition would effectively block an antiviral IRF3-mediated response, an activity independent of eIF-2α phosphorylation. In cancer cells, TBK1 is constitutively engaged by Ras-related protein Ral-B activation (18). Alternatively, it has recently been reported that tumor-selective upregulation of MEK (mitogen-activated protein kinase [MAPK]/extracellular signal-regulated kinase [ERK]) is associated with a block in virus-activated PKR, which would otherwise phosphorylate eIF-2α (19) and thereby have the potential to shift the threshold of sensitivity to the effect of the translated US11.

OncoVEX^{GM-CSF} is a replication-competent HSV-1 constructed from the recently isolated, completely sequenced HSV-1 JS1 strain (ECACC Accession Number 01010209) rather than the generally used, serially passaged 17+ or F strains, the oncolytic potential of which were shown to be attenuated in comparison (5). As postulated, the additional deletion of ICP47, placing US11 under the regulatory control of the immediate–early α47 promoter, significantly increased the oncolytic effectiveness of the JS1/34.5$^-$ virus (Fig. 2), and possibly contributed to a further decrease in normal tissue infectivity (20). In addition, ICP47 blocks antigen presentation to MHC class I molecules by blocking the human transporters associated with antigen presentation, i.e., peptide transporters TAP1 and TAP2 (21, 22). Its deletion was therefore also shown to enhance the antitumor immune response by increasing levels of MHC class I on the surface of tumor cells (5) Insofar as MHC class II CD4$^+$ T cells are required for priming and secondary expansion of antigen-specific CD8$^+$ T cells, it has been shown that following intratumoral injection of ICP34.5-deleted HSV-1 (HSV-1716) tumor-associated dendritic cells and monocytes produce MIG (C-X-C motif chemokine 9) and IP-10 (C-X-C motif chemokine 10), which, mediated by type 1 interferon production, recruit natural killer (NK) and CD8$^+$ T cells (23). Finally, in addition to stimulating cytokine production in immature dendritic cells, ICP34.5-null HSV-1 mutants (R3616) stimulate dendritic cell (DC) maturation and the expression of MHC class II protein (24). Correspondingly, R3616-infected tumor cells demonstrate both invariant chain (Ii) cleavage and a significant increase in MHC class II cell-surface protein accumulation (23).

Tumor cells genetically modified to secrete GM-CSF have consistently demonstrated the most potent induction of antitumor immunity compared to other cytokines (25). In one study, B16 melanoma cells were engineered to secrete either GM-CSF or FLT3 ligand (FL) and their immunological effects were reported (26). Although both cytokines provoked a marked expansion of DCs locally and systemically, GM-CSF stimulated greater levels of protective immunity. Three profound differences have been described which could account for the disparity in response. First, GM-CSF induces a subset of DCs that are more efficient in the phagocytosis of apoptotic tumor cells (27-29). Second, compared to FL, GM-CSF evokes higher levels of costimulatory molecules, which is characteristic of greater functional maturation. This enhanced activity results in more efficient T-cell stimulation, thereby broadening the arsenal of induced lymphocyte effector mechanisms (30). Third, GM-CSF promotes uniformly high levels of CD1d on DCs, in contrast to FL, which triggers a more heterogeneous expression (31). CD1d is a nonclassi-

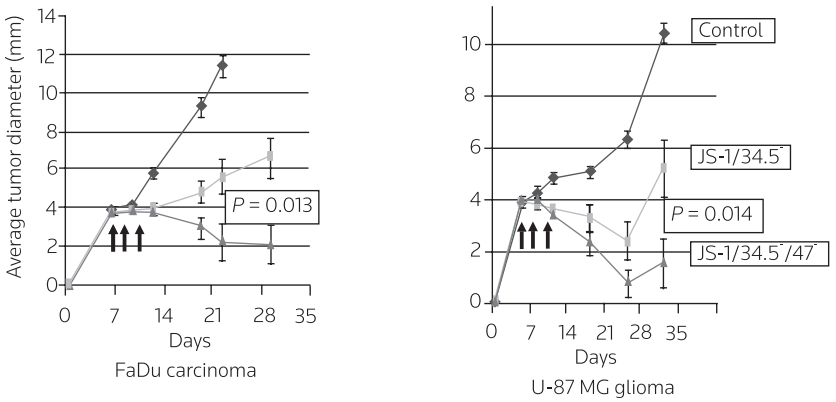

Figure 2. Deletion of ICP47 (transposing US11 to α47 promoter) improves antitumor effects in vivo. The indicated xenografts were generated in the flanks of BALB/c mice. When tumors had reached approximately 0.5 cm in diameter, tumors were injected every other day x 3 (arrows) with 50 µL of a 1 x 10^8 pfu/mL aliquot of the indicated virus and effects on tumor growth measured; n = 10 animals/group. Reprinted by permission from Macmillan Publishers Ltd.: Liu, B.L., Robinson, M., Han, Z.-Q., Branston, R.H., English, C. et al. *ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumor properties. Gene Ther* 2003, 10(4): 292-303, © 2003.

cal MHC class I molecule that presents lipid antigens (32). The CD1d–lipid complex activates NK T cells, a population of lymphocytes that display a restricted class I MHC-like receptor (33). Importantly, NK T cells may play pivotal roles in both endogenous and therapeutic responses to tumors (34). Preclinical in vitro and in vivo evaluation of OncoVEX^{GM-CSF} confirmed GM-CSF enhancement of the immune response (5).

Following intratumoral injections of the HSV-1 mutant G207, Toda (3) showed significant tumor growth reduction in both injected and contralateral uninjected lesions. That the systemic effect was immune-mediated was shown by the fact that, despite bilateral tumor responses, LacZ expression (from G207) was only found in the injected tumor and tumor growth in athymic mice was inhibited only in the injected lesion. Tumor-specific $CD8^+$ cytotoxic T lymphocytes were generated which recognized a dominant tumor-specific MHC class I-restricted epitope (AH1). That this response was dependent on viral infection of the injected tumor was shown by a lack of effectiveness when the virus was administered by the intradermal rather than the intratumoral route. Notably, pre-existing HSV seropositivity did not significantly affect the therapeutic effectiveness of either oncolytic G207 HSV-1 (35) or OncoVEX^{GM-CSF} (5). As a safety factor, OncoVEX^{GM-CSF} retains the gene for thymidine kinase (*TK*), preserving sensitivity to clinically effective antiviral agents (similar to other therapeutic viral constructs, e.g., G207).

PRECLINICAL PHARMACOLOGY

Safety testing of OncoVEX^{GM-CSF} and OncoVEX$^{mGM-CSF}$ demonstrated that (36):

- High and multiple doses, up to 1 x 10^7 plaque-forming units (pfu)/animal (100 µL of 1 x 10^8 pfu/mL or 5 x 10^8 pfu/kg) are tolerated in immune-competent mice following s.c. administration and intratumoral inoculation.
- Sensitivity to aciclovir; thus, patients could be treated with aciclovir to terminate virus replication if necessary.
- Total elimination of virus from major tissues following s.c. administration, including gonads, at 28 days after dosing, with the exception of a positive PCR signal (brain) in 1 animal at 84 days after dosing.
- Good tolerability in three formal toxicity and biodistribution studies in mice given up to 12 s.c. doses at a maximum of 1 x 10^7 pfu. Increased hematopoiesis and lymphoid hyperplasia in the spleen (seen in two studies), increased hematopoiesis in bone marrow (seen in one study) and an inflammatory response at the injection site (seen in three studies) were noted at 24 h after dosing and were reversible upon withdrawal of treatment.
- No evidence of significant toxicity following administration into the rat hepatic artery at doses up to 1 x 10^7 pfu (highest tested), following direct injection into the dog prostate at doses of up to 2.5 x 10^6 pfu (highest tested), or when coadministered in combination with chemotherapy and/or radiation.

Overall, the preclinical studies demonstrated that OncoVEX^{GM-CSF} lyses tumor cells in vitro and eliminates or causes significant shrinkage of both murine and human tumors. OncoVEX^{GM-CSF} affects not only the tumors into which it is injected, but also distant noninjected tumors, demonstrating a beneficial systemic effect from local administration. In addition, OncoVEX^{GM-CSF} prevents tumor recurrence upon rechallenge with the same tumor type and remains effective when animals have undergone previous exposure to wild-type HSV or are immunosuppressed with ciclosporin. OncoVEX^{GM-CSF} has been demonstrated to enhance the effects of radiation and chemotherapy in preclinical studies and may be used in combination with these other modalities for the treatment of cancer. Similar findings were observed in safety studies of OncoVEX$^{mGM-CSF}$ in tumor-bearing mice.

CLINICAL STUDIES

The phase I study (9) evaluating the safety, biodistribution and biological activity of OncoVEX^{GM-CSF} was an open-label evaluation of three dose levels. In part 1 of the study, a single dose of OncoVEX^{GM-CSF} was administered to cohorts of four patients. The first dose group was administered OncoVEX^{GM-CSF} at a dose of 10^6 pfu/mL injected into a single lesion, the second dose group received 10^7 pfu/mL and the third dose group received OncoVEX^{GM-CSF} at a dose of 10^8 pfu/mL. In part 2 of the study, patients received up to 3 doses administered every 14 days at the following dose levels: group A received 10^6, 10^7 and 10^7pfu/mL; group B received 10^8, 10^8 and and 10^8 pfu/mL; and group C received 10^6, 10^8 and and 10^8 pfu/mL. Study drug was administered directly into a cutaneous or subcutaneous tumor. The administered volume was scaled to the tumor diameter, i.e., ≤ 1.5 cm, up to 1 mL; > 1.5 to ≤ 2.5 cm, up to 2 mL; and > 2.5 cm, up to 4 mL. Thirty patients with advanced solid tumors with metastases in the skin or subcutaneous tissue participated in the study (breast cancer, 14; melanoma, 9; SCCHN [squamous cell carcinoma of the head and neck], 4; and other, 3). Patients were categorized at baseline as being seronegative or -positive for HSV-1. The most frequently reported treatment-related adverse effect (AE) was pyrexia, which occurred in 19 of 30 patients (63%). Rigors and post-procedural complications in eight patients (27%) and injection-site reaction in six patients (20%) were also reported as treatment-related. The majority of the AEs were mild or moderate in severity. There were four grade 4 AEs: epigastric pain, epileptic seizures, back surgery and shortness of breath, none of which was considered to be related to OncoVEX^{GM-CSF}. In the first two single-dose groups (10^6 and 10^7 pfu/mL), the four patients (three receiving 10^7 pfu/mL and one receiving 10^6 pfu/mL) who were seronegative for HSV-1 at entry to the study all developed febrile influenza-like syndromes associated with malaise, rigors, pyrexia and erythema around the injected lesion. Two seronegative patients who received OncoVEX^{GM-CSF} 10^7 pfu/mL developed an erythematous skin rash with scattered vesicles in the skin. Virus was detected on the surface of some of the injected nodules at low levels, mainly in patients who were seronegative for HSV and received > 10^6 pfu/mL as their first dose; however, virus was never detected on the outer dressing covering of the injection site or elsewhere. The events were transient, self-limiting and without sequelae. It was therefore concluded that all patients (seropositive or -negative for HSV) should receive an initial dose of 10^6 pfu/mL followed by subsequent doses of 10^6 pfu/mL of OncoVEX^{GM-CSF}, as this was well tolerated by all patients. qPCR blood results were positive at 1 or more time points for 12 of the 30 patients. Urine was positive at one or more time points for two patients. In general, in the second part of the study virus was only noted within 8 h after the injection.

Using RECIST criteria, 8 of the patients (27%) showed stable disease, 19 patients (63%) showed progressive disease and 3 (10%) were not evaluable. While tumor diameter did not decrease, some patients showed tumor flattening, including uninjected lesions in the vicinity of the single lesion which was injected. In addition to clinical observation, the study protocol also defined a response as having occurred if tumor necrosis was observed following biopsy. Biopsies including areas of tumor were taken from 19 patients. Following histopathology, 13 of the tumor-containing biopsies (13/19, 68%) showed evidence of partial or extensive tumor necrosis. One additional tumor-containing biopsy showed apoptosis. Thus, necrosis or apoptosis was seen in 73% of patients for whom tumor-containing biopsies were taken. Using a polyclonal antibody, HSV staining was seen in all biopsies which had areas of necrosis. Non-necrotic and nontumor tissues in the biopsies only very rarely stained for HSV. Measurable quantities of GM-CSF mRNA (qPCR) were obtained in 11 of 13 of the samples tested. In general, there was a positive correlation between the dose of OncoVEX^{GM-CSF} injected and the level of GM-CSF mRNA expressed. There was also a relationship between serum status at the time of injection, with seronegative patients expressing more hGM-CSF mRNA than seropositive patients. GM-CSF blood levels (ELISA) were below the limit of detection, as intended, GM-CSF expression being aimed at locally attracting to and activating antigen-presenting cells within the tumor microenvironment to induce a tumor-specific immune response.

Based on the established safety profile and clinical and histological results of the phase I trial, a phase II open-label evaluation of OncoVEX^{GM-CSF} in 50 patients with stage IIIC or IV melanoma not eligible for surgery was performed (11). Eligible patients received injections of OncoVEX^{GM-CSF} into one or more injectable skin, subcutaneous or nodal melanoma lesions. Initially, the treatment schedule was up to 8 injections given over a 15-week period. If indications of biological activity were observed (injection-site reactions and/or inflammatory response in an uninjected tumor and/or stable disease or better), treatment (injection every 2 weeks) could then continue for up to a maximum of 24 injections. The first injection was administered at a dose of up to 4 mL of 10^6 pfu/mL. Three weeks later, the lesions were injected once every 2 weeks at a concentration of 10^8 pfu/mL for up to a total of 24 injections. Patients with stable disease (SD) or better at that time could then continue on a compassionate dosing extension protocol. Individual tumors could be injected with up to 2.0 mL of OncoVEX^{GM-CSF} and a total of 4.0 mL could be injected at any visit. Patients could continue to receive OncoVEX^{GM-CSF} even with progressive disease (PD) for 120 days, as long as no other therapy was appropriate in consideration of the kinetics of the immune effector response (37). Patient distribution included stages IIIC (n = 10), IVM1a (n = 16), IVM1b (n = 4) and IVM1c (n = 20; LDH greater than upper limits of institutional normal in 13) and Eastern Cooperative Oncology Group (ECOG) status scores of 0 (n = 31) and 1 (n = 19). Seventy-four percent of the patients received one or more prior nonsurgical therapies. Thirteen of the patients were seronegative at baseline, all of whom seroconverted by week 7. There was no correlation of serum status with either response or adverse effects. The median follow-up at the time of publication was 18 months (range: 11-36 months). Patients received a median of 6 sets of injections (mean: 9 sets) and 5 patients the full course of 24 injections. Although eight patients left the study prior to receiving four injections, all patients were evaluated for toxicity and comprised the intent-to-treat population.

There were 14 objective responses to OncoVEX^{GM-CSF} treatment alone, including in the extension study; for all patients: complete response (CR), n = 10 (2 patients on extension study, 1 with prior partial response [PR] and 1 with SD, achieved CR by 24 months); PR, n = 4: response rate (RR), 28%; for stage IV patients: CR, n = 8: PR, n = 2; RR 25%). All responses included changes recorded from both injected and uninjected sites (regional and/or distant [including lung, liver, pancreas, regional and distant lymph nodes, and soft tis-

sue sites]) and were ongoing in 12 of the 13 patients at the time of publication. Interestingly, response onset was from 2 to 10 months after the first dose, with maximum (biopsy-confirmed) overall response at 12 months. Notably, but not unexpectedly (37), transient locoregional or distant progression preceded CR in four patients and PR in two patients. Two additional patients achieved CR with additional surgery: one following craniotomy and resection of a newly diagnosed brain lesion at 4 months and one following surgery and IL-2 retreatment (which the patient had previously failed). Another patient (PR) showed no evidence of disease following surgical resection at 13 months. Overall, 10 patients (20%) attained CR with monomodal OncoVEX^{GM-CSF} and a total of 13 patients (26%) when combined with additional surgery. The 1-year survival for all patients was 58%, 58% for the stage IV subset and 40% for the stage IVM1c subset. The 1-year survival for the 15 patients with CR, surgical CR and PR was 93% (Fig. 3).

Grade 1-2 adverse effects were experienced in 85% of patients and primarily consisted of a mild viral-like syndrome (fever, 52%; chills, 48%; fatigue, 32%; nausea, 30%; vomiting, 20%; and headache, 20%). Grade 3 side effects were limited to six patients with pain (possibly disease-related) and four patients with fatigue and dyspnea. Of the three patients with autoimmune vitiligo, two attained CR and one was responding prior to leaving the study for noncompliance issues.

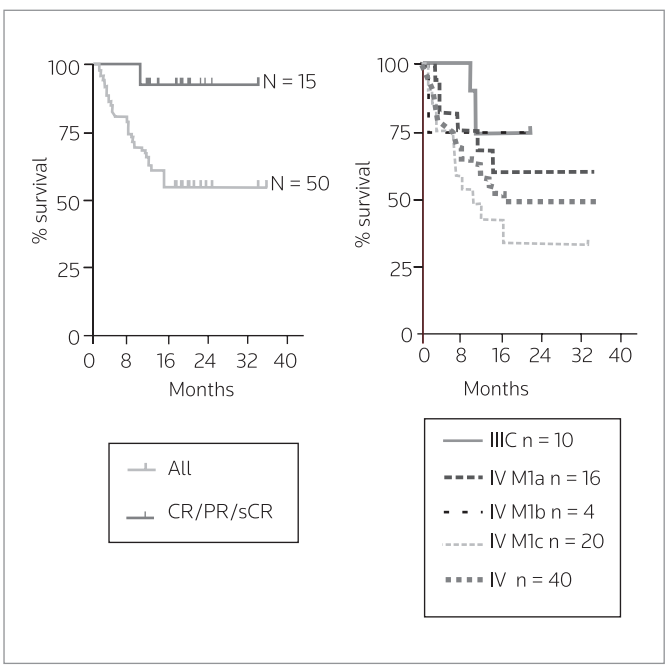

Figure 3. Kaplan-Meier survival analysis for advanced melanoma patients following intratumoral OncoVEX^{GM-CSF}. **A.** Survival curves for all patients enrolled and those who achieved partial response (PR), complete response (CR) or stringent complete response (sCR); **B.** Survival by disease stage and substage (M1a, M1b and M1c). Reprinted with permission © 2008 American Society of Clinical Oncology. Senzer, N.N., Kaufman, H.L., Amatruda, T. et al. *Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second-generation oncolytic herpesvirus in patients with unresectable metastatic melanoma.* J Clin Oncol 2009, 27(34): 5763-71.

Limited immune effector cell and functional analyses were performed on tumor and peripheral blood mononuclear cell (PBMC) samples from 11 patients, 2 of whom provided matched injected and noninjected tumor specimens (38). The results revealed the quantitative discordance between tumor and peripheral blood T-cell subsets, with significantly more regulatory T cells (Tregs; $CD4^+FoxP3^+$), suppressor $CD8^+$ T cells (T_S; $CD8^+FoxP3^+$) and myeloid-derived suppressor cells (MDSC; $CD14^+CD11b^+HLA\text{-}DR^{lo/-}$) in the tumor-infiltrating lymphocytes, emphasizing the necessity for tumor immune assessment in future vaccination studies. ELISpot assay revealed a significant increase in MART-1 (melanoma antigen recognized by T-cells-1)-specific T cells in both tumor-infiltrating lymphocytes and PBMCs from one of the patients with a confirmed CR, confirming that OncoVEX^{GM-CSF} in situ vaccination elicits both local and systemic antitumor-specific immune responses. Melanoma tumor-infiltrating lymphocytes from matched OncoVEX^{GM-CSF}-injected and -uninjected sites in the same patients also recognized MART-1. In addition, tumor-infiltrating lymphocytes from OncoVEX^{GM-CSF}-treated patients showed lower levels of Treg, T_S and MDSC than those from unvaccinated surgically resected patients.

Based on the previous results, an FDA-approved, pivotal, randomized, 2:1 allocation, 360-patient phase III trial comparing OncoVEX^{GM-CSF} to s.c. administered GM-CSF (125 μg/m^2 daily x 14 days every 4 weeks [39]) in patients with stage IIIB, IIIC and IV (no CNS or bone metastases, ≤ 3 visceral lesions, lactate dehydrogenase [LDH] ≤ 1.5 x ULN) has been initiated (ClinicalTrials.gov Identifier NCT00769704). The primary objective is to achieve a statistically significant durable RR, which is defined as the rate of objective response (CR or PR) lasting continuously for 6 or more months as compared to control therapy and beginning at any point within 12 months of initiating therapy. The treatment schedule will be the same as in the completed phase II study, with the dose modified as follows: ≤ 0.5 cm tumor diameter longest diameter, up to 0.1 mL; > 0.5 to ≤ 1.5 cm, up to 0.5 mL; > 1.5 to 2.5 cm, up to 1.0 mL; > 2.5 to 5 cm, up to 2.0 mL; and > 5 cm, up to 4.0 mL. If any injected lesion progresses, the injection frequency can be increased from biweekly to weekly for up to four doses. Patients will continue receiving protocol therapy until clinically relevant disease progression after 24 weeks from initiation. Patients require measurable disease ≥ 10 mm in diameter that is injection-accessible, including through ultrasound guidance for deeper subcutaneous or nodal tumor deposits.

DISCUSSION AND FUTURE PERSPECTIVES

The survival results in the phase II study compare favorably to a recently published meta-analysis of 2,100 stage IV metastatic melanoma patients entered into 42 phase II trials from 1975 through 2005 (40), where the 1-year overall survival (OS) rate was 25.5%, with no trial providing a survival result that was statistically different from the mean (25% in 524 patients). In the same analysis, the 1-year OS for only those 1,024 patients with visceral disease (stage IVM1c) was 23.8%, as compared with 40% of stage IV OncoVEX^{GM-CSF}-treated patients. The median survival time had not been reached at 16+ months for all patients treated with OncoVEX^{GM-CSF} (58% remaining alive), as well as for the stage IV subset (52.5% alive), at the time of publication of the phase II results. The 28% response rate, with impressive durability of response in both injected and

uninjected lesions, including visceral sites, in conjunction with a 58% 1-year overall survival rate is compelling evidence for systemic efficacy.

Ultimately, clinical justification for oncolytic virus immunotherapy hinges on the demonstration of systemic safety, as well as efficacy. With respect to efficacy, experience indicates that significant hurdles need to be overcome, including: 1) the less than 100% efficient infectious process achieved by both wild-type and attenuated viral constructs (41); 2) when administered systemically, pharmacokinetic limitations due to rapid uptake and clearance by nontarget tissues (42); 3) viral activation of the proinflammatory cascade through TNF-α and interferon gamma (IFN-γ) induction that reduces viral survival (43, 44); and 4) activation of adaptive immune responses with increased viral neutralizing antibody titer (44), which has previously been shown to reduce the effectiveness of viral-mediated antitumor approaches, particularly further reducing the viral circulating half-life when administered systemically. Results thus far suggest that the concept of in situ vaccination, not requiring systemic administration to achieve a systemic antitumor effect, in general, and the application of OncoVEX^{GM-CSF} in particular, may overcome these challenges.

SOURCE

BioVex, Inc. (US).

DISCLOSURES

The authors state no conflicts of interest.

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