reovirus as a pre-conditioning regimen performed significantly better than the simultaneous or preceding administration of bsAbs. This combination treatment also induced regressions of non-injected distant lesions, suggesting that this therapy might be effective for metastatic disease.

**Conclusions** Oncolytic reovirus administration represents an effective strategy to induce a local IFN response and strong T cell influx, thereby sensitizing the tumor microenvironment for subsequent CD3-bsAb therapy (figure 1). Our data advocate for the inclusion of oncolytic viruses as a pre-conditioning strategy in T cell engaging antibody trials for solid tumors. Since both CD3-bispecific antibodies and oncolytic viruses are in advanced clinical development as monotherapies, efficient translation of this combination seems feasible.

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**Ethics Approval** All mice studies were approved by the institutional Animal Welfare Body of Leiden University Medical Center and carried out under project licenses AVD1160020187004 or AVD116002015271, issued by the competent authority on animal experiments in the Netherlands (named CDCC).

**REFERENCES**


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**591 COMPARISON OF TWO OHSV VECTORS FOR THE TREATMENT OF Glioblastoma**

**Background** Glioblastoma multiforme (GBM) is the most common human brain cancer. Despite a well-established standard of care, the 5-year mortality rate of GBM patients is 95%, highlighting the need for innovative therapeutic strategies. A variety of oncolytic viruses, including those derived from herpes simplex virus (oHSV), have been designed for GBM therapy, but early-phase clinical trials have reported few complete responses and no evidence of durable anti-tumor immunity. Potential reasons for the lack of efficacy are limited vector potency (i.e., virulence) and the presence of a highly immunosuppressive tumor microenvironment (TME) comprised of few activated lymphocytes, large numbers of immunosuppressive myeloid cells (macrophages, myeloid derived suppressor cells [MDSCs], microglia), and an agglomerate of immunosuppressive cytokines (IL-10, VEGF, MIF, etc.).

Herein we explore these obstacles by comparing the anti-tumor activity two different oHSV designs, an HSV-1 KOS strain derivative designated KG4:T124, and an F strain derivative designated rQNestin34.5v1 (a similar oHSV, rQNestin34.5v2, is currently in a phase I clinical trial for GBM).

**Methods** Using the murine syngeneic GBM models, GL261N4 and CT2A, we compared the anti-tumor activity of KG4:T124 and rQNestin34.5v1. In vitro, we evaluated the viral entry, replication capacity, and cytotoxicity of both oHSVs. In vivo, we measured the impact of both vectors on tumor progression, TME immune cell composition, and animal survival.

**Results** Virus entry into cancer cells of KG4:T124 or rQNestin34.5v1 was relatively similar, but rQNestin34.5v1 replicated more effectively and generally induced greater viral mediated cytotoxicity. In syngeneic mice, rQNestin34.5v1 reduced orthotopic GL261N4 tumor burden and enhanced animal survival compared to KG4:T124. However, preliminary data indicate that multiple injections of KG4:T124 but not rQNestin34.5 enhance GL261N4 survival outcome. Neither oHSV impacted survival outcomes in the more pernicious CT2A model. Analysis of either the GL261N4 or CT2A TME two days post virus administration revealed that both viruses had reduced microglia cell frequency, induced the influx of tumor associated macrophages and polymorphonuclear cells, but did not alter the frequency of monocytes MDSCs, natural killer cells, CD8+ or CD4+ T-cells.

**Conclusions** rQNestin34.5 had greater anti-tumor activity in vivo and in vitro, but did not benefit from multiple oHSV injections. Both viruses induced similar changes in the TME immune cell composition. However, the presence of vital adaptive immune cell types within the TME was not observed at 2 days post oHSV treatment.

**Acknowledgements** Research reported in this abstract was supported by the National Institutes of Health grants P01CA163205 (EAC & JCG) and ST32CA082804-19 (JWJ).

**REFERENCES**


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Methods SENS™ employs proprietary an ionizable cationic lipid and biodegradable and biocompatible polymers. Following complexation with replication-incompetent adenovirus serotype 5 (Ad-vSENS) or replication-competent oncolytic adenovirus serotype 5 (OAd-vSENS), the physicochemical properties of the complexes were characterized by dynamic light scattering (DLS) and electron microscopy. The benefit of vSENS in coxsackievirus and adenovirus receptor (CAR) restricted cellular transduction of adenovirus was evaluated with Ad-vSENS in CAR negative cancer cells. Pharmacokinetic profile of OAd-vSENS was examined in mice following systemic administration to assess the protective effect of vSENS in the presence of pre-existing immunity to Adenoviral proteins. Anti-tumor efficacy was evaluated in syngeneic subcutaneous tumor mice models. The serum level of alanine aminotransferase (ALT) in mice was evaluated by blood chemistry analyzer.

Results Ad-vSENS effectively infected cancer cells in CAR-independent manner, where cancer cell-killing effects of OAd-vSENS were significantly enhanced in CAR negative cancer cells compare with those of naked OAd. When vSENS is complexed with an adenovirus, it encapsulates the virus like a shell shielding the adenovirus. Consistently, in syngenic tumor bearing mice with pre-existing Ad immunity, longer virus blood half-life and longer survival of the mice were observed when administered with OAd-vSENS compared to naked OAd. The hepatotoxicity of OAd was greatly reduced by vSENS formulation as evidenced by the absence of acute spike in serum ALT levels typically seen after systemic administration of OAd.

Conclusions The results show the potential of vSENS as a novel platform technology for delivery of Ad to overcome challenges adeno-virotherapies face in the clinic. vSENS platform is expected to expand the efficacy of the virus from cancer patients with high CAR expression to patients with limited CAR expression often associated as the cancer progresses. The platform is likely to facilitate treatment in patients with high levels of antibodies to adenovirus by shielding the virus from neutralization and increasing the bioavailability.

Ethics Approval The study was approved by Samyang Biopharmaceuticals Institution’s Ethics Board, approval number SYAU2009.

REFERENCES

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TUMORAL MELANOSIS MIMICKING RESIDUAL MELANOMA AFTER T-VEC TREATMENT

Song Park*, Alaa Moshiri, Rouba Had, Austin Green, Jennifer Gardner, Coley Doolittle-Amieva, University of Washington, Seattle, WA, USA

Background Talamogene laherparepvec (T-VEC) has become an increasingly popular treatment option for surgically non-resectable, recurrent melanoma based on its durable efficacy and safety profile. The complete response (CR) rate has been reported to be ~20% with a median of ~9 months to achieve it.1 2 Assessment of treatment response in those studies has predominantly relied on the clinical impression of the size and color of the lesions. However, in the real-world, decrease of tumor size often occurs rapidly within the first 2–3 months, while improvement of the pigmentation takes several more months. Such clinical observation of lasting pigmentation could be explained by tumoral melanosis – a histopathologic term referring to the presence of a melanophage-rich inflammatory infiltrate without remaining viable tumor cells.

Methods We hypothesized that residual pigmentation of stable melanoma lesions while on successful T-VEC treatment may represent tumoral melanosis. We also report practical information of such phenomenon including timeline and clinical features.

Results We report 6 cases of metastatic cutaneous melanoma treated with T-VEC with excellent pathologic responses. Biopsies of 5 cases were performed after observing variable clinical changes in the injected tumors, with some shrinking or becoming flat, while others grew or became raised. The range of time to biopsy was 4–23 months from the initial treatment date. Pathologic evaluation macular lesions demonstrated non-viable tumor tissue with tumoral melanosis in all cases. In an additional case, clinically increased size of the injected tumor prompted surgical excision, which similarly showed tumoral melanosis without viable tumor. Of note, while size of the tumor was increased, SUV max of the lesion decreased from prior assessment on PET-CT. No patient has developed regrowth or recurrent melanoma of the injected lesions to date (table 1).

Conclusions In patients receiving T-VEC treatment, pathologic CR may be achieved within the first 2–3 months, which precedes clinical improvement of pigmentation. To decrease unnecessary additional T-VEC treatment and assess the response correctly, serial biopsy of stable pigmented lesions should be considered to assess for the presence or absence of viable tumor.

Acknowledgements N/A
Trial Registration N/A

593 TUMORAL MELANOSIS MIMICKING RESIDUAL MELANOMA AFTER T-VEC TREATMENT

Abstract 593 Table 1  Summary of patient characteristics

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Abstract 593 Table 1

Summary of patient characteristics