polymer nanoparticle delivery system, so called Stability Enhanced Nano Shells (SENS™) for the delivery of Virus (vSENS).

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 syngeneic 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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593 TUMORAL MELANOSIS MIMICKING RESIDUAL MELANOMA AFTER T-VEC TREATMENT
Song Park*, Ata Moshiri, Rouba Had, Austin Green, Jennifer Gardner, Coley Doolittle-Amieva. University of Washington, Seattle, WA, USA

Background Talmogene 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 3 months, while improvement of the pigmentation takes several 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.

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.

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Trial Registration N/A
Armed Myxoma Virus Demonstrates Therapeutic Activity in Xenograft Models

Lino Torres-Dominguez, Lino Franco, Mario Abrantes, Benjamín Walker, Zachary Tacner, Cassandra Kien, Natalie Elliott, Grant McFadden, Leslie Sharp*.

OncoMyx Therapeutics, Phoenix, AZ, USA

Background Oncolytic Viruses (OV) selectively replicate in and lyse tumor cells and provide stimulation to the immune system. This represents a promising therapeutic option for cancer patients that do not respond well to treatment with immune checkpoint inhibitors. Myxoma virus (MYXV) is a member of the Poxv family of double stranded DNA viruses. The natural host of MYXV is a subset of rabbits and hares, but MYXV can infect cancer cell lines of humans and other species. The genome of MYXV is relatively large and is amenable to engineering for expression of transgenes making it an excellent oncolytic virus for introduction of immunomodulatory proteins.

Methods Armed MYXV were tested for oncolytic activity and transgene production in syngeneic mouse cancer models in vitro and in vivo. In vivo models were further assessed for activity when in combination with immune checkpoint inhibitors and for immune mechanisms of action contributing to the efficacy of armed MYXV.

Results Armed MYXV demonstrated oncolytic activity, transgene production capability and in vivo activity following intratumoral and intravenous administration of armed myxoma viruses in murine cancer models. Additional combination therapy with clinically relevant immune checkpoint inhibitors is demonstrated.

Conclusions Armed Myxoma viruses present an efficacious novel oncolytic viral therapy with the ability to modulate immune responses in murine cancer models.

Ethics Approval Animal studies were approved by OncoMyx and the TD2 IACUC.