ONCR-GBM, a Novel, Armed Oncolytic HSV-1 Vector Engineered for Efficacy and Safety in Glioblastoma

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Introduction

Glioblastoma (GBM) is the most common primary brain tumor, with a 5-year overall survival of only ~15% (1). Oncolytic viruses are a promising and active area of research in GBM with the conditional approval of oncolytic HSV-1 vector, Teparatopavirus (also known as GT-011 and marketed as Delcact by Daiichi Sankyo) in Japan for recurrent GBM based on an overall survival of 12 months and 1 year survival rate of ~80% (2). In 2022, an HSV-1 vector more attenuated than Teparatopavirus, recently demonstrated acceptable tolerability with evidence of responses in children with recurrent or progressive high-grade glioma (3). Both of these vectors rely exclusively on the oncolytic activity of HSV-1, neither express any immune stimulatory transgenes and infect cells via HSV-1 capsule entry receptors, including Nectin-1.

We report here a differentiated oncolytic HSV-1 vector, ONCR-GBM, that is specifically targeted towards EGFRvIII mutations. Antitumor efficacy has been further enhanced through the incorporation of four payloads designed to modulate the immunosuppressive tumor microenvironment of GBM. This includes IL-12 and a PD-1 antagonist nanobody with recurrent or progressive high-grade glioma (3). Both of these vectors rely exclusively on the oncolytic activity of Nectin-1.

ONCR-GBM is a novel, armed oncolytic HSV-1 vector that enhances T cell recruitment and activation, as well as 15-hydroxyprostaglandin dehydrogenase (HPGD) and a novel miR attenuation safety strategy to inhibit viral replication in healthy cell types and which utilizes a microRNA attenuation safety strategy to inhibit viral replication in healthy cell types and which utilizes a microRNA attenuation safety strategy to inhibit viral replication in healthy cell types.

miR Attenuation Strategy

Each miR-T cassette incorporates 4 miR target sequences in tricarinate, and is designed using an algorithm to minimize off-target secondary structure for maximum activity.

ONCR-GBM is Targeted to EGFR and NECTIN-1

Targeting to EGFR was achieved using an anti-EGFR VHH that can bind murine and human EGFR and EGFRvIII, which is engineered into the HSV-1 genome. EGFR targeted HSV can use either NECTIN-1 or EGFR/EGFRvIII as a receptor.

EGFR Targeting and Fusogenic Mutations Improve Spread in GBM Tumor Cell Lines

All viruses express a rOney reporter gene to quantify oncolysis and spread:
- Non-targeted
- Non-fusogenic
- Nectin-1
- Nectin-1 + fusogenic

HKG and MPO-Modulating Ab Payloads Provide Additional Benefit in the GL121 Model

Clear dose response detectable for ONCR-IL-12/PD-1.

miR Attenuation Protects CNS from Viral Replication

Body Weight Change [%]

Reference