Glioblastoma (GBM) is an aggressive primary brain tumor affecting approximately 74,000 people worldwide each year with poor survival rate of 15%. The patients often present with a median overall survival (OS) of 9 months, and GBM is the most common malignant brain tumor. New therapies are urgently needed.

We have developed an adenovirus, Ad-RTS-hIL-12® (Ad-V), administrated intratumorally under the control of the RheoSwitch Therapeutic System® (RTS®), expression platform. Gene expression and Ad-V function production is highly controllable by activator ligand veledimex (V). This technology has consistenly shown a beneficial effect in subjects with recurrent or progressive glioblastoma. The technology has successfully shown a dose-response and corresponding survival benefit in the GL261 mouse glioma model. Influx of cytotoxic CD8+T lymphocytes to drive a cytotoxic immune response against associated antigens significantly improve the function of activated CD8+T lymphocytes and corresponding survival benefit in the GL261 mouse glioma model.

Inclusion Criteria

- Male or female subject ≥ 18 and ≤ 75 years of age must have
- Histologically confirmed diagnosis of GBM or other WHO Grade IV malignancy from archival tissue
- Demonstrate readable tumor response progression by using the tumor response progression criteria and tumor imaging criteria
- Karnovsky performance status ≥ 70
- Adequate bone marrow, liver, and kidney function

Exclusion Criteria

- Radiotherapy within 4 weeks prior to vaccination
- Subsequent administration of an investigational agent or treatment (i.e., non-exempt investigational agent or therapy, investigational device or drug, etc.)

Key Eligibility Criteria

- Male or female subject ≥ 18 and ≤ 75 years of age must have
- Histologically confirmed diagnosis of GBM or other WHO Grade IV malignancy from archival tissue
- Demonstrate readable tumor response progression by using the tumor response progression criteria and tumor imaging criteria
- Karnovsky performance status ≥ 70
- Adequate bone marrow, liver, and kidney function

Phase I Study of IL-12 Gene Therapy in Recurrent or Progressive Glioblastoma/Grade III Malignant Glioma

• Five Days prior to therapy, i.e. GL-261 glioma cells injected at 1×10⁶ cells in the brain of C57BL/6 mice
• On Day 7 a single dose of Ad-RTS-hIL-12® at 515μL q.s. was followed by the activator ligand, veledimex administrated orally for 10 consecutive days.

Phase II Study of IL-12 Gene Therapy in ReCURRENT or PROgressive Glioblastoma/Grade III Malignant Glioma

- Treatment schedule: One dose of intratumoral Ad-RTS-hIL-12® and oral veledimex
- Results clearly show that veledimex is bioavailable and crosses the blood-brain barrier

• Data shows that dose responses and corresponding survival benefits are significant

**References**

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- Franco M. Lebel, John A. Barrett, E. Antonio Chiocca, John Yu, Rimas Vincas Lukas, Priya Kumthekar, Lauren JN Cooper; ZIOPHARM Oncology, Inc., Boston, MA; Brigham and Women’s Hospital, Boston, MA; Cedars-Sinai Medical Center, Los Angeles, CA; University of Chicago, IL; Northwestern Memorial Hospital, Chicago, IL.
- Liao Y, Davis RL, Van Meir EG (2002) Vascular pericyte expression of the proinflammatory cytokine IL-12 significantly improves the function of activated CD8+ T lymphocytes and corresponding survival benefit in the GL261 mouse glioma model.
- We have demonstrated that intratumoral administration of Ad-RTS-hIL-12 results in targeted tumor cytotoxicity and the induction of systemic T cell memory. Ad-RTS-hIL-12, an adenovirus encoding IL-12 gene, has been used to treat glioblastoma multiforme (GBM) patients in clinical trials. The adenovirus is controlled by the RheoSwitch Therapeutic System® (RTS®), a gene expression platform. Gene expression and IL-12 production is tightly controlled by activator ligand veledimex (V). This technology has consistently shown a beneficial effect in subjects with recurrent or progressive glioblastoma. The technology has successfully shown a dose-response and corresponding survival benefit in the GL261 mouse glioma model.
- Early data suggests likely benefit vs. historical control with a favorable trend in survival.
- Intratumoral administration of the viral vector activated by veledimex results in functional IL-12 expression.
- Recombinant IL-12 (rIL-12) has been shown to have a beneficial effect in subjects with recurrent or progressive glioblastoma. The technology has consistently shown a beneficial effect in subjects with recurrent or progressive glioblastoma. The technology has successfully shown a dose-response and corresponding survival benefit in the GL261 mouse glioma model.
- Encouraging dose response of veledimex controlling the RTS® switch in GBM patients.
- Although median OS (mOS) has not been reached, median follow-up 16.2 months with 10 out of 11 alive – 90.9% 1 year survival.
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