Controlled intratumoral viral delivery of Ad-RTS-hIL-12 + oral veledimex suggests a beneficial effect in subjects with recurrent or progressive glioma.

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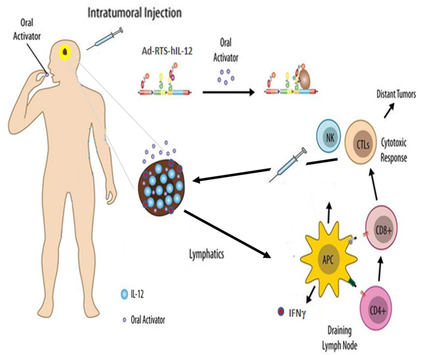
Background

- Glioblastoma (GBM) is an aggressive primary brain tumor affecting approximately 74,000 people worldwide each year with poor overall survival.[i, ii] Recurrent GBM has one of the lowest 3-year survival rates, at 3%, among all cancers.[iii] For patients who have experienced multiple recurrences the prognosis is particularly poor, with a median overall survival (OS) of 6-7 months, while OS in patients that have failed temozolomide and bevacizumab, or equivalent salvage chemotherapy, is approximately 3-5 months.[iv, v] New therapies are urgently needed.

- We have developed an adenoviral vector, Ad-RTS-IL-12 (AD), administered intratumorally under the control of the RheoSwitch Therapeutic System® (RTS®) expression platform. Gene expression and IL-12 protein production is tightly controlled by activator ligand veledimex (V). This technology has consistently shown a dose-response and corresponding survival benefit in the GL261 mouse glioma model.



An adenoviral vector engineered to express IL-12 (Ad-RTS-hIL-12) utilizing the RheoSwitch Therapeutic System® (RTS®) gene switch is injected intratumorally

Expression of IL-12 is controlled through the administration of an oral activator ligand Veledimex

- Localized production of IL-12
- T cell activation toward tumor -associated antigens
- Influx of cytotoxic $CD8^+$ T cells coupled with a reduction in $CD4^+$ regulatory T cells

Regulated intratumoral expression of IL-12 promotes activation of tumor-infiltrating lymphocytes to drive a cytotoxic immune response

Rationale for IL-12 as a Cancer Immunotherapeutic

- Interleukin-12 (IL-12)
  - Pro-inflammatory cytokine
  - Can reverse immune escape mechanisms induced by MDSCs and DCs and significantly improve the function of activated $CD8^+$ T cells resulting in the collapse of the vascularized stroma of solid tumors
  - Expression of functional IL-12 in human subjects by direct intratumoral injection of Ad-RTS-hIL-12 + oral veledimex generates downstream IFNγ production and rapid elevation of IL-10 and IP-10 in melanoma and breast cancer patients
  - We have previously demonstrated that intratumoral administration of Ad-RTS-IL-12 results in targeted tumor cytotoxicity and the induction of systemic T cell memory
  - Ad-RTS-IL-12 + veledimex explores local treatment strategy under the control of the RheoSwitch Therapeutic System® (RTS®) gene switch to extend the IL-12 therapeutic window

References

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[iv] Omuro, A. Glioblastoma and Other Malignant Gliomas. A Clinical Review *JAMA*. *2013* Nov 6;310(17):1842-50.
[v] Iwamoto et al. Patterns or relapse and prognosis after bevacizumab failure in recurrent glioblastoma. Neurology 2009; 73(15):1200-1206
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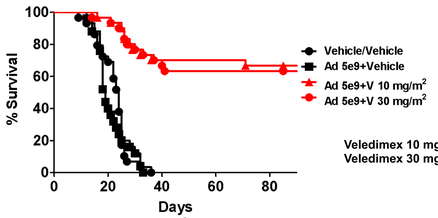
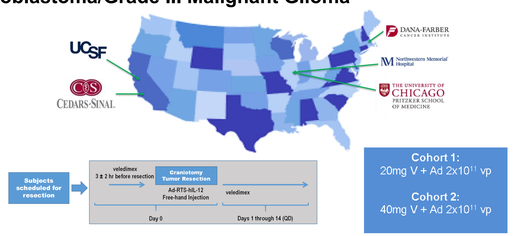
Ad-RTS-mIL-12 + Veledimex Results in Increased Survival in Orthotopic Glioma Mouse Model



Veledimex 10 mg/m² = patient 20 mg flat dose
Veledimex 30 mg/m² = patient 60 mg flat dose

- Five Days prior to therapy $1x10^5$ GL-261 glioma cells volume 3ul were administered into the brain of C57BL/6 mice
- On Day 1 a single dose of Ad-RTS-mIL-12 at $5x10^9$ vp i.t. 5ul followed by the activator ligand, veledimex administered orally for 14 consecutive days.

Phase 1 Study of IL-12 Gene Therapy in Recurrent or Progressive Glioblastoma/Grade III Malignant Glioma



Study Objectives

- **Primary Objective**
  - Determine the safety and tolerability of varying dose levels of intratumoral Ad-RTS-hIL-12 and oral veledimex doses in subjects with recurrent or progressive glioblastoma or Grade III malignant glioma
- **Secondary Objective**
  - Determine the veledimex maximum tolerated dose (MTD) when given with varying doses of intratumoral Ad-RTS-hIL-12
  - Determine the veledimex pharmacokinetic (PK) profile
  - Determine the veledimex concentration ratio between the brain tumor and blood
  - Evaluate cellular and humoral immune responses elicited by Ad-RTS-hIL-12 and Veledimex
  - Determine investigator assessment of response, including tumor objective response rate (ORR) and progression-free survival (PFS)

Key Eligibility Criteria

Inclusion

- Male or female subject ≥ 18 and ≤ 75 years of age must have:
- Histologically confirmed supratentorial glioblastoma or other WHO Grade III or IV malignant glioma from archival tissue
- Evidence of tumor recurrence/progression by MRI according to response assessment in neuro‑oncology (RANO) criteria after standard initial therapy
- Karnofsky performance status ≥ 70
- Adequate bone marrow, liver, and kidney function

Exclusion

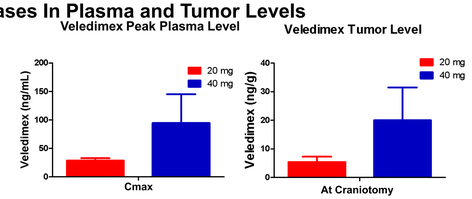
- Radiotherapy treatment within 4 weeks or less prior to veledimex dosing
- Subjects with clinically significant increased intracranial pressure (e.g., impending herniation or requirement for immediate palliative treatment) or uncontrolled seizures
- Known immunosuppressive disease, autoimmune conditions, and/or chronic viral infections [e.g., human immunodeficiency virus (HIV), hepatitis]

Demographics

	Cohort 1 (N=7)	Cohort 2 (N=4)	Total (N=11)
Age in years Median (Min, Max)	39.4 (31.9, 57.9)	51.6 (36.6, 54.5)	39.9 (31.9, 57.9)
Gender Male : Female	4 : 3	2 : 2	6 : 5
First recurrence Multiple recurrences (n)	0 7	3 1	3 8
Prior Lines of Treatment (mean)	2.7	2.0	2.5
Grade at Study Entry	Grade III 1 Grade IV 6	Grade III 0 Grade IV 4	Grade III 1 Grade IV 10
KPS ≥ 90 ≥ 70 and < 90	5 (71%) 2 (29%)	3 (75%) 1 (25%)	8 (72%) 3 (28%)
Veledimex Dosing (days) Expected 15 days Mean % compliance	13 93%	11* 73%	12 83%
Cumulative Steroid Use (Day 0-14) mg Mean (Min, Max)	81 (10, 168)	68 (10, 116)	76 (10, 168)

*One patient was dose reduced from 40 mg of Veledimex to 20 mg starting on Day 5

Veledimex Crosses Blood Brain Barrier: Dose-related Increases In Plasma and Tumor Levels



Peak Serum Levels Post Intratumoral Injection of Ad-RTS-hIL12 + Veledimex

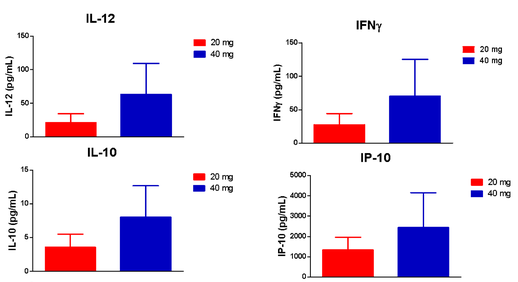
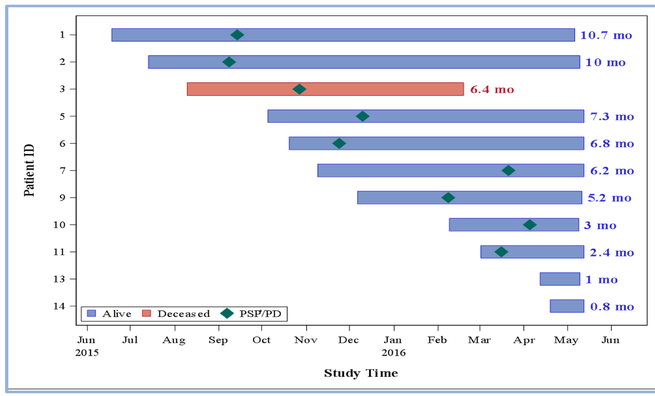


Figure Legend

Upper panel is the plasma C_{max} and tumor levels (Day 0) of the orally administered activator ligand, veledimex at 20 (N=7) and 40 mg (N=4). Results clearly show that veledimex is bioavailable and crosses the blood brain barrier at sufficient levels to turn on the RTS® switch and local generation of IL-12. Depicted in the lower panel are the peak (mean ± SEM) increases in serum cytokines observed on Days 3-7 illustrating the local production of IL-12 results in increases in downstream IFNγ demonstrating biological activity.

Current PFS and Survival by Patient



- All Pseudoprogression/Progression are assumed to trigger PD for PFS analysis at this time (RANO). It is important to note that clinical benefit including long term survival and tumour regression, can still occur after initial disease progression or after the appearance of new lesions in iRANO as reported by Okada et al 2015.[vi]

- Although median OS (mOS) has not been reached, median follow-up is 6.2 month with 10 out of 11 alive
  - In cohort 1: 6 of 7 (86%) patients remain alive with a median follow up of 6.8 months
  - 1 PD died at 193 days (6.4 months)

- Historical control mOS:
  - Failed temozolomide and bevacizumab or equivalent salvage chemotherapy ~ 3-5 months [iv]
  - Multiple recurrences ~6-7 months [iv,v]

Safety Summary N=11

- Overall Ad-RTS-hIL12 + veledimex was well tolerated
- Neurotoxicities were manageable and reversible
- All SAEs and Grade 3 related toxicities are rapidly reversible upon discontinuation of Veledimex
- Common related adverse events (most Grade 1 and 2)include headache, fever, nausea/ vomiting, WBC/leukocyte count decreased, platelet count decreased, and LFTs increased
- Four subjects had related SAEs
  - One with headache, nausea, vomiting, leukopenia, neutropenia, thrombocytopenia
  - One with aseptic meningitis
  - One with mild cytokine release syndrome
  - One with platelet count decreased and ALT increased

Conclusion

- The intracranial administration of Ad-RTS-hIL12 + oral veledimex is clinically feasible
- Early data suggests likely benefit vs. historical control with a favorable trend in survival
- Intratumoral administration of viral vector activated by veledimex results in functional IL-12
- Encouraging dose response of veledimex controlling the RTS® switch in GBM patients.
- Intratumoral regulated IL-12 expression in a salvage GBM population appears to have an acceptable and rapidly reversible side effect profile, as seen previously in Melanoma and Breast studies (N=38)
- Enrollment and dose escalation ongoing

Data Collection is ongoing.