Phase 1 study of intratumoral viral delivery of Ad-RTS-hIL-12 + oral veledimex is well tolerated and suggests survival benefit in recurrent high grade glioma.

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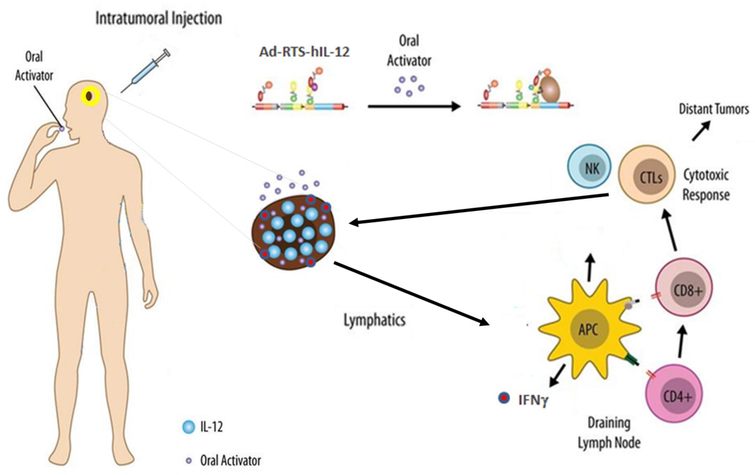
Background

- Glioblastoma (GBM) is an aggressive primary brain tumor affecting approximately 74,000 people worldwide each year with poor overall survival (OS).[i, ii]
- For GBM patients who have experienced multiple recurrences the prognosis is particularly poor, with a median overall survival (mOS) of 6-7 months, while OS in patients that have failed temozolomide and bevacizumab, or equivalent salvage chemotherapy, is approximately 3-5 months.[iii, iv] New therapies are urgently needed.
- Ad-RTS-hIL-12 (Ad) is a novel gene therapy candidate expressing IL-12 under the control of an orally administered activator ligand, veledimex (V), through the proprietary RheoSwitch Therapeutic System® (RTS®) gene switch.
- We have previously demonstrated that intratumoral administration of Ad results in targeted tumor cytotoxicity and the induction of systemic T cell memory.
- Ad + V explores a local treatment strategy under the control of the RTS® gene switch to extend the IL-12 therapeutic window.

Figure 1: Regulated intratumoral expression of IL-12 promotes activation of tumor-infiltrating lymphocytes to drive a sustained cytotoxic immune response.



Key Study Objectives

Primary Objective

- Safety and tolerability

Key Secondary Objectives

- Maximum tolerated dose (MTD)
- Pharmacokinetic (PK) profile
- V ratio of tumor/plasma
- Overall survival

Key Inclusion & Exclusion Criteria

Inclusion

- Male or female 18 to 75 years of age
- Histologically confirmed supratentorial GBM 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 within 4 weeks or less
- Clinically significant increased intracranial pressure or uncontrolled seizures
- Other significant concurrent medical conditions

Study Design

Figure 2: Group 1 design

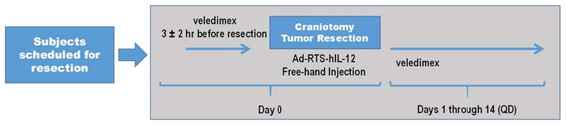


Table 1: Clinical sites in the United States

Cedars-Sinai	Los Angeles, CA
Dana-Farber Cancer Institute	Boston, MA
University of Chicago	Chicago, IL
Northwestern University	Chicago, IL
University of California, San Francisco	San Francisco, CA

References

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viii: Balmaceda C, et al. Multi-institutional phase II study of temozolomide administered twice daily in the treatment of recurrent high-grade gliomas. Cancer. 2008;112(5): 1139–1146.
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x: Stupp R, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomized phase III trial of a novel treatment modality. European J of Cancer. 2012;48:2192-2202.

Study Population

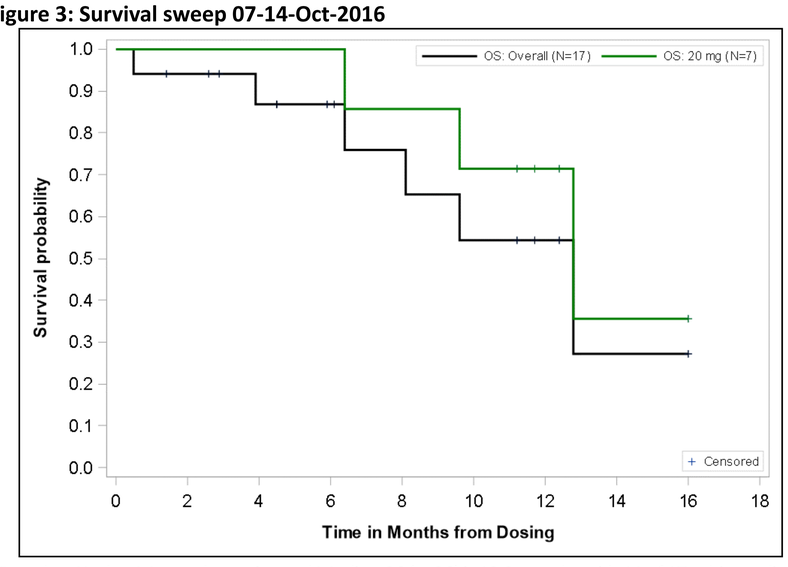
- As of 13-Oct-2016, 17 subjects enrolled. Follow-up is ongoing.

Table 2: Subject characteristics

	Ad 2X10[11] vp			
	20 mg V Cohort (N=7)	30 mg Cohort (N=4)	40 mg Cohort (N=6)	Total (N=17)
Age in years Median (Min, Max)	39.4 (31.9, 57.9)	64.1 (52.0, 74.5)	51.6 (36.4, 58.1)	51.3 (31.9, 74.5)
Gender Male : Female	4 : 3	2 : 2	4 : 2	10 : 7
First recurrence Multiple recurrences (n)	0 7	0 4	1 5	1 16
Prior Lines of Treatment (mean)	2.7	3.0	2.5	2.7
Grade at Study Entry	Grade III 1 Grade IV 6	Grade III 0 Grade IV 4	Grade III 0 Grade IV 6	Grade III 1 Grade IV 16
KPS at Screening ≥ 90 ≥ 70 and < 90	 5 (71%) 2 (29%)	 3 (75%) 1 (25%)	 2 (33%) 4 (67%)	 10 (59%) 7 (41%)
Mean V Dosing in days (15 expected) Dose Holds due to Toxicity (% of subjects)	13 14%	9 75%	9 67%	11 47%
Total Steroid Use (Day 0-14) in mg Mean (Min, Max)	80 (10, 170)	87 (0, 136)	60 (10, 112)	75 (0, 170)

Current Overall Survival

Figure 3: Survival sweep 07-14-Oct-2016



- Based on Kaplan-Meyer plot, estimated Median OS (mOS) is 12.8 months with 11 of 17 subjects alive.
- Current median progression free survival (PFS) is 2.6 months.
  - All pseudo–progression/progression/pseudo-responses are assumed to trigger progressive disease for PFS analysis at this time (RANO). It is important to note that clinical benefit, including long term survival and tumor regression, can still occur after initial disease progression or after the appearance of new lesions in iRANO as reported by Okada et al, 2015[v].

Table 3: ATI001-102 and historical control survival data

Study & Design	Treatment	N	Disease	Median Age	Median # Recurrence	mOS (months)	survival rate %		
							6 months	9 months	12 months
Ziopharm ATI001-102 Open-label Phase I	Ad + V (Overall)	17	16 rGBM 1 AA	43	3	12.8	87	65	54
	Ad+ V (20 mg)	7	6 rGBM 1 AA	39	3	12.8	100	86	71
Randomized Phase II study, BELOB [vii,&]	Bevacizumab	50	rGBM	58	1	8.0	63*	38	26
	Lomustine	46	rGBM	56	1	8.0	68*	43	30
Randomized Multi-Institutional Phase II study [viii]	Temozolomide	68	rGBM	53	1	9.0	71	N/A	35
Randomized Multi-Institutional Phase II study [ix]	Carmustine wafer	110	rGBM: 72 Other: 38	48	N/A	7.2	56	40*	22*
	Polymer placebo	112	rGBM: 73 Other: 39	48	N/A	5.4	36	30*	20*
Novocure Randomized Phase III study, EF-11[x]	NovoTTF-100A	120	rGBM	54	2	6.6	51*	30*	22
	Physician's choice^	117		54		6.0	50*	30*	20

rGBM = recurrent or progressive glioblastoma; AA= anaplastic astrocytoma;
*estimated from published data;
^Physician's choice included (as single agent or combination regimens) bevacizumab, irinotecan, carmustine(BCNU)/lomustine (CCNU), carboplatin, temozolomide or PCV (Procarbazine, CCNU, and Vincristine);
& single agent arms selected for comparison purposes

Pharmacokinetics and Biomarker Results

Figure 4: Veledimex Crosses Blood Brain Barrier with a Tumor to Plasma Ratio of ~35%

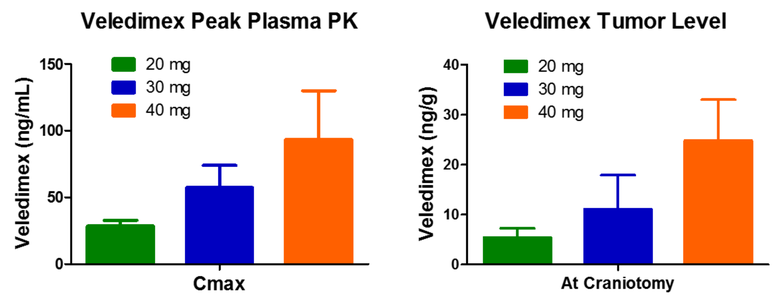
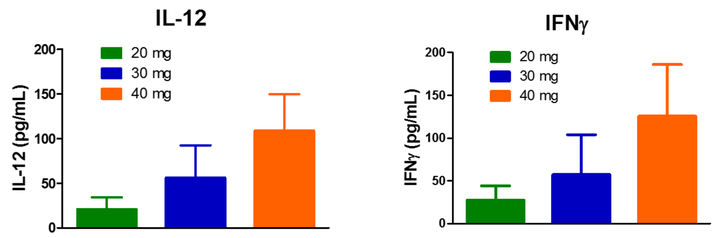


Figure 5: Peak Serum Levels Post Intratumoral Injection of Ad + V (Days 3-7)



Safety Summary (N=17)

Table 4: Treatment related treatment emergent adverse events (TEAEs) and drug related toxicities by cohort

	20 mg, N=7	30 mg, N=4	40 mg, N=6
Related ≥Grade 3 TEAE	2 (29%)	2 (50%)	3 (50%)
Related SAE	2 (29%)	1 (25%)	3 (50%)
Dose discontinuation due to AE	1*(14%)	3 (75%)	4 (67%)
Cytokine release syndrome[vi] – Grade 3	1 (14%)	1 (25%)	3 (50%)

*CYP-3A4 substrate medication taken

- Frequency of drug related toxicity correlated with dose levels.
- The most common related AEs included: pyrexia, lymphopenia, elevated ALT/AST and thrombocytopenia.
- All related SAEs were rapidly reversible upon discontinuation of V:
  - Three with cytokine release syndrome (1 at 30 mg, 2 at 40 mg)
  - One with aseptic meningitis (predominantly lymphocytes)
  - One with headache, nausea, leukopenia, neutropenia, thrombocytopenia
  - One with platelet count decreased and ALT increased
- CNS toxicities were generally mild.

Conclusions

- Ad + 20 mg V is well tolerated and suggests a survival benefit over historical control at 6, 9 and 12 months.
- Based on tolerability and survival benefit, 20 mg has been selected for an expansion cohort.
- Toxicities were tolerable, predictable and reversible upon discontinuing V.
- There is a strong correlation between V dose, BBB penetration, IL-12 intra-tumoral transcription and drug related AEs.
- These data demonstrate that the RTS® gene switch works in humans toggling not only as a switch to turn on and off the production of IL-12, but also as a rheostat to control the level of IL-12.
- A pediatric trial for brain tumors and a combination trial with a checkpoint inhibitor in adult recurrent GBM are planned at the 20 mg dose of V given the strength of the results seen in the mouse model.